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Novel heterocyclic derivatives useful as SHP2 inhibitors

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(56) Related Art
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ABSTRACT

This invention relates to certain novel pyrazine derivatives (Formula I) as **SHP2** inhibitors which is shown as formula I, their synthesis and their use for treating a **SHP2** mediated disorder. More particularly, this invention is directed to fused heterocyclic group derivatives useful as inhibitors of **SHP2,** methods for producing such compounds and methods for treating a SHP2-mediated disorder.

THE DESCRIPTION

NOVEL HETEROCYCLIC DERIVATIVES USEFUL AS SHP2 INHIBITORS

The present application is a divisional of AU 2020267305, which is a divisional of AU 2018239542, which is the national phase entry of PCT/IB2018/051973, the entire disclosures of which are incorporated herein by cross-reference.

Technical Field

This invention relates to certain novel pyrazine derivatives (Formula I, II, III or IV) as SHP2 inhibitors which is shown as Formula I, II, III or IV, their synthesis and their use for treating a SHP2 mediated disorder. More particularly, this invention is directed to fused heterocyclic derivatives useful as inhibitors of SHP2, methods for producing such compounds and methods for treating a SHP2-mediated disorder.

Background Art

SHP2 (The Src Homolgy-2 phosphatease) is a non-receptor protein tyrosine phosphatase encoded by the PTPN11 gene that harbors a classical tyrosine phosphatase domain and two N-terminal Src homology 2 (SH2) domains and a C-terminal tail. The two SH2 domains control the subcellular localization and functional regulation of SHP2. In its inactive state, the N-terminal SH2 domain blocks the PTP domain and this autoinhibition is relieved by binding of the SH2 domains to specific phosphotyrosine sites on receptors or receptor-associated adaptor proteins. The stimulation, for example, by cytokines or growth factors leads to exposure of the catalytic site resulting in enzymatic activation of SHP2.

SHP2 is widely expressed and participated in multiple cell signaling processes, such as the Ras-Erk, PI3K-Akt, Jak-Stat, Met, FGFR, EGFR, and insulin receptors and NF-kB pathways, in which plays an important role in proliferation, differentiation, cell cycle maintenance and migration.

The hyperactivation of SHP2 catalytic activity caused by either germline or somatic mutations in PTPN11 have been identified in patients with Noonan syndrome, Leopard syndrome, juvenile myelomonocytic leukemias, myelodysplastic syndrome, B cell acute lymphoblastic leukemia/lymphoma, and acute myeloid leukemia. In addition, activating mutations of PTPN11 have been found in solid tumors as well, such as lung cancer, colon cancer, melanoma, neuroblastoma, and hepatocellular carcinoma. Therefore, the presence of activated or up-regulated SHP2 protein in human cancers and other disease make SHP2 an excellent target for development of novel therapies. The compounds of the present invention fulfill the need of small molecules in order to inhibit the activity of SHP2.

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It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

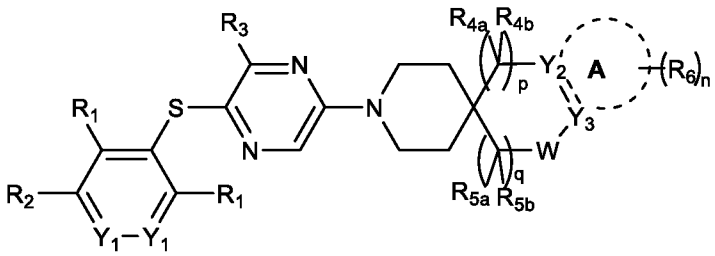
Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

Summary of Invention

The present invention relates to heterocyclic pyrazine compounds useful as SHP2 inhibitors and for the treatment of conditions mediated by SHP2.

In one aspect, the present invention provides a compound of Formula I or pharmaceutically acceptable salt thereof:



I

Wherein,

Each R_1 is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

R_2 is -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; $-N_3$; carboxyl; $-NHC_{1-6}$alkyl; $-N(C_{1-6}alkyl)_2$; $-CONH_2$; $-CONHC_{1-6}$alkyl; $-CON(C_{1-6}alkyl)_2$; $-COC_{1-6}$alkyl; $-NHCOC_{1-6}$alkyl; $-NC_{1-6}alkyl-CO-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{5-10}$heterocyclic; or

R_2 combines with R_1 to which is adjacent to form a 6-10 membered aryl, 5-10 membered heteroaryl or 5-10 membered heterocyclic ring, and each of the ring systems is independently optionally substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-CONH_2$, C_{1-6}alkoxy, C_{1-6}alkyl, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-COOH, $-C_{1-6}$alkylene-$NHCONH_2$, -CO-$N(C_{1-6}alky)_2$, $-C_{1-6}$alkylene-NHCO-C_{1-6}alkyl, -CO-CO-$N(C_{1-6}alkyl)_2$, -CO-C_{1-6}alkyl, $-SONH_2$, $-SO_2NH_2$, $-SOCH_3$, $-SO_2CH_3$, $-C_{5-10}$heterocyclic or $-C_{5-10}$heteroaryl;

Each Y_1 is independently N or CR_{1a};

Each R_{1a} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkoxy, or $-C_{1-6}$alkyl;

R_3 is -H or $-NH_2$;

Each of R_{4a} and R_{4b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form CO, C=NH, or C=N-OH;

p is 0, 1, 2 or 3;

Each of R_{5a} and R_{5b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-10 membered heterocyclic or 5-10 membered heteroaryl or $C=NR_{5c}$, and R_{5c} is -H, or $-C_{1-6}$alkyl; and each of the ring systems is independently optionally substituted with -H, -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkoxy, or $-C_{1-3}$alkyl;

q is 0, 1, 2, 3 or 4;

W is absent, -O, -S or $-NR_w$; and R_w is -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; -CO-C_{1-6}alkyl; -CO-OC_{1-6}alkyl; $-C_{1-6}$alkyl-O- C_{1-6}alkoxy; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-3}$alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with

-F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

Ring A is absent or a 3-10 membered ring;

=== represents a single bond or a double bond;

When ring A is absent, Y_2 is $CR_{2a}R_{2b}$, NR_{2a} or O, and Y_3 is $CR_{3a}R_{3b}$, NR_{3a} or O, and R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-membered heterocyclic ring;

When ring A is a 3-10 membered ring,

i) Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N, when === represents a single bond; or

ii) Y_2 is C, and Y_3 is C, when === represents a double bond;

Each of R_{2a} and R_{2b} is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy;

Each of R_{3a} and R_{3b} is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl or -C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy;

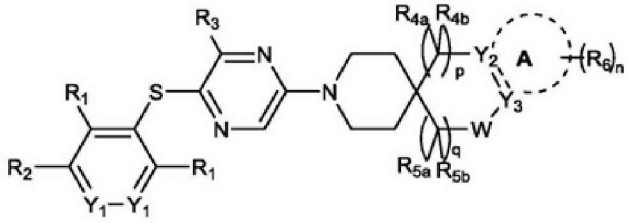
Each R_6 is independently -H, halogen, -$NR_{6a}R_{6b}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, -C_{1-6}alkoxy, -C_{1-6}alkyl, -C_{1-6}alkylene-$NR_{6a}R_{6b}$, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{1-6}alkylene-CO-OR_{6a}, -C_{1-6}alkylene-C_{3-10}heterocyclic, -C_{1-6}alkylene-C_{5-10}heteoaryl, -C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -C_{1-6}alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, -C_{1-6}alkylene-NR_{6a}-CO-C_{1-6}alkyl, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -C_{3-10}carbocyclic, -C_{3-10}heterocyclic, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-C_{3-10}heteocyclic, -O-C_{1-6}alkylene-CO-OR_{6a}, -O-C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -O-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -O-C_{3-10}carbocyclic, -O-C_{3-10}heterocyclic, -NR_{6a}-CO-C_{1-6}alkyl, -NR_{6a}-CO-$NR_{6a}R_{6b}$, -NR_{6a}-CO-C_{5-10}heteoaryl, -NR_{6a}-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -NR_{6a}-C_{1-6}alkylene-C_{3-10}heterocyclic, -NR_{6a}-C_{1-6}alkylene-C_{5-10}heteroaryl, -NR_{6a}-SO_2C_{1-6}alkyl, -S-C_{1-6}alkyl, -SO$NR_{6a}R_{6b}$, -$SO_2NR_{6a}R_{6b}$, -SO-C_{1-6}alkyl, -SO_2C_{1-6}alkyl, -PO(C_{1-6}alkyl)$_2$, -PO(C_{1-6}alkoxy)$_2$, -C_{3-10}heterocyclic or -C_{5-10}heteroaryl;

each of which is independently optionally substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -C_{1-3}alkoxy, or -C_{1-3}alkyl; and n is 0, 1, 2, 3, 4, 5 or 6; or

Two adjacent R_6 can be joined together to form a 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, -C_{3-6}heterocyclic or -C_{3-6}carbocyclic, wherein each of the ring systems is independently optionally substituted with halogen, -NH_2, -CN, -OH, -NO_2, =O, oxo, carboxyl, -$CONH_2$, -$PO(C_{1-6}alkyl)_2$, -C_{1-6}alkoxy or -C_{1-6}alkyl;

Each of R_{6a} and R_{6b} is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-3}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, -carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-3}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

The compounds of the invention have the general structure as Formula I or a pharmaceutically acceptable salt:



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Each R_1 is independently -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl;

R_2 is -H, halogen, -NH_2, -CN, -OH, -NO_2, -N_3, carboxyl, -NHC_{1-6}alkyl, -$N(C_{1-6}alkyl)_2$, -$CONH_2$, -$CONHC_{1-6}$alkyl, -$CON(C_{1-6}alkyl)_2$, -COC_{1-6}alkyl, -$NHCOC_{1-6}$alkyl, -NC_{1-6}alkyl-CO-C_{1-6}alkyl, substituted or unsubstituted -C_{1-6}alkoxy, substituted or unsubstituted -C_{1-6}alkyl or -C_{5-10}heterocyclic; or

R_2 combines with R_1 to which is adjacent to form a 6-10 membered aryl, 5-10 membered heteroaryl or 5-10 membered heterocyclic ring, and each of the ring systems is independently optionally substituted;

Each Y_1 is independently N or CR_{1a};

Each R_{1a} is independently -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl;

R_3 is -H or -NH_2;

Each of R_{4a} and R_{4b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form CO, C=NH, or C=N-OH;

p is 0, 1, 2 or 3;

Each of R_{5a} and R_{5b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-10 membered heterocyclic or 5-10 membered heteroaryl or $C=NR_{5c}$, and R_{5c} is -H, or $-C_{1-6}$alkyl; and each of the ring systems is independently optionally substituted;

q is 0, 1, 2, 3 or 4;

W is absent, -O, -S or -NR_w; and R_w is -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -CO-C_{1-6}alkyl, -CO-OC_{1-6}alkyl, -C_{1-6}alkyl-O- C_{1-6}alkoxy, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl;

Ring A is absent or a 3-10 membered ring;

=== represents a single bond or a double bond;

When ring A is absent, Y_2 is $CR_{2a}R_{2b}$, NR_{2a} or O, and Y_3 is $CR_{3a}R_{3b}$, NR_{3a} or O;

When ring A is a 3-10 membered ring,

i) Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N, when === represents a single bond; or

ii) Y_2 is C, and Y_3 is C, when === represents a double bond;

Each of R_{2a} and R_{2b} is independently -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl;

Each of R_{3a} and R_{3b} is independently -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl;

Each R_6 is independently -H, halogen, -$NR_{6a}R_{6b}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, -C_{1-6}alkoxy, -C_{1-6}alkyl, -C_{1-6}alkylene-$NR_{6a}R_{6b}$, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{1-6}alkylene-CO-OR_{6a}, -C_{1-6}alkylene-C_{3-10}heterocyclic, -C_{1-6}alkylene-C_{5-10}heteoaryl, -C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -C_{1-6}alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, -C_{1-6}alkylene-NR_{6a}-CO-C_{1-6}alkyl, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -C_{3-10}carbocyclic, -C_{3-10}heterocyclic, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-C_{3-10}heteocyclic, -O-C_{1-6}alkylene-CO-OR_{6a}, -O-C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -O-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -O-C_{3-10}carbocyclic, -O-C_{3-10}heterocyclic, -NR_{6a}-CO-C_{1-6}alkyl, -NR_{6a}-CO-$NR_{6a}R_{6b}$, -NR_{6a}-CO-C_{5-10}heteoaryl, -NR_{6a}-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -NR_{6a}-C_{1-6}alkylene-C_{3-10}heterocyclic, -NR_{6a}-C_{1-6}alkylene-C_{5-10}heteroaryl, -NR_{6a}-SO_2C_{1-6}alkyl, -S-C_{1-6}alkyl, -$SONR_{6a}R_{6b}$, -$SO_2NR_{6a}R_{6b}$, -SO-C_{1-6}alkyl, -SO_2C_{1-6}alkyl, -PO(C_{1-6}alkyl)$_2$, -PO(C_{1-6}alkoxy)$_2$, -C_{3-10}heterocyclic or -C_{5-10}heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6; or

Two adjacent R_6 can be joined together to form a 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, -C_{3-6}heterocyclic or -C_{3-6}carbocyclic, and each of the ring systems is independently optionally substituted;

Each of R_{6a} and R_{6b} is independently -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl.

The present invention further provides some preferred technical solutions with regard to compound of Formula I.

In some embodiments of Formula I:

Each R_1 is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted C_{1-6}alkyl;

R_2 is -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, $-N_3$, carboxyl, $-NHC_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, $-CONH_2$, $-CONHC_{1-6}$alkyl, $-CON(C_{1-6}alkyl)_2$, $-COC_{1-6}$alkyl, -NH-CO-C_{1-6}alkyl, $-NC_{1-6}$alkyl-CO-C_{1-6}alkyl, substituted or unsubstituted $-C_{1-6}$alkoxy, substituted or unsubstituted $-C_{1-6}$alkyl or $-C_{5-10}$heterocyclic; or

R_2 combines with R_1 to which is adjacent to form a 5-10 membered heteroaryl or 5-10 membered heterocyclic ring, and each of the ring systems is independently optionally substituted;

Each Y_1 is independently N or CR_{1a};

Each R_{1a} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl;

R_3 is -H or $-NH_2$;

Each of R_{4a} and R_{4b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form CO;

p is 0, 1, 2 or 3;

Each of R_{5a} and R_{5b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-10 membered heterocyclic or 5-10 membered heteroaryl; and each of the ring systems is independently optionally substituted;

q is 1, 2, 3 or 4;

W is absent, O, NR_w or S;

R_w is -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, -CO-C_{1-6}alkyl, -CO-OC_{1-6}alkyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl;

Ring A is absent or a 3-10 membered ring;

=== represents a single or double bond;

When ring A is absent, Y_2 is $-CR_{2a}R_{2b}$, $-NR_{2a}$ or -O, and Y_3 is $-CR_{3a}R_{3b}$, $-NR_{3a}$ or O;

When ring A is a 3-10 membered ring,

i) Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N, when === represents a single bond; or

ii) Y_2 is C, and Y_3 is C , when === represents a double bond;

Each of R_{2a} and R_{2b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl;

Each of R_{3a} and R_{3b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl;

Each R_6 is independently -H, halogen, $-NR_{6a}R_{6b}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{6a}, $-C_{1-6}$alkylene-C_{3-10}heterocyclic, $-C_{1-6}$alkylene-C_{5-10}heteoaryl, $-C_{1-6}$alkylene-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-C_{1-6}alkyl, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-C_{3-10}heteocyclic, -O-C_{1-6}alkylene-CO-OR_{6a}, -O-C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -O-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -O-C_{3-10}carbocyclic, $-NR_{6a}$-CO-C_{1-6}alkyl, $-NR_{6a}$-CO-$NR_{6a}R_{6b}$, $-NR_{6a}$-CO-C_{5-10}heteoaryl, $-NR_{6a}$-C_{1-6}alkylene-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-6}alkylene-C_{3-10}heterocyclic, $-NR_{6a}$-C_{1-6}alkylene-C_{5-10}heteroaryl, -S-C_{1-6}alkyl, $-SONR_{6a}R_{6b}$, $-SO_2NR_{6a}R_{6b}$, -SO-C_{1-6}alkyl, $-SO_2C_{1-6}$alkyl, $-PO(C_{1-6}alkyl)_2$, $-C_{3-10}$heterocyclic or $-C_{5-10}$heteroaryl, and each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6; or

Two adjacent R_6 can be joined together to form a 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, $-C_{3-6}$heterocyclic or $-C_{3-6}$carbocyclic, and each of the ring system is independently optionally substituted;

Each of R_{6a} and R_{6b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula I, each R_1 is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, each R_1 is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-3}$alkyl; $-C_{1-3}$alkoxy; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, each R_1 is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

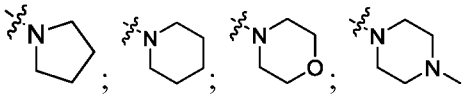
In some embodiments of Formula I, each R_1 is independently -H; -F; -Cl; -Br; -NH_2; -CN; -OH; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; or methyl substituted with one or more substituents each independently selected from -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, each R_1 is independently -Cl, or -H.

In some embodiments of Formula I, R_2 is -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; -N_3; carboxyl; -C_{1-6}alkyl; -C_{1-6}alkoxy; -NHC_{1-6}alkyl; -$N(C_{1-6}alkyl)_2$; -$CONH_2$; -$CONHC_{1-6}$alkyl; -$CON(C_{1-6}alkyl)_2$; -COC_{1-6}alkyl; -$NHCOC_{1-6}$alkyl; -$N(C_{1-6}alkyl)$-CO-C_{1-6}alkyl; -C_{5-10}heterocyclic; -C_{1-6}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

In some embodiments of Formula I, R_2 is -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; -N_3; carboxyl; -C_{1-3}alkyl; -C_{1-3}alkoxy; -NHC_{1-3}alkyl; -$N(C_{1-3}alkyl)_2$; -$CONH_2$; -$CONHC_{1-3}$alkyl; -$CON(C_{1-3}alkyl)_2$; -COC_{1-3}alkyl; -$NHCOC_{1-3}$alkyl; -$N(C_{1-3}alkyl)$-CO-C_{1-3}alkyl; -C_{5-10}heterocyclic; -C_{1-6}alkyl substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

In some embodiments of Formula I, R_2 is -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; -N_3; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; -$NHCH_3$; -$N(CH_3)_2$; -$CONH_2$; -$CONHCH_3$; -$CON(CH_3)_2$; -$COCH_3$; -NH-$COCH_3$; -$N(CH_3)$-$COCH_3$;



; -C_{1-3}alkyl substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, R_2 is -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; or methyl substituted with one or more substituents each independently selected from -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, R_2 is -NH_2.

In some embodiments of Formula I, R_2 combines with R_1 to which is adjacent to form a 5-10 membered heteroaryl or 5-10 membered heterocyclic ring, and each of the ring systems is independently optionally substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$CONH_2$, substituted or unsubstituted -C_{1-6}alkoxy, substituted or unsubstituted -C_{1-6}alkyl, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{1-6}alkylene-COOH, -C_{1-6}alkylene-$NHCONH_2$, -CO-$N(C_{1-6}alky)_2$,

-C_{1-6}alkylene-NHCO-C_{1-6}alkyl, -CO-CO-N(C_{1-6}alkyl)$_2$, -CO-C_{1-6}alkyl, -$SONH_2$, -SO_2NH_2, -$SOCH_3$, -SO_2CH_3, -C_{5-10}heterocyclic or -C_{5-10}heteroaryl.

In some embodiments of Formula I, R_2 combines with R_1 to which is adjacent to form a 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic or 9-membered heterocyclic; and each of the heteroaryl or heterocyclic contains 1 or 2 heteroatoms selected from N or O; and each of the ring systems is independently optionally substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$CONH_2$, substituted or unsubstituted C_{1-3}alkoxy, substituted or unsubstituted C_{1-3}alkyl, -C_{1-3}alkylene-O-C_{1-3}alkyl, -C_{1-3}alkylene-COOH, -C_{1-3}alkylene-$NHCONH_2$, -CO-N(C_{1-3}alky)$_2$, -C_{1-3}alkylene-NHCO-C_{1-3}alkyl, -CO-CO-N(C_{1-3}alkyl)$_2$, -CO-C_{1-3}alkyl, -$SONH_2$, -SO_2NH_2, -$SOCH_3$ or -SO_2CH_3.

In some embodiments of Formula I, R_2 combines with R_1 to which is adjacent to form a 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic or 8-membered heterocyclic; and each of the heteroaryl or heterocyclic contains 1 heteroatom selected from N or O; and each of the ring systems is independently optionally substituted with -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; oxo; =O; -$CONH_2$; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; -CH_2OCH_3; -CH_2COOH; -$CH_2NHCONH_2$; -$CON(CH_3)_2$; -$CH_2NHCOCH_3$; -CO-$CON(CH_3)_2$; -$COCH_3$; -C_{1-3}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2 or carboxyl; or -C_{1-3}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2 or carboxyl.

In some embodiments of Formula I, R_2 combines with R_1 to which is adjacent to form a 5-membered heterocyclic, and optionally substituted with -F or -$COCH_3$.

In some embodiments of Formula I, R_2 and R_1 which is adjacent to, together with the aromatic ring they are attached to form  .

In some embodiments of Formula I, each Y_1 is independently N or CH.

In some embodiments of Formula I, each of R_{4a} and R_{4b} is independently -H, -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl; or R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O, C=NH, or C=N-OH.

In some embodiments of Formula I, each of R_{4a} and R_{4b} is independently -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-3}alkyl; -C_{1-3}alkoxy; -C_{1-6}alkyl substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or C_{1-6}alkoxy substituted with -F,

-Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O.

In some embodiments of Formula I, each of R_{4a} or R_{4b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; C_{1-3}alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O.

In some embodiments of Formula I, each of R_{4a} and R_{4b} is independently -H, $-NH_2$, -OH, methyl, ethyl, methoxy, ethoxy; or R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O.

In some embodiments of Formula I, p is 0, 1, 2 or 3.

In some embodiments of Formula I, each of R_{5a} and R_{5b} is independently -H; -F; -Cl; -Br; -I; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-3}$alkyl; $-C_{1-3}$alkoxy; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; orR_{5a} and R_{5b} together with the carbon atom to which they are both attached form 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic, 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl or 9-membered heteroaryl; and each of the heterocyclic or heteroaryl contains 1 or 2 heteroatoms selected from N or O; and each of the ring systems is independently optionally substituted with -H, -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula I, each of R_{5a} or R_{5b} is independently -H, $-NH_2$, -OH, methyl, ethyl, methoxy or ethoxy; or R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 5-membered heteroaryl or 6-membered heteroaryl; and each of the heterocyclic or heteroaryl contains 1 heteroatoms selected from N or O.

In some embodiments of Formula I, each of R_{5a} or R_{5b} is independently -H or $-NH_2$.

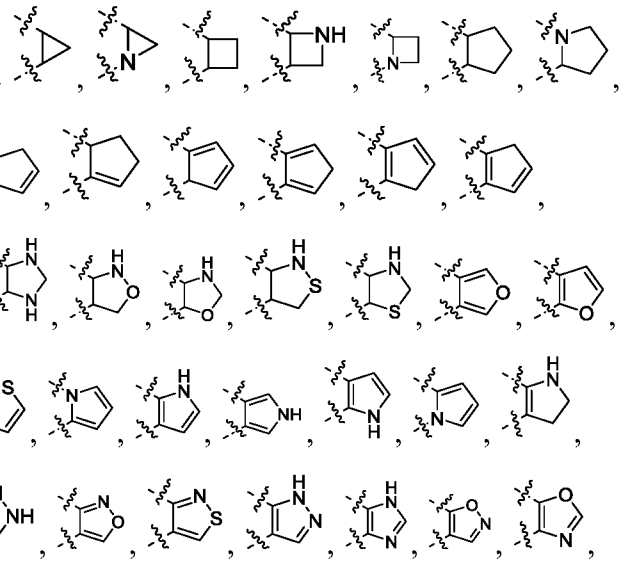
In some embodiments of Formula I, W is absent, O, or NR_w.

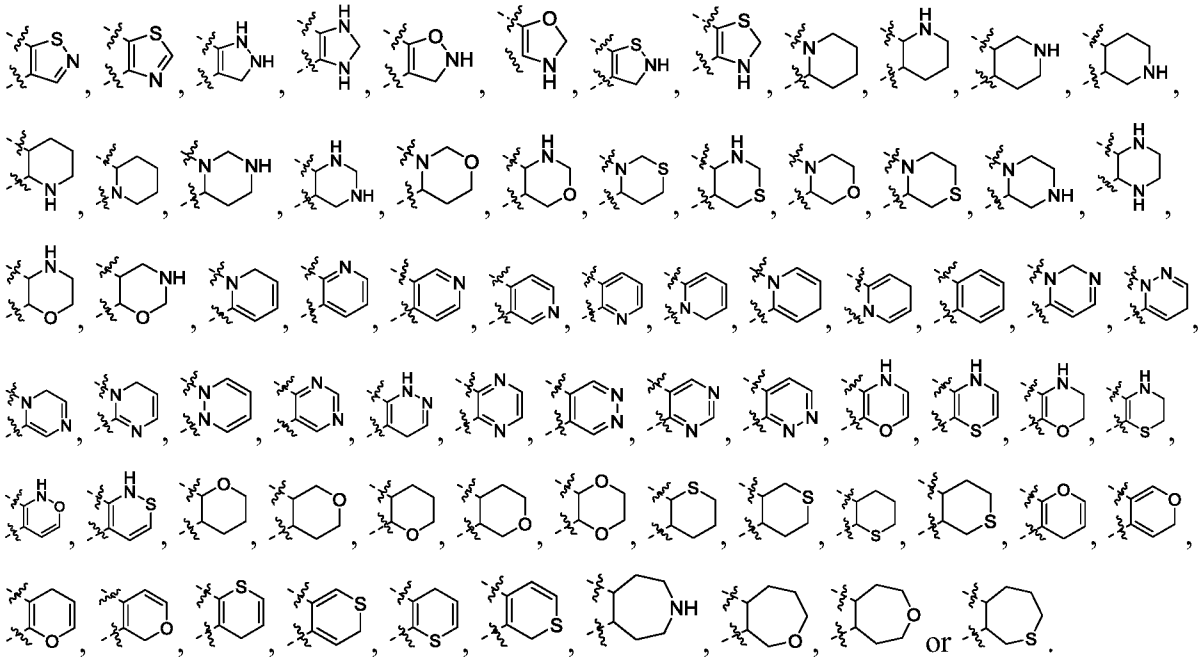
In some embodiments of Formula I, W is NRw, and R_w is -H, -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-CO-C_{1-3}$alkyl, $-COOC_{1-3}$alkyl, $-C_{1-3}$alkyl-$CO-C_{1-3}$alkyl, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

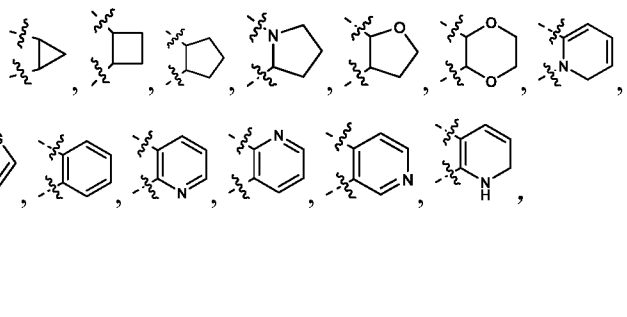
In some embodiments of Formula I, W is NRw, and R_w is -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; methyl-CO- methyl; -C_{1-3}alkyl substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

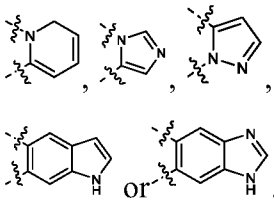
In some embodiments of Formula I, ring A is 6-membered aryl, 7-membered aryl, 8-membered aryl, 9-membered aryl, 10-membered aryl; 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl, 10-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic, 10-membered heterocyclic; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 7-membered carbocyclic, 8-membered carbocyclic, 9-membered carbocyclic or 10-membered carbocyclic; and each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic contains 1, 2 or 3 heteroatoms selected from N or O.

In some embodiments of Formula I, ring A is 6-membered aryl, 7-membered aryl, 8-membered aryl; 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 7-membered carbocyclic or 8-membered carbocyclic; and each of the heteroaryl contains 1 or 2 heteroatoms selected from N, O or S; each of the heterocyclic contains 1 or 2 heteroatoms selected from N or O.

In some embodiments of Formula I, ring A is 



In some embodiments of Formula I, ring A is 



In some embodiments of Formula I, Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N.

In some embodiments of Formula I, Y_2 is CR_{2a} and Y_3 is CR_{3a}.

In some embodiments of Formula I, each of R_{2a} and R_{2b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-3}$alkyl; $-C_{1-3}$alkoxy; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, each of R_{2a} and R_{2b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or $-C_{1-3}$alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, each of R_{2a} and R_{2b} is independently -H or methyl.

In some embodiments of Formula I, R_{2a} is -H or methyl, and R_{2b} is -H.

In some embodiments of Formula I, R_{2a} and R_{2b} are both -H.

In some embodiments of Formula I, Y_2 is CH or N, and Y_3 is CH or N.

In some embodiments of Formula I, Y_2 is CH, and Y_3 is CH.

In some embodiments of Formula I, Y_2 is CH, and Y_3 is N.

In some embodiments of Formula I, Y_2 is N, and Y_3 is CH.

In some embodiments of Formula I, each of R_{3a} and R_{3b} is independently -H, -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, or $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

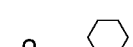
In some embodiments of Formula I, each of R_{3a} and R_{3b} is independently -H.

In some embodiments of Formula I, each R_6 is independently -H, -F, -Cl, -Br, -I, $-NR_{6a}R_{6b}$, -CN, -OH, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{6a}, $-C_{1-6}$alkylene-C_{5-10}heterocyclic, $-C_{1-6}$alkylene-C_{5-10}heteoaryl, $-C_{1-6}$alkylene-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-C_{1-6}alkyl, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -CO-NR_{6a}-C_{5-10}heterocyclic, -CO-NR_{6a}-C_{5-10}heterocyclic, -CO-C_{5-10}heterocyclic, -O-C_{1-6}alkylene-CO-OR_{6a}, -O-C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -O-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -O-C_{5-10}carbocyclic, -NR_{6a}-CO-C_{1-6}alkyl, -NR_{6a}-CO-$NR_{6a}R_{6b}$, -NR_{6a}-CO-C_{5-10}heteoaryl, -NR_{6a}-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -NR_{6a}-C_{1-6}alkylene-C_{3-10}heterocyclic, -NR_{6a}-C_{1-6}alkylene-C_{5-10}heteroaryl, -S-C_{1-6}alkyl, $-SO_2NR_{6a}R_{6b}$, $-SO_2C_{1-6}$alkyl, $-PO(CH_3)_2$, $-C_{5-10}$heterocyclic or $-C_{5-10}$heteroaryl, and each of which is independently optionally substituted -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl; or two adjacent R_6 can be joined together to form a 6-membered aryl; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic; 5-membered heteroaryl, 6-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic or 6-membered heterocyclic; and and each of heteroaryl or heterocyclic contains 1, 2, 3 or 4 heteroatoms selected from N, O or S; and each of the ring system is independently optionally substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, =O, oxo, carboxyl, $-CONH_2$, $-PO(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy or substituted or unsubstituted $-C_{1-6}$alkyl.

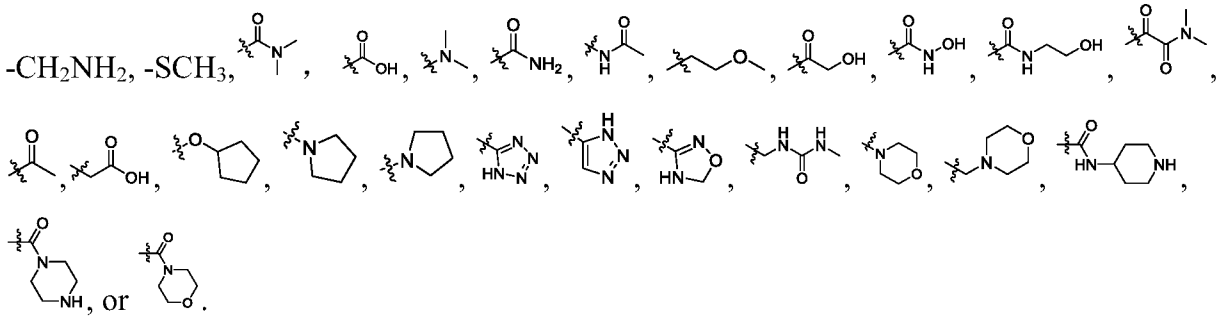
In some embodiments of Formula I, each R_6 is independently -H, -F, -Cl, -Br, $-NR_{6a}R_{6b}$, -CN, -OH, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{6a}, $-C_{1-6}$alkylene-C_{5-10}heterocyclic, $-C_{1-6}$alkylene-C_{5-10}heteoaryl, $-C_{1-6}$alkylene-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -CO-C_{1-6}alkyl, -CO-NR_{6a}-C_{5-10}heterocyclic, -CO-C_{5-10}heterocyclic, -O-C_{5-10}carbocyclic, -NR_{6a}-CO-C_{1-6}alkyl, -NR_{6a}-CO-$NR_{6a}R_{6b}$, -NR_{6a}-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -NR_{6a}-C_{1-6}alkylene-C_{3-10}heterocyclic, -S-C_{1-6}alkyl, $-SO_2NR_{6a}R_{6b}$, $-SO_2C_{1-6}$alkyl,

-C_{5-10}heterocyclic or -C_{5-10}heteroaryl, and each of which is independently optionally substituted -F, -Cl, Br, -NH_2, -OH, carboxyl, oxo, =O, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or two adjacent R_6 can be joined together to form a 6-membered aryl; 5-membered carbocyclic, 5-membered heteroaryl or 5-membered heterocyclic; and and each of heteroaryl or heterocyclic contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring system is independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, =O, oxo, carboxyl, -$CONH_2$, -$PO(CH_3)_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

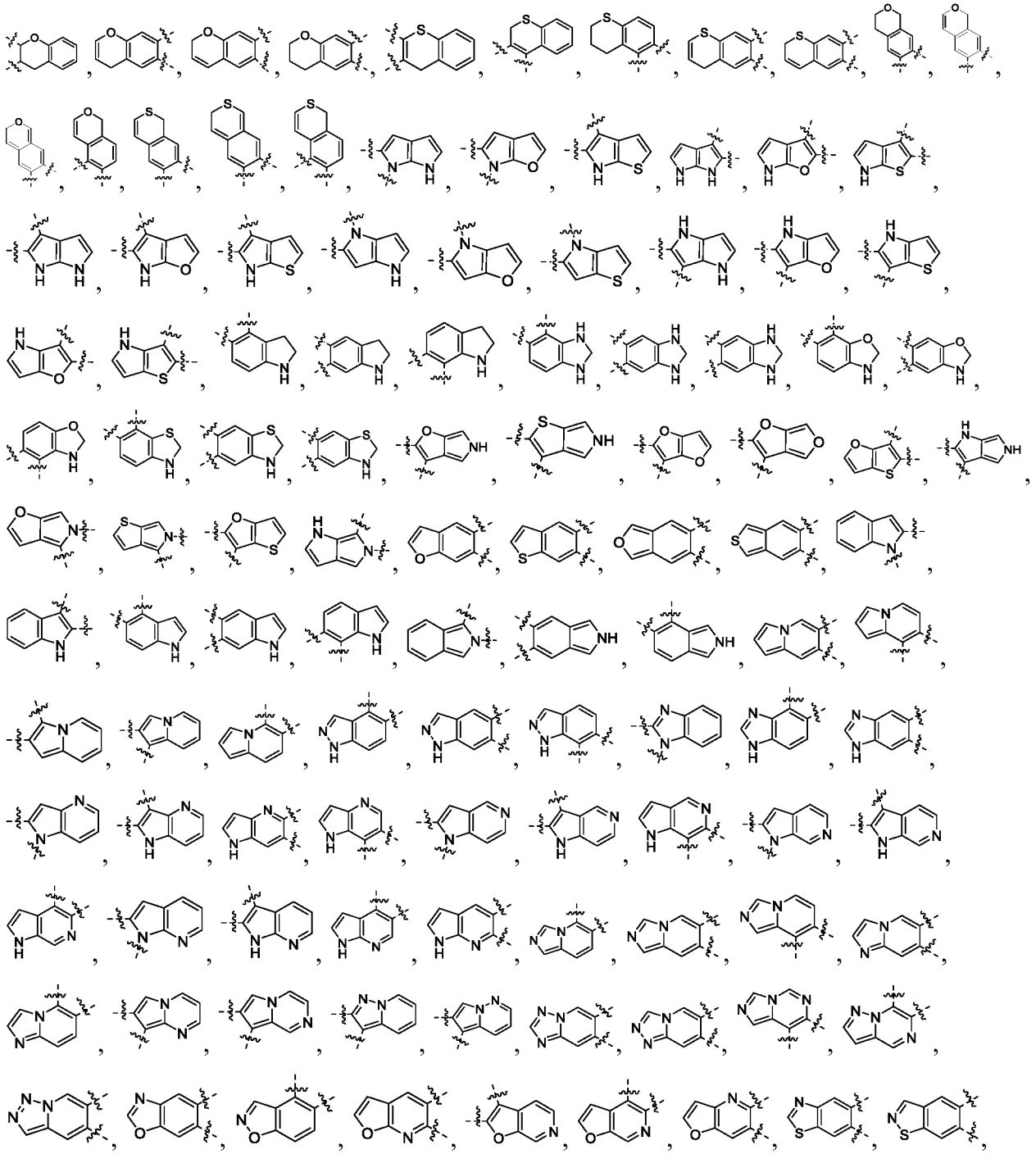
In some embodiments of Formula I, each R_6 is independently -H, -F, -Cl, -Br, -$NR_{6a}R_{6b}$, -CN, -OH, oxo, =O, carboxyl, -C_{1-3}alkoxy, -C_{1-3}alkyl, -C_{1-3}alkylene-$NR_{6a}R_{6b}$, -C_{1-3}alkylene-O-C_{1-3}alkyl, -C_{1-3}alkylene-CO-OR_{6a}, -C_{1-3}alkylene-C_{5-6}heterocyclic, -C_{1-3}alkylene-C_{5-6}heteoaryl, -C_{1-3}alkylene-CO-$NR_{6a}R_{6b}$, -C_{1-3}alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -CO-C_{1-3}alkyl, -CO-NR_{6a}-C_{5-6}heterocyclic, -CO-C_{5-6}heterocyclic, -O-C_{5-6}carbocyclic, -NR_{6a}-CO-C_{1-6}alkyl, -NR_{6a}-CO-$NR_{6a}R_{6b}$, -NR_{6a}-C_{1-3}alkylene-$NR_{6a}R_{6b}$, -NR_{6a}-C_{1-6}alkylene-C_{3-6}heterocyclic, -S-C_{1-3}alkyl, -$SO_2NR_{6a}R_{6b}$, -SO_2C_{1-3}alkyl, -C_{5-6}heterocyclic or -C_{5-6}heteroaryl, and each of which is independently optionally substituted with one or more substituents each independently selected from -F, -Cl, Br, -NH_2, -OH, carboxyl, oxo, =O, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or two adjacent R_6 can be joined together to form a 6-membered aryl; 5-membered carbocyclic, 5-membered heteroaryl or 5-membered heterocyclic; and and each of heteroaryl or heterocyclic contains 1, or 2 heteroatoms selected from N, O or S; and each of the ring system is independently optionally substituted with one or more substituents each independently selected from -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, =O, oxo, carboxyl, -$CONH_2$, -$PO(CH_3)_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

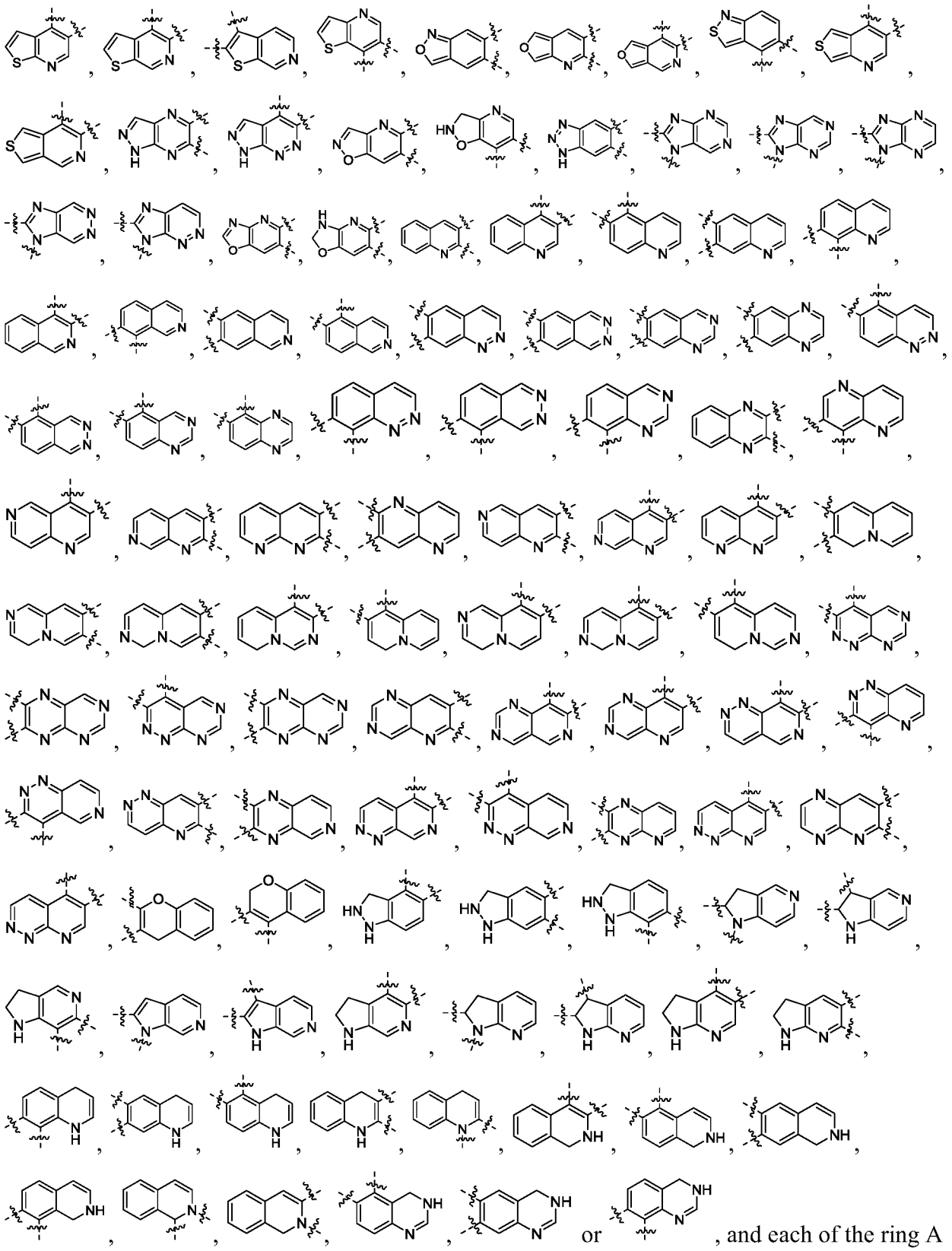
In some embodiments of Formula I, each R_6 is independently -F, -Cl, -Br, =O, -OH, -CN, -NH_2,  , -CH_3,  , -CF_3,  , -OCH_3, -SCH_3, -$SOCH_3$, -SO_2CH_3, -$PO(CH_3)_2$, -$PO(OC_2H_5)_2$, -$NHSO_2CH_3$, -$C(O)NH_2$, ,  , -$NHCOCH_3$, , -$NHCONHCH_3$, , , , , , ,  , , , or two adjacent R_6 can be joined together to form  ,  , or,  .

In some embodiments of Formula I, each R_6 is independently methyl, ethyl, isopropyl, methoxy, ethoxy, =O, oxo, -OH, -CN, -NH_2, -Cl, -Br, -CF_3, -OCF_3, -SO_2NH_2, -SO_2CH_3, -F,

-CH_2NH_2, -SCH_3, 

In some embodiments of Formula I, ring A and the two adjacent R_6 taken together to form





is independently optionally substituted with another one or more R_6.

In some embodiments of Formula I, n is 0, 1, 2 or 3.

In some embodiments of Formula I, each of R_{6a} and R_{6b} is independently -H; -F;- Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1\text{-}3}$alkyl; $-C_{1\text{-}3}$alkoxy; $-C_{1\text{-}3}$alkyl substituted with halogen,

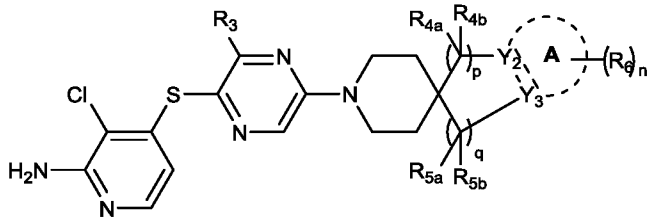
-NH_2, -CN, -OH, -NO_2, -carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-3}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

In some embodiments of Formula I, each of R_{6a} and R_{6b} is independently -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkyl substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or -C_{1-3}alkoxy substituted with -F, -Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, each of R_{6a} and R_{6b} is independently -H; -F; -Cl; -Br; -NH_2; -CN; -OH; carboxyl; methyl; ethyl; isopropyl; methoxy; methyl substituted with -F, -Cl, -NH_2, -OH, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; ethyl substituted with -F, -Cl, -NH_2, -OH, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or propyl substituted with -F, -Cl, -NH_2, -OH, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, each of R_{6a} and R_{6b} is independently -H, -CH_3, -OH, or -CH_2CH_2OH.

In some embodiments of Formula I, the compound is of Formula II:



II

R_3 is -H or -NH_2;

Each of R_{4a} or R_{4b} is independently -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O, C=NH, or C=N-OH;

p is 0, 1, 2 or 3;

Each of R_{5a} or R_{5b} is independently -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-10 membered heterocyclic or 5-10 membered heteroaryl; and each of the ring systems is independently optionally substituted;

q is 0,1, 2, 3 or 4;

Ring A is absent or a 3-10 membered ring;

=== represents a single or double bond;

When ring A is absent, Y_2 is $CR_{2a}R_{2b}$, NR_{2a} or O, and Y_3 is $CR_{3a}R_{3b}$, NR_{3a} or O;

When ring A is a 3-10 membered ring, and,

i) Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N, when === represents a single bond; or

ii) Y_2 is C, and Y_3 is C, when === represents a double bond;

Each of R_{2a} and R_{2b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl;

Each of R_{3a} and R_{3b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl;

Each R_6 is independently -H, halogen, $-NR_{6a}R_{6b}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{6a}, $-C_{1-6}$alkylene-C_{3-10}heterocyclic, $-C_{1-6}$alkylene-C_{5-10}heteoaryl, $-C_{1-6}$alkylene-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-C_{1-6}alkyl, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-C_{3-10}heteocyclic, -O-C_{1-6}alkylene-CO-OR_{6a}, -O-C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -O-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -O-C_{3-10}carbocyclic, $-NR_{6a}$-CO-C_{1-6}alkyl, $-NR_{6a}$-CO-$NR_{6a}R_{6b}$, $-NR_{6a}$-CO-C_{5-10}heteoaryl, $-NR_{6a}$-C_{1-6}alkylene-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-6}alkylene-C_{3-10}heterocyclic, $-NR_{6a}$-C_{1-6}alkylene-C_{5-10}heteroaryl, -S-C_{1-6}alkyl, -SO$NR_{6a}R_{6b}$, $-SO_2NR_{6a}R_{6b}$, -SO-C_{1-6}alkyl, $-SO_2$-C_{1-6}alkyl, -PO(C_{1-6}alkyl)$_2$, $-C_{3-10}$heterocyclic or $-C_{5-10}$heteroaryl, and each of which is independently optionally substituted; and n is 0, 1, 2 or 3; or two adjacent R_6 can be joined together to form a 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, $-C_{3-6}$heterocyclic or $-C_{3-6}$carbocyclic, and each of the ring system is independently optionally substituted;

Each of R_{6a} and R_{6b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula II, each of R_{4a} or R_{4b} is independently -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O.

In some embodiments of Formula II, each of R_{4a} or R_{4b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; carboxyl; methyl; ethyl; methoxy; ethoxy; methyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, methoxy or ethoxy; ethyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, methoxy or ethoxy; methoxy substituted with

-F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, methoxy or ethoxy; or ethoxy substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, methoxy or ethoxy; or R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O.

In some embodiments of Formula II, p is 0, 1 or 2.

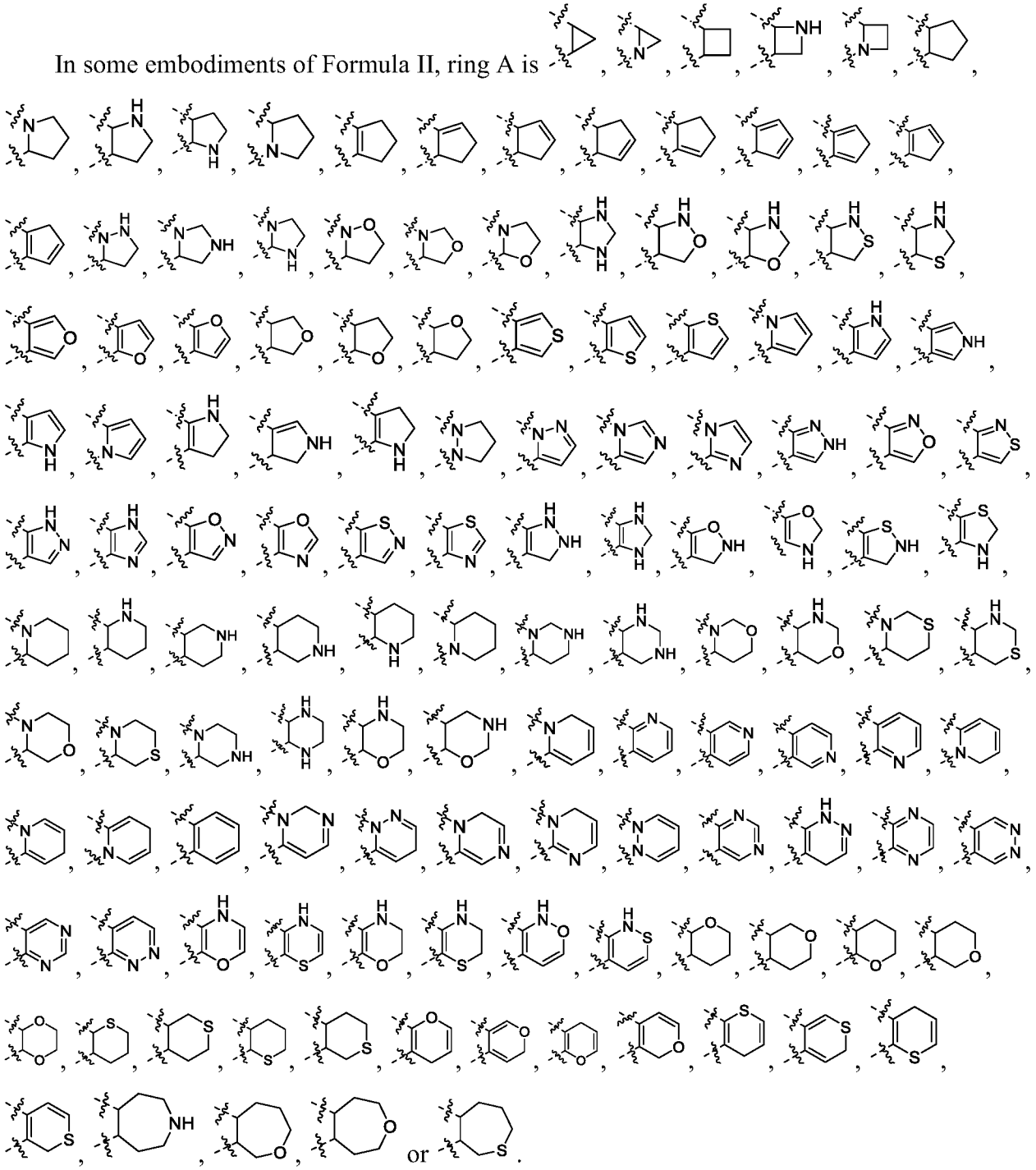
In some embodiments of Formula II, each of R_{5a} and R_{5b} is independently -H; -F; -Cl; -Br; -NH_2; -CN; -OH; carboxyl; -C_{1-3}alkyl;- C_{1-3}alkoxy; -C_{1-3}alkyl substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-3}alkoxy substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic or 6-membered heterocyclic; and each of the heterocyclic contains 1 or 2 heteroatoms selected from N or O; and each of the ring system is independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl, or -C_{1-6}alkoxy.

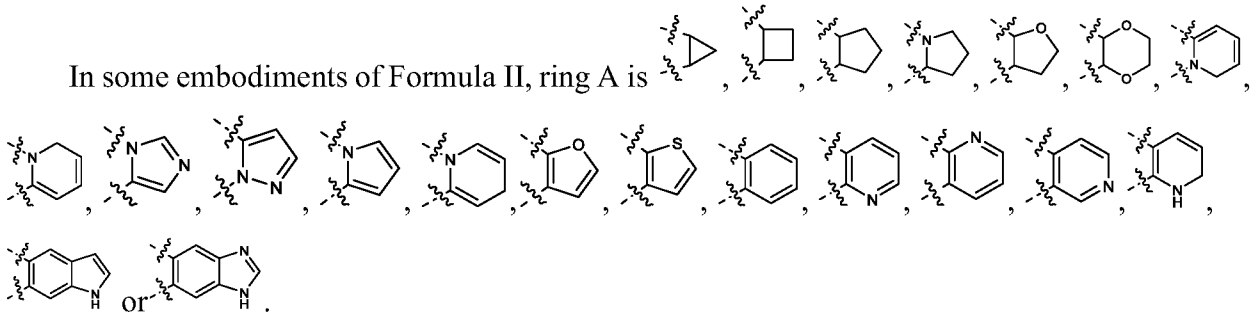
In some embodiments of Formula II, each of R_{5a} or R_{5b} is independently -H; -Cl; -Br; -NH_2; -OH; carboxyl; methyl; ethyl; methoxy; ethoxy; methyl substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl or methoxy; ethyl substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl or methoxy; methoxy substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl or methoxy; or ethoxy substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl or methoxy; or R_{5a} and R_{5b} together with the carbon atom to which they are both attached form  , and *C represents the carbon atom which R_{5a} and R_{5b} attached.

In some embodiments of Formula II, ring A is 6-membered aryl, 7-membered aryl, 8-membered aryl, 9-membered aryl; 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 7-membered carbocyclic, 8-membered carbocyclic or 9-membered carbocyclic; and each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic contains 1, 2 or 3 heteroatoms selected from N or O.

In some embodiments of Formula II, ring A is 6-membered aryl, 7-membered aryl, 8-membered aryl; 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered

carbocyclic, 7-membered carbocyclic or 8-membered carbocyclic; and each of the heteroaryl contains 1 or 2 heteroatoms selected from N, O or S; each of the heterocyclic contains 1 or 2 heteroatoms selected from N or O.

In some embodiments of Formula II, ring A is  .

In some embodiments of Formula II, ring A is  or .

In some embodiments of Formula II, Y_2 is CR_{2a} or N, Y_3 is CR_{3a} or N.

In some embodiments of Formula II, each of R_{2a}, R_{2b}, R_{3a} and R_{3b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or $-C_{1-3}$alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, each of R_{2a}, R_{2b}, R_{3a} and R_{3b} is independently -H or methyl.

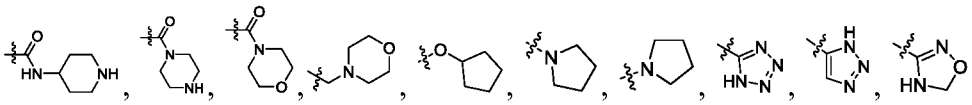
In some embodiments of Formula II, R_{2a}, R_{2b}, R_{3a} and R_{3b} are all -H.

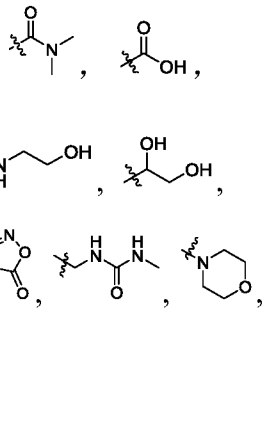
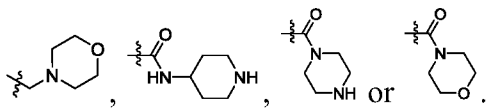
In some embodiments of Formula II, Y_2 is CH or N, and Y_3 is CH or N.

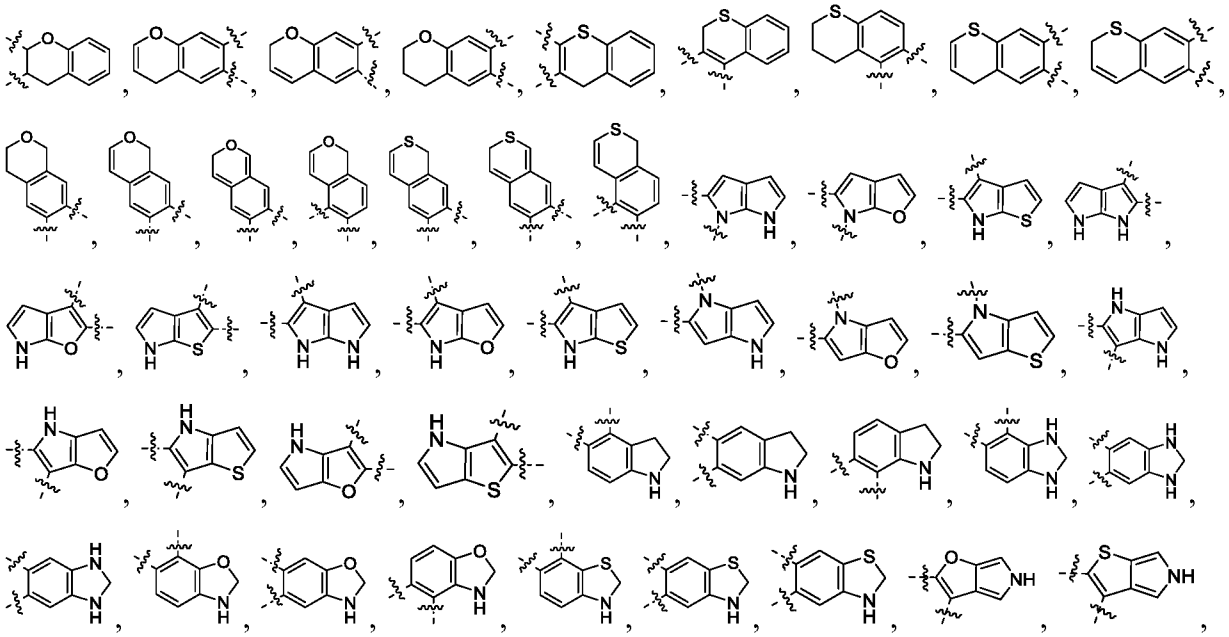
In some embodiments of Formula II, Y_2 is C, and Y_3 is C.

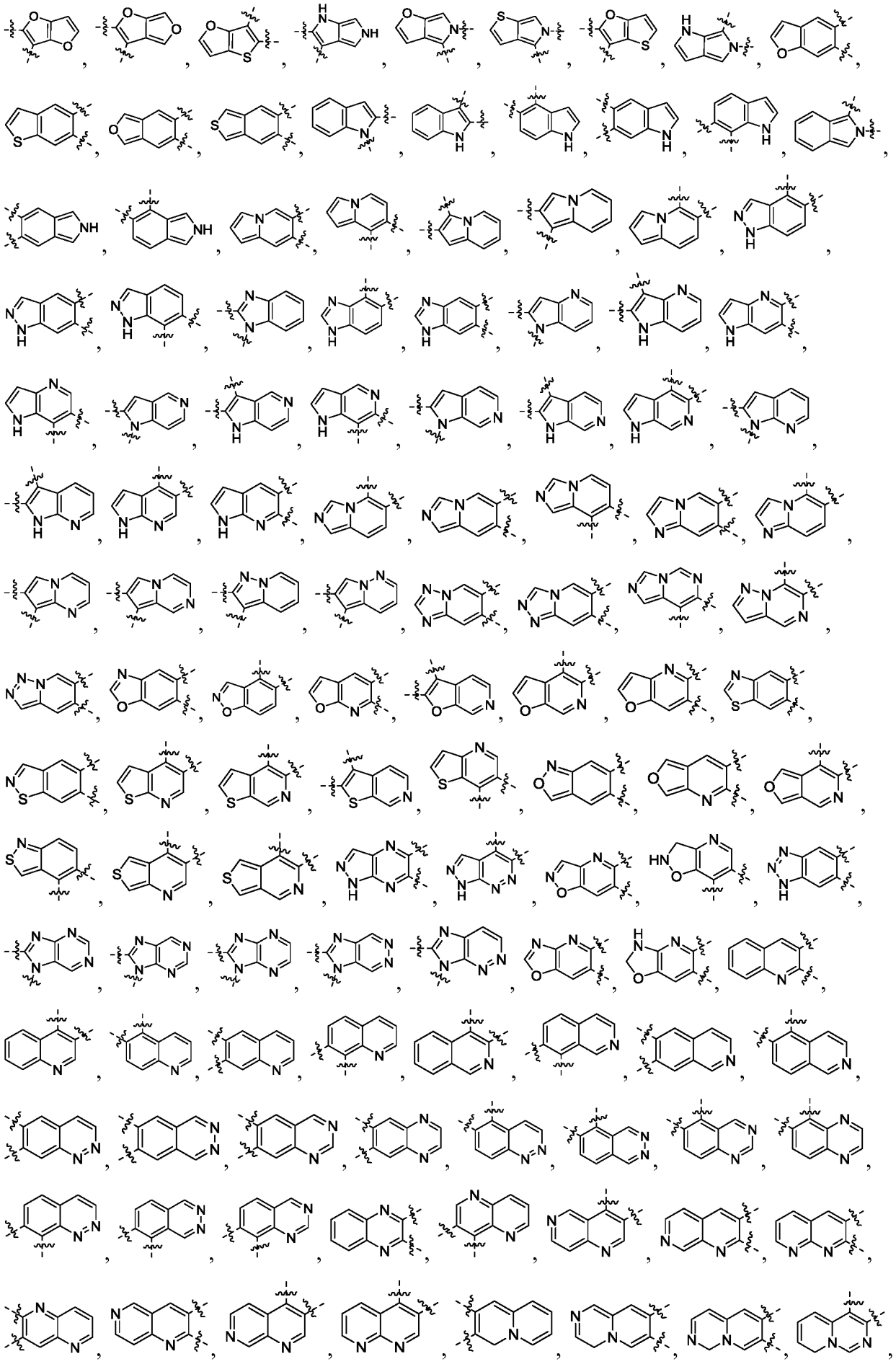
In some embodiments of Formula II, each R_6 is independently -H, -F, -Cl, -Br, $-NH_2$, $-N(CH_3)_2$, -CN, -OH, oxo, =O, carboxyl, $-C_{1-3}$alkoxy, $-C_{1-3}$alkyl, $-CH_2NH_2$, $-C_{1-3}$alkylene-OCH_3, $-CH_2$-COOH, $-CH_2$-COO-C_{1-3}alkyl, $-CH_2$-C_{5-10}heterocyclic, $-C_{1-3}$alkylene-CO-$NR_{6a}R_{6b}$, $-CH_2NH$-CO-$NR_{6a}R_{6b}$, -CO-$NR_{6a}R_{6b}$, -COCO-$NR_{6a}R_{6b}$, -CO-C_{1-3}alkyl, -CONH-C_{5-10}heteocyclic, -CO-5-membered heteocyclic, -CO-6-membered heteocyclic, -O-5-membered carbocyclic, -O-6-membered carbocyclic, -NH-CO-C_{1-3}alkyl, $-NR_{6a}$-CO-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-3}alkylene-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-3}alkylene-C_{5-10}heterocyclic, -S-C_{1-3}alkyl, $-SO_2NH_2$, $-SO_2CH_3$, 5-membered heterocyclic, 6-membered heterocyclic, 5-membered heteroaryl, or 6-membered heteroaryl, and each of which is independently optionally substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, oxo, =O, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl; or two adjacent R_6 can be joined together to form a 6-membered aryl; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 5-membered heteroaryl, 3-membered heterocyclic, 4-membered heterocyclic or 5-membered heterocyclic; and each of heteroaryl or heterocyclic contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring system is independently optionally substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH,

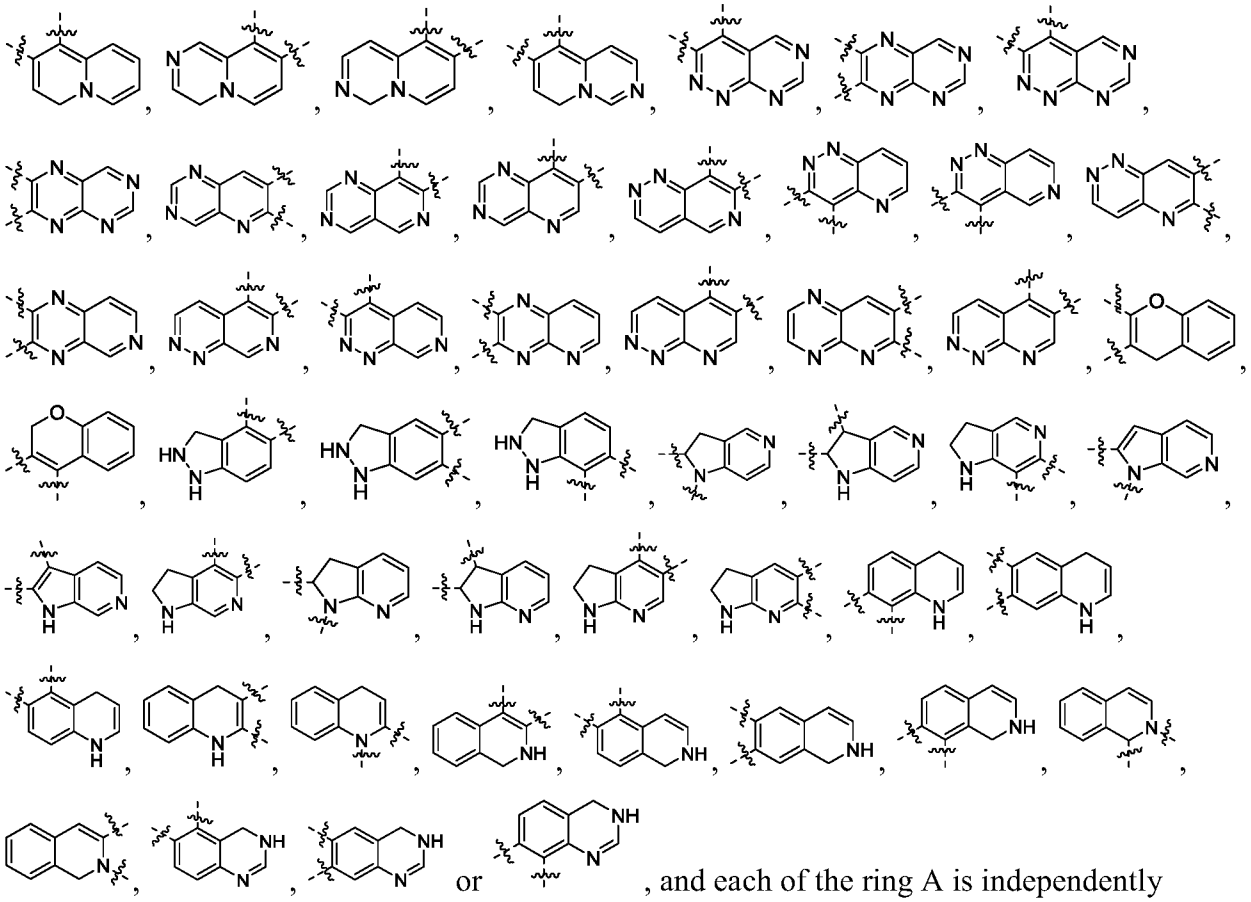
$-NO_2$, =O, oxo, carboxyl, $-CONH_2$, $-PO(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}alkoxy$, or substituted or unsubstituted $-C_{1-3}alkyl$.

In some embodiments of Formula II, each R_6 is independently -F, -Cl, -Br, $-NH_2$, $-N(CH_3)_2$, -CN, -OH, oxo, =O, carboxyl, methoxy, ethoxy, methyl, ethyl, isopropyl, $-CH_2NH_2$, $-CH_2CH_2OCH_3$, $-CH_2$-COOH, $-CH_2NH$-$CONHCH_3$, $-CONH_2$, $-CON(CH_3)_2$, -CONHOH, $-CONHCH_2CH_2OH$, $-CO$-$CON(CH_3)_2$, $-COCH_3$, $-SO_2NH_2$, $-SO_2CH_3$, $-SCH_3$, $-NH$-$COCH_3$,  or  , and each of which is independently optionally substituted with -F, $-NH_2$, -OH, oxo, =O, or substituted or unsubstituted $-C_{1-3}alkyl$.

In some embodiments of Formula II, each R_6 is independently methyl, methoxy, =O, oxo, -OH, -CN, $-NH_2$, -Cl, -Br, $-CF_3$, $-OCF_3$, $-SO_2NH_2$, $-SO_2CH_3$, -F, $-CH_2NH_2$,  or  .

In some embodiments of Formula II, ring A and two adjacent R_6 taken together to form  .





, and each of the ring A is independently optionally substituted with one or more R_6.

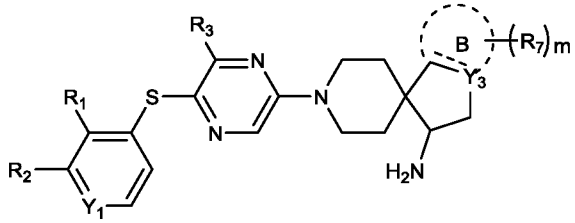
In some embodiments of Formula II, each of R_{6a} and R_{6b} is independently -H, -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula II, each of R_{6a} and R_{6b} is independently -H, -Cl, -Br, $-NH_2$, -OH, carboxyl, methyl, ethyl, methoxy, ethoxy propoxy, isopropoxy, methyl substituted with -OH, or ethyl substituted with -OH.

In some embodiments of Formula II, each of R_{6a} and R_{6b} is independently -H, $-CH_3$, -OH, or $-CH_2CH_2OH$.

In some embodiments of Formula II, n is 0, 1 or 2.

In some embodiments of Formula I, the compound is of III:



III

R_1 is -H, -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl;

R_2 is -H, -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_1 combines with R_2 to which is adjacent to form a 5-10 membered heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-CONH_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, substituted or unsubstituted $-C_{1-6}$alkyl, or $-CO-C_{1-6}$alkyl;

Y_1 is N or CH;

R_3 is -H or $-NH_2$;

Ring B is a 6-membered aryl, 5-6 membered heteroaryl, 3-6 membered carbocyclic or 3-6 membered heterocyclic;

Y_3 is CH, N or C;

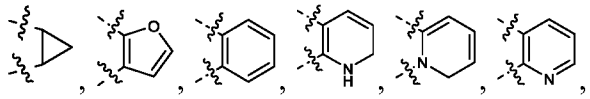
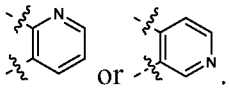
R_7 is halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-CONH_2$, $-NH-COCH_3$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; and m is 0, 1 or 2.

In some embodiments of Formula III, R_1 combines with R_2 to which is adjacent to form a 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic or 10-membered heterocyclic; and each of the heterocyclic contains 1 or 2 heteroatoms selected from N or O; and each of the ring systems is independently optionally substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, oxo, =O, substituted or unsubstituted $-C_{1-3}$alkoxy, substituted or unsubstituted $-C_{1-3}$alkyl, or $-CO-C_{1-3}$alkyl.

In some embodiments of Formula III, R_1 combines with R_2 to which is adjacent to form  ; and the ring systems is independently optionally substituted with -F or $-COCH_3$.

In some embodiments of Formula III, R_1 combines with R_2 to which is adjacent to form  .

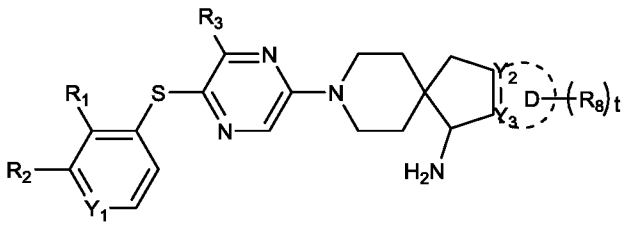
In some embodiments of Formula III, ring B is 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic or 6-membered heterocyclic; and each of the heteroaryl or heterocyclic contains 1, 2 or 3 heteroatoms selected from N, O or S.

In some embodiments of Formula III, ring B is   .

In some embodiments of Formula III, R_7 is $-NH_2$, -CN, oxo, =O, $-CONH_2$, $-NH-COCH_3$, methyl or methoxy.

In some embodiments of Formula III, m is 0 or 1.

In some embodiments of Formula I, the compound is of Formula IV:



IV

R_1 is -H, -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted- C_{1-6}alkyl;

R_2 is -H, -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NHC_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_1 combines with R_2 to which is adjacent to form a 5-12 membered heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-CONH_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, substituted or unsubstituted $-C_{1-6}$alkyl, or $-CO-C_{1-6}$alkyl;

Y_1 is N or CH;

R_3 is -H or $-NH_2$;

Ring D is a 6-membered aryl, 5- membered heteroaryl, 6-membered heteroaryl, 3- membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, or 6-membered heterocyclic;

=== represents a single or double bond; and

i) Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N, when === represents a single bond; or

ii) Y_2 is C, and Y_3 is C, when === represents a double bond;

Each of R_{2a} and R_{3a} is -H, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl;

R_8 is halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-SO_2NR_{8a}R_{8b}$, $-S-C_{1-6}$alkyl, $-SO-C_{1-6}$alkyl, $-SO_2-C_{1-6}$alkyl, $-CO-NR_{8a}R_{8b}$, $-PO(C_{1-6}alkyl)_2$, $-PO(C_{1-6}alkoxy)_2$,

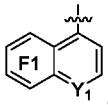
-NR_{8a}-CO-C_{1-6}alkyl, -NR_{8a}-CO-$NR_{8a}R_{8b}$, -O-C_{5-10}carbocyclic, -O-C_{5-10}heterocyclic, -C_{5-10}heterocyclic or -C_{5-10}heteroaryl, -C_{5-10}aryl, -C_{1-6}alkoxy, or -C_{1-6}alkyl; and each of which is independently optionally substituted; and t is 0, 1, 2 or 3; and

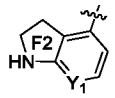
Each of R_{8a} and R_{8b} is independently H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl.

In some embodiments of Formula IV, R_2 is -H, -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl; or R_1 combines with R_2 to which is adjacent to form a 5-10 membered heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$CONH_2$, substituted or unsubstituted -C_{1-6}alkoxy, substituted or unsubstituted -C_{1-6}alkyl, or -CO-C_{1-6}alkyl;

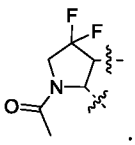
In some embodiments of Formula IV, R_2 is -H, -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -NHC_{1-3}alkyl, -$N(C_{1-3}alkyl)_2$, -C_{1-3}alkoxy, -C_{1-3}alkyl; or R_1 combines with R_2 to which is adjacent to form a 5-,6-, or 7-membered heterocyclic ring contains 1, or 2 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$CONH_2$, methoxy, ethoxy, methyl, ethyl, -CO-methyl, or -CO-ethyl;

In some embodiments of Formula IV, R_2 is -H, -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -$NHCH_3$, -$N(CH_3)_2$, methoxy, ethoxy, methyl, or ethyl; or R_1 combines with R_2 to which is adjacent to form a 5- membered heterocyclic contains 1 heteroatoms selected from N or O, or 6-membered heterocyclic ring contains 1 heteroatoms selected from N or O; and each of the ring systems is independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$CONH_2$, methoxy, ethoxy, methyl, ethyl, -CO-methyl, or -CO-ethyl;

In some embodiments of Formula IV, R_1 and R_2, together with the aromatic ring they are attached to formto 

, or 

and ring F1 or F2 is independently optionally substituted with -F or -$COCH_3$.

In some embodiments of Formula IV, R_1 combines with R_2 to which is adjacent to form 

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In some embodiments of Formula IV, R_2 is -NH_2.

In some embodiments of Formula IV, R_1 is -H, -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-3}alkoxy, or substituted or unsubstituted -C_{1-3}alkyl.

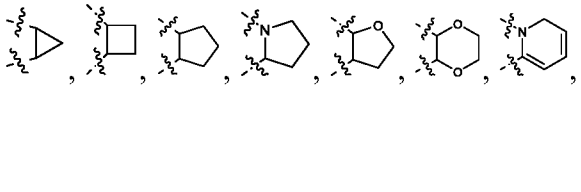
In some embodiments of Formula IV, R_1 is -H, -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methoxy, ethoxy, methyl, or methyl substituted with one or more substituents selected from halogen.

In some embodiments of Formula IV, R_1 is -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methyl; or methyl substituted with one or more substituents selected from -F, -Cl, or -Br.

In some embodiments of Formula IV, R_1 is -Cl.

In some embodiments of Formula IV, ring D is 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic or 6-membered heterocyclic; and each of the heteroaryl or heterocyclic contains 1, 2 or 3 heteroatoms selected from N, O or S.

In some embodiments of Formula IV, ring D is 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 5-membered heterocyclic or 6-membered heterocyclic; and each of the heteroaryl or heterocyclic contains 1 or 2 heteroatoms selected from N, O or S.

In some embodiments of Formula IV, ring D is  .

In some embodiments of Formula IV, Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N.

In some embodiments of Formula IV, each of R_{2a} and R_{3a} is -H, -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted -C_{1-3}alkoxy, or substituted or unsubstituted -C_{1-3}alkyl.

In some embodiments of Formula IV, each of R_{2a} and R_{3a} is -H, methyl or methoxy.

In some embodiments of Formula IV, Y_2 is CH or N, and Y_3 is CH or N.

In some embodiments of Formula IV, both Y_2 and Y_3 are C.

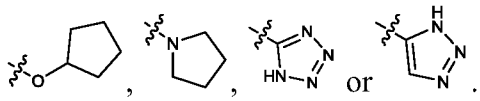
In some embodiments of Formula IV, R_8 is -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-SO_2NR_{8a}R_{8b}$, -S-C_{1-6}alkyl, -CO-$NR_{8a}R_{8b}$, $-NR_{8a}$-CO-C_{1-6}alkyl, $-NR_{8a}$-CO-$NR_{8a}R_{8b}$, -O-C_{5-10}carbocyclic, -C_{5-10}heterocyclic or -C_{5-10}heteroaryl, -C_{1-6}alkoxy, or -C_{1-6}alkyl; and each of which is independently optionally substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, oxo, =O, substituted or unsubstituted -C_{1-3}alkoxy, or substituted or unsubstituted -C_{1-3}alkyl.

In some embodiments of Formula IV, R_8 is -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-SO_2NR_{8a}R_{8b}$, -S-C_{1-3}alkyl, -CO-$NR_{8a}R_{8b}$, -NH-CO-C_{1-3}alkyl, -NH-CO-$NR_{8a}R_{8b}$, -O-C_{5-10}carbocyclic, -C_{5-10}heterocyclic, -C_{5-10}heteroaryl, -C_{1-3}alkoxy, or -C_{1-3}alkyl; and each of which is independently optionally substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, oxo, =O, -C_{1-3}alkoxy, or -C_{1-3}alkyl.

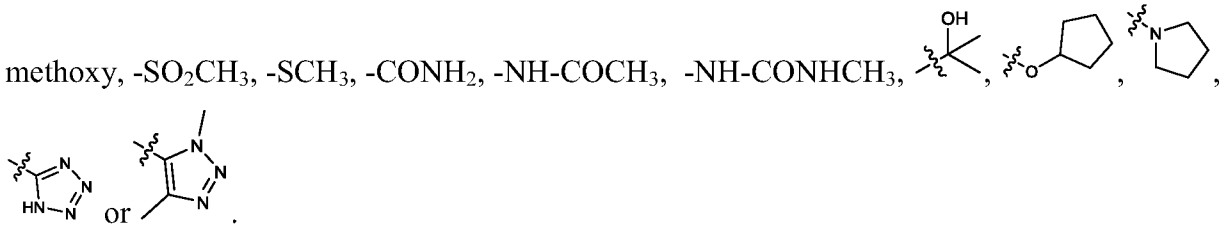
In some embodiments of Formula IV, R_8 is -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, methyl, ethyl, proproyl, isopropoyl, methoxy, ethoxy, propoxy, isopropoxy, $-SO_2NR_{8a}R_{8b}$, -S-C_{1-3}alkyl, -CO-$NR_{8a}R_{8b}$, -NH-CO-C_{1-3}alkyl, -NH-CO-$NR_{8a}R_{8b}$, -O-C_{5-10}carbocyclic, -C_{5-10}heterocyclic or -C_{5-10}heteroaryl; and each of which is independently optionally substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, oxo, =O, methoxy, ethoxy, methyl, or ethyl.

In some embodiments of Formula IV, the C_{5-10}carbocyclic is 5-membered carbocyclic, 6-membered carbocyclic, 7-membered carbocyclic, 8-membered carbocyclic, 9-membered carbocyclic or 10-membered carbocyclic; the C_{5-10}heterocyclic is 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic or 10-membered heterocyclic; and the C_{5-10}heteroaryl is 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl or 10-membered heteroaryl; and each of the heterocyclic or heteroaryl contains 1, 2, 3 or 4 heteroatoms selected from N, O or S.

In some embodiments of Formula IV, R_8 is -F, -Cl, -Br, $-NH_2$, -CN, -OH, oxo, =O, methyl, ethyl, isopropoyl, methoxy, $-SO_2CH_3$, $-SCH_3$, $-CONH_2$, -NH-$COCH_3$, -NH-$CONHCH_3$,



In some embodiments of Formula IV, R_8 is -F, -Cl, -Br, $-NH_2$, -CN, -OH, oxo, =O, methyl, methoxy, $-SO_2CH_3$, $-SCH_3$, $-CONH_2$, -NH-$COCH_3$, -NH-$CONHCH_3$,



In some embodiments of Formula IV, t is 0, 1 or 2.

In some embodiments of Formula I, II, III or IV, the compound is

1	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1, 4'-piperidin]-2-amine
2	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2, 4'-piperidin]-1-amine
3	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-amine
4	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidin]-6-amine
5	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

6	(R)-1-(4-((3-amino-5-(2-amino-2,3-dihydrospiro[indene-1,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
7	1-(4-((3-amino-5-((2R)-2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
8	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine
9	(R)-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7',8'-dihydro-5'H-spiro[piperidine-4,6'-quinolin]-7'-amine
10	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
11	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
12	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine
13	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
14	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
15	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-chloro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
16	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carbonitrile
17	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carboxamide
18	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
19	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
20	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methoxy-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine
21	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine
22	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
23	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
24	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

25	(1S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfinyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
26	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
27	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-N,N-dimethyl-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
28	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
29	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
30	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
31	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-3-amine
32	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-chloro-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
33	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
34	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-yl)dimethylphosphine oxide
35	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
36	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-imidazol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
37	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-pyrrol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
38	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-bromo-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
39	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-difluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
40	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-difluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
41	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)dimethylphosphine oxide
42	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
43	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide

44	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
45	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine
46	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)urea
47	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
48	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
49	(S)-1'-(5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
50	(S)-1'-(5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
51	(S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
52	(S)-1'-(6-amino-5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
53	(S)-1'-(6-amino-5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
54	(S)-1'-(6-amino-5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
55	(S)-1'-(6-amino-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
56	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine
57	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)dimethylphosphine oxide
58	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-((tetrahydro-2H-pyran-4-yl)oxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
59	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)(piperidin-1-yl)methanone
60	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-morpholino-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
61	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
62	(S)-4-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)morpholin-3-one

63	(S)-N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)methanesulfonamide
64	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[b]quinoline-2,4'-piperidin]-1-amine
65	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
66	(S)-1'-(6-amino-5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
67	(1R,3R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,3-diamine
68	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine
69	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine
70	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-5(1H)-one
71	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[indoline-2,4'-piperidin]-3-amine
72	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-6-amine
73	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-chloro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
74	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
75	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(4-methylpiperazin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
76	(S)-1'-(5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
77	(S)-1'-(6-amino-5-((2-(trifluoromethyl)pyridin-3-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
78	(S)-1-(4-((3-amino-5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
79	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-(tert-butyl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine
80	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxylic acid
81	(2R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-2-amine

82	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine
83	(S)-1'-(5-(quinolin-4-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
84	(S)-1'-(6-amino-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
85	(S)-1'-(5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
86	(S)-1'-(5-(pyridin-4-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
87	(S)-1'-(6-amino-5-((3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
88	(S)-1'-(6-amino-5-((3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
89	(S)-1'-(6-amino-5-((3-chloro-2-(methylamino)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
90	diethyl(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)phosphonate
91	(S)-1'-(6-amino-5-((2-amino-3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
92	(S)-1'-(5-((2-amino-3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
93	(S)-1'-(6-amino-5-((3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
94	(S)-1'-(6-amino-5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
95	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
96	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[furo[2,3-b]pyridine-2,4'-piperidin]-3-amine
97	(S)-1'-(5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
98	(S)-1'-(6-amino-5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
99	(S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
100	(S)-1'-(6-amino-5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine

101	(S)-1'-(5-((5-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
102	(S)-1'-(6-amino-5-((5-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
103	(S)-1-(4-((3-amino-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
104	(S)-1'-(5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
105	(S)-1'-(6-amino-5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
106	(S)-1'-(5-((4-chloropyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
107	(S)-1'-(6-amino-5-((4-chloropyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
108	(S)-1'-(5-((3-aminopyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
109	(S)-1'-(6-amino-5-((3-aminopyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
110	(S)-1'-(5-((3,5-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
111	(S)-1'-(6-amino-5-((3,5-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
112	(S)-1'-(5-((2-amino-5-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
113	(S)-1'-(6-amino-5-((2-amino-5-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
114	(S)-1'-(6-amino-5-((2-(trifluoromethyl)pyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
115	(S)-1'-(5-((3-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
116	(S)-1'-(6-amino-5-((3-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
117	(S)-3-((5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)picolinonitrile
118	(S)-3-((3-amino-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)picolinonitrile
119	(S)-1'-(5-((2-chloro-5-(trifluoromethyl)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine

120	(S)-1'-(6-amino-5-((2-chloro-5-(trifluoromethyl)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
121	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
122	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
123	1'-(6-amino-5-((3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
124	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
125	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
126	1'-(6-amino-5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
127	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
128	1'-(5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
129	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
130	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
131	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
132	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
133	(S)-4-((5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol
134	(S)-4-((3-amino-5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol
135	(S)-4-((5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol
136	(S)-4-((3-amino-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol
137	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
138	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-ol

139	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methyl-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
140	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-7(1H)-one (2 mg)
141	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-5(1H)-one
142	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-imino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-amine
143	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-imino-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-amine
144	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(4-imino-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine
145	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-bromo-4-imino-4H,6H-spiro[cyclopenta[c]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine
146	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(4-imino-4H,6H-spiro[cyclopenta[c]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine
147	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(2-bromo-4-imino-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine
148	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
149	(Z)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[indene-2,4'-piperidin]-1(3H)-one oxime
150	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-methoxy-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
151	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
152	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
153	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
154	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
155	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine

156	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine
157	(S)-1'-(6-amino-5-((3-fluoro-1H-indol-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
158	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)ethan-1-one
159	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-yl)ethan-1-one
160	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1-methylspiro[indoline-2,4'-piperidin]-3-amine
161	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
162	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-amine
163	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidin]-6-amine
164	1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine
165	(1'S)-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine
166	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine
167	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine
168	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-6-amine
169	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine
170	(4R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine
171	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-2-amine
172	1'-amino-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-3'-one
173	(1'S)-1'-amino-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-3'-one

174	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-2,4'-piperidin]-3-amine
175	(3R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-2,4'-piperidin]-3-amine
176	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(11-oxa-1,7-diazadispiro[2.0.5^4.3^3]dodecan-7-yl)pyrazin-2-amine
177	1-(4-((3-amino-5-(2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
178	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1-methylspiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-4-amine
179	(4R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1-methylspiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-4-amine
180	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.2.0]heptane-3,4'-piperidin]-2-amine
181	(2R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.2.0]heptane-3,4'-piperidin]-2-amine
182	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydro-1H-spiro[pentalene-2,4'-piperidin]-1-amine
183	(1R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydro-1H-spiro[pentalene-2,4'-piperidin]-1-amine
184	1-(4-((3-amino-5-(2-amino-2,3-dihydrospiro[indene-1,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
185	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
186	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
187	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,5-dihydrospiro[cyclopenta[b]furan-6,4'-piperidin]-5-amine
188	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,5-dihydrospiro[cyclopenta[b]furan-6,4'-piperidin]-5-amine
189	1-(4-((3-amino-5-(11-oxa-1,7-diazadispiro[2.0.5^4.3^3]dodecan-7-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
190	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b][1,4]dioxine-6,4'-piperidin]-5-amine
191	(5S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b][1,4]dioxine-6,4'-piperidin]-5-amine

192	6-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-2(1H)-one
193	(R)-6-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-2(1H)-one
194	2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydro-5H-spiro[indolizine-1,4'-piperidin]-5-one
195	(S)-2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydro-5H-spiro[indolizine-1,4'-piperidin]-5-one
196	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[chromane-4,4'-piperidin]-3-amine
197	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[chromane-4,4'-piperidin]-3-amine
198	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
199	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine
200	1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7',8'-dihydro-5'H-spiro[piperidine-4,6'-quinolin]-7'-amine
201	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[c]pyridine-5,4'-piperidin]-6-amine
202	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[c]pyridine-5,4'-piperidin]-6-amine
203	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine
204	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine
205	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dimethoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
206	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dimethoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
207	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
208	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
209	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine

210	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
211	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
212	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
213	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-ol
214	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-chloro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
215	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
216	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-2,5-diamine
217	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-2,5-diamine
218	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
219	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
220	1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine
221	(S)-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine
222	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine
223	2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carboxamide
224	(R)-2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carboxamide
225	2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carbonitrile
226	(R)-2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carbonitrile
227	N-(2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-4-yl)acetamide

228	(R)-N-(2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-4-yl)acetamide
229	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(pyrrolidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
230	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(pyrrolidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
231	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
232	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
233	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
234	2-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)propan-2-ol
235	(S)-2-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)propan-2-ol
236	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
237	N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide
238	(S)-N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide
239	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
240	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(cyclopentyloxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
241	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(cyclopentyloxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
242	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-7(1H)-one
243	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
244	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
245	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]indole-6,4'-piperidin]-7-amine

246	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]indole-6,4'-piperidin]-7-amine
247	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[indeno[5,6-d]imidazole-6,4'-piperidin]-7-amine
248	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[indeno[5,6-d]imidazole-6,4'-piperidin]-7-amine
249	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-tetrazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
250	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-tetrazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
251	1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)-3-methylurea
252	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)-3-methylurea
253	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine

The present invention also provides a pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt thereof of Formula I, II, III or IV and at least one pharmaceutically acceptable excipient. Furthermore, in the composition, the said compound or pharmaceutically acceptable salt thereof of Formula I, II, III or IV in a weight ratio to the said excipient within the range from about 0.0001 to about 10.

The present invention additionally provided a use of aboved said pharmaceutical composition for the preparation of a medicament.

In some embodiments, the medicament is for treatment or prevention a disease or disorder mediated by the activity of SHP2.

In some embodiments, the disease or disorder mediated by the activity of SHP2 is cancer, cancer metastasis, cardiovascular disease, an immunological disorder, fibrosis, or an ocular disorder.

In some embodiments, the disease or disorder mediated by the activity of SHP2 is one or more selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, head and neck squamous-cell carcinoma, acute myeloid leukemia, breast cancer, esophageal tumor, lung cancer, colon cancer, head cancer, gastric carcinoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combination thereof.

The present invention additionally provided a use of at least one compound or pharmaceutically acceptable salt thereof of Formula I, II, III or IV for the preparation of a medicament.

In some embodiments, the medicament is for treatment or prevention a disease or disorder mediated by the activity of SHP2.

In some embodiments, the disease or disorder mediated by the activity of SHP2 is cancer, cancer metastasis, cardiovascular disease, an immunological disorder, fibrosis, or an ocular disorder.

In some embodiments, the disease or disorderm ediated by the activity of SHP2 is one or more selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, head and neck squamous-cell carcinoma, acute myeloid leukemia, breast cancer, esophageal tumor, lung cancer, colon cancer, head cancer, gastric carcinoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combination thereof.

The present invention additionally provided using at least one compound or pharmaceutically acceptable salt thereof of Formula I, II, III or IV, or pharmaceutical composition described above, which is for the preparation of a medicament.

In some embodiments, the medicament is for treatment or prevention a disease or disorder mediated by the activity of SHP2.

In some embodiments, the disease or disorder mediated by the activity of SHP2 is cancer, cancer metastasis, cardiovascular disease, an immunological disorder, fibrosis, or an ocular disorder.

In some embodiments, the disease or disorder mediated by the activity of SHP2 is one or more selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, head and neck squamous-cell carcinoma, acute myeloid leukemia, breast cancer, esophageal tumor, lung cancer, colon cancer, head cancer, gastric carcinoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combination thereof.

The present invention additionally provided a method of treating a patient having a condition which is mediated by the activity of SHP2, said method comprising administering to the patient a therapeutically effective amount of at least one compound or pharmaceutically acceptable salt thereof of Formula I, II, III or IV, or the pharmaceutical composition described above.

In some embodiments, the condition mediated by the activity of SHP2 is cancer, cancer metastasis, cardiovascular disease, an immunological disorder, fibrosis, or an ocular disorder.

In some embodiments, the condition mediated by the activity of SHP2 is noonan syndrome, leopard syndrome, juvenile myelomonocytic leukemias, liver cancer, neuroblastoma, melanoma,

squamous-cell carcinoma of the head and neck, acute myeloid leukemia, breast cancer, esophageal cancer, lung cancer, colon cancer, head cancer, gastric carcinoma, neuroblastoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combination thereof.

The present invention additionally provided a method of treating cancer selected from the group consisting of noonan syndrome, leopard syndrome, juvenile myelomonocytic leukemias, liver cancer, neuroblastoma, melanoma, squamous-cell carcinoma of the head and neck, acute myeloid leukemia, breast cancer, esophageal cancer, lung cancer, colon cancer, head cancer, gastric carcinoma, neuroblastoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combinations thereof, comprising administering to a mammal in need of such treatment an effective amount of at least one compound or pharmaceutically acceptable salt thereof of Formula I, II, III or IV, or the pharmaceutical composition described above.

The term "halogen", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. The preferred halogen groups include F, Cl and Br. The terms "haloC_{1-6}alkyl", "haloC_{2-6}alkenyl", "haloC_{2-6}alkynyl" and "haloC_{1-6}alkoxy" mean a C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-6}alkoxy in which one or more (in particular, 1,2 or 3) hydrogen atoms have been replaced by halogen atoms, especially fluorine or chlorine atoms. In some embiment, preferred are fluoroC_{1-6}alkyl, fluoroC_{2-6}alkenyl, fluoroC_{2-6}alkynyl and fluoroC_{1-6}alkoxy groups, in particular fluoroC_{1-3}alkyl, for example, CF_3, CHF_2, CH_2F, CH_2CH_2F, CH_2CHF_2, CH_2CF_3 and fluoroC_{1-3}alkoxy groups, for example, OCF_3, $OCHF_2$, OCH_2F, OCH_2CH_2F, OCH_2CHF_2 or OCH_2CF_3, and most especially CF_3, OCF_3 and $OCHF_2$.

As used herein, unless otherwise indicated, alkyl includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, cyclcopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclcobutyl, n-pentyl, 3- (2-methyl) butyl, 2-pentyl, 2-methylbutyl, neopentyl, cyclcopentyl, n- hexyl, 2-hexyl, 2-methylpentyl and cyclohexyl. Similary, C_{1-8}, as in C_{1-8}alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms in a linear or branched arrangement.

Alkylene means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. For example, methylene (i.e., -CH_2-), ethylene (i.e., -CH_2-CH_2- or –$CH(CH_3)$-) and propylene (i.e., -CH_2-CH_2- CH_2-, -$CH(-CH_2-CH_3)$- or –CH_2-$CH(CH_3)$-).

Alkoxy radicals are oxygen ethers formed from the previously described straight, branched chain or cyclic alkyl groups.

The term "aryl", as used herein, unless otherwise indicated, by itself or as part of another substituent refers to a monocyclic or polycyclic aromatic hydrocarbon. Phenyl and naphthyl are preferred aryls. The most preferred aryl is phenyl.

The term "heterocyclic", as used herein, unless otherwise indicated, by itself or as part of another substituent refers to unsubstituted and substituted mono- or polycyclic non-aromatic, partially unsaturated or fully saturated ring system containing one or more heteroatoms. Preferred heteroatoms include N, O, and S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to eight membered and is either fully saturated or has one or more degrees of unsaturation. Multiple degrees of substitution, preferably one, two or three, are included within the present definition.

Examples of such heterocyclic groups include, but are not limited to azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxoazepinyl, azepinyl, tetrahydrofuranyl, dioxolanyl, tetrahydroimidazolyl, tetrahydrothiazolyl, tetrahydrooxazolyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone and oxadiazolyl.

The term "heteroaryl", as used herein, unless otherwise indicated, by itself or as part of another substituent refers to an aromatic ring system containing carbon(s) and at least one heteroatom. Heteroaryl may be monocyclic or polycyclic, substituted or unsubstituted. A monocyclic heteroaryl group may have 1 to 4 heteroatoms in the ring, while a polycyclic heteroaryl may contain 1 to 10 hetero atoms. A polycyclic heteroaryl ring may contain fused, spiro or bridged ring junction, for example, bycyclic heteroaryl is a polycyclic heteroaryl. Bicyclic heteroaryl rings may contain from 8 to 12 member atoms. Monocyclic heteroaryl rings may contain from 5 to 8 member atoms (cabons and heteroatoms). Examples of heteroaryl groups include, but are not limited to thienyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, pyridyl, pyridazinyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, benzofuranyl, benzothienyl, benzisoxazolyl, benzoxazolyl, benzopyrazolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl adeninyl, quinolinyl or isoquinolinyl.

The term "cycloalkyl" as used herein, unless otherwise indicated, by itself or as part of another substituent refers to a substituted or unsubstituted monocyclic, bicyclic or polycyclic non-aromatic saturated or partially unsatureated hydrocarbon group, which optionally includes an alkylene linker through which the cycloalkyl may be attached. Examplary "cycloalkyl" groups includes but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and so on.

The term "carbonyl", "-C=O", "C=O", "-CO", "-C(O) ", and "CO" refer to the group  .

The term "oxo"refers to the radical =O.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralky or dialkylamino) , unless otherwise indicated, by itself or as part of another substituent, it shall be interpreted as including those limitations given above for "alkyl" and "aryl".

Designated numbers of carbon atoms (e.g., C_{1-6}) shall refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The substituents the two "R_1" of Formula I, II, III or IV can be the same or different. Similar to "R_1", and the two "Y_1" of Formula I, II, III or IV can be the same or different.

Compounds described herein, such as certain compounds of Formula I, II, III or IV may contain asymmetrically substituted carbon atoms (or chiral centers) in the R or S configuration. The present invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

The compounds described herein, when specifically designated as the R- or S- isomer, either in a chemical name or in a drawing, should be understood as an enriched R-isomer or S-isomer, respectively. For example, in any of the embodiments described herein, such enriched R- or S-designated isomer can be substantially free (e.g., with less than 5%, less than 1%, or non-detectable, as determined by chiral HPLC) of the other isomer for the respective chiral center. The enriched R- or S-isomers can be prepared by methods exemplified in this application, such as by using a chiral auxiliary such as R- or S-tert-butylsulfinamide in the synthetic process. Other methods for prepaing the enriched R- or S-isomers herein include, but are not limited to, chiral HPLC purifications of a stereoisomeric mixture, such as a racemic mixture. General methods for separating stereoisomers (such as enantiomers and/or diastereomers) using HPLC are known in the art.

Compounds described herein can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, and ^{125}I. Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention. In some embodiments, one or more hydrogen atoms of any of the compounds described herein can be substituted with deuterium to provide the corresponding deterium-labeled or -enriched compounds.

The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "ring systems" as used herein, unless otherwise indicated, include but not limite to a carbocyclic ring, a heterocyclic ring, a heteroaromatic ring, etc., may also include only a

heterocyclic ring, and/or a heteroaromatic ring, and the like, specifically includes which rings need to be determined according to the context, but anyway the "ring systems" do not include the cycloalkyl based on a C_{1-6} alkyl or C_{1-3} alkyl ogroup, and do not include the cycloalkoxy based on a C_{1-6} alkoxy or C_{1-3} alkoxy group.

Compounds of Formula I, II, III or IV may have different isomeric forms. For example, any asymmetric carbon atom may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. Substituents at a double bond or especially a ring may be present m cis-(= Z-) or trans (= E-) form. The compounds may thus be present as mixtures of isomers or preferably as pure isomers, preferably as pure diastereomers or pure enantiomers.

Where the plural form (e.g. compounds, salts) is used, this includes the singular (e.g. a single compound, a single salt). "A compound" does not exclude that (e.g. in a pharmaceutical formulation) more than one compound of the Formula I, II, III or IV (or a salt thereof) is present, the "a" merely representing the indefinite article. "A" can thus preferably be read as "one or more"， less preferably alternatively as "one".

"SHP2" means "Src Homolgy-2 phosphatase" and is also known as SH-PTP2, SH-PTP3, Syp, PTPlD, PTP2C, SAP-2 or PTPNl1.

Cancers harboring "PTPNll mutations" include but are not limited to: N58Y, D61Y, V; E69K; A72V, T, D; E76G, Q, K (ALL); G60A： D61Y; E69V; F71K; A72V; T731; E76G, K; R289G; G503V (AML); G60R, D61Y, V, N; Y62D; E69K; A72T, V; T731; E76K, V, G, A, Q; El39D; G503A, R; Q506P (JMML); G60V; D61V; E69K; F71L; A72V; E76A (MDS), Y63C (CMML); Y62C; E69K; T507K (neuroblastoma); V46L; N58S; E76V (Lung cancer), R138Q (melanoma); E76G (colon cancer)

The term "composition", as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. Accordingly, pharmaceutical compositions containing the compounds of the present invention as the active ingredient as well as methods of preparing the instant compounds are also part of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents and such solvates are also intended to be encompassed within the scope of this invention.

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts". The pharmaceutically acceptable salt forms include

pharmaceutically acceptable acidic/anionic or basic/cationic salts. The pharmaceutically acceptable acidic/anionic salt generally takes a form in which the basic nitrogen is protonated with an inorganic or organic acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic. Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, calcium, chloroprocaine, choline, diethanolamine, ethylenediamine, lithium, magnesium, potassium, sodium and zinc.

The present invention includes within its scope the prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds that are readily converted in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in"Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques know in the art as well as those methods set forth herein.

The present invention includes compounds described can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof.

The above Formula I, II, III or IV is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I, II, III or IV and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautomer of the compound of Formula I, II, III or IV exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically stated otherwise.

When the compound of Formula I, II, III or IV and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Since the compounds of Formula I, II, III or IV are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I, II, III or IV (or a pharmaceutically acceptable salt thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds represented by Formula I, II, III or IV, or a prodrug, or a metabolite, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a

powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in- oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, II, III or IV, or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound, or a pharmaceutically acceptable salt, of Formula I, II, III or IV. The compounds of Formula I, II, III or IV, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen. In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient. For example, a formulation

intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about lmg to about 2g of the active ingredient, typically 25mg, 50mg, l00mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or l000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I, II, III or IV of this invention, or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration and the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as

diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including antioxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, II, III or IV, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of from about 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, inflammation, cancer, psoriasis, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system (CNS), may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

These and other aspects will become apparent from the following written description of the invention.

Examples

The following Examples are provided to better illustrate the present invention. All parts and percentages are by weight and all temperatures are degrees Celsius, unless explicitly stated otherwise. The following abbreviations have been used in the examples:

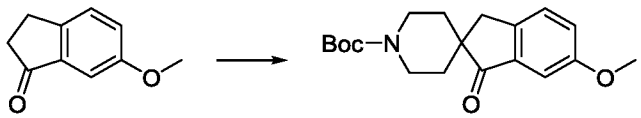
DMF	N,N-Dimethylformamide
EA	Ethyl acetate
Hex	Hexane
MeOH	Methanol
DCM	Dichloromethane
DCE	1,2-Dichloroethane
EtOH	Ethanol
t-BuOH	tert-Butanol
AcOH	Acetic acid glacial
AcONa	Sodium acetate

THF	Tetrahydrofuran
$Ti(OEt)_4$	Titanium ethoxide
NMP	1-Methyl-2-pyrrolidinone
DMSO	Dimethyl sulfoxide
DIEA	N,N-Diisopropylethylamine
$(Boc)_2O$	Di-tert-butyl dicarbonate
LDA	Lithium diisopropylamide
PPA	Polyphosphoric acids
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium

DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
TEA	Triethylamine
CH_3I	Iodomethane
$Pd(OAc)_2$	Palladium diacetate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
HATU	2-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
$Cy_3PH\cdot BF_4$	Tricyclohexylphosphonium tetrafluoroborate
MsCl	Methanesulfonyl chloride

n-BuLi	n-Butyllithium
LAH	Lithium aluminium hydride
t-BuOK	Potassium tert-butoxide
NaOEt	Sodium ethoxide
TFA	Triethylamine
HCl	Hydrochloric acid
RT	Room temperature
min	minute(s)
h	hour(s)
aq	aqueous
sat	saturated
TLC	Thin layer chromatography
Pre-TLC	Preparative thin layer chromatography

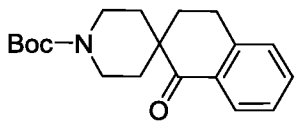
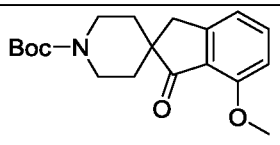
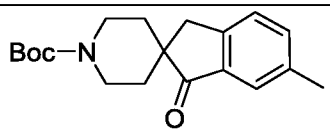
Intermediate A1

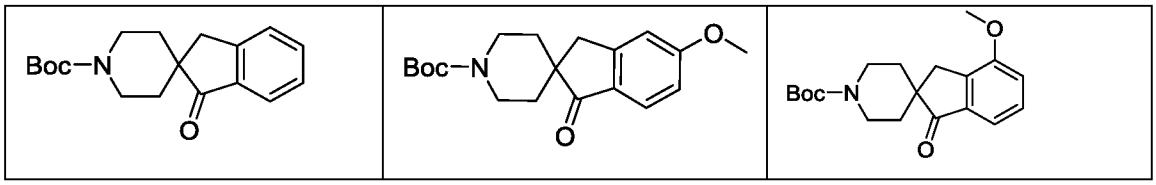


To a solution of 6-methoxy-2,3-dihydro-1H-inden-1-one (1.50 g, 9.25 mmol) in DMF (10 mL) under nitrogen atmosphere was added NaH (60% dispersion in mineral oil, 1.11 g, 27.75 mmol) in portions. The mixture was heated to 60 °C, stirred for 20 min at this temperature. Tert-butyl bis(2-chloroethyl)carbamate (2.46 g, 10.17 mmol) was added dropwise, and the mixture was stirred for 85 min. After cooling to RT, the reaction mixture was diluted with EA (200 mL), washed with brine (3 × 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 12, v/v) to give tert-butyl 6-methoxy-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (557 mg) as a yellow solid. MS: *m/z* 332 $(M+H)^+$.

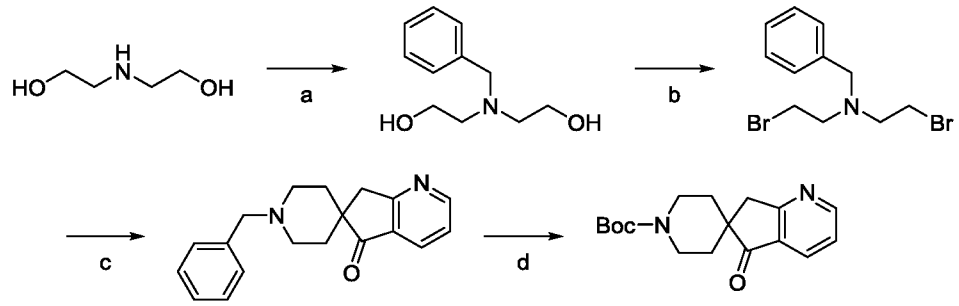
The following compounds were synthesized using the above procedure with the corresponding starting materials.

Table 1



Intermediate A2



Step a: A solution of 2,2'-azanediylbis(ethan-1-ol) (198.15 g, 1.88 mol), K_2CO_3 (520.95 g, 3.77 mol) and (bromomethyl)benzene (386.79 g, 2.26 mol) in acetonitrile (2000 mL) was stirred at 90 °C for 2.5 h. After cooling to RT, the reaction mixture was filtered followed by EA (2 × 100mL) wash. The filtrate was concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with MeOH : DCM = 1 : 10, v/v) to give 2,2'-(benzylazanediyl)bis(ethan-1-ol) (89.44 g) as a colorless oil. MS: *m/z* 196 $(M+H)^+$.

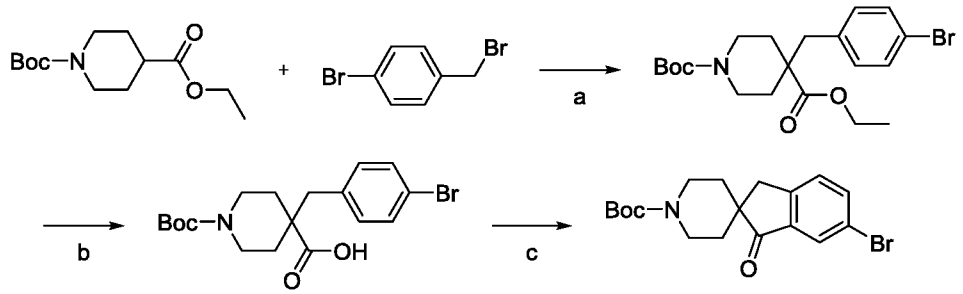
Step b: To a 0 °C solution of 2,2'-(benzylazanediyl)bis(ethan-1-ol) (30.66 g, 0.16 mol) in toluene (300 mL) was added tribromophosphane (69.13 g, 0.26 mol) dropwise. The resulting mixture was stirred at 105 °C for 16 h. After cooling to RT, the volatiles were removed under reduce pressure. The residue was diluted with water (300 mL), and the pH value was adjusted to 9 with NaOH. The resulting mixture was extracted with EA (3 × 150 mL), the organic layers combined, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give N-benzyl-2-bromo-N-(2-bromoethyl) ethan-1-amine (41.58 g) which was used in next step without any further purification. MS: *m/z* 320 $(M+H)^+$.

Step c: To a 0 °C solution of 6,7-dihydro-5H-cyclopenta[b]pyridin-5-one (1.70 g, 12.77 mmol) in DMF (20 mL) under nitrogen atmosphere was added NaH (60% dispersion in mineral oil, 982 mg, 24.55 mmol) in three portions, and the mixture was heated to 60 °C, stirred for 1 h at this temperature. Then N-benzyl-2-bromo-N-(2-bromoethyl)ethan-1-amine (4.54 g, 14.14 mmol) was added and stirred at 60 °C for another 1 h. After cooling to RT, the reaction mixture was quenched with water (80 mL), extracted with EA (3 × 80 mL). The combined organic layers were washed with water (3 × 80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA) to give 1'-benzylspiro[cyclopenta[b]pyridine-6,4'-piperidin]-5(7H)-one (1.14 g). MS: *m/z* 293 $(M+H)^+$.

Step d: To a 0 °C solution of 1'-benzylspiro[cyclopenta[b]pyridine-6,4'-piperidin]-5(7H)-one

(1.05 g, 3.59 mmol) in DCE (10 mL) was added 1-chloroethyl carbonochloridate (903 mg, 6.32 mmol) dropwise. The resulting mixture was stirred at RT for 1.5 h. The volatiles were removed under reduced pressure and the residue was dissolved in MeOH (20 mL), stirred at 80 °C for 4 h. The volatiles were removed under reduced pressure and dissolved in DCM (20 mL). DIEA (1.33 g, 10.32 mmol) and $(Boc)_2O$ (1.38 g, 6.32 mmol) were added. The resulting solution was stirred for 16 h at RT. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 1, v/v) to give tert-butyl 5-oxo-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate (438 mg). MS: *m/z* 303 $(M+H)^+$.

Intermediate A3



Step a: To a -70 °C solution of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate (8.14 g, 31.64 mmol) in THF (80 mL) under nitrogen atmosphere was added LDA (2 M solution in THF/Hex, 24 mL, 48.00mmol) dropwise. After stirred for 70 min at this temperature, 1-bromo-4-(bromomethyl)benzene (7.91 g, 31.64 mmol) was added in portions. The resulting solution was stirred for 3 h at -70°C, and carefully quenched with sat. aq. NH_4Cl (50 mL). The aqueous layer was separated, and extracted with EA (1 × 80 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(tert-butyl) 4-ethyl 4-(4-bromobenzyl)piperidine-1,4-dicarboxylate (14.55 g) as a brown oil which was used in next step without any further purification. MS: *m/z* 426 $(M+H)^+$.

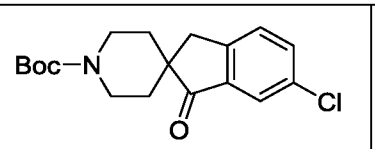
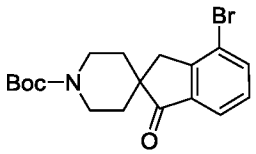
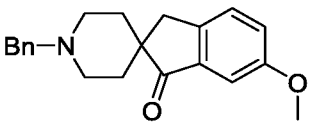
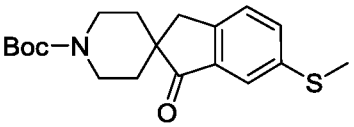
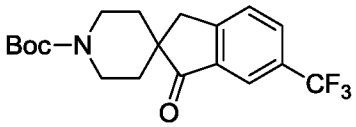
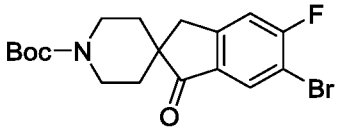
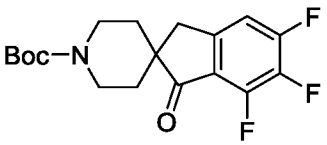
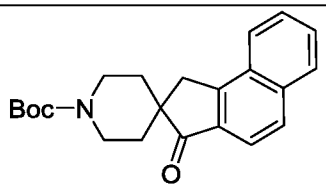
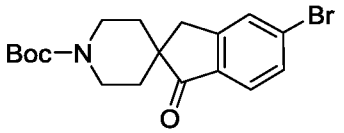
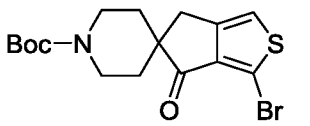
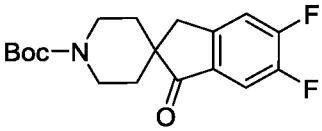
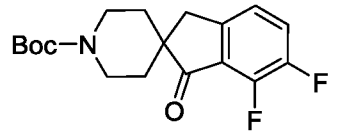
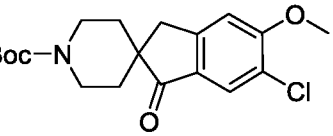
Step b: A solution of 1-(tert-butyl) 4-ethyl 4-(4-bromobenzyl)piperidine-1,4-dicarboxylate (14.55 g, 34.13 mmol) and NaOH (8.12 g, 203.00 mmol) in MeOH (80 mL) and water (80 mL) was stirred for 16.5 h at 75 °C. After cooling to RT, the volatiles were removed under reduced pressure. The resulting mixture was extracted with EA (3 × 80 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 4-(4-bromobenzyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (16.87 g) which was used in next step without any further purification. MS: *m/z* 398 $(M+H)^+$.

Step c: A mixture of 4-(4-bromobenzyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (16.87 g, 42.36 mmol) and PPA (60 mL) was stirred for 30 min at 120 °C. The reaction mixture

was poured into ice/water (300 mL), the pH value was adjusted to 10 with NaOH. Then $(Boc)_2O$ (13.86 g, 63.53 mmol) was added and stirred for 18 h at RT. The reaction mixture was extracted with EA (3 × 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 6-bromo-1-oxo-1,3-dihydrospiro [indene-2,4'-piperidine]-1'-carboxylate (16.87 g) which was used in next step without any further purification. MS: *m/z* 380 $(M+H)^+$.

The following compounds were synthesized using the above procedure or modifications procedure with the corresponding starting materials.

Table 2

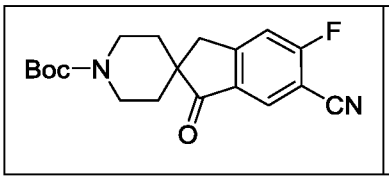
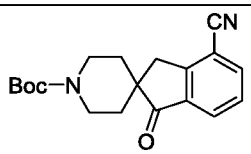
Intermediate A4

A mixture of tert-butyl 6-bromo-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (2.06 g, 5.42 mmol), $Pd(PPh_3)_4$ (626 mg, 0.54 mmol), DBU (252 mg, 1.66 mmol), t-BuOH (15 mL), water (15 mL) and potassium ferrocyanide trihyrate (1.16 g, 2.75 mmol) was stirred for 22.5 h at 90 °C under nitrogen atmosphere. After cooling to RT, the mixture was diluted with EA (30 mL), filtered followed by EA (15 mL) wash. The filtrate was washed with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 10, v/v) to give tert-butyl 6-cyano-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.86 g). MS:

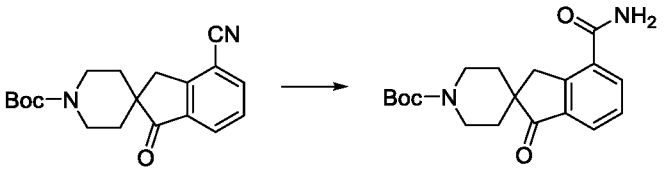
m/z 327 $(M+H)^+$.

The following compounds were synthesized using the above procedure with the corresponding starting materials.

Table 3

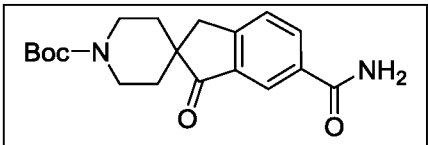
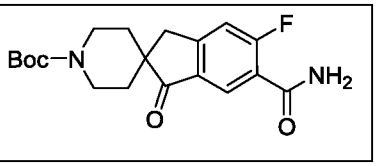
Intermediate A5



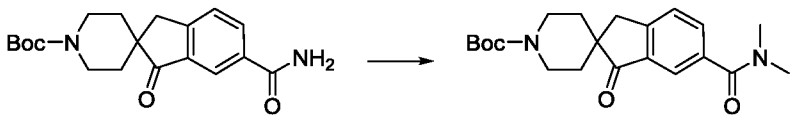
A solution of tert-butyl 4-cyano-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (0.93 g, 2.85 mmol) and KOH (1.60 g, 28.50 mmol) in MeOH (15 mL) and water (15 mL) was stirred for 2 h at 100 °C. After cooling to RT, the reaction mixture was diluted with water (30 mL), extracted with EA (60 mL, 30 mL). The combined organic layers were washed with brine (1 × 80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 4-carbamoyl-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.04 g) which was used in next step without any further purification. MS: *m/z* 345 $(M+H)^+$.

The following compounds were synthesized using the above procedure with the corresponding starting materials.

Table 4

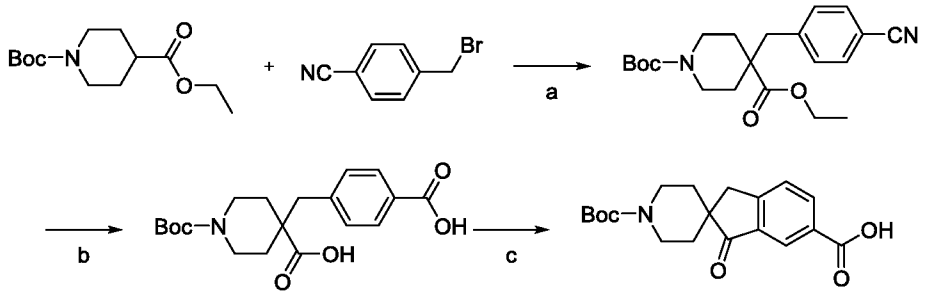
Intermediate A6



To a solution of tert-butyl 6-carbamoyl-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.57 g, 4.56 mmol) in DMF (15 mL) was added NaH (60% dispersion in mineral oil, 0.91 g, 22.79 mmol) followed by the addition of CH_3I (1 mL, 16.06 mmol). The resulting mixture was stirred for 17 h at RT. The reaction was quenched with brine (50 mL), extracted with EA (2 × 50 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by

silica chromatography (eluting with EA : Hex = 1: 3, v/v) to give tert-butyl 6-(dimethylcarbamoyl)-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (0.82 g). MS: *m/z* 373 $(M+H)^+$.

Intermediate A7

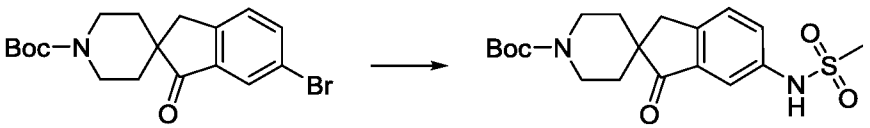


Step a-c: Step (a-c) of Intermediate A 3 was applied to provide 1'-(tert-butoxycarbonyl)-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxylic acid. MS: *m/z* 346 $(M+H)^+$.

Intermediate A8

A 50 mL sealed tube was charged with tert-butyl 6-bromo-1-oxo-1,3-dihydrospiro [indene-2,4'-piperidine]-1'-carboxylate (998 mg, 2.62 mmol), DMSO (8 mL), water (4 mL), CuI (217 mg, 1.14 mmol) and ammonium hydroxide (25%, 4 mL). The resulting mixture was stirred for 5 days at 100 °C. After cooling to RT, the reaction mixture was diluted with brine (20 mL) and EA (30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 6-amino-1-oxo-1,3-dihydrospiro [indene-2,4'-piperidine]-1'-carboxylate (750 mg). MS: *m/z* 317 $(M+H)^+$.

Intermediate A9

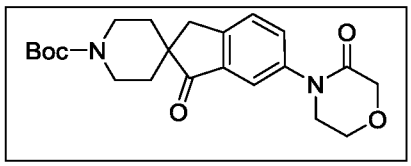


A mixture of tert-butyl 6-bromo-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (534 mg, 1.40 mmol), methanesulfonamide (371 mg, 3.90 mmol), K_2CO_3 (1.10 g, 7.95 mmol), N,N'-dimethyl-1,2-ethanediamine (85 mg, 0.96 mmol), CuI (72 mg, 0.38 mmol) in 1,4-dioxane (20 mL) under nitrogen atmosphere was stirred for 23 h at 110 °C. An additional portion of methanesulfonamide (370 mg, 3.89 mmol), N,N'-dimethyl-1,2-ethanediamine (85 mg, 0.96 mmol), CuI (75 mg, 0.39 mmol) was added, and stirred for another 7 h at the same temperature. After cooling to RT, the reaction was quenched with water (30 mL), extracted with EA (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and

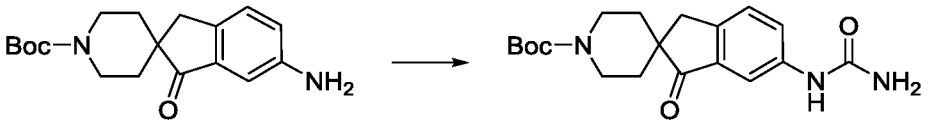
concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 2 : 3, v/v) to give tert-butyl 6-(methylsulfonamido)-1-oxo-1,3-dihydrospiro [indene-2,4'-piperidine]-1'-carboxylate (562 mg). MS: *m/z* 395 $(M+H)^+$.

The following compound was synthesized using the above procedure with the corresponding starting materials.

Table 5

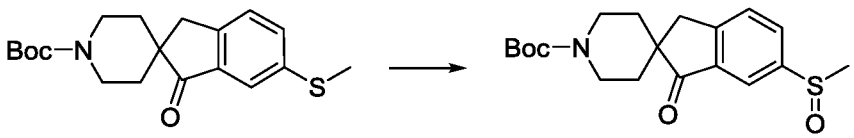


Intermediate A10



To a solution of tert-butyl 6-amino-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (0.66 g, 2.09 mmol) in AcOH (5 mL) and water (10 mL) was added a solution of sodium cyanate (0.28 g, 4.31 mmol) in water (2 mL) dropwise. The resulting mixture was stirred for 4 h at 50 °C. After cooling to RT, the pH value of the reaction mixture was adjusted to 12 with ammonium hydroxide (25%) and extracted with DCM (60 mL, 30 mL). The combined organic layers were washed with brine (1 × 60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 2 :1, v/v) to give tert-butyl 1-oxo-6-ureido-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (0.39 g). MS: *m/z* 360 $(M+H)^+$.

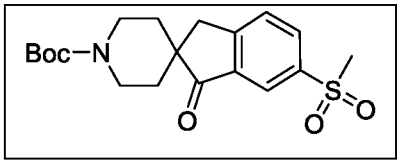
Intermediate A11



To a 0 °C solution of tert-butyl 6-(methylthio)-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (336 mg, 0.97 mmol) in MeOH (20 mL) and water (20 mL) was added potassium peroxymonosulfate (296 mg, 1.76 mmol). The resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (10 mL), the volatiles were removed under reduced pressure. The resulting mixture was extracted with EA (3 × 40 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 4 : 1, v/v) to give tert-butyl 6-(methylsulfinyl)-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (285 mg). MS: *m/z* 364 $(M+H)^+$.

The following compound was synthesized using the above procedure with the corresponding starting materials.

Table 6

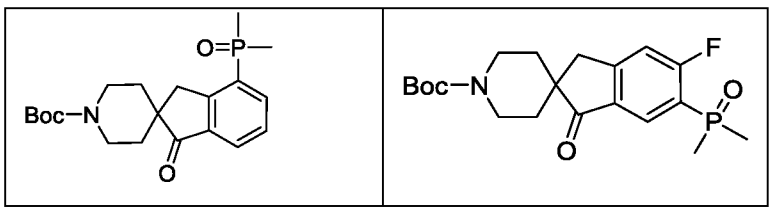


Intermediate A12

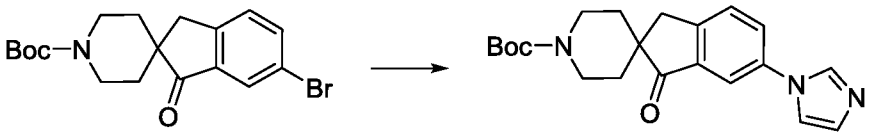
A mixture of tert-butyl 6-bromo-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.51 g, 3.97 mmol), dimethyl(oxo)phosphanium (503 mg, 6.44 mmol), $Pd(OAc)_2$ (92 mg, 0.41 mmol), Xantphos (457 mg, 0.79 mmol), K_3PO_4 (1.57g, 7.40 mmol) and DMF (30 mL) was stirred for 16.5 h at 130 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was quenched with water (120 mL), extracted with EA (3 × 80 mL). The combined organic layers were washed with brine (1 × 120 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with MeOH : DCM = 1 : 30, v/v) to give tert-butyl 6-(dimethylphosphoryl)-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (0.81 g) as a white solid. MS: *m/z* 378 $(M+H)^+$.

The following compounds were synthesized using the above procedure with the corresponding starting materials.

Table 7



Intermediate A13

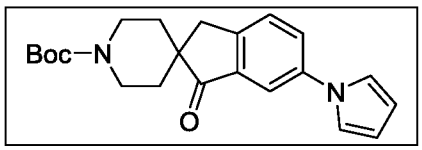


A mixture of tert-butyl 6-bromo-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.09 g, 2.87 mmol), 1H-imidazole (180 mg, 2.64 mmol), CuBr (34 mg, 0.24 mmol), Cs_2CO_3 (851 mg, 2.61 mmol), 1,2,3,4-tetrahydro-8-hydroxyquinoline (74 mg, 0.49 mmol) and DMSO (10 mL) was stirred for 23 h at 110 °C under nitrogen atmosphere. After cooling to RT, the

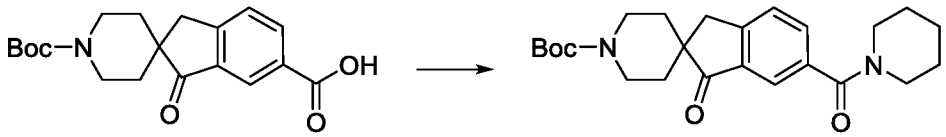
reaction mixture was quenched with water (30 mL), extracted with EA (1 × 40 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA) to give tert-butyl 6-(1H-imidazol-1-yl)-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (142 mg) as a yellow solid. MS: *m/z* 368 $(M+H)^+$.

The following compound was synthesized using the above procedure with the corresponding starting materials.

Table 8

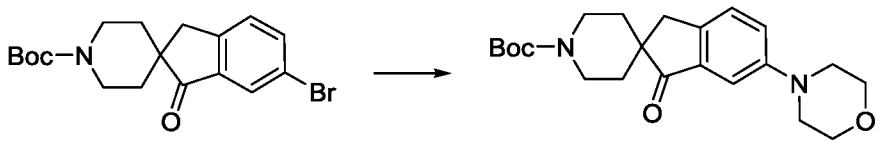


Intermediate A14



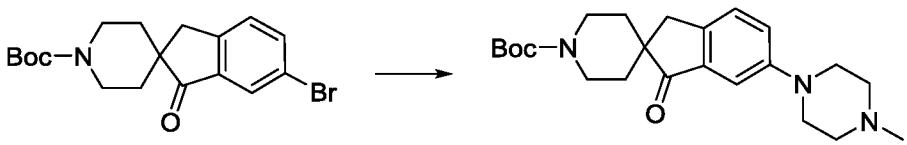
A mixture of 1'-(tert-butoxycarbonyl)-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxylic acid (345 mg, 1.00 mmol), piperidine (129 mg, 1.51 mmol) and HATU (422 mg, 1.11 mmol) in DMF was stirred for 1 h at RT. The reaction mixture was diluted with water (30 mL) and EA (30 mL). The organic layer was separated, washed with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 1-oxo-6-(piperidine-1-carbonyl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (380 mg). MS: *m/z* 413 $(M+H)^+$.

Intermediate A15



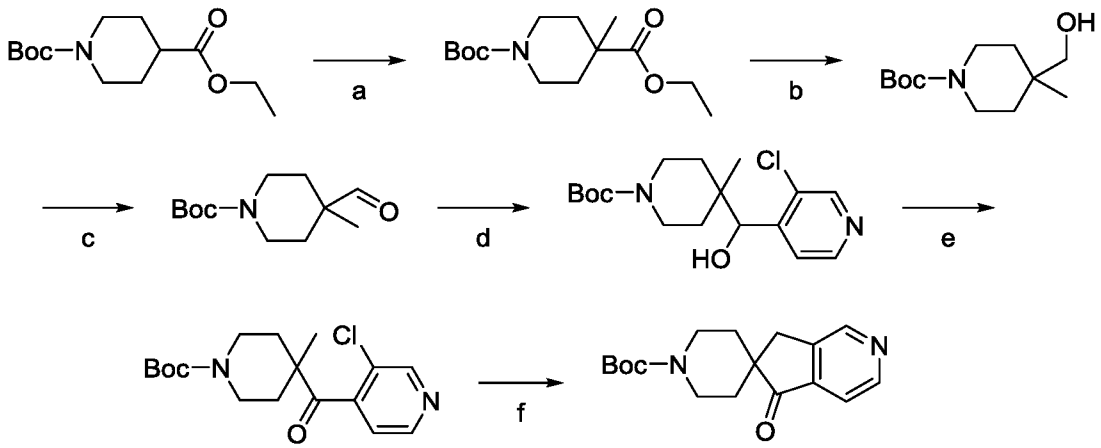
A mixture of tert-butyl 6-bromo-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.02 g, 2.68 mmol), morpholine (0.67 g, 7.69 mmol), $Cu(OAc)_2$ (0.51 g, 2.81 mmol), DBU (1.03 g, 6.77 mmol) in DMSO (10 mL) was stirred for 23 h at 130 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with water (70 mL), extracted with EA (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 1, v/v) to give tert-butyl 6-morpholino-1-oxo-1,3-dihydrospiro [indene-2,4'-piperidine]-1'-carboxylate (467 mg). MS: *m/z* 387 $(M+H)^+$.

Intermediate A16



A mixture of tert-butyl 6-bromo-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (500 mg, 1.31 mmol), 1-methylpiperazine (270 mg, 2.70 mmol), Cs_2CO_3 (1306 mg, 4.01 mmol), $Pd_2(dba)_3$ (66 mg, 0.07 mmol) and XantPhos (75 mg, 0.13 mmol) in 1,4-dioxane (18 mL) was stirred for 0.5 h at 100 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was quenched with water, extracted with EA (2 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 6-(4-methylpiperazin-1-yl)-1-oxo-1,3-dihydrospiro [indene-2,4'-piperidine]-1'-carboxylate (0.87 g, crude) which was used in next step without any further purification. MS: *m/z* 400 $(M+H)^+$.

Intermediate A17



Step a: To a -60 °C solution of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate (15.52 g, 60.31 mmol) in THF (100 ml) was added LDA (2 M solution in THF/Hex, 45.00 mL, 90.00 mmol) dropwise under nitrogen atmosphere. The resulting mixture was allowed to warm to -20 °C and stirred for 50 min. The mixture was cooled to -50 °C, and a solution of CH_3I (8.56 g, 60.31 mmol) in THF (20 mL) was added dropwise. The resulting mixture was stirred for 50 min at this temperature. The reaction mixture was carefully quenched with sat. aq. NH_4Cl (80 mL), extracted with EA (100 mL, 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(tert-butyl) 4-ethyl 4-methylpiperidine-1,4-dicarboxylate (17.70 g) which was used without any further purification. MS: *m/z* 216 $(M+H-56)^+$.

Step b: To a 0 °C solution of 1-(tert-butyl) 4-ethyl 4-methylpiperidine-1,4-dicarboxylate (17.70 g, 65.23 mmol) in THF (150 mL) was added a $LiBH_4$ (2 M solution in THF, 98.00mL,

196.00mmol). The resulting mixture was stirred for 18 h at 70 °C. After cooling to RT, water (100 mL) was added dropwise. The resulting mixture was extracted with EA (200 mL, 100 mL), the combined organic layers were washed with brine (1 × 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 4-(hydroxymethyl)-4-methylpiperidine-1-carboxylate (12.90 g) which was used in next step without any further purification. MS: *m/z* 174 $(M+H-56)^+$.

Step c: To a -78 °C solution of oxalyl chloride (10.71 g, 84.38 mmol) in DCM (150 mL) was added a solution of DMSO (10.99 g, 140.63 mmol) in DCM (30 mL) dropwise, stirred for 30 min at this temperature. A solution of tert-butyl 4-(hydroxymethyl)-4-methylpiperidine-1-carboxylate (12.90 g, 56.25 mmol) in DCM (30 mL) was added dropwise, stirred for 30 min at -78 °C. Triethylamine (22.77 g, 225.02 mmol) was added dropwise, the resulting mixture was allowed to warm to -20 °C, and stirred for 40 min. The reaction mixture was quenched with water (80 mL). The aqueous layer was separated and extracted with DCM (1 × 80 mL). The combined organic layers were washed with brine (1 × 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 20, v/v) to give tert-butyl 4-formyl-4-methylpiperidine-1-carboxylate (11.82 g). MS: *m/z* 172 $(M+H-56)^+$.

Step d: To a -70 °C solution of 3-chloropyridine (2.25 g, 17.64 mmol) in THF (50 mL) was added LDA (2 M solution in THF/Hex, 11.00 mL, 22.00 mmol) dropwise. The resulting mixture was allowed to warm to -60 °C and stirred for 1.5 h. A solution of tert-butyl 4-formyl-4-methylpiperidine-1-carboxylate (3.95 g, 17.37 mmol) in THF (10 mL) was added dropwise at -70 °C. After stirring for 1 h, the mixture was quenched with water (50 mL). The aqueous layer was separated and extracted with EA (60 mL, 30 mL). The combined organic layers were washed with brine (1 × 80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 4-((3-chloropyridin-4-yl)(hydroxy)methyl)-4-methylpiperidine-1-carboxylate (8.10 g) which was used in next step without any further purification. MS: *m/z* 341 $(M+H)^+$.

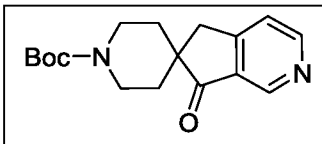
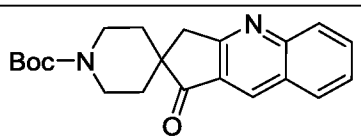
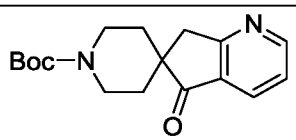
Step e: To a solution of tert-butyl 4-((3-chloropyridin-4-yl)(hydroxy)methyl)-4-methylpiperidine-1-carboxylate (8.10 g, 23.76 mmol) in DCM (50 ml) was added Dess-Martin periodinane (20.12 g, 47.44 mmol). The resulting mixture was stirred for 16 h at RT. The reaction mixture was diluted with DCM (100 mL), washed with aq. $Na_2S_2O_3$ (25%, 1 × 80 mL), sat. aq. $NaHCO_3$ (1 × 80 mL) and brine (1 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica

chromatography (eluting with EA : Hex = 1 :3, v/v) to give tert-butyl 4-(3-chloroisonicotinoyl)-4-methylpiperidine-1-carboxylate (4.81 g). MS: *m/z* 339 $(M+H)^+$.

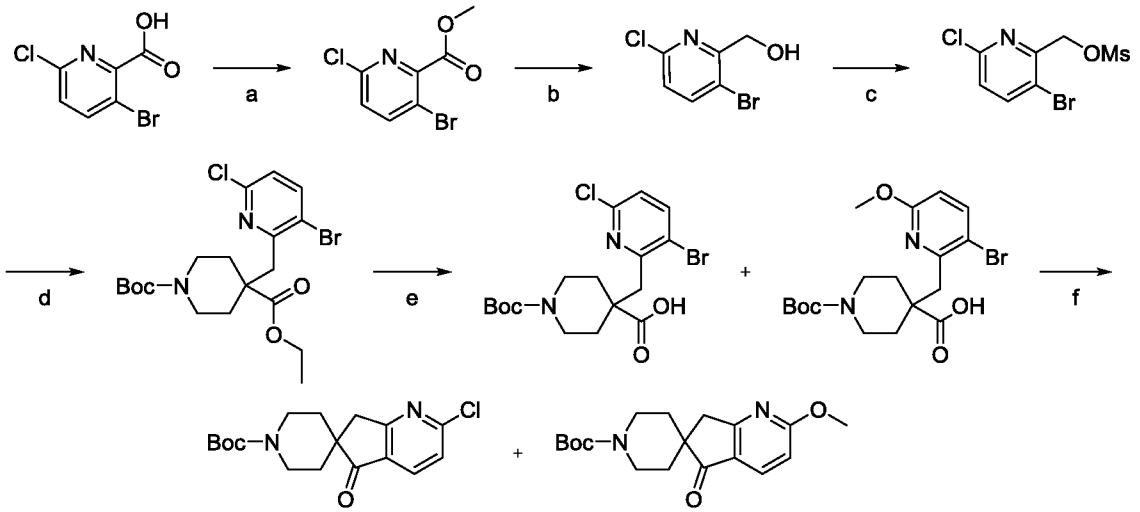
Step f: A mixture of tert-butyl 4-(3-chloroisonicotinoyl)-4-methylpiperidine-1-carboxylate (6.31 g, 18.62 mmol), Cs_2CO_3 (6.72g, 21.90mmol), pivalic_acid (571 mg, 5.60 mmol), $Pd(OAc)_2$ (0.22 g, 0.98 mmol) and $Cy_3PH{\cdot}BF_4$ (0.70 g, 1.90 mmol) in 1,3,5-mesitylene (40 mL) was stirred for 72 h at 140 °C under nitrogen atmosphere. After cooling to RT, the mixture was filtered followed by EA (3 × 40 mL) wash. The filtrate was concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 1, v/v) to give tert-butyl 5-oxo-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidine]-1'-carboxylate (2.82 g). MS: *m/z* 303 $(M+H)^+$.

The following compounds were synthesized using the above procedure with the corresponding starting materials.

Table 9

Intermediate A18



Step a: To a solution of 3-bromo-6-chloropicolinic acid (9.98 g, 42.21 mmol) in MeOH (100 mL) was added H_2SO_4 (98%, 10.00 mL) dropwise. The mixture was stirred for 3 h at 70 °C. After cooling to RT, the pH value of the reaction mixture was adjusted to 9 by ammonium hydroxide (25%). The volatiles were removed under reduced pressure. The mixture was diluted with water (60 mL), extracted with EA (1 × 100 mL). The organic layer was washed with brine (1 × 60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give methyl 3-bromo-6-chloropicolinate (10.14 g) as an off-white solid. MS: *m/z* 250 $(M+H)^+$.

Step b: To a 0 °C solution of methyl 3-bromo-6-chloropicolinate (10.14 g, 40.48 mmol) in

MeOH (150 mL) was added $NaBH_4$ (4.62 g, 122.13 mmol) in portions. The resulting mixture was allowed to warm to RT and stirred for 16 h. The reaction mixture was diluted with brine (110 mL) and MeOH was removed under reduced pressure. The resulting mixture was extracted with EA (100 mL, 80 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give (3-bromo-6-chloropyridin-2-yl)methanol (8.31 g). MS: *m/z* 222 $(M+H)^+$.

Step c: To a -15 °C solution of (3-bromo-6-chloropyridin-2-yl)methanol (8.31 g, 37.35 mmol) and triethylamine (7.63 g, 75.40 mmol) in DCM (100 mL) was added MsCl (4.71 g, 41.12 mmol) dropwise. The resulting mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was quenched with water (50 mL) and the aqueous layer was separated. The organic layer was washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give (3-bromo-6-chloropyridin-2-yl)methyl methanesulfonate (8.54 g). MS: *m/z* 300 $(M+H)^+$.

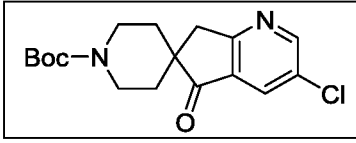
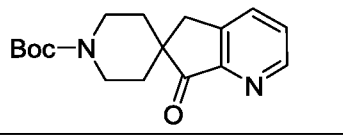
Step d: To a -50 °C solution of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate (9.66 g, 37.54 mmol) in THF (30 mL) was added LDA (2 M solution in THF/Hex, 23.00 mL, 46.00 mmol) dropwise under nitrogen atmosphere. The resulting mixture was stirred for 1 h at this temperature. A solution of (3-bromo-6-chloropyridin-2-yl)methyl methanesulfonate (8.54 g, 28.41 mmol) in THF (15 mL) was added dropwise, the resulting mixture was allowed to warmed to RT and stirred for 1 h. The reaction mixture was quenched with brine (60 mL) and extracted with EA (1 × 30mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(tert-butyl) 4-ethyl 4-((3-bromo-6-chloropyridin-2-yl)methyl)piperidine-1,4-dicarboxylate (17.73 g) which was used in next step without any further purification. MS: *m/z* 461 $(M+H)^+$.

Step e: A solution of 1-(tert-butyl) 4-ethyl 4-((3-bromo-6-chloropyridin-2-yl)methyl) piperidine-1,4-dicarboxylate (17.73 g, 38.39 mmol) and NaOH (8.03 g, 200.75 mmol) in MeOH (100 mL) and water (20 mL) was stirred for 16 h at 65 °C. After cooling to RT, the volatiles were removed under reduced pressure and the resulting mixture was diluted with water (150 mL). The pH value was adjusted to 6 with sat. aq. citric acid. The mixture was extracted with EA (2 × 100 mL), the combined organic layers were washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 10, v/v) to give the mixture of4-((3-bromo-6-chloropyridin-2-yl)methyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid and4-((3-bromo-6-methoxypyridin-2-yl)methyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (18.24 g). MS: *m/z* 433 $(M+H)^+$, MS: *m/z* 429 $(M+H)^+$.

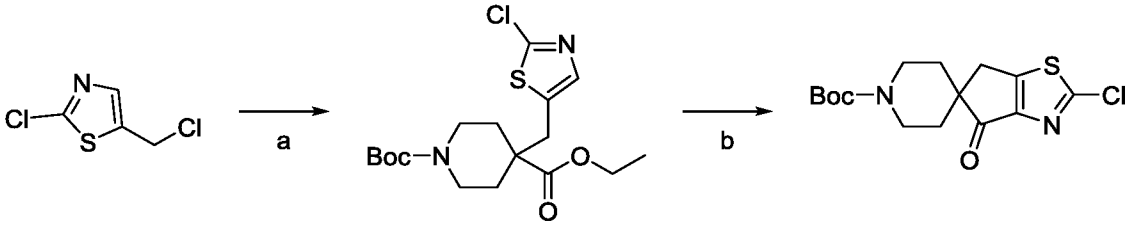
Step f: To a -15 °C solution of 4-((3-bromo-6-chloropyridin-2-yl)methyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid and 4-((3-bromo-6-methoxypyridin-2-yl)methyl)-1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (3.80 g, 8.76 mmol) in THF (20 mL) was added NaH (60 % dispersion in mineral oil, 0.42 g, 10.50 mmol) in portions under nitrogen atmosphere. After stirring for 1 h at this temperature, the mixture was cooled to -60 °C. To the mixture was added n-BuLi (2.5M solution in Hex, 5 mL, 12.50 mmol) dropwise, stirred for 1 h. The reaction mixture was quenched with water (20 mL), extracted with EA (1 × 40 mL). The organic layer was washed with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (EA : Hex = 1 : 10, v/v) to give the mixture of tert-butyl 2-chloro-5-oxo-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate and tert-butyl 2-methoxy-5-oxo-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate (1.48 g). MS: *m/z* 337 $(M+H)^+$. MS: *m/z* 333 $(M+H)^+$.

The following compounds were synthesized using the above procedure or modification procedure with the corresponding starting materials.

Table 10

Intermediate A19

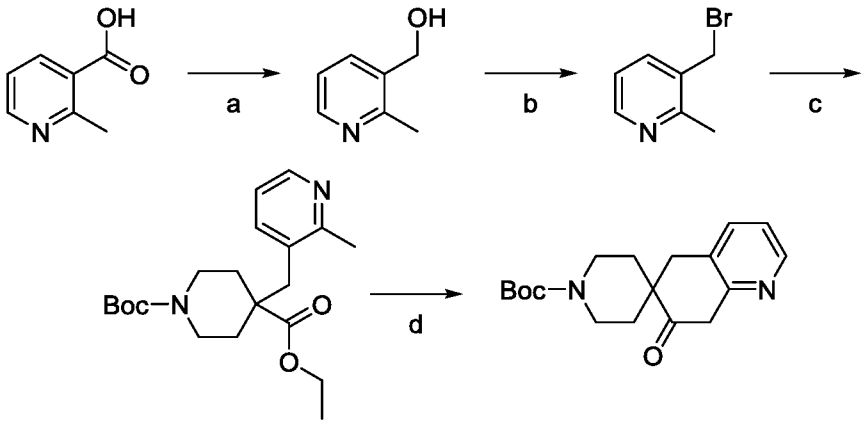


Step a: To a -78 °C solution of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate (2.83 g, 11.00 mmol) in THF (50 mL) was added LDA (2 M solution in THF/Hex, 6.00 mL, 12.00 mmol) dropwise under nitrogen atmosphere. The resulting mixture was stirred for 1 h at this temperature. 2-Chloro-5-(chloromethyl)thiazole (in 3 mL THF, 1.69 g, 10.06 mmol) was added dropwise at -78 °C, and stirred for 1 h. The reaction mixture was quenched with brine (50 mL), extracted with EA (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 20, v/v) to give 1-(tert-butyl) 4-ethyl 4-((2-chlorothiazol-5-yl)methyl) piperidine-1,4-dicarboxylate (1.15 g). MS: *m/z* 389 $(M+H)^+$.

Step b: To a -78 °C solution of 1-(tert-butyl) 4-ethyl 4-((2-chlorothiazol-5-yl)methyl) piperidine-1,4-dicarboxylate (900 mg, 2.31 mmol) in THF (50 mL) was added LDA (2 M solution

in THF/Hex, 3.00 mL, 6.00 mmol) dropwise under nitrogen atmosphere. The resulting mixture was stirred for 30 min at this temperature, quenched with brine (30 mL). The resulting mixture was extracted with EA (2 × 30 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 2-chloro-4-oxo-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate (832 mg). MS: *m/z* 343 $(M+H)^+$.

Intermediate A20



Step a: To a 0 °C solution of 2-methylnicotinic acid (4.56 g, 33.25 mmol) in THF (50 mL) was added LAH (1.51 g, 39.90 mmol). The resulting mixture was allowed to warm to RT and stirred for 4 h. The reaction mixture was diluted carefully with sat. aq. NH_4Cl (50 mL). The resulting mixture was filtered, the organic extract was collected and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give (2-methylpyridin-3-yl) methanol as a yellow oil (1.42 g). MS: *m/z* 124 $(M+H)^+$.

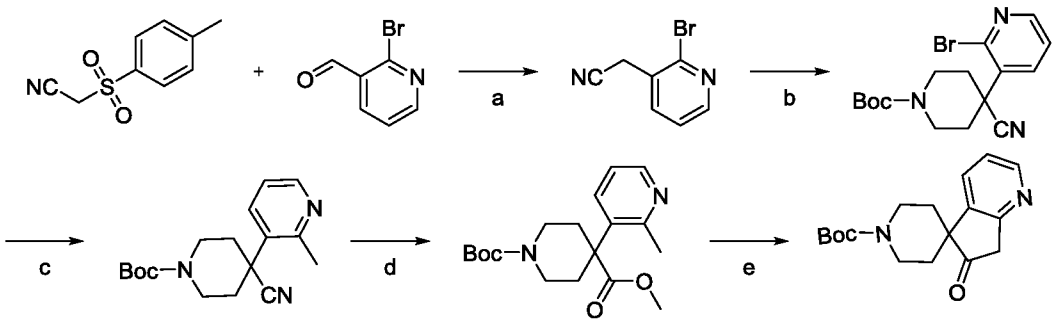
Step b: To a 0 °C mixture of (2-methylpyridin-3-yl) methanol (1.41 g, 11.45 mmol) in DCM (20 mL) was added PBr_3 (1.86 g, 6.87 mmol) dropwise. The resulting mixture was allowed to warm to RT and stirred for 1.5 h. The reaction mixture was taken to pH 8 using aq. NaOH (5 M, 10 mL). The aqueous layer was separated and the organic layer was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 3-(bromomethyl) -2-methylpyridine as a yellow oil (3.52 g) which was used in next step without any further purification. MS: *m/z* 186 $(M+H)^+$.

Step c: To a -50 °C solution of 1-tert-butyl 4-ethyl piperidine-1, 4-dicarboxylate (4.63 g, 18.00 mmol) in THF (30 mL) was added LDA (2 M solution in THF/Hex, 12.00 mL, 24.00 mmol) dropwise, stirred for 1 h at this temperature. 3-(Bromomethyl)-2-methylpyridine (3.25 g, 18.00 mmol) was added, the resulting mixture was allowed to warm to RT and stirred for 16 h. The reaction mixture was diluted carefully with sat. aq. NH_4Cl (50 mL). The aqueous layer was separated and the organic layer was washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4,

filtered and concentrated under reduced pressure to give 1-(tert-butyl) 4-ethyl 4-((2-methylpyridin-3-yl)methyl)piperidine-1,4-dicarboxylate as a red oil (4.87 g) which was used in next step without any further purification. MS: *m/z* 363 $(M+H)^+$.

Step d: To a -20 °C solution of 1-(tert-butyl) 4-ethyl 4-((2-methylpyridin-3-yl)methyl) piperidine-1, 4-dicarboxylate (4.23 g, 11.67 mmol) in THF (40 mL) was added LDA (2 M solution in THF/Hex, 12.00 mL, 24.00 mmol) dropwise, the resulting mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was diluted carefully with brine (50 mL). The aqueous layer was separated and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 1, v/v) to give tert-butyl 7'-oxo-7',8'-dihydro-5'H-spiro[piperidine-4,6'-quinoline]-1-carboxylate (1.23 g) as a yellow oil. MS: *m/z* 317 $(M+H)^+$.

Intermediate A21



Step a: To a -60 °C mixture of t-BuOK (5.92 g, 52.76 mmol) in 1,2-dimethoxyethane (50 mL) was added a solution of 2-tosylacetonitrile (5.08 g, 26.02 mmol) in 1,2-dimethoxyethane (20 mL) dropwise. To the resulting mixture was added a solution of 2-bromonicotinaldehyde (4.81 g, 25.86 mmol) in 1,2-dimethoxyethane (20 mL) dropwise at -60 °C. After stirring for 1 h at this temperature, MeOH was added (50 mL), the resulting mixture was allowed to warm to RT, stirred for 1 h and warmed to 85 °C, stirred for another 1h. After cooling to RT, the volatiles was removed under reduced pressure, diluted with brine (200 mL) and extracted with EA (3 × 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 10, v/v) to give 2-(2-bromopyridin-3-yl)acetonitrile (2.21 g). MS: *m/z* 197 $(M+H)^+$.

Step b: To a 0 °C solution of 2-(2-bromopyridin-3-yl)acetonitrile (2.21 g, 11.21 mmol) in DMF (20 mL) was added NaH (60% dispersion in mineral oil, 1.12 g, 28.03 mmol) in portions. The resulting mixture was warmed to 60 °C and stirred for 1.5 h. Tert-butyl bis(2-chloroethyl)carbamate (3.26 g, 13.46 mmol) was added to the mixture and stirred for 2 h at 60 °C. After cooling to RT, the reaction mixture was quenched with brine (50 mL), extracted with EA (3 × 100 mL). The combined organic layers were washed with brine (3 × 80 mL), dried over

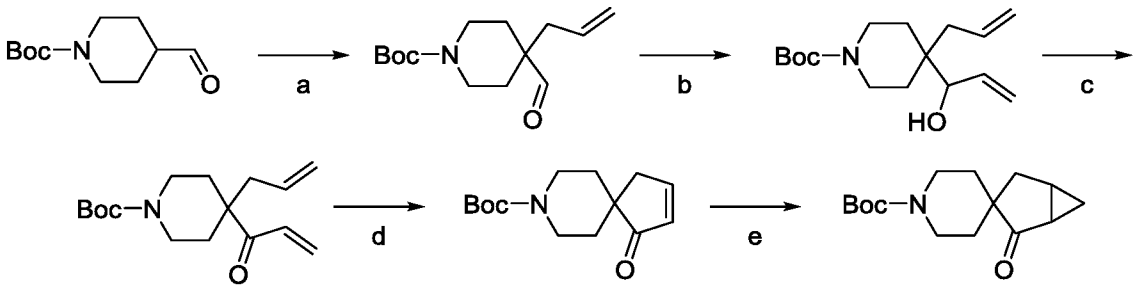
anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 3, v/v) to give tert-butyl 4-(2-bromopyridin-3-yl)-4-cyanopiperidine-1-carboxylate (1.56 g). MS: *m/z* 366 $(M+H)^+$.

Step c: A mixture of tert-butyl 4-(2-bromopyridin-3-yl)-4-cyanopiperidine-1-carboxylate (1.56 g, 4.26 mmol), K_2CO_3 (2.35 g, 17.04 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.07 g, 8.52 mmol) and $Pd(PPh_3)_4$ (47 mg, 0.041 mmol) in 1,4-dioxane (40 mL) and water (8 mL) was stirred for 2 h at 110 °C under nitrogen atmosphere. An additional portion of 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (2.15 g, 17.13 mmol) and $Pd(PPh_3)_4$ (45 mg, 0.039 mmol) was added and stirred for another 3 h at 110 °C. After cooling to RT, the reaction mixture was diluted with brine (100 mL), extracted with EA (3 × 100 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 2 : 1, v/v) to give tert-butyl 4-cyano-4-(2-methylpyridin-3-yl)piperidine-1-carboxylate (1.08 g). MS: *m/z* 302 $(M+H)^+$.

Step d: To a 0 °C solution of tert-butyl 4-cyano-4-(2-methylpyridin-3-yl)piperidine-1-carboxylate (1.08 g, 3.58 mmol) in MeOH (50 mL) was added H_2SO_4 (98 %, 45 mL) dropwise. The resulting mixture was stirred for 18 h at reflux temperature. After cooling to RT, the reaction mixture was poured into ice/water (200 mL), the pH value was adjusted to 9 with sat. aq. NaOH. To the mixture was added $(Boc)_2O$ (11.00 g, 50.40 mmol) and stirred for 2 h at RT. The reaction mixture was extracted with EA (3 × 100 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA) to give 1-(tert-butyl) 4-methyl 4-(2-methylpyridin-3-yl)piperidine-1,4-dicarboxylate (467 mg). MS: *m/z* 335 $(M+H)^+$.

Step e: To a 0 °C solution of 1-(tert-butyl) 4-methyl 4-(2-methylpyridin-3-yl)piperidine-1,4-dicarboxylate (467 mg, 1.40 mmol) in THF (10.50 mL) was potassium bis(trimethylsilyl)amide (1 M solution in THF, 7.00 mL, 7.00 mmol) dropwise under nitrogen atmosphere. The resulting mixture was allowed to warm to RT and stirred for 3.5 h, then quenched with sat.aq.NH_4Cl (10 mL) and extracted with EA (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA) to give tert-butyl 6-oxo-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidine]-1'-carboxylate (170 mg). MS: *m/z* 303 $(M+H)^+$.

Intermediate A22



Step a: To a 0 °C mixture of tert-butyl 4-formylpiperidine-1-carboxylate (15.00 g, 70.33 mmol) in DMF (60 mL) was added lithium 2-methylpropan-2-olate (6.75 g, 84.44 mmol) in portions. The resulting mixture was stirred for 30 min at 0 °C. To the mixture was added 3-bromoprop-1-ene (9.73 g, 80.44 mmol) dropwise at 0 °C and stirred for 1 h at this temperature. The reaction mixture was diluted with brine (100 mL), extracted with EA (3 × 200 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 20, v/v) to give tert-butyl 4-allyl-4-formylpiperidine-1-carboxylate (7.01 g). MS: *m/z* 254 $(M+H)^+$.

Step b: To a –78 °C solution of tert-butyl 4-allyl-4-formylpiperidine-1-carboxylate (7.01 g, 27.63 mmol) in THF (30 mL) was added allylmagnesium bromide (1 M solution in THF, 63.55 mL, 63.55 mmol) dropwise. The resulting mixture was allowed to warm to RT and stirred for 1.5 h. The reaction mixture was quenched with sat. aq. NH_4Cl, extracted with EA (3 × 200 mL). The combined organic layers were washed with brine (1 × 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 4-allyl-4-(1-hydroxyallyl)piperidine-1-carboxylate (7.01 g). MS: *m/z* 282 $(M+H)^+$.

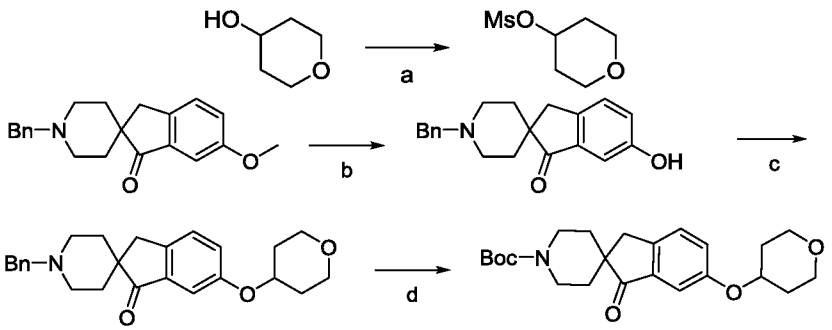
Step c: To a solution of tert-butyl 4-allyl-4-(1-hydroxyallyl)piperidine-1-carboxylate (7.00 g, 24.88 mmol) in DCM (50 mL) was added Dess-Martin periodinane (12.66 g, 29.85 mmol) in portions. After stirring for 1.5 h at RT, the reaction mixture was diluted with brine (150 mL) and extracted with EA (3 × 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (EA : Hex = 1 : 30, v/v) to give tert-butyl 4-acryloyl-4-allylpiperidine-1-carboxylate (5.63 g). MS: *m/z* 280 $(M+H)^+$.

Step d: A mixture of tert-butyl 4-acryloyl-4-allylpiperidine-1-carboxylate (5.63 g, 20.15 mmol), Grubbs II (428 mg, 0.50 mmol) and toluene (30 mL) was stirred for 3.5 h at 85 °C under nitrogen atmosphere. After cooling to RT, the mixture was concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 5, v/v) to give

tert-butyl 1-oxo-8-azaspiro[4.5]dec-2-ene-8-carboxylate (3.61 g). MS: *m/z* 252 $(M+H)^+$.

Step e: To a solution of trimethylsulfoxonium iodide (3.79 g, 17.22 mmol) in DMSO (50 mL) was added NaH (60 % dispersion in mineral oil, 730 mg, 18.25 mmol) in portions. After stirring for 30 min, tert-butyl 1-oxo-8-azaspiro[4.5]dec-2-ene-8-carboxylate (a DMSO solution, 3.61 g, 14.36 mmol) was added dropwise. The resulting mixture was stirred for 1.5 h at RT. The reaction mixture was diluted with brine (200 mL), extracted with EA (3 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 2-oxospiro[bicyclo[3.1.0]hexane-3,4'-piperidine]-1'-carboxylate (3.60 g). MS: *m/z* 266 $(M+H)^+$.

Intermediate A23



Step a: To a -10 °C solution of tetrahydro-2H-pyran-4-ol (3.54 g, 34.66 mmol), triethylamine (4.65 g, 45.95 mmol) in DCM (100 mL) was added MsCl (4.61 g, 40.24 mmol) dropwise. After stirring for 30 min, the reaction mixture was diluted with water (100 mL), extracted with DCM (100 mL, 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tetrahydro-2H-pyran-4-yl methanesulfonate (6.74 g). MS: *m/z* 181 $(M+H)^+$.

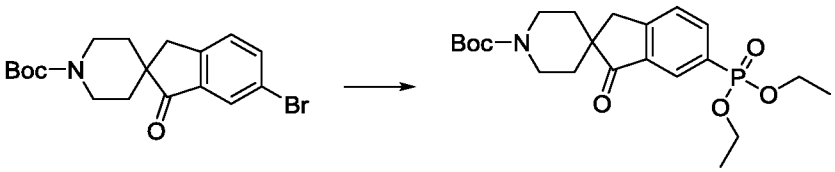
Step b: To a solution of 1'-benzyl-6-methoxyspiro[indene-2,4'-piperidin]-1(3H)-one (4.35 g, 13.53 mmol) in DCM (200 mL) was added BBr_3 (1 M solution in DCM, 15.00 mL, 15.00 mmol), stirred for 13 h at 45 °C. An additional portion of BBr_3 (1 M solution in DCM, 5.00 mL, 5.00 mmol) was added and stirred for 24 h at 45 °C. After cooling to RT, the reaction mixture was diluted with water (150 mL), $NaHCO_3$ (20.00 g) was added in portions. The resulting mixture was extracted with DCM (2 × 100 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1'-benzyl-6-hydroxyspiro[indene-2,4'-piperidin]-1(3H)-one (2.80 g) which was used in next step without any further purification. MS: *m/z* 308 $(M+H)^+$.

Step c: A mixture of 1'-benzyl-6-hydroxyspiro[indene-2,4'-piperidin]-1(3H)-one (2.80 g, 9.11 mmol), tetrahydro-2H-pyran-4-yl methanesulfonate (3.40 g, 18.87 mmol) and K_2CO_3 (8.23 g,

59.55 mmol) in DMF (60 mL) was stirred for 5.5 h at 110 °C. An additional portion of tetrahydro-2H-pyran-4-yl methanesulfonate (1.10 g, 6.10 mmol) and K_2CO_3 (4.55 g, 32.92 mmol) was added and stirred for 1.5 h at 110 °C. After cooling to RT, the mixture was diluted with water (300 mL) and EA (600 mL). The aqueous layer was separated and extracted with EA (1 × 200 mL), the organic layers combined, washed with water (2 × 300 mL) and brine (1 × 300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with MeOH : DCM = 1 : 40, v/v) to give 1'-benzyl-6-((tetrahydro-2H-pyran-4-yl)oxy)spiro[indene-2,4'-piperidin]-1(3H)-one (1.70 g). MS: *m/z* 392 $(M+H)^+$.

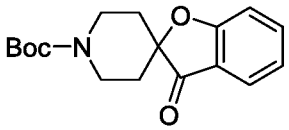
Step d: A mixture of 1'-benzyl-6-((tetrahydro-2H-pyran-4-yl)oxy)spiro[indene-2,4'-piperidin]-1(3H)-one (1.70 g, 4.34 mmol) and $Pd(OH)_2$ (10 % on carbon, 1.21 g) in MeOH was stirred for 3 h at RT under hydrogen atmosphere. The reaction mixture was filtered. To the filtration was added $(Boc)_2O$ (1.10 g, 5.04 mmol) and stirred for 40 h at RT. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 5, v/v) to give tert-butyl 1-oxo-6-((tetrahydro-2H-pyran-4-yl)oxy)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.45 g). MS: *m/z* 402 $(M+H)^+$.

Intermediate A24



A mixture of tert-butyl 6-bromo-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1017 mg, 2.67 mmol), diethyl phosphonate (564 mg, 4.08 mmol), potassium phosphate (1156 mg, 5.45 mmol), $Pd(OAc)_2$ (63 mg, 0.28 mmol) and XantPhos (307 mg, 0.53 mmol) in DMF (10 mL) was stirred for 21 h at 130 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was quenched with water (60 mL), filtered followed by EA (2 × 30 mL) wash. The layers of the filtration was separated, the aqueous layer was extracted with EA (2 × 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA) to give tert-butyl 6-(diethoxyphosphoryl)-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (134 mg) which was used in next step without any further purification. MS: *m/z* 438 $(M+H)^+$.

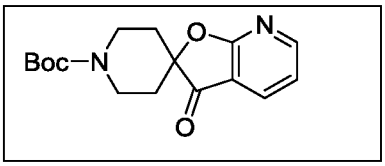
Intermediate A25



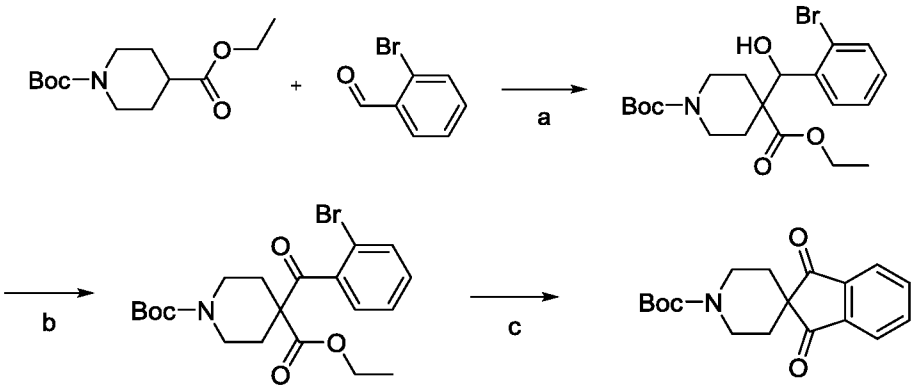
Following procedures of *Y. Uto et al. / Bioorg. Med. Chem. Lett. 20 (2010) 746 – 754*, **intermediate A25** was prepared.

The following compound was synthesized using the above procedure with the corresponding starting materials.

Table 11



Intermediate A26



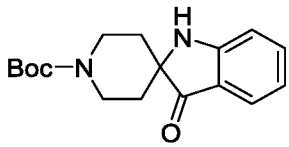
Step a: To a -65 °C solution of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate (5.23 g, 20.32 mmol) in THF (30 ml) was added LDA (2 M solution in THF/Hex, 12.00 mL, 24.00 mmol) dropwise. The resulting mixture was stirred for 1.0 h at this temperature. 2-Bromobenzaldehyde (3.44 g, 18.59 mmol) was added dropwise at -70 °C. After stirring for 1 h, the mixture was quenched with brine (40 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(tert-butyl) 4-ethyl 4-((2-bromophenyl)(hydroxy)methyl)piperidine-1,4-dicarboxylate (9.15 g) which was used in next step without any further purification. MS: *m/z* 442 $(M+H)^+$.

Step b: To a -5 °C solution of 1-(tert-butyl) 4-ethyl 4-((2-bromophenyl)(hydroxy)methyl) piperidine-1,4-dicarboxylate (9.15 g, 20.68 mmol) in DCM (70 ml) was added Dess-Martin periodinane (18.02 g, 42.49 mmol). The resulting mixture was stirred for 2.5 h at RT. The reaction mixture was washed with aq. $Na_2S_2O_3$ (25%, 1 × 80 mL), sat. aq. $NaHCO_3$ (1 × 80 mL) and brine (1 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 5, v/v) to give 1-(tert-butyl) 4-ethyl 4-(2-bromobenzoyl)piperidine-1,4-dicarboxylate (7.16 g).

MS: *m/z* 440 $(M+H)^+$.

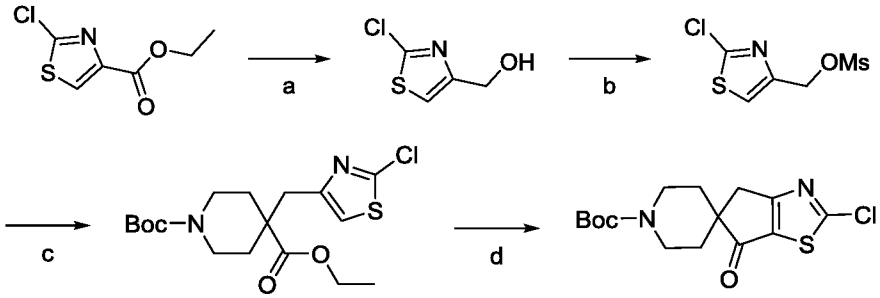
Step d: To a -80 °C solution of 1-(tert-butyl) 4-ethyl 4-(2-bromobenzoyl)piperidine-1,4-dicarboxylate (2.00 g, 4.54 mmol) in THF (20 mL) was added n-BuLi (2.5 M solution in THF/Hex, 1.80 mL, 4.50 mmol) dropwise under nitrogen atmosphere. The resulting mixture was allowed to warm to RT and stirred for 1 h. The reaction mixture was quenched with brine (30 mL) and extracted with EA (1 × 20mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 10, v/v) to give tert-butyl 1,3-dioxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (500 mg). MS: *m/z* 316 $(M+H)^+$.

Intermediate A27



Following procedures of *J. Org. Chem. 1999, 64, 5504-5510*, **intermediate A27** was prepared.

Intermediate A28



Step a: To a 0 °C solution of ethyl 2-chlorothiazole-4-carboxylate (24.95 g, 130.19 mmol) in MeOH (250 mL) was added $NaBH_4$ (17.29 g, 456.97 mmol) in portions. The resulting mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was diluted with water (200 mL) and the volatiles were removed under reduced pressure. The resulting mixture was extracted with EA (2 × 200 mL), the combined organic layers were washed with brine (1 × 400 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give (2-chlorothiazol-4-yl)methanol (18.88 g). MS: *m/z* 150 $(M+H)^+$.

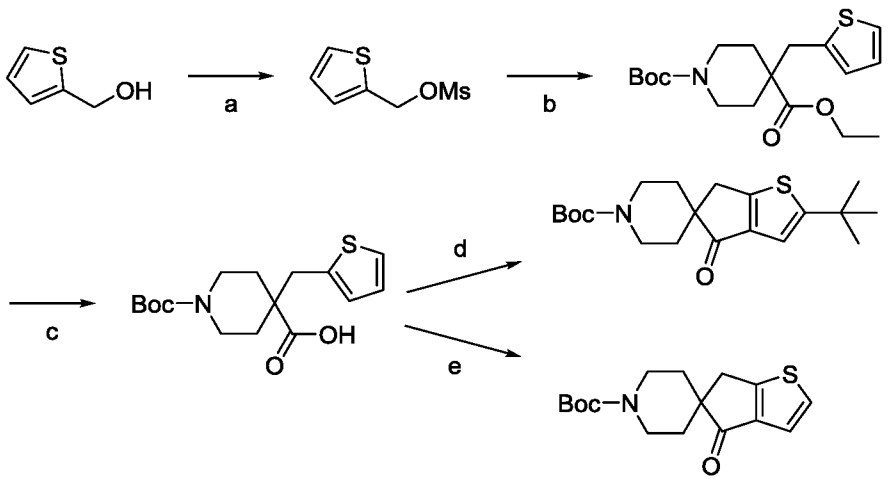
Step b: To a solution of (2-chlorothiazol-4-yl)methanol (18.88 g, 130.19 mmol) and triethylamine (25.56 g, 252.57 mmol) in DCM (200 mL) was added MsCl (15.96 g, 139.30 mmol) dropwise over 15 min. The resulting mixture was stirred for 25 min at RT. The reaction mixture was quenched with brine (200 mL) and the aqueous layer was separated. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give

(2-chlorothiazol-4-yl)methyl methanesulfonate which was used in next step without any further purification. MS: *m/z* 228 $(M+H)^+$.

Step c: To a -60 °C solution of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate (35.67 g, 138.62 mmol) in THF (200 mL) was added LDA (2 M solution in THF/Hex, 75.00 mL, 150.00 mmol) dropwise over 30 min under nitrogen atmosphere. A solution of (2-chlorothiazol-4-yl)methyl methanesulfonate in THF (50 mL) was added dropwise, the resulting mixture was allowed to warmed to RT and stirred for 2 h. The reaction mixture was quenched with brine (300 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 10, v/v) to give 1-(tert-butyl) 4-ethyl 4-((2-chlorothiazol-4-yl)methyl) piperidine-1,4-dicarboxylate (38.12 g). MS: *m/z* 389 $(M+H)^+$.

Step d: To a -60 °C solution of 1-(tert-butyl) 4-ethyl 4-((2-chlorothiazol-4-yl)methyl) piperidine-1,4-dicarboxylate (8.51 g, 21.88 mmol) in THF (80 mL) was added LDA (2 M solution in THF/Hex, 11.00 mL, 22.00 mmol) dropwise under nitrogen atmosphere. Once finished, the reaction mixture was quenched with brine (50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 10, v/v) to give tert-butyl 2-chloro-6-oxo-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate (1.93 g). MS: *m/z* 343 $(M+H)^+$.

Intermediate A29



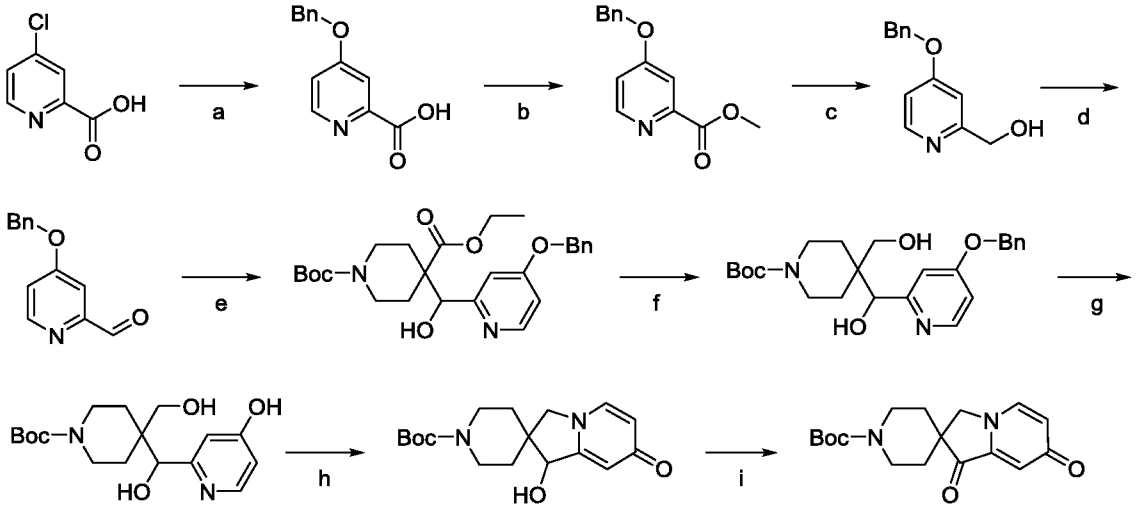
Step (a-c): Step (b-c) of Intermediate A28 and step (b) of Intermediate A3 were applied to provide 1-(tert-butoxycarbonyl)-4-(thiophen-2-ylmethyl)piperidine-4-carboxylic acid.

Step d: A mixture of 1-(tert-butoxycarbonyl)-4-(thiophen-2-ylmethyl)piperidine-4-carboxylic acid (4.92 g, 15.12 mmol) and PPA (30.12 g) was stirred for 5 h at 110 °C. The reaction mixture was poured into ice/water (100 mL), the pH value was adjusted to 10 with NaOH. Then

$(Boc)_2O$ (5.05 g, 23.14 mmol) was added and stirred for 18 h at RT. The reaction mixture was extracted with EA (2 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 2-(tert-butyl)-4-oxo-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidine]-1'-carboxylate (1.70 g). MS: *m/z* 364 $(M+H)^+$.

Step e: A mixture of 1-(tert-butoxycarbonyl)-4-(thiophen-2-ylmethyl)piperidine-4-carboxylic acid (4.88 g, 15.12 mmol) and HCl (4M solution in 1, 4-dioxane, 8 mL) in DCM (50 mL) was stirred for 1 h at RT. The reaction mixture was concentrated under reduced pressure. PPA (21.15 g) was added and the resulting mixture was stirred for 1.5 h at 110 °C. The reaction mixture was poured into ice/water (100 mL), the pH value was adjusted to 10 with NaOH. Then $(Boc)_2O$ (5.12 g, 23.46 mmol) was added and stirred for 18 h at RT. The reaction mixture was extracted with EA (2 × 50 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 10, v/v) to give tert-butyl4-oxo-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidine]-1'-carboxylate(2.71g). MS: *m/z* 308 $(M+H)^+$.

Intermediate A30



Step a: To a solution of phenylmethanol (5.15 g, 47.62 mmol) in DMF (50 mL) was added NaH (60 % dispersion in mineral oil, 3.01 g, 75.25 mmol) in portions, stirred for 20 min. 4-Chloropicolinic acid (2.68 g, 17.01 mmol) was added and stirred for 3.5 h at 85 °C. After cooling to RT, HCl (4 M solution in 1,4-dioxane, 10 mL) was added. The resulting mixture was used in next step. MS: *m/z* 230 $(M+H)^+$.

Step b: The mixture was mixed with $NaHCO_3$ (7.51 g, 89.39 mmol), CH_3I (1.5 mL) and DMF (10 mL). After stirring for 0.5 h, an additional portion of CH_3I (1.5 mL) was added and stirred for

16 h. The reaction mixture was diluted with EA (250 mL), filtered and the filtration was washed with brine (2 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 1, v/v) to give methyl 4-(benzyloxy)picolinate (1.50 g). MS: *m/z* 244 $(M+H)^+$.

Step c: A mixture of methyl 4-(benzyloxy)picolinate (1.50 g, 6.17 mmol), $LiBH_4$ (2M solution in THF, 9.00 mL, 18.00 mmol) in THF (40 mL) was stirred for 1 h at 50 °C. The reaction mixture was diluted with MeOH (15 mL) and water (150 mL), extracted with EA (200 mL, 50 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA) to give (4-(benzyloxy)pyridin-2-yl)methanol (0.50 g). MS: *m/z* 216 $(M+H)^+$.

Step d: A mixture of (4-(benzyloxy)pyridin-2-yl)methanol (0.50 g, 2.32 mmol), dess-martin periodinane (1.25g, 2.95mmol) in DCM (20 mL) was stirred for 1.5 h. The reaction mixture was diluted with sat.aq.$NaHSO_3$, sat.aq.$NaHCO_3$ and DCM (50 mL). The aqueous layer was separated and extracted with DCM (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica chromatography to give 4-(benzyloxy)picolinaldehyde (0.40 g). MS: *m/z* 214 $(M+H)^+$.

Step e: To a 0 °C solution of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate (0.52 g, 2.02 mmol) in THF (15 mL) was added LDA (2 M solution in THF/Hex, 1.30 mL, 2.60 mmol) dropwise. The resulting mixture was cooled to -70 °C, a solution of 4-(benzyloxy)picolinaldehyde (0.40 g, 1.88 mmol) in THF (5 mL) was added. The resulting mixture was allowed to warm to -15 °C and stirred for 30 min, then quenched with sat.aq.NH_4Cl (10 mL), diluted with water (50 mL) and extracted with EA (1 × 100 mL). The organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 1) to give 1-(tert-butyl) 4-ethyl 4-((4-(benzyloxy)pyridin-2-yl)(hydroxy)methyl)piperidine-1,4-dicarboxylate (0.25 g). MS: *m/z* 471 $(M+H)^+$.

Step f: A mixture of 1-(tert-butyl) 4-ethyl 4-((4-(benzyloxy)pyridin-2-yl)(hydroxy) methyl)piperidine-1,4-dicarboxylate (0.25 g, 0.53 mmol), $LiBH_4$ (2 M solution in THF, 1.00 mL, 2.00 mmol) in THF (10 mL) was stirred for 40 min at 55 °C. The reaction mixture was quenched with MeOH (10 mL), the volatiles were removed under reduced pressure. The residue was diluted with water (150 mL), extracted with EA (1 × 50 mL). The organic layer was washed with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to

give tert-butyl 4-((4-(benzyloxy)pyridin-2-yl)(hydroxy)methyl)-4-(hydroxymethyl)piperidine-1-carboxylate (0.22 g). MS: *m/z* 429 $(M+H)^+$.

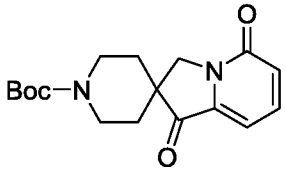
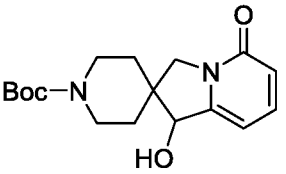
Step g: A mixture of tert-butyl 4-((4-(benzyloxy)pyridin-2-yl)(hydroxy)methyl)-4-(hydroxymethyl)piperidine-1-carboxylate (0.22 g, 0.51 mmol), Pd (10% on carbon, 0.12 g) in MeOH (20 mL) was stirred for 1.5 h under hydrogen atmosphere. The reaction mixture filtrated follow by MeOH wash and the filtration was concentrated under reduced pressure to give tert-butyl 4-(hydroxy(4-hydroxypyridin-2-yl)methyl)-4-(hydroxymethyl)piperidine-1-carboxylate (154 mg). MS: *m/z* 339 $(M+H)^+$.

Step h: To a mixture of tert-butyl 4-(hydroxy(4-hydroxypyridin-2-yl)methyl)-4-(hydroxymethyl)piperidine-1-carboxylate (120 mg, 0.36 mmol) and triphenyl phosphate (175 mg, 0.67 mmol) in THF (10 mL) was added N,N,N',N'-tetramethylazodicarboxamide (158 mg, 0.68 mmol). The mixture was stirred for 30 min at RT. The reaction was purified by silica chromatography (eluting with MeOH : DCM = 1 : 7, v/v) to give tert-butyl 1-hydroxy-7-oxo-1,7-dihydro-3H-spiro[indolizine-2,4'-piperidine]-1'-carboxylate (100 mg). MS: *m/z* 321 $(M+H)^+$.

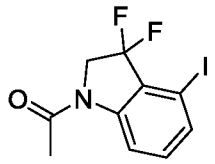
Step i: A mixture of tert-butyl1-hydroxy-7-oxo-1,7-dihydro-3H-spiro[indolizine-2,4'-piperidine]-1'-carboxylate (0.35 g, 1.09 mmol), Dess-Martin periodinane (0.72 g, 1.70 mmol) and DCM (35 mL) was stirred for 2 h at RT. The resulting mixture was washed with sat.aq.Na_2SO_3 (1 × 20 mL) and sat.aq.$NaHCO_3$ (1 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 1,7-dioxo-1,7-dihydro-3H-spiro[indolizine-2,4'-piperidine]-1'-carboxylate (0.33 g). MS: *m/z* 319 $(M+H)^+$.

The following compounds were synthesized using the above procedure with the corresponding starting materials.

Table 12

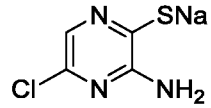
	

Intermediate B1



Following procedures of **WO2017211303 A1**, **intermediate B1** was prepared from 4-iodoindoline-2,3-dione in 3 steps.

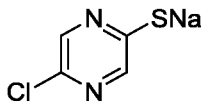
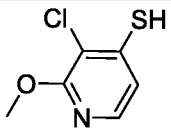
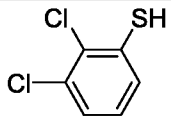
Intermediate B2



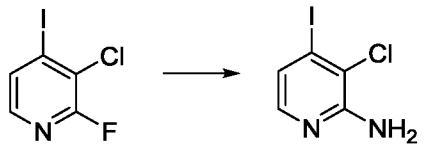
Following procedures of **WO2017211303 A1,intermediate B2** was prepared from 3-bromo-6-chloropyrazin-2-amine in 2 steps.

The following compounds were synthesized using the above procedure or modifications procedure with the corresponding starting materials.

Table 13

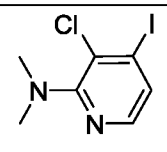
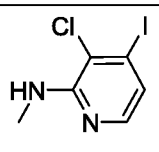
Intermediate B3



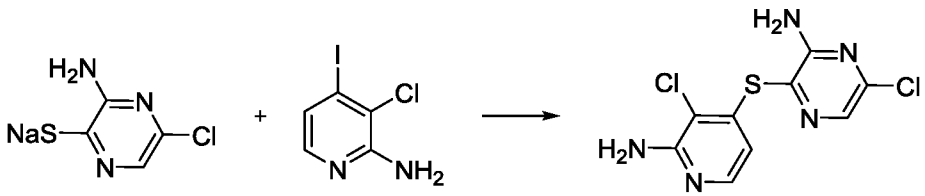
3-Chloro-2-fluoro-4-iodopyridine (10.10 g, 39.23 mmol) and DMSO (50 mL) was added to a sealed tube, ammonium hydroxide (25%, 50 mL) was added dropwise. The resulting mixture was stirred for 16 h at 80 °C. After cooling to RT, the reaction mixture was poured into water (250 mL), the resulting precipitate was collected, dissolved in DCM (280 mL), washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 3-chloro-4-iodopyridin-2-amine (7.01 g). MS: *m/z* 255 $(M+H)^+$.

The following compounds were synthesized using the above procedure or modification procedure with the corresponding starting materials.

Table 14

Intermediate B4

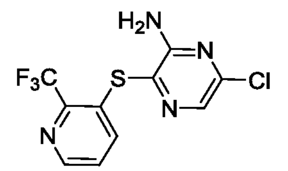
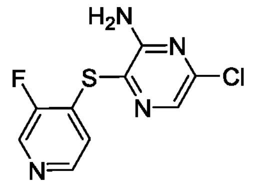
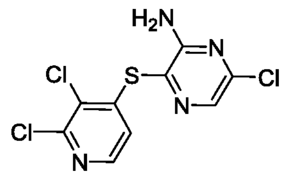
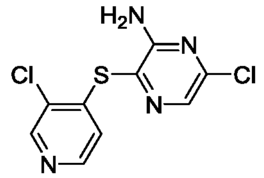
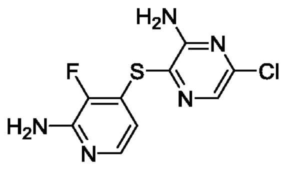
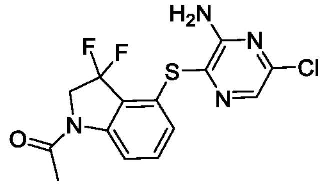
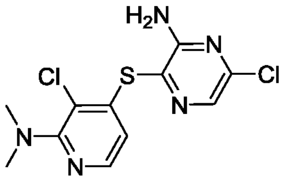
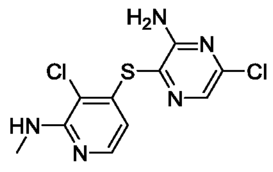
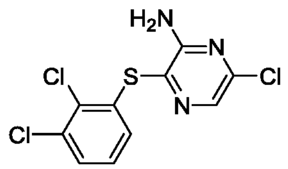
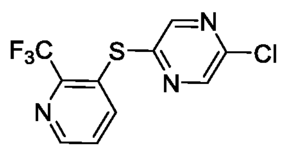
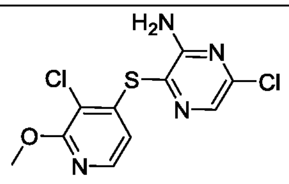
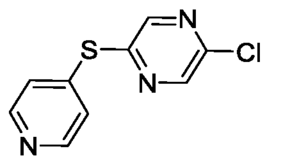
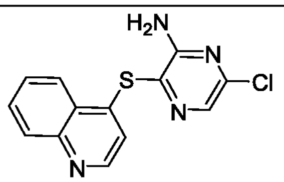
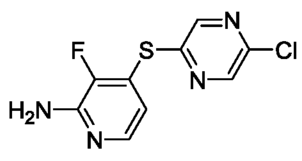
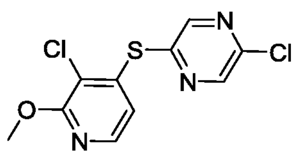
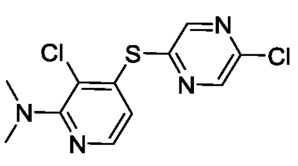
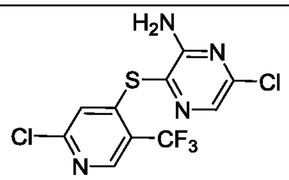
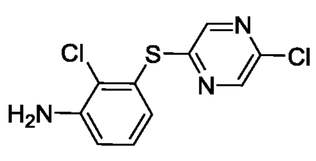
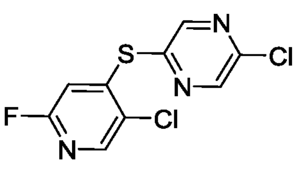
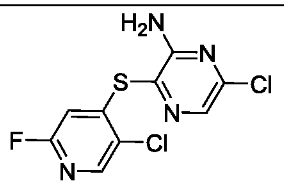
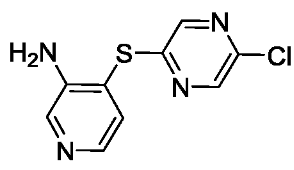


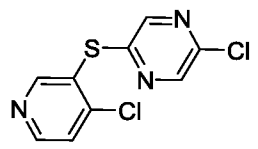
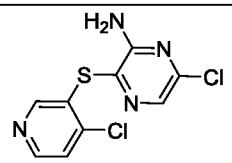
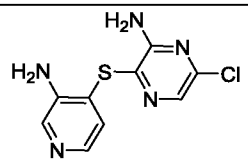
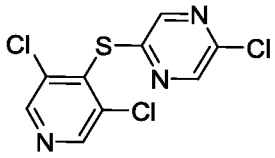
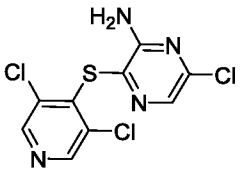
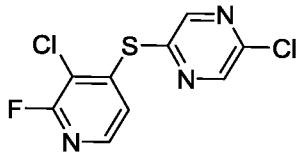
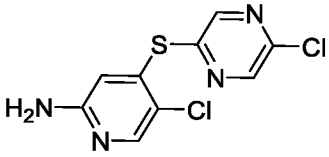
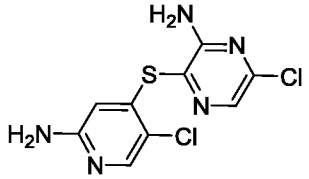
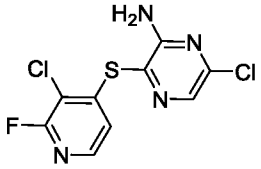
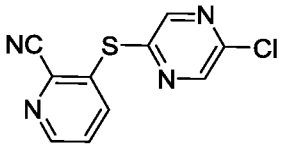
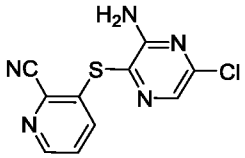
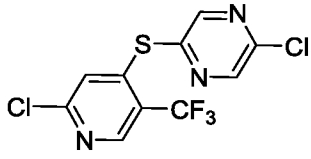
A mixture of 3-chloro-4-iodopyridin-2-amine (25.53 g, 100.33 mmol), sodium 3-amino-5-chloropyrazine-2-thiolate (20.18 g, 109.92 mmol), $Pd_2(dba)_3$ (4.47 g, 4.88 mmol), XantPhos (5.81 g, 10.04 mmol) and DIEA (26.12 g, 202.10 mmol) in 1,4-dioxane (10 mL) was stirred for 1.5 h at

70 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was filtered through a pad of Celite followed by 1,4-dioxane (30 mL) wash and the filtrate was concentrated under reduced pressure. DCM (100 mL) and EA (100 mL) were added and the resulting mixture was stirred for 40 min. The precipitate was collected, dried in a vacuum oven to give 3-((2-amino-3-chloropyridin-4-yl)thio)-6-chloropyrazin-2-amine (13.86 g). MS: *m/z* 288 $(M+H)^+$.

The following compounds were synthesized using the above procedure or modification procedure with the corresponding starting materials.

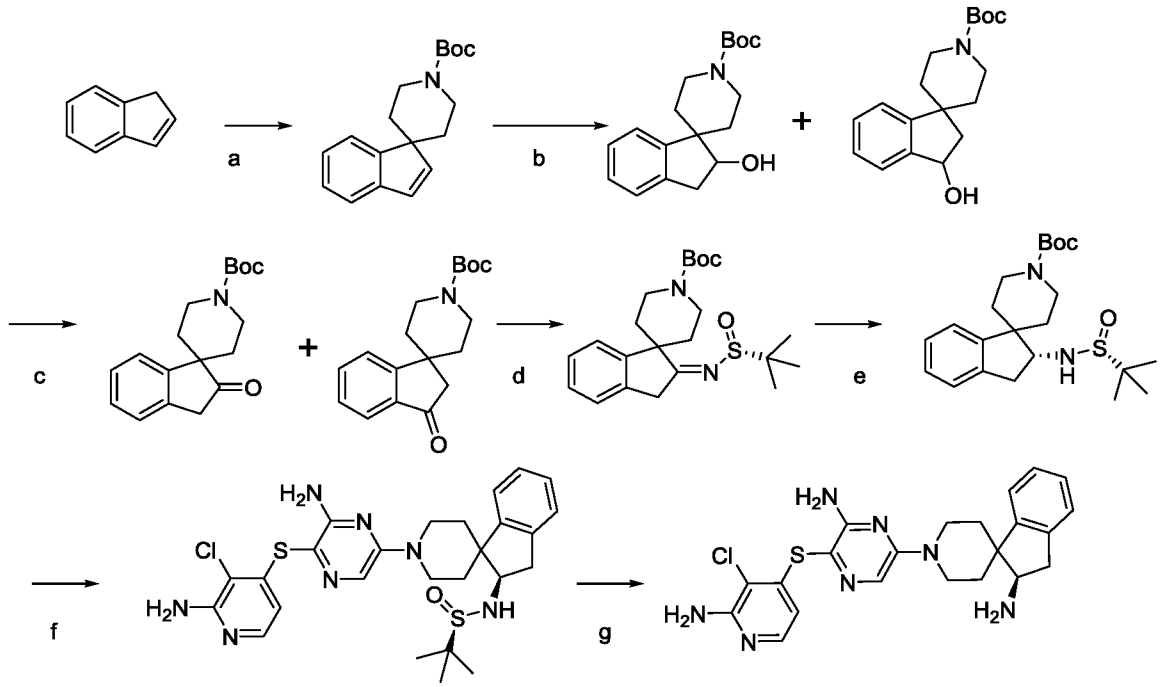
Table 15

EXAMPLE 1

(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine



Step a:A mixture of Compound 1H-indene (11.62g, 0.10mol) and LiHMDS (220mL, 1mol/L in THF) in THF(120mL) was stirred at -50°C for 1 hour. Tert-butyl bis(2-chloroethyl)carbamate (24.21g, 0.10mol) was added to the reaction mixture and stirred at -50°C for 1hr. The reaction was quenched with brine (300mL). The organic extracts were dried with anhydrous Na_2SO_4, and

concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford Compound tert-butyl spiro[indene-1,4'-piperidine]-1'-carboxylate as a yellow solid (10.36g, 36%). MS: 286 $(M+H)^+$.

Step b:A mixture of Compound tert-butyl spiro[indene-1,4'-piperidine]-1'-carboxylate (117.02g, 0.41mol) and borane-methyl sulfide complex (10mol/L, 220mL) in THF (800mL) was stirred at 0°Cfor 3 hours. NaOH (2mol/L, 1.2L) and H_2O_2 (300mL) was added and stirred at 0°C for 1 hour. The organic extracts were collected, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure in vacuo to afford the mixture of tert-butyl 2-hydroxy-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate and tert-butyl 3-hydroxy-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate as a yellow oil (130.33g, crude). MS: 304 $(M+H)^+$.

Step c:A mixture of tert-butyl 2-hydroxy-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate and tert-butyl 3-hydroxy-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate (130.02g, 0.43mol) and Dess-Martin periodinane (364.76g, 0.86mol) in DCM (2L) was stirred at 25°C for 12 hours. The reaction mixture was filtered and the filtrate was washed by saturated sodium bicarbonate solution (1L) and brine (1L). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford Compound tert-butyl 3-oxo-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate as a white solid (41.75g, 34%, 2 steps). MS: 302 $(M+H)^+$.

Step d:To a solution of Compound tert-butyl 3-oxo-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate (41.01g, 0.14mol) in Titanium(IV) ethoxide (80mL) was added R-(+)-tert-Butylsulfinamide (49.46g, 0.41mol). The resulting mixture was stirred at 85°C for 2 hours. EA (0.5L) and water (0.5L) was added to the reaction mixture. The reaction mixture was filtered and organic extracts were collected. The aqueous solution was extracted with EA (200mL×2). The combined organic extracts were washed with brine (500mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure in vacuo to afford Compound tert-butyl 3-oxo-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate (132.05g crude). MS: 405$(M+H)^+$. Without purification to next step.

Step e:A mixture of Compound tert-butyl 3-oxo-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate (132.02g, 0.33mol) in THF (200mL) was stirred at -50°C. $NaBH_4$ (7.71g, 0.51mol) was added to the reaction mixture and allowed to return to room temperature. Reaction was quenched with saturated ammonium chloride solution (100mL). The organic extracts were collected, dried over anhydrous Na_2SO_4, and

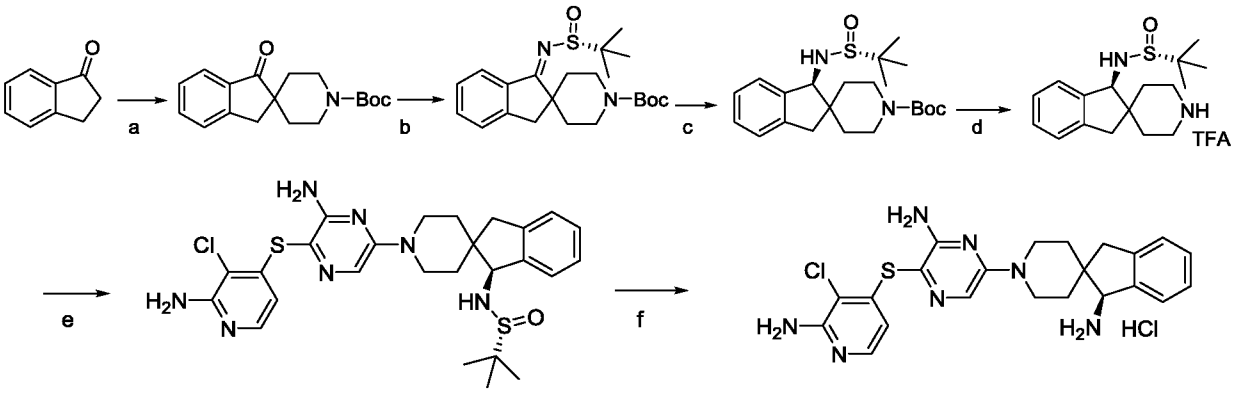
concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford Compound tert-butyl (R)-2-(((R)-tert-butylsulfinyl)amino)-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate as a white solid (27.25g, 49%, 2 steps). MS: 407 $(M+H)^+$.

Step f:A mixture of Compound tert-butyl (R)-2-(((R)-tert-butylsulfinyl)amino)-2,3-dihydrospiro[indene-1,4'-piperidine]-1'-carboxylate (1.16g, 3.98mmol), CF_3COOH (3.6mL) in DCM (20mL) was stirred at 25°C for 1.5 hours. The reaction mixture was concentrated under reduced pressure, The residue was dissolved in NMP (15mL), then 3-((2-amino-3-chloropyridin-4-yl)thio)-6- chloropyrazin-2-amine (1.03g, 3.59mmol) and K_2CO_3 (6.60g, 47.76mmol) was added to mixture and stirred at 90°C for 16 hours. H_2O (30mL) was added to the reaction mixture and the precipitate was filtered. The filter cake dissolved in DCM (40mL) and washed with brine (40mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure in vacuo to afford the Compound (R)-N-((R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-yl)-2-methylpropane-2-sulfinamide (1.55g, 70%) as a yellow solid.

Step g:To a solution of Compound (R)-N-((R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-yl)-2-methylpropane-2-sulfinamide (1.52g，2.72mmol) in DCM (20mL) was added HCl/Dixoane (2mL, 4mol/L). The resulting mixture was stirred at 25°C for 1hour and the precipitate was filtered. The filter cake dispersed in DCM (30mL) and Ammonium hydroxide (5mL) was added to adjust pH>10. The mixture was washed with brine (40mL), dried over anhydrous Na2SO4 and concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford Compound (R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine as a yellow solid (530mg, 42%). MS: 454 $(M+H)^+$. ^1H NMR (400 MHz, *DMSO-d6*) δ 7.64 - 7.66 (m, 2H), 7.30 (d, 1H), 7.20 (d, 1H), 7.13 - 7.15 (m, 2H), 6.78 (d, 1H), 4.05 - 4.09 (m, 1H), 3.91 - 3.95 (m, 1H), 3.54 - 3.60 (m, 3H), 3.12 - 3.18 (m, 1H), 2.57 - 2.63 (m, 1H), 1.91 - 2.09 (m, 2H), 1.66 - 1.76 (m, 1H), 1.49 - 1.58 (m, 1H).

EXAMPLE 2

(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine



Step a:NaH(60%) (3.63g, 90.80mmol) was added into the solution of Compound 2,3-dihydro-1H-inden-1-one (4.00g, 30.27mmol) in DMF (80mL). The mixture was stirred for 30 min at 16°C. Tert-butyl bis(2-chloroethyl) carbamate (8.06g, 33.29mmol) was added dropwise. And then the mixture was stirred for 16 hours at 60°C. The mixture was quenched with brine (200mL), extracted with EA (100mL×2). The organic layers were combined and washed with brine (100mL×2), dried over anhydrous Na_2SO4. After concentrated, the residue was purified by column chromatography to afford the Compound tert-butyl 1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.21g, 13%) as a dark red oil. MS: 302 $(M+H)^+$.

Step b:After the Titanium(IV) ethoxide (12.00g) was warmed into 90°C, the compound tert-butyl 1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.21g, 4.01mmol) and (R)-2-methylpropane-2-sulfinamide (1.22g, 12.04mmol) were added. After stirred for 19hrs at 90°C. The mixture was poured into EA (200mL), and brine (200mL) was added. After stirred for 15 mins, the solids were filtrated out. The liquid was separated. The organic layer was washed with brine (200mL×2), and dried over anhydrous Na_2SO_4. The solids were filtrated out, and the filtration was concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford the compound tert-butyl (R,E)-1-((tert-butylsulfinyl)imino)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.01g, 62%) as a black solid. MS: 405 $(M+H)^+$.

Step c:The solution of the compound tert-butyl (R,E)-1-((tert-butylsulfinyl)imino)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (1.01g, 2.50mmol) in THF (10mL) was cooled in -50°C. $NaBH_4$ (142mg, 3.74mmol) was added in portionwise. The mixture was stirred for 15.5 hours with natural warming to room temperature, and then poured into EA (100mL). The mixture was washed with brine (100mL×3). The organic layer was dried over anhydrous Na2SO4 and concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford the Compound tert-butyl (S)-1-(((R)-tert-butylsulfinyl)amino)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate

(580mg, 57%) as a yellow oil. MS: 407 $(M+H)^+$.

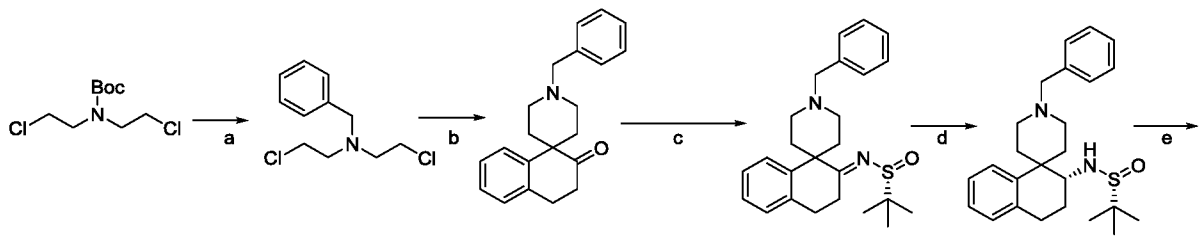
Step d:The mixture of the compound tert-butyl (S)-1-(((R)-tert-butylsulfinyl)amino)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (580mg, 1.43mmol) and TFA (1mL) in DCM (5mL) was stirred for 40 mins at 20°C. The solution was concentrated to afford the compound (R)-N-((S)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-yl)-2-methylpropane-2-sulfinamide (520mg, 90%) as a yellow oil. MS: 307 $(M+H)^+$.

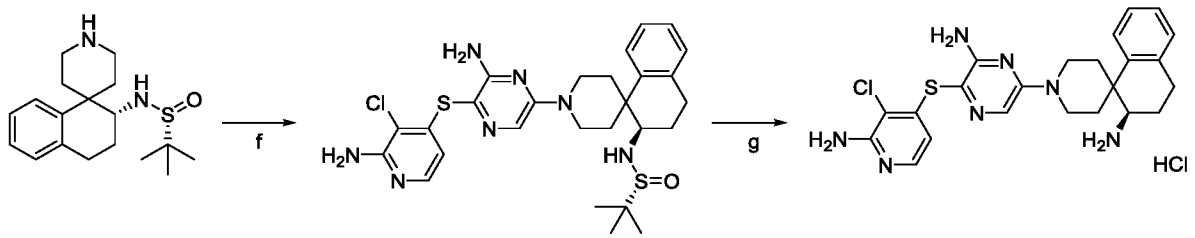
Step e:The mixture of (R)-N-((S)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-yl)-2-methylpropane-2-sulfinamide (260mg, 0.62mmol), 3-((2-amino-3-chloropyridin-4-yl) thio)-6-chloropyrazin-2-amine (196mg, 0.68mmol) and K_2CO3 (427mg, 3.09mmol) in NMP（8mL） were stirred for 16 hours at 100°C. The mixture poured into EA (200mL) and washed with brine (200mL×3). The organic layer was dried over anhydrous Na2SO4 and concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford the Compound (R)-N-((S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-yl)-2-methylpropane-2-sulfinamide (260mg, 65%) as a yellow solid. MS: 558 $(M+H)^+$.

Step f:The compound (R)-N-((S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-yl)-2-methylpropane-2-sulfinamide (260mg, 0.47mmol) was dissolved in DCM (5mL) and HCl/Dixoane (4mol/L, 5mL) was added dropwise. The mixture was stirred for 30 mins at 20 °C. The mixture was concentrated and the residue was dissolved in methanol (2mL). And EA (5mL) was added. The solids were collected by filtration to afford the compound (S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine (123mg, 54%) as an off-white solid. MS: 454 $(M+H)^+$. ^1H NMR (400 MHz, *DMSO-d6*) δ 7.81 (d, 1H), 7.72 (s, 1H), 7.62 (d, 1H), 7.27 - 7.36 (m, 3H), 6.12 (d, 1H), 4.21 - 4.35 (m, 3H), 2.97 - 3.24 (m, 4H), 1.77 - 1.91 (m, 2H), 1.49 - 1.59 (m, 2H).

EXAMPLE 3

(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-amine





Step a:The solution of the compound tert-butyl bis(2-chloroethyl)carbamate (11.00g,45.43mmol) in HCl/Dixoane (4mol/L, 200mL) was stirred for 1h at 20°C. The solution was concentrated and the residue was dissolved in DCE (200mL). Triethylamine (22.95g, 227.14mmol) and benzaldehyde (7.23g, 68.14mmol) was added to the mixture. And then $NaBH(OAc)_3$ (24.07g, 113.57mmol) was added in portionwise. The mixture was stirred for 54 hours at 20°C, and then EA(300mL) and brine (200mL) was added. The organic layer was concentrated under reduced pressure in vacuo. The residue was dissolved in HCl solution (2mol/L, 200mL) and extracted with EA (100mL). The pH value of the aqueous layer was adjusted to 9 with saturated Na_2CO_3 solution. The mixture was extracted with EA (200mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the compound N-benzyl-2-chloro-N-(2-chloroethyl)ethan-1-amine (8.52g, 81%) as a colorless oil.

Step b:Into the solution of the compound N-benzyl-2-chloro-N-(2-chloroethyl)ethan-1-amine (8.52g, 36.70mmol) and 3,4-dihydronaphthalen-2(1H)-one (4.88g, 33.36mmol) in THF (80mL) and DMSO (50mL) was added Potassium tert-butylate (9.36g, 83.14mmol). The mixture was stirred for 20 hours at 20°C. The mixture was concentrated and diluted with EA (200mL). And then the mixture was washed with brine (200mL×3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography to afford 1'-benzyl-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-one (2.32g, 21%) as a black oil. MS: 306 $(M+H)^+$.

Step c:Into Titanium(IV) ethoxide was added the compound 1'-benzyl-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-one (2.32g, 7.60mmol) and (R)-2-methylpropane-2-sulfinamide (2.76g, 22.79mmol). The mixture was stirred for 19h at 100°C. EA (200mL) and water (200mL) was added. The solids were filtrated out. The liquid mixture was separated. The organic layer was washed with brine (100mL×5), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford the compound (R,E)-N-(1'-benzyl-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-ylidene)-2-methylpropane-2-sulfinamide (660mg, 21%) as a yellow oil. MS: 409 $(M+H)^+$.

Step d:The solution of the compound (R,E)-N-(1'-benzyl-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-ylidene)-2-methylpropan

e-2-sulfinamide (660mg, 1.62mmol) in THF (10mL) was cooled into -50°C. And then NaBH4 (122mg, 3.23mmol)was added in portionwise. The mixture was stirred for 18h with natural warming to room temperature. The mixture was quenched with water (50mL) and extracted with EA (50mL×2). The organic layers were combined and washed with brine (50mL×2), dried over anhydrous Na2SO4 and concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford the compound (R)-N-((R)-1'-benzyl-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-yl)-2-methylpropane-2-sulfinamide (195mg, 29%) as a yellow oil. MS: 411 $(M+H)^+$.

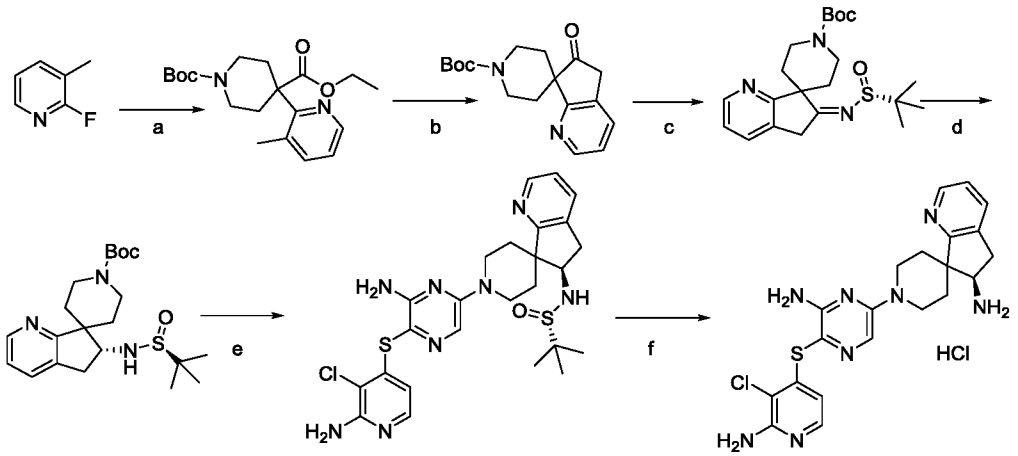
Step e:Into the solution of the compound (R)-N-((R)-1'-benzyl-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-yl)-2-methylpropane-2-sulfinamide (195mg, 0.47mmol) in methanol (5mL) was added palladium hydroxide(20%, 120mg). The mixture was stirred for 18h at 40°C under hydrogen atmosphere. The mixture was filtrated and the filtration was concentrated to afford the compound (R)-N-((R)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-yl)-2-methylpropane-2-sulfinamide (92mg, 60%). MS: 321 $(M+H)^+$.

Step f:The compound (R)-N-((R)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-yl)-2-methylpropane-2-sulfinamide (92mg, 0.29mmol) was dissolved in NMP (3mL). 3-((2-amino-3-chloropyridin-4-yl)thio)-6-chloropyrazin-2-amine (91mg, 0.32mmol) and K_2CO_3 (198mg, 1.44mmol) were added into. The mixture was stirred for 3 hours at 100°C, and diluted with EA(30mL) ,washed with brine (30mL×3). The organic layer was dried with anhydrous Na_2SO_4. The residue was purified with Pre-TLC to afford the compound (R)-N-((R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-yl)-2-methylpropane-2-sulfinamide (18mg, 11%) as an off-white solid.

Step g:In to the solution of the compound (R)-N-((R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-yl)-2-methylpropane-2-sulfinamide (18mg, 0.03mmol) in 1,4-dioxane (2mL)was added HCl/Dixoane (4mol/L, 2mL). The mixture was stirred for 30 mins. The resulted mixture was concentrated and washed with EA for twice. The solid was dried in high vacuum to afford the compound (R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-amine (14mg, 88%) as an off-white solid. MS: 468 $(M+H)^+$.

EXAMPLE 4

(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidin]-6-amine



Step a:NaHMDS (38ml, 2mol/L in THF) was added to the mixture of the compound 2-fluoro-3-methylpyridine (5.56g, 50.00mmol), 1-tert-butyl 4-ethyl piperidine-1,4-dicarboxylate (14.15g, 55.00mmol) in toluene (50mL) dropwise at 0°C, then naturally warmed to 20°C and stirred for 24 hours. Reaction mixture was quenched with brine (100mL). The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford the compound 1-(tert-butyl) 4-ethyl 4-(3-methylpyridin-2-yl)piperidine-1,4-dicarboxylate (6.32g, 36%) as a yellow oil. MS: 349 $(M+H)^+$.

Step b:A mixture of the compound 1-(tert-butyl) 4-ethyl 4-(3-methylpyridin-2-yl)piperidine-1,4-dicarboxylate (4.80g, 13.78mmol), LDA (2mol/L,17mL) in THF (48mL) was stirred at 0°C for 0.5 hour. The mixture was removed under reduced pressure in vacuo. The residue was purified by column chromatography to afford the compound tert-butyl 6-oxo-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidine]-1'-carboxylate (0.95g, 23%) as a red oil. MS: 303 $(M+H)^+$.

Step c:To a solution of the compound tert-butyl 6-oxo-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidine]-1'-carboxylate (0.94g, 3.11mol) in Titanium(IV) ethoxide (5mL) was added R-(+)-tert-Butylsulfinamide（1.13g, 9.33mmol）. The resulting mixture was stirred at 80°C for 1 hour. EA (30mL) and water (20mL) was added to the reaction mixture. The reaction mixture was filtered and organic extracts were collected. The aqueous solution was extracted with EA (10mL×2). The combined organic extracts were washed with brine (50mL), dried over Na_2SO_4 and concentrated under reduced pressure in vacuo to afford the compound tert-butyl (R,Z)-6-((tert-butylsulfinyl)imino)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidine]-1'-ca

rboxylate (2.51g, crude) as a red oil. Without purification to next step.MS: 406$(M+H)^+$.

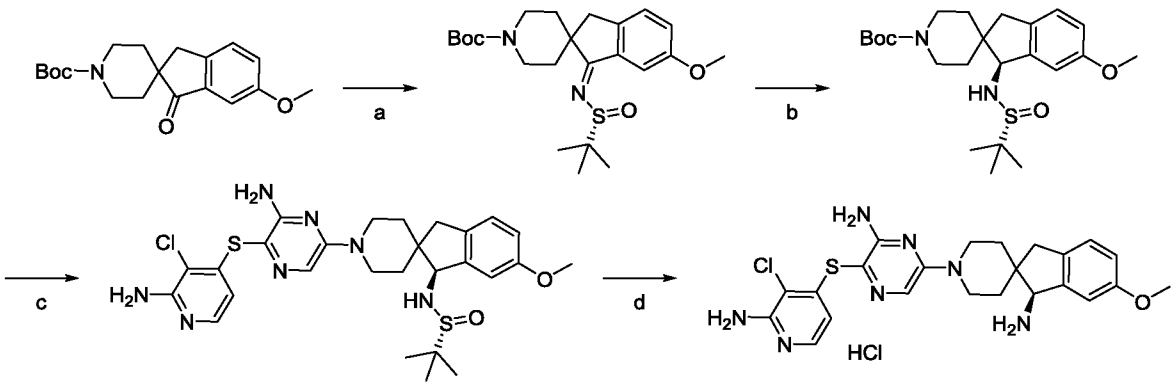
Step d:A solution of the compound tert-butyl (R,Z)-6-((tert-butylsulfinyl)imino)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidine]-1'-carboxylate (2.12g, crude) in THF (20mL) was stirred at -50°C. $NaBH_4$ (176mg, 4.66mmol) was added to the reaction mixture and naturally warmed to room temperature. Reaction was quenched with saturated ammonium chloride solution (30mL). The organic extracts were collected and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure in vacuo. The residue was purified by column chromatography to afford the compound tert-butyl (R)-6-(((S)-tert-butylsulfinyl)amino)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidine]-1'-carboxylate (0.21g, 17%, 2 steps) as a yellow solid. MS: 408 $(M+H)^+$.

Step e:A mixture of the compound tert-butyl (R)-6-(((S)-tert-butylsulfinyl)amino)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidine]-1'-carboxylate (204mg, 0.50mmol), CF_3COOH (1mL) in DCM(10mL) was stirred at 25°C for 1.5 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in NMP(10mL), then 3-((2-amino-3-chloropyridin-4-yl)thio)-6-chloropyrazin-2-amine (144mg, 0.50mmol) and K_2CO_3 (0.82g, 6.00mmol) was added to mixture and stirred at 95°C for 16 hours. H_2O (50mL) was added to the reaction mixture. The aqueous solution was extracted with EA (30mL×2). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure in vacuo to afford the compound (S)-N-((R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidin]-6-yl)-2-methylpropane-2-sulfinamide (302mg, crude). Without purification to next step. MS: 559 $(M+H)^+$.

Step f:To a solution of the compound (S)-N-((R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidin]-6-yl)-2-methylpropane-2-sulfinamide (302mg, 0.54mmol) in DCM (10mL) was added HCl/Dixoane (4mol/L, 1mL). The resulting mixture was stirred at 25°C for 1 hour and the precipitate was filtered. The filter cake dissolved in MeOH (2mL), then DCM (15mL) was added into. The mixture was stirred for 0.5 hour and filtered to afford the compound (R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidin]-6-amine (163mg, 71%, 2 steps) as a yellow solid. MS: 455 $(M+H)^+$. ^1H NMR (600 MHz,*MeOH-d4*) δ 8.69 (d, 1H), 8.54 (d, 1H), 7.92 - 7.96 (m, 1H), 7.88(s,1H), 7.75(d,1H), 6.58(d,1H), 4.54 - 4.67 (m, 3H), 3.89 - 3.95 (m, 1H), 3.37 - 3.61 (m, 3H), 2.79 - 2.86 (m, 1H), 1.93 - 2.20 (m, 3H).

EXAMPLE 5

(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-1,3-dihydro spiro[indene-2,4'-piperidin]-1-amine



Step a: A mixture of tert-butyl 6-methoxy-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (557 mg, 1.68 mmol) and (R)-(+)-2-Methyl-2-propanesulfinamide (610 mg, 5.04 mmol) in $Ti(OEt)_4$ (5 mL) was stirred for 16 h at 100 °C. After cooling to RT, the reaction mixture was diluted with EA (20 mL) and water (30 mL). The resulting mixture was filtered through a pad of Celite followed by EA wash. The filtrate was washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl (R,Z)-1-((tert-butylsulfinyl)imino)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (0.98 g) which was used in next step without any further purification. MS: *m/z* 435 $(M+H)^+$.

Step b: To a -50 °C solution of tert-butyl (R,Z)-1-((tert-butylsulfinyl)imino)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (0.98 g, 2.25 mmol) in THF (10 mL) was added $NaBH_4$ (0.17 g, 4.51 mmol). The resulting mixture was allowed to warm to RT and stirred for 24 h. The reaction mixture was diluted with EA (50 mL) and water (50 mL), the organic layer was separated, washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 5, v/v) to give tert-butyl (S)-1-(((R)-tert-butylsulfinyl)amino)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (380 mg). MS: *m/z* 437 $(M+H)^+$.

Step c: To solution of tert-butyl (S)-1-(((R)-tert-butylsulfinyl)amino)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (380 mg, 0.87 mmol) in DCM (10 mL) was added TFA (2 mL), and stirred for 1.5 h at RT. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in NMP (10 mL), 3-((2-amino-3-chloropyridin-4-yl)thio)-6-chloropyrazin-2-amine (301 mg, 1.04 mmol) and K_2CO_3 (601 mg, 4.35 mmol) was added. The resulting mixture was stirred for 16 h at 100 °C. After cooling to RT, the reaction mixture was diluted with water (50 mL) and EA (50 mL). The aqueous layer was separated, the organic layer was washed with brine (2 × 50 mL), dried over

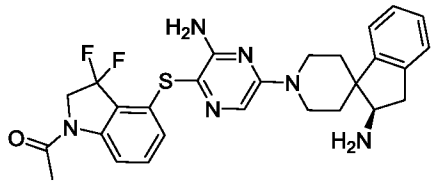
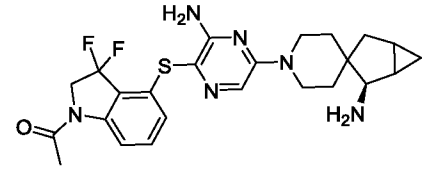
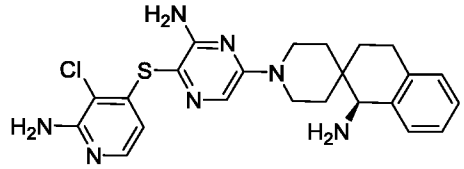
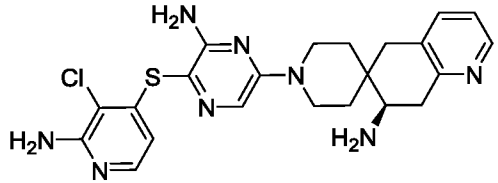
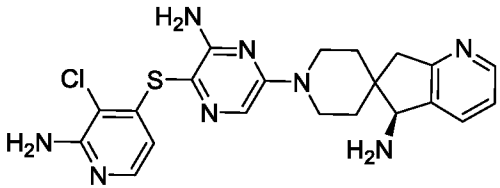
anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with MeOH : DCM = 1 : 20, v/v) to give (R)-N-((S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-3-yl)-2-methylpropane-2-sulfinamide (254 mg). MS: *m/z* 588 $(M+H)^+$.

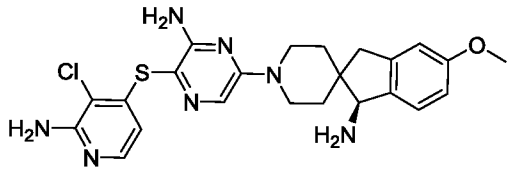
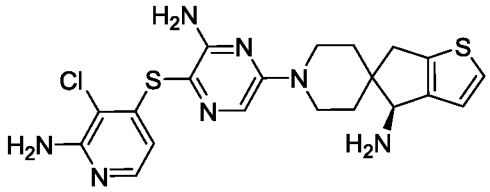
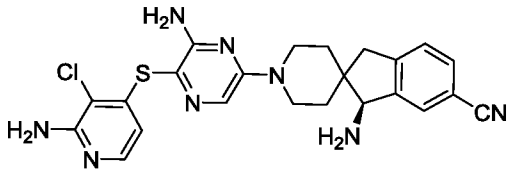
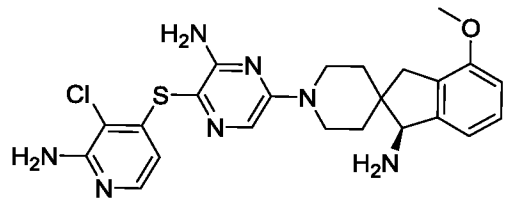
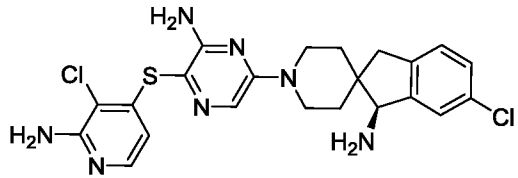
Step d: To a solution of (R)-N-((S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-3-yl)-2-methylpropane-2-sulfinamide (254 mg, 0.43 mmol) in 1, 4-dioxane (3 mL) was added HCl (4M solution in 1, 4-dioxane, 3 mL) dropwise and stirred for 30 min at RT. The reaction mixture was filtered and the collected precipitate was dried in a vacuum oven to give (S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine (221 mg) as a HCl salt. MS: *m/z* 484 $(M+H)^+$. ^1H NMR (600 MHz, *MeOH-d4*) δ 7.90 (s, 1H), 7.76 (d, 1H), 7.28 (d, 1H), 7.12 (d, 1H), 6.95 - 6.89 (m, 1H), 6.58 (d, 1H), 4.50 - 4.35 (m, 3H), 3.82 (s, 3H), 3.49 - 3.40 (m, 2H), 3.16 - 3.08 (m, 2H), 2.01 - 1.66 (m, 4H).

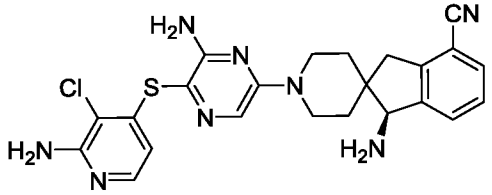
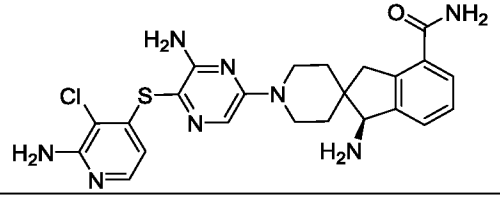
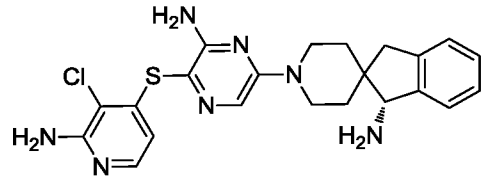
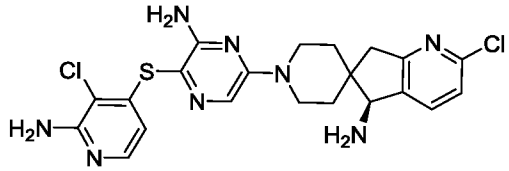
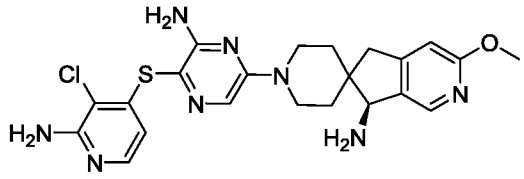
The following examples were synthesized using the above procedure or modification procedure using the corresponding Intermediate A and Intermediate B.

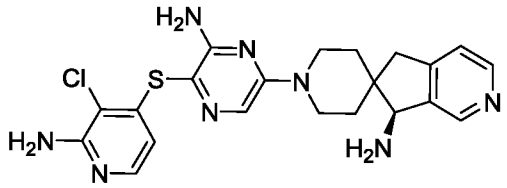
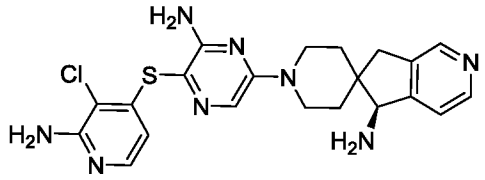
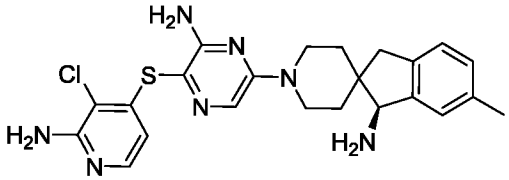
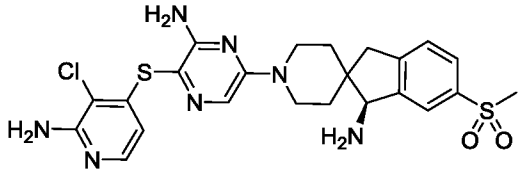
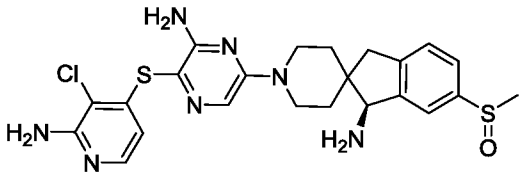
The following examples are compounds with **free base**, or a pharmaceutically acceptable salt.

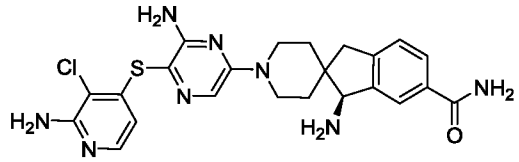
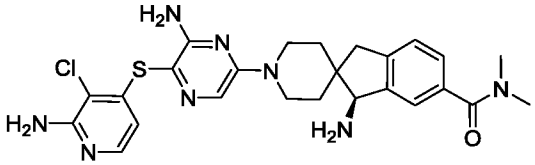
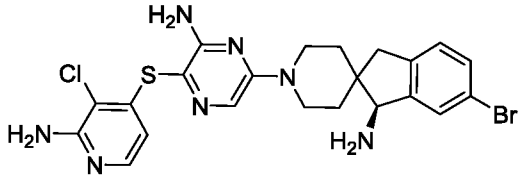
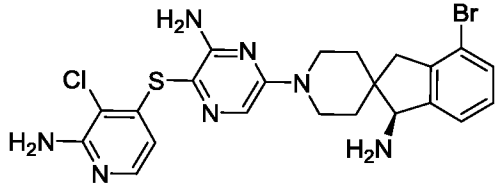
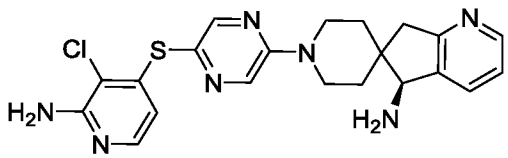
Table 16

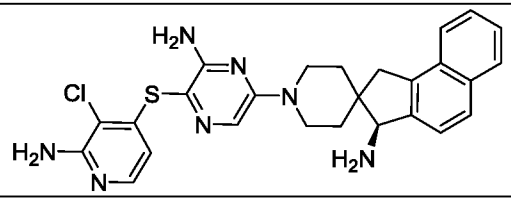
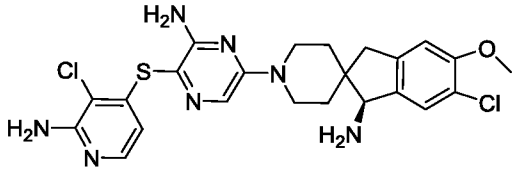
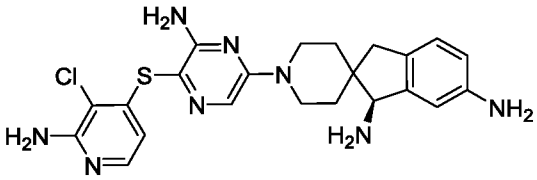
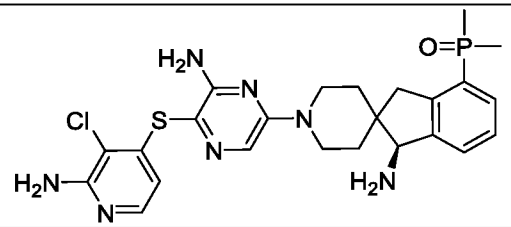
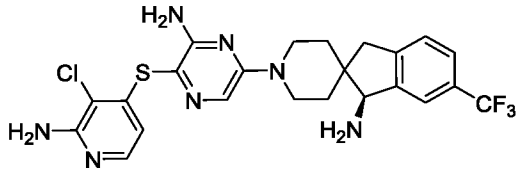
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
6	(R)-1-(4-((3-amino-5-(2-amino-2,3-dihydrospiro[indene-1,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one		^{1}H NMR (600 MHz, *MeOH-d4*) δ 8.07 (d, 1H), 7.60 (s, 1H), 7.3 - 7.30 (m, 5H), 6.64 (d, 1H), 4.52 (t, 2H), 4.28 - 4.12 (m, 3H), 3.57 - 3.53(m, 3H), 3.00 (d, 1H), 2.28 (s, 3H), 2.01 - 1.65 (m, 4H). MS: 523$(M+H)^+$.
7	1-(4-((3-amino-5-((2R)-2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one		^{1}H NMR (600 MHz, *MeOH-d4*) δ 8.05 (d, 1H), 7.51 (s, 1H), 7.3((t, 1H), 6.51 (d, 1H), 4.51 (t, 2H), 4.25 - 4.10 (m, 2H), 3.32 (d, 1H), 3.24 (d, 1H), 3.05 - 2.97 (m, 2H), 2.27 (s, 3H), 1.91 (d, 1H) 1.71 - 1.39 (m, 8H). MS: 487$(M+H)^+$.
8	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine		^{1}H NMR (600 MHz, *MeOH-d4*) δ 7.89 (s, 1H), 7.76 (d, 1H), 7.4 (d, 1H), 7.39 - 7.28 (m, 3H), 6.57 (d, 1H), 4.33 (s, 1H), 4.26 (d, 1H), 4.08 (d, 1H), 3.74 - 3.56 (m, 2H), 3.07 - 2.92 (m, 2H), 2.2 - 2.19 (m, 1H), 1.97 - 1.90 (m, 2H), 1.81 - 1.52 (m, 3H). MS: 468$(M+H)^+$.
9	(R)-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7',8'-dihydro-5'H-spiro[piperidine-4,6'-quinolin]-7'-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.75 (d, 1H), 8.52 (d, 1H), 7.9 - 7.95 (m, 1H), 7.91 (s, 1H), 7.77 (d, 1H), 6.59 (d, 1H), 4.34 (t, 2H), 3.93 (t, 1H), 3.83 - 3.76 (m, 2H), 3.53 - 3.35 (m, 4H), 2.01 1.94 (m, 2H), 1.83 (d, 1H), 1.71(d, 1H). MS: 469$(M+H)^+$.
10	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.31 (d, 1H), 7.67 - 7.63 (m, 3H), 7.17 (m, 1H), 5.76 (d, 1H), 4.22 (d, 2H), 3.90 (s, 1H), 3.20 3.08 (m, 3H), 2.75 (d, 1H), 1.80 - 1.66 (m, 2H), 1.53 (d, 1H), 1.1 (d, 1H). MS: 455$(M+H)^+$.

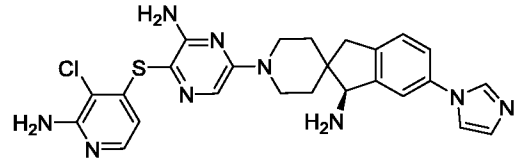
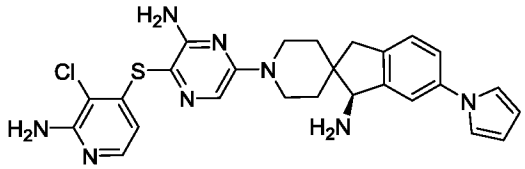
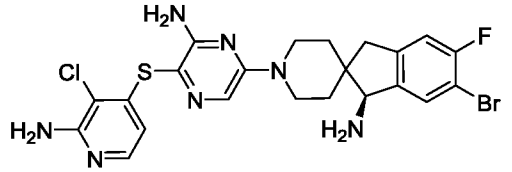
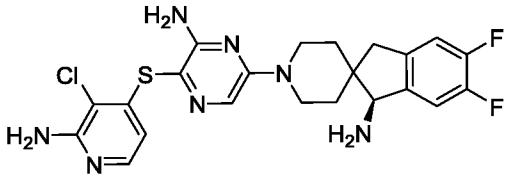
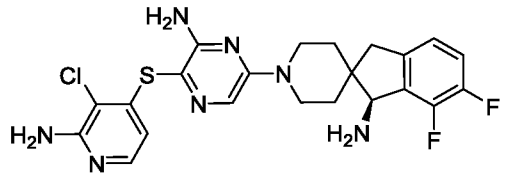
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
11	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.80 (d, 1H), 7.72 (s, 1H), 7.5((d, 1H), 6.92 - 6.79 (m, 2H), 6.11 (d, 1H), 4.37 - 4.15 (m, 3H), 3.76 (s, 3H), 3.25 - 3.10 (m, 3H), 2.97 (d, 1H), 1.84 - 1.67 (m, 2H), 1.66 - 1.57 (m, 1H), 1.51 - 1.41 (m, 1H). MS: 484$(M+H)^+$.
12	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.87 (s, 1H), 7.73 (d, 1H), 7.4: (d, 1H), 7.07 (d, 1H), 6.53 (d, 1H), 4.51 (d, 1H), 4.39 (d, 1H), 4.30 (s, 1H), 3.47 - 3.12 (m, 4H), 2.11 - 1.78 (m, 4H). MS: 460$(M+H)^+$.
13	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile		^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.05 (s, 1H), 7.83 (d, 1H), 7.9((d, 1H), 7.72 (s, 1H), 7.55 (d, 1H), 6.11 (d, 1H), 4.47 (s, 1H), 4.3: (d, 1H), 4.23 (d, 1H), 3.40 - 3.07 (m, 4H), 1.79 - 1.72 (m, 2H), 1.58 - 1.49 (m, 2H). MS: 479$(M+H)^+$.
14	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.89 (s, 1H), 7.75 (d, 1H), 7.3: (t, 1H), 7.12 (d, 1H), 7.01 (d, 1H), 6.58 (d, 1H),4.48 (d, 1H), 4.4((s, 1H), 4.37 (d, 1H), 3.87 (s, 3H), 3.51 - 3.38 (m, 2H), 3.19 - 3.0: (m, 2H), 1.99 - 1.87 (m, 2H), 1.79 (d, 1H), 1.66 (d, 1H). MS: 484$(M+H)^+$.
15	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-chloro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.80 (d, 1H), 7.72 (s, 1H), 7.7((s, 1H), 7.41 - 7.35 (m, 2H), 6.12 (d, 1H), 4.39 (s, 1H), 4.32 (d, 1H), 4.24 (d, 1H), 3.23 - 2.94 (m, 4H), 1.86 - 1.70 (m, 2H), 1.58 1.49 (m, 2H). MS: 488$(M+H)^+$.

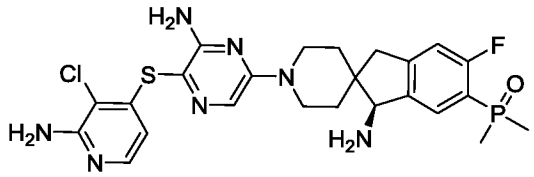
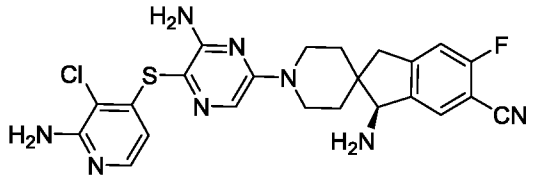
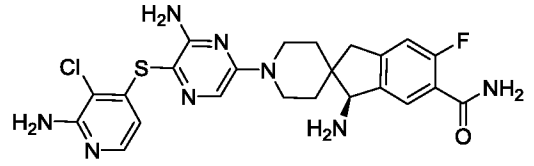
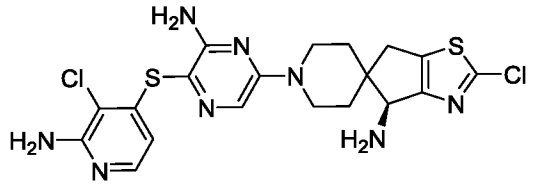
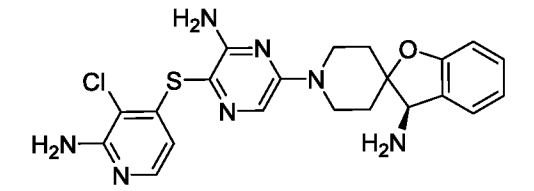
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
16	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carbonitrile		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.89 - 7.76 (m, 3H), 7.72 (d, 1H), 7.55 (t, 1H), 6.49 (d, 1H), 4.60 (s, 1H), 4.47 (d, 1H), 4.36 (d 1H), 3.52 - 3.36 (m, 4H), 1.99 - 1.86 (m, 2H), 1.85 - 1.75 (m, 1H) 1.73 - 1.61 (m, 1H). MS: 479$(M+H)^+$.
17	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carboxamide		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.78 - 7.60 (m, 4H), 7.52 - 7.4 (m, 1H), 5.97 (d, 1H), 4.49 - 4.35 (m, 2H), 4.30 (d, 1H), 3.45 - 3.25 (m, 4H), 1.95 - 1.56 (m, 4H). MS: 497$(M+H)^+$.
18	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 454$(M+H)^+$.
19	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.86 - 7.80 (m, 1H), 7.66 - 7.5 (m, 2H), 7.34 (d, 1H), 5.96 (d, 1H), 4.41 - 4.29 (m, 2H), 4.08 (s, 1H), 3.32 - 3.18 (m, 3H), 2.97 (d,1H), 1.93 - 1.79 (m, 2H), 1.65 (d, 1H), 1.49 (d, 1H). MS: 489$(M+H)^+$.
20	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methoxy-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.08 (d, 1H), 7.82 (s, 1H), 7.7 (d, 1H), 7.02 (d, 1H), 6.47 (d, 1H), 4.49 (d, 2H), 4.37 (d, 1H), 4.06 (s, 3H), 3.47 - 3.34 (m, 4H), 2.05 - 1.95 (m, 1H), 1.93 - 1.8 (m, 2H), 1.71 (d, 1H). MS: 485$(M+H)^+$.

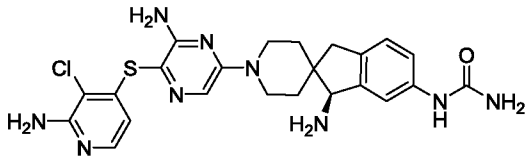
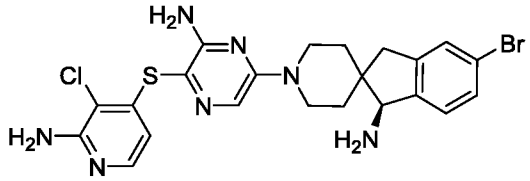
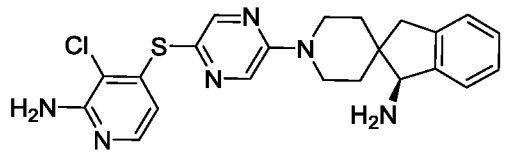
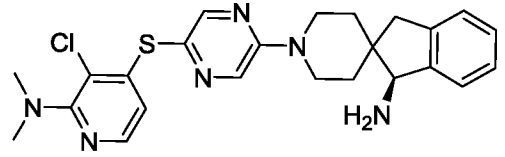
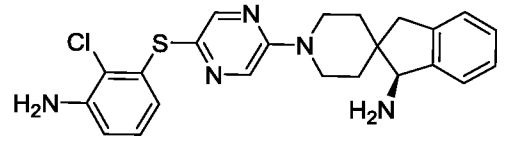
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
21	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 9.16 (s, 1H), 8.88 (d, 1H), 8.0- (d, 1H), 7.81 (d, 1H), 7.74 (s, 1H), 6.11 (d, 1H), 4.72 (s, 1H), 4.4- - 4.13 (m, 2H), 3.73 - 3.12 (m, 4H), 1.91 - 1.75 (m, 2H), 1.72 - 1.64 (m, 1H), 1.53 - 1.40 (m, 1H). MS: 455$(M+H)^+$.
22	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.92 (d, 2H), 8.26 (d, 1H), 7.8- (s, 1H), 7.72 (s, 1H), 6.49 (d, 1H), 4.97 (s, 1H), 4.52 (t, 2H), 3.7((d, 1H), 3.46 - 3.29 (m, 3H), 2.19 - 1.65 (m, 4H). MS: 455$(M+H)^+$.
23	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.80 (d, 1H), 7.71 (s, 1H), 7.4((s, 1H), 7.25 - 7.10 (m, 2H), 6.12 (d, 1H), 4.40 - 4.13 (m, 3H), 3.28 - 3.04 (m, 3H), 2.98 - 2.85 (d, 1H), 2.31 (s, 3H), 1.87 - 1.6- (m, 2H), 1.62 - 1.40 (m, 2H). MS: 468$(M+H)^+$.
24	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.08 (s, 1H), 7.92 (d, 1H), 7.7- - 7.54 (m, 3H), 5.98 (d, 1H), 4.47 - 4.31 (m, 2H), 4.27 (s, 1H), 3.34 - 3.20 (m, 3H), 3.17 (s, 3H), 3.02 (d, 1H), 1.97 - 1.80 (m, 2H), 1.72 - 1.48 (m, 2H). MS: 532$(M+H)^+$.
25	(1S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfinyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.86 - 7.79 (m, 1H), 7.72 - 7.5- (m, 3H), 7.55 (d, 1H), 5.96 (d, 1H), 4.40 - 4.26 (m, 3H), 3.32 - 3.11 (m, 4H), 2.84 (s, 3H), 1.95 - 1.77 (m, 2H), 1.76 - 1.58 (m, 2H). MS: 516$(M+H)^+$.

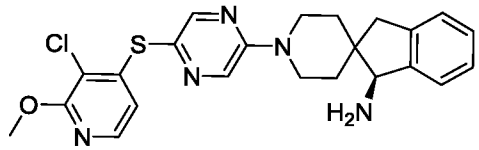
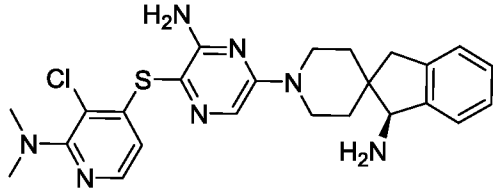
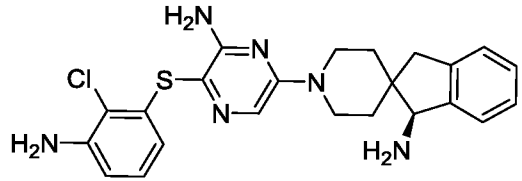
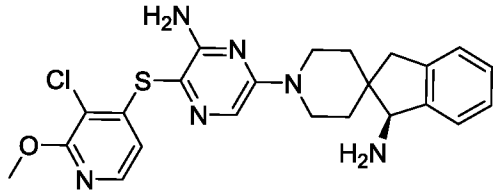
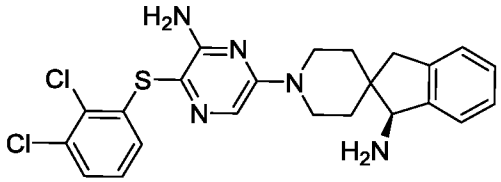
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
26	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.02 (s, 1H), 7.89 (d, 1H), 7.62 - 7.61(m, 2H), 7.47 (d, 1H), 5.92 (d, 1H), 4.44 (s, 1H), 4.39 - 4.26 (m, 2H), 3.35 - 3.17 (m, 4H), 1.81 - 1.77 (m, 2H), 1.70 (d, 1H), 1.61 (d, 1H). MS: 497$(M+H)^+$.
27	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-N,N-dimethyl-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.61 (s, 2H), 7.53 (s, 1H), 7.43 (s, 2H), 5.93 (d, 1H), 4.36 - 4.28 (m, 3H), 3.34 - 3.26 (m, 2H), 3.22 - 3.15 (d, 2H), 3.11 (s, 3H), 3.03 (s, 3H), 1.88 - 1.76 (m, 2H) 1.68 - 1.59 (m, 2H). MS: 525$(M+H)^+$.
28	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (600 MHz, *MeOH-d4*) δ 7.75 (s, 1H), 7.74 (s, 1H), 7.70 (d, 1H), 7.62 - 7.57 (m, 1H), 7.36 (d, 1H), 6.37 (d, 1H), 4.49 (s, 1H), 4.46 (d, 1H), 4.35 (d, 1H), 3.42 - 3.35 (m, 2H), 3.24 - 3.15 (m, 2H), 1.98 - 1.81 (m, 2H), 1.77 (d, 1H), 1.67 (d, 1H). MS: 532$(M+H)^+$.
29	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.77 (s, 1H), 7.68 (d, 1H), 7.61 (d, 1H), 7.52 (d, 1H), 7.30 (t, 1H), 6.39 (d, 1H), 4.57 (s, 1H), 4.44 (d, 1H), 4.33 (d, 1H), 3.46 - 3.34 (m, 2H), 3.21 (s, 2H), 2.03 - 1.62 (m, 4H). MS: 532$(M+H)^+$.
30	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.39 (d, 1H), 8.37 (d, 1H), 8.28 (d, 1H), 7.86 (d, 1H), 7.60 (d, 1H), 7.31 - 7.28 (m, 1H), 5.95 (d, 1H), 4.42 - 4.36 (m, 2H), 4.12 (s, 1H), 3.37 - 3.33 (m, 2H), 3.26 (d, 1H), 3.00 (d, 1H), 1.94 - 1.81 (m, 2H), 1.69 - 1.45 (m, 2H). MS: 440$(M+H)^+$.

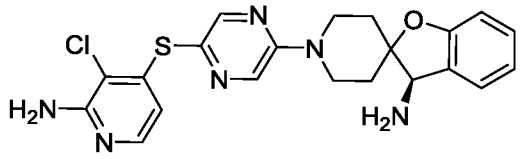
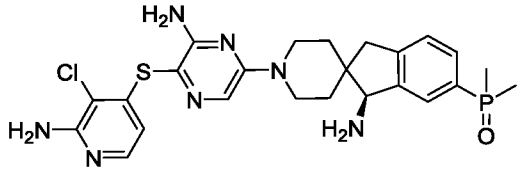
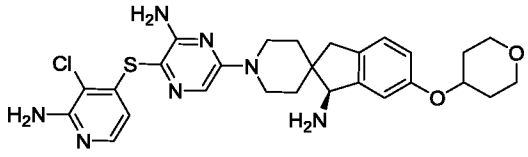
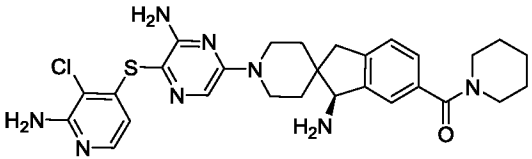
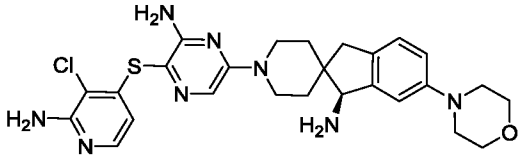
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
31	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-3-amine		^{1}H NMR (600MHz, *MeOH-d4*) δ 8.01 - 7.58 (m, 8H), 6.51 (d, 1H), 4.64 (s, 1H), 4.54 (d, 1H), 4.39 (d, 1H), 3.65 - 3.48 (m, 4H) 2.11 - 1.89 (m, 3H), 1.73 (d, 1H). MS: 504$(M+H)^+$.
32	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-chloro-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.64 - 7.63 (m, 2H), 7.25 (s, 1H), 7.14 (s, 1H), 5.75 (d, 1H), 4.21 (d, 2H), 3.89 (s, 1H), 3.83 (s 3H), 3.13 - 3.06 (m, 2H), 3.01 (d, 1H), 2.63 (d, 1H), 1.76 - 1.71 (m, 1H), 1.66 - 1.60 (m, 1H), 1.50 (d, 1H), 1.17 (d, 1H). MS: 518$(M+H)^+$.
33	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine		^{1}H NMR (600MHz, *MeOH-d4*) δ 7.64 (d, 2H), 7.13 (d, 1H), 6.8 (s, 1H), 6.81 (d, 1H), 5.96 (d, 1H), 4.41 (d, 1H), 4.30 (d, 2H), 3.3 - 3.26 (m, 2H), 3.08 (d, 2H), 1.90 - 1.83 (m, 1H), 1.76 (d, 2H), 1.65 (d, 1H). MS: 469$(M+H)^+$.
34	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-yl)dimethylphosphine oxide		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.80 - 7.68 (m, 2H), 7.67 - 7.5 (m, 2H), 7.51 (t, 1H), 5.96 (d, 1H), 4.41 - 4.24 (m, 3H), 3.48 - 3.31(m, 4H), 1.96 - 1.79 (m, 8H), 1.71 - 1.55 (m, 2H). MS: 530$(M+H)^+$.
35	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.03 (s, 1H), 7.78 (d, 1H), 7.7 - 7.71 (m, 2H), 7.55 (d, 1H), 6.09 (d, 1H), 4.49 (d, 1H), 4.34 -4.2 (m, 2H), 3.37 - 3.31(d, 1H), 3.21 - 3.14 (m, 2H), 3.09 - 3.05 (d, 1H), 1.82 - 1.76 (m, 2H), 1.56 - 1.53 (m, 2H). MS: 522$(M+H)^+$.

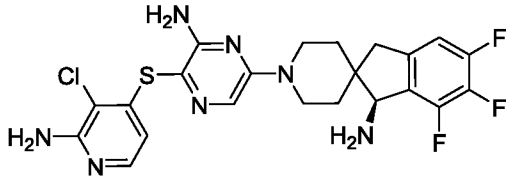
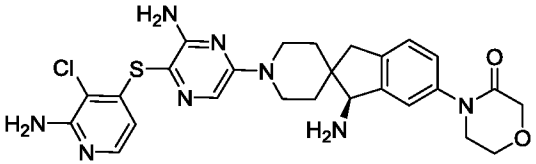
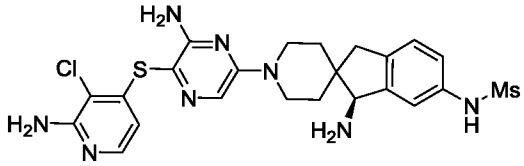
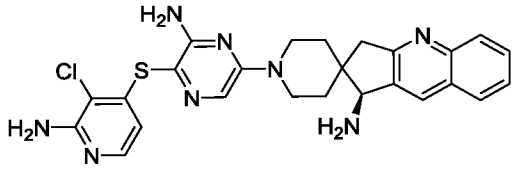
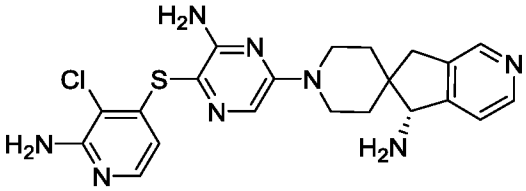
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
36	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-imidazol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 9.22 (s, 1H), 7.99 (s, 1H), 7.7 - 7.52 (m, 5H), 6.15 (d, 1H), 4.22 (d, 2H), 3.63 - 3.23 (m, 4H), 2.88 (d, 1H), 1.91 (d, 2H), 1.68 (d, 1H), 1.48 (d, 1H). MS: 520$(M+H)^+$.
37	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-pyrrol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.81 (s, 1H), 7.75 - 7.70 (m, 2H), 7.66 (d, 1H), 7.58 - 7.53 (m, 1H), 7.48 (d, 1H), 7.22 - 7.19 (m, 1H), 6.46 - 6.43 (m, 1H), 6.34 - 6.29 (m, 2H), 4.53 (s, 1H), 4.47 (d, 1H), 4.37 (d, 1H), 3.42 (d, 2H), 3.24 (d, 2H), 1.98 - 1.9((m, 2H), 1.81 (d, 1H), 1.72 (d, 1H). MS: 519$(M+H)^+$.
38	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-bromo-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (600 MHz, *MeOH-d4*) δ 7.84 (s, 1H), 7.81 (d, 1H), 7.7 (d, 1H), 7.28 (d, 1H), 6.50 (d, 1H), 4.51 - 4.42 (m, 2H), 4.35 (d, 1H), 3.47 - 3.39 (m, *2*H), 3.27 - 3.20 (m, *2*H),2.00 - 1.93 (m, 1H) 1.92 - 1.84 (m, 1H), 1.84 - 1.73 (m, 1H), 1.72 - 1.63 (m, 1H). MS 550$(M+H)^+$.
39	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-difluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.82 (d, 1H), 7.76 - 7.73 (m, 1H), 7.72 (s, 1H), 7.42 - 7.38 (m, 1H), 6.11 (d, 1H), 4.36 - 4.20 (m, 3H), 3.22 - 3.10 (m, 3H), 2.99 - 2.95 (d, 1H), 1.81 - 1.75 (m 2H) , 1.61 - 1.51 (m, 2H). MS: 490$(M+H)^+$.
40	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-difluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.65 - 7.63 (m, 2H), 7.30 - 7.2 (m, 2H), 5.75 (d, 1H), 4.22 - 4.17 (m, 2H), 3.83 (s, 1H), 3.16 - 3.02 (m, 3H), 2.62 (d, 1H), 1.78 - 1.71 (m, 1H), 1.68 - 1.55 (m, 1H), 1.51 (d, 1H), 1.11 (d, 1H). MS: 490$(M+H)^+$.

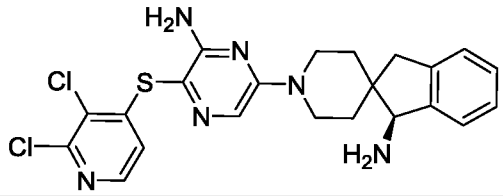
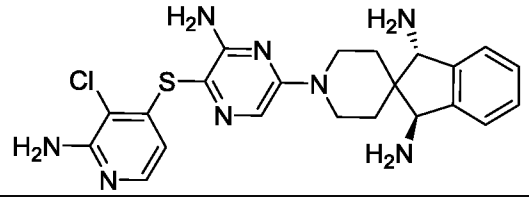
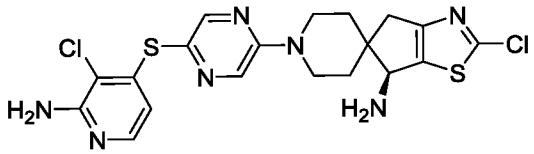
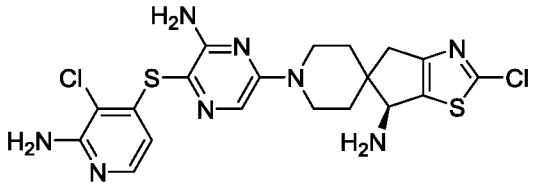
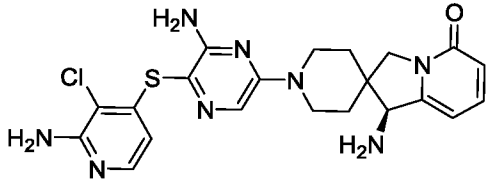
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
41	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)dimethylphosphine oxide		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.97 - 7.92 (m, 1H), 7.64 - 7.63(m, 2H), 7.34 - 7.31 (m, 1H), 5.96 (d, 1H), 4.44 - 4.38 (m, 2H), 4.31 (d, 1H), 3.34 - 3.21 (m, 4H), 1.93 - 1.80 (m, 8H), 1.75 1.71 (m, 1H), 1.66 - 1.62 (m,1H). MS: 548$(M+H)^+$.
42	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.90 (d, 1H), 7.79 (s, 1H), 7.7((d, 1H), 7.43 (d, 1H), 6.43 (d, 1H), 4.54 (s, 1H), 4.44 (d, 1H), 4.3 (d, 1H), 3.47 - 3.20 (m, 4H), 2.01 - 1.82 (m, 2H), 1.82 - 1.72 (m 1H), 1.71 - 1.60 (m, 1H). MS: 497$(M+H)^+$.
43	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.87 (d, 1H), 7.68 - 7.59 (m, 2H), 7.15 (d, 1H), 5.96 (d, 1H), 4.31 - 4.26 (d, 2H), 4.04 (s, 1H) 3.39 - 3.18 (m, 3H), 2.90 - 2.86 (d, 1H), 1.96 - 1.74 (m, 2H), 1.6 - 1.57 (m, 1H), 1.44 - 1.41 (m, 1H). MS: 515$(M+H)^+$.
44	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.65 (s, 1H), 7.64 (d, 1H), 5.7 (d, 1H), 4.06 - 3.96 (m, 2H), 3.80 (s, 1H), 3.41- 3.28 (m, 2H), 2.91 - 2.76 (m, 2H), 1.91 - 1.82 (m, 1H), 1.66 - 1.47 (m, 3H). MS 495$(M+H)^+$.
45	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.70 (s, 1H), 7.65 (d, 1H), 7.4 (d, 1H), 7.20 (t, 1H), 6.90 (t, 1H), 6.84 (d, 1H), 5.77 (d, 1H), 4.3 - 4.20 (m, 3H), 3.33 - 3.29 (m, 2H), 1.99 - 1.90 (m, 1H), 1.84 - 1.70 (m, 3H). MS: 456$(M+H)^+$.

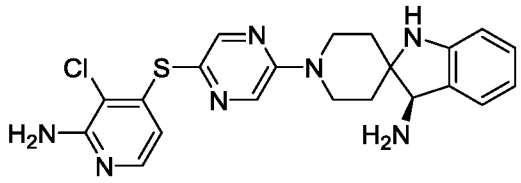
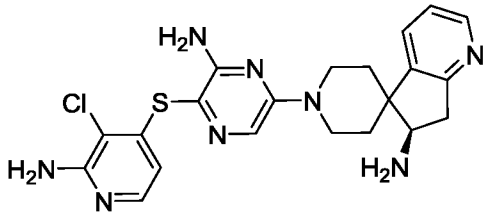
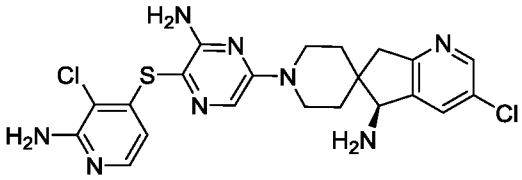
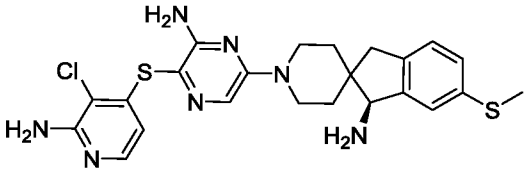
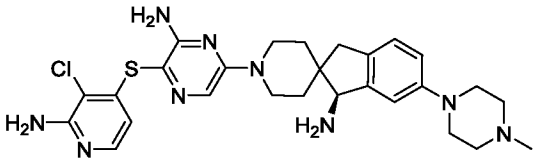
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
46	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)urea		^{1}H NMR (400 MHz, MeOH-d4) δ 7.68 (s, 1H), 7.64 - 7.59 (m, 2H), 7.31- 7.25 (m, 2H), 5.93 (d, 1H), 4.43 - 4.25 (m, 3H), 3.31 3.11 (m, 4H), 1.88 - 1.60 (m, 4H). MS: 512(M+H)+.
47	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.84 (s, 1H), 7.74 (d, 1H), 7.58 (s, 1H), 7.53 - 7.41 (m, 2H), 6.51 (d, 1H), 4.50 - 4.28 (m, 3H), 3.51 - 3.35 (m, 2H), 3.30 - 3.17 (m, 2H), 2.02 - 1.83 (m, 2H), 1.8 - 1.71 (m, 1H), 1.70 - 1.57 (m, 1H). MS: 532(M+H)$^+$.
48	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.55 (s, 1H), 8.38 (s, 1H), 7.80 (d, 1H), 7.60 (d, 1H), 7.35 - 7.28 (m, 3H), 6.23 (d, 1H), 4.43 - 4.31 (m, 3H), 3.38 - 3.23 (m, 3H), 3.03 - 2.99 (d, 1H), 1.93 - 1.78 (m, 2H), 1.61 - 1.54 (m, 2H). MS: 439(M+H)$^+$.
49	(S)-1'-(5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (600 MHz, *MeOH-d4*) δ 8.50 (s, 1H), 8.36 (s, 1H), 7.78 (d 1H), 7.54 (d, 1H), 7.44 - 7.39 (m, 2H), 7.34 (m, 1H), 6.60 (d, 1H), 4.51 (d, 1H), 4.45 (s, 1H), 4.38 (d, 1H), 3.51 - 3.40 (m, 2H), 3.33 (s 6H), 3.28 - 3.19 (m, 2H), 2.00 - 1.93 (m, 1H), 1.92 - 1.85 (m, 1H), 1.80 (d, 1H), 1.68 (d, 1H). MS: 467(M+H)$^+$.
50	(S)-1'-(5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.43 (s, 1H), 8.19 (s, 1H), 7.59 (d, 1H), 7.35 - 7.29 (m, 3H), 6.97 (t, 1H), 6.78 (d, 1H), 6.22 (d, 1H), 4.35 (s, 1H), 4.32 - 4.22 (m, 2H), 3.28 - 3.19 (m, 3H), 3.02 2.98 (d, 1H), 1.82 - 1.71 (m, 2H), 1.60 - 1.46 (m, 2H). MS: 438(M+H)$^+$.

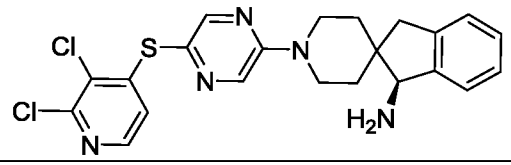
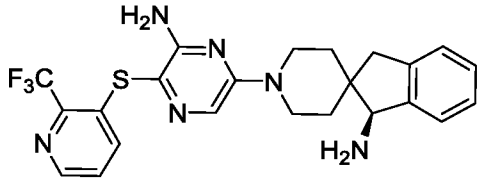
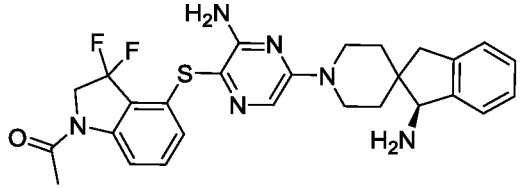
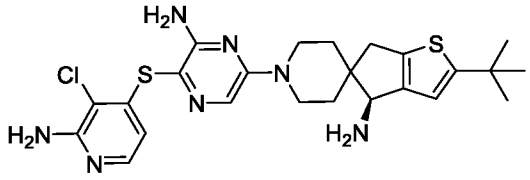
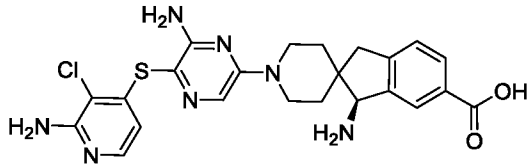
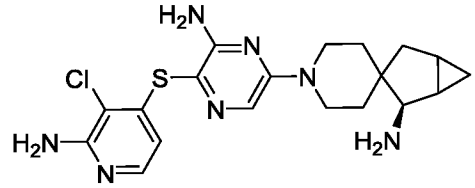
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
51	(S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.52 (d, 1H), 8.34 (s, 1H), 7.8 (d, 1H), 7.59 (d, 1H), 7.39 - 7.26 (m, 3H), 6.33 (d, 1H), 4.39 (m 2H), 4.30 (d, 1H), 3.94 (d, 3H), 3.23 (m, 3H), 3.07 - 2.95 (m, 1H) 1.87 - 1.71 (m, 2H), 1.63 - 1.49 (m, 2H). MS: 454$(M+H)^+$.
52	(S)-1'-(6-amino-5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.89 (d, 1H), 7.72 (s, 1H), 7.6 (d, 1H), 7.41 - 7.20 (m, 3H), 6.24 (d, 1H), 4.35 (s, 1H), 4.33 (d, 1H), 4.23 (d, 1H), 3.27 - 3.11 (m, 3H), 3.05 (s, 6H), 3.02 - 2.93 (d 1H), 1.85 - 1.70 (m, 2H), 1.62 - 1.46 (m, 2H). MS: 482$(M+H)^+$.
53	(S)-1'-(6-amino-5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.61 (d, 1H), 7.35 - 7.27 (m, 4H), 7.00 - 6.93 (t, 1H), 6.79 (d, 1H), 6.07 (d, 1H), 4.35 (s, 1H), 4.30 (d, 1H), 4.20 (d, 1H), 3.19 - 3.28 (m, 3H), 3.21 (d, 1H), 1.8 - 1.73 (m, 2H), 1.59 - 1.48 (m, 2H). MS: 453$(M+H)^+$.
54	(S)-1'-(6-amino-5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.87 (d, 1H), 7.66 (s, 1H), 7.3 - 7.32 (m, 1H), 7.22 - 7.17 (m, 3H), 6.19 (d, 1H), 4.22 (d, 2H), 3.92 (s, 4H), 3.19 - 3.06 (m, 3H), 2.71 - 2.67 (d, 1H), 1.82 - 1.5 (m, 2H), 1.48 - 1.39 (m, 1H) , 1.19 - 1.16 (m, 1H). MS: 469$(M+H)^+$.
55	(S)-1'-(6-amino-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.69(s, 1H), 7.59 (d, 1H), 7.4 (d, 1H), 7.39 - 7.27 (m, 3H), 7.23 (t, 1H), 6.60(d, 1H), 4.36 (s, 1H), 4.31 (d, 1H), 4.21 (d, 1H), 3.22 - 3.13 (m, 3H), 3.02 - 2.98 (d, 1H), 1.80 - 1.71 (m, 2H), 1.57 - 1.48 (m, 2H). MS: 472$(M+H)^+$.

EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
56	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine		^{1}H NMR (600 MHz, *MeOH-d4*) δ 8.38 (d, 1H), 8.30 (s, 1H), 7.6 (d, 1H), 7.42 (d, 1H), 7.24 (t, 1H), 6.94 (t, 1H), 6.85 (d, 1H), 5.9 (d, 1H), 4.53 (d, 1H), 4.40 (d, 1H), 4.24 (s, 1H), 3.54 - 3.45 (m, 2H), 2.01 - 1.83 (m, 4H). MS: 441$(M+H)^+$.
57	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)dimethylphosphine oxide		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.77 (d, 1H), 7.69 - 7.63 (m, 1H), 7.61 - 7.59 (m, 2H), 7.44 - 7.42 (m, 1H), 5.94 (d, 1H), 4.3 - 4.27 (m, 2H), 4.01 (s, 1H), 3.32 - 3.23 (m, 2H), 2.86 (d, 1H), 2.58 (d, 1H), 1.94 - 1.73 (m, 8H) , 1.51 (d, 1H), 1.37 (d, 1H). MS 530$(M+H)^+$.
58	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-((tetrahydro-2H-pyran-4-yl)oxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.62 - 7.60 (m, 2H), 7.26 (d, 1H) 7.13 (d, 1H), 7.07 - 6.97 (m, 1H), 5.92 (d, 1H), 4.59 - 4.54 (m, 2H) 4.37 (d, 1H), 4.32 (s, 1H), 4.28 (d, 1H), 3.98 - 3.93 (m, 2H), 3.63 - 3.56 (m, 2H), 3.35 - 3.22 (m, 2H), 3.14 - 3.03 (m, 2H), 2.06 - 2.01 (m, 2H), 1.86 - 1.58 (m, 5H). MS: 554$(M+H)^+$.
59	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)(piperidin-1-yl)methanone		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.61 (t, 2H), 7.51 (s, 1H), 7.4 - 7.38 (m, 2H), 5.93 (d, 1H), 4.39 - 4.27 (m, 3H), 3.80 - 3.64 (m 2H), 3.43 - 3.37 (m, 2H), 3.32 - 3.25 (m, 2H), 3.24 (d, 1H), 3.1 (d, 1H), 1.88 - 1.50 (m, 10H). MS: 565$(M+H)^+$.
60	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-morpholino-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.62 - 7.58 (m, 2H), 7.18 (d, 1H), 7.06 (d, 1H), 6.94 -6.91 (m, 1H), 5.92 (d, 1H), 4.33 - 4.24 (m, 2H), 4.10 (s, 1H), 3.83 (t, 4H), 3.24 (t, 2H), 3.12 (t, 4H), 3.07 (d, 1H), 2.88 (d, 1H), 1.82 - 1.73 (m, 2H), 1.62 - 1.53 (m,

EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
			2H). MS: 539$(M+H)^+$.
61	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.63 (d, 2H), 7.27 - 7.17 (m, 1H), 5.95 (d, 1H), 4.67 (s, 1H), 4.39 (d, 1H), 4.27 (d, 1H), 3.30 - 3.12 (m, 4H), 1.94 - 1.88 (m, 1H), 1.85 - 1.70 (m, 2H), 1.61 (d, 1H). MS: 508$(M+H)^+$.
62	(S)-4-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)morpholin-3-one		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.68 - 7.55 (m, 2H), 7.45 - 7.3 (m, 3H), 5.92 (d, 1H), 4.45 - 4.25 (m, 5H), 4.05 (t, 2H), 3.79 (d 2H), 3.35 (s, 2H), 3.20 (d, 1H), 3.07 (d, 1H), 1.90 - 1.60 (m, 4H) MS: 553$(M+H)^+$.
63	(S)-N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)methanesulfonamide		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.59 (t, 2H), 7.36 (s, 1H), 7.2 (d, 1H), 7.15 - 7.12 (m, 1H), 5.92 (d, 1H), 4.29 (t, 2H), 4.11 (s, 1H), 3.30 - 3.21 (m, 2H), 3.14 (d, 1H), 2.96 (s, 3H), 2.89 (d, 1H) 1.85 - 1.75 (m, 2H), 1.62 - 1.49 (m, 2H). MS: 547$(M+H)^+$.
64	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[b]quinoline-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 9.26 (s, 1H), 8.42 (d, 1H), 8.3 - 8.20 (m, 2H), 8.02 (t, 1H), 7.83 (s, 1H), 7.71 (d, 1H), 6.46 (d, 1H), 5.01 (s, 1H), 4.54 (d, 1H), 4.43 (d, 1H), 3.98 (d, 1H), 3.78 (d, 1H), 3.45 (t, 2H), 2.06 (t, 2H), 1.97 - 1.83 (m, 2H). MS: 505$(M+H)^+$.
65	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.53 (s, 1H), 8.49 (d, 1H), 7.6 - 7.52 (m, 3H), 5.93 (d, 1H), 4.40 - 4.33 (m, 3H), 3.55 - 3.02 (m 4H), 1.92 - 1.53 (m, 4H). MS: 455$(M+H)^+$.

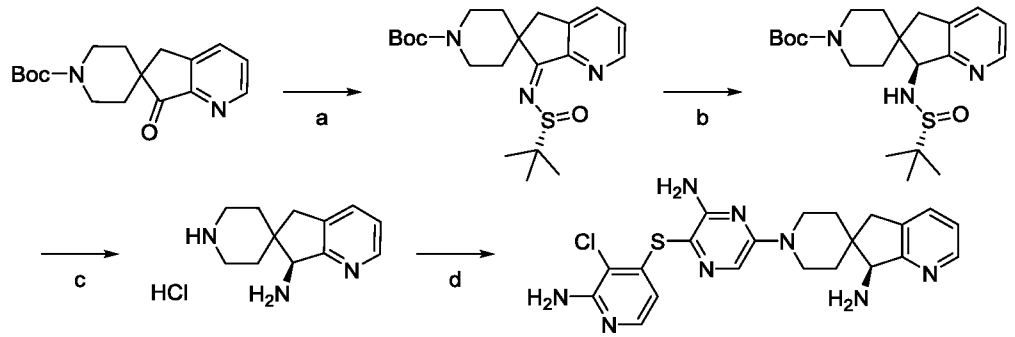
EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
66	(S)-1'-(6-amino-5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.05 (d, 1H), 7.74 (s, 1H), 7.5 (d, 1H), 7.42 - 7.32 (m, 3H), 6.73 (d, 1H), 4.45 - 4.43 (m, 3H), 3.42 - 3. 20 (m, 4H), 2.02 - 1.62 (m, 4H). MS: 473$(M+H)^+$.
67	(1R,3R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,3-diamine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.74 - 7.62 (m, 4H), 7.62 - 7.5 (m, 2H), 5.98 (d, 1H), 4.97 (s, 2H), 4.02 - 3.82 (m, 4H), 1.96 - 1.84 (m, 2H), 1.84 - 1.72 (m, 2H). MS: 469$(M+H)^+$.
68	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.49 (d, 1H), 8.29 (d, 1H), 7.66 (d, 1H), 5.83 (d, 1H), 4.26 - 4.09 (m, 2H), 4.03 (s, 1H), 3.4 - 3.23 (m, 2H), 2.91 - 2.71 (m, 2H), 1.92 - 1.77 (m, 1H), 1.74 - 1.54 (m, 3H). MS: 480$(M+H)^+$.
69	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine		MS: 495$(M+H)^+$.
70	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-5(1H)-one		^{1}H NMR (600 MHz, *MeOH-d4*) δ 7.84 (d, 1H), 7. 91 - 7. 87 (m, 1H), 7.77 (d, 1H), 6.97 (d, 1H), 6.84 (d, 1H), 6.68 (d, 1H), 4.92 (s, 1H), 4. 61 - 4. 38 (m, 4H), 3.50 - 3. 40 (m, 2H), 2. 27 - 2. 16 (m, 1H), 2.10 – 2.00 (m, 1H), 1.99 (d, 1H), 1.81 (d, 1H). MS: 471$(M+H)^+$.

EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
71	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[indoline-2,4'-piperidin]-3-amine		^{1}H NMR (600 MHz, *MeOH-d4*) δ 8.37 (d, 1H), 8.30 (d, 1H), 7.6 (d, 1H), 7.30 (d, 1H), 7.11 (t, 1H),6.75- 6.69 (m, 2H), 5.95(d, 1H), 4.38 - 4.26 (m, 2H), 4.13 (s, 1H), 3.52 - 3.49 (m, 2H), 1.83 1.74 (m, 4H).MS: 440$(M+H)^+$.
72	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-6-amine		MS: 455$(M+H)^+$.
73	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-chloro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 489$(M+H)^+$.
74	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 500$(M+H)^+$.
75	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(4-methylpiperazin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 552$(M+H)^+$.

EX No	Chemical Name	Structure	^{1}HNMR & MS: $(M+H)^+$
76	(S)-1'-(5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 458$(M+H)^+$.
77	(S)-1'-(6-amino-5-((2-(trifluoromethyl)pyridin-3-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 473$(M+H)^+$.
78	(S)-1-(4-((3-amino-5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one		MS: 523$(M+H)^+$.
79	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-(tert-butyl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine		MS: 516$(M+H)^+$.
80	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxylic acid		MS: 498$(M+H)^+$.
81	(2R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-2-amine		MS: 418$(M+H)^+$.

EXAMPLE 82

(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine



Step a: A mixture of tert-butyl 7-oxo-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate (936 mg, 3.10 mmol) and (R)-(+)-2-Methyl-2-propanesulfinamide (1045 mg, 8.62 mmol) in $Ti(OEt)_4$ (8 mL) was stirred for 2 h at 100 °C. After cooling to RT, the reaction mixture was diluted with EA (50 mL) and water (50 mL). The resulting mixture was filtered through a pad of Celite followed by EA wash. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl (R,Z)-7-((tert-butylsulfinyl)imino)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate (1.41 g). MS: *m/z* 406 $(M+H)^+$.

Step b: To a -40 °C solution of tert-butyl (R,Z)-7-((tert-butylsulfinyl)imino)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate (1.41 g, 3.48 mmol) in THF (50 mL) was added BH_3 (1 M solution in THF, 10.00 mL, 10.00 mmol). The resulting mixture was allowed to warm to RT and stirred for 1 h. The reaction mixture was quenched with brine (100 mL). The aqueous layer was separated, extracted with EA (1 × 60 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (100 mL) and stirred for 15 h at 80 °C. After cooling to RT, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with MeOH : DCM = 1 : 60, v/v) to give tert-butyl (S)-7-(((R)-tert-butylsulfinyl)amino)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate (309 mg). MS: *m/z* 408 $(M+H)^+$.

Step c: To solution of tert-butyl (S)-7-(((R)-tert-butylsulfinyl)amino)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate (309 mg, 0.76 mmol) in DCM (20 mL) was added HCl (4 M solution in EA, 2 mL, 8.00 mmol), and stirred for 1.5 h at RT. The resulting mixture was concentrated under reduced pressure to give (S)-5,7-dihydrospiro [cyclopenta [b] pyridine-6,4'-piperidin]-7-amine (227 mg). MS: *m/z* 204 $(M+H)^+$.

Step d: A mixture of (S)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine

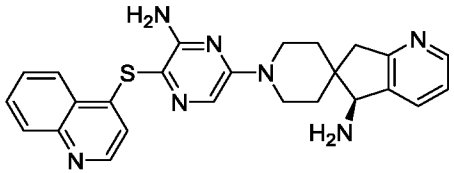
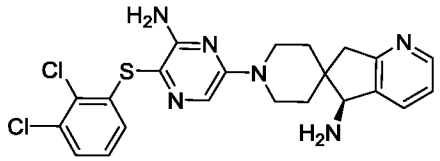
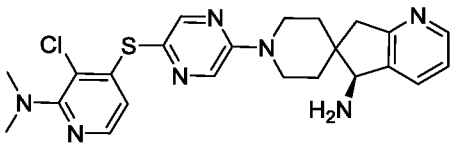
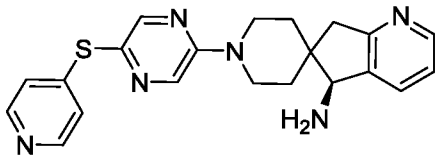
(HCl salt, 227 mg, 1.12 mmol), 3-((2-amino-3-chloropyridin-4-yl)thio)-6-chloropyrazin-2-amine (249 mg, 0.86 mmol) and K_2CO_3 (1149 mg, 8.31 mmol) in acetonitrile (15 mL) was stirred for 44 h at reflux temperature. After cooling to RT, the reaction mixture was diluted with brine (100 mL), extracted with EA (2 × 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with MeOH : DCM = 1 : 6, v/v) to give (S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine (77 mg). MS: *m/z* 455 $(M+H)^+$. ^1H NMR (400 MHz, *MeOH-d4*) δ 8.51 (s, 1H), 7.81 (d, 1H), 7.63 (s, 2H), 7.38 (s, 1H), 5.94 (d, 1H), 4.49 - 4.30 (m, 3H), 3.37 - 3.09 (m, 4H), 2.05 - 1.95 (m, 1H), 1.85 - 1.70 (m, 2H), 1.60 - 1.50 (m, 1H).

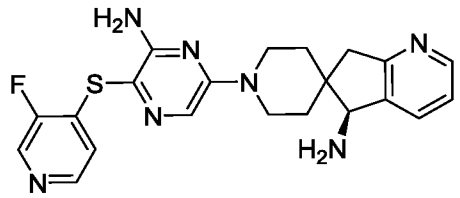
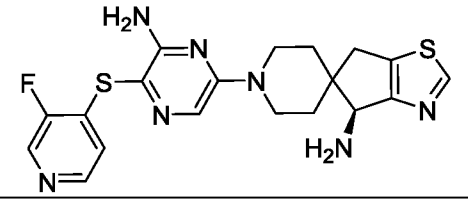
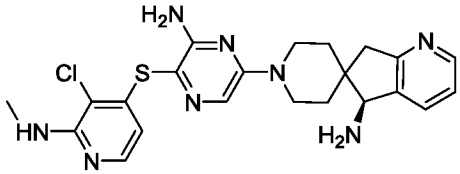
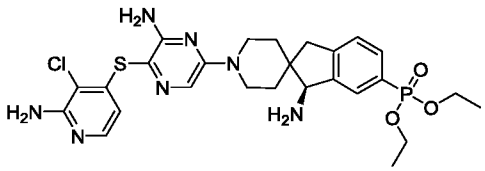
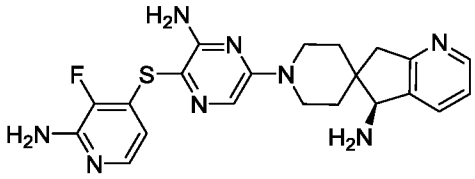
The following examples were synthesized using the above procedure or modification procedure using the corresponding Intermediate **A** and Intermediate **B**.

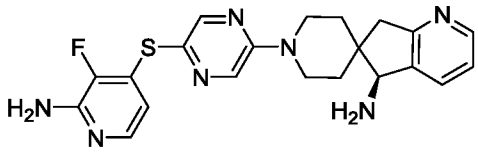
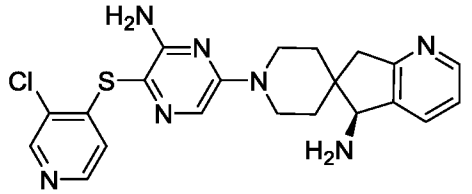
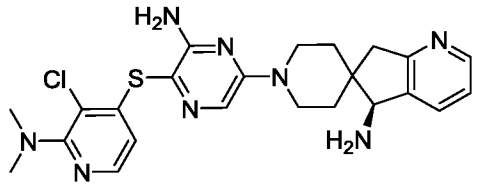
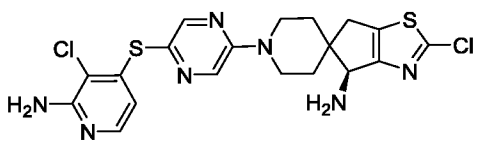
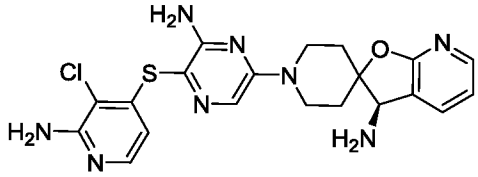
2-Methylpropane-2-sulfinamide, instead of (R)-(+)-2-Methyl-2-Propanesulfinamide, was used in step (a) of Example 82 to give the racemic compounds.

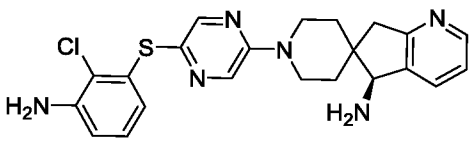
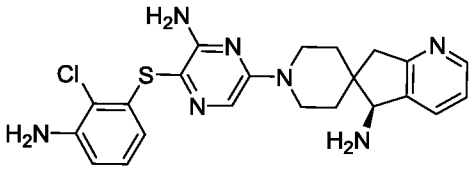
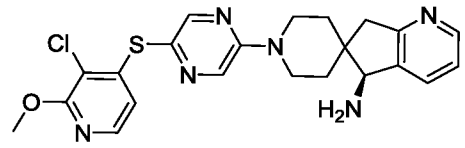
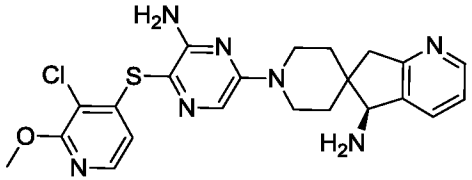
The following examples are compounds with **free base**, or a pharmaceutically acceptable salt.

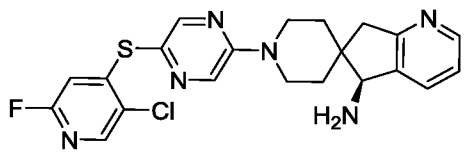
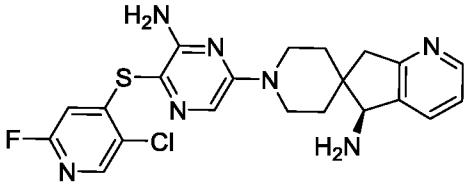
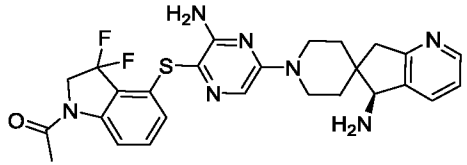
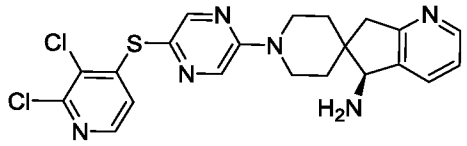
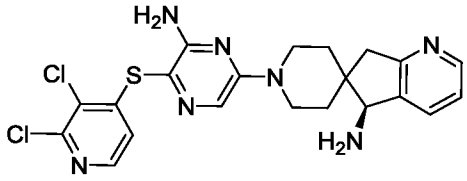
Table 17

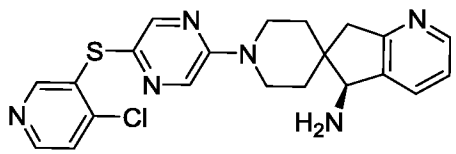
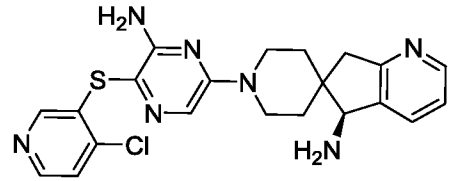
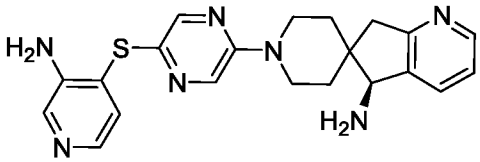
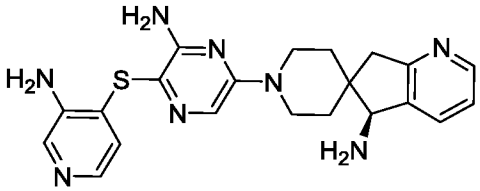
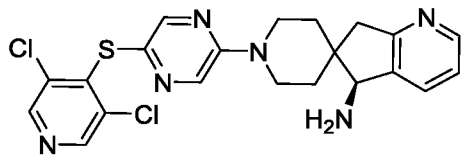
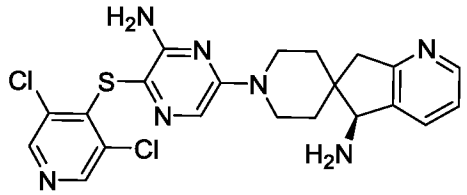
EX No	Chemical Name	Structure	MS: $(M+H)^+$ & ^{1}HNMR
83	(S)-1'-(6-amino-5-(quinolin-4-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.57 (d, 1H), 8.42 - 8.38 (m, 1H), 8.34 - 8.29 (m, 1H), 8.06 (d, 1H), 7.90 - 7.82 (m, 2H), 7.75 - 7.67 (m, 2H), 7.35 - 7.29 (m, 1H), 6.89 (d, 1H), 4.38 (d, 2H), 4.10 (s, 1H), 3.34 - 3.23 (m, 3H), 2.98 - 2.94 (d, 1H), 1.98 - 1.83 (m, 2H), 1.68 (d, 1H), 1.48 (d, 1H). MS: 456$(M+H)^+$.
84	(S)-1'-(6-amino-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.39 - 8.34 (m, 1H), 7.85 (d, 1H) 7.62 (s, 1H), 7.34 - 7.26 (m, 2H), 7.16 - 7.10 (t, 1H), 6.70 - 6.63 (m, 1H), 4.33 (d, 2H), 4.05 (s, 1H), 3.32 - 3.19 (m, 3H), 2.94 - 2.90 (d, 1H), 1.95 - 1.79 (m, 2H), 1.64 (d, 1H), 1.43 (d, 1H). MS: 473$(M+H)^+$
85	(S)-1'-(5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.50 - 8.46 (m, 1H), 8.39 (d, 1H) 8.32 (d, 1H), 7.94 (d, 1H), 7.84 (d, 1H), 7.40 - 7.34 (m, 1H), 6.22 (d, 1H), 4.51 - 4.36 (m, 2H), 4.33 (s, 1H), 3.43 - 3.29 (m, 3H), 3.17 - 3.10 (d, 1H), 2.97 (s, 6H), 1.96 - 1.85 (m, 2H), 1.74 - 1.61 (m, 2H). MS: 468$(M+H)^+$.
86	(S)-1'-(5-(pyridin-4-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.46 (d, 1H), 8.33 - 8. 28 (m, 3H) 7.94 (d, 1H), 7.66 - 7.61 (m, 1H), 7.36 - 7.32 (m, 1H), 7.16 - 7.12 (m, 1H), 7.07 (d, 1H), 4.43 - 4. 31 (m, 3H), 3.36 - 3. 28 (m, 3H), 3.10 (d, 1H), 1.92 - 1. 84 (m, 2H), 1.67 - 1.60 (m, 2H). MS: 391$(M+H)^+$.

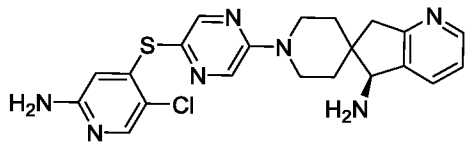
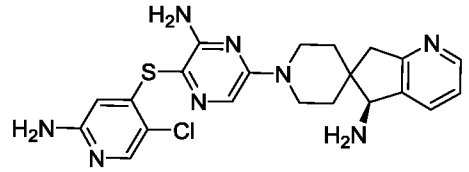
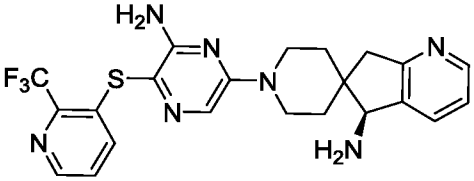
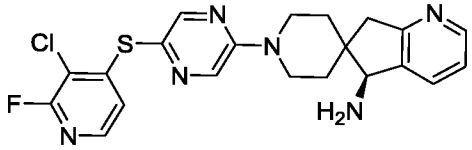
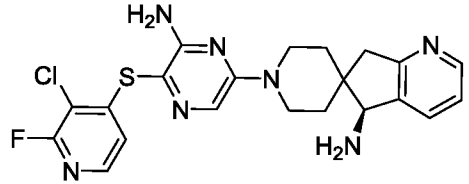
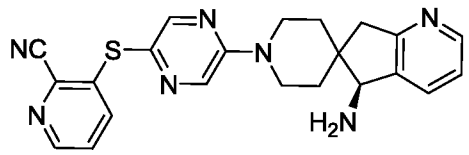
87	(S)-1'-(6-amino-5-((3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.58 (d, 1H), 8.34 (s, 1H), 8.15 (d 1H), 8.03 (d, 1H), 7.69 (s, 1H), 7.48 - 7.39 (m, 1H), 6.87 - 6.77 (m, 1H), 4.54 (s, 1H), 4.47 (d, 1H), 4.37 (d, 1H), 3.33 - 3.20 (m, 4H), 1.9 - 1.81 (m, 2H), 1.81 - 1.62 (m, 2H). MS: 424(M+H)$^+$.
88	(S)-1'-(6-amino-5-((3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 9.02 (s, 1H), 8.35 (s, 1H), 8.16 (s 1H), 7.70 (s, 1H), 6.83 (s, 1H), 4.43 - 4.28 (m, 3H), 3.32 - 3.05 (m, 4H), 2.09 - 1.72 (m, 4H). MS: 430(M+H)$^+$
89	(S)-1'-(6-amino-5-((3-chloro-2-(methylamino)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.39 (d, 1H), 7.87 (d, 1H), 7.70 (d, 1H), 7.62 (s, 1H), 7.35 - 7.28 (m, 1H), 5.90 (d, 1H), 4.40 - 4.31 (m, 2H), 4.11 (s, 1H), 3.33 - 3.23 (m, 3H), 2.97 - 2.94 (d, 1H), 2.93 (s, 3H),1.95 - 1.80 (m, 2H), 1.65 (d, 1H), 1.47 (d, 1H). MS: 469(M+H)$^+$.
90	diethyl(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)phosphonate		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.93 (d, 1H), 7.81 - 7.76 (m, 1H) 7.61 - 7.53 (m, 3H), 5.92 (d, 1H), 4.42 (s, 1H), 4.37 (d, 1H), 4.29 (d 1H), 4.18 - 4.09 (m, 4H), 3.38 - 3.13 (m, 4H), 1.90 - 1.80 (m, 2H), 1.70 - 1.60 (m, 2H), 1.36 (t, 6H). MS: 590(M+H)$^+$.
91	(S)-1'-(6-amino-5-((2-amino-3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.40 (s, 1H), 7.88 (d, 1H), 7.63 (s 1H), 7.53 (d, 1H), 7.39 - 7.27 (m, 1H), 6.10 - 5.97 (m, 1H), 4.36 (d, 2H), 4.10 (s, 1H), 3.28 - 3.16 (m, 3H), 2.98 (d, 1H), 1.98 - 1.77 (m, 2H), 1.67 (d, 1H), 1.47 (d, 1H). MS: 439(M+H)$^+$.

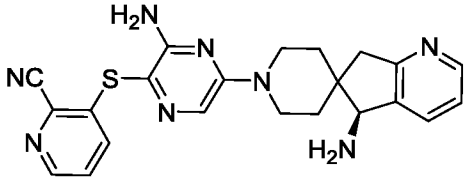
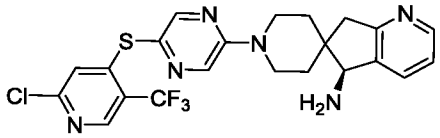
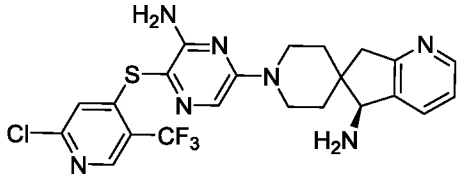
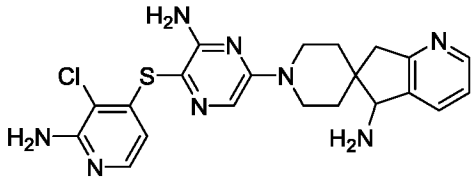
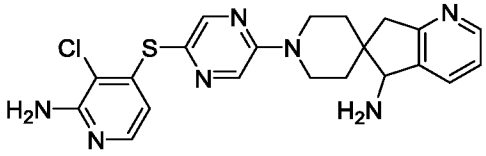
92	(S)-1'-(5-((2-amino-3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.42 - 8.37 (m, 1H), 8.34 (d, 1H), 8.31 (d, 1H), 7.88 (d, 1H), 7.55 (d, 1H), 7.35 - 7.29 (m, 1H), 6.14 - 6.10 (m, 1H), 4.45 - 4.35 (m, 2H), 4.11 (s, 1H), 3.38 - 3.27 (m, 2H), 3.22 (d, 1H), 3.00 (d, 1H), 1.99 - 1.82 (m, 2H), 1.75 - 1.65 (m, 1H), 1.54 - 1.46 (m, 1H). MS: 424(M+H)$^+$.
93	(S)-1'-(6-amino-5-((3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.43 (d, 1H), 8.39 (s, 1H), 8.16 (d 1H), 7.92 (d, 1H), 7.64 (s, 1H), 7.33 (t, 1H), 6.70 (d, 1H), 4.38 - 4.25 (m, 3H), 3.40 - 3.00 (m, 4H), 1.92 - 1.79 (m, 2H), 1.65 - 1.54(m, 2H). MS: 440(M+H)$^+$.
94	(S)-1'-(6-amino-5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.41 (d, 1H), 7.88 (d, 1H), 7.84 (d 1H), 7.63 (s, 1H), 7.36 - 7.28 (m, 1H), 6.21 (d, 1H), 4.41 - 4.31 (m, 2H), 4.14 (s, 1H), 3.34 - 3.23 (m, 3H), 3.02 - 2.99 (d, 1H) 2.98 (s, 6H), 1.95 - 1.80 (m, 2H), 1.65 (d, 1H), 1.50 (d, 1H). MS: 483(M+H)$^+$
95	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.49 (s, 1H), 8.29 (s, 1H), 7.66 (s 1H), 5.84 (s, 1H), 4.20 - 3.95 (m, 2H), 3.85 (s, 1H), 3.58 - 3.40 (m, 2H), 3.02 - 2.71 (m, 2H), 1.76 - 1.48 (m, 3H), 1.34 - 1.09 (m, 1H). MS: 480 (M+H)$^+$.
96	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[furo[2,3-b]pyridine-2,4'-piperidin]-3-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.07 (d, 1H), 7.90 (d, 1H), 7.69 (s 1H)， 7.64 (d, 1H), 7.08 - 6.99 (m, 1H), 6.00 (d, 1H), 4.52 (d, 1H), 4.43 (d, 1H), 4.28 (s, 1H), 3.58 - 3.41 (m, 2H), 2.16 - 1.81 (m, 4H). MS: 457 (M+H)$^+$.

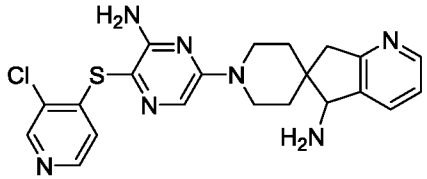
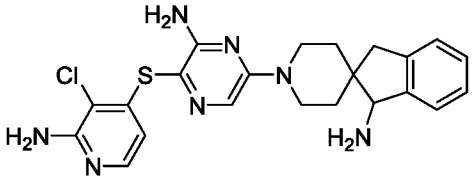
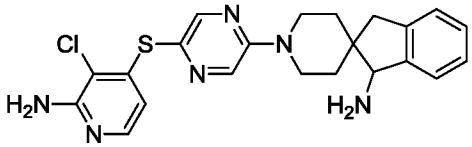
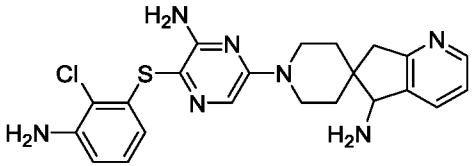
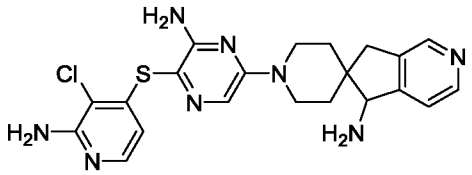
97	(S)-1'-(5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.37 (d, 1H), 8.24 (s, 1H), 8.14 (s, 1H), 7.85 (d, 1H), 7.38 - 7.20 (m, 1H), 6.98 - 6.85 (m, 1H), 6.70 (d, 1H) 6.27 (d, 1H), 4.41 - 4.21 (m, 2H), 4.08 (s, 1H), 3.44 - 3.19 (m, 3H), 3.0 - 2.89 (m, 1H), 1.98 - 1.72 (m, 2H), 1.73 - 1.58 (m, 1H), 1.55 - 1.38 (m 1H). MS: 439 $(M+H)^+$.
98	(S)-1'-(6-amino-5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.43 (d, 1H), 7.90 (d, 1H), 7.56 (s 1H), 7.41 - 7.26 (m, 1H), 6.95 - 6.79 (m, 1H), 6.63 (d, 1H), 6.03 (d, 1H), 4.41 - 4.26 (m, 2H), 4.23 (s, 1H), 3.39 - 3.15 (m, 3H), 3.10 - 2.96 (m, 1H), 1.92 - 1.74 (m, 2H), 1.70 - 1.59 (m, 1H), 1.58 - 1.47 (m 1H). MS: 454 $(M+H)^+$.
99	(S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.46 - 8.37 (m, 2H), 8.33 (d, 1H), 7.88 (d, 1H), 7.83 (d, 1H), 7.38 - 7.26 (m, 1H), 6.33 (d, 1H), 4.50 - 4.34 (m, 2H), 4.12 (s, 1H), 4.01 (s, 3H), 3.47 - 3.24 (m, 3H), 3.06 - 2.94 (m, 1H), 2.02 - 1.79 (m, 2H), 1.78 - 1.65 (m, 1H), 1.60 - 1.44 (m 1H). MS: 455 $(M+H)^+$.
100	(S)-1'-(6-amino-5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.41 (d, 1H), 7.87 (d, 1H), 7.79 (d 1H), 7.63 (s, 1H), 7.36 - 7.24 (m, 1H), 6.25 (d, 1H), 4.43 - 4.29 (m, 2H), 4.16 (s, 1H), 3.98 (s, 3H), 3.43 - 3.17 (m, 3H), 3.09 - 2.95 (m, 1H), 1.93 - 1.76 (m, 2H), 1.70 - 1.59 (m, 1H), 1.56 - 1.42 (m, 1H). MS: 470 $(M+H)^+$.

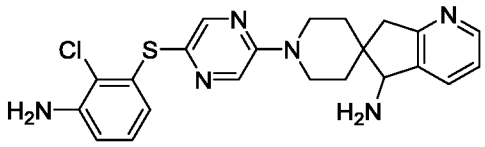
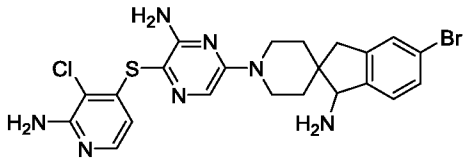
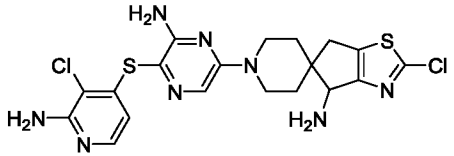
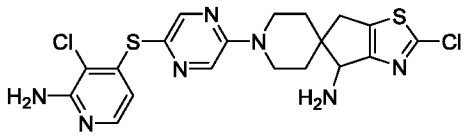
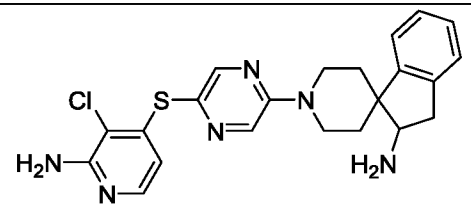
101	(S)-1'-(5-((5-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.44 (d, 1H), 8.39 (d, 1H), 8.36 (d 1H), 8.14 (s, 1H), 7.87 (d, 1H), 7.38 - 7.24 (m, 1H), 6.42 (d, 1H), 4.54 - 4.36 (m, 2H), 4.11 (s, 1H), 3.48 - 3.23 (m, 3H), 3.07 - 2.93 (m, 1H) 2.04 - 1.80 (m, 2H), 1.77 - 1.66 (m, 1H), 1.56 - 1.44 (m, 1H). MS: 443 $(M+H)^+$.
102	(S)-1'-(6-amino-5-((5-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.40 (d, 1H), 8.13 (s, 1H), 7.87 (d 1H), 7.70 (s, 1H), 7.40 - 7.25 (m, 1H), 6.28 (s, 1H), 4.40 (d, 2H), 4.11 (s, 1H), 3.47 - 3.16 (m, 3H), 3.08 - 2.89 (m, 1H), 2.00 - 1.81 (m, 2H) 1.72 - 1.60 (m, 1H), 1.54 - 1.42 (m, 1H). MS: 458 $(M+H)^+$.
103	(S)-1-(4-((3-amino-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.34 (d, 1H), 8.07 (d, 1H), 7.83 (d 1H), 7.58 (s, 1H), 7.33 (t, 1H),7.28 - 7.25 (m, 1H), 6.64 (d, 1H), 4.52 (t, 2H), 4.30 (d, 2H), 4.04(s, 1H), 3.25 - 3.21 (m, 3H), 2.92(d, 1H), 2.28(s, 3H), 1.90 - 1.80 (m, 2H), 1.62 (d, 1H), 1.41(d, 1H). MS: 524 $(M+H)^+$.
104	(S)-1'-(5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.39 (s, 1H), 8.37 (d, 1H), 8.32 (s 1H), 8.00 (d, 1H), 7.84 (d, 1H), 7.30 - 7.26 (m, 1H), 6.71 (d, 1H), 4.42 - 4.37 (m, 2H), 4.08 (s, 1H), 3.40 - 3.24 (m, 3H), 2.96 (d, 1H), 1.96 - 1.81 (m, 2H), 1.67 (d, 1H), 1.48 (d, 1H). MS: 459 $(M+H)^+$.
105	(S)-1'-(6-amino-5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.34 (d, 1H), 8.00 (d, 1H), 7.82 (d 1H), 7.63 (s, 1H), 7.28 - 7.24 (m, 1H), 6.64 (d, 1H), 4.32 (d, 2H), 4.03 (s, 1H), 3.31 - 3.21 (m, 3H), 2.92 (d, 1H), 1.94 - 1.77 (m, 2H), 1.62 (d, 1H),1.41 (d, 1H). MS: 474 $(M+H)^+$.

106	(S)-1'-(5-((4-chloropyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.36 - 8.32 (m, 2H), 8.27 (d, 2H), 8.22 (s, 1H), 7.83 (d, 1H), 7.53 (d, 1H), 7.30 - 7.27 (m, 1H), 4.34 (d 2H), 4.06 (s, 1H), 3.36 - 3.23 (m, 3H), 2.95 (d, 1H), 1.94 - 1.80 (m, 2H), 1.66 (d, 1H), 1.45 (d, 1H). MS: 425 $(M+H)^+$.
107	(S)-1'-(6-amino-5-((4-chloropyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.36 (d, 1H), 8.26 (d, 1H), 7.88 (s 1H), 7.84 (d, 1H), 7.62 (s, 1H), 7.47 (d, 1H), 7.30 - 7.26 (m, 1H), 4.34 (d, 2H), 4.06 (s, 1H), 3.36 - 3.23 (m, 3H), 2.95 (d, 1H), 1.94 - 1.80 (m, 2H), 1.66 (d, 1H), 1.45 (d, 1H). MS: 440 $(M+H)^+$.
108	(S)-1'-(5-((3-aminopyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.48 (d, 1H), 8.28 (d, 1H), 8.21 (d 1H), 8.03 (s, 1H), 7.96 (d, 1H), 7.73 (d, 1H), 7.41 - 7.33 (m, 1H), 7.09 (d, 1H), 4.44 - 4.28 (m, 3H), 3.34 - 3.26 (m, 3H), 3.11 (d, 1H), 1.95 - 1.84 (m, 2H), 1.72 - 1.59 (m, 2H). MS: 406 $(M+H)^+$.
109	(S)-1'-(6-amino-5-((3-aminopyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.40 (d, 1H), 7.96 (s, 1H), 7.88 (d 1H), 7.68 (d, 1H), 7.60 (s, 1H), 7.35 - 7.27 (m, 1H), 6.84 (d, 1H), 4.38 - 4.27 (m, 2H), 4.11 (s, 1H), 3.32 - 3.20 (m, 3H), 2.98 (d, 1H), 1.96 - 1.78 (m, 2H), 1.64 (d, 1H), 1.46 (d, 1H). MS: 421 $(M+H)^+$.
110	(S)-1'-(5-((3,5-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.53 (s, 2H), 8.36 (d, 1H), 8.15 (d 1H), 8.11 (s, 1H), 7.83 (d, 1H), 7.30 - 7.26 (m, 1H), 4.29 - 4.25 (m, 2H), 4.06 (s, 1H), 3.36 - 3.21 (m, 3H), 2.94 (d, 1H), 1.92 - 1.78 (m, 2H), 1.63 (d, 1H), 1.44 (d, 1H). MS: 459 $(M+H)^+$.
111	(S)-1'-(6-amino-5-((3,5-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 474 $(M+H)^+$.

112	(S)-1'-(5-((2-amino-5-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.37 (s, 2H), 8.29 (d, 1H), 7.85 (d 1H), 7.84 (s, 1H), 7.31 - 7.27 (m, 1H), 5.91 (s, 1H), 4.40 - 4.37 (m, 2H), 4.10 (s, 1H), 3.37 - 3.24 (m, 3H), 2.97 (d, 1H), 1.92 - 1.84 (m, 2H), 1.68 (d, 1H), 1.58 (d, 1H). MS: 440 $(M+H)^+$.
113	(S)-1'-(6-amino-5-((2-amino-5-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.36 (d, 1H), 7.84 (d, 1H), 7.74 (s 1H), 7.62 (s, 1H), 7.30 - 7.26 (m, 1H), 5.90 (s, 1H), 4.32 (d, 2H), 4.07 (s, 1H), 3.35 - 3.21 (m, 3H), 2.94 (d, 1H), 1.92 - 1.78 (m, 2H), 1.62 (d, 1H), 1.43 (d, 1H). MS: 455 $(M+H)^+$.
114	(S)-1'-(6-amino-5-((2-(trifluoromethyl)pyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.40 (d, 1H), 8.37 (d, 1H), 7.84 (d, 1H), 7.63 (s, 1H), 7.46 - 7.40 (m, 2H), 7.30 - 7.27 (m, 1H), 4.35 - 4.30 (m, 2H), 4.09 (s, 1H), 3.31 - 3.22 (m, 3H), 2.96 (d, 1H), 1.88 - 1.78 (m, 2H), 1.62 (d, 1H), 1.44 (d, 1H).MS: 474 $(M+H)^+$.
115	(S)-1'-(5-((3-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 443 $(M+H)^+$.
116	(S)-1'-(6-amino-5-((3-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.36 (d, 1H), 7.84 (d, 1H), 7.78 (d 1H), 7.61 (s, 1H), 7.30 - 7.26 (m, 1H), 6.24 (d, 1H), 4.33 (d, 2H), 4.07 (s, 1H), 3.35 - 3.22 (m, 3H), 2.94 (d, 1H), 1.89 - 1.81 (m, 2H), 1.62 (d, 1H),1.44 (d, 1H).MS: 458 $(M+H)^+$.
117	(S)-3-((5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)picolinonitrile		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.53-8.51 (m, 1H), 8.45 (d, 1H) 8.31 - 8.28 (m, 2H), 7.90 (d, 1H), 7.77 - 7.74 (m, 1H), 7.55 - 7.52 (m,1H), 7.35 - 7.32 (m, 1H), 4.41 - 4.27 (m, 3H), 3.35 - 3.25 (m, 3H), 3.18 (d, 1H), 1.89 - 1.83 (m, 2H), 1.67 - 1.57 (m, 2H) .MS: 416 $(M+H)^+$.

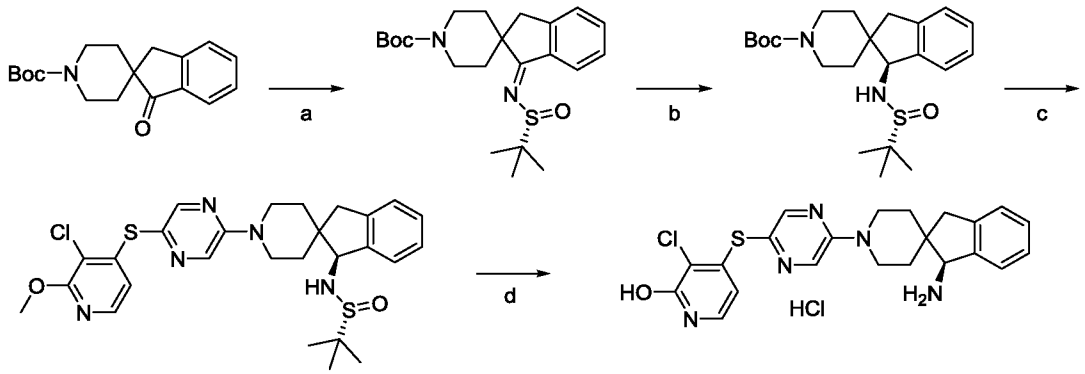
118	(S)-3-((3-amino-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)picolinonitrile		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.43 - 8.42 (m, 1H), 8.37 (d, 1H) 7.85 (d, 1H), 7.61 (s, 1H), 7.49 - 7.45 (m, 1H), 7.41 - 7.39 (m, 1H),7.30 - 7.27 (m, 1H), 4.34 - 4.30 (m, 2H), 4.10 (s, 1H), 3.32 - 3.22 (m, 3H), 2.96 (d, 1H), 1.91 - 1.78 (m, 2H), 1.62 (d, 1H),1.45 (d 1H). MS: 431 $(M+H)^+$.
119	(S)-1'-(5-((2-chloro-5-(trifluoromethyl)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 493 $(M+H)^+$.
120	(S)-1'-(6-amino-5-((2-chloro-5-(trifluoromethyl)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.54 (s, 1H), 8.38 (d, 1H), 7.86 (d 1H), 7.69 (s, 1H), 7.31 - 7.28 (m, 1H), 6.77 (d, 1H), 4.42 - 4.34 (m, 2H), 4.14 (s,1H), 3.35 - 3.24 (m, 3H), 2.99 (d, 1H), 1.93 - 1.81 (m, 2H), 1.64 (d, 1H), 1.49 (d, 1H). MS: 508 $(M+H)^+$.
121	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.41 (d, 1H), 7.89 (d, 1H), 7.73 - 7.57 (m, 2H), 7.38 - 7.25 (m, 1H), 5.97 (d, 1H), 4.45 - 4.27 (m, 2H), 4.14 (s, 1H), 3.46 - 3.18 (m, 3H), 3.09 - 2.93 (m, 1H), 2.00 - 1.78 (m 2H), 1.72 - 1.60 (m, 1H), 1.55 - 1.45 (m, 1H). MS: 455 $(M+H)^+$.
122	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.45 - 8.35 (m, 2H), 8.32 (s, 1H), 7.89 (d, 1H), 7.64 (d, 1H), 7.39 - 7.27 (m, 1H), 5.99 (d, 1H), 4.52 - 4.33 (m, 2H), 4.14 (s, 1H), 3.48 - 3.18 (m, 3H), 3.11 - 2.94 (m, 1H), 2.01 - 1.82 (m, 2H), 1.76 - 1.65 (m, 1H), 1.59 - 1.46 (m, 1H). MS: 440 $(M+H)^+$.

123	1'-(6-amino-5-((3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.36 (d, 1H), 8.25 (d, 1H), 7.87 (s 1H), 7.84 (d, 1H), 7.61 (s, 1H), 7.48(d,1H),7.30 - 7.26 (m,1H), 4.34 - 4.30 (m, 2H), 4.09 (s, 1H), 3.29 - 3.21 (m, 3H), 2.95 (d, 1H), 1.88 - 1.79 (m, 2H), 1.62 (d, 1H), 1.45 (d, 1H). MS: 440 $(M+H)^+$.
124	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.68 - 7.57 (m, 2H), 7.50 (d, 1H), 7.41 - 7.26 (m, 3H), 5.95 (d, 1H), 4.43 - 4.21 (m, 3H), 3.41 - 3.16 (m 3H), 3.15 - 3.00 (m, 1H), 1.91 - 1.74 (m, 2H), 1.74 - 1.58 (m, 2H). MS: 454 $(M+H)^+$.
125	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.33 (d, 1H), 8.27 (d, 1H), 7.60 (d, 1H), 7.37 (d, 1H), 7.23 - 7.18 (m, 3H), 5.95 (d, 1H), 4.34 (d, 2H) 3.95 (s, 1H), 3.34 - 3.15 (m, 3H), 2.81 (d, 1H), 1.88 - 1.84 (m, 2H), 1.63 (d, 1H), 1.45 (d, 1H). MS: 439 $(M+H)^+$.
126	1'-(6-amino-5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.38 (d, 1H), 7.85 (d, 1H), 7.55 (s 1H), 7.31-7.27 (m, 1H), 6.85 (t, 1H), 6.63 - 6.60 (m, 1H), 6.03 (d, 1H), 4.32 - 4.27 (m, 2H), 4.12 (s, 1H), 3.35 - 3.22 (m, 3H), 2.98 (d 1H), 1.89 - 1.78 (m, 2H), 1.62 (d, 1H), 1.47 (d, 1H).MS: 454 $(M+H)^+$.
127	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ8.43（s，1H)，8.41 (d,1H), 7.6((t, 2H), 7.48 (d, 1H), 5.93 (d, 1H), 4.36 - 4.31 (m, 2H), 4.11 (s,1H) 3.35 - 3.21 (m, 3H), 2.90 (d, 1H), 1.91 - 1.89 (m, 1H), 1.77 - 1.72 (m 1H), 1.66 (d, 1H), 1.34 (d, 1H).MS: 455 $(M+H)^+$.

128	1'-(5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.39 (d, 1H), 8.23 (d, 1H), 8.13 (d, 1H), 7.85 (d,1H), 7.31 - 7.28 (m, 1H), 6.91 (t, 1H), 6.69 (d, 1H), 6.27 (d, 1H), 4.34 - 4.28 (m, 2H), 4.13 (s, 1H), 3.35 - 3.26 (m, 3H), 3.00 (d, 1H), 1.92 - 1.80 (m, 2H), 1.65 (d, 1H), 1.49 (d, 1H). MS: 43^9 $(M+H)^+$.
129	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.59 (t, 2H), 7.47 (s, 1H), 7.43 - 7.33 (m, 2H), 5.93 (d, 1H), 4.33 - 4.25 (m, 2H), 4.10 (s, 1H), 3.35 - 3.15 (m, 3H), 2.95 (d, 1H), 1.81 - 1.76 (m, 2H), 1.59 (d, 1H), 1.53 (d, 1H). MS: 532 $(M+H)^+$.
130	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.62 - 7.58 (m, 2H), 5.93 (d, 1H) 4.27 - 4.09 (m, 2H), 3.95 (s, 1H), 3.48 - 3.30 (m, 3H), 3.00 (d, 1H) 1.92 - 1.71 (m, 4H). MS: 495 $(M+H)^+$.
131	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.37 (s, 1H), 8.31 (s, 1H), 7.61 (d 1H), 5.95 (d, 1H), 4.44 - 4.28 (m, 2H), 4.12 (s,1H), 3.35 - 3.31 (m, 3H), 3.10 (d, 1H), 1.98 - 1.78 (m, 4H). MS: 480 $(M+H)^+$.
132	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.38 (d, 1H), 8.32 (s, 1H), 7.61 (d 1H), 7.42 - 7.28 (m, 4H), 5.97 (d, 1H), 4.36 - 4.14 (m, 3H), 3.67 - 3.52 (m, 3H), 2.99 (d, 1H), 2.29 - 2.23 (m, 1H), 1.97 - 1.70 (m, 3H) MS: 439 $(M+H)^+$.

EXAMPLE 133

(S)-4-((5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol



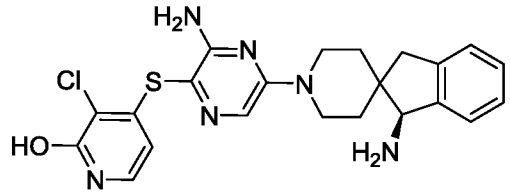
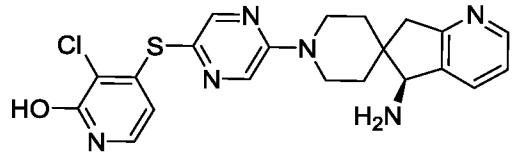
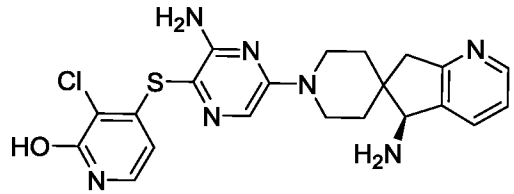
Step a-c: Step (a-c) of Example 5 was applied to provide (R)-N-((S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2, 4'-piperidin]-1-yl)-2-methylpropane-2-sulfinamide. MS: *m/z* 558 $(M+H)^+$.

Step d: A mixture of (R)-N-((S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2, 4'-piperidin]-1-yl)-2-methylpropane-2-sulfinamide (112 mg, 0.20 mmol), DCM (5 mL) and HCl (4 M solution in 1,4-dioxane, 10 mL) was stirred for 17 h at RT. The mixture was concentrated under reduced pressure, dissolved in MeOH (10 mL) and stirred for another 23 h at 60 °C. After cooling to RT, the reaction mixture was concentrated under reduced pressure. The residue was suspended in MeOH (2 mL) and EA (20 mL), the resulting precipitate was collected by filtration and dried under reduced pressure to give (S)-4-((5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol (73 mg). MS: *m/z* 440 $(M+H)^+$. ^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.51 (s, 1H), 8.34 (s, 1H), 7.59 (d, 1H), 7.37 - 7.28 (m, 3H), 7.23 (d, 1H), 5.52 (d, 1H), 4.40 - 4.28 (m, 3H), 3.38 - 3.21 (m, 3H), 3.02 - 2.99 (d, 1H), 1.82- 1.75 (m, 2H), 1.60 - 1.52 (m, 2H).

The following examples were synthesized using the above procedure with the corresponding starting materials.

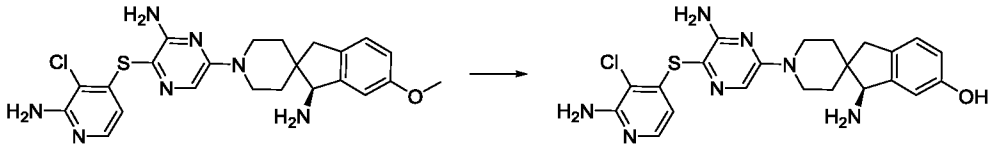
The following examples are compounds, or a pharmaceutically acceptable salt.

Table 18

EX No.	Chemical Name	Structure	MS: $(M+H)^+$ & ^{1}HNMR
134	(S)-4-((3-amino-5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.68 (s, 1H), 7.52 (d, 1H), 7.39 - 7.29 (m, 3H), 7.23 (d, 1H), 5.45 (d, 1H), 4.36 (s, 1H), 4.29 (d, 1H), 4.21 (d, 1H), 3.19 - 3.00 (m, 4H), 1.78 - 1.63 (m, 2H), 1.46 - 1.58 (m, 2H). MS: 455$(M+H)^+$.
135	(S)-4-((5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol		^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.38 - 8.32 (m, 3H), 7.84 (d, 1H), 7.31 - 7.27 (m, 1H), 7.19 (d,1H), 5.76 (d, 1H), 4.42 - 4.38 (d, 2H), 4.10 (s, 1H), 3.31 - 3.25 (m, 3H), 2.99 (d,1H), 1.95 - 1.82 (m, 2H), 1.68 (d,1H), 1.48 (d,1H). MS: 441$(M+H)^+$.
136	(S)-4-((3-amino-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.41 (d, 1H), 7.89 (d, 1H), 7.64 (s, 1H), 7.38 - 7.28 (m, 1H), 7.24 (d, 1H), 5.77 (d, 1H), 4.44 - 4.29 (m, 2H), 4.15 (s, 1H), 3.43 - 3.19 (m, 3H), 3.08 - 2.92 (m, 1H), 1.99 - 1.78 (m, 2H), 1.74 - 1.58 (m, 1H), 1.56 - 1.43 (m, 1H). MS: 456$(M+H)^+$.

EXAMPLE 137

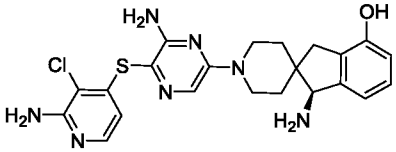
(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol



To a mixture of (S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine (74 mg, 0.14 mmol) in DCM (2 mL) was added BBr3 (1 M solution in DCM, 0.71 mL). The resulting mixture was stirred for 6 h at RT. The volatiles were removed under reduced pressure, the residue suspended in water, the resulting solid was filtered off and the pH value of the filtrate was adjusted to 7 with sat.aq.NaHCO3. The resulting precipitate was collected by filtration and dried in a vacuum oven to give (S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol (7 mg). MS: m/z 470 $(M+H)^+$.

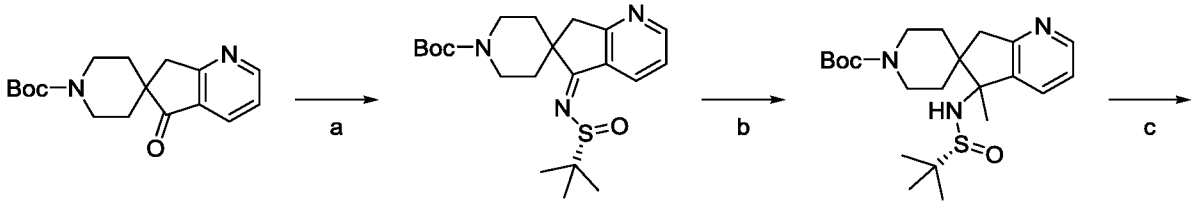
The following example was synthesized using the above procedure with the corresponding starting materials.

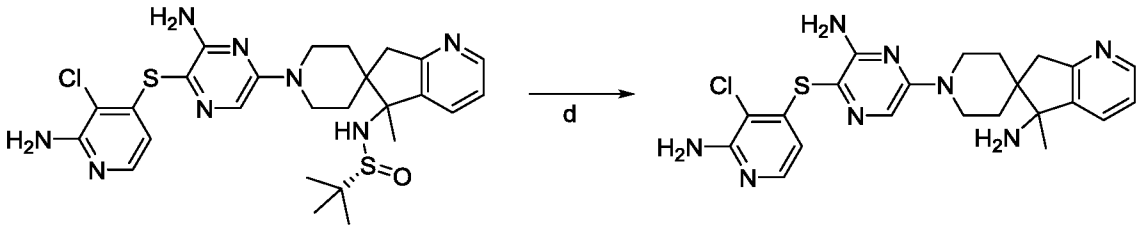
Table 19

EX No.	Chemical name	Structure	MS: $(M+H)^+$ & ^{1}HNMR
138	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-ol		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.58 - 7.51 (m, 2H), 7.05 (t, 1H), 6.87 (d, 1H), 6.65 (d, 1H), 5.94 (d, 1H), 4.27 (d, 2H), 3.9 (s, 1H), 3.36 - 3.18 (m, 2H), 3.08 (d, 1H), 2.69 (d, 1H), 1.88 - 1.68 (m, 2H), 1.57 (d, 1H), 1.43 (d, 1H). MS: 470$(M+H)^+$.

EXAMPLE 139

1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methyl-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine





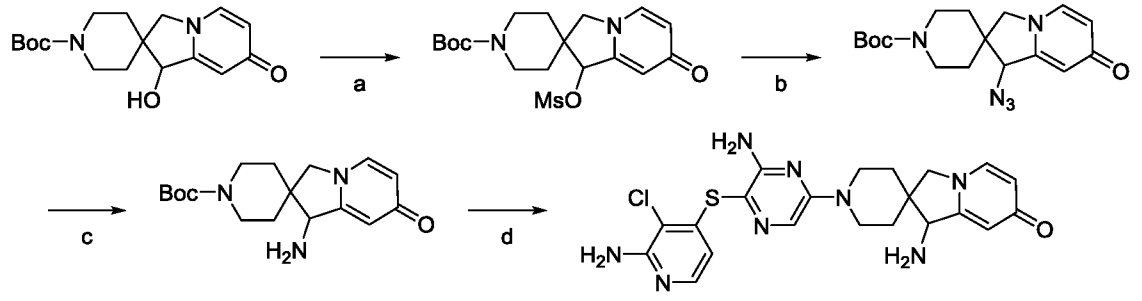
Step a: Step (a) of Example 5 was applied to provide tert-butyl (R,Z)-5-((tert-butylsulfinyl)imino)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate. MS: *m/z* 406 $(M+H)^+$.

Step b: To a -60 °C solution of tert-butyl (R,Z)-5-((tert-butylsulfinyl)imino)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate (1.49 g, 3.67 mmol) in THF (15 mL) was added methyllithium (1.3 M solution in diethyl ether, 14 mL, 18.20 mmol) dropwise. The resulting mixture was allowed to warm to RT and stirred for 20 h. The reaction mixture was diluted with water (10 mL) and EA (20 mL). The aqueous layer was collected, NaOH (1.00 g, 25.00 mmol) and $(Boc)_2O$ (0.50 mL) was added. The mixture was stirred for 1.5 h at RT. The reaction mixture was extracted with EA (2 × 50 mL), the organic layers combined, washed with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 1, v/v) to give tert-butyl 5-(((S)-tert-butylsulfinyl)amino)-5-methyl-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-1'-carboxylate (823 mg). MS: *m/z* 422 $(M+H)^+$.

Step (c-d): Step (c-d) of Example 5 was applied to provide 1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methyl-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine (71 mg). MS: *m/z* 469 $(M+H)^+$.^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.50 - 8.44 (m, 1H), 7.93 - 7.87 (m, 1H), 7.67 - 7.61 (m, 2H), 7.41 - 7.35 (m, 1H), 5.97 (d, 1H), 4.54 (m, 2H), 3.35 (d, 1H), 3.23 - 3.08 (m, 3H), 1.92 - 1.78 (m, 2H), 1.57 - 1.48 (m, 2H), 1.44 (s, 3H) .

EXAMPLE 140

1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-7(1H)-one



Step a: To a -10 °C solution of tert-butyl 1-hydroxy-7-oxo-1,7-dihydro-3H-spiro[indolizine-

2,4'-piperidine]-1'-carboxylate (100 mg, 0.31 mmol), triethylamine (157 mg, 1.55 mmol) in THF (10 mL) and DCM (2 mL) was added MsCl (66 mg, 0.58 mmol). The resulting sloution was stirred for 1 h at RT. The reaction solution was diluted with water (50 mL), extracted with DCM (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give tert-butyl 1-((methylsulfonyl)oxy)-7-oxo-1,7-dihydro-3H-spiro[indolizine-2,4'-piperidine]-1'-carboxylate (155 mg). MS: *m/z* 399 $(M+H)^+$.

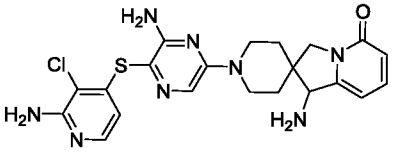
Step b: A mixture of tert-butyl 1-((methylsulfonyl)oxy)-7-oxo-1,7-dihydro-3H-spiro[indolizine-2,4'-piperidine]-1'-carboxylate (155 mg, 0.39 mmol), sodium azide (136 mg, 2.09 mmol) and DMF (5 mL) was stirred for 1 h at 75 °C and 4 h at 85 °C. After cooling to RT, the reaction mixture was diluted with EA (30 mL), filtered and the filtration was concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with MeOH : DCM = 1 : 10, v/v) to give tert-butyl 1-azido-7-oxo-1,7-dihydro-3H-spiro[indolizine-2,4'-piperidine]-1'-carboxylate (32 mg). MS: *m/z* 346 $(M+H)^+$.

Step c: A mixture of tert-butyl 1-azido-7-oxo-1,7-dihydro-3H-spiro[indolizine-2,4'-piperidine]-1'-carboxylate (32 mg, 0.093 mmol), Pd (10% on carbon, 15 mg) in EtOH (6 mL) was stirred for 3 h under hydrogen atmosphere. The reaction mixture filtrated follow by EtOH wash and the filtration was concentrated under reduced pressure to give tert-butyl 1-amino-7-oxo-1,7-dihydro-3H-spiro[indolizine-2,4'-piperidine]-1'-carboxylate (26 mg). MS: m/z 320 $(M+H)^+$.

Step d: To solution of tert-butyl 1-amino-7-oxo-1,7-dihydro-3H-spiro[indolizine-2,4'-piperidine]-1'-carboxylate (26 mg, 0.081 mmol) in DCM (2 mL) was added TFA (2 mL), and stirred for 30 min at RT. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in NMP (2.5 mL), 3-((2-amino-3-chloropyridin-4-yl)thio)-6-chloropyrazin-2-amine (46 mg, 0.16 mmol) and K_2CO_3 (395 mg, 2.86 mmol) was added, stirred for 16 h at 95 °C. After cooling to RT, the reaction mixture was diluted DCM (30 mL), filtered and concentrated under reduced pressure. The residue was purified by Pre-TLC (eluting with MeOH : DCM = 1 : 3, v/v) to give 1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-7(1H)-one (2 mg). MS: *m/z* 471 $(M+H)^+$.

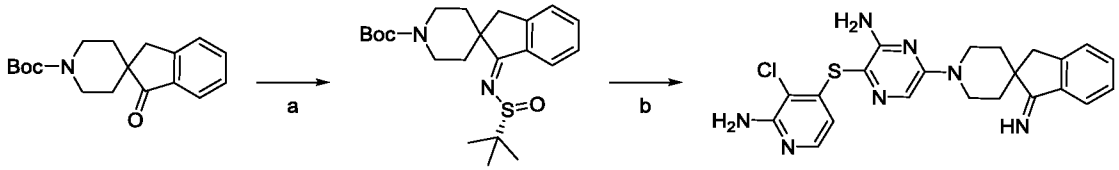
The following example was synthesized using the above procedure with the corresponding starting materials.

Table 20

EX No.	Chemical Name	Structure	MS: $(M+H)^+$ & ^{1}HNMR
141	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-5(1H)-one		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.61 - 7.57 (m, 3H), 6.53 (d, 1H), 6.45 (d, 1H), 5.93 (d, 1H), 4.46 (d, 1H), 4.39 - 4.32 (m, 2H), 4.14 - 4.08 (m, 1H), 3.84 (d, 1H), 3.28 - 3.11 (m, 2H), 1.99 - 1.91 (m, 1H), 1.83 - 1.75 (m, 1H), 1.70 (d, 1H), 1.30 (d, 1H). MS: 471$(M+H)^+$.

EXAMPLE 142

3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-imino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-amine

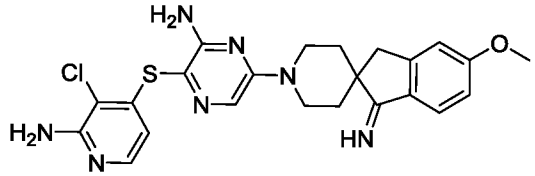
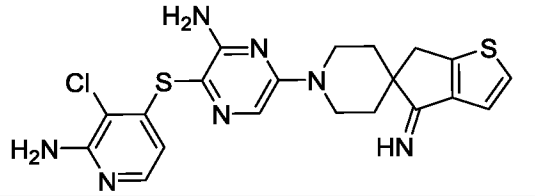
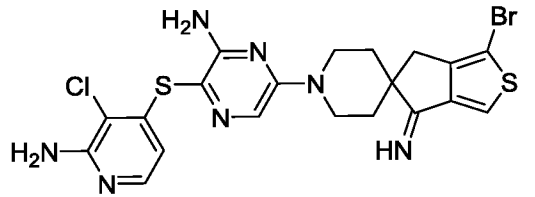
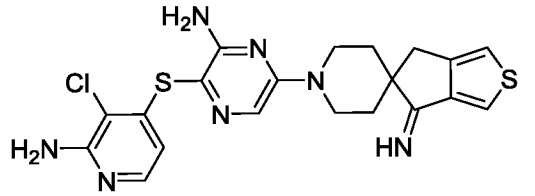
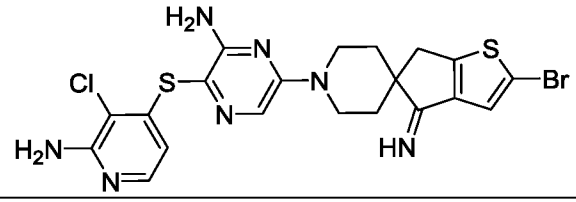


Step a: Step (a) of Example 5 was applied to provide tert-butyl (R,Z)-1-((tert-butylsulfinyl)imino)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate. MS: *m/z* 405 $(M+H)^+$.

Step b: To solution of tert-butyl (R,Z)-1-((tert-butylsulfinyl)imino)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (405 mg, 1.00 mmol) in DCM (10 mL) was added TFA (1 mL), and stirred for 1.5 h at RT. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in NMP (10 mL), 3-((2-amino-3-chloropyridin-4-yl)thio)-6-chloropyrazin-2-amine (288 mg, 1.00 mmol) and K_2CO_3 (1.38 g, 10.00 mmol) was added. The resulting mixture was stirred for 18 h at 100 °C. After cooling to RT, the reaction mixture was diluted with water (50 mL) and extracted with EA (3 × 30 mL). The combined organic layers were washed with brine (1X 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with MeOH : DCM = 1 : 5, v/v) to give 3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-imino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl) pyrazin-2-amine (50 mg). MS: *m/z* 452 $(M+H)^+$. ^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.83 (d, 1H), 7.74 - 7.37 (m, 5H), 5.96 (d, 1H), 4.58 - 4.43 (m, 2H), 3.28 - 3.12 (m, 4H), 2.06 - 2.01 (m, 2H), 1.60 - 1.56 (m, 2H).

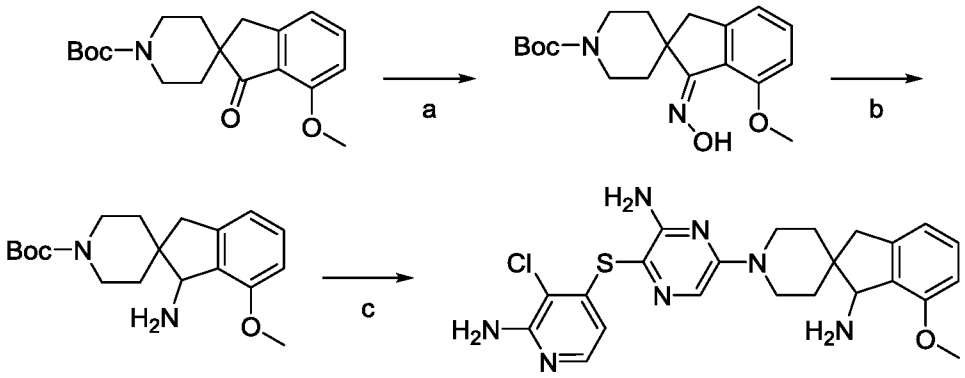
The following examples were synthesized using the above procedure with the corresponding starting materials.

Table 21

EX No.	Chemical Name	Structure	MS: $(M+H)^+$ & ^{1}HNMR
143	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-imino-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 7.81 (d, 1H), 7.65 (s, 1H), 7.61(d, 1H), 7.06 (s, 1H), 7.00 (dd, 1H), 5.95 (d, 1H), 4.57 (d, 2H), 3.91 (s, 3H), 3.26 (s, 2H), 3.21 - 3.14 (m, 2H), 2.05 - 1.98 (m, 2H), 1.61 (d, 2H). MS: 482$(M+H)^+$.
144	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(4-imino-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.83 (d, 1H), 7.70 (s, 1H), 7.66 (d, 1H), 7.46 (d, 1H), 6.04 (d, 1H), 4.68 (d, 2H), 3.59 (s, 2H), 3.21 (t, 2H), 2.14 - 2.07 (m, 2H), 1.91 (d, 2H). MS: 458$(M+H)^+$.
145	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-bromo-4-imino-4H,6H-spiro[cyclopenta[c]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.69 (s, 1H), 7.65 (d, 1H), 6.15 (s, 1H), 5.81 - 5.74 (m, 1H), 4.49 - 4.32 (m, 2H), 3.17 - 2.93 (m, 4H), 1.90 - 1.80 (m, 1H), 1.79 - 1.66 (m, 1H), 1.61 - 1.43 (m, 2H). MS: 536$(M+H)^+$.
146	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(4-imino-4H,6H-spiro[cyclopenta[c]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.69 (s, 1H), 7.65 (d, 1H), 6.20 - 6.12 (m, 2H), 5.80 - 5.73 (m, 1H), 4.51 - 4.28 (m, 2H), 3.13 - 2.96 (m, 4H), 1.83 - 1.66 (m, 2H), 1.59 - 1.46 (m, 2H). MS: 458$(M+H)^+$.
147	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(2-bromo-4-imino-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine		MS: 536$(M+H)^+$.

EXAMPLE 148

1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine



Step a: To a solution oftert-butyl 7-methoxy-1-oxo-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (552 mg, 1.07 mmol) in MeOH (10 mL) was added hydroxylamine hydrochloride (348 mg, 5.01 mmol) and AcONa (822 mg, 10.02 mmol). The resulting mixture was stirred for 4 h at RT. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EA (15 mL) and water (15 mL), the organic layer was separated, washed with brine (1 × 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl (Z)-1-(hydroxyimino)-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (520 mg) as a yellow solid. MS: *m/z* 347 $(M+H)^+$.

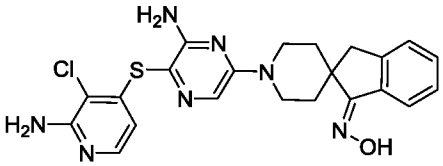
Step b: A suspension oftert-butyl (Z)-1-(hydroxyimino)-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (510 mg, 1.47 mmol) and PtO_2 (30 mg) in AcOH (10 mL) was stirred for 17 h at 60 °C under hydrogen atmosphere. After cooling to RT, the reaction mixture was diluted with EA (45 mL) and water (45 mL), the aqueous layer was separated and the pH value was taken to 10 with K_2CO_3 solid. The resulting mixture was extracted with DCM (2 × 30 mL), the combined organic layers were washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 1-amino-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (202 mg) as a colorless oil. MS: *m/z* 333 $(M+H)^+$.

Step c: To solution oftert-butyl 1-amino-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (199 mg, 0.60 mmol) in DCM (10 mL) was added TFA (1 mL), and stirred for 1.5 h at RT. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in NMP (5 mL), 3-((2-amino-3-chloropyridin-4-yl)thio)-6-chloropyrazin-2-amine (144 mg, 0.50 mmol) and

K_2CO_3 (691 mg, 5.90 mmol) was added. The resulting mixture was stirred for 3 h at 95 °C. After cooling to RT, the reaction mixture was diluted with water (50 mL) and extracted with EA (1 × 50 mL). The organic layer was washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Pre-TLC (eluting with MeOH : DCM = 1 : 5, v/v) to give 1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine (20 mg). MS: *m/z* 484 $(M+H)^+$. ^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.66 (s, 1H), 7.64 (d, 1H), 7.36 - 7.28 (m, 1H), 6.90 (d, 1H), 6.88 (d, 1H), 5.75 (d, 1H), 4.29 (s, 1H), 4.20 (d, 1H), 4.09 (d, 1H), 3.83 (s, 3H), 3.30 - 3.15 (m, 2H), 3.10 (d, 1H), 2.96 (d, 1H), 1.87 - 1.76 (m,1H), 1.70 - 1.54 (m, 2H), 1.41 (d, 1H).

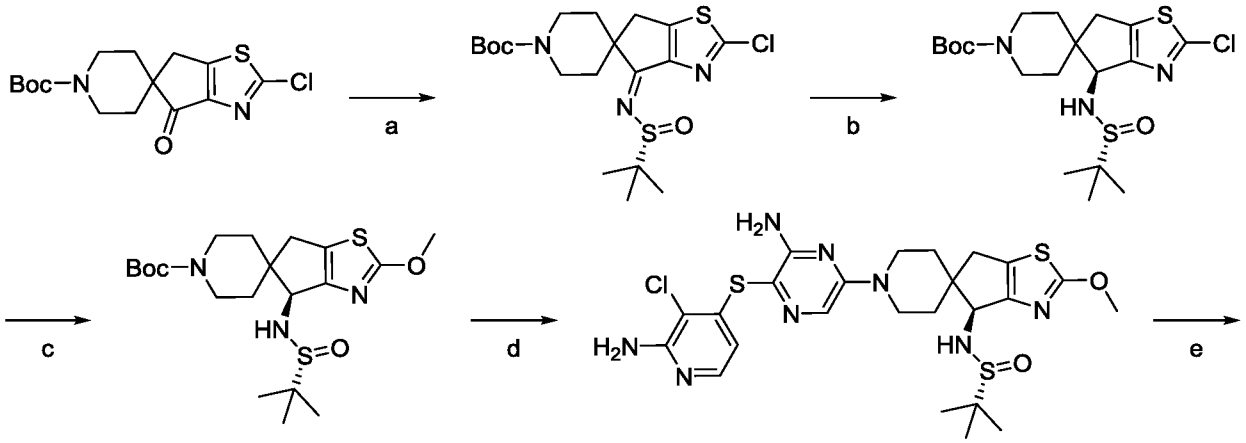
The following example was synthesized using the above procedure with the corresponding starting materials.

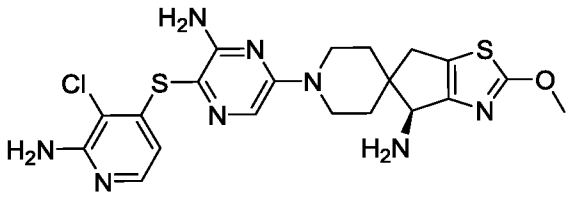
Table 22

EX No.	Chemical Name	Structure	MS: $(M+H)^+$ & ^{1}HNMR
149	(Z)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[indene-2,4'-piperidin]-1(3H)-one oxime		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.40 (d, 1H), 7.63 - 7.58 (m, 3H), 7.41 - 7.34 (m, 2H), 5.96 (d, 1H), 4.38 (d, 2H), 3.31 - 3.14 (m, 4H), 1.96 - 1.92 (m, 2H), 1.72 - 1.63 (m, 2H). MS: 468$(M+H)^+$.

EXAMPLE 150

(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-methoxy-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine





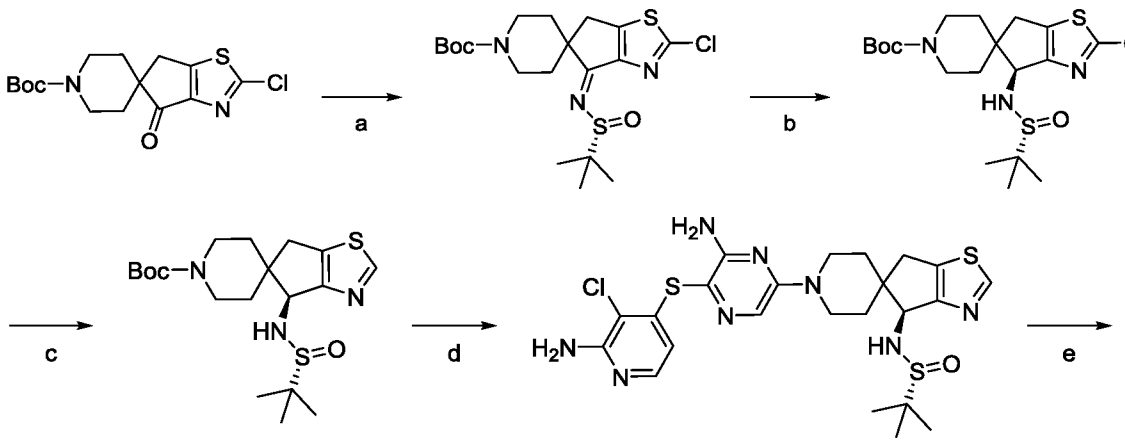
Step (a-b): Step (a-b) of Example 5 was applied to provide tert-butyl (S)-4-(((R)-tert-butylsulfinyl)amino)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate. MS: *m/z* 448 $(M+H)^+$.

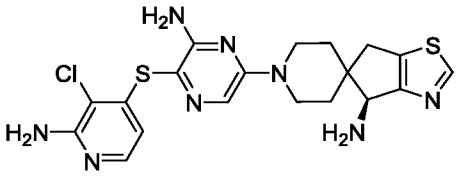
Step c: A mixture of tert-butyl(S)-4-(((R)-tert-butylsulfinyl)amino)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate (403 mg, 0.90 mmol) and NaOH (358 mg, 8.95 mmol) in MeOH (15 mL) was stirred for 5 h at 65 °C. After cooling to RT, the volatiles were removed under reduced pressure. The residue was dissolved in water and the pH value was taken to 7 by the addition of aq. citric acid. The resulting mixture was extracted with EA (3 × 30 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl(S)-4-(((R)-tert-butylsulfinyl)amino)-2-methoxy-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate (360 mg) as a brown oil. MS: *m/z* 444 $(M+H)^+$.

Step (d-e): Step (c-d) of Example 5 was applied to provide(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-methoxy-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine. MS: *m/z* 491 $(M+H)^+$.

EXAMPLE 151

(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine





Step (a-b): Step (a-b) of Example 5 was applied to provide tert-butyl (S)-4-(((R)-tert-butylsulfinyl)amino)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate. MS: *m/z* 448 $(M+H)^+$.

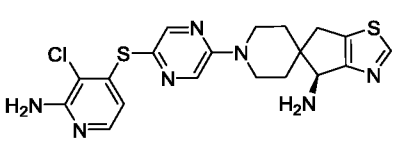
Step c: A suspension of tert-butyl (S)-4-(((R)-tert-butylsulfinyl)amino)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate (2.50 g, 5.58 mmol), TEA (2 mL) and Pd (10 % on carbon, 690 mg) in MeOH (50 mL) was stirred for 24 h at 40 °C under hydrogen atmosphere. The resulting mixture was filtered, and an additional portion of Pd (10 on carbon, 1.32 g) was added to the filtration. The resulting mixture was stirred for another 16 h at 50 °C under hydrogen atmosphere. The resulting mixture was filtered, the filtration was concentrated under reduced pressure. The residue was purified by silica chromatography (eluting with EA : Hex = 1 : 1, v/v) to give tert-butyl (4S)-4-((tert-butylsulfinyl)amino)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate (1.28 g). MS: *m/z* 414 $(M+H)^+$.

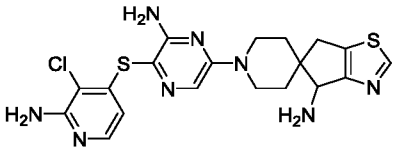
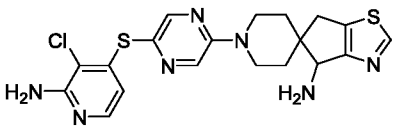
Step (d-e):Step (c-d) of Example 5 was applied to provide(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine. MS: *m/z* 461 $(M+H)^+$. ^{1}H NMR (400 MHz, *DMSO-d6*) δ 8.94 (s, 1H), 7.66 - 7.63 (m, 2H), 5.76 (d, 1H), 4.07 - 3.99 (m, 2H), 3.87 (s, 1H), 3.38 - 3.28 (m, 2H), 2.93 - 2.78 (m, 2H), 1.87 - 1.47 (m, 4H).

2-Methylpropane-2-sulfinamide, instead of (R)-(+)-2-Methyl-2-Propanesulfinamide, was used in step (a) of Example 5 to give the racemic compounds.

The following example was synthesized using the above procedure with the corresponding starting materials.

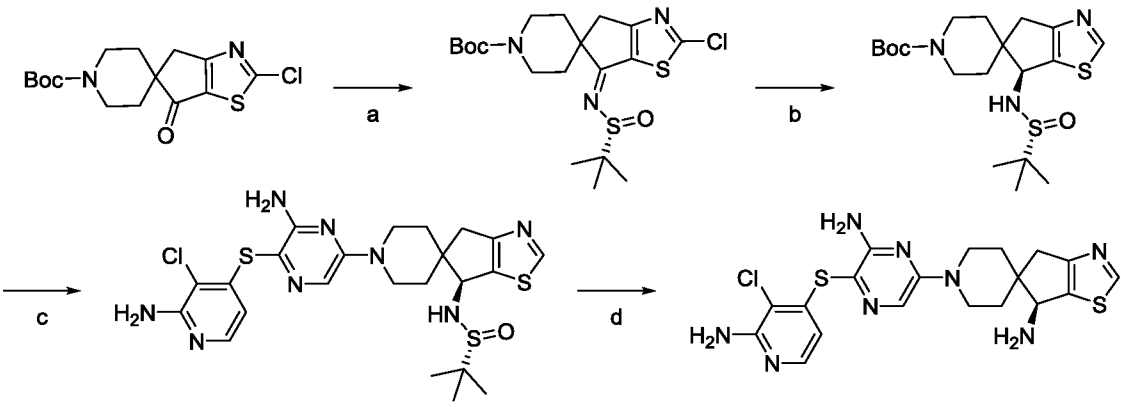
Table 23

EX No.	Chemical Name	Structure	MS: $(M+H)^+$ & ^{1}HNMR
152	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.97 (s, 1H), 8.34 (d, 2H), 7.60 (d, 1H), 5.94 (d, 1H), 4.43 (d, 1H), 4.33 (d, 1H), 4.23 (s, 1H), 3.48 - 3.31 (m, 2H), 3.12 - 3.09 (m, 2H), 2.01 - 1.79 (m, 4H). MS: 446$(M+H)^+$.

153	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.88 (s, 1H), 7.62 - 7.58 (d, 2H), 5.94 (d, 1H), 4.33 - 4.14 (m, 2H), 3.98 (s, 1H), 3.44 - 3.30 (m, 2H), 3.05 - 2.95 (m, 2H), 1.96 - 1.69 (m, 4H). MS: 461 $(M+H)^+$.
154	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 8.91 (s, 1H), 8.36 (d, 1H), 8.30 (d, 1H), 7.61 (d,1H), 5.95 (d, 1H), 4.35 - 4.24 (m,2H), 4.06 (s, 1H), 3.52 - 3.38 (m, 2H), 3.06 (s, 2H), 2.00 - 1.75 (m, 4H). MS: 446 $(M+H)^+$.

EXAMPLE 155

(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine



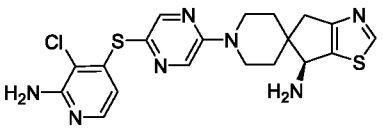
Step a: Step (a) of Example 5 was applied to provide tert-butyl (R,Z)-6-((tert-butylsulfinyl)imino)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate. MS: *m/z* 446 $(M+H)^+$.

Step b: To a -50 °C solution of tert-butyl (R,Z)-6-((tert-butylsulfinyl)imino)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate (4.25 g, 9.53 mmol) in THF (30 mL) was added BH_3 (1 M solution in THF, 30.00 mL, 30.00 mmol). The resulting mixture was allowed to warm to RT and stirred for 18 h. The reaction mixture was quenched with brine (50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica chromatography eluting with(EA : Hex = 1 : 2, v/v) to give tert-butyl (S)-6-(((R)-tert-butylsulfinyl)amino)-4,6-dihydrospiro [cyclopenta[d]thiazole-5,4'-piperidine]-1'-carboxylate (1.12 g). MS: *m/z* 414 $(M+H)^+$.

Step (c-d): Step (c-d) of Example 5 was applied to provide (S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine. ^{1}H NMR (400 MHz, *DMSO-d6*) δ 9.01 (s, 1H), 7.66 - 7.63 (m, 2H) 5.76 (d, 1H), 4.23 - 4.19 (m, 2H), 4.09 (s, 1H), 3.32 - 3.15 (m, 2H), 2.93 - 2.80 (m, 2H), 1.87 - 1.60 (m, 4H). MS: *m/z* 461 $(M+H)^+$.

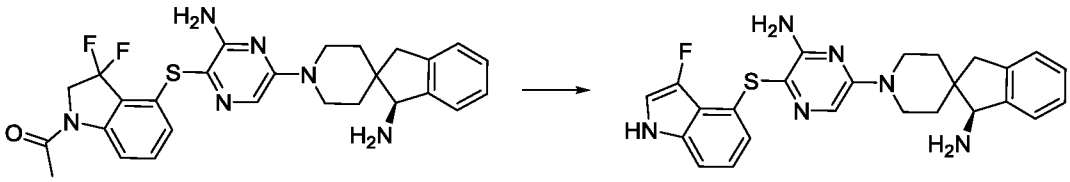
The following example was synthesized using the above procedure or modification procedure with the corresponding starting materials.

Table 24

EX No.	Chemical Name	Structure	MS: $(M+H)^+$ & ^{1}HNMR
156	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine		^{1}H NMR (400 MHz, *MeOH-d4*) δ 9.07 (s, 1H), 8.37 (d, 1H), 8.30 (d, 1H), 7.60 (d, 1H), 5.95 (d, 1H), 4.48 (d, 1H), 4.38 - 4.34 (m, 2H), 3.45 - 3.27(m, 2H), 3.13 - 3.02 (m, 2H), 2.00 - 1.76 (m, 4H). MS: 446$(M+H)^+$.

EXAMPLE 157

(S)-1'-(6-amino-5-((3-fluoro-1H-indol-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

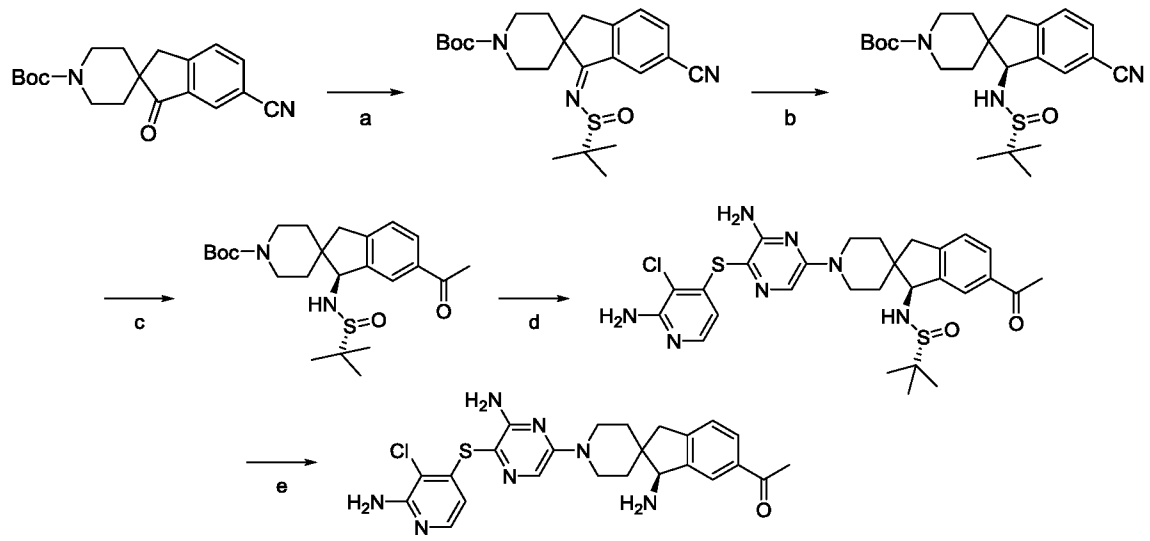


A mixture of (S)-1-(4-((3-amino-5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one (86 mg, 0.14 mmol), DCM (5 mL) and HCl (4 M solution in 1,4-dioxane, 0.50 mL) was stirred for 0.5 h at RT. The mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (8 mL) and NaOH (17 mg, 0.43 mmol) was added. The resulting mixture was stirred for another 21 h at 65 °C. After cooling to RT, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and EA (20 mL). The separated organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under pressure. EA (5 mL) and Hex (3 mL) was added and the resulting precipitate was collected by filtration and dried under reduced pressure to give (S)-1'-(6-amino-5-((3-fluoro-1H-indol-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine (14 mg). ^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.59 (s, 1H), 7.37 - 7.21 (m, 5H), 7.13

(d, 1H), 7.00 - 6.93 (m, 1H), 6.40 (d, 1H), 4.18 (d, 2H), 3.97 (s, 1H), 3.09 (m, 3H), 2.72 (m, 1H), 1.77 - 1.62 (m, 2H), 1.50 - 1.47 (m, 1H) , 1.20 - 1.16 (m, 1H) MS: 461$(M+H)^+$.

EXAMPLE 158

(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)ethan-1-one



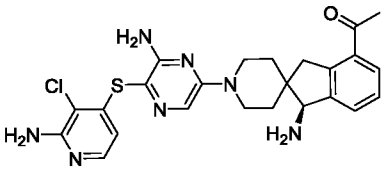
Step a-b: Step (a-b) of Example 5 was applied to provide tert-butyl (1S)-1-((tert-butylsulfinyl)amino)-6-cyano-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate. MS: m/z 432 $(M+H)^+$.

Step c: To a -50 °C solution of tert-butyl (1S)-1-((tert-butylsulfinyl)amino)-6-cyano-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (430 mg, 1.00 mmol) in THF (10 mL) was added methylmagnesium bromide (3 M solution in THF/Hex, 0.50 mL, 1.50 mmol) dropwise. The resulting mixture was allowed to warmed to RT and stirred for 24 h. The reaction mixture was quenched with brine (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl (1S)-6-acetyl-1-((tert-butylsulfinyl)amino)-1,3-dihydrospiro[indene-2,4'-piperidine]-1'-carboxylate (0.72 g) which was used in next step without any further purification. MS: m/z 449 $(M+H)^+$.

Step d-e: Step (c-d) of Example 5 was applied to provide (S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)ethan-1-one. MS: 496$(M+H)^+$.

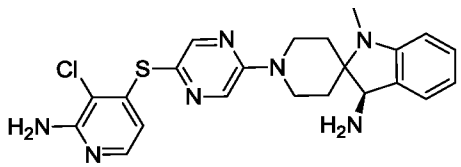
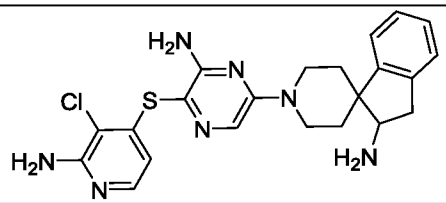
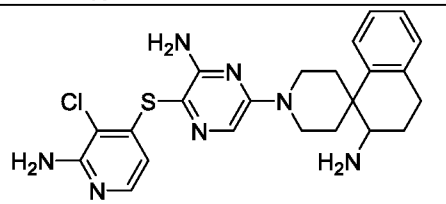
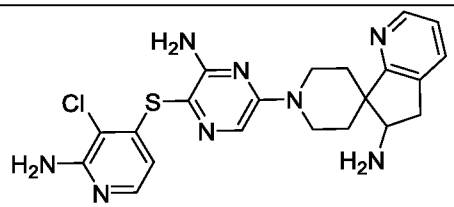
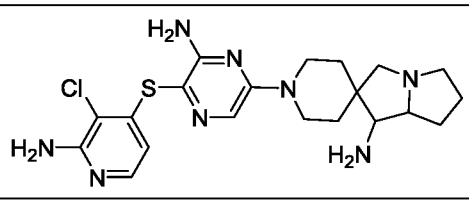
The following example was synthesized using the above procedure or modification procedure with the corresponding starting materials.

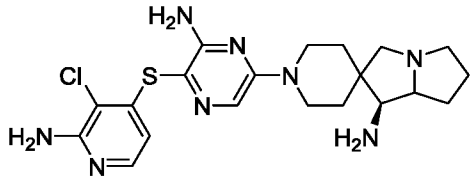
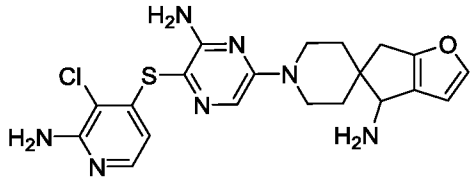
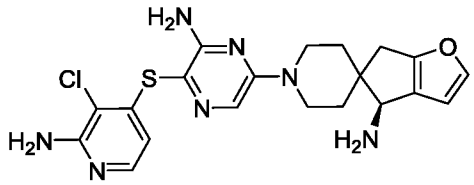
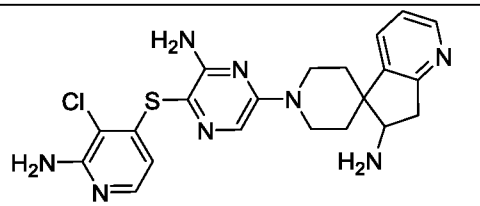
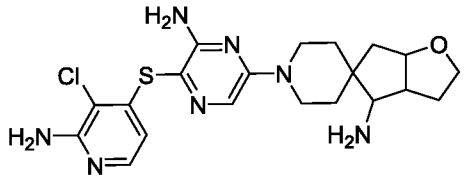
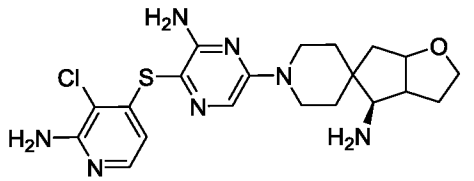
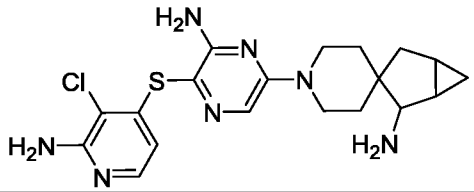
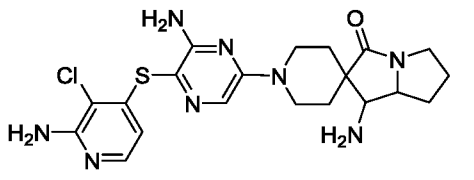
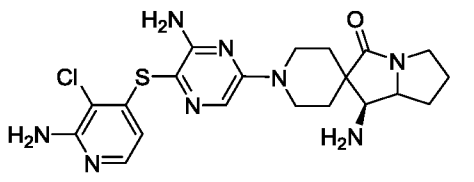
Table 25

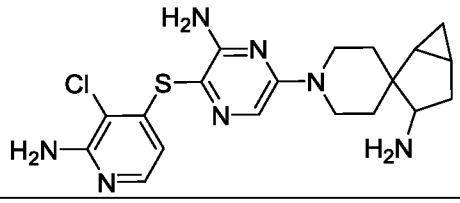
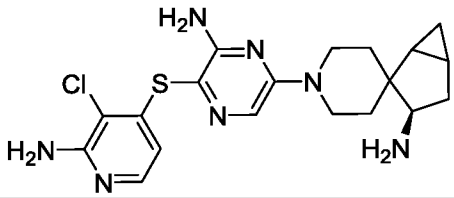
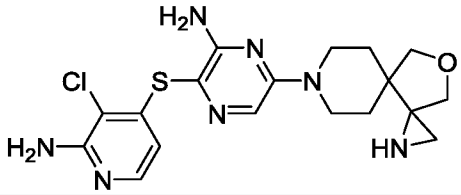
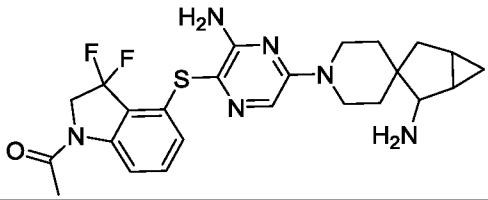
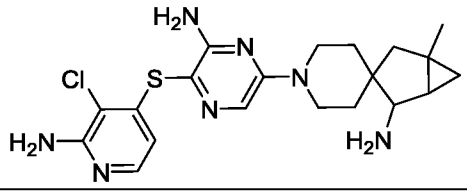
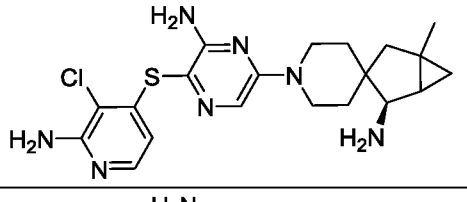
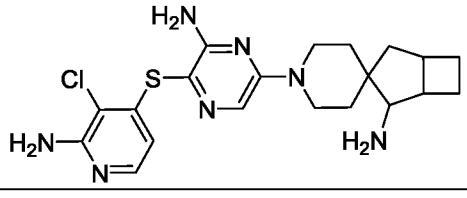
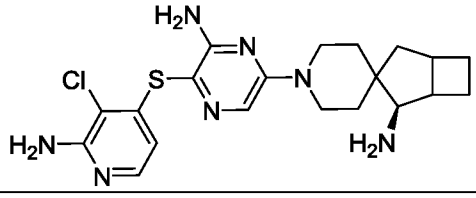
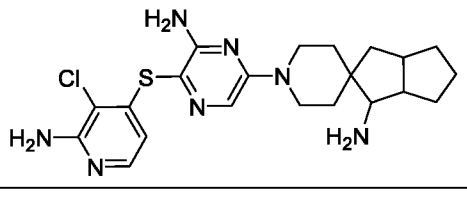
EX No.	Chemical Name	Structure	MS: $(M+H)^+$ & ^{1}HNMR
159	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-yl)ethan-1-one		^{1}H NMR (400 MHz, *DMSO-d6*) δ 7.99 (d, 1H), 7.73 (d, 1H), 7.67 (s, 1H), 7.64 (d, 1H), 7.50 (t, 1H), 5.75 (d, 1H), 4.40 (s, 1H), 4.24 (d, 1H), 4.16 (d, 1H), 3.41 - 3.17 (m, 4H), 2.60 (s, 3H), 1.74 - 1.66 (m, 2H) , 1.53 - 1.45 (m, 2H). MS: 496$(M+H)^+$.

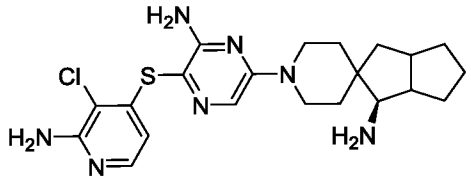
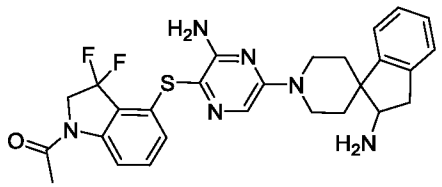
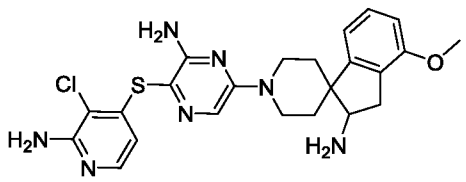
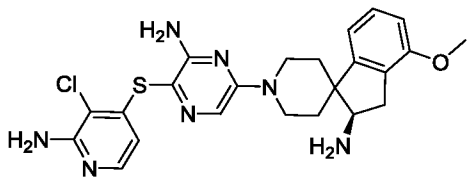
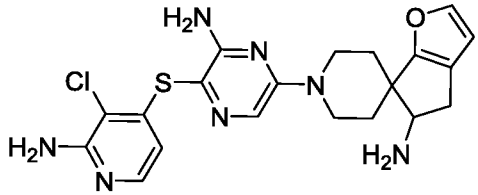
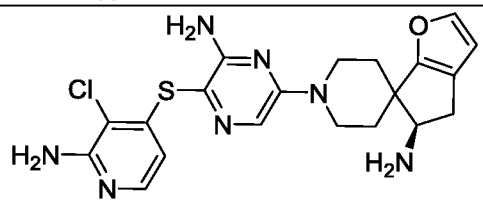
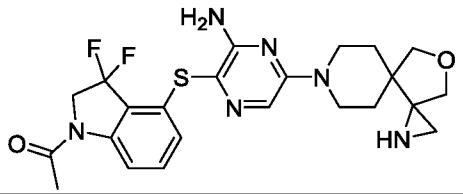
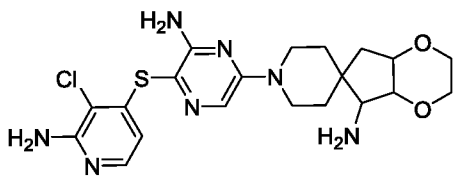
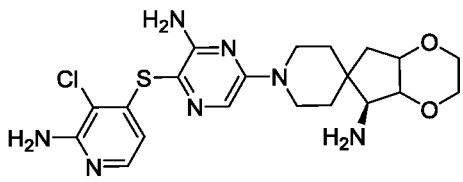
The following examples can be synthesized using the above methods and appropriate starting materials:

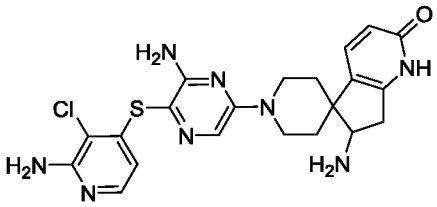
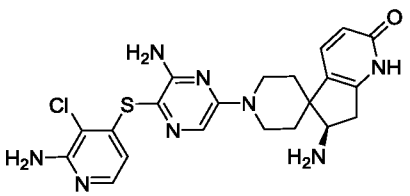
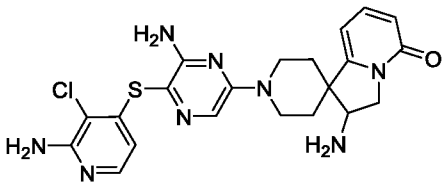
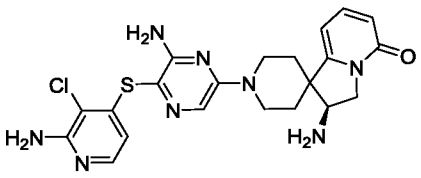
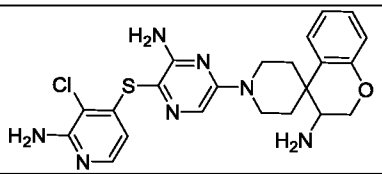
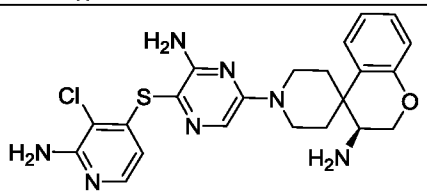
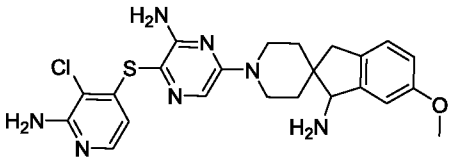
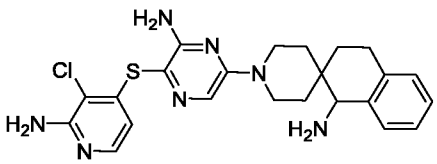
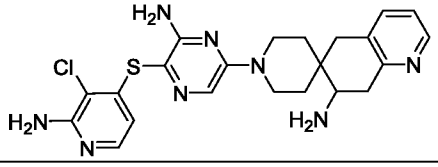
Table 26

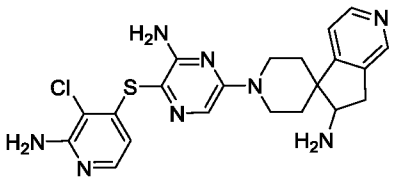
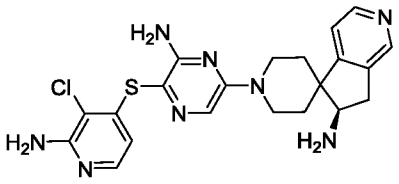
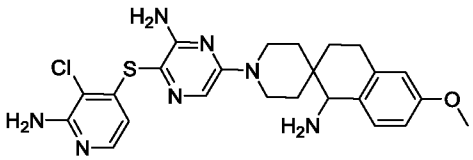
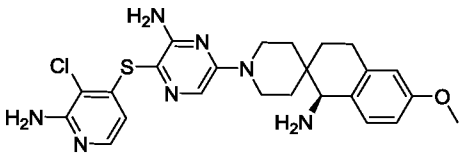
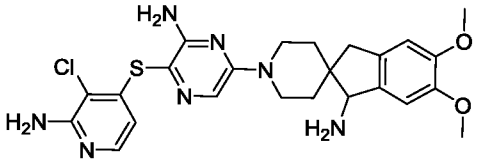
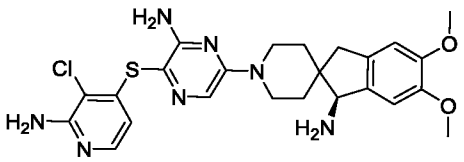
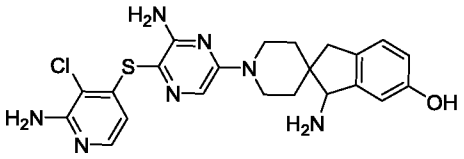
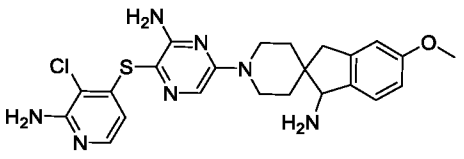
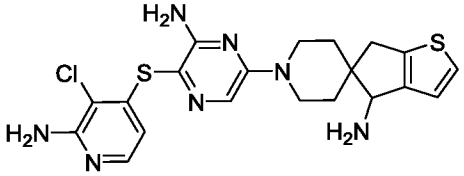
EX No.	Chemical Name	Structure	MS(M+H)+
160	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1-methylspiro[indoline-2,4'-piperidin]-3-amine		454
161	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine		454
162	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-amine		468
163	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidin]-6-amine		455
164	1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine		447

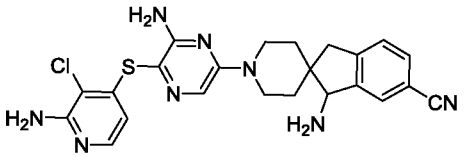
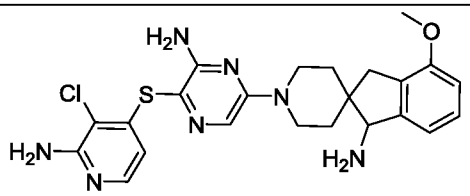
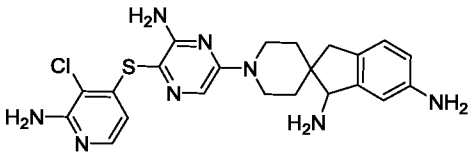
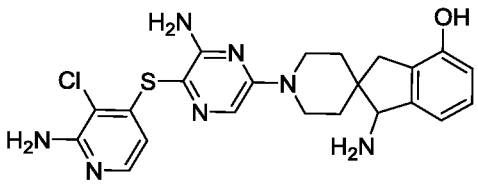
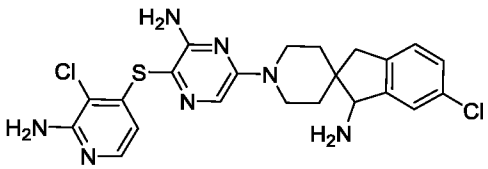
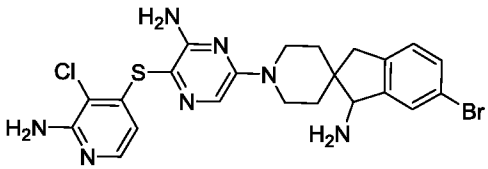
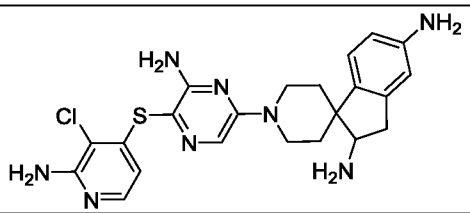
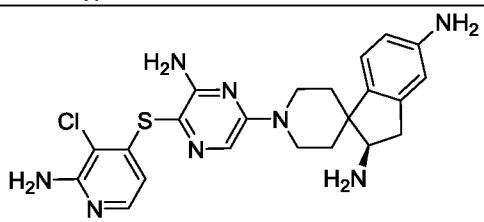
EX No.	Chemical Name	Structure	MS(M+H)+
165	(1'S)-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine		447
166	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine		444
167	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine		444
168	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-6-amine		455
169	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine		448
170	(4R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine		448
171	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-2-amine		418
172	1'-amino-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-3'-one		461
173	(1'S)-1'-amino-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-3'-one		461

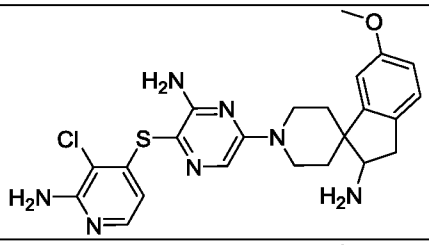
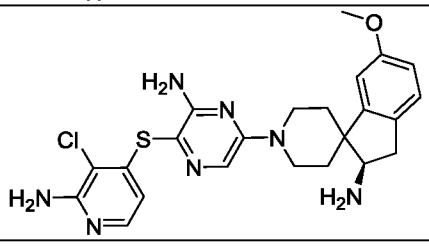
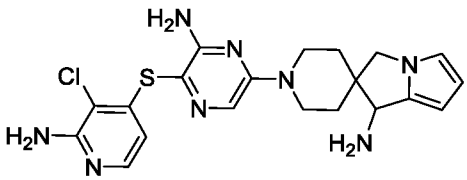
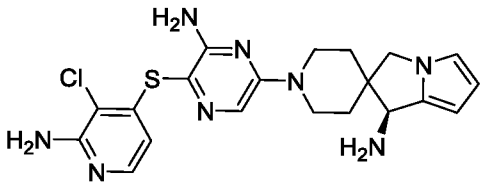
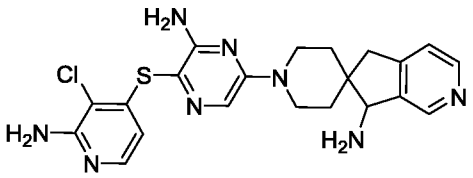
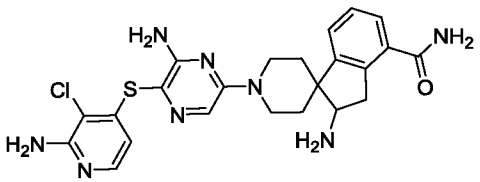
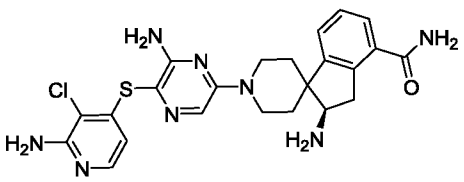
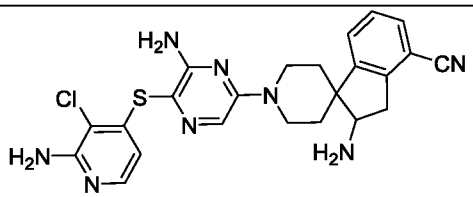
EX No.	Chemical Name	Structure	MS(M+H)+
174	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-2,4'-piperidin]-3-amine		418
175	(3R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-2,4'-piperidin]-3-amine		418
176	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(11-oxa-1,7-diazadispiro[2.0.5^4.3^3]dodecan-7-yl)pyrazin-2-amine		420
177	1-(4-((3-amino-5-(2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one		487
178	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1-methylspiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-4-amine		432
179	(4R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1-methylspiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-4-amine		432
180	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.2.0]heptane-3,4'-piperidin]-2-amine		432
181	(2R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.2.0]heptane-3,4'-piperidin]-2-amine		432
182	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydro-1H-spiro[pentalene-2,4'-piperidin]-1-amine		446

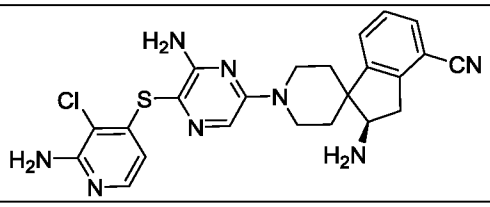
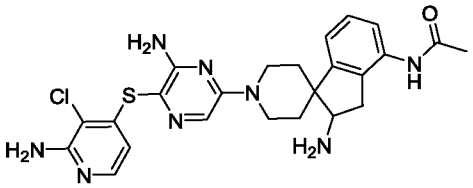
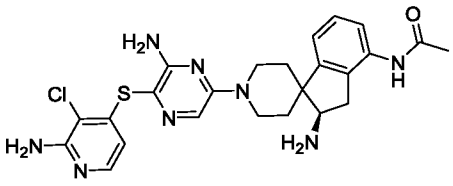
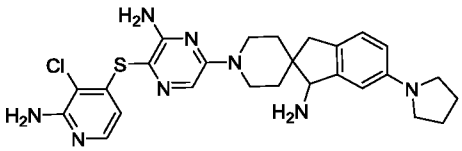
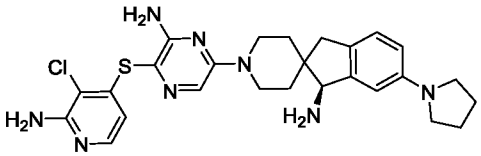
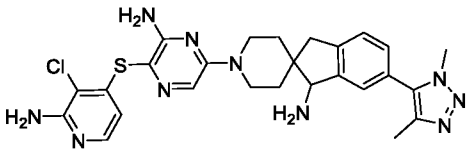
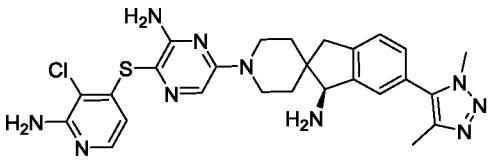
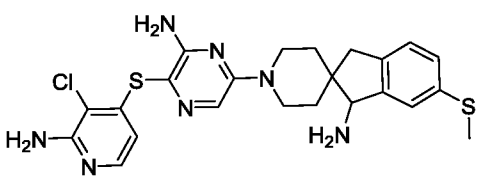
EX No.	Chemical Name	Structure	MS(M+H)+
183	(1R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydro-1H-spiro[pentalene-2,4'-piperidin]-1-amine		446
184	1-(4-((3-amino-5-(2-amino-2,3-dihydrospiro[indene-1,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one		523
185	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine		484
186	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine		484
187	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,5-dihydrospiro[cyclopenta[b]furan-6,4'-piperidin]-5-amine		444
188	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,5-dihydrospiro[cyclopenta[b]furan-6,4'-piperidin]-5-amine		444
189	1-(4-((3-amino-5-(11-oxa-1,7-diazadispiro[2.0.5^4.3^3]dodecan-7-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one		489
190	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b][1,4]dioxine-6,4'-piperidin]-5-amine		464
191	(5S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b][1,4]dioxine-6,4'-piperidin]-5-amine		464

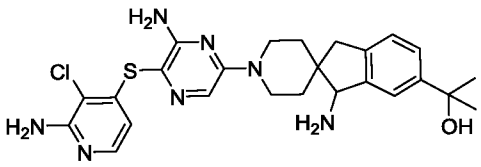
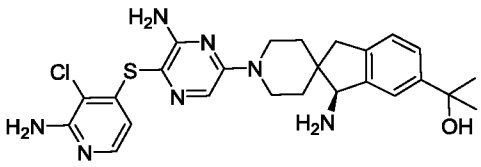
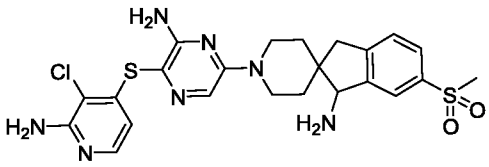
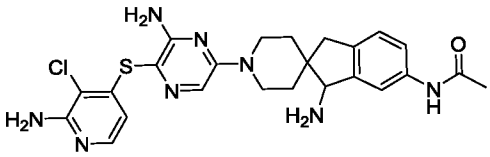
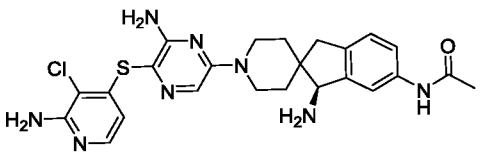
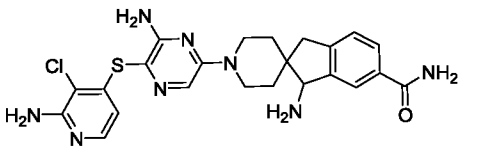
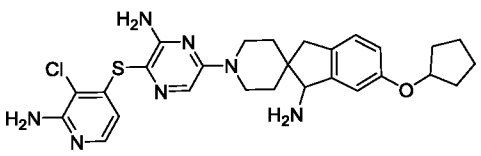
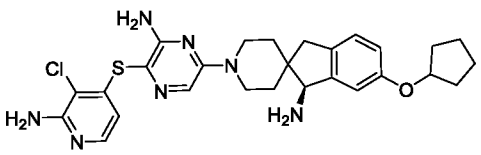
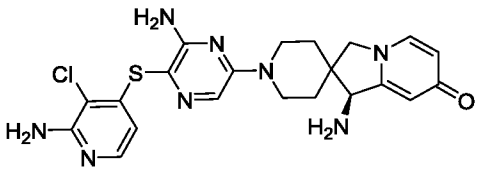
EX No.	Chemical Name	Structure	MS(M+H)+
192	6-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-2(1H)-one		471
193	(R)-6-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-2(1H)-one		471
194	2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydro-5H-spiro[indolizine-1,4'-piperidin]-5-one		471
195	(S)-2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydro-5H-spiro[indolizine-1,4'-piperidin]-5-one		471
196	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[chromane-4,4'-piperidin]-3-amine		470
197	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[chromane-4,4'-piperidin]-3-amine		470
198	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		484
199	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine		468
200	1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7',8'-dihydro-5'H-spiro[piperidine-4,6'-q		469

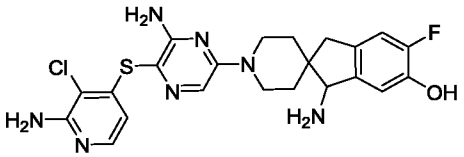
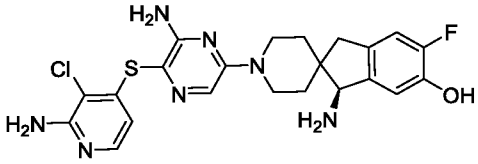
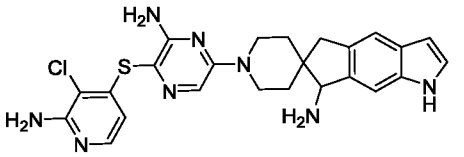
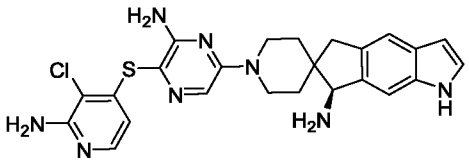
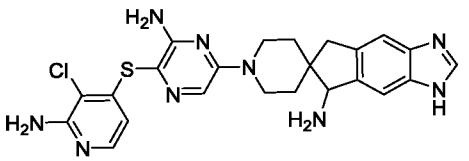
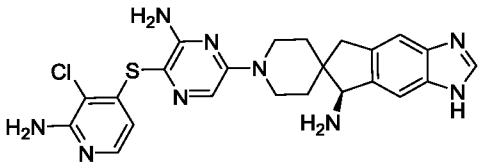
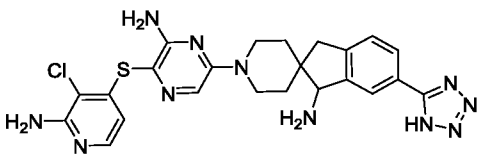
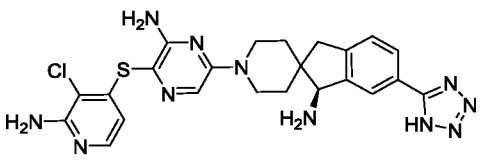
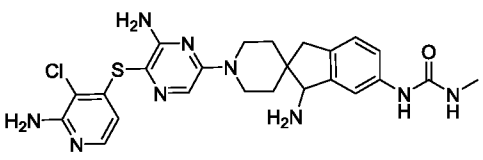
EX No.	Chemical Name	Structure	MS(M+H)+
	uinolin]-7'-amine		
201	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[c]pyridine-5,4'-piperidin]-6-amine		455
202	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[c]pyridine-5,4'-piperidin]-6-amine		455
203	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine		498
204	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine		498
205	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dimethoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		514
206	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dimethoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		514
207	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol		470
208	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		484
209	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine		460

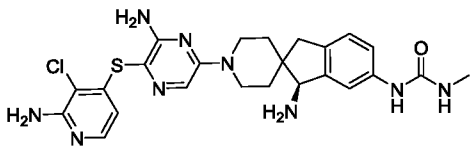
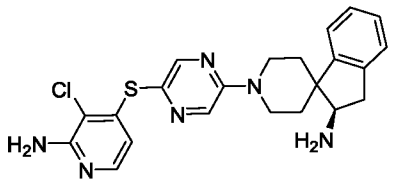
EX No.	Chemical Name	Structure	MS(M+H)+
210	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile		479
211	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		484
212	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine		469
213	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-ol		470
214	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-chloro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		488
215	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		532
216	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-2,5-diamine		469
217	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-2,5-diamine		469

EX No.	Chemical Name	Structure	MS(M+H)+
218	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine		484
219	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine		484
220	1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine		443
221	(S)-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine		443
222	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine		455
223	2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carboxamide		497
224	(R)-2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carboxamide		497
225	2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carbonitrile		479

EX No.	Chemical Name	Structure	MS(M+H)+
226	(R)-2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carbonitrile		479
227	N-(2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-4-yl)acetamide		511
228	(R)-N-(2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-4-yl)acetamide		511
229	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(pyrrolidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		523
230	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(pyrrolidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		523
231	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		549
232	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		549
233	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		500

EX No.	Chemical Name	Structure	MS(M+H)+
234	2-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)propan-2-ol		512
235	(S)-2-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)propan-2-ol		512
236	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		532
237	N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide		511
238	(S)-N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide		511
239	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide		497
240	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(cyclopentyloxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		538
241	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(cyclopentyloxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		538
242	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-7(1H)-one		471

EX No.	Chemical Name	Structure	MS(M+H)+
243	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol		488
244	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol		488
245	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]indole-6,4'-piperidin]-7-amine		493
246	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]indole-6,4'-piperidin]-7-amine		493
247	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[indeno[5,6-d]imidazole-6,4'-piperidin]-7-amine		494
248	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[indeno[5,6-d]imidazole-6,4'-piperidin]-7-amine		494
249	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-tetrazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		522
250	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-tetrazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		522
251	1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)-3-methylurea		526

EX No.	Chemical Name	Structure	MS(M+H)+
252	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)-3-methylurea		526
253	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine		439

PHARMACOLOGICAL TESTING

Example A. Phosphatase Assay (single dose inhibition)

Assay Protocol:

For single dose inhibition assays using 6,8-difluoro-4-methylumbelliferyl phosphate (DiFMUP) as a substrate, SHP2 samples (diluted to 0.5 nM in reaction buffer) were incubated with dPEG8 peptide for 30 min in reaction buffer[60 mM 3,3-dimethyl glutarate (pH7.2), 75 mM NaCl, 75 mM KCl, and 1 mM EDTA, 0.05% Tween 20, 2mM dithiothreitol （DTT）] to active the PTP. DMSO [0.5% (v/v)] or compounds (100nM) were added to the mixture and incubated for 30 min at room temperature. Reactions were initiated by the addition of DiFMUP (12 μM; total reaction volume of 100 μL), and the fluorescence (excitation at 340 nm, emission at 450 nm) of the resulting solutions was measured on a 2104-0020 EnVision Xcite Multilabel Reader (PerkinElmer) after 30min. The experiment is carried out in triplicate. The value for the control sample (DMSO) was set to 100%, and the values for the compound-treated samples were expressed as activity relative to the control sample. The inhibition of SHP2 by compounds of the invention were shown in table A

Table A

Example	SHP2 inhibition (%)@0.1μM
1	87
2	75
3	42
4	20
5	84

Example	SHP2 inhibition (%)@0.1μM
6	66
7	81
8	60
9	54
11	74

Example	SHP2 inhibition (%)@0.1μM
12	76
13	72
14	82
15	83
16	75

Example	SHP2 inhibition (%)@0.1μM
17	81
18	35
19	86
20	86
21	49
22	30
23	71
24	70
25	72
26	57
27	79
28	75
29	77
31	70
32	85
33	81
34	71
35	70
36	65
37	76
38	75
39	67
40	74
41	69
42	49
43	79
44	88
45	68
46	69

Example	SHP2 inhibition (%)@0.1μM
47	81
48	81
49	85
50	77
51	85
53	84
54	69
56	71
57	55
58	73
59	69
60	70
61	74
62	76
63	93
64	66
65	0
66	72
67	63
68	82
69	89
70	30
71	86
72	28
73	80
74	76
75	16
78	67
79	58

Example	SHP2 inhibition (%)@0.1μM
80	75
81	75
82	72
83	91
89	90
90	71
91	88
92	92
93	94
94	64
95	73
96	66
97	86
98	81
99	89
100	88
101	83
102	81
103	76
104	87
106	82
107	77
108	71
109	71
110	61
111	82
112	87
113	80
114	96

Example	SHP2 inhibition (%)@0.1μM
115	86
116	79
117	81
118	81
119	61
120	87
122	88
123	50
124	84
125	86
126	81
127	83
128	84
129	74

Example	SHP2 inhibition (%)@0.1μM
130	94
131	83
132	78
133	76
134	78
135	86
136	83
137	89
138	82
140	14
141	41
142	17
143	72
144	80

Example	SHP2 inhibition (%)@0.1μM
145	79
146	82
148	72
149	28
150	84
151	86
153	82
154	82
156	80
157	78
158	90
159	88

Example B. Phosphatase Assays (IC50)

IC_{50} values were estimated using 6,8-difluoro-4-methylumbelliferyl phosphate (DiFMUP) as a substrate, SHP2 samples (diluted to 0.5 nM in reaction buffer) were incubated with dPEG8 peptide for 30 min in reaction buffer[60 mM 3,3-dimethyl glutarate (pH7.2), 75 mM NaCl, 75 mM KCl, and 1 mM EDTA, 0.05% Tween 20, 2mM dithiothreitol（DTT）] to active the PTP. DMSO [0.5% (v/v)] or compounds (concentrations ranging from 0.3 nM to 1 μM) were added to the mixture and incubated for 30 min at room temperature. Reactions were initiated by the addition of DiFMUP (12 μM; total reaction volume of 100 μL), and the fluorescence (excitation at 340 nm, emission at 450 nm) of the resulting solutions was measured on a 2104-0020 EnVision Xcite Multilabel Reader (PerkinElmer) after 30min. The IC_{50} results of the compounds of the invention were shown by table B.

Table B

Example	IC_{50}(nM)
1	8
2	4

Example	IC_{50}(nM)
5	6
7	22

Example	IC_{50}(nM)
10	7
19	7

Example	IC_{50}(nM)
26	11
30	3
44	4
57	16
81	8

Example	IC_{50}(nM)
84	3
85	6
86	14
87	9
88	36

Example	IC_{50}(nM)
121	56
146	12
151	7
152	3
155	3

Example C. Cell Proliferation Assay

MV-4-11 (4000 cells/well) were plated onto 96-well plates in 100μL medium (IMDM containing 3% FBS, Gibco). For drug treatment, compounds of the invention at various concentrations were added 24 hours after cell plating. At day 8, 30μL MTS/PMS reagents (Promega/Sigma) were added, and the absorbance value was determined according to the supplier's instruction (Promega). The IC_{50} results of the compounds of the invention were shown by table C.

Table C

Example	IC_{50}(nM)
2	2.7
5	4.8
10	4.0
14	6.0
30	2.2
44	7.4
45	2.5
56	10.4
64	8.1

Example	IC_{50}(nM)
68	4.9
69	4.0
71	13.0
83	16.0
89	5.0
91	12.0
92	9.0
93	11.0
94	10.9

Example	IC_{50}(nM)
95	10.0
99	18.0
100	30.0
104	9.0
105	11.0
112	30.0
137	3.3
156	46.1

Example D. p-ERK cellular assay

ERK1/2 activation is determined by immunoblotting analysis of cell lysates with an anti-p-ERK1/2 antibody. In brief, MV-4-11 cells were treated with a series of compounds (concentrations ranging from 0.3 nM to 100 nM) for 2 hours. Total protein was extracted using a RIPA buffer with Halt Protease Inhibitor Cocktail (Thermo Fisher Scientific, Rockford, IL, USA). 10 μL of total protein was resolved by SDS-PAGE under reducing conditions and transferred onto

polyvinylidene difluoride membranes (Bio-Rad). After blocking in Tris-buffered saline containing 5% BSA, the membrane was incubated overnight with primary antibodies at 4°C, followed by 1 h incubation with horseradish peroxidase (HRP)-conjugated secondary antibody. The bound secondary antibody was detected using chemiluminescence.

Example E. MV-4-11 xenograft model

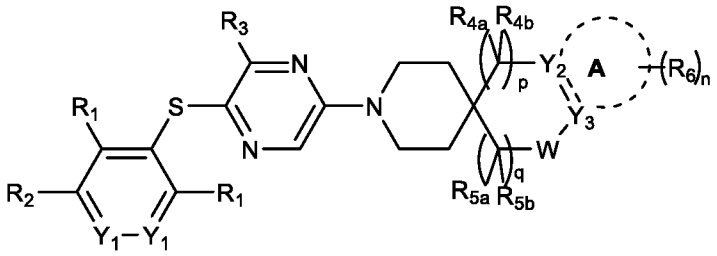
MV-4-11 cells were expanded in culture, harvested and injected subcutaneously into 5-8 week old female NOD/SCID mice (5×10^6 cells/each mouse, n=6-10/group). Subsequent administration of compound by oral gavage (0.1-10 mpk/dose) started when the mean tumor size reached approximately 100-200 mm^3. During the treatment(once or twice a day for 2-4 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.

The compounds of the present invention are preferably formulated as pharmaceutical compositions administered by a variety of routes. Most preferably, such compositions are for oral administration. Such pharmaceutical compositions and processes for preparing the same are well known in the art. See, e.g., REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro, et al, eds., 19th ed., Mack Publishing Co., 1995). The compounds of Formula I, II, III or IV are generally effective over a wide dosage range.

In summary, the most of compounds descripted here is very potent and selective, with IC50 below 10 nM. They also showed a great anti-tumor efficacy in in vivo models. For example, dosages per day normally fall within the range of about 0.2 mg to about 100 mg total daily dose, preferably 0.2 mg to 50 mg total daily dose, more preferably 0.2 mg to 20 mg total daily dose. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed. The above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of Formula I or pharmaceutically acceptable salt thereof:



I

Wherein,

Each R_1 is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy;

R_2 is -H; halogen; -NH_2; -CN; -OH; -NO_2; -N_3; carboxyl; -NHC_{1-6}alkyl; -N(C_{1-6}alkyl)$_2$; -$CONH_2$; -CONHC_{1-6}alkyl; -CON(C_{1-6}alkyl)$_2$; -COC_{1-6}alkyl; -NHCOC_{1-6}alkyl; -NC_{1-6}alkyl-CO-C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{5-10}heterocyclic; or

R_2 combines with R_1 to which is adjacent to form a 6-10 membered aryl, 5-10 membered heteroaryl or 5-10 membered heterocyclic ring, and each of the ring systems is independently optionally substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$CONH_2$, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{1-6}alkylene-COOH, -C_{1-6}alkylene-$NHCONH_2$, -CO-N(C_{1-6}alky)$_2$, -C_{1-6}alkylene-NHCO-C_{1-6}alkyl, -CO-CO-N(C_{1-6}alkyl)$_2$, -CO-C_{1-6}alkyl, -$SONH_2$, -SO_2NH_2, -$SOCH_3$, -SO_2CH_3, -C_{5-10}heterocyclic or -C_{5-10}heteroaryl;

Each Y_1 is independently N or CR_{1a};

Each R_{1a} is independently -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkoxy, or -C_{1-6}alkyl;

R_3 is -H or -NH_2;

Each of R_{4a} and R_{4b} is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form CO, C=NH, or C=N-OH;

p is 0, 1, 2 or 3;

Each of R_{5a} and R_{5b} is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-10 membered heterocyclic or 5-10 membered heteroaryl or C=NR_{5c}, and R_{5c} is -H, or -C_{1-6}alkyl; and each of the ring systems is independently optionally substituted with -H, -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkoxy, or -C_{1-3}alkyl;

q is 0, 1, 2, 3 or 4;

W is absent, -O, -S or -NR_w; and R_w is -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -CO-C_{1-6}alkyl; -CO-OC_{1-6}alkyl; -C_{1-6}alkyl-O- C_{1-6}alkoxy; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-3}alkyl substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

Ring A is absent or a 3-10 membered ring;

=== represents a single bond or a double bond;

When ring A is absent, Y_2 is $CR_{2a}R_{2b}$, NR_{2a} or O, and Y_3 is $CR_{3a}R_{3b}$, NR_{3a} or O, and R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-membered heterocyclic ring;

When ring A is a 3-10 membered ring,

i) Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N, when === represents a single bond; or

ii) Y_2 is C, and Y_3 is C, when === represents a double bond;

Each of R_{2a} and R_{2b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

Each of R_{3a} and R_{3b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

Each R_6 is independently -H, halogen, $-NR_{6a}R_{6b}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{6a}, $-C_{1-6}$alkylene-C_{3-10}heterocyclic, $-C_{1-6}$alkylene-C_{5-10}heteoaryl, $-C_{1-6}$alkylene-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-C_{1-6}alkyl, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, $-C_{3-10}$carbocyclic, $-C_{3-10}$heterocyclic, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-C_{3-10}heteocyclic, -O-C_{1-6}alkylene-CO-OR_{6a}, -O-C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -O-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -O-C_{3-10}carbocyclic, -O-C_{3-10}heterocyclic, $-NR_{6a}$-CO-C_{1-6}alkyl, $-NR_{6a}$-CO-$NR_{6a}R_{6b}$, $-NR_{6a}$-CO-C_{5-10}heteoaryl, $-NR_{6a}$-C_{1-6}alkylene-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-6}alkylene-C_{3-10}heterocyclic, $-NR_{6a}$-C_{1-6}alkylene-C_{5-10}heteroaryl, $-NR_{6a}$-SO_2C_{1-6}alkyl, -S-C_{1-6}alkyl, -SO$NR_{6a}R_{6b}$, $-SO_2NR_{6a}R_{6b}$, -SO-C_{1-6}alkyl, $-SO_2C_{1-6}$alkyl, -PO(C_{1-6}alkyl)$_2$, -PO(C_{1-6}alkoxy)$_2$, $-C_{3-10}$heterocyclic or $-C_{5-10}$heteroaryl; each of which is independently optionally substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-C_{1-3}$alkoxy, or $-C_{1-3}$alkyl; and n is 0, 1, 2, 3, 4, 5 or 6; or

Two adjacent R_6 can be joined together to form a 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, $-C_{3-6}$heterocyclic or $-C_{3-6}$carbocyclic, wherein each of the ring systems is independently optionally substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, =O, oxo, carboxyl, $-CONH_2$, -PO(C_{1-6}alkyl)$_2$, $-C_{1-6}$alkoxy or $-C_{1-6}$alkyl;

Each of R_{6a} and R_{6b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-3}$alkyl substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, -carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-3}$alkoxy substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

2. The compound or pharmaceutically acceptable salt thereof of claim 1, wherein:

Each R_1 is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; C_{1-6}alkyl; -C_{1-6}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy;

R_2 is -H; halogen; -NH_2; -CN; -OH; -NO_2; -N_3; carboxyl; -NHC_{1-6}alkyl; -N(C_{1-6}alkyl)$_2$; -$CONH_2$; -CONHC_{1-6}alkyl; -CON(C_{1-6}alkyl)$_2$; -COC_{1-6}alkyl; -NH-CO-C_{1-6}alkyl; -NC_{1-6}alkyl-CO-C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{5-10}heterocyclic; or

R_2 combines with R_1 to which is adjacent to form a 5-10 membered heteroaryl or 5-10 membered heterocyclic ring, and each of the ring systems is independently optionally substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$CONH_2$, C_{1-6}alkoxy, C_{1-6}alkyl, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{1-6}alkylene-COOH, -C_{1-6}alkylene-$NHCONH_2$, -CO-N(C_{1-6}alky)$_2$, -C_{1-6}alkylene-NHCO-C_{1-6}alkyl, -CO-CO-N(C_{1-6}alkyl)$_2$, -CO-C_{1-6}alkyl, -$SONH_2$, -SO_2NH_2, -$SOCH_3$, -SO_2CH_3, -C_{5-10}heterocyclic or -C_{5-10}heteroaryl;

Each Y_1 is independently N or CR_{1a};

Each R_{1a} is independently -H, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkoxy, or -C_{1-6}alkyl;

R_3 is -H or -NH_2;

Each of R_{4a} and R_{4b} is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form CO;

p is 0, 1, 2 or 3;

Each of R_{5a} and R_{5b} is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-10 membered heterocyclic or 5-10 membered heteroaryl; and each of the ring systems is independently optionally substituted with -H, -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkoxy, or $-C_{1-3}$alkyl;

q is 1, 2, 3 or 4;

W is absent, O, NR_w or S;

R_w is -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-CO-C_{1-6}$alkyl; $-CO-OC_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-3}$alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

Ring A is absent or a 3-10 membered ring;

=== represents a single or double bond;

When ring A is absent, Y_2 is $-CR_{2a}R_{2b}$, $-NR_{2a}$ or -O, and Y_3 is $-CR_{3a}R_{3b}$, $-NR_{3a}$ or O, and R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-membered heterocyclic ring;

When ring A is a 3-10 membered ring,

i) Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N, when === represents a single bond; or

ii) Y_2 is C, and Y_3 is C , when === represents a double bond;

Each of R_{2a} and R_{2b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

Each of R_{3a} and R_{3b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

Each R_6 is independently -H, halogen, $-NR_{6a}R_{6b}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{6a}, $-C_{1-6}$alkylene-C_{3-10}heterocyclic, $-C_{1-6}$alkylene-C_{5-10}heteoaryl, $-C_{1-6}$alkylene-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-C_{1-6}alkyl, $-CO-NR_{6a}R_{6b}$, $-CO-CO-NR_{6a}R_{6b}$, $-CO-C_{1-6}$alkyl,

-CO-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-C_{3-10}heteocyclic, -O-C_{1-6}alkylene-CO-OR_{6a}, -O-C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -O-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -O-C_{3-10}carbocyclic, -NR_{6a}-CO-C_{1-6}alkyl, -NR_{6a}-CO-$NR_{6a}R_{6b}$, -NR_{6a}-CO-C_{5-10}heteoaryl, -NR_{6a}-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -NR_{6a}-C_{1-6}alkylene-C_{3-10}heterocyclic, -NR_{6a}-C_{1-6}alkylene-C_{5-10}heteroaryl, -S-C_{1-6}alkyl, -$SONR_{6a}R_{6b}$, -$SO_2NR_{6a}R_{6b}$, -SO-C_{1-6}alkyl, -SO_2C_{1-6}alkyl, -$PO(C_{1-6}alkyl)_2$, -C_{3-10}heterocyclic or -C_{5-10}heteroaryl, wherein each of which is independently optionally substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -C_{1-3}alkoxy, or -C_{1-3}alkyl; and n is 0, 1, 2, 3, 4, 5 or 6; or

Two adjacent R_6 can be joined together to form a 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, -C_{3-6}heterocyclic or -C_{3-6}carbocyclic, wherein each of the ring system is independently optionally substituted with halogen, -NH_2, -CN, -OH, -NO_2, =O, oxo, carboxyl, -$CONH_2$, -$PO(C_{1-6}alkyl)_2$, -C_{1-6}alkoxy or -C_{1-6}alkyl;

Each of R_{6a} and R_{6b} is independently -H; halogen; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{1-3}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, -carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-3}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

3. The compound or pharmaceutically acceptable salt thereof of claims 1 or 2, wherein

each R_1 is independently -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkyl; -C_{1-6}alkoxy; -C_{1-6}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy;

R_2 is -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; -N_3; carboxyl; -C_{1-6}alkyl; -C_{1-6}alkoxy; -NHC_{1-6}alkyl; -$N(C_{1-6}alkyl)_2$; -$CONH_2$; -$CONHC_{1-6}$alkyl; -$CON(C_{1-6}alkyl)_2$; -COC_{1-6}alkyl; -$NHCOC_{1-6}$alkyl; -N(C_{1-6}alkyl)-CO-C_{1-6}alkyl; -C_{5-10}heterocyclic; -C_{1-6}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or

R_2 combines with R_1 to which is adjacent to form a 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic,

8-membered heterocyclic or 9-membered heterocyclic; and each of the heteroaryl or heterocyclic contains 1 or 2 heteroatoms selected from N or O; and each of the ring systems is independently optionally substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-CONH_2$, C_{1-3}alkoxy, C_{1-3}alkyl, -C_{1-3}alkylene-O-C_{1-3}alkyl, -C_{1-3}alkylene-COOH, -C_{1-3}alkylene-$NHCONH_2$, -CO-N(C_{1-3}alky)$_2$, -C_{1-3}alkylene-NHCO-C_{1-3}alkyl, -CO-CO-N(C_{1-3}alkyl)$_2$, -CO-C_{1-3}alkyl, $-SONH_2$, $-SO_2NH_2$, $-SOCH_3$ or $-SO_2CH_3$;

each of R_{4a} and R_{4b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; -C_{1-3}alkyl; -C_{1-3}alkoxy; -C_{1-6}alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O;

each of R_{5a} and R_{5b} is independently -H; -F; -Cl; -Br; -I; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; -C_{1-3}alkyl; -C_{1-3}alkoxy; -C_{1-6}alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic, 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl or 9-membered heteroaryl; and each of the heterocyclic or heteroaryl contains 1 or 2 heteroatoms selected from N or O; and each of the ring systems is independently optionally substituted with -H, -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, -C_{1-3}alkoxy, or -C_{1-3}alkyl;

W is absent, O, or NR_w;

or any combination thereof.

4. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-3, wherein

each R_1 is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl,

methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

R_2 is -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; $-N_3$; carboxyl; $-C_{1-3}$alkyl; $-C_{1-3}$alkoxy; $-NHC_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; $-CONH_2$; $-CONHC_{1-3}$alkyl; $-CON(C_{1-3}alkyl)_2$; $-COC_{1-3}$alkyl; $-NHCOC_{1-3}$alkyl; $-N(C_{1-3}alkyl)-CO-C_{1-3}$alkyl; $-C_{5-10}$heterocyclic; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or

R_2 combines with R_1 to which is adjacent to form a 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic or 8-membered heterocyclic; and each of the heteroaryl or heterocyclic contains 1 heteroatom selected from N or O; and each of the ring systems is independently optionally substituted with -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; oxo; =O; $-CONH_2$; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; $-CH_2OCH_3$; $-CH_2COOH$; $-CH_2NHCONH_2$; $-CON(CH_3)_2$; $-CH_2NHCOCH_3$; $-CO-CON(CH_3)_2$; $-COCH_3$; $-C_{1-3}$alkyl substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$ or carboxyl; or $-C_{1-3}$alkoxy substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$ or carboxyl;

each of R_{4a} or R_{4b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; C_{1-3}alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O;

each of R_{5a} or R_{5b} is independently -H, $-NH_2$, -OH, methyl, ethyl, methoxy or ethoxy; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic,

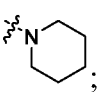
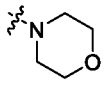
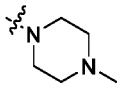
6-membered heterocyclic, 5-membered heteroaryl or 6-membered heteroaryl; and each of the heterocyclic or heteroaryl contains 1 heteroatoms selected from N or O;

W is NR_w, and R_w is -H, -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-CO-C_{1-3}$alkyl, $-COOC_{1-3}$alkyl, C_{1-3}alkoxy, or C_{1-3}alkyl; $-C_{1-3}$alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

or any combination thereof.

5. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-4, wherein

each R_1 is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; or methyl substituted with one or more substituents each independently selected from -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

R_2 is -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; $-N_3$; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; $-NHCH_3$; $-N(CH_3)_2$; $-CONH_2$; $-CONHCH_3$; $-CON(CH_3)_2$; $-COCH_3$; $-NH-COCH_3$; $-N(CH_3)-COCH_3$;  ;  ;  ;  ; $-C_{1-3}$alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or

R_2 combines with R_1 to which is adjacent to form a 5-membered heterocyclic, and optionally substituted with -F or $-COCH_3$;

each of R_{4a} and R_{4b} is independently -H, $-NH_2$, -OH, methyl, ethyl, methoxy, ethoxy; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O

each of R_{5a} or R_{5b} is independently -H or $-NH_2$;

W is NR_w, and R_w is -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkyl substituted with -F,

-Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or C_{1-3}alkoxy substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

or any combination thereof.

6. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-5, wherein

ring A is 6-membered aryl, 7-membered aryl, 8-membered aryl, 9-membered aryl, 10-membered aryl; 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl, 10-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic, 10-membered heterocyclic; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 7-membered carbocyclic, 8-membered carbocyclic, 9-membered carbocyclic or 10-membered carbocyclic; and each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic contains 1, 2 or 3 heteroatoms selected from N or O;

Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N;

each R_6 is independently -H, -F, -Cl, -Br, -I, -$NR_{6a}R_{6b}$, -CN, -OH, oxo, =O, carboxyl, -C_{1-6}alkoxy, -C_{1-6}alkyl, -C_{1-6}alkylene-$NR_{6a}R_{6b}$, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{1-6}alkylene-CO-OR_{6a}, -C_{1-6}alkylene-C_{5-10}heterocyclic, -C_{1-6}alkylene-C_{5-10}heteoaryl, -C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -C_{1-6}alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, -C_{1-6}alkylene-NR_{6a}-CO-C_{1-6}alkyl, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -CO-NR_{6a}-C_{5-10}heterocyclic, -CO-NR_{6a}-C_{5-10}heterocyclic, -CO-C_{5-10}heterocyclic, -O-C_{1-6}alkylene-CO-OR_{6a}, -O-C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -O-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -O-C_{5-10}carbocyclic, -NR_{6a}-CO-C_{1-6}alkyl, -NR_{6a}-CO-$NR_{6a}R_{6b}$, -NR_{6a}-CO-C_{5-10}heteoaryl, -NR_{6a}-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -NR_{6a}-C_{1-6}alkylene-C_{3-10}heterocyclic, -NR_{6a}-C_{1-6}alkylene-C_{5-10}heteroaryl, -S-C_{1-6}alkyl, -$SO_2NR_{6a}R_{6b}$, -SO_2C_{1-6}alkyl, -$PO(CH_3)_2$, -C_{5-10}heterocyclic or -C_{5-10}heteroaryl, wherein each of which is independently optionally substituted -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -C_{1-3}alkoxy, or -C_{1-3}alkyl; or

Two adjacent R_6 can be joined together to form a 6-membered aryl; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic; 5-membered heteroaryl, 6-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic or 6-membered heterocyclic; and wherein each of heteroaryl or heterocyclic contains 1, 2, 3 or 4 heteroatoms selected from N, O or S; and each of the ring system is independently optionally substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, =O, oxo, carboxyl, $-CONH_2$, $-PO(C_{1-6}alkyl)_2$, $-C_{1-6}alkoxy$ or $-C_{1-6}alkyl$;

or any combination thereof.

7. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-6, wherein

ring A is 6-membered aryl, 7-membered aryl, 8-membered aryl; 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 7-membered carbocyclic or 8-membered carbocyclic; and each of the heteroaryl contains 1 or 2 heteroatoms selected from N, O or S; each of the heterocyclic contains 1 or 2 heteroatoms selected from N or O;

Y_2 is CR_{2a} and Y_3 is CR_{3a};

each R_6 is independently -H, -F, -Cl, -Br, $-NR_{6a}R_{6b}$, -CN, -OH, oxo, =O, carboxyl, $-C_{1-6}alkoxy$, $-C_{1-6}alkyl$, $-C_{1-6}alkylene-NR_{6a}R_{6b}$, $-C_{1-6}alkylene-O-C_{1-6}alkyl$, $-C_{1-6}alkylene-CO-OR_{6a}$, $-C_{1-6}alkylene-C_{5-10}heterocyclic$, $-C_{1-6}alkylene-C_{5-10}heteoaryl$, $-C_{1-6}alkylene-CO-NR_{6a}R_{6b}$, $-C_{1-6}alkylene-NR_{6a}-CO-NR_{6a}R_{6b}$, $-CO-NR_{6a}R_{6b}$, $-CO-CO-NR_{6a}R_{6b}$, $-CO-C_{1-6}alkyl$, $-CO-NR_{6a}-C_{5-10}heterocyclic$, $-CO-C_{5-10}heterocyclic$, $-O-C_{5-10}carbocyclic$, $-NR_{6a}-CO-C_{1-6}alkyl$, $-NR_{6a}-CO-NR_{6a}R_{6b}$, $-NR_{6a}-C_{1-6}alkylene-NR_{6a}R_{6b}$, $-NR_{6a}-C_{1-6}alkylene-C_{3-10}heterocyclic$, $-S-C_{1-6}alkyl$, $-SO_2NR_{6a}R_{6b}$, $-SO_2C_{1-6}alkyl$, $-C_{5-10}heterocyclic$ or $-C_{5-10}heteroaryl$, wherein each of which is independently optionally substituted -F, -Cl, Br, $-NH_2$, -OH, carboxyl, oxo, =O, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or

Two adjacent R_6 can be joined together to form a 6-membered aryl; 5-membered carbocyclic, 5-membered heteroaryl or 5-membered heterocyclic; and wherein each of

heteroaryl or heterocyclic contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring system is independently optionally substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, =O, oxo, carboxyl, $-CONH_2$, $-PO(CH_3)_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

or any combination thereof.

8. The compound or pharmaceutically acceptable salt thereof of claim 6 or 7, wherein each R_6 is independently -H, -F, -Cl, -Br, $-NR_{6a}R_{6b}$, -CN, -OH, oxo, =O, carboxyl, $-C_{1-3}$alkoxy, $-C_{1-3}$alkyl, $-C_{1-3}$alkylene-$NR_{6a}R_{6b}$, $-C_{1-3}$alkylene-O-C_{1-3}alkyl, $-C_{1-3}$alkylene-CO-OR_{6a}, $-C_{1-3}$alkylene-C_{5-6}heterocyclic, $-C_{1-3}$alkylene-C_{5-6}heteoaryl, $-C_{1-3}$alkylene-CO-$NR_{6a}R_{6b}$, $-C_{1-3}$alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -CO-C_{1-3}alkyl, -CO-NR_{6a}-C_{5-6}heterocyclic, -CO-C_{5-6}heterocyclic, -O-C_{5-6}carbocyclic, $-NR_{6a}$-CO-C_{1-6}alkyl, $-NR_{6a}$-CO-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-3}alkylene-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-6}alkylene-C_{3-6}heterocyclic, -S-C_{1-3}alkyl, $-SO_2NR_{6a}R_{6b}$, $-SO_2C_{1-3}$alkyl, $-C_{5-6}$heterocyclic or $-C_{5-6}$heteroaryl, wherein each of which is independently optionally substituted with one or more substituents each independently selected from -F, -Cl, Br, $-NH_2$, -OH, carboxyl, oxo, =O, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or

Two adjacent R_6 can be joined together to form a 6-membered aryl; 5-membered carbocyclic, 5-membered heteroaryl or 5-membered heterocyclic; and wherein each of heteroaryl or heterocyclic contains 1, or 2 heteroatoms selected from N, O or S; and each of the ring system is independently optionally substituted with one or more substituents each independently selected from -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, =O, oxo, carboxyl, $-CONH_2$, $-PO(CH_3)_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

9. The compound or pharmaceutically acceptable salt thereof of claims 1-8, wherein

each of R_{2a} and R_{2b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or $-C_{1-3}$alkoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy;

each of R_{3a} and R_{3b} is independently -H, -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl, -C_{1-3}alkoxy, or -C_{1-6}alkyl or -C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; and/or

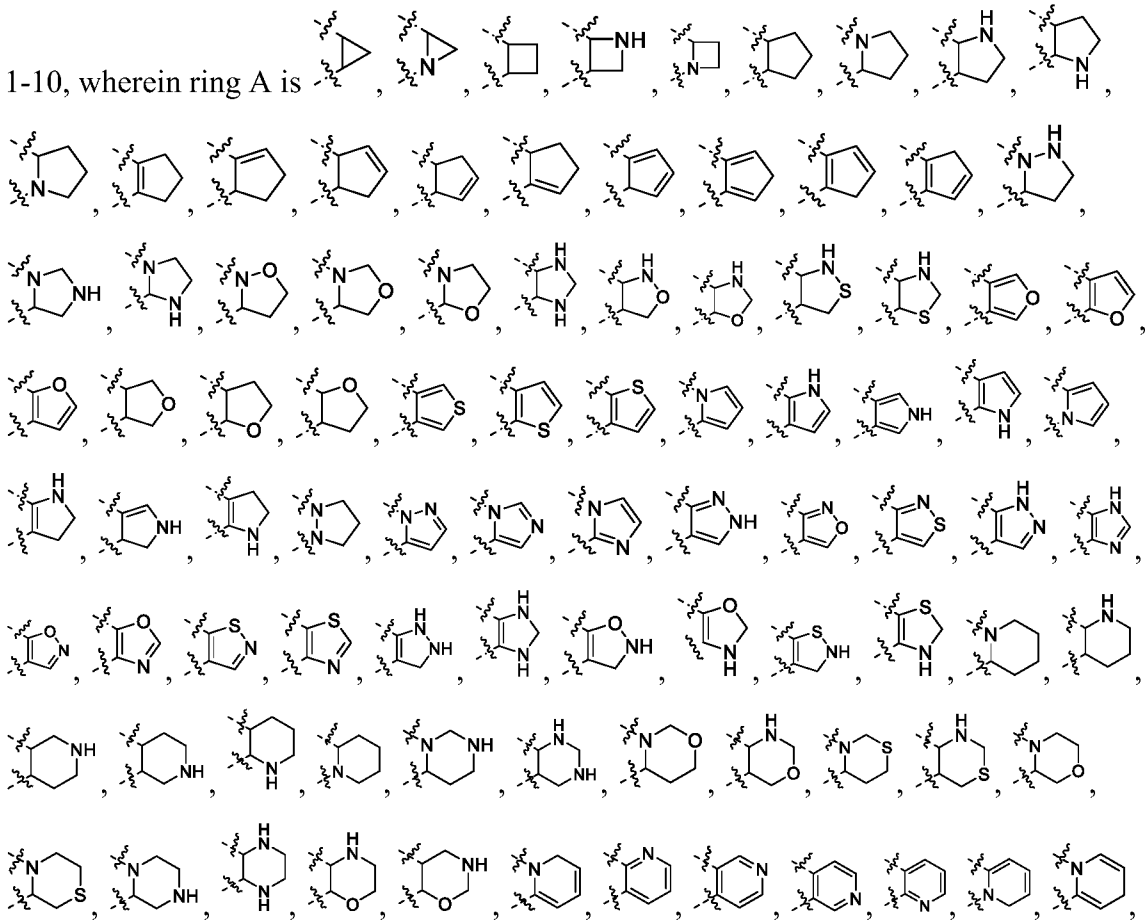
each of R_{6a} and R_{6b} is independently -H; -F; -Cl; -Br; -NH_2; -CN; -OH; carboxyl; methyl; ethyl; isopropyl; methoxy; methyl substituted with -F, -Cl, -NH_2, -OH, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; ethyl substituted with -F, -Cl, -NH_2, -OH, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or propyl substituted with -F, -Cl, -NH_2, -OH, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

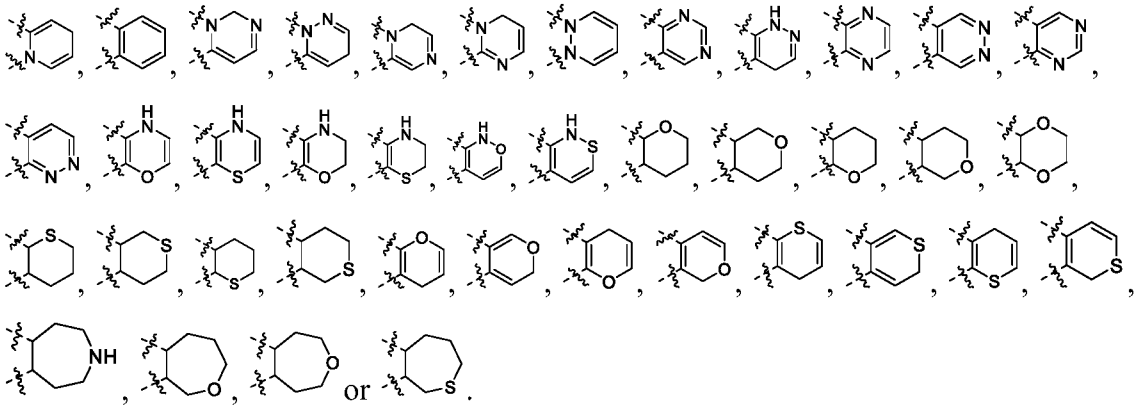
10. The compound or pharmaceutically acceptable salt thereof of claim 9, wherein

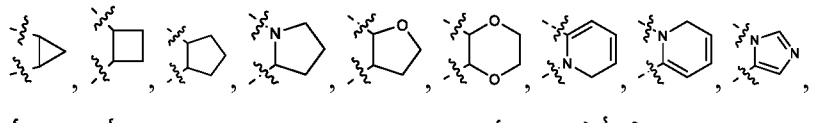
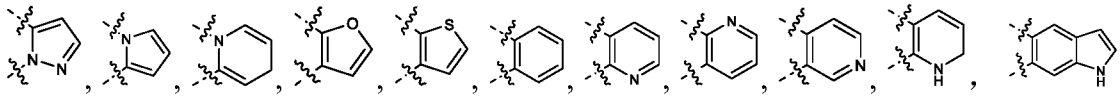
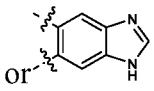
each of R_{2a} and R_{2b} is independently -H or methyl;

each of R_{3a} and R_{3b} is independently –H; and/or

each of R_{6a} and R_{6b} is independently -H, -CH_3, -OH, or -CH_2CH_2OH.

11. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-10, wherein ring A is 



12. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-11, wherein ring A is 


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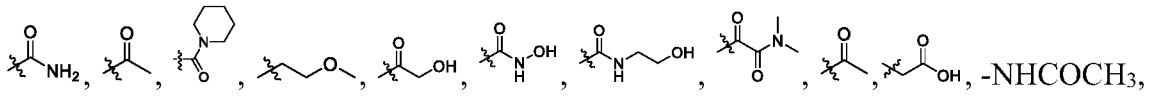
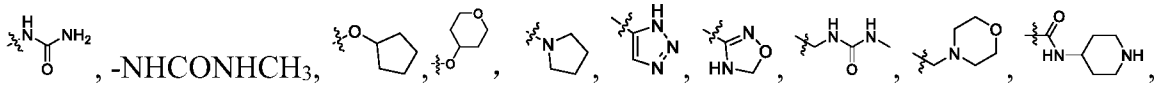
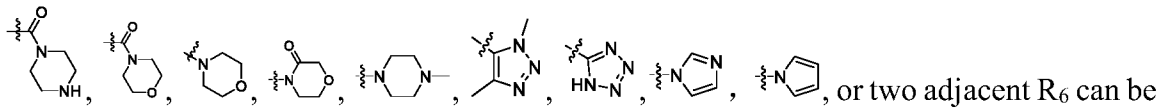
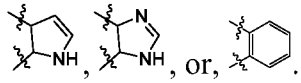
13. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-12, wherein each R_6 is independently -F, -Cl, -Br, =O, oxo, -OH, -CN, $-NH_2$,  , $-CH_3$, ethyl, isopropyl,  , $-CF_3$, $-OCF_3$,  , $-OCH_3$, ethoxy, $-SCH_3$, $-SOCH_3$, $-SO_2CH_3$, $-PO(CH_3)_2$, $-PO(OC_2H_5)_2$, $-NHSO_2CH_3$, $-C(O)NH_2$, $-SO_2NH_2$, $-CH_2NH_2$, 

, $-NHCOCH_3$,

, $-NHCONHCH_3$,

, or two adjacent R_6 can be joined together to form 
, or,
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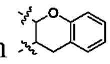
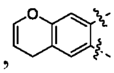
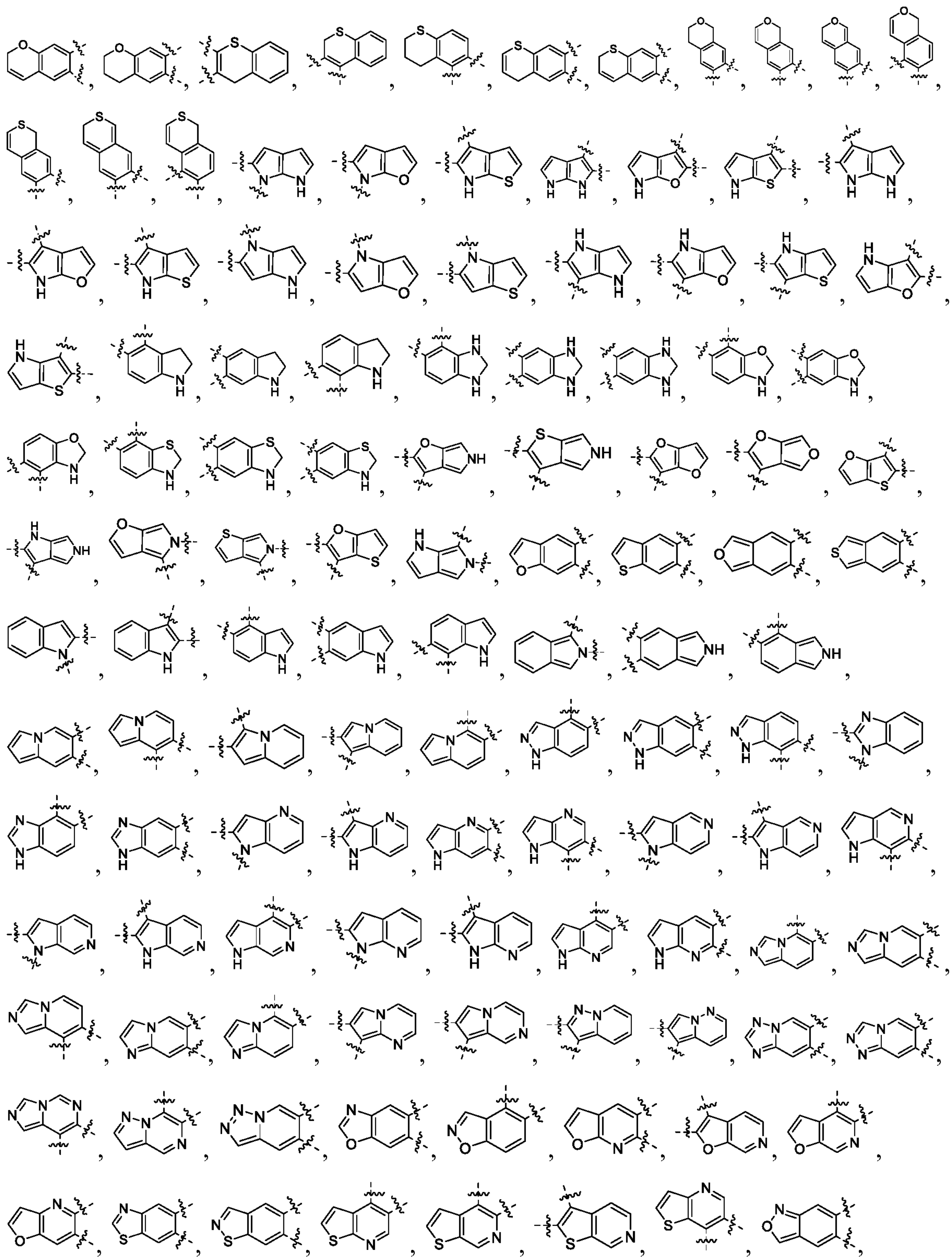
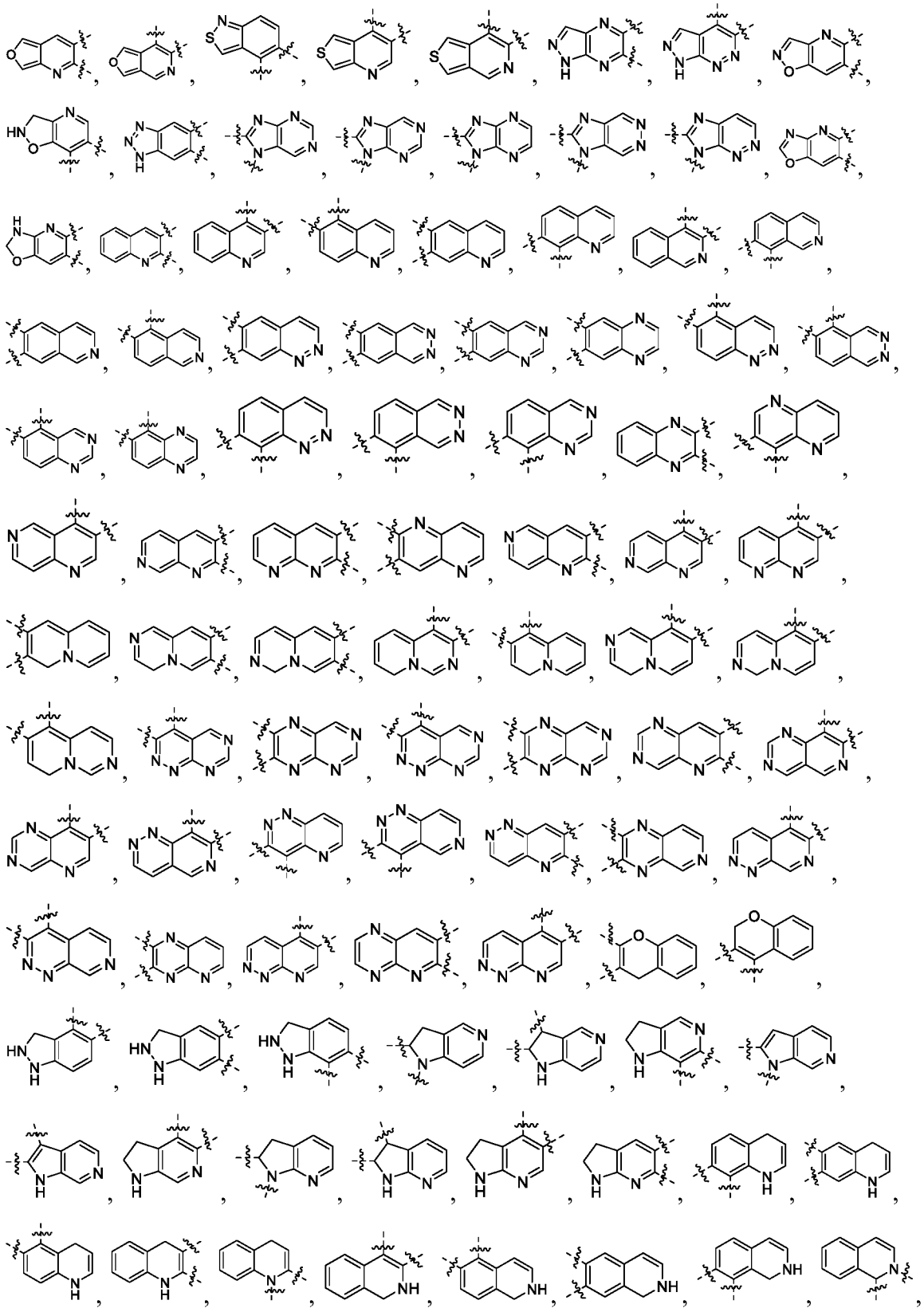
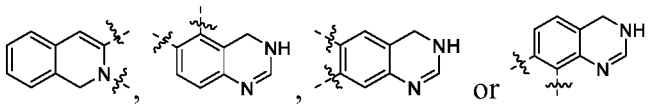
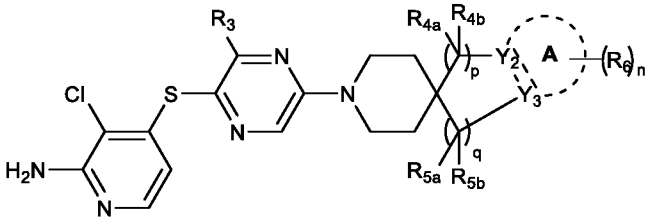
14. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-13, wherein ring A and the two adjacent R_6 taken together to form  ,  ,






, wherein each of the ring A is independently optionally substituted with another one or more R_6.

15. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-14, wherein the compound is of Formula II:



II

Wherein,

R_3 is -H or $-NH_2$;

Each of R_{4a} or R_{4b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O, C=NH, or C=N-OH;

p is 0, 1, 2 or 3;

Each of R_{5a} or R_{5b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-10 membered heterocyclic or 5-10 membered heteroaryl; and each of the ring systems is independently optionally substituted with -H, -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkoxy, or $-C_{1-3}$alkyl;

q is 0,1, 2, 3 or 4;

Ring A is absent or a 3-10 membered ring;

=== represents a single or double bond;

When ring A is absent, Y_2 is $CR_{2a}R_{2b}$, NR_{2a} or O, and Y_3 is $CR_{3a}R_{3b}$, NR_{3a} or O, and R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-membered heterocyclic ring;

When ring A is a 3-10 membered ring, wherein,

i) Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N, when ≡ represents a single bond; or

ii) Y_2 is C, and Y_3 is C, when ≡ represents a double bond;

Each of R_{2a} and R_{2b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

Each of R_{3a} and R_{3b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

Each R_6 is independently -H, halogen, $-NR_{6a}R_{6b}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{1-6}$alkylene-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{6a}, $-C_{1-6}$alkylene-C_{3-10}heterocyclic, $-C_{1-6}$alkylene-C_{5-10}heteoaryl, $-C_{1-6}$alkylene-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-$NR_{6a}R_{6b}$, $-C_{1-6}$alkylene-NR_{6a}-CO-C_{1-6}alkyl, -CO-$NR_{6a}R_{6b}$, -CO-CO-$NR_{6a}R_{6b}$, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -CO-NR_{6a}-C_{3-10}heterocyclic, -CO-C_{3-10}heteocyclic, -O-C_{1-6}alkylene-CO-OR_{6a}, -O-C_{1-6}alkylene-CO-$NR_{6a}R_{6b}$, -O-C_{1-6}alkylene-$NR_{6a}R_{6b}$, -O-C_{3-10}carbocyclic, $-NR_{6a}$-CO-C_{1-6}alkyl, $-NR_{6a}$-CO-$NR_{6a}R_{6b}$, $-NR_{6a}$-CO-C_{5-10}heteoaryl, $-NR_{6a}$-C_{1-6}alkylene-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-6}alkylene-C_{3-10}heterocyclic, $-NR_{6a}$-C_{1-6}alkylene-C_{5-10}heteroaryl, -S-C_{1-6}alkyl, -SO$NR_{6a}R_{6b}$, $-SO_2NR_{6a}R_{6b}$, -SO-C_{1-6}alkyl, $-SO_2$-C_{1-6}alkyl, $-PO(C_{1-6}alkyl)_2$, $-C_{3-10}$heterocyclic or $-C_{5-10}$heteroaryl, wherein each of which is independently optionally substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-C_{1-3}$alkoxy, or $-C_{1-3}$alkyl; and n is 0, 1, 2 or 3; or

Two adjacent R_6 can be joined together to form a 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, $-C_{3-6}$heterocyclic or $-C_{3-6}$carbocyclic, wherein each of the ring system is independently optionally substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, =O, oxo, carboxyl, $-CONH_2$, $-PO(C_{1-6}alkyl)_2$, $-C_{1-6}$alkoxy or $-C_{1-6}$alkyl;

Each of R_{6a} and R_{6b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-3}$alkyl substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, -carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-3}$alkoxy substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

16. The compound or pharmaceutically acceptable salt thereof of claim 15, wherein

each of R_{4a} or R_{4b} is independently -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or C_{1-6}alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O;

each of R_{5a} and R_{5b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; carboxyl; $-C_{1-3}$alkyl;- C_{1-3}alkoxy; $-C_{1-3}$alkyl substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-3}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form a 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic or 6-membered heterocyclic; and each of the heterocyclic contains 1 or 2 heteroatoms selected from N or O; and each of the ring system is independently optionally substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl, or $-C_{1-6}$alkoxy;

or any combination thereof.

17. The compound or pharmaceutically acceptable salt thereof of claims 15 or 16, wherein

each of R_{4a} or R_{4b} is independently -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; carboxyl; methyl; ethyl; methoxy; ethoxy; methyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, methoxy or ethoxy; ethyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, methoxy or ethoxy; methoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, methoxy or ethoxy; or ethoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, methoxy or ethoxy; or

R_{4a} and R_{4b} together with the carbon atom to which they are both attached form C=O;

each of R_{5a} or R_{5b} is independently -H; -Cl; -Br; $-NH_2$; -OH; carboxyl; methyl; ethyl; methoxy; ethoxy; methyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl or methoxy; ethyl substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl or methoxy; methoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl or methoxy; or ethoxy substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl or methoxy; or

R_{5a} and R_{5b} together with the carbon atom to which they are both attached form  , and *C represents the carbon atom which R_{5a} and R_{5b} attached;

or any combination thereof.

18. The compound or pharmaceutically acceptable salt thereof of any one of claims 15-17, wherein

ring A is 6-membered aryl, 7-membered aryl, 8-membered aryl, 9-membered aryl; 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 7-membered carbocyclic, 8-membered carbocyclic or 9-membered carbocyclic; and each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic contains 1, 2 or 3 heteroatoms selected from N or O;

Y_2 is CR_{2a} or N, Y_3 is CR_{3a} or N;

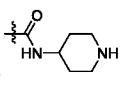
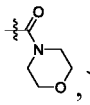
each R_6 is independently -H, -F, -Cl, -Br, $-NH_2$, $-N(CH_3)_2$, -CN, -OH, oxo, =O, carboxyl, $-C_{1-3}$alkoxy, $-C_{1-3}$alkyl, $-CH_2NH_2$, $-C_{1-3}$alkylene-OCH_3, $-CH_2$-COOH, $-CH_2$-COO-C_{1-3}alkyl, $-CH_2$-C_{5-10}heterocyclic, $-C_{1-3}$alkylene-CO-$NR_{6a}R_{6b}$, $-CH_2NH$-CO-$NR_{6a}R_{6b}$, -CO-$NR_{6a}R_{6b}$, -COCO-$NR_{6a}R_{6b}$, -CO-C_{1-3}alkyl, -CONH-C_{5-10}heteocyclic, -CO-5-membered heteocyclic, -CO-6-membered heteocyclic, -O-5-membered carbocyclic, -O-6-membered carbocyclic, -NH-CO-C_{1-3}alkyl, $-NR_{6a}$-CO-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-3}alkylene-$NR_{6a}R_{6b}$, $-NR_{6a}$-C_{1-3}alkylene-C_{5-10}heterocyclic, -S-C_{1-3}alkyl, $-SO_2NH_2$, $-SO_2CH_3$, 5-membered heterocyclic, 6-membered heterocyclic, 5-membered heteroaryl, or 6-membered heteroaryl, wherein each of which is

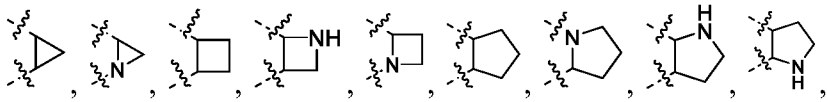
independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, oxo, =O, -C_{1-3}alkoxy, or -C_{1-3}alkyl; or

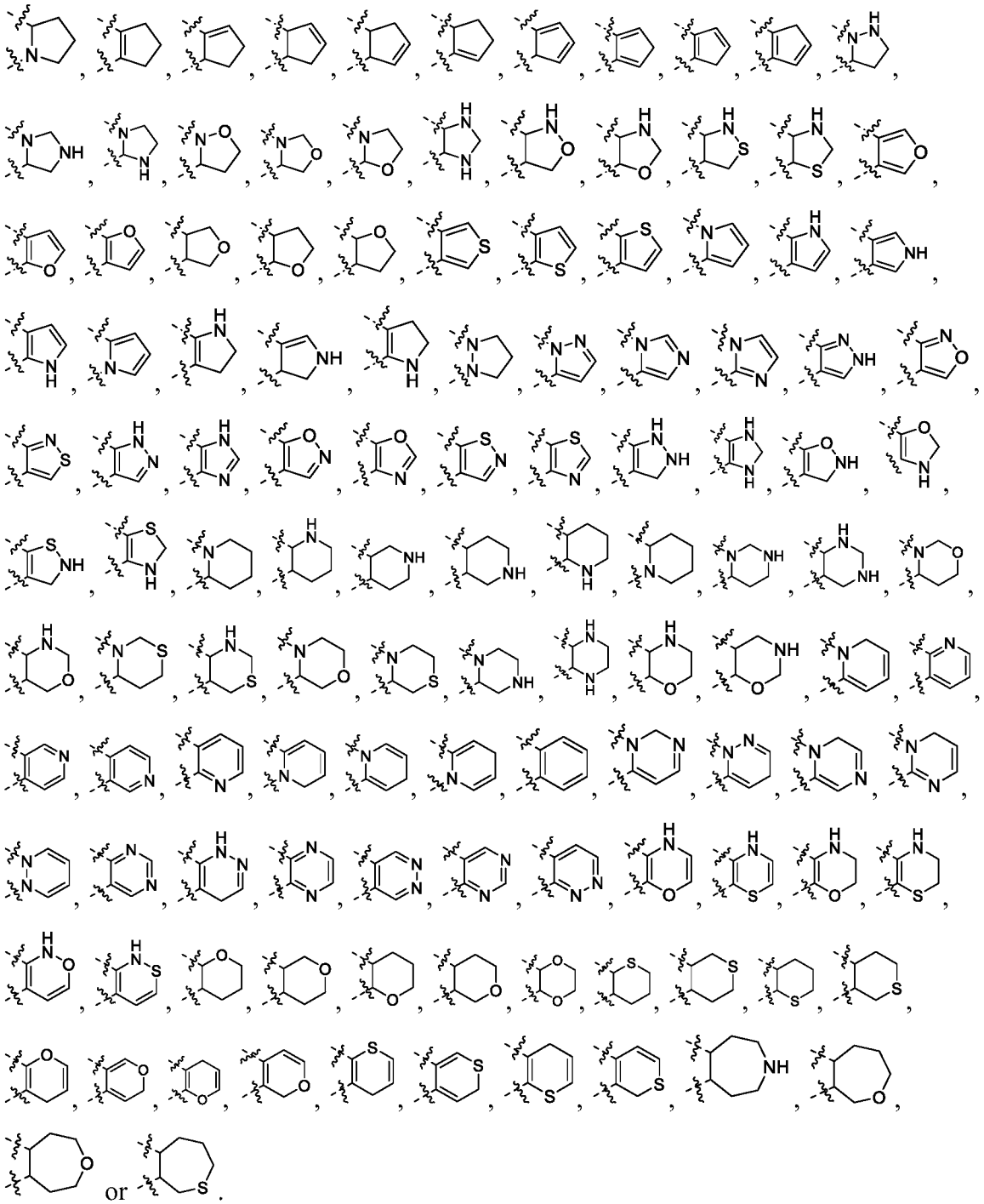
Two adjacent R_6 can be joined together to form a 6-membered aryl; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 5-membered heteroaryl, 3-membered heterocyclic, 4-membered heterocyclic or 5-membered heterocyclic; and wherein each of heteroaryl or heterocyclic contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring system is independently optionally substituted with -F, -Cl, -Br, -I, -NH_2, -CN, -OH, -NO_2, =O, oxo, carboxyl, -$CONH_2$, -$PO(C_{1-3}alkyl)_2$, -C_{1-3}alkoxy, or -C_{1-3}alkyl;

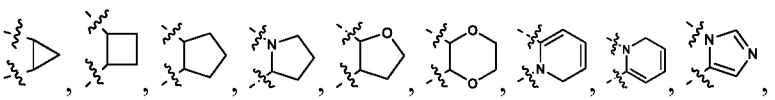
or any combination thereof.

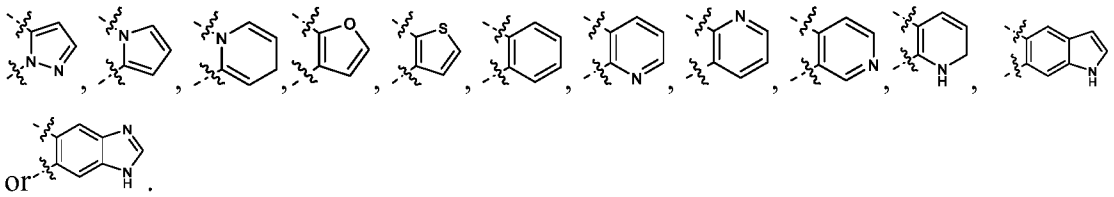
19. The compound or pharmaceutically acceptable salt thereof of any one of claims 15-18, wherein ring A is 6-membered aryl, 7-membered aryl, 8-membered aryl; 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl; 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic; 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 7-membered carbocyclic or 8-membered carbocyclic; and each of the heteroaryl contains 1 or 2 heteroatoms selected from N, O or S; each of the heterocyclic contains 1 or 2 heteroatoms selected from N or O; and/or

each R_6 is independently -F, -Cl, -Br, -NH_2, -$N(CH_3)_2$, -CN, -OH, oxo, =O, carboxyl, methoxy, ethoxy, methyl, ethyl, isopropyl, -CH_2NH_2, -$CH_2CH_2OCH_3$, -CH_2-COOH, -CH_2NH-$CONHCH_3$, -$CONH_2$, -$CON(CH_3)_2$, -CONHOH, -$CONHCH_2CH_2OH$, -CO-$CON(CH_3)_2$, -$COCH_3$, -SO_2NH_2, -SO_2CH_3, -SCH_3, -NH-$COCH_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  , wherein each of which is independently optionally substituted with -F, -NH_2, -OH, oxo, =O, or -C_{1-3}alkyl.

20. The compound or pharmaceutically acceptable salt thereof of any one of claims 15-19, wherein ring A is  ,



21. The compound or pharmaceutically acceptable salt thereof of any one of claims 15-20, wherein ring A is  ,



22. The compound or pharmaceutically acceptable salt thereof of any one of claims 15-19, wherein

each of R_{2a}, R_{2b}, R_{3a} and R_{3b} is independently -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methyl; ethyl; propyl; isopropyl; methoxy; ethoxy; propoxy; isopropoxy; -$C_{1\text{-}3}$alkyl substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; or -$C_{1\text{-}3}$alkoxy substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; and/or

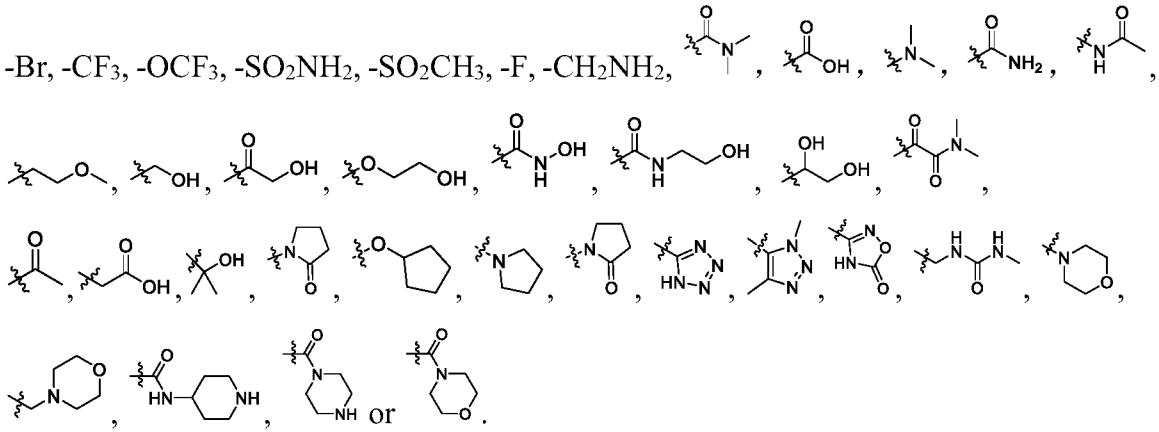
each of R_{6a} and R_{6b} is independently -H, -Cl, -Br, -NH_2, -OH, carboxyl, methyl, ethyl, methoxy, ethoxy propoxy, isopropoxy, methyl substituted with -OH, or ethyl substituted with -OH..

23. The compound or pharmaceutically acceptable salt thereof of any one of claims 15-19, and 22, wherein

each of R_{2a}, R_{2b}, R_{3a} and R_{3b} is independently -H or methyl; and/or

each of R_{6a} and R_{6b} is independently -H, -CH_3, -OH, or -CH_2CH_2OH.

24. The compound or pharmaceutically acceptable salt thereof of any one of claims 15-23, wherein each R_6 is independently methyl, methoxy, =O, oxo, -OH, -CN, -NH_2, -Cl, -Br, -CF_3, -OCF_3, -SO_2NH_2, -SO_2CH_3, -F, -CH_2NH_2,



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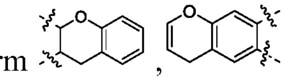
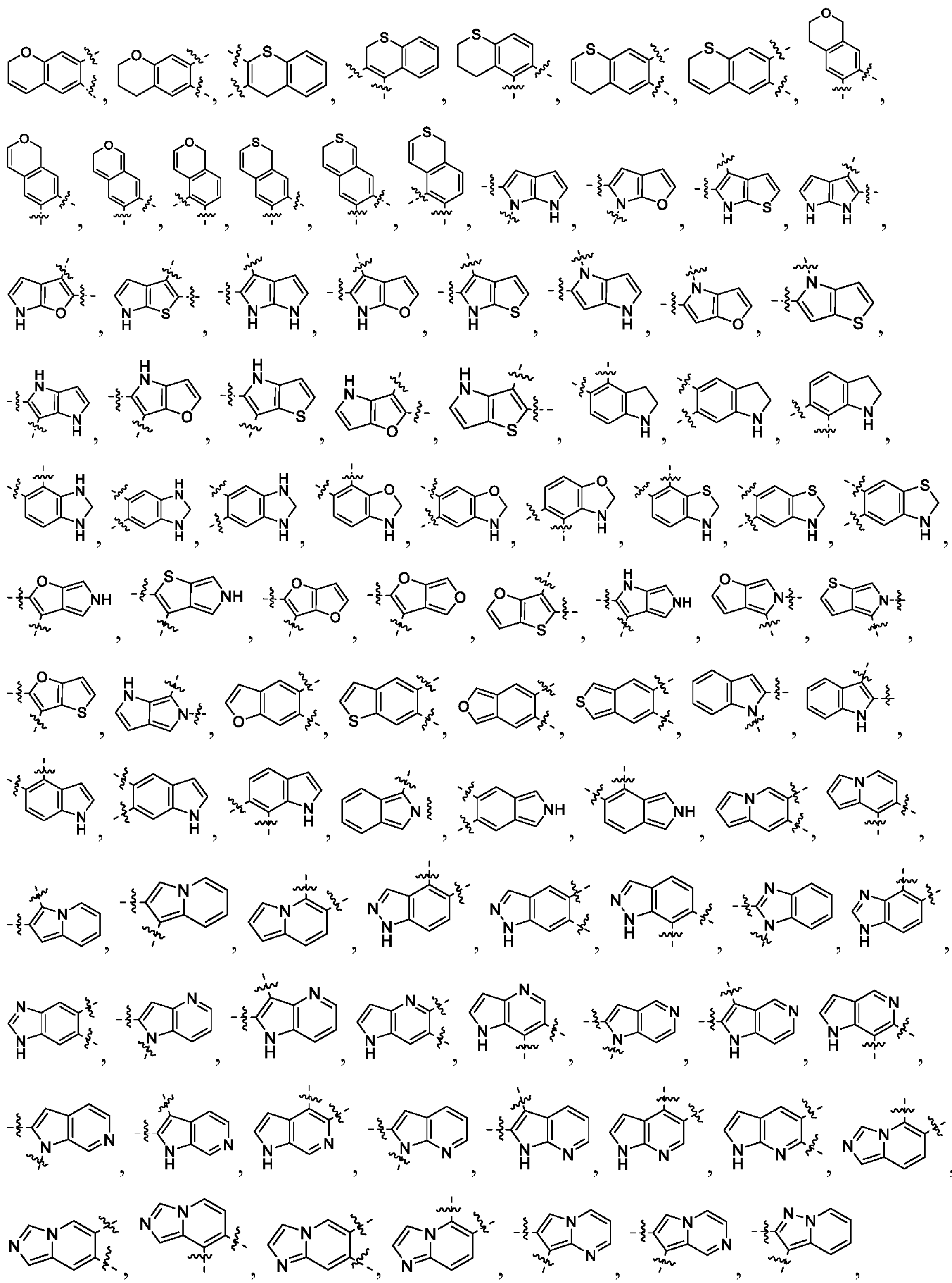
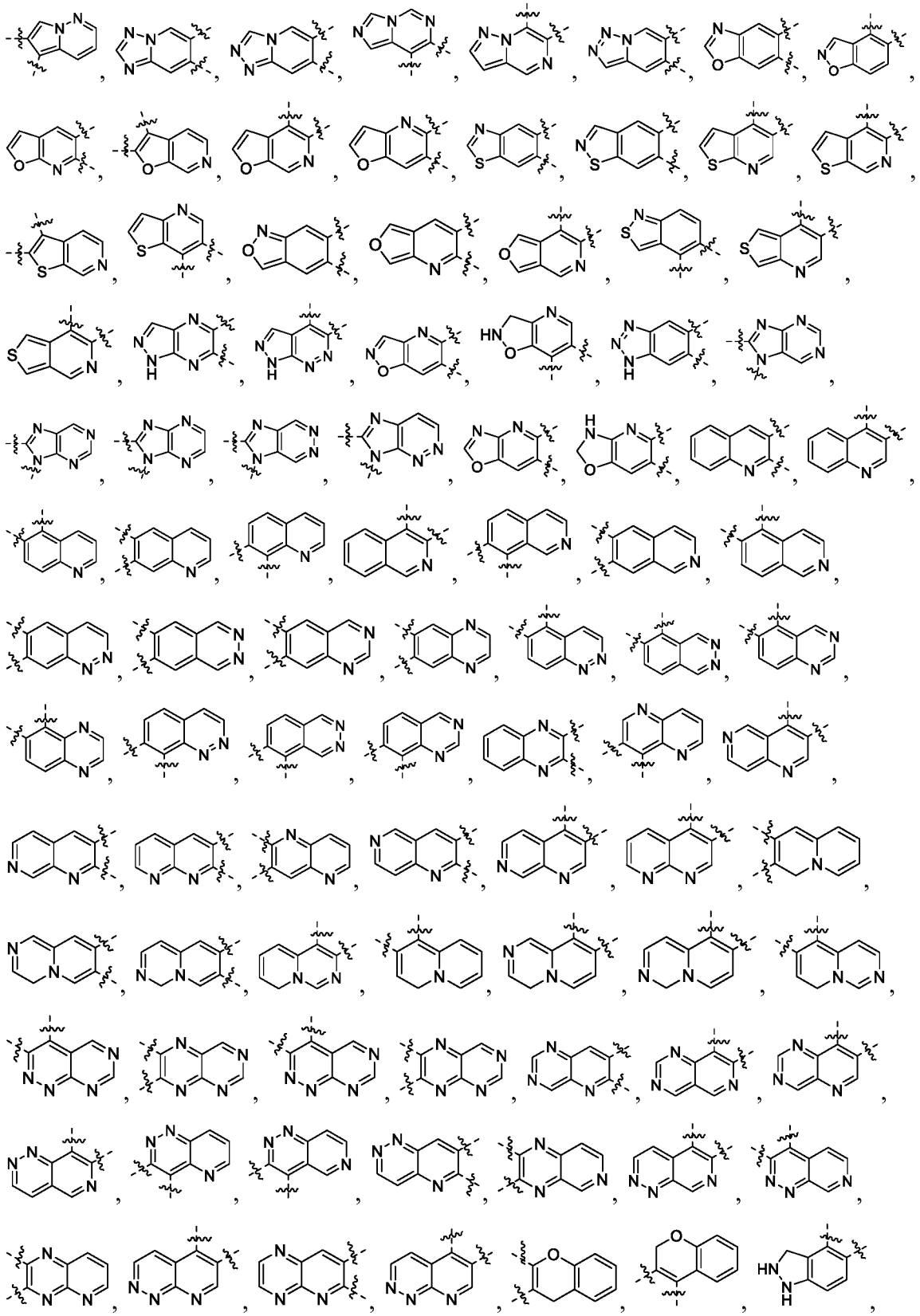
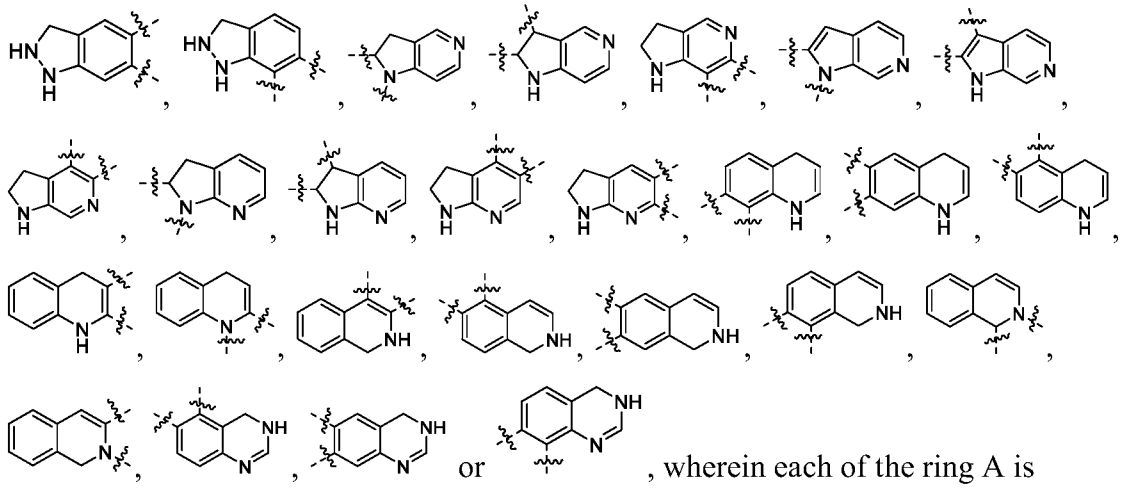
25. The compound or pharmaceutically acceptable salt thereof of any one of claims 15-24, wherein ring A and two adjacent R_6 taken together to form  ,







or , wherein each of the ring A is independently optionally substituted with one or more R_6.

26. The compound or pharmaceutically acceptable salt thereof of any one of claims 15-25, wherein

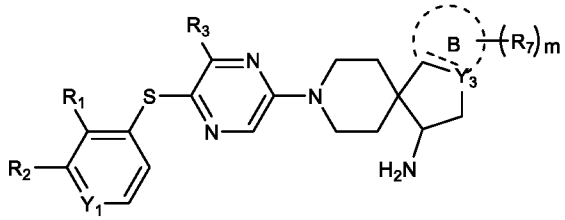
p is 0, 1, or 2;

Y_2 is C, and Y_3 is C;

n is 0, 1, or 2;

or any combination thereof.

27. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-14, wherein the compound is of Formula III:



III

wherein,

R_1 is -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-6}$alkoxy substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

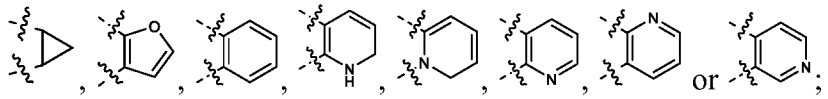
R_2 is -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or

-C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or

R_1 combines with R_2 to which is adjacent to form a 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic or 10-membered heterocyclic; and each of the heterocyclic contains 1 or 2 heteroatoms selected from N or O; and each of the ring systems is independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, oxo, =O, C_{1-3}alkoxy, C_{1-3}alkyl, or -CO-C_{1-3}alkyl;

Y_1 is N or CH;

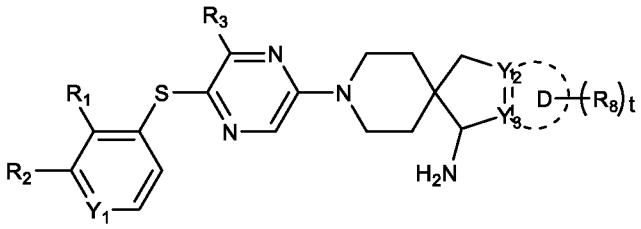
R_3 is -H or -NH_2;

Ring B is  ;

Y_3 is CH, N or C;

R_7 is -NH_2, -CN, oxo, =O, -$CONH_2$, -NH-$COCH_3$, methyl or methoxy; and m is 0 or 1.

28. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-14, wherein the compound is of Formula IV:



IV

wherein,

R_1 is -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; -C_{1-6}alkoxy; - C_{1-6}alkyl; -C_{1-6}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy;

R_2 is -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; -NHC_{1-6}alkyl; -N(C_{1-6}alkyl)$_2$; -C_{1-6}alkoxy; -C_{1-6}alkyl; -C_{1-6}alkyl substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or -C_{1-6}alkoxy substituted with halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy; or

R_1 combines with R_2 to which is adjacent to form a 5-10 membered heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-CONH_2$, C_{1-6}alkoxy, C_{1-6}alkyl, or $-CO-C_{1-6}$alkyl;

Y_1 is N or CH;

R_3 is -H or $-NH_2$;

Ring D is a 6-membered aryl, 5- membered heteroaryl, 6-membered heteroaryl, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 6-membered carbocyclic, 3-membered heterocyclic, 4-membered heterocyclic, 5-membered heterocyclic, or 6-membered heterocyclic; and each of the heteroaryl or heterocyclic contains 1, 2 or 3 heteroatoms selected from N, O or S;

=== represents a single or double bond; and

i) Y_2 is CR_{2a} or N, and Y_3 is CR_{3a} or N, when === represents a single bond; or

ii) Y_2 is C, and Y_3 is C, when === represents a double bond;

Each of R_{2a} and R_{3a} is -H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy substituted with -F, -Cl, -Br, -I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy;

R_8 is halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, oxo, =O, $-SO_2NR_{8a}R_{8b}$, $-S-C_{1-6}$alkyl, $-SO-C_{1-6}$alkyl, $-SO_2-C_{1-6}$alkyl, $-CO-NR_{8a}R_{8b}$, $-PO(C_{1-6}alkyl)_2$, $-PO(C_{1-6}alkoxy)_2$, $-NR_{8a}-CO-C_{1-6}$alkyl, $-NR_{8a}-CO-NR_{8a}R_{8b}$, $-O-C_{5-10}$carbocyclic, $-O-C_{5-10}$heterocyclic, $-C_{5-10}$heterocyclic or $-C_{5-10}$heteroaryl, $-C_{5-10}$aryl, $-C_{1-6}$alkoxy, or $-C_{1-6}$alkyl; and each of which is independently optionally substituted with -F, -Cl, -Br, $-NH_2$, -CN, -OH, oxo, =O, $-C_{1-3}$alkoxy, or $-C_{1-3}$alkyl; and t is 0, 1, 2 or 3;

Each of R_{8a} and R_{8b} is independently H; halogen; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-6}$alkoxy; $-C_{1-6}$alkyl; $-C_{1-3}$alkyl substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, -carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy; or $-C_{1-3}$alkoxy substituted with halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

29. The compound or pharmaceutically acceptable salt thereof of claim 28, wherein

R_1 is -H; -F; -Cl; -Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-C_{1-3}$alkoxy; $-C_{1-3}$alkyl; or methyl substituted with one or more substituents selected from halogen;

R_2 is -H, -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -NHC_{1-3}alkyl, -$N(C_{1-3}alkyl)_2$, -C_{1-3}alkoxy, -C_{1-3}alkyl; or

R_1 combines with R_2 to which is adjacent to form a 5-,6-, or 7-membered heterocyclic ring contains 1, or 2 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$CONH_2$, methoxy, ethoxy, methyl, ethyl, -CO-methyl, or -CO-ethyl;

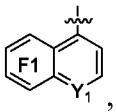
30. The compound or pharmaceutically acceptable salt thereof of any one of claims 28 or 29, wherein

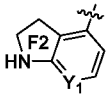
R_1 is -H; -F; -Cl; -Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methyl; or methyl substituted with one or more substituents selected from -F, -Cl, or –Br;

R_2 is -H, -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -$NHCH_3$, -$N(CH_3)_2$, methoxy, ethoxy, methyl, or ethyl; or

R_1 combines with R_2 to which is adjacent to form a 5- membered heterocyclic contains 1 heteroatoms selected from N or O, or 6-membered heterocyclic ring contains 1 heteroatoms selected from N or O; and each of the ring systems is independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$CONH_2$, methoxy, ethoxy, methyl, ethyl, -CO-methyl, or -CO-ethyl;

31. The compound or pharmaceutically acceptable salt thereof of any one of claims 28-30, wherein R_1, and R_2, together with the aromatic ring they are attached to form to



, or


wherein ring F1 or F2 is independently optionally substituted with -F or -$COCH_3$.

32. The compound or pharmaceutically acceptable salt thereof of any one of claims 28-31, wherein

ring D is 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, 3-membered carbocyclic, 4-membered carbocyclic, 5-membered carbocyclic, 5-membered heterocyclic or 6-membered heterocyclic; and each of the heteroaryl or heterocyclic contains 1 or 2 heteroatoms selected from N, O or S;

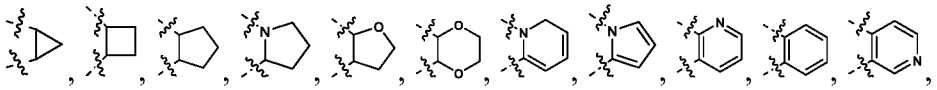
each of R_{2a} and R_{3a} is -H, methyl or methoxy;

R_8 is -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, -$SO_2NR_{8a}R_{8b}$, -S-C_{1-3}alkyl, -CO-$NR_{8a}R_{8b}$, -NH-CO-C_{1-3}alkyl, -NH-CO-$NR_{8a}R_{8b}$, -O-C_{5-10}carbocyclic,

-C_{5-10}heterocyclic, -C_{5-10}heteroaryl, -C_{1-3}alkoxy, or -C_{1-3}alkyl; wherein each of which is independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, oxo, =O, -C_{1-3}alkoxy, or -C_{1-3}alkyl;

or any combination thereof.

33. The compound or pharmaceutically acceptable salt thereof of any one of claims 28-32, wherein

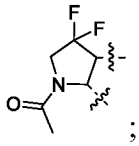
ring D is  ,  or  ; and/or

R_8 is -F, -Cl, -Br, -NH_2, -CN, -OH, -NO_2, carboxyl, oxo, =O, methyl, ethyl, proproyl, isopropoyl, methoxy, ethoxy, propoxy, isopropoxy, -$SO_2NR_{8a}R_{8b}$, -S-C_{1-3}alkyl, -CO-$NR_{8a}R_{8b}$, -NH-CO-C_{1-3}alkyl, -NH-CO-$NR_{8a}R_{8b}$, -O-C_{5-10}carbocyclic, -C_{5-10}heterocyclic or -C_{5-10}heteroaryl; wherein each of which is independently optionally substituted with -F, -Cl, -Br, -NH_2, -CN, -OH, oxo, =O, methoxy, ethoxy, methyl, or ethyl.

34. The compound or pharmaceutically acceptable salt thereof of any one of claims 28-33, wherein

R_1 is –Cl;

R_2 is -NH_2; or

R_1 combines with R_2 to which is adjacent to form  ;

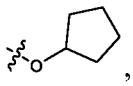
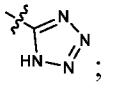
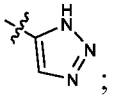
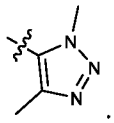
both Y_2 and Y_3 are C;

t is 0, 1 or 2;

or any combination thereof.

35. The compound or pharmaceutically acceptable salt thereof of of any one of claims 28-34, wherein the C_{5-10}carbocyclic is 5-membered carbocyclic, 6-membered carbocyclic, 7-membered carbocyclic, 8-membered carbocyclic, 9-membered carbocyclic or 10-membered carbocyclic; the C_{5-10}heterocyclic is 5-membered heterocyclic, 6-membered heterocyclic, 7-membered heterocyclic, 8-membered heterocyclic, 9-membered heterocyclic or 10-membered heterocyclic; and the C_{5-10}heteroaryl is

5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl or 10-membered heteroaryl; and each of the heterocyclic or heteroaryl contains 1, 2, 3 or 4 heteroatoms selected from N, O or S.

36. The compound or pharmaceutically acceptable salt thereof of any one of claims 28-35, wherein R_8 is -F, -Cl, -Br, $-NH_2$, -CN, -OH, oxo, =O, methyl, ethyl, isopropoyl, methoxy, $-SO_2CH_3$, $-SCH_3$, $-CONH_2$, -NH-$COCH_3$, -NH-$CONHCH_3$,  ;  ,  ,  ;  ; ,or  .

37. The compound or pharmaceutically acceptable salt thereof of claim 1-36, wherein the compound is

1	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
2	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
3	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-amine
4	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidin]-6-amine
5	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
6	(R)-1-(4-((3-amino-5-(2-amino-2,3-dihydrospiro[indene-1,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
7	1-(4-((3-amino-5-((2R)-2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
8	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine
9	(R)-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7',8'-dihydro-5'H-spiro[piperidine-4,6'-quinolin]-7'-amine
10	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
11	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

12	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine
13	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
14	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
15	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-chloro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
16	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carbonitrile
17	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carboxamide
18	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
19	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
20	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methoxy-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine
21	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine
22	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
23	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
24	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
25	(1S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfinyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
26	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
27	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-N,N-dimethyl-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
28	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
29	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-bromo-1,3-dihyd

	rospiro[indene-2,4'-piperidin]-1-amine
30	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
31	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-3-amine
32	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-chloro-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
33	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
34	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-yl)dimethylphosphine oxide
35	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
36	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-imidazol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
37	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-pyrrol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
38	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-bromo-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
39	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-difluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
40	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-difluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
41	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)dimethylphosphine oxide
42	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
43	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
44	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
45	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine
46	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)urea

47	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
48	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
49	(S)-1'-(5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
50	(S)-1'-(5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
51	(S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
52	(S)-1'-(6-amino-5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
53	(S)-1'-(6-amino-5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
54	(S)-1'-(6-amino-5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
55	(S)-1'-(6-amino-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
56	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine
57	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)dimethylphosphine oxide
58	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-((tetrahydro-2H-pyran-4-yl)oxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
59	(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)(piperidin-1-yl)methanone
60	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-morpholino-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
61	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
62	(S)-4-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)morpholin-3-one
63	(S)-N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)methanesulfonamide
64	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[c

	yclopenta[b]quinoline-2,4'-piperidin]-1-amine
65	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
66	(S)-1'-(6-amino-5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
67	(1R,3R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,3-diamine
68	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine
69	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine
70	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-5(1H)-one
71	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[indoline-2,4'-piperidin]-3-amine
72	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-6-amine
73	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-chloro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
74	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
75	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(4-methylpiperazin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
76	(S)-1'-(5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
77	(S)-1'-(6-amino-5-((2-(trifluoromethyl)pyridin-3-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
78	(S)-1-(4-((3-amino-5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
79	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-(tert-butyl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine
80	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxylic acid
81	(2R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-2-amine

82	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine
83	(S)-1'-(5-(quinolin-4-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
84	(S)-1'-(6-amino-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
85	(S)-1'-(5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
86	(S)-1'-(5-(pyridin-4-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
87	(S)-1'-(6-amino-5-((3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
88	(S)-1'-(6-amino-5-((3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
89	(S)-1'-(6-amino-5-((3-chloro-2-(methylamino)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
90	diethyl(S)-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)phosphonate
91	(S)-1'-(6-amino-5-((2-amino-3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
92	(S)-1'-(5-((2-amino-3-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
93	(S)-1'-(6-amino-5-((3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
94	(S)-1'-(6-amino-5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
95	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
96	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[furo[2,3-b]pyridine-2,4'-piperidin]-3-amine
97	(S)-1'-(5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
98	(S)-1'-(6-amino-5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
99	(S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclope

	nta[b]pyridine-6,4'-piperidin]-5-amine
100	(S)-1'-(6-amino-5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
101	(S)-1'-(5-((5-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
102	(S)-1'-(6-amino-5-((5-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
103	(S)-1-(4-((3-amino-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
104	(S)-1'-(5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
105	(S)-1'-(6-amino-5-((2,3-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
106	(S)-1'-(5-((4-chloropyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
107	(S)-1'-(6-amino-5-((4-chloropyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
108	(S)-1'-(5-((3-aminopyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
109	(S)-1'-(6-amino-5-((3-aminopyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
110	(S)-1'-(5-((3,5-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
111	(S)-1'-(6-amino-5-((3,5-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
112	(S)-1'-(5-((2-amino-5-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
113	(S)-1'-(6-amino-5-((2-amino-5-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
114	(S)-1'-(6-amino-5-((2-(trifluoromethyl)pyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
115	(S)-1'-(5-((3-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
116	(S)-1'-(6-amino-5-((3-chloro-2-fluoropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine

117	(S)-3-((5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)picolinonitrile
118	(S)-3-((3-amino-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)picolinonitrile
119	(S)-1'-(5-((2-chloro-5-(trifluoromethyl)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
120	(S)-1'-(6-amino-5-((2-chloro-5-(trifluoromethyl)pyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
121	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
122	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
123	1'-(6-amino-5-((3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
124	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
125	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
126	1'-(6-amino-5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
127	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
128	1'-(5-((3-amino-2-chlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
129	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
130	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
131	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
132	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
133	(S)-4-((5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol
134	(S)-4-((3-amino-5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)t

	hio)-3-chloropyridin-2-ol
135	(S)-4-((5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol
136	(S)-4-((3-amino-5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chloropyridin-2-ol
137	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
138	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-ol
139	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methyl-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
140	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-7(1H)-one (2 mg)
141	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-5(1H)-one
142	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-imino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-amine
143	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-imino-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-amine
144	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(4-imino-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine
145	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(1-bromo-4-imino-4H,6H-spiro[cyclopenta[c]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine
146	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(4-imino-4H,6H-spiro[cyclopenta[c]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine
147	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(2-bromo-4-imino-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-amine
148	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
149	(Z)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[indene-2,4'-piperidin]-1(3H)-one oxime
150	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2-methoxy-4,6-dihydrospiro[cyclopenta[d]thiazole-

	5,4'-piperidin]-4-amine
151	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
152	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
153	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
154	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
155	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine
156	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine
157	(S)-1'-(6-amino-5-((3-fluoro-1H-indol-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
158	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)ethan-1-one
159	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-yl)ethan-1-one
160	(R)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1-methylspiro[indoline-2,4'-piperidin]-3-amine
161	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
162	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-2H-spiro[naphthalene-1,4'-piperidin]-2-amine
163	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dihydrospiro[cyclopenta[b]pyridine-7,4'-piperidin]-6-amine
164	1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine
165	(1'S)-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine

166	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine
167	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine
168	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-6-amine
169	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine
170	(4R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b]furan-5,4'-piperidin]-4-amine
171	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-2-amine
172	1'-amino-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-3'-one
173	(1'S)-1'-amino-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)tetrahydro-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-3'-one
174	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-2,4'-piperidin]-3-amine
175	(3R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.1.0]hexane-2,4'-piperidin]-3-amine
176	3-((2-amino-3-chloropyridin-4-yl)thio)-6-(11-oxa-1,7-diazadispiro[2.0.5^4.3^3]dodecan-7-yl)pyrazin-2-amine
177	1-(4-((3-amino-5-(2-aminospiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
178	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1-methylspiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-4-amine
179	(4R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1-methylspiro[bicyclo[3.1.0]hexane-3,4'-piperidin]-4-amine
180	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.2.0]heptane-3,4'-piperidin]-2-amine
181	(2R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[bicyclo[3.2.0]heptane-3,4'-piperidin]-2-amine
182	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydro-1H-spiro[pe

	ntalene-2,4'-piperidin]-1-amine
183	(1R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydro-1H-spiro[pentalene-2,4'-piperidin]-1-amine
184	1-(4-((3-amino-5-(2-amino-2,3-dihydrospiro[indene-1,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
185	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
186	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
187	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,5-dihydrospiro[cyclopenta[b]furan-6,4'-piperidin]-5-amine
188	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,5-dihydrospiro[cyclopenta[b]furan-6,4'-piperidin]-5-amine
189	1-(4-((3-amino-5-(11-oxa-1,7-diazadispiro[2.0.5^4.3^3]dodecan-7-yl)pyrazin-2-yl)thio)-3,3-difluoroindolin-1-yl)ethan-1-one
190	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b][1,4]dioxine-6,4'-piperidin]-5-amine
191	(5S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)hexahydrospiro[cyclopenta[b][1,4]dioxine-6,4'-piperidin]-5-amine
192	6-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-2(1H)-one
193	(R)-6-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-2(1H)-one
194	2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydro-5H-spiro[indolizine-1,4'-piperidin]-5-one
195	(S)-2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydro-5H-spiro[indolizine-1,4'-piperidin]-5-one
196	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[chromane-4,4'-piperidin]-3-amine
197	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)spiro[chromane-4,4'-piperidin]-3-amine
198	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

199	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine
200	1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-7',8'-dihydro-5'H-spiro[piperidine-4,6'-quinolin]-7'-amine
201	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[c]pyridine-5,4'-piperidin]-6-amine
202	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6,7-dihydrospiro[cyclopenta[c]pyridine-5,4'-piperidin]-6-amine
203	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine
204	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-1-amine
205	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dimethoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
206	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,6-dimethoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
207	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
208	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
209	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine
210	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
211	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
212	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
213	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-4-ol
214	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-chloro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
215	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-bromo-1,3-dihydros

	piro[indene-2,4'-piperidin]-1-amine
216	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-2,5-diamine
217	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-2,5-diamine
218	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
219	(R)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-methoxy-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
220	1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine
221	(S)-1-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1'H,3'H-spiro[piperidine-4,2'-pyrrolizin]-1'-amine
222	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine
223	2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carboxamide
224	(R)-2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carboxamide
225	2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carbonitrile
226	(R)-2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidine]-4-carbonitrile
227	N-(2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-4-yl)acetamide
228	(R)-N-(2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-4-yl)acetamide
229	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(pyrrolidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
230	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(pyrrolidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
231	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

232	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
233	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
234	2-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)propan-2-ol
235	(S)-2-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)propan-2-ol
236	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
237	N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide
238	(S)-N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide
239	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
240	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(cyclopentyloxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
241	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(cyclopentyloxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
242	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-7(1H)-one
243	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
244	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
245	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]indole-6,4'-piperidin]-7-amine
246	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]indole-6,4'-piperidin]-7-amine
247	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[indeno[5,6-d]imidazole-6,4'-piperidin]-7-amine
248	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-sp

	iro[indeno[5,6-d]imidazole-6,4'-piperidin]-7-amine
249	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-tetrazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
250	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-tetrazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
251	1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)-3-methylurea
252	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)-3-methylurea
253	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine

38. A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1-37 and at least one pharmaceutically acceptable excipient.

39. The pharmaceutical composition according to claim 38, wherein, the said compound or pharmaceutically acceptable salt thereof in a weight ratio to the said excipient within the range from about 0.0001 to about 10.

40. Use of a pharmaceutical composition of as defined in claim 38 or 39 and/or at least one compound or pharmaceutically acceptable salt thereof any one of claims 1-37 for the preparation of a medicament.

41. The use according to claim 40, wherein the medicament is for treatment or prevention a disease or disorder mediated by the activity of SHP2.

42. The use according to claim 40 or 41, wherein, the disease or disorder mediated by the activity of SHP2 is cancer, cancer metastasis, cardiovascular disease, an immunological disorder, fibrosis, or an ocular disorder.

43. The use according to claim 41 or 42, wherein, the disease or disorder mediated by the activity of SHP2 is one or more selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, head and neck squamous-cell carcinoma, acute myeloid leukemia, breast cancer, esophageal tumor, lung cancer, colon cancer, head cancer, gastric carcinoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combination thereof.

44. A method of treating a patient having a condition which is mediated by the activity of SHP2, said method comprising administering to the patient a therapeutically effective amount of at least one compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1-37, or the pharmaceutical composition of claim 38 or 39.

45. The method according to claim 44 wherein the condition mediated by the activity of SHP2 is cancer, cancer metastasis, cardiovascular disease, an immunological disorder, fibrosis, or an ocular disorder.

46. The method according to claim 44, wherein the condition mediated by the activity of SHP2 is noonan syndrome, leopard syndrome, juvenile myelomonocytic leukemias, liver cancer, neuroblastoma, melanoma, squamous-cell carcinoma of the head and neck, acute myeloid leukemia, breast cancer, esophageal cancer, lung cancer, colon cancer, head cancer, gastric carcinoma, neuroblastoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combination thereof.

47. A method of treating cancer selected from the group consisting of noonan syndrome, leopard syndrome, juvenile myelomonocytic leukemias, liver cancer, neuroblastoma, melanoma, squamous-cell carcinoma of the head and neck, acute myeloid leukemia, breast cancer, esophageal cancer, lung cancer, colon cancer, head cancer, gastric carcinoma, neuroblastoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combinations thereof, comprising administering to a mammal in need of such treatment an effective amount of at least one compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1-37, or the pharmaceutical composition of claim 38 or 39.

22	(R)-N-(2-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-4-yl)acetamide
22	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(pyrrolidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
23	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(pyrrolidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
23	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
23	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
23	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
23	2-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)propan-2-ol
23	(S)-2-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)propan-2-ol
23	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
23	N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide
23	(S)-N-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide
23	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide

24	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(cyclopentyloxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
24	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(cyclopentyloxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
24	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3H-spiro[indolizine-2,4'-piperidin]-7(1H)-one
24	1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
24	(S)-1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
24	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]indole-6,4'-piperidin]-7-amine
24	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[cyclopenta[f]indole-6,4'-piperidin]-7-amine
24	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[indeno[5,6-d]imidazole-6,4'-piperidin]-7-amine
24	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydro-1H-spiro[indeno[5,6-d]imidazole-6,4'-piperidin]-7-amine
24	1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-tetrazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
25	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-6-(1H-tetrazol-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
25	1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydr

	ospiro[indene-2,4'-piperidin]-6-yl)-3-methylurea
25	(S)-1-(1-amino-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)-3-methylurea
25	1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine

38. A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1-37 and at least one pharmaceutically acceptable excipient.

39. The pharmaceutical composition according to claim 38, wherein, the said compound or pharmaceutically acceptable salt thereof in a weight ratio to the said excipient within the range from about 0.0001 to about 10.

40. Use of a pharmaceutical composition of as defined in claim 38 or 39 and/or at least one compound or pharmaceutically acceptable salt thereof any one of claims 1-37 for the preparation of a medicament.

41. The use according to claim 40, wherein the medicament is for treatment or prevention a disease or disorder mediated by the activity of SHP2.

42. The use according to claim 40 or 41, wherein, the disease or disorder mediated by the activity of SHP2 is cancer, cancer metastasis, cardiovascular disease, an immunological disorder, fibrosis, or an ocular disorder.

43. The use according to claim 41 or 42, wherein, the disease or disorder mediated by the activity of SHP2 is one or more selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, head and neck squamous-cell carcinoma, acute myeloid leukemia, breast cancer, esophageal tumor, lung cancer, colon cancer, head cancer, gastric carcinoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combination thereof.

44. A method of treating a patient having a condition which is mediated by the activity of SHP2, said method comprising administering to the patient a therapeutically effective amount of at least one compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1-37, or the pharmaceutical composition of claim 38 or 39.

45. The method according to claim 44 wherein the condition mediated by the activity of SHP2 is cancer, cancer metastasis, cardiovascular disease, an immunological disorder, fibrosis, or an ocular disorder.

46. The method according to claim 44, wherein the condition mediated by the activity of SHP2 is noonan syndrome, leopard syndrome, juvenile myelomonocytic leukemias, liver cancer, neuroblastoma, melanoma, squamous-cell carcinoma of the head and neck, acute myeloid leukemia, breast cancer, esophageal cancer, lung cancer, colon cancer, head cancer, gastric carcinoma, neuroblastoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combination thereof.

47. A method of treating cancer selected from the group consisting of noonan syndrome, leopard syndrome, juvenile myelomonocytic leukemias, liver cancer, neuroblastoma, melanoma, squamous-cell carcinoma of the head and neck, acute myeloid leukemia, breast cancer, esophageal cancer, lung cancer, colon cancer, head cancer, gastric carcinoma, neuroblastoma, lymphoma, glioblastoma, gastric cancer, pancreatic cancer, and combinations thereof, comprising administering to a mammal in need of such treatment an effective amount of at least one compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1-37, or the pharmaceutical composition of claim 38 or 39.