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(54) Titre : INHIBITEURS DE SHP2 ET LEURS UTILISATIONS  
(54) Title: SHP2 INHIBITORS AND USES THEREOF



(1)

(57) **Abrégé/Abstract:**

Compounds of Formula (1) as inhibitors of protein tyrosine phosphatase SHP2 are disclosed. The pharmaceutical compositions comprising compounds of Formula 1, methods of synthesis of these compounds, methods of treatment for diseases associated with the aberrant activity of SHP2 such as cancer using these compounds or compositions containing these compounds are also disclosed.

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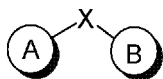
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## (54) Title: SHP2 INHIBITORS AND USES THEREOF



(1)

(57) Abstract: Compounds of Formula (1) as inhibitors of protein tyrosine phosphatase SHP2 are disclosed. The pharmaceutical compositions comprising compounds of Formula 1, methods of synthesis of these compounds, methods of treatment for diseases associated with the aberrant activity of SHP2 such as cancer using these compounds or compositions containing these compounds are also disclosed.

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## **SHP2 INHIBITORS AND USES THEREOF**

### **CROSS-REFERENCE TO RELATED APPLICATION**

This application claims the benefit of U.S. Provisional Application No. 62/646,107, filed March  
5 21, 2018; which is incorporated by reference by its entirety.

### **FIELD**

The present disclosure relates to inhibitors of protein tyrosine phosphatase SHP2 (Src Homolgy-2 phosphatase) and their use in treating SHP2 mediated disorders. More specifically, this disclosure is directed to compounds that inhibit SHP2 and compositions comprising these compounds,  
10 methods of treating diseases associated with the aberrant activity of SHP2, and methods of synthesizing these compounds.

### **BACKGROUND**

Tyrosyl phosphorylation regulates human cellular processes from cell differentiation to growth and apoptosis etc. Tyrosyl phosphorylation is regulated by protein-tyrosine kinases (PTK)  
15 and protein-tyrosine phosphatases (PTP). The imbalance of regulation governed by PTK and PTP activity leads to various diseases.

SHP2 is a non-receptor protein tyrosine phosphatase (PTP) encoded by the Protein-tyrosine phosphatase non-receptor type 11 (PTPN11) gene. It contains two N-terminal Src homology 2 domains (N-SH2 and C-SH2), a catalytic domain, and a C-terminal tail. The protein exists in an  
20 inactive, auto-inhibited basal conformation that blocks the active site. This self-inhibition state is stabilized by a binding network involving residues from both the N-SH2 and catalytic domains. Stimulation by, for example, cytokines or growth factors results in enzymatic activation of SHP2 and makes the active site available for dephosphorylation of PTPN11 substrates.

SHP2 is widely expressed in most tissues and contributes to various cellular functions including  
25 proliferation, differentiation, cell cycle maintenance and migration. It is involved in signaling through the Ras-mitogen-activated protein kinase, the JAK-STAT, EGFR, or the phosphoinositol 3-kinase-AKT pathways.

Mutations in the PTPN11 gene and subsequently in SHP2 lead to hyperactivation of SHP2 catalytic activity, and have been identified in several human diseases, such as Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, acute myeloid leukemia and cancers of the breast, lung, melanoma, neuroblastoma, hepatocellular carcinoma, and colon. These mutations disrupt the auto-inhibition between the N-SH2 domains and the catalytic site allowing constitutive access of substrates to the catalytic site of the enzyme.

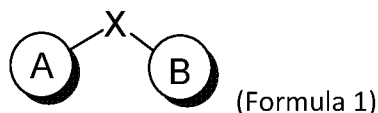
Additionally, there is growing evidence that PTPN11/SHP2 may be implicated in immune evasion during tumorigenesis, and hence a SHP2 inhibitor could stimulate the immune response in cancer patients.

Furthermore, SHP2 plays an important role in JAK/STAT3 pathway, with clear correlation between its phosphatase activity and systemic autoimmunity, thus a SHP2 inhibitor could be used to treat autoimmune diseases such as Lupus and Rheumatoid Arthritis.

Therefore, SHP2 represents a highly attractive target for the development of novel therapies for the treatment of various diseases associated with the aberrant activity of SHP2. The compounds of the present disclosure that are capable of inhibiting the activity of SHP2, possess great potential as novel small molecule therapies for the treatment of various diseases mentioned above.

### SUMMARY

This disclosure relates to compounds represented by Formula 1:



or a pharmaceutically acceptable salt thereof; wherein X is S, O,  $\text{NR}^A$ ,  $\text{CHR}^A$ , SO,  $\text{SO}_2$ , CO, or a bond; Ring A is an optionally substituted aryl, heteroaryl, or bicyclic ring system; Ring B is an optionally substituted heterocyclic ring system, including non-aromatic ring system and heteroaryl, comprising a mono-cyclic ring, a bicyclic ring system, a tricyclic ring system, or a tetracyclic ring system, wherein the heterocyclic ring system contains at least 2 ring nitrogen atoms; and  $\text{R}^A$  is H or  $\text{C}_{1-6}$  hydrocarbyl.

Some embodiments include a method of treating diseases, disorders, or conditions associated with the aberrant activity of SHP2, such as but not limited to, cancer, and autoimmune disorders,

comprising administering a therapeutically effective amount of a compound described herein, or any optionally substituted compound represented in Table I below, or a pharmaceutically acceptable salt thereof (referred to collectively herein as a “subject compound”), to a patient in need thereof.

Some embodiments include use of a compound described herein, such as a compound of  
5 Formula 1, a subject compound described herein in the manufacture of a medicament for the treatment of cancer, autoimmune diseases, inflammatory diseases, autoinflammatory conditions, and other SHP2 mediated disorders in a mammal.

Some embodiments include a pharmaceutical composition comprising a therapeutically effective amount of a subject compound described herein, or a pharmaceutically acceptable salt  
10 thereof, in combination with at least one pharmaceutically acceptable vehicle, diluent, or carrier.

Some embodiments include a process for making a pharmaceutical composition comprising combining a subject compound described herein and at least one pharmaceutically acceptable carrier.

Some embodiments include a medicament comprising a composition comprising a therapeutically effective amount of a subject compound.

15 Some embodiments include a kit comprising a medicament of above and a label indicating that the medicament is for treating a disease, disorders, or condition associated with the aberrant activity of SHP2.

### DESCRIPTION

Unless otherwise indicated, any reference to a compound herein by structure, name, or any  
20 other means, includes pharmaceutically acceptable salts, such as sodium, potassium, and ammonium salts, or HCl, H<sub>2</sub>SO<sub>4</sub>, HCO<sub>2</sub>H, and CF<sub>3</sub>CO<sub>2</sub>H salts; prodrugs, such as ester prodrugs; alternate solid forms, such as polymorphs, solvates, hydrates, etc.; tautomers; or any other chemical species that may rapidly convert to a compound described herein under conditions in which the compounds are used as described herein.

25 If stereochemistry is not indicated, a name or structural depiction includes any stereoisomer or any mixture of stereoisomers.

Unless otherwise indicated, when a compound or chemical structural feature such as aryl is referred to as being “optionally substituted,” it includes a feature that has no substituents (i.e.

unsubstituted), or a feature that is “substituted,” meaning that the feature has one or more substituents. The term “substituent” is broad, and includes a moiety that occupies a position normally occupied by one or more hydrogen atoms attached to a parent compound or structural feature. In some embodiments, a substituent may be an ordinary organic moiety known in the art, which may have a molecular weight (e.g. the sum of the atomic masses of the atoms of the substituent) of 15 g/mol to 50 g/mol, 15 g/mol to 100 g/mol, 15 g/mol to 150 g/mol, 15 g/mol to 200 g/mol, 15 g/mol to 300 g/mol, or 15 g/mol to 500 g/mol. In some embodiments, a substituent may be an ordinary organic moiety known in the art, which may have a molecular weight of 15 g/mol to 200 g/mol. In some embodiments, a substituent comprises, or consists of: 0-30, 0-20, 0-10, or 0-5 carbon atoms; and 0-30, 0-20, 0-10, or 0-5 heteroatoms, wherein each heteroatom may independently be: N, O, S, P, Si, F, Cl, Br, or I; provided that the substituent includes one C, N, O, S, P, Si, F, Cl, Br, or I atom. Examples of substituents include, but are not limited to, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, acyl, acyloxy, alkylcarboxylate, thiol, alkylthio, cyano, halo, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxyl, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, phosphonic acid, etc.

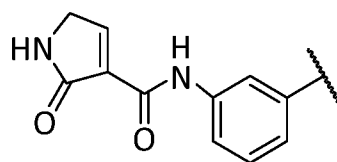
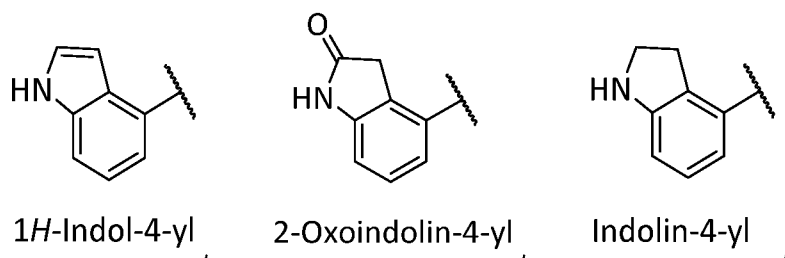
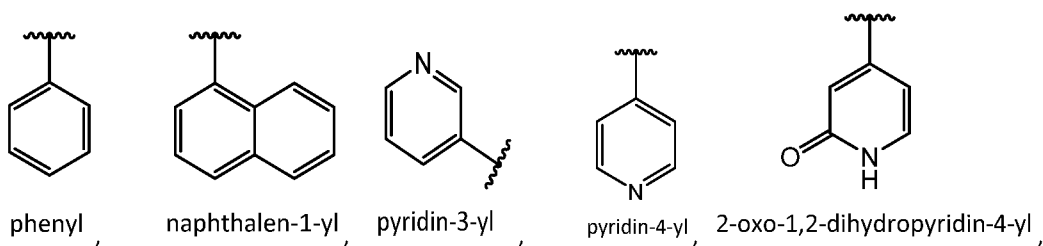
For convenience, the term “molecular weight” is used with respect to a moiety or part of a molecule to indicate the sum of the atomic masses of the atoms in the moiety or part of a molecule, even though it may not be a complete molecule.

The term “treating” or “treatment” includes the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals.

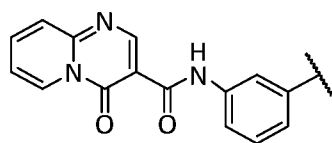
A hydrogen atom in any position of a compound of Formula 1 may be replaced by a deuterium. In some embodiments, a compound of Formula 1 contains a deuterium atom or multiple deuterium atoms.

With respect to Formula 1, in some embodiments Ring A is: optionally substituted phenyl, optionally substituted naphthalen-1-yl, optionally substituted pyridin-3-yl, optionally substituted pyridin-4-yl, optionally substituted 2-oxo-1,2-dihydropyridin-4-yl, optionally substituted 1*H*-indol-4-

yl, optionally substituted 2-oxoindolin-4-yl, optionally substituted indolin-4-yl, optionally substituted 3-(2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxamido)phenyl, optionally substituted 3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamido)phenyl, optionally substituted 3-(4-oxo-4*H*-pyrazino[1,2-*a*]pyrimidine-3-carboxamido)phenyl, optionally substituted 3-(5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine-6-  
 5 carboxamido)phenyl, optionally substituted 3-(5-oxo-1,5-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxamido)phenyl, or optionally substituted 3-(4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamido)phenyl. For example, Ring A may be 2,3-dichlorophenyl, 2,3-dichloropyridin-4-yl, or 2-amino-3-chloropyridin-4-yl.

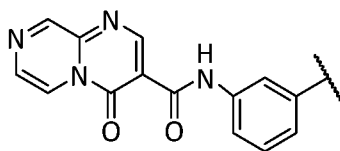


3-(2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxamido)phenyl,

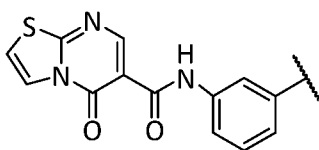


3-(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamido)phenyl,

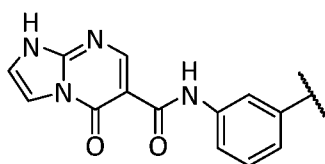




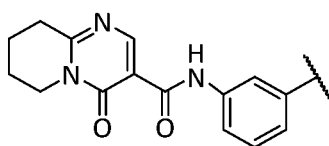
3-(4-oxo-4H-pyrazino[1,2-a]pyrimidine-3-carboxamido)phenyl ,



3-(5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carboxamido)phenyl ,



3-(5-oxo-1,5-dihydroimidazo[1,2-a]pyrimidine-6-carboxamido)phenyl ,



3-(4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-3-carboxamido)phenyl .

5 In some embodiments, Ring A is unsubstituted.

In some embodiments, Ring A has a Cl substituent.

In some embodiments, Ring A has two Cl substituents.

In some embodiments, Ring A has two Cl substituents at 2- and 3-positions; for example, Ring A is 2,3-dichlorophenyl.

10 In some embodiments, Ring A has a CF<sub>3</sub> substituent.

In some embodiments, Ring A has a CF<sub>3</sub> substituent at 2-position.

In some embodiments, Ring A has an NH<sub>2</sub> substituent.

In some embodiments, Ring A has an NH<sub>2</sub> substituent and a Cl substituent.

15 In some embodiments, Ring A has an NH<sub>2</sub> substituent and a Cl substituent with Cl at 2-position and NH<sub>2</sub> at 5-position.

In some embodiments, Ring A has an NH<sub>2</sub> substituent and a Cl substituent with Cl at 2-position and NH<sub>2</sub> at 3-position.

In some embodiments, Ring A has an NH<sub>2</sub> substituent and a Cl substituent with Cl at 3-position and NH<sub>2</sub> at 2-position.

5 In some embodiments, Ring A has an -OCH<sub>3</sub> substituent.

In some embodiments, Ring A has an -OCH<sub>3</sub> substituent and a Cl substituent.

In some embodiments, Ring A has an -OCH<sub>3</sub> substituent and a Cl substituent with Cl at 2-position and -OCH<sub>3</sub> at 3-position.

In some embodiments, Ring A has an F substituent.

10 In some embodiments, Ring A has two F substituents.

In some embodiments, Ring A has two F substituents at same position.

In some embodiments, Ring A has two F substituents at 2- and 3-positions.

In some embodiments, Ring A has an F substituent and a Cl substituent.

15 In some embodiments, Ring A has an F substituent and a Cl substituent with Cl at 2-position and F at 3-position.

In some embodiments, Ring A has an acetyl substituent.

In some embodiments, Ring A has a CH<sub>3</sub> substituent.

In some embodiments, Ring A has two CH<sub>3</sub> substituents that are at same position.

In some embodiments, Ring A has a CH<sub>3</sub> substituent and a Cl substituent.

20 In some embodiments, Ring A has a CH<sub>3</sub> substituent and a Cl substituent with Cl at 2-position and CH<sub>3</sub> at 4-position.

In some embodiments, Ring A has a CH<sub>3</sub> substituent and a Cl substituent with Cl at 2-position and CH<sub>3</sub> at 3-position.

In some embodiments, Ring A has a CH<sub>3</sub> substituent and two F substituents.

25 In some embodiments, Ring A has a CH<sub>3</sub> substituent and two F substituents with two F at same position.

In some embodiments, Ring A has an OH substituent.

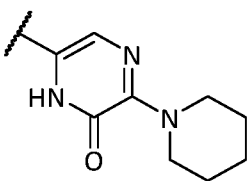
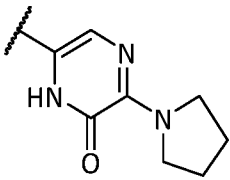
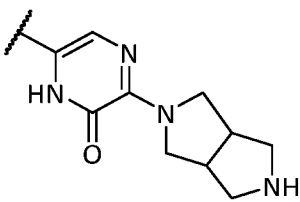
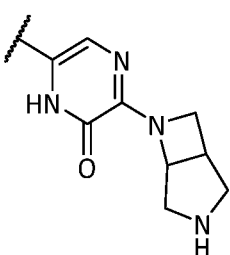
In some embodiments, Ring A has an OH substituent and a Cl substituent.

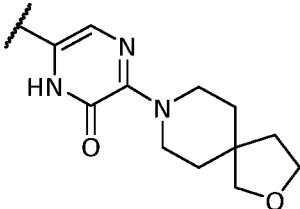
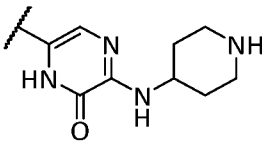
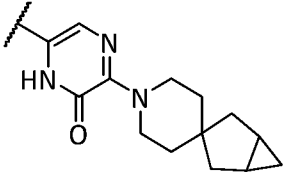
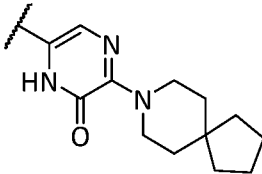
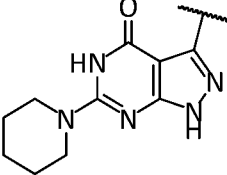
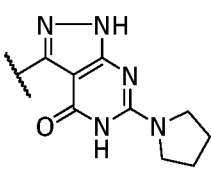
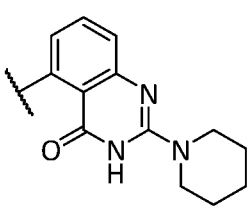
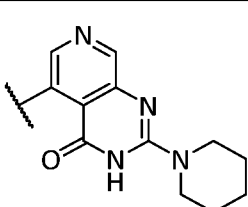
In some embodiments, Ring A has multiple substituents with any combination of the above substituents.

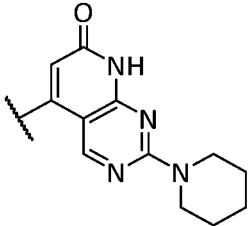
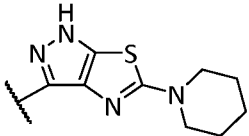
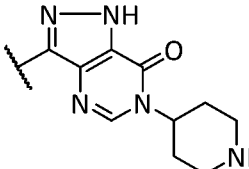
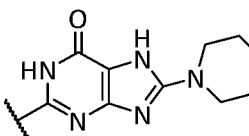
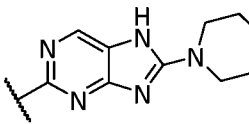
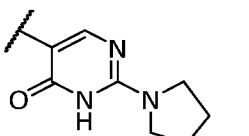
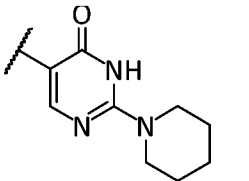
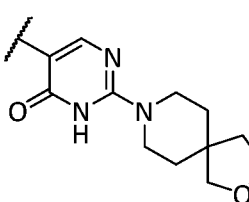
With respect to Formula 1, in some embodiments Ring B is: optionally substituted 6-oxo-5-(piperidin-1-yl)-1,6-dihydropyrazin-2-yl, optionally substituted 6-oxo-5-(pyrrolidin-1-yl)-1,6-dihydropyrazin-2-yl, optionally substituted 5-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrazin-2-yl, optionally substituted 5-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrazin-2-yl, optionally substituted 6-oxo-5-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1,6-dihydropyrazin-2-yl, optionally substituted 6-oxo-5-(piperidin-4-ylamino)-1,6-dihydropyrazin-2-yl, 6-oxo-5-(spiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-1,6-dihydropyrazin-2-yl, optionally substituted 6-oxo-5-(8-azaspiro[4.5]decan-8-yl)-1,6-dihydropyrazin-2-yl, optionally substituted 4-oxo-6-(piperidin-1-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl, 4-oxo-6-(pyrrolidin-1-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl, optionally substituted 4-oxo-2-(piperidin-1-yl)-3,4-dihydroquinazolin-5-yl, optionally substituted 4-oxo-2-(piperidin-1-yl)-3,4-dihydropyrido[3,4-d]pyrimidin-5-yl, optionally substituted 7-oxo-2-(piperidin-1-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-5-yl, optionally substituted 5-(piperidin-1-yl)-1H-pyrazolo[4,3-d]thiazol-3-yl, optionally substituted 7-oxo-6-(piperidin-4-yl)-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-3-yl, optionally substituted 6-oxo-8-(piperidin-1-yl)-6,7-dihydro-1H-purin-2-yl, optionally substituted 8-(piperidin-1-yl)-7H-purin-2-yl, optionally substituted 6-oxo-2-(pyrrolidin-1-yl)-1,6-dihydropyrimidin-5-yl, optionally substituted 6-oxo-2-(piperidin-1-yl)-1,6-dihydropyrimidin-5-yl, optionally substituted 6-oxo-2-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1,6-dihydropyrimidin-5-yl, optionally substituted 2-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, optionally substituted 2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, optionally substituted 2-(3-azabicyclo[3.2.0]heptan-3-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, optionally substituted 6-oxo-2-(2-azaspiro[3.4]octan-2-yl)-1,6-dihydropyrimidin-5-yl, optionally substituted 2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, optionally substituted 6-oxo-2-(2-azaspiro[3.4]octan-2-yl)-1,6-dihydropyrimidin-5-yl, optionally substituted 5-oxo-6-(2-oxa-8-azaspiro[4.5]decan-8-yl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl, optionally substituted 5-oxo-6-(piperidin-1-yl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl, optionally substituted 6-(piperidin-1-yl)-

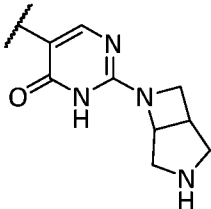
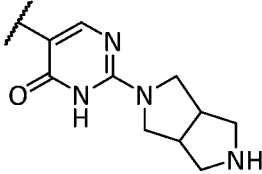
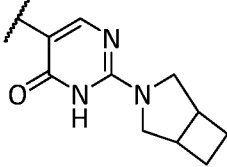
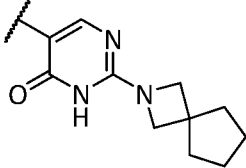
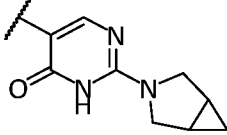
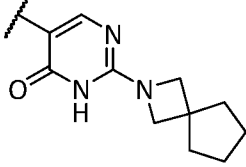
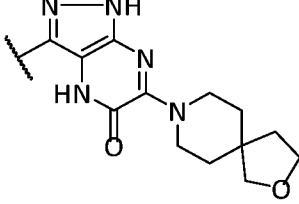
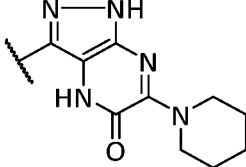
1H-pyrazolo[3,4-d]pyrimidin-3-yl, optionally substituted 6-oxo-5-(2-azaspiro[3.4]octan-2-yl)-1,6-dihydropyrazin-2-yl, optionally substituted 1-cyclohexyl-2-oxo-1,2-dihydropyridin-4-yl, optionally substituted 5-(3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-dihydropyrazin-2-yl, optionally substituted 6-oxo-5-(3H-spiro[benzofuran-2,4'-piperidin]-1'-yl)-1,6-dihydropyrazin-2-yl, optionally substituted 4-oxo-2-(2-oxa-8-azaspiro[4.5]decan-8-yl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl, optionally substituted 5-(5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, optionally substituted 5-(1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, optionally substituted 5-(4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, or optionally substituted 6-oxo-5-(spiro[indoline-2,4'-piperidin]-1'-yl)-1,6-dihydropyrazin-2-yl. The core structures for some suitable Ring B groups are listed in Table 1A below.

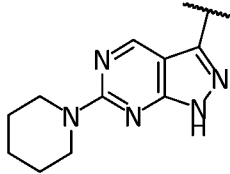
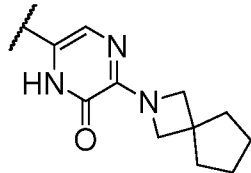
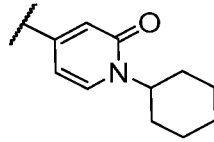
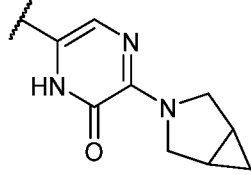
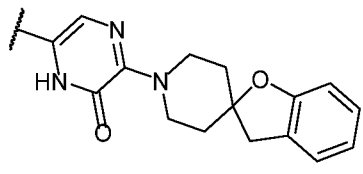
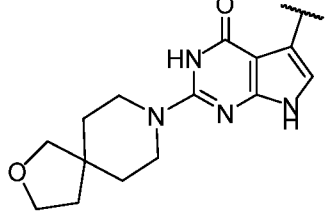
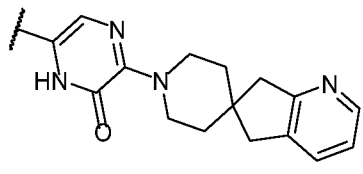
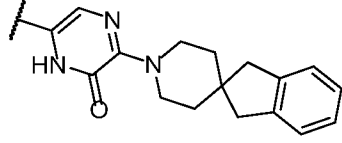
Table 1A.

Structure	Name
	6-oxo-5-(piperidin-1-yl)-1,6-dihydropyrazin-2-yl
	6-oxo-5-(pyrrolidin-1-yl)-1,6-dihydropyrazin-2-yl
	5-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrazin-2-yl
	5-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrazin-2-yl

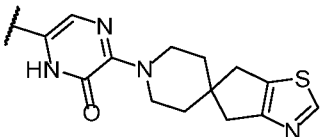
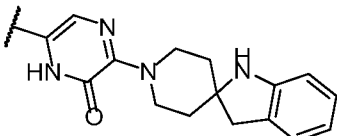
Structure	Name
	6-oxo-5-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1,6-dihydropyrazin-2-yl
	6-oxo-5-(piperidin-4-ylamino)-1,6-dihydropyrazin-2-yl
	6-oxo-5-(spiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-1,6-dihydropyrazin-2-yl
	6-oxo-5-(8-azaspiro[4.5]decan-8-yl)-1,6-dihydropyrazin-2-yl
	4-oxo-6-(piperidin-1-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl
	4-oxo-6-(pyrrolidin-1-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl
	4-oxo-2-(piperidin-1-yl)-3,4-dihydroquinazolin-5-yl
	4-oxo-2-(piperidin-1-yl)-3,4-dihydropyrido[3,4-d]pyrimidin-5-yl

Structure	Name
	7-oxo-2-(piperidin-1-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-5-yl
	5-(piperidin-1-yl)-1H-pyrazolo[4,3-d]thiazol-3-yl
	7-oxo-6-(piperidin-4-yl)-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-3-yl
	6-oxo-8-(piperidin-1-yl)-6,7-dihydro-1H-purin-2-yl
	8-(piperidin-1-yl)-7H-purin-2-yl
	6-oxo-2-(pyrrolidin-1-yl)-1,6-dihydropyrimidin-5-yl
	6-oxo-2-(piperidin-1-yl)-1,6-dihydropyrimidin-5-yl
	6-oxo-2-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1,6-dihydropyrimidin-5-yl

Structure	Name
	2-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrimidin-5-yl
	2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrimidin-5-yl
	2-(3-azabicyclo[3.2.0]heptan-3-yl)-6-oxo-1,6-dihydropyrimidin-5-yl
	6-oxo-2-(2-azaspiro[3.4]octan-2-yl)-1,6-dihydropyrimidin-5-yl
	2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-dihydropyrimidin-5-yl
	6-oxo-2-(2-azaspiro[3.4]octan-2-yl)-1,6-dihydropyrimidin-5-yl
	5-oxo-6-(2-oxa-8-azaspiro[4.5]decan-8-yl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl
	5-oxo-6-(piperidin-1-yl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl

Structure	Name
	6-(piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl
	6-oxo-5-(2-azaspiro[3.4]octan-2-yl)-1,6-dihydropyrazin-2-yl
	1-cyclohexyl-2-oxo-1,2-dihydropyridin-4-yl
	5-(3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-dihydropyrazin-2-yl
	6-oxo-5-(3H-spiro[benzofuran-2,4'-piperidin]-1'-yl)-1,6-dihydropyrazin-2-yl
	4-oxo-2-(2-oxa-8-azaspiro[4.5]decan-8-yl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl
	5-(5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl
	5-(1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl



Structure	Name
	5-(4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl
	6-oxo-5-(spiro[indoline-2,4'-piperidin]-1'-yl)-1,6-dihydropyrazin-2-yl

In some embodiments, Ring B is unsubstituted.

In some embodiments, Ring B has a -CH<sub>3</sub> substituent.

In some embodiments, Ring B has a -CH<sub>2</sub>NH<sub>2</sub> substituent.

In some embodiments, Ring B has a -NH<sub>2</sub> substituent.

5 In some embodiments, Ring B has a -CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> substituent.

In some embodiments, Ring B has a 1-aminopropan-2-yl substituent.

In some embodiments, Ring B has a -CN substituent.

In some embodiments, Ring B has an -F substituent.

In some embodiments, Ring B has a -Cl substituent.

10 In some embodiments, Ring B has a -CH<sub>2</sub>F substituent.

In some embodiments, Ring B has an -OH substituent.

In some embodiments, Ring B has an -OCH<sub>3</sub> substituent.

In some embodiments, Ring B has multiple substituents with any combination of the above substituents.

15 With respect to Formula 1, in some embodiments, X is S, O, NR<sup>A</sup>, CHR<sup>A</sup>, SO, SO<sub>2</sub>, CO, or a bond.

In some embodiments, X is S. In some embodiments, X is a bond. In some embodiments, X is O.

In some embodiments, X is NH. In some embodiments, X is -CH(CH<sub>3</sub>). In some embodiments, X is CH<sub>2</sub>.

20 With respect to Formula 1, in some embodiments, R<sup>A</sup> is H or C<sub>1-6</sub> hydrocarbyl. In some embodiments, R<sup>A</sup> is H. In some embodiments, R<sup>A</sup> is CH<sub>3</sub>.

In Appendix A below, various possibilities for Ring A are depicted. Ring A could be any core structure in any of these depicted possibilities, wherein these core structures are optionally

substituted.

# Appendix A:

Phenyl,

2,3-dichlorophenyl,

5 naphthalen-1-yl,

2-(trifluoromethyl)phenyl,

2-(trifluoromethyl)pyridin-3-yl,

5-amino-2-chlorophenyl,

5-amino-2-chloropyridin-3-yl,

10 3-amino-2-chlorophenyl,

2-amino-3-chloropyridin-4-yl,

2-chloro-3-methoxyphenyl,

3-chloro-2-methoxypyridin-4-yl,

3-fluoro-1H-indol-4-yl,

15 3,3-difluoro-2-oxoindolin-4-yl,

1-acetyl-3,3-difluoroindolin-4-yl,

2-chloro-3-(4-hydroxy-1,5,5-trimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxamido)phenyl,

2-chloro-3-(2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamido)phenyl,

2-chloro-3-(2-hydroxy-4-oxo-4H-pyrazino[1,2-a]pyrimidine-3-carboxamido)phenyl,

20 2-chloro-3-(7-hydroxy-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carboxamido)phenyl,

2-chloro-3-(7-hydroxy-5-oxo-1,5-dihydroimidazo[1,2-a]pyrimidine-6-carboxamido)phenyl,

2-chloro-3-(2-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-3-carboxamido)phenyl,

2,3-dichloropyridin-4-yl,

2,3-difluorophenyl,

25 3-chloro-2-fluoropyridin-4-yl,

2,3-difluoropyridin-4-yl,

2-chloro-3-methylphenyl,

3-chloro-2-methylpyridin-4-yl,

3,3-difluoro-1-methyl-2-oxoindolin-4-yl,

3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl, or

2-chloro-3-fluorophenyl.

In Appendix B below, various possibilities for Ring B are depicted. Ring B could be any core structure in any of these depicted possibilities, wherein these core structures are optionally substituted.

#### Appendix B:

5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 10 5-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 (S)-5-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 6-oxo-5-(piperidin-4-ylamino)-1,6-dihydropyrazin-2-yl,  
 5-(2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-((1R,3R)-1-amino-3-methyl-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 15 (6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl)amino,  
 6-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl,  
 7-amino-2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-4-oxo-3,4-dihydroquinazolin-5-yl,  
 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-4-oxo-3,4-dihydropyrido[3,4-d]pyrimidin-5-yl,  
 20 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-5-yl,  
 5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-1H-pyrazolo[4,3-d]thiazol-3-yl,  
 6-(1-(1-aminopropan-2-yl)piperidin-4-yl)-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-3-yl,  
 8-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-6,7-dihydro-1H-purin-2-yl,  
 6-amino-8-(4-(aminomethyl)-4-methylpiperidin-1-yl)-7H-purin-2-yl,  
 25 4-amino-2-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-6-oxo-1,6-dihydropyrimidin-5-yl,  
 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-4-cyano-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl,  
 4-amino-2-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrimidin-5-yl,  
 4-amino-2-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrimidin-5-yl,  
 4-amino-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrimidin-5-yl,

- 4-amino-2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrimidin-5-yl,  
 4-amino-2-(6-amino-3-azabicyclo[3.2.0]heptan-3-yl)-6-oxo-1,6-dihydropyrimidin-5-yl,  
 4-amino-2-(6-amino-2-azaspiro[3.4]octan-2-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl,  
 4-amino-2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-dihydropyrimidin-5-yl,  
 5 4-amino-2-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-oxo-1,6-dihydropyrimidin-5-yl,  
 5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 (S)-5-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-(2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl,  
 10 5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-((1R,3R)-1-amino-3-methyl-8-azaspiro[4.5]decan-8-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 15 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl,  
 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl,  
 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-oxo-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl,  
 6-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-5-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl,  
 20 d]pyrimidin-3-yl,  
 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl,  
 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl,  
 4-amino-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl,  
 25 4-amino-2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrimidin-5-yl,  
 4-amino-2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl,  
 4-amino-2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl,

- 4-amino-2-(6-amino-3-azabicyclo[3.2.0]heptan-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl,  
 5-(4-(aminomethyl)-4-fluoropiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-(4-(aminomethyl)-4-hydroxypiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 (R)-5-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5 (S)-5-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 1-(3-aminocyclohexyl)-2-oxo-1,2-dihydropyridin-4-yl,  
 (R)-5-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-(4-amino-4-(fluoromethyl)piperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 10 (R)-5-(1-amino-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 (R)-5-(3-amino-3H-spiro[benzofuran-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-  
 pyrrolo[2,3-d]pyrimidin-5-yl,  
 15 2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-  
 d]pyrimidin-5-yl,  
 (R)-5-(1-amino-3,3-difluoro-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-((1R)-1-amino-3-fluoro-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 (S)-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-oxo-1,6-  
 20 dihydropyrazin-2-yl,  
 (S)-5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl,  
 (S)-5-(4-amino-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-6-oxo-1,6-  
 dihydropyrazin-2-yl,  
 (R)-5-(3-aminospiro[indoline-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, or  
 25 (S)-5-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-  
 yl.

Some embodiments include one of the compounds in **Table 1**, wherein any of the compounds in **Table 1** below may be optionally substituted.

Table 1

Compound ID	Structure	Compound name
1		3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-(2,3-dichlorophenyl)pyrazin-2(1H)-one
2		3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
3		3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one
4		3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-(2,3-dichlorophenoxy)pyrazin-2(1H)-one
5		3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2,3-dichlorophenyl)amino)pyrazin-2(1H)-one
6		3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-(2,3-dichlorophenoxy)-1-methylpyrazin-2(1H)-one

Compound ID	Structure	Compound name
7		3-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
8		6-((2,3-dichlorophenyl)thio)-3-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrazin-2(1H)-one
9		3-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
10		3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
11		6-((2,3-dichlorophenyl)thio)-3-(piperidin-4-ylamino)pyrazin-2(1H)-one
12		3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-(naphthalen-1-ylthio)pyrazin-2(1H)-one

Compound ID	Structure	Compound name
13		3-((2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
14		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
15		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one
16		3-((1R,3R)-1-amino-3-methyl-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
17		3-((4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2-(trifluoromethyl)phenyl)thio)pyrazin-2(1H)-one
18		3-((4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2-(trifluoromethyl)pyridin-3-yl)thio)pyrazin-2(1H)-one



Compound ID	Structure	Compound name
19		6-((5-amino-2-chlorophenyl)thio)-3-(4-(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one
20		6-((5-amino-2-chloropyridin-3-yl)thio)-3-(4-(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one
21		6-((3-amino-2-chlorophenyl)thio)-3-(4-(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one
22		6-((2-amino-3-chloropyridin-4-yl)thio)-3-(4-(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one
23		3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2-chloro-3-methoxyphenyl)thio)pyrazin-2(1H)-one
24		3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2(1H)-one

Compound ID	Structure	Compound name
25		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-fluoro-1H-indol-4-yl)thio)pyrazin-2(1H)-one
26		4-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-3,3-difluoroindolin-2-one
27		6-((1-acetyl-3,3-difluoroindolin-4-yl)thio)-3-(4-(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one
28		N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-4-hydroxy-1,5,5-trimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxamide
29		N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamide

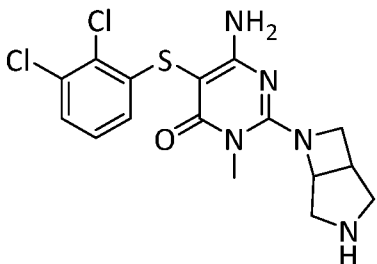
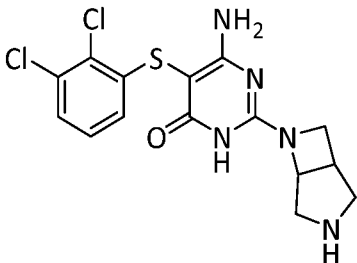
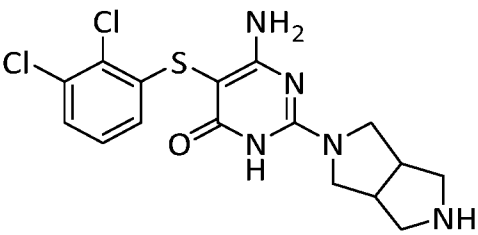
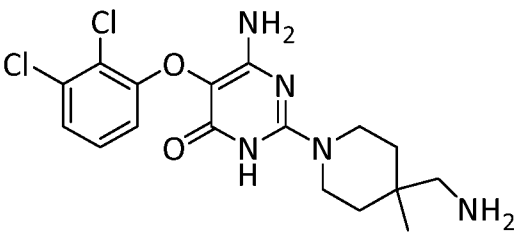
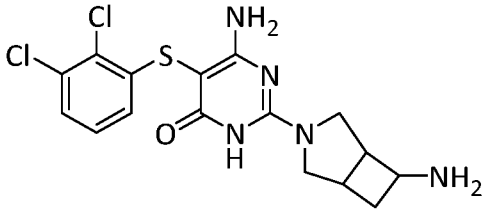
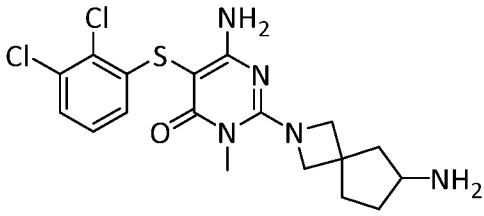
Compound ID	Structure	Compound name
30		N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-2-hydroxy-4-oxo-4H-pyrazino[1,2-a]pyrimidine-3-carboxamide
31		N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-7-hydroxy-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carboxamide
32		N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-7-hydroxy-5-oxo-1,5-dihydroimidazo[1,2-a]pyrimidine-6-carboxamide
33		N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-2-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-3-carboxamide
34		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-((2,3-dichlorophenyl)amino)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-

Compound ID	Structure	Compound name
		4-one
35		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenoxy)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
36		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-((2,3-dichlorophenyl)amino)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
37		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenoxy)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
38		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenoxy)-4-methyl-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one
39		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenoxy)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one
40		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenyl)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one

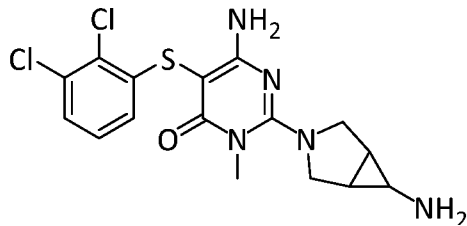
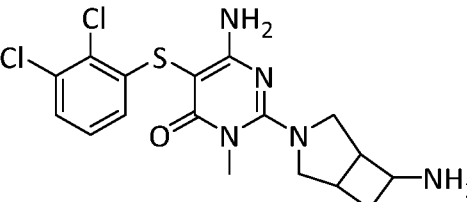
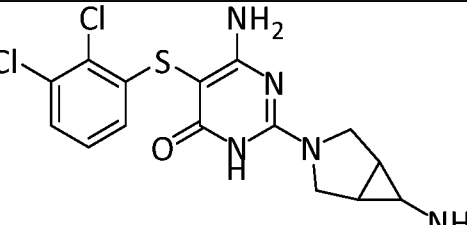
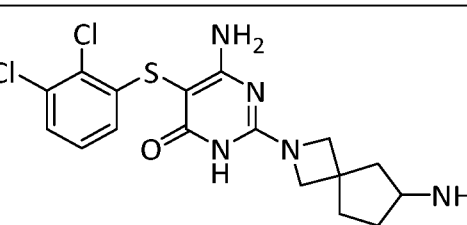
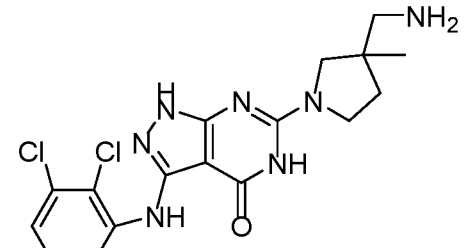
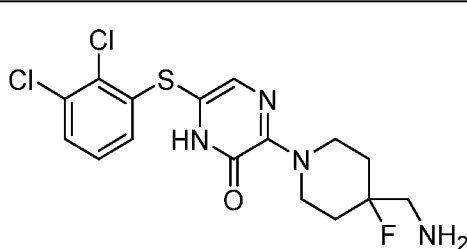
Compound ID	Structure	Compound name
41		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-((2,3-dichlorophenyl)thio)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one
42		6-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-3-(2,3-dichlorophenoxy)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
43		6-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-3-(2,3-dichlorophenoxy)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
44		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(1-(2,3-dichlorophenyl)ethyl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
45		6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorobenzyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
46		7-amino-2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-((2,3-dichlorophenyl)thio)quinazolin-4(3H)-one

Compound ID	Structure	Compound name
47		2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-((2,3-dichlorophenyl)thio)pyrido[3,4-d]pyrimidin-4(3H)-one
48		2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-((2,3-dichlorophenyl)thio)pyrido[2,3-d]pyrimidin-7(8H)-one
49		(1-(3-((2,3-dichlorophenyl)thio)-1H-pyrazolo[4,3-d]thiazol-5-yl)-4-methylpiperidin-4-yl)methanamine
50		6-(1-(1-aminopropan-2-yl)piperidin-4-yl)-3-((2,3-dichlorophenyl)thio)-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one
51		5-(1-(1-aminopropan-2-yl)piperidin-4-yl)-3-((2,3-dichlorophenyl)thio)-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one
52		6-amino-2-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidin-4(3H)-one

Compound ID	Structure	Compound name
		one
53		6-amino-5-((2,3-dichlorophenyl)thio)-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-methylpyrimidin-4(3H)-one
54		6-amino-2-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one
55		2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(2,3-dichlorophenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carbonitrile
56		6-amino-2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(2,3-dichlorophenoxy)pyrimidin-4(3H)-one
57		6-amino-2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(2,3-dichlorophenoxy)-3-methylpyrimidin-4(3H)-one

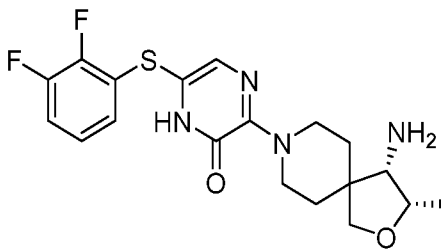
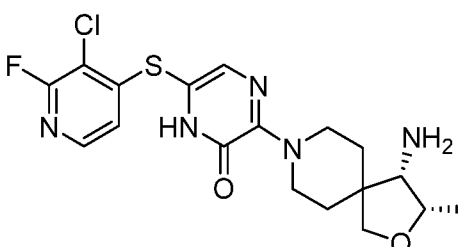
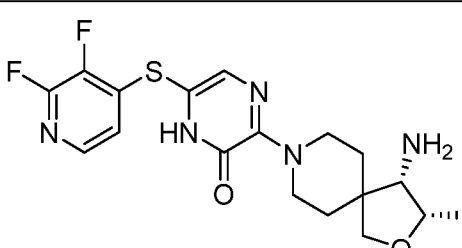
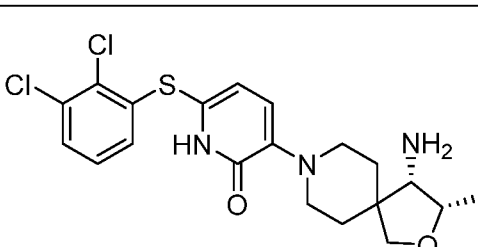
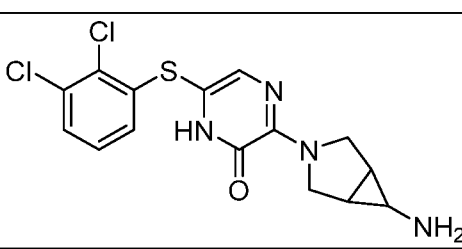
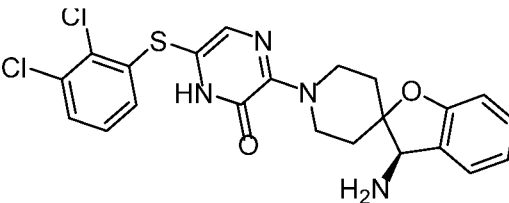
Compound ID	Structure	Compound name
58		6-amino-2-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidin-4(3H)-one
59		6-amino-2-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one
60		6-amino-5-((2,3-dichlorophenyl)thio)-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4(3H)-one
61		6-amino-2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(2,3-dichlorophenoxy)pyrimidin-4(3H)-one
62		6-amino-2-(6-amino-3-azabicyclo[3.2.0]heptan-3-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one
63		6-amino-2-(6-amino-2-azaspiro[3.4]octan-2-yl)-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidin-4(3H)-one

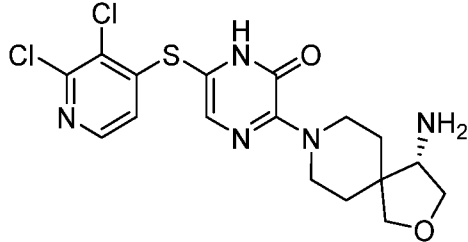
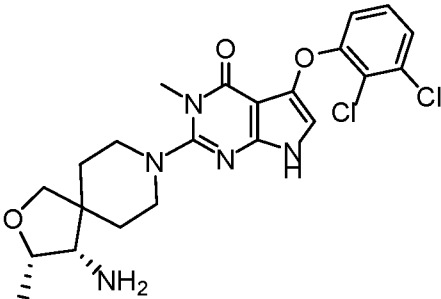
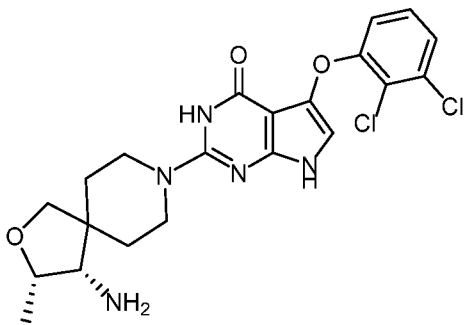
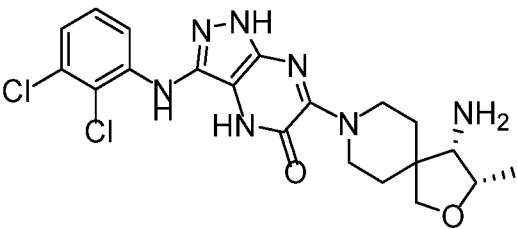
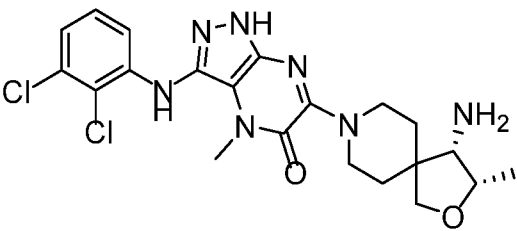


Compound ID	Structure	Compound name
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65		6-amino-2-(6-amino-3-azabicyclo[3.2.0]heptan-3-yl)-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidin-4(3H)-one
66		6-amino-2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one
67		6-amino-2-(6-amino-2-azaspiro[3.4]octan-2-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one
68		6-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-3-((2,3-dichlorophenyl)amino)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
69		3-(4-(aminomethyl)-4-fluoropiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one

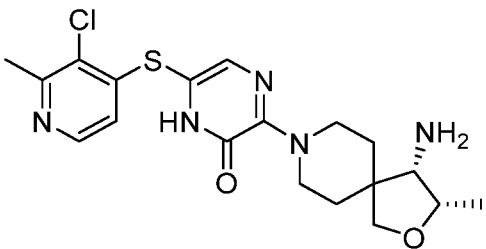
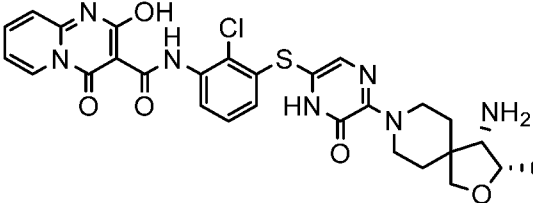
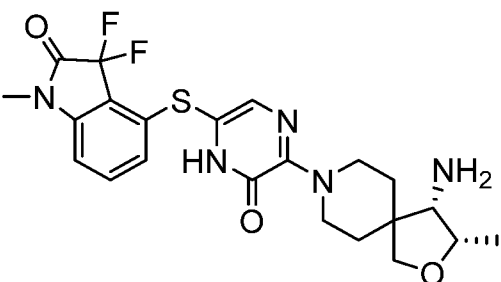
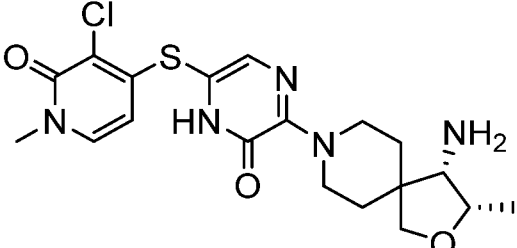
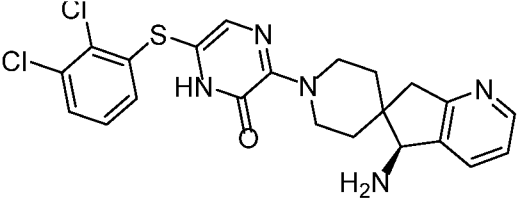
Compound ID	Structure	Compound name
70		3-(4-(aminomethyl)-4-hydroxypiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
71		(R)-3-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
72		(S)-3-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
73		(S)-3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
74		1-(3-aminocyclohexyl)-4-(2,3-dichlorophenyl)pyridin-2(1H)-one
75		(R)-3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one

Compound ID	Structure	Compound name
76		3-(4-amino-4-(fluoromethyl)piperidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
77		6-((2-amino-3-chloropyridin-4-yl)thio)-3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)pyrazin-2(1H)-one
78		(R)-3-(1-amino-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
79		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2-chloro-3-methoxyphenyl)thio)pyrazin-2(1H)-one
80		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2(1H)-one
81		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichloropyridin-4-yl)thio)pyrazin-2(1H)-one

Compound ID	Structure	Compound name
82		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-difluorophenyl)thio)pyrazin-2(1H)-one
83		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2(1H)-one
84		4-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-3,3-difluoroindolin-2-one
85		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyridin-2(1H)-one
86		3-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
87		(R)-3-(3-amino-3H-spiro[benzofuran-2,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one

Compound ID	Structure	Compound name
88		(S)-3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichloropyridin-4-yl)thio)pyrazin-2(1H)-one
89		2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(2,3-dichlorophenoxy)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
90		2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(2,3-dichlorophenoxy)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
91		6-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-((2,3-dichlorophenyl)amino)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one
92		6-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-((2,3-dichlorophenyl)amino)-4-methyl-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one

Compound ID	Structure	Compound name
93		2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-((2,3-dichlorophenyl)amino)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
94		2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-((2,3-dichlorophenyl)amino)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
95		(R)-3-(1-amino-3,3-difluoro-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
96		3-((1R)-1-amino-3-fluoro-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
97		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2-chloro-3-methylphenyl)thio)pyrazin-2(1H)-one

Compound ID	Structure	Compound name
98		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-2-methylpyridin-4-yl)thio)pyrazin-2(1H)-one
99		N-(3-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamide
100		4-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-3,3-difluoro-1-methylindolin-2-one
101		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)thio)pyrazin-2(1H)-one
102		(S)-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one

Compound ID	Structure	Compound name
103		(S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2,3-dichloropyridin-4-yl)thio)pyrazin-2(1H)-one
104		(S)-3-(4-amino-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
105		(R)-3-(3-aminospiro[indoline-2,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
106		(S)-3-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one
107		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-2-oxo-1,2-dihydropyridin-4-yl)thio)pyrazin-2(1H)-one
108		(S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one



Compound ID	Structure	Compound name
109		3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2-chloro-3-fluorophenyl)thio)pyrazin-2(1H)-one
110		(1-(3-((2,3-dichlorophenyl)thio)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)methanamine
111		3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one
112		3-(2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one
113		3-((1R,3R)-1-amino-3-methyl-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one
114		6-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(2,3-dichlorophenoxy)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one

Compound ID	Structure	Compound name
		one

An example, not as an attempt to limit the scope of the disclosure, of a useful composition for a dosage form containing about 10-1000 mg of compound **83** is shown in **Table 1B** below:

**Table 1B.** Example of dosage form of compound **83**

Component	Amount (wt/wt)
Compound <b>83</b>	30-70%
lubricant	1-10%
diluent	20-70%
disintegrant	1-10%

A pharmaceutical composition comprising a compound of Formula 1 may be adapted for oral, or parental, such as intravenous, intramuscular, topical, intraperitoneal, nasal, buccal, sublingual, or subcutaneous administration, or for administration via respiratory tract in the form of, for example, an aerosol or an air-suspended fine powder. The dosage of a compound of Formula 1 may vary depending on the route of administration, body weight, age, the type and condition of the disease being treated. A pharmaceutical composition provided herein may optionally comprise two or more compounds of the Formula 1 without an additional therapeutic agent, or may comprise an additional therapeutic agent (i.e., a therapeutic agent other than a compound provided herein). For example, the subject compounds can be administered simultaneously, sequentially, or separately in combination with at least one other therapeutic agent. The other therapeutic agent can be a small molecule, an antibody-drug conjugate, or a biologic. Therapeutic agents suitable for combination with a subject compound include, but are not limited to antibiotics, antiemetic agents, antidepressants, and antifungal agents, anti-inflammatory agents, antiviral agents, and anticancer agents that are known in the art. In some embodiments, the other therapeutic agents are chemotherapy agents, for example, mitotic inhibitors such as a taxane, a vinca alkaloid, paclitaxel; or tyrosine kinase inhibitors, for example Erlotinib; ALK inhibitors such as Crizotinib; BRAF inhibitors such as Vemurafanib; MEK inhibitors such as trametinib; or other anticancer agents, i.e. cisplatin, flutamide,

gemcitabine, CTLA-4 inhibitors, PD-1 inhibitors and PD-L1 inhibitors. Such combination may offer significant advantages, including synergistic activity, in therapy. The pharmaceutical composition may be used for the treatment of cancer, autoimmune diseases, inflammatory diseases, autoinflammatory conditions, and other SHP2 mediated disorders in patients. The term "patient" herein means a mammal (e.g., a human or an animal). In some embodiments, the patient has cancer.

The pharmaceutical composition described herein can be prepared by combining a compound of Formula 1 with at least one pharmaceutical acceptable inert ingredient, such as a carrier, excipient, filler, lubricant, flavoring agent, buffer, etc., selected on the basis of the chosen route of administration and standard pharmaceutical practice as described, for example, in Remington's Pharmaceutical Sciences, 2005, the disclosure of which is hereby incorporated herein by reference, in its entirety. The relative proportions of active ingredient and carrier may be determined, for example, by the solubility and chemical nature of the compounds, chosen route of administration and standard pharmaceutical practice.

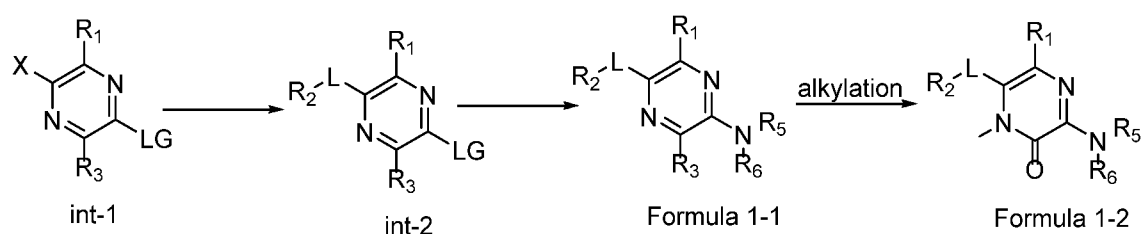
Some embodiments include a method of treating a SHP2 mediated disease or disorder comprising administering a therapeutically effective amount of a compound of Formula 1, or any compound described herein, or a pharmaceutically acceptable salt thereof ("subject compound"), or a pharmaceutical composition comprising a subject compound to a patient in need thereof. The term a "therapeutically effective amount" herein refers to an amount of a subject compound, or a pharmaceutical composition containing a subject compound, sufficient to be effective in inhibiting SHP2 and thus providing a benefit in the treatment of cancer, autoimmune diseases, inflammatory diseases, autoinflammatory conditions, and other SHP2 mediated disorders in patients, such as to delay or minimize symptoms associated with cancer, autoimmune, inflammatory diseases, and autoinflammatory conditions, or to ameliorate a disease or infection or cause thereof, or to prevent the further development of a disorder, or reducing the severity of symptoms that are otherwise expected to develop without treatment.

## **EXPERIMENTAL:**

### **GENERAL SYNTHETIC METHODS:**

The compounds of the present invention, or their pharmaceutically acceptable salts, can be synthesized using the methods described below in schemes **1-6**. It will be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by the person skilled in the art, using routine optimization procedures. Additionally, one skilled in the art will recognize that in many cases, these compounds will be mixtures of stereoisomers that may be separated at various stages of the synthetic schemes using conventional techniques, such as, but limited to, crystallization, normal-phase chromatography, reversed phase chromatography and chiral chromatography, to afford single enantiomers. For all the protection and deprotection methods, see Philip J. Kocienski, in "Protecting Groups", Georg Thieme Verlag Stuttgart, New York, 1994 and, Theodora W. Greene and Peter G. M. Wuts in "Protective Groups in Organic Synthesis", Wiley Interscience, 3rd Edition 1999. The schemes **1-6** are representative of methods useful in synthesizing the compounds of the present invention. They are not to constrain the scope of the invention in any way.

Scheme 1

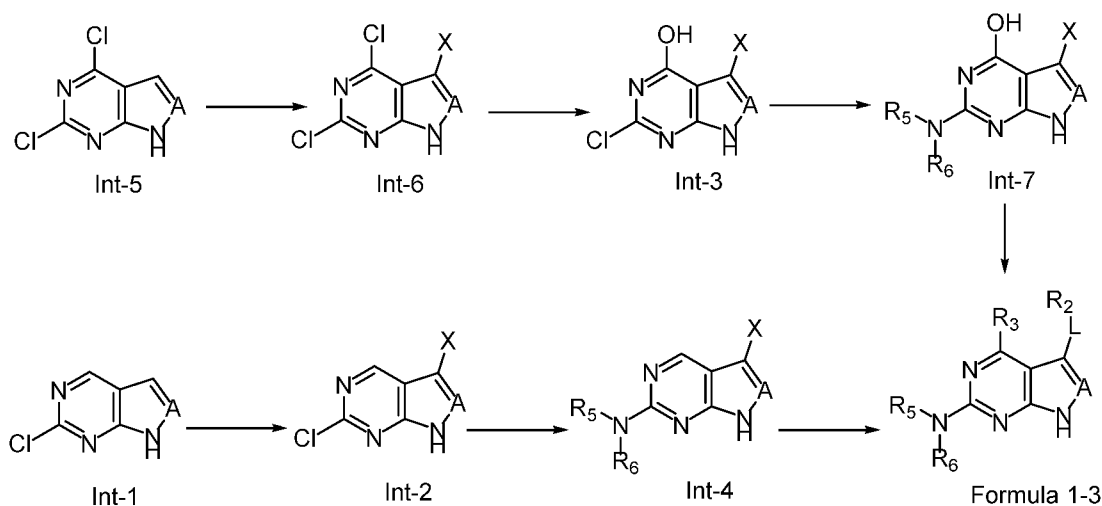


Scheme **1** illustrates a method for preparing compounds of Formula **1**. In which L is S, O, N or a bond; R<sub>1</sub> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, NH<sub>2</sub>, or CN; R<sub>2</sub> is aryl, heterocycloalkyl or heteroaryl; R<sub>3</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl, OR<sub>1</sub>; R<sub>5</sub> is alkyl, H; R<sub>6</sub> is alkyl, H; R<sub>5</sub> and R<sub>6</sub> together with the atom or atoms to which they are attached, can combine to form a monocyclic or polycyclic C<sub>3</sub>-C<sub>12</sub> cycloalkyl or heterocycle.

Compound **int-1** is treated with aryl or alkyl boronic acids or esters or salts (where L is a bond) under suitable metal catalysts (such Pd<sub>2</sub>(dba)<sub>3</sub>, or the like), suitable ligands (such as dppf, or the like),

suitable bases (such as  $\text{Cs}_2\text{CO}_3$ , or the like), suitable solvents (such as DMF, or the like) to provide a product of **int-2**. In other cases, where the L of Formula **1** is O, N or S, compound **int-1** was reacted with corresponding phenols, thiophenols, thioalcohols or amines under suitable metal catalysts (such as CuI,  $\text{Pd}_2(\text{dba})_3$ ), suitable ligands (such as TMEDA, XPHOS, Xantphos, or the like), suitable salts or bases (such as  $\text{Cs}_2\text{CO}_3$ ,  $\text{K}_3\text{PO}_4$  or the like), suitable solvents (such as DMF, dioxane or the like) to provide a product of **int-2**. The reaction temperature is ranged from  $80^\circ\text{C}$  to  $140^\circ\text{C}$ , and the reaction takes 1 - 24 hours to complete. Compound **int-2** reacted with amines with or without bases (such as DIPEA), in suitable solvents (such as DMF, NMP or the like) under the temperature range from  $80^\circ\text{C}$  to  $140^\circ\text{C}$  to offer compound of Formula **1**. If desired, further transformations may be performed to provide a product of Formula **1-2**. For example, the compound of Formula **1-1** wherein  $\text{R}_3 = \text{OH}$  may be subjected to an alkylation reaction to provide a compound of Formula **1-2**.

Scheme 2

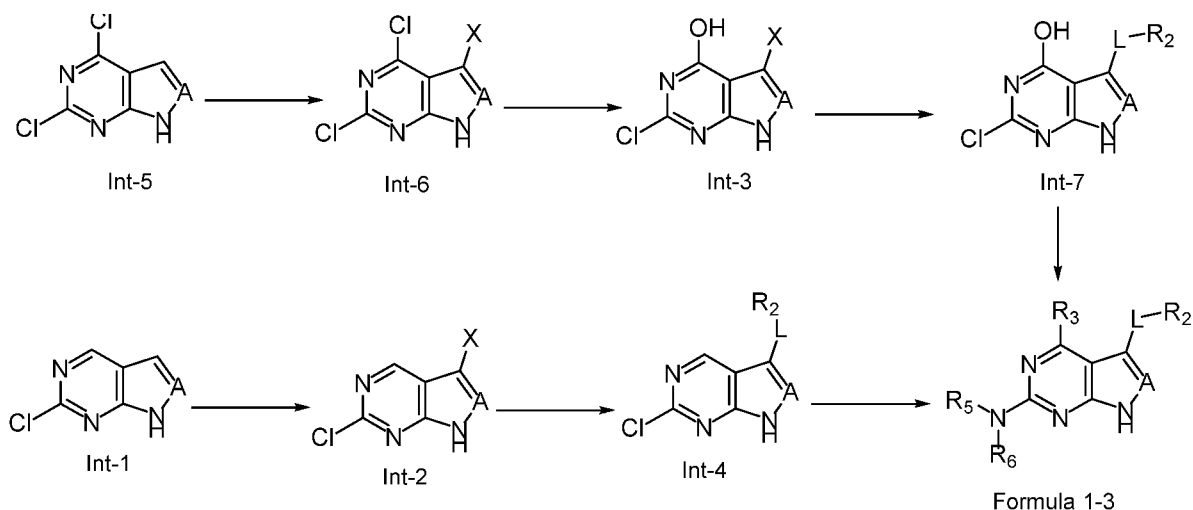


Scheme 2 illustrates a method for preparing compounds of Formula **1-3**. Compound **Int-1** was first halogenated to provide intermediate **Int-2**. The activated chlorine in **Int-2** was displaced by an amine to afford **Int-4**. **Int-4** reacted with an aryl amine or phenol to provide target compounds of Formula **1-3** ( $\text{R}_3 = \text{H}$ ).

For the compounds of Formula **1-3** where  $\text{R}_3$  was OH, **Int-6** was regioselectively hydrolyzed to provide **Int-3**, and then followed by substitutions and couplings to offer target compounds.

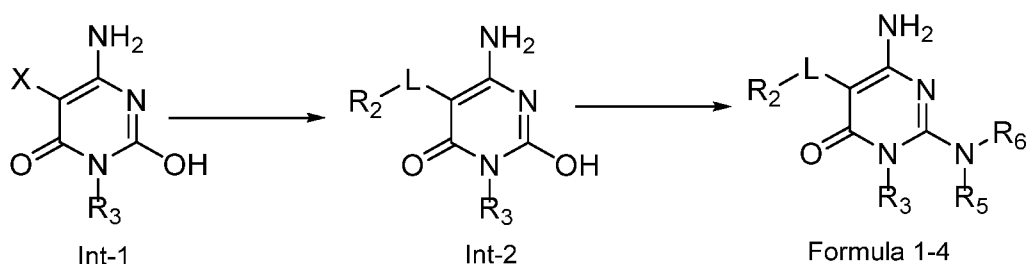
Deprotection steps can be incorporated either before or after the coupling reactions.

Scheme 3



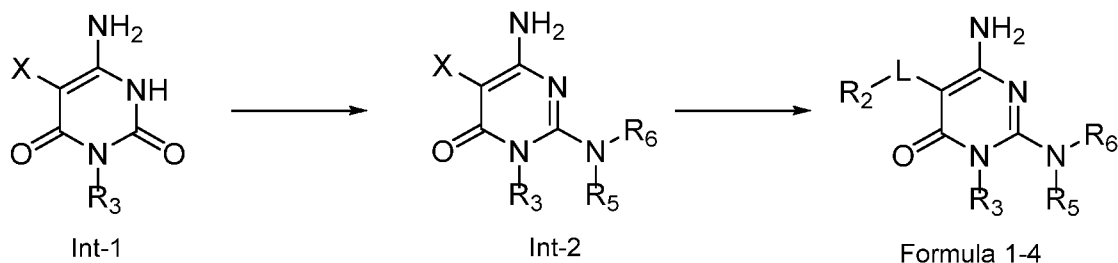
Additionally, the compounds of Formula **1-3** can be synthesized using an alternative way, as illustrated in Scheme **3**. The order of reaction steps may alter. Coupling reactions may occur before the amine displacement.

Scheme 4



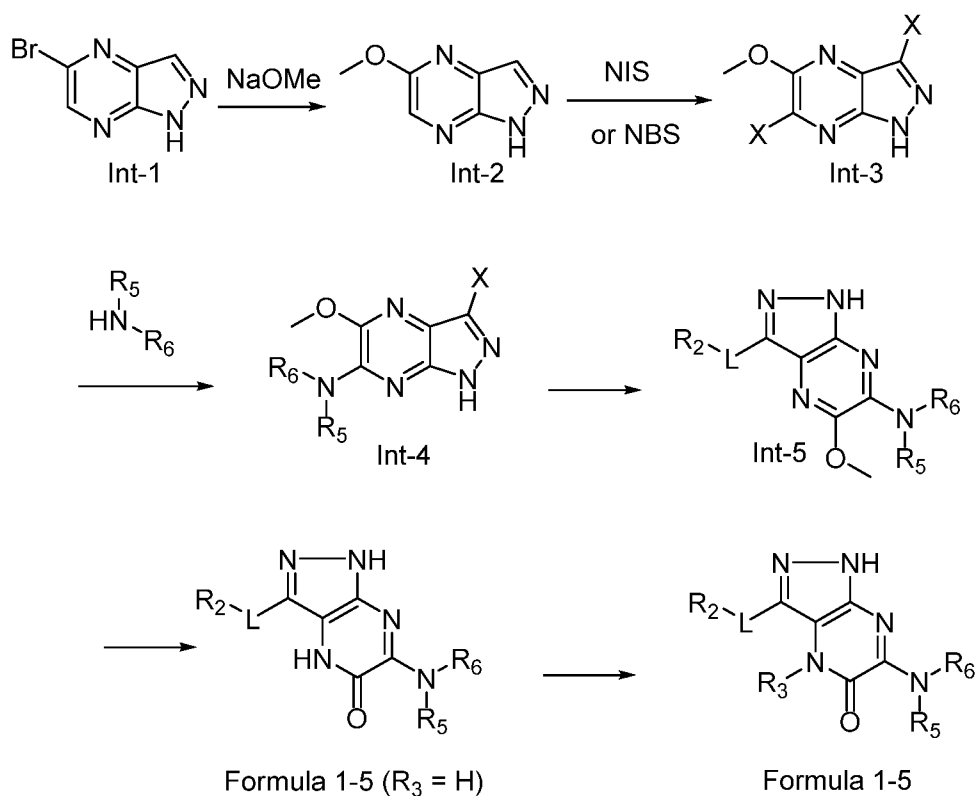
Scheme **4** illustrates a method for preparing compounds of Formula **1-4**. **Int-1** was reacted with an aryl amine or phenol in the presence of a suitable metal catalyst (such as CuI, or the like), a suitable ligand (such as TMEDA, TMHD, or the like), a suitable salt (such as K<sub>3</sub>PO<sub>4</sub>, or the like) and a suitable solvent (such as dioxane or the like). The reaction proceeds at a temperature ranged 80 °C to 140 °C, with the reaction time from 1 - 24 hours. **Int-2** reacted with an amine in the presence of a suitable coupling reagent (such as BOP-Cl, or the like), a suitable base (such DIEPA, DBU, or the like), and a suitable solvent (such as DMF, THF or the like). The reaction proceeded at temperature 80°C to 130°C with 1 - 24 hours to finish.

Scheme 5



Alternatively, as illustrated in Scheme 5, the order of reactions can be modified to change the overall synthesis to allow for variations at different positions of the molecule at different stages of the preparation. For example, in Scheme 5, compound of Formula **Int-1** is activated and reacted with an amine to provide **Int-2** first, and then followed with the coupling reaction, to provide compound of Formula **1-4**.

Scheme 6



Scheme 6 illustrates a method for preparing compounds of Formula **1-5**.

10 Bromine of **Int-1** was displaced with methoxy group to afford **Int-2**, and then **Int-2** was halogenated with NBS or NIS to offer **Int-3**. From **Int-3**, after the substitution, coupling and deprotection compounds of formula **1-5** (R<sub>3</sub> = H) were synthesized. The compound of Formula **1-5**

wherein  $R_3 = H$  may be subjected to an alkylation reaction to provide another series compound of Formula 1-5.

### EXPERIMENTAL PROCEDURES AND EXAMPLES

Experiments were generally carried out under inert atmosphere (nitrogen or argon), particularly in cases where oxygen- or moisture-sensitive reagents or intermediates were employed. Commercial solvents and reagents were generally used without further purification, including anhydrous solvents where appropriate. Products were generally dried under vacuum before being carried on to further reactions or submitted for biological testing. Mass spectrometry data is reported from liquid chromatography-mass spectrometry (LCMS) instrumentation. Mass spectra, MS ( $m/z$ ), were recorded using either electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). Where relevant and unless otherwise stated the  $m/z$  data provided are for isotopes  $^{19}F$ ,  $^{35}Cl$ ,  $^{79}Br$  and  $^{127}I$ . Chemical shifts for nuclear magnetic resonance (NMR) data are expressed in parts per million (ppm,  $\delta$ ) referenced to residual peaks from the deuterated solvents employed, using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used for common solvents:  $CDCl_3$ , deuteriochloroform;  $d_6$ -DMSO, deuterodimethylsulphoxide; and  $CD_3OD$ , deuteromethanol.

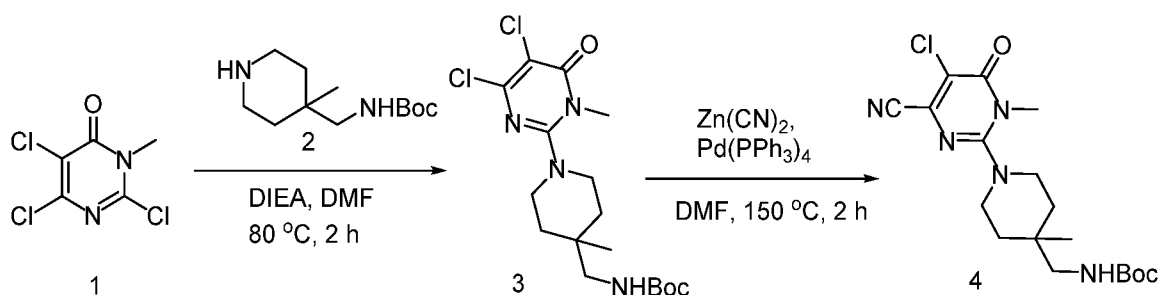
In general, reactions were followed by thin layer chromatography (TLC) and/or liquid chromatography-mass spectrometry (LCMS) and subjected to work-up when appropriate.

Purification was carried out by chromatographic and/or HPLC.

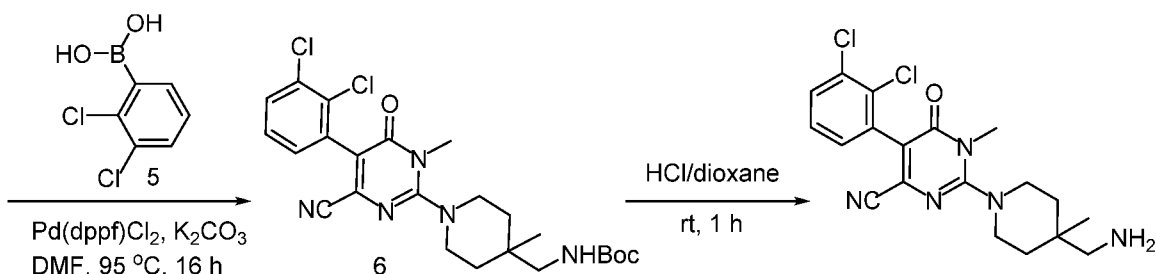
Unless noted otherwise, all reactants were obtained commercially.

#### Example 1

Preparation of 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(2,3-dichlorophenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carbonitrile







Step 1: preparation of tert-butyl ((1-(4,5-dichloro-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-4-methylpiperidin-4-yl)methyl)carbamate (**3**)

To a mixture of compound **1** (1.4 g, 1.0 eq) and compound **2** (1.5 g, 1.0 eq) in DMF (25 mL) was added DIEA (3.2 mL, 2.0 eq). The mixture was degassed and protected with nitrogen. The reaction was stirred at 80 °C for 2 h. EtOAc (150 mL) was added to the mixture under r.t. After standard work up procedure, the residue was purified by column chromatography to give compound **3** as a white solid (1.9 g, 71%).

Step 2: preparation of tert-butyl ((1-(5-chloro-4-cyano-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-4-methylpiperidin-4-yl)methyl)carbamate (**4**)

A mixture of compound **3** (200 mg, 1.0 eq), Zn(CN)<sub>2</sub> (57.9 g, 1.0 eq) and Pd(PPh<sub>3</sub>)<sub>4</sub> (56 mg, 0.1 eq) in DMF was stirred at 150 °C for 2 h, and the mixture was cooled to rt. EtOAc was added, after standard work up procedure the residue was purified by prep-TLC to give compound **4** as a white solid (60 mg, 31%).

Step 3: preparation of tert-butyl ((1-(4-cyano-5-(2,3-dichlorophenyl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-4-methylpiperidin-4-yl)methyl)carbamate (**6**)

To a mixture of compound **4** (60 mg, 1.0 eq), K<sub>2</sub>CO<sub>3</sub> (42 mg, 2 eq) and compound **5** (86 mg, 3.0 eq) in DMF (10 mL) was added Pd(dppf)Cl<sub>2</sub> (11 mg, 0.1 eq). The resulting mixture was stirred at 95 °C overnight. The mixture was diluted with EtOAc. After standard work up procedure, the residue was purified by prep-TLC to give compound **6** as a white solid (20 mg, 26%).

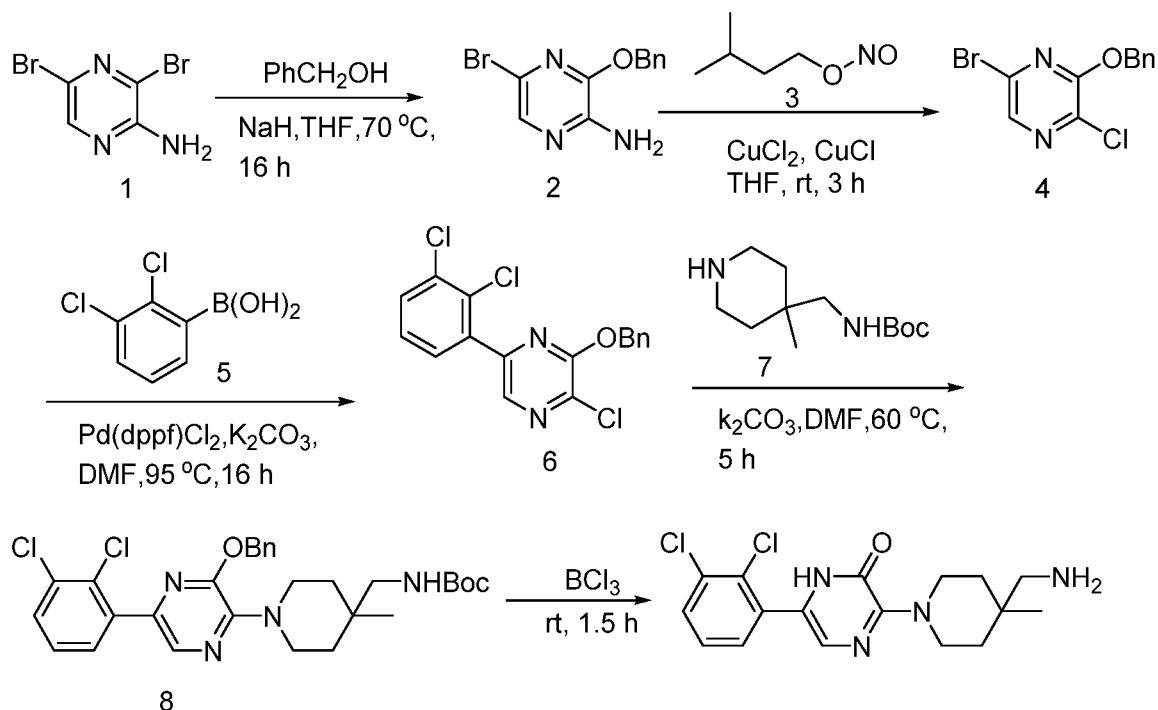
Step 4: preparation of 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(2,3-dichlorophenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carbonitrile

HCl/dioxane (0.5 mL, 10.0 eq) was added to a solution of compound **6** (19 mg, 1.0 eq) in DCM (5.0 mL), and then the reaction was stirred at rt for 1 h. The mixture was concentrated and neutralized with ammonium hydroxide, purified by prep-HPLC to give the desired compound as a white solid (2.5

mg, 17%). **LC-MS:**  $[M+H]^+$ : 406.1.  **$^1H$  NMR** (400 MHz,  $CD_3OD$ )  $\delta$  7.65 (dd,  $J = 8.0, 1.6$  Hz, 1H), 7.40 (t,  $J = 8.0$  Hz, 1H), 7.33 (dd,  $J = 8.0, 1.2$  Hz, 1H), 3.55 - 3.48 (m, 4H), 3.34 - 3.31 (m, 2H), 2.66 (s, 1H), 1.71 - 1.66 (m, 2H), 1.55 - 1.52 (m, 2H), 1.10 (s, 3H).

### Example 2

#### 5 Preparation of 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-(2,3-dichlorophenyl) pyrazin-2(1H)-one



#### Step 1: Preparation of 3-(benzyloxy)-5-bromopyrazin-2-amine (**2**)

To a solution of benzyl alcohol (13.5 g, 1.05 eq) in THF (300 mL) was added NaH (60%, 5.7 g, 1.2 eq) at rt. The mixture was stirred at rt for 30 min. Compound **1** (30.0 g, 118 mmol, 1.0 eq) was added to the mixture. The mixture was heated to 70 °C and stirred overnight. The reaction was quenched by water, worked up under standard operation to give compound **2** as a yellow solid (25.0 g, 75%).

#### Step 2: preparation of 3-(benzyloxy)-5-bromo-2-chloropyrazine (**4**)

To a solution of compound **2** (9.0 g, 1.0 eq) in THF (30 mL) was added  $CuCl_2$  (12.96 g, 3.0 eq) and  $CuCl$  (5.75 g, 2.0 eq) at rt. Compound **3** (12.9 mL, 3.0 eq) was added dropwise to the mixture 10 min later. The reaction was worked up under standard operation to give compound **4** as a yellow oil (4.0 g, 41%).

Step 3: preparation of 3-(benzyloxy)-2-chloro-5-(2,3-dichlorophenyl)pyrazine (**6**)

To a solution of compound **4** (3.0 g, 1.0 eq) in DMF (30 mL) was added K<sub>2</sub>CO<sub>3</sub> (4.14 g, 3.0 eq), compound **5** (1.9 g, 1.0 eq) and Pd(dppf)Cl<sub>2</sub> (0.73 g, 0.1 eq). The resulting mixture was stirred at 95 °C under N<sub>2</sub> atmosphere overnight. The reaction was quenched by water and worked up under standard operation to give compound **6** as a yellow solid (1.5 g, 40%).

Step 4: preparation of tert-butyl ((1-(3-(benzyloxy)-5-(2,3-dichlorophenyl)pyrazin-2-yl)-4-methylpiperidin-4-yl)methyl)carbamate (**8**)

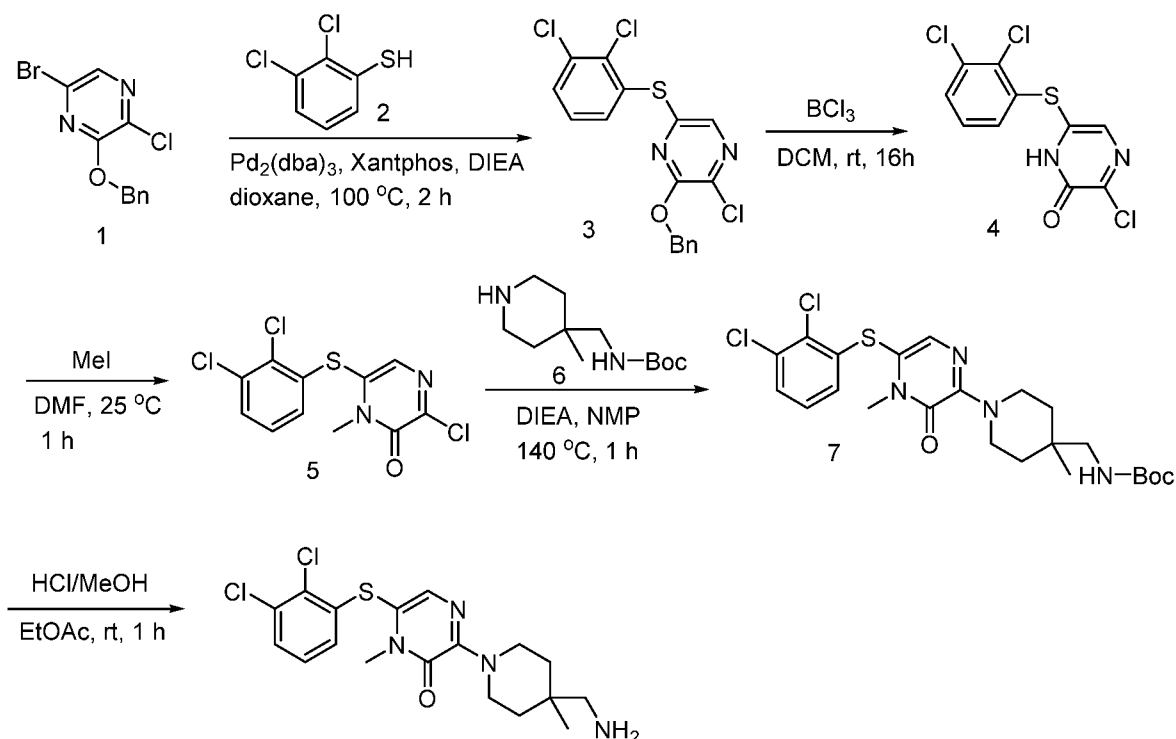
To a solution of compound **6** (500 mg, 1.0 eq) in DMF (5 mL) were added compound **7** (342 mg, 1.1 eq) and K<sub>2</sub>CO<sub>3</sub> (660 mg, 3.5 eq). The mixture was stirred at 60 °C under N<sub>2</sub> atmosphere for 5 h. The reaction was quenched by water and worked up under standard operation to give compound **8** as a white solid (400 mg, 53%).

## Step 5: preparation of 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-(2,3-dichlorophenyl)-pyrazin-2(1H)-one

To a solution of compound **8** (100 mg, 1.0 eq) in DCM (5 mL) was added BCl<sub>3</sub> (1M in DCM, 5.0 eq). The mixture was stirred at rt for 1.5 h. The reaction was quenched by MeOH (5 mL) and the mixture was concentrated and purified by prep-HPLC to give target compound as a white solid (7 mg, 10%). **LC-MS**: [M+H]<sup>+</sup> = 367. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.67 (d, *J* = 7.4 Hz, 1H), 7.52 - 7.34 (m, 2H), 6.91 (s, 1H), 4.10 - 4.03 (m, 2H), 3.45 - 3.32 (m, 2H), 2.88 (d, *J* = 6.0 Hz, 1H), 2.39 (s, 1H), 1.50 - 1.41 (m, 2H), 1.26 - 1.24 (m, 2H), 0.90 (d, *J* = 9.2 Hz, 3H).

**Example 3**

Preparation of 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one



Step 1: preparation of 3-(benzyloxy)-2-chloro-5-((2,3-dichlorophenyl)thio)pyrazine (**3**)

To a mixture of compound **1** (3.0 g, 1.0 eq), compound **2** (1.79 g, 1.0 eq), Pd<sub>2</sub>(dba)<sub>3</sub> (300 mg) and Xantphos (300 mg) in dioxane (50 mL) was added DIEA (3.0 mL, 1.8 eq), and then the mixture was degassed and protected with nitrogen. EtOAc (150 mL) was added to the mixture 2 hours later. After standard work up procedure the residue was purified by column chromatography to give compound **3** as a colorless oil (2.9 g, 73%).

Step 2: preparation of 3-chloro-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one (**4**)

BCl<sub>3</sub> (10.0 mL, 1M in DCM, 1.99 eq) was added to a solution of compound **3** (2.0 g, 1.0 eq) in DCM at rt and then the reaction was stirred at rt overnight. The reaction was quenched by sat. NaHCO<sub>3</sub> and stirred for 1 h. The suspension was then filtered and the solid was washed with DCM and water. The solid was dried to give the crude product **4** as a yellow solid. (3.0 g, 78%).

Step 3: preparation of 3-chloro-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one (**5**)

MeI (1 mL) was added to a mixture of crude **4** (2.0 g, 1.0 eq) and K<sub>2</sub>CO<sub>3</sub> (2.0 g, 5.6 eq) in DMF (10 mL) and the resulting mixture was stirred at 25 °C for 1 h. The mixture was diluted with EtOAc and then was washed with brine. The organic solution was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by column chromatography to give compound **5** as a white solid (505 mg, 60%).

Step 4: preparation of tert-butyl ((1-(5-((2,3-dichlorophenyl)thio)-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)-4-methylpiperidin-4-yl)methyl)carbamate (**7**)

A mixture of compound **5** (96 mg, 1.0 eq), compound **6** (73 mg, 1.07 eq) and DIEA (0.7 mL, 1.8 eq) in NMP (2 mL) was stirred at 140 °C for 1 h. The mixture was diluted with EtOAc and then washed with brine. The organic solution was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by column chromatography to give compound **7** as an off-white solid (140 mg, 91%)

Step 3: preparation of 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one

HCl/MeOH (1.0 mL, 10.0 eq) was added to the solution of compound **7** (51 mg, 1.0 eq) in EtOAc (2.0 mL) and then the reaction was stirred at rt for 1 h. The reaction solution was kept for 2 days and the obtained suspension was filtered. The solid was washed with EtOAc and the solid was dried to give the desired compound as HCl salt, white solid (24 mg, 53%). **LC-MS: [M+H]<sup>+</sup> : 413.1. <sup>1</sup>H NMR** (400 MHz, CD<sub>3</sub>OD) δ 7.45 (d, *J* = 8.0 Hz, 1H), 7.30-7.25 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 4.48-4.43 (m, 2H), 3.88-3.81 (m, 2H), 3.46 (s, 3H), 2.96 (s, 2H), 1.81-1.67 (m, 4H), 1.23 (s, 3H).

The compounds in Table A below were synthesized in the similar manner using appropriate reagents and conditions. The compounds listed in Table A are merely non-limiting examples. Other subject compounds could also be made using similar methods.

**Table A**

Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
<b>7</b>	<b>LC-MS: [M+H]<sup>+</sup> : 385.1</b> <b><sup>1</sup>H NMR</b> (400 MHz, CD <sub>3</sub> OD) δ 7.34 (d, <i>J</i> = 8.4 Hz, 1H), 7.20 (t, <i>J</i> = 8.0 Hz, 1H), 7.13 (s, 1H), 6.93 (d, <i>J</i> = 7.6 Hz, 1H), 4.00 - 3.90 (m, 2H), 3.80 - 3.66 (m, 2H), 2.72 (s, 2H), 1.96 - 1.85 (m, 1H), 1.77 - 1.72 (m, 1H), 1.15 (s, 3H).
<b>2</b>	<b>LC-MS: [M+H]<sup>+</sup> : 399.1</b> <b><sup>1</sup>H NMR</b> (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 12.11 (br s, 1H), 7.97 (br s, 3H), 7.49 (d, <i>J</i> = 8.0 Hz, 1H), 7.35-7.31 (m, 1H), 7.22 (s, 1H), 6.95 (d, <i>J</i> = 8.0 Hz, 1H), 4.27-4.24 (m, 2H), 3.58-3.53 (m, 2H), 2.76 (s, 2H), 1.58-1.41 (m, 4H), 1.08 (s, 3H).
<b>4</b>	<b>LC-MS: [M+H]<sup>+</sup> : 383</b> <b><sup>1</sup>H NMR</b> (400 MHz, CD <sub>3</sub> OD) δ 8.57 (s, 1H), 7.33 (d, <i>J</i> = 8.0 Hz, 1H), 7.26 (t, <i>J</i> = 8.0 Hz, 1H), 7.06 (d, <i>J</i> = 7.6 Hz, 1H), 6.96 (s, 1H), 3.67 (br s, 2H), 3.15 (br s, 2H), 2.86 (br s, 2H), 1.66 (s, 2H), 1.53-1.50 (m, 2H), 1.12 (s, 3H).
<b>6</b>	<b>LC-MS: [M+H]<sup>+</sup> : 397</b>

Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.47 (d, <i>J</i> = 8.4 Hz, 1H), 7.37 (t, <i>J</i> = 8.4 Hz, 1H), 7.21 (d, <i>J</i> = 8.4 Hz, 1H), 6.42 (s, 1H), 3.94-3.91 (m, 2H), 3.53 (s, 3H), 3.28-3.25 (m, 2H), 2.86 (br s, 2H), 1.68-1.61 (m, 2H), 1.54-1.51 (m, 2H), 1.13 (s, 3H).
5	LC-MS: [M+H] <sup>+</sup> : 382.2 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.14 (t, <i>J</i> = 8.0 Hz, 1H), 7.03 (d, <i>J</i> = 8.0 Hz, 1H), 6.95 - 6.90 (m, 2H), 4.03 - 3.96 (m, 2H), 3.40 - 3.31 (m, 2H), 2.90 (s, 2H), 1.70 - 1.64 (m, 2H), 1.69 - 1.63 (m, 2H), 1.16 (s, 3H).
12	LC-MS: [M+H] <sup>+</sup> : 381.2 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.53 (s, 1H), 8.34 (d, <i>J</i> = 8.4 Hz, 1H), 7.91 (d, <i>J</i> = 7.6 Hz, 1H), 7.82 (d, <i>J</i> = 8.0 Hz, 1H), 7.64 - 7.51 (m, 2H), 7.51 - 7.37 (m, 2H), 7.17 (s, 1H), 4.29-4.24(m, 2H), 3.48 - 3.42 (m, 2H), 2.85 (s, 2H), 1.67 - 1.55 (m, 2H), 1.52 - 1.48 (m, 2H), 1.15 (s, 3H).
8	LC-MS: [M+H] <sup>+</sup> : 383 <sup>1</sup> H NMR (400 MHz, DMSO) δ 7.46 (d, <i>J</i> = 8.0 Hz, 1H), 7.32 (d, <i>J</i> = 8.0 Hz, 1H), 7.13 (s, 1H), 6.94 (d, <i>J</i> = 8.4 Hz, 1H), 3.99-3.97 (m, 2H), 3.68 - 3.65 (m, 2H), 2.95 - 2.91 (m, 2H), 2.76 - 2.74 (m, 2H), 2.66 - 2.63 (m, 2H).
9	LC-MS: [M+H] <sup>+</sup> : 369.1 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.35 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.20 (t, <i>J</i> = 8.0 Hz, 1H), 7.11 (s, 1H), 6.93 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 5.27 - 5.22 (m, 1H), 4.42 - 4.38 (m, 1H), 3.95 - 3.91 (m, 1H), 3.63 - 3.60 (m, 1H), 3.29 - 3.25 (m, 1H), 3.24 - 3.20 (m, 1H), 2.88 - 2.85 (m, 1H), 2.79 - 2.77 (m, 1H).
11	LC-MS: [M+H] <sup>+</sup> : 371 <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.32 (s, 1H), 7.53 (d, <i>J</i> = 7.6 Hz, 1H), 7.48 - 7.46 (m, 1H), 7.31 (t, <i>J</i> = 8.0 Hz, 1H), 7.14 (s, 1H), 6.96 - 6.93 (m, 1H), 3.96 - 3.94(m, 1H), 3.11 - 3.08 (m, 2H), 2.74 - 2.67 (m, 2H), 1.88 - 1.85 (m, 2H), 1.65 - 1.56 (m, 2H).
17	LC-MS: [M+H] <sup>+</sup> : 399.2 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.53 (s, 1H), 7.71 (d, <i>J</i> = 7.6 Hz, 1H), 7.51 (t, <i>J</i> = 7.6 Hz, 1H), 7.36 (t, <i>J</i> = 7.6 Hz, 1H), 7.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.21 (s, 1H), 4.39 - 4.34 (m, 2H), 3.57 - 3.50 (m, 2H), 2.86 (s, 2H), 1.65 - 1.59 (m, 2H), 1.55 - 1.51 (m, 2H), 1.17 (s, 3H).
19	LC-MS: [M+H] <sup>+</sup> : 380.2 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.20 (s, 1H), 7.07 (d, <i>J</i> = 8.6 Hz, 1H), 6.53 (dd, <i>J</i> = 8.4, 2.6 Hz, 1H), 6.38 (d, <i>J</i> = 2.6 Hz, 1H), 4.35-4.32 (m, 2H), 3.54-3.48 (m, 2H), 2.89 (s, 4H), 1.70-1.45 (m, 4H), 1.17 (s, 3H).
21	LC-MS: [M+H] <sup>+</sup> : 380 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.53 (s, 1H), 7.19 (s, 1H), 6.94 (t, <i>J</i> = 8.0 Hz, 1H), 6.66 (dd, <i>J</i> = 8.1, 1.2 Hz, 1H), 6.26 (dd, <i>J</i> = 7.8, 1.2 Hz, 1H), 4.42 - 4.24 (m, 2H), 3.51 (m, 2H), 2.86 (s, 2H), 1.61 (m, 2H), 1.52 (m, 2H), 1.16 (s, 3H).
10	LC-MS: [M+H] <sup>+</sup> : 427 <sup>1</sup> H NMR (400 MHz, DMSO) δ 8.26 (s, 1H), 7.48 (dd, <i>J</i> = 6.8 Hz, 1.2 Hz, 1H), 7.33 (t, <i>J</i> = 8.0 Hz, 1H), 7.22 (s, 1H), 6.95 (dd, <i>J</i> = 6.8 Hz, 1.2 Hz, 1H), 4.47-4.43 (m, 2H), 3.95(t, <i>J</i> = 8.4 Hz, 1H), 3.71 (d, <i>J</i> = 8.4 Hz, 1H), 3.61 (d, <i>J</i> = 8.8 Hz, 1H), 3.30-3.28 (m, 3 H), 3.09-3.07 (m, 1H), 1.70-1.61 (m, 2H), 1.44-1.43 (m, 2H).
18	LC-MS: [M+H] <sup>+</sup> : 400

Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
	<sup>1</sup> H NMR (400 MHz, DMSO) δ 8.52 (d, <i>J</i> = 3.2 Hz, 1H), 8.31 (s, 1H), 7.39-7.62 (m, 2H), 7.22 (s, 1H), 4.24-4.21 (m, 2H), 3.57-3.48 (m, 2H), 2.58 (s, 2H), 1.53-1.47 (m, 2H), 1.36-1.33 (m, 2H), 0.99 (s, 3H).
20	LC-MS: [M+H] <sup>+</sup> : 381.2 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.52 (d, <i>J</i> = 2.8 Hz, 1H), 7.23 (s, 1H), 6.71 (d, <i>J</i> = 2.8 Hz, 1H), 4.28-4.23 (m, 2H), 3.53- 3.47 (m, 2H), 2.61 (s, 2H), 1.62-1.55 (m, 2H), 1.47-1.43 (m, 2H), 1.07 (s, 3H).
24	LC-MS: [M+H] <sup>+</sup> : 396 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.51 (s, 1H), 7.88 (d, <i>J</i> = 5.5 Hz, 1H), 7.25 (s, 1H), 6.50 (d, <i>J</i> = 5.5 Hz, 1H), 4.41 (d, <i>J</i> = 13.9 Hz, 2H), 3.97 (s, 3H), 3.56 (m, 2H), 2.88 (s, 2H), 1.61 (m, 4H), 1.18 (s, 3H).
69	LC-MS: [M+H] <sup>+</sup> : 403.2 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.50 (s, 1H), 7.37 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.26 (s, 1H), 7.21 (t, <i>J</i> = 8.0 Hz, 1H), 6.94 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 4.82-4.79 (m, 2H), 3.37-3.34 (m, 2H), 3.14 (d, <i>J</i> = 19.8 Hz, 2H), 2.06-1.75 (m, 4H).
70	LC-MS: [M+H] <sup>+</sup> : 437 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.50 (s, 1H), 7.63 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.42 (t, <i>J</i> = 7.8 Hz, 1H), 7.34 (dd, <i>J</i> = 7.6, 1.4 Hz, 1H), 4.68 (s, 2H), 4.36-4.24 (m, 1H), 4.05-3.92 (m, 1H), 3.85 (d, <i>J</i> = 9.1 Hz, 1H), 3.78-3.62 (m, 2H), 3.44 (t, <i>J</i> = 12.0 Hz, 1H), 3.08 (dt, <i>J</i> = 24.9, 6.9 Hz, 2H), 2.05-1.82 (m, 3H), 1.75 (d, <i>J</i> = 12.9 Hz, 1H), 1.32 (d, <i>J</i> = 6.5 Hz, 3H).1
71	LC-MS: [M+H] <sup>+</sup> : 397 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.54 (s, 1H), 7.35 (dd, <i>J</i> = 8.0, 1.4 Hz, 1H), 7.25 -7.18 (m, 1H), 7.14 (s, 1H), 6.93 (dd, <i>J</i> = 8.0, 1.3 Hz, 1H), 3.30 (d, <i>J</i> = 1.6 Hz, 3H), 3.26 (s, 2H), 1.91 (s, 2H), 1.75 (t, <i>J</i> = 10.0 Hz, 2H), 1.62 (d, <i>J</i> = 9.2 Hz, 2H).
72	LC-MS: [M+H] <sup>+</sup> : 397 <sup>1</sup> H NMR (400 MHz, DMSO) δ 8.36 (s, 1H), 7.47 (dd, <i>J</i> = 8.0, 1.3 Hz, 1H), 7.32 (t, <i>J</i> = 8.0 Hz, 1H), 7.12 (d, <i>J</i> = 5.2 Hz, 1H), 6.95 (d, <i>J</i> = 8.0 Hz, 1H), 5.67 (s, 1H), 3.53 (dd, <i>J</i> = 167.4, 77.9 Hz, 7H), 1.66 (dd, <i>J</i> = 37.8, 25.8 Hz, 4H), 1.44 (s, 2H).
14	LC-MS: [M+H] <sup>+</sup> : 441.2 <sup>1</sup> H NMR (400 MHz, DMSO) δ 8.53 (s, 1H), 7.36 (d, <i>J</i> = 8.0 Hz, 1H), 7.21 (dd, <i>J</i> = 15.9, 7.8 Hz, 2H), 6.92 (d, <i>J</i> = 8.0 Hz, 1H), 4.65-4.39 (m, 2H), 4.35-4.14 (m, 1H), 3.92 (d, <i>J</i> = 8.9 Hz, 1H), 3.79 (d, <i>J</i> = 8.9 Hz, 1H), 3.31-3.21 (m, 3H), 2.01-1.57 (m, 4H), 1.27 (d, <i>J</i> = 6.4 Hz, 3H).
15	LC-MS: [M+H] <sup>+</sup> : 441.2 <sup>1</sup> H NMR (400 MHz, DMSO) δ 8.53 (s, 1H), 7.36 (d, <i>J</i> = 8.0 Hz, 1H), 7.21 (dd, <i>J</i> = 15.9, 7.8 Hz, 2H), 6.92 (d, <i>J</i> = 8.0 Hz, 1H), 4.65-4.39 (m, 2H), 4.35-4.14 (m, 4H), 3.92 (d, <i>J</i> = 8.9 Hz, 1H), 3.79 (d, <i>J</i> = 8.9 Hz, 1H), 3.31-3.21 (m, 3H), 2.01-1.57 (m, 4H), 1.27 (d, <i>J</i> = 6.4 Hz, 3H).
22	LC-MS: [M+H] <sup>+</sup> : 381.2 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.50 (s, 1H), 7.69 (d, <i>J</i> = 5.6 Hz, 1H), 7.23 (s, 1H), 6.17 (d, <i>J</i> = 5.6 Hz, 1H), 4.58 (s, 1H), 4.41 (d, <i>J</i> = 14.0 Hz, 2H), 3.64-3.48 (m, 2H), 2.89 (s, 2H), 1.63-1.58 (m, 4H), 1.18 (s, 3H).

Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
73	<b>LC-MS:</b> [M+H] <sup>+</sup> : 427 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.49 (s, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.22 (dd, J = 16.3, 8.3 Hz, 2H), 6.92 (d, J = 8.1 Hz, 1H), 4.69-4.52 (m, 2H), 4.15 (dd, J = 10.1, 5.8 Hz, 1H), 3.90 (dd, J = 18.7, 9.1 Hz, 2H), 3.73 (d, J = 10.3 Hz, 1H), 3.46 (s, 3H), 1.83 (d, J = 9.8 Hz, 2H), 1.71 (d, J = 13.8 Hz, 2H).
75	<b>LC-MS:</b> [M+H] <sup>+</sup> : 427 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.53 (s, 1H), 7.36 (dd, J = 8.0, 1.3 Hz, 1H), 7.22 (dd, J = 15.0, 7.0 Hz, 2H), 6.92 (dd, J = 8.1, 1.3 Hz, 1H), 4.71-4.50 (m, 2H), 4.13 (dd, J = 9.7, 6.1 Hz, 1H), 3.86 (s, 2H), 3.63 (dd, J = 9.7, 4.1 Hz, 1H), 3.35 (d, J = 11.1 Hz, 2H), 3.24-3.15 (m, 1H), 1.81 (td, J = 15.0, 4.0 Hz, 2H), 1.65 (d, J = 14.4 Hz, 2H).
76	<b>LC-MS:</b> [M+H] <sup>+</sup> : 403 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.49 (s, 1H), 7.37 (dd, J = 8.0, 1.3 Hz, 1H), 7.30-7.17 (m, 2H), 6.94 (dd, J = 8.1, 1.3 Hz, 1H), 3.36-3.31 (m, 2H), 3.30-3.24 (m, 2H), 3.16 (d, J = 19.9 Hz, 2H), 2.04-1.72 (m, 4H).
77	<b>LC-MS:</b> [M+H] <sup>+</sup> : 423.2 <sup>1</sup> H NMR (400 MHz, MeOD) δ 7.69 (d, J = 5.4 Hz, 1H), 7.24 (s, 1H), 6.17 (d, J = 5.5 Hz, 1H), 4.65-4.55 (m, 4H), 4.35-4.22 (m, 1H), 3.94 (d, J = 9.0 Hz, 1H), 3.83 (d, J = 9.0 Hz, 1H), 3.31-3.21 (m, 1H), 1.93-1.49 (m, 4H), 1.28 (d, J = 6.5 Hz, 3H).
78	<b>LC-MS:</b> [M+H] <sup>+</sup> : 425 <sup>1</sup> H NMR (400 MHz, MeOD) δ 7.36-7.34 (m, 1H), 7.22-7.18 (m, 2H), 6.92-6.90 (m, 1H), 4.38-4.34 (m, 1H), 3.27-3.25 (m, 2H), 3.10-3.03 (m, 2H), 2.16-2.13 (m, 1H), 1.97-1.87 (m, 1H), 1.87-1.66 (m, 8H),
79	<b>LC-MS:</b> [M+H] <sup>+</sup> : 437.2 <sup>1</sup> H NMR (400 MHz, DMSO) δ 7.22 (s, 1H), 7.18 (t, J = 8.2 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 4.70-4.60 (m, 4H), 4.30-4.27 (m, 1H), 3.97 (d, J = 9.2 Hz, 1H), 3.86 (d, J = 11.6 Hz, 1H), 3.41 (d, J = 4.1 Hz, 1H), 3.26-3.08 (m, 2H), 1.94-1.61 (m, 4H), 1.31 (d, J = 6.5 Hz, 3H).
80	<b>LC-MS:</b> [M+H] <sup>+</sup> : 438 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.49 (s, 1H), 7.88 (d, J = 5.5 Hz, 1H), 7.25 (s, 1H), 6.50 (d, J = 5.5 Hz, 1H), 4.75-4.58 (m, 2H), 4.27 (dd, J = 6.5, 4.4 Hz, 1H), 4.06-3.90 (m, 4H), 3.84 (d, J = 9.1 Hz, 1H), 3.36 (s, 1H), 3.28-3.11 (m, 2H), 1.86 (dd, J = 17.1, 7.3 Hz, 3H), 1.67 (d, J = 13.5 Hz, 1H), 1.29 (d, J = 6.5 Hz, 3H).
81	<b>LC-MS:</b> [M+H] <sup>+</sup> : 442 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.56-8.32 (m, 1H), 8.10 (d, J = 5.3 Hz, 1H), 7.40-7.19 (m, 1H), 6.95 (d, J = 5.3 Hz, 1H), 4.77-4.62 (m, 2H), 4.33-4.20 (m, 1H), 3.97 (d, J = 9.1 Hz, 1H), 3.86 (d, J = 9.1 Hz, 1H), 3.43 (t, J = 16.6 Hz, 1H), 3.23 (m, 2H), 1.96-1.79 (m, 3H), 1.69 (d, J = 13.2 Hz, 1H), 1.31 (d, J = 6.5 Hz, 3H).
84	<b>LC-MS:</b> [M+H] <sup>+</sup> : 410.3 <sup>1</sup> H NMR (400 MHz, DMSO) δ 8.32 (s, 2H), 7.91 (d, J = 5.3 Hz, 1H), 7.25 (s, 1H), 7.05 (t, J = 5.1 Hz, 1H), 4.32-4.28 (m, 2H), 4.13-4.01 (m, 2H), 3.69 (d, J = 8.4 Hz, 1H), 3.51 (d, J = 8.5 Hz, 1H), 2.97 (d, J = 5.1 Hz, 1H), 1.79-1.65 (m, 2H), 1.59-1.42 (m, 2H), 1.10 (d, J = 6.4 Hz, 3H).

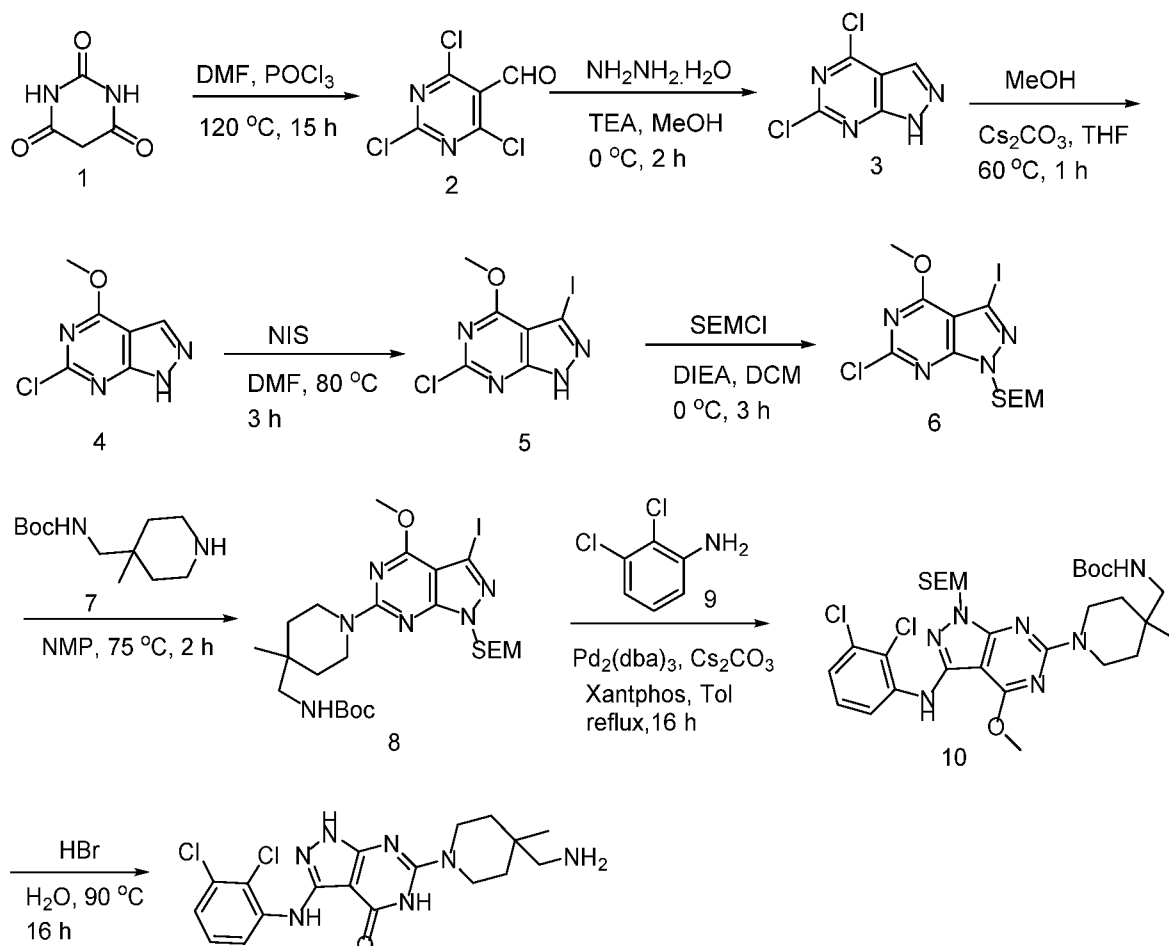


Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
107	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 424</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, MeOD) δ 8.52 (s, 1H), 7.35-7.18 (m, 2H), 5.98 (d, <i>J</i> = 7.1 Hz, 1H), 4.60 (m, 2H), 4.34-4.19 (m, 1H), 3.92 (d, <i>J</i> = 9.0 Hz, 1H), 3.81 (d, <i>J</i> = 9.0 Hz, 1H), 3.37 (d, <i>J</i> = 10.2 Hz, 1H), 3.28-3.18 (m, 2H), 1.84 (m, 3H), 1.66 (d, <i>J</i> = 13.3 Hz, 1H), 1.27 (d, <i>J</i> = 6.5 Hz, 3H).</p>
109	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 425</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, MeOD) δ 7.32 (m, 1H), 7.21m7.08 (m, 3H), 4.83m4.76 (m, 1H), 4.69 (d, <i>J</i> = 13.4 Hz, 1H), 4.32 (m, 1H), 4.01 (d, <i>J</i> = 9.2 Hz, 1H), 3.88 (d, <i>J</i> = 9.2 Hz, 1H), 3.70-3.46 (m, 3H), 2.09 (t, <i>J</i> = 10.7 Hz, 2H), 2.03-1.94 (m, 1H), 1.83 (d, <i>J</i> = 13.2 Hz, 1H), 1.33 (d, <i>J</i> = 6.5 Hz, 3H).</p>
82	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 409</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, MeOD) δ 8.49 (s, 1H), 7.25 (s, 1H), 7.14 (m, 2H), 6.99 (m, 1H), 4.64-4.46 (m, 2H), 4.34-4.20 (m, 1H), 3.93 (d, <i>J</i> = 9.1 Hz, 1H), 3.82 (d, <i>J</i> = 9.1 Hz, 1H), 3.29-3.06 (m, 3H), 1.91-1.73 (m, 3H), 1.65 (d, <i>J</i> = 13.2 Hz, 1H), 1.28 (d, <i>J</i> = 6.5 Hz, 3H).</p>
83	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 426.3</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, DMSO) δ 8.26 (s, 1H), 8.03 (s, 1H), 7.27 (s, 1H), 6.98 (s, 1H), 4.45-4.31 (m, 2H), 4.15-4.09 (m, 1H), 3.75 (d, <i>J</i> = 8.6 Hz, 1H), 3.58 (d, <i>J</i> = 8.6 Hz, 1H), 3.20-3.10 (m, 3H), 1.86-1.41 (m, 4H), 1.13 (d, <i>J</i> = 6.5 Hz, 3H).</p>
26	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 422</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, MeOD) δ 7.36 (t, <i>J</i> = 8.0 Hz, 1H), 7.23 (s, 1H), 6.77 (t, <i>J</i> = 7.8 Hz, 2H), 4.43-4.29 (m, 2H), 3.54 (m, 2H), 2.89 (s, 2H), 1.70-1.59 (m, 2H), 1.54 (d, <i>J</i> = 13.7 Hz, 2H), 1.18 (s, 3H).</p>
85	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 439</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, DMSO) δ 7.53-7.48 (m, 1H), 7.33 (t, <i>J</i> = 8.0 Hz, 1H), 6.85 (d, <i>J</i> = 7.9 Hz, 1H), 6.74 (d, <i>J</i> = 7.4 Hz, 1H), 6.60 (d, <i>J</i> = 7.5 Hz, 1H), 4.31-4.06 (m, 1H), 3.79 (d, <i>J</i> = 8.8 Hz, 1H), 3.70-3.47 (m, 3H), 3.28 (s, 1H), 2.73-2.58 (m, 2H), 1.79 (m, 2H), 1.62 (dm, 2H), 1.21 (t, <i>J</i> = 10.4 Hz, 3H).</p>
13	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 437.1</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, DMSO) δ 7.48 (d, <i>J</i> = 7.4 Hz, 1H), 7.32 (t, <i>J</i> = 8.0 Hz, 1H), 7.21 (d, <i>J</i> = 1.2 Hz, 1H), 6.94 (m, 1H), 4.79-4.45 (m, 2H), 3.38 (d, <i>J</i> = 5.4 Hz, 1H), 3.21-2.81 (m, 3H), 2.09-1.71 (m, 2H), 1.70-1.32 (m, 6H), 0.75-0.33 (m, 2H)</p>
86	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 369.0</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, MeOD) δ 7.42 (d, <i>J</i> = 7.8 Hz, 1H), 7.33-7.12 (m, 2H), 7.05 (s, 1H), 4.72-4.16 (m, 2H), 4.21-3.92 (m, 2H), 2.60 (s, 1H), 2.33 (s, 2H).</p>
108	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 473.1</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, DMSO) δ 12.16 (s, 1H), 8.47 (s, 3H), 7.58 (d, <i>J</i> = 7.3 Hz, 1H), 7.50 (dd, <i>J</i> = 8.0, 1.3 Hz, 1H), 7.39-7.17 (m, 5H), 6.98 (m, 1H), 4.76 (s, 2H), 4.35 (d, <i>J</i> = 5.1 Hz, 1H), 3.33-3.13 (m, 3H), 3.00 (d, <i>J</i> = 16.2 Hz, 1H), 1.88-1.74 (m, 2H), 1.52 (t, <i>J</i> = 15.3 Hz, 2H).</p>
87	<p><b>LC-MS:</b> [M+H]<sup>+</sup>: 475.1</p> <p><b><sup>1</sup>H NMR</b> (400 MHz, MeOD) δ 7.54 (d, <i>J</i> = 7.4 Hz, 1H), 7.41 (m, 2H), 7.24 (d, <i>J</i> = 16.0 Hz, 2H), 7.12-7.04 (m, 2H), 7.00 (d, <i>J</i> = 8.2 Hz, 1H), 5.11 (d, <i>J</i> = 12.3 Hz, 1H), 4.83-4.76 (m, 1H), 4.68 (s, 1H), 3.70-3.41 (m, 2H), 2.28 (td, <i>J</i> = 12.9, 4.6 Hz, 1H), 2.10 (m, 1H), 2.03-1.87 (m, 2H).</p>

Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
88	<b>LC-MS:</b> [M+H] <sup>+</sup> : 428.1 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.17 (d, <i>J</i> = 4.4 Hz, 1H), 7.27-7.20 (m, 2H), 4.68-4.63 (m, 1H), 4.22-4.18 (m, 1H), 4.00-3.83 (m, 3H), 3.73-3.57 (m, 4H), 2.09-2.01 (m, 2H), 1.92-1.84 (m, 2H)
27	<b>LC-MS:</b> [M+H] <sup>+</sup> : 492.2 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.18 (d, <i>J</i> = 8.3 Hz, 1H), 7.47 (t, <i>J</i> = 8.2 Hz, 1H), 7.10 (s, 1H), 7.03 (d, <i>J</i> = 7.9 Hz, 1H), 4.78 (s, 1H), 4.68-4.45 (m, 3H), 4.30 (m, 1H), 3.99 (d, <i>J</i> = 9.3 Hz, 1H), 3.88 (d, <i>J</i> = 9.2 Hz, 1H), 3.57-3.42 (m, 3H), 2.28 (s, 3H), 2.09-1.92 (m, 3H), 1.79 (d, <i>J</i> = 13.8 Hz, 1H), 1.32 (d, <i>J</i> = 6.5 Hz, 3H).

**Example 4**

Preparation of 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-((2, 3-dichlorophenyl) amino)-1, 5-dihydro-4H-pyrazolo [3, 4-d] pyrimidin-4-one



5

Step 1: preparation of 2, 4, 6-trichloropyrimidine-5-carbaldehyde (2)

A mixture of compound **1** (25.6 g, 1.0 eq) with POCl<sub>3</sub> (100 mL) and DMF (30 mL) was heated at 120 °C for 15 h, and then DMF was evaporated. Ice water was added to the residue and the solid formed was collected and dried to give compound **2** (9.2 g, 21%).

Step 2: preparation of 4, 6-dichloro-1H-pyrazolo [3, 4-d] pyrimidine (**3**)

5 To a solution of compound **2** (16.0 g, 1.0 eq) in methanol (80 mL) was added dropwise a solution of hydrazine monohydrate (4.55 g, 1.2 eq) in methanol at 0 °C, and then a solution of triethylamine (15.28 g, 2.0eq) in methanol was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h, then evaporated in vacuo. The residue was suspended in hot isopropyl alcohol and the insoluble materials were removed by filtration. The combined filtrate was concentrated in vacuo to  
10 give the title compound **3** as a yellow solid (9.0 g, 62%).

Step 3: preparation of 6-chloro-4-methoxy-1H-pyrazolo [3, 4-d] pyrimidine (**4**)

To a solution of compound **3** (480 mg, 2.54 mmol, 1.0 eq) in THF was added cesium carbonate (1.65 g, 2.0 eq) and methanol (3.0 mL), and the mixture was heated to 60 °C. The reaction was quenched with water (10 mL) and worked up under standard procedure to afford compound **4** as a  
15 brown solid (468 mg, 99%).

Step 4: preparation of 6-chloro-3-iodo-4-methoxy-1H-pyrazolo [3, 4-d] pyrimidine (**5**)

To a solution of compound **4** (468 mg, 1.0eq) in dry DMF (12 mL) was added N-iodosuccinimide (857mg, 1.5eq) and the reaction mixture was heated to 80 °C under stirring for 3 h. The reaction was quenched with water (10 mL) and worked up under standard process to afford  
20 compound **5** as a brown solid (522 mg, 66%).

Step 5: preparation of 6-chloro-3-iodo-4-methoxy-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-pyrazolo [3, 4-d] pyrimidine (**6**)

To a solution of compound **5** (2.6 g, 1.0 eq) in DCM (20 mL) was added DIEA (2.37 g, 2.2 eq) at 0 °C, and then SEMCl (1.67 g, 1.2 eq) was added dropwise. The reaction was quenched with water  
25 (10 mL) and worked up under standard process to afford compound **6** as a brown solid (1.55 g, 42%).

Step 6: preparation of tert-butyl ((1-(3-iodo-4-methoxy-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-pyrazolo [3, 4-d] pyrimidin-6-yl)-4-methylpiperidin-4-yl) methyl) carbamate (**8**)

To a solution of compound **6** (520 mg, 1.0 eq) in NMP (10 mL) was added compound **7** (296 mg, 1.1 eq) at RT, and then the mixture was stirred at 75 °C for 2 h. The reaction was quenched with

water (10 mL) and worked up under standard process to afford compound **8** as a white solid (450 mg, 60%).

Step 7: preparation of tert-butyl ((1-(3-((2,3-dichlorophenyl)amino)-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)methyl)carbamate (**10**)

To a solution of compound **8** (200 mg, 1.0 eq) in toluene was added compound **9** (61.5 mg, 1.2 eq), cesium carbonate (123.7 mg, 1.2 eq) and xantphos (183.1 mg, 1.0 eq). After that, Pd<sub>2</sub>(dba)<sub>3</sub> (5.0 mg) was added under the atmosphere of Ar. The mixture was stirred at 120 °C for 16 h. The reaction was quenched with water and worked up under standard process to give compound **10** as a white solid (42 mg, 20%).

Step 8: preparation of 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-((2, 3-dichlorophenyl) amino)-1, 5-dihydro-4H-pyrazolo [3, 4-d] pyrimidin-4-one

To a mixture of compound **10** (97.0 mg, 1.0 eq) in H<sub>2</sub>O (4 mL) was added HBr (40%, 2 mL), and then the mixture was stirred at 90 °C for 16 h. The reaction was quenched by water followed by standard work up process. The crude product was purified by prep-HPLC to give desired compound, as HCOOH salt (white solid, 9.79 mg, 16%). **LC-MS**: [M+H]<sup>+</sup> = 422.2. **<sup>1</sup>H NMR** (400 MHz, CD<sub>3</sub>OD): δ 8.53 (brs, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 7.24 (t, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 4.03 - 3.98 (m, 2H), 3.50-3.43 (m, 2H), 2.87 (s, 2H), 1.64 - 1.56 (m, 4H), 1.17 (s, 3H).

The compounds in Table B below were synthesized in the similar manner using appropriate reagents and conditions. The compounds listed in Table B are merely non-limiting examples. Other subject compounds could also be made using similar methods.

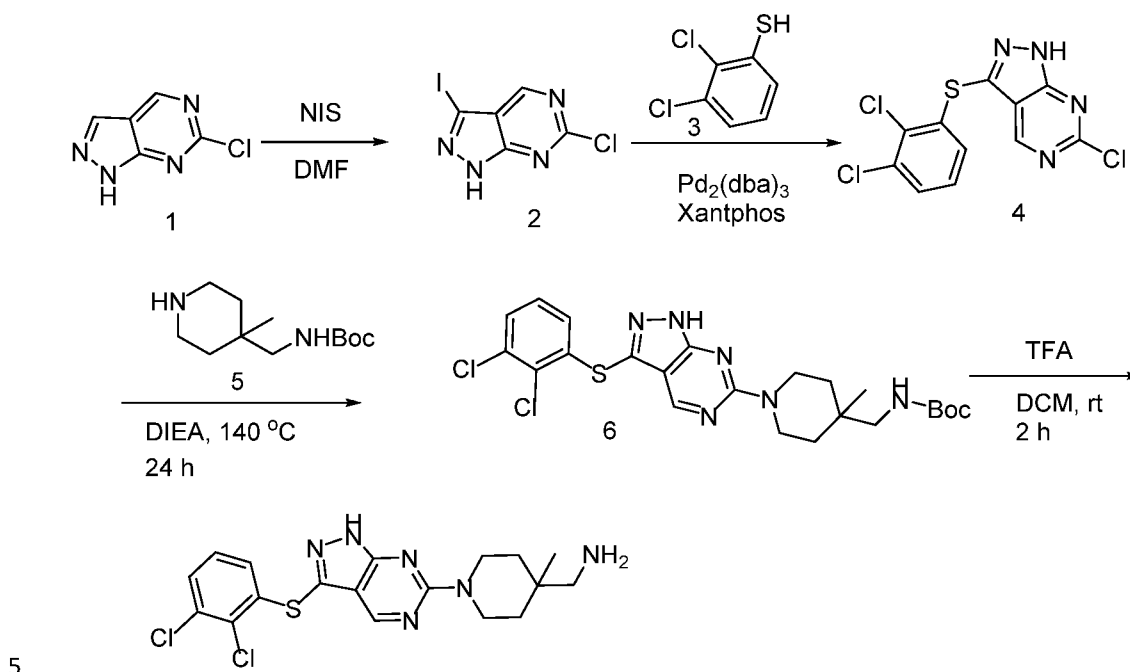
**Table B**

Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
<b>35</b>	<b>LC-MS</b> : [M+H] <sup>+</sup> : 423.1 <b><sup>1</sup>H NMR</b> (400 MHz, CD <sub>3</sub> OD) δ 8.52 (br s, 3H), 7.38 (d, <i>J</i> = 8.0 Hz, 1H), 7.27 (t, <i>J</i> = 8.2 Hz, 1H), 7.14 (d, <i>J</i> = 8.8 Hz, 1H), 4.08-3.99 (m, 2H), 3.60-3.43 (m, 2H), 2.88 (s, 2H), 1.62-1.56 (m, 4H), 1.18 (s, 3H).
<b>68</b>	<b>LC-MS</b> : [M+H] <sup>+</sup> : 408 <b><sup>1</sup>H NMR</b> (400 MHz, DMSO) δ 12.21 (s, 1H), 8.67-8.21 (m, 3H), 7.96 (s, 1H), 7.34 (t, <i>J</i> = 8.2 Hz, 1H), 7.13 (d, <i>J</i> = 7.8 Hz, 1H), 3.55 (s, 2H), 3.44 (d, <i>J</i> = 10.9 Hz, 1H), 3.20

Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
	(d, <i>J</i> = 10.8 Hz, 1H), 2.58 (s, 2H), 1.89 (s, 1H), 1.66 (d, <i>J</i> = 5.5 Hz, 1H), 1.05 (s, 3H).

**Example 5**

Preparation of (1-(3-((2,3-dichlorophenyl)thio)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)methanamine



Step 1: preparation of 6-chloro-3-iodo-1H-pyrazolo[3,4-d]pyrimidine (**2**)

To a solution of compound **1** (780 mg, 1.0 eq) in DMF was added NIS (1300 mg, 1.2 eq) in portion at rt. The mixture was heated to 80 °C and stirred for 4 h. The reaction was quenched by water and worked up under standard operation to afford compound **2** as yellow solid (560 mg, 68%).

Step 2: preparation of 1-(3-((2,3-dichlorophenyl)thio)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)methanamine (**4**)

To a solution of compound **2** (280 mg, 1.0 eq) in dioxane were added Pd<sub>2</sub>(dba)<sub>3</sub> (46 mg, 0.05 eq), XantPhos (58 mg, 0.1 eq) and DIEA (200 mg, 1.5 eq) at rt. The mixture was heated to 90 °C and stirred for 14 h. The reaction was quenched by water and worked up under standard operation to afford compound **4** as yellow solid (140 mg, 48%).

Step 3: preparation of tert-butyl ((1-(3-((2,3-dichlorophenyl)thio)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)methyl)carbamate (**6**)

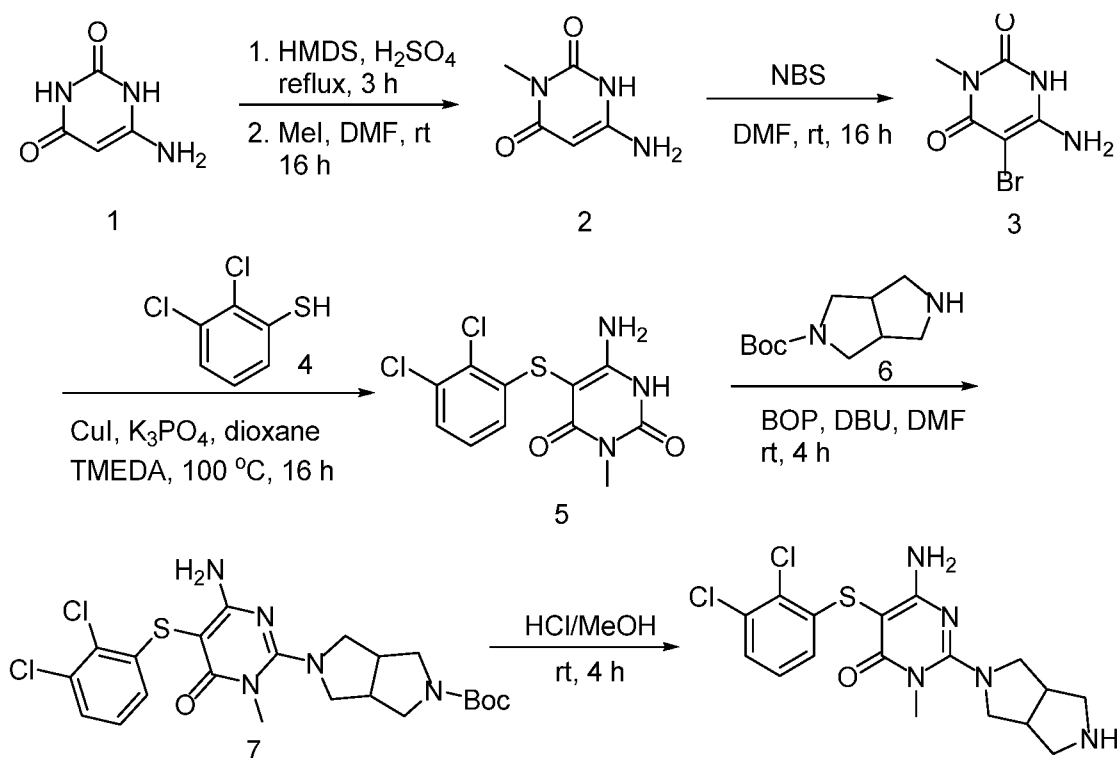
To a solution of compound **4** (145mg, 1.0 eq) in DIEA was added compound **5** (300 mg, 3.0 eq) at rt. The mixture was heated at 140 °C for 24 h. The reaction was quenched by water and worked up under standard operation to give compound **6** as a yellow oil (110 mg, 48%).

Step 4: preparation of (1-(3-((2,3-dichlorophenyl)thio)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)methanamine

To a solution of compound **6** (110 mg, 1.0 eq) in DCM was added TFA (1 mL). The mixture was stirred at rt for 2 h. The mixture was concentrated and neutralized with ammonium hydroxide (pH = 7-8), purified by prep-HPLC to give the target compound as a white solid (HCOOH salt, 6 mg, 7%). **LC-MS**:  $[M+H]^+ = 423.2$ . **<sup>1</sup>H NMR** (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.54 (s, 1H), 7.41 (dd,  $J = 8.0, 1.2$  Hz, 1H), 7.14 (t,  $J = 8.0$  Hz, 1H), 6.92 (dd,  $J = 8.0, 1.2$  Hz, 1H), 4.62 (br, 1H), 4.42 - 4.36 (m, 2H), 3.61 - 3.54 (m, 2H), 2.89 (s, 2H), 1.60 - 1.50 (m, 4H), 1.20 (s, 3H).

#### Example 6

Preparation of 6-amino-5-((2,3-dichlorophenyl)thio)-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-methylpyrimidin-4(3H)-one



Step 1: Preparation of 6-amino-3-methylpyrimidine-2,4(1H,3H)-dione (**2**)

To a solution of compound **1** (31.08 g, 1.0 eq) in HMDS (150 mL) was added *conc.* H<sub>2</sub>SO<sub>4</sub> (0.6 mL) at room temperature. The mixture was heated to reflux for 3 h. Then the mixture was concentrated in vacuo. The residue was dissolved in DMF (150 mL) and MeI (115.8 g, 3.4 eq) was added at rt. The mixture was stirred at rt for 16 h. The reaction was quenched by water and worked up under standard operation to give compound **2** as a white solid (16 g, 47%).

Step 2: preparation of 6-amino-5-bromo-3-methylpyrimidine-2,4(1H,3H)-dione (**3**)

To a solution of compound **2** (5.0 g, 1.0 eq) in DMF (50 mL) was added NBS (7.9 g, 1.25 eq) and the mixture was stirred at rt overnight. The reaction was quenched by water and worked up under standard operation to give compound **3** as a white solid (4.7 g, 60%).

Step 3: preparation of 6-amino-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidine-2,4(1H,3H)-dione (**5**)

To a solution of compound **3** (500 mg, 1.0 eq) in dioxane (10 mL) was added compound **4** (813 mg, 2.0 eq), K<sub>3</sub>PO<sub>4</sub> (1445 mg, 3.0 eq), TMEDA (105 mg, 0.4 eq) and CuI (86 mg, 0.2 eq). The resulting mixture was stirred at 100 °C under N<sub>2</sub> atmosphere for 2 h. The reaction was quenched by water and worked up under standard operation to give compound **5** as a brown solid (210 mg, 29%).

Step 4: preparation of tert-butyl 5-(4-amino-5-((2,3-dichlorophenyl)thio)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (**7**)

To a solution of compound **5** (60 mg, 1.0 eq) in DMF (2 mL) was added compound **6** (60 mg, 1.5 eq), BOP (250 mg, 3.0 eq) and DBU (143 mg, 5.0 eq). The reaction was quenched by water and worked up under standard operation to give compound **7** as a white solid (55 mg, 57%).

Step 5: preparation of 6-amino-5-((2,3-dichlorophenyl)thio)-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-methylpyrimidin-4(3H)-one

A solution of compound **7** (50 mg, 1.0 eq) in HCl/MeOH (3 M, 3 mL) was stirred at rt for 4 h. The mixture was concentrated and purified by pre-HPLC to give the desired compound as HCOOH salt (white solid, 21 mg, 53%). **LC-MS:** [M+H]<sup>+</sup> = 412. **<sup>1</sup>H NMR** (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.52 (br s, 1H), 7.24 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.74-3.61 (m, 4H), 3.60-3.50 (m, 2H), 3.45 (s, 3H), 3.30-3.13 (m, 4H).

The compounds in Table C below were synthesized in the similar manner using appropriate reagents and conditions. The compounds listed in Table C are merely non-limiting examples. Other subject compounds could also be made using similar methods.

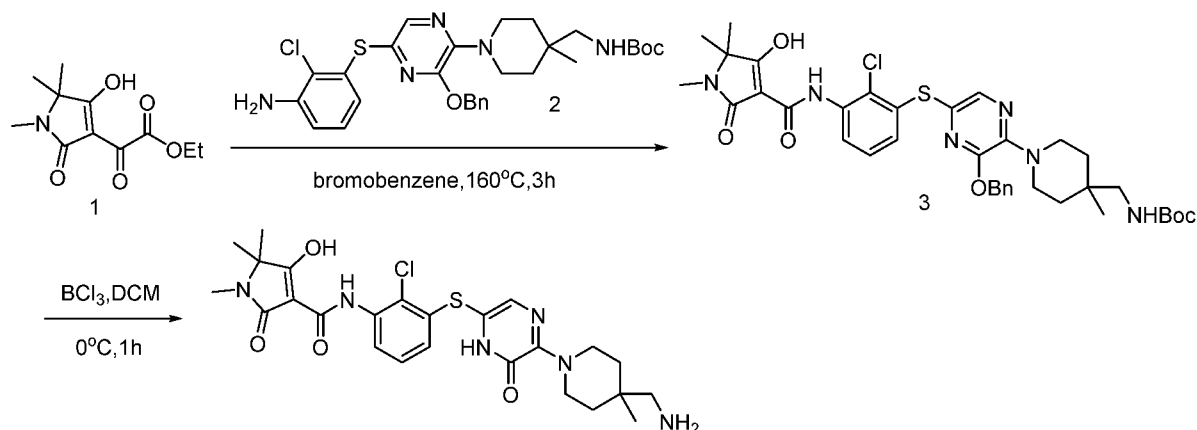
Table C

Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
52	<b>LC-MS:</b> [M+H] <sup>+</sup> : 414.2 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.23 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 7.09 (t, <i>J</i> = 8.0 Hz, 1H), 6.76 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 3.77-3.70 (m, 2H), 3.56 (d, <i>J</i> = 10.8 Hz, 1H), 3.42 (s, 3H), 3.34-3.24 (m, 1H), 2.69 (s, 2H), 1.95-1.84 (m, 1H), 1.82-1.70 (m, 1H), 1.15 (s, 3H).
60	<b>LC-MS:</b> [M+H] <sup>+</sup> : 398.1 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.23 (dd, <i>J</i> = 8.0 Hz, 1.2 Hz, 1H), 7.10 (t, <i>J</i> = 8.0 Hz, 1H), 6.79 (d, <i>J</i> = 8.0 Hz, 1.2 Hz, 1H), 3.77-3.72 (m, 2H), 3.49-3.46 (m, 2H), 3.17-3.12 (m, 2H), 3.00 (br s, 2H), 2.82-2.80 (m, 2H).
54	<b>LC-MS:</b> [M+H] <sup>+</sup> : 400.1 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.22 (d, <i>J</i> = 8.0 Hz, 1H), 7.10 (t, <i>J</i> = 8.0 Hz, 1H), 6.81 (d, <i>J</i> = 8.0 Hz, 1H), 3.61 (br s, 2H), 3.42-3.39 (m, 1H), 3.25-3.23 (m, 1H), 2.67 (s, 2H), 1.96-1.93 (m, 1H), 1.79-1.76 (m, 1H), 1.14 (s, 3H).
63	<b>LC-MS:</b> [M+H] <sup>+</sup> : 426.1 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.22 (d, <i>J</i> = 7.6 Hz, 1H), 7.09 (t, <i>J</i> = 8.0 Hz, 1H), 6.76 (d, <i>J</i> = 8.0 Hz, 1H), 4.25-4.19 (m, 2H), 4.16-4.10 (m, 2H), 3.39-3.31 (m, 1H), 3.30 (s, 3H), 2.32-2.27 (m, 1H), 2.10-1.92 (m, 3H), 1.71-1.66 (m, 1H), 1.49-1.45 (m, 1H).
64	<b>LC-MS:</b> [M+H] <sup>+</sup> : 398.1 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.25 (d, <i>J</i> = 7.6 Hz, 1H), 7.10 (t, <i>J</i> = 7.6 Hz, 1H), 6.78 (d, <i>J</i> = 7.6 Hz, 1H), 3.94 (br s, 3H), 3.45-3.33 (m, 5H), 1.93 (br s, 2H).
66	<b>LC-MS:</b> [M+H] <sup>+</sup> : 384 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.24 (d, <i>J</i> = 8.0 Hz, 1H), 7.11 (t, <i>J</i> = 8.0 Hz, 1H), 6.84 (d, <i>J</i> = 8.0 Hz, 1H), 3.76-3.72 (m, 2H), 3.66-3.63 (m, 2H), 2.52 (t, <i>J</i> = 7.2 Hz, 1H), 1.83-1.82 (m, 2H).
67	<b>LC-MS:</b> [M+H] <sup>+</sup> : 412.1 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.23 (dd, <i>J</i> = 8.0 Hz, 2.0 Hz, 1H), 7.10 (t, <i>J</i> = 8.0 Hz, 1H), 6.79 (dd, <i>J</i> = 8.0 Hz, 2.0 Hz, 1H), 4.06-4.04 (m, 2H), 3.96-3.95 (m, 2H), 3.43-3.39 (m, 1H), 2.33-2.27 (m, 1H), 2.07-2.02 (m, 2H), 1.96-1.92 (m, 1H), 1.74-1.68 (m, 1H), 1.52-1.49 (m, 1H).
58	<b>LC-MS:</b> [M+H] <sup>+</sup> : 398.1 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.22 (d, <i>J</i> = 8.0, 1H), 7.08 (t, <i>J</i> = 8.0 Hz, 1H), 6.76 (d, <i>J</i> = 8.0, 1H), 5.17-5.15 (m, 1H), 4.42 (t, <i>J</i> = 8.4 Hz, 1H), 4.09-4.05 (m, 1H), 3.36 (s, 3H), 3.31-3.27 (m, 1H), 3.18 (d, <i>J</i> = 12.0 Hz, 1H), 3.08-3.05 (m, 1H), 2.77-2.72 (m, 1H), 2.62-2.61 (m, 1H), 2.59-2.58 (m, 1H).
59	<b>LC-MS:</b> [M+H] <sup>+</sup> : 384.1 <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 7.22 (d, <i>J</i> = 8.0 Hz, 1H), 7.10 (t, <i>J</i> = 8.0 Hz, 1H), 6.79 (d, <i>J</i> = 8.0 Hz, 1H), 4.94-4.91 (m, 1H), 4.17 (t, <i>J</i> = 8.8 Hz, 1H), 3.71-3.68 (m, 1H), 3.45 (d, <i>J</i> = 12.8 Hz, 1H), 3.15-3.11 (m, 2H), 2.74-2.70 (m, 1H), 2.58-2.54 (m, 1H).

**Example 7:**

Preparation of N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-4-hydroxy-1,5,5-trimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxamide





Step 1: preparation of tert-butyl ((1-(3-(benzyloxy)-5-((2-chloro-3-(4-hydroxy-1,5,5-trimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxamido)phenyl)thio)pyrazin-2-yl)-4-methylpiperidin-4-yl)methyl)carbamate (**3**)

To a mixture of compound **1** (80 mg, 1.0 eq) in bromobenzene (5 mL) was added compound **2** (107 mg, 0.5 eq) at r.t. and the mixture was degassed and protected with nitrogen. The reaction was stirred at 160 °C for 3 h. Solvent was removed to give crude compound **3** as an oil (140 mg, 100%).

Step 2: preparation of N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-4-hydroxy-1,5,5-trimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxamide

To a solution of compound **3** (140 mg, 1.0 eq) in DCM (3 mL) was added BCl<sub>3</sub> (1.9 mL, 1.0 mol/L in DCM, 10.0 eq) at room temperature. The mixture was stirred at r.t. for 1 h. The mixture was quenched by MeOH (3 mL) followed by standard work up process. Desired compound was obtained after prep-HPLC as a slightly red solid (25 mg, 12%). **LC-MS**: [M+H]<sup>+</sup> = 547. **<sup>1</sup>H NMR** (400 MHz, DMSO)  $\delta$  11.37 (br s, 1 H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.30 (s, 1H), 7.18 (s, 1H), 7.09 (s, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 4.24-4.21 (m, 2H), 3.55-3.48 (m, 2H), 2.74 (s, 3H), 2.65 (s, 2H), 1.55-1.50 (m, 2H), 1.38-1.33 (m, 2H), 1.12 (s, 6H), 1.02 (s, 3H).

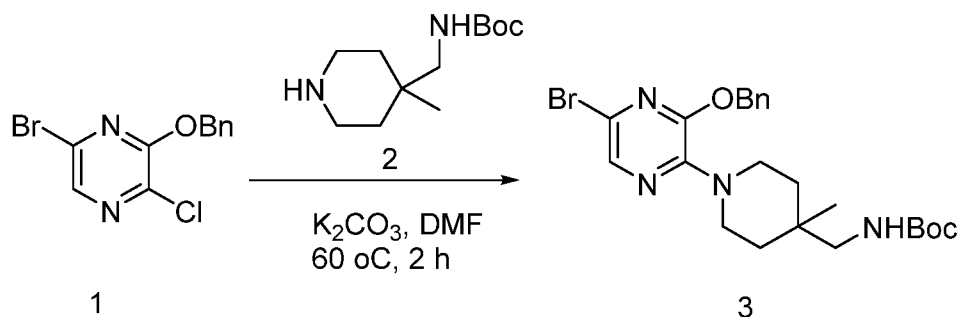
The compounds in Table D below were synthesized by similar manners using appropriate reagents and conditions. The compounds listed in Table D are merely non-limiting examples. Other subject compounds could also be made using similar methods.

**Table D**

Compound ID	<sup>1</sup> H-NMR & MS [M+1] <sup>+</sup>
31	<b>LC-MS:</b> [M+H] <sup>+</sup> : 574 <sup>1</sup> H NMR (400 MHz, DMSO) δ 13.28 (br s, 1 H), 8.42 (d, <i>J</i> = 7.6 Hz, 1H), 8.16 (s, 1H), 7.68 (d, <i>J</i> = 4.4 Hz, 1H), 7.21-7.17 (m, 2H), 7.01-6.98 (m, 1H), 6.54 (d, <i>J</i> = 8.0 Hz, 1H), 4.27-4.21 (m, 2H), 3.59-3.50 (m, 2H), 2.79 (s, 2H), 1.58-1.54 (m, 2H), 1.43-1.40 (m, 2H), 1.07 (s, 3H).
29	<b>LC-MS:</b> [M+H] <sup>+</sup> : 568.3 <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 12.15 (brs, 1H), 9.06 (d, <i>J</i> = 6.4 Hz, 1H), 8.30-8.17 (m, 1H), 7.72 (brs, 1H), 7.58 (brs, 2H), 7.46 (t, <i>J</i> = 6.4 Hz, 1H), 7.34 (brs, 2H), 7.22 (s, 1H), 6.76 (brs, 1H), 4.30-4.24 (m, 2H), 3.57-3.51 (m, 2H), 2.81-2.75 (m, 2H), 1.59-1.51 (m, 2H), 1.43-1.40 (m, 2H), 1.07 (s, 3H).
32	<b>LC-MS:</b> [M+H] <sup>+</sup> : 557 <sup>1</sup> H NMR (400 MHz, DMSO) δ 12.74 (br s, 1 H), 8.42-8.35 (m, 1H), 8.20 (s, 1H), 7.34 (s, 1H), 7.21 (s, 2H), 6.97-6.92 (m, 1H), 6.61-6.57 (m, 1H), 4.28-4.21 (m, 2H), 3.58-3.48 (m, 2H), 2.75 (s, 2H), 1.58-1.52 (m, 2H), 1.42-1.36 (m, 2H), 1.06 (s, 3H).
30	<b>LC-MS:</b> [M+H] <sup>+</sup> : 568.3 <sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 12.15 (brs, 1H), 9.06 (d, <i>J</i> = 6.4 Hz, 1H), 8.30-8.17 (m, 1H), 7.72 (brs, 1H), 7.58 (brs, 2H), 7.46 (t, <i>J</i> = 6.4 Hz, 1H), 7.34 (brs, 2H), 7.22 (s, 1H), 6.76 (brs, 1H), 4.30-4.24 (m, 2H), 3.57-3.51 (m, 2H), 2.81-2.75 (m, 2H), 1.59-1.51 (m, 2H), 1.43-1.40 (m, 2H), 1.07 (s, 3H).
33	<b>LC-MS:</b> [M+H] <sup>+</sup> : 572.2 <sup>1</sup> H NMR (400 MHz, MeOD) δ 8.31 (s, 1H), 7.25 (s, 2H), 6.81 (s, 1H), 4.39 (d, <i>J</i> = 13.3 Hz, 2H), 3.99 (s, 2H), 3.76-3.43 (m, 2H), 2.96-2.87 (m, 4H), 2.01-1.92 (m, 4H), 1.76-1.37 (m, 4H), 1.18 (s, 3H).

**Example 8:**

Preparation of intermediate tert-butyl ((1-(3-(benzyloxy)-5-bromopyrazin-2-yl)-4-methylpiperidin-4-yl)methyl)carbamate

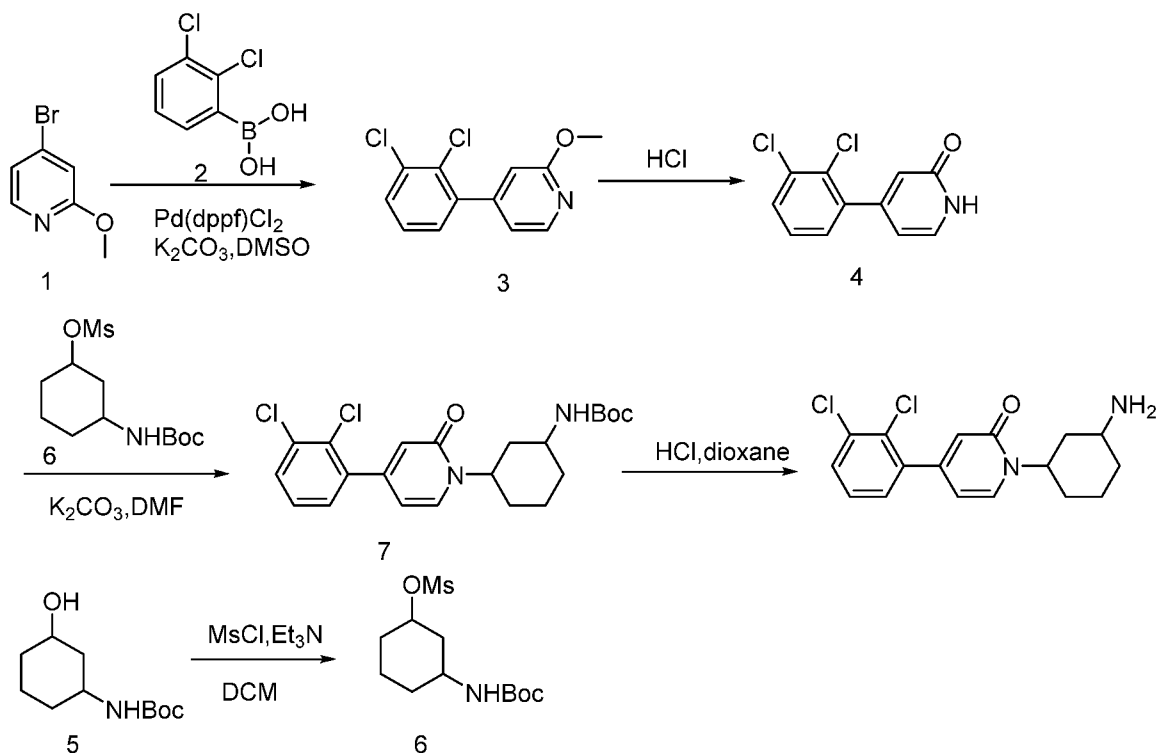


To a solution of compound **1** (320 mg, 1.0 eq) in DMF (5 mL) was added compound **2** (292 mg, 1.2 eq) and K<sub>2</sub>CO<sub>3</sub> (441 mg, 3.0 eq) at rt. The reaction mixture was stirred at 60 °C under Ar atmosphere for 2 hours before it was quenched by water. The desired compound was obtained after

standard work up process as a white solid (140 mg, 26%).

### Example 9:

Preparation of 1-(3-aminocyclohexyl)-4-(2,3-dichlorophenyl)pyridin-2(1H)-one



#### 5 Step 1: Preparation of 4-(2,3-dichlorophenyl)-2-methoxypyridine (**3**)

To a solution of compound **1** (2.0g, 1eq) in DMSO were added compound **2** (1 g, 1eq),  $\text{PdCl}_2(\text{dppf})$  (0.77 g, 0.1eq) and  $\text{K}_2\text{CO}_3$  (2.9g, 2eq). The mixture was stirred at 95 °C overnight. The reaction was quenched by water, and worked up under standard procedure. The residue was purified by flash column chromatography to give the title compound (2.1 g, yield: 78.9%).

#### 10 Step 2: Preparation of 4-(2,3-dichlorophenyl)pyridin-2(1H)-one (**4**)

The mixture of compound **3** (1.0g, 1eq) in conc. HCl (20 mL) was stirred at 150 °C overnight. Ice-water was added into the mixture and pH was adjusted to 7. After standard work up procedure, title compound (0.94 g, yield: 100%) was obtained.

#### Step 3: Preparation of 3-((tert-butoxycarbonyl)amino)cyclohexyl methanesulfonate (**6**)

15 To a solution of compound **5** (1.0g, 1.0 eq),  $\text{Et}_3\text{N}$  (1 ml, 1.5 eq) in DCM (20 mL) was added  $\text{MsCl}$ . The mixture was quenched with water (30 mL) 2 hours later. After standard work up procedure, the

residue was purified by flash column chromatography to give the title compound (1.0 g, yield: 73.5%).

Step 4: Preparation of tert-butyl (3-(4-(2,3-dichlorophenyl)-2-oxopyridin-1(2H)-yl)cyclohexyl)carbamate (**7**)

To a solution of compound **4** (1.0 g, 1.0 eq) in DMF (10 mL) was added K<sub>2</sub>CO<sub>3</sub> (1.7 g, 3.0eq) and compound **6** (1.7 g, 1.2eq), and the mixture was stirred at 110 °C overnight. The reaction was quenched with water (30 mL), followed by standard work up procedure. The residue was purified by flash column chromatography to give the title compound (170 mg, yield: 9.34%).

Step 5: Synthesis of 1-(3-aminocyclohexyl)-4-(2,3-dichlorophenyl)pyridin-2(1H)-one

The solution of compound **7** (170 mg, 1.0 eq) in 4M HCl/dioxane(5mL) was stirred at room temperature for 30 min. NaOH solution was added to the mixture at 0 °C, and the mixture was extracted with EA (3 x 30 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The final compound was obtained after Pre-HPLC as HCOOH salt (100mg, yield: 76.3%). **LC-MS:** [M+H]<sup>+</sup> = 338.2. **<sup>1</sup>H NMR** (400 MHz, CD<sub>3</sub>OD) δ 8.22-8.21 (d, *J* = 4.8 Hz 1H), 7.63-7.61(d, *J* = 7.6 Hz, 1H), 7.4- (m, 1H), 7.33-7.31 (m, 2H), 6.85(s, 1H), 5.54(s, 1H), 3.53 (m, 1H), 2.48-2.44 (d, *J* = 13.2 Hz, 1H), 2.082-2.01(m, 2H), 1.79 (m, 3H), 1.66 (m 3H).

### Pharmacological Testing

Some of the compounds disclosed herein were assessed for their ability to selectively inhibit SHP2 activity. The inhibitory properties of the compounds described herein can be evidenced by testing in the following assays.

#### SHP2 Phosphatase Assays

IC<sub>50</sub> values were determined at room temperature in 384-well black polystyrene plate, using a final reaction volume of 15 μL and the following assay buffer conditions: 60 mM Hepes (pH = 7.2), 75 mM NaCl, 75 mM KCl, and 1 mM EDTA, 0.05% P-20, 5 mM dithiothreitol (DTT). Full length SHP2 enzyme (diluted to 0.1 nM in reaction buffer) were co-incubated with 1 uM IRS-1 peptide and 0.01 nM to 10 μM compounds of the disclosure for 60 min. The surrogate substrate DiFMUP (5 μL, 100 μM) was added, and incubated at rt for 60 min. The reaction was then quenched by the addition of 5 μL of a 40 μM solution of bpV(Phen). The fluorescence signal was monitored using a microplate reader (Envision, Perkin-Elmer) using excitation and emission wavelengths of 360 nm and 450 nm,

respectively. The inhibitor dose–response curves were analyzed using normalized IC<sub>50</sub> regression curve fitting with control-based normalization. The inhibitory activity results of the compounds of the disclosure is shown in **Table 2**.

**Table 2.** IC<sub>50</sub>: +++: ≤ 50 nM; ++: ≤ 100 nM; +: ≤ 1 μM;

Compound ID	IC <sub>50</sub>
2	+++
35	+++
52	+++
34	+++
77	+++
31	+++
29	+++
32	+++
28	+++
30	+++
14	+++
73	+++
74	+++
33	+++
79	+++
80	+++
81	+++
84	+++
107	+++
109	+++
82	+++
83	+++
13	+++
86	+++
108	+++
87	+++
88	+++
73	+++

#### 5 p-ERK/total ERK Cellular Assay

Cells were seeded in 384-well cell culture plate and incubated overnight. Test compounds were added to the cell plate and the plate was incubated for 2-6 hours. To detect p-ERK, the cell plate

was used AlphaLISA SureFire Ultra p-ERK kit; to detect total ERK, the cell plate was used total ERK HTRF kit. The plate was read on the Envision. The inhibitory activity results of the compounds of the disclosure is shown in **Table 3**.

**Table 3.** IC<sub>50</sub>: +++: ≤ 0.1 μM; ++: ≤ 0.5 μM; +: ≤ 1 μM;

Compound ID	IC <sub>50</sub>
2	++
35	++
34	++
10	+++
31	+++
29	+++
30	+++
14	+++
73	+++
33	+++
79	+++
80	+++
81	+++
84	+++
109	+++
82	+++
83	+++

## 5 Cell Proliferation Assay

Firstly, the cells were seeded in 384-well cell culture plate and incubate overnight. The test compounds were added to the cell plate and incubated for 3-5 days. The cell plate was then detected using CellTiter Glo reagents. The inhibitory activity results of the compounds of the disclosure is shown in **Table 4**.

10 **Table 4.** IC<sub>50</sub>: +++: ≤ 1 μM; ++: ≤ 5 μM; +: ≤ 10 μM

Compound ID	IC <sub>50</sub>
2	++
10	++
31	++
29	++
14	+++

Compound ID	IC <sub>50</sub>
73	++
81	+++
84	+++
109	++
82	++
83	+++

### **KYSE-520 Xenograft Model**

KYSE-520 cells were expanded in culture, harvested and injected subcutaneously into 6-8 weeks old female BALB/c nude mice (5 x 10<sup>6</sup> cell/each mouse, supplemented with Matrigel (1:1) for tumor development, n = 9 per group). Subsequent administration of a compound by oral gavage started when the mean tumor size reached approximately 150-200 mm<sup>3</sup>. During the treatment (once a day for 4 weeks), the tumor volumes were measured using a caliper. Statistical analysis of difference in tumor volume among the groups were evaluated using a one-way ANOVA. Vehicle alone was the negative control.

Many of the compounds described herein is very potent and selective, with enzymatic IC<sub>50</sub> less than 10 nM. The compounds tested also displayed superior anti-tumor activities in the *in vivo* animal models. In some embodiments, the dose amount per day falls within the range of 3-100 mg/kg to achieve the tumor regression or >80% tumor growth inhibition.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and etc. used in herein are to be understood as being modified in all instances by the term "about." Each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Accordingly, unless indicated to the contrary, the numerical parameters may be modified according to the desired properties sought to be achieved, and should, therefore, be considered as part of the disclosure. At the very least, the examples shown herein are for illustration only, not as an attempt to limit the scope of the disclosure.

The terms "a," "an," "the" and similar referents used in the context of describing embodiments of the present disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly

contradicted by context. All methods described herein may be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illustrate embodiments of the present disclosure and does not pose a limitation on the scope of any  
5 claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the embodiments of the present disclosure.

Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated  
10 that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability.

Certain embodiments are described herein, including the best mode known to the inventors for carrying out the embodiments. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The  
15 inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the embodiments of the present disclosure to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated  
20 herein or otherwise clearly contradicted by context.

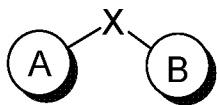
In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments  
25 precisely as shown and described.



## CLAIMS

**What Is Claimed Is:**

1. A compound represented by a formula:



- 5 or a pharmaceutically acceptable salt thereof;

wherein X is S, O, NR<sup>A</sup>, CHR<sup>A</sup>, SO, SO<sub>2</sub>, CO, or a bond;

Ring A is an optionally substituted aryl, heteroaryl, or bicyclic ring system;

- Ring B is an optionally substituted heterocyclic ring system, comprising a mono-cyclic ring, a bicyclic ring system, a tricyclic ring system, or a tetracyclic ring system, wherein the heterocyclic ring system contains heteroaryl and at least 2 ring nitrogen atoms; and

R<sup>A</sup> is H or C<sub>1-6</sub> hydrocarbyl.

2. The compound of claim 1, wherein Ring A is optionally substituted phenyl.
3. The compound of claim 1, wherein Ring A is optionally substituted naphthalen-1-yl.
4. The compound of claim 1, wherein Ring A is optionally substituted pyridin-3-yl.
- 15 5. The compound of claim 1, wherein Ring A is optionally substituted pyridin-4-yl.
6. The compound of claim 1, wherein Ring A is optionally substituted 2-oxo-1,2-dihydropyridin-4-yl.
7. The compound of claim 1, wherein Ring A is optionally substituted 1*H*-indol-4-yl.
8. The compound of claim 1, wherein Ring A is optionally substituted 2-oxoindolin-4-yl.
- 20 9. The compound of claim 1, wherein Ring A is optionally substituted indolin-4-yl.
10. The compound of claim 1, wherein Ring A is optionally substituted 3-(2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxamido)phenyl.
11. The compound of claim 1, wherein Ring A is optionally substituted 3-(4-oxo-4*H*-pyrido[1,2- $\alpha$ ]pyrimidine-3-carboxamido)phenyl.
- 25 12. The compound of claim 1, wherein Ring A is optionally substituted 3-(4-oxo-4*H*-pyrazino[1,2- $\alpha$ ]pyrimidine-3-carboxamido)phenyl.
13. The compound of claim 1, wherein Ring A is optionally substituted 3-(5-oxo-5*H*-thiazolo[3,2- $\alpha$ ]pyrimidine-6-carboxamido)phenyl.

14. The compound of claim 1, wherein Ring A is optionally substituted 3-(5-oxo-1,5-dihydroimidazo[1,2- $\alpha$ ]pyrimidine-6-carboxamido)phenyl.
15. The compound of claim 1, wherein Ring A is optionally substituted 3-(4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2- $\alpha$ ]pyrimidine-3-carboxamido)phenyl.
- 5 16. The compound of claim 1, wherein Ring A is optionally substituted 2,3-dichlorophenyl.
17. The compound of claim 1, wherein Ring A is optionally substituted 2,3-dichloro-pyridin-4-yl.
18. The compound of claim 1, wherein Ring A is optionally substituted 2-amino-3-chloropyridin-4-yl
19. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring A is unsubstituted.
- 10 20. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring A has a Cl substituent.
21. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring A has two Cl substituents.
22. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring  
15 A has a CF<sub>3</sub> substituent.
23. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring A has an NH<sub>2</sub> substituent.
24. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring A has a -OCH<sub>3</sub> substituent.
- 20 25. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring A has an F substituent.
26. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring A has an acetyl substituent.
27. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring  
25 A has a CH<sub>3</sub> substituent.
28. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring A has an OH substituent.

29. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18, wherein Ring A has multiple substituents with any combination of the substituent of claim 20, 21, 22, 23, 24, 25, 26, 27, or 28, at any positions that are chemically permissible.

30. The compound of claim 1, wherein Ring A is any one of the following: phenyl, 2,3-dichlorophenyl, naphthalen-1-yl, 2-(trifluoromethyl)phenyl, 2-(trifluoromethyl)pyridin-3-yl, 5-amino-2-chlorophenyl, 5-amino-2-chloropyridin-3-yl, 3-amino-2-chlorophenyl, 2-amino-3-chloropyridin-4-yl, 2-chloro-3-methoxyphenyl, 3-chloro-2-methoxypyridin-4-yl, 3-fluoro-1H-indol-4-yl, 3,3-difluoro-2-oxoindolin-4-yl, 1-acetyl-3,3-difluoroindolin-4-yl, 2-chloro-3-(4-hydroxy-1,5,5-trimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxamido)phenyl, 2-chloro-3-(2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamido)phenyl, 2-chloro-3-(2-hydroxy-4-oxo-4H-pyrazino[1,2-a]pyrimidine-3-carboxamido)phenyl, 2-chloro-3-(7-hydroxy-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carboxamido)phenyl, 2-chloro-3-(7-hydroxy-5-oxo-1,5-dihydroimidazo[1,2-a]pyrimidine-6-carboxamido)phenyl, 2-chloro-3-(2-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-3-carboxamido)phenyl, 2,3-dichloropyridin-4-yl, 2,3-difluorophenyl, 3-chloro-2-fluoropyridin-4-yl, 2,3-difluoropyridin-4-yl, 2-chloro-3-methylphenyl, 3-chloro-2-methylpyridin-4-yl, 3,3-difluoro-1-methyl-2-oxoindolin-4-yl, 3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl, or 2-chloro-3-fluorophenyl.

31. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-5-(piperidin-1-yl)-1,6-dihydropyrazin-2-yl.

32. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-5-(pyrrolidin-1-yl)-1,6-dihydropyrazin-2-yl.

33. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrazin-2-yl.

34. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrazin-2-yl.

35. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-5-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1,6-dihydropyrazin-2-yl.

36. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-5-(piperidin-4-ylamino)-1,6-dihydropyrazin-2-yl.

37. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-5-(spiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-1,6-dihydropyrazin-2-yl.

38. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-5-(8-azaspiro[4.5]decan-8-yl)-1,6-dihydropyrazin-2-yl.

39. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 4-oxo-6-(piperidin-1-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl.

40. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 4-oxo-6-(pyrrolidin-1-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl.

41. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 4-oxo-2-(piperidin-1-yl)-3,4-dihydroquinazolin-5-yl.

42. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 4-oxo-2-(piperidin-1-yl)-3,4-dihydropyrido[3,4-d]pyrimidin-5-yl.

43. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 7-oxo-2-(piperidin-1-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-5-yl.

44. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-(piperidin-1-yl)-1H-pyrazolo[4,3-d]thiazol-3-yl.

45. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 7-oxo-6-(piperidin-4-yl)-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-3-yl.

46. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-8-(piperidin-1-yl)-6,7-dihydro-1H-purin-2-yl.

47. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 8-(piperidin-1-yl)-7H-purin-2-yl.

48. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-2-(pyrrolidin-1-yl)-1,6-dihydropyrimidin-5-yl.

49. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-2-(piperidin-1-yl)-1,6-dihydropyrimidin-5-yl.

50. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-2-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1,6-dihydropyrimidin-5-yl.

51. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 2-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrimidin-5-yl.

52. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrimidin-5-yl.

53. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 2-(3-azabicyclo[3.2.0]heptan-3-yl)-6-oxo-1,6-dihydropyrimidin-5-yl.

54. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-2-(2-azaspiro[3.4]octan-2-yl)-1,6-dihydropyrimidin-5-yl.

55. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 2-(3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-dihydropyrimidin-5-yl.

56. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-2-(2-azaspiro[3.4]octan-2-yl)-1,6-dihydropyrimidin-5-yl.

57. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-oxo-6-(2-oxa-8-azaspiro[4.5]decan-8-yl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl.

58. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-oxo-6-(piperidin-1-yl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl.

59. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-(piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl.

60. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-5-(2-azaspiro[3.4]octan-2-yl)-1,6-dihydropyrazin-2-yl.

61. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 1-cyclohexyl-2-oxo-1,2-dihydropyridin-4-yl.

62. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-(3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-dihydropyrazin-2-yl.

63. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-5-(3H-spiro[benzofuran-2,4'-piperidin]-1'-yl)-1,6-dihydropyrazin-2-yl.

64. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 4-oxo-2-(2-oxa-8-azaspiro[4.5]decan-8-yl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl.

65. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-(5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl.

66. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-(1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl.

67. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-(4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl.

68. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 6-oxo-5-(spiro[indoline-2,4'-piperidin]-1'-yl)-1,6-dihydropyrazin-2-yl.

69. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is optionally substituted 5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl.

70. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B is unsubstituted.

71. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has a -CH<sub>3</sub> substituent.

72. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has an -CH<sub>2</sub>NH<sub>2</sub> substituent.

5 73. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has an -NH<sub>2</sub> substituent.

74. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,  
10 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has a -CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> substituent.

75. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,  
24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50,  
15 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has a 1-aminopropan-2-yl substituent.

76. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,  
24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50,  
51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has a -CN  
20 substituent.

77. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,  
24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50,  
51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has an -F  
substituent.

25 78. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,  
24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50,  
51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has a -Cl  
substituent.



79. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has a  $-CH_2F$  substituent.

5 80. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has an  $-OH$  substituent.

81. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 10 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has an  $-OCH_3$  substituent.

82. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 15 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69, wherein Ring B has multiple substituents with any combination of the substituent of claim 72, 73, 74, 75, 76, 77, 78, 79, 80, or 81, at any positions that are chemically permissible.

83. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, wherein Ring B is any one of the following: 5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (S)-5-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 6-oxo-5-(piperidin-4-ylamino)-1,6-dihydropyrazin-2-yl, 5-(2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-((1R,3R)-1-amino-3-methyl-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl)amino, 6-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl, 7-amino-2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-4-oxo-3,4-dihydroquinazolin-5-yl, 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-4-oxo-3,4-

dihydropyrido[3,4-d]pyrimidin-5-yl, 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-7-oxo-7,8-  
 dihydropyrido[2,3-d]pyrimidin-5-yl, 5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-1H-pyrazolo[4,3-  
 d]thiazol-3-yl, 6-(1-(1-aminopropan-2-yl)piperidin-4-yl)-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-  
 d]pyrimidin-3-yl, 8-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-6,7-dihydro-1H-purin-2-yl, 6-  
 5 amino-8-(4-(aminomethyl)-4-methylpiperidin-1-yl)-7H-purin-2-yl, 4-amino-2-(3-(aminomethyl)-3-  
 methylpyrrolidin-1-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-  
 4-cyano-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl, 4-amino-2-(4-amino-2-oxa-8-  
 azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, 4-amino-2-(3,6-  
 diazabicyclo[3.2.0]heptan-6-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, 4-amino-2-(hexahydropyrrolo[3,4-  
 10 c]pyrrol-2(1H)-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, 4-amino-2-(4-(aminomethyl)-4-methylpiperidin-  
 1-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, 4-amino-2-(6-amino-3-azabicyclo[3.2.0]heptan-3-yl)-6-oxo-  
 1,6-dihydropyrimidin-5-yl, 4-amino-2-(6-amino-2-azaspiro[3.4]octan-2-yl)-1-methyl-6-oxo-1,6-  
 dihydropyrimidin-5-yl, 4-amino-2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-  
 dihydropyrimidin-5-yl, 4-amino-2-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-oxo-1,6-dihydropyrimidin-  
 15 5-yl, 5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl, 5-(4-  
 amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (S)-5-(4-amino-2-oxa-8-  
 azaspiro[4.5]decan-8-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl, 5-(2-  
 aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl, 5-  
 ((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-  
 20 ((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl,  
 5-((1R,3R)-1-amino-3-methyl-8-azaspiro[4.5]decan-8-yl)-1-methyl-6-oxo-1,6-dihydropyrazin-2-yl, 5-  
 (4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 6-(4-(aminomethyl)-4-  
 methylpiperidin-1-yl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl, 6-(4-(aminomethyl)-4-  
 methylpiperidin-1-yl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl, 6-(4-  
 25 (aminomethyl)-4-methylpiperidin-1-yl)-5-oxo-4,5-dihydro-1H-pyrazolo[3,4-b]pyrazin-3-yl, 6-(3-  
 (aminomethyl)-3-methylpyrrolidin-1-yl)-5-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-  
 yl, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-  
 d]pyrimidin-3-yl, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl, 4-  
 amino-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl, 4-

amino-2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrimidin-5-yl, 4-amino-2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl, 4-amino-2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl, 4-amino-2-(6-amino-3-azabicyclo[3.2.0]heptan-3-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-5-yl, 5-(4-(aminomethyl)-4-fluoropiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-(4-(aminomethyl)-4-hydroxypiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (R)-5-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (S)-5-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 1-(3-aminocyclohexyl)-2-oxo-1,2-dihydropyridin-4-yl, (R)-5-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-(4-amino-4-(fluoromethyl)piperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (R)-5-(1-amino-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (R)-5-(3-amino-3H-spiro[benzofuran-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl, 2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl, (R)-5-(1-amino-3,3-difluoro-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl, 5-((1R)-1-amino-3-fluoro-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (S)-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (S)-5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (S)-5-(4-amino-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, (R)-5-(3-aminospiro[indoline-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl, or (S)-5-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-oxo-1,6-dihydropyrazin-2-yl.

84. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, or 83, wherein X is S.

85. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, or 83, wherein X is a bond.
- 5 86. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, or 83, wherein X is O.
87. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,  
10 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, or 83, wherein X is NH.
88. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,  
24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50,  
15 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, or 83, wherein X is CH(CH<sub>3</sub>).
89. The compound of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,  
24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50,  
51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77,  
20 78, 79, 80, 81, 82, or 83, wherein X is CH<sub>2</sub>.
90. The compound of any preceding claim, wherein R<sup>A</sup> is H.
91. The compound of any preceding claim, wherein R<sup>A</sup> is CH<sub>3</sub>.
92. The compound of any preceding claim, or a pharmaceutically acceptable salt thereof, wherein the compound is optionally substituted at any position that is chemically permissible.
- 25 93. The compound of any one of the preceding claims, wherein the compound is an R-enantiomer.
94. The compound of any one of the preceding claims, wherein the compound is an S-enantiomer.
95. The compound of any one of the preceding claims, wherein the compound is deuterated.

96. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is any one of the following compounds that is optionally substituted: 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-(2,3-dichlorophenyl)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2,3-dichlorophenoxy)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2,3-dichlorophenyl)amino)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-(2,3-dichlorophenoxy)-1-methylpyrazin-2(1H)-one, 3-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 6-((2,3-dichlorophenyl)thio)-3-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrazin-2(1H)-one, 3-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 6-((2,3-dichlorophenyl)thio)-3-(piperidin-4-ylamino)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-(naphthalen-1-ylthio)pyrazin-2(1H)-one, 3-(2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one, 3-((1R,3R)-1-amino-3-methyl-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2-(trifluoromethyl)phenyl)thio)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2-(trifluoromethyl)pyridin-3-yl)thio)pyrazin-2(1H)-one, 6-((5-amino-2-chlorophenyl)thio)-3-(4-(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one, 6-((5-amino-2-chloropyridin-3-yl)thio)-3-(4-(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one, 6-((3-amino-2-chlorophenyl)thio)-3-(4-(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one, 6-((2-amino-3-chloropyridin-4-yl)thio)-3-(4-(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((2-chloro-3-methoxyphenyl)thio)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-fluoro-1H-indol-4-yl)thio)pyrazin-2(1H)-one, 4-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-3,3-difluoroindolin-2-one, 6-((1-acetyl-3,3-difluoroindolin-4-yl)thio)-3-(4-

(aminomethyl)-4-methylpiperidin-1-yl)pyrazin-2(1H)-one, N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-4-hydroxy-1,5,5-trimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxamide, N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamide, N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-2-hydroxy-4-oxo-4H-pyrazino[1,2-a]pyrimidine-3-carboxamide,

N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-7-hydroxy-5-oxo-5H-thiazolo[3,2-a]pyrimidine-6-carboxamide, N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-7-hydroxy-5-oxo-1,5-dihydroimidazo[1,2-a]pyrimidine-6-carboxamide, N-(3-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-2-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-3-carboxamide, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-((2,3-dichlorophenyl)amino)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenoxy)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-((2,3-dichlorophenyl)amino)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenoxy)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenoxy)-4-methyl-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenoxy)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorophenyl)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-((2,3-dichlorophenyl)thio)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one, 6-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-3-(2,3-dichlorophenoxy)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, 6-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-3-(2,3-dichlorophenoxy)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(1-(2,3-dichlorophenyl)ethyl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, 6-(4-(aminomethyl)-4-methylpiperidin-1-yl)-3-(2,3-dichlorobenzyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, 7-amino-2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-((2,3-

dichlorophenyl)thio)quinazolin-4(3H)-one, 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-((2,3-dichlorophenyl)thio)pyrido[3,4-d]pyrimidin-4(3H)-one, 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-((2,3-dichlorophenyl)thio)pyrido[2,3-d]pyrimidin-7(8H)-one, (1-(3-((2,3-dichlorophenyl)thio)-1H-pyrazolo[4,3-d]thiazol-5-yl)-4-methylpiperidin-4-yl)methanamine, 6-(1-(1-aminopropan-2-yl)piperidin-4-yl)-3-((2,3-dichlorophenyl)thio)-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(1-(1-aminopropan-2-yl)piperidin-4-yl)-3-((2,3-dichlorophenyl)thio)-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 6-amino-2-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidin-4(3H)-one, 6-amino-5-((2,3-dichlorophenyl)thio)-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-methylpyrimidin-4(3H)-one, 6-amino-2-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one, 2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(2,3-dichlorophenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carbonitrile, 6-amino-2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(2,3-dichlorophenoxy)pyrimidin-4(3H)-one, 6-amino-2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(2,3-dichlorophenoxy)-3-methylpyrimidin-4(3H)-one, 6-amino-2-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidin-4(3H)-one, 6-amino-2-(3,6-diazabicyclo[3.2.0]heptan-6-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one, 6-amino-5-((2,3-dichlorophenyl)thio)-2-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4(3H)-one, 6-amino-2-(4-(aminomethyl)-4-methylpiperidin-1-yl)-5-(2,3-dichlorophenoxy)pyrimidin-4(3H)-one, 6-amino-2-(6-amino-3-azabicyclo[3.2.0]heptan-3-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one, 6-amino-2-(6-amino-2-azaspiro[3.4]octan-2-yl)-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidin-4(3H)-one, 6-amino-2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidin-4(3H)-one, 6-amino-2-(6-amino-3-azabicyclo[3.2.0]heptan-3-yl)-5-((2,3-dichlorophenyl)thio)-3-methylpyrimidin-4(3H)-one, 6-amino-2-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one, 6-amino-2-(6-amino-2-azaspiro[3.4]octan-2-yl)-5-((2,3-dichlorophenyl)thio)pyrimidin-4(3H)-one, 6-(3-(aminomethyl)-3-methylpyrrolidin-1-yl)-3-((2,3-dichlorophenyl)amino)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, 3-(4-(aminomethyl)-4-fluoropiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-(4-(aminomethyl)-4-hydroxypiperidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, (R)-3-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-((2,3-

dichlorophenyl)thio)pyrazin-2(1H)-one, (S)-3-(6-amino-2-azaspiro[3.4]octan-2-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, (S)-3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 1-(3-aminocyclohexyl)-4-(2,3-dichlorophenyl)pyridin-2(1H)-one, (R)-3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 5 3-(4-amino-4-(fluoromethyl)piperidin-1-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 6-((2-amino-3-chloropyridin-4-yl)thio)-3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)pyrazin-2(1H)-one, (R)-3-(1-amino-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2-chloro-3-methoxyphenyl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichloropyridin-4-yl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-difluorophenyl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2(1H)-one, 4-((5-(4-(aminomethyl)-4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-3,3-difluoroindolin-2-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyridin-2(1H)-one, 3-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, (R)-3-(3-amino-3H-spiro[benzofuran-2,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, (S)-3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichloropyridin-4-yl)thio)pyrazin-2(1H)-one, 2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(2,3-dichlorophenoxy)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one, 2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-(2,3-dichlorophenoxy)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one, 6-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-((2,3-dichlorophenyl)amino)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one, 6-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-((2,3-dichlorophenyl)amino)-4-methyl-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one, 2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-((2,3-dichlorophenyl)amino)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one, 2-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-5-((2,3-dichlorophenyl)amino)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one, (R)-3-(1-amino-3,3-difluoro-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-((1R)-1-amino-3-fluoro-8-



azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2-chloro-3-methylphenyl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-2-methylpyridin-4-yl)thio)pyrazin-2(1H)-one, N-(3-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-2-chlorophenyl)-2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxamide, 4-((5-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-oxo-1,6-dihydropyrazin-2-yl)thio)-3,3-difluoro-1-methylindolin-2-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)thio)pyrazin-2(1H)-one, (S)-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, (S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2,3-dichloropyridin-4-yl)thio)pyrazin-2(1H)-one, (S)-3-(4-amino-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, (R)-3-(3-aminospiro[indoline-2,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, (S)-3-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((3-chloro-2-oxo-1,2-dihydropyridin-4-yl)thio)pyrazin-2(1H)-one, (S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazin-2(1H)-one, 3-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2-chloro-3-fluorophenyl)thio)pyrazin-2(1H)-one, (1-(3-((2,3-dichlorophenyl)thio)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpiperidin-4-yl)methanamine, 3-(4-amino-2-oxa-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one, 3-(2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one, 3-((1R,3R)-1-amino-3-methyl-8-azaspiro[4.5]decan-8-yl)-6-((2,3-dichlorophenyl)thio)-1-methylpyrazin-2(1H)-one, or 6-((3S,4S)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(2,3-dichlorophenoxy)-1,4-dihydro-5H-pyrazolo[3,4-b]pyrazin-5-one.

97. The compound of claim 1, wherein any substituent of the compound has a molecular weight of about 15 g/mol to about 200 g/mol.

98. A pharmaceutical composition comprising a compound of any preceding claims or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, diluent, or carrier.

99. A method of treating a mammal, including a human, having a disease, disorders, or condition associated with the aberrant activity of SHP2, including cancer and autoimmune disorders, comprising administering to a mammal in need thereof a therapeutically effective amount of the compound of any preceding claim.

100. A medicament comprising a composition comprising a therapeutically effective amount of the compound of any preceding claim.

101. A kit comprising a medicament of claim 100 and a label indicating that the medicament is for treating a disease, disorders, or condition associated with the aberrant activity of SHP2.