

FUSED PYRAZOLE DERIVATIVES, PREPARATION METHOD THEREOF, AND USE
THEREOF IN TREATMENT OF CANCERS, INFLAMMATION AND IMMUNE
DISEASES

5 TECHNICAL FIELD

The present invention relates to novel fused pyrazole derivatives and their pharmaceutically acceptable salts thereof or pharmaceutical compositions comprising these compounds, and to methods of preparing these compounds. The present invention also relates to use of the fused pyrazole derivatives and their pharmaceutically acceptable salts thereof or the pharmaceutical
10 compositions comprising these compounds in the preparation of therapeutic agents, especially as a Bruton tyrosine kinase inhibitor, and to use of the fused pyrazole derivatives and their pharmaceutically acceptable salts thereof or the pharmaceutical compositions in the preparation of medicaments for treating and/or preventing tumors and inflammatory diseases.

15 BACKGROUND

Bruton tyrosine kinase (BTK) is an important member of Tec tyrosine kinase family, which is present in plasmocytes including B cells, mastocytes and macrophages, and plays a decisive role in the B cell receptor (BCR) mediated signal pathway. When BTK is activated by upstream Src family kinases, it phosphorylates downstream phospholipases C (PLC), thereby activating
20 the PI3 and DAG signal pathway. This signal pathway promotes the proliferation, adhesion and survival of cells, and plays an important role in the development of B cell lymphomas.

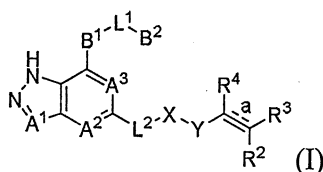
By inhibiting the activity of BTK, BTK inhibitors can inhibit the proliferation of B cell lymphoma cells, destroy the adhesion of tumor cells, and promote the apoptosis of tumor cells, so that BTK becomes a drug target of interest in B cells-associated cancers, especially B cell
25 lymphoma and leukemia, for example, non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and mantle cell lymphoma (MCL), etc. Currently, the only drug with BTK specific inhibition in market is Ibrutinib from Pharmacyclics/JNJ. Ibrutinib is an irreversible small molecule BTK inhibitor, which has significant efficacy on the treatment of MCL, CLL, WM, etc., and is safe. Other BTK inhibitors entering clinical trials for targeting cell lymphomas
30 comprise CC-292 from Celgene company, ACP-196 from Acerta company, ONO-4059 from ONO Company, and BGB-3111 from Beigene Company, and so on.

In addition to anti-B cell lymphomas and anti-leukemia effects, BTK inhibitors can further inhibit the production of B cell autoantibodies and cytokines. Mutations in BTK can lead to a rare genetic disease – X-Linked Agammaglobulinemia (XLA). Because the function of BTK is inhibited in this disease, resulting in inhibition of the production or maturation of B cells and reduction of the circulating antibodies, the patients are prone to serious and even fatal infections. Pre-clinical animal model studies showed that BTK gene-deficient mice can resist to collagen-induced arthritis, and clinical results also demonstrated that Rituxan, an antibody drug for B cell depletion, is efficacious for the treatment of immune disorders. Therefore, the BTK inhibitors can also be used for treating autoimmune-related diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), anaphylactic diseases (such as, esophagitis, eosinophilic esophagitis), and so on. Currently, there are not yet a BTK specific inhibitor for use in immune diseases in the market, but several are in clinical stages, for example, CC-292 from Celgene Company, HM-71224 from Hanmi, PRN-1008 from Principia, and a compound from Pharmacyclics.

As BTK plays an important role in a plurality of signaling pathways, the development of BTK inhibitors has attracted attention from many biopharmaceutical companies. A series of patent applications on BTK inhibitors have been disclosed, including WO2007087068, WO2010126960, WO2011019780, WO2011090760, WO2012135801, WO2012158764, WO2013060098, WO2013081016, WO2013010869, WO2013113097, CN103113375, WO2014068527, WO2014125410, WO2014173289, WO2013118986, WO2015017502, WO2015048689, etc. However, there is still a need to develop new compounds with better efficacy. With continuous efforts, the inventor designs a compound having the structure of formula (I), and finds that the compounds having such structure exhibit excellent effects and functions.

SUMMARY OF THE INVENTION

The present invention is to provide a compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof, or a pharmaceutically acceptable salt thereof:



wherein:

A^1 , A^2 and A^3 are each independently selected from the group consisting of CR^1 or N;

B^1 is independently selected from the group consisting of C_{3-8} cyclic, 3- to 8-membered
 5 heterocyclic group, aryl, or heteroaryl, wherein cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^1 ;

B^2 is independently selected from the group consisting of H, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, or heteroaryl, wherein cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^2 ;

10 L^1 is independently selected from the group consisting of $-C_{0-2}$ alkyl-, $-CR^5R^6-$, $-C_{1-2}$ alkyl(R^5)(OH)-, $-C(O)-$, $-CR^5R^6O-$, $-OCR^5R^6-$, $-SCR^5R^6-$, $-CR^5R^6S-$, $-NR^5-$, $-NR^5C(O)-$, $-C(O)NR^5-$, $-NR^5CONR^6-$, $-CF_2-$, $-O-$, $-S-$, $-S(O)_m-$, $-NR^5S(O)_2-$ or $-S(O)_2NR^5-$;

L^2 is independently selected from the group consisting of $-C_{0-4}$ alkyl-, $-C(O)-$, $-O-$, $-NR^7-$, $-NR^7C(O)-$ or $-NR^7S(O)_2-$;

15 X is independently selected from the group consisting of C_{0-4} alkyl, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, or heteroaryl, wherein alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^3 ;

Y is independently selected from the group consisting of $-C(O)-$, $-NR^8C(O)-$, $-S(O)_m-$ or $-NR^8S(O)_m-$;

20 R^1 is independently selected from the group consisting of H, D, C_{0-4} alkyl, halogen or cyano;

bond $\equiv$ is a double bond or a triple bond;

when bond $\equiv$ is a double bond, R^2 , R^3 and R^4 are each independently selected from the group consisting of H, D, cyano, halogen, alkyl, cyclic group, heterocyclic group, aryl, or
 25 heteroaryl, wherein alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^4 ; when bond $\equiv$ is a triple bond, R^3 and R^4 are absent, and R^2 is independently selected from the group consisting of H, D, cyano, halogen, alkyl, cyclic group, heterocyclic group, aryl, or heteroaryl, wherein alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^4 ; wherein R^3 and R^2 or R^3 and R^4 ,

together with the carbon atom attached thereto, can form a ring which contains optionally heteroatom(s);

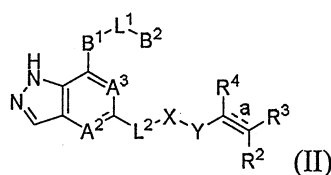
R^5 , R^6 , R^7 and R^8 are each independently selected from the group consisting of H, D, C_{0-8} alkyl, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, or heteroaryl, wherein alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^5 ;

G^1 , G^2 , G^3 , G^4 and G^5 are each independently selected from the group consisting of H, D, halogen, cyano, alkyl, alkenyl, alkynyl, cyclic group, heterocyclic group, aryl, heteroaryl, $-OR^9$, $-OC(O)NR^9R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^9R^{10}$, $-C(O)R^9$, $-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-NR^9C(O)NR^{10}R^{11}$, $-S(O)_mR^{10}$ and $-NR^9S(O)_mR^{10}$, wherein alkyl, alkenyl, alkynyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more substituents selected from the group consisting of D, halogen, cyano, C_{1-8} alkyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclic group, $-OR^{12}$, $-OC(O)NR^{12}R^{13}$, $-C(O)OR^{12}$, $-C(O)NR^{12}R^{13}$, $-C(O)R^{12}$, $-NR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, $-NR^{12}C(O)NR^{13}R^{14}$, $-S(O)_mR^{12}$, or $-NR^{12}S(O)_mR^{13}$;

R^9 , R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_1 - C_6 heteroalkyl, C_{3-8} cycloalkyl, 3- to 8-membered monocyclic heterocyclic group, monocyclic heteroaryl or monocyclic aryl; and

m is 1 or 2.

In an embodiment of the present invention, a compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof is a compound represented by formula (II), or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof:



wherein:

A^2 and A^3 are each independently selected from the group consisting of CH or N;

B^1 is independently selected from the group consisting of C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, or heteroaryl, wherein cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^1 ;

B^2 is independently selected from the group consisting of H, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, or heteroaryl, wherein cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^2 ;

L^1 is independently selected from the group consisting of $-C_{0-2}$ alkyl-, $-CR^5R^6$ -, $-C_{1-2}$ alkyl(R^5)(OH)-, $-C(O)$ -, $-CR^5R^6O$ -, $-OCR^5R^6$ -, $-SCR^5R^6$ -, $-CR^5R^6S$ -, $-NR^5$ -, $-NR^5C(O)$ -, $-C(O)NR^5$ -, $-NR^5CONR^6$ -, $-CF_2$ -, $-O$ -, $-S$ -, $-S(O)_m$ -, $-NR^5S(O)_2$ - or $-S(O)_2NR^5$ -;

L^2 is independently selected from the group consisting of $-C_{0-4}$ alkyl-, $-C(O)$ -, $-O$ -, $-NR^7$ -, $-NR^7C(O)$ - or $-NR^7S(O)_2$ -;

X is independently selected from the group consisting of C_{0-4} alkyl, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, or heteroaryl, wherein alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^3 ;

Y is independently selected from the group consisting of $-C(O)$ -, $-NR^8C(O)$ -, $-S(O)_m$ - or $-NR^8S(O)_m$ -;

bond $\equiv$ is a double bond or a triple bond;

when bond $\equiv$ is a double bond, R^2 , R^3 and R^4 are each other independently selected from the group consisting of H, D, cyano, halogen, alkyl, cyclic group, heterocyclic group, aryl or heteroaryl, wherein alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^4 ; and when bond $\equiv$ is a triple bond, R^3 and R^4 are absent, and R^2 is independently selected from the group consisting of H, D, cyano, halogen, alkyl, cyclic group, heterocyclic group, aryl, or heteroaryl, wherein alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^4 ; wherein R^3 and R^2 or R^3 and R^4 , together with the carbon atom attached thereto, can form a ring which contains optionally heteroatom(s);

R^5 , R^6 , R^7 and R^8 are each independently selected from the group consisting of H, D, C_{0-8} alkyl, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, or heteroaryl, wherein alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^5 ;

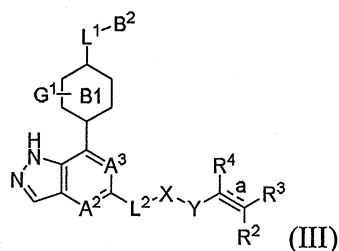
G^1 , G^2 , G^3 , G^4 and G^5 are each independently selected from the group consisting of H, D, halogen, cyano, alkyl, alkenyl, alkynyl, cyclic group, heterocyclic group, aryl, heteroaryl, $-OR^9$, $-OC(O)NR^9R^{10}$, $-C(O)OR^{10}$, $-C(O)NR^9R^{10}$, $-C(O)R^9$, $-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-NR^9C(O)NR^{10}R^{11}$, $-S(O)_mR^{10}$ and $-NR^9S(O)_mR^{10}$, wherein alkyl, alkenyl, alkynyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more substituents selected from the group

consisting of D, halogen, cyano, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclic group, -OR¹², -OC(O)NR¹²R¹³, -C(O)OR¹², -C(O)NR¹²R¹³, -C(O)R¹², -NR¹²R¹³, -NR¹²C(O)R¹³, -NR¹²C(O)NR¹³R¹⁴, -S(O)_mR¹², or -NR¹²S(O)_mR¹³;

R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₃₋₈ cycloalkyl, 3- to 8-membered monocyclic heterocyclic group, monocyclic heteroaryl or monocyclic aryl; and

m is 1 or 2.

In another embodiment of the present invention, a compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof is a compound represented by formula (III), or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof:

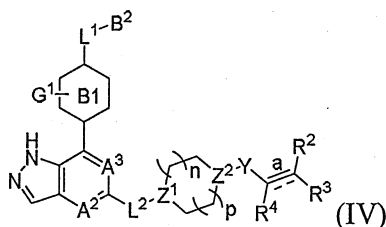


wherein:

B¹ is a phenyl ring or a 6-membered heteroaryl ring;

A², A³, B², L¹, L², X, Y, bond $\equiv$, R², R³, R⁴ and G¹ are as defined in claim 1 or 2.

In another embodiment of the present invention, a compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof is a compound represented by formula (IV), or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof:



wherein:

Z¹ and Z² are each independently selected from the group consisting of C(R^a), or N;

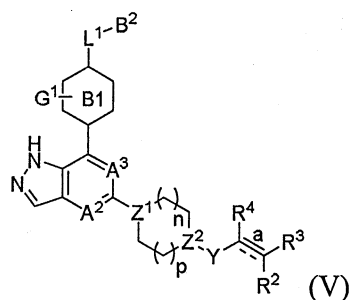
R^a is H or alkyl;

n and p are each independently selected from the group consisting of 0, 1 or 2;

A^2 , A^3 , B^1 , B^2 , L^1 , L^2 , Y, bond $\equiv$, R^2 , R^3 , R^4 and G^1 are as defined in any one of claims

1-3.

In another embodiment of the present invention, a compound represented by formula (I) or
5 its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof is a compound represented by formula (V), or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof:



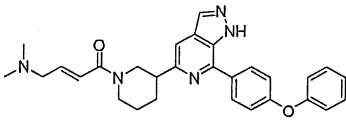
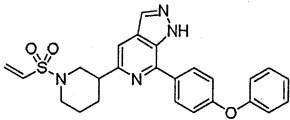
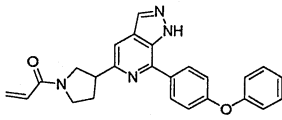
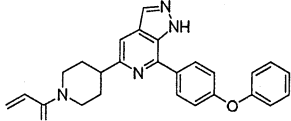
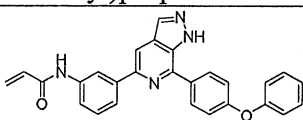
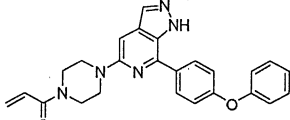
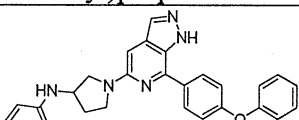
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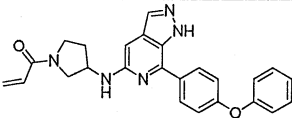
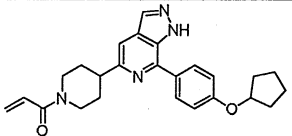
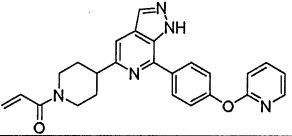
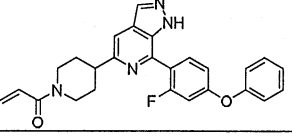
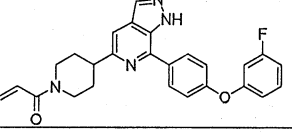
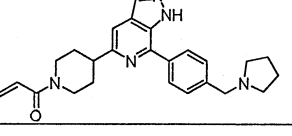
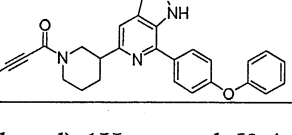
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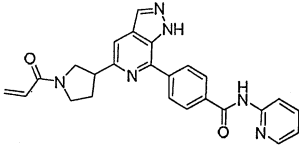
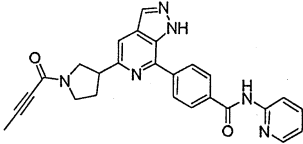
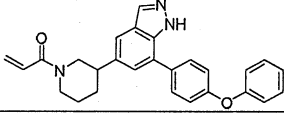
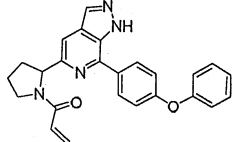
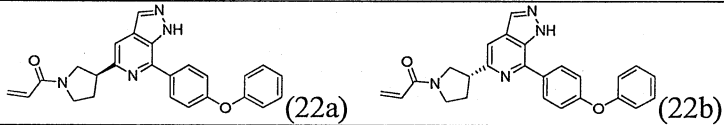
A^2 , A^3 , B^1 , B^2 , L^1 , Y, bond $\equiv$, R^2 , R^3 , R^4 , G^1 , Z^1 , Z^2 , n and p are as defined in any one of claims 1-4.

Representative compounds of the present invention include, but are not limited to:

Compound No.	Compound Structure and Nomenclature
1.	
	1-(3-(7-(4-(morpholinomethyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one
2.	
	1-(3-(7-(4-(oxetan-3-oxy)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one
3.	
	1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one

4.	 (E)-4-(dimethylamino)-1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)but-2-en-1-one
5.	 7-(4-phenoxyphenyl)-5-(1-(ethenylsulfonyl)piperidin-3-yl)-1H-pyrazolo[3,4-c]pyridine
6.	 1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one
7.	 1-(4-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one
8.	 N-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)phenyl)acrylamide
9.	 1-(4-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperazin-1-yl)prop-2-en-1-one
10.	 N-(1-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-3-yl)acrylamide

11.	
	1-(3-((7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one
12.	
	1-(4-(7-(4-(cyclopentyloxy)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one
13.	
	1-(4-(7-(4-(pyridin-2-oxy)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one
14.	
	1-(4-(7-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one
15.	
	1-(4-(7-(4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one
16.	
	1-(4-(7-(4-(pyrrolidin-1-ylmethyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one
17.	
	1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)but-2-en-1-one

18.	
	4-(5-(1-acryloylpyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)-N-(pyridin-2-yl)benzamide
19.	
	4-(5-(1-(but-2-ynoyl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)-N-(pyridin-2-yl)benzamide
20.	
	1-(3-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)piperidin-1-yl)prop-2-en-1-one
21.	
	1-(2-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one
22.	
	(S)-1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one 22a and (R)-1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one 22b

or their tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and pharmaceutically acceptable salts thereof.

The present invention is further directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

Another aspect of the present invention relates to use of the compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same in the preparation of Bruton tyrosine kinase inhibitors.

5 Another aspect of the present invention relates to use of the compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising the same in the preparation of a medicament for treating and/or preventing tumors, inflammatory diseases, and the like.

10 The present invention also relates to a method of treating and/or preventing tumors, inflammatory diseases, and the like, comprising administering a therapeutically effective amount of a compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same to a patient in need thereof.

15 Another aspect of the present invention relates to a compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof and a pharmaceutically acceptable salt thereof for use as a medicament for treating and/or preventing tumors, inflammatory diseases, and the like.

20 DETAILED DESCRIPTION

The terms as used in the description and claims have the following meanings, unless otherwise indicated.

The expression "C_{x-y}" as used herein means the range of carbon atoms, wherein both x and y are an integer. For Example, C₃₋₈ cyclic group means a cyclic group having 3-8 carbon atoms,
25 and -C₀₋₂ alkyl means an alkyl group having 0-2 carbon atoms, wherein -C₀ alkyl refers to a single chemical bond.

"Alkyl" refers to a saturated aliphatic hydrocarbon group, including straight and branched groups having 1-20 carbon atoms, e.g., straight or branched groups having 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. Non-limiting
30 examples include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, 1,1-dimethyl-propyl, 1,2-dimethyl-propyl, 2,2-dimethyl-propyl, 1-ethyl-propyl,

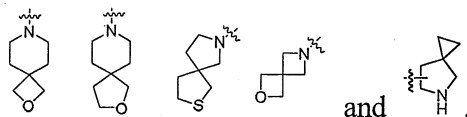
2-methyl-butyl, 3-methyl-butyl, *n*-hexyl, 1-ethyl-2-methyl-propyl, 1,1,2-trimethyl-propyl, 1,1-dimethyl-butyl, 1,2-dimethyl-butyl, 2,2-dimethyl-butyl, 1,3-dimethyl-butyl, 2-ethyl-butyl, and any branched isomer thereof, etc. Alkyl can be optionally substituted or unsubstituted.

“Cyclic group” refers to saturated or partially unsaturated, mono-cyclic or multi-cyclic hydrocarbon substituents containing 3-12 ring atoms, such as, 3-12, 3-10, or 3-6 ring atoms, or the cyclic group can be a 3-, 4-, 5-, or 6-membered ring. Non-limiting examples of mono-cyclic groups comprise cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl, and the like. Cyclic group can be optionally substituted or unsubstituted.

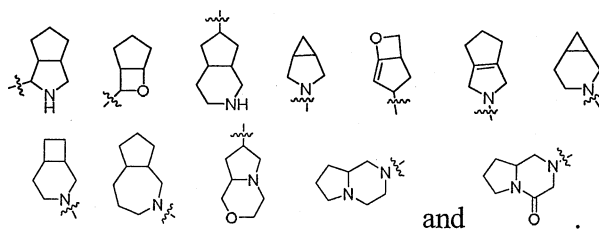
“Heterocyclic group” refers to saturated or partially unsaturated, mono-cyclic or multi-cyclic hydrocarbon substituents containing 3-20 ring atoms, such as, 3-16, 3-12, 3-10, or 3-6 ring atoms, in which one or more ring atoms are heteroatom(s) selected from the group consisting of nitrogen, oxygen and S(O)_m (wherein m is an integer from 0 to 2), excluding the case that any ring moiety is -O-O-, -O-S- or -S-S-, and the remainder ring atoms are carbon. Preferably, the heterocyclic group comprises 3-12 ring atoms, of which 1-4 ring atoms are heteroatoms; more preferably, the heterocycloalkyl ring contains 3-10 ring atoms; and most preferably, the heterocyclic group comprises a 5- or 6-membered ring, wherein 1-4 atoms are heteroatoms, more preferably 1-3 atoms are heteroatoms, and most preferably 1-2 atoms are heteroatoms. Non-limiting examples of mono-cyclic heterocyclic group comprise pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, sulfomorpholinyl, homopiperazinyl and the like. Multi-cyclic heterocyclic groups comprise those comprising spiro-ring, fused-ring, and bridged ring.

“Spiro-heterocyclic group” refers to a 5- to 20-membered, multi-cyclic heterocyclic group wherein a plurality of monocyclic rings shares a common atom (namely, a spiro atom), and wherein one or more ring atoms are heteroatom(s) selected from the group consisting of nitrogen, oxygen, and S(O)_m (wherein m is an integer from 0 to 2), and the remainder ring atoms are carbon. The monocyclic rings can contain one or more double bonds, but none of the monocyclic rings has a completely conjugated π -electron system. It is preferably a 6- to 14-membered ring, and more preferably 7- to 10-membered ring. Depending on the number of common spiro-atoms, the spirocycloalkyl groups are classified as mono-spiro heterocyclic groups, bis-spiro heterocyclic groups, or multi-spiro heterocyclic groups, with

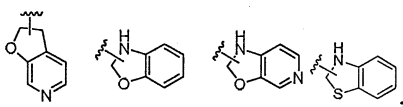
mono-spirocycloalkyl and bis-spirocycloalkyl preferred. More preferred are 4-/4-membered, 4-/5-membered, 4-/6-membered, 5-/5-membered, or 5-membered/6-membered mono-spirocycloalkyl groups. Non-limiting examples of spirocycloalkyl groups comprise:



- 5 “Fused-heterocyclic group” refers to a 5- to 20-membered multi-cyclic heterocyclic group wherein each ring in the system comprises a pair of adjacent atoms shared with other rings in the system, wherein one or more rings can contain one or more double bonds, but none of the rings comprises a completely conjugated π -electron subsystem, and wherein one or more ring atoms are heteroatom(s) selected from the group consisting of nitrogen, oxygen, and S(O)_m (wherein m is an integer from 0 to 2), and the remainder ring atoms are carbon. It is preferably a 7- to 14-membered ring, and more preferably 7- to 10-membered ring. Depending on the number of the rings, the fused heterocyclic groups are classified as bicyclic, tricyclic, tetracyclic, or polycyclic fused heterocycloalkyl groups, with bicyclic or tricyclic fused heterocyclic groups preferred. More preferred are 5-/5-membered and 5-/6-membered bicyclic fused heterocyclic groups. Non-limiting examples of fused heterocyclic groups comprise:



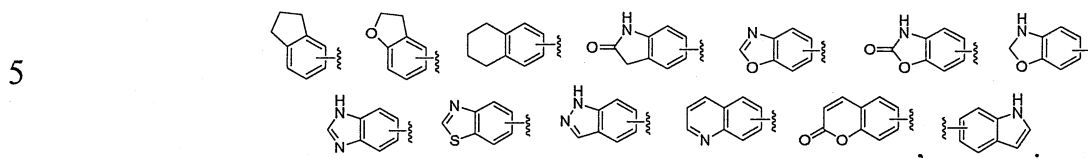
- The heterocyclic ring can be fused to an aryl, a heteroaryl or a cycloalkyl ring, wherein the ring attached to the parent structure is a heterocyclic ring. Non-limiting examples thereof
- 20 comprise:



and the like. The heterocyclic group can be optionally substituted or unsubstituted.

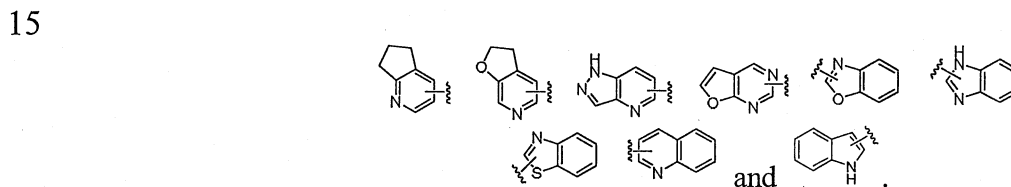
- “Aryl” refers to a 6- to 14-membered full carbon mono-cyclic or a fused-polycyclic (i.e., rings sharing a pair of adjacent carbon atoms) group, a polycyclic group (i.e., rings having a pair of adjacent carbon atoms) having conjugated π electron system. It is preferably a 6- to
- 25

10-membered aryl, such as, phenyl and naphthyl, and most preferably phenyl. The aryl ring can be fused to a heteroaryl, a heterocyclic or a cycloalkyl ring, wherein the ring attached to the parent structure is an aryl ring. Non-limiting examples thereof comprise:



Aryl can be optionally substituted or unsubstituted.

“Heteroaryl” refers to a heteroaromatic system having 1 to 4 heteroatoms and 5 to 14 ring atoms, wherein the heteroatoms comprise oxygen, sulfur and nitrogen. It is preferably a 5- to 10-membered heteroaryl. More preferably, the heteroaryl is a 5- or 6-membered heteroaryl, such as, furyl, thienyl, pyridyl, pyrrolyl, N-alkylpyrrolyl, pyrimidyl, pyrazinyl, imidazolyl, tetrazolyl, oxazolyl, isoxazolyl, and the like. The heteroaryl ring can be fused to an aryl, a heterocyclic or a cycloalkyl ring, wherein the ring attached to the parent structure is a heteroaryl ring. Non-limiting examples thereof comprise:



Heteroaryl can be optionally substituted or unsubstituted.

“Halogen” refers to fluorine, chlorine, bromine, or iodine.

20 “Cyano” refers to -CN.

“Optional” or “optionally” means that the event or environment with reference to such term(s) may (but not necessarily) occur, including the situations that such event or environment occurs or does not occur. For example, “a heterocyclic group optionally substituted with an alkyl group” means that the alkyl group may be but not necessarily present, including the situations that the heterocyclic group is substituted with the alkyl and that the heterocyclic group is not substituted with the alkyl.

“Substituted” means that one or more hydrogen atoms, preferably up to 5 hydrogen atoms, and more preferably 1-3 hydrogen atoms in a group, are each independently substituted with the corresponding number of substituent(s). Apparently, the substituents are merely present in their possible positions, and persons skilled in the art can determine possible or impossible

substitutions (by experiments or theory) without paying much effort. For example, the binding between an amino or hydroxyl group having free hydrogen and carbon atoms having unsaturated (e.g., olefinic) bond may be unstable.

“Pharmaceutical composition” refers to a mixture comprising one or more compounds as described herein or a physiologically/pharmaceutically acceptable salt or prodrug thereof and other chemical components, as well as other components such as, a physiologically/pharmaceutically acceptable carrier and excipient. The pharmaceutical composition aims to promote the administration to a living body and facilitate the absorption of active ingredients, thereby exerting the biological activity.

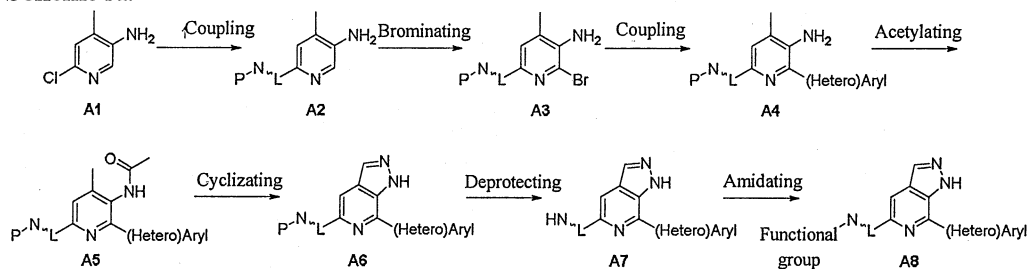
SYNTHETIC METHOD

The present invention further provides a method of preparing the compounds. The compound represented by formula (I) of the present invention can be prepared in according with the following exemplary methods and examples, which should not however be construed as limiting the scope of the present invention in any manner. The inventive compounds can also be synthesized by any synthetic technique that is well known by persons skilled in the art, or by a combination of the known methods with the methods of the present invention. The product produced in each step can be obtained by any known separation techniques in the art, comprising but not limited to extraction, filtration, distillation, crystallization, chromatography and so on. Starting materials and chemical agents as required by synthesis may be routinely prepared according to literatures (available from SciFinder) or commercially available.

The fused pyrazole compounds represented by formula (I) of the present invention can be prepared according to Scheme A: 1) reacting a starting material A1 reacted with a precursor bearing boric acid or borate $(RO)_2B-L-N-P$ (wherein L~N-P is a functional group having a protected amino, and P is a protecting group of the amino) via Suzuki coupling reaction to produce A2, or with a precursor bearing an amino L~N-P (wherein L comprises -NH) via Buchwald coupling reaction to produce A2; 2) brominating A2 to produce A3; 3) reacting A3 with a (hetero)aryl boric acid or borate via Suzuki coupling to produce A4; 4) acetylating the amino group in A4 to produce A5; 5) further cyclizing A5 to produce A6; 6) deprotecting the amino group in A6 to produce A7; and 7) derivating the amino group in A7 with a chemical agent containing a functional group capable of reacting with cysteine residue(s) in the binding

domain of a kinase ligand (e.g., acryloyl chloride etc.), to produce a target compound **A8**.

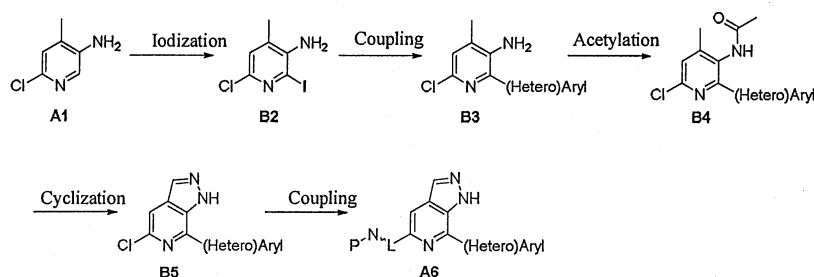
Scheme A:



5

A6 can also be prepared according to Scheme B: subjecting **B2** to undergo Buchwald coupling reaction to produce **B3**, followed by acetylation, cyclization, and coupling to produce an intermediate **A6**.

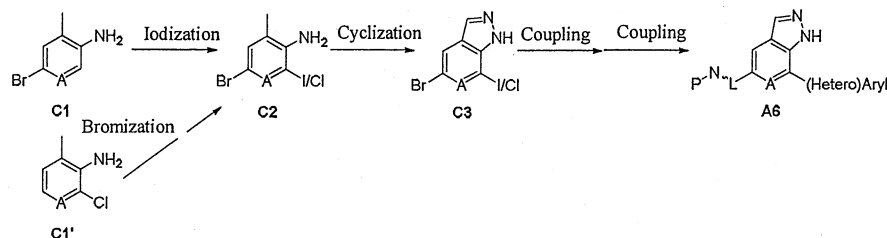
Scheme B:



10

A6 can also be prepared according to Scheme C: subjecting **C1** or **C1'** to iodization or bromination, followed by cyclization to produce **C3**. In accordance with the requirements of synthesis, an iodine-containing **C3** is subject to a coupling reaction with a (hetero)aryl boric acid (or borate) via Suzuki coupling, following by a second coupling reaction with $((RO)_2B-)L-N-P$, to produce **A6**; or a bromine-containing **C3** is subject to a first coupling reaction with $((RO)_2B-)L-N-P$, followed by a second coupling reaction with a (hetero)aryl boric acid (or borate), to produce **A6**.

Scheme C:



20

EXAMPLES

The compound of formula (I) or a pharmaceutically acceptable salt thereof can be prepared by the exemplary methods as described in the following examples and the associated publications referenced by persons skilled in the art. However, these examples are not to limit
5 the scope of the present invention.

The structure of compounds are identified by nuclear magnetic resonance (NMR) or mass spectrum (MS). NMR measurements are conducted on a Bruker AVANCE-400 or Varian Oxford-300 NMR instrument, using DMSO-d₆, CDCl₃, CD₃OD as solvent, tetramethylsilane (TMS) as an internal standard, and a chemical shift of 10⁻⁶ppm.

10 MS measurements are conducted on an Agilent SQD (ESI) mass spectrometer (manufacturer: Agilent, Model: 62100) or a Shimadzu SQD (ESI) mass spectrometer (manufacturer: Shimadzu, Model: 2020).

HPLC measurements are conducted on an Agilent 1200 DAD high pressure liquid chromatograph (Sunfire C18, 150 × 4.6mm, 5 μm chromatographic column), and Waters
15 2695-2996 high pressure liquid chromatograph (Gimini C18 150 × 4.6mm, 5 μm chromatographic column).

The used silica gel plate is Qingdao Haiyang GF254 silica gel plate. The silica gel plate has a specification of 0.15 mm - 0.2 mm when used in the thin layer chromatography (TLC), and a specification of 0.4 mm-0.5 mm during the separation and purification of product by thin layer
20 chromatography.

Column chromatography usually employs Qingdao Haiyang 200-300 mesh silica gel as carrier.

The known starting materials of the present invention can be prepared by or in accordance with the methods known in the art, or commercially available from ABCR GmbH&Co. KG,
25 Acros Organics, Aldrich Chemical Company, Accela ChemBio, Beijing Ouhe Chemical Company, and so on.

The reactions in the examples are carried out under an argon or nitrogen atmosphere unless otherwise indicated.

Argon or nitrogen atmosphere means that the reaction flask is connected to an argon or
30 nitrogen balloon having a 1L volume.

Hydrogen atmosphere means that the reaction flask is connected to a hydrogen balloon

having a 1L volume.

Pressurized hydrogenation reaction is carried out by using a GCD-500G high-purity hydrogen generator and BLT-2000 medium-pressure hydrogenation instrument available from Beijing Jiawei Kechuang Technology Co., Ltd.

- 5 Hydrogenation reaction is usually carried out by vacuuming the reactor and charging it with hydrogen, and the aforesaid steps are repeated three times.

Microwave reaction is conducted on a CEM Discover-SP-type microwave reactor.

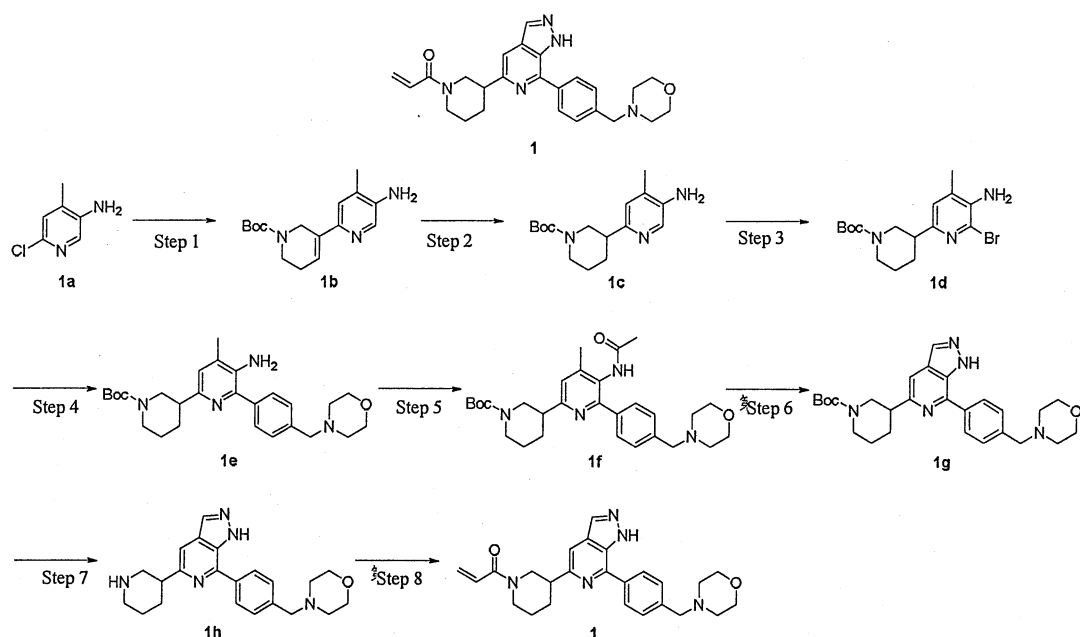
The reaction temperature in the examples is room temperature ranging from 20°C to 30°C unless otherwise indicated.

- 10 The reaction progress in the examples is monitored with thin layer chromatography (TLC). The developer system used in the reaction comprises: A: dichloromethane and methanol system; and B: petroleum ether and ethyl acetate system, wherein the volumetric ratio of solvents is adjusted in accordance with the polarity of compounds.

- 15 The eluent system in column chromatography and the developer system in thin layer chromatography for use in the purification of compounds comprise: A: dichloromethane and methanol system; and B: petroleum ether and ethyl acetate system, wherein the volumetric ratio of solvents is adjusted in accordance with the polarity of compounds, and a small amount of triethylamine and an acidic or alkaline reagent may be added for adjustment.

20 EXAMPLE 1

1-(3-(7-(4-(morpholinomethyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one



Step 1

Tert-butyl 5-amino-4-methyl-5',6'-dihydro-[2,3'-dipyridyl]-1'(2'H)-carboxylate

Compound 6-chloro-4-methylpyridin-3-amine **1a** (568 mg, 4.0 mmol), *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.22 g, 4.0 mmol), cesium carbonate (3.8 g, 12 mmol), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride dichloromethane adduct (146 mg, 0.2 mmol), 1,4-dioxane (30 mL), and water (7 mL) were mixed, degassed, and heated to reflux under nitrogen for 16 hrs. The mixture was cooled to room temperature and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20/1 to 2/1) to produce the target compound *tert*-butyl 5-amino-4-methyl-5',6'-dihydro-[2,3'-dipyridyl]-1'(2'H)-carboxylate **1b** (401 mg, yellow oil), yield: 34%.

MS m/z (ESI): 290[M+1]

Step 2

Tert-butyl 3-(5-amino-4-methylpyridin-2-yl)piperidin-1-carboxylate

Compound *tert*-butyl 5-amino-4-methyl-5',6'-dihydro-[2,3'-dipyridyl]-1'(2'H)-carboxylate **1b** (401 mg, 0.45 mmol), Pd/C (106 mg), and ethanol (100 mL) were mixed, degassed, and stirred under hydrogen atmosphere at room temperature for 16 hrs. The mixture was filtered and concentrated to remove solvent under reduced pressure to give the crude target product *tert*-butyl 3-(5-amino-4-methylpyridin-2-yl)piperidin-1-carboxylate **1c** (400 mg, yellow oil) which was used for the next reaction without further purification.

MS m/z (ESI):292[M+1]

Step 3

Tert-butyl 3-(5-amino-6-bromo-4-methylpyridin-2-yl)piperidin-1-carboxylate

Compound *tert*-butyl 3-(5-amino-4-methylpyridin-2-yl)piperidin-1-carboxylate **1c** (400 mg, crude), N-bromosuccinimide (244 mg, 1.4 mmol), and dichloromethane (5 mL) were mixed at 0°C, and then stirred at 0°C for 1 hr. Saturated sodium bicarbonate (10 mL) was added and the mixture was extracted with dichloromethane (20 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 6/1) to give a target product *tert*-butyl 3-(5-amino-6-bromo-4-methylpyridin-2-yl)piperidin-1-carboxylate **1d** (290 mg, brown oil), yield: two-step 57%.

MS m/z (ESI):370[M+1]

Step 4

Tert-butyl

3-(5-amino-4-methyl-6-(4-(morpholinomethyl)phenyl)pyridin-2-yl)piperidin-1-carboxylate

Compound *tert*-butyl 3-(5-amino-6-bromo-4-methylpyridin-2-yl)piperidin-1-carboxylate **1d** (300 mg, 0.81 mmol), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylmorpholine (295 mg, 0.97 mmol), cesium carbonate (792 mg, 2.4 mmol), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride dichloromethane adduct (50 mg, 0.2 mmol), 1,4-dioxane (15 mL), and water (5 mL) were mixed, degassed, and heated to reflux under nitrogen for 16 hrs. The mixture was cooled to room temperature and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 20/1 to 1/1) to produce a target compound *tert*-butyl 3-(5-amino-4-methyl-6-(4-(morpholinomethyl)phenyl)pyridin-2-yl)piperidin-1-carboxylate **1e** (300 mg, yellow oil), yield: 80%.

MS m/z (ESI):467[M+1]

Step 5

Tert-butyl

3-(5-acetamido-4-methyl-6-(4-(morpholinomethyl)phenyl)pyridin-2-yl)piperidin-1-carboxylate

Compound

tert-butyl

3-(5-amino-4-methyl-6-(4-(morpholinomethyl)phenyl)pyridin-2-yl)piperidin-1-carboxylate **1e**
 (300 mg, 0.64 mmol), acetic anhydride (130 mg, 1.3 mmol), and anhydrous toluene (20 mL)
 were mixed, heated to 100°C under stirring for 14 hrs. The mixture was cooled to room
 temperature and concentrated to remove solvent under reduced pressure to give a target crude
 product

tert-butyl

3-(5-acetamido-4-methyl-6-(4-(morpholinomethyl)phenyl)pyridin-2-yl)piperidin-1-carboxylate
1f (350 mg, yellow viscous oil) which was directly used in the next reaction without further
 purification.

MS m/z (ESI):509[M+1]

Step 6

Tert-butyl

3-(7-(4-(morpholinomethyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-carboxylate

A

mixture

of

tert-butyl

3-(5-acetamido-4-methyl-6-(4-(morpholinomethyl)phenyl)pyridin-2-yl)piperidin-1-carboxylate
1f (350 mg, crude), acetic anhydride (208 mg, 2.0 mmol), potassium acetate (87 mg, 0.88 mmol),
 and benzene (20 mL) was heated to 78°C. Isoamyl nitrite (117 mg, 1.0 mmol) was added
 immediately and the resulting mixture was stirred for 18 hrs. The mixture was cooled to room
 temperature and concentrated to remove solvent under reduced pressure. The residue was
 dissolved in a mixture of water (5 mL), and ethanol (15 mL) and lithium hydroxide
 monohydrate (100 mg) was added. The mixture was stirred at room temperature for 2 hrs and
 concentrated to remove solvent under reduced pressure. The residue was dispersed in water (10
 mL), and extracted with ethyl acetate (50 mL×3). The organic phases were combined, dried over
 anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent
 under reduced pressure. The residue was purified by column chromatography on silica gel
 (petroleum ether/ethyl acetate = 1/1 to 1/2) to give a target product *tert*-butyl
 3-(7-(4-(morpholinomethyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-carboxylate **1g**
 (130 mg, yellow solid), yield: two-step 40%.

MS m/z (ESI):478[M+1]

Step 7

4-(4-(5-(piperidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)phenyl)morpholine

Compound

tert-butyl

3-(7-(4-(morpholinomethyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-carboxylate **1g** (130 mg, 0.27 mmol), trifluoroacetic acid (3 mL), and dichloromethane (3 mL) were mixed and stirred at room temperature for 14 hrs. Saturated sodium bicarbonate solution (30 mL) was added, and the mixture was extracted with dichloromethane (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/methanol = 10/1) to give a target product 4-(4-(5-(piperidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)phenmethyl)morpholine **1h** (100 mg, yellow viscous oil), yield: 98%.

MS *m/z* (ESI):378[M+1]

Step 8

1-(3-(7-(4-(morpholinomethyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one

Compound

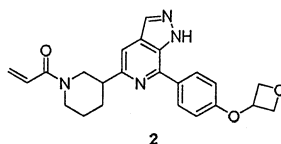
4-(4-(5-(piperidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)phenmethyl)morpholine **1h** (0.15 g, 0.40 mmol), acryloyl chloride (91 mg, 0.56 mmol), solid sodium bicarbonate (86 mg, 0.86 mmol), water (5 mL), and tetrahydrofuran (15 mL) were mixed and stirred at room temperature for 2 hrs. The mixture was extracted with ethyl acetate (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/methanol = 10/1) to give a target product 1-(3-(7-(4-(morpholinomethyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one **1** (20 mg, white solid), yield: 23%.

MS *m/z* (ESI):432[M+1]

¹H NMR (400 MHz, CD₃OD) δ 8.30 - 8.22 (m, 3H), 7.77 (dd, *J* = 8.3, 2.3 Hz, 2H), 7.73 (d, *J* = 10.0 Hz, 1H), 4.79 (m, 0.5H), 4.52 (m, 2.5H), 4.17 (m, 1H), 4.01 (m, 2H), 3.84 (m, 2H), 3.53 (dd, *J* = 13.3, 11.0 Hz, 1H), 3.36 (m, 2H), 3.29 - 2.98 (m, 3H), 2.93 - 2.78 (m, 1H), 2.19 (s, 3H), 2.15 (s, 1H), 2.08 (s, 1H), 1.95 (d, *J* = 3.3 Hz, 1H), 1.78 - 1.62 (m, 1H).

EXAMPLE 2

1-(3-(7-(4-(oxetan-3-oxy)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one



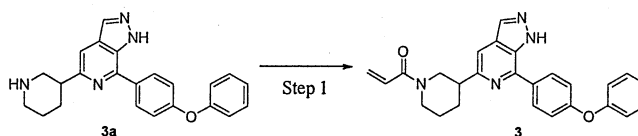
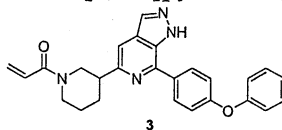
5 Example 2 was synthesized following the procedures in Example 1, except that 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine was replaced with 4,4,5,5-tetramethyl-2-(4-(oxetan-3-oxy)phenyl)-1,3,2-dioxaborolane in Step 4.

MS m/z (ESI):405[M+1]

¹H NMR (400 MHz, CDCl₃) δ 11.04 (s, 1H), 8.15 (d, *J* = 6.9 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 12.8 Hz, 1H), 6.98 - 6.82 (m, 2H), 6.68 (dd, *J* = 16.6, 10.7 Hz, 1H), 6.31 (t, *J* = 15.1 Hz, 1H), 5.69 (dd, *J* = 27.8, 10.4 Hz, 1H), 5.31 (s, 1H), 5.09 - 4.98 (m, 2H), 4.89 - 4.74 (m, 2.5H), 4.70 (d, *J* = 11.4 Hz, 0.5H), 4.29 (d, *J* = 12.3 Hz, 0.5H), 4.05 (d, *J* = 13.3 Hz, 0.5H), 3.51 (t, *J* = 12.1 Hz, 0.5H), 3.20 (dd, *J* = 29.8, 16.8 Hz, 2H), 2.83 (t, *J* = 12.3 Hz, 0.5H), 2.22 (d, *J* = 11.2 Hz, 1H), 2.14 - 1.97 (m, 1H), 1.89 (s, 1H), 1.71 (s, 1H).

EXAMPLE 3

1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one



20 Example 3a was synthesized following the procedures described in Steps 1-7 of Example 1, except that 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine was replaced with (4-phenoxyphenyl) boric acid in Step 4.

MS m/z (ESI):371[M+1]

¹H NMR (400 MHz, CD₃OD) δ 8.35 - 8.28 (m, 1H), 8.10 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 12.2 Hz, 1H), 7.52 - 7.40 (m, 2H), 7.23 (dd, *J* = 7.8, 4.2 Hz, 3H), 7.18 - 7.09 (m, 2H), 3.68 (d, *J* = 10.1 Hz, 1H), 3.47 (d, *J* = 11.6 Hz, 3H), 3.22 - 3.09 (m, 1H), 2.26 (d, *J* = 12.9 Hz, 1H), 2.17 - 1.92 (m, 3H).

Step 1

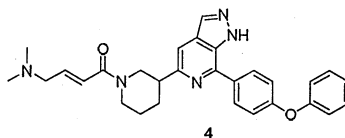
Compound 7-(4-phenoxyphenyl)-5-(piperidin-3-yl)-1H-pyrazolo[3,4-c]pyridine **3a** (0.13 g, 0.40 mmol), acryloyl chloride (34 mg, 0.37 mmol), solid sodium bicarbonate (63 mg, 0.75 mmol), water (5 mL), and tetrahydrofuran (15 mL) were mixed and stirred at room temperature for 2 hrs. The mixture was extracted with ethyl acetate (50mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/methanol = 10/1) to give a target product **3** 1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one (120 mg, white solid), yield: 83%.

MS m/z (ESI):425[M+1]

¹H NMR (400 MHz, CDCl₃) δ 10.81 (brs, 1H), 8.18 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 2H), 7.49 (s, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 6.9 Hz, 3H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 7.0 Hz, 1H), 6.38 - 6.26 (m, 1H), 5.69 (dd, *J* = 25.2, 10.5 Hz, 1H), 4.84 (s, 0.5H), 4.71 (d, *J* = 11.9 Hz, 0.5H), 4.30 (d, *J* = 13.5 Hz, 0.5H), 4.05 (d, *J* = 12.8 Hz, 0.5H), 3.57 - 3.48 (m, 0.5H), 3.28 - 3.12(m, 2H), 2.84 - 2.74(m, 0.5H), 2.25 - 2.16(m, 1H), 2.11 - 2.0(s, 1H), 1.95 - 1.85(m, 1H), 1.75 - 1.65(m, 1H).

EXAMPLE 4

(E)-4-(dimethylamino)-1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)but-2-en-1-one



Compound 7-(4-phenoxyphenyl)-5-(piperidin-3-yl)-1H-pyrazolo[3,4-c]pyridine **3a** (100 mg, 0.28 mmol), (E)-4-(dimethylamino)but-2-enic acid (53 mg, 0.32 mmol), 2-(7-azobenzotriazole)-N,N,N',N'-tetramethylurea hexafluorophosphate (154 mg, 0.41 mmol), triethylamine (82 mg, 0.81 mmol), and N,N-dimethylformamide (15 mL) were mixed and stirred at room temperature for 3 hrs. The mixture was desolventized under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/methanol = 30/1 to 10/1) to give a target product (E)-4-(dimethylamino)-1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-

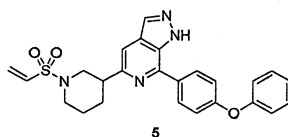
yl)but-2-en-1-one **4** (45 mg, white solid), yield: 33%.

MS *m/z* (ESI): 482 [*M*+1]

¹H NMR (300 MHz, DMSO-*d*₆) δ 13.55 (brs, 1H), 8.26 (s, 3H), 7.60 (s, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.31 - 7.06 (m, 5H), 6.59 (s, 2H), 4.48 (s, 1H), 4.23 (s, 1H), 3.13 - 2.97 (m, 5H),
 5 2.21 (s, 7H), 2.08 - 1.96 (m, 1H), 1.88 (d, *J* = 13.2 Hz, 1H), 1.70 - 1.50 (m, 1H).

EXAMPLE 5

7-(4-phenoxyphenyl)-5-(1-(ethenylsulfonyl)piperidin-3-yl)-1H-pyrazolo[3,4-*c*]pyridine



10

Compound 7-(4-phenoxyphenyl)-5-(piperidin-3-yl)-1H-pyrazolo[3,4-*c*]pyridine **3a** (100 mg, 0.27 mmol), 2-chloroethanesulfonyl chloride (52 mg, 0.32 mmol), triethylamine (82 mg, 0.81 mmol), and dichloromethane (3 mL) were mixed and stirred for at room temperature for 1 hr. The mixture was concentrated to remove solvent under reduced pressure and the residue was
 15 purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1 to 1/3) to give a target product 7-(4-phenoxyphenyl)-5-(1-(ethenylsulfonyl)piperidin-3-yl)-1H-pyrazolo[3,4-*c*]pyridine **5** (20 mg, white solid), yield: 16%.

MS *m/z* (ESI): 461 [*M*+1]

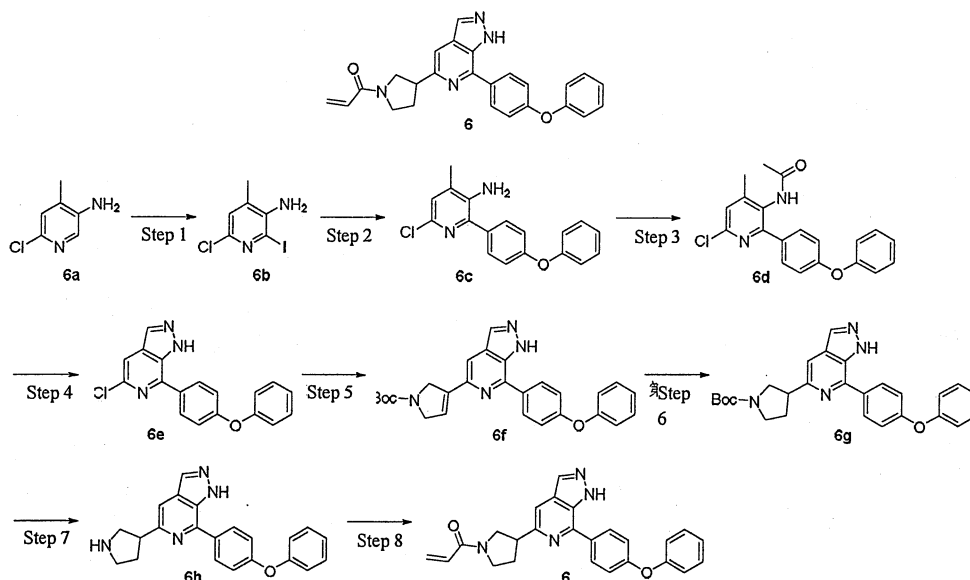
20 ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.59 (s, 1H), 7.43 (dd, *J* = 8.4, 7.5 Hz, 2H), 7.22 (dd, *J* = 7.9, 6.4 Hz, 3H), 7.17 - 7.09 (m, 2H), 6.51 (dd, *J* = 16.7, 9.9 Hz, 1H), 6.27 (d, *J* = 16.6 Hz, 1H), 6.05 (d, *J* = 9.9 Hz, 1H), 3.95 - 3.86 (m, 1H), 3.75 - 3.79 (m, 1H), 3.20 - 3.10 (m, 2H), 2.90 - 2.75 (m, 1H), 2.20 - 2.09 (m, 1H), 1.99 - 1.85 (m, 2H), 1.65 - 1.50 (m, 2H).

25

EXAMPLE 6

1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*c*]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-on

e



Step 1

6-chloro-2-iodo-4-methylpyridin-3-amine

- 5 Compound 6-chloro-4-methylpyridin-3-amine **6a** (6.75 g, 47.3 mmol), N-iodosuccinimide (12.95 g, 57.6 mmol), and N,N-dimethylformamide (100 mL) were mixed at 0°C and stirred at room temperature for 15 hrs. Next, water (100 mL) was added, and the mixture was extracted with ethyl acetate (150 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 10/1) to give a target product 6-chloro-2-iodo-4-methylpyridin-3-amine **6b** (6.5 g, yellow solid), yield: 47%.

MS m/z (ESI):269[M+1]

Step 2

- 15 6-chloro-4-methyl-2-(4-phenoxyphenyl)pyridine -3-amine

Referring to the procedure for **1e** of Example 1, 1,6-chloro-2-iodo-4-methylpyridin-3-amine **6b** (3.0 g, 11.2 mmol) was used as starting material to give a target product 6-chloro-4-methyl-2-(4-phenoxyphenyl)pyridine -3-amine **6c** (3.5 g, yellow solid), yield: 100%.

- 20 MS m/z (ESI):311[M+1]

Step 3

N-(6-chloro-4-methyl-2-(4-phenoxyphenyl)pyridine -3-yl)acetamide

Referring to the procedure for **1f** of Example 1, 6-chloro-4-methyl-2-(4-phenoxyphenyl)pyridin-3-amine **6c** (3.5 g, 11.2 mmol) was used as starting material to give a target product N-(6-chloro-4-methyl-2-(4-phenoxyphenyl)pyridin-3-yl)acetamide **6d** (4.0 g, yellow solid),
 5 yield: 100%.

MS m/z (ESI):353[M+1]

Step 4

5-chloro-7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridine

Referring to the procedure for **1g** of Example 1,
 10 N-(6-chloro-4-methyl-2-(4-phenoxyphenyl)pyridine -3-yl)acetamide **6d** (3.4 g, 9.6 mmol) was used as starting material to give a target product 5-chloro-7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridine **6e** (1.5 g, yellow solid), yield: 40%.

MS m/z (ESI):322[M+1]

Step 5

15 *Tert*-butyl

3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate

Referring to the procedure for **1b** of Example 1, 5-chloro-7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridine **6e** (850 mg, 2.64 mmol), and *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate
 20 (1.95 g, 6.6 mmol) were used as starting materials to give a target product *tert*-butyl 3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **6f** (700 mg, yellow solid), yield: 58%.

MS m/z (ESI):455[M+1]

Step 6

25 *Tert*-butyl

3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidine-1-carboxylate

Referring to the procedure for **1c** of Example 1, *tert*-butyl 3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **6f** (700 mg, 1.54 mmol) was used as starting material to give a target
 30 product *tert*-butyl 3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidine-1-carboxylate **6g** (270 mg, yellow solid), yield: 39%.

MS m/z (ESI):457[M+1]

Step 7

7-(4-phenoxyphenyl)-5-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridine

Referring to the procedure for **1h** of Example 1, *tert*-butyl
 5 3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidine-1-carboxylate **6g** (250 mg, 0.327 mmol) was used as starting material to give a target product *tert*-butyl 7-(4-phenoxyphenyl)-5-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridine **6h** (95 mg, yellow solid), yield: 82%.

MS m/z (ESI):357[M+1]

10 Step 8

1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one

e

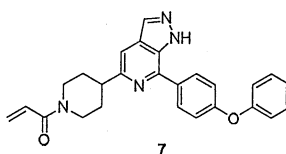
Referring to the procedure for **1** of Example 1,
 1,7-(4-phenoxyphenyl)-5-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridine **6h** (95 mg, 0.267 mmol)
 15 was used as starting material to give a target product 1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one **6** (45 mg, yellow solid), yield: 82%.

MS m/z (ESI):411[M+1]

¹H NMR (400 MHz, CDCl₃) δ 10.86 (brs, 1H), 8.18 (s, 1H), 7.99 (t, *J* = 9.3 Hz, 2H), 7.50
 20 (d, *J* = 8.2 Hz, 1H), 7.45 - 7.38 (m, 2H), 7.20 (dd, *J* = 11.5, 8.7 Hz, 3H), 7.15 - 7.09 (m, 2H), 6.58 - 6.36 (m, 2H), 5.71 (ddd, *J* = 14.7, 10.0, 2.3 Hz, 1H), 4.20 - 4.07 (m, 1H), 4.00 - 3.60 (m, 4H), 2.58 - 2.30 (m, 2H).

EXAMPLE 7

25 1-(4-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one



Example 7 was synthesized following the procedures in Example 6, except that *tert*-butyl
 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate was
 30 replaced with *tert*-butyl

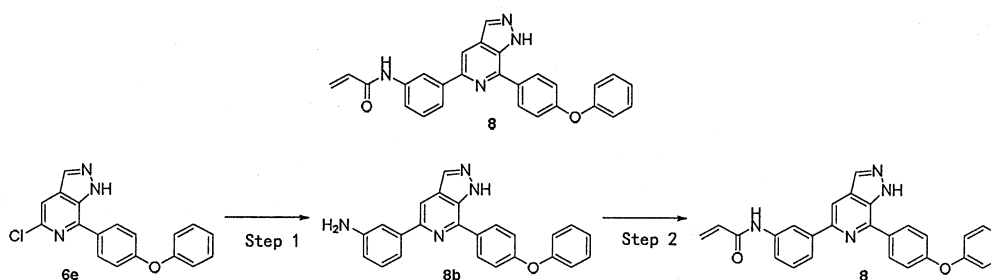
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate in Step 5.

MS m/z (ESI):371[M+1]

¹H NMR (400 MHz, DMSO-d₆) δ 13.65(s, 1H), 8.23 (s, 1H), 8.09 - 8.08(m, 2H), 7.57 - 7.44(m, 3H), 7.23 - 7.11(m, 5H), 6.90 - 6.84 (m, 1H), 6.13(d, *J* = 12.8 Hz, 1H), 5.68 (d, *J* = 10.4 Hz, 1H), 4.62 - 4.59 (m, 1H), 4.23 - 4.19 (m, 1H), 3.02 - 3.12(m, 2H), 2.83 - 2.77(m, 1H), 2.02 - 1.99(m, 2H), 1.76 - 1.70 (m, 2H).

EXAMPLE 8

10 N-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)phenyl)acrylamide



Step 1

15 3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)aniline

Referring to the procedure for **1b** of Example 1, 5-chloro-7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridine (100 mg, 0.34 mmol), and (3-aminophenyl)boric acid **6e** (51 mg, 0.37 mmol) were used as starting materials to give a target product 3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)aniline **8b** (80 mg, grey solid), yield: 68%.

MS m/z (ESI):379[M+1]

Step 1

N-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)phenyl)acrylamide

Referring to the procedure for **1** of Example 1, 3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)aniline **8b** (80 mg, 0.21 mmol) was used as starting material to give N-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)phenyl)acrylamide **8** (13 mg, yellow solid), yield: 15%.

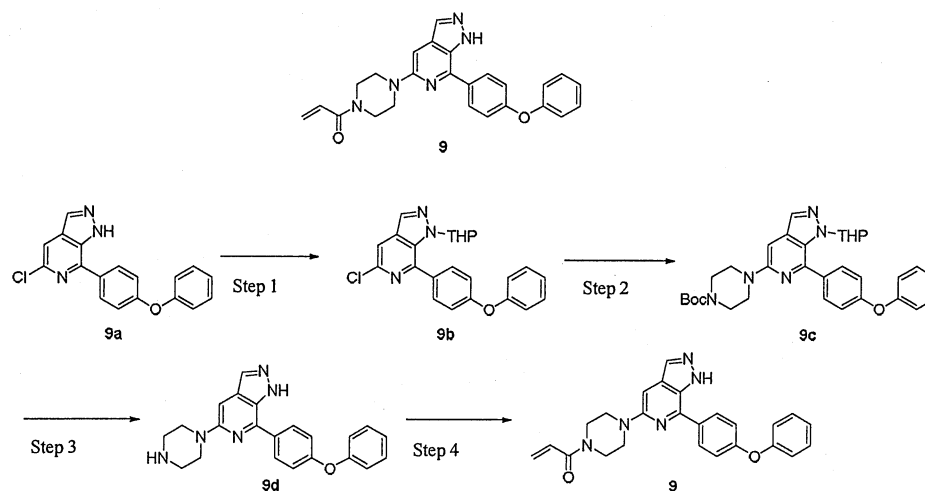
MS m/z (ESI):433[M+1]

¹H NMR (400 MHz, DMSO-d₆) δ 13.82 (s, 1H), 10.28 (s, 1H), 8.46 (s, 1H), 8.37 (s, 1H), 8.23 - 8.19 (m, 3H), 7.89 - 7.79 (m, 2H), 7.49 - 7.43 (m, 3H), 7.25 - 7.15 (m, 5H), 6.50 - 6.46 (m, 1H), 6.31 - 6.27 (m, 1H), 5.79 - 5.77 (m, 1H).

5

EXAMPLE 9

1-(4-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperazin-1-yl)prop-2-en-1-one



10

Step 1

5-chloro-7-(4-phenoxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridine

Compound 5-chloro-7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridine **9a** (500 mg, 1.56 mmol), 3,4-dihydro-2H-pyran (393 mg, 4.68 mmol), and dichloromethane (20 mL) were mixed at 0°C, and then *p*-toluenesulfonic acid (50 mg, 0.29 mmol) was added. The mixture was stirred at room temperature for 15 hrs. A saturated solution of sodium bicarbonate (10 mL) was added, and the mixture was extracted with dichloromethane (20 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 5/1) to give a target product 5-chloro-7-(4-phenoxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridine **9b** (350 mg, pale yellow solid), yield: 55%.

MS m/z (ESI): 406[M+1]

Step 2

tert-butyl

4-(7-(4-phenoxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperazine-1-carboxylate

Compound

- 5 5-chloro-7-(4-phenoxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridine **9b**
 (350 mg, 0.864 mmol), *tert*-butylpiperazine-1-carboxylate (344 mg, 1.73 mmol), cesium
 carbonate (562 mg, 1.73 mmol),
 (2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)] palladium (II)
 chloride methyl *tert*-butyl ether adduct (68 mg, 0.09 mmol), and 1,4-dioxane (20 mL) were
 10 mixed, degassed, and heated in microwave at 150°C under nitrogen for 5 hrs. The mixture was
 cooled to room temperature, and concentrated to remove solvent under reduced pressure. The
 residue was purified by column chromatography on silica gel (dichloromethane/methanol =
 20/1), to produce a target compound *tert*-butyl
 4-(7-(4-phenoxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperazin
 15 e-1-carboxylate **9c** (50 mg, yellow oil), yield: 18%.

MS m/z (ESI):556[M+1]

Step 3

7-(4-phenoxyphenyl)-5-(piperazin-1-yl)-1H-pyrazolo[3,4-c]pyridine

Compound

tert-butyl

- 20 4-(7-(4-phenoxyphenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperazin
 e-1-carboxylate **9c** (50 mg, 0.0899 mmol), and dichloromethane (3 mL) were mixed, and then a
 solution of hydrogen chloride in ethanol (4 M, 1 mL, 4 mmol) was added. The mixture was
 stirred at room temperature for 14 hrs, and concentrated to remove solvent under reduced
 pressure to give a target product
 25 7-(4-phenoxyphenyl)-5-(piperazin-1-yl)-1H-pyrazolo[3,4-c]pyridine **9d** (crude, pale yellow
 solid) which was directly used in the next reaction without further purification.

MS m/z (ESI):372[M+1]

Step 4

1-(4-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperazin-1-yl)prop-2-en-1-one

- 30 Referring to the procedure for 1 of Example 1,
 7-(4-phenoxyphenyl)-5-(piperazin-1-yl)-1H-pyrazolo[3,4-c]pyridine **9d** (crude) was used as the

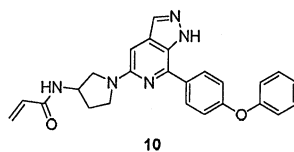
starting material to give
 1-(4-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperazin-1-yl)prop-2-en-1-one 9
 (10 mg, nearly white solid), yield: two-step 26%.

MS m/z (ESI):426[M+1]

5 ^1H NMR (400 MHz, CDCl_3) δ 10.62 (s, 1H), 8.02 (t, $J = 18.6$ Hz, 3H), 7.42 (t, $J = 7.9$ Hz, 2H), 7.16 (dd, $J = 31.1, 8.2$ Hz, 5H), 6.89 (s, 1H), 6.66 (dd, $J = 16.8, 10.5$ Hz, 1H), 6.47 - 6.29 (m, 1H), 5.78 (d, $J = 10.6$ Hz, 1H), 3.89 (d, $J = 51.8$ Hz, 4H), 3.61 (d, $J = 30.3$ Hz, 4H).

EXAMPLE 10

10 N-(1-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-3-yl)acrylamide



Example 10 was synthesized following the procedures in Example 9, except that *tert*-butyl piperazine-1-carboxylate was replaced with *tert*-butyl pyrrolidin-3-yl carbamate in Step 2.

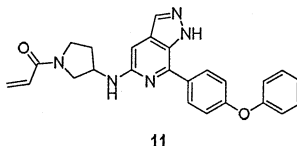
15 MS m/z (ESI):426[M+1]

^1H NMR (400 MHz, CDCl_3) δ 10.42 (s, 1H), 7.99 (d, $J = 8.7$ Hz, 3H), 7.41 (t, $J = 8.0$ Hz, 2H), 7.16 (dt, $J = 8.6, 7.7$ Hz, 4H), 6.57 (s, 1H), 6.35 (dd, $J = 16.9, 1.2$ Hz, 1H), 6.21 - 5.84 (m, 2H), 5.68 (dd, $J = 10.3, 1.2$ Hz, 1H), 4.80 (s, 1H), 3.92 - 3.56 (m, 4H), 2.43 (dd, $J = 13.5, 6.5$ Hz, 1H), 2.13 (d, $J = 4.8$ Hz, 1H).

20

EXAMPLE 11

1-(3-(((7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one



25

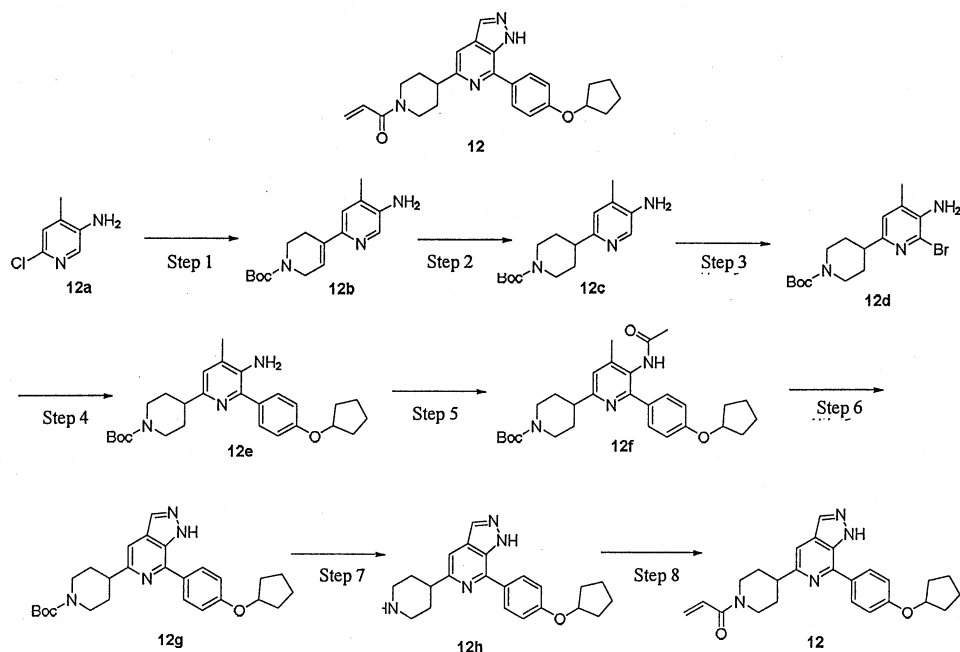
Example 11 was synthesized following the procedures in Example 9, except that *tert*-butyl piperazine-1-carboxylate was replaced with *tert*-butyl 3-aminopyrrolidine-1-carboxylate in Step 2.

MS m/z (ESI):426[M+1]

¹H NMR (400 MHz, CD₃OD) δ 8.07 - 7.93 (m, 2H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.24 - 7.06 (m, 4H), 6.65 (ddd, *J* = 27.4, 24.5, 16.1 Hz, 2H), 6.29 (ddd, *J* = 16.9, 7.6, 2.0 Hz, 1H), 5.75 (ddd, *J* = 16.4, 10.4, 1.9 Hz, 1H), 4.61 - 4.44 (m, 1H), 4.09 (dd, *J* = 10.6, 6.1 Hz, 1H), 3.99 - 3.85 (m, 1H),
5 3.78 (dt, *J* = 15.1, 6.9 Hz, 1H), 3.63 (ddd, *J* = 25.3, 14.2, 6.2 Hz, 2H), 2.25 (m, 3H).

EXAMPLE 12

1-(4-(7-(4-(pyridin-2-oxyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one



Example 12 was synthesized following the procedures in Example 1, except that *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate was replaced with *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate in Step 1, and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylmorpholine was replaced with 4,4,5,5-tetramethyl-2-(4-(oxetan-3-yl)phenyl)-1,3,2-dioxaborolane in Step 4.

MS m/z (ESI):417[M+1]

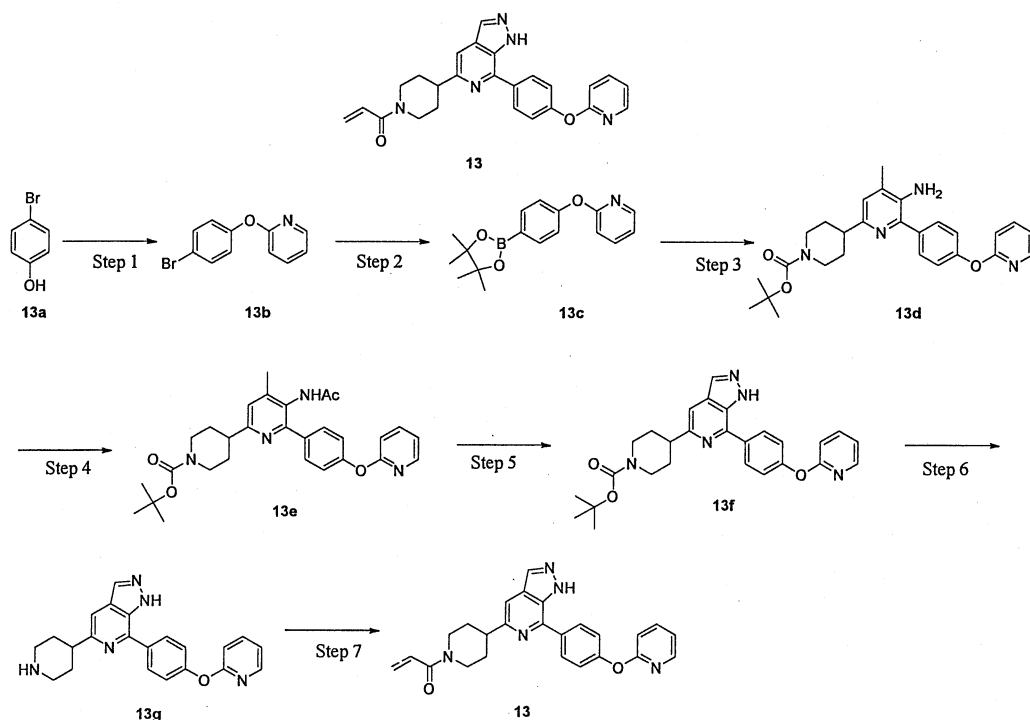
¹H NMR (400 MHz, DMSO-*d*₆) δ 13.62 (s, 1H), 8.21 (s, 1H), 8.02 (d, *J* = 7.0 Hz, 2H), 7.51 (s, 1H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.88 (dd, *J* = 16.7, 10.5 Hz, 1H), 6.13 (dd, *J* = 16.7, 2.5 Hz, 1H), 5.69 (dd, *J* = 10.4, 2.5 Hz, 1H), 4.93 (dd, *J* = 7.1, 4.5 Hz, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 4.21 (d, *J* = 12.6 Hz, 1H), 3.23 (t, *J* = 12.2 Hz, 1H), 3.09 (s, 1H), 2.80 (s, 1H), 1.99 (dd, *J* = 8.5,

5.5 Hz, 4H), 1.83 - 1.55 (m, 8H).

EXAMPLE 13

1-(4-(7-(4-(pyridin-2-oxy)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en

5 -1-one



Step 1

2-(4-bromophenoxy)pyridine

- 10 Compound 4-bromophenol **13a** (5.00 g, 28.9 mmol), 2-bromopyridine (4.60 g, 28.9 mmol), copper powder (184 mg, 2.89 mmol), cuprous iodide (550 mg, 2.89 mmol), potassium carbonate (11.9 g, 86.7 mmol), and N-methylpiperidin-2-one (30 mL) were mixed and heated to 150°C under stirring for 15 hrs. The mixture was cooled to room temperature, and then water (90 mL) was added. The mixture was extracted with dichloromethane (80 mL×3). The organic phases
- 15 were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 5/1) to give a target product 2-(4-bromophenoxy)pyridine **13b** (2.60 g, pale yellow oil), yield: 36%.

MS m/z (ESI): 250, 252[M+1]

20

Step 2

2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyridine

Compound 2-(4-bromophenoxy)pyridine **13b** (1.3 g, 5.24 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-di(1,3,2-dioxaborolanyl) (1.59 g, 6.28 mmol), potassium acetate (1.03 g, 10.50 mmol), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (380 mg, 0.524 mmol), and 1,4-dioxane (70 mL) were mixed, degassed, and heated at 90°C under nitrogen for 15 hrs. The mixture was cooled to room temperature, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 10/1), to produce a target compound 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyridine **13c** (1.30 g, yellow oil), yield: 79%.

MS m/z (ESI): 298[M+1]

Steps 3 to 7

1-(4-(7-(4-(pyridin-2-oxy)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one

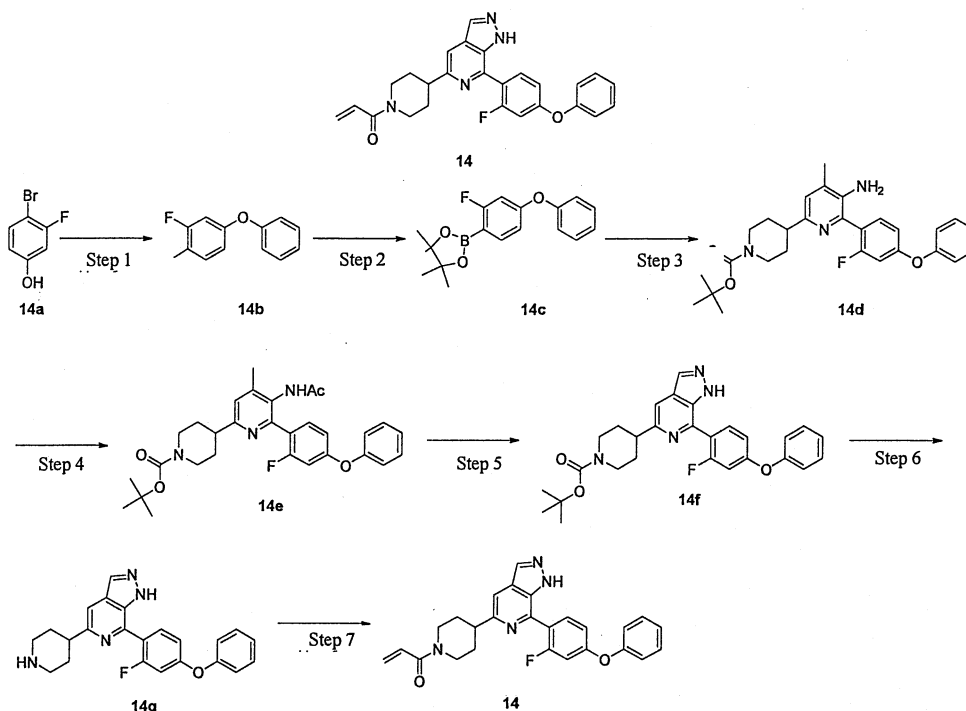
13 was prepared following the procedures described in Steps 4 to 8 of Example 12, except that 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine and *tert*-butyl 3-(5-amino-6-bromo-4-methylpyridin-2-yl)piperidin-1-carboxylate were replaced with 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyridine and *tert*-butyl 4-(5-amino-6-bromo-4-methylpyridin-2-yl)piperidin-1-carboxylate in Step 3.

MS m/z (ESI): 426[M+1]

¹H NMR (400 MHz, CD₃OD) δ 8.19 (s, 1H), 8.06 (d, *J* = 7.0 Hz, 2H), 7.59 (s, 1H), 7.41 (dd, *J* = 15.1, 8.2 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (dt, *J* = 19.0, 8.5 Hz, 4H), 6.24 (dd, *J* = 16.8, 1.4 Hz, 1H), 5.77 (d, *J* = 10.7 Hz, 1H), 4.77 (d, *J* = 13.0 Hz, 1H), 4.30 (d, *J* = 13.1 Hz, 1H), 3.38 (s, 1H), 3.21 (s, 1H), 2.93 (t, *J* = 12.6 Hz, 1H), 2.14 (s, 2H), 1.91 (s, 2H).

EXAMPLE 14

1-(4-(7-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one



Step 1

1-bromo-2-fluoro-4-phenoxybenzene

Compound 3-fluoro-4-bromophenol **14a** (3.00 g, 15.7 mmol), phenylboronic acid (3.82 g, 31.4 mmol), cupric acetate (2.85 g, 15.7 mmol), triethylamine (4.8 g, 47.1 mmol), molecular sieve (5 g), and dichloromethane (120 mL) were mixed and stirred at room temperature for 15 hrs. The mixture was filtered to remove the molecular sieve, and desolventized under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 5/1) to give a target product 1-bromo-2-fluoro-4-phenoxybenzene **14b** (3.30 g, white solid), yield: 78%.

^1H NMR (400 MHz, CDCl_3) δ 7.48 (t, J = 8.3 Hz, 1H), 7.41 (t, J = 7.9 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.80 (dd, J = 9.8, 2.7 Hz, 1H), 6.73 (dd, J = 8.8, 2.7 Hz, 1H).

Step 2

2-(2-fluoro-4-phenoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Following the synthetic procedures for **12c** in Example 12, 1-bromo-2-fluoro-4-phenoxybenzene (3.30 g, 12.3 mmol) was used as starting material to produce 2-(2-fluoro-4-phenoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **13c** (1.40 g, pale yellow solid), yield: 36%.

^1H NMR (400 MHz, CDCl_3) δ 7.73 - 7.67 (m, 1H), 7.40 (t, J = 7.9 Hz, 2H), 7.20 (t, J = 7.4

Hz, 1H), 7.07 (d, $J = 7.8$ Hz, 2H), 6.78 (dd, $J = 8.3, 2.2$ Hz, 1H), 6.64 (dd, $J = 10.7, 2.2$ Hz, 1H), 1.37 (s, 12H).

Steps 3 to 7

1-(4-(7-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one

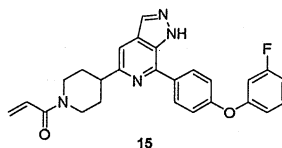
14 was prepared following the procedures described in Steps 4 to 8 of Example 12, except that 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine and *tert*-butyl 3-(5-amino-6-bromo-4-methylpyridin-2-yl)piperidin-1-carboxylate were replaced with 2-(2-fluoro-4-phenoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and *tert*-butyl 4-(5-amino-6-bromo-4-methylpyridin-2-yl)piperidin-1-carboxylate in Step 3.

MS m/z (ESI): 443[M+1]

^1H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1H), 7.75 (t, $J = 8.4$ Hz, 1H), 7.67 (s, 1H), 7.47 (t, $J = 8.0$ Hz, 2H), 7.25 (t, $J = 7.4$ Hz, 1H), 7.21 - 7.11 (m, 2H), 7.01 (dd, $J = 8.5, 2.0$ Hz, 1H), 6.89 (ddd, $J = 27.5, 14.2, 6.4$ Hz, 2H), 6.23 (dd, $J = 16.8, 2.0$ Hz, 1H), 5.77 (dd, $J = 10.7, 1.9$ Hz, 1H), 4.76 (d, $J = 12.5$ Hz, 1H), 4.29 (d, $J = 14.0$ Hz, 1H), 3.35 (d, $J = 11.0$ Hz, 1H), 3.21 (t, $J = 11.8$ Hz, 1H), 2.92 (t, $J = 12.7$ Hz, 1H), 2.13 (s, 2H), 1.89 (td, $J = 12.2, 5.3$ Hz, 2H).

EXAMPLE 15

1-(4-(7-(4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)prop-2-en-1-one



15 was prepared following the procedures of Example 14, except that 3-fluoro-4-bromophenol and phenylboronic acid were replaced with *p*-bromophenol and *m*-fluorophenylboronic acid in Step 1.

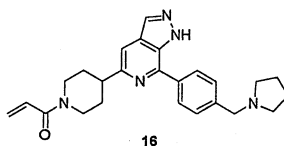
MS m/z (ESI): 443[M+1]

^1H NMR (400 MHz, CD_3OD) δ 8.38 (s, 1H), 8.22 (dd, $J = 5.0, 1.3$ Hz, 1H), 8.13 (d, $J = 7.7$ Hz, 2H), 7.99 - 7.82 (m, 2H), 7.42 (d, $J = 8.6$ Hz, 2H), 7.23 (dd, $J = 6.8, 5.4$ Hz, 1H), 7.14 (d, $J = 8.3$ Hz, 1H), 6.87 (dd, $J = 16.8, 10.7$ Hz, 1H), 6.25 (dd, $J = 16.8, 2.0$ Hz, 1H), 5.79 (dd, $J = 10.7, 2.0$ Hz, 1H), 4.81 (d, $J = 13.4$ Hz, 1H), 4.35 (d, $J = 13.4$ Hz, 1H), 3.38 (d, $J = 12.9$ Hz, 2H),

2.94 (s, 1H), 2.18 (s, 2H), 1.99 - 1.84 (m, 2H).

EXAMPLE 16

1-(4-(7-(4-(pyrrolidin-1-ylmethyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)propan-2-one



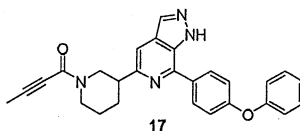
16 was prepared following the procedures described in Steps 4 to 8 of Example 13, except that 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyridine was replaced with 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)pyrrolidine as starting material.

MS m/z (ESI): 416[M+1]

^1H NMR (400 MHz, CD_3OD) δ 8.20 (s, 1H), 8.07 (d, $J = 8.0$ Hz, 2H), 7.69 - 7.57 (m, 3H), 6.85 (dd, $J = 16.8, 10.7$ Hz, 1H), 6.24 (dd, $J = 16.8, 1.9$ Hz, 1H), 5.77 (dd, $J = 10.6, 1.9$ Hz, 1H), 4.76 (d, $J = 12.9$ Hz, 1H), 4.30 (d, $J = 13.5$ Hz, 1H), 3.98 (s, 2H), 3.36 (d, $J = 14.7$ Hz, 1H), 3.20 (ddd, $J = 15.4, 7.7, 3.7$ Hz, 1H), 3.00 - 2.80 (m, 5H), 2.13 (t, $J = 9.9$ Hz, 2H), 2.04 - 1.81 (m, 6H).

EXAMPLE 17

1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)piperidin-1-yl)but-2-yn-1-one



17 was prepared following the procedures of Example 4, except that (E)-4-(dimethylamino)but-2-enoic acid was replaced with but-2-ynoic acid.

MS m/z (ESI): 416[M+1]

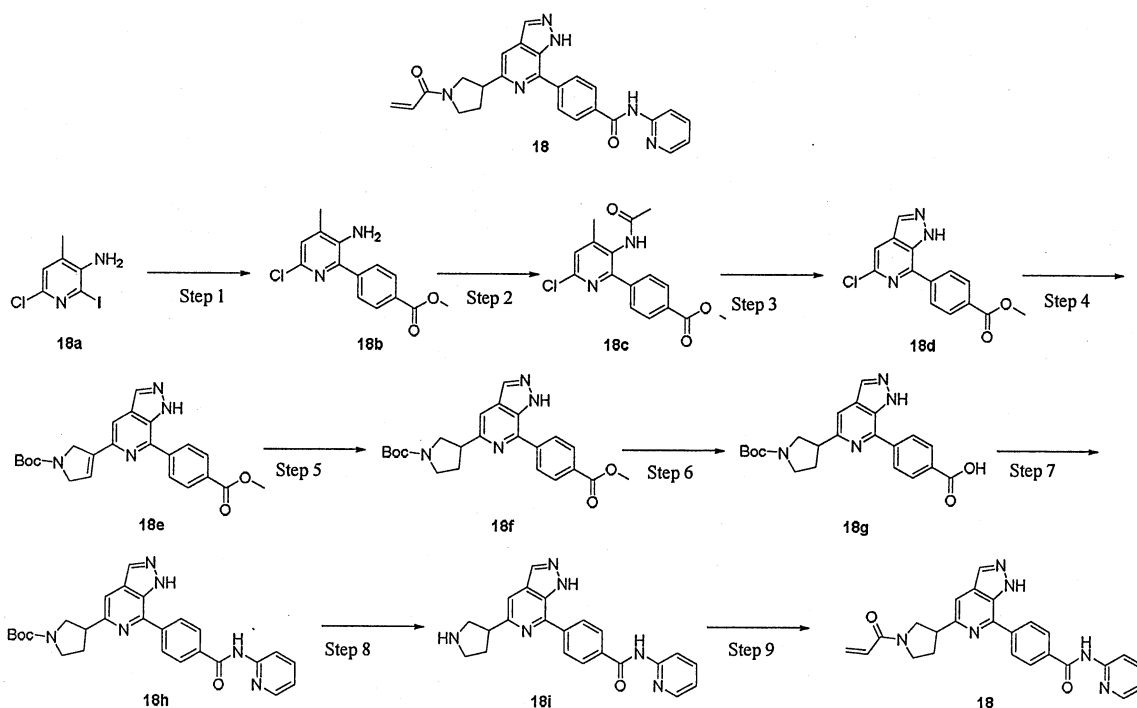
^1H NMR (400 MHz, CD_3OD) δ 8.19 (d, $J = 7.0$ Hz, 1H), 8.07 (t, $J = 8.6$ Hz, 2H), 7.62 (d, $J = 10.3$ Hz, 1H), 7.43 (t, $J = 7.9$ Hz, 2H), 7.20 (dd, $J = 8.2, 4.1$ Hz, 3H), 7.12 (d, $J = 8.2$ Hz, 2H), 4.69 (t, $J = 9.3$ Hz, 1H), 4.54 - 4.41 (m, 1H), 3.61 - 3.52 (m, 0.5H), 3.28 (s, 0.5H), 3.24 - 3.16 (m, 0.5H), 3.15 - 2.95 (m, 1H), 2.91 - 2.86 (m, 0.5H), 2.23 - 2.18 (m, 1H), 2.15 - 1.88 (m, 5H), 1.80 - 1.58 (m, 1H).

EXAMPLE 18

4-(5-(1-acryloylpyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)-N-(pyridin-2-yl)

benzamide

5



Steps 1 to 5

10

Tert-butyl

3-(7-(4-(methoxycarbonyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidine-1-carboxylate

18f was prepared following the procedures described in Steps 2 to 6 of Example 6, except that (4-phenoxyphenyl) boric acid was replaced with methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoate in Step 1.

15

MS m/z (ESI): 423[M+1]

Step 6

4-(5-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl) benzoic acid

Compound

tert-butyl

3-(7-(4-(methoxycarbonyl)phenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidine-1-carboxylate

20

18f (422 mg, 1.0 mmol), lithium hydroxide (52 mg, 10.0 mmol), water (10 mL), and

tetrahydrofuran (10 mL) were mixed and stirred at room temperature for 14 hrs. The reaction solution was adjusted to pH= 6 with 1 M diluted hydrochloric acid, and extracted with dichloromethane (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure to give a target product 4-(5-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-*c*]pyridin-7-yl)benzoic acid **18g** (300mg, crude), which was directly used in the next reaction without further purification.

MS m/z (ESI):409[M+1]

Step 7

Tert-butyl

3-(7-(4-(pyridin-2-ylcarbamoyl)phenyl)-1H-pyrazolo[3,4-*c*]pyridin-5-yl)pyrrolidine-1-carboxylate

Compound 4-(5-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-*c*]pyridin-7-yl)benzoic acid **18g** (204 mg, 0.5 mmol), triethylamine (194 mg, 3.0 mmol), and dichloromethane (20 mL) were mixed, and then 2,4,6-tripropyl-1,3,5,2,4,6-trioxotriphosphoric acid-2,4,6-trioxide (477 mg, 1.5 mmol) was added. The mixture was stirred at room temperature for 14 hrs, and then a saturated solution of sodium bicarbonate (10 mL) was added. The reaction mixture was extracted with dichloromethane (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1) to give a target product *tert*-butyl 3-(7-(4-(pyridin-2-ylcarbamoyl)phenyl)-1H-pyrazolo[3,4-*c*]pyridin-5-yl)pyrrolidine-1-carboxylate **18h** (80 mg, yellow solid), yield: 33%.

MS m/z (ESI):485[M+1]

Step 8

N-(pyridin-2-yl)-4-(5-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-*c*]pyridin-7-yl) benzamide

Following the synthetic procedure for **1h** of Example 1, *tert*-butyl 3-(7-(4-(pyridin-2-ylcarbamoyl)phenyl)-1H-pyrazolo[3,4-*c*]pyridin-5-yl)pyrrolidine-1-carboxylate (80 mg, 0.17 mmol) was used as starting material to produce N-(pyridin-2-yl)-4-(5-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-*c*]pyridin-7-yl)benzamide **18i** (50 mg, crude).

MS m/z (ESI):385[M+1]

Step 9

4-(5-(1-acryloylpyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)-N-(pyridin-2-yl)benzamide
e

5 Following the synthetic procedure for 1 of Example 1, N-(pyridin-2-yl)-4-(5-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)benzamide **18i** (50 mg, 0.13 mmol) was used as starting material to produce a target product 4-(5-(1-acryloylpyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)-N-(pyridin-2-yl)benzamide **18** (12 mg, yellow solid), yield: 12%.

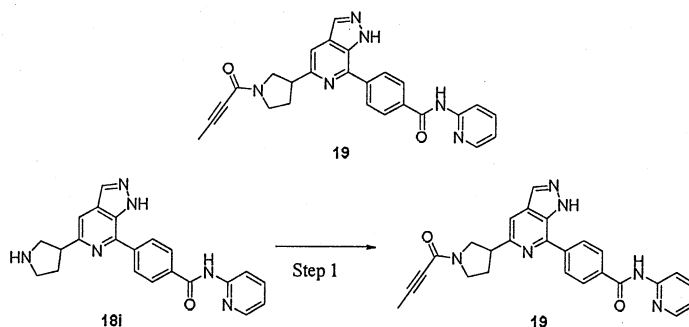
10 MS m/z (ESI):439[M+1]

¹H NMR (400 MHz, CDCl₃) δ 11.13 (s, 1H), 9.69 (s, 1H), 8.66 - 8.56 (m, 1H), 8.36 (s, 1H), 8.30 - 8.14 (m, 3H), 7.96 (s, 1H), 7.80 (s, 1H), 7.57 (t, *J* = 10.6 Hz, 1H), 7.23 (s, 1H), 6.93 - 6.79 (m, 1H), 6.51 (tdd, *J* = 16.8, 12.4, 8.0 Hz, 2H), 5.78 - 5.66 (m, 1H), 4.22 - 4.05 (m, 1H), 4.03 - 3.60 (m, 4H), 2.46 (dt, *J* = 32.0, 7.5 Hz, 2H).

15

EXAMPLE 19

4-(5-(1-(but-2-ynoyl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)-N-(pyridin-2-yl)benzamide



20

Compound

N-(pyridin-2-yl)-4-(5-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)benzamide **18i** (384 mg, 1.0 mmol), but-2-ynoyl chloride (113 mg, 1.1 mmol), solid sodium bicarbonate (232 mg, 3.0 mmol), water (4 mL), and tetrahydrofuran (16 mL) were mixed and stirred at room temperature for 1 hr. The mixture was extracted with ethyl acetate (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column

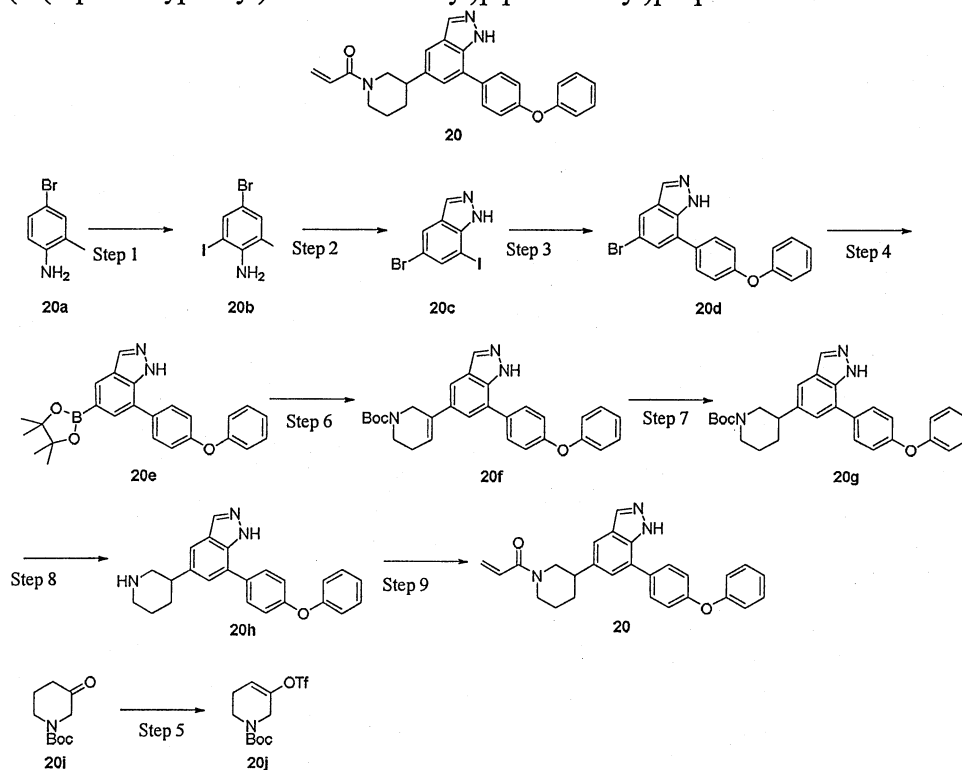
chromatography on silica gel (dichloromethane/methanol = 20/1) to give a target product 4-(5-(1-(but-2-ynacyl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-c]pyridin-7-yl)-N-(pyridin-2-yl)benzamide **19** (72 mg, white solid), yield: 16%.

MS m/z (ESI): 439[M+1]

- 5 ^1H NMR (400 MHz, CD_3OD) δ 8.53 (t, J = 7.4 Hz, 2H), 8.47 (d, J = 5.8 Hz, 1H), 8.43 - 8.33 (m, 4H), 8.03 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 8.9 Hz, 1H), 7.71 (t, J = 6.9 Hz, 1H), 4.28 (dd, J = 10.9, 7.4 Hz, 0.5H), 3.95 (m, 4H), 3.66 - 3.56 (m, 0.5H), 2.63 - 2.36 (m, 2H), 2.06 (d, J = 20.4 Hz, 3H).

10 EXAMPLE 20

1-(3-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)piperidin-1-yl)prop-2-en-1-one



Step 1

4-bromo-2-iodo-6-methylaniline

- 15 Compound 4-bromo-2-methylaniline **20a** (5 g, 26.87 mmol), N-iodosuccinimide (6.05 g, 26.87 mmol), *p*-toluenesulfonic acid (0.5 g, 2.91 mmol), and acetonitrile (100 mL) were mixed at room temperature and stirred for 3 hrs, and then saturated sodium bicarbonate (50 mL) was added. The mixture was extracted with ethyl acetate (50 mL $\times$ 2). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and

concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give a target product 4-bromo-2-iodo-6-methylaniline **20b** (3.5 g, white solid), yield: 42%.

MS m/z (ESI):312, 314[M+1]

5 Step 2

5-bromo-7-iodo-1H-indazole

Compound 4-bromo-2-iodo-6-methylaniline **20b** (3.5 g, 11.2 mmol), acetic acid (45 mL), and water (2.1 mL) were mixed at room temperature, and then sodium nitrite (851 mg, 12.3 mmol) was added. The mixture was stirred at room temperature for another 1 hr, and then water (200 mL) was added. The mixture was adjusted to pH = 9 by using a saturated solution of sodium bicarbonate, and extracted with ethyl acetate (200 mL×2). The organic phases were combined, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 5/1) to give a target product 5-bromo-7-iodo-1H-indazole **20c** (2.5 g, brown solid), yield: 69%.

15 MS m/z (ESI):323, 325[M+1]

Step 3

5-bromo-7-(4-phenoxyphenyl)-1H-indazole

Compound 5-bromo-7-iodo-1H-indazole **20c** (2.0 g, 6.2 mmol), (4-phenoxyphenyl)boric acid (1.46 g, 6.8mmol), cesium carbonate (4.04 g, 12.4 mmol), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (453 mg, 0.62 mmol), 1,4-dioxane (50 mL), and water (10 mL) were mixed, degassed, and heated at 100°C under nitrogen for 12 hrs. The mixture was cooled to room temperature, and then water (100 mL) was added. Next, the mixture was extracted with ethyl acetate (100 mL×2). The organic phases were combined, and desolventized under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/methanol = 30/1), to produce a target compound 5-bromo-7-(4-phenoxyphenyl)-1H-indazole **20d** (1.6 g, white solid), yield: 71%.

MS m/z(ESI):365, 367[M+1]

Step 4

7-(4-phenoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole

30 Compound 5-bromo-7-(4-phenoxyphenyl)-1H-indazole **20d** (730 mg, 2 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-di(1,3,2-dioxaborolanyl) (1.22g, 4.0 mmol), potassium acetate

(589 mg, 6 mmol), [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (146 mg, 0.2 mmol), and 1,4-dioxane (20 mL) were mixed, degassed, and heated at 90°C under nitrogen for 12 hrs. The mixture was cooled to room temperature, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 5/1), to produce a target compound 7-(4-phenoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole **20e** (480 mg, white solid), yield: 34%.

MS m/z (ESI):413[M+1]

Step 5

Tert-butyl 5-(((trifluoromethyl)sulfonyl)oxo)-3,6-dihydropyridine-1(2H)-carboxylate

Compound *tert*-butyl 3-carboxylpiperidin-1-carboxylate **20i** (10 g, 50 mmol) was dissolved in tetrahydrofuran (200 mL) under nitrogen protection and cooled to -78°C, and then a solution of lithium di-isopropyl amide in tetrahydrofuran (2 M, 30mL) was added. The mixture was stirred at the aforesaid temperature for 1 hr, and then N-phenyl-bis(trifluoromethanesulfonimide) (19.6 g, 55 mmol) was added. Next, the mixture was gradually warmed to room temperature and stirred for another 3 hrs. The reaction was quenched with water (5 mL). The reaction mixture was poured into water (300 mL), and extracted with ethyl acetate (300 mL×2). The organic phases were combined and concentrated to remove solvent under reduced pressure to give a target product *tert*-butyl 5-(((trifluoromethyl)sulfonyl)oxo)-3,6-dihydropyridine-1(2H)-carboxylate **20j** (4.8 g, brown oil), yield: 29%.

¹H NMR (400 MHz, CDCl₃) δ 5.97-5.89 (m, 1H), 4.07-4.00 (m, 2H), 3.52-3.44 (m, 2H), 2.34- 2.26 (m, 2H), 1.48 (s, 9H).

Step 6

Tert-butyl

5-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate

Compound

7-(4-phenoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole **20e** (2.3 g, 5.58 mmol), *tert*-butyl

5-(((trifluoromethyl)sulfonyl)oxo)-3,6-dihydropyridine-1(2H)-carboxylate **20j** (2.8 g, 8.37 mmol), cesium carbonate (3.6 g, 11.16 mmol), [1,1'-bis(diphenylphosphine)ferrocene]palladium

dichloride (408 mg, 0.2 mmol), 1,4-dioxane (80 mL), and water (16 mL) were mixed, degassed, and heated at 100°C under nitrogen for 12 hrs. The mixture was cooled to room temperature and concentrated to remove solvent. The residue was dispersed in water (50 mL) and extracted with ethyl acetate (300 mL×2). The organic phases were combined, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1), to produce a target compound *tert*-butyl 5-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate **20f** (2.2 g, white solid), yield: 85%.

MS m/z (ESI):468[M+1]

10 Step 7

Tert-butyl 3-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)piperidin-1-carboxylate

Compound

tert-butyl

5-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate **20f** (1.4 g, 2.99 mmol), Pd-C (400mg), and methanol (30 mL) were mixed, degassed, and stirred at room temperature under hydrogen atmosphere for 16 hrs. The mixture was filtered, and concentrated to remove solvent under reduced pressure to produce a target product *tert*-butyl 3-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)piperidin-1-carboxylate **20g** (1.3 g, brown oil), yield: 92%.

MS m/z (ESI): 470[M+1]

20 Step 8

7-(4-phenoxyphenyl)-5-(piperidin-3-yl)-1H-indazole

Compound *tert*-butyl 3-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)piperidin-1-carboxylate **20g** (1.1 g, 2.3 mmol) was dissolved in a solution of hydrogen chloride in ethyl acetate (1 M, 25 mL, 25 mmol), and stirred at room temperature for 12 hrs. The mixture was concentrated to remove solvent under reduced pressure to produce a target product 7-(4-phenoxyphenyl)-5-(piperidin-3-yl)-1H-indazole **20h** (1.1 g, yellow solid), yield 100%.

MS m/z (ESI):370[M+1]

Step 9

1-(3-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)piperidin-1-yl)prop-2-en-1-one

30 Compound 7-(4-phenoxyphenyl)-5-(piperidin-3-yl)-1H-indazole **20h** (500 mg, 1.23 mmol), acryloyl chloride (111 mg, 1.23 mmol), solid sodium bicarbonate (210 mg, 2.46 mmol), water

(12.5 mL), and tetrahydrofuran (12.5 mL) were mixed and stirred at room temperature for 2 hrs. The mixture was extracted with ethyl acetate (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1) to give a target product 1-(3-(7-(4-phenoxyphenyl)-1H-indazol-5-yl)piperidin-1-yl)prop-2-en-1-one **20** (20 mg, white solid), yield: 40%.

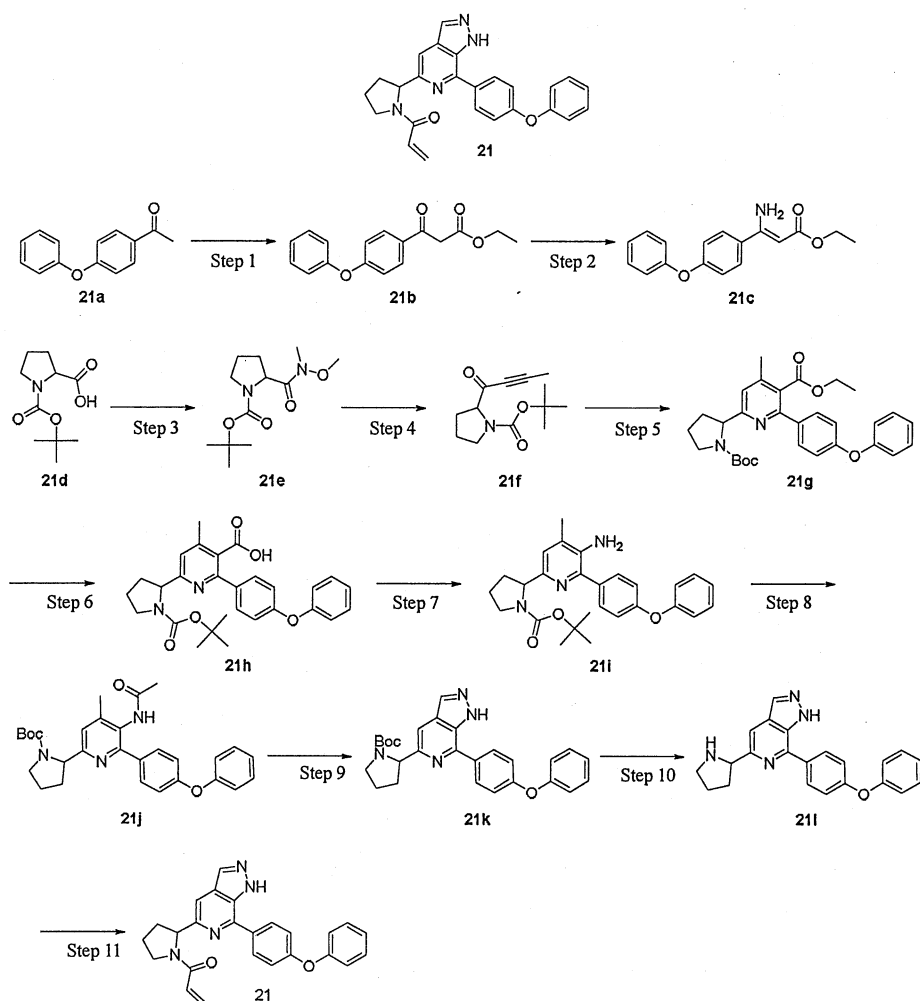
MS m/z (ESI):424[M+1]

¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.68 - 7.62 (m, 2H), 7.60 (s, 1H), 7.42 (dd, *J* = 8.3, 7.6 Hz, 2H), 7.35 (s, 1H), 7.19 (d, *J* = 8.2 Hz, 3H), 7.13 (dd, *J* = 8.6, 0.9 Hz, 2H), 6.65 (d, *J* = 10.6 Hz, 1H), 6.33 (d, *J* = 16.9 Hz, 1H), 5.77 - 5.64 (m, 1H), 4.86 (dd, *J* = 45.3, 12.8 Hz, 1H), 4.22 - 4.06 (m, 1H), 3.27 - 3.11 (m, 1H), 2.91 (d, *J* = 10.6 Hz, 1H), 2.80 - 2.68 (m, 1H), 2.21 (d, *J* = 13.2 Hz, 1H), 1.98 - 1.81 (m, 2H), 1.75 - 1.63 (m, 1H).

15 EXAMPLE 21

1-(2-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-on

e



Step 1

Ethyl 3-carbonyl-3-(4-phenoxyphenyl)propionate

A mixture of 1-(4-phenoxyphenyl)ethanone **21a** (4.24 g, 20 mmol), sodium hydride (60%, 2.0 g, 50 mmol), and toluene (30 mL) was heated to 90°C, and then compound diethyl carbonate (5.9 g, 50 mmol) was added. The reaction mixture was stirred at reflux for 45 min. The mixture was cooled to room temperature, and adjusted with a saturated ammonium chloride solution to neutral and extracted with ethyl acetate (100 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 100/1) to give a target product ethyl 3-carbonyl-3-(4-phenoxyphenyl) propionate **21b** (4.0 g, white solid), yield: 50%.

MS m/z (ESI): 283[M-1]

Step 2

Ethyl (Z)-3-amino-3-(4-phenoxyphenyl)acryloyl acid ester

Compound ethyl 3-carbonyl-3-(4-phenoxyphenyl) propionate **21b** (2.84 g, 10.0 mmol), ammonium formate (3.15 g, 50.0 mmol), molecular sieve (2.0 g), and ethanol (50 mL) were mixed and heated to reflux for 16 hrs. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give a target product ethyl (Z)-3-amino-3-(4-phenoxyphenyl)acryloyl acid ester **21c** (1.8 g, white solid), yield: 64%.

MS m/z (ESI):284[M+1]

Step 3

Tert-butyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate

Compound (*tert*-butoxy carbonyl)proline **21d** (5 g, 23 mmol), methoxymethyl amine hydrochloride (2.5 g, 25 mmol), 2-(7-azobenzotriazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate (9.7 g, 25 mmol), diisopropyl ethyl amine (11.5 mL, 69 mmol), and dichloromethane (100 mL) were mixed and stirred at room temperature for 15 hrs. The mixture was desolventized under reduced pressure. The residue was dissolved in ethyl acetate (200 mL), and washed with saturated saline. The organic phase was desolventized under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate= 5/1 to 1/1) to give a target product *tert*-butyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate **21e** (5.7 g, colorless oil), yield: 96%.

¹H NMR (400 MHz, CDCl₃) δ 4.78 - 4.57 (m, 1H), 3.77 (d, *J* = 25.5 Hz, 3H), 3.59 (m, 1H), 3.54 - 3.38 (m, 1H), 3.22 (s, 3H), 2.20 (m, 1H), 1.93 (m, 3H), 1.46 (d, *J* = 17.8 Hz, 9H).

Step 4

tert-butyl 2-(but-2-ynacyl)pyrrolidine-1-carboxylate

Compound *tert*-butyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate **21e** (3.5 g, 13.5mmol) was dissolved in tetrahydrofuran (100 mL). The mixture was cooled to -78°C, and then a propynyl magnesium bromide solution (0.5 M, 54 mL, 27 mmol) was dropwise added. After completion of addition, the mixture was gradually warmed to room temperature and stirred for another 15 hrs. After the completion of reaction, a saturated ammonium chloride solution was added to quench the reaction. The mixture was desolventized under reduced pressure. The residue was diluted with ethyl acetate (200 mL), and washed with saturated saline. The organic phase was desolventized under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give a target product

tert-butyl 2-(but-2-ynacyl)pyrrolidine-1-carboxylate **21f** (2.45 g, colorless oil), yield: 78%.

¹H NMR (400 MHz, CDCl₃) δ 4.33 (ddd, *J* = 13.9, 8.7, 4.8 Hz, 1H), 3.55 (d, *J* = 6.7 Hz, 2H), 2.33 - 2.12 (m, 1H), 2.04 (d, *J* = 2.2 Hz, 3H), 2.03 - 1.80 (m, 3H), 1.46 (d, *J* = 19.1 Hz, 9H).

5 Step 5

Ethyl 6-(1-(*tert*-butoxy carbonyl)pyrrolidin-2-yl)-4-methyl-2-(4-phenoxyphenyl)nicotine acid ester

Compound ethyl (Z)-3-amino-3-(4-phenoxyphenyl)acryloyl acid ester **21c** (980 mg, 3.5 mmol), *tert*-butyl 2-(but-2-ynacyl)pyrrolidine-1-carboxylate **21f** (907 mg, 3.8 mmol), ammonium acetate (267 mg, 3.5 mmol), and ethanol (30 mL) were mixed and heated with stirring at 100°C for 15 hrs. After the completion of reaction, the mixture was cooled to room temperature, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give a target product ethyl 6-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-4-methyl-2-(4-phenoxyphenyl)nicotine acid ester **21g** (540 mg, yellow solid), yield: 31%.

MS *m/z* (ESI): 503[M+1]

Step 6

6-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-4-methyl-2-(4-phenoxyphenyl)nicotinic acid

20 Compound ethyl 6-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-4-methyl-2-(4-phenoxyphenyl)nicotine acid ester **21g** (140 mg, 0.28 mmol), sodium hydroxide (1.1 g, 28 mmol), water (5 mL), and ethanol (8 mL) were mixed, heated to 88°C, and stirred for 15 hrs. After the completion of reaction, the reaction mixture was adjusted by hydrochloric acid to pH = 3, and extracted with ethyl acetate (100 mL). The organic phase was concentrated to remove solvent under reduced pressure, and the residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1) to give a target product 6-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-4-methyl-2-(4-phenoxyphenyl)nicotinic acid **21h** (130 mg, colorless oil), yield: 90%.

30 MS *m/z* (ESI): 475[M+1]

Step 7

tert-butyl 2-(5-amino-4-methyl-6-(4-phenoxyphenyl)pyridin-2-yl)pyrrolidine-1-carboxylate
Compound

6-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-4-methyl-2-(4-phenoxyphenyl)nicotinic acid **21h**
(130 mg, 0.27 mmol), diphenylphosphoryl azide (98 mg, 0.324 mmol), triethylamine (36 mg,
5 0.324 mmol), and acetonitrile (10 mL) were mixed and heated with stirring at 90°C under Ar
atmosphere for 5 hrs. The mixture was cooled to room temperature, and then water was added (2
mL). The mixture was heated for 1 hr at 90°C under Ar atmosphere. After the completion of
reaction, the reaction mixture was concentrated to remove solvent under reduced pressure. The
residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate =
10 1/1) to give a target product *tert*-butyl
2-(5-amino-4-methyl-6-(4-phenoxyphenyl)pyridin-2-yl)pyrrolidine-1-carboxylate **21i** (60 mg,
colorless oil), yield: 60%.

MS *m/z* (ESI):446[M+1]

Step 8

15 *Tert*-butyl

2-(5-acetamido-4-methyl-6-(4-phenoxyphenyl)pyridin-2-yl)pyrrolidine-1-carboxylate

Compound

tert-butyl

2-(5-amino-4-methyl-6-(4-phenoxyphenyl)pyridin-2-yl)pyrrolidine-1-carboxylate **21i** (80 mg,
0.18 mmol), acetic anhydride (37 mg, 0.36 mmol), and toluene (10 mL) were mixed and heated
20 with stirring at 90°C for 15 hrs. The reaction was cooled to room temperature, and concentrated
to remove solvent under reduced pressure. The residue was purified by column chromatography
on silica gel (petroleum ether/ethyl acetate= 5/1) to give a target product *tert*-butyl
2-(5-acetamido-4-methyl-6-(4-phenoxyphenyl)pyridin-2-yl)pyrrolidine-1-carboxylate **21j** (44
mg, colorless oil), yield: 50%.

25 MS *m/z* (ESI):488[M+1]

Step 9

Tert-butyl

2-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*c*]pyridin-5-yl)pyrrolidine-1-carboxylate

A

mixture

of

tert-butyl

30 2-(5-acetamido-4-methyl-6-(4-phenoxyphenyl)pyridin-2-yl)pyrrolidine-1-carboxylate **21j** (44
mg, 0.09 mmol), acetic anhydride (28 mg, 0.27 mmol), potassium acetate (12 mg, 0.12 mmol),

and benzene (20 mL) was heated to 78°C, and isoamyl nitrite was immediately added (17 mg, 0.14 mmol). The mixture was stirred for 18 hrs, and then cooled to room temperature. The mixture was desolventized under reduced pressure. The residue was dissolved in a mixture of water (5 mL), and ethanol (15 mL), and then lithium hydroxide monohydrate (100 mg) was added and stirred at room temperature for 2 hrs. The mixture was concentrated to remove solvent under reduced pressure, and the residue was dispersed in water (10 mL). The mixture was extracted with ethyl acetate (50 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1 to 1/2) to give a target product *tert*-butyl 2-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidine-1-carboxylate **21k** (10 mg, yellow solid), yield: 24%.

MS m/z (ESI):457[M+1]

Step 10

7-(4-phenoxyphenyl)-5-(pyrrolidin-2-yl)-1H-pyrazolo[3,4-c]pyridine

Compound

tert-butyl

2-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidine-1-carboxylate **20k** (10 mg, 0.02 mmol), dichloromethane (5 mL), and a solution of hydrogen chloride in ethanol (4 M, 1 mL, 4 mmol) were mixed and stirred at room temperature for 2 hrs. The mixture was desolventized under reduced pressure to produce a target product 7-(4-phenoxyphenyl)-5-(pyrrolidin-2-yl)-1H-pyrazolo[3,4-c]pyridine **21l** (5 mg, crude). The product was directly used in the next reaction without further purification.

MS m/z (ESI):357[M+1]

Step 11

1-(2-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one

e

Compound 7-(4-phenoxyphenyl)-5-(pyrrolidin-2-yl)-1H-pyrazolo[3,4-c]pyridine **20l** (5 mg, crude), acryloyl chloride (2 mg, 0.02 mmol), solid sodium bicarbonate (20 mg, 0.24 mmol), water (10 mL), and tetrahydrofuran (20 mL) were mixed and stirred at room temperature for 2 hrs. The mixture was extracted with ethyl acetate (20 mL×3). The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove the desiccant, and

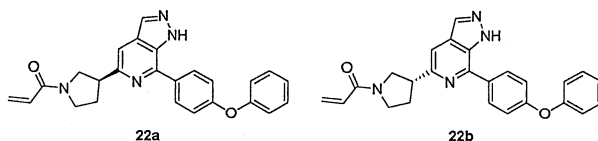
concentrated to remove solvent under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/methanol = 20/1) to give a target product 1-(2-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one **21** (1 mg, white solid), yield: 17%.

5 MS m/z (ESI): 411[M+1]

¹H NMR (400 MHz, CD₃OD) δ 8.19 (d, J = 12.2 Hz, 1H), 8.03 (dd, J = 12.4, 8.7 Hz, 2H), 7.53 (d, J = 4.5 Hz, 1H), 7.48 - 7.37 (m, 2H), 7.25 - 7.17 (m, 2H), 7.13 (d, J = 8.3 Hz, 1.5H), 6.80 (dd, J = 16.8, 10.5 Hz, 0.5H), 6.39 (dd, J = 16.9, 10.1 Hz, 0.5H), 6.24 (m, 1H), 5.79 (dd, J = 10.4, 1.9 Hz, 0.5H), 5.53 (dd, J = 10.3, 2.0 Hz, 0.5H), 5.46 (s, 1H), 5.36 (t, J = 4.7 Hz, 0.5H), 4.09 (d, J = 6.3 Hz, 0.5H), 4.00 - 3.85 (m, 1H), 3.82 - 3.74 (m, 0.5H), 2.49 (m, 1H), 2.23 (m, 2H), 2.11 - 1.98 (m, 2H).

EXAMPLE 22

(S)-1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one **22a** and
 15 (R)-1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one **22b**



20

Compound

1-(3-(7-(4-phenoxyphenyl)-1H-pyrazolo[3,4-c]pyridin-5-yl)pyrrolidin-1-yl)prop-2-en-1-one **6** (1.34 g) was resolved by chiral preparative liquid chromatography (chiral column: CHIRALCEL OD-H; gauge: 0.46 cm I.D. $\times$ 15 cm L; mobile phase: n-hexane/ethanol = 70/30; flow rate: 1.0 mL/min; temperature: 35°C) to give two optical isomers (one component with a retention time of 7.428 min, 0.61 g; and the other component with a retention time of 10.601 min, 0.70 g). The two optical isomers correspond to **22a** and **22b**, respectively, but the absolute configurations thereof were not yet identified.

30

BTK ENZYME ACTIVITY TESTING

An *in vitro* kinase assay is used to evaluate the effect of the inventive compounds on Bruton tyrosine kinase (BTK) activity.

The experimental method is generally described as follows:

In vitro activity of BTK is measured by detecting ADP produced in a kinase reaction with
5 an ADP-Glo™ kinase assay kit from Promega Company. In the kinase assay, the kinase consumes ATP to phosphorylate the substrate, while producing ADP. ADP-Glo reagent then terminates the kinase reaction and completely consumes the remaining ATP. Finally, a kinase detection reagent is added to convert generated ADP into new ATP. Luciferase in the detection
10 reagent is capable of catalyzing fluorescein with the participation of ATP and O₂ to produce oxidized fluorescein, AMP, and generate light quantum, thereby converting a chemical signal into an optical signal (Luminescence). The intensity of optical signal is positively correlated with the production of ADP in the kinase reaction, so that the activity of kinase BTK can be thereby quantitatively determined.

All assays are conducted at a constant temperature of 23°C, using a Corning 3674 Type
15 white 384-well plate; the BTK kinase (full length with His-Tag) is expressed and purified internally by the company; the substrate of kinase is polypeptide (4:1 Glu,Tyr) (from SignalChem) and ATP (from Sigma); and a microplate reader EnVision (Perkin Elmer) is used for reading an optical signal. The assay buffer includes 40 mM Tris-HCl (pH 7.5), 10 mM MgCl₂ (Sigma), 2 mM MnCl₂ (Sigma), 0.05 mM DTT (Sigma), and 0.01% BSA (Sigma); the
20 BTK kinase is diluted with the assay buffer to a concentration of 1.6 ng/uL as a kinase reaction solution; and the substrate reaction solution comprises 0.2 mg/mL polypeptide substrate and 50 uM ATP.

Compound's IC₅₀ is calculated from 10 concentration points by the following method. The compound is dissolved and diluted in 100% DMSO to a concentration of 1 mM, followed by a
25 serial 3X dilution with DMSO to a minimum concentration of 0.05 uM. Each concentration stock is further diluted 40X with the assay buffer. To a 384-well assay plate are added 1 uL of a series of compound solutions and 2 uL of the kinase reaction solution, followed by mixing homogeneously, and incubating in the dark at room temperature. After in the dark for 30 min, 2 uL of the substrate reaction solution is added to allowed the total reaction volume to 5uL. The
30 reaction mixture is incubated in the dark at room temperature in the dark for another 60 min. An equal volume of 5 uL ADP-Glo™ reagent is then added to terminate the reaction. The resulting

mixture is homogeneously mixed, and stands at room temperature for 40 min. Finally, 10 uL of the kinase detection reagent is added, stands at room temperature for 30 min, and then a value is read on Envision.

Percent inhibition is calculated based on the following equation:

$$\text{Inhibition \%} = [1 - (\text{RLU}_{\text{compound}} - \text{RLU}_{\text{min}}) / (\text{RLU}_{\text{max}} - \text{RLU}_{\text{min}})] \times 100$$

wherein $\text{RLU}_{\text{compound}}$ is the luminescence reading at a given concentration of compound, RLU_{min} is the luminescence reading in the absence of kinase, and RLU_{max} is the luminescence reading in the absence of compound. IC_{50} of the compound is calculated by using a XLfit program in Excel.

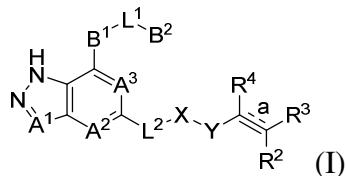
Compound No.	$\text{IC}_{50}(\text{nM})$	Compound No.	$\text{IC}_{50}(\text{nM})$
1	B	2	B
3	A	4	A
5	A	6	A
7	A	8	A
9	A	10	A
11	A	12	A
13	A	14	A
15	A	16	C
17	B	18	A
19	B	20	A
21	A	22a	A
22b	A		

A < 100nM; B = 100 to 500nM; C > 500nM

Conclusion: the compounds of the present invention exhibit a significant inhibitory effect on the activity of Bruton tyrosine kinase.

CLAIMS

1. A compound represented by formula (I),



5 or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof, or a pharmaceutically acceptable salt thereof:

wherein:

A^1 , A^2 and A^3 are each independently selected from the group consisting of CR^1 and N;

10 B^1 is independently selected from the group consisting of C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, and heteroaryl, wherein the cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^1 ;

B^2 is independently selected from the group consisting of H, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl and heteroaryl, wherein the cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^2 ;

15 L^1 is independently selected from the group consisting of $-C_{0-2}$ alkyl-, $-CR^5R^6$ -, $-C_{1-2}$ alkyl $(R^5)(OH)$ -, $-C(O)$ -, $-CR^5R^6O$ -, $-OCR^5R^6$ -, $-SCR^5R^6$ -, $-CR^5R^6S$ -, $-NR^5$ -, $-NR^5C(O)$ -, $-C(O)NR^5$ -, $-NR^5CONR^6$ -, $-CF_2$ -, $-O$ -, $-S$ -, $-S(O)_m$ -, $-NR^5S(O)_2$ - and $-S(O)_2NR^5$;

L^2 is independently selected from the group consisting of $-C_{0-4}$ alkyl-, $-C(O)$ -, $-O$ -, $-NR^7$ -, $-NR^7C(O)$ - and $-NR^7S(O)_2$;

20 X is independently selected from the group consisting of C_{0-4} alkyl, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl and heteroaryl, wherein the alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^3 ;

Y is independently selected from the group consisting of $-C(O)$ -, $-NR^8C(O)$ -, $-S(O)_m$ - and $-NR^8S(O)_m$;

25 R^1 is independently selected from the group consisting of H, D, C_{0-4} alkyl, halogen and cyano; bond $\equiv$ is a double bond or a triple bond;

when bond $\equiv$ is a double bond, R^2 , R^3 and R^4 are each independently selected from the group consisting of H, D, cyano, halogen, alkyl, cyclic group, heterocyclic group, aryl, and

heteroaryl, wherein the alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G⁴; and when bond $\equiv$ is a triple bond, R³ and R⁴ are absent, and R² is independently selected from the group consisting of H, D, cyano, halogen, alkyl, cyclic group, heterocyclic group, aryl and heteroaryl, wherein the alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G⁴; wherein R³ and R², together with the carbon atom attached thereto, can form a ring which contains optionally a heteroatom;

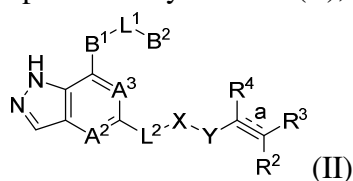
R⁵, R⁶, R⁷ and R⁸ are each independently selected from the group consisting of H, D, C₀₋₈ alkyl, C₃₋₈ cyclic group, 3- to 8-membered heterocyclic group, aryl, and heteroaryl, wherein the alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G⁵;

G¹, G², G³, G⁴ and G⁵ are each independently selected from the group consisting of H, D, halogen, cyano, alkyl, alkenyl, alkynyl, cyclic group, heterocyclic group, aryl, heteroaryl, -OR⁹, -OC(O)NR⁹R¹⁰, -C(O)OR¹⁰, -C(O)NR⁹R¹⁰, -C(O)R⁹, -NR⁹R¹⁰, -NR⁹C(O)R¹⁰, -NR⁹C(O)NR¹⁰R¹¹, -S(O)_mR¹⁰ and -NR⁹S(O)_mR¹⁰, wherein the alkyl, alkenyl, alkynyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more substituents selected from the group consisting of D, halogen, cyano, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclic group, -OR¹², -OC(O)NR¹²R¹³, -C(O)OR¹², -C(O)NR¹²R¹³, -C(O)R¹², -NR¹²R¹³, -NR¹²C(O)R¹³, -NR¹²C(O)NR¹³R¹⁴, -S(O)_mR¹², and -NR¹²S(O)_mR¹³;

R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁-C₆ heteroalkyl, C₃₋₈ cycloalkyl, 3- to 8-membered monocyclic heterocyclic group, monocyclic heteroaryl and monocyclic aryl; and

m is 1 or 2.

2. The compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof or a pharmaceutically acceptable salt thereof of claim 1, wherein the compound is represented by formula (II),



wherein:

A^2 and A^3 are each independently selected from the group consisting of CH and N;

B^1 is independently selected from the group consisting of C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, and heteroaryl, wherein the cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^1 ;

B^2 is independently selected from the group consisting of H, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, and heteroaryl, wherein the cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^2 ;

L^1 is independently selected from the group consisting of $-C_{0-2}$ alkyl-, $-CR^5R^6$ -, $-C_{1-2}$ alkyl(R^5)(OH)-, $-C(O)$ -, $-CR^5R^6O$ -, $-OCR^5R^6$ -, $-SCR^5R^6$ -, $-CR^5R^6S$ -, $-NR^5$ -, $-NR^5C(O)$ -, $-C(O)NR^5$ -, $-NR^5CONR^6$ -, $-CF_2$ -, $-O$ -, $-S$ -, $-S(O)_m$ -, $-NR^5S(O)_2$ - and $-S(O)_2NR^5$;

L^2 is independently selected from the group consisting of $-C_{0-4}$ alkyl-, $-C(O)$ -, $-O$ -, $-NR^7$ -, $-NR^7C(O)$ - and $-NR^7S(O)_2$;

X is independently selected from the group consisting of C_{0-4} alkyl, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, and heteroaryl, wherein the alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^3 ;

Y is independently selected from the group consisting of $-C(O)$ -, $-NR^8C(O)$ -, $-S(O)_m$ - and $-NR^8S(O)_m$;

bond $\equiv$ is a double bond or a triple bond;

when bond $\equiv$ is a double bond, R^2 , R^3 and R^4 are each independently selected from the group consisting of H, D, cyano, halogen, alkyl, cyclic group, heterocyclic group, aryl and heteroaryl, wherein the alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^4 ; and when bond $\equiv$ is a triple bond, R^3 and R^4 are absent, R^2 is independently selected from the group consisting of H, D, cyano, halogen, alkyl, cyclic group, heterocyclic group, aryl, and heteroaryl, wherein the alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more G^4 ; wherein R^3 and R^2 , together with the carbon atom attached thereto, can form a ring which contains optionally a heteroatom;

R^5 , R^6 , R^7 and R^8 are each independently selected from the group consisting of H, D, C_{0-8} alkyl, C_{3-8} cyclic group, 3- to 8-membered heterocyclic group, aryl, and heteroaryl, wherein the alkyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more

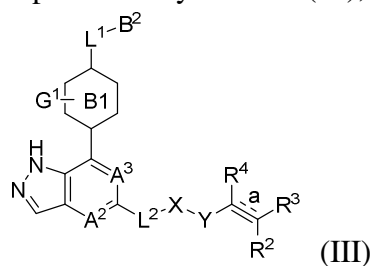
G⁵;

G¹, G², G³, G⁴ and G⁵ are each independently selected from the group consisting of H, D, halogen, cyano, alkyl, alkenyl, alkynyl, cyclic group, heterocyclic group, aryl, heteroaryl, -OR⁹, -OC(O)NR⁹R¹⁰, -C(O)OR¹⁰, -C(O)NR⁹R¹⁰, -C(O)R⁹, -NR⁹R¹⁰, -NR⁹C(O)R¹⁰, -NR⁹C(O)NR¹⁰R¹¹, -S(O)_mR¹⁰ and -NR⁹S(O)_mR¹⁰, wherein the alkyl, alkenyl, alkynyl, cyclic group, heterocyclic group, aryl or heteroaryl is optionally substituted with one or more substituents selected from the group consisting of D, halogen, cyano, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclic group, -OR¹², -OC(O)NR¹²R¹³, -C(O)OR¹², -C(O)NR¹²R¹³, -C(O)R¹², -NR¹²R¹³, -NR¹²C(O)R¹³, -NR¹²C(O)NR¹³R¹⁴, -S(O)_mR¹², and -NR¹²S(O)_mR¹³;

R⁹, R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁-C₆ heteroalkyl, C₃₋₈ cycloalkyl, 3- to 8-membered monocyclic heterocyclic group, monocyclic heteroaryl and monocyclic aryl; and

m is 1 or 2.

3. The compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof or a pharmaceutically acceptable salt thereof of claim 1, wherein the compound is represented by formula (III),

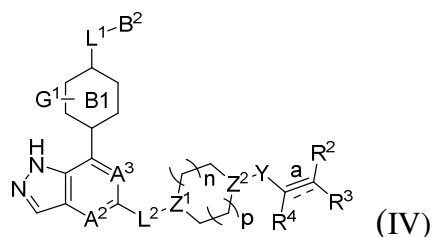


wherein:

B¹ is a phenyl ring or 6-membered heteroaryl ring;

A², A³, B², L¹, L², X, Y, bond $\equiv$, R², R³, R⁴ and G¹ are defined as in claim 1.

4. The compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof or a pharmaceutically acceptable salt thereof of claim 1, wherein the compound is represented by formula (IV),



wherein:

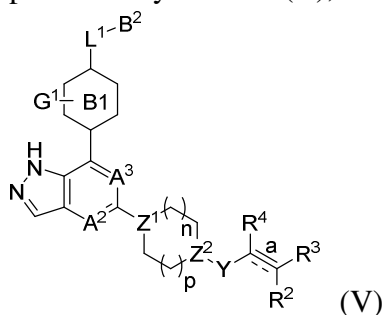
Z^1 and Z^2 are each independently selected from the group consisting of $C(R^a)$ and N;

R^a is H or alkyl;

5 n and p are each independently selected from the group consisting of 0, 1 and 2;

A^2 , A^3 , B^1 , B^2 , L^1 , L^2 , Y, bond $\equiv$, R^2 , R^3 , R^4 and G^1 are defined as in claim 1.

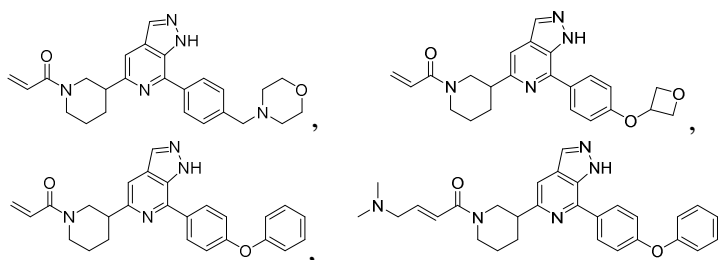
5. The compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof or a pharmaceutically acceptable salt thereof of claim 1, wherein the compound is represented by formula (V),

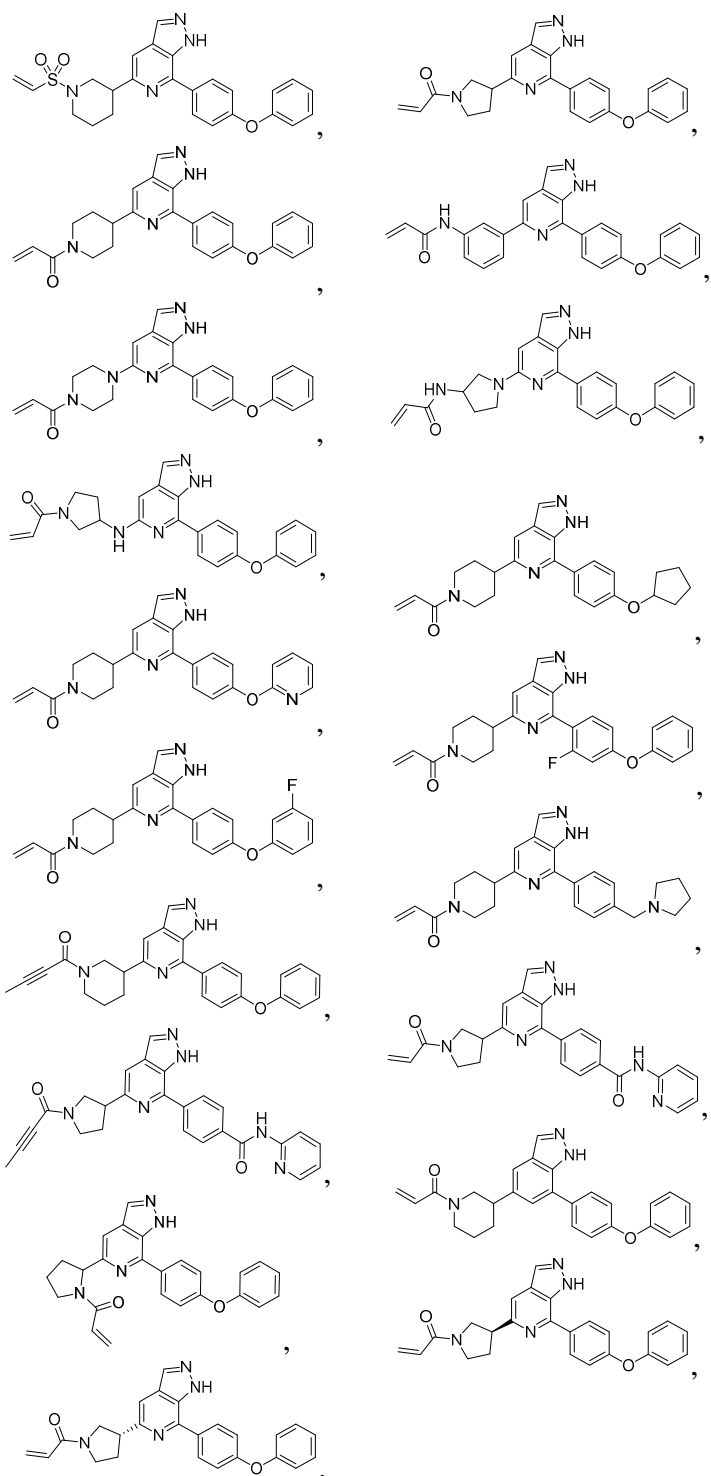


wherein:

A^2 , A^3 , B^1 , B^2 , L^1 , Y, bond $\equiv$, R^2 , R^3 , R^4 , G^1 , Z^1 , Z^2 , n and p are defined as in claim 1.

15 6. The compound represented by formula (I) or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof or a pharmaceutically acceptable salt thereof of claim 1, wherein the compound is:





7. A pharmaceutical composition comprising a therapeutically effective amount of a compound represented by formula (I) of claim 1, or its tautomers, mesomers, racemates, enantiomers, diastereoisomers, mixtures thereof, and a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, and excipient.