

TITLE OF INVENTION

PYRROLOTRIAZINE DERIVATIVES AS KINASE INHIBITOR

TECHNICAL FIELD

The present relates to a pyrrolotriazine derivative having kinase inhibitory
5 activity, a process for preparing the same and use thereof.

BACKGROUND OF ART

Protein kinase is an enzyme that catalyzes phosphorylation of specific
residues of other proteins, and plays an important role in signal-transduction pathways
that transduce extracellular signals to the nucleus. Further, it is involved in various
10 diseases in vivo. In the onset or development of inflammatory disease, autoimmune
disease, proliferative disease or hyperproliferative disease, and/or immunity mediated
disease, there is various evidence that T-cells (or T-lymphocytes) and B-cells (or B-
lymphocytes) play an important role.

15 Janus kinase (hereinafter referred to as "JAK") is a cytoplasmic protein
tyrosine kinase that plays pivotal roles in regulating cell function in the lympho-
hematopoietic system. Cytokines are known to play an important role in regulating
inflammation, immunity and normal cell function, and JAK activates STAT (Signal
Transducer and Activators of Transcription) proteins through tyrosine phosphorylation
20 to provide rapid signaling pathways to cytokines. JAK/STAT signaling is known to be
associated with allergies, asthma, autoimmune diseases (e.g., transplant rejection,
rheumatoid arthritis, amyotrophic lateral sclerosis, multiple sclerosis etc.), solid
cancers, blood cancers (e.g., leukemia, lymphoma and so on).

25 The JAK family is classified into four members: JAK 1, JAK 2, JAK 3, and
TYK 2. Members of the JAK family pair with each other to mediate signals from a
variety of cytokines. It includes JAK2 and JAK1 associated with hematopoietic
growth factor signaling, and a combination of TYK2 and AK2 is important for
interferon signaling and contributes to host tolerance. JAK2 can induce anemia,
30 thrombocytopenia, leukopenia, especially when it is involved in the hematopoietic

growth factor signaling and causes excessive inhibition.

The expression of JAK1, JAK2, and TYK2 was found to be widely distributed, whereas the expression of JAK3 was restricted to lymphocytes and is associated with signaling for the common gamma chains, members of IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 receptors, particularly the common gamma chain of the IL-2 family. As soon as the cytokine is bound, the receptor carries adjacent JAK3 nearby, which induces autophosphorylation of the β -chain C-terminus. As a result, it causes activation of the STAT protein, which is an important step in retransmitting the signal to the nucleus. JAK3 controls the signal pathways of various cytokines through this process. This makes JAK3 as an attractive target for immunosuppression.

B cells play an important role in the development of autoimmune and/or inflammatory diseases. Protein-based therapeutic agents that reduce B cells, for example Rituxan, are effective in autoantibody-induced inflammatory diseases such as rheumatoid arthritis. Thus, protein kinase inhibitors that play a role in B cell activation are useful therapeutic agents for the treatment of B cell-mediated diseases, for example, for the production of autoantibodies.

Signal transduction through B cell receptor (BCR) regulates various B cell responses, including proliferation and differentiation into mature antibody-producing cells. BCR is an important regulatory element of B cell activity, and abnormal signal transduction can cause the formation of pathogenic autoantibodies leading to a plurality of autoimmune and/or inflammatory diseases and the proliferation of deregulated B cell.

Bruton's tyrosine kinase (hereinafter, referred to as "BTK") is an important regulator of the development, activation, signaling and survival of B-cells. BTK is involved in signal transduction pathways initiated by binding various extracellular ligands to their cell surface receptors. Following ligation of the B cell antigen receptor

(BCR), the activity of BTK by the coincident action of the protein tyrosine kinases Lyn and Syk is required for the induction of the phospholipase C- γ 2-mediated calcium mobilization. Therefore, inhibition of BTK can be a useful therapeutic approach in blocking the onset process of B-cell mediated diseases.

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As mentioned above, Janus kinase and TEC-based kinases plays an important role in the activation of T-cells and/or B-cells involved in the development of inflammatory diseases, autoimmune diseases, proliferative diseases or hyperproliferative diseases, and immunity mediated diseases. Therefore, the development of substances that effectively inhibit these diseases can be useful as a related therapeutic agent. Specific examples of the diseases which can be treated and prevented include cancer, transplant rejection, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, psoriasis, asthma, allergic dermatitis, atopic dermatitis, eczema, type I diabetes, diabetic complication, ulcerative colitis, Crohn's disease, autoimmune thyroid disorder, systemic depilation, Sjogren's syndrome and the like.

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JAK3 kinase inhibitor, tofacitinib (CP-690550) (Pfizer Inc.) is currently approved and marketed for the treatment of rheumatoid arthritis. In addition, a BTK kinase inhibitor, ibrutinib (PCI-32765) (Pharmacyclics) is in a clinical stage, but severe side effects such as skin rash and diarrhea have been reported in clinical cases. Thus, there is a need to develop a more stable and effective substance that inhibits JAK and/or BTK (see, Nat Rev Rheumatol. 2009 Jun 5(6) 317-24; Expert Opin Investig Drugs. 2014 Aug 23(8) 1067-77; Drug Discov Today 2014 Aug 19(8) 1200-4; WO2002/096909; WO2010-009342).

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Therefore, the present inventors have found a new pyrrolotriazine derivative having an excellent inhibitory activity as a kinase inhibitor, thereby completing the present invention.

DETAILED DESCRIPTION OF THE INVENTION

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TECHNICAL PROBLEM

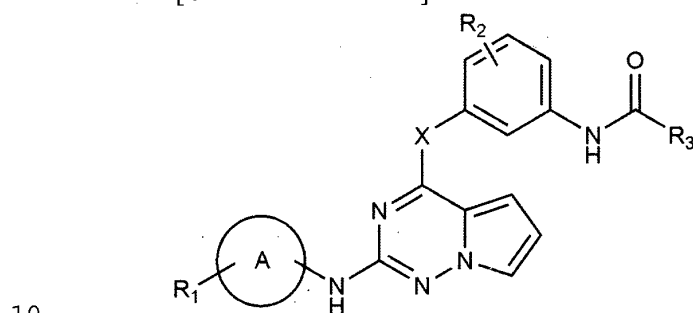
It is one object of the present invention to provide a new pyrrolotriazine derivative having kinase inhibitory activity, and a process for preparing the same.

It is another object of the present invention to provide a pharmaceutical composition comprising the pyrrolotriazine derivative as an active ingredient.

5 TECHNICAL SOLUTION

In order to achieve the above objects, the present invention provides a compound represented by the following Chemical Formula 1, or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]



in Chemical Formula 1,

X is O, or NH,

A is a divalent C₆₋₁₀ aromatic ring, or a divalent C₂₋₁₀ heteroaromatic ring containing one to three heteroatoms each independently selected from the group consisting of N, O and S,

R₁ is hydrogen; C₁₋₄ alkyl unsubstituted or substituted with one substituent selected from the group consisting of C₁₋₄ alkoxy, N(C₁₋₄ alkyl)₂, cyano, and (C₁₋₄ alkyl)-NHCO; C₁₋₄ alkoxy; C₁₋₄ haloalkyl; C₃₋₆ cycloalkyl; N(C₁₋₄ alkyl)₂; benzoyl;

pyrazolyl unsubstituted or substituted with one or two C₁₋₄ alkyl; or

20 wherein Y₁ is NH, N(C₁₋₄ alkyl), or O; Y₂ is CH or N; L is a bond, C₁₋₄ alkylene, or CO,

R₂ is hydrogen, C₁₋₄ alkyl, or halogen, and

R₃ is C₁₋₄ alkyl substituted by halogen or cyano; C₂₋₄ alkenyl unsubstituted or substituted with halogen; or C₂₋₄ alkynyl.

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Preferably, A is a divalent ring selected from the group consisting of benzene, benzothiazole, isothiazole, isoxazole, pyrazole, pyridine, pyrrole, thiazole, thiophene, and 4,5,6,7-tetrahydropyrazolo [1,5-a]pyrazine.

5 Preferably, R₁ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxyethyl, dimethylaminomethyl, diethylaminoethyl, cyanomethyl, methylaminocarbonylmethyl, methoxy, difluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, cyclopropyl, dimethylamino, benzoyl, or 3,5-dimethyl-1H-pyrazol-1-yl.

10 Preferably, R₁ is piperidin-4-yl, 1-methyl-piperidin-4-yl, 4-methylpiperazin-1-yl, tetrahydro-2H-pyran-4-yl, morpholino, 2-morpholinoethyl, or morpholine-4-carbonyl.

Preferably, R₂ is hydrogen, methyl, chloro, or fluoro.

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Preferably, R₃ is -CH₂-Cl, -CH=CH₂, -CH=CHCH₂CH₃, -CH=CHCH₂Cl, or -C≡CCH₂CH₃.

Typical examples of the compounds represented by Chemical Formula 1 are
20 as follows:

- 1) N-(3-((2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 2) N-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 25 3) N-(3-((2-((1-methyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 4) N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 5) N-(3-((2-((3-methylisothiazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-
30 4-yl)oxy)phenyl)acrylamide,

- 6) N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 7) N-(4-fluoro-3-((2-((3-methylisothiazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 5 8) N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 9) N-(4-fluoro-3-((2-((1-methyl-1H-pyrrol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 10) N-(4-fluoro-3-((2-((1-isobutyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 10 f)[1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 11) N-(3-((2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 12) N-(3-((2-((4-(dimethylamino)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 15 13) N-(4-fluoro-3-((2-((4-phenoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 14) N-(3-((2-((benzo[d]thiazol-6-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 15) N-(4-fluoro-3-((2-((pyridin-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 20 yl)oxy)phenyl)acrylamide,
- 16) N-(3-((2-((4-isopropylphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 17) N-(3-((2-((4-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 25 18) N-(3-((2-((4-(morpholine-4-carbonyl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 19) N-(3-((2-((thiophen-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 20) N-(3-((2-((1-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 30 f)[1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,

- 21) N-(3-((2-((4-((dimethylamino)methyl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 22) N-(3-((2-((4-morpholinophenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 5 23) N-(3-((2-((4-(dimethylamino)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 24) N-(3-((2-((5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 25) N-(4-fluoro-3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 10 yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 26) N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 27) N-(4-fluoro-3-((2-((1-methyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 15 28) N-(4-fluoro-3-((2-((4-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 29) N-(4-fluoro-3-((2-((4-(morpholine-4-carbonyl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 30) N-(4-fluoro-3-((2-((thiophen-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 20 yl)oxy)phenyl)acrylamide,
- 31) N-(4-fluoro-3-((2-((4-morpholinophenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 32) N-(4-fluoro-3-((2-((1-propyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 25 33) N-(3-((2-((1-(difluoromethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 34) N-(4-fluoro-3-((2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 35) N-(4-fluoro-3-((2-((1-(2-morpholinoethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 30 yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,

- 36) N-(4-fluoro-3-((2-((1-isopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 37) N-(4-fluoro-3-((2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 5 38) N-(4-fluoro-3-((2-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 39) N-(3-((2-((4-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 40) N-(4-fluoro-3-((2-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 10 41) 2-chloro-N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acetamide,
- 42) 2-chloro-N-(4-fluoro-3-((2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acetamide,
- 15 43) 2-chloro-N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acetamide,
- 44) (E)-4-chloro-N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)but-2-enamide,
- 45) N-(4-fluoro-3-(2-(isoxazol-4-ylamino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 20 46) N-(4-chloro-3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 47) N-(5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-2-methylphenyl)acrylamide,
- 25 48) N-(5-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-2-methylphenyl)acrylamide, and
- 49) N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)pent-2-ynamide.

30 In addition, the compounds of the present invention may exist in the form of

salts, especially pharmaceutically acceptable salts. As salts, salts commonly used in the art, such as acid addition salts formed by pharmaceutically acceptable free acids can be used without limitation. The term "pharmaceutically acceptable salt" as used herein refers to any organic or inorganic addition salt of the compound represented by

5 Chemical Formula 1, whose concentration is relatively non-toxic and harmless to a patient and activates effectively and whose side effects do not degrade the beneficial efficacy of the above compound.

Pharmaceutically acceptable salts can be obtained by conventional methods

10 using inorganic or organic acids. For example, the pharmaceutically acceptable salt can be prepared by dissolving the compound represented by Chemical Formula 1 in a water-miscible organic solvent, e.g., acetone, methanol, ethanol or acetonitrile, followed by adding an organic acid or an inorganic acid, and filtering and drying the precipitated crystals. Alternatively, it may be prepared by subjecting a solvent or an

15 excessive amount of acid from the acid-added reaction mixture to reduced pressure and then drying the residue, or by adding a different organic solvent and then filtering the precipitated salt. At this time, the preferred salts may include salts derived from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, acetic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid,

20 fumaric acid, malic acid, mandelic acid, tartaric acid, citric acid, ascorbic acid, palmitic acid, maleic acid, hydroxymaleic acid, benzoic acid, hydroxybenzoic acid, phenylacetic acid, cinnamic acid, salicylic acid, methanesulfonic acid, benzenesulfonic acid or toluenesulfonic acid, and the like.

25 A pharmaceutically unacceptable salt or solvate of the compound of Chemical Formula 1 may be used as an intermediate in the production of the compound of Chemical Formula 1, or the pharmaceutically acceptable salt or the solvate thereof.

The compound of Chemical Formula 1 according to the present invention

30 includes not only pharmaceutically acceptable salts thereof, but all solvates and

hydrates that can be prepared therefrom, and includes all possible stereoisomers as well. The solvate, the hydrate and the stereoisomer of the compound represented by Chemical Formula 1 may be prepared and used from the compound of Chemical Formula 1 using common methods.

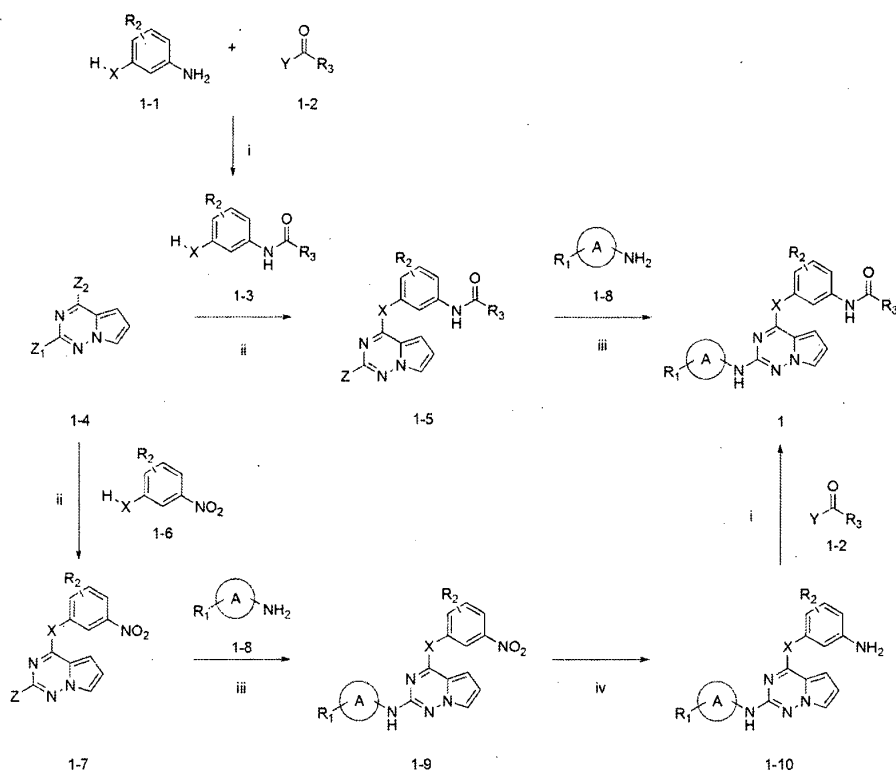
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In addition, the compound represented by Chemical Formula 1 according to the present invention may be prepared either in a crystalline form or in a non-crystalline form, and when the compound represented by Chemical Formula 1 is prepared in a crystalline form, it may be optionally hydrated or solvated. In the present invention, the compound represented by Chemical Formula 1 may not only include a stoichiometric hydrate, but include a compound containing various amounts of water. The solvate of the compound represented by Chemical Formula 1 according to the present invention includes both stoichiometric solvates and non-stoichiometric solvates.

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Furthermore, as an example, the present invention can produce the compound represented by Chemical Formula 1 through Reaction Scheme 1 below.

[Reaction Scheme 1]



(in Reaction Scheme 1, X, A and R_1 to R_3 are as previously defined, Z_1 and Z_2 are each independently halogen, and Y is halogen, or OH)

- 5 Step i is a step of preparing a compound represented by Chemical Formula 1-3 or Chemical Formula 1 by reacting a compound represented by Chemical Formula 1-1 or 1-10 with a compound (Y=Cl) represented by Chemical Formula 1-2. The reaction is preferably carried out under the conditions of triethylamine or sodium hydrogencarbonate. The reaction temperature is preferably -20°C to 0°C , and the
- 10 reaction time is preferably 30 minutes to 24 hours. The solvent for the reaction is preferably a mixed solution of dichloromethane or tetrahydrofuran and water.

 Alternatively, Step i can be carried out by reacting Y = OH instead of Y = Cl in Chemical Formula 1-2. In this case, the reaction is preferably carried out under the

15 conditions of diisopropylethylamine, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (O-HATU) at room temperature for 24 hours, and the solvent for the reaction is preferably tetrahydrofuran, dimethylformamide, or

dimethylsulfoxide.

Step ii is a step of preparing a compound represented by Chemical Formula 1-5 or 1-7 by reacting a compound represented by Chemical Formula 1-4 with a compound
5 represented by Chemical Formula 1-3 or 1-6. The reaction is preferably carried out in the presence of a base. In addition, the reaction temperature is preferably room temperature or 40 to 60°C. Further, the reaction time is preferably 1 hour to 6 hours. The solvent for the reaction is preferably dimethylformamide, 1,4-dioxane, dimethylsulfoxide, or toluene. Further, the base is preferably potassium carbonate,
10 cesium carbonate, diisopropylamine, or sodium hydride.

Step iii is a step of preparing a compound represented by Chemical Formula 1 or 1-9 by reacting a compound represented by Chemical Formula 1-5 or 1-7 with a compound represented by Chemical Formula 1-8. The reaction can be carried out in the
15 presence of a base such as tris(dibenzylideneacetone)dipalladium ($\text{Pd}_2(\text{dba})_3$), palladium acetate ($\text{Pd}(\text{OAc})_2$), or [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride ($(\text{Pd}(\text{Dppf})\text{Cl}_2)$) under basic conditions. The reaction temperature is preferably 50°C to 150°C. In addition, the reaction solvent is preferably 1,4-dioxane, toluene, t-butanol or dimethylformamide. Further, the base is preferably an inorganic alkali such as cesium
20 carbonate, calcium carbonate, sodium carbonate, potassium phosphate or the like.

Step iv is a step of preparing a compound represented by Chemical Formula 1-10 by reducing the compound represented by Chemical Formula 1-9. The reaction is preferably carried out in a mixture of ammonium chloride, 1,4-dioxane and water in the
25 presence of tin. In addition, the reaction temperature is preferably 0°C to room temperature. Further, the reaction time is preferably 30 minutes to 3 hours. Further, the reaction can be carried out by using methanol in the presence of 10% palladium/carbon or by using metal (iron) or metal salt (stannous chloride) in hydrochloric acid or ethanol.

30 Further, the present invention provides a pharmaceutical composition for

preventing or treating diseases which is beneficial for kinase inhibitory actions, comprising the compound represented by Chemical Formula 1, or a pharmaceutically acceptable salt, hydrate, solvate or isomer thereof as an active ingredient.

5 In this case, the diseases which are associated with kinase inhibitory actions includes inflammatory diseases, autoimmune diseases, proliferative diseases or hyperproliferative diseases, and immunity mediated diseases, cancers, tumors or the like.

 The term "prevention" as used herein refers to any act to delay or inhibit
10 occurrence, spread or recurrence of the above-mentioned diseases by administration of the composition of the present invention, and the term "treatment" as used herein refers to any act to improve or change the symptoms of the above diseases for the better by administration of the composition of the present invention.

15 The pharmaceutical composition of the present invention can be formulated in types for oral or parenteral administrations according to a standard pharmaceutical practice. These formulations may contain additives such as pharmaceutically acceptable carrier, adjuvant or diluent in addition to the active ingredient.

20 Suitable carriers include, for example, physiological saline, polyethylene glycol, ethanol, vegetable oil, and isopropyl myristate and the like. Diluents include, for example, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine and the like, but are not limited thereto. Further, the compounds of the present invention can be dissolved in oils, propylene glycol or other solvents commonly used in the preparation
25 of injection solutions. Furthermore, the compounds of the present invention can be formulated in ointments or creams for topical application.

 Pharmaceutical dosage forms of the compounds of the present invention may include using the compounds in the form of pharmaceutically acceptable salts or
30 solvates thereof, and using the compounds alone or as a combination and/or a suitable

mixture together with other pharmaceutically active compounds.

The compounds of the present invention can be formulated into injection solutions by dissolving, suspending or emulsifying the compounds in a water-soluble solvent such as normal saline, 5% dextrose or a non-aqueous solvent such as synthetic fatty acid glyceride, higher fatty acid ester or propylene glycol. Formulations of the present invention may include conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

A preferred dose of the compound of the present invention may be varied according to the condition and weight of a patient, the severity of a disease, the type of a drug, and the route and duration of administration, but it may be suitably selected by those skilled in the art. In order to achieve the desirable effects, however, the compound of the present invention may be administrated daily at a dose of 0.0001 to 100 mg/kg (body weight), and preferably 0.001 to 100 mg/kg (body weight). The administration may be performed once a day or in divided doses each day through an oral or parenteral route. Depending on the method of administration, the composition may contain the compound of the present invention in an amount of 0.001 to 99% by weight, preferably 0.01 to 60% by weight.

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The pharmaceutical composition according to the present invention may be administered to mammals such as a rat, a mouse, a domestic animal, a human, through various routes. The administration may be carried out through all possible methods, for example, oral, rectal, intravenous, intramuscular, subcutaneous, intra-endometrial, intracerebroventricular injection.

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ADVANTAGEOUS EFFECTS

The compound represented by Chemical Formula 1 according to the present invention or a pharmaceutically acceptable salt, hydrate, solvate or isomer thereof can be usefully used for the prevention or treatment of diseases which are associated with kinase inhibitory actions.

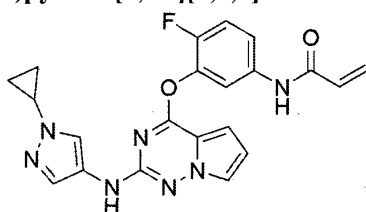
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DETAILED DESCRIPTION OF THE EMBODIMENTS

Below, the present invention will be described in more detail by way of examples. However, these examples are provided for illustrative purposes only, and should not be construed as limiting the scope of the present invention to these examples.

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Example 1: Preparation of N-(3-((2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide



Step 1) Preparation of N-(4-fluoro-3-hydroxyphenyl)acrylamide

10 After 5-amino-2-fluorophenol (1,000.0 mg, 1.0 eq) and sodium bicarbonate (712.0 mg, 1.5 eq) were dissolved in THF/distilled water (15.0 mL/3.0 mL), acryloyl chloride (712.0 mg, 1.0 eq) was added thereto. After the reaction solution was stirred at room temperature for 24 hours, the reaction was terminated. Extraction was performed by adding dichloromethane and then adding an ammonium chloride aqueous solution. Then, the extracts were dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (ethyl acetate: hexane = 1:1) to obtain N-(4-fluoro-3-hydroxyphenyl)acrylamide (1,135.0 mg, 79.6%).

15 ¹H NMR (500 MHz, CD₃OD) δ 7.40-7.39 (m, 1H), 6.99-6.98 (m, 2H), 6.44-6.33 (m, 2H), 5.77-5.75 (m, 1H)

Step 2) Preparation of N-(3-((2-chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide

25 After N-(4-fluoro-3-hydroxyphenyl)acrylamide (505.9 mg, 1.1 eq) and 2,4-dichloropyrrolo[2,1-f][1,2,4]triazine (500.0 mg, 1.0 eq) were dissolved in N,N-dimethylformamide (10.0 mL), K₂CO₃ (385.9 mg, 1.1 eq) was added thereto. The reaction solution was stirred at 50°C for 2 hours, and then cooled to room temperature.

Extraction was carried out by adding dichloromethane and then adding distilled water. Then, the extracts was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (ethyl acetate: hexane=1:1) to obtain N-(3-((2-chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide 640.0 mg, 72.3%).

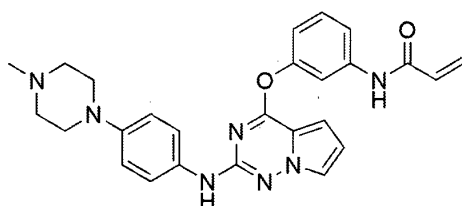
¹H NMR (500 MHz, CD₃OD) δ 7.92-7.91 (m, 1H), 7.85-7.83 (m, 1H), 7.56-7.52 (m, 1H), 7.29 (t, 1H), 7.14-7.13 (m, 1H), 6.96-6.95 (m, 1H), 6.44-6.34 (m, 2H), 5.79 (dd, 1H)

Step 3) Preparation of N-(3-((2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide

After N-(3-((2-chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide (30.0 mg, 1.0 eq.) and 1-cyclopropyl-1H-pyrazol-4-amine (11.1 mg, 1.0 eq) were dissolved in 1.0 mL of 1,4-dioxane. After adding Pd(OAc)₂ (1.0 mg, 0.05 eq), Xanthphos (5.2 mg, 0.1 eq) and Cs₂CO₃ (58.6 mg, 2.0 eq), N₂ gas purge was done for 30 minutes. The reaction solution was reacted using a microwave (150°C, 30 minutes, normal). The reaction solution was filtered, and the filtrate was concentrated under reduced pressure. The obtained concentrated residue was purified by column chromatography (ethyl acetate: hexane = 1:1) to obtain N-(3-((2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide (3.5 mg, 9.3%).

¹H NMR (500 MHz, CD₃OD) δ 7.80-7.78 (m, 2H), 7.66-7.65 (m, 1H), 7.58-7.55 (m, 1H), 7.37 (s, 1H), 7.27 (t, 1H), 6.89 (dd, 1H), 6.66 (dd, 1H), 6.44-6.34 (m, 2H), 5.79 (dd, 1H), 3.53-3.50 (m, 1H), 1.00-0.99 (m, 4H)

Example 2: Preparation of N-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide

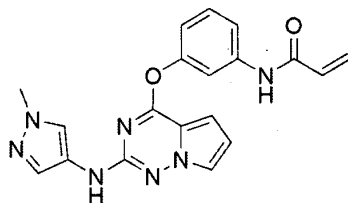


A title compound (12.8 mg, yield: 28.6%) was obtained in the same manner as in Example 1, except that 4-(4-methylpiperazin-1-yl)aniline was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.70 (s, 1H), 7.58 (s, 1H), 7.56-7.54 (m, 1H), 7.47-7.45 (m, 2H), 7.43-7.40 (m, 1H), 7.04-7.03 (m, 1H), 6.90-6.86 (m, 2H), 6.84-6.83 (m, 1H), 6.62-6.61 (m, 1H), 6.46-6.35 (m, 2H), 5.79-5.77 (m, 1H), 3.11-3.09 (m, 4H), 2.64-2.62 (m, 4H), 2.35 (s, 3H)

10

Example 3: Preparation of N-(3-((2-((1-methyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide

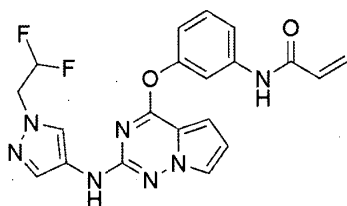


A title compound (3.7 mg, yield: 10.3%) was obtained in the same manner as in Example 1, except that 1-methyl-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.74 (br s, 1H), 7.69 (s, 1H), 7.61 (s, 1H), 7.56-7.54 (m, 1H), 7.43 (t, 1H), 7.36 (s, 1H), 7.04-7.02 (m, 1H), 6.85-6.84 (m, 1H), 6.63-6.62 (m, 1H), 6.45-6.34 (m, 2H), 5.79-5.77 (m, 1H), 3.79 (s, 3H)

20

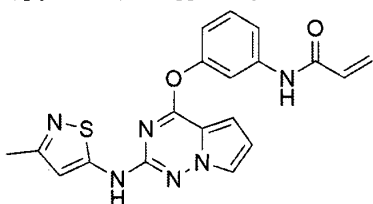
Example 4: Preparation of N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (4.1 mg, yield: 10.1%) was obtained in the same manner as in Example 1, except that 1-(2,2-difluoroethyl)-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.88 (br s, 1H), 7.70 (s, 1H), 7.63 (s, 1H), 7.56-7.54 (m, 1H), 7.45-7.41 (m, 2H), 7.05-7.03 (m, 1H), 6.86-6.85 (m, 1H), 6.64-6.63 (m, 1H), 6.45-6.34 (m, 2H), 6.21-5.98 (m, 1H), 5.78 (dd, 1H), 4.43 (td, 2H)

Example 5: Preparation of N-(3-((2-((3-methylisothiazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



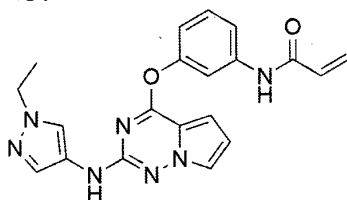
An intermediate N-(3-((2-N-chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide was prepared in the same manner as in Example 1, except that 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

N-(3-((2-N-chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide (50.0 mg, 1.0 eq) was dissolved in t-butanol/N,N-dimethylformamide (3.0 mL/0.6 mL). After adding 3-methylisothiazol-5-amine (16.3 mg, 0.9 eq), Pd₂(dba)₃ (7.3 mg, 0.05 eq), Xphos (7.6 mg, 0.1 eq) and K₂CO₃ (48.3 mg, 2.2 eq), N₂ gas purge was done for 30 minutes. The reaction solution was stirred at 150°C for 16 hours and the reaction was terminated. The reaction solution was concentrated under reduced pressure. Extraction was performed by adding ethyl acetate and distilled water. Then, the extracts were dried over anhydrous sodium sulfate, and concentrated under

reduced pressure. The resulting residue was purified by column chromatography (ethyl acetate: hexane = 1: 1) to obtain N-(3-((2-((3-methylisothiazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide (3.5 mg, 6.2%).

¹H NMR (500 MHz, CD₃OD) δ 7.75-7.74 (m, 2H), 7.55-7.53 (m, 1H), 7.44 (t, 1H), 7.06-7.05 (m, 1H), 6.99-6.98 (m, 1H), 6.76-6.75 (m, 1H), 6.50 (s, 1H), 6.45-6.34 (m, 2H), 5.78 (dd, 1H), 2.28 (s, 3H)

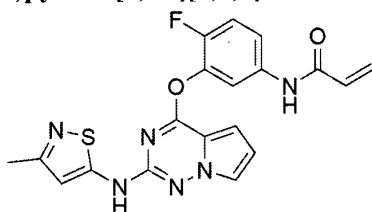
Example 6: Preparation of N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (7.3 mg, yield: 19.7%) was obtained in the same manner as in Example 1, except that 1-ethyl-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazole-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.75 (br s, 1H), 7.70 (s, 1H), 7.61 (s, 1H), 7.57-7.55 (m, 1H), 7.43 (t, 1H), 7.37 (s, 1H), 7.04-7.03 (m, 1H), 6.85-6.84 (m, 1H), 6.63-6.62 (m, 1H), 6.45-6.34 (m, 2H), 5.79-5.77 (m, 1H), 4.06-4.04 (m, 2H), 1.38 (t, 3H)

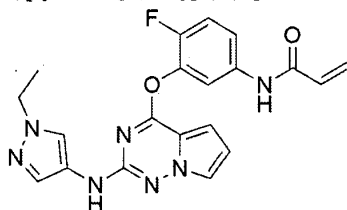
Example 7: Preparation of N-(4-fluoro-3-((2-((3-methylisothiazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (3.6 mg, yield: 6.5%) was obtained in the same manner as in Example 5, except that 5-amino-2-fluorophenol was used instead of 5-amino-phenol in Example 5.

¹H NMR (500 MHz, CD₃OD) δ 7.87-7.86 (m, 1H), 7.78 (s, 1H), 7.56-7.55 (m, 1H), 7.29 (t, 1H), 7.03-7.02 (m, 1H), 6.79 (s, 1H), 6.51 (s, 1H), 6.44-6.35 (m, 2H), 5.79-5.78 (m, 1H), 2.28 (s, 3H)

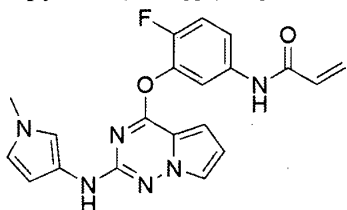
Example 8: Preparation of N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide



A title compound (4.9 mg, yield: 13.3%) was obtained in the same manner as in Example 1, except that 1-ethyl-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.80-7.78 (m, 2H), 7.65 (s, 1H), 7.57-7.54 (m, 1H), 7.39 (s, 1H), 7.27 (t, 1H), 6.89-6.88 (m, 1H), 6.66-6.64 (m, 1H), 6.40-6.35 (m, 2H), 5.80-5.77 (m, 1H), 4.07 (q, 2H), 1.40 (t, 3H)

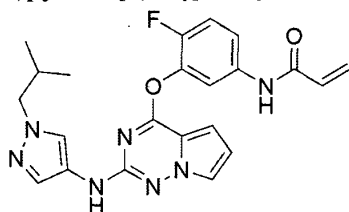
Example 9: Preparation of N-(4-fluoro-3-((2-((1-methyl-1H-pyrrol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (9.6 mg, yield: 20.0%) was prepared in the same manner as in Example 1, except that 1-methyl-1H-pyrrole-3-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.76-7.74 (m, 1H), 7.59-7.54 (m, 2H), 7.26 (t, 1H), 6.95 (br s, 1H), 6.84 (dd, 1H), 6.61 (dd, 1H), 6.42-6.35 (m, 3H), 5.89-5.88 (m, 1H), 5.78 (dd, 1H), 3.57 (s, 3H)

Example 10: Preparation of N-(4-fluoro-3-((2-((1-isobutyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,

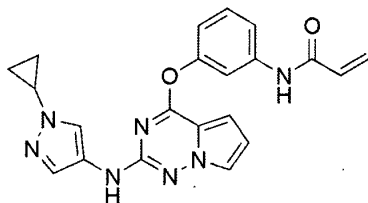


A title compound (2.0 mg, yield: 5.1%) was obtained in the same manner as in
 5 Example 1, except that 1-isobutyl-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.79-7.78 (m, 1H), 7.72-7.71 (m, 1H), 7.65 (s, 1H), 7.59-7.57 (m, 1H), 7.40-7.38 (m, 1H), 7.28 (t, 1H), 6.89 (d, 1H), 6.66-6.65 (m, 1H), 6.46-6.35 (m, 2H), 5.79 (dd, 1H), 3.93 (dd, 1H), 3.81 (d, 2H), 2.03-2.02 (m, 6H)

10

Example 11: Preparation of N-(3-((2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide

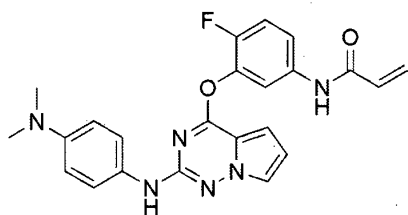


A title compound (7.8 mg, yield: 15.3%) was obtained in the same manner as in
 15 Example 1, except that 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.76 (br s, 1H), 7.70-7.69 (m, 1H), 7.62 (t, 1H), 7.56 (d, 1H), 7.43 (t, 1H), 7.36 (s, 1H), 7.03 (dd, 1H), 6.85 (dd, 1H), 6.63 (dd, 1H), 6.45-6.34 (m, 2H), 5.78 (dd, 1H), 3.50-3.49 (m, 1H), 0.99-0.97 (m, 4H)

20

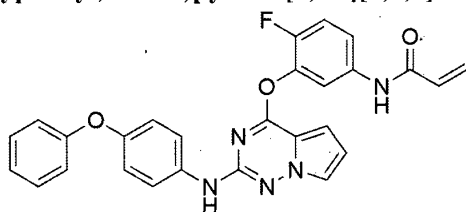
Example 12: Preparation of N-(3-((2-((4-(dimethylamino)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide



A title compound (5.3 mg, yield: 13.6%) was obtained in the same manner as in Example 1, except that N,N' -dimethylbenzene-1,4-diamine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.78 (dd, 1H), 7.60-7.59 (m, 1H), 7.57-7.54 (m, 1H), 7.42-7.40 (m, 2H), 7.26 (t, 1H), 6.87-6.86 (m, 1H), 6.77-6.74 (m, 2H), 6.64-6.63 (m, 1H), 6.44-6.35 (m, 2H), 5.78 (dd, 1H), 2.84 (s, 6H)

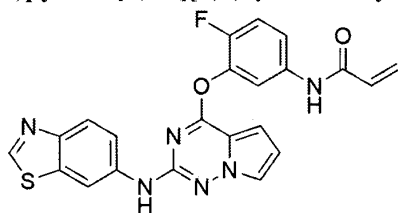
Example 13: Preparation of N-(4-fluoro-3-((2-((4-phenoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (9.2 mg, yield: 21.2%) was obtained in the same manner as in Example 1, except that 4-phenoxyaniline was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.81-7.79 (m, 1H), 7.64-7.63 (m, 1H), 7.57-7.51 (m, 3H), 7.31-7.24 (m, 3H), 7.03 (t, 1H), 6.91-6.86 (m, 5H), 6.66 (dd, 1H), 6.40-6.34 (m, 2H), 5.78 (dd, 1H)

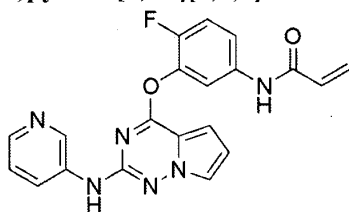
Example 14: Preparation of N-(3-((2-((benzo[d]thiazol-6-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide



A title compound (8.6 mg, yield: 21.4%) was prepared in the same manner as in Example 1, except that 4-benzo[d]thiazol-6-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 9.01 (s, 1H), 8.55 (d, 1H), 7.86-7.84 (m, 2H), 7.76-7.75 (m, 1H), 7.59-7.56 (m, 1H), 7.50 (dd, 1H), 7.30 (t, 1H), 6.98 (dd, 1H), 6.73 (dd, 1H), 6.41-6.35 (m, 2H), 5.78 (dd, 1H)

Example 15: Preparation of N-(4-fluoro-3-((2-((pyridin-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide

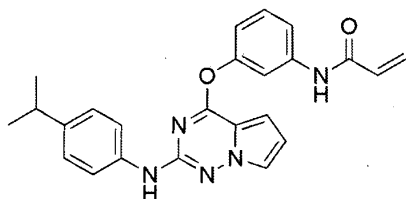


The same procedures as in Example 1 were carried out except that the step 3 in Example 1 was changed to the following process.

N-(3-((2-chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide (20.0 mg, 1.0 eq) and pyridine-3-amine (9.6 mg, 1.7 eq) were dissolved in 2.0 mL of 1,4-dioxane. After adding Pd(OAc)₂ (1.2 mg, 0.09 eq), BINAP (6.4 mg, 0.2 eq) and Cs₂CO₃ (50.9 mg, 2.6 eq), the reaction solution was allowed to react under reflux for 24 hours. Extraction was carried out by adding ethyl acetate and then adding distilled water. Then, the extracts were dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (ethyl acetate: hexane=1:1) to obtain N-(4-fluoro-3-((2-((pyridin-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide (3.0 mg, 12.8%).

¹H NMR (500 MHz, CD₃OD) δ 8.70 (s, 1H), 8.20-8.19 (m, 1H), 8.07-8.06 (m, 1H), 7.83-7.82 (m, 1H), 7.73 (s, 1H), 7.55-7.53 (m, 1H), 7.33-7.27 (m, 2H), 6.96-6.95 (m, 1H), 6.74-6.73 (m, 1H), 6.44-6.35 (m, 2H), 5.79 (dd, 1H)

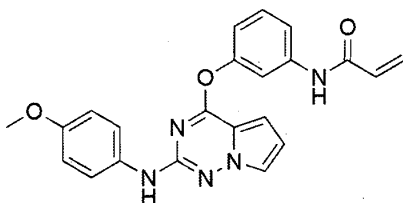
Example 16: Preparation of N-(3-((2-((4-isopropylphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (6.2 mg, yield: 15.7%) was prepared in the same manner as in
 5 Example 1, except that 4-isopropylaniline was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 3-aminophenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.71-7.70 (m, 1H), 7.62-7.61 (m, 1H), 7.57-7.55 (m, 1H), 7.47 (d, 2H), 7.46 (t, 1H), 7.08-7.04 (m, 3H), 6.86 (dd, 1H), 6.65-6.63 (m,
 10 1H), 6.46-6.35 (m, 2H), 5.78 (dd, 1H), 2.85-2.79 (m, 1H), 1.20 (d, 6H)

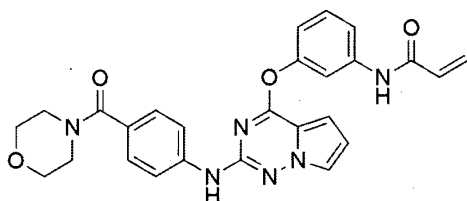
Example 17: Preparation of N-(3-((2-((4-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (3.5 mg, yield: 24.8%) was obtained in the same manner as in
 15 Example 1, except that 4-methoxyaniline was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.70 (s, 1H), 7.58 (s, 1H), 7.55-7.53 (m, 1H),
 20 7.46 (d, 2H), 7.42 (t, 1H), 7.04 (dd, 1H), 6.84 (dd, 1H), 6.78 (d, 2H), 6.62-6.61 (m, 1H), 6.46-6.35 (m, 2H), 5.78 (dd, 1H), 3.74 (s, 3H)

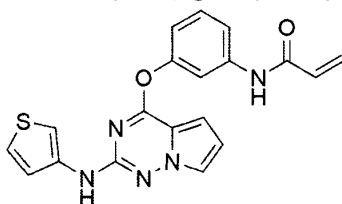
Example 18: Preparation of N-(3-((2-((4-(morpholine-4-carbonyl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (4.0 mg, yield: 8.7%) was prepared in the same manner as in Example 1, except that (4-aminophenyl)(morpholino)methanone was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.72-7.68 (m, 4H), 7.55 (d, 1H), 7.44 (t, 1H), 7.30 (d, 2H), 7.06 (dd, 1H), 6.90 (dd, 1H), 6.70-6.68 (m, 1H), 6.46-6.35 (m, 2H), 5.78 (dd, 1H), 3.67-3.34 (m, 8H)

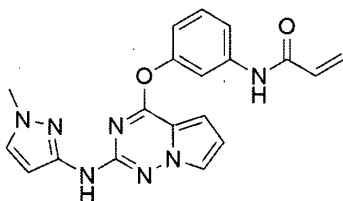
Example 19: Preparation of N-(3-((2-((thiophen-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (7.8 mg, yield: 21.7%) was obtained in the same manner as in Example 1, except that thiophen-3-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.69 (s, 1H), 7.65 (t, 1H), 7.55-7.51 (m, 2H), 7.44-7.40 (m, 1H), 7.20 (dd, 1H), 7.04 (dd, 1H), 6.93 (dd, 1H), 6.86 (dd, 1H), 6.65 (dd, 1H), 6.46-6.34 (m, 2H), 5.78 (dd, 1H)

Example 20: Preparation of N-(3-((2-((1-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide

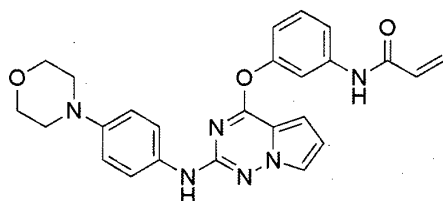


¹H NMR (500 MHz, CD₃OD) δ 7.70 (s, 1H), 7.62 (s, 1H), 7.55 (d, 1H), 7.42 (t, 1H), 7.35 (d, 1H), 7.04 (dd, 1H), 6.87-6.86 (m, 1H), 6.65-6.64 (m, 1H), 6.45-6.34 (m, 3H), 5.77 (dd, 1H), 3.73 (s, 3H)

CN(C)Cc1ccc(cc1)Nc2nc3ccccc3n2Oc4ccc(cc4)N(C=O)C=C

¹H NMR (500 MHz, CD₃OD) δ 7.72-7.70 (m, 1H), 7.66-7.63 (m, 3H), 7.56-7.54 (m, 1H), 7.45-7.42 (m, 2H), 7.22 (d, 1H), 7.06 (dd, 1H), 6.89 (dd, 1H), 6.68 (dd, 1H), 6.46-6.35 (m, 2H), 5.79 (dd, 1H), 3.73 (s, 2H), 2.46 (s, 6H)

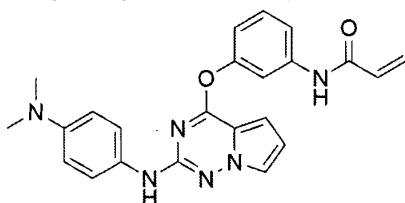
Example 22: Preparation of N-(3-((2-((4-morpholinophenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (3.9 mg, yield: 9.0%) was obtained in the same manner as in Example 1, except that 4-morpholinoaniline was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in
5 Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.69 (t, 1H), 7.59-7.55 (m, 2H), 7.48-7.46 (m, 2H), 7.42 (t, 1H), 7.04 (dd, 1H), 6.88-6.84 (m, 3H), 6.63 (dd, 1H), 6.43-6.35 (m, 2H), 5.78 (dd, 1H), 3.81 (t, 4H), 3.04 (t, 4H)

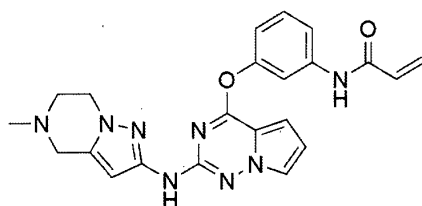
10 **Example 23: Preparation of N-(3-((2-((4-(dimethylamino)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide**



A title compound (1.8 mg, yield: 4.6%) was obtained in the same manner as in
15 Example 1, except that N¹,N¹-dimethylbenzene-1,4-diamine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.69 (t, 1H), 7.57-7.55 (m, 2H), 7.44-7.40 (m, 3H), 7.04 (dd, 1H), 6.84 (dd, 1H), 6.75 (d, 2H), 6.61 (dd, 1H), 6.46-6.35 (m, 2H), 5.78
20 (dd, 1H), 2.84 (s, 6H)

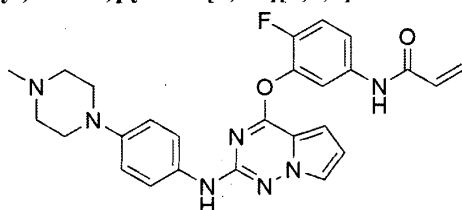
Example 24: Preparation of N-(3-((2-((5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (6.7 mg, yield: 16.3%) was obtained in the same manner as in Example 1, except that 5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-phenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.68-7.67 (m, 1H), 7.63-7.59 (m, 2H), 7.44 (s, 1H), 7.05-7.03 (m, 1H), 6.88 (dd, 1H), 6.66 (dd, 1H), 6.43-6.38 (m, 2H), 6.20 (s, 1H), 5.79 (dd, 1H), 4.00 (t, 2H), 3.58 (s, 2H), 2.92 (t, 2H), 2.47 (s, 3H)

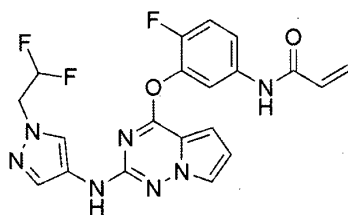
Example 25: Preparation of N-(4-fluoro-3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (14.6 mg, yield: 33.2%) was obtained in the same manner as in Example 1, except that 4-(4-methylpiperazin-1-yl)aniline was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.78 (dd, 1H), 7.61 (s, 1H), 7.57-7.54 (m, 1H), 7.46 (d, 2H), 7.26 (t, 1H), 6.89-6.87 (m, 3H), 6.65-6.64 (m, 1H), 6.44-6.34 (m, 2H), 5.78 (dd, 1H), 3.12 (t, 4H), 2.64 (t, 4H), 2.36 (s, 3H)

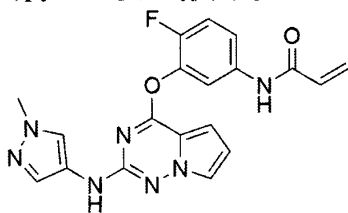
Example 26: Preparation of N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide



A title compound (16.7 mg, yield: 14.8%) was obtained in the same manner as in Example 1, except that 1-(2,2-difluoroethyl)-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.90 (s, 1H), 7.79 (dd, 1H), 7.66-7.65 (m, 1H), 7.56-7.53 (m, 1H), 7.46 (s, 1H), 7.26 (t, 1H), 6.89 (dd, 1H), 6.65 (dd, 1H), 6.44-6.34 (m, 2H), 6.10 (td, 1H), 5.79 (dd, 1H), 4.44 (td, 2H)

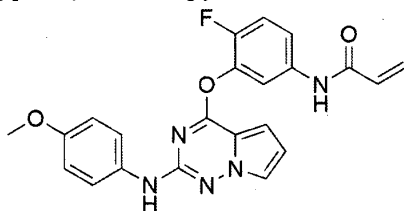
Example 27: Preparation of N-(4-fluoro-3-((2-((1-methyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (12.6 mg, yield: 35.5%) was obtained in the same manner as in Example 1, except that 1-methyl-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.79-7.77 (m, 2H), 7.65-7.64 (m, 1H), 7.56-7.53 (m, 1H), 7.37 (s, 1H), 7.26 (t, 1H), 6.88 (dd, 1H), 6.64 (dd, 1H), 6.44-6.34 (m, 2H), 5.78 (dd, 1H), 3.79 (s, 3H)

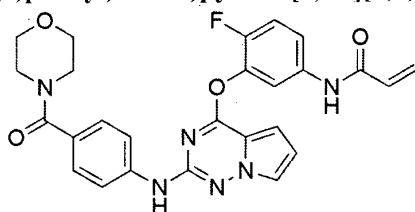
Example 28: Preparation of N-(4-fluoro-3-((2-((4-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (9.0 mg, yield: 23.8%) was obtained in the same manner as in Example 1, except that 4-methoxyaniline was instead of 1-cyclopropyl-1H-pyrazol-4-amine.

¹H NMR (500 MHz, CD₃OD) δ 7.78 (dd, 1H), 7.61 (s, 1H), 7.56-7.53 (m, 1H),
 5 7.46 (d, 2H), 7.27 (t, 1H), 6.88 (dd, 1H), 6.79 (d, 2H), 6.66-6.64 (m, 1H), 6.44-6.35 (m, 2H), 5.79 (dd, 1H), 3.74 (s, 3H)

Example 29: Preparation of N-(4-fluoro-3-((2-((4-(morpholine-4-carbonyl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide

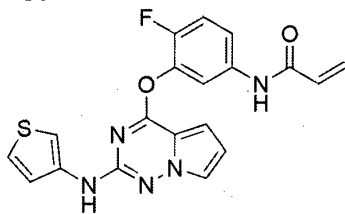


10

A title compound (14.2 mg, yield: 31.3%) was obtained in the same manner as in Example 1, except that (4-aminophenyl)(morpholino)methanone was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.81 (dd, 1H), 7.71-7.67 (m, 3H), 7.57-7.52 (m,
 15 1H), 7.39-7.27 (m, 3H), 6.94 (dd, 1H), 6.73-6.71 (m, 1H), 6.44-6.35 (m, 2H), 5.79 (dd, 1H), 3.70-3.62 (m, 8H)

Example 30: Preparation of N-(4-fluoro-3-((2-((thiophen-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



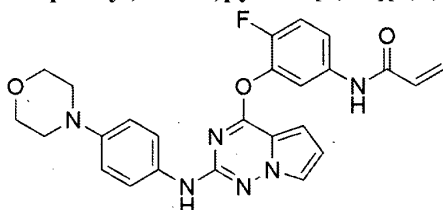
20

A title compound (8.2 mg, yield: 22.7%) was obtained in the same manner as in Example 1, except that thiophen-3-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.79 (dd, 1H), 7.69-7.56 (m, 1H), 7.56-7.52 (m,

2H), 7.27 (t, 1H), 7.20 (dd, 1H), 6.92 (qd, 2H), 6.68 (dd, 1H), 6.44-6.34 (m, 2H), 5.77 (dd, 1H)

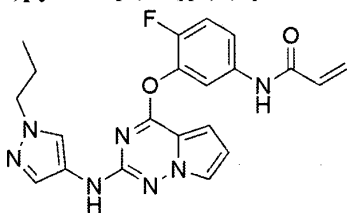
Example 31: Preparation of N-(4-fluoro-3-((2-((4-morpholinophenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (5.6 mg, yield: 13.1%) was obtained in the same manner as in Example 1, except that 4-morpholinoaniline was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.78 (dd, 1H), 7.62-7.61 (m, 1H), 7.57-7.54 (m, 1H), 7.46 (d, 2H), 7.27 (t, 1H), 6.89-6.86 (m, 3H), 6.65 (dd, 1H), 6.44-6.35 (m, 2H), 5.79 (dd, 1H), 3.81 (t, 4H), 3.04 (t, 4H)

Example 32: Preparation of N-(4-fluoro-3-((2-((1-propyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide

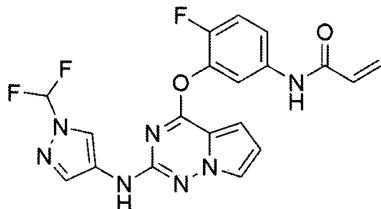


A title compound (6.5 mg, yield: 17.1%) was obtained in the same manner as in Example 1, except that 1-propyl-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.79 (dd, 1H), 7.78 (s, 1H), 7.65-7.64 (m, 1H), 7.58-7.55 (m, 1H), 7.38 (s, 1H), 7.27 (t, 1H), 6.89 (dd, 1H), 6.65 (dd, 1H), 6.44-6.35 (m, 2H), 5.78 (dd, 1H), 3.98 (t, 2H), 1.80 (q, 2H), 0.88 (t, 3H)

Example 33: Preparation of N-(3-((2-((1-(difluoromethyl)-1H-pyrazol-4-

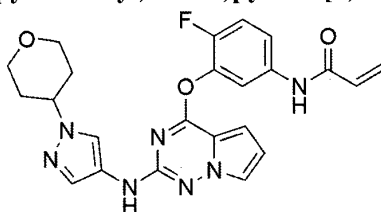
yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide



A title compound (6.1 mg, yield: 15.8%) was obtained in the same manner as in Example 1, except that 1-(difluoromethyl)-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 8.17 (s, 1H), 7.81 (dd, 1H), 7.71 (s, 1H), 7.60 (s, 1H), 7.55-7.52 (m, 1H), 7.37-7.34 (m, 1H), 7.26 (t, 1H), 6.92 (d, 1H), 6.69 (dd, 1H), 6.44-6.31 (m, 2H), 5.78 (dd, 1H)

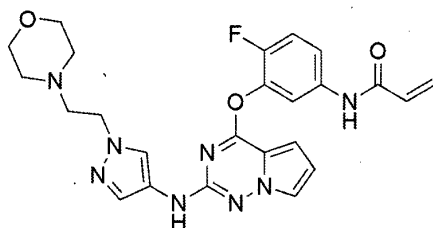
Example 34: Preparation of N-(4-fluoro-3-((2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (3.5 mg, yield: 8.4%) was obtained in the same manner as in Example 1, except that 1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.81-7.79 (m, 2H), 7.65-7.64 (m, 1H), 7.58-7.56 (m, 1H), 7.40 (s, 1H), 7.27 (t, 1H), 6.88 (dd, 1H), 6.66-6.64 (m, 1H), 6.44-6.34 (m, 2H), 5.78 (dd, 1H), 4.26-4.22 (m, 1H), 4.04-4.02 (m, 2H), 3.56-3.50 (m, 2H), 1.99-1.94 (m, 4H)

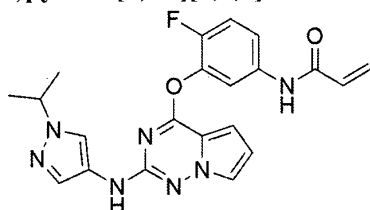
Example 35: Preparation of N-(4-fluoro-3-((2-((1-(2-morpholinoethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (5.4 mg, yield: 12.2%) was obtained in the same manner as in Example 1, except that 1-(2-morpholinoethyl)-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

5 ^1H NMR (500 MHz, CD_3OD) δ 7.89 (s, 1H), 7.78 (dd, 1H), 7.65 (s, 1H), 7.58-7.55 (m, 1H), 7.39 (s, 1H), 7.27 (t, 1H), 6.89 (dd, 1H), 6.65 (dd, 1H), 6.44-6.34 (m, 2H), 5.79 (dd, 1H), 4.19 (t, 2H), 3.67 (t, 4H), 2.75 (t, 2H), 2.46 (t, 4H)

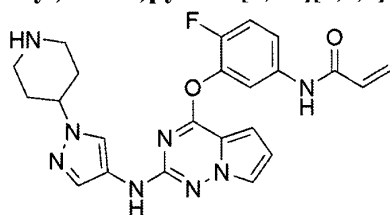
10 **Example 36: Preparation of N-(4-fluoro-3-((2-((1-isopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide**



A title compound (16.6 mg, yield: 43.7%) was obtained in the same manner as in Example 1, except that 1-isopropyl-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

15 ^1H NMR (500 MHz, CD_3OD) δ 7.80-7.78 (m, 2H), 7.65-7.64 (m, 1H), 7.57-7.55 (m, 1H), 7.41 (s, 1H), 7.26 (t, 1H), 6.88-6.87 (m, 1H), 6.65-6.64 (m, 1H), 6.44-6.35 (m, 2H), 5.78 (dd, 1H), 4.41-4.38 (m, 1H), 1.43 (d, 6H)

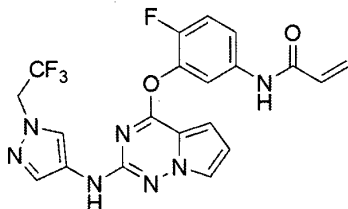
20 **Example 37: Preparation of N-(4-fluoro-3-((2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide**



A title compound (1.0 mg, yield: 2.4%) was obtained in the same manner as in Example 1, except that tert-butyl 4-(4-amino-1H-pyrazol-1-yl) piperidine-1-carboxylate was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.81-7.80 (m, 1H), 7.75-7.74 (m, 1H), 7.64-7.54 (m, 2H), 7.42 (s, 1H), 7.28 (t, 1H), 6.90-6.89 (m, 1H), 6.67-6.66 (m, 1H), 6.44-6.35 (m, 2H), 5.79 (dd, 1H), 4.17-4.16 (m, 1H), 3.20-3.16 (m, 4H), 2.78-2.73 (m, 4H)

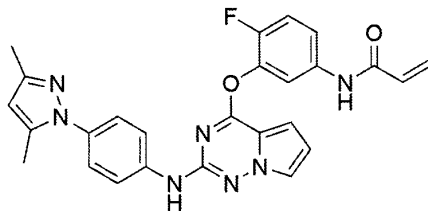
Example 38: Preparation of N-(4-fluoro-3-((2-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (7.5 mg, yield: 18.0%) was obtained in the same manner as in Example 1, except that 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.97 (br s, 1H), 7.78 (dd, 1H), 7.68-7.67 (m, 1H), 7.57-7.54 (m, 1H), 7.49 (s, 1H), 7.27 (t, 1H), 6.91-6.90 (m, 1H), 6.68-6.66 (m, 1H), 6.44-6.34 (m, 2H), 5.79 (dd, 1H), 4.82-4.79 (m, 2H)

Example 39: Preparation of N-(3-((2-((4-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide

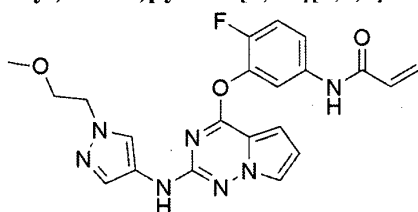


A title compound (6.0 mg, yield: 13.7%) was obtained in the same manner as in Example 1, except that 4-(3,5-dimethyl-1H-pyrazol-1-yl)aniline was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.83-7.81 (m, 1H), 7.73-7.70 (m, 3H), 7.56-

7.53 (m, 1H), 7.30-7.26 (m, 1H), 7.23-7.22 (m, 2H), 6.94-6.93 (m, 1H), 6.72-6.70 (m, 1H), 6.45-6.34 (m, 2H), 6.01 (s, 1H), 5.79-5.77 (m, 1H), 2.22-2.21 (m, 6H)

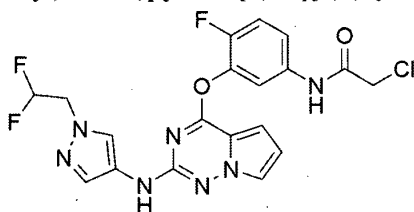
Example 40: Preparation of N-(4-fluoro-3-((2-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (1.8 mg, yield: 4.6%) was obtained in the same manner as in Example 1, except that 1-(2-methoxyethyl)-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.82-7.77 (m, 2H), 7.66-7.65 (m, 1H), 7.57-7.55 (m, 1H), 7.41 (s, 1H), 7.27 (t, 1H), 6.89-6.88 (m, 1H), 6.66-6.65 (m, 1H), 6.44-6.34 (m, 2H), 5.79 (dd, 1H), 4.19 (t, 2H), 3.69 (t, 2H), 2.01 (s, 3H)

Example 41: Preparation of 2-chloro-N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acetamide



Step 1) Preparation of 2-chloro-4-(2-fluoro-5-nitrophenoxy)pyrrolo[2,1-f][1,2,4]triazine

After 2,4-dichloropyrrolo[2,1-f][1,2,4]triazine (500.0 mg, 1.0 eq) and 2-fluoro-5-nitrophenol (438.7 mg, 1.05 eq) were dissolved in N,N-dimethylformamide (10.0 mL), K₂CO₃ (385.9 mg, 1.05 eq) was added thereto. The reaction solution was stirred at 50°C for 2 hours, and then cooled to room temperature. Extraction was performed by adding dichloromethane and then adding distilled water. Then, the extracts were dried over anhydrous sodium sulfate, and concentrated under reduced

pressure. The resulting residue was purified by column chromatography (ethyl acetate: hexane=1:1) to obtain 2-chloro-4-(2-fluoro-5-nitrophenoxy)pyrrolo[2,1-f][1,2,4]triazine (800.7 mg, 97.6%).

¹H NMR (500 MHz, CD₃OD) δ 8.44-8.42 (m, 1H), 8.36-8.33 (m, 1H), 7.96-7.95 (m, 1H), 7.61 (t, 1H), 7.20-7.19 (m, 1H), 6.70-6.99 (m, 1H)

Step 2) Preparation of N-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)-4-(2-fluoro-5-nitrophenoxy)pyrrolo[1,2-b]triazin-2-amine

2-Chloro-4-(2-fluoro-5-nitrophenoxy)pyrrolo[2,1-f][1,2,4]triazine (200.0 mg, 1.0 eq) and 1-(2,2-difluoroethyl)-1H-pyrazol-4-amine (95.3 mg, 1.0 eq) were dissolved in 9.0 mL of 1,4-dioxane. After adding Pd(OAc)₂ (7.3 mg, 0.05 eq), Xanthphos (37.5 mg, 0.1 eq) and Cs₂CO₃ (422.3 mg, 2.0 eq), N₂ gas purge was done for 30 minutes. The reaction solution was reacted using a microwave (150°C, 30 minutes, normal). The reaction solution was filtered, and the filtrate was concentrated under reduced pressure. The obtained concentrated residue was purified by column chromatography (ethyl acetate: hexane = 1:1) to obtain N-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)-4-(2-fluoro-5-nitrophenoxy)pyrrolo[1,2-b]triazin-2-amine (210.0 mg, 77.5%).

¹H NMR (500 MHz, CD₃OD) δ 8.40-8.39 (m, 1H), 8.32-8.30 (m, 1H), 8.03-7.99 (m, 1H), 7.71 (s, 1H), 7.59 (t, 1H), 7.48 (s, 1H), 6.94-6.93 (m, 1H), 6.69-6.68 (m, 1H), 6.24-6.01 (m, 1H), 4.47 (td, 2H)

Step 3) Preparation of 4-(5-amino-2-fluorophenoxy)-N-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-2-amine

N-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)-4-(2-fluoro-5-nitrophenoxy)pyrrolo[1,2-b]triazin-2-amine (210.0 mg, 1.0 eq) was dissolved in 1,4-dioxane/distilled water (3.0 mL / 3.0 mL), and then NH₄Cl (214.7 mg, 8.0 eq) was added thereto. The reaction solution was cooled to 0°C and Zn powder (262.6 mg, 8.0 eq) was added thereto. After stirring at room temperature for 1 hour, the reaction solution was filtered. Extraction was performed by adding dichloromethane to the filtrate and then adding distilled water. Then, the extracts were dried over anhydrous

sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (ethyl acetate: hexane=1:1) to obtain 4-(5-amino-2-fluorophenoxy)-N-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-2-amine (145.4 mg, 74.6%).

5 ¹H NMR (500 MHz, CD₃OD) δ 7.90 (br s, 1H), 7.46 (s, 1H), 7.13 (t, 1H), 6.95 (m, 1H), 6.88-6.85 (m, 2H), 6.72-6.63 (m, 1H), 6.23-5.99 (m, 1H), 4.45 (td, 2H)

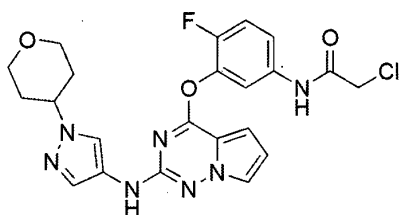
Step 4) Preparation of 2-chloro-N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acetamide

10 4-(5-amino-2-fluorophenoxy)-N-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-2-amine (20.0 mg, 1.0 eq) and 2-chloroacetic acid (6.7 mg, 1.2 eq) were dissolved in 5.0 mL of THF. O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (O-HATU, 27.0 mg, 1.2 eq) and N,N-diisopropylethylamine (15.3 mg, 2.0 eq) were added thereto. The reaction solution was stirred at room temperature for 24 hours and then the reaction was terminated. Extraction was performed by adding ethyl acetate and then adding distilled water. Then, the extracts were dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (ethyl acetate: hexane=1:1) to obtain 2-chloro-N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acetamide (9.3 mg, 33.8%).

20 ¹H NMR (500 MHz, CD₃OD) δ 7.90 (br s, 1H), 7.72-7.70 (m, 1H), 7.66-7.65 (m, 1H), 7.53-7.50 (m, 1H), 7.46 (s, 1H), 7.27 (t, 1H), 6.89-6.88 (m, 1H), 6.66-6.65 (m, 1H), 6.11 (tt, 1H), 4.45 (td, 2H), 4.18 (s, 2H)

25

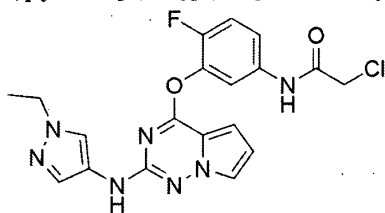
Example 42: Preparation of 2-chloro-N-(4-fluoro-3-((2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acetamide



A title compound (9.0 mg, yield: 37.9%) was obtained in the same manner as in Example 41, except that 1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-amine was used instead of 1-(2,2-difluoroethyl)-1H-pyrazol-4-amine in Example 41.

¹H NMR (500 MHz, CD₃OD) δ 7.79-7.71 (m, 2H), 7.66 (s, 1H), 7.55-7.53 (m, 1H), 7.40 (s, 1H), 7.29 (t, 1H), 6.89-6.88 (m, 1H), 6.66-6.65 (m, 1H), 4.30-4.24 (m, 1H), 4.18 (s, 2H), 4.06-4.04 (m, 2H), 3.58-3.53 (m, 2H), 2.03-1.96 (m, 4H)

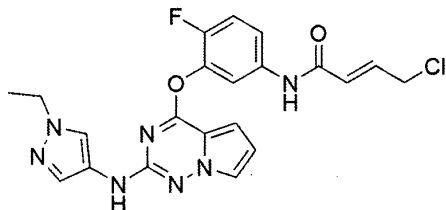
Example 43: Preparation of 2-chloro-N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acetamide



A title compound (9.1 mg, yield: 43.3%) was obtained in the same manner as in Example 41, except that 1-ethyl-1H-pyrazol-4-amine was used instead of 1-(2,2-difluoroethyl)-1H-pyrazol-4-amine in Example 41.

¹H NMR (500 MHz, CD₃OD) δ 7.77 (br s, 1H), 7.72-7.70 (m, 1H), 7.66-7.65 (m, 1H), 7.54-7.51 (m, 1H), 7.39 (s, 1H), 7.28 (t, 1H), 6.89-6.87 (m, 1H), 6.65-6.64 (m, 1H), 4.18 (s, 2H), 4.08 (q, 2H), 1.40 (t, 3H)

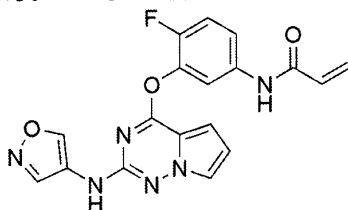
Example 44: Preparation of (E)-4-chloro-N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)but-2-enamide



A title compound (8.1 mg, yield: 36.4%) was obtained in the same manner as in Example 41, except that 1-ethyl-1H-pyrazol-4-amine was used instead of 1-(2,2-difluoroethyl)-1H-pyrazol-4-amine, and (E)-4-chlorobut-2-enoic acid was used instead of 2-chloroacetic acid.

¹H NMR (500 MHz, CD₃OD) δ 7.77 (s, 1H), 7.70-7.68 (m, 1H), 7.65-7.64 (m, 1H), 7.49-7.47 (m, 1H), 7.38 (s, 1H), 7.25 (t, 1H), 6.88-6.87 (m, 1H), 6.65-6.64 (m, 1H), 6.35-6.33 (m, 1H), 6.13-6.10 (m, 1H), 4.07 (q, 2H), 3.39-3.37 (m, 2H), 1.40 (t, 3H)

Example 45: Preparation of N-(4-fluoro-3-(2-(isoxazol-4-ylamino)pyrrolo[2,1-f][1,2,4]triazin-4-yloxy)phenyl)acrylamide



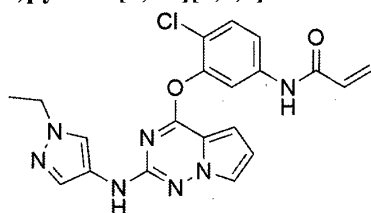
An intermediate N-(4-(5-amino-2-fluorophenoxy)pyrrolo[2,1-f][1,2,4]triazin-2-yl)isoxazol-4-amine was prepared in the same manner as in Example 41, except that isoxazol-4-amine was used instead of 1-(2,2-difluoroethyl)-1H-pyrazol-4-amine in Example 41.

N-(4-(5-amino-2-fluorophenoxy)pyrrolo[2,1-f][1,2,4]triazin-2-yl)isoxazol-4-amine (7.5 mg, 1.0 eq) was dissolved in 1.0 mL of dichloromethane and then cooled to 0°C. N,N-diisopropylethylamine (5.9 mg, 2.0 eq) was added and then acryloyl chloride (2.2 mg, 1.05 eq) was added dropwise. The reaction solution was stirred at 0°C for 30 minutes to terminate the reaction. Extraction was performed by adding ethyl acetate and then adding distilled water. Then, the extracts were dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (dichloromethane: methanol=10:1) to obtain N-(4-fluoro-3-(2-(isoxazol-4-ylamino)pyrrolo[2,1-f][1,2,4]triazin-4-yloxy)phenyl)acrylamide (1.7 mg, 19.5%).

¹H NMR (500 MHz, CD₃OD) δ 8.95 (br s, 1H), 8.32 (s, 1H), 7.81 (dd, 1H),

7.74-7.73 (m, 1H), 7.54-7.53 (m, 1H), 7.27 (t, 1H), 6.94-6.93 (m, 1H), 6.71-6.70 (m, 1H), 6.44-6.35 (m, 2H), 5.79 (dd, 1H)

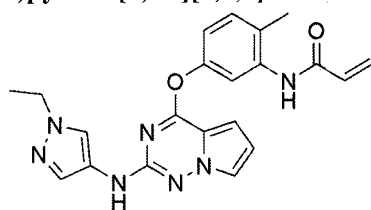
Example 46: Preparation of N-(4-chloro-3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide



A title compound (1.4 mg, yield: 3.8%) was obtained in the same manner as in Example 1, except that ethyl-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 5-amino-2-chlorophenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500MHz, CD₃OD) δ 7.83-7.81 (m, 1H), 7.72-7.70 (m, 1H), 7.66-7.65 (m, 1H), 7.61-7.56 (m, 1H), 7.51-7.50 (m, 1H), 7.37-7.36 (m, 1H), 6.90-6.89 (m, 1H), 6.66-6.65 (m, 1H), 6.44-6.36 (m, 2H), 5.80 (dd, 1H), 4.09-4.05 (m, 2H), 1.44-1.41 (m, 3H)

Example 47: Preparation of N-(5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-2-methylphenyl)acrylamide

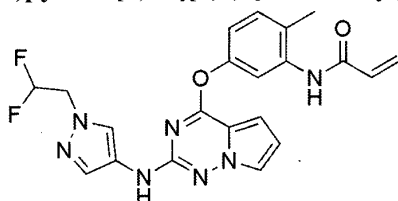


A title compound (3.4 mg, yield: 9.2%) was obtained in the same manner as in Example 1, except that 1-ethyl-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 3-amino-4-methylphenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.77 (br s, 1H), 7.61-7.60 (m, 1H), 7.49-7.48 (m, 1H), 7.38 (s, 1H), 7.35-7.34 (m, 1H), 7.08-7.06 (m, 1H), 6.84-6.83 (m, 1H), 6.62-

6.61 (m, 1H), 6.53-6.51 (m, 1H), 6.39-6.35 (m, 1H), 5.79 (dd, 1H), 4.07 (q, 2H), 2.31 (s, 3H), 1.39 (t, 3H)

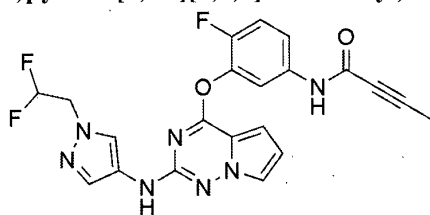
Example 48: Preparation of N-(5-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-2-methylphenyl)acrylamide



A title compound (6.3 mg, yield: 15.7%) was obtained in the same manner as in Example 1, except that 1-(2,2-difluoroethyl)-1H-pyrazol-4-amine was used instead of 1-cyclopropyl-1H-pyrazol-4-amine, and 3-amino-4-methylphenol was used instead of 5-amino-2-fluorophenol in Example 1.

¹H NMR (500 MHz, CD₃OD) δ 7.87 (br s, 1H), 7.62-7.61 (m, 1H), 7.48-7.44 (m, 2H), 7.35-7.33 (m, 1H), 7.08-7.06 (m, 1H), 6.85-6.84 (m, 1H), 6.63-6.62 (m, 1H), 6.56-6.51 (m, 1H), 6.39-6.35 (m, 1H), 6.20-5.98 (m, 1H), 5.80-5.78 (m, 1H), 4.43 (td, 2H), 2.31 (s, 3H)

Example 49: Preparation of N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)pent-2-ynamide



A title compound (2.1 mg, yield: 7.6%) was obtained in the same manner as in Example 41, except that pent-2-enoic acid was used instead of 2-chloroacetic acid in Example 41.

¹H NMR (500 MHz, CD₃OD) δ 7.91 (br s, 1H), 7.67-7.65 (m, 2H), 7.53-7.50 (m, 1H), 7.47 (s, 1H), 7.25 (t, 1H), 6.92-6.88 (m, 1H), 6.68-6.65 (m, 1H), 6.23-5.99 (m, 1H), 4.45 (td, 2H), 2.41 (q, 2H), 1.23 (t, 3H)

Experimental Example: Measurement of JAK 3 and BTK Enzyme inhibitory activity

JAK3 and BTK kinase inhibitory activities were measured for the compounds prepared in the above Examples through in vitro analysis on the ADP Glow (Glo) platform.

Specifically, the inhibitory activities of JAK3 and BTK kinase were measured using a JAK3 kinase assay kit (Promega, V9441) and a BTK kinase assay kit (Promega, V9071) which were purchased from Promega. Recombinant purified human JAK3 and BTK were diluted with 1 x kinase reaction buffer (JAK3: 40 mM Tris-Cl, pH 7.5, 20 mM MgCl₂, 0.1 mg/mL BSA and 50 uM DTT/BTK: 40 mM Tris-Cl, pH 7.5, 20 mM MgCl₂, 0.1 mg/mL BSA, 2 mM MnCl₂ and 50 uM DTT) and added to a 96 well plate (JAK3: final concentration of 4 ng per reaction/BTK: final concentration of 8 ng per reaction). The compounds were treated so as to be finally a 1% DMSO aqueous solution, and a substrate cocktail containing ATP (JAK3: final concentration of 5 uM/BTK: final concentration of 10 uM) and 0.2 ug/uL of Poly(Glu4, Tyr1)peptide (JAK3 and BTK final concentration) in the total 25 uL reactants was added to a 96-well plate to initiate enzymatic reaction. After incubation (30°C) for 1 hour, equivalent volume (25 uL per reaction) of ADP Glo was added and incubated (30°C) for 40 minutes at room temperature. Then, a kinase detection reagent (50 uL per reaction) was added and incubated (30°C) for 30 minutes at room temperature. The kinase activity was measured by chemiluminescence according to the instructions of ADP Glo kinase assay kit, and the inhibitory activity of the compounds according to the present invention was calculated. For the analysis of the results of each compound, Microsoft Excel was used, and IC₅₀ values were calculated by SigmaPlot software. The results are shown in Table 1 below.

[Table 1]

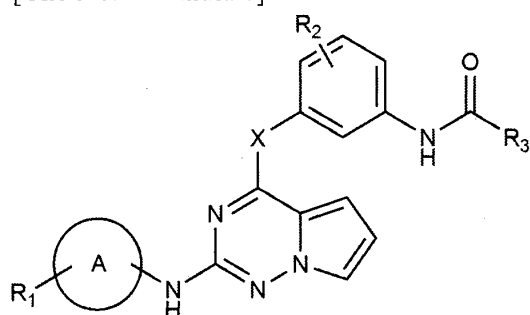
Example No.	JAK3 IC ₅₀ (nM)	BTK IC ₅₀ (nM)	Example No.	JAK3 IC ₅₀ (nM)	BTK IC ₅₀ (nM)	Example No.	JAK3 IC ₅₀ (nM)	BTK IC ₅₀ (nM)
1	1.1	13.6	21	11.7	103.8	41	0.7	1.2
2	2.8	22.7	22	5.3	35.4	42	0.5	1.3

3	0.6	12.7	23	10.4	60.2	43	0.7	1.2
4	0.7	13.4	24	18.8	166.4	44	99.5	114.2
5	0.6	8.7	25	1.4	7.9	45	32	205.8
6	0.5	10.0	26	0.9	6.2	46	56.8	269.1
7	0.5	10.7	27	0.7	5.0	47	13.0	52.2
8	0.6	7.7	28	9.2	52.0	48	13.8	73.4
9	16.8	243.4	29	2.0	23.1	49	>400	30
10	9.6	112.9	30	7.6	66.6	Tofacitinib	1.1~3.3	-
11	10.3	107.2	31	4.5	27.4	Ibrutinib	-	0.5~2.7
12	0.7	7.5	32	1.4	9.1			
13	41.7	622.4	33	2.8	15.3			
14	9.8	43.3	34	0.5	2.4			
15	15.5	103.5	35	0.7	3.5			
16	20.0	123.1	36	1.1	4.4			
17	5.9	68.6	37	11.5	63.6			
18	2.2	37.8	38	1.8	16.5			
19	5.3	62.9	39	23.5	111.3			
20	57.7	647.3	40	2.8	23.0			

WHAT IS CLAIMED IS:

1. A compound represented by the following Chemical Formula 1, or a pharmaceutically acceptable salt thereof:

5 [Chemical Formula 1]



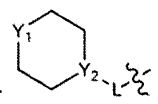
in Chemical Formula 1,

X is O, or NH,

A is a divalent C₆₋₁₀ aromatic ring, or a divalent C₂₋₁₀ heteroaromatic ring
 10 containing one to three heteroatoms each independently selected from the group consisting of N, O and S,

R₁ is hydrogen; C₁₋₄ alkyl unsubstituted or substituted with one substituent selected from the group consisting of C₁₋₄ alkoxy, N(C₁₋₄ alkyl)₂, cyano, and (C₁₋₄ alkyl)-NHCO; C₁₋₄ alkoxy; C₁₋₄ haloalkyl; C₃₋₆ cycloalkyl; N(C₁₋₄ alkyl)₂; benzoyl;

15 pyrazolyl unsubstituted or substituted with one or two C₁₋₄ alkyl; or



wherein Y₁ is NH, N(C₁₋₄ alkyl), or O; Y₂ is CH or N; L is a bond, C₁₋₄ alkylene, or CO,

R₂ is hydrogen, C₁₋₄ alkyl, or halogen, and

R₃ is C₁₋₄ alkyl substituted by halogen or cyano; C₂₋₄ alkenyl unsubstituted or
 20 substituted with halogen; or C₂₋₄ alkynyl.

2. The compound, or a pharmaceutically acceptable salt thereof according to claim 1, wherein

A is a divalent ring selected from the group consisting of benzene,

benzothiazole, isothiazole, isoxazole, pyrazole, pyridine, pyrrole, thiazole, thiophene, and 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine.

3. The compound, or a pharmaceutically acceptable salt thereof according to
5 claim 1, wherein

R_1 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxyethyl, dimethylaminomethyl, diethylaminoethyl, cyanomethyl, methylaminocarbonylmethyl, methoxy, difluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, cyclopropyl, dimethylamino, benzoyl, or 3,5-dimethyl-1H-pyrazol-1-yl.

10

4. The compound, or a pharmaceutically acceptable salt thereof according to claim 1, wherein

R_1 is piperidin-4-yl, 1-methyl-piperidin-4-yl, 4-methylpiperazin-1-yl, tetrahydro-2H-pyran-4-yl, morpholino, 2-morpholinoethyl, or morpholine-4-carbonyl.

15

5. The compound, or a pharmaceutically acceptable salt thereof according to claim 1, wherein

R_2 is hydrogen, methyl, chloro, or fluoro.

6. The compound, or a pharmaceutically acceptable salt thereof according to
20 claim 1, wherein

R_3 is $-\text{CH}_2\text{-Cl}$, $-\text{CH}=\text{CH}_2$, $-\text{CH}=\text{CHCH}_2\text{CH}_3$, $-\text{CH}=\text{CHCH}_2\text{Cl}$, or $-\text{C}\equiv\text{CCH}_2\text{CH}_3$.

7. The compound, or a pharmaceutically acceptable salt thereof according to
25 claim 1, wherein

the compound represented by Chemical Formula 1 is any one selected from the group consisting of:

1) N-(3-((2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-
30 f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,

- 2) N-(3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 3) N-(3-((2-((1-methyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 5 4) N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 5) N-(3-((2-((3-methylisothiazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 6) N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-10 4-yl)oxy)phenyl)acrylamide,
- 7) N-(4-fluoro-3-((2-((3-methylisothiazol-5-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 8) N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 15 9) N-(4-fluoro-3-((2-((1-methyl-1H-pyrrol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 10) N-(4-fluoro-3-((2-((1-isobutyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 11) N-(3-((2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 20 12) N-(3-((2-((4-(dimethylamino)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 13) N-(4-fluoro-3-((2-((4-phenoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 25 14) N-(3-((2-((benzo[d]thiazol-6-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 15) N-(4-fluoro-3-((2-((pyridin-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 16) N-(3-((2-((4-isopropylphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-30 yl)oxy)phenyl)acrylamide,

- 17) N-(3-((2-((4-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 18) N-(3-((2-((4-(morpholine-4-carbonyl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 5 19) N-(3-((2-((thiophen-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 20) N-(3-((2-((1-methyl-1H-pyrazol-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 21) N-(3-((2-((4-((dimethylamino)methyl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 10 22) N-(3-((2-((4-morpholinophenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 23) N-(3-((2-((4-(dimethylamino)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 15 24) N-(3-((2-((5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 25) N-(4-fluoro-3-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 26) N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 20 27) N-(4-fluoro-3-((2-((1-methyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 28) N-(4-fluoro-3-((2-((4-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 25 29) N-(4-fluoro-3-((2-((4-(morpholine-4-carbonyl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 30) N-(4-fluoro-3-((2-((thiophen-3-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 31) N-(4-fluoro-3-((2-((4-morpholinophenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 30

- 32) N-(4-fluoro-3-((2-((1-propyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 33) N-(3-((2-((1-(difluoromethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 5 34) N-(4-fluoro-3-((2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 35) N-(4-fluoro-3-((2-((1-(2-morpholinoethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 36) N-(4-fluoro-3-((2-((1-isopropyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 10 37) N-(4-fluoro-3-((2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 38) N-(4-fluoro-3-((2-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 15 39) N-(3-((2-((4-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acrylamide,
- 40) N-(4-fluoro-3-((2-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 41) 2-chloro-N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acetamide,
- 20 42) 2-chloro-N-(4-fluoro-3-((2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acetamide,
- 43) 2-chloro-N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)acetamide,
- 25 44) (E)-4-chloro-N-(3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)but-2-enamide,
- 45) N-(4-fluoro-3-(2-(isoxazol-4-ylamino)pyrrolo[2,1-f][1,2,4]triazin-4-yloxy)phenyl)acrylamide,
- 46) N-(4-chloro-3-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)phenyl)acrylamide,
- 30

- 47) N-(5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-2-methylphenyl)acrylamide,
- 48) N-(5-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-2-methylphenyl)acrylamide, and
- 5 49) N-(3-((2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)pyrrolo[2,1-f][1,2,4]triazin-4-yl)oxy)-4-fluorophenyl)pent-2-ynamide.

8. A pharmaceutical composition for the prevention or treatment of inflammatory disease, autoimmune disease, proliferative disease, hyperproliferative
10 disease, immunity mediated disease, cancer or tumor, comprising the compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof.