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(54) Title: AMINO-METHYL PIPERIDINE DERIVATIVE AS KINASE INHIBITOR

(54) 발명의 명칭: 카이네이즈 저해제로서의 아미노-메틸피페리딘 유도체

(57) Abstract: The present invention relates to a compound represented by chemical formula (1) or pharmaceutically acceptable salts thereof. The compound according to the present invention can be utilized for preventing or treating diseases that benefit from kinase inhibitory action.

(57) 요약서: 본 발명은 화학식 1로 표시되는 화합물, 또는 이의 약학적으로 허용가능한 염에 관한 것으로, 본 발명에 따른 화합물은 카이네이즈 저해 작용이 유익한 질환의 예방 또는 치료에 유용하게 사용할 수 있다.

WO 2019/132561 A1

## 【DESCRIPTION】

### 【Invention Title】

AMINO-METHYLPIPERIDINE DERIVATIVES AS KINASE INHIBITOR

### 5   【Technical Field】

The present invention relates to an amino-methylpiperidine derivative having kinase inhibitory activity, a process for preparing the same and use thereof.

### 【Background Art】

10       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 diseases *in vivo*. In the onset or development of inflammatory disease, autoimmune disease, proliferative disease or 15 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.

Janus kinase (hereinafter referred to as "JAK") is a cytoplasmic protein tyrosine kinase that plays pivotal roles in regulating cell function in the 20 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 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 5 etc.), solid cancers, blood cancers (e.g., leukemia, lymphoma and so on).

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 10 JAK1 associated with hematopoietic growth factor signaling, and a combination of TYK2 and JAK2 is important for interferon signaling and contributes to host tolerance. JAK2 can induce anemia, thrombocytopenia, leukopenia, especially when it is involved in the hematopoietic growth factor signaling and causes excessive 15 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, 20 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  $\beta$ -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 25 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- $\gamma$ 2-mediated calcium mobilization. Therefore, inhibition of BTK can be a useful therapeutic approach in blocking the onset process of B-cell mediated diseases.

As mentioned above, Janus kinase and TEC-based kinases play 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 5 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, 10 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.

JAK3 kinase inhibitor, tofacitinib (CP-690550) (Pfizer Inc.) is 15 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 20 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).

Therefore, the present inventors have found a new amino- 25 methylpiperidine derivative having an excellent inhibitory activity as

a kinase inhibitor, thereby completing the present invention.

The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters 5 formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to be interpreted as specifying 10 the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

### **【DETAILED DESCRIPTION OF THE INVENTION】**

#### **【Technical Problem】**

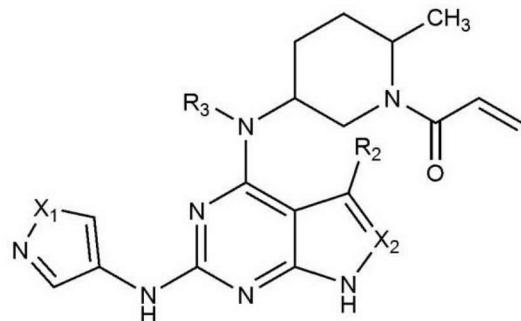
It would be desirable to provide an amino-methylpiperidine having an inhibitory ability against kinase, particularly tyrosine kinase, a process for preparing the same and use thereof.

It would also be desirable to provide a pharmaceutical composition comprising 20 the amino-methylpiperidine derivative as an active ingredient.

#### **【Technical Solution】**

The present invention provides a compound represented by the following Chemical Formula 1, or a pharmaceutically acceptable salt thereof is provided herein:

#### **25 [Chemical Formula 1]**



wherein, in Chemical Formula 1,

X<sub>1</sub> is N-R<sub>1</sub>, O, or S,

X<sub>2</sub> is CH, or N,

R<sub>1</sub> is C<sub>1-5</sub> alkyl, C<sub>3-6</sub> cycloalkyl, or C<sub>1-5</sub> alkyl substituted with (tert-butoxycarbonyl)amino,

5 R<sub>2</sub> is hydrogen, C<sub>1-5</sub> alkyl, or halogen, and

R<sub>3</sub> is hydrogen or C<sub>1-5</sub> alkyl.

Preferably, R<sub>1</sub> is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or 2-((tert-butoxycarbonyl)amino)ethyl.

Preferably, R<sub>2</sub> is hydrogen, methyl, bromo, fluoro, or chloro.

Preferably, R<sub>3</sub> is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, or neopentyl.

Preferably, X<sub>1</sub> is N-R<sub>1</sub> and X<sub>2</sub> is CH.

15

Representative examples of the compound represented by the Chemical Formula 1 are as follows:

1) 1-((2S,5R)-5-((5-chloro-2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,

20 2) 1-((2S,5R)-5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,

3) 1-((2S,5R)-5-((2-((1-isobutyl-1H-pyrazol-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-

1-one,

4) 1-((2S,5R)-5-((2-((1-cyclopentyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,

5 5) tert-butyl 2-(4-((4-((3R,6S)-1-acryloyl-6-methylpiperidin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)ethylcarbamate,

6) 1-((2S,5R)-5-((5-chloro-2-(isothiazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-10 1-one,

7) 1-((2S,5R)-5-((5-chloro-2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,

8) 1-((2S,5R)-5-((5-chloro-2-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,

9) 1-((2S,5R)-5-((5-chloro-2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,

20 10) 1-((2S,5R)-5-((2-(1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one, and

11) 1-((2S,5R)-5-((3-chloro-6-((1-ethyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one.

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 5 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 Chemical Formula 1 whose concentration has effective action because it is relatively non-toxic and harmless to 10 the patients and whose side effects do not degrade the beneficial efficacy of the above compound.

Pharmaceutically acceptable salts can be obtained by conventional methods using inorganic or organic acids. For example, the pharmaceutically acceptable salt can be prepared by dissolving 15 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 excessive amount of acid 20 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, 25 lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid,

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 5 toluenesulfonic acid, and the like.

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.

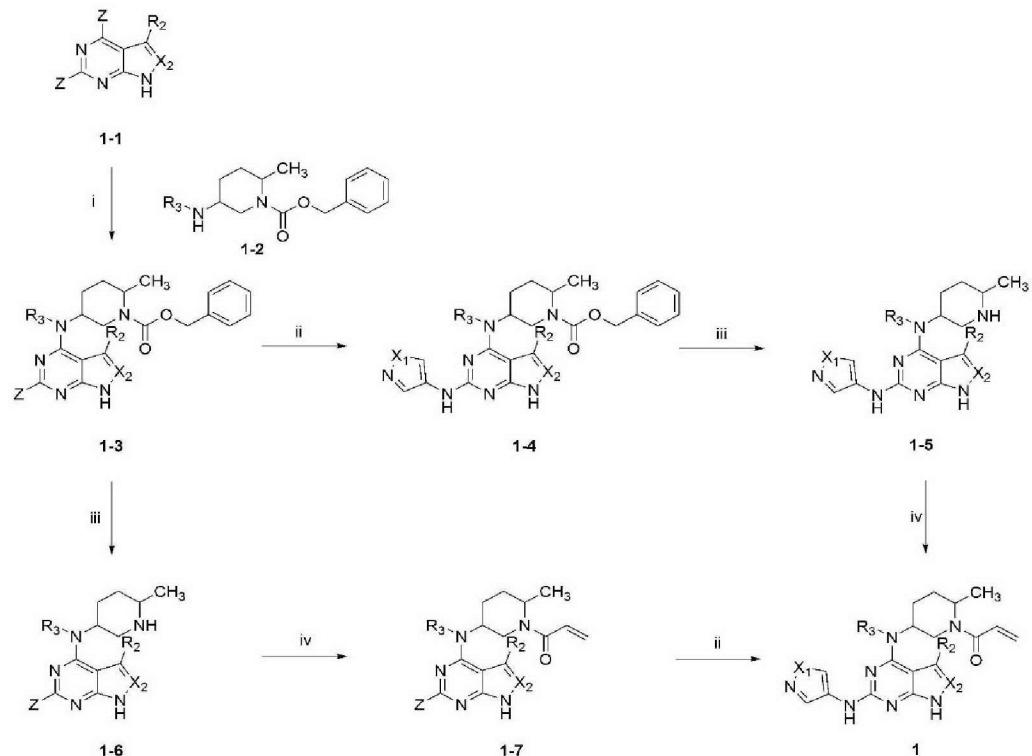
10 The compound of Chemical Formula 1 according to the present invention includes not only pharmaceutically acceptable salts thereof, but all solvates and hydrates that can be prepared therefrom, and includes all possible stereoisomers as well. The solvate, the hydrate and the stereoisomer of the compound represented by Chemical 15 Formula 1 may be prepared and used from the compound of Chemical Formula 1 using common methods.

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 20 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 25 by Chemical Formula 1 according to the present invention includes

both stoichiometric solvates and non-stoichiometric solvates.

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

5 [Reaction Scheme 1]



(in Reaction Scheme 1,  $X_1$  to  $X_2$ , and  $R_1$  to  $R_3$  are as previously defined,  $Z$  is halogen, and preferably  $Z$  is chloro)

Step i is a step of preparing a compound represented by 10 Chemical Formula 1-3 by reacting a compound represented by Chemical Formula 1-1 with a compound represented by Chemical Formula 1-2. The reaction is preferably carried out at  $0^{\circ}\text{C}$  or less or at room temperature to high temperature in the presence of sodium

hydride or diisopropylethylamine, and the solvent is preferably tetrahydrofuran, ethanol, or dimethylformamide.

Step ii is a step of preparing a compound represented by Chemical Formula 1-4 by reacting a compound represented by Chemical Formula 1-3 with an amine. The reaction is preferably carried out at 100°C to 120°C in the presence of a ligand, a palladium catalyst, or a base, or carried out at a high temperature in the presence of trifluoroacetic acid, and the solvent is preferably 1,4-dioxane, tert-butanol or 2-butanol.

Step iii is a reaction for removing the protecting group of the compound represented by Chemical Formula 1-4, which is a step for preparing the compound represented by Chemical Formula 1-5. The reaction is preferably carried out with palladium in the presence of hydrogen, or carried out at high temperature under acidic conditions, preferably under 6N hydrochloric acid conditions.

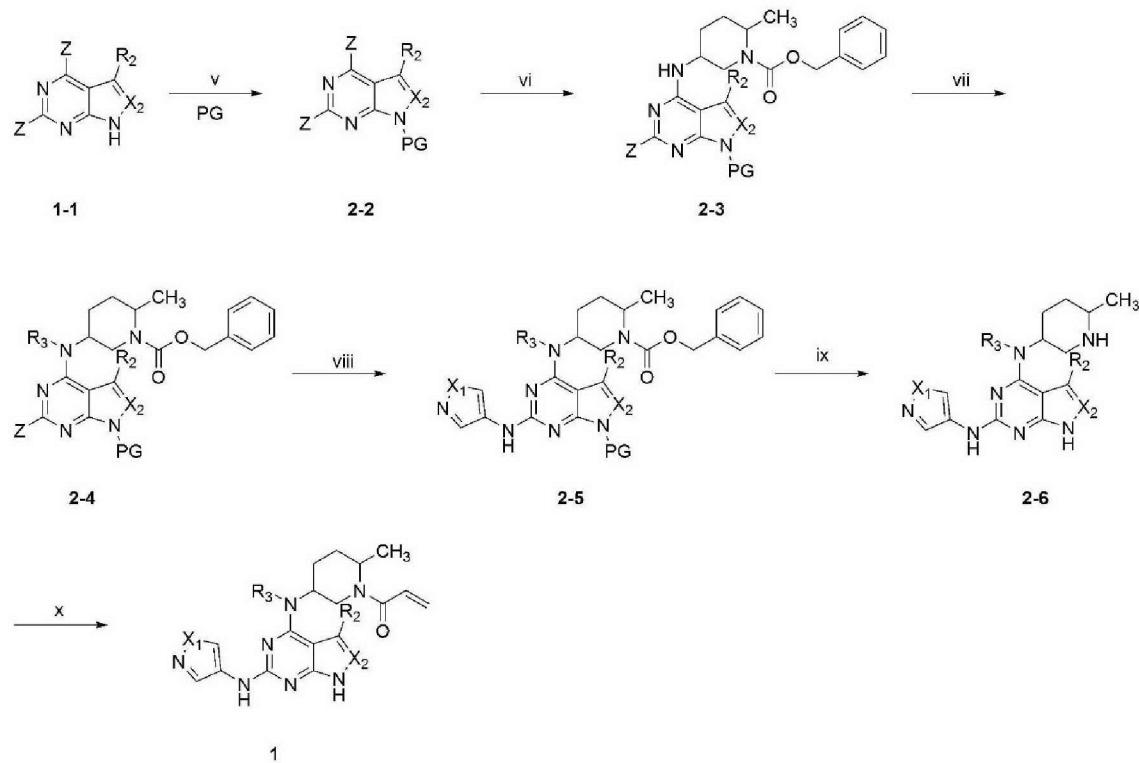
Step iv is a step of preparing a compound represented by Chemical Formula 1 by reacting a compound represented by Chemical Formula 1-5 with acyl chloride. The reaction is preferably carried out at -20°C to 0°C in the presence of triethylamine or sodium hydrogen carbonate. Further, the solvent is preferably a mixture of dichloromethane or tetrahydrofuran and water.

Further, as shown in the Reaction Scheme 1, a compound represented by Chemical Formula 1-3, a compound represented by Chemical Formula 1-6, a compound represented by Chemical Formula 1-7, and a compound represented by Chemical Formula 1

may also be prepared in this order, and each step iii, iv, and ii is the same as described above, except for the reactants.

Further, as an example, the present invention can produce the 5 compound represented by Chemical Formula 1 through Reaction Scheme 2 below.

[Reaction Scheme 2]



(in Reaction Scheme 2,  $X_1$  to  $X_2$ , and  $R_1$  to  $R_3$  are as 10 previously defined, PG is hydropyran or 2-(trimethylsilyl)ethoxymethyl as a protecting group, and Z is halogen. Preferably, Z is chloro.)

Step v is a step of preparing a compound represented by

Chemical Formula 2-2 by reacting a compound represented by Chemical Formula 1-1 with a protecting group. The reaction is preferably carried out with dihydropyran under acid conditions, or carried out with 2-(trimethylsilyl)ethoxymethyl chloride under basic 5 conditions, and the solvent is preferably dichloromethane or dimethylformamide.

Step vi is a step of preparing a compound represented by Chemical Formula 2-3 from the compound represented by Chemical Formula 2-2, and is the same as step i of the Reaction Scheme 1 10 except for the reactants.

Step vii is a step of preparing a compound represented by Chemical Formula 2-4 by reacting a compound represented by Chemical Formula 2-3 and R<sub>3</sub>-I. The reaction is preferably carried out at 0°C or less, or at room temperature in the presence of a base, 15 preferably in the presence of sodium hydride, and the solvent is preferably dimethylformamide.

Step viii is a step of preparing a compound represented by Chemical Formula 2-5 from a compound represented by Chemical Formula 2-4, and is the same as step ii of the Reaction Scheme 1 20 except for the reactants.

Step ix is a reaction for removing the protecting group of the compound represented by Chemical Formula 2-5, which is a step for preparing the compound represented by Chemical Formula 2-6. The reaction is preferably carried out at a high temperature under acidic 25 conditions (preferably, trifluoroacetic acid), or carried out with

fluoride, preferably tetrabutylammonium fluoride, under basic conditions, and the solvent is preferably methanol, tetrahydrofuran, or 1,4-dioxane.

Step x is a step for preparing a compound represented by 5 Chemical Formula 1 from a compound represented by Chemical Formula 2-6, and is the same as step iv of the Reaction Scheme 1 except for the reactants.

According to another embodiment of the present invention, there is provided a pharmaceutical composition for preventing or 10 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.

In this case, the diseases which is associated with kinase 15 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 occurrence, spread or recurrence of the above-mentioned 20 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.

The pharmaceutical composition of the present invention can 25 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.

Suitable carriers include, for example, physiological saline, 5 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 10 commonly used in the preparation 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 15 pharmaceutically acceptable salts or 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 20 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, 25 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.

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.

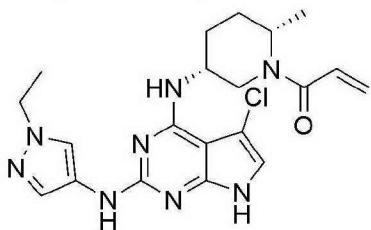
#### **[ADVANTAGEOUS EFFECTS]**

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.

## **[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.

### **Example 1: Preparation of 1-((2S,5R)-5-((5-chloro-2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**



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### **Step 1: Preparation of benzyl(2S,5R)-5-((2,5-dichloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate**

After 2,4,5-trichloro-7H-pyrrolo[2,3-d]pyrimidine (11.1 g, 50.0 mmol) was dissolved in ethanol (10.0 mL), N,N-diisopropylethylamine (26.1 mL, 150.0 mmol) and benzyl(2S,5R)-5-amino-2-methylpiperidine-1-carboxylate (14.9 g, 60.0 mmol) were added thereto. The reaction mixture was stirred at 110°C for 12 hours. After adding ethyl acetate, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography to

obtain 19.9 g (yield: 91.7%) of the title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.40-7.20(m, 5H), 7.03(s, 1H), 5.18-5.06(m, 2H), 4.50-4.30(m, 2H), 4.16-4.04(m, 1H), 2.94-2.85(m, 1H), 1.95-1.77(m, 3H), 1.70-1.60(m, 1H), 1.24-1.20(m, 3H)

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**Step 2: Preparation of benzyl (2S,5R)-5-((5-chloro-2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)-2-methylpiperidine-1-carboxylate**

Benzyl(2S,5R)-5-((2,5-dichloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (19.9 g, 46.0 mmol) and 1-ethyl-1H-pyrazol-4-amine (3.9 g, 35.0 mmol) were dissolved in 2-butanol (190.0 mL). After adding trifluoroacetic acid (3.2 mL, 42.0 mmol), the reaction mixture was reacted at 110°C for 12 hours, and then the solvent was concentrated. The reaction product was neutralized by adding 7N ammonia solution dissolved in methanol, and then the residue was separated by column chromatography to obtain 4.7 g (yield: 26.5%) of the title compound.

1H NMR (500MHz, CD<sub>3</sub>OD) δ 7.90(s, 1H), 7.51(s, 1H), 7.40-7.20(m, 5H), 6.78(s, 1H), 5.18-5.06(m, 2H), 4.54-4.38(m, 2H), 4.27-4.10(m, 1H), 4.10-4.00(m, 2H), 2.94-2.85(m, 1H), 1.99-1.70(m, 4H), 1.43-1.35(m, 3H), 1.28-1.20(m, 3H)

**Step 3: Preparation of 5-chloro-N<sup>2</sup>-(1-ethyl-1H-pyrazol-4-yl)-N<sup>4</sup>-((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine**

6N hydrochloric acid solution (47.0 mL, excess) dissolved in methanol was added to benzyl (2S,5R)-5-((5-chloro-2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidine-4-yl)amino)-2-methylpiperidine-1-carboxylate (4.7 g, 9.5 mmol). After stirring at 5 80°C for 6 hours, the reaction product was concentrated and then the next reaction was carried out without separation.

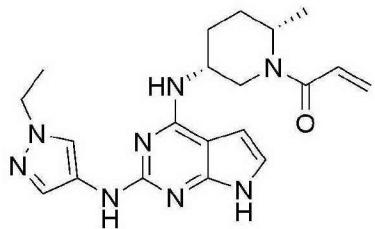
10 **Step 4: Preparation of 1-((2S,5R)-5-((5-chloro-2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**

15 After 5-chloro-N<sup>2</sup>-(1-ethyl-1H-pyrazol-4-yl)-N<sup>4</sup>-((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine (3.3 g, 9.0 mmol) and sodium bicarbonate (599.8 mg, 6.9 mmol) were dissolved in tetrahydrofuran / distilled water (15.0 mL/3.0 mL), acryloyl chloride (720.0 uL, 9.0 mmol) was added thereto at 0°C. The reaction mixture was stirred at 0°C for 1 hour. After adding ethyl acetate, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The 20 residue was separated by column chromatography to obtain 1.4 mg (yield: 36.8%) of the title compound.

25 <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.95(s, 1H), 7.50(s, 1H), 6.94-6.55(m, 2H), 6.33-6.06(m, 1H), 5.86-5.53(m, 1H), 4.56-4.14(m, 2H), 4.13-4.00(m, 2H), 3.14-2.67(m, 1H), 2.18-2.12(m, 1H), 2.04-1.98(m, 1H), 1.97-1.76(m, 3H), 1.46-1.38(m, 3H), 1.37-1.17(m, 3H)

**Example 2: Preparation of 1-((2S,5R)-5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**

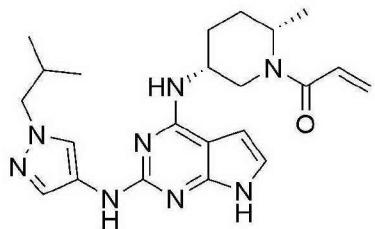
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5.4 mg (yield: 46.1%) of the title compound was obtained in the same manner as in Example 1, except that 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine was used instead of 2,4,5-trichloro-7H-pyrrolo[2,3-d]pyrimidine in Example 1.

10  $^1\text{H}$  NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.96-7.91(m, 1H), 7.52-7.47(m, 1H), 6.88-6.57(m, 2H), 6.40-6.38(m, 1H), 6.23-6.13(m, 1H), 5.79-5.56(m, 1H), 4.47-4.07(m, 4H), 3.00-2.70(m, 1H), 2.01-1.81(m, 4H), 1.44-1.41(m, 3H), 1.35-1.34(m, 1H), 1.26-1.22(m, 2H)

15 **Example 3: Preparation of 1-((2S,5R)-5-((2-((1-isobutyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**



**Step 1: Preparation of benzyl (2S,5R)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate**

After benzyl (2R,5S)-5-amino-2-methylpiperidine-1-carboxylate (10.0 g, 40.27 mmol) was dissolved in ethanol (500.0 mL), N,N-diisopropylethylamine (35.1 mL, 201.4 mmol) and 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (9.1 g, 48.3 mmol) were added thereto. The reaction mixture was stirred at 110°C for 12 hours. After adding ethyl acetate, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography to obtain 14.6 mg (yield: 90.7%) of the title compound.

1H NMR (500 MHz, CDCl<sub>3</sub>) δ 11.00(s, 1H), 7.48-7.30(m, 5H), 7.03(s, 1H), 6.38(s, 1H), 5.41-4.93(m, 2H), 4.63-4.41(m, 2H), 4.22-4.19(m, 1H), 2.77-2.75(m, 1H), 2.09-2.06(m, 1H), 1.98-1.83(m, 1H), 1.78-1.45(m, 2H), 1.39-1.10(m, 3H)

**Step 2: Preparation of 2-chloro-N-((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine**

After benzyl (2S,5R)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (14.4 g 36.0 mmol) was dissolved in ethanol (500.0 mL), palladium/carbon (1.4 g) was added thereto, and the reactor was sealed. The air inside the reactor was removed using a vacuum pump, and a palladium-

mediated hydrogenation reaction was carried out through hydrogen gas substitution. After the reaction was allowed to proceed at room temperature for about 3 hours, palladium was removed through a celite filter, and ethanol was concentrated under reduced pressure.

5 6.9 g (yield: 60.2%) of the title compound was obtained without further purification.

10 **Step 3: Preparation of 1-((2S,5R)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**

15 After 2-chloro-N-((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (6.8 g, 25.7 mmol) and sodium bicarbonate (4.3 g, 51.3 mmol) were dissolved in tetrahydrofuran/distilled water (300.0 mL/30.0 mL), acryloyl chloride (2.1 mL, 25.7 mol) was added thereto at 0°C. The reaction mixture was stirred at 0°C for 1 hour. After adding ethyl acetate, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated 20 by column chromatography to obtain 3.3 mg (yield: 40.2%) of the title compound.

25  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  11.82(s, 1H), 7.08-7.06(m, 1H), 6.95-6.48(m, 1H), 6.45-6.16(m, 2H), 5.74-5.72(m, 1H), 5.50(s, 1H), 5.02(s, 1H), 4.46(s, 1H), 4.11-4.09(m, 1H), 2.88(s, 1H), 2.10-2.08(m, 1H), 1.95-1.61(m, 4H), 1.45-1.03(m, 3H)

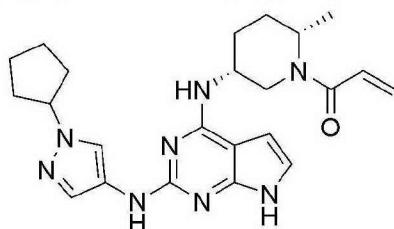
**Step 4: Preparation of 1-((2S,5R)-5-((2-((1-isobutyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**

5           Tert-butanol (2.0 mL) was added to 1-((2S,5R)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one (100.0 mg, 0.3 mmol) and 1-isobutyl-1H-pyrazol-4-amine (45.3 mg, 0.3 mmol). Tris(dibenzylidineacetone)dipalladium (28.6 mg, 0.03 mmol), 2-dicyclohexylphosphino-2',4',6'-trisopropylbiphenyl (22.4 mg, 0.05 mmol) and potassium carbonate (86.4 mg, 0.6 mmol) were added thereto, and the mixture was stirred at 150°C for 2 to 3 hours and then cooled to room temperature. After adding ethyl acetate, distilled water was added and the organic layer was separated. The separated organic layer  
10          was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography to obtain 15.0 mg (yield: 11.4%) of the title compound.

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1H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.43(s, 1H), 7.82(s, 1H), 7.53-20 7.44(m, 1H), 6.74(s, 1H), 6.65-6.62(m, 1H), 6.40(s, 1H), 6.33-6.30(m, 1H), 6.24(s, 1H), 5.70-5.68(m, 1H), 5.03(s, 1H), 4.72-4.70(m, 1H), 4.34(s, 1H), 4.17-4.06(m, 1H), 3.94-3.73(m, 2H), 2.86(s, 2H), 2.28-2.07(m, 3H), 1.95-1.81(m, 1H), 1.79-1.58(m, 6H), 1.40-1.15(m, 8H), 1.00-0.83(m, 6H)

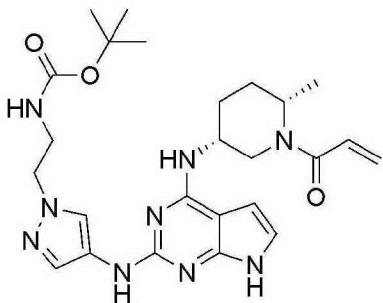
**Example 4: Preparation of 1-((2S,5R)-5-((2-((1-cyclopentyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**



5 25.8 mg (yield: 18.4%) of the title compound was obtained in the same manner as in Example 3, except that 1-cyclopentyl-1H-pyrazol-4-amine was used instead of 1-isobutyl-1H-pyrazol-4-amine in Example 3.

10  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.09(s, 1H), 7.86(s, 1H), 7.50-7.48(m, 1H), 6.75-6.53 (m, 2H), 6.44(s, 1H), 6.32-6.29(m, 1H), 6.21(s, 1H), 5.67(s, 1H), 4.99(s, 1H), 4.74-4.70(m, 1H), 4.58-4.55(m, 1H), 2.82(s, 1H), 2.45-2.21(m, 1H), 2.12-1.56(m, 6H), 1.32-1.07(m, 4H), 0.92-0.76(m, 3H)

15 **Example 5: Preparation of tert-butyl 2-((4-((3R,6S)-1-acryloyl-6-methylpiperidin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)ethylcarbamate**

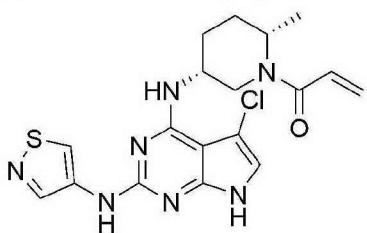


111.5 mg (yield: 69.7%) of the title compound was obtained in the same manner as in Example 3, except that tert-butyl(2-(4-amino-1H-pyrazol-1-yl)ethyl)carbamate was used instead of 1-isobutyl-1H-pyrazol-4-amine in Example 3.

1H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.00(s, 1H), 7.82-7.79(m, 1H), 7.50(s, 1H), 6.71(s, 1H), 6.65-6.59(m, 1H), 6.33-6.29(m, 1H), 6.23(s, 1H), 5.72-5.69(m, 1H), 4.14-4.10(m, 4H), 3.52-3.48(m, 2H), 2.04-2.02(m, 2H), 1.95-1.60(m, 4H), 1.50-1.47(m, 9H), 1.22-1.19(m, 3H)

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**Example 6: Preparation of 1-((2S,5R)-5-((5-chloro-2-(isothiazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**



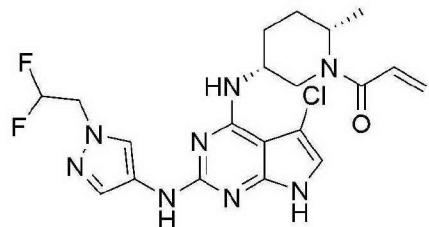
15 5.9 mg (yield: 25.6%) of the title compound was obtained in the same manner as in Example 1, except that isothiazol-4-amine

was used instead of 1-ethyl-1H-pyrazol-4-amine in Example 1.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 8.95-8.80(m, 1H), 8.62-8.50(m, 1H), 6.90-6.60(m, 2H), 6.33-6.10(m, 1H), 5.80-5.60(m, 1H), 4.65-4.08(m, 2H), 3.18-2.70(m, 1H), 2.10-1.75(m, 5H), 1.30-1.20(m, 3H)

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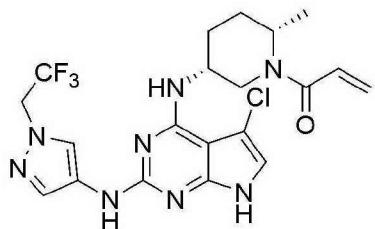
**Example 7: Preparation of 1-((2S,5R)-5-((5-chloro-2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**



10 9.9 mg (yield: 39.3%) of the title compound 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-ethyl-1H-pyrazol-4-amine in Example 1.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 8.15-7.95(m, 1H), 7.70-7.50 (m, 1H), 6.90-6.55(m, 2H), 6.30-5.95(m, 2H), 5.80-5.55(m, 1H), 4.60-4.38(m, 3H), 4.30-4.10(m, 1H), 3.18-2.65(m, 1H), 2.05-1.65(m, 5H), 1.40-1.20(m, 3H)

**Example 8: Preparation of 1-((2S,5R)-5-((5-chloro-2-((2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**

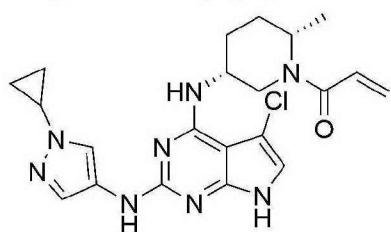


9.2 mg (yield: 35.3%) of the title compound was obtained in the same manner as in Example 1, except that 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine was used instead of 1-ethyl-1H-pyrazol-4-amine in Example 1.

1H NMR (500MHz, CD<sub>3</sub>OD) δ 8.17-8.12(m, 1H), 7.58-7.55(m, 1H), 6.86-6.72(m, 2H), 6.28-6.18(m, 1H), 5.79-5.66(m, 1H), 4.82-4.81(m, 2H), 4.50-4.48(m, 1H), 4.26-4.15(m, 1H), 3.05-2.77(m, 1H), 2.01-1.83(m, 4H), 1.35-1.23(m, 4H)

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**Example 9: Preparation of 1-((2S,5R)-5-((5-chloro-2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**

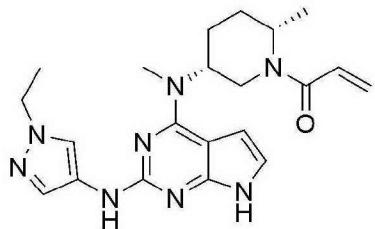


15 5.0 mg (yield: 21.0%) of the title compound was obtained in the same manner as in Example 1, except that 1-cyclopropyl-1H-pyrazol-4-amine was used instead of 1-ethyl-1H-pyrazol-4-amine in Example 1.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.98(s, 1H), 7.48(s, 1H), 6.82-6.64(m, 2H), 6.21-6.18(m, 1H), 5.75-5.61(m, 1H), 4.58-4.56(m, 1H), 4.26-4.19(m, 1H), 3.52-3.50(m, 1H), 3.05-2.77(m, 1H), 2.05-1.82(m, 4H), 1.36-1.31(m, 4H), 1.03-0.98(m, 4H)

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**Example 10: Preparation of 1-((2S,5R)-5-((2-(1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**



10 **Step 1: Preparation of 2,4-dichloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine**

2,4-Dichloro-7H-pyrrolo[2,3-d]pyrimidine (400.0 mg, 2.1 mmol) and sodium hydride (93.6 mg, 2.3 mmol) were dissolved in N,N-dimethylformamide (4.0 mL), and then the mixture was stirred at 0°C for 10 minutes. 2-(Trimethylsilyl)ethoxymethyl chloride (415.0 uL, 2.3 mmol) was added to the reaction mixture, followed by stirring at 0°C for 30 minutes. After adding ethyl acetate to the mixture, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography to obtain 585.0 mg (yield: 80.4%) of the

title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.66-7.65(m, 1H), 6.72-6.71(m, 1H), 5.63(s, 2H), 3.59-3.56(m, 2H), 0.91-0.88(m, 2H), 0.07(s, 9H)

5                   **Step 2: Preparation of benzyl (2S,5R)-5-((2-chloro-7-((2-  
(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-  
yl)amino)-2-methylpiperidine-1-carboxylate**

After       benzyl       (2S,5R)-5-amino-2-methylpiperidine-1-  
carboxylate   (390.1   mg,   1.6   mmol),   2,4-dichloro-7-((2-  
10           (trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (500.0 mg,  
1.6 mmol) and N, N-diisopropyl (821.0 uL, 4.7 mmol) were dissolved  
in ethanol (3.0 mL), the temperature was raised to 150°C and the  
mixture was stirred for 12 hours. The solution was concentrated  
under reduced pressure, and the resulting residue was separated by  
15           column chromatography to obtain 717.8 mg (yield: 86.2%) of the title  
compound.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.40-7.29(m, 5H), 7.13-7.12(m,  
1H), 6.61-6.60(m, 1H), 5.48(s, 2H), 5.18-5.12(m, 2H), 4.49-4.47(m,  
1H), 4.36-4.34(m, 1H), 4.12-4.10(m, 1H), 3.54-3.53(m, 2H), 2.85-  
20           2.80(m, 1H), 1.93-1.70(m, 3H), 1.25-1.22(m, 4H), 0.88-0.85(m, 2H),  
0.07(s, 9H)

25                   **Step 3: Preparation of benzyl(2S,5R)-5-((6-chloro-1-((2-  
(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-  
yl)amino)-2-methylpiperidine-1-carboxylate**

After **benzyl** **(2S,5R)-5-((2-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate** (170.0 mg, 0.3 mmol) was dissolved in N,N-dimethylformamide (2.0 mL), sodium hydride (25.7 mg, 0.6 mmol) was added thereto and then stirred at 0°C for 10 minutes. Then, methyl iodide (30.0 uL, 0.5 mmol) was added and further stirred at 0°C for 2 hours. After adding ethyl acetate to the mixture, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography to obtain 165.2 mg (yield: 94.7%) of the title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.35-7.23(m, 5H), 7.13-7.07(m, 1H), 6.61-6.58(m, 1H), 5.47(s, 2H), 5.17-5.06 (m, 2H), 4.61-4.60(m, 1H), 4.46-4.44(m, 1H), 3.54-3.50(m, 2H), 3.25(s, 3H), 3.17-3.14(m, 1H), 2.15-2.12(m, 1H), 1.87-1.65(m, 3H), 1.24-1.21(m, 4H), 0.88-0.84(m, 2H), 0.07(s, 9H)

**Step 4: Preparation of benzyl (2S,5R)-5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidine-1-carboxylate**

Tert-butanol (4.0 mL) was added to benzyl(2S,5R)-5-((6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (165.2 mg,

0.3 mol) and 1-ethyl-1H-pyrazol-4-amine (30.4 mg, 0.3 mmol). Tris(dibenzylidineacetone)dipalladium (13.9 mg, 0.02 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (14.5 mg, 0.03 mmol) and potassium carbonate (92.3 mg, 0.7 mmol) were added 5 thereto, and the mixture was stirred at 150°C for 12 hours and then cooled to room temperature. After adding ethyl acetate, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated 10 by column chromatography to obtain 149.4 mg (yield: 79.5%) of the title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.93(s, 1H), 7.54-7.21(m, 6H), 6.87-6.83(m, 1H), 6.53-6.51(m, 1H), 5.49(s, 2H), 5.19-5.05 (m, 2H), 4.49-4.48(m, 1H), 4.13-4.07(m, 3H), 3.25(s, 3H), 3.15-3.10(m, 1H), 15 2.15-2.11(m, 1H), 1.93-1.75(m, 4H), 1.43-1.40(m, 3H), 1.28-1.24(m, 3H), 0.90-0.87(m, 2H), 0.01(s, 9H)

**Step 5: Preparation of benzyl (2S,5R)-5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidine-1-carboxylate**

Benzyl (2S,5R)-5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidine-1-carboxylate (133.5 mg, 0.2 mmol), ethylenediamine (43.7 uL, 0.6 mmol), and 1.0M 25 tetrabutylammonium fluoride (647.1 uL, 0.6 mmol) dissolved in

tetrahydrofuran solution were dissolved in tetrahydrofuran (2.0 mL), and then the mixture was stirred at 160°C for 12 hours. After adding ethyl acetate, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography to obtain 72.3 mg (yield: 68.6%) of the title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.82(s, 1H), 7.47(s, 1H), 7.35-7.19(m, 5H), 6.74-6.71(m, 1H), 6.40-6.38(m, 1H), 5.15-5.01(m, 2H), 4.83-4.80(m, 1H), 4.43-4.41(m, 1H), 4.03-4.00(m, 3H), 3.22(s, 3H), 3.09-3.06(m, 1H), 1.82-1.65(m, 3H), 1.36-1.34(m, 3H), 1.25-1.21(m, 4H)

**Step 6: Preparation of N<sup>2</sup>-(1-ethyl-1H-pyrazol-4-yl)-N<sup>4</sup>-methyl-N<sup>4</sup>-((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine**

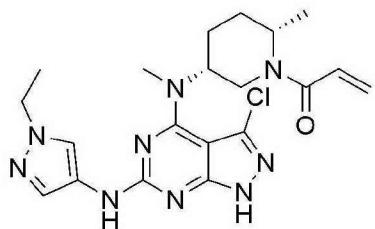
After adding methanol to benzyl (2S,5R)-5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidine-1-carboxylate (72.3 mg, 0.1 mmol) and palladium/carbon (7.0 mg), the air was replaced by hydrogen and the mixture was stirred at room temperature for 12 hours. After filtering under reduced pressure through celite, the residue was concentrated under reduced pressure to obtain 53.0 mg (yield: 100.0%) of the title compound, and the next reaction was carried out without further separation.

**Step 7: Preparation of 1-((2S,5R)-5-((2-(1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**

5        After  $N^2$ -(1-ethyl-1H-pyrazol-4-yl)- $N^4$ -methyl- $N^4$ -((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine (53.0 mg, 0.1 mmol) and sodium bicarbonate (37.3 mg, 0.4 mmol) were dissolved in tetrahydrofuran/distilled water (0.75 mL/0.25 mL), acryloyl chloride (12.0  $\mu$ L, 0.1 mmol) was added thereto at 0°C. The 10 reaction mixture was stirred at room temperature for 1 hour. After adding ethyl acetate, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography to obtain 15 29.0 mg (yield: 48.0%) of the title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  7.90(s, 1H), 7.55(s, 1H), 6.84-6.61(m, 1H), 6.26-6.19(m, 1H), 5.75-5.68(m, 1H), 4.63-4.61(m, 1H), 4.51-4.42(m, 1H), 4.13-4.01(m, 3H), 3.41-3.06(m, 4H), 2.21-2.18(m, 1H), 1.88-1.81(m, 3H), 1.44-1.41(m, 3H), 1.35-1.30(m, 3H)

20        **Example 11: Preparation of 1-((2S,5R)-5-((3-chloro-6-((1-ethyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**



**Step 1: Preparation of 3,4,6-trichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine**

3,4,6-Trichloro-1H-pyrazolo[3,4-d]pyrimidine (600.0 mg, 2.7 mmol), dihydropyran (735.0  $\mu$ L, 8.1 mmol) and p-toluenesulfonic acid (51.1 mg, 0.3 mmol) were dissolved in dichloromethane (10.0 mL), and then stirred at 120°C for 2 hours. The reaction mixture was concentrated under reduced pressure, and then the resulting residue was separated by column chromatography to obtain 715.9 mg (yield: 86.7%) of the title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD)  $\delta$  5.98-5.95(m, 1H), 4.05-4.02(m, 1H), 3.81-3.76(m, 1H), 2.46-2.43(m, 1H), 2.14-2.10(m, 1H), 1.98-1.95(m, 1H), 1.82-1.62(m, 3H)

**Step 2: Preparation of benzyl (2S,5R)-5-((3,6-dichloro-1-tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate**

Benzyl (2S,5R)-5-amino-2-methylpiperidine-1-carboxylate (242.2 mg, 1.0 mmol), 3,4,6-trichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (300.0 mg, 1.0 mmol) and N,N-diisopropyl (203.9  $\mu$ L, 1.2 mmol) were dissolved in ethanol (2.0 mL) and then stirred at 190°C for 5 hours. The reaction product was

concentrated under reduced pressure, and then the resulting residue was separated by column chromatography to obtain 446.3 mg (yield: 92.0%) of the title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.39-7.29(m, 5H), 5.80-5.78(m, 5 1H), 5.18-5.10(m, 2H), 4.48-4.46(m, 1H), 4.29-4.22(m, 2H), 4.04-4.02(m, 1H), 3.78-3.75(m, 1H), 3.02-3.00(m, 1H), 2.41-2.33(m, 1H), 2.08-1.61(m, 9H), 1.25-1.22(m, 3H)

10 **Step 3: Preparation of benzyl (2S,5R)-5-((3,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidine-1-carboxylate**

15 After benzyl (2S,5R)-5-((3,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (200.0 mg, 0.4 mmol) was dissolved in N,N-dimethylformamide (2.0 mL), sodium hydride (30.8 mg, 0.8 mmol) was added thereto and then stirred at 0°C for 5 minutes. Methyl iodide (40.0 uL, 0.6 mmol) was added and stirred at 0°C for 6 hours. After adding distilled water, the mixture was filtered under reduced pressure to obtain 205.4 mg (yield: 100.0%) of the title compound.

20 1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.36-7.31(m, 5H), 5.87-5.85(m, 1H), 5.14-5.09(m, 2H), 4.47-4.45(m, 2H), 4.18-4.13(m, 1H), 4.03-4.01(m, 1H), 3.79-3.77(m, 1H), 3.32(s, 3H), 3.18-3.16(m, 1H), 2.39-1.59(m, 10H), 1.28-1.26(m, 3H)

25 **Step 4: Preparation of benzyl (2S,5R)-5-((3-chloro-6-((1-**

**ethyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)(methyl) amino)-2-methylpiperidine-1-carboxylate**

After benzyl (2S,5R)-5-((3,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidine-1-carboxylate (200.0 mg, 0.4 mmol) and 1-ethyl-1H-pyrazol-4-amine (32.0 mg, 0.3 mmol) were dissolved in 2-butanol (3.0 mL), trifluoroacetic acid (26.5 uL, 0.3 mmol) was added thereto, and the mixture was reacted 200 °C for 6 hours. The reaction product was concentrated and then neutralized by adding 7N ammonia / methanol solution, and the residue was separated by column chromatography to obtain 92.3 mg (yield: 61.1%) of the title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.92-7.89(m, 1H), 7.56-7.53(m, 1H), 7.37-7.24(m, 5H), 5.18-5.04(m, 2H), 4.59-4.45(m, 2H), 4.17-4.07(m, 3H), 3.29(s, 3H), 3.18-3.16(m, 1H), 2.17-2.13(m, 1H), 1.88-1.76(m, 3H), 1.45-1.42(m, 3H), 1.28-1.25(m, 3H)

**Step 5: Preparation of 3-chloro-N<sup>6</sup>-(1-ethyl-1H-pyrazol-4-yl)-N<sup>4</sup>-methyl-N<sup>4</sup>-((3R,6S)-6-methylpiperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine**

Benzyl (2S,5R)-5-((3-chloro-6-((1-ethyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidine-1-carboxylate (39.0 mg, 0.1 mmol) and trifluoroacetic acid (3.0 mL) were dissolved in 2-butanol (1.0 mL), and then stirred at 190 °C for 18 hours. The reaction product was

concentrated and then neutralized by adding 7N ammonia / methanol solution, and concentrated under reduced pressure to obtain 29.0 mg (yield: 100.0%) of the title compound, and the next reaction was carried out without further separation.

5

**Step 6: Preparation of 1-((2S,5R)-5-((3-chloro-6-((1-ethyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one**

10            After        3-chloro-N<sup>6</sup>-(1-ethyl-1H-pyrazol-4-yl)-N<sup>4</sup>-methyl-N4-((3R,6S)-6-methylpiperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine (29.0 mg, 0.1 mmol) and sodium bicarbonate (38.8 mg, 0.2 mmol) were dissolved in tetrahydrofuran / distilled water (0.75 mL / 0.25 mL), acryloyl chloride (6.0 uL, 0.1 mmol) was added thereto at 15 0 °C. The reaction mixture was stirred at room temperature for 1 hour. After adding ethyl acetate, distilled water was added and the organic layer was separated. The separated organic layer was treated with sodium sulfate, filtered and concentrated under reduced pressure. The residue was separated by column chromatography to 20 obtain 13.1 mg (yield: 39.7%) of the title compound.

1H NMR (500 MHz, CD<sub>3</sub>OD) δ 7.84-7.83(m, 1H), 7.48(s, 1H), 6.84-6.52(m, 2H), 6.45-6.44(m, 1H), 6.24-6.06(m, 1H), 5.77-5.56(m, 1H), 4.59-4.41(m, 1H), 4.11-3.91(m, 3H), 3.34(s, 3H), 3.29-3.00(m, 1H), 2.18-2.11(m, 1H), 1.85-1.72(m, 3H), 1.42-1.38(m, 3H), 1.34-25 1.33(m, 1H), 1.25-1.23(m, 3H)

## **Experimental Example 1: Measurement of Inhibitory Activity against JAK3 and BTK Enzymes**

JAK3 and BTK kinases inhibitory activities were measured for 5 the compounds prepared in the Examples through in vitro analysis on the ADP Glow (Glo) platform.

Specifically, the inhibitory activities against JAK3 and BTK kinase were measured using a JAK3 kinase assay kit (Promega, V9441) and a BTK kinase assay kit (Promega, V9071) which were 10 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 MgCl<sub>2</sub>, 0.1 mg/mL BSA and 50 uM DTT/BTK: 40 mM Tris-Cl, pH 7.5, 20 mM MgCl<sub>2</sub>, 0.1 mg/mL BSA, 2 mM MnCl<sub>2</sub> and 50 uM DTT) and added to 96 well plates (JAK3: final concentration 15 of 4 ng per reaction/BTK: final concentration of 8 ng per reaction). The compounds prepared in the previous Examples 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 20 (JAK3 and BTK final concentration) in the total 25 uL reactants was added to 96-well plates 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) 25 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 5 of each compound, Microsoft Excel was used, and IC<sub>50</sub> values were calculated by SigmaPlot software. The results are shown in Table 1 below. Further, for comparison, Tofacitinib and Ibrutinib were evaluated in a similar way.

【Table 1】

Example No.	JAK3 IC <sub>50</sub> (nM)	BTK IC <sub>50</sub> (nM)
1	0.3	1.2
2	0.4	1.3
3	1.8	3.5
4	2.2	5.4
5	1.2	5.3
6	0.6	3.4
7	0.3	1.6
8	0.3	1.8
9	0.3	2.0
10	2.4	3.3
11	5.7	0.9

Tofacitinib	3.5	-
Ibrutinib	-	0.6

**Experimental Example 2: JAK3-Mediated Cell Assay (HT-2/IL-2 Assay)**

The inhibitory activities against JAK3 kinase at the cellular level were measured for the compounds prepared in the Examples through in vitro analysis of STAT5 phosphorylation induced by IL-2 stimulation in HT-2 cells. Specifically, STAT5 phosphorylation was analyzed using HTRF®phospho-STAT5 (Tyr694) assay kit (Cisbio, 64AT5PEG), which was purchased from Cisbio. HT-2 cells were cultured for 2 hours in growth factor-free medium. The cultured HT-2 cells were dispensed into 96-well plates by 50 ul so as to be a density of  $2.5 \times 10^5$  cells/well. The compounds prepared in the previous Examples were prepared so as to be finally a 0.3% DMSO aqueous solution, and HT-2 cells was treated with the compounds for 30 minutes. After the compound treatment, IL-2 was prepared so as to be finally a concentration of 20 ng/ml, and HT-2 cells was treated for 10 minutes. The cells were then disrupted by treating lysis buffers for 30 minutes. The level of STAT5 phosphorylation was measured according to the instructions of HTRF® phospho-STAT5 assay kit, and the inhibitory activity of the compounds according to the invention was calculated. For the analysis of the results of each compound, Microsoft Excel was used, and IC<sub>50</sub> values were

calculated by SigmaPlot software.

**【Table 2】**

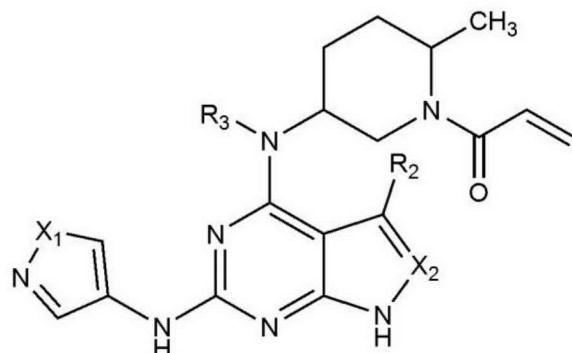
Example No.	JAK3 Cell IC <sub>50</sub> (nM)
1	90.9
2	360.4

The claims defining the invention are as follows:

【Claim 1】

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

[Chemical Formula 1]



10

wherein, in Chemical Formula 1,

X<sub>1</sub> is N-R<sub>1</sub>, O, or S,

X<sub>2</sub> is CH, or N,

15 R<sub>1</sub> is ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-((tert-butoxycarbonyl)amino)ethyl, 2,2-difluoroethyl(-CH<sub>2</sub>CHF<sub>2</sub>) or 2,2,2-trifluoroethyl(-CH<sub>2</sub>CF<sub>3</sub>),

R<sub>2</sub> is hydrogen, C<sub>1-5</sub> alkyl, or halogen, and

R<sub>3</sub> is hydrogen or C<sub>1-5</sub> alkyl.

20

【Claim 2】

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

25 wherein R<sub>2</sub> is hydrogen, methyl, bromo, fluoro, or chloro.

【Claim 3】

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

wherein R<sub>3</sub> is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, or neopentyl.

5

【Claim 4】

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

wherein X<sub>1</sub> is N-R<sub>1</sub> and X<sub>2</sub> is CH.

10

【Claim 5】

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

wherein the compounds represented by the Chemical Formula 1 is any one selected from the group consisting of the following:

- 1) 1-((2S,5R)-5-((5-chloro-2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,
- 2) 1-((2S,5R)-5-((2-((1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,
- 3) 1-((2S,5R)-5-((2-((1-isobutyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,
- 4) 1-((2S,5R)-5-((2-((1-cyclopentyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,
- 5) tert-butyl 2-(4-((4-((3R,6S)-1-acryloyl-6-methylpiperidin-3-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-1H-pyrazol-1-yl)ethylcarbamate,
- 6) 1-((2S,5R)-5-((5-chloro-2-(isothiazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,
- 7) 1-((2S,5R)-5-((5-chloro-2-((1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,
- 8) 1-((2S,5R)-5-((5-chloro-2-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,

- 9) 1-((2S,5R)-5-((5-chloro-2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one,
- 10) 1-((2S,5R)-5-((2-(1-ethyl-1H-pyrazol-4-yl)amino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one, and
- 5 11) 1-((2S,5R)-5-((3-chloro-6-((1-ethyl-1H-pyrazol-4-yl)amino)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)(methyl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one.

【Claim 6】

10 A pharmaceutical composition for the prevention or treatment of inflammatory disease, autoimmune disease, proliferative disease, hyperproliferative disease, immunity mediated disease, cancer or tumor, comprising the compound according to any one of claims 1, 2 to 5 or a pharmaceutically acceptable salt thereof.