

COMPOUND INHIBITING ACTIVITIES OF BTK AND/OR JAK3 KINASES

TECHNICAL FIELD

5 The present invention relates to a compound for inhibiting activities of BTK (Bruton's tyrosine kinase) and/or JAK3 (Janus kinase 3) kinases, a pharmaceutical composition thereof, the use thereof in the manufacture of a medicament, a method of using the compound in inhibiting BTK and/or JAK3 activities and a method of using the compound in the treatment and/or prevention of BTK- and/or JAK3-mediated diseases or disorders in mammals, especially in humans.

10 BACKGROUND ART

Protein kinase is one of the largest families in human enzymes, and more than 500 kinds of protein kinases have been identified in the human body to date. These protein kinases modulate the activities of particular proteins by transferring phosphate groups to the proteins, and then control complex signaling pathways. Aberrant activities of protein kinases are correlated with
15 many diseases including cancers, autoimmune disorders, and so on. Because of the essential role of protein kinases in signaling pathways and the correlation between the kinase activities and many diseases, kinase inhibitors have now become a hot topic for the research and discovery of new chemical entities.

BTK (Bruton's tyrosine kinase) is a non-receptor tyrosine kinase of TEC family. BTK is an
20 essential media of B cell receptor (BCR) signaling pathway and it is a key modulator of early B cell development, and activation, signaling and survival of mature B cells. Thus, BTK inhibitors can be used for treating diseases associated with aberrant activation of B cells, for example, autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus, etc. The efficacy for treating autoimmune diseases by BTK inhibitors has been preliminary demonstrated
25 in the preclinical animal models (Honigberg, L. A. et al, *Proceedings of the National Academy of Sciences of the United States of America*, 2010, 107, 13075-13080). Besides B cells, there are experimental evidences showing that BTK also takes part in the signal pathways of monocytes, macrophages, neutrophils and mast cells. BTK inhibitors can depress FcγR-induced release of cytokines including TNFα, IL-1β and IL-6, from monocytes and macrophages, and can also
30 reduce the FcγR-induced degranulation of mast cells (Chang B. Y. et al, *Arthritis Research & Therapy*, 2011, 13, R115).

The B cell receptor (BCR)-mediated signaling pathway is vital to the survival of many

lymphomas. As a key kinase in the BCR pathway, BTK is therefore a potential therapeutic target of lymphomas. In clinical trials, BTK inhibitors show significant effects in the treatment of chronic lymphocytic leukemia (CLL). BTK inhibitors also exhibit significant effects on other lymphomas such as diffused large B-cell lymphoma and mantle cell lymphoma, etc. (Buggy, J. J. et al, *International Reviews of Immunology*, 2012, 31, 119-132).

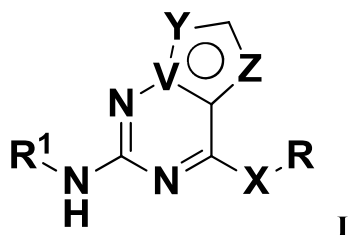
Janus kinases are essential tyrosine kinases for modulating the cellular function of lymphatic and hematopoietic cells. Janus kinases include four known members, which are JAK1, JAK2, JAK3 and TYK2, respectively, and wherein JAK3 (Janus tyrosine kinase 3) is mainly expressed in lymphocytes and natural killer cells. JAK3 is constitutively bound to the common γ c chain, which is a common receptor subunit for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 (Ghoreschi K. et al, *Immunological Reviews*, 2009, 228, 273-87). These cytokines, mediated through JAK3, are essential for the proliferation, differentiation and functions of lymphocytes. The function loss of the JAK3 kinase will result in the immunodeficiency of both human and mice. Because of the essential role of JAK3 kinase in the immune system, JAK3 kinase is a very attractive target for the treatment of immune-associated diseases, for example, autoimmune diseases like rheumatoid arthritis or allograft rejection in the patients with organ transplantation. Selective JAK3 inhibitors show significant efficacy in the clinical trials of rheumatoid arthritis.

In addition to the individual efficacy of BTK inhibitors and JAK3 inhibitors, simultaneously inhibiting both BTK pathway and JAK3 pathway will potentially have synergetic effects in clinical application. For example, via experiments, Cetkovic-Cvrlje M et al prove that the combination of using BTK and JAK3 inhibitors may improve the survival rates of animals in Graft-Versus-Host Disease (GVHD) models (Cetkovic-Cvrlje M. et al, *British Journal of Haematology*, 2004, 126, 821-827).

Therefore, it is necessary to develop novel compounds aiming at BTK and/or JAK3 pathways, wherein the novel compounds show good efficacy and can be orally available, which also exhibit pharmacokinetic properties favorable to the therapeutic applications and show sufficiently low toxic and side effects *in vivo*.

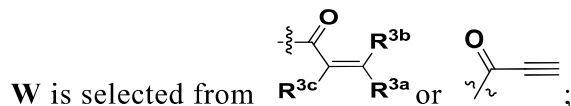
SUMMARY OF THE INVENTION

According to one aspect of the present invention, the present invention provides a compound represented by formula I (hereinafter sometimes referred to as a compound of formula I):



wherein:

- R** is selected from C₃₋₈ cycloalkyl substituted by -NR²W; a 4- to 10-membered saturated *N*-heterocyclcyl group which contains only one nitrogen atom on its ring and the nitrogen atom is substituted by **W**; or C₁₋₄ alkyl substituted by a 4- to 10-membered saturated *N*-heterocyclcyl group which contains only one nitrogen atoms on its ring and the nitrogen atom is substituted by **W**;



V is selected from C or N;

- X** is selected from O, S, or NR⁴;

Y is selected from CH, O, or S;

Z is selected from CH, O, S, or NR⁵;

R¹ is C₆₋₁₂ aryl or 5- to 12-membered heteroaryl, optionally substituted by one or more **R**⁶;

- R**² is selected from hydrogen or C₁₋₈ aliphatic;

R^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl;

R⁴ is selected from hydrogen or C₁₋₈ aliphatic;

R⁵ is selected from hydrogen or C₁₋₈ aliphatic;

- each **R**⁶ is independently selected from the group consisting of halogen, nitro, cyano, heterocyclcyl, C₆₋₁₂ aryl, 5- to 12-membered heteroaryl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclcyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyloxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, carboxy C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticacylamino C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticoxycarbonyl C₁₋₈ aliphatic, aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfinyl C₁₋₈ aliphatic, C₁₋₈ aliphatic sulfonylamino, C₁₋₈ aliphaticsulfonylamino C₁₋₈ aliphatic, sulfamoyl C₁₋₈ aliphatic, C₁₋₈

aliphaticaminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminosulfonyl C₁₋₈ aliphatic,
 di(C₁₋₈ aliphatic)phosphonyl C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy, heterocyclyloxy,
 heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈
 aliphaticoxy, amino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticamino C₁₋₈ aliphaticoxy, di(C₁₋₈
 5 aliphatic)amino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticacylamino C₁₋₈ aliphaticoxy, C₁₋₈
 aliphaticcarbonyl C₁₋₈ aliphaticoxy, aminoacyl C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticaminoacyl
 C₁₋₈ aliphaticoxy, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphaticoxy, amino, C₁₋₈
 aliphaticamino, di(C₁₋₈ aliphatic)amino, heterocyclylamino, heterocyclyl C₁₋₈
 aliphaticamino, hydroxy C₁₋₈ aliphaticamino, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticamino, amino
 10 C₁₋₈ aliphaticamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino C₁₋₈
 aliphaticamino, C₁₋₈ aliphaticacylamino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl C₁₋₈
 aliphaticamino, aminoacyl C₁₋₈ aliphaticamino, C₁₋₈ aliphaticaminoacyl C₁₋₈
 aliphaticamino, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphaticamino, C₁₋₈ aliphaticacylamino,
 heterocyclyl C₁₋₈ aliphaticacylamino, heterocyclylacylamino, hydroxy C₁₋₈
 15 aliphaticacylamino, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticacylamino, amino C₁₋₈
 aliphaticacylamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticacylamino, di(C₁₋₈ aliphatic)amino
 C₁₋₈ aliphaticacylamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, heterocyclyl C₁₋₈
 aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, heterocyclyl C₁₋₈ aliphaticoxycarbonyl,
 di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl,
 20 di(C₁₋₈ aliphatic)aminoacyl, heterocyclyl C₁₋₈ aliphaticaminoacyl, heterocyclylaminoacyl,
 hydroxy C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticaminoacyl, amino C₁₋₈
 aliphaticaminoacyl, C₁₋₈ aliphaticamino C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)amino
 C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticsulphydryl, heterocyclylsulphydryl, heterocyclyl C₁₋₈
 aliphaticsulphydryl, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, heterocyclylsulfonyl,
 25 heterocyclylsulfinyl, heterocyclyl C₁₋₈ aliphaticsulfonyl, heterocyclyl C₁₋₈
 aliphaticsulfinyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl,
 heterocyclyl C₁₋₈ aliphaticaminosulfonyl, heterocyclylaminosulfonyl, di(C₁₋₈
 aliphatic)amino C₁₋₈ aliphaticaminosulfonyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl,
 di(C₁₋₈ aliphatic)aminosulfinyl, heterocyclylaminosulfinyl and di(C₁₋₈
 30 aliphatic)phosphonyl, wherein:

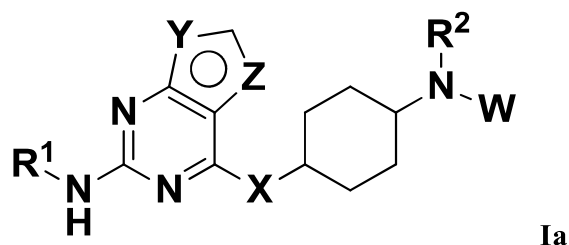
heterocyclyl, as an independent group or a part of other group(s), represents a
 saturated or partially unsaturated 3- to 12-membered heterocyclyl group containing one or
 more heteroatoms selected from the group consisting of N, O, and S; optionally, each
 heterocyclyl is independently substituted by one or more substituents selected from the
 35 group consisting of halogen, C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈

aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, heterocyclyl, 5- to 12-membered heteroaryl, hydroxy, C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, heterocyclyl C₁₋₈ aliphaticcarbonyl, hydroxy C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticcarbonyl, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, heterocyclylsulfonyl, heterocyclylsulfinyl, heterocyclyl C₁₋₈ aliphaticsulfonyl, heterocyclyl C₁₋₈ aliphaticsulfinyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, and di(C₁₋₈ aliphatic)aminosulfonyl; and

optionally, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl are independently substituted by one or more substituents selected from the group consisting of halogen, C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino and di(C₁₋₈ aliphatic)amino,

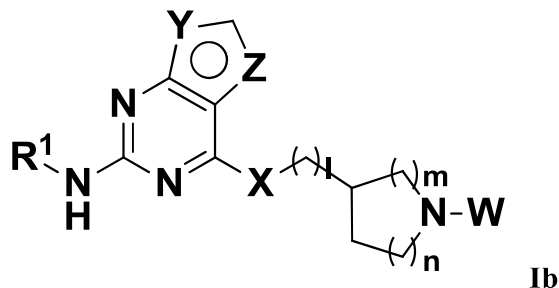
wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

In some embodiments, the present invention provides a compound represented by formula **Ia** (hereinafter sometimes referred to as a compound of formula **Ia**):



wherein, X, Y, Z, W, R¹, and R² are all defined as in formula **I**, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

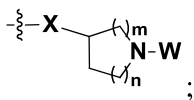
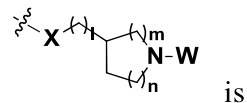
In some embodiments, the present invention provides a compound represented by formula **Ib** (hereinafter sometimes referred to as a compound of formula **Ib**):



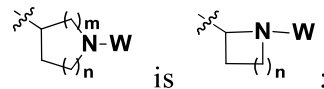
wherein:

X, **Y**, **Z**, **W**, and **R¹** are all defined as in formula **I**;

l is selected from 0, 1, 2, 3, or 4, wherein when **l** is 0,

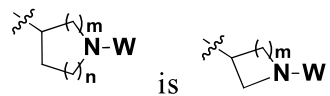


m is selected from 0, 1, 2, 3, or 4; wherein when **m** is 0,



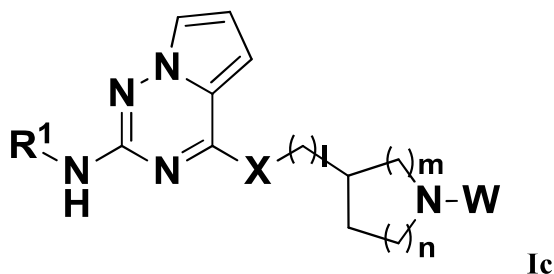
and

n is selected from 0, 1, 2, or 3; wherein when **n** is 0,



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

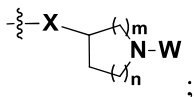
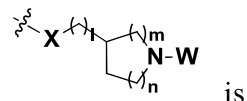
In some embodiments, the present invention provides a compound represented by
10 formula **Ic** (hereinafter sometimes referred to as a compound of formula **Ic**):



wherein:

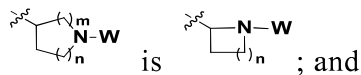
X, **W**, and **R¹** are all defined as in formula **I**;

l is selected from 0, 1, 2, 3, or 4; wherein when **l** is 0,

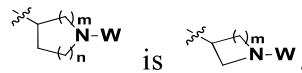


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m is selected from 0, 1, 2, 3, or 4; wherein when **m** is 0,



n is selected from 0, 1, 2, or 3; wherein when **n** is 0,



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

Another aspect of the present invention relates to a pharmaceutical composition
20 comprising one or more compounds of formula **I** (especially compounds of formulae **Ia**,

Ib and **Ic**) of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients.

The pharmaceutical composition of the present invention further comprises one or more agents selected from the group consisting of immunosuppressants, corticosteroids, nonsteroidal anti-inflammatory drugs, Cox-2 specific inhibitors, TNF- α binding proteins, interferons and interleukins.

Another aspect of the present invention relates to use of the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting BTK and/or JAK3 activities.

Another aspect of the present invention relates to use of the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention or treatment of BTK- and/or JAK3-mediated diseases.

Another aspect of the present invention relates to use of the pharmaceutical composition of the present invention comprising one or more compounds of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients in the manufacture of a medicament for inhibiting BTK and/or JAK3 activities. In some embodiments, the pharmaceutical composition further comprises, in addition to the above-mentioned compounds, one or more agents selected from the group consisting of immunosuppressants, corticosteroids, nonsteroidal anti-inflammatory drugs, Cox-2 specific inhibitors, TNF- α binding proteins, interferons and interleukins.

Another aspect of the present invention relates to use of the pharmaceutical composition of the present invention comprising one or more compounds of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or stereoisomers, tautomers, solvates, or pharmaceutically acceptable salts thereof, and pharmaceutically acceptable excipients in the manufacture of a medicament for the prevention or treatment of BTK- and/or JAK3-mediated diseases. In some embodiments, the pharmaceutical composition further comprises, in addition to the above-mentioned compounds, one or more agents selected from the group consisting of immunosuppressants, corticosteroids, nonsteroidal anti-inflammatory drugs, Cox-2 specific inhibitors, TNF- α binding proteins, interferons and interleukins.

Another aspect of the present invention relates to a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, for inhibiting BTK and/or JAK3 activities.

5 Another aspect of the present invention relates to a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of BTK- and/or JAK3-mediated diseases.

10 Another aspect of the present invention relates to a pharmaceutical composition comprising a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, for inhibiting BTK and/or JAK3 activities.

15 Another aspect of the present invention relates to a pharmaceutical composition comprising a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of BTK- and/or JAK3-mediated diseases.

20 Another aspect of the present invention relates to a method of inhibiting BTK and/or JAK3 activities in a biological system comprising bringing the biological system into contact with a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, or with a pharmaceutical composition comprising a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

25 Another aspect of the present invention relates to a method of preventing or treating BTK- and/or JAK3-mediated diseases comprising administering to a mammal (especially a human) in need thereof a therapeutically effective amount of a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, or of a
30 pharmaceutical composition comprising a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

35 Another aspect of the present invention relates to use of a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, in

combination with one or more active agents selected from the group consisting of immunosuppressants, corticosteroids, nonsteroidal anti-inflammatory drugs, Cox-2 specific inhibitors, TNF- α binding proteins, interferons and interleukins in the manufacture of a medicament for treating BTK- and/or JAK3-mediated diseases.

- 5 In the present application, the BTK- and/or JAK3-mediated diseases are selected from the group consisting of autoimmune diseases, inflammatory diseases, heteroimmune conditions or diseases, thromboembolic diseases and cancers.

BRIEF DESCRIPTION OF THE DRAWINGS

- 10 Figure 1 shows the inhibiting effect of compound **132** on the BTK pathway in Ramos cells.
Figure 2 shows the scores of compound **132** in mCIA model.
Figure 3 shows the scores of compound **132** in rAIA model.

DETAILED DESCRIPTION OF THE EMBODIMENTS

- 15 Unless otherwise indicated, scientific and technical terms used herein have the same meanings as those commonly understood by an ordinary skilled person in the art.

It should be understood that the above-outlined contents and the following detailed description are exemplary only for illustration purposes without limiting the subject matter of the present invention in any way.

- 20 All literatures or sections of literatures including but not limited to, patents, patent applications, articles, books, manuals and theses as cited in the present application are incorporated herein by reference in its entirety.

- 25 The total number of carbon atoms present in a chemical group as defined herein is represented by a shorthand notation before the group. For example, C₁₋₈ aliphatic refers to an aliphatic group as defined hereinafter having 1 to 8 carbon atoms in total; C₁₋₈ alkyl refers to an alkyl group as defined hereinafter having 1 to 8 carbon atoms in total; C₃₋₈ cycloalkyl refers to a cycloalkyl group as defined hereinafter having 3 to 8 carbon atoms in total; C₆₋₁₂ aryl refers to an aryl group as defined hereinafter having 6 to 12 carbon atoms in total. Carbon atoms that may exist in the substituents of the chemical group are not included in the total number of carbon
30 atoms in the shorthand notation.

Unless otherwise indicated in this specification, all combined groups according to the present invention (i.e., groups comprised of two or more groups) are attached to the rest of the molecule in such a way that the lastly described group acts as the point of attachment. By way of

example, “heterocyclyl aliphatic” means that the heterocyclyl group is attached to the rest of the molecule via the aliphatic group; “aliphaticoxy” means that the aliphatic group is attached to the rest of the molecule via an oxy group; etc.

In addition to the above-mentioned, as used in the specification and claims, unless otherwise indicated, the following terms have the meanings as set forth below:

“Amino” refers to the -NH_2 group.

“Cyano” refers to the -CN group.

“Hydroxy” refers to the -OH group.

“Nitro” refers to the -NO_2 group.

“Oxo” refers to the =O substituent.

“Carbonyl” or “acyl” refers to the -C(=O)- group.

“Sulphydryl” refers to the -S group.

“Sulfonyl” refers to the $\text{-S(=O)}_2\text{-}$ group.

“Sulfinyl” refers to the -S(=O)- group.

“Phosphonyl” refers to the -P(=O)(OH)_2 group.

“Aminoacyl” refers to the -C(=O)-NH_2 group.

“Sulfamoyl” refers to the $\text{-S(=O)}_2\text{-NH}_2$ group.

“Aminosulfinyl” refers to the -S(=O)-NH_2 group.

In the present application, the term “halogen” refers to fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

In the present application, as an independent group or a part of other group(s), the term “aliphatic” or “aliphatic group” refers to a saturated or unsaturated group having the fundamental properties of an aliphatic compound, consisting solely of carbon atoms and hydrogen atoms, and which is attached to the rest of the molecules by a single bond. An aliphatic group includes straight or branched alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl groups, wherein alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are as defined hereinafter. In the present application, aliphatic refers to alkyl, alkenyl, alkynyl, cycloalkyl and/or cycloalkenyl, preferably refers to alkyl and/or cycloalkyl. All hydrogen atoms on an aliphatic group are optionally replaced with any suitable groups, for example, halogen, hydroxy, amino, mono-substituted amino, di-substituted amino, alkoxy, heterocyclyl, and the like.

In the present application, as an independent group or a part of other group(s), the term “alkyl” or “alkyl group” refers to a straight or branched group consisting solely of carbon and hydrogen atoms, containing no unsaturated bond, and which is attached to the rest of the molecule by a single bond. An alkyl group may comprise, for example, from 1

to 18, preferably 1 to 12, more preferably 1 to 8 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, *n*-pentyl, 2-pentyl, hexyl, heptyl, 2-methylhexyl, 3-methylhexyl, octyl, nonyl, decyl and the like, preferably methyl, ethyl, propyl, isopropyl, and *n*-butyl, more preferably methyl, ethyl, propyl and isopropyl. All hydrogen atoms on an alkyl group are optionally replaced with any suitable groups, for example, halogen, hydroxy, amino, mono-substituted amino, di-substituted amino, alkoxy, heterocyclyl, and the like.

In the present application, as an independent group or a part of other group(s), the term “alkenyl” or “alkenyl group” refers to a straight or branched hydrocarbon chain group, consisting solely of carbon and hydrogen atoms, containing at least one double bond, having for example from 2 to 18, preferably 2 to 10, more preferably 2 to 8 carbon atoms, and which is attached to the rest of the molecule by a single bond, which includes but is not limited to, ethenyl, propenyl, allyl, but-1-enyl, but-2-enyl, pent-1-enyl, pent-2-enyl, pent-1,4-dienyl and the like, preferably ethenyl and propenyl. All hydrogen atoms on an alkenyl group may optionally be replaced with any suitable groups, for example, halogen, hydroxy, amino, mono-substituted amino, di-substituted amino, alkoxy, heterocyclyl, and the like.

In the present application, as an independent group or a part of other group(s), the term “alkynyl” or “alkynyl group” refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing at least one triple bond and optionally containing one or more double bonds, having for example from 2 to 18, preferably 2 to 10, more preferably 2 to 8 carbon atoms, and which is attached to the rest of the molecule by a single bond. Examples of alkynyl include, but are not limited to, ethynyl, prop-1-ynyl, pent-1-en-4-ynyl, and the like. All hydrogen atoms on an alkynyl group are optionally replaced with any suitable groups, for example, halogen, hydroxy, amino, alkoxy, heterocyclyl, and the like.

In the present application, as an independent group or a part of other group(s), the term “cycloalkyl” or “cycloalkyl group” refers to a stable saturated non-aromatic monocyclic or polycyclic hydrocarbon group consisting solely of carbon and hydrogen atoms, which may include fused or bridged cyclic systems, having for example from 3 to 15, preferably 3 to 10, more preferably 3 to 8 carbon atoms, and which is attached to the rest of the molecule by a single bond via any suitable carbon atom on the ring. A cycloalkyl group includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, 7,7-dimethyl-bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.1.1]heptyl,

bicyclo[3.2.1]octyl, adamantyl, and the like, preferably cyclobutyl, cyclopentyl, and cyclohexyl groups. All hydrogen atoms on a cycloalkyl group may be optionally replaced with any suitable groups, for example, halogen, hydroxy, amino, mono-substituted amino, di-substituted amino, alkyl, alkoxy, heterocyclyl, and the like.

5 In the present application, as an independent group or a part of other group(s), the term “cycloalkenyl” refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon group consisting solely of carbon and hydrogen atoms, and containing at least one double bond, which may include fused or bridged cyclic systems with for example, from 3 to 15, preferably 3 to 10, more preferably 3 to 8 carbon atoms, and which is attached to the rest
10 of the molecule by a single bond via any suitable carbon atom on the ring. Examples of cycloalkenyl include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1,3-cyclohexadiene, 1,4-cyclohexadiene, 1*H*-indenyl, 2,3-dihydro-indenyl, 1,2,3,4-tetrahydro-naphthyl, 5,6,7,8-tetrahydro-naphthyl, 8,9-dihydro-7*H*-benzocyclohepten-6-yl, 6,7,8,9-tetrahydro-5*H*-benzocycloheptenyl, 15 5,6,7,8,9,10-hexahydro-benzocyclooctenyl, fluorenyl, bicyclo[2.2.1]heptenyl, bicyclo[2.2.2]octyl, bicyclo[2.2.2]octenyl, bicyclo[3.2.1]octenyl, octahydro-4,7-methylene-1*H*-indenyl, octahydro-2,5-methylene-pentadienyl, and the like. All hydrogen atoms on a cycloalkenyl group are optionally replaced with any suitable groups, for example, halogen, hydroxy, amino, mono-substituted amino, di-substituted
20 amino, alkyl, alkoxy, heterocyclyl, and the like.

In the present application, the term “halo aliphatic” refers to an aliphatic group, as defined above, which is substituted by one or more halogen atoms. Examples of halo aliphatic include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, 1,1-difluoroethyl, chloromethyl, chloroethyl, dichloromethyl,
25 1,2-dichloroethyl, fluoroethenyl, fluorocyclopentyl, fluorocyclohexyl, chlorocyclohexenyl, and the like, preferably fluoroethyl.

In the present application, the term “hydroxy aliphatic” refers to an aliphatic group, as defined above, substituted by one or more hydroxy groups. Examples of hydroxy aliphatic include, but are not limited to, 1-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxy-cyclopentyl, 4-hydroxy-cyclohexyl, 3,4-dihydroxy-cyclohexyl, and the like,
30 preferably 1-hydroxyethyl.

In the present application, the term “amino aliphatic” refers to an aliphatic group, as defined above, substituted by one or more amino groups.

In the present application, as an independent group or a part of other group(s), the
35 term “aliphaticoxy” refers to a group as represented by formula -OR_a, wherein R_a is an

aliphatic group as defined above. The aliphatic moiety of the aliphaticoxy group may be optionally substituted as described above for an aliphatic group. Examples of aliphaticoxy include, but are not limited to, methoxy, ethoxy, isobutoxy, *n*-butoxy, isobutoxy, *tert*-butoxy, ethenyloxy, 1-propenyloxy, 1-propynyloxy, cyclopentyloxy, cyclohexyloxy, and the like, preferably methoxy and ethoxy.

In the present application, the term “hydroxy aliphaticoxy” refers to an aliphaticoxy group, as defined above, wherein the aliphatic moiety is substituted by one or more hydroxy groups. Examples of hydroxy aliphaticoxy include, but are not limited to, 1-hydroxyethoxy, 1-hydroxypropoxy, 3-hydroxy-cyclopentyloxy, 3,4-dihydroxy cyclohexyloxy, and the like, preferably 1-hydroxyethoxy.

In the present application, as an independent group or a part of other group(s), the term “aliphaticcarbonyl” refers to a group of the formula -C(=O)-R_a , wherein R_a is an aliphatic group as defined above. The aliphatic moiety of the aliphaticcarbonyl group may be optionally substituted as described above for an aliphatic group. Aliphaticcarbonyl includes alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, cycloalkylcarbonyl and cycloalkenylcarbonyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are as defined above. In the present application, aliphaticcarbonyl preferably refers to alkylcarbonyl and/or cycloalkylcarbonyl. Examples of aliphaticcarbonyl include, but are not limited to, methylcarbonyl (also referred to as acetyl), ethylcarbonyl (also referred to as propionyl), isopropylcarbonyl, butylcarbonyl, ethenylcarbonyl, propenylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, and the like, preferably methylcarbonyl.

In the present application, as an independent group or a part of other group(s), the term “aliphaticamino” refers to a group of the formula -NHR_a , wherein R_a is an aliphatic group as defined above. An aliphaticamino group includes alkylamino, alkenylamino, alkynylamino, cycloalkylamino and cycloalkenylamino groups, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moieties are all defined as above. In the present application, an aliphaticamino group preferably refers to alkylamino and/or cycloalkylamino groups. Examples include, but are not limited to, methylamino, ethylamino, isopropylamino, ethenylamino, propenylamino, propynylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, cyclohexenylamino, and the like, preferably methylamino, ethylamino, and cyclohexylamino.

In the present application, as an independent group or a part of other group(s), the term “dialiphaticamino” refers to an amino group on which two hydrogen atoms are, respectively, replaced with an aliphatic group, and which can be represented by formula $\text{-NR}_a\text{R}_b$, wherein R_a and R_b are independently an aliphatic group as defined above. In the

present application, a dialiphaticamino group preferably refers to a dialkylamino group. Examples of dialkylamino include, but are not limited to, dimethylamino, diethylamino, dipropylamino, methylethylamino, and the like, preferably dimethylamino.

5 In the present application, as an independent group or a part of other group(s), the term “aliphaticoxy aliphaticoxy” refers to an aliphaticoxy group as defined above, wherein the aliphatic moiety is substituted by an aliphaticoxy group as defined above. An aliphaticoxy aliphaticoxy group preferably refers to alkoxyalkoxy, alkoxycycloalkoxy and/or cycloalkoxyalkoxy groups. Examples of aliphaticoxy aliphaticoxy include, but are not limited to, methoxyethoxy, ethoxyethoxy, methoxycyclopentyloxy, methoxy
10 cyclohexyloxy, cyclopentyloxy methoxy, and the like.

In the present application, as an independent group or a part of other group(s), the term “aliphaticamino aliphatic” refers to an aliphatic group, as defined above, which is substituted by an aliphaticamino group as defined above.

15 In the present application, as an independent group or a part of other group(s), the term “dialiphaticamino aliphatic” refers to an aliphatic group, as defined above, which is substituted by a dialiphaticamino group as defined above. Examples of dialiphaticamino aliphatic include, but are not limited to, dimethylamino ethyl, diethylamino ethyl, (methyl)(ethyl)amino ethyl, and the like, preferably dimethylamino ethyl.

20 In the present application, as an independent group or a part of other group(s), the term “dialiphaticamino aliphaticamino” refers to an aliphaticamino group as defined above, wherein the aliphatic moiety is substituted by a dialiphaticamino group as defined above. Examples of dialiphaticamino aliphaticamino include, but are not limited to, dimethylamino ethylamino, diethylamino ethylamino, (methyl)(ethyl)amino ethylamino, and the like, preferably dimethylamino ethylamino.

25 In the present application, as an independent group or a part of other group(s), the term “aliphaticaminoacyl” refers to an aminoacyl group wherein one hydrogen atom on the amino moiety is replaced with an aliphatic group as defined above, and which can be represented by formula $-C(=O)-NH-R_a$, wherein R_a is an aliphatic group as defined above. Examples of aliphaticaminoacyl include, but are not limited to, $-C(=O)-NH-CH_3$,
30 $-C(=O)-NH-C_2H_5$, cyclohexylaminoacyl, and the like, preferably $-C(=O)-NH-CH_3$.

In the present application, as an independent group or a part of other group(s), the term “heterocyclyl” refers to a stable 3- to 18-membered non-aromatic ring group comprising 1 to 6 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur. Unless indicated otherwise specifically in the specification, the heterocyclyl
35 group may be a monocyclic, bicyclic, tricyclic or polycyclic ring system, which may

include fused or bridged ring systems. For purpose of the present invention, heterocyclyl is preferably a stable 3- to 12-membered non-aromatic monocyclic or bicyclic ring group comprising 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur, more preferably a stable 3- to 8-membered non-aromatic monocyclic ring group comprising 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur. The nitrogen, carbon or sulphur atom in the heterocyclyl group may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl group may be partially or fully saturated. The heterocyclyl group may be attached to the rest of the molecule by a single bond via a carbon atom or a heteroatom. In a heterocyclyl group containing fused rings, one or more rings may be aryl or heteroaryl, provided that the point of attachment of the heterocyclyl group to the rest of the molecule is through an atom on the non-aromatic ring. Examples of such heterocyclyl groups include, but are not limited to, azetidiny, pyranly, tetrahydropyranly, thiopyranly, tetrahydrofuranly, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, oxazinyl, dioxolanly, tetrahydroisoquinolinyl, decahydroisoquinolinyl, imidazolinyl, imidazolidinyl, quinolizinyl, thiazolidinyl, isothiazolidinyl, isoxazolidinyl, indolinyl, octahydroindolyl, octahydroisoindolyl, pyrrolidinyl, pyrazolidinyl, phthalimido, and the like, preferably piperazinyl, piperidyl, tetrahydropyranly, and morpholinyl. A heterocyclyl group may be optionally substituted by any suitable substituents including, but not limited to, halogen, hydroxy, amino, alkyl, alkoxy, alkylcarbonyl, and the like.

In the present application, “*N*-heterocyclyl” refers to a heterocyclyl group, as defined above, containing at least one nitrogen atom on its ring.

In the present application, as an independent group or a part of other group(s), the term “heterocyclyloxy” refers to a group of the formula $-OR_h$, wherein R_h is a heterocyclyl group as defined above. The heterocyclyl moiety of the heterocyclyloxy group may be optionally substituted as described above for a heterocyclyl group.

In the present application, as an independent group or a part of other group(s), the term “heterocyclylcarbonyl” refers to a group of the formula $-C(=O)-R_h$, wherein R_h is a heterocyclyl group as defined above. The heterocyclyl moiety of the heterocyclylcarbonyl group may be optionally substituted as described above for a heterocyclyl group.

In the present application, as an independent group or a part of other group(s), the term “heterocyclylamino” refers to a group of the formula R_h-NH- , wherein R_h is a heterocyclyl group as defined above. The heterocyclyl moiety of the heterocyclylamino group may be optionally substituted as described above for a heterocyclyl group.

In the present application, as an independent group or a part of other group(s), the

term “heterocyclylaminoacyl” refers to an aminoacyl group as defined above, wherein one hydrogen on the amino moiety is replaced with a heterocyclyl group as defined above, and which can be represented by formula $-C(=O)-NH-R_h$, wherein R_h is a heterocyclyl group as defined above. The heterocyclyl moiety of the heterocyclylaminoacyl group may be optionally substituted as described above for a heterocyclyl group.

In the present application, as an independent group or a part of other group(s), the term “heterocyclyl aliphatic” refers to an aliphatic group, as defined above, that is substituted by a heterocyclyl group as defined above. The heterocyclyl moiety of the heterocyclyl aliphatic group may be optionally substituted as described above for a heterocyclyl group, and the aliphatic moiety of the heterocyclyl aliphatic group may be optionally substituted as described above for an aliphatic group.

In the present application, as an independent group or a part of other group(s), the term “heterocyclyl aliphaticoxy” refers to an aliphaticoxy group as defined above, wherein the aliphatic moiety is substituted by a heterocyclyl group as defined above. The heterocyclyl moiety of the heterocyclyl aliphaticoxy group may be optionally substituted as described above for heterocyclyl, and the aliphatic moiety of the heterocyclyl aliphaticoxy group may be optionally substituted as described above for an aliphatic group.

In the present application, as an independent group or a part of other group(s), the term “aryl” refers to a system group having from 6 to 18, preferably 6 to 12 carbon atoms and at least one aromatic ring. For the purpose of the present invention, the aryl group may be a monocyclic, bicyclic, tricyclic or polycyclic ring system, which may include a fused or bridged ring system. The aryl group is attached to the rest of the molecule by a single bond via an atom on the aromatic ring. Examples of such aryl groups include, but are not limited to, phenyl, naphthyl, anthryl, phenanthryl, fluorenyl, 2-benzoxazolinone, 2*H*-1,4-benzoxazin-3(4*H*)-one-7-yl, and the like; preferably phenyl.

In the present application, as an independent group or a part of other group(s), the term “heteroaryl” refers to a 5- to 16-membered ring system group containing 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur on its ring, and at least one aromatic ring. Unless otherwise indicated in the present specification, the heteroaryl group may be a monocyclic, bicyclic, tricyclic or polycyclic ring system, which may include a fused or bridged ring system, provided that the point of attachment is through an atom on the aromatic ring. The nitrogen, carbon or sulphur atoms in the heteroaryl group may be optionally oxidized; and the nitrogen atom may be optionally quaternized. For the purpose of the present invention, the heteroaryl group is

preferably a stable 5- to 12-membered aromatic monocyclic or bicyclic ring group containing 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur, more preferably a stable 5- to 8-membered aromatic monocyclic or bicyclic ring group containing 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur, and most preferably a stable 5- to 6-membered aromatic monocyclic ring group containing 1 to 2 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur. Examples of such heteroaryl groups include, but are not limited to, thienyl, furyl, pyrrolyl, imidazolyl, benzimidazolyl, pyrazolyl, benzopyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, triazinyl, pyrimidinyl, pyridazinyl, indoliziny, indolyl, isoindolyl, indazolyl, isoindazolyl, purinyl, quinolyl, isoquinolyl, naphthyridinyl, naphthyridinyl, quinoxalinyl, pteridinyl, carbazolyl, carbolinyl, phenanthridinyl, phenanthrolinyl, acridinyl, phenazinyl, thiazolyl, isothiazolyl, benzothiazolyl, benzothienyl, oxazolyl, isoxazolyl, oxadiazolyl, oxatriazolyl, cinnolinyl, quinazolinyl, phenylthio, indoliziny, phenanthrolinyl, phenoxazinyl, phenothiazinyl, 4,5,6,7-tetrahydro-benzo[*b*]thienyl, naphthopyridinyl, imidazo[1,2-*a*]pyridinyl, and the like, preferably pyrrolyl, pyrazolyl, imidazolyl, thienyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, and imidazo[1,2-*a*]pyridinyl, and more preferably pyrazolyl, thienyl, isoxazolyl, thiazolyl, and isothiazolyl.

In the present application, “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, “alkyl optionally substituted by one or more halogens” means the alkyl group is unsubstituted or substituted by one or more halogens, and that the description includes both substituted alkyl groups and unsubstituted alkyl groups.

A “stereoisomer” refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures. The present invention contemplates various stereoisomers and mixtures thereof.

As the compounds of formula **I** of the present invention contain an olefinic double bond, and unless specified otherwise, it is intended that the compounds include both E- and Z-geometric isomers.

A “tautomer” refers to an isomer resulted from a proton shift from one atom of a molecule to another atom of the same molecule. All tautomeric forms of the compound of formula **I** of the present invention are included within the scope of the present invention.

In the present application, the term “pharmaceutically acceptable salt” includes both pharmaceutically acceptable acid and base addition salts.

“Pharmaceutically acceptable acid addition salt” refers to those salts which are capable of retaining the biological effectiveness of the free bases without any undesirable effects, and which are formed with inorganic acid or organic acids. The inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; and the organic acids include, but are not limited to, formic acid, acetic acid, trifluoroacetic acid, propionic acid, caprylic acid, caproic acid, capric acid, undecylenic acid, glycolic acid, gluconic acid, lactic acid, oxalic acid, sebacic acid, adipic acid, glutaric acid, malonic acid, maleic acid, succinic acid, fumaric acid, tartaric acid, citric acid, palmitic acid, stearic acid, oleic acid, cinnamic acid, lauric acid, malic acid, glutamic acid, pyroglutamic acid, aspartic acid, benzoic acid, methanesulfonic acid, p-toluene sulfonic acid, alginic acid, ascorbic acid, salicylic acid, 4-amino salicylic acid, naphthalene disulfonic acid, and the like. These salts can be prepared by the methods known in the art.

“Pharmaceutically acceptable base addition salt” refers to those salts which are capable of retaining the biological effectiveness of free acids without any undesirable effects. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, triethanolamine, dimethylethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins, and the like.

Depending on the number of the charged function groups and the valency of cations or anions, the compound of the present invention may contain a plurality of cations or anions.

Often crystallizations produce a solvate of the compound of the present invention. In the present application, a “solvate” refers to an aggregate that comprises one or more molecules of a compound of the present invention with one or more molecules of solvent. They either react with each other in the solvent or precipitate or crystallize from the

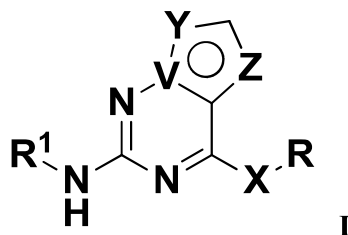
solvent. The solvent may be water, in which case the solvate is a hydrate. Alternatively, the solvent may be an organic solvent. The solvates of the compounds of the present invention are also within the scope of the present invention.

In the present application, a “pharmaceutical composition” refers to a formulation of a compound of the present invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, e.g., humans. Said a medium includes pharmaceutically acceptable excipients. The pharmaceutical composition of the present invention may be a single formulation, or may be a combination of a plurality of formulations.

In the present application, “pharmaceutically acceptable excipient” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dyes/colorant, flavoring agent, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent or emulsifier which has been approved by relevant state authorities as being acceptable for use in humans or domestic animals.

In the present application, “therapeutically effective amount” refers to that amount of a compound of the present invention which, when administered to a mammal, e.g., a human, is sufficient to effect treatment of a disease or disorder in the mammal, e.g., a human. The amount of a compound of the invention which constitutes a “therapeutically effective amount” will vary depending on the particular compound used, the particular disorder to be treated, cause of the disorder, targets of the drug, severity of the disease, the manner of administration, and the age, weight, physical conditions, and the like of the mammal to be treated, but can be routinely determined by one skilled in the art having regard to his own knowledge and to the disclosure of the present application.

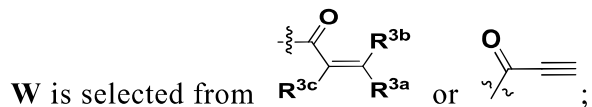
According to one aspect of the present invention, the present invention provides a compound represented by formula I:



wherein:

R is selected from C₃₋₈ cycloalkyl substituted by -NR²W; a 4- to 10-membered saturated *N*-heterocyclyl group, which contains only one nitrogen atom on its ring, and the nitrogen atom is substituted by **W**; or C₁₋₄ alkyl substituted by a 4- to 10-membered saturated *N*-heterocyclyl

group which contains only one nitrogen atom on its ring and the nitrogen atom is substituted by W;



V is selected from C or N;

5 X is selected from O, S, or NR⁴;

Y is selected from CH, O, or S;

Z is selected from CH, O, S, or NR⁵;

R¹ is a C₆₋₁₂ aryl or a 5- to 12-membered heteroaryl group, optionally substituted by one or more R⁶;

10 R² is selected from hydrogen or C₁₋₈ aliphatic;

R^{3a}, R^{3b}, and R^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl;

R⁴ is selected from hydrogen or C₁₋₈ aliphatic;

R⁵ is selected from hydrogen or C₁₋₈ aliphatic;

15 Each R⁶ is independently selected from the group consisting of halogen, nitro, cyano, heterocyclyl, C₆₋₁₂ aryl, 5- to 12-membered heteroaryl, C₁₋₈ aliphatic, C₁₋₈ haloaliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyloxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, carboxyl C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticacylamino C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticoxycarbonyl C₁₋₈ aliphatic, aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfinyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonylamino, C₁₋₈ aliphaticsulfonylamino C₁₋₈ aliphatic, sulfamoyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic) phosphonyl C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy, heterocyclloxy, heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, amino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticamino C₁₋₈ aliphaticoxy, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticacylamino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphaticoxy, aminoacyl C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphaticoxy, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, heterocyclyl amino, heterocyclyl C₁₋₈ aliphaticamino, hydroxy C₁₋₈ aliphaticamino, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticamino, amino

C₁₋₈ aliphaticamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino C₁₋₈
 aliphaticamino, C₁₋₈ aliphaticacylamino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl C₁₋₈
 aliphaticamino, aminoacyl C₁₋₈ aliphaticamino, C₁₋₈ aliphaticaminoacyl C₁₋₈
 aliphaticamino, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphaticamino, C₁₋₈ aliphaticacylamino,
 5 heterocyclyl C₁₋₈ aliphaticacylamino, heterocyclylacylamino, hydroxy C₁₋₈
 aliphaticacylamino, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticacylamino, amino C₁₋₈
 aliphaticacylamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticacylamino, di(C₁₋₈ aliphatic)amino
 C₁₋₈ aliphaticacylamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, heterocyclyl C₁₋₈
 aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, heterocyclyl C₁₋₈ aliphaticoxycarbonyl,
 10 di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl,
 di(C₁₋₈ aliphatic)aminoacyl, heterocyclyl C₁₋₈ aliphaticaminoacyl, heterocyclylaminoacyl,
 hydroxy C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticaminoacyl, amino C₁₋₈
 aliphaticaminoacyl, C₁₋₈ aliphaticamino C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)amino
 C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticsulphydryl, heterocyclylsulphydryl, heterocyclyl C₁₋₈
 15 aliphaticsulphydryl, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, heterocyclylsulfonyl,
 heterocyclylsulfinyl, heterocyclyl C₁₋₈ aliphaticsulfonyl, heterocyclyl C₁₋₈
 aliphaticsulfinyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl,
 heterocyclyl C₁₋₈ aliphaticaminosulfonyl, heterocyclylaminosulfonyl, di(C₁₋₈
 aliphatic)amino C₁₋₈ aliphaticaminosulfonyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl,
 20 di(C₁₋₈ aliphatic)aminosulfinyl, heterocyclylaminosulfinyl and di(C₁₋₈
 aliphatic)phosphonyl, wherein:

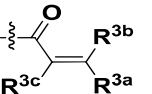
heterocyclyl, as an independent group or a part of other group(s), represents a
 saturated or partially unsaturated 3- to 12-membered heterocyclyl group containing one or
 more heteroatoms selected from the group consisting of N, O, and S; optionally, each
 25 heterocyclyl is independently substituted by one or more substituents selected from the
 group consisting of halogen, C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈
 aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino
 C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, heterocyclyl, 5- to 12-membered heteroaryl,
 hydroxy, C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, C₁₋₈
 30 aliphaticcarbonyl, heterocyclylcarbonyl, heterocyclyl C₁₋₈ aliphaticcarbonyl, hydroxy C₁₋₈
 aliphaticcarbonyl, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticcarbonyl, di(C₁₋₈ aliphatic)amino C₁₋₈
 aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈
 aliphatic)aminoacyl, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, heterocyclylsulfonyl,
 heterocyclylsulfinyl, heterocyclyl C₁₋₈ aliphaticsulfonyl, heterocyclyl C₁₋₈
 35 aliphaticsulfinyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, and di(C₁₋₈

aliphatic)aminosulfonyl; and

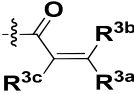
optionally, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl are independently substituted by one or more substituents selected from the group consisting of halogen, C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, and di(C₁₋₈ aliphatic)amino;

- 5 wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

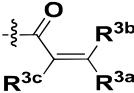
- In some embodiments of the compound of formula **I**, **R** is C₃₋₈ cycloalkyl substituted
10 by -NR²W, wherein **R**² is selected from hydrogen or C₁₋₈ aliphatic; and **W** is selected

from  or , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl, wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

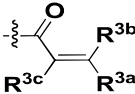
- 15 In some embodiments of the compound of formula **I**, **R** is cyclohexyl substituted by -NR²W, wherein **R**² is selected from hydrogen or C₁₋₈ aliphatic; and **W** is selected from

 or , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl, wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈
20 alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **I**, **R** is cyclohexyl substituted by -NR²W, wherein **R**² is selected from hydrogen or C₁₋₈ alkyl; and **W** is selected from

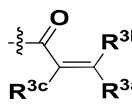
 or , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen.

- 25 In some embodiments of the compound of formula **I**, **R** is a 4- to 10-membered saturated *N*-heterocyclyl group which contains only one nitrogen atom on its ring and the

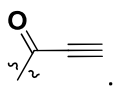
nitrogen atom is substituted by **W**, wherein **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl, wherein C₁₋₈ aliphatic is selected from the group consisting of

C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

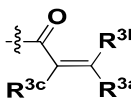
In some embodiments, **R** is a 4- to 10-membered saturated *N*-heterocyclyl group, which contains only one nitrogen atom on its ring, and the nitrogen atom is substituted by

W, wherein **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen.

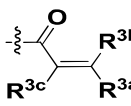
5 In some embodiments of the compound of formula **I**, **R** is a 4- to 10-membered saturated *N*-heterocyclyl group which contains only one nitrogen atom on its ring, and the

nitrogen atom is substituted by **W**, wherein **W** is .

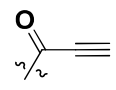
In some embodiments of the compound of formula **I**, **R** is C₁₋₄ alkyl substituted by a 4- to 10-membered saturated *N*-heterocyclyl group which contains only one nitrogen atom

10 on its ring, and the nitrogen atom is substituted by **W**, wherein **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl, wherein C₁₋₈ aliphatic is selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

15 In some embodiments of the compound of formula **I**, **R** is C₁₋₄ alkyl substituted by a 4- to 10-membered saturated *N*-heterocyclyl group which contains only one nitrogen atom

on its ring, and the nitrogen atom is substituted by **W**, wherein **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen.

20 In some embodiments of the compound of formula **I**, **R** is C₁₋₄ alkyl substituted by a 4- to 10-membered saturated *N*-heterocyclyl group which contains only one nitrogen atom

on its ring, and the nitrogen atom is substituted by **W**, wherein **W** is .

In some embodiments of the compound of formula **I**, **X** is O. In some other embodiments of the compound of formula **I**, **X** is S. In yet some other embodiments of the compound of formula **I**, **X** is NR⁴, **R**⁴ is selected from hydrogen or C₁₋₈ aliphatic, wherein
25 C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl. In some embodiments, **X** is NR⁴, **R**⁴ is selected from hydrogen or C₁₋₈ alkyl, and is more preferably selected from

hydrogen or methyl.

In some embodiments of the compound of formula **I**, **V** is C. In some other embodiments of the compound of formula **I**, **V** is N.

5 In some embodiments of the compound of formula **I**, **Y** is CH. In some other embodiments of the compound of formula **I**, **Y** is O. In yet some other embodiments of the compound of formula **I**, **Y** is S.

10 In some embodiments of the compound of formula **I**, **Z** is CH. In some other embodiments of the compound of formula **I**, **Z** is O. In yet some other embodiments of the compound of formula **I**, **Z** is S. In some other embodiments of the compound of formula **I**, **Z** is NR^5 , R^5 is selected from hydrogen or C_{1-8} aliphatic, wherein C_{1-8} aliphatic is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl and C_{4-8} cycloalkenyl. In some embodiments, R^5 is selected from hydrogen or C_{1-8} alkyl, and is more preferably selected from hydrogen or methyl.

15 In some embodiments of the compound of formula **I**, at least one of **V**, **Y** and **Z** is a heteroatom.

20 In some embodiments of the compound of formula **I**, R^1 is C_{6-12} aryl or 5- to 12-membered heteroaryl, optionally substituted by one or more R^6 , wherein each R^6 is independently selected from the group consisting of halogen, heterocyclyl, C_{1-8} aliphatic, C_{1-8} halo aliphatic, heterocyclyl C_{1-8} aliphatic, hydroxy C_{1-8} aliphatic, C_{1-8} aliphaticoxy C_{1-8} aliphatic, amino C_{1-8} aliphatic, C_{1-8} aliphaticamino C_{1-8} aliphatic, di(C_{1-8} aliphatic)amino C_{1-8} aliphatic, C_{1-8} aliphaticoxy, heterocycliloxy, heterocyclyl C_{1-8} aliphaticoxy, hydroxy C_{1-8} aliphaticoxy, C_{1-8} aliphaticoxy C_{1-8} aliphaticoxy, C_{1-8} aliphaticamino, di(C_{1-8} aliphatic)amino, heterocyclylamino, amino C_{1-8} aliphaticamino, C_{1-8} aliphaticamino C_{1-8} aliphaticamino, di(C_{1-8} aliphatic)amino C_{1-8} aliphaticamino, C_{1-8} aliphaticcarbonyl, heterocyclylcarbonyl, aminoacyl, C_{1-8} aliphaticaminoacyl, di(C_{1-8} aliphatic)aminoacyl, heterocyclylaminoacyl, sulfamoyl, C_{1-8} aliphaticaminosulfonyl, di(C_{1-8} aliphatic)aminosulfonyl, heterocyclylaminosulfonyl, aminosulfinyl, C_{1-8} aliphaticamino sulfinyl, di(C_{1-8} aliphatic)aminosulfinyl, and heterocyclylaminosulfinyl, wherein:

30 heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more substituents selected from the group consisting of hydroxy, C_{1-8} aliphatic, C_{1-8} aliphaticoxy, amino, and C_{1-8} aliphaticcarbonyl;

35

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **I**, **R**¹ is C₆₋₁₂ aryl or 5- to 12-membered heteroaryl, optionally substituted by one or more **R**⁶; each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyloxy, heterocyclyl C₁₋₈ aliphaticoxy, heterocyclylamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, and heterocyclylaminoacyl, wherein: heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more C₁₋₈ aliphatic substituents.

In some embodiments of the compound of formula **I**, **R**¹ is C₆₋₁₂ aryl, optionally substituted by one or more **R**⁶; each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, C₁₋₈ aliphaticoxy, heterocyclyloxy, heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, heterocyclylamino, amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, heterocyclylaminoacyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, heterocyclylaminosulfonyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl, di(C₁₋₈ aliphatic)aminosulfinyl, and heterocyclylaminosulfinyl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more substituents selected from the group consisting of hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, amino, and C₁₋₈ aliphaticcarbonyl;

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **I**, **R**¹ is phenyl, optionally substituted by one or more **R**⁶; each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, heterocyclyloxy,

heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, heterocyclylamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, and heterocyclylaminoacyl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more, preferably one or two, heteroatoms selected from the group consisting of N, O, and S, preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl, and tetrahydropyranyl; optionally, each heterocyclyl is independently substituted by one or more, preferably one or two, substituents selected from the group consisting of hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, and C₁₋₈ aliphaticcarbonyl;

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **I**, **R**¹ is phenyl, optionally substituted by one or more **R**⁶; each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphaticoxy, heterocyclylamino, heterocyclylcarbonyl, and heterocyclylaminoacyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S, preferably selected from the group consisting of piperidinyl, piperazinyl, and morpholinyl; optionally, each heterocyclyl is independently substituted by one or two C₁₋₈ aliphatic substituents, wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl.

In some embodiments of the compound of formula **I**, **R**¹ is a 5- to 12-membered heteroaryl group, optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, and heterocyclylxy, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; optionally, each

heterocyclyl is independently substituted by one or more substituents selected from the group consisting of hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, amino, and C₁₋₈ aliphaticcarbonyl;

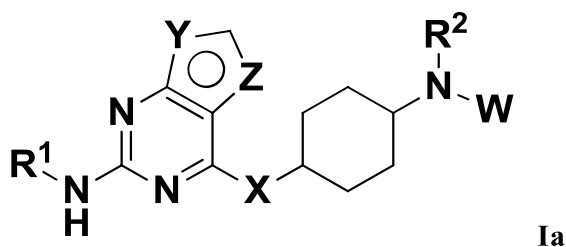
5 wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **I**, **R**¹ is a 5- to 10-membered heteroaryl group, optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, and C₁₋₈ aliphaticcarbonyl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more, preferably one or two, heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more, preferably one or two, C₁₋₈ aliphatic substituents;

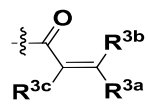
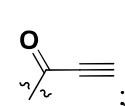
wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **I**, the compound of formula **I** is represented by formula **Ia**:



wherein, **X**, **Y**, **Z**, **W**, **R**¹, and **R**² are all defined as in formula **I**.

In some embodiments of the compound of formula **Ia**, each group in the formula **Ia** is defined as follows:

25 **W** is selected from  or  ;

X is selected from S, O, or NR⁴;

Y is selected from CH, O, or S;

Z is selected from CH, O, S, or NR⁵;

R¹ is C₆₋₁₂ aryl or 5- to 12-membered heteroaryl, optionally substituted by one or

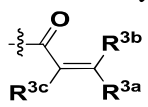
- more **R**⁶;
- R**² is selected from hydrogen or C₁₋₈ aliphatic;
- R**^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl;
- 5 **R**⁴ is selected from hydrogen or C₁₋₈ aliphatic;
- R**⁵ is selected from hydrogen or C₁₋₈ aliphatic;
- each **R**⁶ is independently selected from the group consisting of halogen, nitro, cyano, heterocyclyl, C₆₋₁₂ aryl, 5- to 12-membered heteroaryl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyloxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticacylamino C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticoxycarbonyl C₁₋₈ aliphatic, aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfinyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonylamino C₁₋₈ aliphatic, sulfamoyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)phosphonyl C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy, heterocycliloxy, heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, amino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticamino C₁₋₈ aliphaticoxy, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticacylamino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphaticoxy, aminoacyl C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphaticoxy, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, heterocyclylamino, heterocyclyl C₁₋₈ aliphaticamino, hydroxy C₁₋₈ aliphaticamino, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticamino, amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticacylamino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphaticamino, aminoacyl C₁₋₈ aliphaticamino, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphaticamino, C₁₋₈ aliphaticacylamino, heterocyclyl C₁₋₈ aliphaticacylamino, heterocyclylacylamino, hydroxy C₁₋₈ aliphaticacylamino, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticacylamino, amino C₁₋₈ aliphaticacylamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticacylamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticacylamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, heterocyclyl C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, heterocyclyl C₁₋₈ aliphaticoxycarbonyl, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, heterocyclyl C₁₋₈ aliphaticaminoacyl, heterocyclylaminoacyl,

hydroxy C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticaminoacyl, amino C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticamino C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticsulphydryl, heterocyclysulphydryl, heterocycl C₁₋₈ aliphaticsulphydryl, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, heterocyclsulfonyl, heterocyclsulfinyl, heterocycl C₁₋₈ aliphaticsulfonyl, heterocycl C₁₋₈ aliphaticsulfinyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, heterocycl C₁₋₈ aliphaticaminosulfonyl, heterocyclaminosulfonyl, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticaminosulfonyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl, di(C₁₋₈ aliphatic)aminosulfinyl, heterocyclaminosulfinyl, and di(C₁₋₈ aliphatic)phosphonyl, wherein:

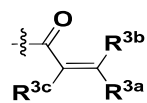
heterocycl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 12-membered heterocycl group containing one or more heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocycl is independently substituted by one or more substituents selected from the group consisting of halogen, C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocycl C₁₋₈ aliphatic, heterocycl, 5- to 12-membered heteroaryl, hydroxy, C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, C₁₋₈ aliphaticcarbonyl, heterocyclcarbonyl, heterocycl C₁₋₈ aliphaticcarbonyl, hydroxy C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticcarbonyl, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, heterocyclsulfonyl, heterocyclsulfinyl, heterocycl C₁₋₈ aliphaticsulfonyl, heterocycl C₁₋₈ aliphaticsulfinyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, and di(C₁₋₈ aliphatic)aminosulfonyl; and

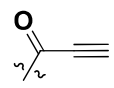
optionally, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl are independently substituted by one or more substituents selected from the group consisting of halogen, C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, and di(C₁₋₈ aliphatic)amino;

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **Ia**, **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen,

and di(C₁₋₈ aliphatic)aminomethyl, wherein C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈

cycloalkenyl. In some embodiments, **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen.

5 In some embodiments of the compound of formula **Ia**, **W** is .

In some embodiments of the compound of formula **Ia**, **X** is S. In other some embodiments of the compound of formula **Ia**, **X** is O. In yet other some embodiments of the compound of formula **Ia**, **X** is **NR**⁴, wherein **R**⁴ is selected from hydrogen or C₁₋₈ aliphatic, wherein C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl. In some
10 embodiments, **X** is **NR**⁴, wherein **R**⁴ is selected from hydrogen or C₁₋₈ alkyl, more preferably selected from hydrogen or methyl, and most preferably hydrogen.

In some embodiments of the compound of formula **Ia**, **Y** is CH. In some other embodiments of the compound of formula **Ia**, **Y** is O. In yet other some embodiments of
15 the compound of formula **Ia**, **Y** is S.

In one embodiment of the compound of formula **Ia**, **Z** is CH. In other some embodiments of the compound of formula **Ia**, **Z** is O. In yet other some embodiments of the compound of formula **Ia**, **Z** is S. In yet some other embodiments of the compound of formula **Ia**, **Z** is **NR**⁵, wherein **R**⁵ is selected from hydrogen or C₁₋₈ aliphatic, wherein
20 C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl. In yet some other embodiments, **Z** is **NR**⁵, wherein **R**⁵ is preferably selected from hydrogen or C₁₋₈ alkyl, more preferably selected from hydrogen or methyl, and most preferably hydrogen.

In some embodiments of the compound of formula **Ia**, at least one of **Y** and **Z** is a
25 heteroatom.

In some embodiments of the compound of formula **Ia**, **Y** is S, and **Z** is CH.

In some embodiments of the compound of formula **Ia**, **Y** is O, and **Z** is CH.

In some embodiments of the compound of formula **Ia**, **Y** is CH, and **Z** is S. In some other embodiments of the compound of formula **Ia**, **Y** is CH, and **Z** is O.

30 In some embodiments of the compound of formula **Ia**, **Y** is CH, **Z** is **NR**⁵, wherein **R**⁵ is selected from hydrogen or C₁₋₈ aliphatic, wherein C₁₋₈ aliphatic is selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈

cycloalkenyl. In some embodiments, **Y** is CH, and **Z** is NR⁵, wherein **R**⁵ is hydrogen.

In some embodiments of the compound of formula **Ia**, **R**¹ is a C₆₋₁₂ aryl or 5- to 12-membered heteroaryl group, optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, heterocycliloxy, heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, heterocyclylamino, amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticamino, heterocyclylcarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, heterocyclylaminoacyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, heterocyclylaminosulfonyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl, di(C₁₋₈ aliphatic)aminosulfinyl, and heterocyclylaminosulfinyl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more, preferably one or two, heteroatoms selected from the group consisting of O, N and S; optionally, which is independently substituted by one or more, optionally by one or two, substituents selected from the group consisting of C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticcarbonyl,

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **Ia**, **R**¹ is C₆₋₁₂ aryl, optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, heterocycliloxy, heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, heterocyclylamino, amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl di(C₁₋₈ aliphatic)aminoacyl, heterocyclylaminoacyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, heterocyclylaminosulfonyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl, di(C₁₋₈ aliphatic)aminosulfinyl and heterocyclylaminosulfinyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially

5 unsaturated 3- to 8-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of O, N and S; optionally, heterocyclyl is independently substituted by one or two substituents selected from the group consisting of C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticcarbonyl, and wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

10 In some embodiments of the compound of formula **Ia**, **R**¹ is phenyl, optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, heterocycliloxy, heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, di(C₁₋₈ aliphatic)amino, C₁₋₈ aliphaticamino, heterocyclylamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, C₁₋₈ aliphaticaminoacyl and heterocyclylaminoacyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 15 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of O, N and S, preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl and tetrahydropyranyl; optionally, each heterocyclyl is independently substituted by one or more substituents selected from the group consisting of C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticcarbonyl, and 20 wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl.

In some embodiments of the compound of formula **Ia**, **R**¹ is phenyl, optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, heterocycliloxy, heterocyclyl C₁₋₈ 25 aliphaticoxy, heterocyclylamino, heterocyclylcarbonyl and heterocyclylaminoacyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of O, N and S, preferably selected from the group consisting of piperidinyl, piperazinyl and morpholinyl; optionally, each 30 heterocyclyl is independently substituted by one or two C₁₋₈ aliphatic substituents, and wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl.

In some embodiments of the compound of formula **Ia**, **R**¹ is phenyl, optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group 35 consisting of fluorine, chlorine, methyl, methoxy, dimethylamino, methylaminoacyl,

hydroxyethyloxy, methoxyethyloxy, dimethylaminoethylamino, heterocyclylethyloxy, heterocyclyl, cyclohexylamino, heterocyclylamino, heterocyclyloxy, heterocyclylcarbonyl and heterocyclylaminoacyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of O, N and S, preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl and tetrahydropyranyl; optionally, each heterocyclyl is independently substituted by one or more substituents selected from the group consisting of methyl, methylcarbonyl, hydroxy, methoxy and isopropyl.

In some embodiments of the compound of formula **Ia**, **R¹** is phenyl, optionally substituted by one or more **R⁶**, wherein each **R⁶** is independently selected from the group consisting of fluorine, chlorine, methyl, heterocyclyl, heterocyclylethyloxy, heterocyclylamino, heterocyclyloxy, heterocyclylcarbonyl and heterocyclylaminoacyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of O, N and S, preferably selected from the group consisting of piperidinyl, piperazinyl and morpholinyl; optionally, each heterocyclyl is independently substituted by methyl or isopropyl.

In some embodiments of the compound of formula **Ia**, **R¹** is a 5- to 12-membered heteroaryl group, optionally substituted by one or more **R⁶**, wherein each **R⁶** is independently selected from the group consisting of heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of O, N and S; optionally, each heterocyclyl is independently substituted by one or more C₁₋₈ aliphatic groups, and wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **Ia**, **R¹** is a 5- to 10-membered heteroaryl group, optionally substituted by one or more **R⁶**, wherein each **R⁶** is independently selected from the group consisting of heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy and

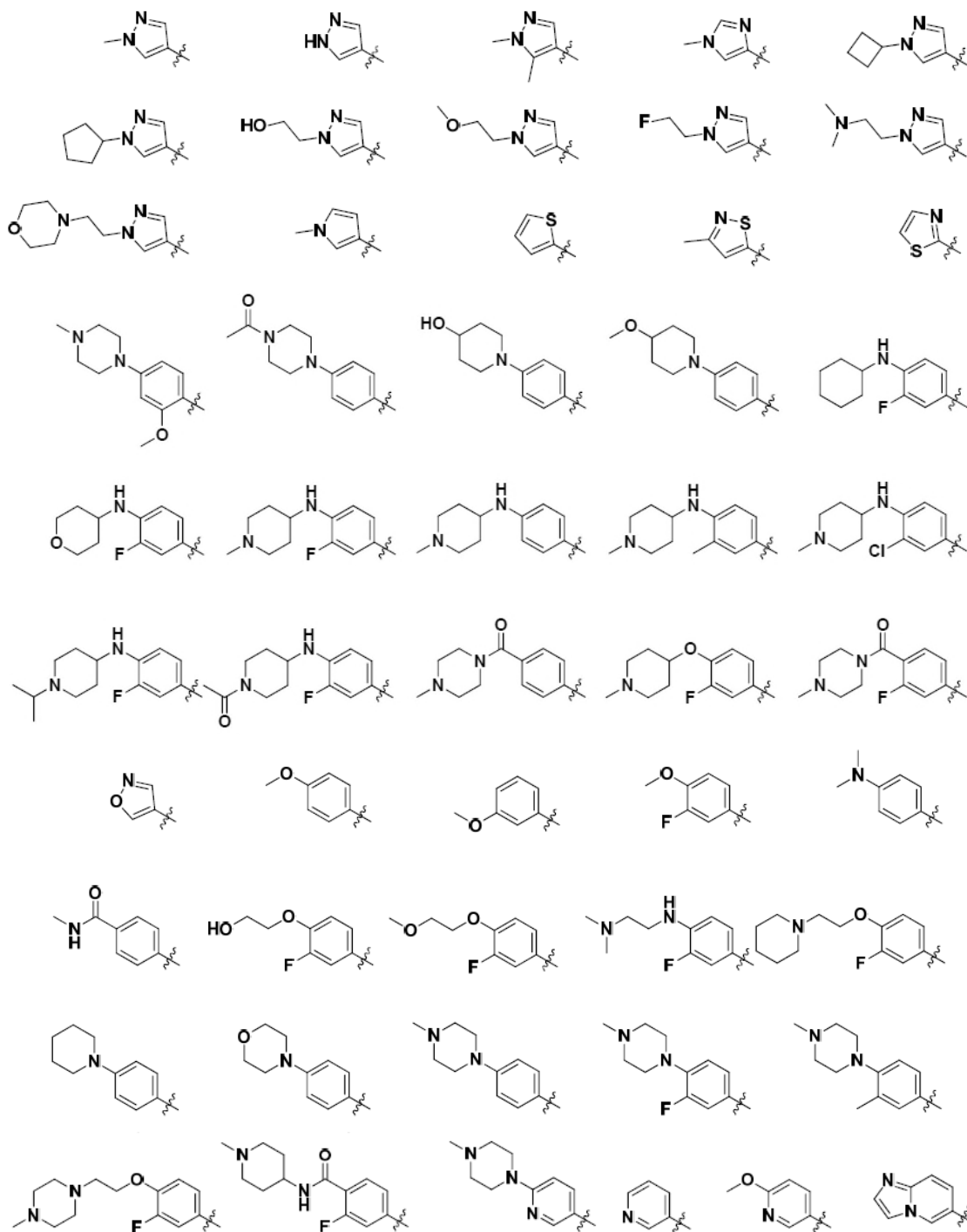
C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of O, N and S, preferably selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and tetrahydropyranyl; optionally, each heterocyclyl is independently substituted by one or more C₁₋₈ aliphatic groups, and wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl.

In some embodiments of the compound of formula **Ia**, **R**¹ is a 5- to 10-membered heteroaryl group, preferably selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, thienyl, thiazolyl, isothiazolyl, isoxazolyl, pyridinyl, and imidazo[1,2-*a*]pyridinyl, which is optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of methyl, cyclobutyl, cyclopentyl, hydroxyethyl, methoxy, methoxyethyl, fluoroethyl, dimethylaminoethyl, 1-methyl-piperazin-4-yl and morpholin-4-yl-ethyl.

In some embodiments of the compound of formula **Ia**, **R**¹ is a 5-membered heteroaryl group, preferably selected from the group consisting of pyrazolyl, thienyl, thiazolyl, isothiazolyl and isoxazolyl, which is optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic and C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of O, N and S; optionally, each heterocyclyl is independently substituted by one or more C₁₋₈ aliphatic groups, and wherein C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl.

In some embodiments of the compound of formula **Ia**, **R**¹ is a 5-membered heteroaryl group, preferably selected from the group consisting of pyrazolyl, thienyl, thiazolyl, isothiazolyl and isoxazolyl, which is optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of methyl, cyclobutyl, cyclopentyl, hydroxy ethyl, methoxy ethyl, fluoroethyl, dimethylaminoethyl and morpholin-4-yl-ethyl.

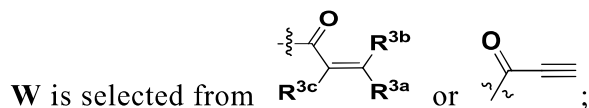
In some embodiments of the compound of formula **Ia**, **R**¹ is selected from the group consisting of:



5 In some embodiments of the compound of formula **Ia**, R^2 is selected from hydrogen or C_{1-8} aliphatic, wherein C_{1-8} aliphatic is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl and C_{4-8} cycloalkenyl. In some embodiments, R^2 is selected from hydrogen or C_{1-8} alkyl. In some embodiments, R^2 is selected from hydrogen or methyl. In some embodiments, R^2 is hydrogen.

10 In some embodiments of the compound of formula **Ia**, each group in the formula **Ia**

is defined as follows:



X is selected from O, S, or NR^4 ;

Y is selected from CH, O, or S;

5 **Z** is selected from CH, O, S, or NR^5 ;

R¹ is C₆₋₁₂ aryl or 5- to 12-membered heteroaryl, optionally substituted by one or more **R**⁶;

R² is hydrogen;

R^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen;

10 **R**⁴ is selected from hydrogen or C₁₋₈ aliphatic;

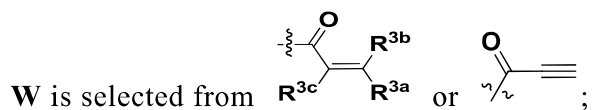
R⁵ is hydrogen;

each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, heterocycliloxy, heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, heterocyclylamino, amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, heterocyclylaminoacyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, heterocyclylaminosulfonyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl, di(C₁₋₈ aliphatic)aminosulfinyl and heterocyclylaminosulfinyl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 12-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more substituents selected from the group consisting of hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticcarbonyl;

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **Ia**, each group in the formula **Ia** is defined as follows:



X is NR⁴;

Y is CH;

Z is O or S;

5 R¹ is a C₆₋₁₂ aryl or 5- to 12-membered heteroaryl group, optionally substituted by one or more R⁶;

R² is hydrogen;

R^{3a}, R^{3b}, and R^{3c} are all hydrogen;

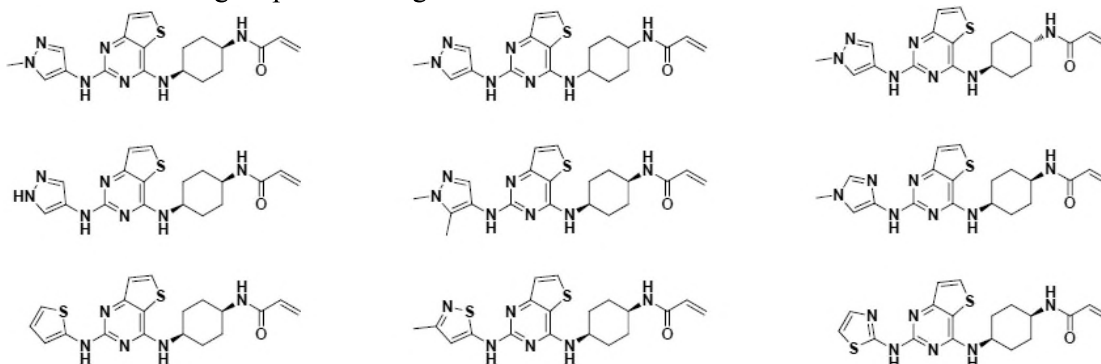
R⁴ is hydrogen;

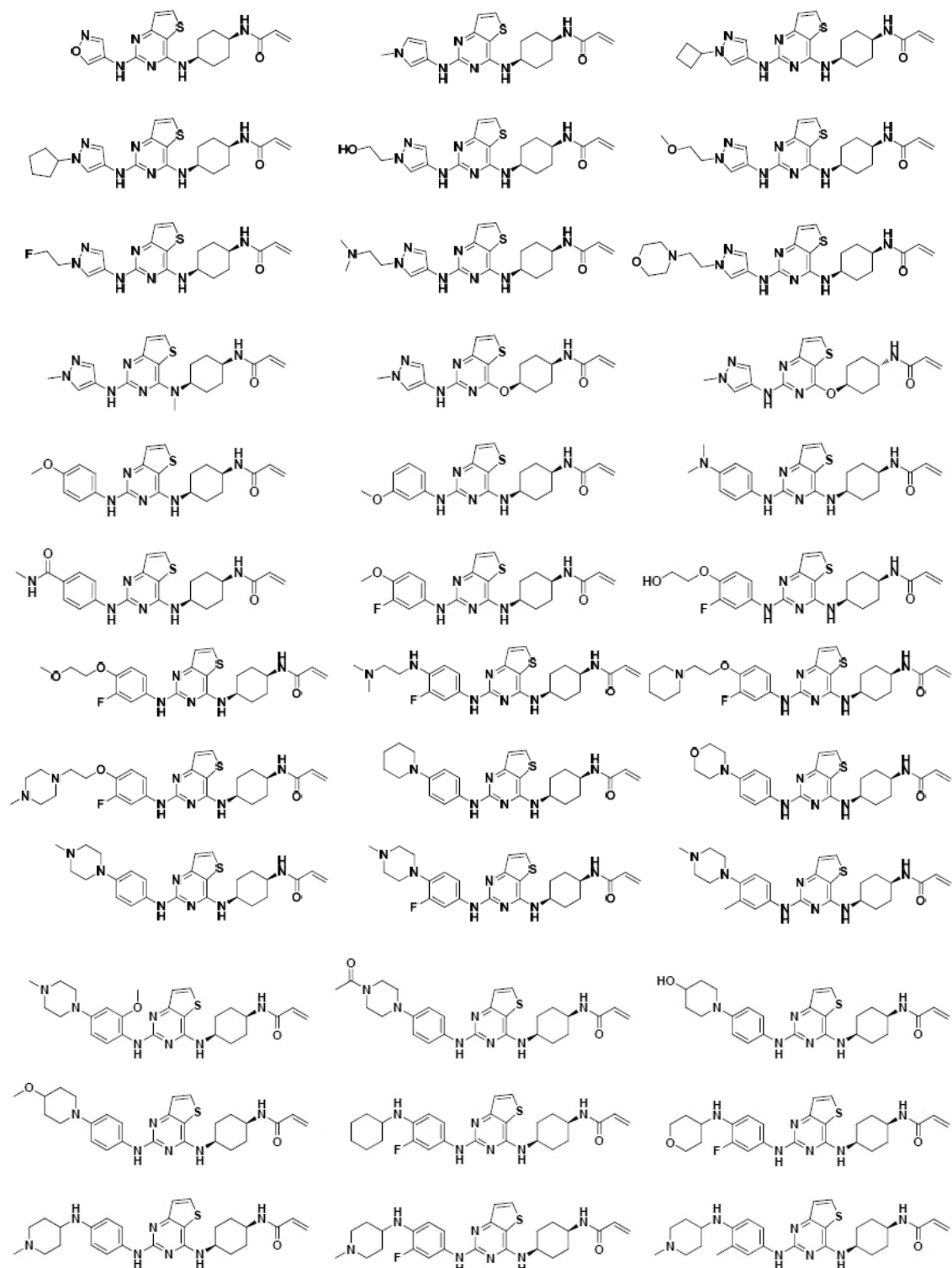
10 each R⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclloxy, heterocyclyl C₁₋₈ aliphaticoxy, heterocyclylamino, heterocyclylcarbonyl and heterocyclylaminoacyl, wherein:

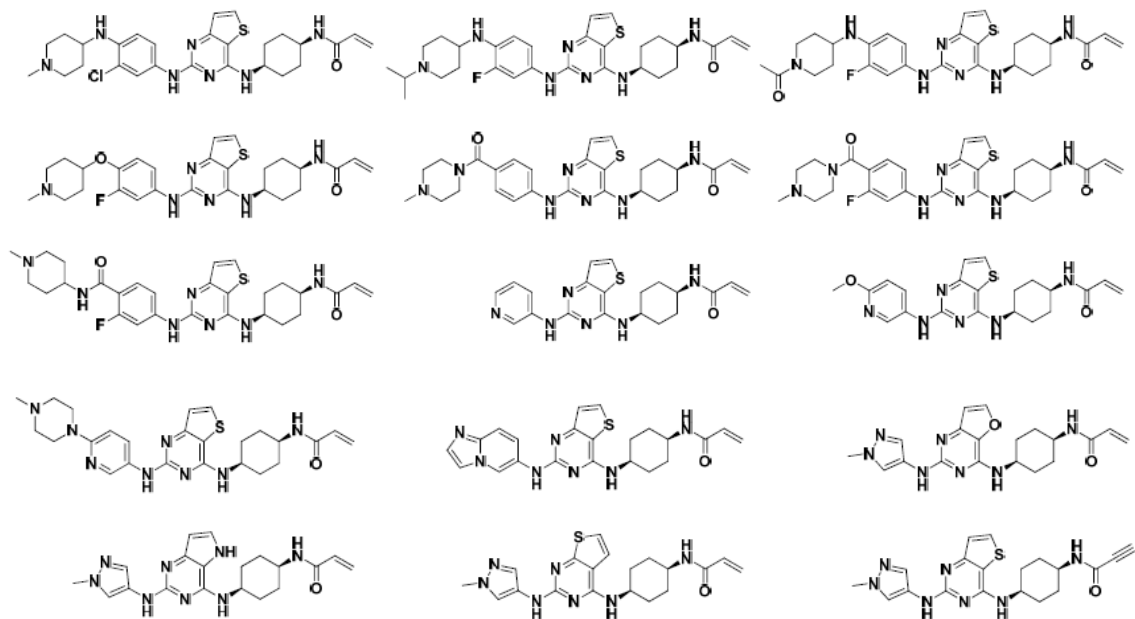
15 heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more C₁₋₈ aliphatic substituents,

20 wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

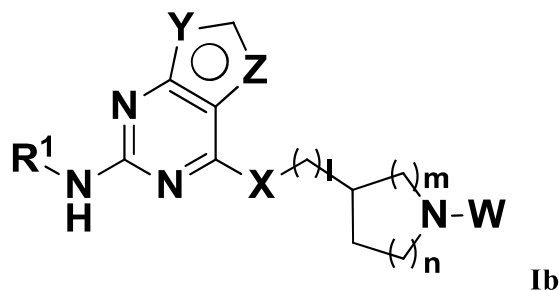
In some embodiments of the compound of formula **1a**, the compound of formula **1a** is selected from the group consisting of:







In some embodiments of the compound of formula **I**, the compound of formula **I** is represented by formula **Ib**:

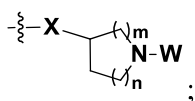
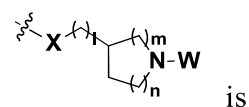


5

wherein:

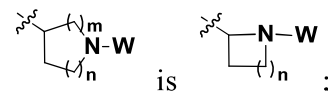
X, **Y**, **Z**, **W**, and **R**¹ are all defined as in formula **I**;

l is selected from 0, 1, 2, 3, or 4, wherein when **l** is 0,



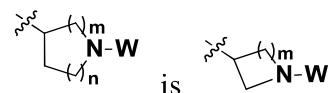
10

m is selected from 0, 1, 2, 3, or 4; wherein when **m** is 0,



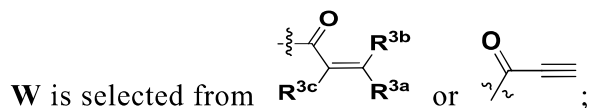
and

n is selected from 0, 1, 2 or 3; wherein when **n** is 0,



In some embodiments of the compound of formula **Ib**, each group in the formula **Ib**

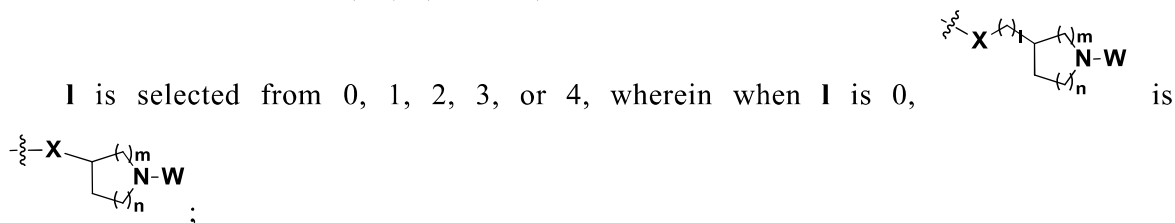
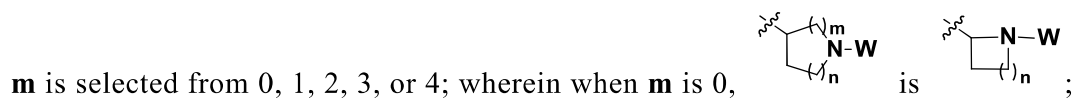
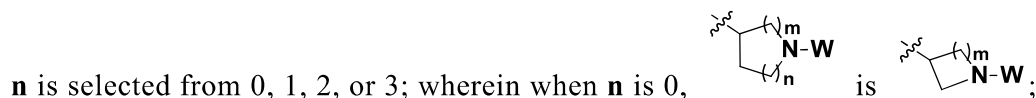
is defined as follows:



X is selected from O, S, or NR⁴;

Y is selected from CH, O, or S;

5 **Z** is selected from CH, O, S, or NR⁵;



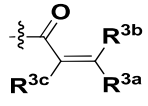
10 **R**¹ is a 5- to 6-membered heteroaryl group, optionally substituted by one or more **R**⁶;
R^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl;

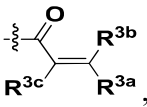
R⁴ is selected from hydrogen or C₁₋₈ aliphatic;

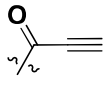
R⁵ is selected from hydrogen or C₁₋₈ aliphatic;

15 each **R**⁶ is independently selected from the group consisting of halogen, nitro, cyano, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticoxycarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyloxy C₁₋₈ aliphatic, aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticacylamino C₁₋₈ aliphatic, C₁₋₈ aliphatic sulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfinyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonylamino C₁₋₈ aliphatic, sulfamoyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminosulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticsulfonyl, C₁₋₈ alkylsulfinyl, C₁₋₈ aliphaticsulfonylamino, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, heterocyclyl, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a

saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; each heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticcarbonyl; and optionally, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl are independently substituted by one or more substituents selected from the group consisting of halogen and C₁₋₈ aliphatic, wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **Ib**, **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl, wherein C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈

cycloalkenyl. In some embodiments, **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen.

In some embodiments of the compound of formula **Ib**, **W** is .

In some embodiments of the compound of formula **Ib**, **X** is O.

In some embodiments of the compound of formula **Ib**, **X** is NR⁴, wherein **R**⁴ is selected from hydrogen or C₁₋₈ aliphatic, wherein C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl. In some embodiments, **X** is NR⁴, wherein **R**⁴ is selected from hydrogen or C₁₋₈ alkyl. In some embodiments, **X** is NR⁴, wherein **R**⁴ is selected from hydrogen or methyl.

In some embodiments of the compound of formula **Ib**, **Y** is CH. In some other embodiments of the compound of formula **Ib**, **Y** is S. In some other embodiments of the compound of formula **Ib**, **Y** is O.

In some embodiments of the compound of formula **Ib**, **Z** is CH. In some other embodiments of the compound of formula **Ib**, **Z** is S. In yet some other embodiments of the compound of formula **Ib**, **Z** is O. In yet some other embodiments of the compound of formula **Ib**, **Z** is NR⁵, wherein **R**⁵ is selected from hydrogen or C₁₋₈ aliphatic, wherein C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈

alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl. In some embodiments, **Z** is NR⁵, wherein **R**⁵ is selected from hydrogen or C₁₋₈ alkyl. In some embodiments, **Z** is NR⁵, wherein **R**⁵ is selected from hydrogen or methyl.

5 In some embodiments of the compound of formula **Ib**, at least one of **Y** and **Z** is a heteroatom.

In some embodiments of the compound of formula **Ib**, **Y** is S, and **Z** is CH. In some other embodiments, **Y** is O, and **Z** is CH.

10 In some embodiments of the compound of formula **Ib**, **Y** is CH, and **Z** is S. In some other embodiments, **Y** is CH, and **Z** is O. In yet some other embodiments, **Y** is CH, and **Z** is NR⁵, wherein **R**⁵ is selected from hydrogen or C₁₋₈ aliphatic, wherein C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl. In yet some other embodiments, **Y** is CH, and **Z** is NR⁵, wherein **R**⁵ is selected from hydrogen or C₁₋₈ alkyl, and preferably selected from hydrogen or methyl.

15 In some embodiments of the compound of formula **Ib**, **R**¹ is a 5- to 6-membered heterocyclyl group, optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, and heterocyclyloxy, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; optionally, each
25 heterocyclyl is independently substituted by one or more substituents selected from the group consisting of hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, amino, and C₁₋₈ aliphaticcarbonyl,

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

30 In some embodiments of the compound of formula **Ib**, **R**¹ is a 5-membered heterocyclyl group, preferably selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, thienyl, isoxazolyl, thiazolyl and isothiazolyl, and **R**¹ is optionally substituted by one or two **R**⁶; wherein each **R**⁶ is independently selected from the group consisting of halogen, C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino
35 aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl, and heterocyclyloxy, wherein:

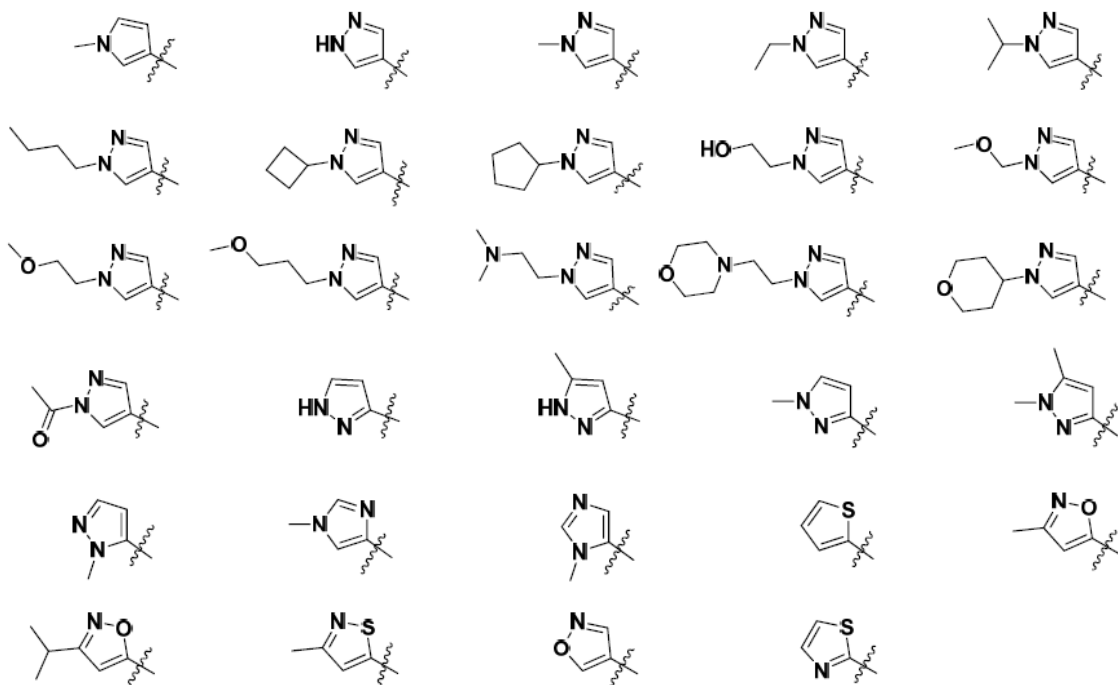
C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl and heterocyclyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S, preferably selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and tetrahydropyranyl; each heterocyclyl is optionally substituted by one or more C₁₋₈ aliphatic substituents, and wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl.

In some embodiments of the compound of formula **Ib**, **R**¹ is a 5-membered heterocyclyl group, preferably selected from the group consisting of pyrazolyl, thienyl, isoxazolyl, thiazolyl and isothiazolyl, and **R**¹ is optionally substituted by one or two **R**⁶; wherein each **R**⁶ is independently selected from the group consisting of C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl, heterocyclyl and heterocyclyl C₁₋₈ aliphatic, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S, preferably selected from the group consisting of morpholinyl and tetrahydropyranyl, wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl.

In some embodiments of the compound of formula **Ib**, **R**¹ is a 5-membered heterocyclyl group, preferably selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, thienyl, isoxazolyl, thiazolyl and isothiazolyl, and **R**¹ is optionally substituted by one or two **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of methyl, ethyl, isopropyl, *n*-butyl, hydroxyethyl, methoxymethyl, methoxyethyl, methoxypropyl, cyclobutyl, cyclopentyl, dimethylaminoethyl, morpholin-4-yl-ethyl, tetrahydropyran-4-yl and methylcarbonyl.

In some embodiments of the compound of formula **Ib**, **R**¹ is a 5-membered heterocyclyl group, preferably selected from the group consisting of pyrazolyl, thienyl, isoxazolyl, thiazolyl and isothiazolyl, and **R**¹ is optionally substituted by one or two **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of methyl, ethyl, isopropyl, cyclobutyl, cyclopentyl, methoxymethyl, methoxyethyl, methoxypropyl, dimethylaminoethyl, morpholin-4-yl-ethyl, tetrahydropyran-4-yl and methylcarbonyl.

In some embodiments of the compound of formula **Ib**, **R**¹ is selected from the group consisting of:



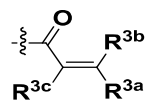
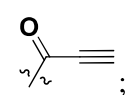
In some embodiments of the compound of formula **Ib**, **l** is selected from 0, 1 or 2.

In some embodiments of the compound of formula **Ib**, **m** is selected from 0, 1, 2 or 3.

5 In some embodiments of the compound of formula **Ib**, **n** is selected from 0, 1 or 2.

In some embodiments of the compound of formula **Ib**, **m** and **n** are not 0 simultaneously.

In some embodiments of the compound of formula **Ib**, each group in the formula **Ib** is defined as follows:

10 **W** is selected from  or  ;

X is selected from O, S, or NR⁴;

Y is selected from CH, O, or S;

Z is selected from CH, O, S, or NR⁵;

l is selected from 0, 1 or 2;

15 **m** is selected from 0, 1, 2 or 3;

n is selected from 0, 1 or 2;

R¹ is a 5- to 6-membered heteroaryl group, optionally substituted by one or more **R**⁶;

R^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen;

R⁴ is selected from hydrogen or C₁₋₈ aliphatic;

20 **R**⁵ is selected from hydrogen or C₁₋₈ aliphatic;

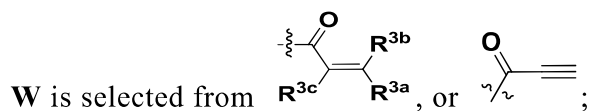
each **R**⁶ is independently selected from the group consisting of halogen, C₁₋₈ aliphatic,

hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl and heterocyclyl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; each heterocyclyl is optionally substituted by one or more C₁₋₈ aliphatic substituents;

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **Ib**, each group in the formula **Ib** is defined as follows:



X is selected from O, or NR⁴;

Y is selected from CH, or S;

Z is selected from CH, O, or S;

l is selected from 0, 1 or 2;

m is selected from 0, 1, 2 or 3;

n is selected from 0, 1 or 2;

R¹ is a 5-membered heteroaryl group, optionally substituted by one or more **R**⁶;

R^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen;

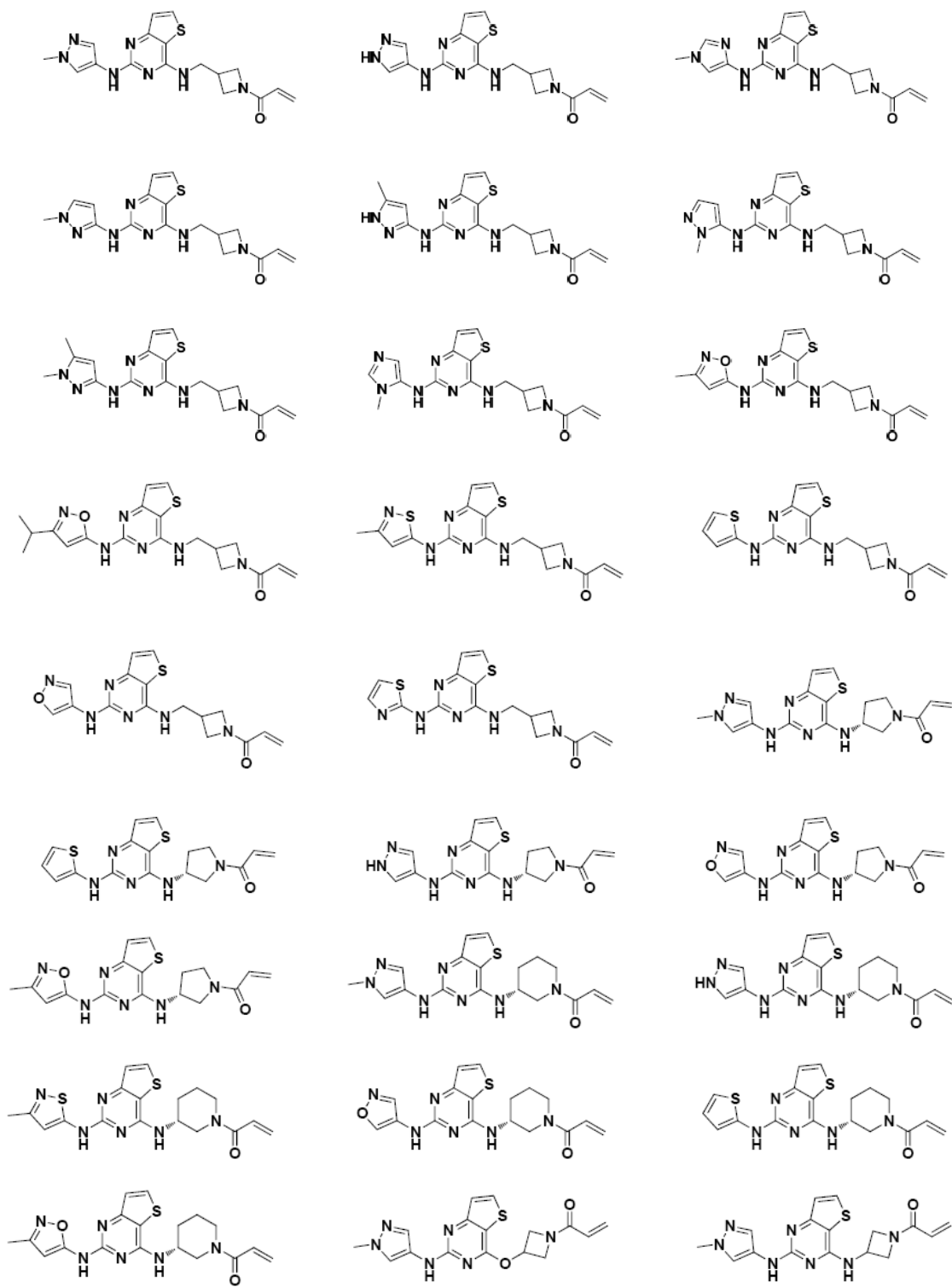
R⁴ is selected from hydrogen or C₁₋₈ aliphatic;

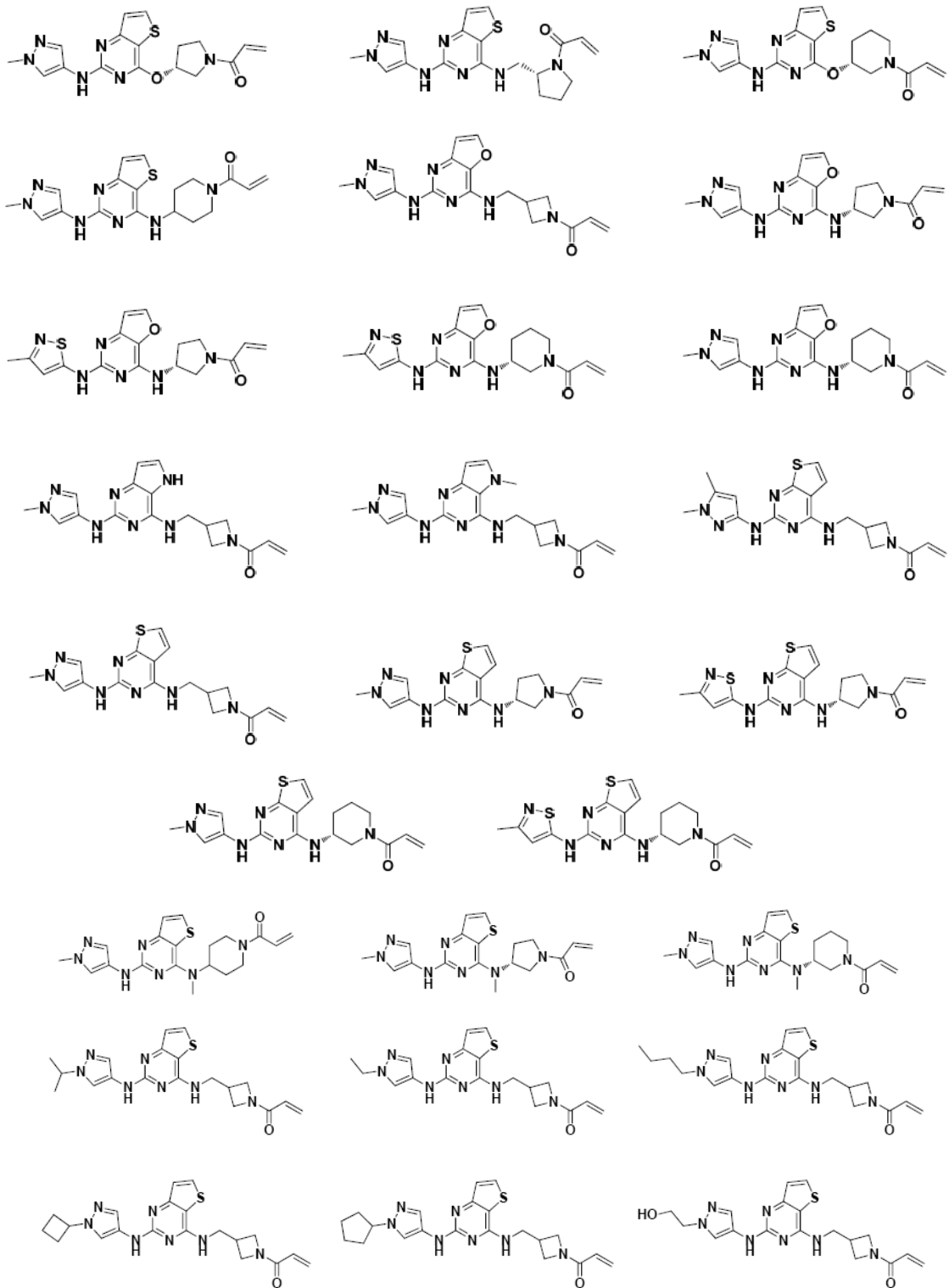
each **R**⁶ is independently selected from the group consisting of halogen, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl and heterocyclyl, wherein:

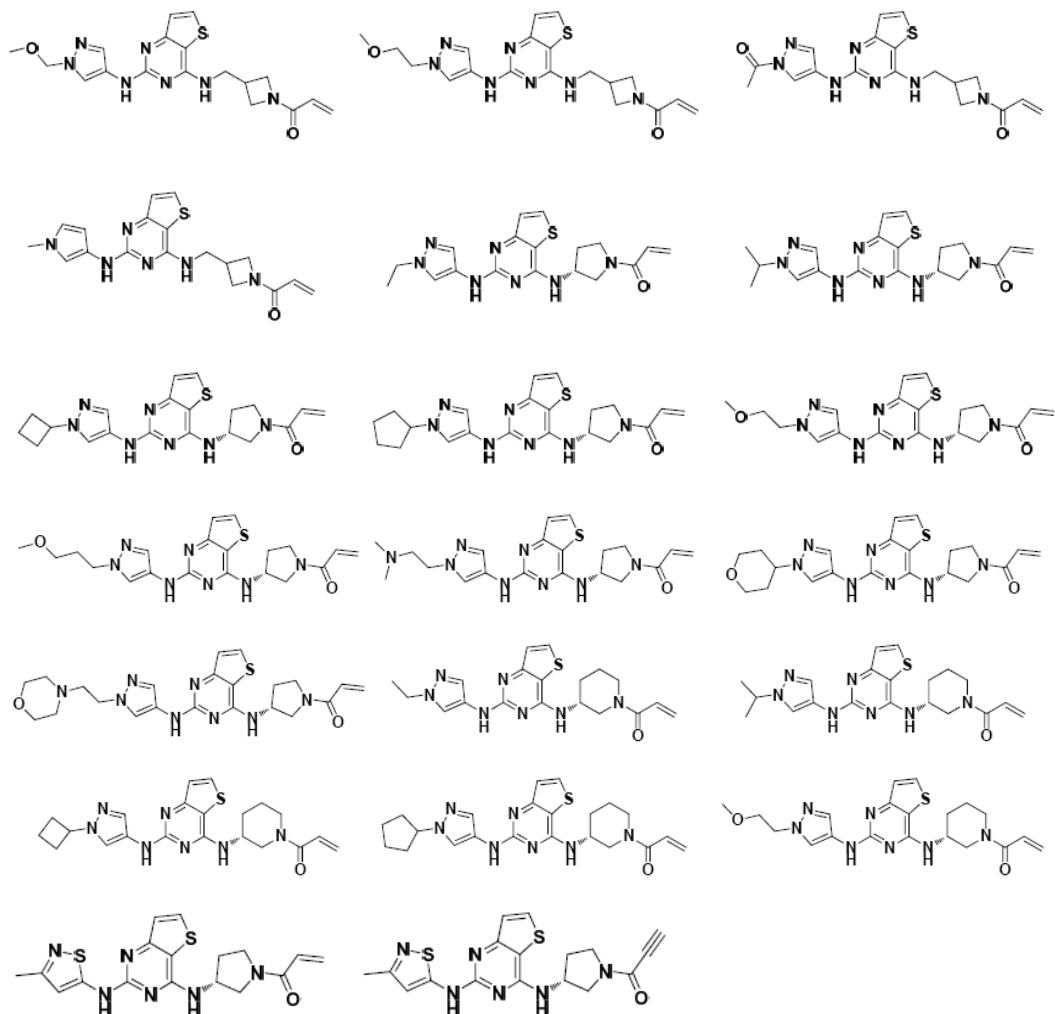
heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; each heterocyclyl is optionally substituted by one or more C₁₋₈ aliphatic substituents;

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl.

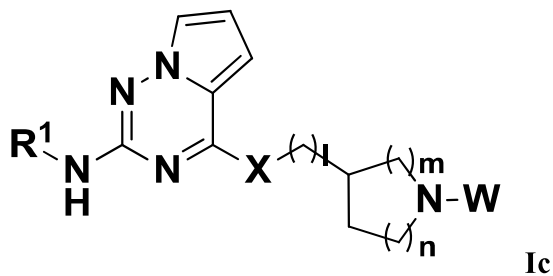
In some embodiments of the compound of formula **Ib**, the compound of formula **Ib** is selected from the group consisting of:







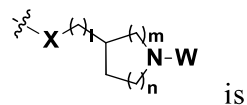
In yet some other embodiments of the compound of formula **I**, the compound of
 5 formula **I** is represented by formula **Ic**:

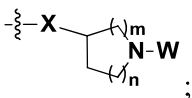


wherein:

X, **W**, and **R¹** are all defined as in formula **I**;

l is selected from 0, 1, 2, 3 or 4; wherein when **l** is 0,

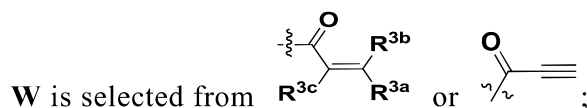




m is selected from 0, 1, 2, 3 or 4; wherein when **m** is 0,  is ; and

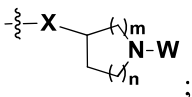
n is selected from 0, 1, 2 or 3; wherein when **n** is 0,  is .

In some embodiments of the compound of formula **1c**, each group in the formula **1c** is
5 defined as follows:



X is selected from O, S, or NR^4 ;

l is selected from 0, 1, 2, 3 or 4; wherein when **l** is 0, $\frac{1}{n}$ is



m is selected from 0, 1, 2, 3 or 4; wherein when **m** is 0, $\left(\begin{matrix} N \\ n \end{matrix} \right)$ is $\left(\begin{matrix} N \\ 0 \end{matrix} \right)$;

n is selected from 0, 1, 2 or 3; wherein when **n** is 0, is ; is ; is ;

R¹ is a 5- to 6-membered heteroaryl group, optionally substituted by one or more **R⁶**;

R^{3a}, **R^{3b}**, and **R^{3c}** are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl;

15 **R⁴** is selected from hydrogen or C₁₋₈ aliphatic;

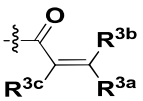
each **R**⁶ is independently selected from the group consisting of halogen, nitro, cyano, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticoxycarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyloxy C₁₋₈ aliphatic, aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticacylamino C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfinyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonylamino C₁₋₈ aliphatic, sulfamoyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminosulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticsulfonyl,

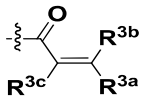
C₁₋₈ aliphaticsulfinyl, C₁₋₈ aliphaticsulfonylamino, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, heterocyclyl, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; each heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticcarbonyl; and

optionally, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl are independently substituted by one or more substituents selected from the group consisting of halogen and C₁₋₈ aliphatic,

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **Ic**, **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl, wherein C₁₋₈ aliphatic is selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

In some embodiments of the compound of formula **Ic**, **W** is , wherein **R**^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen.

In some embodiments of the compound of formula **Ic**, **W** is .

In some embodiments of the compound of formula **Ic**, **X** is O. In some other embodiments of the compound of formula **Ic**, **X** is S. In yet some other embodiments of the compound of formula **Ic**, **X** is NR⁴, wherein **R**⁴ is selected from hydrogen or C₁₋₈ aliphatic, wherein C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl. In yet some other embodiments, **X** is NR⁴, wherein **R**⁴ is selected from hydrogen or C₁₋₈ alkyl. In yet some other embodiments, **X** is NR⁴, wherein **R**⁴ is hydrogen or methyl. In yet some other embodiments, **X** is NR⁴, wherein **R**⁴ is hydrogen.

In some embodiments of the compound of formula **Ic**, **R**¹ is a 5- to 6-membered heteroaryl group, preferably selected from the group consisting of pyridinyl, pyrrolyl,

pyrazolyl, imidazolyl, thienyl, isoxazolyl, thiazolyl and isothiazolyl, which is optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of halogen, nitro, cyano, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticoxycarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyloxy C₁₋₈ aliphatic, aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticacylamino C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfinyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonylamino C₁₋₈ aliphatic, sulfamoyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminosulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, C₁₋₈ aliphaticsulfonylamino, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, heterocyclyl, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; each heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticcarbonyl; and

optionally, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl are independently substituted by one or more substituents selected from the group consisting of halogen and C₁₋₈ aliphatic,

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

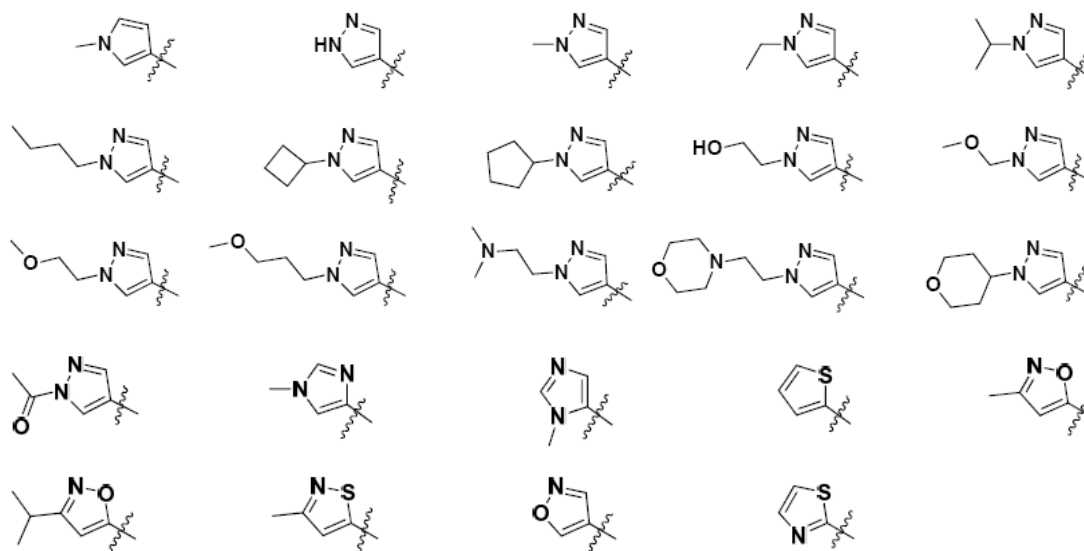
In some embodiments of the compound of formula **Ic**, **R**¹ is a 5-membered heteroaryl group, preferably selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, thienyl, isoxazolyl, thiazolyl and isothiazolyl, which is optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of halogen, C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl and heterocyclyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S, and

preferably selected from the group consisting of piperidinyl, piperazinyl, morpholinyl and tetrahydropyranyl; each heterocyclyl is optionally substituted by one or more C₁₋₈ aliphatic substituents; and wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl.

5 In some embodiments of the compound of formula **Ic**, **R**¹ is a 5-membered heteroaryl group, preferably selected from the group consisting of pyrazolyl and isothiazolyl, which is optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of halogen and C₁₋₈ aliphatic.

10 In some embodiments of the compound of formula **Ic**, **R**¹ is a 5-membered heteroaryl group, preferably selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, thienyl, isoxazolyl, thiazolyl and isothiazolyl, which is optionally substituted by one or more **R**⁶, wherein each **R**⁶ is independently selected from the group consisting of methyl, ethyl, isopropyl, *n*-butyl, hydroxyethyl, methoxymethyl, methoxyethyl, methoxypropyl, dimethylaminoethyl, morpholin-4-yl-ethyl, tetrahydropyran-4-yl, cyclobutyl, cyclopentyl, 15 methylcarbonyl, and more preferably is methyl.

In some embodiments of the compound of formula **Ic**, **R**¹ is selected from the group consisting of:



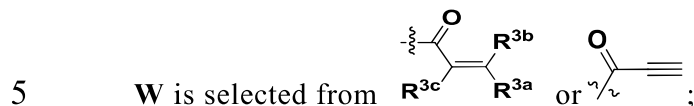
20 In some embodiments of the compound of formula **Ic**, **l** is selected from 0, 1 or 2, more preferably selected from 0 or 1.

In some embodiments of the compound of formula **Ic**, **m** is selected from 0, 1, 2 or 3, preferably selected from 1, 2 or 3.

25 In some embodiments of the compound of formula **Ic**, **n** is selected from 0, 1 or 2, and more preferably is 0.

In some embodiments of the compound of formula **Ic**, **m** and **n** are not 0 simultaneously.

In some embodiments of the compound of formula **Ic**, each group in the formula **Ic** is defined as follows:



X is NR^4 ;

l is selected from 0, 1 or 2;

m is selected from 0, 1, 2 or 3;

n is selected from 0, 1 or 2;

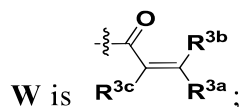
10 **R**¹ is a 5- to 6-membered heteroaryl group, optionally substituted by one or more **R**⁶;
R^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen;

R⁴ is hydrogen;

each **R**⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic and C₁₋₈ aliphaticcarbonyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S; each heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of halogen and C₁₋₈ aliphatic,

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl.

25 In some embodiments of the compound of formula **Ic**, each group in the formula **Ic** is defined as follows:



X is NR^4 ;

l is selected from 0, 1 or 2;

m is selected from 0, 1, 2 or 3;

30 **n** is selected from 0, 1 or 2;

R¹ is a 5-membered heteroaryl group, optionally substituted by one or more **R**⁶;

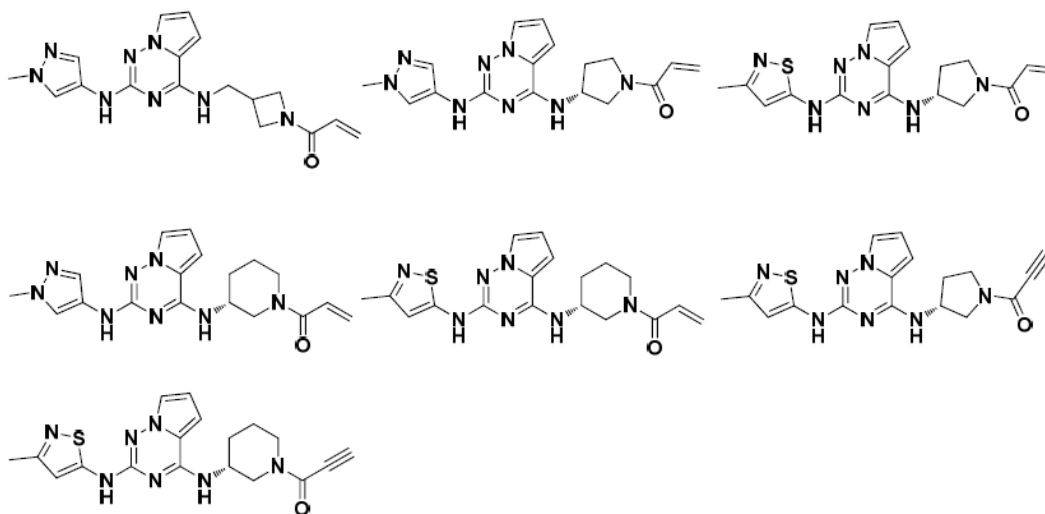
R^{3a}, **R**^{3b}, and **R**^{3c} are all hydrogen;

R^4 is hydrogen;

each R^6 is independently C_{1-8} aliphatic,

wherein C_{1-8} aliphatic is selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl and C_{4-8} cycloalkenyl.

5 In some embodiments of the compound of formula **Ic**, the compound of formula **Ic** is selected from the group consisting of:



The compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a pharmaceutically acceptable salt thereof may contain one or
10 more chiral carbon atoms, and each of the asymmetric carbon atom may form a R- or S-configuration, both configurations are within the scope of the present invention. Accordingly, the compounds may exist in the form of enantiomers, diastereomers or mixtures thereof. The above compounds may be prepared from racemates, diastereomers or enantiomers as starting materials or intermediates. Optically active isomers may be
15 prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chiral chromatography or fractional crystallization.

Conventional techniques for the preparation/isolation of individual isomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid
20 chromatography, see, for example, Gerald Gübitz and Martin G. Schmid (Eds.), Chiral Separations, Methods and Protocols, *Methods in Molecular Biology*, Vol. 243, 2004; A.M. Stalcup, Chiral Separations, *Annu. Rev. Anal. Chem.* 3:341-63, 2010; Fumiss et al. (eds.), VOGEL'S ENCYCLOPEDIA OF PRACTICAL ORGANIC CHEMISTRY 5. sup. TH Ed., Longman Scientific and Technical Ltd., Essex, 1991, 809-816; and Heller, *Acc. Chem.*
25 *Res.* 1990, 23, 128.

Another aspect of the present invention relates to a pharmaceutical composition comprising one or more compounds of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients.

5 The pharmaceutical composition of the present invention may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols.

10 The pharmaceutical composition of the present invention may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection may be prepared by combining a compound of formula **I**, especially compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a pharmaceutically acceptable salt or prodrug thereof with sterile, distilled water, so as to form a solution. A surfactant may be added to facilitate the formation of a
15 homogeneous solution or suspension. Actual methods of preparing a pharmaceutical composition are known to those skilled in the art; for example, see *The Science and Practice of Pharmacy*, 20th Edition (Philadelphia College of Pharmacy and Science, 2000).

20 The routes of administration of the pharmaceutical composition of the present invention include, but are not limited to, oral, topical, transdermal, intramuscular, intravenous, inhalation, parenteral, sublingual, rectal, vaginal and intranasal. For example, dosage forms suitable for oral administration include capsules, tablets, granules, syrups, and the like. The compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, included in these dosage forms may be solid powders or
25 granules; solutions or suspensions in aqueous or non-aqueous liquids; emulsions of water-in-oil type or oil-in-water type; and the like. The above-mentioned dosage forms may be prepared from active compounds together with one or more carriers or excipients by conventional pharmaceutical methods. The above-mentioned carriers are required to be compatible with the active compounds or the other excipients. For solid formulations,
30 commonly used non-toxic carriers include, but are not limited to, mannitol, lactose, starch, magnesium stearate, cellulose, glucose, sucrose, and the like. Carriers for liquid formulations include, but are not limited to, water, physiological saline, aqueous solution of glucose, ethylene glycol, polyethylene glycol, and the like. The active compound may form a solution or a suspension with the above carriers. The specific route of
35 administration and dosage form depend on the physical and chemical properties of the

compounds per se and the severity of the diseases to be treated, etc. The specific route of administration can be determined by one skilled in the art based on the above-mentioned factors in combination with his own knowledge. See, for example, Li jun, "Clinical pharmacology", People's Medical Publishing House, 2008.06; Ding Yufeng, Discussion on Clinical Dosage Form factors and Drug Rational use in Hospital, *Herald of Medicine*, 26(5), 2007; Howard C. Ansel, Loyd V. Allen, Jr., Nicholas G. Popovich ed., Jiang Zhiqiang translated, "Pharmaceutical Dosage Forms and Drug Delivery System", China Medical Science Press, 2003.05.

The compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a pharmaceutical composition comprising the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, may be used in association or combination with one or more other drugs. Drugs to be used in combination with the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or the pharmaceutical composition comprising the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, include, but are not limited to:

- 1) Immunosuppressants such as methotrexate, cyclophosphamide, and the like;
- 2) Corticosteroids such as dexamethasone, betamethasone, and the like;
- 3) Nonsteroidal anti-inflammatory drugs such as salicylates, aryl alkanoic acid, and the like;
- 4) Cox-2 specific inhibitors such as rofecoxib, celecoxib, and the like;
- 5) TNF- α binding proteins such as infliximab, adalimumab, and the like;
- 6) Interferons such as interferon- β and interferon- γ ; interleukins such as interleukin-2; and the like.

Another aspect of the present invention relates to a compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, for inhibiting the activities of BTK and/or JAK3.

Another aspect of the present invention relates to a compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, for the prevention and/or treatment of BTK- and/or JAK3-mediated diseases.

Another aspect of the present invention relates to a pharmaceutical composition comprising the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a

pharmaceutically acceptable salt thereof, for inhibiting the activities of BTK and/or JAK3.

Another aspect of the present invention relates to a pharmaceutical composition comprising the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, for the prevention and/or treatment of BTK- and/or JAK3-mediated diseases.

Another aspect of the present invention relates to use of the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or the pharmaceutically acceptable salt thereof or of the pharmaceutical composition comprising the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inhibiting the activities of BTK and/or JAK3.

Another aspect of the present invention relates to use of the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition comprising the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment and/or prevention of BTK- and/or JAK3-mediated diseases.

Another aspect of the present invention relates to use of the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition comprising the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment and/or prevention BTK- and/or JAK3-mediated diseases.

Another aspect of the present invention relates to a method of inhibiting the activities of BTK and/or JAK3 in a biological system comprising bringing the biological system into contact with the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, or with the pharmaceutical composition comprising said compound. In some embodiments, the biological system is an enzyme, a cell, or a mammal. Examples of mammals include, but are not limited to, humans;

non-human primates such as chimpanzee, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like.

5 Another aspect of the present invention relates to a method of inhibiting BTK and/or JAK3 in a mammal, especially in a human, comprising administering to the mammal, especially the human, in need thereof a therapeutically effective amount of the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, or of
10 the pharmaceutical composition comprising said compound.

Another aspect of the present invention relates to a method of treating and/or preventing BTK- and/or JAK3-mediated diseases comprising administering to a mammal, especially a human, in need thereof a therapeutically effective amount of the compound of formula **I**, especially the compounds of formulae **Ia**, **Ib** and **Ic**, of the present invention, a
15 stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition comprising said compound.

In the present application, the BTK- and/or JAK3-mediated diseases are selected from the group consisting of autoimmune diseases, inflammatory diseases, heteroimmune conditions or diseases, thromboembolic diseases and cancers. The autoimmune diseases
20 and inflammatory diseases are selected from the group consisting of rheumatoid arthritis, osteoarthritis, juvenile arthritis, chronic obstructive pulmonary diseases, multiple sclerosis, systemic lupus erythematosus, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, and the like. The cancers are selected from the group consisting of B-cell chronic lymphocytic leukemia, acute lymphocytic leukemia,
25 non-Hodgkin's lymphoma, Hodgkin's lymphoma, acute myelogenous leukemia, diffuse large B-cell lymphoma, multiple myeloma, mantle cell lymphoma, small lymphocytic lymphoma, and the like.

The composition of the present invention is formulated, quantified and administered in a manner conforming to the guidelines of medical practices. The "therapeutically
30 effective amount" of the compound of the present invention is determined depending on the specific disorders to be treated, individuals being treated, causes of the disorders, targets of the drug, and the modes of administration. Typically, the dose for parenteral administration may be from 1 to 200 mg/kg, and the dose for oral administration may be from 1 to 1000 mg/kg.

35 The ranges of the effective doses provided herein are not intended to limit the scope

of the invention, but represent preferred dose ranges. However, the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one skilled in the art (see, for example, Berkow et. al. eds., The Merck Manual, 16th edition, Merck Company, Rahway, N. J., 1992).

5

Preparation of the Compound of the Invention

The following Reaction Schemes, taking the compounds of formulas **Ia**, **Ib** and **Ic** as examples, illustrate methods to make the compounds of formula **I** of the present invention.

10 It is understood by those skilled in the art that in the following description, combinations of substituents are permissible only if such combinations result in stable compounds.

It will also be appreciated by those skilled in the art that in the process described below the functional groups of immediate compounds may need to be protected by
15 suitable protecting groups "PGs". Said functional groups include hydroxyl, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxyl include trialkylsilyl or diarylalkylsilyl (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable
20 protecting groups for mercapto include -C(O)-R" (wherein R" is alkyl, aryl or arylalkyl), p-methoxybenzyl, trityl, and the like. Suitable protecting groups for carboxyl include alkyl, aryl or arylalkyl esters.

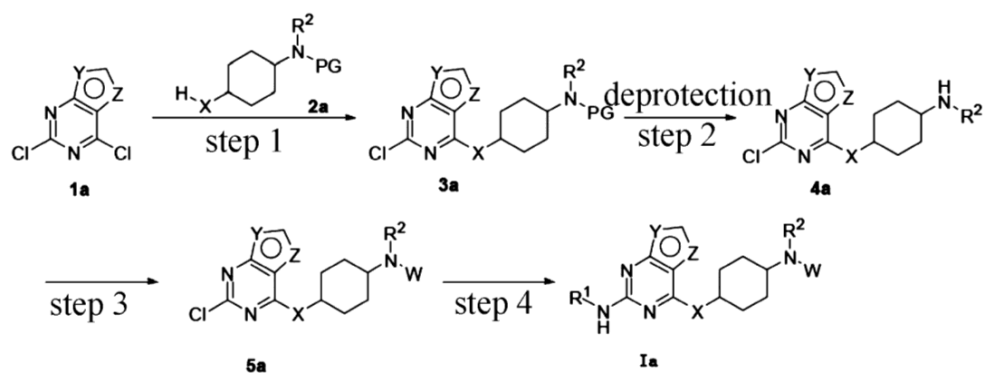
Protecting groups may be introduced and removed in accordance with standard techniques, which are known to those skilled in the art and as described herein.

25 The use of protecting groups is described in detail in Greene, T. W. and P. G. M. Wuts, Protective Groups in Organic Synthesis, (1999), 4th Ed., Wiley. The Protecting group may also be a polymer resin.

The compounds of formula **Ia**, **Ib** and **Ic** of the present invention may be prepared following the procedures illustrated in the following reaction scheme **I**.

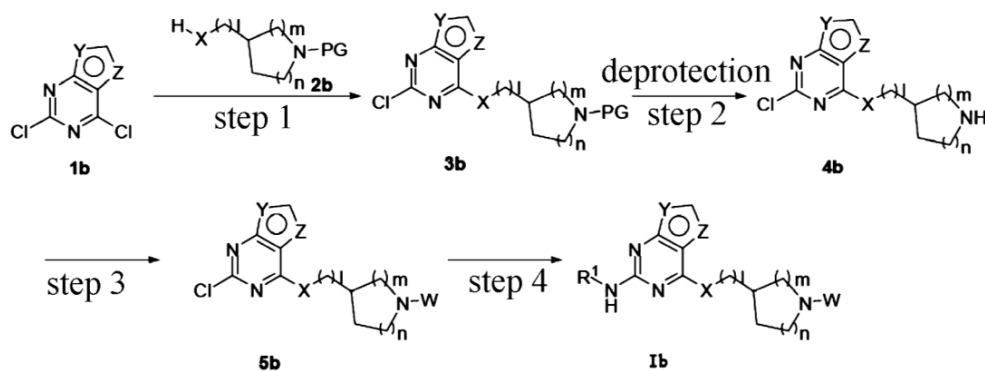
30

Reaction Scheme I



wherein, **X**, **Y**, **Z**, **W**, **R¹**, and **R²** in their respective formulas are all defined as in formula **Ia** above;

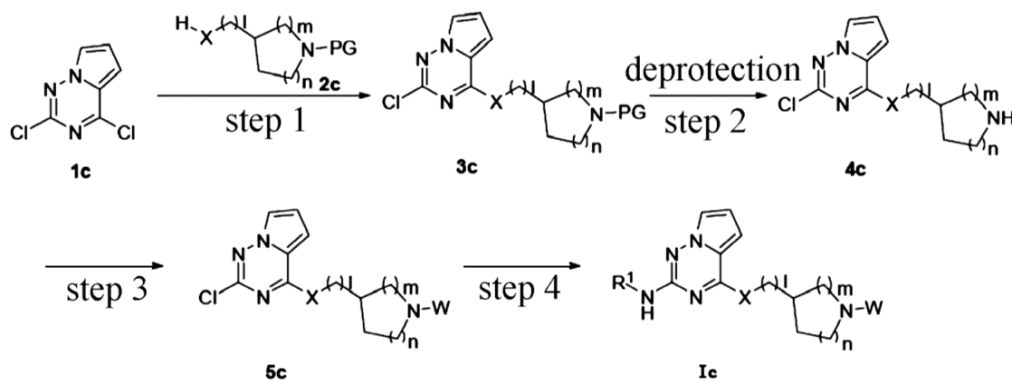
or



5

wherein, **X**, **Y**, **Z**, **W**, **R¹**, **l**, **m** and **n** in their respective formulas are all defined as in formula **Ib** above;

or



10 wherein, **X**, **Y**, **Z**, **W**, **R¹**, **l**, **m** and **n** in their respective formulas are all defined as in formula **Ic** above.

Reaction scheme **I** comprises the steps of:

Step 1: subjecting the compound of formula **1a**, **1b** or **1c**, respectively, to substitution reaction with the compound of formula **2a**, **2b** or **2c** to prepare the compound of formula **3a**, formula **3b** or formula **3c**.

5 In this step, the reaction is preferably carried out in the presence of a base. The base used in the reaction may be an organic base selected from the group consisting of triethylamine, *N,N*-diisopropylethylamine, pyridine, and the like. The base used in the reaction may also be an inorganic base selected from the group consisting of sodium carbonate, potassium carbonate, sodium hydroxide, and the like. The reaction may also be
10 carried out in the presence of an acid or under a neutral condition. The acid used in the reaction may be selected from the group consisting of hydrochloric acid, trifluoroacetic acid, a solution of hydrogen chloride in 1,4-dioxane, acetic acid, sulfuric acid, and the like. The reaction temperature is in a range from -80°C to 120°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, tetrahydrofuran,
15 dichloromethane, toluene, methanol, ethanol, isopropanol, butanol, and the like.

Step 2: removing the protecting group PG from the compound of formula **3a**, **3b** or **3c** to prepare the compound of formula **4a**, **4b** or **4c**.

The protecting group (PG) of the compound of formula **3a**, **3b** or **3c** may be *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, or the like. The deprotecting reaction
20 may be carried out under an acid catalysis condition. The acid used in the reaction may be selected from the group consisting of hydrochloric acid, trifluoroacetic acid, a solution of hydrogen chloride in 1,4-dioxane, acetic acid, sulfuric acid, and the like. The reaction may also be carried out by catalytic hydrogenation using a palladium catalyst under an acidic or a neutral condition. The palladium catalyst used in the present invention may be
25 selected from the group consisting of palladium on carbon and palladium hydroxide. The acid used in the reaction may be selected from the group consisting of hydrochloric acid, trifluoroacetic acid, a solution of hydrogen chloride in 1,4-dioxane, sulfuric acid, and the like. The reaction temperature is in a range from -80°C to 120°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, tetrahydrofuran,
30 dichloromethane, toluene, ethanol, and the like.

Step 3: Subjecting the compound of formula **4a**, **4b** or **4c** to condensation reaction to obtain the compound of formula **5a**, **5b** or **5c**.

In this step, the condensation reagent may be selected from the group consisting of carbonyldiimidazole (CDI), *O*-benzotriazol-1-yl-*N,N,N'*-tetramethyluronium
35 tetrafluoroborate (TBTU), dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-

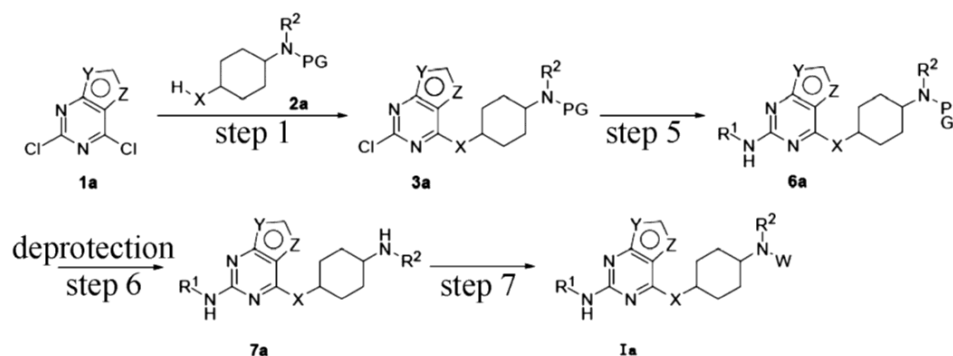
3-ethyl-carbodiimide (EDCI), and the like. The base used in the reaction may be selected from the group consisting of triethylamine, *N,N*-diisopropyl ethylamine, pyridine, sodium hydride, and the like. The reaction temperature is in a range from 0°C to 80°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, tetrahydrofuran, dichloromethane, toluene, and the like.

Step 4: subjecting the compound of formula **5a**, **5b** or **5c** to substitution reaction to obtain the corresponding compound of formula **Ia**, **Ib** or **Ic**.

In this step, the reaction may be carried out in the presence of an acid or under a neutral condition. The acid used in the reaction may be selected from the group consisting of hydrochloric acid, trifluoroacetic acid, a solution of hydrogen chloride in 1,4-dioxane, acetic acid, sulfuric acid, and the like. The reaction may also be carried out in the presence of a base. The base used in the reaction may be a strong base selected from the group consisting of sodium hydroxide, cesium carbonate, sodium *tert*-butoxide, sodium hydride, and the like. The reaction may also be carried out in the presence of a palladium catalyst. The palladium catalyst which may be used in the present invention is selected from the group consisting of bis(triphenylphosphine)palladium dichloride ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$), tris(dibenzylidenepropanone)dipalladium ($\text{Pd}_2(\text{dba})_3$), tetra(triphenylphosphine)palladium ($\text{Pd}(\text{PPh}_3)_4$), palladium acetate ($\text{Pd}(\text{OAc})_2$), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium ($\text{Pd}(\text{dppf})\text{Cl}_2$) and palladium chloride (PdCl_2). The base which may be useful under this condition is preferably an inorganic base, such as sodium carbonate, potassium carbonate, potassium phosphate, cesium carbonate, and the like. The reaction temperature is in a range from 80°C to 160°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, toluene, ethanol, isopropanol, butanol, 2-butanol, water, and mixtures thereof.

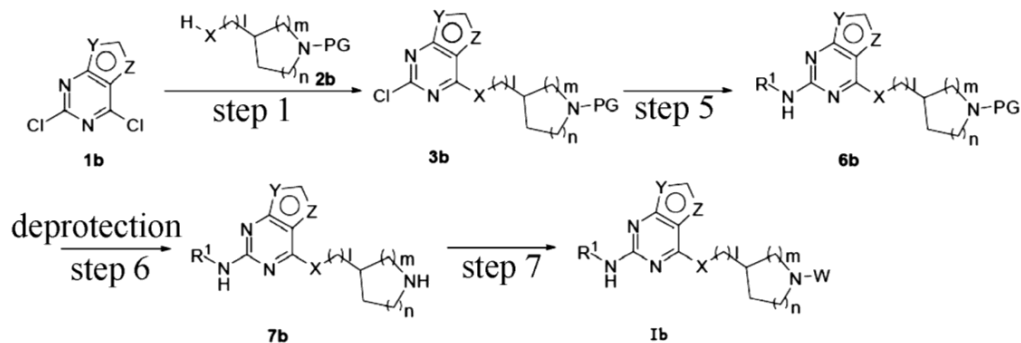
The compounds of formulas **Ia**, **Ib**, and **Ic** of the present invention may be prepared following the procedures illustrated in the following reaction scheme **II**.

Reaction Scheme II



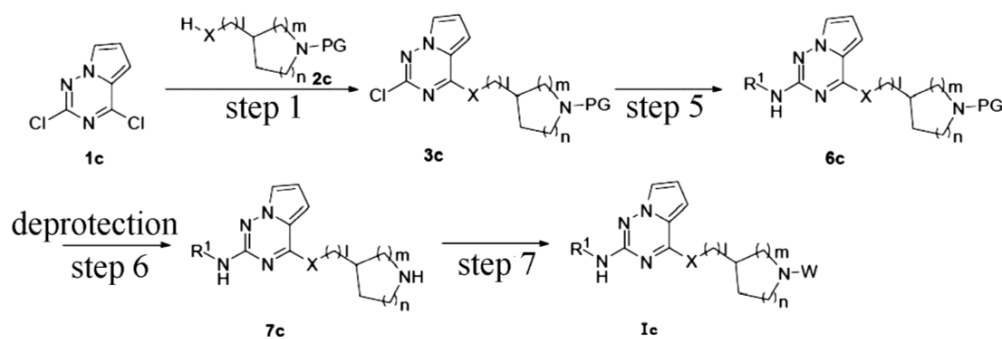
wherein, **X**, **Y**, **Z**, **W**, **R¹** and **R²** in their respective formulas are all defined as above in formula **1a**;

or



5 wherein, **X**, **Y**, **Z**, **W**, **R¹**, **l**, **m** and **n** in their respective formulas are all defined as above in formula **1b**;

or



10 wherein, **X**, **Y**, **Z**, **W**, **R¹**, **l**, **m** and **n** in their respective formulas are all defined as above in formula **1c**.

Reaction scheme **II** comprises the steps of:

Step 1: subjecting the compound of formula **1a**, **1b** or **1c**, respectively, to substitution reaction with the compound of formula **2a**, **2b** or **2c** to prepare the compound of formula **3a**, **3b** or **3c**.

15 In this step, the reaction is preferably carried out in the presence of a base. The base used in the reaction may be an organic base selected from the group consisting of triethylamine, *N,N*-diisopropylethylamine, pyridine, and the like. The base used in the reaction may also be an inorganic base selected from the group consisting of sodium carbonate, potassium carbonate, sodium hydroxide, and the like. The reaction may also be
20 carried out in the presence of an acid or under a neutral condition. The acid used in the

reaction may be selected from the group consisting of hydrochloric acid, trifluoroacetic acid, a solution of hydrogen chloride in 1,4-dioxane, acetic acid, sulfuric acid, and the like. The reaction temperature is in a range from -80°C to 120°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, tetrahydrofuran, dichloromethane, toluene, methanol, ethanol, isopropanol, butanol, and the like.

Step 5: subjecting the compound of formula **3a**, **3b** or **3c** to substitution reaction to obtain the compound of formula **6a**, **6b** or **6c**.

In this step, the reaction may be carried out in the presence of an acid or under a neutral condition. The acid used in the reaction may be selected from the group consisting of hydrochloric acid, trifluoroacetic acid, a solution of hydrogen chloride in 1,4-dioxane, acetic acid, sulfuric acid, and the like. The reaction may also be carried out in the presence of a base. The base used in the reaction may be a strong base selected from the group consisting of sodium hydroxide, sodium *tert*-butoxide, sodium hydride, and the like. The reaction may also be carried out in the presence of a palladium catalyst. The palladium catalyst that may be used in the present invention is selected from the group consisting of bis(triphenylphosphine)palladium dichloride ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$), tris(dibenzylidenepropanone)dipalladium ($\text{Pd}_2(\text{dba})_3$), tetra(triphenylphosphine)palladium ($\text{Pd}(\text{PPh}_3)_4$), palladium acetate ($\text{Pd}(\text{OAc})_2$), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium ($\text{Pd}(\text{dppf})\text{Cl}_2$), and palladium chloride (PdCl_2). The base which may be useful under this condition is preferably an inorganic base, such as sodium carbonate, potassium carbonate, potassium phosphate, cesium carbonate, and the like. The reaction temperature is in a range from 80°C to 160°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, toluene, ethanol, isopropanol, butanol, 2-butanol, water, and mixtures thereof.

Step 6: removing the protecting group PG of the compound of formula **6a**, **6b** or **6c** to prepare the compound of formula **7a**, **7b** or **7c**.

The protecting group (PG) of the compound of formula **6a**, **6b** or **6c** may be *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, or the like. The deprotecting reaction may be carried out under an acid catalysis condition. The acid used in the reaction may be selected from the group consisting of hydrochloric acid, trifluoroacetic acid, a solution of hydrogen chloride in 1,4-dioxane, acetic acid, sulfuric acid, and the like. The reaction may also be carried out by catalytic hydrogenation using a palladium catalyst under an acidic or a neutral condition. The palladium catalyst used in the present invention is selected from the group consisting of palladium on carbon and palladium hydroxide, and the acid used in the reaction may be selected from the group consisting of hydrochloric

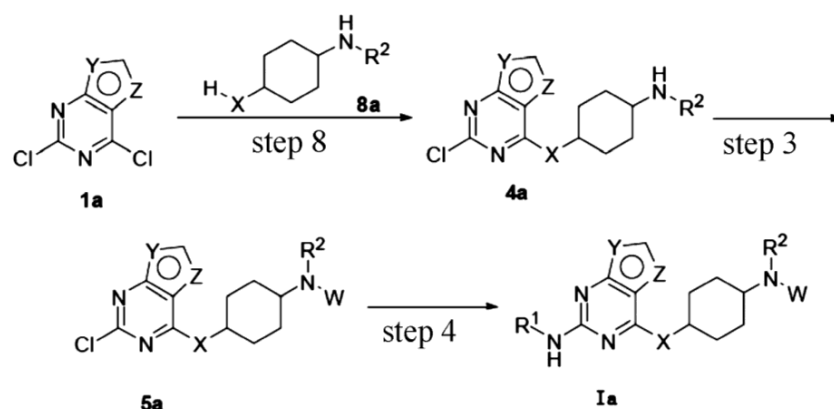
acid, a solution of hydrogen chloride in 1,4-dioxane, sulfuric acid, and the like. The reaction temperature is in a range from -80°C to 120°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, tetrahydrofuran, dichloromethane, toluene, methanol, ethanol, and the like.

5 Step 7: subjecting the compound of formula **7a**, **7b** or **7c** to condensation reaction to obtain the corresponding compound of formula **1a**, **1b** or **1c**.

In this step, the condensation reagent may be selected from the group consisting of carbonyldiimidazole (CDI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDCI), and the like. The base used in the reaction may be selected from the group consisting of triethylamine, *N,N*-diisopropylethylamine, pyridine, and the like. The reaction temperature is in a range from 0°C to 80°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, tetrahydrofuran, dichloromethane, toluene, and the like.

15 The compound of formula **1a** of the present invention may be prepared following the procedures illustrated in the following reaction scheme **III**.

Reaction Scheme **III**



20 wherein, **X**, **Y**, **Z**, **W**, **R¹** and **R²** in their respective formulas are all defined as above in formula **1a**.

Reaction scheme **III** comprises the steps of:

Step 8: subjecting the compound of formula **1a** to substitution reaction with the compound of formula **8a** to prepare the compound of formula **4a**.

25 In this step, the reaction is preferably carried out in the presence of a base. The base used in the reaction may be an organic base selected from the group consisting of triethylamine, *N,N*-diisopropylethylamine, pyridine, and the like, and the base used in the

reaction may also be an inorganic base selected from the group consisting of sodium carbonate, potassium carbonate, sodium hydroxide, and the like. The reaction may also be carried out in the presence of an acid or in the neutral condition. The acid used in the reaction may be selected from the group consisting of hydrochloric acid, trifluoroacetic acid, a solution of hydrogen chloride in 1,4-dioxane, acetic acid, sulfuric acid, and the like. The reaction temperature is in a range from -80°C to 120°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, tetrahydrofuran, dichloromethane, toluene, methanol, ethanol, isopropanol, butanol, and the like.

Step 3: subjecting the compound of formula **4a** to condensation reaction to obtain the compound of formula **5a**.

In this step, the condensation reagent may be selected from the group consisting of carbonyldiimidazole (CDI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU), dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDCI), and the like. The base used in the reaction may be selected from the group consisting of triethylamine, *N,N*-diisopropyl ethylamine, pyridine, and the like. The reaction temperature is in a range from 0°C to 80°C. The solvent used in the reaction may be selected from the group consisting of 1,4-dioxane, tetrahydrofuran, dichloromethane, toluene, and the like.

Step 4: subjecting the compound of formula **5a** to substitution reaction to obtain the corresponding compound of formula **1a**.

In this step, the reaction may be carried out in the presence of an acid or in the neutral condition, and the acid used in the reaction may be selected from the group consisting of hydrochloric acid, trifluoroacetic acid, a solution of hydrogen chloride in 1,4-dioxane, acetic acid, sulfuric acid, and the like. The reaction may be carried out in the presence of a base, and the base used in the reaction may be a strong base selected from the group consisting of sodium hydroxide, sodium *tert*-butoxide, sodium hydride, and the like. The reaction may also be carried out in the presence of a palladium catalyst. The palladium catalyst that may be used in the present invention is selected from the group consisting of bis(triphenylphosphine)palladium dichloride (Pd(PPh₃)₂Cl₂), tris(dibenzylidenepropanone)dipalladium (Pd₂(dba)₃), tetra(triphenylphosphine)palladium (Pd(PPh₃)₄), palladium acetate (Pd(OAc)₂), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (Pd(dppf)Cl₂), and palladium chloride (PdCl₂). The base that may be useful under this condition is preferably an inorganic base, such as sodium carbonate, potassium carbonate, potassium phosphate, cesium carbonate, and the like. The reaction temperature is in a range from 80°C to 160°C. The solvent used in the reaction may be

selected from the group consisting of 1,4-dioxane, toluene, ethanol, isopropanol, butanol, 2-butanol, water, and mixtures thereof.

It will be appreciated by those skilled in the art that the above reaction schemes and preparation methods are only for a simple and clear illustration purpose, and are not intended to be limiting, and that the compound of formula **I** of the present invention may also be obtained by similar methods as described above by selecting appropriate starting materials, which may be commercially available, or obtainable by using methods well known in the art.

10 Examples

The following experiments, synthetic methods and intermediates involved are provided as an illustration of the present invention, and are not intended to limit the scope of the present invention.

The starting materials used in the present invention are purchased from reagent suppliers or prepared from known materials by methods as known in the art. Unless otherwise specifically indicated, the following conditions are applied in the examples:

Temperature is expressed in degrees Celsius (°C); and room temperature is defined as 18-25 °C;

The organic solvent was dried over anhydrous magnesium sulfate or anhydrous sodium sulfate, and concentrated to dryness using a rotary evaporator under reduced pressure at elevated temperature (e.g. 15 mmHg, 30°C);

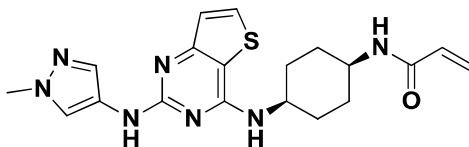
200-300 Mesh silica gel was used as a carrier in the separation and purification by column chromatography, and TLC refers to thin layer chromatography;

Typically, the progress of a reaction was monitored by TLC or LC-MS;

Identification of the final product was performed by NMR (Bruker AVANCE 300, 300 MHz) and LC-MS (Bruker esquire 6000, Agilent 1200 series) spectrometry.

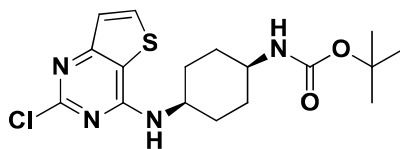
Example 1

Preparation of *N*-(*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide



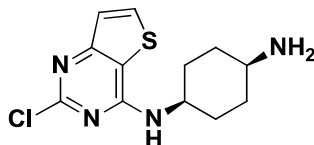
Step 1: preparation of *tert*-butyl *cis*-4-((2-chloro-thieno[3,2-*d*]pyrimidin-4-

yl)amino)cyclohexyl carbamate



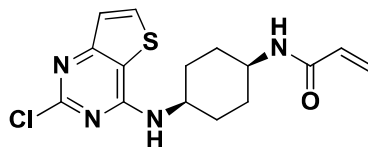
2,4-Dichloro-thieno[3,2-*d*]pyrimidine (678 mg, 3.31 mmol) and *tert*-butyl *cis*-4-aminocyclohexyl carbamate (849 mg, 3.97 mmol) were dissolved in tetrahydrofuran (10 mL), followed by the addition of *N,N*-diisopropylethylamine (0.9 mL, 4.97 mmol). The reaction solution was reacted at 70°C overnight, and then concentrated. The residue was added with water (20 mL), and extracted with ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, and concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: n-hexane: ethyl acetate = 1 : 5) to give a white solid (1.07 g). Yield: 84.7%. MS (ESI, *m/z*): [M+H]⁺: 383.4; ¹H-NMR (300 MHz, CDCl₃) δ: 7.74 (d, 1H, *J* = 5.4 Hz), 7.35 (d, 1H, *J* = 5.4 Hz), 5.00 (s, 1H), 4.59 (s, 1H), 4.31-4.38 (m, 1H), 3.72-3.74 (m, 1H), 1.62-2.04 (m, 8H), 1.45 (s, 9H).

Step 2: preparation of *cis*-*N*'-(2-chloro-thieno[3,2-*d*]pyrimidin-4-yl)cyclohexyl-1,4-diamine



The product obtained in step 1 (840 mg, 2.2 mmol) was dissolved in dichloromethane (10 mL), followed by the slow addition of trifluoroacetic acid (2 mL, 30.8 mmol). The reaction solution was reacted at room temperature for 2 hours. The reaction solution was concentrated, and the crude product thus obtained was used directly in the next step without further purification. MS (ESI, *m/z*): [M+H]⁺: 282.9.

Step 3: preparation of *N*-(*cis*-4-((2-chloro-thieno[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide



The product obtained in step 2 (620 mg, 2.20 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (440 mg, 4.4 mmol). A solution of acryloyl chloride (0.2 mL, 2.42 mmol) dissolved in dichloromethane (5 mL) was added dropwise to the above solution at 0°C. The reaction solution was reacted at room temperature overnight. The reaction solution was washed with water (20 mL), and

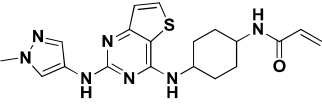
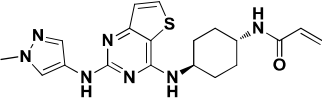
the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 70 : 1), to give a white solid (0.56 g). Yield: 75.8%. MS (ESI, m/z): $[M+H]^+$: 337.2; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 7.76 (d, 1H, $J = 5.4$ Hz), 7.36 (d, 1H, $J = 5.4$ Hz), 6.07-6.35 (m, 2H), 5.65-5.69 (m, 2H), 5.23 (bs, 1H), 4.34-4.38 (m, 1H), 4.09-4.13 (m, 1H), 1.68-2.02 (m, 8H).

Step 4: preparation of *N*-(*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide

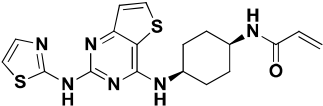
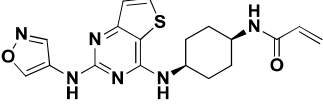
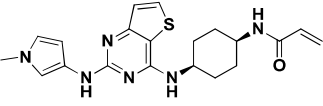
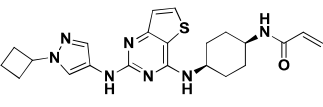
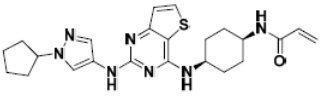
The product obtained in step 3 (54 mg, 0.162 mmol) and 1-methyl-1*H*-pyrazole-4-amine (23 mg, 0.244 mmol) was dissolved in 1,4-dioxane (2 mL). The pH of the reaction solution was adjusted to 5 with trifluoroacetic acid, and the reaction mixture was reacted at 90°C under microwave irradiation for 0.5 hours. The reaction solution was cooled to room temperature, and adjusted to pH 8 with 1N solution of sodium hydroxide. The resulting mixture was extracted with ethyl acetate (10 mL $\times$ 3), and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1) to give a pale yellow solid (32 mg). Yield: 49.8%. MS (ESI, m/z): $[M+H]^+$: 398.3; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.66-7.69 (m, 3H), 6.99-7.19 (m, 2H), 6.32 (dd, 1H, $J = 1.5$ Hz, $J = 16.8$ Hz), 6.15 (dd, 1H, $J = 10.2$ Hz, $J = 16.8$ Hz), 5.89-5.91 (m, 2H), 5.66 (dd, 1H, $J = 1.5$ Hz, $J = 10.2$ Hz), 4.23-4.38 (m, 1H), 4.08-4.16 (m, 1H), 3.88 (s, 3H), 1.75-2.05 (m, 8H).

The following compounds (in Table 1) were prepared from similar starting materials by similar synthetic methods to those as described in Example 1.

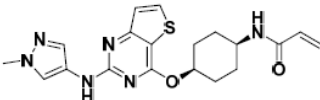
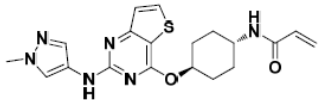
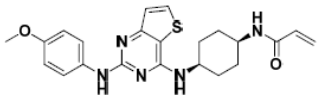
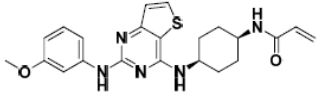
Table 1

Example	Structure	Characterization data
2		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.96 (d, 1H, $J = 5.4$ Hz), 7.86 (s, 1H), 7.63 (s, 1H), 7.17 (d, 1H, $J = 5.4$ Hz), 6.22-8.43 (m, 2H), 5.67 (dd, 1H, $J = 2.1$ Hz, $J = 17.1$ Hz), 4.27-4.28 (m, 1H), 4.27-4.28 (m, 1H), 4.01-4.04 (m, 1H), 2.03 (s, 3H), 1.78-1.97 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 398.3$
3		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.06 (d, 1H, $J = 5.4$ Hz), 7.87 (s, 1H), 7.67 (s, 1H), 7.22 (d, 1H, $J = 5.4$ Hz), 6.25-6.27 (m, 2H), 5.66-5.70 (m, 1H),

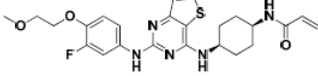
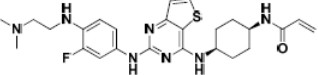
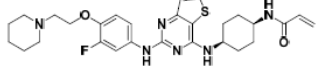
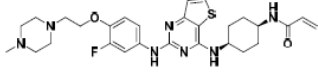
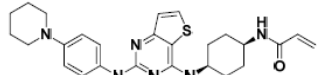
		4.20-4.24 (m, 1H), 3.96 (s, 3H), 3.75-3.89 (m, 1H), 2.07-2.20 (m, 4H), 1.42-1.68 (m, 4H); LC-MS(ESI, m/z): $[M+H]^+ = 398.3$
4		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.91 (d, 1H, $J = 5.4$ Hz), 7.83 (s, 2H), 7.14 (d, 1H, $J = 5.4$ Hz), 6.43 (q, 1H, $J = 6.9$ Hz), 6.25 (dd, 1H, $J = 2.1$ Hz, $J = 17.1$ Hz), 5.66 (dd, 1H, $J = 2.1$ Hz, $J = 10.2$ Hz), 4.26 (m, 1H), 4.05 (m, 1H), 1.72-2.02 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 384.2$
5		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.90 (d, 1H, $J = 2.4$ Hz), 7.51 (s, 1H), 7.63 (s, 1H), 7.99 (d, 1H, $J = 5.4$ Hz), 6.19-6.39 (m, 2H), 5.65 (dd, 1H, $J = 2.1$ Hz, $J = 9.9$ Hz), 4.23 (s, 1H), 3.99 (s, 1H), 3.81 (s, 3H), 2.22 (s, 3H), 1.73-1.91 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 412.3$
6		$^1\text{H-NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ : 8.05-8.16 (m, 2H), 7.97 (d, 1H, $J = 6.3$ Hz), 7.35 (d, 1H, $J = 5.4$ Hz), 6.32-8.41 (m, 1H), 6.08 (dd, 1H, $J = 2.4$ Hz, $J = 17.1$ Hz), 5.57 (dd, 1H, $J = 2.4$ Hz, $J = 10.2$ Hz), 4.27-4.28 (m, 1H), 4.01-4.04 (m, 1H), 2.03 (s, 3H), 1.78-1.80 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 398.3$
7		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.90 (d, 1H, $J = 5.4$ Hz), 7.16 (d, 1H, $J = 5.4$ Hz), 6.85-6.91 (m, 2H), 6.70-6.72 (m, 1H), 6.22-8.43 (m, 2H), 5.68 (dd, 1H, $J = 2.1$ Hz, $J = 9.9$ Hz), 4.45-4.55 (m, 1H), 4.00-4.10 (m, 1H), 1.79-2.05 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 400.3$
8		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.89 (d, 1H, $J = 5.4$ Hz), 7.20 (d, 1H, $J = 5.4$ Hz), 6.63 (s, 1H), 6.22-8.43 (m, 2H), 5.67 (dd, 1H, $J = 2.4$ Hz, $J = 9.9$ Hz), 4.40-4.54 (m, 1H), 4.05-4.13 (m, 1H), 1.79-2.03 (m, 8H);

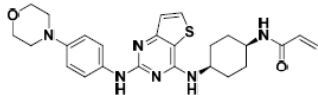
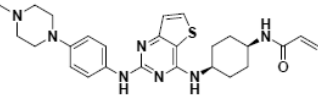
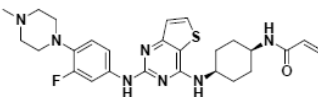
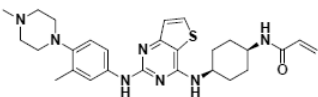
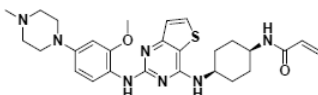
		LC-MS(ESI, m/z): $[M+H]^+ = 415.3$
9		$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 8.05 (d, 1H, $J = 5.4$ Hz), 7.97 (d, 1H, $J = 6.3$ Hz), 7.37 (d, 1H, $J = 3.9$ Hz), 7.18 (d, 1H, $J = 5.4$ Hz), 7.06 (d, 1H, $J = 3.6$ Hz), 6.33-6.42 (m, 1H), 6.09 (dd, 1H, $J = 2.4$ Hz, $J = 17.1$ Hz), 5.68 (dd, 1H, $J = 2.4$ Hz, $J = 10.2$ Hz), 4.31 (s, 1H), 3.87 (s, 1H), 1.63-1.90 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 401.2$
10		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 9.03 (s, 1H), 8.57 (s, 1H), 7.84 (d, 1H, $J = 5.4$ Hz), 7.16 (d, 1H, $J = 5.4$ Hz), 6.22-8.41 (m, 2H), 5.67 (dd, 1H, $J = 2.1$ Hz, $J = 9.9$ Hz), 4.20-4.32 (m, 1H), 4.00-4.10 (m, 1H), 1.70-2.02 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 385.4$
11		$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 9.11 (s, 1H), 7.98-8.20 (m, 3H), 7.15 (d, 1H, $J = 5.4$ Hz), 7.03 (s, 1H), 6.58 (s, 1H), 6.33-6.42 (m, 1H), 6.00-6.12 (m, 2H), 5.55-5.59 (m, 1H), 4.34 (m, 1H), 4.13-4.15 (m, 1H), 3.60 (s, 3H), 1.54-1.91 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 397.2$
12		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.93 (s, 1H), 7.85 (d, 1H, $J = 5.4$ Hz), 7.63 (s, 1H), 7.11 (d, 1H, $J = 5.4$ Hz), 6.35 (m, 1H), 6.23 (m, 1H), 5.65 (dd, 1H, $J = 2.4$ Hz, $J = 9.9$ Hz), 4.78 (m, 1H), 4.28 (m, 1H), 4.00 (m, 1H), 2.50 (m, 4H), 1.90 (m, 10H); LC-MS(ESI, m/z): $[M+H]^+ = 438.3$
13		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.00 (m, 1H), 7.90 (d, 1H, $J = 3.0$ Hz), 7.64 (d, 1H, $J = 3.0$ Hz), 7.20 (m, 1H), 6.20-6.41 (m, 2H), 5.66 (m, 1H), 4.72 (m, 1H), 4.28 (s, 1H), 4.00 (s, 1H), 3.21 (m, 1H), 2.19 (s, 2H), 1.75-2.03 (m, 13H); LC-MS(ESI, m/z): $[M+H]^+ = 452.4$

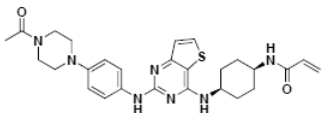
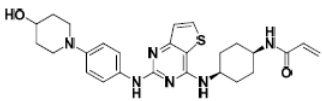
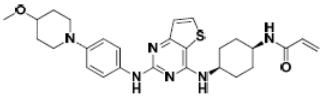
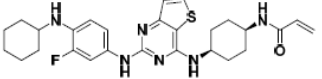
14		¹ H-NMR (300 MHz, CD ₃ OD) δ: 7.91-8.05 (m, 2H), 7.66 (s, 1H), 7.14-7.28 (m, 1H), 6.22-8.44 (m, 2H), 5.64-5.68 (m, 1H), 3.91-3.14 (m, 3H), 3.32-3.36 (m, 3H), 1.85-2.04 (m, 8H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 428.4
15		¹ H-NMR (300 MHz, CD ₃ OD) δ: 8.02 (d, 1H, <i>J</i> = 5.4 Hz), 7.95 (s, 1H), 7.67 (s, 1H), 7.20 (d, 1H, <i>J</i> = 5.4 Hz), 6.22-8.42 (m, 2H), 5.68 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 9.9 Hz), 4.31-4.35 (m, 3H), 4.00-4.08 (m, 1H), 3.79 (t, 2H, <i>J</i> = 4.8 Hz), 3.40 (s, 3H), 1.79-2.01 (m, 8H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 442.4
16		¹ H-NMR (300 MHz, CD ₃ OD) δ: 7.96 (s, 1H), 7.84 (d, 1H, <i>J</i> = 5.4 Hz), 7.65 (s, 1H), 7.11 (d, 1H, <i>J</i> = 5.4 Hz), 6.36 (m, 1H), 6.22 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 16.8 Hz), 5.65 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 9.9 Hz), 4.83 (m, 1H), 4.67 (m, 1H), 4.48 (m, 1H), 4.39 (m, 1H), 4.26 (s, 1H), 4.00 (s, 1H), 1.82 (m, 8H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 430.3
17		¹ H-NMR (300 MHz, CD ₃ OD) δ: 8.02 (m, 2H), 7.80 (s, 1H), 7.44 (m, 1H), 7.23 (d, 1H, <i>J</i> = 5.4 Hz), 6.30 (m, 2H), 5.65 (dd, 1H, <i>J</i> = 1.8 Hz, <i>J</i> = 8.1 Hz), 4.59 (m, 2H), 4.29 (m, 1H), 4.02 (m, 1H), 3.63 (m, 2H), 3.02 (s, 6H), 1.78-1.99 (m, 8H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 455.3
18		¹ H-NMR (300 MHz, CD ₃ OD) δ: 8.00 (m, 2H), 7.70 (s, 1H), 7.21 (d, 1H, <i>J</i> = 5.4 Hz), 6.40 (m, 1H), 6.24 (m, 1H), 5.67 (m, 1H), 4.38 (t, 2H, <i>J</i> = 6.3 Hz), 4.30 (m, 1H), 4.04 (m, 1H), 3.75 (m, 4H), 3.02 (t, 2H, <i>J</i> = 6.3 Hz), 2.69 (m, 4H), 1.79-2.01 (m, 8H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 497.4
19		¹ H-NMR (300 MHz, CD ₃ OD) δ: 8.02 (d, 1H, <i>J</i> = 5.7 Hz), 7.80 (s, 1H), 7.60 (s, 1H), 7.19 (d, 1H, <i>J</i> =

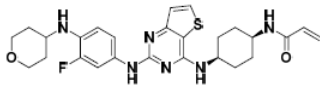
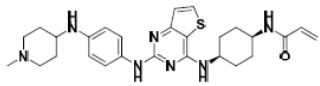
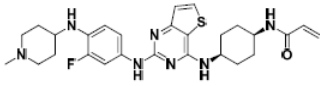
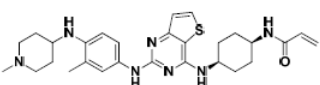
		<p>5.7 Hz), 6.41-6.50 (m, 1H), 6.25 (dd, 1H, $J = 1.8$ Hz, $J = 17.1$ Hz), 5.67 (dd, 1H, $J = 1.8$ Hz, $J = 10.2$ Hz), 4.18 (s, 1H), 3.90 (s, 3H), 3.42 (s, 1H), 1.74-2.05 (m, 8H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 412.3$</p>
20		<p>$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ: 7.85 (s, 1H), 7.73 (d, 1H, $J = 5.4$ Hz), 7.52 (s, 1H), 7.23 (d, 1H, $J = 5.4$ Hz), 6.91 (bs, 1H), 6.31 (dd, 1H, $J = 1.5$ Hz, $J = 16.8$ Hz), 6.10 (dd, 1H, $J = 10.2$ Hz, $J = 16.8$ Hz), 5.66 (dd, 1H, $J = 1.5$ Hz, $J = 10.2$ Hz), 5.58-5.61 (m, 1H), 5.47 (bs, 1H), 3.98-4.09 (m, 1H), 3.91 (s, 3H), 2.10-2.17 (m, 2H), 1.67-2.05 (m, 8H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 399.2$</p>
21		<p>$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ: CDCl_3 δ: 7.79 (s, 1H), 7.73 (d, 1H, $J = 5.4$ Hz), 7.60 (s, 1H), 7.20 (d, 1H, $J = 5.4$ Hz), 7.07 (bs, 1H), 6.31 (dd, 1H, $J = 0.9$ Hz, $J = 16.8$ Hz), 6.10 (dd, 1H, $J = 10.2$ Hz, $J = 16.8$ Hz), 5.66 (dd, 1H, $J = 1.2$ Hz, $J = 10.2$ Hz), 5.56-5.58 (m, 1H), 5.16-5.23 (m, 1H), 3.95-3.99 (m, 1H), 3.91 (s, 3H), 2.16-2.28 (m, 4H), 1.67-1.76 (m, 2H), 1.33-1.45 (m, 2H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 399.2$</p>
22		<p>$^1\text{H-NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ: 9.23 (s, 1H), 7.98-8.03 (s, 3H), 7.62 (d, 2H, $J = 8.7$ Hz), 7.15 (d, 1H, $J = 5.4$ Hz), 7.89 (d, 2H, $J = 8.7$ Hz), 6.33-6.42 (m, 1H), 6.06-6.12 (m, 1H), 5.55-5.59 (m, 1H), 4.08-4.10 (m, 1H), 3.86 (m, 1H), 3.73 (s, 3H), 1.77-1.85 (m, 6H), 1.59-1.62 (m, 2H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 424.3$</p>
23		<p>$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ: 8.12 (bs, 1H), 7.60 (d, 1H, $J = 5.4$ Hz), 7.43-7.45 (m, 1H), 7.09-7.23 (m, 3H), 6.57-6.60 (m, 1H), 6.12-8.35 (m, 2H), 5.95 (bs, 1H), 5.65 (dd, 1H, $J = 1.8$ Hz, $J = 9.9$ Hz), 5.49 (bs, 1H), 4.30 (bs, 1H), 4.15 (bs, 1H),</p>

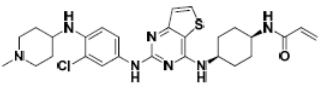
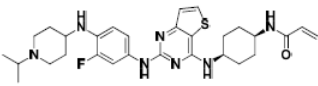
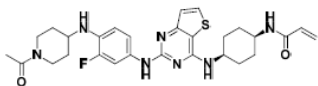
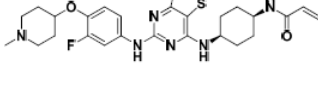
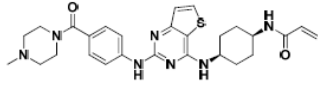
		3.81 (s, 3H), 1.70-2.08 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 424.3$
24		$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 9.58 (s, 1H), 8.52 (s, 1H), 8.10 (d, 1H, $J = 5.4$ Hz), 8.00 (d, 1H, $J = 6.3$ Hz), 7.42 (d, 2H, $J = 8.4$ Hz), 7.20 (d, 1H, $J = 5.4$ Hz), 6.78 (d, 2H, $J = 8.7$ Hz), 6.33-6.42 (m, 1H), 6.06-6.12 (m, 1H), 5.55-5.59 (m, 1H), 4.02-4.09 (m, 1H), 3.86 (m, 1H), 2.90 (s, 6H), 1.77-1.99 (m, 6H), 1.56-1.62 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 437.3$
25		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.13 (d, 1H, $J = 5.1$ Hz), 7.86-7.90 (m, 2H), 7.71-7.75 (m, 2H), 7.28 (d, 1H, $J = 5.7$ Hz), 6.36 (dd, 1H, $J = 9.9$ Hz, $J = 17.1$ Hz), 6.24 (dd, 1H, $J = 2.1$ Hz, $J = 17.1$ Hz), 5.66 (dd, 1H, $J = 2.4$ Hz, $J = 9.9$ Hz), 4.26 (bs, 1H), 4.03 (bs, 1H), 2.94 (s, 3H), 1.72-2.02 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 451.4$
26		$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 10.09 (s, 1H), 8.77 (s, 2H), 8.15 (d, 1H, $J = 5.4$ Hz), 8.02 (d, 1H, $J = 6.3$ Hz), 7.70 (dd, 1H, $J = 2.4$ Hz, $J = 13.8$ Hz), 7.13-7.30 (m, 3H), 6.34-6.43 (m, 1H), 6.10 (dd, 1H, $J = 2.4$ Hz, $J = 17.4$ Hz), 5.58 (dd, 1H, $J = 2.4$ Hz, $J = 10.2$ Hz), 4.07 (d, 1H, $J = 3.3$ Hz), 3.84 (s, 3H), 1.58-1.91 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 472.3$
27		$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 9.12 (s, 1H), 7.97 (m, 2H), 7.87-7.93 (m, 1H), 7.61 (s, 1H), 7.03 (d, 1H, $J = 8.7$ Hz), 7.14 (d, 1H, $J = 5.1$ Hz), 7.07 (t, 1H, $J = 9.3$ Hz), 6.32-8.42 (m, 1H), 6.06-6.12 (m, 1H), 5.55-5.59 (m, 1H), 4.87 (s, 1H), 4.10-4.12 (m, 1H), 3.99-4.02 (m, 2H), 3.86 (m, 1H), 3.71-3.76 (m, 2H), 1.78-1.91 (m, 6H), 1.61-1.65 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 472.3$

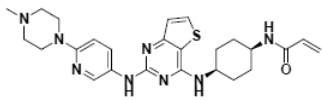
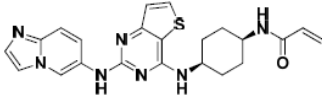
28		¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆) δ: 9.37 (s, 1H), 7.82-8.04 (m, 4H), 7.34 (d, 1H, <i>J</i> = 8.7 Hz), 7.07-7.18 (m, 2H), 6.33-6.42 (m, 1H), 6.07-6.13 (m, 1H), 5.56-5.60 (m, 1H), 4.11-4.14 (m, 3H), 3.87 (m, 1H), 3.64-3.68 (m, 2H), 3.32 (s, 3H), 1.79-1.87 (m, 6H), 1.61-1.64 (m, 2H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 486.3
29		¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆) δ: 10.14 (m, 2H), 8.86 (m, 1H), 8.17 (d, 1H, <i>J</i> = 5.4 Hz), 8.06 (d, 1H, <i>J</i> = 6.3 Hz), 7.59 (d, 1H, <i>J</i> = 13.8 Hz), 7.15-7.25 (m, 2H), 6.87 (t, 1H, <i>J</i> = 9.6 Hz), 6.35-6.44 (m, 1H), 6.06-6.13 (m, 1H), 5.56-5.60 (m, 1H), 4.02-4.08 (m, 1H), 3.87 (m, 1H), 3.17-3.61 (m, 4H), 2.83 (s, 3H), 1.78-1.99 (m, 6H), 1.58-1.61 (m, 2H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 498.4
30		¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆) δ: 9.07 (s, 1H), 7.95-8.01 (m, 3H), 7.41-7.49 (m, 2H), 7.10-7.17 (m, 2H), 6.33-6.42 (m, 1H), 6.06-6.12 (m, 1H), 5.55-5.59 (m, 1H), 4.36 (m, 2H), 4.11-4.13 (m, 1H), 3.87 (m, 1H), 3.41 (m, 3H), 3.04 (m, 2H), 1.62-1.91 (m, 15H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 539.4
31		¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆) δ: 9.03 (s, 1H), 7.92-8.01 (m, 3H), 7.37-7.48 (m, 2H), 7.04-7.13 (m, 2H), 6.33-6.42 (m, 1H), 6.06-6.12 (m, 1H), 5.55-5.60 (m, 1H), 4.10-4.13 (m, 3H), 3.87 (m, 1H), 3.08 (m, 4H), 2.81 (m, 4H), 2.67 (m, 5H), 1.81-1.91 (m, 6H), 1.62-1.65 (m, 2H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 554.4
32		¹ H-NMR (300 MHz, CD ₃ OD) δ: 7.88 (d, 1H, <i>J</i> = 5.4 Hz), 7.45 (d, 2H, <i>J</i> = 8.7 Hz), 7.12 (d, 1H, <i>J</i> = 5.4 Hz), 7.00 (d, 2H, <i>J</i> = 5.4 Hz), 6.38 (m, 1H), 6.23 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 17.1 Hz), 5.65 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 9.9 Hz), 4.19 (s, 1H), 4.01 (s,

		1H), 3.11 (m, 4H), 1.56-1.91 (m, 14H); LC-MS(ESI, m/z): $[M+H]^+ = 477.4$
33		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.13 (d, 1H, $J = 5.4$ Hz), 7.58 (d, 2H, $J = 9.0$ Hz), 7.32 (d, 1H, $J = 5.4$ Hz), 7.17 (d, 2H, $J = 9.0$ Hz), 6.35-6.55 (m, 2H), 5.81 (dd, 1H, $J = 2.1$ Hz, $J = 9.6$ Hz), 4.40 (s, 1H), 4.16 (s, 1H), 4.01 (t, 4H, $J = 4.8$ Hz), 2.17 (s, 5H), 1.85-2.09 (m, 7H); LC-MS(ESI, m/z): $[M+H]^+ = 479.4$
34		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.99 (d, 1H, $J = 5.4$ Hz), 7.52 (d, 1H, $J = 9.0$ Hz), 7.21 (d, 1H, $J = 5.4$ Hz), 7.08 (d, 1H, $J = 9.0$ Hz), 6.38-6.47 (m, 1H), 6.22-8.28 (m, 1H), 5.67 (dd, 1H, $J = 1.8$ Hz, $J = 9.9$ Hz), 4.18-4.28 (m, 1H), 4.00-4.08 (m, 1H), 3.37-3.45 (m, 8H), 2.94 (s, 3H), 1.71-1.94 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 492.4$
35		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.90 (d, 1H, $J = 5.4$ Hz), 7.81 (dd, 1H, $J = 15$ Hz, 2.1 Hz), 7.23-7.26 (m, 1H), 7.16-7.18 (m, 1H), 7.02-7.08 (m, 1H), 6.22-8.46 (m, 2H), 5.65-5.69 (m, 1H), 3.59-3.67 (m, 3H), 3.23-3.41 (m, 7H), 2.93 (s, 3H), 1.74-2.01 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 510.4$
36		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.99 (s, 1H), 7.96-8.02 (m, 2H), 7.55-7.64 (m, 3H), 7.11 (d, 1H, $J = 5.1$ Hz), 6.97 (d, 1H, $J = 8.7$ Hz), 6.33-6.42 (m, 1H), 6.05-6.12 (m, 1H), 5.55-5.59 (m, 1H), 4.14 (m, 1H), 3.86 (m, 1H), 3.08-3.18 (m, 8H), 2.82 (s, 3H), 2.26 (s, 3H), 1.80-1.91 (m, 6H), 1.60-1.65 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 506.4$
37		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.08 (d, 1H, $J = 9.0$ Hz), 7.85 (d, 1H, $J = 5.4$ Hz), 7.09 (d, 1H, $J =$

		<p>5.4 Hz), 6.71 (d, 1H, $J = 2.4$ Hz), 6.60 (dd, 1H, $J = 2.4$ Hz, $J = 9.0$ Hz), 6.36 (dd, 1H, $J = 9.6$ Hz, $J = 16.8$ Hz), 6.23 (dd, 1H, $J = 2.1$ Hz, $J = 16.8$ Hz), 5.66 (dd, 1H, $J = 2.4$ Hz, $J = 9.9$ Hz), 4.22 (bs, 1H), 4.02 (bs, 1H), 3.90 (s, 3H), 3.00-3.08 (m, 4H), 2.64 (s, 3H), 1.70-2.00 (m, 8H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 522.4$</p>
38		<p>$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ: 7.89 (d, 1H, $J = 5.4$ Hz), 7.48 (d, 1H, $J = 8.4$ Hz), 7.13 (d, 1H, $J = 5.4$ Hz), 7.00 (d, 1H, $J = 8.1$ Hz), 6.19-6.41 (m, 2H), 5.63-5.67 (m, 1H), 4.01-4.21 (m, 2H), 3.67-3.75 (m, 4H), 3.05-3.21 (m, 4H), 2.15 (s, 3H), 1.70-1.92 (m, 8H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 520.5$</p>
39		<p>$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ: 8.10 (d, 1H, $J = 5.4$ Hz), 7.45 (d, 2H, $J = 9.0$ Hz), 7.18-7.25 (m, 3H), 6.36 (dd, 1H, $J = 9.9$ Hz, $J = 17.1$ Hz), 6.24 (dd, 1H, $J = 2.1$ Hz, $J = 17.1$ Hz), 5.66 (dd, 1H, $J = 2.1$ Hz, $J = 9.9$ Hz), 4.23 (bs, 1H), 4.01 (bs, 1H), 3.82-3.88 (m, 1H), 3.63-3.70 (m, 2H), 3.04-3.13 (m, 2H), 1.69-2.02 (m, 12H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 493.4$</p>
40		<p>$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ: 9.92 (s, 1H), 7.57 (d, 1H, $J = 4.8$ Hz), 7.44 (d, 1H, $J = 8.4$ Hz), 7.12 (s, 1H), 6.92 (d, 1H, $J = 8.4$ Hz), 6.29-6.48 (m, 3H), 5.59-5.63 (m, 1H), 4.10-4.28 (m, 2H), 3.39-3.55 (m, 5H), 2.87-3.02 (m, 2H), 1.68-2.05 (m, 12H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 507.5$</p>
41		<p>$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ: 7.90 (d, 1H, $J = 5.4$ Hz), 7.42 (dd, 1H, $J = 2.1$ Hz, $J = 13.5$ Hz), 7.13 (d, 1H, $J = 5.4$ Hz), 7.04 (d, 1H, $J = 7.8$ Hz), 6.76 (t, 1H, $J = 9.3$ Hz), 6.19-6.40 (m, 2H), 5.64 (dd, 1H, $J = 2.1$ Hz, $J = 9.9$ Hz), 4.19 (s, 1H), 4.00 (s, 1H), 3.24 (s, 1H), 1.64-2.04 (m, 15H), 1.42 (m,</p>

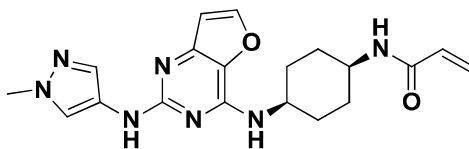
		3H); LC-MS(ESI, m/z): $[M+H]^+ = 509.4$
42		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.95 (d, 1H, $J = 5.4$ Hz), 7.40 (dd, 1H, $J = 1.8$ Hz, $J = 13.2$ Hz), 7.16 (d, 1H, $J = 5.4$ Hz), 7.05 (d, 1H, $J = 8.4$ Hz), 6.83 (t, 1H, $J = 9.3$ Hz), 6.37 (m, 1H), 6.23 (dd, 1H, $J = 2.1$ Hz, $J = 17.1$ Hz), 5.65 (dd, 1H, $J = 2.1$ Hz, $J = 9.9$ Hz), 4.20 (s, 1H), 3.97 (m, 3H), 3.55 (m, 3H), 1.68-2.01 (m, 10H), 1.55 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 511.4$
43		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.12-8.14 (m, 1H), 7.27-7.31 (m, 3H), 6.82-8.85 (m, 2H), 6.41-6.47 (m, 1H), 6.26-6.32 (m, 1H), 5.69-5.73 (m, 1H), 4.25 (m, 1H), 4.08 (m, 1H), 3.61-3.80 (m, 3H), 3.42-3.58 (m, 2H), 2.96 (s, 3H), 1.72-2.43 (m, 12H); LC-MS(ESI, m/z): $[M+H]^+ = 506.4$
44		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 10.13 (s, 1H), 9.70 (s, 1H), 8.43 (s, 1H), 8.02-8.11 (m, 2H), 7.60-7.65 (m, 1H), 7.14-7.20 (m, 2H), 6.77-6.83 (m, 1H), 6.35-6.44 (m, 1H), 6.06-6.13 (m, 1H), 5.56-5.60 (m, 1H), 5.23 (s, 1H), 4.07-4.09 (m, 1H), 3.86 (m, 1H), 3.20-3.48 (m, 2H), 3.06 (m, 2H), 2.75 (s, 3H), 1.59-2.11 (m, 12H); LC-MS(ESI, m/z): $[M+H]^+ = 524.5$
45		$^1\text{H-NMR}$ (300 MHz, $\text{DMSO}-d_6$) δ : 10.32 (s, 1H), 9.97 (s, 1H), 8.92 (s, 1H), 8.17 (d, 1H, $J = 5.1$ Hz), 8.04 (d, 1H, $J = 6.3$ Hz), 7.16-7.22 (m, 3H), 6.66 (d, 1H, $J = 8.4$ Hz), 6.34-6.43 (m, 1H), 6.06-6.12 (m, 1H), 5.55-5.60 (m, 1H), 4.02-4.04 (m, 1H), 3.85 (m, 1H), 3.09 (m, 3H), 2.75 (s, 3H), 1.99-2.21 (m, 6H), 1.76-1.86 (m, 8H), 1.55-1.58 (m, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 520.4$

46		¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆) δ: 10.07 (m, 1H), 8.78 (m, 1H), 8.16 (d, 1H, <i>J</i> = 7.2 Hz), 8.02 (d, 1H, <i>J</i> = 6.0 Hz), 7.75 (s, 1H), 7.28 (d, 1H, <i>J</i> = 8.7 Hz), 7.21 (d, 1H, <i>J</i> = 5.4 Hz), 6.86 (d, 1H, <i>J</i> = 9.0 Hz), 6.33-6.42 (m, 1H), 6.06-6.12 (m, 1H), 5.56-5.60 (m, 1H), 5.04 (m, 1H), 4.08 (m, 1H), 3.85 (m, 1H), 3.09 (m, 3H), 2.76 (s, 3H), 2.08-2.09 (m, 3H), 1.76-1.87 (m, 8H), 1.58 (m, 3H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 540.6
47		¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆) δ: 7.87 (d, 1H, <i>J</i> = 5.4 Hz), 7.59 (d, 1H, <i>J</i> = 13.8 Hz), 7.12 (d, 2H, <i>J</i> = 5.4 Hz), 6.85 (t, 1H, <i>J</i> = 9.3 Hz), 6.33 (m, 2H), 5.66 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 9.9 Hz), 4.23 (m, 1H), 4.02 (m, 1H), 3.35 (s, 1H), 3.26 (m, 2H), 3.05-3.65 (m, 3H), 2.30 (m, 2H), 1.73-1.94 (m, 10H), 1.40 (d, 6H, <i>J</i> = 6.9 Hz); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 552.5
48		¹ H-NMR (300 MHz, CD ₃ OD) δ: 7.91 (d, 1H, <i>J</i> = 5.4 Hz), 7.47 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 13.5 Hz), 7.12 (m, 2H), 6.85 (t, 1H, <i>J</i> = 9.0 Hz), 6.31 (m, 2H), 5.65 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 9.9 Hz), 4.46 (m, 1H), 4.21 (m, 1H), 3.97 (m, 2H), 3.34 (m, 2H), 3.23 (m, 1H), 2.85 (m, 1H), 2.27 (m, 1H), 2.12 (s, 3H), 2.08 (m, 2H), 1.92 (m, 4H), 1.72 (m, 4H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 552.5
49		¹ H-NMR (300 MHz, CD ₃ OD) δ: 8.00 (d, 1H, <i>J</i> = 5.4 Hz), 7.75 (dd, 1H, <i>J</i> = 2.4 Hz, <i>J</i> = 13.5 Hz), 7.21 (m, 3H), 6.20-6.41 (m, 2H), 5.66 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 9.9 Hz), 4.60 (s, 1H), 4.18 (s, 1H), 4.02 (s, 1H), 3.40 (m, 4H), 2.93 (t, 3H), 2.18 (m, 4H), 1.71-1.95 (m, 8H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 525.4
50		¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆) δ: 9.28 (s, 1H), 7.88-7.99 (m, 3H), 7.34 (d, 2H, <i>J</i> = 8.4 Hz), 7.15 (d, 1H, <i>J</i> = 5.4 Hz), 6.37 (dd, 1H, <i>J</i> = 10.2 Hz, <i>J</i> =

		Hz), 5.87-5.90 (m, 1H), 5.65 (dd, 1H, $J = 1.8$ Hz, $J = 10.8$ Hz), 5.36-5.39 (m, 1H), 4.05-4.30 (m, 2H), 3.93 (s, 3H), 1.68-2.00 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 425.3$
55		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.77 (d, 2H, $J = 5.4$ Hz), 7.31 (d, 1H, $J = 5.4$ Hz), 6.68 (d, 1H, $J = 9.9$ Hz), 6.31 (d, 1H, $J = 16.8$ Hz), 6.11 (dd, 1H, $J = 10.2$ Hz, $J = 17.1$ Hz), 5.59-5.74 (m, 2H), 4.23 (bs, 1H), 4.09 (bs, 1H), 3.75-3.90 (m, 4H), 3.05-3.25 (m, 4H), 2.78 (s, 3H), 1.60-2.10 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 493.4$
56		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 9.51 (s, 1H), 8.01 (s, 1H), 7.84-7.95 (m, 2H), 7.68-7.80 (m, 2H), 7.22 (d, 1H, $J = 5.4$ Hz), 6.30-6.43 (m, 2H), 5.67 (dd, 1H, $J = 2.1$ Hz, $J = 9.9$ Hz), 4.20-4.34 (m, 1H), 3.96-4.08 (m, 1H), 1.68-2.01 (m, 8H); LC-MS(ESI, m/z): $[M+H]^+ = 434.3$

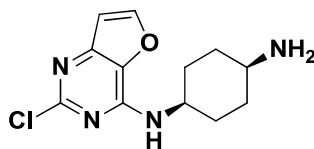
Example 57

Preparation of *N*-(*cis*-4-((2-(((1-methyl-1*H*-pyrazol-4-yl)amino)furo[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide



5

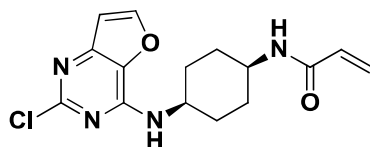
Step 1: preparation of *cis*-*N*¹-(2-chloro-furo[3,2-*d*]pyrimidin-4-yl)cyclohexyl-1,4-diamine



2,4-Dichloro-furo[3,2-*d*]pyrimidine (188 mg, 1 mmol) was dissolved in dichloromethane (5 mL), and dropwise added to a solution of *cis*-1,4-cyclohexanediamine (456 mg, 4.0 mmol) in dichloromethane (10 mL). The reaction solution was stirred at room temperature overnight, and then concentrated. The residue was added with water (20

mL), and extracted with ethyl acetate (20 mL $\times$ 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and was purified by silica gel column chromatography (eluent: n-hexane: ethyl acetate = 1 : 1), to give a pale yellow solid (140 mg). Yield: 52.6%. MS (ESI, m/z): $[M+H]^+$: 267.1; $^1\text{H-NMR}$ (300 MHz, CD_3OD): 8.01-8.00 (d, 1H, $J = 2.1$ Hz), 6.78-6.77 (d, 1H, $J = 2.1$ Hz), 4.24-2.22 (m, 1H), 3.07-3.03 (m, 1H), 1.91-1.66 (m, 8H).

Step 2: preparation of *N*-(*cis*-4-((2-chloro-furo[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide



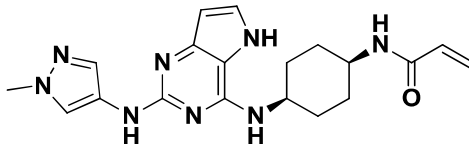
The product obtained in step 1 (120 mg, 0.45 mmol) and triethylamine (188 μL , 1.36 mmol) were dissolved in dichloromethane (20 mL), followed by the addition of acryloyl chloride (53 μL , 0.54 mmol). The reaction solution was reacted at room temperature overnight. After concentration, the residue was purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1), to give an orange solid (0.13 g). Yield: 90.3%. MS (ESI, m/z): $[M+H]^+$: 321.1; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$): 8.24-8.21 (d, 1H, $J = 6.3$ Hz), 7.99-7.97 (d, 1H, $J = 6.3$ Hz), 6.41-6.32 (dd, 2H, $J = 10.2$ Hz, $J = 17.1$ Hz), 5.68-5.64 (dd, 1H, $J = 2.4$ Hz, $J = 17.1$ Hz), 5.59-5.55 (dd, 1H, $J = 2.1$ Hz, $J = 10.2$ Hz), 4.11-4.09 (m, 1H), 3.09-3.05 (m, 1H), 1.81-1.61 (m, 8H).

Step 3: preparation of *N*-(*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)furo[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide

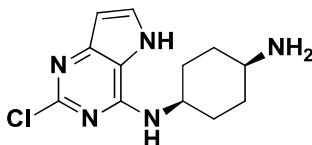
The product obtained in step 2 (25 mg, 0.078 mmol) and 1-methyl-1*H*-pyrazole-4-amine (8.4 mg, 0.086 mmol) were dissolved in isopropanol (2 mL), followed by the addition of trifluoroacetic acid (250 mg, 2.2 mmol). The reaction solution was reacted at 90°C under microwave irradiation for 1 hour. The reaction solution was cooled to room temperature, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1), to give a brown solid (10 mg). Yield: 33.7%. MS (ESI, m/z): $[M+H]^+$: 382.2; $^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.94-7.93 (d, 1H, $J = 2.1$ Hz), 7.86 (s, 1H), 7.60 (s, 1H), 6.76-6.75 (d, 1H, $J = 2.1$ Hz), 6.44-6.35 (t, 1H, $J = 10.2$ Hz, $J = 17.1$ Hz), 6.26-6.20 (dd, 1H, $J = 2.1$ Hz, $J = 17.1$ Hz), 5.67-5.63 (dd, 1H, $J = 2.1$ Hz, $J = 10.2$ Hz), 4.23-4.21 (m, 1H), 4.02-4.01 (m, 1H), 3.90 (s, 3H), 1.90-1.74 (m, 8H).

Example 58

Preparation of *N*-(*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide

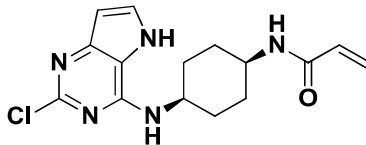


- 5 Step 1: preparation of *cis*-*N*¹-(2-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)cyclohexyl-1,4-diamine



- 2,4-Dichloro-pyrrolo[3,2-*d*]pyrimidine (187 mg, 1 mmol) was dissolved in dichloromethane (5 mL), and then added dropwise to a solution of *cis*-1,4-cyclohexanediamine (456 mg, 4.0 mmol) in dichloromethane (10 mL). The reaction solution was stirred at room temperature overnight, and then concentrated. The residue was added with water (20 mL), and extracted with ethyl acetate (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: *n*-hexane: ethyl acetate = 1 : 1), to give a pale yellow solid (150 mg). Yield: 56.6%. MS (ESI, *m/z*): [M+H]⁺: 266.1; ¹H-NMR (300 MHz, CD₃OD): 7.41-7.40 (d, 1H, *J* = 3.0 Hz), 6.62-8.61 (d, 1H, *J* = 3.0 Hz), 4.31 (s, 1H), 3.09 (s, 1H), 2.01-1.70 (m, 8H).

Step 2: preparation of *N*-(*cis*-4-((2-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide



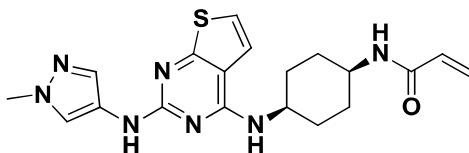
- 20 The product obtained in step 1 (120 mg, 0.45 mmol) and triethylamine (188 μL, 1.36 mmol) were dissolved in dichloromethane (20 mL), followed by the addition of acryloyl chloride (53 μL, 0.54 mmol). The reaction solution was reacted at room temperature overnight. After concentration, the residue was purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1), to give a pale yellow solid (0.1 g). Yield: 69.7%. MS (ESI, *m/z*): [M+H]⁺: 320.1; ¹H-NMR (300 MHz, CDCl₃): 7.40-7.38 (d, 1H, *J* = 7.8 Hz), 7.29-7.21 (m, 1H), 6.73-6.70 (d, 1H, *J* = 7.8 Hz), 6.24-6.20 (m, 1H), 5.57-5.53 (m, 1H), 4.41 (s, 1H), 3.97 (s, 1H), 1.84-1.72 (m, 8H).

Step 3: preparation of *N*-(*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide

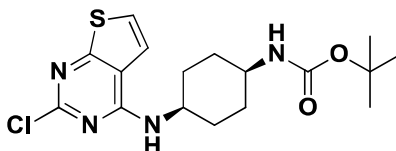
The product obtained in step 2 (25 mg, 0.078 mmol) and 1-methyl-1*H*-pyrazole-4-amine (8.4 mg, 0.086 mmol) were dissolved in isopropanol (2 mL), followed by the addition of trifluoroacetic acid (250 mg, 2.2 mmol). The reaction solution was reacted at 90°C under microwave irradiation for 1 hour. The reaction solution was cooled to room temperature, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10: 1), to give a brown solid (12 mg). Yield: 40.5%. MS (ESI, *m/z*): [M+H]⁺: 381.2; ¹H-NMR (300 MHz, CD₃OD) δ: 7.86 (s, 1H), 7.64 (s, 1H), 7.43 (s, 1H), 6.43-6.34 (m, 1H), 6.29-6.21 (m, 1H), 5.69-5.65 (m, 1H), 4.46-4.35 (m, 1H), 4.01-4.95 (m, 1H), 3.94 (s, 3H), 1.99-1.61 (m, 8H).

Example 59

Preparation of *N*-(*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)-thieno[2,3-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide



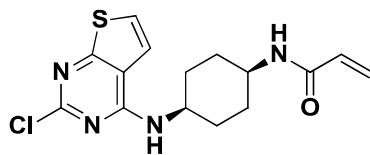
Step 1: preparation of *tert*-butyl (*cis*-4-((2-chloro-thieno[2,3-*d*]pyrimidin-4-yl)amino)cyclohexyl)carbamate



2,4-Dichloro-thieno[2,3-*d*]pyrimidine (204 mg, 1 mmol) and *tert*-butyl *cis*-4-amino-cyclohexyl carbamate (215 mg, 1 mmol) were dissolved in tetrahydrofuran (10 mL), followed by the addition of *N,N*-diisopropylethylamine (0.4 mL, 2 mmol). The reaction solution was reacted at 70°C overnight, and then concentrated. The residue was added with water (20 mL), and extracted with ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: *n*-hexane: ethyl acetate = 1 : 5) to give a pale yellow solid (150 mg). Yield: 56.6 %. MS (ESI, *m/z*): [M+H]⁺: 383.1; ¹H-NMR (300 MHz, DMSO-*d*₆): 7.74-7.72 (d, 1H, *J* = 6.0 Hz), 7.58-7.56 (d, 1H, *J* = 6.0 Hz), 4.03 (s, 1H), 3.46 (m, 1H), 1.81-1.55 (m, 8H), 1.40 (s, 9H).

Step 2: preparation of *N*-(*cis*-4-((2-chloro-thieno[2,3-*d*]pyrimidin-4-yl)amino)

cyclohexyl)acrylamide



The product obtained in step 1 (50 mg, 0.13 mmol) was dissolved in methanol (2 mL), followed by the addition of 4N solution of hydrogen chloride in 1,4-dioxane (4 mL, 1 mmol). The reaction solution was reacted at room temperature for 2 hours. The reaction solution was concentrated, and the remaining viscous liquid was dissolved in dichloromethane (5 mL) followed by the addition of triethylamine (54 μ L, 0.39 mmol). To the above solution acryloyl chloride (14 μ L, 0.14 mmol) was added dropwise at 0°C. The reaction solution was reacted at room temperature overnight. The reaction solution was washed with water (10 mL), and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 8 : 1) to give a white solid (40 mg). Yield: 91.5 %. MS (ESI, m/z): $[M+H]^+$: 337.1; $^1\text{H-NMR}$ (300 MHz, DMSO- d_6): 7.75-7.73 (d, 1H, J = 6.0 Hz), 7.57-7.55 (d, 1H, J = 6.0 Hz), 6.38-6.29 (dd, 1H, J = 10.2 Hz, J = 17.1 Hz), 6.11-6.04 (dd, 1H, J = 2.4 Hz, J = 17.1 Hz), 5.57-5.53 (dd, 1H, J = 2.1 Hz, J = 10.2 Hz), 4.05-4.03 (m, 1H), 3.09-3.05 (m, 1H), 1.97-1.61 (m, 8H).

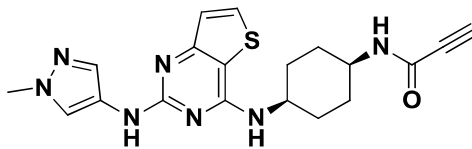
Step 3: preparation of *N*-(*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[2,3-*d*]pyrimidin-4-yl)amino)cyclohexyl)acrylamide

The product obtained in step 2 (25 mg, 0.078 mmol) and 1-methyl-1*H*-pyrazole-4-amine (8.4 mg, 0.086 mmol) were dissolved in isopropanol (2 mL), followed by the addition of trifluoroacetic acid (250 mg, 2.2 mmol). The reaction solution was reacted at 90°C under microwave irradiation for 1 hour. The reaction solution was cooled to room temperature, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1) to give a brown solid (10 mg). Yield: 33.7 %. MS (ESI, m/z): $[M+H]^+$: 398.3; $^1\text{H-NMR}$ (300 MHz, DMSO- d_6) δ : 10.51 (s, 1H), 9.08 (s, 1H), 8.20 (d, 1H, J = 5.1 Hz), 8.02 (d, 1H, J = 6.0 Hz), 7.87 (s, 1H), 7.57 (s, 1H), 7.21 (d, 1H, J = 5.4 Hz), 6.32-8.41 (m, 1H), 6.07 (dd, 1H, J = 2.1 Hz, J = 17.1 Hz), 5.57 (dd, 1H, J = 2.4 Hz, J = 9.9 Hz), 4.14 (d, 1H, J = 5.4 Hz), 3.84 (s, 3H), 1.25-1.64 (m, 8H).

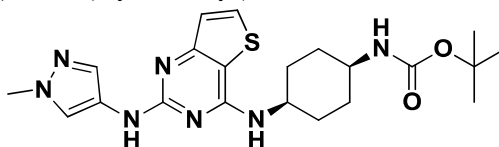
Example 60

Preparation of *N*-(*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[3,2-*d*]

pyrimidin-4-yl)amino)cyclohexyl)propynamide



Step 1: preparation of *tert*-butyl (*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)carbamate

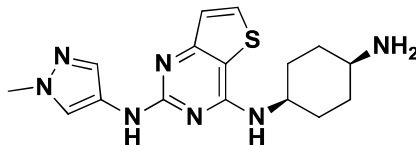


5

The product obtained in step 1 of Example 1 (120 mg, 0.31 mmol) and 1-methyl-1*H*-pyrazole-4-amine (52 mg, 0.62 mmol) were suspended in isopropanol (2 mL), followed by the addition of two drops of trifluoroacetic acid. The mixture was reacted for 25 minutes under microwave at a temperature of 90°C. To the system was added a saturated sodium carbonate solution, and the pH of the reaction solution was adjusted to about 8. The reaction mixture was concentrated, and purified by silica gel column chromatography (eluent: dichloromethane: methanol = 20 : 1) to give a yellow solid (120 mg). Yield: 87.4%. MS (ESI, *m/z*): [M+H]⁺: 444.3.

Step 2: preparation of *N*⁴-(*cis*-4-aminocyclohexyl)-*N*²-(1-methyl-1*H*-pyrazol-4-yl)thieno[3,2-*d*]pyrimidine-2,4-diamine

15



The product obtained in the above step 1 (120 mg, 0.27 mmol) was dissolved in dichloromethane (10 mL), followed by the dropwise addition of 4*N* solution of hydrogen chloride in 1,4-dioxane (675 μ L, 2.7 mmol). The reaction solution was reacted at room temperature for 2 hours. The reaction solution was concentrated, and the resulting crude product was used directly in the next step without further purification. MS (ESI, *m/z*): [M+H]⁺: 344.2.

20

Step 3: preparation of *N*-(*cis*-4-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)cyclohexyl)propynamide

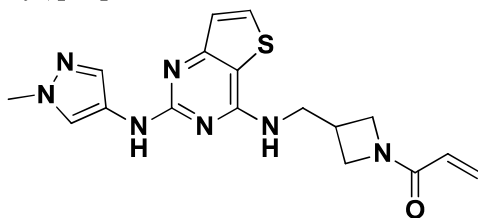
25

The product obtained in step 2 (38 mg, 0.10 mmol) and propiolic acid (8.4 mg, 0.12 mmol) were dissolved in tetrahydrofuran (10 mL), followed by the addition of *N,N*-diisopropylethylamine (53 μ L). The mixture was stirred at room temperature for 30 minutes, followed by the addition of TBTU (4 mg). The mixture was stirred at room

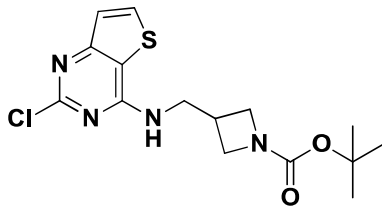
temperature overnight, concentrated, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1) to give a pale yellow solid (2.45 mg). Yield: 6.2%. MS (ESI, m/z): $[M+H]^+$: 396.2; $^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.93 (d, 1H, J = 5.4 Hz), 7.85 (s, 1H), 7.61 (s, 1H), 7.16 (d, 1H, J = 5.4 Hz), 3.91 (s, 3H), 3.54-3.61 (m, 2H), 1.74-2.01 (m, 8H).

Example 61

Preparation of 1-(3-(((2-((1-methyl-1H-pyrazol-4-yl)amino)thieno[3,2- d]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one

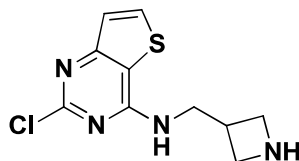


Step 1: preparation of *tert*-butyl 3-(((2-chloro-thieno[3,2- d]pyrimidin-4-yl)amino)methyl)azetidine-1-carboxylate



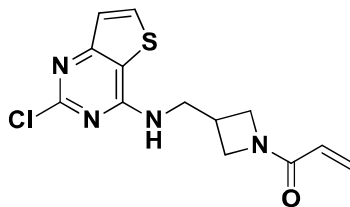
2,4-Dichloro-thieno[3,2- d]pyrimidine (205 mg, 1 mmol) and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate (186 mg, 1 mmol) were dissolved in tetrahydrofuran (5 mL), followed by the addition of *N,N*-diisopropylethylamine (258 mg, 2 mmol). The reaction solution was reacted at 70°C overnight, and then concentrated. The residue was added with water (20 mL), and extracted with ethyl acetate (10 mL $\times$ 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: *n*-hexane: ethyl acetate = 5 : 1) to give a white solid (340 mg). Yield: 96.0%. MS (ESI, m/z): $[M+H]^+$: 355.1; $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.76 (d, 1H, J = 5.4 Hz), 7.37 (d, 1H, J = 5.4 Hz), 5.49 (s, 1H), 4.05-4.09 (m, 2H), 3.87-3.91 (m, 2H), 3.71-3.75 (m, 2H), 2.94 (m, 1H), 1.44 (s, 9H).

Step 2: preparation of *N*-(azetidin-3-ylmethyl)-2-chloro-thieno[3,2- d]pyrimidine-4-amine



The product obtained in step 1 (340 mg, 0.96 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of 4N solution of hydrogen chloride in 1,4-dioxane (2.5 mL, 10 mmol). The reaction solution was reacted at room temperature for 2 hours. The reaction solution was concentrated, and the resulting crude product was used directly in the next step without further purification. MS (ESI, m/z): [M+H]⁺: 254.9.

Step 3: preparation of 1-(3-(((2-chloro-thieno[3,2-d]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one



The product obtained in step 2 (1.22 g, 4.80 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (0.969 g, 9.60 mmol). A solution of acryloyl chloride (0.434 g, 4.80 mmol) dissolved in dichloromethane (5 mL) was added dropwise to the above solution at 0°C. The reaction solution reacted at room temperature overnight. The reaction solution was washed with water (10 mL), and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 70 : 1), to give a white solid (1.00 g). Yield: 67.6%. [M+H]⁺: 309.0; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.50-8.53 (m, 1H), 8.19 (d, 1H, *J* = 5.1 Hz), 7.35 (d, 1H, *J* = 5.4 Hz), 6.25-6.34 (m, 1H), 6.05-6.12 (m, 1H), 5.63-5.68 (m, 1H), 4.27-4.33 (m, 1H), 3.97-4.03 (m, 2H), 3.67-3.75 (m, 3H), 2.89-2.98 (m, 1H).

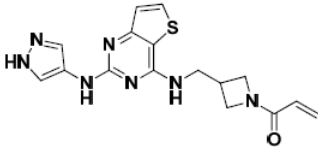
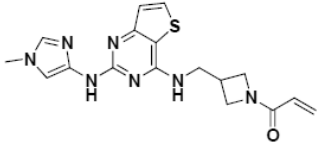
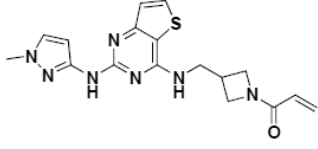
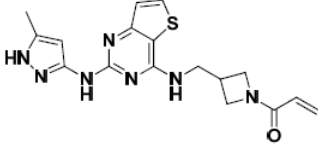
Step 4: preparation of 1-(3-(((2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one

The product obtained in step 3 (50 mg, 0.162 mmol) and 1-methyl-1*H*-pyrazole-4-amine (23 mg, 0.244 mmol) were dissolved in 1,4-dioxane (2 mL). The pH of the reaction solution was adjusted to 5 with trifluoroacetic acid. The reaction solution was reacted at 90°C under microwave irradiation for 0.5 hours. The reaction solution was cooled to room temperature, adjusted with 1N sodium hydroxide solution to pH 8, and extracted with ethyl acetate (10 mL × 3). The organic phase was

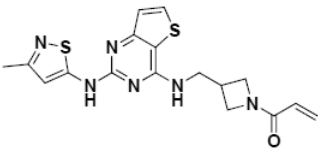
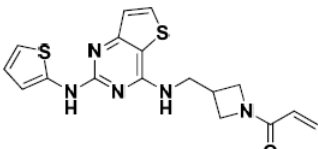
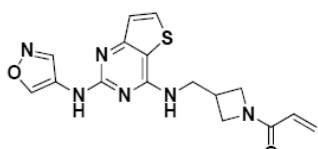
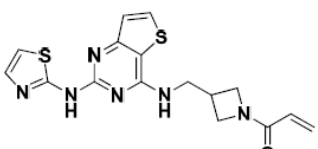
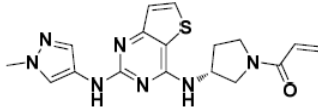
dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1) to give a yellow solid (15 mg). Yield: 25.4%. MS (ESI, m/z): $[M+H]^+$: 370.2; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 7.83 (s, 1H), 7.60 (d, 1H, $J = 5.4$ Hz), 7.52 (s, 1H), 7.18 (d, 1H, $J = 5.4$ Hz), 7.12 (s, 1H), 6.31-6.37 (m, 1H), 6.13-6.22 (m, 1H), 5.65-5.69 (m, 1H), 5.53 (s, 1H), 4.01-4.35 (m, 3H), 3.81-3.93 (m, 6H), 3.07 (m, 1H).

The following compounds (in Table 2) were prepared from similar starting materials by similar synthetic methods to those described in Example 61.

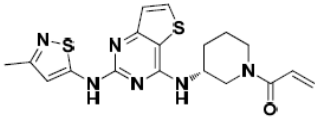
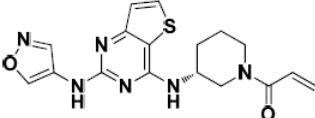
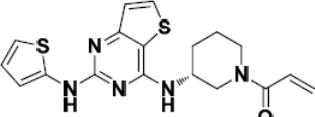
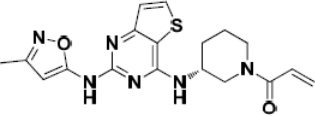
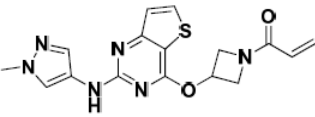
Table 2

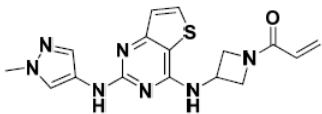
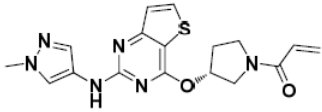
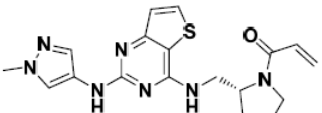
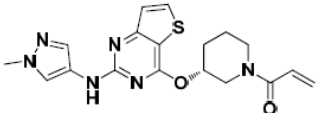
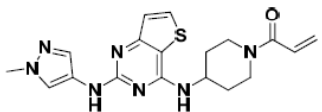
Example	Structure	Characterization data
62		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.83 (m, 3H), 7.13 (d, 1H, $J = 5.4$ Hz), 6.27 (m, 2H), 5.73 (dd, 1H, $J = 2.4$ Hz, $J = 9.9$ Hz), 4.41 (t, 1H, $J = 9.0$ Hz), 4.16 (m, 2H), 3.85-3.95 (m, 3H), 3.18-3.20 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 356.3$
63		$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 8.54 (s, 1H), 8.11 (d, 1H, $J = 5.4$ Hz), 8.02 (s, 1H), 7.60 (s, 1H), 6.94 (s, 1H), 6.27-6.36 (m, 2H), 6.08 (dd, 1H, $J = 2.4$ Hz, $J = 16.8$ Hz), 5.65 (dd, 1H, $J = 2.1$ Hz, $J = 10.2$ Hz), 4.30 (t, 1H, $J = 8.4$ Hz), 3.99-4.06 (m, 2H), 3.63-3.83 (m, 3H), 3.05-3.14 (m, 1H), 1.99 (s, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 370.2$
64		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.16 (d, 1H, $J = 5.4$ Hz), 7.81 (d, 1H, $J = 2.4$ Hz), 7.44 (d, 1H, $J = 5.4$ Hz), 6.21-6.27 (m, 1H), 6.08-6.14 (m, 1H), 5.97 (d, 1H, $J = 2.4$ Hz), 5.61-5.65 (m, 1H), 4.34-4.38 (m, 1H), 4.04-4.12 (m, 2H), 3.91 (s, 3H), 3.74-3.90 (m, 3H), 3.02-3.12 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 370.2$
65		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.87 (d, 1H, $J = 5.4$ Hz), 7.14 (d, 1H, $J = 5.1$ Hz), 6.29 (m, 2H), 6.10 (s, 1H), 5.73 (dd, 1H, $J = 2.4$ Hz, $J = 9.6$ Hz), 4.40 (t, 1H, $J = 8.7$ Hz), 4.16 (m, 2H), 3.88 (m, 3H),

		3.13 (m, 1H), 2.27 (s, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 370.2$
66		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.66 (d, 1H, $J = 5.4$ Hz), 7.45 (d, 1H, $J = 1.8$ Hz), 7.18 (d, 1H, $J = 5.1$ Hz), 7.11 (s, 1H), 6.29-6.38 (m, 2H), 6.13-6.22 (m, 1H), 5.66-5.70 (m, 1H), 5.54-5.55 (m, 1H), 4.13-4.31 (m, 2H), 3.68-3.97 (m, 7H), 2.98-3.03 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 370.2$
67		$^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 8.74 (m, 1H), 7.81-8.40 (m, 2H), 7.43-7.80 (m, 1H), 7.01-7.35 (m, 1H), 6.26-6.35 (m, 1H), 6.05-6.12 (m, 1H), 5.63-5.67 (m, 1H), 4.29 (m, 1H), 4.00-4.04 (m, 2H), 3.70-3.80 (m, 6H), 2.98-3.01 (m, 1H), 2.24-2.27 (m, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 384.3$
68		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.38 (bs, 1H), 7.88 (d, 1H, $J = 5.4$ Hz), 7.32 (s, 1H), 7.13 (d, 1H, $J = 5.4$ Hz), 6.21-6.40 (m, 2H), 5.74 (dd, 1H, $J = 2.4$ Hz, $J = 9.9$ Hz), 4.37-4.42 (m, 1H), 4.07-4.16 (m, 2H), 3.77-3.90 (m, 3H), 3.74 (s, 3H), 3.06-3.10 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 370.2$
69		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.88 (d, 1H, $J = 5.4$ Hz), 7.21 (d, 1H, $J = 5.1$ Hz), 6.20-6.38 (m, 3H), 5.72 (dd, 1H, $J = 2.4$ Hz, $J = 9.6$ Hz), 4.40 (t, 1H, $J = 8.7$ Hz), 4.10-4.20 (m, 2H), 3.83-3.96 (m, 2H), 3.03-3.23 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 371.2$
70		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.89 (d, 1H, $J = 5.4$ Hz), 7.23 (d, 1H, $J = 5.4$ Hz), 6.20-6.39 (m, 3H), 5.73 (dd, 1H, $J = 2.4$ Hz, $J = 9.9$ Hz), 4.41 (t, 1H, $J = 8.7$ Hz), 4.08-4.15 (m, 2H), 3.86-3.95 (m, 3H), 2.97-2.01 (m, 1H), 3.13-3.15 (m, 1H), 2.03

		(s, 6H); LC-MS(ESI, m/z): $[M+H]^+ = 399.3$
71		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.91 (d, 1H, $J = 5.4$ Hz), 7.23 (d, 1H, $J = 5.1$ Hz), 6.63 (s, 1H), 6.21-6.37 (m, 1H), 5.71-5.75 (m, 1H), 4.42-4.45 (m, 1H), 4.17-4.21 (m, 2H), 3.93-3.99 (m, 3H), 3.18-3.25 (m, 1H), 2.36 (s, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 387.3$
72		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.85 (d, 1H, $J = 5.4$ Hz), 7.13 (d, 1H, $J = 5.4$ Hz), 6.75-6.84 (m, 2H), 6.63-6.65 (m, 1H), 6.17-6.36 (m, 2H), 5.70 (dd, 1H, $J = 2.4$ Hz, $J = 9.6$ Hz), 4.40 (t, 1H, $J = 8.7$ Hz), 4.04-4.22 (m, 3H), 3.91-3.97 (m, 2H), 3.08-3.28 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 372.2$
73		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 9.04 (s, 1H), 8.54 (s, 1H), 7.83 (d, 1H, $J = 5.4$ Hz), 7.17 (d, 1H, $J = 5.4$ Hz), 6.20-6.38 (m, 2H), 5.73 (dd, 1H, $J = 2.4$ Hz, $J = 9.9$ Hz), 4.41 (t, 1H, $J = 8.7$ Hz), 4.10-4.17 (m, 2H), 3.84-3.95 (m, 3H), 3.03-3.23 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 357.1$
74		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.91 (d, 1H, $J = 5.4$ Hz), 7.33-7.36 (m, 2H), 6.99 (d, 1H, $J = 3.6$ Hz), 6.16-6.34 (m, 2H), 5.68 (dd, 1H, $J = 2.4$ Hz, $J = 9.6$ Hz), 4.38 (t, 1H, $J = 8.7$ Hz), 4.05-4.17 (m, 2H), 3.88-3.92 (m, 3H), 3.05-3.14 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 373.2$
75		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.61-7.81 (m, 3H), 7.21 (d, 1H, $J = 5.4$ Hz), 6.39-6.64 (m, 2H), 5.69-5.78 (m, 1H), 3.61-3.99 (m, 8H), 2.10-2.45 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 370.2$

76		¹ H-NMR (300 MHz, CD ₃ OD) δ: 7.84-7.86 (m, 1H), 7.12-7.15 (m, 1H), 6.83-6.86 (m, 1H), 6.77-6.80 (m, 1H), 6.55-6.73 (m, 2H), 6.26-6.35 (m, 1H), 5.72-5.81 (m, 1H), 5.07-5.11 (m, 1H), 3.99-4.23 (m, 1H), 3.62-3.92 (m, 4H), 2.16-2.53 (m, 2H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 372.2
77		¹ H-NMR (300 MHz, CD ₃ OD) δ: 7.98 (m, 1H), 7.85 (s, 2H), 7.18 (d, 1H, <i>J</i> = 12.3 Hz), 6.55-6.72 (m, 1H), 6.26-6.34 (m, 1H), 5.77 (td, 1H, <i>J</i> = 1.8 Hz, <i>J</i> = 10.2 Hz), 3.53-3.99 (m, 5H), 2.19-2.47 (m, 2H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 356.2
78		¹ H-NMR (300 MHz, CD ₃ OD) δ: 9.07 (s, 1H), 8.56 (s, 1H), 7.85 (dd, 1H, <i>J</i> = 0.9 Hz, <i>J</i> = 5.4 Hz), 7.18 (dd, 1H, <i>J</i> = 1.8 Hz, <i>J</i> = 5.4 Hz), 6.56-6.72 (m, 1H), 6.26-6.34 (m, 1H), 5.73-5.81 (m, 1H), 3.57-4.01 (m, 5H), 2.12-2.52 (m, 2H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 357.1
79		¹ H-NMR (300 MHz, CD ₃ OD) δ: 7.89 (dd, 1H, <i>J</i> = 1.5 Hz, <i>J</i> = 5.4 Hz), 7.22 (dd, 1H, <i>J</i> = 2.1 Hz, <i>J</i> = 5.1 Hz), 6.57-6.72 (m, 1H), 6.27-6.34 (m, 2H), 5.73-5.81 (m, 1H), 3.61-4.15 (m, 5H), 2.16-2.47 (m, 4H), 2.26 (s, 3H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 371.2
80		¹ H-NMR (300 MHz, CDCl ₃) δ: 7.78 (s, 1H), 7.56-7.67 (m, 2H), 7.21 (d, 1H, <i>J</i> = 5.4 Hz), 6.28-6.69 (m, 2H), 5.55-5.82 (m, 1H), 4.34 (bs, 1H), 4.00-4.12 (m, 1H), 3.88 (s, 3H), 3.30-3.80 (m, 3H), 1.60-2.20 (m, 4H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 384.3
81		¹ H-NMR (300 MHz, CD ₃ OD) δ: 7.90 (s, 1H), 7.81 (s, 2H), 7.15 (m, 1H), 6.52-6.88 (m, 1H), 6.08-6.29 (m, 1H), 5.54-5.82 (m, 1H), 4.80 (m,

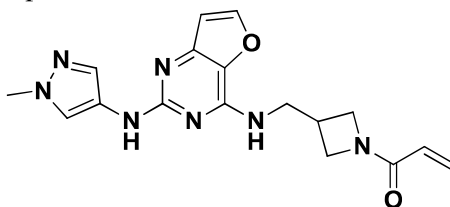
		1H), 4.66 (m, 1H), 4.15-4.40 (m, 2H), 3.15 (m, 1H), 3.87 (m, 1H), 2.52 (m, 1H), 2.22 (m, 1H), 1.95 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 370.2$
82		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.82 (d, 1H, $J = 4.5$ Hz), 7.15 (s, 1H), 6.54-6.80 (m, 2H), 6.06-6.27 (m, 1H), 5.53-5.76 (m, 1H), 4.77 (m, 1H), 4.05-4.46 (m, 2H), 3.10 (m, 1H), 2.84 (m, 1H), 2.31 (s, 3H), 2.22 (s, 1H), 1.66-2.00 (m, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 401.3$
83		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 9.02 (d, 1H, $J = 6.9$ Hz), 8.54 (d, 1H, $J = 6.6$ Hz), 7.82 (d, 1H, $J = 5.1$ Hz), 7.15 (d, 1H, $J = 5.1$ Hz), 6.72 (m, 1H), 6.20 (dd, 1H, $J = 15.6$ Hz, $J = 46.5$ Hz), 5.68 (dd, 1H, $J = 10.8$ Hz, $J = 69.3$ Hz), 4.05-4.29 (m, 3H), 3.08-3.36 (m, 2H), 2.17 (m, 1H), 1.93 (d, 1H, $J = 12.6$ Hz), 1.79 (t, 1H, $J = 12.0$ Hz), 1.61 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 371.2$
84		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.65 (d, 1H, $J = 5.4$ Hz), 7.19 (d, 1H, $J = 5.4$ Hz), 6.84-6.87 (m, 1H), 6.75-6.77 (m, 1H), 6.59 (bs, 1H), 6.18-6.49 (m, 1H), 5.65-5.85 (m, 1H), 5.49-5.52 (m, 1H), 4.57 (bs, 1H), 3.83-4.03 (m, 2H), 3.68-3.79 (m, 1H), 3.47-3.60 (m, 2H), 2.00-2.25 (m, 2H), 1.70-1.89 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 386.2$
85		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.86-7.89 (m, 1H), 7.35-7.40 (m, 1H), 7.21 (d, 1H, $J = 5.1$ Hz), 6.63-6.90 (m, 1H), 6.11-6.30 (m, 1H), 5.56-5.82 (m, 1H), 3.61-4.15 (m, 5H), 2.16-2.47 (m, 4H), 2.23 (s, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 385.2$
86		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.72-7.74 (m, 2H), 7.48 (m, 1H), 7.17 (s, 1H), 6.31 (dd, 1H, $J =$

		<p>1.8 Hz, $J = 16.8$ Hz), 6.13 (dd, 1H, $J = 10.2$ Hz, $J = 17.1$ Hz), 5.65 (dd, 1H, $J = 1.8$ Hz, $J = 10.2$ Hz), 5.50-5.53 (m, 1H), 4.56-4.62 (m, 1H), 4.43-4.49 (m, 1H), 4.26-4.31 (m, 1H), 4.16-4.21 (m, 1H), 3.85 (s, 3H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 357.2$</p>
87		<p>$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ: 7.86 (s, 1H), 7.78 (d, 1H, $J = 5.4$ Hz), 7.57 (s, 1H), 7.11 (d, 1H, $J = 5.4$ Hz), 6.22-6.39 (m, 2H), 5.71-5.76 (m, 1H), 4.48-4.98 (m, 1H), 4.63-4.69 (m, 1H), 4.41-4.47 (m, 1H), 4.21-4.26 (m, 1H), 4.06-4.11 (m, 1H), 3.87 (s, 3H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 356.2$</p>
88		<p>$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ: 7.80 (bs, 1H), 7.65-7.69 (m, 1H), 7.47 (s, 1H), 7.14-7.16 (m, 1H), 6.94 (bs, 1H), 6.32-6.43 (m, 2H), 5.61-5.76 (m, 2H), 3.63-3.91 (m, 8H), 2.24-2.36 (m, 2H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 371.2$</p>
89		<p>$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ: 8.09 (s, 1H), 7.76 (s, 1H), 7.64 (d, 1H, $J = 5.1$ Hz), 7.18 (d, 1H, $J = 5.4$ Hz), 6.48 (d, 2H, $J = 6.3$ Hz), 5.78 (d, 1H, $J = 6.0$ Hz), 4.63-4.69 (m, 1H), 3.89 (s, 3H), 3.54-3.83 (m, 4H), 2.02-2.14 (m, 3H), 1.86-1.90 (m, 1H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 384.3$</p>
90		<p>$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ: 7.89 (m, 2H), 7.54 (d, 1H, $J = 6.0$ Hz), 7.16 (m, 1H), 6.46-6.84 (m, 1H), 5.99-6.20 (m, 1H), 5.44-5.76 (m, 1H), 5.34 (m, 1H), 4.10 (m, 1H), 3.88 (m, 4H), 3.70 (m, 1H), 3.20-3.34 (m, 1H), 1.84-2.16 (m, 3H), 1.65 (m, 1H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 385.2$</p>
91		<p>$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ: 7.74 (s, 1H), 7.54 (d, 1H, $J = 5.4$ Hz), 7.47 (s, 1H), 7.12 (d, 1H, $J =$</p>

		5.4 Hz), 6.54 (dd, 1H, $J = 10.5$ Hz, $J = 16.8$ Hz), 6.24 (dd, 1H, $J = 1.8$ Hz, $J = 16.8$ Hz), 5.65 (dd, 1H, $J = 1.8$ Hz, $J = 10.5$ Hz), 4.60-4.80 (m, 2H), 4.29-4.35 (m, 1H), 3.97-4.04 (m, 1H), 3.15-3.25 (m, 1H), 2.70-2.90 (m, 2H), 2.11-2.21 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 384.3$
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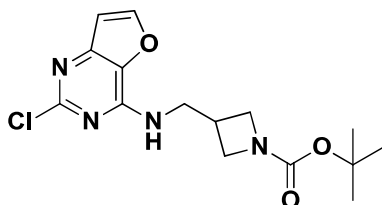
Example 92

Preparation of 1-(3-(((2-((1-methyl-1*H*-pyrazol-4-yl)amino)furo[3,2-*d*]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one



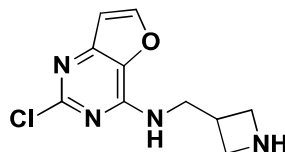
5

Step 1: preparation of *tert*-butyl 3-(((2-chloro-furo[3,2-*d*]pyrimidin-4-yl)amino)methyl)azetidine-1-carboxylate



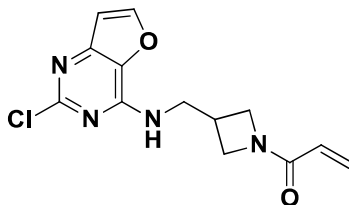
2,4-Dichloro-furo[3,2-*d*]pyrimidine (189 mg, 1 mmol) and *tert*-butyl 3-
 10 (aminomethyl)azetidine-1-carboxylate (186 mg, 1 mmol) were dissolved in tetrahydrofuran (20 mL), followed by the addition of *N,N*-diisopropylethylamine (258 mg, 2 mmol). The reaction solution was reacted under reflux overnight, then cooled to room temperature, and concentrated. The residue was added with water (20 mL), and extracted with ethyl acetate (10 mL $\times$ 3). The organic phase was dried over anhydrous sodium
 15 sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: n-hexane: ethyl acetate = 6 : 1), to give a white solid (283 mg). Yield: 83.5%. MS (ESI, m/z): $[M+H]^+ : 339.1$.

Step 2: preparation of *N*-(azetidin-3-ylmethyl)-2-chloro-furo[3,2-*d*]pyrimidine-4-amine



5 The compound obtained in step 1 (283 mg, 0.84 mmol) was dissolved in dichloromethane (2 mL), followed by the slow and dropwise addition of a solution of trifluoroacetic acid (1.43 g, 12.5 mmol) in methylene chloride (1 mL) in an ice bath. The reaction solution was reacted at room temperature for 1 hour, and then concentrated. The resulting crude product was used directly in the next step without further purification. MS (ESI, m/z): [M+H]⁺: 238.9.

Step 3: preparation of 1-(3-(((2-chloro-furo[3,2-d]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one



10

The product obtained in step 2 (0.84 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (254 mg, 2.51 mmol). A solution of acryloyl chloride (83.1 mg, 0.92 mmol) dissolved in dichloromethane (5 mL) was dropwise added to the above solution in an ice-bath. The reaction solution was reacted at room temperature overnight. The reaction solution was washed with water (10 mL), and the organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 70 : 1), to give a white solid (176 mg). Yield: 72.0%. MS (ESI, m/z): [M+H]⁺: 293.0.

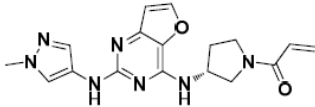
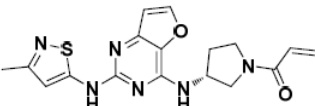
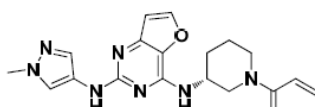
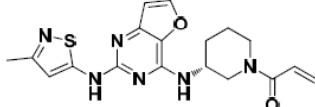
20 Step 4: preparation of 1-(3-(((2-((1-methyl-1H-pyrazol-4-yl)amino)furo[3,2-d]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one

The compound obtained in step 3 (29.3 mg, 0.1 mmol) and 1-methyl-1H-pyrazole-4-amine (14.6 mg, 0.15 mmol) were dissolved in isopropanol (2 mL). The reaction solution was adjusted to pH 5 with trifluoroacetic acid, and reacted at 90°C under microwave irradiation for 0.5 hours. The reaction solution was cooled to room temperature, adjusted with 1N sodium hydroxide solution to pH 8, and extracted with ethyl acetate (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1) to give a yellow solid (15.5

mg). Yield: 43.9%. MS (ESI, m/z): $[M+H]^+$: 354.2; $^1\text{H-NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ : 7.80 (s, 1H), 7.61 (d, 1H, $J = 2.1$ Hz), 7.49 (s, 1H), 7.04 (s, 1H), 6.66 (d, 1H, $J = 1.8$ Hz), 6.33 (dd, 1H, $J = 1.8$ Hz, $J = 17.1$ Hz), 6.12-6.21 (m, 1H), 5.67 (dd, 1H, $J = 2.1$ Hz, $J = 10.2$ Hz), 4.00-4.35 (m, 3H), 3.87 (s, 3H), 3.79-3.92 (m, 3H), 3.01-3.06 (m, 1H).

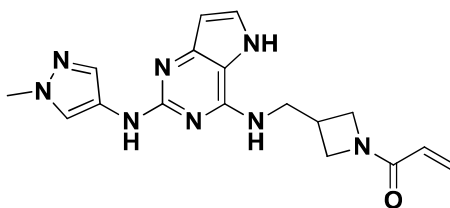
5 The following compounds (in Table 3) were prepared from similar starting materials by similar synthetic methods to those described in Example 92.

Table 3

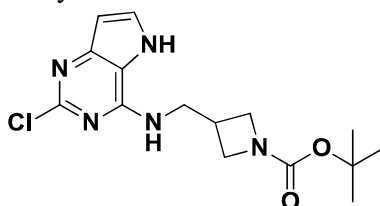
Example	Structure	Characterization data
93		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.83-7.87 (m, 2H), 7.55-7.57 (m, 1H), 6.54-6.71 (m, 2H), 6.26-6.34 (m, 1H), 5.73-5.80 (m, 1H), 3.88 (s, 1H), 3.57-4.01 (m, 5H), 2.12-2.44 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 354.3$
94		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.89 (s, 1H), 6.54-6.72 (m, 3H), 6.26-6.33 (m, 1H), 5.71-5.80 (m, 1H), 3.97-4.19 (m, 1H), 3.59-3.1 (m, 4H), 2.14-2.53 (m, 2H), 2.34 (s, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 371.2$
95		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.83-7.91 (m, 2H), 7.50 (d, 1H, $J = 11.4$ Hz), 6.50-6.89 (m, 2H), 6.08-6.29 (m, 1H), 5.52-5.81 (m, 1H), 4.05-4.21 (m, 2H), 3.78-3.89 (m, 1H), 3.84 (s, 3H), 2.77-3.36 (m, 2H), 2.14-2.20 (m, 1H), 1.90-1.97 (m, 1H), 1.59-1.82 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 368.2$
96		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.88 (d, 1H, $J = 4.2$ Hz), 6.56-6.68 (m, 3H), 6.07-6.27 (m, 1H), 5.50-5.57 (m, 1H), 4.02-4.71 (m, 3H), 2.88-3.36 (m, 2H), 2.33 (s, 3H), 2.14-2.27 (m, 1H), 1.94-1.99 (m, 1H), 1.59-1.85 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 385.2$

Example 97

10 Preparation of 1-(3-(((2-((1-methyl-1H-pyrazol-4-yl)amino)-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one

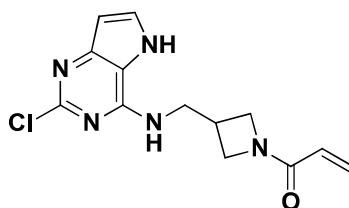


Step 1: preparation of *tert*-butyl 3-(((2-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)amino)methyl)azetidine-1-carboxylate



5 2,4-Dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidine (360 mg, 1.92 mmol) and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate (374 mg, 2.01 mmol) were dissolved in methanol (20 mL), followed by the addition of *N,N*-diisopropylethylamine (667 μ L, 3.83 mmol) under stirring at room temperature. The reaction solution was refluxed for 3 hours, and then concentrated, re-dissolved in dichloromethane (50 mL), washed with water (30 mL)
10 and concentrated to give a white solid (350 mg). Yield: 51.2%. MS (ESI, m/z): $[M+H]^+$: 338.2.

Step 2: preparation of 1-(3-(((2-chloro-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one



15 The product obtained in step 1 (222 mg, 0.66 mmol) was dissolved in dichloromethane (5 mL), followed by the addition of trifluoroacetic acid (2 mL) under stirring at room temperature. After stirring for 3 hours, the reaction solution was concentrated under reduced pressure to remove most of trifluoroacetic acid, and re-dissolved in dichloromethane (30 mL). *N,N*-diisopropylethylamine (229 μ L, 1.31 mmol)
20 was added under stirring at room temperature, and then a solution of acryloyl chloride (59 μ L, 0.66 mmol) in dichloromethane (10 mL) was slowly, dropwise added in an ice bath. After 5 hours, water (50 mL) was added to the reaction system, and the organic phase was separated, dried over anhydrous sodium sulfate, and concentrated to give a pale yellow solid, which was then purified by silica gel column chromatography (eluent:

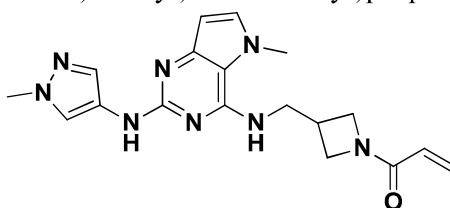
dichloromethane / methanol = 70 : 1), to give a white solid (150 mg). Yield: 77.7%. MS (ESI, m/z): [M+H]⁺: 292.0.

Step 3: preparation of 1-(3-(((2-((1-methyl-1*H*-pyrazol-4-yl)amino)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one

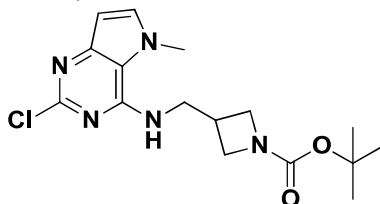
5 The compound obtained in step 2 (40 mg, 0.14 mmol) and 1-methyl-1*H*-pyrazole-4-amine (15 mg, 0.15 mmol) were dissolved in isopropanol (2 mL). The reaction solution was adjusted to pH 5 with trifluoroacetic acid, and then reacted under microwave irradiation at 90°C for 0.5 hours. The reaction solution was cooled to room temperature, adjusted with 1N sodium hydroxide solution to pH 8, and extracted with ethyl acetate (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1) to give a yellow solid (2 mg). Yield: 4.1%. MS (ESI, m/z): [M+H]⁺: 353.2; ¹H-NMR (300 MHz, DMSO-*d*₆) δ: 7.52 (s, 2H), 7.41 (s, 1H), 6.98 (d, 1H, *J* = 3.0 Hz), 6.13-6.19 (m, 2H), 5.98 (d, 1H, *J* = 3.0 Hz), 10 5.67 (dd, 1H, *J* = 2.4 Hz, *J* = 9.6 Hz), 4.25-4.35 (m, 1H), 4.04-4.08 (m, 2H), 3.80-3.85 (m, 2H), 3.74 (s, 3H), 3.65-3.73 (m, 1H), 2.95-3.05 (m, 1H).

Example 98

Preparation of 1-(3-(((5-methyl-2-((1-methyl-1*H*-pyrazol-4-yl)amino)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one



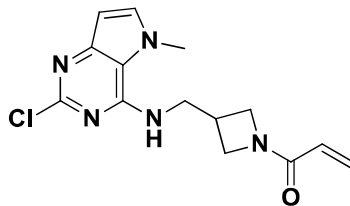
Step 1: preparation of *tert*-butyl 3-(((2-chloro-5-methyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yl)amino)methyl)azetidine-1-carboxylate



25 2,4-Dichloro-5-methyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (300 mg, 1.48 mmol) and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate (290 mg, 1.56 mmol) were dissolved in tetrahydrofuran (10 mL), followed by the addition of *N,N*-diisopropylethylamine (258 mg, 2 mmol). The reaction solution was reacted under reflux overnight, and then cooled

to room temperature. The reaction solution was concentrated and the residue was added with water (50 mL), and extracted with ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: n-hexane: ethyl acetate = 6 : 1), to give a colorless liquid (300 mg). Yield: 50.7%. MS (ESI, m/z): [M+H]⁺: 352.2.

Step 2: preparation of 1-(3-(((2-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino)methyl)azetidin-1-yl) prop-2-en-1-one



The product obtained in step 1 (229 mg) was dissolved in dichloromethane (4 mL), followed by the addition of trifluoroacetic acid (1.5 mL) under stirring at room temperature. After stirring for 3 hours, the reaction solution was concentrated under reduced pressure to remove most of trifluoroacetic acid, and was then re-dissolved in dichloromethane (20 mL). To the solution, *N,N*-diisopropylethylamine (276 μL, 1.59 mmol) was added under stirring at room temperature, and then a solution of acryloyl chloride (64 μL, 0.66 mmol) in dichloromethane (10 mL) was slowly, dropwise added in an ice bath. After 5 hours, water (50 mL) was added to the reaction system. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated to give a pale yellow solid, which was then purified by silica gel column chromatography (eluent: dichloromethane / methanol = 70 : 1), to give a white solid (180 mg). Yield: 90.5%. MS (ESI, m/z): [M+H]⁺: 306.1.

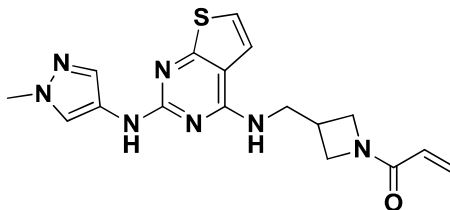
Step 3: preparation of 1-(3-(((5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one

The compound obtained in step 2 (50 mg, 0.16 mmol) and 1-methyl-1H-pyrazole-4-amine (18 mg, 0.18 mmol) were dissolved in isopropanol (2 mL). The reaction solution was adjusted to pH 5 with trifluoroacetic acid, and reacted under microwave irradiation at 90°C for 0.5 hours. The reaction solution was cooled to room temperature, adjusted with 1N sodium hydroxide solution to pH 8, and extracted with ethyl acetate (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1) to give a pale yellow solid (3 mg). Yield: 5%. MS (ESI, m/z): [M+H]⁺: 367.3; ¹H-NMR (300 MHz, DMSO-*d*₆) δ: 7.59 (d, 1H, *J* =

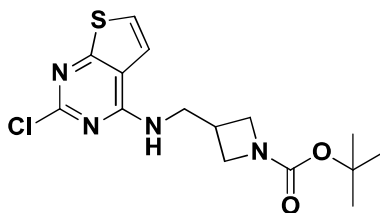
3.0 Hz), 7.54 (s, 1H), 6.89 (d, 1H, $J = 3.0$ Hz), 6.77 (bs, 1H), 6.11-6.30 (m, 3H), 5.68 (dd, 1H, $J = 1.8$ Hz, $J = 10.2$ Hz), 4.31-4.37 (m, 1H), 4.11-4.18 (m, 1H), 3.90-4.06 (m, 5H), 3.83 (s, 3H), 3.70-3.80 (m, 2H), 3.05-3.17 (m, 1H).

5 Example 99

Preparation of 1-(3-(((2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[2,3-*d*]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one

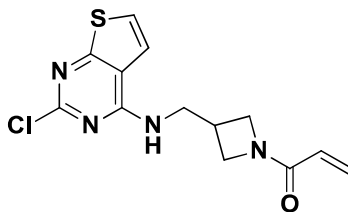


Step 1: preparation of *tert*-butyl 3-(((2-chloro-thieno[2,3-*d*]pyrimidin-4-yl)amino)methyl)azetidine-1-carboxylate



2,4-Dichloro-thieno[2,3-*d*]pyrimidine (300 mg, 1.46 mmol) and *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate (272 mg, 1.46 mmol) were dissolved in tetrahydrofuran (25 mL), followed by the addition of *N,N*-diisopropylethylamine (258 mg, 2 mmol). The reaction solution was reacted at 70°C overnight, and then concentrated. The residue was added with water (50 mL), and extracted with ethyl acetate (20 mL $\times$ 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: *n*-hexane: ethyl acetate = 1: 5) to give a white solid (425 mg). Yield: 81.9%. MS (ESI, m/z): $[M+H]^+$: 355.2.

Step 2: preparation of 1-(3-(((2-chloro-thieno[2,3-*d*]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one



The product obtained in step 1 (425 mg, 1.20 mmol) was dissolved in

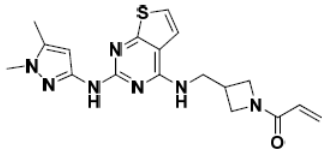
dichloromethane (10 mL), followed by the addition of trifluoroacetic acid (3 mL) under stirring at room temperature. After stirring for 3 hours, the reaction solution was concentrated under reduced pressure to remove most of trifluoroacetic acid, and was then re-dissolved in dichloromethane (30 mL), followed by the addition of *N,N*-diisopropylethylamine (417 μ L, 2.40 mmol) under stirring at room temperature. Then a solution of acryloyl chloride (140 μ L, 1.73 mmol) in dichloromethane (20 mL) was slowly, dropwise added in an ice bath. After 5 hours, water (50 mL) was added to the reaction system, and the organic phase was separated, dried over anhydrous sodium sulfate, and concentrated to give a pale yellow solid, which was purified by silica gel column chromatography (eluent: dichloromethane / methanol = 70 : 1), to give a white solid (300 mg). Yield: 81.1%. MS (ESI, m/z): $[M+H]^+$: 309.1.

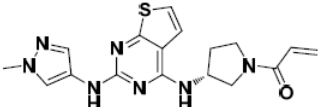
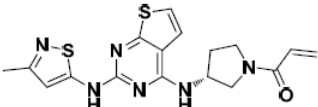
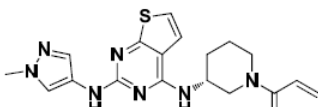
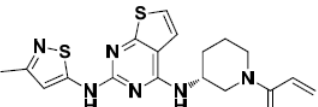
Step 3: preparation of 1-(3-(((2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[2,3-*d*]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one

The product obtained in step 2 (40 mg, 0.13 mmol), 1-methyl-1*H*-pyrazole-4-amine (19 mg, 0.19 mmol), tris(dibenzylidenepropanone)dipalladium (12 mg, 0.013 mmol), ($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (12 mg, 0.019 mmol) and cesium carbonate (127 mg, 0.39 mmol) were suspended in 1,4-dioxane (1.5 mL), followed by the addition of water (300 μ L). Argon air was purged to remove air, and the reaction was carried out with the assistance of microwave at 100°C for half an hour. The reaction mixture was filtered through celite, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1), to give a yellow solid (9 mg). Yield: 18.8%. MS (ESI, m/z): $[M+H]^+$: 370.2; $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.79 (bs, 1H), 7.07 (s, 1H), 6.97 (d, 1H, $J = 6.0$ Hz), 6.91 (s, 1H), 6.82 (d, 1H, $J = 6.0$ Hz), 6.75 (bs, 1H), 6.26 (dd, 1H, $J = 1.8$ Hz, $J = 16.8$ Hz), 6.10 (dd, 1H, $J = 10.2$ Hz, $J = 16.8$ Hz), 5.60 (dd, 1H, $J = 1.8$ Hz, $J = 10.2$ Hz), 4.21-4.27 (m, 1H), 4.08-4.14 (m, 1H), 3.92-3.97 (m, 1H), 3.78-3.86 (m, 5H), 3.65-3.76 (m, 1H), 2.95-3.05 (m, 1H).

The following compounds (in Table 4) were prepared from similar starting materials by similar synthetic methods to those described in Example 99.

Table 4

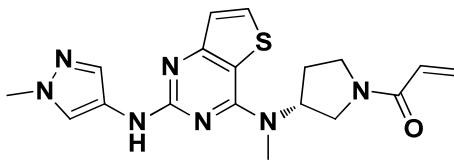
Example	Structure	Characterization Data
100		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.04 (d, 1H, $J = 6.0$ Hz), 6.90 (d, 1H, $J = 6.0$ Hz), 6.53 (s, 1H), 6.32 (dd, 1H, $J = 2.1$ Hz, $J = 16.8$ Hz), 6.16 (dd, 1H, $J = 10.2$ Hz, $J = 16.8$ Hz), 5.65 (dd, 1H, $J = 2.1$ Hz, $J = 10.2$ Hz), 4.26-4.32 (m, 1H),

		4.15-4.22 (m, 1H), 4.04-4.09 (m, 1H), 3.85-3.96 (m, 2H), 3.72-3.81 (m, 1H), 3.67 (s, 3H), 3.05-3.10 (m, 1H), 2.26 (s, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 384.2$
101		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.90 (s, 1H), 7.58 (s, 1H), 7.35-7.37 (m, 1H), 6.96-6.98 (m, 1H), 6.56-6.72 (m, 1H), 6.27-6.34 (m, 1H), 5.73-5.81 (m, 1H), 4.80-4.88 (m, 1H), 3.96-4.14 (m, 1H), 3.88 (s, 3H), 3.58-3.86 (m, 3H), 2.14-2.47 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 370.2$
102		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.37-7.46 (m, 2H), 7.12-7.15 (m, 1H), 6.56-6.73 (m, 2H), 6.27-6.35 (m, 1H), 5.73-5.81 (m, 1H), 5.00-5.10 (m, 1H), 4.00-4.24 (m, 1H), 3.62-3.91 (m, 3H), 2.13-2.55 (m, 5H); LC-MS(ESI, m/z): $[M+H]^+ = 387.2$
103		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.87-7.94 (m, 1H), 7.51 (d, 1H, $J = 11.7$ Hz), 7.32 (t, 1H, $J = 6.0$ Hz), 6.93-6.96 (m, 1H), 6.50-6.88 (m, 1H), 6.08-6.30 (m, 1H), 5.51-5.81 (m, 1H), 4.07-4.26 (m, 2H), 3.83 (s, 3H), 2.66-3.27 (m, 2H), 2.15-2.20 (m, 1H), 1.90-1.95 (m, 1H), 1.60-1.81 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 384.2$
104		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.35-7.42 (m, 1H), 7.07-7.12 (m, 1H), 6.57-6.85 (m, 2H), 6.17 (dd, 1H, $J = 16.8$ Hz, $J = 50.4$ Hz), 5.50-5.80 (m, 1H), 4.80 (bs, 1H), 4.50 (bs, 1H), 4.06-4.22 (m, 2H), 2.70-3.43 (m, 2H), 2.34 (s, 3H), 2.21-2.27 (m, 1H), 1.58-2.05 (m, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 401.3$

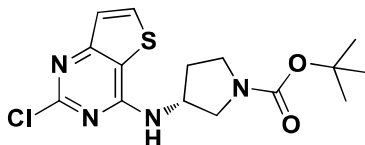
Example 105

Preparation of (*R*)-1-(3-(methyl(2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[3,2-*d*]

pyrimidin-4-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one



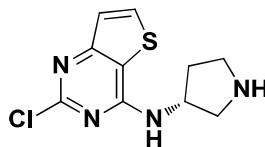
Step 1: preparation of *tert*-butyl (*R*)-3-((2-chloro-thieno[3,2-*d*]pyrimidin-4-yl)amino)pyrrolidin-1-yl carboxylate



5

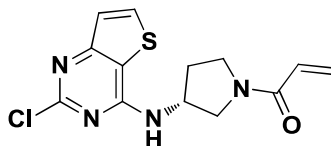
2,4-Dichloro-thieno[3,2-*d*]pyrimidine (2.26 g, 0.011 mol) and *tert*-butyl (*R*)-3-amino pyrrolidin-1-yl carboxylate (2.25 g, 0.012 mol) were dissolved in tetrahydrofuran (50 mL), followed by the addition of *N,N*-diisopropylethylamine (2.838 g, 0.022 mol). The reaction solution was reacted at 70°C overnight, and then concentrated. The residue was added
10 with water (50 mL), and extracted with ethyl acetate (50 mL × 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: *n*-hexane: ethyl acetate = 5 : 1), to give a white solid (3.8 g). Yield: 97.4%. MS (ESI, *m/z*): [M+H]⁺: 355.1; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.05 (d, 1H, *J* = 6.3 Hz), 8.02 (d, 1H, *J* = 5.4 Hz), 7.35 (d, 1H, *J* = 6.3 Hz),
15 4.60-4.48 (m, 1H), 3.60-3.67 (m, 1H), 3.22-3.48 (m, 3H), 2.15-2.19 (m, 1H), 1.91-2.01 (m, 1H), 1.40 (s, 9H).

Step 2: preparation of (*R*)-2-chloro-*N*-(pyrrolidin-3-yl)thieno[3,2-*d*]pyrimidine-4-amine



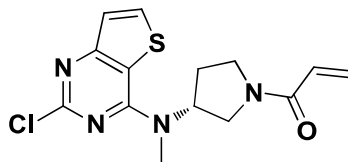
20 The compound obtained in step 1 (0.3 g, 0.845 mmol) was dissolved in ethanol (10 mL), followed by the addition of 4N solution of hydrogen chloride in 1,4-dioxane (2 mL, 8 mmol). The reaction solution was reacted at 80°C for 4 hours, and then concentrated. The resulting crude product was used directly in the next step without further purification. MS (ESI, *m/z*): [M+H]⁺: 254.9.

25 Step 3: preparation of (*R*)-1-(3-((2-chloro-thieno[3,2-*d*]pyrimidin-4-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one



The compound obtained in step 2 (0.497 g, 1.96 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of triethylamine (0.396 g, 3.92 mmol). A solution of acryloyl chloride (0.195 g, 2.15 mmol) dissolved in dichloromethane (5 mL) was added dropwise to the above solution at 0°C. The reaction solution was reacted at room temperature overnight, and then washed with water (20 mL). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 70 : 1), to give a white solid (0.44 g). Yield: 72.8%. MS (ESI, m/z): [M+H]⁺: 309.0; ¹H-NMR (300 MHz, DMSO-*d*₆): 8.52-8.55 (m, 1H), 8.20 (m, 1H), 7.35 (m, 1H), 6.52-6.67 (m, 1H), 6.11-6.19 (m, 1H), 5.64-5.71 (m, 1H), 4.63-4.80 (m, 1H), 3.43-3.97 (m, 4H), 2.00-2.23 (m, 2H).

Step 4: preparation of (R)-1-(3-((2-chloro-thieno[3,2-*d*]pyrimidin-4-yl)methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one



To a solution of the compound obtained in step 3 (100 mg, 0.32 mmol) and sodium hydride (60%, in mineral oil, 39 mg, 0.97 mmol) in tetrahydrofuran (15 mL) was added iodomethane (24 µL, 0.39 mmol), and was stirred at room temperature for 3 hours. The reaction solution was concentrated, and then purified by silica gel column chromatography (eluent: dichloromethane / methanol = 30 : 1) to give a white solid (80 mg). Yield: 76.5%. MS (ESI, m/z): [M+H]⁺: 323.1; ¹H-NMR (300 MHz, CDCl₃): 7.79-7.82 (m, 1H), 7.36-7.38 (m, 1H), 6.40-6.54 (m, 1H), 5.58-5.77 (m, 1H), 3.81-4.03 (m, 2H), 3.48-3.70 (m, 2H), 3.40 (s, 3H), 2.12-2.40 (m, 2H).

Step 5: preparation of (R)-1-(3-(methyl(2-((1-methyl-1*H*-pyrazol-4-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one

The compound obtained in step 4 (40 mg, 0.12 mmol), 1-methyl-1*H*-pyrazole-4-amine (13 mg, 0.14 mmol) and trifluoroacetic acid (20 mg, 0.18 mmol) were dissolved in 2-butanol (1.2 mL), and reacted under microwave at 100°C for 40 minutes, and then purified by silica gel column chromatography (eluent: dichloromethane / methanol = 20 : 1), to give a brown solid (22 mg). Yield: 46.3%. MS (ESI, m/z): [M+H]⁺: 384.3; ¹H-NMR

(300 MHz, CDCl₃): δ : 7.79 (d, 1H, J = 9.9 Hz), 7.68 (d, 1H, J = 5.4 Hz), 7.50 (d, 1H, J = 5.7 Hz), 7.22 (d, 1H, J = 5.7 Hz), 6.42-6.48 (m, 2H), 5.70-5.77 (m, 1H), 5.47-5.56 (m, 1H), 3.79-3.98 (m, 5H), 3.49-3.67 (m, 2H), 3.35 (d, 3H, J = 5.4 Hz), 2.12-2.34 (m, 2H).

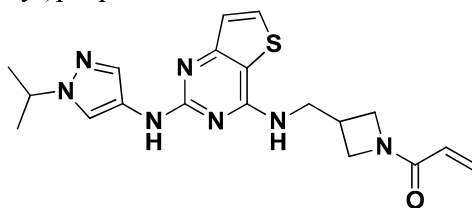
The following compounds (in Table 5) were prepared from similar starting materials by similar synthetic methods to those described in Example 105.

Table 5

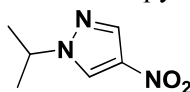
Example	Structure	Characterization Data
106		¹ H-NMR (300 MHz, CDCl ₃) δ : 7.75 (s, 1H), 7.69 (d, 1H, J = 5.4 Hz), 7.47-7.52 (m, 1H), 7.22 (d, 1H, J = 5.4 Hz), 6.50-6.69 (m, 1H), 6.29-6.37 (m, 1H), 5.63-5.76 (m, 1H), 4.70-4.82 (m, 2H), 4.06-4.15 (m, 1H), 3.85 (s, 3H), 3.37 (s, 3H), 2.50-3.18 (m, 2H), 1.94-2.04 (m, 2H); LC-MS(ESI, m/z): [M+H] ⁺ = 398.3
107		¹ H-NMR (300 MHz, CDCl ₃) δ : 7.76-7.78 (m, 1H), 7.64-7.65 (m, 2H), 7.29 (s, 1H), 6.62 (dd, 1H, J = 10.5 Hz, J = 16.8 Hz), 6.33 (dd, 1H, J = 1.8 Hz, J = 16.8 Hz), 5.75 (dd, 1H, J = 1.8 Hz, J = 10.5 Hz), 4.89-5.08 (m, 2H), 4.17-4.21 (m, 1H), 3.89 (s, 3H), 3.32 (s, 3H), 3.20-3.30 (m, 2H), 2.71-2.79 (m, 1H), 1.69-1.90 (m, 4H); LC-MS(ESI, m/z): [M+H] ⁺ = 398.3

Example 108

Preparation of 1-(3-(((2-(((1-isopropyl-1H-pyrazol-4-ylamino)thieno[3,2-d]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one



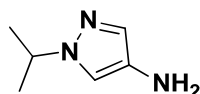
Step 1: preparation of 1-isopropyl-4-nitro-1H-pyrazole



4-Nitro-1H-pyrazole (226 mg, 2 mmol) and 2-iodopropane (340 mg, 2 mmol) were

dissolved in *N,N*-dimethylformamide (5 mL), followed by the addition of potassium carbonate (276 mg, 2 mmol). The reaction solution was reacted at 70°C for 2 hours, then poured into water (20 mL), and extracted with ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: *n*-hexane / ethyl acetate = 5 : 1) to give a white solid (250 mg). Yield: 80.0%. MS (ESI, *m/z*): [M+H]⁺: 155.8; ¹H-NMR (300 MHz, CDCl₃) δ: 8.16 (s, 1H), 8.08 (s, 1H), 4.48-4.57 (m, 1H), 1.57 (s, 3H), 1.55 (s, 3H).

Step 2: preparation of 1-isopropyl-1*H*-pyrazole-4-amine



The product obtained in step 1 (250 mg, 1.61 mmol) was dissolved in ethanol (10 mL), followed by the addition of palladium on carbon (25 mg), and reacted under hydrogen atmosphere for 2 hours at room temperature. The reaction solution was filtered and concentrated, and the resulting crude product was used directly in the next step. MS (ESI, *m/z*): [M+H]⁺: 125.9.

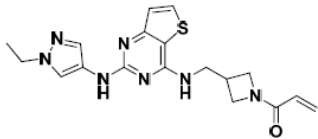
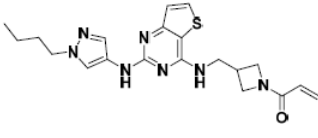
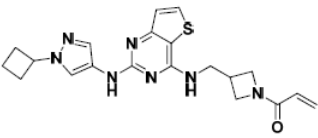
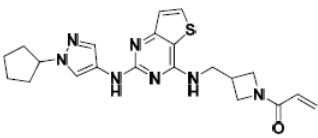
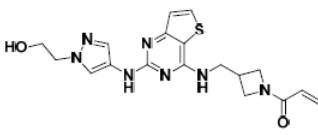
Step 3: preparation of 1-(3-(((2-((1-isopropyl-1*H*-pyrazol-4-yl-amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)methyl)azetidin-1-yl)prop-2-en-1-one

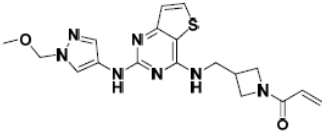
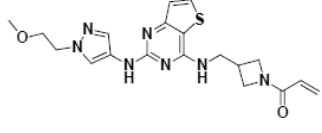
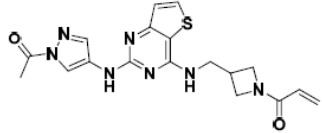
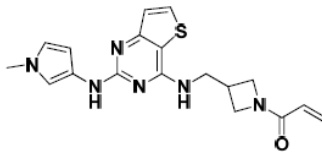
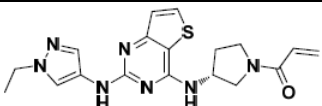
The product obtained in step 3 of Example 61 (30 mg, 0.1 mmol) and 1-isopropyl-1*H*-pyrazole-4-amine (19 mg, 0.15 mmol) were dissolved in 1,4-dioxane (2 mL). The reaction solution was adjusted to pH 5 with trifluoroacetic acid, and reacted under microwave irradiation at 90°C for 0.5 hours. The reaction solution was cooled to room temperature, adjusted with 1N sodium hydroxide solution to pH 8, and extracted with ethyl acetate (10 mL × 3). The organic phase was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 20 : 1) to give a yellow solid (15 mg). Yield: 37.8%. MS (ESI, *m/z*): [M+H]⁺: 398.3; ¹H-NMR (300 MHz, DMSO-*d*₆) δ: 7.81 (s, 1H), 7.64 (d, 1H, *J* = 5.4 Hz), 7.60 (s, 1H), 7.20 (d, 1H, *J* = 5.4 Hz), 6.31-6.37 (m, 1H), 6.13-6.22 (m, 1H), 5.66-5.70 (m, 1H), 4.31-4.37 (m, 1H), 4.18-4.24 (m, 1H), 4.00-4.05 (m, 1H), 3.81-3.95 (m, 3H), 3.09 (m, 1H), 1.53 (s, 3H), 1.51 (s, 3H).

The following compounds (in Table 6) were prepared from similar starting materials by similar synthetic methods to those described in Example 108.

Table 6

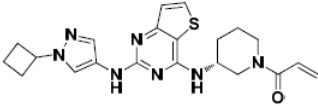
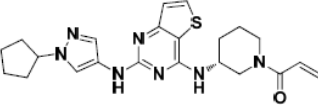
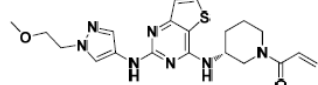
Example	Structure	Characterization Data
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109		¹ H-NMR (300 MHz, CD ₃ OD) δ: 8.17 (m, 2H), 7.74 (s, 1H), 7.28 (d, 1H, <i>J</i> = 5.1 Hz), 6.28 (m, 2H), 5.73 (q, 1H, <i>J</i> = 3.9 Hz), 4.22 (q, 2H, <i>J</i> = 7.2 Hz), 4.35 (m, 1H), 3.95 (m, 1H), 3.71 (m, 1H), 3.40-3.53 (m, 3H), 2.63 (m, 1H), 1.50 (t, 3H, <i>J</i> = 7.2 Hz); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 384.3
110		¹ H-NMR (300 MHz, CD ₃ OD) δ: 8.19 (d, 2H, <i>J</i> = 5.1 Hz), 8.14 (s, 1H), 7.28 (d, 1H, <i>J</i> = 5.4 Hz), 6.22-6.36 (m, 2H), 5.72 (dd, 1H, <i>J</i> = 2.4 Hz, <i>J</i> = 8.7 Hz), 4.31-4.37 (m, 1H), 4.18 (t, 2H, <i>J</i> = 7.2 Hz), 3.92-3.99 (m, 1H), 3.71-3.77 (m, 1H), 3.52 (d, 2H, <i>J</i> = 6.6 Hz), 3.41-3.48 (m, 1H), 2.62-2.67 (m, 1H), 1.85-1.90 (m, 2H), 1.30-1.40 (m, 3H), 8.19 (t, 3H, <i>J</i> = 7.5 Hz); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 412.3
111		¹ H-NMR (300 MHz, CDCl ₃) δ: 8.22 (s, 1H), 7.81 (s, 1H), 7.65 (m, 2H), 7.20 (d, 1H, <i>J</i> = 5.1 Hz), 6.32-6.38 (m, 1H), 6.14-6.23 (m, 1H), 6.11 (s, 1H), 5.68-5.71 (m, 1H), 4.71-4.76 (m, 1H), 4.33-4.38 (m, 1H), 4.19-4.25 (m, 1H), 4.03-4.07 (m, 1H), 3.83-3.97 (m, 3H), 3.12 (m, 1H), 2.36-2.59 (m, 4H), 1.84-1.92 (m, 2H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 410.4
112		¹ H-NMR (300 MHz, CDCl ₃) δ: 9.94 (s, 1H), 8.41-8.45 (m, 1H), 8.16 (d, 1H, <i>J</i> = 5.4 Hz), 7.81 (d, 1H, <i>J</i> = 2.4 Hz), 7.44 (d, 1H, <i>J</i> = 5.4 Hz), 6.22-6.31 (m, 1H), 6.08-6.15 (m, 1H), 5.97 (d, 1H, <i>J</i> = 2.4 Hz), 5.61-5.65 (m, 1H), 4.58-4.64 (m, 1H), 3.56-4.02 (m, 5H), 1.67-2.36 (m, 10 H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 424.5
113		¹ H-NMR (300 MHz, CD ₃ OD) δ: 8.18 (d, 2H, <i>J</i> = 5.4 Hz), 7.79 (s, 1H), 7.25 (d, 1H, <i>J</i> = 5.4 Hz), 6.28 (m, 2H), 5.72 (dd, 1H, <i>J</i> = 3.0 Hz, <i>J</i> = 9.0 Hz), 4.35 (dd, 1H, <i>J</i> = 4.5 Hz, <i>J</i> = 12.3 Hz), 4.26

		(t, 2H, $J = 5.1$ Hz), 4.11 (m, 1H), 3.95 (m, 3H), 3.73 (m, 1H), 3.52 (d, 1H, $J = 6.6$ Hz), 3.43 (m, 1H), 2.65 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 400.3$
114		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.11 (s, 1H), 7.86 (d, 1H, $J = 5.4$ Hz), 7.69 (s, 1H), 7.15 (d, 1H, $J = 5.1$ Hz), 6.20-6.38 (m, 2H), 5.71-5.75 (m, 1H), 5.38 (s, 2H), 4.38-4.44 (m, 1H), 4.13-4.20 (m, 2H), 3.85-3.94 (m, 3H), 3.34 (s, 3H), 3.14 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 400.3$
115		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.95 (s, 1H), 7.77 (d, 1H, $J = 5.1$ Hz), 7.58 (s, 1H), 7.09 (d, 1H, $J = 5.4$ Hz), 6.19-6.34 (m, 2H), 5.68-5.72 (m, 1H), 4.34-4.39 (m, 1H), 4.24 (t, 2H, $J = 5.1$ Hz), 4.10-4.18 (m, 2H), 3.87-3.93 (m, 1H), 3.81-3.85 (m, 2H), 3.72 (t, 2H, $J = 5.1$ Hz), 3.33 (s, 3H), 3.04-3.18 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 414.3$
116		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.17 (m, 2H), 7.74 (s, 1H), 7.28 (d, 1H, $J = 5.1$ Hz), 6.28 (m, 2H), 5.73 (q, 1H, $J = 3.9$ Hz), 4.35 (m, 1H), 3.95 (m, 1H), 3.71 (m, 1H), 3.40-3.53 (m, 3H), 2.85 (s, 3H), 2.63 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 398.3$
117		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.01 (d, 1H, $J = 5.4$ Hz), 7.20 (d, 1H, $J = 5.4$ Hz), 6.65-6.67 (m, 1H), 6.21-6.36 (m, 2H), 6.08-6.11 (m, 1H), 5.72-5.76 (m, 1H), 4.38-4.44 (m, 1H), 4.08-4.22 (m, 2H), 3.87-3.96 (m, 3H), 3.69 (s, 3H), 3.61-3.77 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 369.2$
118		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.93 (s, 1H), 7.85 (dd, 1H, $J = 1.2$ Hz, $J = 5.4$ Hz), 7.61 (s,

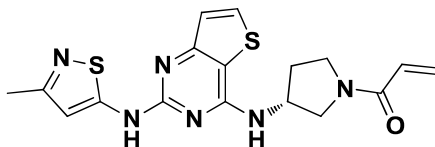
		1H), 7.14 (d, 1H, $J = 5.1$ Hz), 6.55-6.71 (m, 1H), 6.26-6.34 (m, 1H), 5.73-5.80 (m, 1H), 4.09 (q, 2H, $J = 6.9$ Hz), 3.72-4.01 (m, 3H), 3.57-3.67 (m, 2H), 2.12-2.53 (m, 2H), 1.47 (t, 3H, $J = 7.2$ Hz); LC-MS(ESI, m/z): $[M+H]^+ = 384.3$
119		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.62-7.81 (m, 3H), 7.20 (d, 1H, $J = 5.1$ Hz), 6.44 (d, 1H, $J = 6.0$ Hz), 6.38 (d, 1H, $J = 6.0$ Hz), 5.67-5.76 (m, 1H), 4.87-4.95 (m, 1H), 4.42-4.51 (m, 1H), 3.57-3.98 (m, 4H), 2.28-2.39 (m, 1H), 1.50-1.52 (m, 6H), 1.42-1.45 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 398.4$
120		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.86 (d, 1H, $J = 8.4$ Hz), 7.58-7.62 (m, 2H), 7.16-7.20 (m, 1H), 6.37-6.46 (m, 2H), 5.66-5.75 (m, 1H), 4.67-4.92 (m, 2H), 3.58-4.02 (m, 5H), 2.42-2.62 (m, 4H), 2.26-2.37 (m, 2H), 2.07-2.15 (m, 1H), 1.78-1.93 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 410.4$
121		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.84 (d, 1H, $J = 6.0$ Hz), 7.56-7.61 (m, 2H), 7.16-7.19 (m, 1H), 6.37-6.46 (m, 2H), 5.66-5.75 (m, 1H), 4.83-4.94 (m, 1H), 4.57-4.66 (m, 1H), 3.56-4.02 (m, 5H), 1.67-2.36 (m, 10H); LC-MS(ESI, m/z): $[M+H]^+ = 424.4$
122		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.97(s, 1H), 7.87 (dd, 1H, $J = 1.8\text{Hz}$, $J = 5.4$ Hz), 7.62 (s, 1H), 7.13 (d, 1H, $J = 5.4$ Hz), 6.55-6.71 (m, 1H), 6.26-6.34 (m, 1H), 5.73-5.80 (m, 1H), 4.28-4.31 (m, 2H), 4.11-4.26 (m, 1H), 3.59-3.98 (m, 6H), 3.31 (s, 3H), 2.17-2.48 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 414.4$
123		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.90 (m, 2H), 7.62 (s, 1H), 7.15 (d, 1H, $J = 6.0$ Hz), 6.61 (m,

		1H), 6.31 (m, 1H), 5.77 (t, 1H, $J = 10.5$ Hz), 3.60-4.25 (m, 8H), 3.38 (s, 3H), 2.03-2.36 (m, 5H); LC-MS(ESI, m/z): $[M+H]^+ = 428.3$
124		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 8.03 (m, 2H), 7.73 (s, 1H), 7.29 (d, 1H, $J = 5.4$ Hz), 6.64 (m, 1H), 6.31 (m, 1H), 5.78 (m, 1H), 4.63 (m, 2H), 4.13 (m, 1H), 4.04 (m, 1H), 3.85 (m, 1H), 3.60-3.80 (m, 4H), 3.47 (s, 1H), 3.36 (s, 3H), 2.20-2.50 (m, 3H), 2.02 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 427.4$
125		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.93-8.00 (m, 2H), 7.64 (s, 1H), 7.18 (d, 1H, $J = 5.4$ Hz), 6.54-6.71 (m, 1H), 6.31 (m, 1H), 6.27-6.34 (m, 1H), 5.73-5.81 (m, 1H), 3.58-4.13 (m, 8H), 2.00-2.48 (m, 6H), 1.29-1.35 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 440.4$
126		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.99 (s, 1H), 7.90 (m, 1H), 7.66 (s, 1H), 7.16 (dd, 1H, $J = 0.4$ Hz, $J = 5.4$ Hz), 6.63 (m, 1H), 6.30 (m, 1H), 5.77 (m, 1H), 4.34 (m, 2H), 4.13 (m, 1H), 3.75-4.01 (m, 2H), 3.72 (m, 4H), 3.65 (m, 1H), 2.95 (m, 2H), 2.63 (m, 4H), 2.19-2.43 (m, 2H); LC-MS(ESI, m/z): $[M+H]^+ = 469.3$
127		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.91 (m, 2H), 7.55 (d, 1H, $J = 13.5$ Hz), 7.14 (d, 1H, $J = 5.1$ Hz), 6.49-6.90 (m, 1H), 6.07-6.31 (m, 1H), 5.53-5.83 (m, 1H), 4.83 (m, 1H), 4.12-4.33 (m, 4H), 3.19 (q, 1H, $J = 12.0$ Hz), 2.74-3.01 (m, 1H), 2.17 (d, 1H, $J = 12.0$ Hz), 1.94 (d, 1H, $J = 13.2$ Hz), 1.80 (m, 1H), 1.60 (m, 1H), 1.42 (m, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 398.3$
128		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.93 (m, 2H), 7.58 (d, 1H, $J = 7.8$ Hz), 7.17 (t, 1H, $J = 5.1$ Hz),

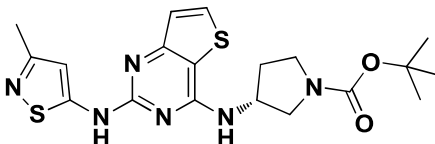
		<p>6.52-6.92 (m, 1H), 6.07-6.30 (m, 1H), 5.55-5.83 (m, 1H), 4.80 (dd, 1H, $J = 4.2$ Hz, $J = 12.9$ Hz), 4.51 (q, 1H, $J=6.9$Hz), 4.32 (m, 1H), 4.12 (m, 1H), 3.25 (m, 1H), 2.78-3.00 (m, 1H), 2.19 (m, 1H), 1.97 (m, 1H), 1.82 (m, 1H), 1.65 (m, 1H), 1.47 (m, 6H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 412.4$</p>
129		<p>$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ: 7.98 (s, 1H), 7.93 (t, 1H, $J = 5.1$ Hz), 7.59 (d, 1H, $J = 2.1$ Hz), 7.15 (d, 1H, $J = 5.4$ Hz), 6.47-6.92 (m, 1H), 6.01-6.33 (m, 1H), 5.51-5.85 (m, 1H), 4.80 (m, 1H), 4.10-4.37 (m, 3H), 3.19 (t, 1H, $J = 10.5$ Hz), 2.77-2.95 (m, 1H), 2.44-2.59 (m, 4H), 2.19 (d, 1H, $J = 12.0$ Hz), 1.78-1.99 (m, 4H), 1.59-1.68 (m, 1H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 424.4$</p>
130		<p>$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ: 7.95 (d, 1H, $J = 9.9$ Hz), 7.83 (d, 1H, $J = 5.4$ Hz), 7.54 (d, 1H, $J = 6.9$ Hz), 7.11 (d, 1H, $J = 5.4$ Hz), 6.51-6.91 (m, 1H), 6.06-6.31 (m, 1H), 5.52-5.83 (m, 1H), 4.85 (m, 1H), 4.62 (m, 1H), 4.31 (m, 1H), 4.14 (m, 1H), 3.21 (m, 1H), 2.74-3.01 (m, 1H), 2.16 (m, 3H), 1.65-2.03 (m, 9H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 438.5$</p>
131		<p>$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ: 8.00 (d, 1H, $J = 10.8$ Hz), 7.86 (d, 1H, $J = 1.8$Hz, $J = 5.4$ Hz), 7.58 (d, 1H, $J = 10.8$ Hz), 7.13 (d, 1H, $J = 5.4$ Hz), 6.52-6.90 (m, 1H), 6.08-6.32 (m, 1H), 5.53-5.84 (m, 1H), 4.10-4.27 (m, 5H), 3.67-3.76 (m, 3H), 3.32 (s, 3H), 3.07-3.27 (m, 1H), 2.17-2.23 (m, 1H), 1.93-2.02 (m, 1H), 1.62-1.86 (m, 2H);</p> <p>LC-MS(ESI, m/z): $[M+H]^+ = 428.5$</p>

Example 132

Preparation of (*R*)-1-(3-((2-((3-methyl-isothiazol-5-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one

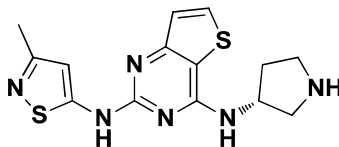


Step 1: preparation of *tert*-butyl (*R*)-3-((2-((3-methyl-isothiazol-5-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)pyrrolidine-1-carboxylate



The product obtained in step 1 of Example 105 (35.6 g, 0.1 mol) and 3-methyl-isothiazole-5-amine hydrochloride (16.3 g, 0.11 mol) were dissolved in 1,4-dioxane / water (700 mL, 20 : 1), followed by the addition of tris (dibenzylidenepropanone)dipalladium (7.3 g, 8 mmol), ($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (7.5 g, 12 mmol) and cesium carbonate (130 g, 0.4 mol) under nitrogen atmosphere, and refluxed at 100°C overnight. The reaction solution was cooled to room temperature, and filtered through celite. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane: methanol = 30 : 1) to give a crude yellow solid (44 g). To the crude product was added a solvent mixture (*n*-hexane: dichloromethane: ethyl acetate = 3 : 1 : 1) (500 mL). The mixture was stirred at 70°C for 1 hour, cooled in an ice bath, and filtered to give a pale yellow solid (35 g). Yield: 80.6%. MS (ESI, *m/z*): [*M*+*H*]⁺: 433.3; ¹H-NMR (300 MHz, CDCl₃) δ : 7.69 (d, 1H, *J* = 3.6 Hz), 7.22 (s, 1H), 6.46 (s, 1H), 5.00-5.30 (m, 2H), 3.46-3.87 (m, 4H), 2.37-2.40 (m, 4H), 2.12 (m, 1H), 1.84-1.86 (m, 1H), 1.49 (s, 9H).

Step 2: preparation of (*R*)-*N*²-(3-methyl-isothiazol-5-yl)-*N*⁴-(pyrrolidin-3-yl)thieno[3,2-*d*]pyrimidine-2,4-diamine



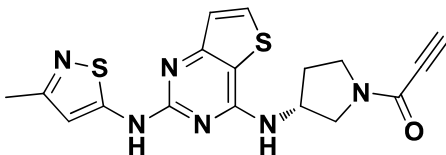
The product obtained in step 1 (35 g, 0.081 mol) was dissolved in dichloromethane (1.5 L), and to solubilize it methanol (1 L) was added, followed by the addition of 4N solution of hydrogen chloride in 1,4-dioxane (200 mL, 0.8 mol), and then reacted at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and used directly in the next step. MS (ESI, *m/z*): [*M*+*H*]⁺: 333.1.

Step 3: preparation of (*R*)-1-(3-((2-((3-methyl-isothiazol-5-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one

The product obtained in step 2 (26.9 g, 0.081 mol) was dissolved in dichloromethane (500 mL), followed by the addition of triethylamine (16.36 g, 0.162 mol) in an ice bath, and then the dropwise addition of a solution of acryloyl chloride (7.33 g, 0.081 mol) in dichloromethane (50 mL) in the ice bath, and reacted at room temperature overnight. The reaction solution was concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 30 : 1) to give a white solid (15 g). Yield: 47.9%. MS (ESI, *m/z*): [*M*+*H*]⁺: 387.2; ¹H-NMR (300 MHz, DMSO-*d*₆) δ: 8.06-8.14 (m, 2H), 7.23 (s, 1H), 6.53-6.70 (m, 2H), 6.12-6.20 (m, 1H), 5.64-5.72 (m, 1H), 4.88 (s, 1H), 3.51-4.09 (m, 4H), 2.05-2.66 (m, 6H).

Example 133

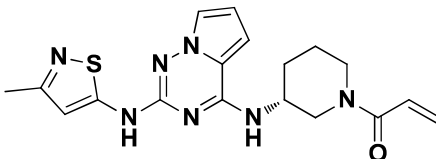
Preparation of (*R*)-1-(3-((2-((3-methyl-isothiazol-5-yl)amino)thieno[3,2-*d*]pyrimidin-4-yl)amino)pyrrolidin-1-yl)prop-2-yn-1-one



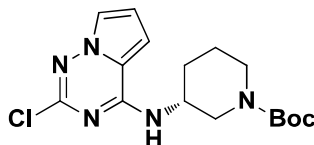
The product obtained in step 2 of Example 132 (33 mg, 0.10 mmol) and propiolic acid (8.4 mg, 0.12 mmol) were dissolved in tetrahydrofuran (10 mL), followed by the addition of *N,N*-diisopropylethylamine (53 μL). The mixture was stirred at room temperature for 30 minutes, followed by the addition of TBTU (4 mg). The mixture was stirred at room temperature overnight, concentrated and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1) to give a pale yellow solid (6.4 mg). Yield: 16.7%. MS (ESI, *m/z*): [*M*+*H*]⁺: 385.2; ¹H-NMR (300 MHz, CD₃OD) δ: 7.89-7.92 (m, 1H), 7.22 (d, 1H, *J* = 5.1 Hz), 6.62 (s, 1H), 5.04 (s, 1H), 3.53-4.86 (m, 5H), 2.42-2.50 (m, 1H), 2.35 (s, 3H), 2.20-2.28 (m, 1H).

Example 134

Preparation of (*R*)-1-(3-((2-((3-methyl-isothiazol-5-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one

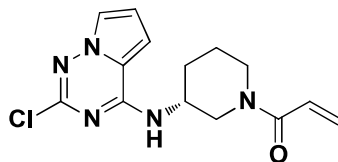


Step 1: preparation of *tert*-butyl (*R*)-3-((2-chloro-pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)piperidine-1-carboxylate



2,4-Dichloro-pyrrolo[2,1-*f*][1,2,4]triazine (325 mg, 1.73 mmol) and
 5 (*R*)-1-*tert*-butoxycarbonyl-3-amino piperidine (364 mg, 1.80 mmol) were dissolved in tetrahydrofuran (50 mL), followed by the addition of *N,N*-diisopropylethylamine (603 μ L, 3.46 mmol) under stirring at room temperature, and refluxed for 3 hours. The reaction solution was concentrated, re-dissolved in dichloromethane (50 mL), washed with water (30 mL), concentrated, and dried over anhydrous sodium sulfate to give a crude product
 10 (640 mg). MS (ESI, *m/z*): $[M+H]^+$: 352.2.

Step 2: preparation of (*R*)-1-(3-((2-chloro-pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one



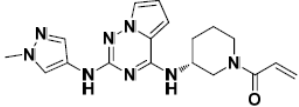
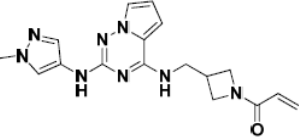
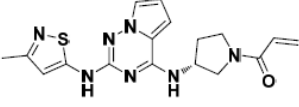
The crude product obtained in step 1 (640 mg) was dissolved in dichloromethane (3
 15 mL), followed by the addition of trifluoroacetic acid (1.5 mL) under stirring at room temperature. After stirring for 3 hours, the reaction solution was concentrated under reduced pressure to remove most of trifluoroacetic acid. The residue was re-dissolved in dichloromethane (30 mL), followed by the addition of *N,N*-diisopropylethylamine (603 μ L, 3.46 mmol) under stirring at room temperature. A solution of acryloyl chloride (140 μ L,
 20 1.73 mmol) in dichloromethane (20 mL) was slowly, dropwise added in an ice bath. After 5 hours, water (50 mL) was added to the reaction system. The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated to give a pale yellow solid, which was purified by silica gel column chromatography (eluent: dichloromethane / methanol = 70 : 1) to give a white solid (408 mg). Yield: 77.14%. MS (ESI, *m/z*): $[M+H]^+$:
 25 306.2.

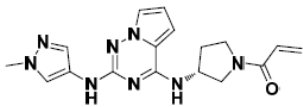
Step 3: preparation of (*R*)-1-(3-((2-((3-methyl-isothiazol-5-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one

The product obtained in step 2 (31 mg, 0.1 mmol), 3-methyl-isothiazole-5-amine hydrochloride (15 mg, 0.1 mmol), tris(dibenzylideneacetone)dipalladium (9 mg, 0.01
 30 mmol), 4,5-bis-diphenylphosphine-9,9-dimethylxanthene (9 mg, 0.015 mmol) and cesium

- carbonate (130 mg, 0.4 mmol) were suspended in 1,4-dioxane (1.5 mL), and added with water (300 μ L), purged with argon, reacted at 100°C under microwave for half an hour. The reaction mixture was filtered through celite, and the filtrate was purified by silica gel column chromatography (eluent: dichloromethane / methanol = 30 : 1) to give a yellow solid (20 mg). Yield: 51.44%. MS (ESI, m/z): $[M+H]^+$: 384.3; $^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.43 (s, 1H), 6.70-6.89 (m, 2H), 6.52-6.56 (m, 2H), 6.20 (dd, 1H, $J = 16.8$ Hz, $J = 40.2$ Hz), 5.71 (dd, 1H, $J = 10.8$ Hz, $J = 55.5$ Hz), 4.78-4.82 (m, 1H), 4.08-4.46 (m, 2H), 2.82-3.46 (m, 2H), 2.34 (s, 3H), 2.18-2.30 (m, 1H), 1.90-2.02 (m, 1H), 1.60-1.85 (m, 2H).
- The following compounds (in Table 7) were prepared from similar starting materials by similar synthetic methods to those described in Example 134.

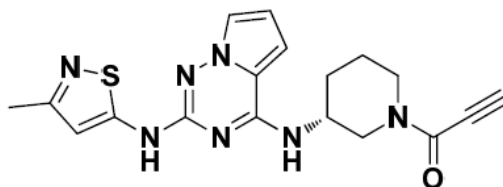
Table 7

Examples	Structures	Characterization Data
135		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.92 (s, 1H), 7.49 (d, 1H, $J = 6.3$ Hz), 7.35 (s, 1H), 6.66-6.87 (m, 2H), 6.41-6.43 (m, 1H), 6.11-6.30 (m, 1H), 5.61-5.81 (m, 1H), 4.06-4.28 (m, 3H), 3.86 (s, 3H), 3.07-3.20 (m, 1H), 2.68-2.76 (m, 1H), 2.10-2.22 (m, 1H), 1.52-1.98 (m, 3H); LC-MS(ESI, m/z): $[M+H]^+ = 367.3$
136		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.87 (s, 1H), 7.47 (s, 1H), 7.41 (s, 1H), 6.55 (bs, 1H), 6.45-6.48 (m, 1H), 6.36 (dd, 1H, $J = 1.8$ Hz, $J = 17.1$ Hz), 6.20 (dd, 1H, $J = 1.8$ Hz, $J = 10.2$ Hz), 5.69 (dd, 1H, $J = 1.8$ Hz, $J = 10.2$ Hz), 4.31-4.37 (m, 1H), 4.17-4.23 (m, 1H), 4.01-4.05 (m, 1H), 3.93-3.97 (m, 1H), 3.91 (s, 3H), 3.79-3.87 (m, 2H), 3.00-3.12 (m, 1H); LC-MS(ESI, m/z): $[M+H]^+ = 353.2$
137		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 7.41-7.43 (m, 1H), 6.85-6.87 (m, 1H), 6.50-6.71 (m, 3H), 6.26-6.34 (m, 1H), 5.73-5.80 (m, 1H), 4.90-5.05 (m, 2H), 3.97-4.20 (m, 1H), 3.63-3.93 (m, 3H), 2.19-2.50 (m, 5H); LC-MS(ESI, m/z): $[M+H]^+ = 370.2$

138		¹ H-NMR (300 MHz, CD ₃ OD) δ: 7.91 (d, 1H, <i>J</i> = 2.7 Hz), 7.52 (s, 1H), 7.35 (d, 1H, <i>J</i> = 1.5 Hz), 6.74 (d, 1H, <i>J</i> = 3.3 Hz), 6.53-6.67 (m, 1H), 6.41-6.42 (m, 1H), 6.23-6.33 (m, 1H), 5.71-5.78 (m, 1H), 4.77-4.87 (m, 1H), 3.91-4.13 (m, 1H), 3.86 (s, 3H), 3.55-3.81 (m, 3H), 2.03-2.41 (m, 2H); LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 353.2
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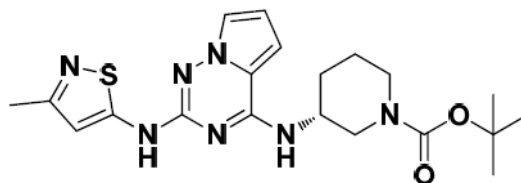
Example 139

Preparation of (*R*)-1-(3-((2-((3-methyl-isothiazol-5-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)piperidin-1-yl)prop-2-yn-1-one



5

Step 1: preparation of *tert*-butyl (*R*)-3-((2-((3-methyl-isothiazol-5-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)piperidine-1-carboxylate

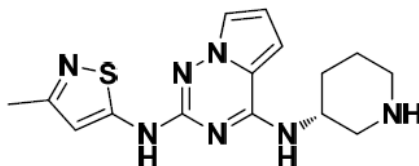


The product obtained in step 1 of Example 134 (352 mg, 1 mmol) and 3-methyl-isothiazole-5-amine hydrochloride (163 mg, 1.1 mmol) were dissolved in 1,4-dioxane / water (21 mL, 20 : 1), followed by the addition of tris(dibenzylidenepropanone)dipalladium (46 mg, 0.05 mmol), (±)-2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl (63 mg, 0.1 mmol) and cesium carbonate (650 mg, 2 mmol) under nitrogen atmosphere, and refluxed at 100 °C overnight. The reaction solution was cooled to room temperature, and filtered through celite. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (eluent: dichloromethane: methanol = 30 : 1) to give a pale yellow solid (349 mg). Yield: 81.2%. MS (ESI, *m/z*): [M+H]⁺: 430.2.

15

Step 2: preparation of (*R*)-*N*²-(3-methyl-isothiazol-5-yl)-*N*⁴-(piperidin-3-yl)

pyrrolo[2,1-*f*][1,2,4]triazine-2,4-diamine



The product obtained in step 1 (64 mg, 0.2 mmol) was dissolved in dichloromethane (15 mL), and to solubilize it methanol (10 mL) was added. Then 4N solution of hydrogen chloride in 1,4-dioxane (0.5 mL, 2 mmol) was added, and the mixture was reacted at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and used directly into the next step. MS (ESI, *m/z*): [M+H]⁺: 330.1.

Step 3: preparation of (*R*)-1-(3-((2-((3-methyl-isothiazol-5-yl)amino)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)piperidine-1-yl)prop-2-yn-1-one

The product obtained in step 2 (33 mg, 0.10 mmol) and propiolic acid (8.4 mg, 0.12 mmol) were dissolved in tetrahydrofuran (10 mL), followed by the addition of *N,N*-diisopropylethylamine (53 μL). The mixture was stirred at room temperature for 30 minutes, added with TBTU (4 mg), and then stirred at room temperature overnight. The reaction solution was concentrated, and purified by silica gel column chromatography (eluent: dichloromethane / methanol = 10 : 1) to give a pale yellow solid (6.1 mg). Yield: 16.1%. MS (ESI, *m/z*): [M+H]⁺: 382.2.

The following compounds (in Table 8) were prepared from similar starting materials by similar synthetic methods to those described in Example 139.

Table 8

Example	Structure	Characterization Data
140		LC-MS(ESI, <i>m/z</i>): [M+H] ⁺ = 368.2

Pharmacological evaluation

Test sample 1: BTK kinase activity inhibition assay

The BTK kinase (purchased from Invitrogen, No.: PV3363) was diluted with reaction buffer (40 mM Tris-HCl, pH 7.5; 20 mM MgCl₂, 0.1 mg/ml BSA; 1 mM DTT; 2 mM MnCl₂) to 2 times of the final concentration (which is 1.1 ng/μL) and added with 5 μL/well to a 96-well plate. The compounds of the present invention were serial diluted with deionized water to four times (i.e., 40 μM, 4 μM, 0.4 μM, 80 nM, 16 nM, 3.2 nM,

respectively) of the final concentrations (10 μ M, 1 μ M, 0.1 μ M, 20 nM, 4 nM, 0.8 nM, respectively), and added at 2.5 μ L/well to the test wells of the 96-well plate. After incubation at 25°C for 10 minutes, ATP (50 μ M) (purchased from Promega, No.: V9102) and 0.2 μ g/ μ L of Poly E4Y1 (purchased from Sigma, No.: P0275-25MG) were added with 2.5 μ L/well and incubated at 25°C for 120 minutes. After the reaction was completed, 10 μ L of the ADP-Glo reagent (ADP-Glo™ kinase assay kit, purchased from Promega, No.: V9102) was added to each well, and reacted at 25°C for 40 minutes. Then 20 μ L of the ADP-Glo kinase detection reagent was added to each well and reacted at 25°C for 30 minutes. The kinase activity was detected by luminescence using the ADP-Glo kinase assay kit according to the manufacture's instruction, and IC₅₀ values of the compounds of the present invention were calculated. The results are shown in Table 9.

Table 9 Results from the BTK kinase activity inhibition assay

Compound	BTK	Compound	BTK	Compound	BTK
1	+++	62	+++	104	+++
2	+++	65	+++	105	+++
4	+++	69	+++	108	+++
8	+++	70	++	111	+++
12	+++	71	+++	112	+++
13	+++	72	+++	114	+++
14	+++	73	+++	115	+++
15	+++	74	++	116	+++
16	+++	75	+++	118	+++
17	++	76	+++	119	+++
18	+++	77	+++	120	+++
30	++	78	++	121	+++
31	+++	79	+	122	+++
33	++	80	+++	123	+++
34	+++	81	+++	124	+++
35	+++	82	+++	125	+++
36	++	83	+++	126	+++
43	+++	84	+++	127	+++
44	+++	85	++	128	+++
45	++	88	++	129	+++
46	+++	92	+++	130	+++

47	+++	93	+++	131	+++
49	+++	94	+++	132	+++
50	+++	95	+++	134	+++
51	+++	96	+++	135	+++
52	++	99	++	136	+++
57	+++	101	++	137	+++
60	+++	102	+++	138	+++
61	+++	103	+++		

Table 9 shows the activity of the selected compounds of the present invention in the BTK activity inhibition assay, wherein "+++" means that the compound designated by it has an $IC_{50} \leq 50$ nM; "++" means that the compound designated by it has an $50 < IC_{50} \leq 100$ nM; and "+" means that the compound designated by it has an $100 < IC_{50} < 1000$ nM.

Test example 2: JAK3 kinase activity inhibition assay

The JAK3 kinase (purchased from SignalChem, No.: J03-11G) was diluted with reaction buffer (40 mM Tris-HCl, pH 7.5; 20 mM $MgCl_2$, 0.1 mg/ml BSA; 1 mM DTT) to 2 times of the final concentration (which is 0.5 ng/ μ L) and added with 5 μ L/well to a 96-well plate. The compounds of the present invention were serial diluted with deionized water to four times (i.e., 40 μ M, 4 μ M, 0.4 μ M, 80 nM, 16 nM, 3.2 nM, respectively) of the final concentrations (10 μ M, 1 μ M, 0.1 μ M, 20 nM, 4 nM, 0.8 nM, respectively), and added with 2.5 μ L/well to the test wells of the 96-well plate. After incubation at 25°C for 10 minutes, 10 μ M of ATP (purchased from Promega, No.: V9102) and 0.2 μ g/ μ L of Poly E4Y1 (purchased from Sigma, No.: P0275-25MG) were added at 2.5 μ L/well and reacted at 25°C for 60 minutes. After the reaction was completed, 10 μ L of the ADP-Glo reagent (ADP-Glo™ kinase assay kit, purchased from Promega, No.: V9102) was added to each well and reacted at 25°C for 40 minutes. Then 20 μ L of the ADP-Glo kinase detection reagent was added to each well and reacted at 25°C for 30 minutes. The kinase activity was detected by luminescence using the ADP-Glo kinase assay kit according to the manufacture's instruction, and IC_{50} values of the compounds of the present invention were calculated. The results are shown in Table 10.

Table 10 Results from the JAK3 kinase activity inhibition assay

Compound	JAK3	Compound	JAK3	Compound	JAK3
61	+++	85	++	118	++

62	++	88	++	119	++
65	++	92	+	120	++
69	++	93	++	121	++
70	++	94	+++	122	+++
71	+++	95	++	123	++
72	++	96	+++	124	++
73	++	99	++	125	+++
74	+	101	+	126	++
75	++	102	++	127	+++
76	++	103	+	128	++
77	++	104	++	129	++
78	++	105	++	130	++
79	++	108	+++	131	++
80	++	111	++	132	+++
81	++	112	++	134	+++
82	+++	114	++	135	++
83	+++	115	++	137	+++
84	++	116	++	138	++

Table 10 shows the activity of the selected compounds of the present invention in the JAK3 activity inhibition assay, wherein "+++" means that the compound designated by it has an $IC_{50} \leq 10$ nM; "++" means that the compound designated by it has an $10 < IC_{50} \leq 100$ nM; and "+" means that the compound designated by it has an $100 < IC_{50} < 1000$ nM.

Test example 3: IL-2 induced CTLL-2 cell proliferation assay

The compounds of the present invention were serial diluted with RPMI-1640 complete medium (purchased from Gibco, No.: 22440) to three times (i.e., 3 μ M, 0.6 μ M, 120 nM, 24 nM, 4.8 nM, 0.96 nM, respectively) of the final concentrations (1 μ M, 0.2 μ M, 40 nM, 8 nM, 1.6 nM, 0.32 nM, respectively), and added at 50 μ L/well to the test wells of a 96-well plate. Control wells with IL-2 (referred to as IL-2⁺) (IL-2 was purchased from R & D, No.: 402-ML-020/CF) and without IL-2 (referred to as IL-2⁻) (with addition of 50 μ L of the medium). CTLL-2 cells (purchased from ATCC, No.: TIB-214) at the logarithmic growth phase were rinsed with PBS buffer (pH 7.2), then resuspended in RPMI-1640 complete medium without IL-2, and seeded at 50000 cells/50 μ L/well in the

96-well plate. The plate was placed at 37°C, 5% CO₂ and pre-incubated for 1 hour. Then, to the test wells and the IL-2⁺ control well RPMI-1640 complete medium containing IL-2 (50 µL/well) was added, while to the IL-2⁻ control well RPMI-1640 complete medium without IL-2 (50 µL/well) was added. The cells were stimulated for 24 hours at 37°C, 5% CO₂. After this, the 96-well plate was taken out from the incubator. To each well 15 µL of CCK-8 reagent (purchased from DOJINDO, No.: DOJINDO-CK04) was added, and then the plate was placed in the incubator again and cultured for another 1-4 hours. Absorption was determined at 450 nm of wavelength, and IC₅₀ values of the compounds of the present invention were thereby calculated. The results are shown in Table 11.

Table 11 Results of the IL-2 induced CTLL-2 cell proliferation assay

Compound	CTLL-2
134	+++
137	++

Table 12 shows the activity of the selected compounds of the present invention in the CTLL-2 cell proliferation assay, wherein "+++" means that the compound designated by it has an IC₅₀ ≤100 nM; "++" means that the compound designated by it has an IC₅₀ of 100<IC₅₀<1000 nM.

Test example 4: p-BTK and p-PCL-γ2 inhibition assay in Ramos cells (Western blot assay)

Ramos cells (purchased from the Beijing Union Medical College) with starvation culture for 1 hour were treated with the compounds of the present invention for 1 hour, and then rinsed with PBS buffer (pH 7.2) to remove the compounds. Then they were resuspended in 100 µL of serum-free culture medium containing 1 µM of anti-human IgM F(ab')₂ (purchased from SBA company, No.: 2022-01) and stimulated on ice for 10 minutes. The cells were rinsed with PBS buffer (pH 7.2) to remove IgM and resuspended in 100 µL of protein lysis buffer (purchased from Sigma, No.: C2978), and then prepared and quantified the protein sample. 100 µg of the protein sample were taken and loaded on polyacrylamide gels for electrophoresis under 200V of voltage. After electrophoresis, protein blots were transferred to a PVDF membrane. The membrane was blocked with 3% BSA at room temperature for 2 hours and incubated overnight with the corresponding anti-p-BTK (pY223) (purchased from CST, No.: 5082S); anti-BTK (purchased from Abcam, No.: ab118156); anti-p-PLCγ2 (pY1217) (purchased from CST, No.: 3871S); anti-PLCγ2 (purchase from CST, No.: 3872S); and anti-β-actin (purchased from CWBIO,

No.: CW0096A)) antibodies at 4°C, and then incubated with horseradish peroxidase-conjugated IgG secondary antibody (purchased from CWBIO, No.: CW0103A) for 1 hour. The protein expression was detected by coloration using ECL substrate (purchased from GE, No.: RPN2109).

5 By the above method, compound **132** of the present application was tested. The results showed that compound **132** can significantly inhibit the expressions of p-BTK and p-PLC γ 2 in Ramos cells in a dose-dependent manner.

The result is shown in Figure 1.

10 **Test example 5: Type II collagen-induced arthritis (CIA) model in DBA/1J mice**

The CIA model is a widely-used animal model in the study of drugs for the treatment of rheumatoid arthritis in human. The experimental animals used in this experiment are DBA/1J mice (male, 6 to 8 weeks of age, purchased from Shanghai Silaike Laboratory Animal Co., Ltd., China). Mice were housed in an IVC system.

15 In order to induce the mice CIA model, a bovine type II collagen (CII) (purchased from Chondrex company, No.: 20022) solution was emulsified with the same volume of complete Freund's adjuvant (CFA) (purchased from Sigma-Aldrich, No.: F5881) using an electronic homogenizer to prepare an emulsion. Then, 70 μ L of the prepared emulsion was intradermally injected into the base of the tail of the mice as a primary immunization.

20 Three weeks after the primary immunization, one booster immunization was carried out. A bovine type II collagen solution was emulsified with the same volume of incompletely Freund's adjuvant (IFA) (purchased from Sigma-Aldrich, No.: F5506) to prepare an emulsion, and then 70 μ L of the prepared emulsion was intradermally injected in a single point into the hind back to complete the immunization. According to the following

25 criteria, Mice were evaluated for the severity of arthritis using an established scoring system ranging from 0 to 4 (0 score: no evidence of edema or swelling; 1 score: mild edema and redness confined to the ankle joint or tarsal; 2 scores: mild edema and redness, from the ankle joint to the tarsal; 3 scores: moderate edema and redness, from the ankle joint to the metatarsal; and 4 scores: severe edema and redness, from the ankle to the

30 whole instep and toes, or ankylosis of the ankle or wrist joints). The scores for the four limbs of each mouse were added together and the highest score was 16 (4×4).

According to their arthritis scores, 5 to 7 mice were assigned to each group of three groups, one model control group and two administration groups. Treatment starts when the average arthritis severity scores in each group were about 1-2. Two doses of 3 mg/kg and

35 10 mg/kg were designed and orally administrated once a day for 14 days. At the same

time, a normal control group was established. The results from the test groups were compared with the results of the normal control group and the model control group, so as to determine the therapeutic effect of the test compounds on arthritis in the model.

By comparison of the arthritis severity scores, compound **132** of the present invention was confirmed to have a good therapeutic effect on arthritis in the CIA model at the designed doses in a dose dependent manner.

The results are shown in Figure 2.

Test example 6: Adjuvant-induced arthritis (AIA) model in rats

100 mg of inactivated *Mycobacterium tuberculosis* (purchased from BD Difco, No.: 231141) accurately weighed and dissolved in 5 mL of incomplete Freund's adjuvant (IFA) (purchased from Sigma, No.: F5506), and then with 5 mL of physiological saline added, was homogeneously emulsified into 10 mg/mL of complete Freund's adjuvant (CFA). In order to induce the AIA model in rats, 50 Lewis rats in SPF grade (purchased from Beijing Vital River Laboratories (VRL), animal production license number: SCXK (Beijing) 2012-0001), male, weighing 180-200g, and adaptively feeding for 7 days, were injected with the complete Freund's adjuvant containing the inactivated *Mycobacterium tuberculosis* (H37RA, 10 mg/ml) at a dose of 0.1 ml/rat at the dorsal base of the tail to induce arthritis in rats. At the same time, three non-immunized rats were used as a normal control group. Rats were evaluated for the severity of arthritis using an established scoring system ranging from 0 to 4 as follows: 0 = no evidence of erythema or swelling; 1 = slight erythema or swelling of one of the toe joints; 2 = erythema or swelling of more than one toe; 3 = swelling of the ankle or wrist joint; 4 = swelling of all toes including the ankle joint. All four paws of the rat were scored individually, and the highest score was 16.

The paw volumes of the rats were measured by the drainage method using a plethysmometer (Plethysmometer PV-200, Chengdu Taimeng Science and Technology Co., Ltd.) to determine the volumes below the ankle joints (in mL). The rats were measured for paw volumes every other day from day 10 after primary immunization, i.e. day 1 of the administration. The volumes of the four limbs of each rat were added together, and then divided by 4 to give an average value. Two doses of 30 mg/kg and 100 mg/kg were designed and orally administrated once a day for 7 days. At the same time, a normal control group and a model control group were established, and the results from the test groups were compared with the results from the normal control group and the model control group, so as to determine the therapeutic effect of the test compounds on arthritis

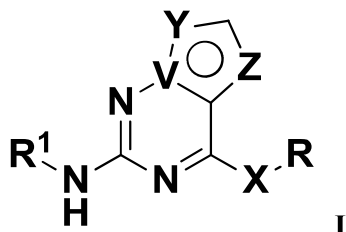
in the model.

By comparison of the arthritis severity scores, compound **132** of the present invention was confirmed to have a good therapeutic effect on arthritis in the AIA model at the designed doses.

5 The results are shown in Figure 3.

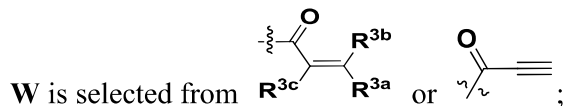
What is claimed is:

1. A compound represented by formula I:



5 wherein:

R is selected from C₃₋₈ cycloalkyl substituted by -NR²W; a 4- to 10-membered saturated N-heterocyclyl group, which contains only one nitrogen atom on its ring, and the nitrogen atom is substituted by **W**; or C₁₋₄ alkyl substituted by a 4- to 10-membered saturated N-heterocyclyl group which contains only one nitrogen atoms on its ring and the nitrogen atom is substituted by **W**;



V is selected from C or N;

X is selected from NR⁴, O or S;

Y is selected from CH, S or O;

15 **Z** is selected from CH, S, O or NR⁵;

R¹ is selected from C₆₋₁₂ aryl or 5- to 12-membered heteroaryl, optionally substituted by one or more **R**⁶;

R² is selected from hydrogen or C₁₋₈ aliphatic;

20 **R**^{3a}, **R**^{3b}, and **R**^{3c} are independently selected from the group consisting of hydrogen, halogen, and di(C₁₋₈ aliphatic)aminomethyl;

R⁴ is selected from hydrogen or C₁₋₈ aliphatic;

R⁵ is selected from hydrogen or C₁₋₈ aliphatic;

25 each **R**⁶ is independently selected from the group consisting of halogen, nitro, cyano, heterocyclyl, C₆₋₁₂ aryl, 5- to 12-membered heteroaryl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyloxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticacylamino C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticoxycarbonyl C₁₋₈ aliphatic, aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphatic, C₁₋₈

aliphaticsulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfinyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonylamino, C₁₋₈ aliphaticsulfonylamino C₁₋₈ aliphatic, sulfamoyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)phosphonyl C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy, heterocyclyloxy, heterocyclyl C₁₋₈ aliphaticoxy, hydroxy

5 C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, amino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticamino C₁₋₈ aliphaticoxy, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticacylamino C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphaticoxy, aminoacyl C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphaticoxy, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, heterocyclylamino,

10 heterocyclyl C₁₋₈ aliphaticamino, hydroxy C₁₋₈ aliphaticamino, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticamino, amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticacylamino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphaticamino, aminoacyl C₁₋₈ aliphaticamino, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphaticamino, C₁₋₈ aliphaticacylamino,

15 heterocyclyl C₁₋₈ aliphaticacylamino, heterocyclylacylamino, hydroxy C₁₋₈ aliphaticacylamino, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticacylamino, amino C₁₋₈ aliphaticacylamino, C₁₋₈ aliphaticamino C₁₋₈ aliphaticacylamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticacylamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, heterocyclyl C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, heterocyclyl C₁₋₈ aliphaticoxycarbonyl, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticoxycarbonyl,

20 aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, heterocyclyl C₁₋₈ aliphaticaminoacyl, heterocyclylaminoacyl, hydroxy C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticaminoacyl, amino C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticamino C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticaminoacyl, C₁₋₈ aliphaticsulphydryl, heterocyclylsulphydryl, heterocyclyl C₁₋₈ aliphaticsulphydryl, C₁₋₈ aliphaticsulfonyl, C₁₋₈

25 aliphaticsulfinyl, heterocyclylsulfonyl, heterocyclylsulfinyl, heterocyclyl C₁₋₈ aliphaticsulfonyl, heterocyclyl C₁₋₈ aliphaticsulfinyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, heterocyclyl C₁₋₈ aliphaticaminosulfonyl, heterocyclylaminosulfonyl, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticaminosulfonyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl, di(C₁₋₈ aliphatic)aminosulfinyl, heterocyclyl C₁₋₈ aliphaticaminosulfinyl,

30 heterocyclylaminosulfinyl, and di(C₁₋₈ aliphatic)phosphonyl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 12-membered heterocyclyl group containing one or more heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more substituents selected from the group consisting of

35 halogen, C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈

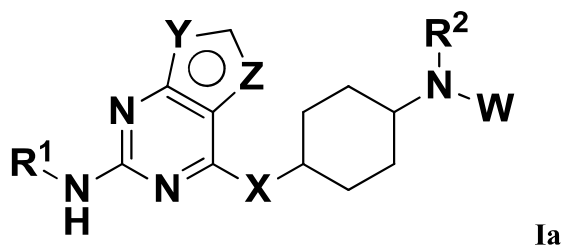
aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, heterocyclyl, 5- to 12-membered heteroaryl, hydroxy, C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, heterocyclyl C₁₋₈ aliphaticcarbonyl, hydroxy C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticcarbonyl, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, heterocyclylsulfonyl, heterocyclylsulfinyl, heterocyclyl C₁₋₈ aliphaticsulfonyl, heterocyclyl C₁₋₈ aliphaticsulfinyl, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, and di(C₁₋₈ aliphatic)aminosulfonyl; and

optionally, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl are independently substituted by one or more substituents selected from the group consisting of halogen, C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino and di(C₁₋₈ aliphatic)amino,

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein the compound is represented by formula

Ia:



wherein, X, Y, Z, W, R¹, and R² are all defined as in claim 1, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 2, wherein:

R¹ is selected from phenyl or 5- to 12-membered heteroaryl, optionally substituted by one or more R⁶;

each R⁶ is independently selected from the group consisting of halogen, heterocyclyl, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, heterocyclyl C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy, heterocycliloxy, heterocyclyl C₁₋₈ aliphaticoxy, hydroxy C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticoxy C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino,

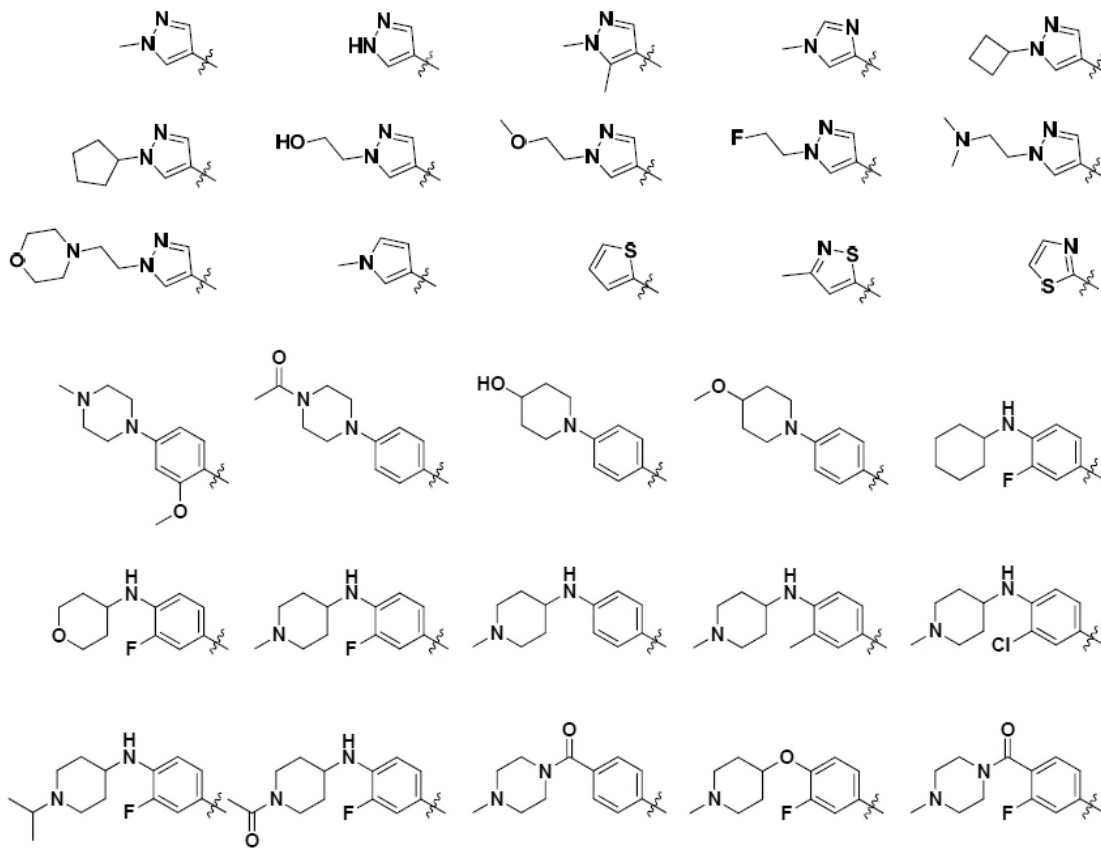
di(C₁₋₈ aliphatic)amino, heterocyclylamino, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphaticamino, C₁₋₈ aliphaticcarbonyl, heterocyclylcarbonyl, C₁₋₈ aliphaticaminoacyl, heterocyclylaminoacyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl, di(C₁₋₈ aliphatic)aminosulfinyl and heterocyclylaminosulfinyl, wherein heterocyclyl, as an independent group or a part of other

5 group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more substituents selected from the group consisting of halogen, C₁₋₈ aliphatic, hydroxy, C₁₋₈ aliphaticoxy, amino, C₁₋₈ aliphaticamino, di(C₁₋₈ aliphatic)amino and C₁₋₈ aliphaticcarbonyl;

10 wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 2 or 3, wherein R¹ is selected from the group

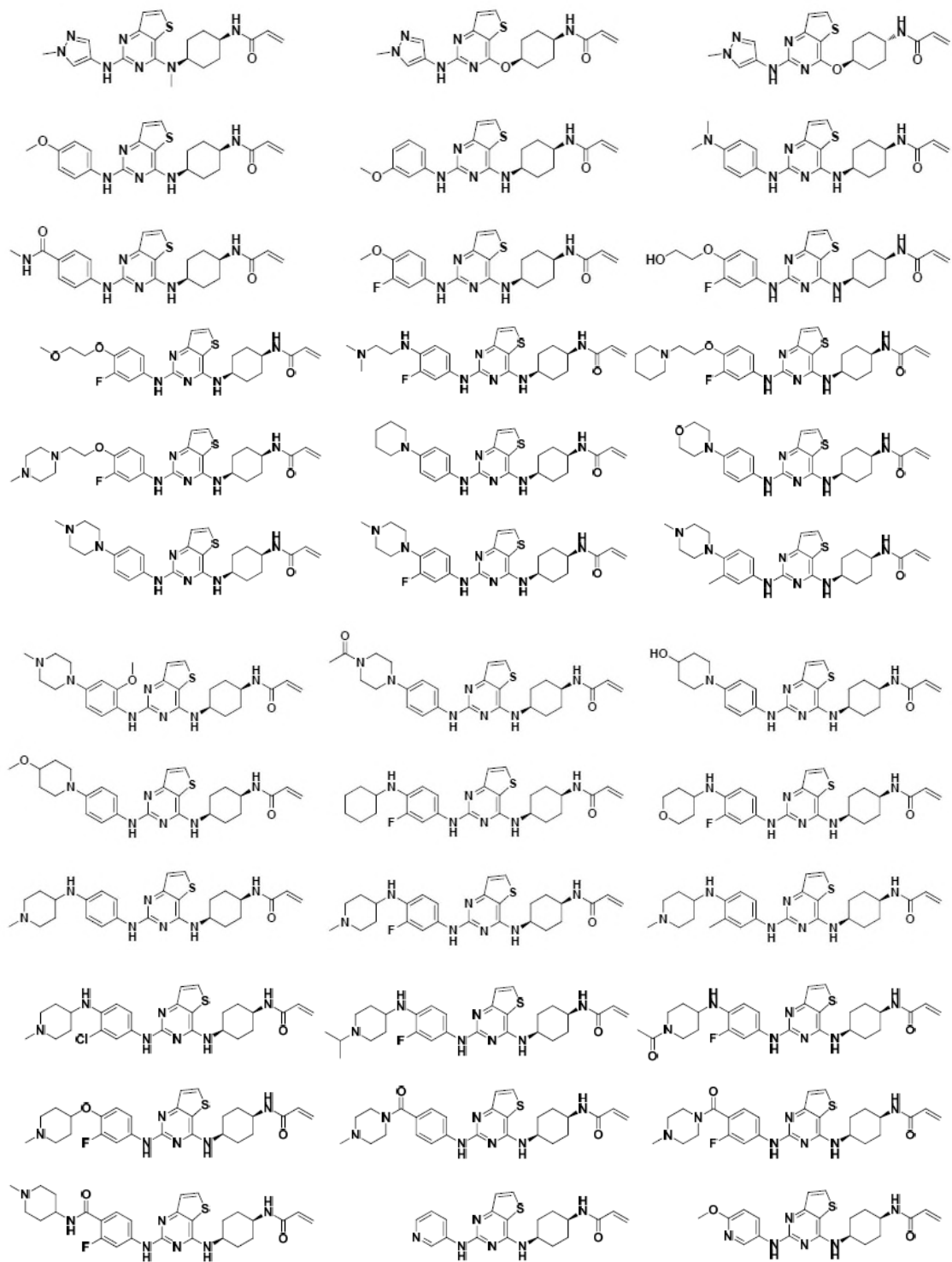
15 consisting of:

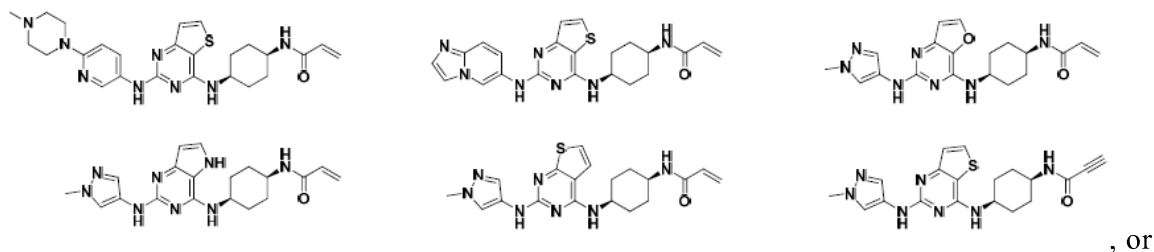




5. The compound according to any one of claims 2 to 4, wherein the compound is selected from the group consisting of:



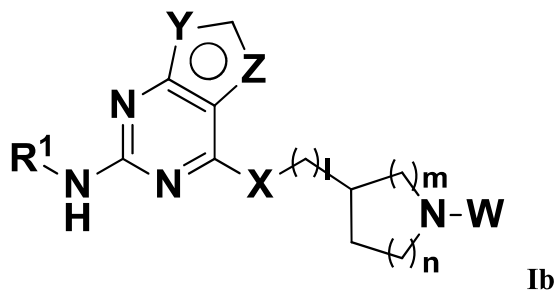




a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, wherein the compound is represented by formula

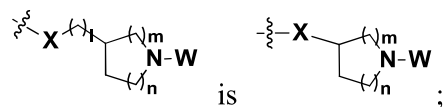
Ib:



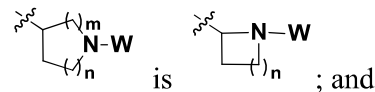
wherein:

X, Y, Z, W, and R¹ are all defined as in claim 1;

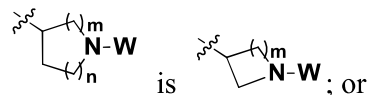
I is selected from 0, 1, 2, 3, or 4, wherein when **I** is 0,



m is selected from 0, 1, 2, 3, or 4; wherein when **m** is 0,



n is selected from 0, 1, 2, or 3; wherein when **n** is 0,



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

7. The compound according to claim 6, wherein:

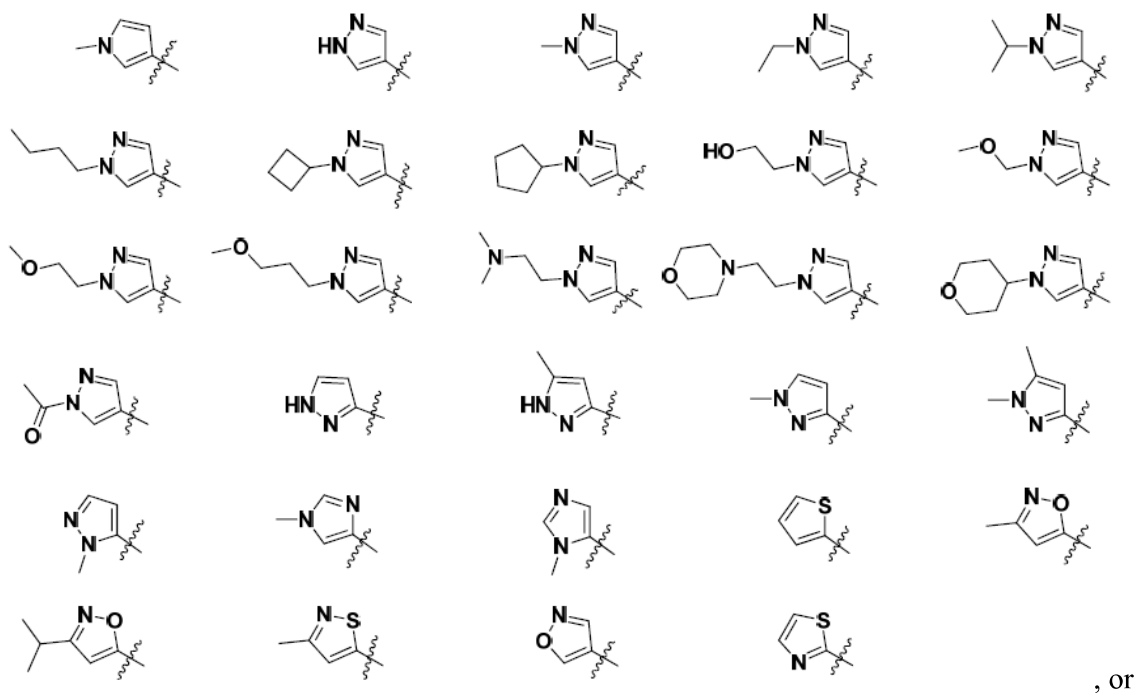
R¹ is a 5- to 6-membered heteroaryl group, optionally substituted by one or more **R⁶**;

each **R⁶** is independently selected from the group consisting of halogen, nitro, cyano, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocycl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticoxycarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyloxy C₁₋₈ aliphatic, aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticacylamino C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfinyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonylamino

C₁₋₈ aliphatic, sulfamoyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminosulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, C₁₋₈ aliphaticsulfonylamino, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, aminosulfinyl, C₁₋₈ aliphaticaminosulfinyl, di(C₁₋₈ aliphatic)aminosulfinyl, heterocyclylaminosulfinyl, heterocyclyl, C₆₋₁₂ aryl and 5-12 membered heteroaryl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more substituents selected from the group consisting of halogen, hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticcarbonyl; and C₆₋₁₂ aryl or 5- to 12-membered heteroaryl is optionally substituted by one or more substituents selected from the group consisting of halogen and C₁₋₈ aliphatic; wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

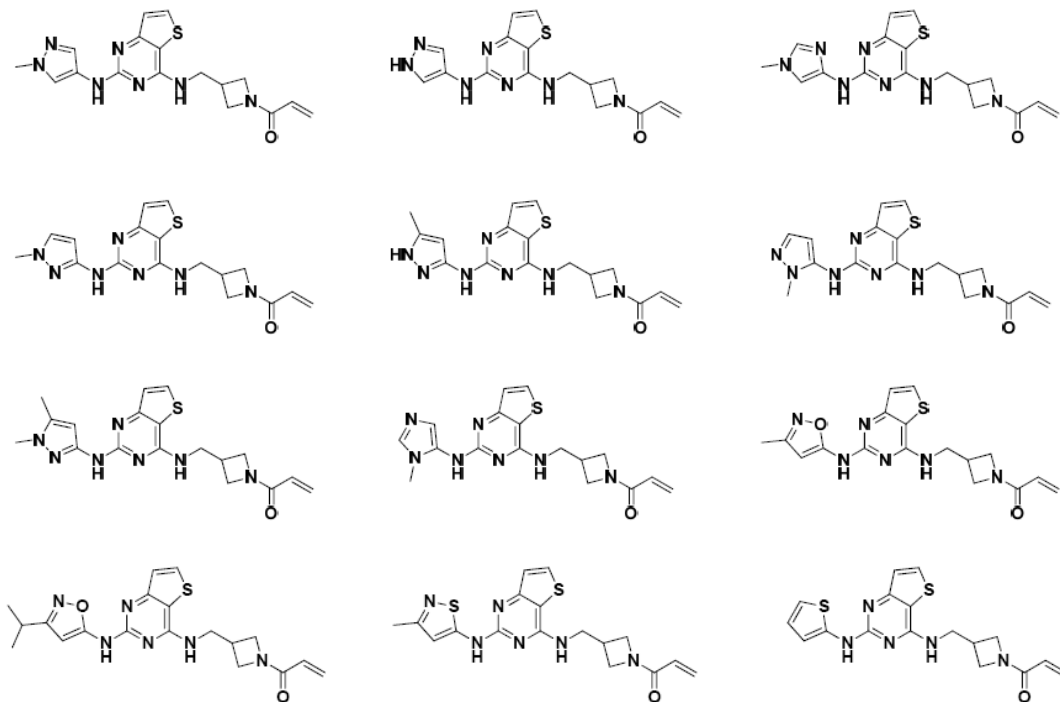
8. The compound according to claim 6 or 7, wherein R¹ is a 5-membered heteroaryl group, preferably selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, thienyl, isoxazolyl, thiazolyl and isothiazolyl, and R¹ is optionally substituted by one or two R⁶; each R⁶ is independently selected from the group consisting of C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl and heterocyclyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 5- to 6-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S; optionally, each heterocyclyl is independently substituted by one or more C₁₋₈ aliphatic substituents, wherein C₁₋₈ aliphatic is independently selected from the group consisting of C₁₋₈ alkyl and C₃₋₈ cycloalkyl, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of claims 6 to 8, wherein R¹ is selected from the group consisting of:

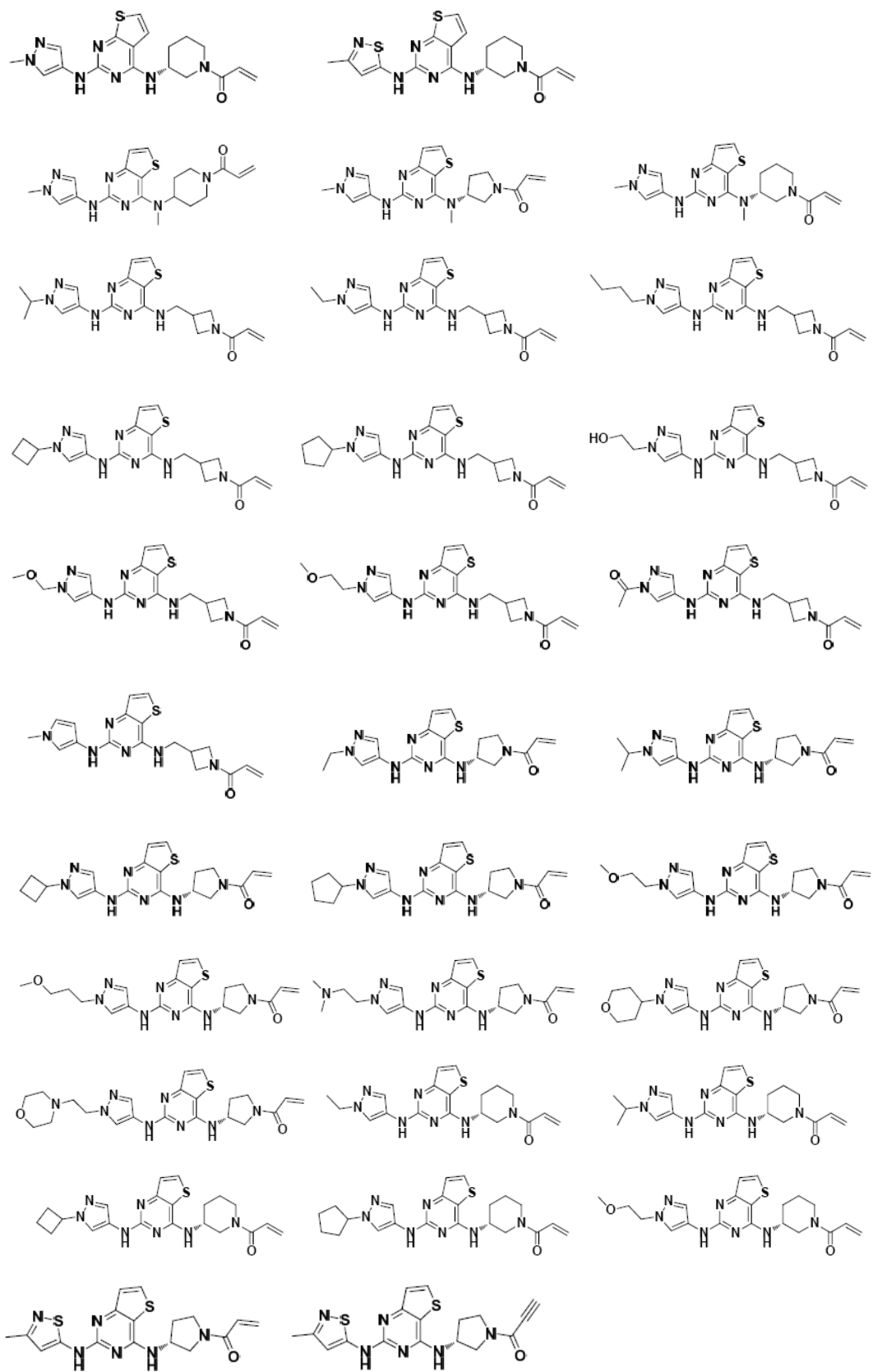


a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

- 5 10. The compound according to any one of claims 6 to 9, wherein the compound is selected from the group consisting of:





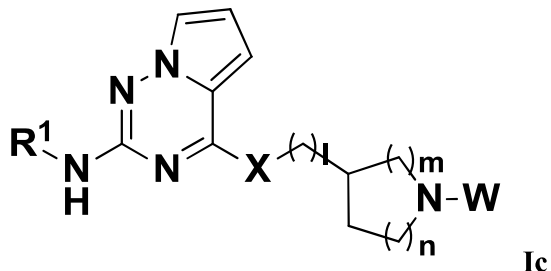


5

, or

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

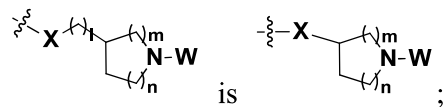
11. The compound according to claim 1, wherein the compound is represented by formula **Ic**:



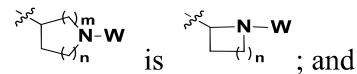
wherein:

X, **W**, and **R¹** are all defined as in claim 1;

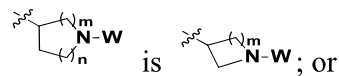
l is selected from 0, 1, 2, 3, or 4; wherein when **l** is 0,



m is selected from 0, 1, 2, 3, or 4; wherein when **m** is 0,



n is selected from 0, 1, 2, or 3; wherein when **n** is 0,



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

12. The compound according to claim 11, wherein:

R¹ is a 5- to 6-membered heteroaryl group, optionally substituted by one or more **R⁶**;

each **R⁶** is independently selected from the group consisting of halogen, nitro, cyano, C₁₋₈ aliphatic, C₁₋₈ halo aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticoxycarbonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyloxy C₁₋₈ aliphatic, aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminoacyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminoacyl C₁₋₈ aliphatic, C₁₋₈ aliphaticacylamino C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfinyl C₁₋₈ aliphatic, C₁₋₈ aliphaticsulfonylamino C₁₋₈ aliphatic, sulfamoyl C₁₋₈ aliphatic, C₁₋₈ aliphaticaminosulfonyl C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)aminosulfonyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl, C₁₋₈ aliphaticoxycarbonyl, aminoacyl, C₁₋₈ aliphaticaminoacyl, di(C₁₋₈ aliphatic)aminoacyl, C₁₋₈ aliphaticoxy, C₁₋₈ aliphaticsulfonyl, C₁₋₈ aliphaticsulfinyl, C₁₋₈ aliphatic sulfonylamino, sulfamoyl, C₁₋₈ aliphaticaminosulfonyl, di(C₁₋₈ aliphatic)aminosulfonyl, aminosulfinyl, C₁₋₈

aliphaticaminosulfinyl, di(C₁₋₈ aliphatic)aminosulfinyl, heterocyclylaminosulfinyl, heterocyclyl, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl, wherein:

heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S; each heterocyclyl is optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxy, C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy and C₁₋₈ aliphaticcarbonyl; and

optionally, C₆₋₁₂ aryl and 5- to 12-membered heteroaryl are independently substituted by one or more substituents selected from the group consisting of halogen and C₁₋₈ aliphatic;

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

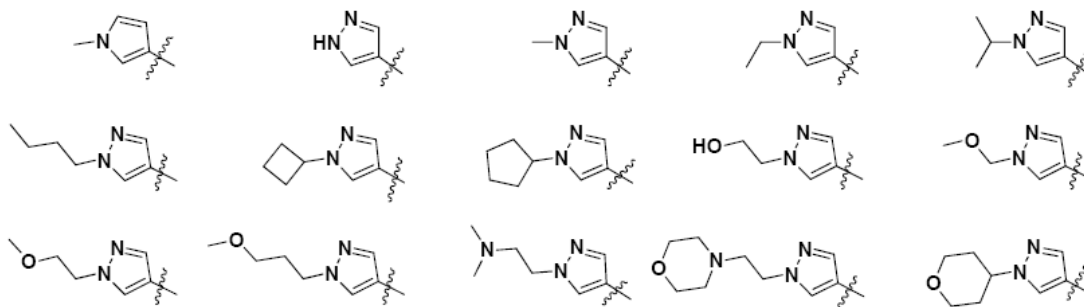
13. The compound according to claim 11 or 12, wherein:

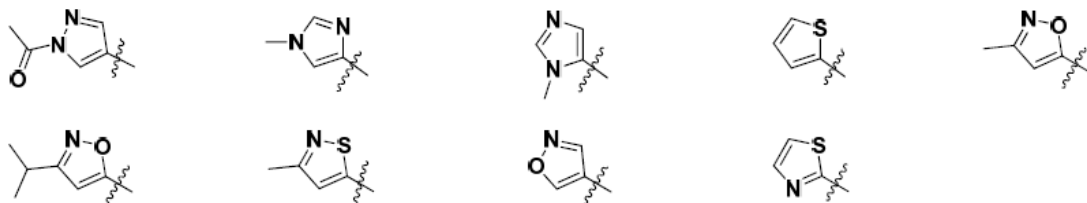
R¹ is a 5-membered heteroaryl group, optionally substituted by one or two **R**⁶;

each **R**⁶ is independently selected from the group consisting of C₁₋₈ aliphatic, hydroxy C₁₋₈ aliphatic, C₁₋₈ aliphaticoxy C₁₋₈ aliphatic, amino C₁₋₈ aliphatic, C₁₋₈ aliphaticamino C₁₋₈ aliphatic, di(C₁₋₈ aliphatic)amino C₁₋₈ aliphatic, heterocyclyl C₁₋₈ aliphatic, C₁₋₈ aliphaticcarbonyl and heterocyclyl, wherein heterocyclyl, as an independent group or a part of other group(s), represents a saturated or partially unsaturated 3- to 8-membered heterocyclyl group containing one or two heteroatoms selected from the group consisting of N, O, and S; each heterocyclyl is optionally substituted by one or more C₁₋₈ aliphatic substituents;

wherein C₁₋₈ aliphatic, at each occurrence, is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl and C₄₋₈ cycloalkenyl, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof.

14. The compound according to any one of claims 11 to 13, wherein **R**¹ is selected from the group consisting of:

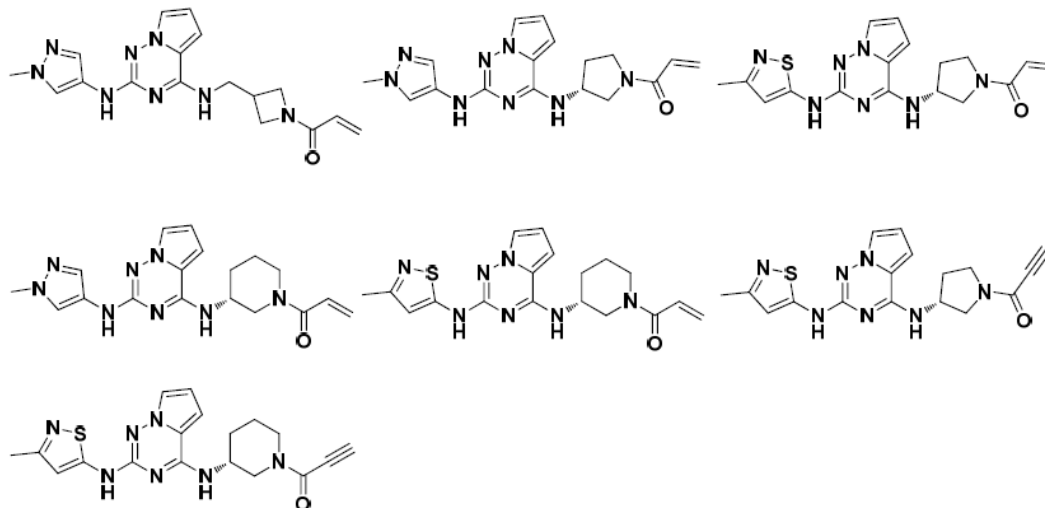




, or

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

15. The compound according to any one of claims 11 to 14, wherein the compound is
5 selected from the group consisting of:



, or

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

16. A pharmaceutical composition comprising the compound according to any one of
10 claims 1 to 15, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients.

17. The pharmaceutical composition according to claim 16, further comprising one or
15 more agents selected from the group consisting of an immunosuppressant, a corticosteroid, a nonsteroidal anti-inflammatory drug, a Cox-2 specific inhibitor, a TNF- α binding protein, an interferon, and an interleukin.

18. Use of the compound according to any one of claims 1 to 15 or a stereoisomer, a
20 tautomer, a solvate, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for inhibiting BTK and/or JAK3 activities.

19. Use of the compound according to any one of claims 1 to 15 or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the prevention or treatment of a BTK- and/or JAK3-mediated disease.

20. The use according to claim 19, wherein the disease is selected from the group consisting of an autoimmune disease, an inflammatory disease, a heteroimmune condition or disease, a thromboembolic disease, and a cancer.

21. The use according to claim 19, wherein the disease is selected from the group consisting of rheumatoid arthritis, osteoarthritis, juvenile arthritis, chronic obstructive pulmonary diseases, multiple sclerosis, systemic lupus erythematosus, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and irritable bowel syndrome.

22. The use according to claim 21, wherein the cancer is selected from the group consisting of B-cell chronic lymphocytic leukemia, acute lymphocytic leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, acute myelogenous leukemia, diffuse large B-cell lymphoma, multiple myeloma, mantle cell lymphoma, and small lymphocytic lymphoma.

23. A method of inhibiting BTK and/or JAK3 activities in a biological system comprising bringing the biological system into contact with the compound according to any one of claims 1 to 15, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, or with the pharmaceutical composition according to claim 16 or 17, wherein the biological system is an enzyme or a cell.

24. Use of the compound according to any one of claims 1 to 15, or a stereoisomer, a tautomer, a solvate, or a pharmaceutically acceptable salt thereof, in combination with one or more active agents selected from the group consisting of an immunosuppressant, a corticosteroid, a nonsteroidal anti-inflammatory drug, a Cox-2 specific inhibitor, a TNF- α binding protein, an interferon and an interleukin in the manufacture of a medicament for treating a BTK- and/or JAK3- mediated disease.