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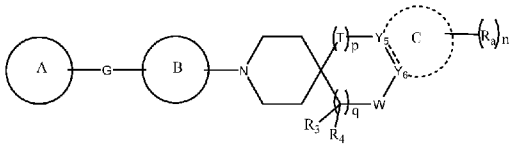
(54) Title: NOVEL HETEROCYCLIC DERIVATIVES USEFUL AS SHP2 INHIBITORS



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(57) Abstract: Provided is a compound of formula I, their synthesis and their use for treating a SHP2 mediated disorder. More particularly, provided is a pharmaceutical composition comprising the said compound.

THE DESCRIPTION

NOVEL HETEROCYCLIC DERIVATIVES USEFUL AS SHP2 INHIBITORS

Technical Field

This invention relates to certain novel heterocyclic 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 derivatives useful as inhibitors of SHP2, methods for producing such compounds and methods for treating a SHP2-mediated disorder.

Background Art

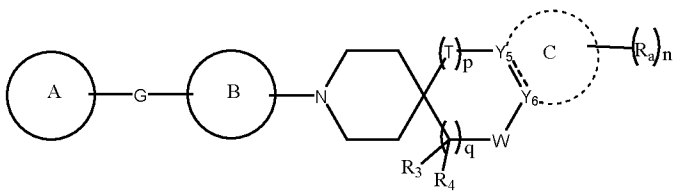
SHP2 (The Src Homolgy-2 phosphatease) is a non-receptor protein tyrosine phosphatase encoded by the PTPN11 gene that harbors a classical tyrosine phosphatase domain and two N-terminal Src homology 2 (SH2) domains and a C-terminal tail. The two SH2 domains control the subcellular localization and functional 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 mutation s 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.

Summary of Invention

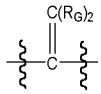
The present invention relates to certain novel heterocyclic compounds useful as SHP2 inhibitors and their use for treating a SHP2 mediated disorder. The compounds of the invention have the general structure as Formula I or a pharmaceutically acceptable salt:



I

ring A is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered

heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-, -NR_G-SO_2-,  , -$C(R_G)_2$- or -SO_2-NR_G-;

each of R_G is independently selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy, and each of which is independently optionally substituted or unsubstituted;

ring B is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring, a 3-10 membered carbocyclic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

T is absent, O, NR_1 or CR_1R_2;

each of R_1 and R_2 is independently selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -NH-C_{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 and R_2 together with the carbon atom to which they are both attached form CO or C=NR_5;

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

each of R_3 and R_4 is independently selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -NH-C_{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_3 and R_4 together with the carbon atom to which they are both attached form a 3-12 membered heterocyclic ring or a 5-12 membered heteroaromatic ring or C=NR_5, and each of the ring systems is independently optionally substituted or unsubstituted;

each of R_5 is independently selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy;

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

W is absent, O, S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -CO-C_{1-6}alkyl, -CO-OC_{1-6}alkyl, -C_{1-6}alkylene-O-C_{1-6}alkoxy, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl;

ring C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

when ring C is absent, Y_5 is $CR_{5a}R_{5b}$, NR_{5a} or O, and Y_6 is $CR_{6a}R_{6b}$, NR_{6a} or O;

when ring C is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring;

i) Y_5 is CR_{5a} or N, and Y_6 is CR_{6a} or N, when the "------" in the term "^{Y_5}------^{Y_6}" represents a single bond; or

ii) Y_5 is C, and Y_6 is C, when the "------" in the term "^{Y_5}------^{Y_6}" represents a double bond;

each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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_a is independently selected from hydrogen, deuterium, halogen, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{3-8}$cycloalkyl,$-C_{1-6}$alkylene-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-$CO-OR_{a1}$, $-C_{1-6}$alkylene-(3-10 membered heterocyclic), $-C_{1-6}$alkylene-(5-10 membered heteroaryl), $-C_{1-6}$alkylene-$CO-NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-$CO-NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-CO-C_{1-6}alkyl, $-CO-NR_{a1}R_{a2}$, $-CO-CO-NR_{a1}R_{a2}$, $-C_{3-10}$carbocyclic, -5-10 membered heteroaryl, -3-10 membered heterocyclic, $-CO-C_{1-6}$alkyl, $-COO-C_{1-6}$alkyl, $-CO-C_{1-6}$alkylene-$NR_{a1}R_{a2}$, $-CO-NR_{a1}$-(3-10 membered heterocyclic), $-CO-NR_{a1}$-(3-10 membered heterocyclic), -CO-(3-10 membered heterocyclic), $-O-C_{1-6}$alkylene-$CO-OR_{a1}$, $-O-C_{1-6}$alkylene-$CO-NR_{a1}R_{a2}$, $-O-C_{1-6}$alkylene-$NR_{a1}R_{a2}$, $-O-C_{3-10}$carbocyclic, -O-(3-10 membered heterocyclic), $-NR_{a1}$-$CO-C_{1-6}$alkyl, $-NR_{a1}$-$CO-NR_{a1}R_{a2}$, $-NR_{a1}$-CO-(5-10 membered heteroaryl), $-NR_{a1}$-$CO-C_{3-8}$cycloalkyl,$-NR_{a1}$-C_{1-6}alkylene-$NR_{a1}R_{a2}$, $-NR_{a1}$-C_{1-6}alkylene-(3-10 membered heterocyclic), $-NR_{a1}$-C_{1-6}alkylene-(5-10 membered heteroaryl), $-NR_{a1}$-SO_2C_{1-6}alkyl, -S-C_{1-6}alkyl, $-SONR_{a1}R_{a2}$, $-SO_2NR_{a1}R_{a2}$, -SO-C_{1-6}alkyl, $-SO_2$-C_{1-6}alkyl, $-PO(C_{1-6}alkyl)_2$, $-PO(C_{1-6}alkoxy)_2$, -3-10 membered heterocyclic or -5-10 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6; or

two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted; or

R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, 3-10 membered heteroaromatic ring or 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted;

each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

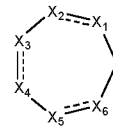
In some embodiments of Formula I, ring A is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring A is a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring A is a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a

10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring A is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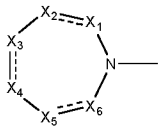
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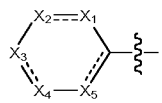
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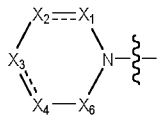
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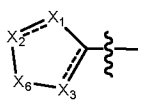
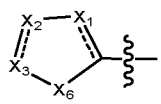
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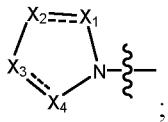

;

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

X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1};

each of R_{X1} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO;

each of R_{X2} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3};

each of R_{X3} is independently selected from hydrogen, deuterium, halogen, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl, $-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted ;

X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4};

each of R_{X4} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or a 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, oxo, =O,$-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5};

each of R_{X5} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$;

each of R_{X6} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, or

R_{X5} and R_{X6} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently

selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}alkylene-C_{3-8}$cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}alkylene-C_{3-8}$cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$,CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-4}$alkyl, $-C_{1-3}$alkoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}alkylene-C_{3-6}$cycloalkyl or 3-6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxy, ethoxy, propoxy, isopropoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}alkylene-C_{3-6}$cycloalkyl, 3 membered heterocyclic, 4 membered

heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxy, ethoxy, propoxy, isopropoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}$alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{X1} and R_{X2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{X1} and R_{X2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl, $-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl,$-O-C_{1-6}$alkylene-C_{1-6}alkyl, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl, $-O-C_{1-3}$alkylene-C_{1-3}alkyl, $-O-C_{5-6}$aryl or $-O-C_{1-3}$alkylene-C_{5-6}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl, $-O-C_{1-3}$alkylene-C_{1-3}alkyl, $-O-C_{5-6}$aryl or $-O-C_{1-3}$alkylene-C_{5-6}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl, $-O-C_{1-3}$alkylene-C_{1-3}alkyl, $-O-C_{5-6}$aryl or $-O-C_{1-3}$alkylene-C_{5-6}aryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{X2} and R_{X3} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{X2} and R_{X3} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8

membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, an 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, -NHCO-(5-10 membered heterocyclyl) or 5-10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, R_{X3} and R_{X4} together with the ring to which they are attached

form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{X3} and R_{X4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{X3} and R_{X4} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently

selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{X4} and R_{X5} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{X4} and R_{X5} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

In some embodiments of Formula I, X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-3}alkyl or -C_{1-3}alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently

selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

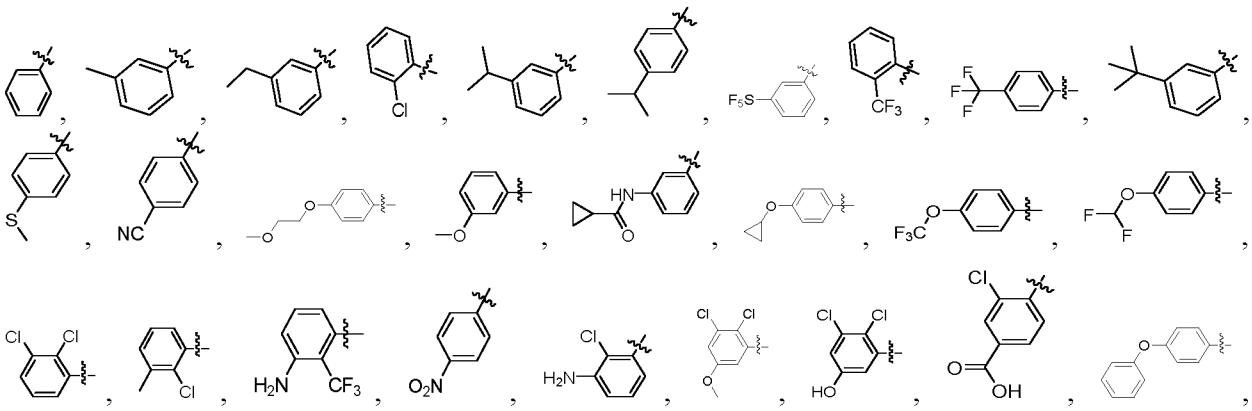
In some embodiments of Formula I, X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

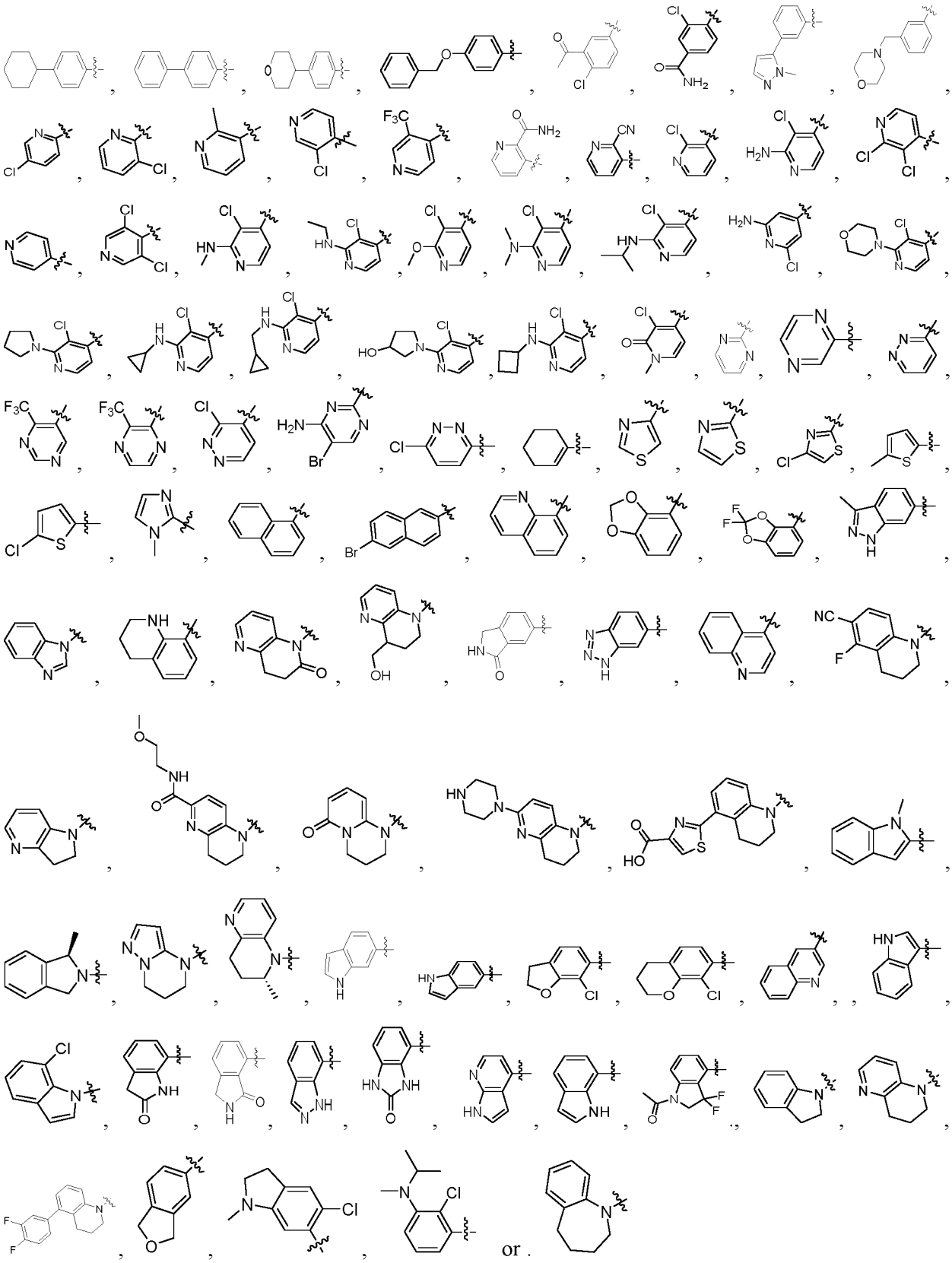
In some embodiments of Formula I, R_{X5} and R_{X6} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

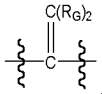
In some embodiments of Formula I, R_{X5} and R_{X6} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered. heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

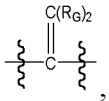
In some embodiments of Formula I, R_{X5} and R_{X6} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

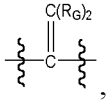
In some embodiments of Formula I, ring A is selected from





In some embodiments of Formula I, G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-, -NR_G-SO_2-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy, and each of which is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-, -NR_G-SO_2-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy, and each of which is independently optionally substituted or unsubstituted.

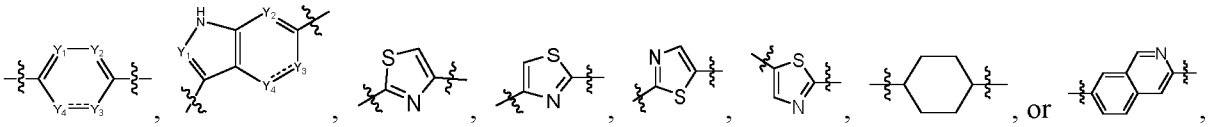
In some embodiments of Formula I, G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-, -NR_G-SO_2-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring B is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring, a 3-10 membered carbocyclic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2,3, 4, 5 or 6 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2, 3, 4, 5 or 6heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, wherein ring B is a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring, a 3-10 membered carbocyclic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2,3, 4, 5 or 6 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2, 3, 4, 5 or 6 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring B is a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered carbocyclic ring, a 6 membered carbocyclic ring, a 7 membered carbocyclic ring, a 8 membered carbocyclic ring, a 9 membered carbocyclic ring, a 10 membered carbocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, a 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2, 3 or 4 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2, 3 or 4 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring B is



Y_1 is N or CR_{Y1};

R_{Y1} is selected from hydrogen, deuterium, halogen, -NH_2, -OH, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6}alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is

independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

Y_2 is N or CR_{Y2};

R_{Y2} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

when the "======" in the term "^{Y_3}======^{Y_4}" represents a single bond, Y_3 is NR_{Y3} or $C(R_{Y3})_2$, and Y_4 is CO, $C(R_{Y4})_2$ or NR_{Y4};

when the "======" in the term "^{Y_3}======^{Y_4}" represents a double bond, Y_3 is N or CR_{Y3}, and Y_4 is N or CR_{Y4};

R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, halogen, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH ,$-C_{1-6}$alkylene-OH, $-CO-C_{3-8}$heterocyclic ring, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl, $-C_{1-6}$alkyl substituted with –OH, or $-C_{1-6}$alkoxy; or

R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F,

Cl, Br, I, -NH_2, -OH, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6} alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

In some embodiments of Formula I, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6} alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-3}alkyl, -C_{1-3}alkoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, wherein R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8

membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH, $-CO-C_{3-8}$heterocyclic ring, $-C_{1-6}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl, $-C_{1-6}$alkyl substituted with –OH, or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH, $-C_{1-6}$alkylene-OH, $-CO-C_{3-8}$heterocyclic ring, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-3}$alkyl, carboxyl, $-COO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkylene-OH, $-C_{1-3}$alkylene-OH, $-CO-C_{3-8}$heterocyclic ring, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl, $-C_{1-3}$alkyl substituted with -OH or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, methyl, ethyl, propyl, isopropyl, carboxyl, $-COO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkylene-OH, $-C_{1-3}$alkylene-OH, $-CO-C_{3-8}$heterocyclic ring, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, ethyl substituted with –OH, methoxy, ethoxy, propoxy or isopropoxy.

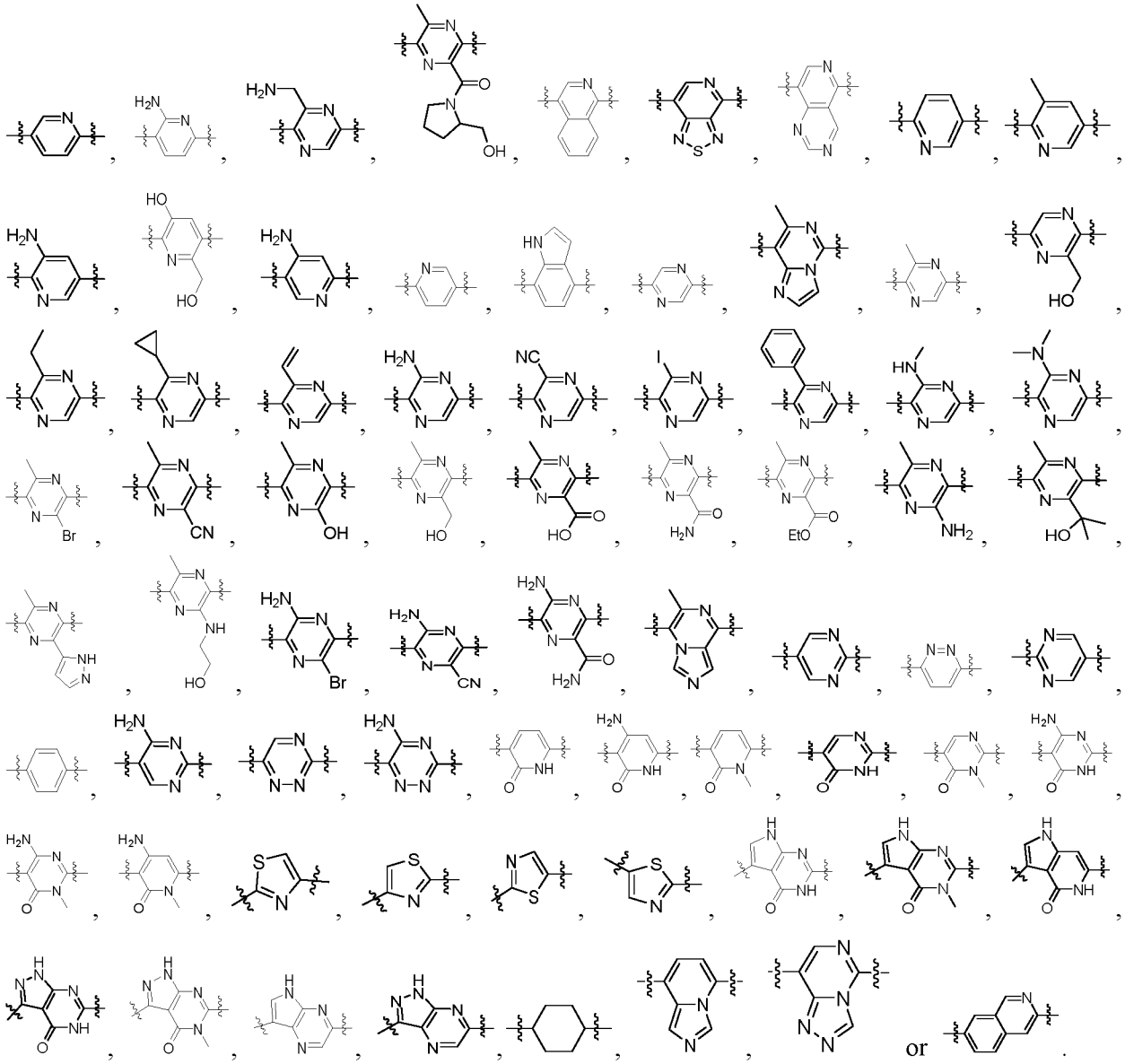
In some embodiments of Formula I, R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of

the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring B is selected from



In some embodiments of Formula I, each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula I, each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}$alkyl, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula I, each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl 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_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, R_1 and R_2 together with the carbon atom to which they are both attached form CO or $C=NR_5$.

In some embodiments of Formula I, R_1 and R_2 together with the carbon atom to which they are both attached form CO.

In some embodiments of Formula I, R_1 and R_2 together with the carbon atom to which they are both attached form $C=NR_5$.

In some embodiments of Formula I, each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula I, each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}$alkyl, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula I, each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl 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_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, R_3 and R_4 together with the carbon atom to which they are both attached form 3-12 membered heterocyclic ring or 5-12 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the

heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_3 and R_4 together with the carbon atom to which they are both attached form 3-10 membered heterocyclic ring or 5-10 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, R_3 and R_4 together with the carbon atom to which they are both attached form 3 membered heterocyclic ring, 4 membered heterocyclic ring, 5 membered heterocyclic ring, 6 membered heterocyclic ring, 7 membered heterocyclic ring, 8 membered heterocyclic ring, 9 membered heterocyclic ring, 10 membered heterocyclic ring, 5 membered heteroaromatic ring, 6 membered heteroaromatic ring, 7 membered heteroaromatic ring, 8 membered heteroaromatic ring, 9 membered heteroaromatic ring, 10 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, each of R_5 is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, each of R_5 is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, each of R_5 is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula I, W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-CO-C_{1-6}$alkyl, $-CO-OC_{1-6}$alkyl, $-C_{1-6}$alkylene-O-C_{1-6}alkoxy, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula I, W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-CO-C_{1-3}$alkyl, $-CO-OC_{1-3}$alkyl, $-C_{1-3}$alkylene-O-C_{1-3}alkoxy, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula I, W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN;-OH; $-NO_2$; carboxyl; $-CO-C_{1-3}$alkyl; $-CO-OC_{1-3}$alkyl; $-C_{1-3}$alkylene-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl 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, W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN;-OH; $-NO_2$; carboxyl; $-CO-C_{1-3}$alkyl; $-CO-OC_{1-3}$alkyl; $-C_{1-3}$alkylene-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl;

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

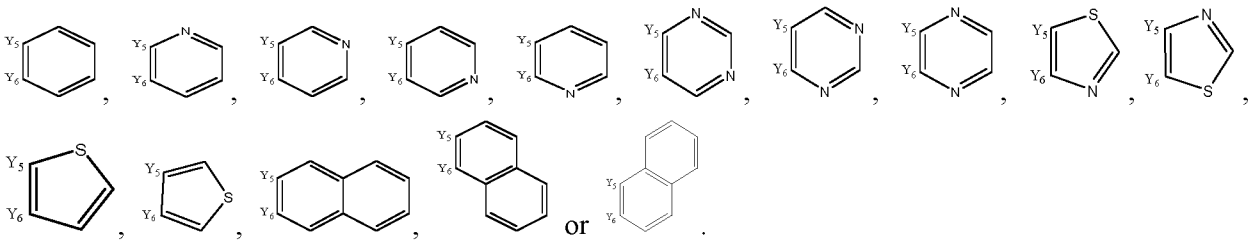
In some embodiments of Formula I, W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN;-OH; -NO_2; carboxyl; -CO-C_{1-3}alkyl; -CO-OC_{1-3}alkyl; -C_{1-3}alkylene-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; -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.

In some embodiments of Formula I, ring C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring C is absent, a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring C is absent, a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula I, ring C is selected from



In some embodiments of Formula I, each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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.

In some embodiments of Formula I, each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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 I, each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl 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_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -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; -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.

In some embodiments of Formula I, each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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.

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

In some embodiments of Formula I, each of R_a is independently hydrogen, deuterium, F, Cl, Br, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, -C_{1-3}alkoxy, -C_{1-4}alkyl, -C_{3-6}cycloalkyl,-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-O-C_{1-6}alkyl, -C_{1-3}alkylene-CO-OR_{a1}, -C_{1-3}alkylene-(3-8 membered heterocyclic), -C_{1-3}alkylene-(5-8 membered heteroaryl), -C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, -C_{3-8}carbocyclic, -5-8 membered heteroaryl, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2-C_{1-3}alkyl, -$PO(C_{1-3}alkyl)_2$, -$PO(C_{1-3}alkoxy)_2$, -3-8 membered

heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

In some embodiments of Formula I, each of R_a is independently hydrogen, deuterium, F, Cl, Br, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, methoxy, ethoxy, propoxy, isopropoxy methyl, ethyl, propyl, isopropyl, butyl, isobutyl, $-C_{3-6}$cycloalkyl,$-C_{1-3}$alkylene-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-O-C_{1-6}alkyl, $-C_{1-3}$alkylene-CO-OR_{a1}, $-C_{1-3}$alkylene-(3-8 membered heterocyclic), $-C_{1-3}$alkylene-(5-8 membered heteroaryl), $-C_{1-3}$alkylene-CO-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, $-C_{3-8}$carbocyclic, -5-8 membered heteroaryl, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), $-NR_{a1}$-CO-C_{1-3}alkyl, $-NR_{a1}$-CO-$NR_{a1}R_{a2}$, $-NR_{a1}$-CO-(5-8 membered heteroaryl), $-NR_{a1}$-CO-C_{3-6}cycloalkyl,$-NR_{a1}$-C_{1-3}alkylene-$NR_{a1}R_{a2}$, $-NR_{a1}$-C_{1-3}alkylene-(3-8 membered heterocyclic), $-NR_{a1}$-C_{1-3}alkylene-(5-8 membered heteroaryl), $-NR_{a1}$-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, $-SONR_{a1}R_{a2}$, $-SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, $-SO_2$-C_{1-3}alkyl, $-PO(C_{1-3}alkyl)_2$, $-PO(C_{1-3}alkoxy)_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

In some embodiments of Formula I, two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3 membered heterocyclic ring, a 4 membered heterocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 3 membered carbocyclic ring, a 4 membered carbocyclic ring, a 5 membered carbocyclic ring, a 6 membered carbocyclic ring, wherein each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, 3-10 membered heteroaromatic ring or 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted with deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula I, R_a and R_w with the atom to which they are both attached form a

3-10 membered aromatic ring, 3-10 membered heteroaromatic ring or 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, 3-10 membered heteroaromatic ring or 3-10 membered heterocyclic ring; each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula I, R_a and R_w with the atom to which they are both attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 5 membered heteroaryl ring, a 6 membered heteroaryl ring, a 5 membered heterocyclic ring or a 6 membered heterocyclic ring; each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

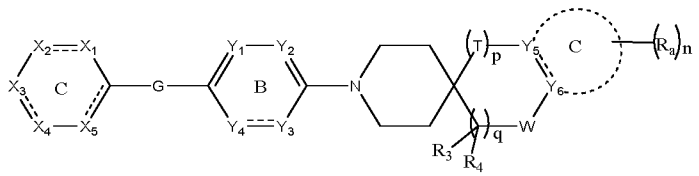
In some embodiments of Formula I, each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula I, each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, 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 I, each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl 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_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

The present invention further provides the compound of Formula II or a pharmaceutically acceptable salt thereof:



II

X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1};

each of R_{X1} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO;

each of R_{X2} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3};

each of R_{X3} is independently selected from hydrogen, deuterium, halogen, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl, $-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted ;

X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4};

each of R_{X4} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl,$-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5};

each of R_{X5} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

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

G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$, $-NR_G-SO_2-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$;

each of R_G is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted or unsubstituted;

Y_1 is N or CR_{Y1};

R_{Y1} is selected from hydrogen, deuterium, halogen, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

Y_2 is N or CR_{Y2};

R_{Y2} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

when the "======" in the term "Y_3======Y_4" represents a single bond, Y_3 is NR_{Y3} or $C(R_{Y3})_2$, and Y_4 is CO, $C(R_{Y4})_2$ or NR_{Y4};

when the "======" in the term "Y_3======Y_4" represents a double bond, Y_3 is N or CR_{Y3}, and Y_4 is N or CR_{Y4};

R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, halogen, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH ,$-C_{1-6}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

T is absent, O, NR_1 or CR_1R_2;

each of R_1 and R_2 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH,

$-NO_2$, carboxyl, $-NH-C_{1-6}$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 and R_2 together with the carbon atom to which they are both attached form CO or $C=NR_5$;

p is 0, 1, 2 or 3;

each of R_3 and R_4 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_3 and R_4 together with the carbon atom to which they are both attached form a 3-12 membered heterocyclic ring or a 5-12 membered heteroaromatic ring or $C=NR_5$, and each of the ring systems is independently optionally substituted or unsubstituted;

each of R_5 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

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

W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen, deuterium, 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 C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

when ring C is absent, Y_5 is $CR_{5a}R_{5b}$, NR_{5a} or O, and Y_6 is $CR_{6a}R_{6b}$, NR_{6a} or O;

when ring C is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring;

i) Y_5 is CR_{5a} or N, and Y_6 is CR_{6a} or N, when the "======" in the term "^{Y_5}======Y_6" represents a single bond; or

ii) Y_5 is C, and Y_6 is C, when the "======" in the term "^{Y_5}======Y_6" represents a double bond;

each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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_a is independently hydrogen, deuterium, halogen, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{3-8}$cycloalkyl,$-C_{1-6}$alkylene-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{a1}, $-C_{1-6}$alkylene-(3-10 membered heterocyclic), $-C_{1-6}$alkylene-(5-10 membered heteroaryl), $-C_{1-6}$alkylene-CO-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-CO-C_{1-6}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, $-C_{3-10}$carbocyclic, -5-10 membered heteroaryl, -3-10 membered heterocyclic, $-CO-C_{1-6}$alkyl, $-COO-C_{1-6}$alkyl, $-CO-C_{1-6}$alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-(3-10 membered heterocyclic), $-O-C_{1-6}$alkylene-CO-OR_{a1}, $-O-C_{1-6}$alkylene-CO-$NR_{a1}R_{a2}$, $-O-C_{1-6}$alkylene-$NR_{a1}R_{a2}$, $-O-C_{3-10}$carbocyclic, -O-(3-10 membered heterocyclic), $-NR_{a1}-CO-C_{1-6}$alkyl, $-NR_{a1}-CO-NR_{a1}R_{a2}$, $-NR_{a1}-CO-$(5-10 membered

heteroaryl), -NR_{a1}-CO-C_{3-8}cycloalkyl,-NR_{a1}-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-6}alkylene-(3-10 membered heterocyclic), -NR_{a1}-C_{1-6}alkylene-(5-10 membered heteroaryl), -NR_{a1}-SO_2C_{1-6}alkyl, -S-C_{1-6}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-6}alkyl, -SO_2-C_{1-6}alkyl, -$PO(C_{1-6}alkyl)_2$, -$PO(C_{1-6}alkoxy)_2$, -3-10 membered heterocyclic or -5-10 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6; or

two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaomatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted;

each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, 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, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -$CONH_2$, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

In some embodiments of Formula II, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -$CONH_2$, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -$CONH_2$, -CN, -C_{1-3}alkyl or -C_{1-3}alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -$CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -$CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -CO-C_{1-6}alkyl, -NH-C_{1-6}alkyl, -N-$(C_{1-6}alkyl)_2$, -SF_5, -NHCO-C_{3-8}cycloalkyl, -NH-C_{3-8}cycloalkyl,

-C_{1-6}alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), -NH-C_{1-6}alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -oxo, =O,-NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

In some embodiments of Formula II, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -CO-C_{1-6}alkyl, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -SF_5, -NHCO-C_{3-8}cycloalkyl, -NH-C_{3-8}cycloalkyl, -C_{1-6}alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), -NH-C_{1-6}alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -oxo, =O, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

In some embodiments of Formula II, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-3}alkyl, -C_{1-3}alkoxy, -CO-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -SF_5, -NHCO-C_{3-6}cycloalkyl, -NH-C_{3-6}cycloalkyl, -C_{1-3}alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), -NH-C_{1-3}alkylene-C_{3-6}cycloalkyl or 3-6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -oxo, =O, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

In some embodiments of Formula II, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -CO-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -SF_5, -NHCO-C_{3-6}cycloalkyl, -NH-C_{3-6}cycloalkyl, -C_{1-3}alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), -NH-C_{1-3}alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -oxo, =O, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -CO-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -SF_5, -NHCO-C_{3-6}cycloalkyl, -NH-C_{3-6}cycloalkyl, -C_{1-3}alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), -NH-C_{1-3}alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -oxo, =O, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered

heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{X1} and R_{X2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{X1} and R_{X2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl,$-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula II, X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl, $-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl, $-O-C_{1-3}$alkylene-C_{1-3}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is

independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl or $-O-C_{1-3}$alkylene-C_{1-3}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-3}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl or $-O-C_{1-3}$alkylene-C_{1-3}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-3}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{X2} and R_{X3} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{X2} and R_{X3} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula II, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy,

-NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula II, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, -NHCO-(5-10 membered heterocyclyl) or 5-10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula II, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{X3} and R_{X4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{X3} and R_{X4} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8

membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula II, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

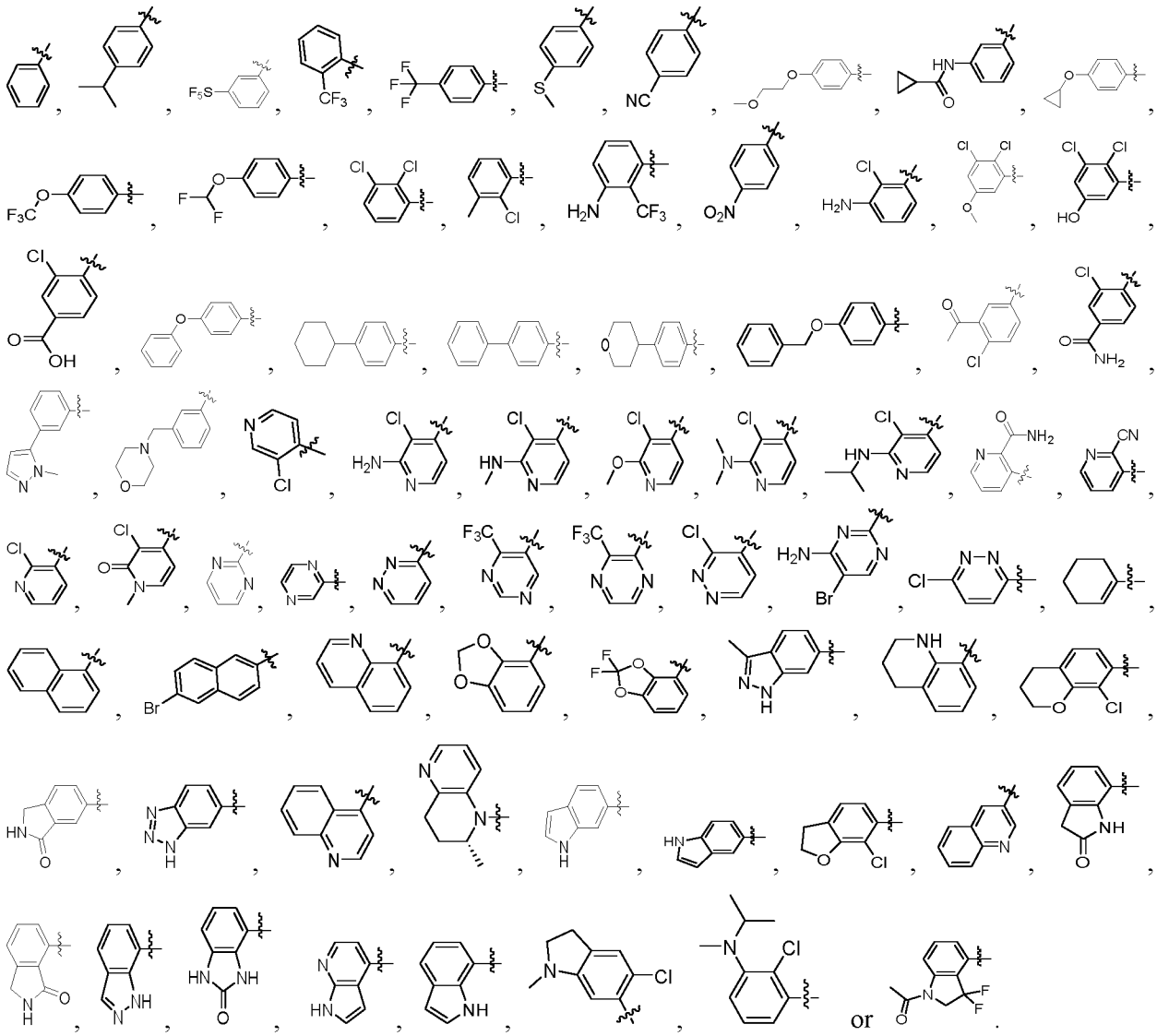
In some embodiments of Formula II, R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

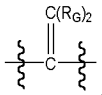
In some embodiments of Formula II, R_{X4} and R_{X5} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of

the ring systems is independently optionally substituted or unsubstituted.

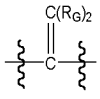
In some embodiments of Formula II, R_{X4} and R_{X5} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

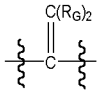
In some embodiments of Formula II, ring A is selected from



In some embodiments of Formula II, G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$, $-NR_G-SO_2-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently

optionally substituted or unsubstituted.

In some embodiments of Formula II, G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-, -NR_G-SO_2-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy, and each of which is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-, -NR_G-SO_2-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6}alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

In some embodiments of Formula II, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6}alkenyl, -C_{3-8}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-3}alkyl, -C_{1-3}alkoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6} alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

In some embodiments of Formula II, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6} alkenyl, -C_{3-8}cycloalkyl or

-C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-3}alkyl, -C_{1-3}alkoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, carboxyl, -COO-C_{1-6}alkyl, -NH-C_{1-6}alkylene-OH, -C_{1-6}alkylene-OH, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

In some embodiments of Formula II, R_{Y3} and R_{Y4} are independently selected from hydrogen,

deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH, $-C_{1-6}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 II, R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-3}$alkyl, carboxyl, $-COO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkylene-OH, $-C_{1-3}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

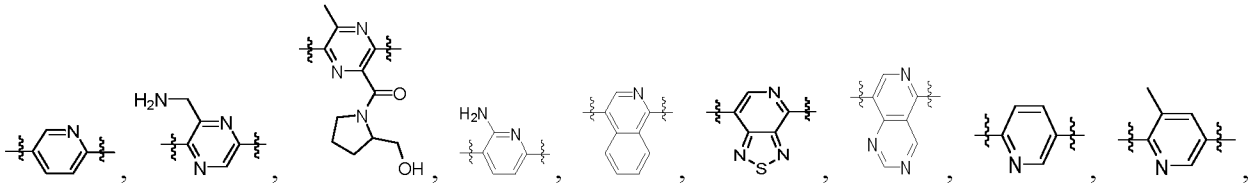
In some embodiments of Formula II, R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, methyl, ethyl, propyl, isopropyl, carboxyl, $-COO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkylene-OH, $-C_{1-3}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

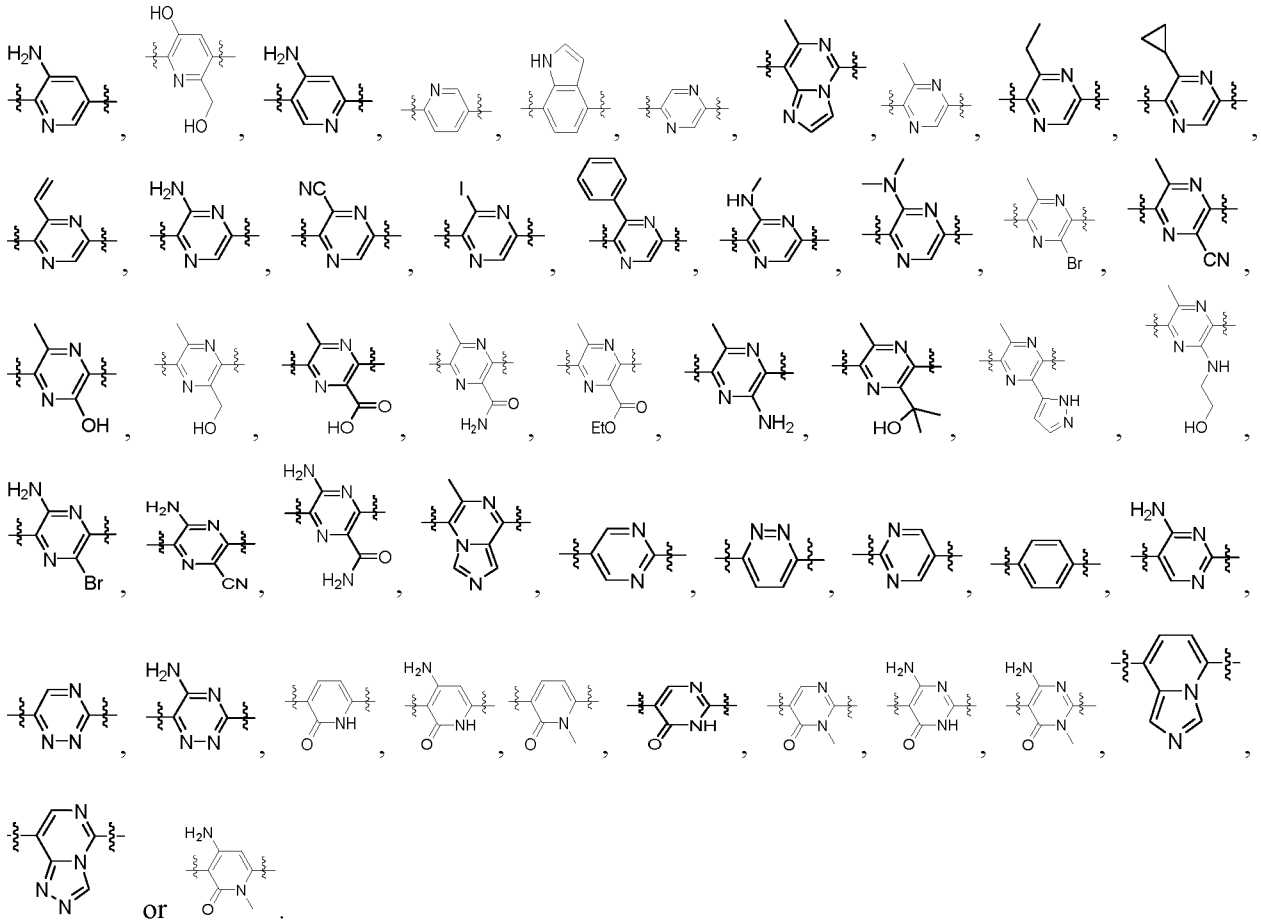
In some embodiments of Formula II, R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, ring B is selected from





In some embodiments of Formula II, each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula II, each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}$alkyl, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula II, each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula II, each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, R_1 and R_2 together with the carbon atom to which they are both attached form CO or $C=NR_5$.

In some embodiments of Formula II, R_1 and R_2 together with the carbon atom to which they are both

attached form CO.

In some embodiments of Formula II, R_1 and R_2 together with the carbon atom to which they are both attached form $C=NR_5$.

In some embodiments of Formula II, each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula II, each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}$alkyl, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula II, each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula II, each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, R_3 and R_4 together with the carbon atom to which they are both attached form a 3-12 membered heterocyclic ring or a 5-12 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_3 and R_4 together with the carbon atom to which they are both attached form a 3-10 membered heterocyclic ring or a 5-10 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, R_3 and R_4 together with the carbon atom to which they are both attached form a 3 membered heterocyclic ring, a 4 membered heterocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, each of R_5 is independently selected from hydrogen, deuterium,

F, Cl, Br, -NH_2, -CN, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy.

In some embodiments of Formula II, each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy.

In some embodiments of Formula II, each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, -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.

In some embodiments of Formula II, W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -CO-C_{1-3}alkyl, -CO-OC_{1-3}alkyl, -C_{1-3}alkyl-O-C_{1-3}alkoxy, substituted or unsubstituted -C_{1-3}alkoxy, or substituted or unsubstituted -C_{1-3}alkyl.

In some embodiments of Formula II, W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN;-OH; -NO_2; carboxyl; -CO-C_{1-3}alkyl; -CO-OC_{1-3}alkyl; -C_{1-3}alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula II, W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN;-OH; -NO_2; carboxyl; -CO-C_{1-3}alkyl; -CO-OC_{1-3}alkyl; -C_{1-3}alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula II, W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN;-OH; -NO_2; carboxyl; -CO-C_{1-3}alkyl; -CO-OC_{1-3}alkyl; -C_{1-3}alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

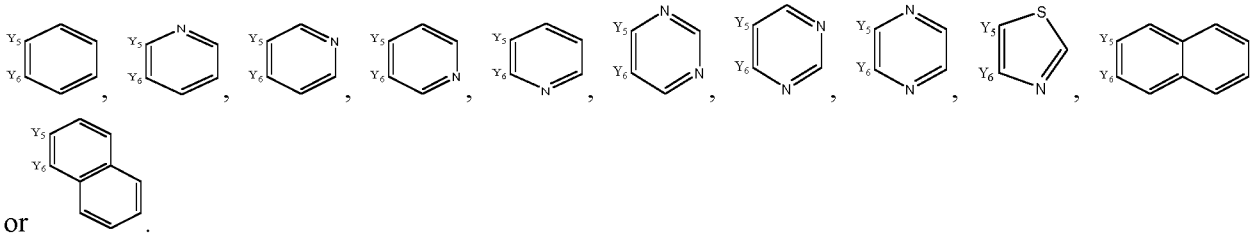
In some embodiments of Formula II, ring C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, ring C is absent, a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or

3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, ring C is absent, a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, a 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula II, ring C is selected from



or .

In some embodiments of Formula II, each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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.

In some embodiments of Formula II, each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula II, each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula II, each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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.

In some embodiments of Formula II, each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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 selected from hydrogen;

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

In some embodiments of Formula II, each of R_{6a} and R_{6b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

In some embodiments of Formula II, each of R_a is independently selected from hydrogen, deuterium, F, Cl, Br, -$NR_{a1}R_{a2}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, -C_{1-3}alkoxy, -C_{1-3}alkyl, -C_{3-6}cycloalkyl,-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-O-C_{1-6}alkyl, -C_{1-3}alkylene-CO-OR_{a1}, -C_{1-3}alkylene-(3-8 membered heterocyclic), -C_{1-3}alkylene-(5-8 membered heteroaryl), -C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, -C_{3-8}carbocyclic, -5-10 membered heteroaryl, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -PO(C_{1-3}alkyl)$_2$, -PO(C_{1-3}alkoxy)$_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

In some embodiments of Formula II, each of R_a is independently selected from hydrogen, deuterium, F, Cl, Br, -$NR_{a1}R_{a2}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, methoxy, ethoxy, propoxy, isopropoxy methyl, ethyl, propyl, isopropyl, -C_{3-6}cycloalkyl,-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-O-C_{1-6}alkyl, -C_{1-3}alkylene-CO-OR_{a1}, -C_{1-3}alkylene-(3-8 membered heterocyclic), -C_{1-3}alkylene-(5-8 membered heteroaryl), -C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, -C_{3-8}carbocyclic, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -PO(C_{1-3}alkyl)$_2$, -PO(C_{1-3}alkoxy)$_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

In some embodiments of Formula II, two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula II, two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula II, two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3 membered heterocyclic ring, a 4 membered heterocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 3 membered carbocyclic ring, a 4 membered carbocyclic ring, a 5 membered carbocyclic ring, a 6 membered carbocyclic ring, wherein each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

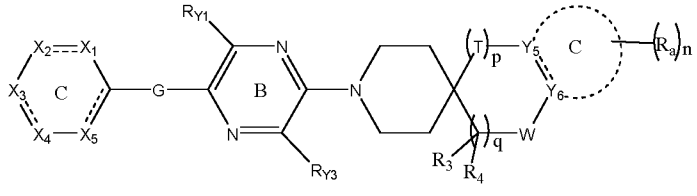
In some embodiments of Formula II, each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula II, each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, 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_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula II, each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

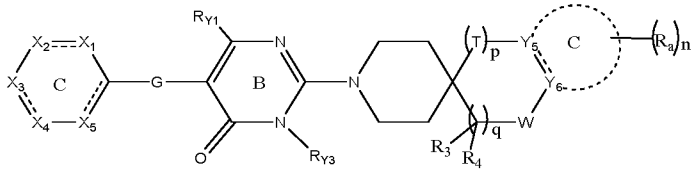
In some embodiments of Formula II, the compound is of Formula II-a:



II-a

X_1, X_2, X_3, X_4, X_5, G, R_{Y1}, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined herein.

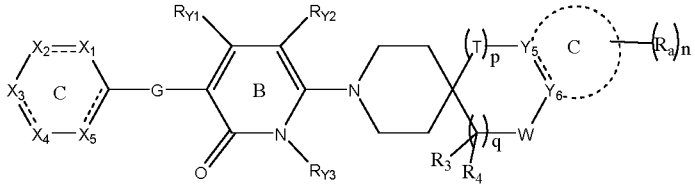
In some embodiments of Formula II, the compound is of Formula II-b



II-b

X_1, X_2, X_3, X_4, X_5, G, R_{Y1}, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined herein.

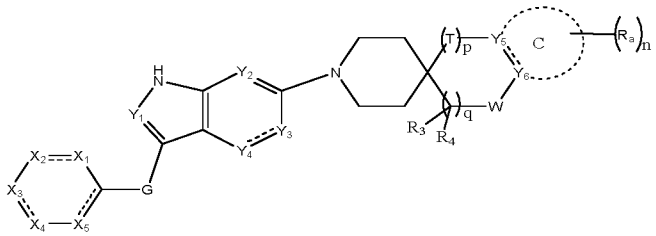
In some embodiments of Formula II, the compound is of Formula II-c



II-c

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y1}, R_{Y2}, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined herein.

The present invention further provides the compound of Formula III or a pharmaceutically acceptable salt thereof:



III

X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1};

each of R_{X1} is selected from hydrogen, deuterium, halogen, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO;

each of R_{X2} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is

independently optionally substituted or unsubstituted;

X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3};

each of R_{X3} is independently selected from hydrogen, deuterium, halogen, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl,$-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl or $-O-C_{1-6}$alkylene-C_{1-6}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted ;

X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4};

each of R_{X4} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

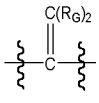
R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_5 is N, NR_{X5} $C(R_{X5})_2$ or CR_{X5};

each of R_{X5} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

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

G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$, $-NR_G-SO_2-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$;

each of R_G is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted or unsubstituted;

Y_1 is N or $CR_{Y1;}$

R_{Y1} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

Y_2 is N or CR_{Y2};

R_{Y2} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

when the "======" in the term "^{Y_3}======^{Y_4}" represents a single bond, Y_3 is NR_{Y3}, and Y_4 is CO;

when the "======" in the term "^{Y_3}======^{Y_4}" represents a double bond, Y_3 is N or CR_{Y3}, and Y_4 is N or CR_{Y4};

R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, halogen, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH ,$-C_{1-6}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

T is absent, O, NR_1 or CR_1R_2;

each of R_1 and R_2 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$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 and R_2 together with the carbon atom to which they are both attached form CO or $C=NR_5$;

p is 0, 1, 2 or 3;

each of R_3 and R_4 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_3 and R_4 together with the carbon atom to which they are both attached form a 3-12 membered heterocyclic ring or 5-12 membered heteroaromatic ring or $C=NR_5$, and each of the ring systems is independently optionally substituted or unsubstituted;

each of R_5 is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

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

W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen, deuterium, 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 C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

when ring C is absent, Y_5 is $CR_{5a}R_{5b}$, NR_{5a} or O, and Y_6 is $CR_{6a}R_{6b}$, NR_{6a} or O;

when ring C is 5-12 membered aromatic ring, 5-12 membered heteroaromatic ring or 5-12 membered heterocyclic ring;

i) Y_5 is CR_{5a} or N, and Y_6 is CR_{6a} or N, when the "======" in the term "^{Y_5}======^{Y_6}"

represents a single bond; or

ii) Y_5 is C, and Y_6 is C, when the "======" in the term "^{Y_5}======^{Y_6}" represents a double bond;

each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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_a is independently hydrogen, deuterium, halogen, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{3-8}$cycloalkyl,$-C_{1-6}$alkylene-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{a1}, $-C_{1-6}$alkylene-(3-10 membered heterocyclic), $-C_{1-6}$alkylene-(5-10 membered heteroaryl), $-C_{1-6}$alkylene-CO-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-CO-C_{1-6}alkyl, -CO-$NR_{a1}R_{a2}$, -COO-C_{1-6}alkyl, -CO-CO-$NR_{a1}R_{a2}$, $-C_{3-10}$carbocyclic, -5-10 membered heteroaryl, -3-10 membered heterocyclic, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-(3-10 membered heterocyclic), -O-C_{1-6}alkylene-CO-OR_{a1}, -O-C_{1-6}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-10}carbocyclic, -O-(3-10 membered heterocyclic), $-NR_{a1}$-CO-C_{1-6}alkyl, $-NR_{a1}$-CO-$NR_{a1}R_{a2}$, $-NR_{a1}$-CO-(5-10 membered heteroaryl), $-NR_{a1}$-CO-C_{3-8}cycloalkyl,$-NR_{a1}$-C_{1-6}alkylene-$NR_{a1}R_{a2}$, $-NR_{a1}$-C_{1-6}alkylene-(3-10 membered heterocyclic), $-NR_{a1}$-C_{1-6}alkylene-(5-10 membered heteroaryl), $-NR_{a1}$-SO_2C_{1-6}alkyl, -S-C_{1-6}alkyl, -SO$NR_{a1}R_{a2}$, $-SO_2NR_{a1}R_{a2}$, -SO-C_{1-6}alkyl, $-SO_2C_{1-6}$alkyl, $-PO(C_{1-6}alkyl)_2$, $-PO(C_{1-6}alkoxy)_2$, -3-10 membered heterocyclic or -5-10 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6; or

two adjacent R_a can be joined together to form a 6-membered aromatic ring, 5-membered heteroaromatic ring, 6-membered heteroaromatic ring, -3-6 membered heterocyclic ring or -3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted; or

R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, 3-10 membered heteroaromatic ring or 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted;

each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, 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 III, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula III, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is

independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}alkylene-C_{3-8}$cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula III, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}alkylene-C_{3-8}$cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-4}$alkyl, $-C_{1-3}$alkoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}alkylene-C_{3-6}$cycloalkyl or 3-6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxy, ethoxy, propoxy, isopropoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}$alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxy, ethoxy, propoxy, isopropoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}$alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, R_{X1} and R_{X2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, R_{X1} and R_{X2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$,

-C_{1-6}alkyl, -C_{1-6}alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, -S-C_{1-6}alkyl, 3-12 membered heterocyclyl, -O-C_{3-8}cycloalkyl or -O-C_{1-6}alkylene-C_{1-6}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

In some embodiments of Formula III, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, -NO_2, -NH_2, -CN, -$CONH_2$, -C_{1-6}alkyl, -C_{1-6}alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, -S-C_{1-6}alkyl, 3-12 membered heterocyclyl, -O-C_{3-8}cycloalkyl or -O-C_{1-6}alkylene-C_{1-6}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, -NO_2, -NH_2, -CN, -$CONH_2$, -C_{1-3}alkyl,-C_{1-3}alkoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, -S-C_{1-3}alkyl, 3-10 membered heterocyclyl, -O-C_{3-6}cycloalkyl or -O-C_{1-3}alkylene-C_{1-3}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, -NO_2, -NH_2, -CN, -$CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, -S-C_{1-3}alkyl, 3-10 membered heterocyclyl, -O-C_{3-6}cycloalkyl or -O-C_{1-3}alkylene-C_{1-3}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, -NO_2, -NH_2, -CN, -$CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, -S-C_{1-3}alkyl, 3-10 membered heterocyclyl, -O-C_{3-6}cycloalkyl or -O-C_{1-3}alkylene-C_{1-3}alkyl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, R_{X2} and R_{X3} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, R_{X2} and R_{X3} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl,, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula III, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl,$-C_{1-3}$alkoxy, -NHCO-(5-10 membered heterocyclyl) or 5-10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, , -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or

isopropoxy.

In some embodiments of Formula III, R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, R_{X3} and R_{X4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, R_{X3} and R_{X4} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula III, X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl,

Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

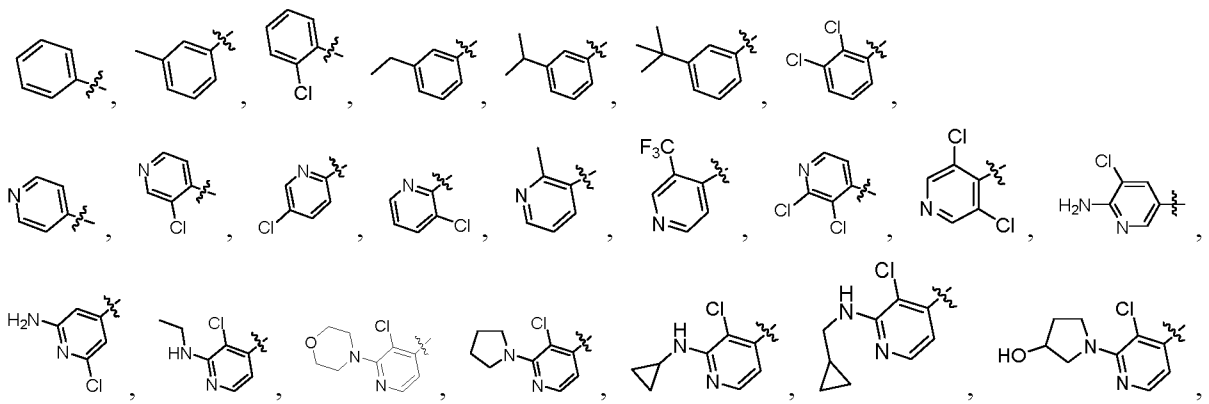
In some embodiments of Formula III, X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

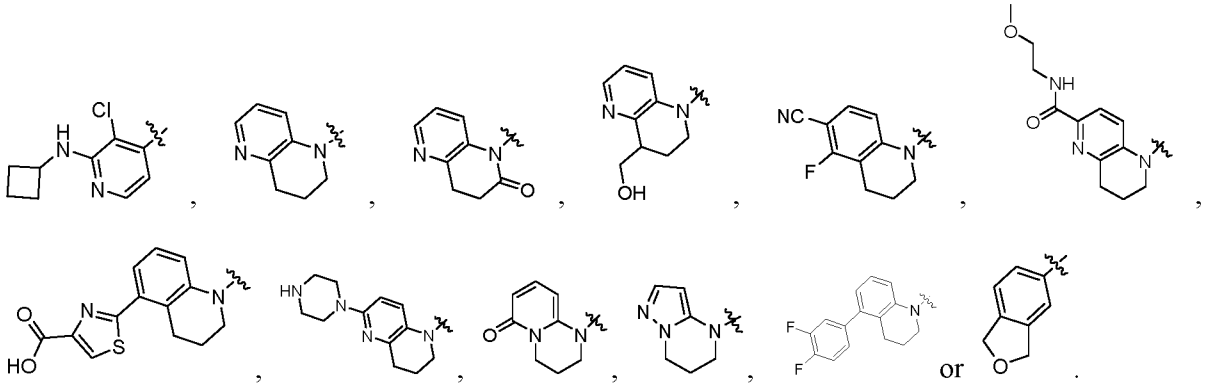
In some embodiments of Formula III, R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

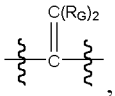
In some embodiments of Formula III, R_{X4} and R_{X5} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

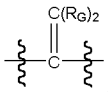
In some embodiments of Formula III, R_{X4} and R_{X5} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

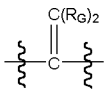
In some embodiments of Formula III, ring A is selected from





In some embodiments of Formula III, G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$; each of R_G is independent selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$; each of R_G is independent selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$; each of R_G is independent selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula III, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula III, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH ,$-C_{1-6}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

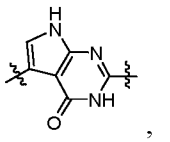
In some embodiments of Formula III, R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH ,$-C_{1-6}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, R_{Y3} and R_{Y4} are independently selected from hydrogen,

deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-3}$alkyl, carboxyl, $-COO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkylene-OH ,$-C_{1-3}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, 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 III, R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, methyl, ethyl, propyl, isopropyl, carboxyl, $-COO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkylene-OH ,$-C_{1-3}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, ring B is selected from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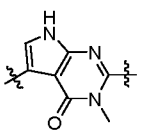
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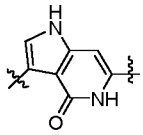
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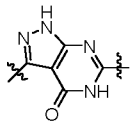
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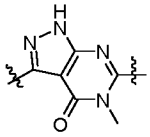
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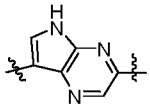
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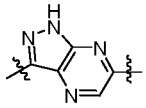
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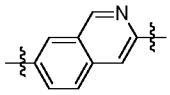
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In some embodiments of Formula III, each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula III, each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}$alkyl, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula III, each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula III, each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, R_1 and R_2 together with the carbon atom to which they are both attached form CO or $C=NR_5$.

In some embodiments of Formula III, R_1 and R_2 together with the carbon atom to which they are both attached form CO.

In some embodiments of Formula III, R_1 and R_2 together with the carbon atom to which they are

both attached form $C=NR_5$.

In some embodiments of Formula III, each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

In some embodiments of Formula III, each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}$alkyl, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula III, each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula III, each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, R_3 and R_4 together with the carbon atom to which they are both attached form 3-12 membered heterocyclic ring or 5-12 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, R_3 and R_4 together with the carbon atom to which they are both attached form 3-10 membered heterocyclic ring or 5-10 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, R_3 and R_4 together with the carbon atom to which they are both attached form 3 membered heterocyclic ring, 4 membered heterocyclic ring, 5 membered heterocyclic ring, 6 membered heterocyclic ring, 7 membered heterocyclic ring, 8 membered heterocyclic ring, 9 membered heterocyclic ring, 10 membered heterocyclic ring, 5 membered heteroaromatic ring, 6 membered heteroaromatic ring, 7 membered heteroaromatic ring, 8 membered heteroaromatic ring, 9 membered heteroaromatic ring, 10 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula III, each of R_5 is independently selected from hydrogen,

deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -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.

In some embodiments of Formula III, W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-CO-C_{1-3}$alkyl, $-CO-OC_{1-3}$alkyl, $-C_{1-3}$alkyl-O-C_{1-3}alkoxy, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

In some embodiments of Formula III, W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN;-OH; $-NO_2$; carboxyl; $-CO-C_{1-3}$alkyl; $-CO-OC_{1-3}$alkyl; $-C_{1-3}$alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula III, W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN;-OH; $-NO_2$; carboxyl; $-CO-C_{1-3}$alkyl; $-CO-OC_{1-3}$alkyl; $-C_{1-3}$alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula III, W is absent, -O, -S or $-C(Rw)_2-$; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN;-OH; $-NO_2$; carboxyl; $-CO-C_{1-3}$alkyl; $-CO-OC_{1-3}$alkyl; $-C_{1-3}$alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

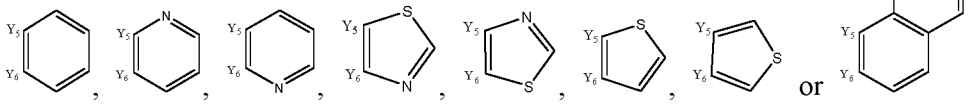
In some embodiments of Formula III, ring C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, ring C is absent, a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally

substituted or unsubstituted.

In some embodiments of Formula III, ring C is absent, a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, a 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

In some embodiments of Formula III, ring C is selected from



In some embodiments of Formula III, each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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.

In some embodiments of Formula III, each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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 III, each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula III, each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

In some embodiments of Formula III, each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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.

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

C_{1-3}alkoxy.

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

In some embodiments of Formula III, each of R_a is independently selected from hydrogen, deuterium, F, Cl, Br, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-3}$alkoxy, $-C_{1-4}$alkyl, $-C_{3-6}$cycloalkyl,$-C_{1-3}$alkylene-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-O-C_{1-6}alkyl, $-C_{1-3}$alkylene-CO-OR_{a1}, $-C_{1-3}$alkylene-(3-8 membered heterocyclic), $-C_{1-3}$alkylene-(5-8 membered heteroaryl), $-C_{1-3}$alkylene-CO-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, $-C_{3-8}$carbocyclic, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -$PO(C_{1-3}alkyl)_2$, -$PO(C_{1-3}alkoxy)_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

In some embodiments of Formula III, each of R_a is independently selected from hydrogen, deuterium, F, Cl, Br, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, methoxy, ethoxy, propoxy, isopropoxy methyl, ethyl, propyl, isopropyl, butyl, isobutyl, $-C_{3-6}$cycloalkyl,$-C_{1-3}$alkylene-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-O-C_{1-6}alkyl, $-C_{1-3}$alkylene-CO-OR_{a1}, $-C_{1-3}$alkylene-(3-8 membered heterocyclic), $-C_{1-3}$alkylene-(5-8 membered heteroaryl), $-C_{1-3}$alkylene-CO-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, $-C_{3-8}$carbocyclic, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -$PO(C_{1-3}alkyl)_2$, -$PO(C_{1-3}alkoxy)_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

In some embodiments of Formula III, two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently

optionally substituted with deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula III, two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3 membered heterocyclic ring, a 4 membered heterocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 3 membered carbocyclic ring, a 4 membered carbocyclic ring, a 5 membered carbocyclic ring, a 6 membered carbocyclic ring, wherein each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, a 3-10 membered heteroaromatic ring or 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted with deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

In some embodiments of Formula III, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, 3-10 membered heteroaromatic ring or 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, a 3-10 membered heteroaromatic ring or a 3-10 membered heterocyclic ring; each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, R_a and R_w with the atom to which they are both attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 5 membered heteroaryl ring, a 6 membered heteroaryl ring, a 5 membered heterocyclic ring or a 6 membered heterocyclic ring; each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

In some embodiments of Formula III, each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, 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.

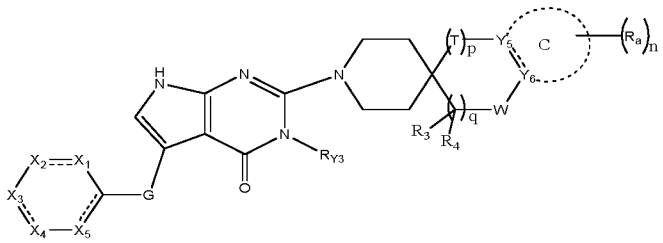
In some embodiments of Formula III, each of R_{a1} and R_{a2} is independently selected from hydrogen,

deuterium, 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 III, each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

In some embodiments of Formula III, each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

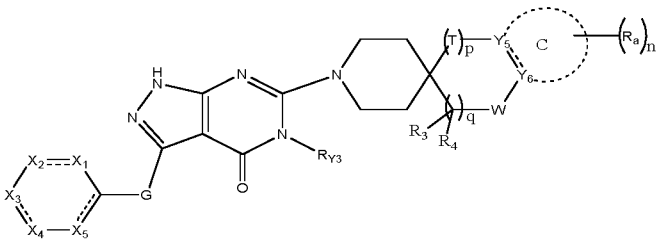
In some embodiments of Formula III, the compound is of Formula III-a:



III-a

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined herein.

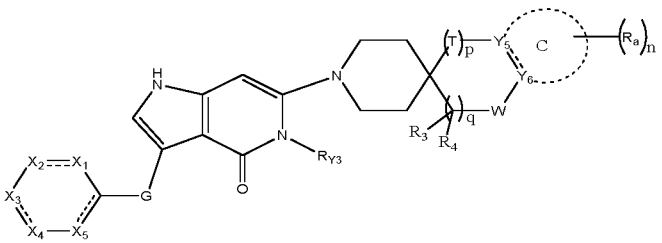
In some embodiments of Formula II, the compound is of Formula III-b:



III-b

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined herein.

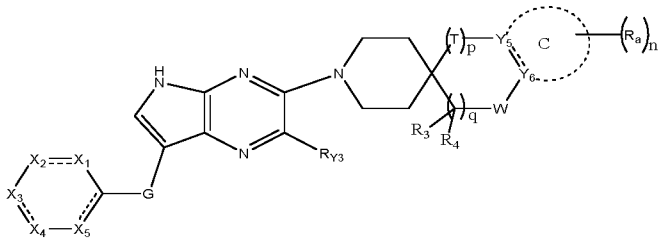
In some embodiments of Formula III, the compound is of Formula III-c:



III-c

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined herein.

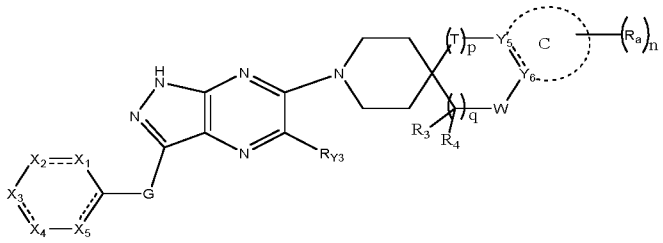
In some embodiments of Formula III, the compound is of Formula III-d:



III-d

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined herein.

In some embodiments of Formula III, the compound is of Formula III-e:



III-e

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined herein.

In some embodiments, the present invention provides a compound selected from the group consisting of:

1	ethyl (S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5--2-carboxylate
2	(S)-1'-(5-(2,3-dichlorophenyl)-6-methylpyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
3	(S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazine-2-carboxylic acid
4	(S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazine-2-carboxamide
5	ethyl (S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2-amino-3-chloropyridin-4-yl)thio)-5-methylpyrazine-2-carboxylate
6	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)-6-methylpyrazin-2-yl)-1,3-dihydrospiro[indene-2 4'-piperidin]-1-amine
7	(S)-1'-(6-amino-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
8	(S)-1'-(4-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrimidin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
9	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
10	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)-6-(methylamino)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
11	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)-6-(dimethylamino)pyrazin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine

12	(S)-1'-(6-amino-5-(thiazol-4-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
13	(S)-1'-(6-amino-5-(thiazol-2-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
14	(S)-1'-(6-amino-5-(quinolin-3-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
15	(S)-5-amino-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidine]-3-carbonitrile
16	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-N-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
17	(S)-1'-(5-((3,5-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
18	(S)-1-amino-1'-(2-((2-cyanopyridin-3-yl)thio)pyrimidin-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carbonitrile
19	(S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro [indene-2,4'-piperidin]-1-amine
20	(S)-1-(5-((5-(4-amino-2-(tert-butyl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-2-chlorophenyl)ethan-1-one
21	(S)-1'-(5-((3-chloro-2-(isopropylamino)pyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
22	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b] pyridine-6,4'-piperidin]-7,7-d2-5-amine
23	(S)-(3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methyl pyrazin-2-yl)methanol
24	(S)-(3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2-amino-3-chloropyridin-4-yl)thio)-5-methylpyrazin-2-yl)methanol
25	(S)-1'-(3-bromo-5-(2,3-dichlorophenyl)-6-methylpyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b] pyridine-6,4'-piperidin]-5-amine
26	(S)-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazine-2-carbonitrile
27	(S)-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazine-2-carboxamide
28	(S)-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazin-2-ol
29	(S)-1'-(6-amino-3-bromo-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
30	(S)-5-amino-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazine-2-carbonitrile
31	(S)-5-amino-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazine-2-carboxamide

32	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
33	(S)-1'-(6-((2-amino-3-chloropyridin-4-yl)thio)pyridin-3-yl)-5,7-dihydrospiro[cyclopenta[b] pyridine-6,4'-piperidin]-5-amine
34	(S)-1'-(4-((2-amino-3-chloropyridin-4-yl)thio)phenyl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6, 4'-piperidin]-5-amine
35	(S)-1'-(4-((2-amino-3-chloropyridin-4-yl)thio)isoquinolin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
36	(S)-6-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-3-(2,3-dichlorophenyl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
37	(S)-6-(1-amino-6-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(2,3-dichlorophenyl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
38	(S)-6-(1-amino-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-methyl-3-(5-methylthiophen-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
39	(S)-2-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-5-(2,3-dichlorophenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
40	(S)-6-amino-2-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-((2-amino-3-chloropyridin-4-yl)thio)-3-methylpyrimidin-4(3H)-one
41	(S)-1'-(6-amino-5-((4-chlorothiazol-2-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d] thiazole-5,4'-piperidin]-4-amine
42	(S)-1-amino-1'-(5-((4-amino-5-bromopyrimidin-2-yl)thio)-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
43	(S)-6-(1-amino-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-((3-chloro-2-methoxypyridin-4-yl)thio)-1-methylpyridin-2(1H)-one
44	(S)-1-amino-1'-(4-(6-bromonaphthalen-2-yl)thiazol-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
45	(S)-1'-(6-amino-5-(2-chloro-3-methylphenyl)pyrazin-2-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
46	(S)-1'-(5-(3-amino-2-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
47	(S)-1'-(6-amino-5-(2-chloro-3-methylphenyl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
48	(S)-1'-(6-(5-chlorothiophen-2-yl)pyridazin-3-yl)-5-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
49	(S)-1'-(6'-chloro-[3,3'-bipyridazin]-6-yl)-5-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
50	(S)-1'-(3-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
51	(R)-1'-(5-(2,3-dichloro-5-methoxyphenyl)pyridin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine

52	(S)-6'-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1'-methyl-2'-oxo-1',2'-dihydro-[3,3'-bipyridine]-2-carbonitrile
53	(S)-6'-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1'-methyl-2'-oxo-1',2'-dihydro-[3,3'-bipyridine]-2-carboxamide
54	(S)-1'-(4-(3-methoxyphenyl)cyclohexyl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
55	(S)-1-amino-1'-(6-((3-amino-2-chlorophenyl)thio)-1,2,4-triazin-3-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
56	1-(5-((5-((1S)-1-amino-6-(methylsulfinyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-2-chlorophenyl)ethan-1-one
57	(S)-1'-(5-(pyrimidin-2-ylthio)pyrazin-2-yl)-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
58	(S)-6-bromo-5-fluoro-1'-(5-(quinolin-4-ylthio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
59	(S)-6-(4-amino-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)-3-(3-(trifluoromethyl)pyridin-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
60	(S)-2-(1-amino-6-chloro-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(3,5-dichloropyridin-4-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
61	(S)-1'-(7-(5-chloropyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-3-amine
62	(S)-1'-(7-(3-chloropyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-1H,3H-spiro[phenalene-2,4'-piperidin]-1-amine
63	(R)-1'-(3-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-3-amine
64	(S)-6-amino-2-(1-amino-7-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-phenylpyrimidin-4(3H)-one
65	(S)-1-amino-1'-(4-amino-6-oxo-5-(pyridazin-3-ylthio)-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-7-carbonitrile
66	(S)-1-amino-1'-(1-methyl-6-oxo-5-(pyrazin-2-yl)-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-7-carbonitrile
67	(S)-2-(1-amino-6-chloro-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-((4-isopropylphenyl)thio)pyrimidin-4(3H)-one
68	(S)-4-amino-6-(1-amino-6-bromo-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(2-chloro-3-methylphenyl)-1-methylpyridin-2(1H)-one
69	(S)-6-(4-acetyl-1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-4-amino-3-(4-(trifluoromethyl)phenyl)pyridin-2(1H)-one
70	(S)-6'-(1-amino-4-hydroxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-2'-oxo-1',2'-dihydro-[3,3'-bipyridine]-2-carbonitrile
71	(S)-1'-(3-bromo-5-(1H-indol-6-yl)-6-methylpyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine

72	(S)-3-(4-amino-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-5-methyl-6-(2-oxoindolin-7-yl)pyrazine-2-carbonitrile
73	(S)-1'-(5-amino-6-((2-amino-3-chloropyridin-4-yl)thio)-1,2,4-triazin-3-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
74	(S)-1'-(5-amino-6-((2-amino-3-chloropyridin-4-yl)thio)pyridin-3-yl)-6-chloro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
75	(S)-1'-(4-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
76	(S)-1'-(5-((2,3-dichlorophenyl)thio)thiazol-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine
77	(R)-1'-(4-((3-chloropyridin-4-yl)thio)thiazol-2-yl)spiro[indoline-2,4'-piperidin]-3-amine
78	(R)-1'-(2-(7-chloro-1H-indol-1-yl)thiazol-4-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
79	(R)-1'-(2-((2-(trifluoromethyl)phenyl)thio)thiazol-5-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine
80	(S)-(5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)(2,3-dichlorophenyl)methanone
81	(S)-2-(1-amino-6-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(indolin-1-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
82	(S)-1'-(5-((1,2,3,4-tetrahydroquinolin-8-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[b]naphthalene-2,4'-piperidin]-1-amine
83	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-1-amine
84	1'-(5-((3-amino-2-chlorophenyl)thio)-6-methylpyrazin-2-yl)-1-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
85	(R)-1'-(7-((2-amino-3-chloropyridin-4-yl)thio)-1H-indol-4-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine
86	(S)-1'-(7-((2-amino-3-chloropyridin-4-yl)thio)isoquinolin-3-yl)-5,6-dibromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
87	(S)-4-((5-(5-acetyl-1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-aminopyrazin-2-yl)thio)-3-chloro-1-methylpyridin-2(1H)-one
88	(S)-5-(1-amino-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-2-((2,3-dichlorophenyl)thio)-6-(hydroxymethyl)pyridin-3-ol
89	(S)-6-bromo-1'-(5-(2,3-dichlorophenyl)-6-methylimidazo[1,5-a]pyrazin-8-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
90	(S)-1'-(7-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,5]thiadiazolo[3,4-c]pyridin-4-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
91	(S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)pyrido[4,3-d]pyrimidin-5-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

92	(S)-3-(5-(1-amino-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyridin-2-yl)-4,5-dichlorophenol
93	(S)-1-amino-1'-(5-(5-methylthiophen-2-yl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
94	(S)-1'-(5-(1H-indol-7-yl)pyrazin-2-yl)-5-ethyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
95	(S)-1'-(5-(cyclohex-1-en-1-yl)pyrazin-2-yl)-5-isopropyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
96	(S)-N-(1-amino-1'-(5-(2-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)methanesulfonamide
97	(S)-1'-(5-((4-(trifluoromethyl)pyrimidin-5-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine
98	(S)-1'-(5-((2-chloropyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
99	(S)-4-((5-(5-amino-5,7-dihydrospiro[cyclopenta[d]pyrimidine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chlorobenzoic acid
100	(S)-1'-(5-((3-(trifluoromethyl)pyrazin-2-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine
101	(S)-1'-(5-((3-chloropyridazin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[d]pyrimidine-6,4'-piperidin]-7-amine
102	(S)-4-((5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyrazine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chlorobenzamide
103	(S)-(1-amino-1'-(5-((3-chloro-2-(methylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)dimethylphosphine oxide
104	(S)-1-amino-1'-(6-amino-5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-5-carboxylic acid
105	ethyl (S)-1-amino-1'-(5-((3-chloro-2-(methylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-5-carboxylate
106	(S)-1'-(5-((3-(morpholinomethyl)phenyl)thio)pyrazin-2-yl)-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
107	(S)-6-bromo-5-fluoro-1'-(5-((3-(pentafluoro-l6-sulfanyl)phenyl)thio)pyrazin-2-yl)-1,3 -dihydrospiro[indene-2,4'-piperidin]-1-amine
108	(S)-N-(3-((5-(1-amino-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)phenyl)cyclopropanecarboxamide
109	(S)-6-(6-amino-1-bromo-4H,6H-spiro[cyclopenta[c]thiophene-5,4'-piperidin]-1'-yl)-3-(m-tolyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
110	(S)-2-(1-amino-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(3-ethylphenyl)-3 -methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one

111	(R)-1'-(3-(3-(tert-butyl)phenyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3,4-dihydro-1H-spiro [naphthalene-2,4'-piperidin]-3-amine
112	(S)-2-(3-amino-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-1'-yl)-5-(3-isopropylphenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
113	(S)-1-amino-1'-(3-(3-chloro-2-morpholinopyridin-4-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c] pyridin-6-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
114	(S)-1'-(7-(3-chloro-2-(cyclobutylamino)pyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-3-amine
115	(S)-1'-(3-(3-chloro-2-(cyclopropylamino)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-N6-methyl-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
116	(S)-5-amino-1'-(3-(3-chloro-2-(pyrrolidin-1-yl)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-2-fluoro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-3-carboxamide
117	1-(4-(6-((S)-4-amino-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-3-chloropyridin-2-yl)pyrrolidin-3-ol
118	(S)-1'-(3-(3-chloro-2-((cyclopropylmethyl)amino)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl) -N6,N6-dimethyl-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
119	(S)-1'-(3-(2-amino-6-chloropyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-2-(tert-butyl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine
120	(S)-2-chloro-1'-(3-(1,3-dihydroisobenzofuran-5-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine
121	(S)-3-chloro-1'-(3-((2-chlorophenyl)thio)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
122	(S)-1'-(3-(3-chloro-2-(ethylamino)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine
123	(R)-1'-(7-(methyl(pyridin-4-yl)amino)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-3H-spiro[furo[2,3-b] pyridine-2,4'-piperidin]-3-amine
124	(R)-1'-(3-((3-chloropyridin-4-yl)amino)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-6,7-dihydrospiro [cyclopenta[b]pyridine-5,4'-piperidin]-6-amine
125	(S)-2-methoxy-1'-(3-(1-phenylvinyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro [cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
126	(R)-1-(3-benzyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1',3'-dihydrospiro[piperidine-4,2'-pyrrolo [2,3-b]pyridin]-3'-amine
127	(S)-(6-(6-amino-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-1H-pyrazolo [3,4-b]pyrazin-3-yl)(phenyl)methanone
128	(4S)-1'-(3-(1-phenylethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta [d]thiazole-5,4'-piperidin]-4-amine
129	1-(6-((S)-5-amino-2-methoxy-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-1-phenylethan-1-ol
130	(S)-1'-(3-((2,3-dichloropyridin-4-yl)oxy)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine

131	(S)-6-bromo-1'-(3-(5-(3,4-difluorophenyl)-3,4-dihydroquinolin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
132	(S)-6-amino-2-(1-amino-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(4-cyclopropoxyphenyl)-3-methylpyrimidin-4(3H)-one
133	(S)-N-(1-amino-1'-(4-amino-5-((4-(methylthio)phenyl)thio)-6-oxo-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide
134	(S)-2-(1-amino-6-(methylamino)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(4-(benzyloxy)phenyl)-3-methylpyrimidin-4(3H)-one
135	(S)-2-(7-acetyl-1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(benzo[d][1,3]dioxol-4-ylthio)pyrimidin-4(3H)-one
136	4-amino-6-((1S)-1-amino-7-(1-hydroxyethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(4-(difluoromethoxy)phenyl)-1-methylpyridin-2(1H)-one
137	(S)-1-amino-1'-(4-amino-6-oxo-5-(4-phenoxyphenyl)-1,6-dihydropyridin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carbonitrile
138	(S)-6-(1-amino-4-hydroxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(4-cyclohexylphenyl)-1-methylpyridin-2(1H)-one
139	(S)-3-([1,1'-biphenyl]-4-yl)-6-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyridin-2(1H)-one
140	(S)-6-amino-2-(1-amino-6-(2-oxopiperidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-(4-(trifluoromethoxy)phenyl)pyrimidin-4(3H)-one
141	(S)-1-(1-amino-1'-(4-amino-5-((4-cyanophenyl)thio)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)urea
142	(S)-4-amino-6-(1-amino-6-chloro-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1-methyl-3-(4-(tetrahydro-2H-pyran-4-yl)phenyl)pyridin-2(1H)-one
143	(S)-6-(1-amino-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(4-(2-methoxyethoxy)phenyl)-1-methylpyridin-2(1H)-one
144	(S)-6-amino-2-(1-amino-6-(piperidine-1-carbonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-(quinolin-8-ylthio)pyrimidin-4(3H)-one
145	(S)-6-amino-2-(1-amino-6-morpholino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-((4-nitrophenyl)thio)pyrimidin-4(3H)-one
146	(S)-6-amino-2-(5-amino-3-nitro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-3-methyl-5-(quinolin-8-ylthio)pyrimidin-4(3H)-one
147	(S)-6-(5-amino-3-(4-methylpiperazin-1-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-1-methyl-3-(naphthalen-1-ylthio)pyridin-2(1H)-one
148	(S)-2-(1-amino-6-(1H-pyrrol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-((2,2-difluorobenzo[d][1,3]dioxol-4-yl)thio)pyrimidin-4(3H)-one
149	(S)-7-(5-(1-amino-6-(1H-imidazol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(hydroxymethyl)-3-methylpyrazin-2-yl)isoindolin-1-one
150	(S)-3-(1-amino-6-(ethylamino)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(1H-indol-5-yl)-5-methylpyrazine-2-carboxamide

151	(S)-N-(1-amino-1'-(3-bromo-5-(1H-indol-6-yl)-6-methylpyrazin-2-yl)-1,3-dihydrospiro [indene-2,4'-piperidin]-6-yl)cyclopropanecarboxamide
152	(S)-4-(6-amino-5-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methylpyrazin-2-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one
153	(S)-3-(1-amino-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-methyl-6-(2-oxoindolin-7-yl)pyrazine-2-carbonitrile
154	(S)-N-(5-(1-amino-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2-hydroxyethyl)amino)-3-methylpyrazin-2-yl)benzenesulfonamide
155	(S)-1'-(6-methyl-3-(1H-pyrazol-5-yl)-5-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
156	(S)-2-(3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(8-chlorochroman-7-yl)-5-methylpyrazin-2-yl)propan-2-ol
157	(S)-6-chloro-1'-(5-(7-chloro-2,3-dihydrobenzofuran-6-yl)pyrazin-2-yl)-1,3-dihydrospiro [indene-2,4'-piperidin]-1-amine
158	(S)-4-bromo-1'-(5-(3-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrazin-2-yl)-1,3-dihydrospiro [indene-2,4'-piperidin]-1-amine
159	(S)-1-amino-1'-(6-cyano-5-(1H-indazol-7-yl)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
160	(S)-1'-(5-(1H-indol-3-yl)-6-iodopyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
161	(R)-6-(5-(7'-amino-7',8'-dihydro-5'H-spiro[piperidine-4,6'-quinolin]-1-yl)-3-vinylpyrazin-2-yl) isoindolin-1-one
162	(R)-1-(4-(5-(6-amino-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-1'-yl)-3-ethylpyrazin-2-yl)-3,3-difluoroindolin-1-yl)ethan-1-one
163	(S)-1'-(5-(3-methyl-1H-indazol-6-yl)-6-phenylpyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b] pyridine-6,4'-piperidin]-5-amine
164	(S)-1'-(5-(1H-benzo[d][1,2,3]triazol-6-yl)-6-cyclopropylpyrazin-2-yl)-6-((tetrahydro-2H-pyran-4-yl)oxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
165	(S)-1-amino-1'-(3-((1-methyl-1H-imidazol-2-yl)thio)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
166	(S)-1'-(3-(1H-benzo[d]imidazol-1-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
167	(S)-1-(6-(1-amino-5-chloro-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one
168	(1-(6-((S)-1-amino-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo [3,4-b]pyrazin-3-yl)-1,2,3,4-tetrahydro-1,5-naphthyridin-4-yl)methanol
169	1-(6-((1S)-1-amino-6-(methylsulfinyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoro-1,2,3,4-tetrahydroquinoline-6-carbonitrile
170	(S)-6-chloro-1'-(3-(2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl) -5-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

171	(S)-5-(6-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-N-(2-methoxyethyl)-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carboxamide
172	(S)-1-amino-5-fluoro-1'-(3-(6-(piperazin-1-yl)-3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
173	(S)-2-(1-(6-(1-amino-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-1,2,3,4-tetrahydroquinolin-5-yl)thiazole-4-carboxylic acid
174	(S)-1'-(6-(aminomethyl)-5-(2,3-dichloropyridin-4-yl)pyrazin-2-yl)-6-(1H-imidazol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
175	(1S)-1-amino-1'-(5-(2,3-dichloropyridin-4-yl)-3-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)-6-methylpyrazin-2-yl)-N,N-dimethyl-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
176	(S)-1'-(8-(2-amino-3-chloropyridin-4-yl)-7-methylimidazo[1,2-c]pyrimidin-5-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
177	(S)-1'-(5-(1-methyl-1H-indol-2-yl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-3,3-d2-1-amine
178	(S)-1-(6-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrimidin-6-one
179	(S)-1'-(3-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
180	(3-((S)-1-amino-6-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((R)-1-methylisoindolin-2-yl)pyrazin-2-yl)methanol
181	(S)-1'-(3-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5,5-d2-7-amine
182	(S)-4-(difluoromethyl)-1'-(5-methyl-6-((R)-2-methyl-3,4-dihydro-1,5-naphthyridin-1(2H)-yl)pyridin-3-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
183	(S)-1'-(8-(2-chloro-3-(isopropyl(methyl)amino)phenyl)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-2,3,6,8-tetrahydrospiro[indeno[5,6-b][1,4]dioxine-7,4'-piperidin]-6-amine
184	(S)-1-(5-amino-1'-(8-((5-chloro-1-methylindolin-6-yl)thio)imidazo[1,5-a]pyridin-5-yl)-2,3,5,7-tetrahydro-1H-spiro[cyclopenta[b]pyrrolo[3,2-e]pyridine-6,4'-piperidin]-1-yl)ethan-1-one

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The present invention further provides a pharmaceutical composition comprising at least one compound or a pharmaceutically acceptable salt thereof as defined herein and at least one pharmaceutically acceptable excipient.

In some embodiments, the compound in a weight ratio to the said excipient within the range from about 0.0001 to about 10.

The present invention additionally provides a combination pharmaceutical product comprising the compound or a pharmaceutically acceptable salt thereof mentioned above, together with one or more other therapeutically active agents.

The present invention further provides use of the above-mentioned compound or a pharmaceutically acceptable salt thereof, the above-mentioned pharmaceutical composition, or the above-mentioned combination pharmaceutical product for the preparation of a medicament.

In some embodiments, the medicament is used for the treatment or prevention of cancer, cancer metastasis , cardiovascular disease, an immunological disorder or an ocular disorder.

The present invention additionally provides use, in the manufacture of a medicament for use as an inhibitor of SHP2, of at least one above-mentioned compound or a pharmaceutically acceptable salt thereof, the above-mentioned pharmaceutical composition, or the above-mentioned combination pharmaceutical product.

The present invention further provides use of the above-mentioned compound or a pharmaceutically acceptable salt thereof, the above-mentioned pharmaceutical composition, or the above-mentioned combination pharmaceutical product for the preparation of a medicament in the treatment of diseases or conditions mediated by the activity of SHP2.

In some embodiments, wherein the diseases or conditions mediated by the activity of SHP2 is cancer.

In some embodiments, the diseases or conditions mediated by the activity of SHP2 is selected from 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, anaplastic large-cell lymphoma and glioblastoma.

The present invention additionally provides a method for preventing or treating a disease, lessening a disease symptoms, delaying the progression or onset of a disease, comprising administering to the patient in need thereof a therapeutically effective amount of the above-mentioned compound or the pharmaceutically acceptable salt thereof, the above-mentioned pharmaceutical composition, or the above-mentioned combination pharmaceutical product, and the disease is cancer, cancer metastasis, cardiovascular disease, an immunological disorder or an ocular disorder.

The present invention further provides a method for inhibiting the activity of SHP2 level, comprising administering to the patient in need thereof a therapeutically effective amount of the above-mentioned compound or the pharmaceutically acceptable salt thereof, or the above-mentioned pharmaceutical composition, or the above-mentioned combination pharmaceutical product.

The present invention additionally provides a method for preventing or treating a disease, lessening a disease symptoms, delaying the progression or onset of a disease, comprising administering to the patient in need thereof a therapeutically effective amount of the above-mentioned compound or the pharmaceutically acceptable salt thereof, the above-mentioned pharmaceutical composition, or the above-mentioned combination pharmaceutical product, and the disease is mediated by the activity of SHP2.

In some embodiments, the disease mediated by the activity of SHP2 is cancer.

In some embodiments, the disease mediated by the activity of SHP2 is selected from 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, anaplastic large-cell lymphoma and glioblastoma.

The present invention further provides the above-mentioned compound or the pharmaceutically acceptable salt thereof, the above-mentioned pharmaceutical composition, or the above-mentioned combination pharmaceutical product for use in preventing or treating a disease, lessening a disease symptom, delaying the progression or onset of a disease, wherein the disease is cancer, cancer metastasis , cardiovascular disease, an immunological disorder or an ocular disorder.

The present invention additionally provides the above-mentioned compound or the pharmaceutically acceptable slat thereof, the above-mentioned pharmaceutical composition , or the above-mentioned combination pharmaceutical product, for use in inhibiting the activity of SHP2.

The present invention further provides the above-mentioned compound or the pharmaceutically acceptable salt thereof, the above-mentioned pharmaceutical composition, or the above-mentioned combination pharmaceutical product for use in preventing or treating a disease, lessening a disease symptom, delaying the progression or onset of a disease, and the disease is mediated by the activity of SHP2.

In some embodiments, the disease mediated by the activity of SHP2 is cancer.

In some embodiments, the disease mediated by the activity of SHP2 is selected from 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, anaplastic large-cell lymphoma and glioblastoma.

Definition

As used herein, the singular form "a", "an", and "the" include plural references unless indicated otherwise. For example, "a" substituent includes one or more substituents.

As used herein, the term "alkyl" is defined to include saturated aliphatic hydrocarbons including straight chains and branched chains. In some embodiments, the alkyl group has 1 to 20 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. For example, the term "C_{1-6} alkyl," as well as the alkyl moieties of other groups referred to herein (e.g., C_{1-6} alkoxy) refers to linear or branched radicals of 1 to 6 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, or n-hexyl). For yet another example, the term "C_{1-4} alkyl" refers to linear or branched aliphatic hydrocarbon chains of 1 to 4 carbon atoms; the term "C_{1-3} alkyl" refers to linear or branched aliphatic hydrocarbon chains of 1 to 3 carbon atoms; the term "C_{1-2} alkyl" refers to methyl and/or ethyl; and the term "C1 alkyl" refers to methyl. An alkyl group optionally can be substituted by one or more (e.g., 1 to 5) suitable substituents.

As used herein, the term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. For example, the term "C_{1-6} alkoxy" or "C_{1-6} alkyloxy" refers to an -O-(C_{1-6} alkyl) group; and the term "C_{1-4} alkoxy" or "C_{1-4} alkyloxy" refers to an -O-(C_{1-4} alkyl) group; For another example, the term "C_{1-2} alkoxy" or "C_{1-2} alkyloxy" refers to an -O-(C_{1-2} alkyl) group. Examples of alkoxy include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), tert-butoxy, and the like. The alkoxy or alkyloxy group optionally can be substituted by 1 or more (e.g., 1 to 5) suitable substituents.

As used herein, the term "Alkylene" refers to a divalent hydrocarbyl group having the specified

number of carbon atoms which can link two other groups together. Sometimes it refers to a group -$(CH_2)_t$- where t is 1-8, and preferably t is 1-4. Where specified, an alkylene can also be substituted by other groups and may include one or more degrees of unsaturation (i.e., an alkenylene or alkynlene moiety) or rings. The open valences of an alkylene need not be at opposite ends of the chain. Thus branched alkylene groups such as -CH(Me)- , -CH_2CH(Me)- and -$C(Me)_2$- are also included within the scope of the term "alkylenes" as are cyclic groups such as cyclopropan-1,1-diyl and unsaturated groups such as ethylene (-CH=CH-) or propylene (-CH_2-CH=CH-). Where an alkylene group is described as optionally substituted, the substituents include those typically present on alkyl groups as described herein.

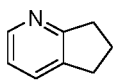
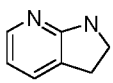
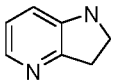
As used herein, the term "halo" or "halogen" refers to fluoro (which may be depicted as -F), chloro (which may be depicted as -Cl), bromo (which may be depicted as -Br), or iodo (which may be depicted as -I). The preferred halogen groups include F, Cl and Br. The terms "haloC_{1-6}alkyl", "haloC_{2-6}alkenyl", "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 to 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, the term "n-membered", where n is an integer, typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, pyridine is an example of a 6-membered heteroaryl ring and thiophene is an example of a 5-membered heteroaryl group.

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual sub-combination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to include C_1 alkyl (methyl), C_2 alkyl (ethyl), C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl. For another example, the term "a 5- to 12-membered heteroaryl group" is specifically intended to include any 5-, 6-, 7-, 8-, 9-, 10-, 11- or 12-membered heteroaryl group.

As used herein, the term "oxo" refers to =O. When an oxo is substituted on a carbon atom, they together form a carbonyl moiety [-C(=O)-]. When an oxo is substituted on a sulfur atom, they together form a sulfinyl moiety [-S(=O)-]; when two oxo groups are substituted on a sulfur atom, they together form a sulfonyl moiety [-$S(=O)_2$-].

As used herein, the term "aryl" or "aromatic" refers to an optionally substituted monocyclic or fused bicyclic or polycyclic ring system having the well-known characteristics of aromaticity, wherein at least one ring contains a completely conjugated pi-electron system. Typically, aryl groups contain 6 to 20 carbon atoms ("C_6-C_{20} aryl") as ring members, preferably 6 to 14 carbon atoms ("C_6-C_{14} aryl") or more preferably, 6 to 12 carbon atoms ("C_6-C_{12} aryl"). Fused aryl groups may include an aryl ring (e.g., a phenyl ring) fused to another aryl or heteroaryl ring, or fused to a saturated or partially unsaturated carbocyclic or heterocyclic ring, provided the point of attachment to the base molecule on such fused ring systems is an atom of the aromatic portion of the ring system. Examples, without limitation, of aryl groups include phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and tetrahydronaphthyl. The aryl group is unsubstituted or substituted as further described herein.

As used herein, the term "heteroaryl" or "heteroaromatic" refers to monocyclic or fused bicyclic or polycyclic ring systems having the well-known characteristics of aromaticity that contain the specified number of ring atoms and include at least one heteroatom selected from N, O and S as a ring member in an aromatic ring. The inclusion of a heteroatom permits aromaticity in 5-membered rings as well as 6-membered rings. Typically, heteroaryl groups contain 5 to 20 ring atoms ("5-20 membered heteroaryl"), preferably 5 to 14 ring atoms ("5-14 membered heteroaryl"), and more preferably 5 to 12 ring atoms ("5-12 membered heteroaryl"). Heteroaryl rings are attached to the base molecule via a ring atom of the heteroaromatic ring, such that aromaticity is maintained. Thus, 6-membered heteroaryl rings may be attached to the base molecule via a ring C atom, while 5-membered heteroaryl rings may be attached to the base molecule via a ring C or N atom. Heteroaryl groups may also be fused to another aryl or heteroaryl ring, or fused to a saturated or partially unsaturated carbocyclic or heterocyclic ring, provided the point of attachment to the base molecule on such fused ring systems is an atom of the heteroaromatic portion of the ring system. Examples of unsubstituted heteroaryl groups often include, but are not limited to, pyrrole, furan, thiophene, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, oxadiazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, benzofuran, benzothiophene, indole, benzimidazole, indazole, indazole,  ,  ,  , quinoline, isoquinoline, purine, triazine, naphthryidine and carbazole. In frequent preferred embodiments, 5- or 6-membered heteroaryl groups are selected from the group consisting of pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, pyridinyl and pyrimidinyl, pyrazinyl or pyridazinyl rings. The heteroaryl group is unsubstituted or substituted as further described herein.

As used herein, the term "heterocyclyl", "heterocyclic" or "heteroalicyclic" used interchangeably herein refers to a non-aromatic, saturated or partially unsaturated ring system containing the specified number of ring atoms, including at least one heteroatom selected from N, O and S as a ring member, where ring S atoms are optionally substituted by one or two oxo groups (i.e., $S(O)_x$, where x is 0, 1 or 2) and where the heterocyclic ring is connected to the base molecule via a ring atom, which may be C or N. Heterocyclic rings include rings which are spirocyclic, bridged, or fused to one or more other heterocyclic or carbocyclic rings, where such spirocyclic, bridged, or fused rings may themselves be saturated, partially unsaturated or aromatic to the extent unsaturation or aromaticity makes chemical sense, provided the point of attachment to the base molecule is an atom of the heterocyclic portion of the ring system. Preferably, heterocyclic rings contain 1 to 4 heteroatoms selected from N, O, and $S(O)_q$ as ring members, and more preferably 1 to 2 ring heteroatoms, provided that such heterocyclic rings do not contain two contiguous oxygen atoms. Heterocyclyl groups are unsubstituted or substituted by suitable substituent groups, for example the same groups that are described herein as suitable for alkyl, aryl or heteroaryl. Such substituents may be present on the heterocycylic ring attached to the base molecule, or on a spirocyclic, bridged or fused ring attached thereto. In addition, ring N atoms are optionally substituted by groups suitable for an amine, e.g., alkyl, acyl, carbamoyl, sulfonyl substituents, and the like.

As used herein, the term "cycloalkyl" refers to a non-aromatic, saturated or partially unsaturated carbocyclic ring system containing the specified number of carbon atoms, which may be a monocyclic, spirocyclic, bridged or fused bicyclic or polycyclic ring system that is connected to the base molecule

through a carbon atom of the cycloalkyl ring. Typically, the cycloalkyl groups of the invention contain 3 to 12 carbon atoms ("C_3-C_{12} cycloalkyl"), preferably 3 to 8 carbon atoms ("C3-C8 cycloalkyl"). Representative examples include, e.g., cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, cycloheptatriene, adamantane, and the like. Cycloalkyl groups are unsubstituted or substituted by the same groups that are described herein as suitable for alkyl.

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 deuterium-labeled or -enriched compounds.

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.

"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 “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 "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 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 is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I 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) 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) 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) 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 (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, 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, 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. The compounds of Formula I, 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 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 wherein 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, 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

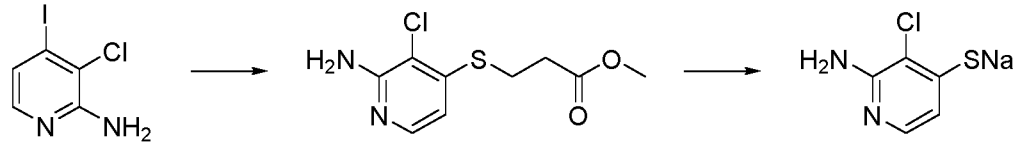
The following Examples are provided to better illustrate the present invention. All parts and percentages are by weight and all temperatures are degrees Celsius, unless explicitly stated otherwise. The following abbreviations have been used in the examples:

DMF	N,N-Dimethylformamide
EA	Ethyl acetate
Hex	Hexane
MeOH	Methanol
DCM	Dichloromethane
DCE	1,2-Dichloroethane
EtOH	Ethanol
t-BuOH	tert-Butanol
iPrOH	Propan-2-ol

CD_3I	Iodomethane-d3
LiHMDS	Lithium bis(trimethylsilyl)amide
THF	Tetrahydrofuran
$Ti(OEt)_4$	Titanium ethoxide
NMP	1-Methyl-2-pyrrolidinone
DIPEA	N,N-Diisopropylethylamine
$(Boc)_2O$	Di-tert-butyl dicarbonate
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
PPA	Polyphosphoric acids
TEA	Triethylamine
PPh_3	Triphenylphosphane
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
BINAP	2,2'-Bis(diphenylphosphanyl)-1,1'-binaphthalene
DavePhos	2'-(dicyclohexylphosphanyl)-N,N-dimethyl-[1,1'-biphenyl]-2-amine
$Pd(OAc)_2$	Palladium diacetate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex
BOP	Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate
PyBOP	Benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
$K_4Fe(CN)_6 \cdot 3H_2O$	Potassium ferrocyanide trihyrate
$Cy_3PH \cdot BF_4$	Tricyclohexylphosphonium tetrafluoroborate
t-BuOK	Potassium tert-butoxide
NaOEt	Sodium ethoxide
NCS	N-Chlorosuccinimide
NBS	N-Bromosuccinimide
NIS	N-Iodosuccinimide
TFA	2,2,2-Trifluoroacetic acid
RT	Room temperature
min	minute(s)
h	hour(s)
aq	aqueous
sat	saturated

TLC	Thin layer chromatography
Prep - TLC	Preparative thin layer chromatography

Intermediate A1

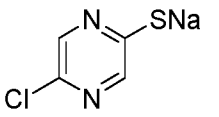
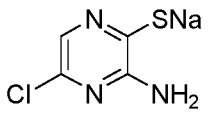
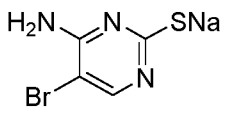
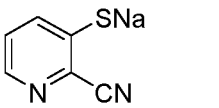
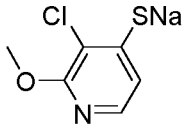


A1-1 **A1**

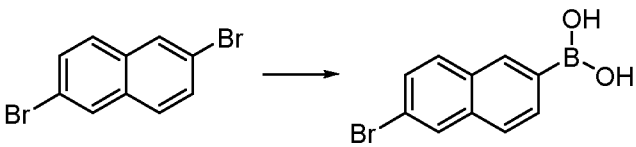
A mixture of 3-chloro-4-iodopyridin-2-amine (25.55 g, 100.41 mmol), methyl 3-mercaptopropanoate (12.72 g, 105.85 mmol), $Pd_2(dba)_3$ (0.96 g, 1.05 mmol), XantPhos (1.21 g, 2.09 mmol) and DIPEA (26.01 g, 201.25 mmol) in 1,4-dioxane (80 mL) was stirred for 18 h at 100 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with EA (80 mL), filtered and concentrated under reduced pressure. The residue was diluted with EA (50 mL) and Hex (250 mL), the resulting suspension was stirred for 10 min and filtered. The filter cake was collected. The filtration was concentrated under reduced pressure and the residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 1, v/v). The product was combined with the filter cake to give compound **A1-1** (21.62 g). MS: 247 $[M+1]^+$.

Sodium (2.48 g, 107.83 mmol) was dissolved in EtOH (200 mL) and added to a suspension of compound **A1-1** (21.62 g, 87.63 mmol) in EtOH (100 mL) dropwise at 0 °C. The resulting mixture was allowed to warm to RT and stirred for 2 h. The mixture was diluted with EtOH (20 mL) and DCM (200 mL), stirred for another 20 min, filtered and washed with DCM (30 mL). The filter cake was collected and dried in an high vacuum oven to afford intermediate **A1** (12.72 g). MS: 161 $[M-Na+2H]^+$.

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

Intermediate A2

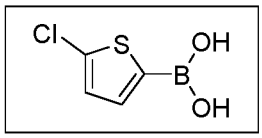


A2

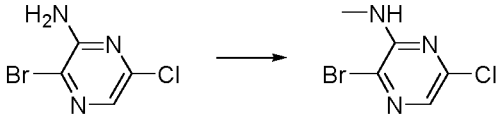
To a - 80 °C solution of 2,6-dibromonaphthalene (994 mg, 3.48 mmol) in THF (20 mL) under nitrogen atmosphere was added n-BuLi (2.5 M, 1.60 mL, 4.00 mmol) dropwise. The resulting mixture was stirred for 50 min at - 80 °C. Then triisopropyl borate (789 mg, 4.20 mmol) was added and the resulting mixture was allowed to warm to RT and stirred for 16 h. Hydrochloric acid (1 M, 10.00 mL)

was added and stirred for 1 h. The reaction mixture was diluted with brine. The layers were separated and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate **A2** (922 mg) as an off - white solid.

The following compound was synthesized using the above procedure with 2-bromo-5-chlorothiophene.



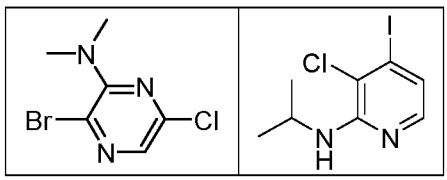
Intermediate B1



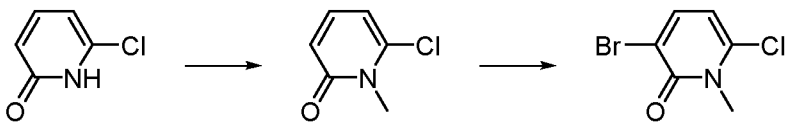
B1

To a 0 °C mixture of 3-bromo-6-chloropyrazin-2-amine (511 mg, 2.45 mmol) in DMF (5 mL) under nitrogen atmosphere was added NaH (60%, 153 mg, 3.83 mmol). The resulting mixture was allowed to warm to RT and stirred for 30 min. Then CH_3I (453 mg, 3.19 mmol) was added and the resulting mixture was stirred for 1 h at RT. The reaction mixture was quenched with brine (50 mL) and extracted with EA (80 mL). The organic layer was washed with brine (3 × 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give intermediate **B1** (503 mg) as a brown solid which was used in next step without further purification. MS: 222 $[M+1]^+$.

The following compounds were synthesized using with corresponding starting materials.



Intermediate B2

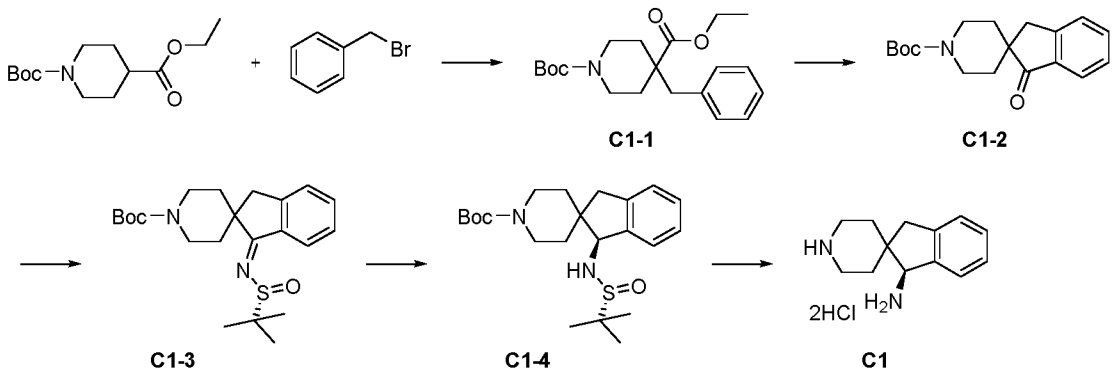


B2-1 **B2**

A mixture of 6-chloropyridin-2(1H)-one (5.03 g, 38.83 mmol), CH_3I (8.49 g, 66.86 mmol), K_2CO_3 (8.99 g, 65.05 mmol) and EtOH (25 mL) in a sealed tube was stirred for 17 h at 70 °C. After cooling to RT, the reaction mixture was poured into water (200 mL) and extracted with EA (2 A 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **B2-1** (4.35 g) as a yellow solid. MS: 144 $[M+1]^+$.

Following procedures of **WO 2007146824**, intermediate **B2** was prepared from compound **B2-1**.

Intermediate C1



To a - 70 °C solution of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate (26.02 g, 101.18 mmol) in THF (100 mL) under nitrogen atmosphere was added LDA (2 M, 65.00 mL, 130.00 mmol) dropwise. The resulting mixture was stirred for 1 h at - 70 °C. Then (bromomethyl)benzene (17.98 g, 105.12 mmol) was added and the resulting mixture was stirred for 30 min. The reaction mixture was quenched by the addition of brine (100 mL) dropwise. The layers were separated and the organic layer was washed with brine (1 × 80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **C1-1** (38.05 g, crude) as a yellow oil. MS: 348 $[M+1]^+$.

A mixture of compound **C1-1** (38.05 g, 0.11 mol) and PPA (50.00 g) was stirred for 1.5 h at 130 °C. After cooling to RT, the reaction mixture was poured into ice / water and the pH value of the resulting mixture was adjusted to 9 with NaOH. $(Boc)_2O$ (40.12 g, 0.18 mol) was added and the resulting mixture was stirred for 16 h at RT. The reaction mixture was extracted with EA (3 × 150 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 10, v/v) to give compound **C1-2** (10.00 g). MS: 302 $[M+1]^+$.

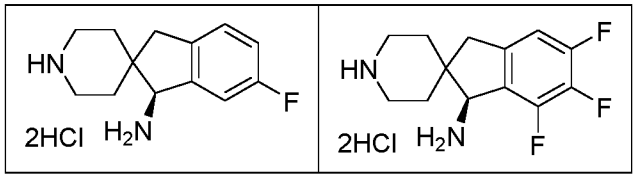
A mixture of compound **C1-2** (10.00 g, 0.033 mol) and (R)-(+)-2-methyl-2-propanesulfinamide (8.33 g, 0.069 mol) in $Ti(OEt)_4$ (50 mL) was stirred for 2 h at 120 °C. The reaction mixture was poured into water (100 mL) and diluted with EA (300 mL). The resulting mixture was filtered through a pad of Celite, the filtrate was separated and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **C1-3** (18.49 g, crude) as a yellow oil. MS: 405 $[M+1]^+$.

To a - 50 °C solution of compound **C1-3** (18.49 g, 0.046 mol) in THF (100 mL) was added BH_3 / THF (1 M, 125.00 mL, 0.13 mol) dropwise. The resulting mixture was allowed to warm to RT and stirred for 16 h. The reaction mixture was quenched by the addition of brine dropwise. The layers were separated and the organic layer was washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 2, v/v) to give compound **C1-4** (8.06 g) as a yellow oil. MS: 407 $[M+1]^+$.

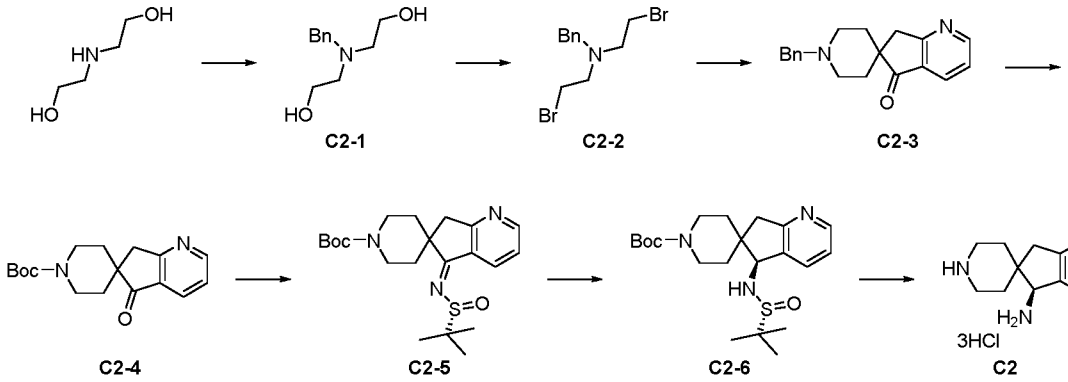
A mixture of compound **C1-4** (8.06 g, 0.020 mol) and HCl / EA (4 M, 20.00 mL, 80.00 mmol) in DCM (120 mL) was stirred for 1 h at RT. Another portion of HCl / EA (4 M, 10.00 mL, 40.00 mmol) was added and stirred for 1.5 h at RT. The reaction mixture was filtered followed by EA (50 mL) wash. The filter cake was collected, dried under high vacuum to give intermediate **C1** (4.57 g) as a white solid. MS: 203 $[M+1]^+$.

The following compounds were synthesized using the above procedure or modified procedure with

the corresponding starting materials.



Intermediate C2



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 gel chromatography (eluting with MeOH : DCM = 1 : 10, v/v) to give compound **C2-1** (89.44 g) as a colorless oil. MS: 196 $[M+H]^+$.

To a 0 °C solution of compound **C2-1** (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 compound **C2-2** (41.58 g) which was used in next step without any further purification. MS: 320 $[M+H]^+$.

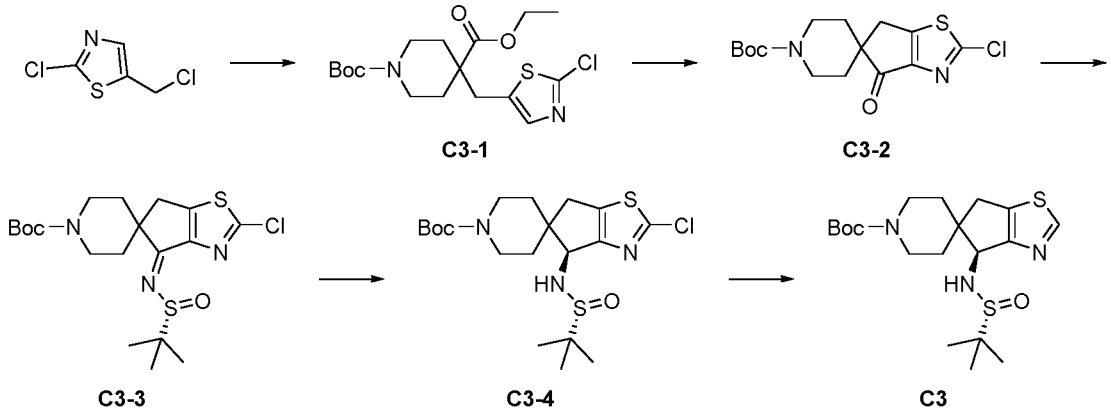
To a 0 °C solution of compound **C2-2** (1.70 g, 12.77 mmol) in DMF (20 mL) under nitrogen atmosphere was added NaH (60% dispersion in mineral oil, 982 mg, 24.55 mmol) in three portions, and the mixture was heated to 60 °C, stirred for 1 h at this temperature. Then N-benzyl-2-bromo-N-(2-bromoethyl)ethan-1-amine (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 gel chromatography (eluting with EA) to give compound **C2-3** (1.14 g). MS: 293 $[M+H]^+$.

To a 0 °C solution of compound **C2-3** (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). DIPEA (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 gel chromatography (eluting with EA : Hex = 1 : 1, v/v) to give compound **C2-4** (438 mg). MS: 303 $[M+H]^+$.

Intermediate **C2** was synthesized in the manner similar to intermediate **C1**, except compound **C1-2** was replaced with compound **C2-4**.

Intermediate C3



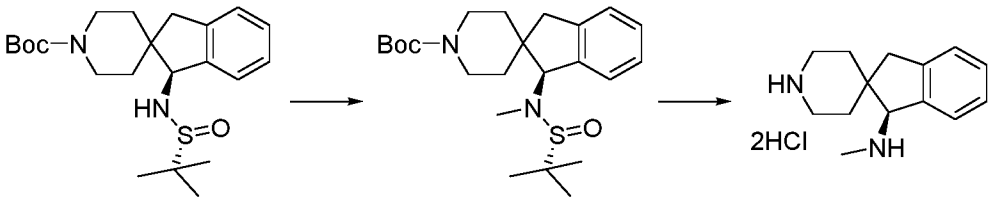
To a -78 °C solution of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate (2.83 g, 11.00 mmol) in THF (50 mL) was added LDA (2 M, 6.00 mL, 12.00 mmol) dropwise under nitrogen atmosphere. The resulting mixture was stirred for 1 h at this temperature. Then 2-chloro-5-(chloromethyl)thiazole (in 3 mL THF, 1.69 g, 10.06 mmol) was added dropwise 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 gel chromatography (eluting with EA : Hex = 1 : 20, v/v) to give compound **C3-1** (1.15 g). MS: 389 $[M+H]^+$.

To a -78 °C solution of compound **C3-1** (900 mg, 2.31 mmol) in THF (50 mL) was added LDA (2 M, 3.00 mL, 6.00 mmol) dropwise under nitrogen atmosphere. The resulting mixture was stirred for 30 min at this temperature, and 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 compound **C3-2** (832 mg). MS: 343 $[M+1]^+$.

Compound **C3-4** was synthesized in the manner similar to intermediate **C1-4**, except compound **C1-2** was replaced with compound **C3-2**.

A suspension of compound **C3-4** (2.50 g, 5.58 mmol), TEA (2 mL) and Pd / C (10 %, 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 / C (10 %, 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 gel chromatography (eluting with EA : Hex = 1 : 1, v/v) to give intermediate **C3** (1.28 g). MS: 414 $[M+H]^+$.

Intermediate C4

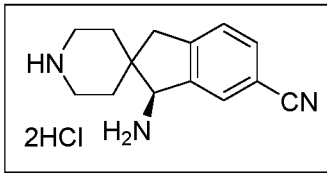
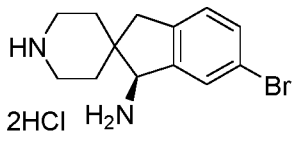
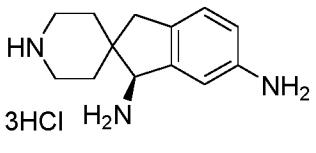
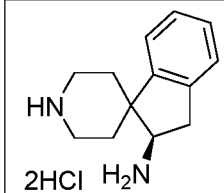
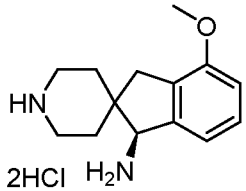
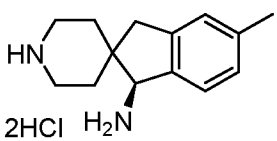
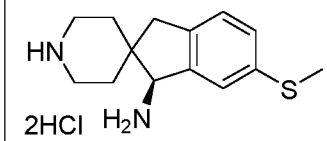
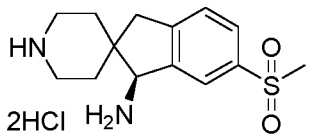
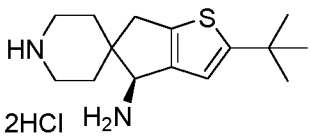


C1-4 C4-1 C4

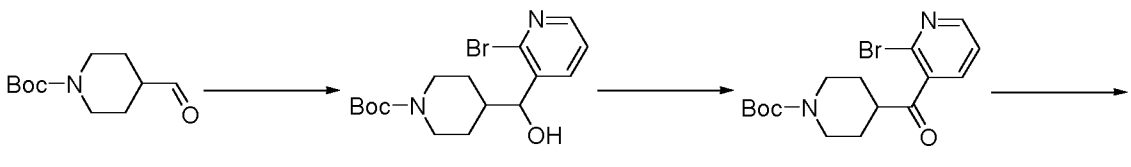
To a -30 °C solution of compound **C1-4** (695 mg, 1.71 mmol) in DMF (6 mL) was added LiHMDS (1 M, 2.10 mL, 2.10 mmol) dropwise. The resulting mixture was stirred for 1.5 h at this temperature. Then CH_3I (496 mg, 3.49 mmol) was added dropwise. The resulting mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was quenched with water and extracted with EA. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (EA : Hex = 2 : 5, v/v) to give compound **C4-1** (232 mg) as a yellow solid. MS: 421 $[M+1]^+$.

A mixture of compound **C4-1** (232 mg, 0.55 mmol) and HCl / EA (4 M, 2.00 mL, 8.00 mmol) in EA (5 mL) was stirred for 1.5 h at RT. The reaction mixture was filtered. The filter cake was collected, dried under high vacuum to give intermediate **C4** (50 mg) as a white solid. MS: 217 $[M+1]^+$.

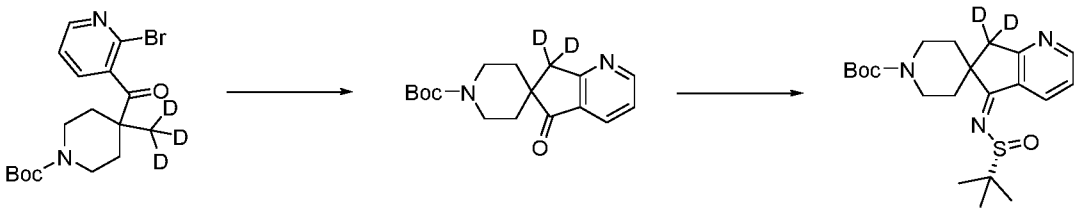
Following procedures of **WO2018172984**, the following intermediates were prepared with corresponding starting materials.

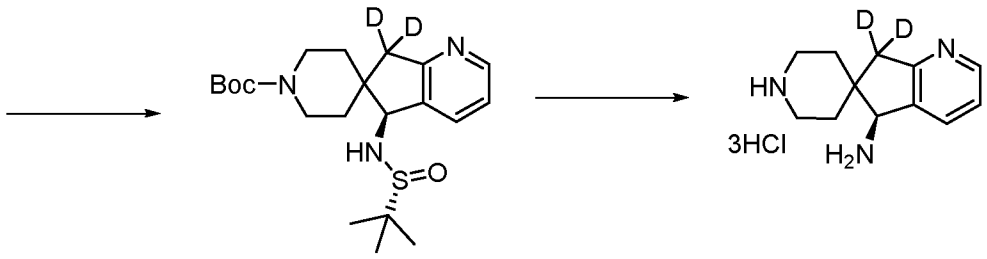
Intermediate C5



C5-1 C5-2 C5-3



C5-4 C5-5 C5-6



C5-7 **C5**

To a solution of 2,3-dibromopyridine (47.38 g, 0.20 mol) in THF (300 ml) was added isopropylmagnesium chloride (2 M solution in THF, 110 mL) dropwise at RT under nitrogen atmosphere. The reaction mixture was stirred for 1.5 h, and **C5-1** (46.93 g in 130 mL THF, 0.22 mol) was added at RT. The reaction mixture was stirred for 1 h and quenched with brine (300 mL), and then the mixture was filtered. The filtrate was separated and the organic layer was collected. The aqueous layer was extracted with EA (1 × 200 mL).The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **C5-2** (87.67 g) which was used without any further purification. MS: 371 $(M+H)^+$.

To a solution of **C5-2** (64.77 g, 17.45 mmol) in DCM (500 mL) was added Dess-Martin (90.12 g, 21.25 mmol) below 30 °C. The resulting mixture was stirred for 4 h, and then saturated sodium bicarbonate solution (500 mL) and saturated sodium carbonate solution (300 mL) were added. The organic layer was collected and washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was added to the solution of EA (60 mL) and Hex (300 mL) and stirred for 27 h. The mixture was filtered, and the filter cake was collected to give **C5-3** (30.57 g) as an off-white solid. MS: 369 $(M+H)^+$.

To a -30 °C solution of **C5-3** (10.16 g, 27.52 mmol) in THF (80 mL) were added LiHMDS (1 M solution in THF, 31.00 mL) and CD_3I under nitrogen atmosphere. The resulting mixture was allowed to warm to RT and stirred for 20 h. The reaction mixture was quenched with brine (80 mL), and the organic layer was collected. 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 **C5-4** (8.40 g). MS: 386 $(M+H)^+$.

A mixture of **C5-4** (8.40 g, 21.74 mmol), Cs_2CO_3 (7.04g, 21.61 mmol), pivalic acid (672 mg, 6.58 mmol), $Pd(OAc)_2$ (248 mg, 1.10 mmol) and $Cy_3PH{\cdot}BF_4$ (809 mg, 2.20 mmol) in 1,3,5-mesitylene (40 mL) was stirred for 16 h at 140 °C under nitrogen atmosphere. 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 **C5-5** (3.80 g). MS:305 $(M+H)^+$.

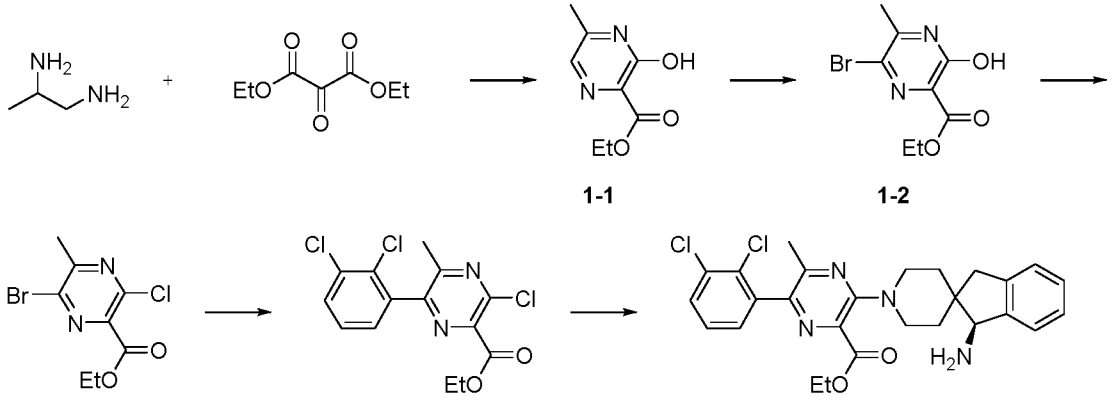
A mixture of **C5-5** (3.80 g, 12.48 mmol) and (R)-(+)-2-Methyl-2-propanesulfinamide (3.03 g, 25.00 mmol) in $Ti(OEt)_4$ (38 mL) was stirred for 2 h at 100 °C. After cooling to RT, the reaction mixture was diluted with EA (200 mL) and water (40 mL). The resulting mixture was filtered through a pad of Celite followed by EA (40 mL) wash. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **C5-6** (5.50 g). MS: 408 $(M+H)^+$.

To a -40 °C solution of **C5-6** (5.40 g, 13.25 mmol) in THF (50 mL) was added BH_3 (1 M solution in THF, 40.00 mL). The resulting mixture was allowed to warm to RT and stirred for 3 h. The reaction

mixture was quenched with MeOH (150 mL) and stirred at 80 °C for 20 h. After cooling to 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 **C5-7** (3.78 g). MS: 410 $(M+H)^+$.

To solution of **C5-7** (3.70 g, 9.03 mmol) in EA (40 mL) was added HCl (4 M solution in EA, 15 mL), and stirred at RT for 17 h. The resulting mixture was filtered followed by EA (10 *2 mL) wash, and then the filter cake was concentrated under reduced pressure to give **C5** (3.30 g) as a white solid. MS: 206 $(M+H)^+$.

Example 1



A solution of propane-1,2-diamine (11.00 mL, 129.11 mmol) in EtOH (220 mL) was cooled to 0 °C. Diethyl 2-oxomalonate (20.00 mL, 131.15 mmol) was added to the solution dropwise. Then the cooling bath was removed. The solution was allowed to warmed to RT and stirred for 1 h. The clear solution had become a thick mixture. The mixture was warmed to reflux temperature and stirred for 24 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure to give compound **1-1** (27.12 g, crude) as a solid. MS: 183 $[M+1]^+$.

To a 0 °C solution of compound **1-1** (27.12 g, crude) in DMF (100 mL) under nitrogen atmosphere was added NBS (21.30 g, 0.12 mol). The resulting mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was diluted with brine (100 mL) and EA (400 mL). The organic layer was separated, washed with water (2 × 100 mL) and brine (3 × 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 100, v/v) to give compound **1-2** (7.75 g) as a yellow solid. MS: 261 $[M+1]^+$. ^{1}HNMR (400 MHz, DMSO – d_6) δ 12.72 (brs, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.28 (t, J = 7.1 Hz, 1H).

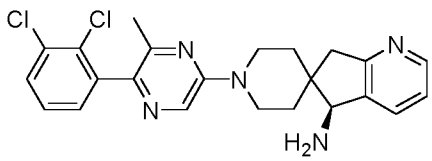
To a solution of PPh_3 (31.03 g, 80.18 mmol) in 1,4-dioxane (280 mL) was added NCS (10.77 g, 80.66 mmol). The resulting mixture was stirred for 30 min at RT. Compound **1-2** (6.96 g, 26.66 mmol) was added, the resulting mixture was warmed to 100 °C and stirred for 1 h. After cooling to RT, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 5, v/v) to give compound **1-3** (6.66 g) as a yellow oil. MS: 279 $[M+1]^+$.

A mixture of compound **1-3** (1.19 g, 4.26 mmol), (2,3-dichlorophenyl)boronic acid (1.21 g, 6.34 mmol), K_2CO_3 (2.42 g, 17.51 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.44 g, 0.54 mmol) in CH_3CN / H_2O (15 mL / 1 mL) was stirred for 2.5 h at 100 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with EA (50 mL) and washed with brine (2 × 50 mL). The organic layer was dried

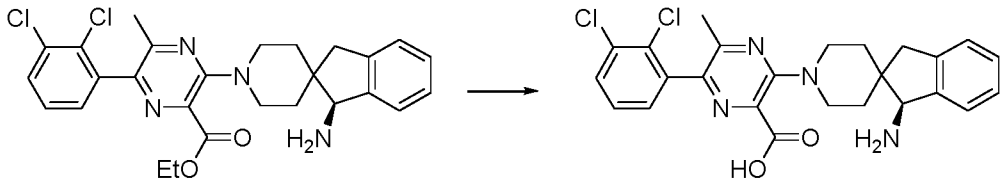
over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 30, v/v) to give compound **1-4** (0.67 g). MS: 345 $[M+1]^+$.

A mixture of compound **1-4** (0.67 g, 1.94 mmol), intermediate **C1** (0.64 g, 2.33 mmol) and K_2CO_3 (2.70 g, 19.54 mmol) in CH_3CN (15 mL) was stirred for 24 h at 100 °C. After cooling to RT, the reaction mixture was diluted with EA (60 mL) and water (100 mL). The organic layer was separated, the aqueous layer was extracted with EA (1 × 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 gel chromatography (eluting with MeOH : DCM = 1 : 50, v/v) to give example **1** (468 mg) as a yellow solid. MS: 511 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.65 (dd, J = 7.9, 1.6 Hz, 1H), 7.47 - 7.34 (m, 3H), 7.29 - 7.14 (m, 3H), 4.40 (q, J = 7.1 Hz, 2H), 4.02 - 3.91 (m, 3H), 3.41 - 3.37 (m, 1H), 3.32 - 3.30 (m, 1H), 3.19 - 3.15 (m, 1H), 2.85 - 2.81 (m, 1H), 2.27 (s, 3H), 1.94 - 1.82 (m, 2H), 1.62 - 1.55 (m, 1H), 1.46 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H).

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

Ex No.	Chemical Name	Structure	MS & ^{1}HNMR
2	(S)-1'-(5-(2,3-dichlorophenyl)-6-methylpyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 440 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.34 (d, J = 4.6 Hz, 1H), 8.05 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.61 (dd, J = 8.0, 1.5 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.32 - 7.25 (m, 2H), 4.38 - 4.33 (m, 2H), 4.03 (s, 1H), 3.29 - 3.22 (m, 3H), 2.96 - 2.90 (m, 1H), 2.19 (s, 3H), 1.96 - 1.80 (m, 2H), 1.68 - 1.62 (m, 1H), 1.46 - 1.39 (m, 1H).

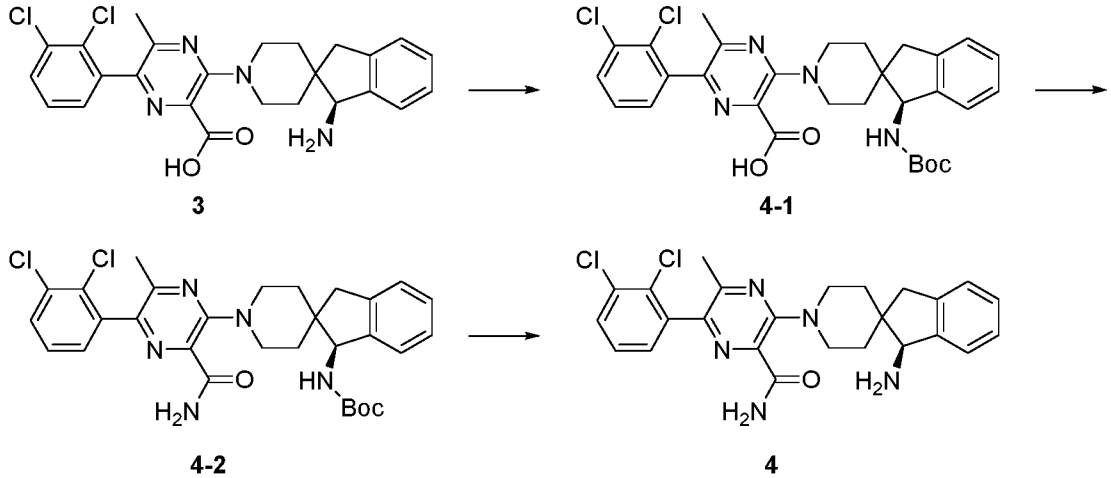
Example 3



1 **3**

A mixture of example **1** (302 mg, 0.59 mmol) and LiOH (81 mg, 3.38 mmol) in MeOH / H_2O (20 mL / 3 mL) was stirred for 4 h at 60 °C. After cooling to RT, MeOH was removed under reduced pressure. The residue was dissolved in brine (50 mL), extracted with EA (3 × 40 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give example **3** (258 mg) as a light yellow solid. MS: 483 $[M+1]^+$.

Example 4

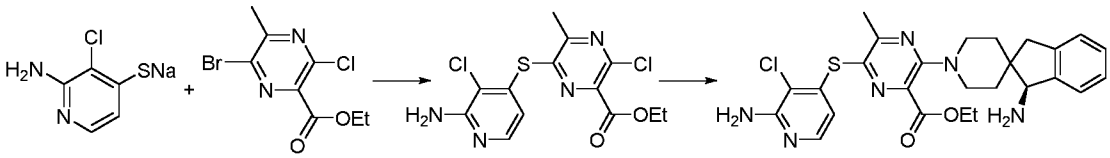


A solution of example **3** (60 mg, 0.12 mmol), $(Boc)_2O$ (0.50 mL, 2.18 mmol) and DIPEA (1.00 mL, 6.05 mmol) in DCM was stirred for 1 h at 40 °C. The reaction solution was concentrated under reduced pressure to give compound **4-1** (0.39 g, crude), which was used in next step without further purification. MS: 583 $[M+1]^+$.

A solution of compound **4-1** (0.39 g, crude), NH_4Cl (466 mg, 8.71 mmol), PyBOP (194 mg, 0.37 mmol) and DIPEA (0.50 mL, 3.03 mmol) in NMP (8 mL) was stirred for 2 h at 80 °C. The reaction solution was diluted with EA (40 mL) and washed with brine (3 × 30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **4-2** (0.37 g, crude) as a yellow oil, which was used in next step without further purification. MS: 582 $[M+1]^+$.

A mixture of compound **4-2** (0.37 g, crude) and HCl / EA (4 M, 3.00 mL, 12.00 mmol) in DCM (20 mL) was stirred for 2.5 h at RT. The reaction mixture was diluted with brine (50 mL) and the pH value was taken to 9 with $NH_3 \cdot H_2O$ (25 %). The resulting mixture was extracted with DCM (1 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 10, v/v) to give example **4** (9 mg) as a light yellow solid. MS: 482 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.66 (d, J = 9.4 Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.48 - 7.29 (m, 5H), 4.39 (s, 1H), 4.13 - 4.00 (m, 2H), 3.39 - 3.35 (m, 1H), 3.31 - 3.28 (m, 1H), 3.24 - 3.12 (m, 2H), 2.29 (s, 3H), 2.03 - 1.88 (m, 2H), 1.73 - 1.62 (m, 2H).

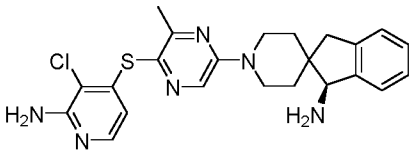
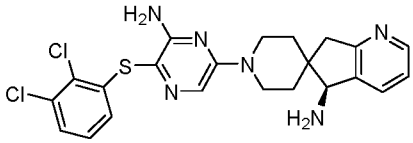
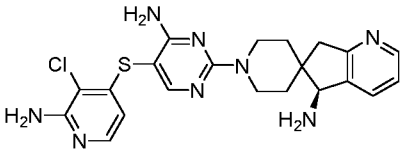
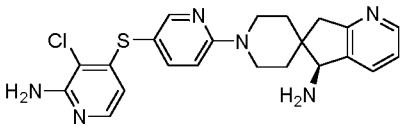
Example 5

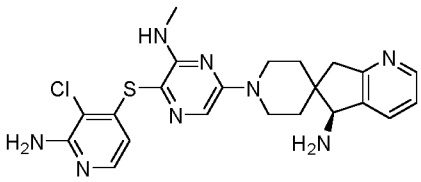
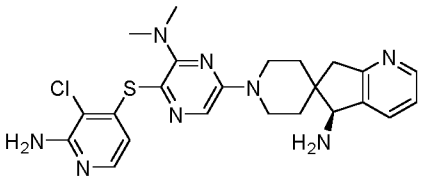
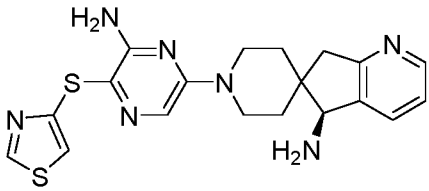
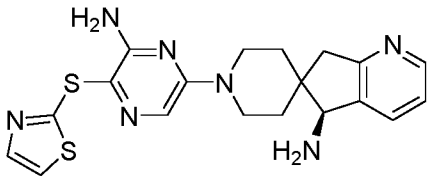


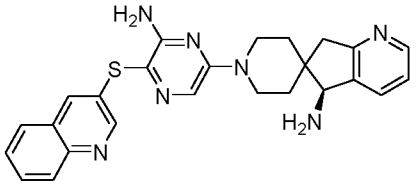
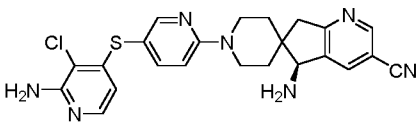
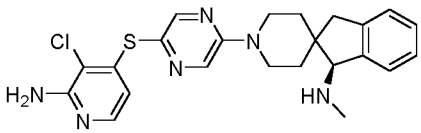
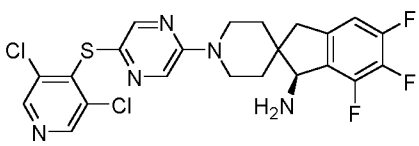
A mixture of intermediate **A1** (504 mg, 2.76 mmol), compound **1-3** (769 mg, 2.75 mmol), $Pd_2(dba)_3$ (127 mg, 0.14 mmol), XantPhos (144 mg, 0.25 mmol) and DIPEA (1.10 g, 8.51 mmol) in 1,4-dioxane (20 mL) was stirred for 3 h at 110 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was quenched with brine (100 mL), extracted with EA (1 × 60 mL), the organic layer dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 2, v/v) to give compound **5-1** (489 mg) as a yellow solid. MS: 359 $[M+1]^+$.

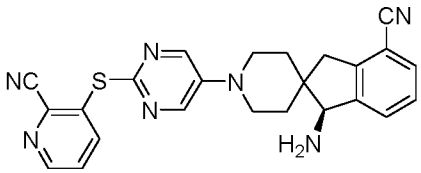
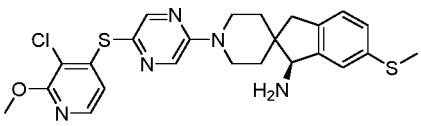
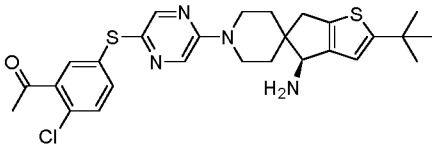
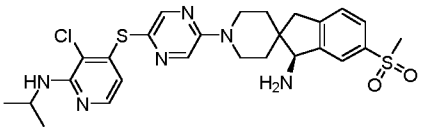
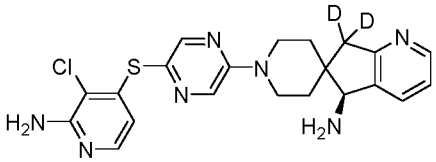
Example **5** was synthesized in the manner similar to example **1**, except compound **1-4** was replaced with compound **5-1**. MS: 525 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.63 (d, J = 5.5 Hz, 1H), 7.47 - 7.34 (m, 1H), 7.26 - 7.19 (m, 3H), 5.91 (d, J = 5.5 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 4.06 - 3.98 (m, 2H), 3.97 (s, 1H), 3.43 - 3.35 (m, 2H), 3.18 - 3.14 (m, 1H), 2.85 - 2.81 (m, 1H), 2.49 (s, 3H), 1.96 - 1.76 (m, 2H), 1.64 - 1.57 (m, 1H), 1.48 - 1.42 (m, 1H), 1.39 (t, J = 8.0 Hz, 3H).

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

EX No	Chemical Name	Structure	MS & ^{1}HNMR
6	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)-6-methylpyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 453 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.16 (s, 1H), 7.60 - 7.32 (m, 5H), 5.80 (s, 1H), 4.46 - 4.25 (m, 3H), 3.46 - 3.35 (m, 2H), 3.23 - 3.08 (m, 2H), 2.45 (s, 3H), 1.89 - 1.57 (m, 4H).
7	(S)-1'-(6-amino-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 473 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.36 (d, J = 4.7 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 7.62 (s, 1H), 7.37 - 7.22 (m, 2H), 7.13 (t, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 4.33 (d, J = 13.4 Hz, 2H), 4.05 (s, 1H), 3.29 - 3.17 (m, 3H), 2.94 (d, J = 16.5 Hz, 1H), 1.98 - 1.75 (m, 2H), 1.70 - 1.57 (m, 1H), 1.48 - 1.37 (m, 1H).
8	(S)-1'-(4-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrimidin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 455 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.41 (d, J = 4.4 Hz, 1H), 7.96 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 5.5 Hz, 1H), 7.31 (dd, J = 7.6, 5.2 Hz, 1H), 6.03 (d, J = 5.5 Hz, 1H), 4.62 (t, J = 13.3 Hz, 2H), 4.19 (s, 1H), 3.24 (m, 3H), 3.09 - 2.95 (m, 1H), 1.92 - 1.63 (m, 2H), 1.63 - 1.42 (m, 2H).
9	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5		MS: 439 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.38 (d, J = 4.5 Hz, 1H), 8.21 (s, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.72 - 7.55 (m, 2H), 7.38 - 7.26 (m, 1H), 6.97 (d, J = 9.0 Hz, 1H), 5.92 (d, J = 5.5 Hz, 1H), 4.43 - 4.26 (m,

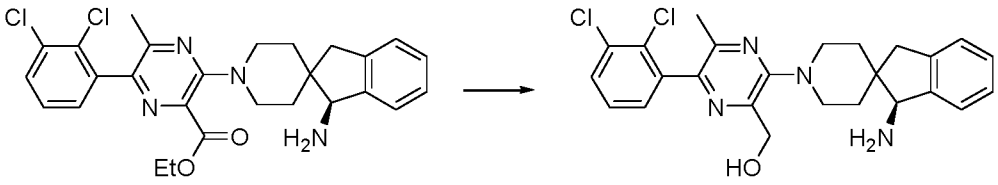
	-amine		2H), 4.10 (s, 1H), 3.32 - 3.19 (m, 3H), 3.03 - 2.91 (m, 1H), 1.98 - 1.79 (m, 2H), 1.70 - 1.60 (m, 1H), 1.54 - 1.44 (m, 1H).
10	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)-6-(methylamino)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 469 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.36 (d, J = 4.3 Hz, 1H), 7.83 (d, J = 10.6 Hz, 1H), 7.73 - 7.71,7.51 - 7.49 (m, 1H), 7.59 (dd, J = 9.9, 4.4 Hz, 1H), 7.29 (dd, J = 7.4, 5.2 Hz, 1H), 5.89 - 5.84 (m, 1H), 4.45 - 4.13 (m, 2H), 4.06 (s, 1H), 3.31 - 3.13 (m, 3H), 3.07 (s, 1H), 2.88 (s, 3H), 2.00 - 1.77 (m, 2H), 1.67 - 1.63 (m, 1H), 1.47 - 1.43 (m, 1H).
11	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)-6-(dimethylamino)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 483 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.36 (d, J = 4.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.72 - 7.50 (m, 1H), 7.64 - 7.57 (m, 1H), 7.29 (dd, J = 7.5, 5.2 Hz, 1H), 5.89 - 5.84 (m, 1H), 4.36 (t, J = 15.0 Hz, 2H), 4.07 (s, 1H), 3.31 - 3.16 (m, 3H), 3.10 (s, 3H), 3.06 (s, 1H), 2.88 (s, 3H), 1.98 - 1.77 (m, 2H), 1.71 - 1.57 (m, 1H), 1.71 - 1.44 (m, 1H).
12	(S)-1'-(6-amino-5-(thiazol-4-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 412 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 9.00 (d, J = 2.0 Hz, 1H), 8.49 (d, J = 4.3 Hz, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.53 (s, 1H), 7.40 - 7.34 (m, 1H), 7.20 (d, J = 2.0 Hz, 1H), 4.40 - 4.23 (m, 3H), 3.28 - 3.06 (m, 4H), 1.90 - 1.79 (m, 2H), 1.68 - 1.56 (m, 2H).
13	(S)-1'-(6-amino-5-(thiazol-2-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 412 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.41 (d, J = 4.7 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 3.4 Hz, 1H), 7.60 (s, 1H), 7.45 (d, J = 3.4 Hz, 1H), 7.32 (dd, J = 7.5, 5.2 Hz, 1H), 4.45 - 4.29 (m, 2H), 4.17 (s, 1H), 3.31 - 3.20 (m, 3H), 3.08 - 2.96 (m, 1H), 1.97 - 1.78 (m, 2H), 1.70 -

			1.59 (m, 1H), 1.55 - 1.44 (m, 1H).
14	(S)-1'-(6-amino-5-(quinolin-3-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		MS: 456 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.69 (d, J = 2.1 Hz, 1H), 8.42 (d, J = 4.6 Hz, 1H), 8.09 (d, J = 1.6 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.74 (t, J = 7.2 Hz, 1H), 7.62 (t, J = 7.1 Hz, 2H), 7.33 (dd, J = 7.4, 5.2 Hz, 1H), 4.34 (t, J = 11.8 Hz, 2H), 4.17 (s, 1H), 3.30 - 3.19 (m, 3H), 3.08 - 2.95 (m, 1H), 1.92 - 1.82 (m, 2H) , 1.64 (d, J = 12.5 Hz, 1H), 1.51 (d, J = 12.2 Hz, 1H).
15	(S)-5-amino-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-3-carbonitrile		MS: 464 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.20 (d, J = 2.3 Hz, 1H), 7.74 (s, 1H), 7.67 – 7.56 (m, 2H), 7.45 (d, J = 7.8 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 5.91 (d, J = 5.6 Hz, 1H), 4.37 – 4.27 (m, 2H), 4.07 (s, 1H), 3.29 – 3.19 (m, 3H), 2.98 – 2.93 (m, 1H), 1.95 – 1.85 (m, 2H), 1.79 – 1.74 (m, 1H), 1.63 – 1.60 (m, 1H).
16	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-N-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 453 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.36 (s, 1H), 8.31 (s, 1H), 7.63 (d, J = 5.6 Hz, 1H), 7.46 (d, J = 7.3 Hz, 1H), 7.38 – 7.21 (m, 3H), 5.96 (d, J = 5.6 Hz, 1H), 4.37 – 4.27 (m, 1H), 4.25 – 4.16 (m, 1H), 3.86 (s, 1H), 3.53 – 3.39 (m, 2H), 3.09 (dd, J = 38.1, 15.9 Hz, 2H), 2.56 (s, 3H), 2.00 – 1.92 (m, 1H),1.60 – 1.51 (m, 2H), 1.37 – 1.29 (m, 1H).
17	(S)-1'-(5-((3,5-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 512 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.54 (s, 2H), 8.19 – 8.05 (m, 2H), 7.06 – 6.97 (m, 1H), 4.33 – 3.97 (m, 3H), 3.46 – 3.34 (m, 2H), 3.09 (d, J = 16.3 Hz, 1H), 2.90 (d, J = 16.2 Hz, 1H), 1.95 – 1.84 (m, 1H), 1.76 – 1.60 (m, 2H), 1.59 – 1.46 (m, 1H).

18	(S)-1-amino-1'-(2-((2-cyanopyridin-3-yl)thio)pyrimidin-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carbonitrile		MS: 440 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.52 (s, 2H), 7.87 – 7.82 (m, 2H), 7.80 – 7.76 (m, 2H), 7.56 – 7.52 (m, 2H), 3.91 – 3.68 (m, 3H), 3.28 – 3.08 (m, 4H), 1.86 – 1.78 (m, 2H), 1.76 – 1.63 (m, 2H).
19	(S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 500 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.30 (s, 1H), 8.26 (s, 1H), 7.50 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.85 (s, 1H), 4.43 (d, J = 13.8 Hz, 1H), 4.31 (d, J = 13.9 Hz, 1H), 4.13 (s, 1H), 3.28 – 3.21 (m, 1H), 3.11 (dd, J = 33.5, 15.9 Hz, 3H), 2.60 (s, 3H), 1.94 – 1.74 (m, 4H), 1.40 (s, 9H).
20	(S)-1-(5-((5-(4-amino-2-(tert-butyl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-2-chlorophenyl)ethan-1-onez		MS: 527 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.30 (s, 1H), 8.26 (s, 1H), 7.50 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.85 (s, 1H), 4.43 (d, J = 13.8 Hz, 1H), 4.31 (d, J = 13.9 Hz, 1H), 4.13 (s, 1H), 3.28 – 3.21 (m, 1H), 3.20 – 3.01 (m, 3H), 2.60 (s, 3H), 1.94 – 1.74 (m, 4H), 1.45 – 1.36 (s, 9H).
21	(S)-1'-(5-((3-chloro-2-(isopropylamino)pyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 559 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.37 (s, 1H), 8.31 (s, 1H), 8.02 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.71 (d, J = 5.5 Hz, 1H), 7.65 (d, J = 5.7 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 5.91 (d, J = 5.5 Hz, 1H), 4.28 – 4.18 (m, 1H), 4.13 (s, 1H), 3.66 – 3.56 (m, 5H), 3.40 – 3.37 (m, 1H), 3.15 (s, 3H), 1.88 – 1.82 (m, 2H), 1.72 – 1.67 (m, 2H), 1.27 (d, J = 6.5 Hz, 6H).
22	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro		MS: 442 $[M+1]^+$. ^{1}HNMR (400 MHz, DMSO-*d6*) δ 8.49 (s, 1H), 8.35 (d, 1H), 8.29 (s, 1H), 7.70 (d, 1H), 7.67 (d, 1H), 7.20 (dd, 1H), 6.34 (s, 2H),

	[cyclopenta[b]pyridine-6,4'-piperidin]-7,7-d2-5-amine		5.83 (d, 1H), 4.31 (d, 2H), 3.98 (s, 1H), 3.30 – 3.20 (m, 2H), 3.15 (s, 2H), 1.85 – 1.67 (m, 2H), 1.57 (d, 1H), 1.22 (d, 1H).

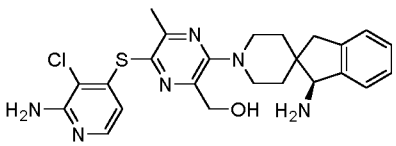
Example 23



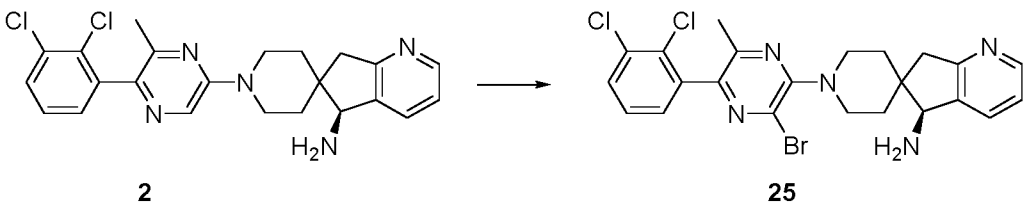
1 **23**

To a 0 °C solution of example **1** (132 mg, 0.26 mmol) in THF (8 mL) under nitrogen atmosphere was added $LiBH_4$ (2M / THF, 0.30 mL, 0.60 mmol). The resulting mixture was stirred for 16 h at 70 °C. After cooling to RT, the reaction mixture was quenched with brine (50 mL), extracted with EA (3 × 40 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 16, v/v) to give example **23** (11 mg). MS: 469 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.63 (dd, J = 7.9, 1.3 Hz, 1H), 7.50 - 7.39 (m, 2H), 7.37 - 7.24 (m, 4H), 4.69 (s, 2H), 4.29 (s, 1H), 3.80 - 3.58 (m, 2H), 3.26 - 2.96 (m, 4H), 2.26 (s, 3H), 3.01 - 1.89 (m, 2H), 1.74 - 1.59 (m, 2H).

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

EX No	Chemical Name	Structure	MS & ^{1}HNMR
24	(S)-(3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2-amino-3-chloropyridin-4-yl)thio)-5-methylpyrazin-2-yl)methanol		MS: 483 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.62 (d, J = 5.5 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.39 - 7.36 (m, 3H), 5.93 (d, J = 5.5 Hz, 1H), 4.68 (s, 2H), 4.38 (s, 1H), 4.14 - 3.85 (m, 4H), 3.21 - 3.14 (m, 2H), 2.51 (s, 3H), 1.76 - 1.72 (m, 2H), 1.64 - 1.57 (m, 2H).

Example 25

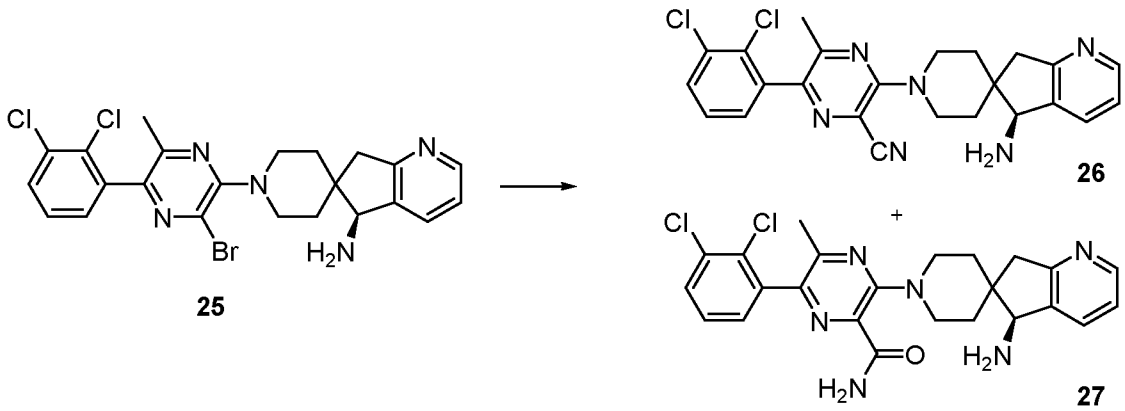


2 **25**

To a 0 °C solution of example **2** (0.57 g, 1.29 mmol) in DCM (20 mL) was added NBS (0.35 g, 1.97 mmol). The resulting mixture was stirred for 4 h at RT. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 :

30, v/v) to give example **25** (451 mg). MS: 518 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.34 (d, J = 4.5 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.65 (dd, J = 8.0, 1.5 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.36 - 7.32 (m, 1H), 7.29 - 7.25 (m, 1H), 4.09 - 4.07 (m, 1H), 3.97 - 3.92 (m, 2H), 3.25 - 3.16 (m, 3H), 2.95 - 2.89 (m, 1H), 2.68 (s, 3H), 2.03 - 1.99 (m, 2H), 1.70 - 1.65 (m, 1H), 1.51 - 1.47 (m, 1H).

Example 26 & Example 27

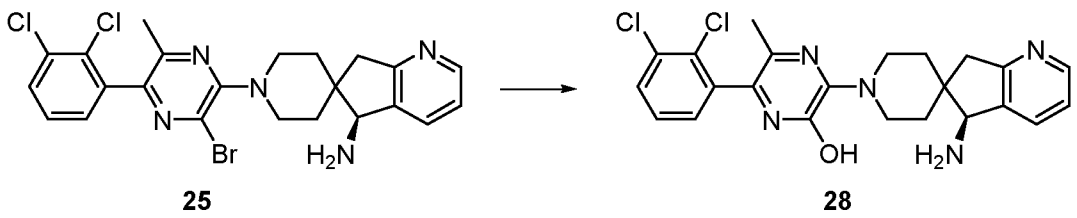


A mixture of example **25** (155 mg, 0.30 mmol), $K_4Fe(CN)_6{\cdot}3H_2O$ (156 mg, 0.37 mmol), DBU (242 mg, 1.59 mmol) and $Pd(PPh_3)_4$ (39 mg, 0.034 mmol) in t-BuOH / H_2O (6 mL / 6 mL) was stirred for 3.5 h at 100 °C under nitrogen atmosphere. After cooling to RT, the resulting mixture was quenched with brine (50 mL) and extracted with EA (2 × 30 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 8, v/v) to give example **26** (19 mg) and example **27** (25 mg).

Example **26**: MS: 465 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.39 (d, J = 4.7 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.66 (dd, J = 8.0, 1.4 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.35 (dd, J = 7.6, 1.4 Hz, 1H), 7.32 - 7.28 (m, 1H), 4.55 - 4.49 (m, 2H), 4.18 (s, 1H), 3.52 - 3.43 (m, 2H), 3.26 – 3.24 (m, 1H), 3.04 - 2.99 (m, 1H), 2.29 (s, 3H), 2.03 - 1.91 (m, 2H), 1.76 - 1.66 (m, 1H), 1.60 - 1.54 (m, 1H).

Example **27**: MS: 483 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.42 (d, J = 4.5 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.62 (dd, J = 7.3, 2.3 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.32 (dd, J = 7.5, 5.2 Hz, 1H), 4.24 (s, 1H), 4.13 - 3.97 (m, 2H), 3.39 - 3.33 (m, 1H), 3.29 - 3.20 (m, 2H), 3.09 - 2.99 (m, 1H), 2.26 (s, 3H), 2.02 - 1.87 (m, 2H), 1.66 - 1.50 (m, 2H).

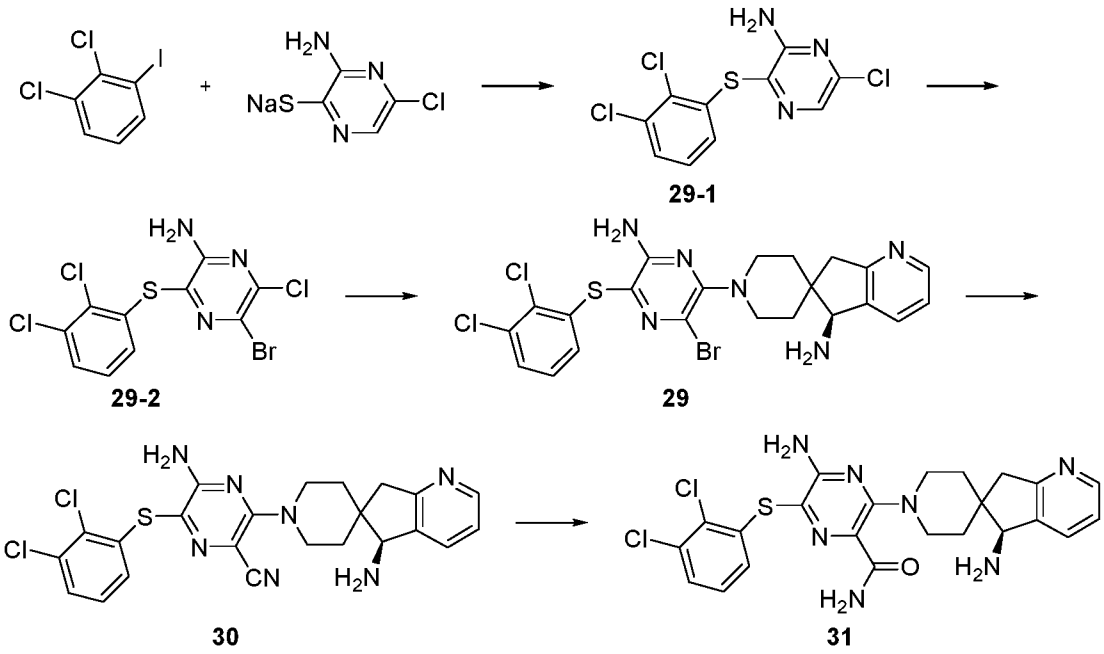
Example 28



A mixture of example **25** (64 mg, 0.12 mmol) and HCl / EA (4 M, 4 mL) was stirred for 1 h at RT. The reaction mixture was filtered followed by EA wash. The solid was dissolved in EA (20 mL) and washed with $NH_3{\cdot}H_2O$ (10 %, 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and dried under high vacuum for 2 h to give example **28** (17 mg) as a yellow solid. MS: 456 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.37 (d, J = 4.7 Hz, 1H), 7.87 (d, J

= 7.5 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.38 - 7.34 (m, 1H), 7.32 - 7.28 (m, 1H), 4.11 (s, 1H), 4.04 - 3.99 (m, 2H), 3.28 - 3.21 (m, 3H),2.98 - 2.93 （m, 1H）, 2.27 (s, 3H), 2.10 - 1.98 (m, 2H), 1.73 - 1.67(d, *J* = 11.9 Hz, 2H).

Example 29 & Example 30 & Example 31



A mixture of 1,2-dichloro-3-iodobenzene (575 mg, 3.13 mmol), sodium 3-amino-5-chloropyrazine-2-thiolate (813 mg, 2.98 mmol), $Pd_2(dba)_3$ (134 mg, 0.15 mmol), XantPhos (176 mg, 0.30 mmol) and DIPEA (1.41 g, 10.92 mmol) in 1,4-dioxane (20 mL) was stirred for 3 h at 110 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 10, v/v) to give compound **29-1** (0.41 g). MS: 306 $[M+1]^+$.

To a 0 °C solution of compound **29-1** (0.40 g, 1.31 mmol) in DCM (20 mL) was added NBS (0.32 g, 1.80 mmol). The resulting mixture was stirred for 17 h at RT. The reaction mixture was diluted with EA (50 mL) and brine (100 mL). The aqueous layer was separated, extracted with EA (1 × 50 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **29-2** (0.43 g) as a brown solid.

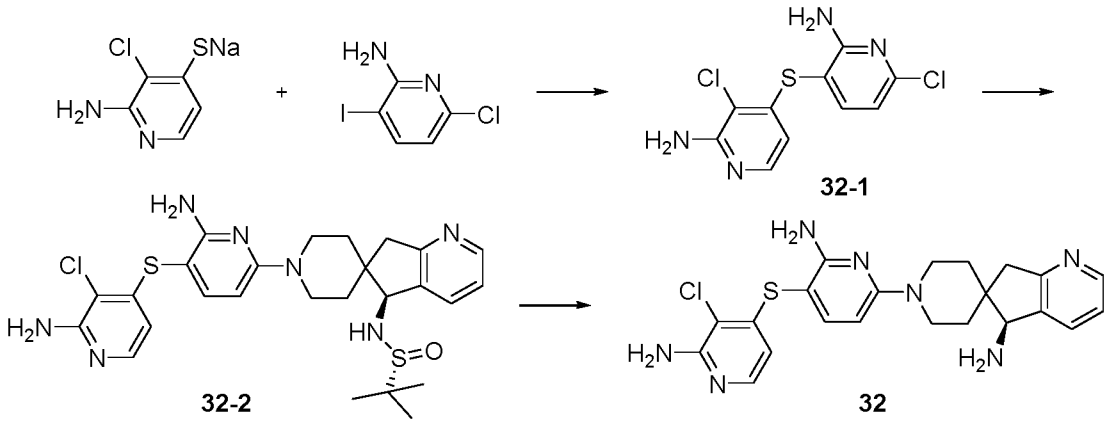
A mixture of compound **29-2** (0.43 g, 1.11 mmol), intermediate **C2** (0.43 g, 1.38 mmol) and K_2CO_3 (1.60 g, 11.58 mmol) in CH_3CN (20 mL) was stirred for 5 h at 100 °C. After cooling to RT, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 20, v/v) to give example **29** (191 mg) an a brown solid. MS: 551 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.35 (d, *J* = 4.6 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.28 (dd, *J* = 7.5, 5.2 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.77 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.14 - 3.95 (m, 3H), 3.28 - 3.12 (m, 3H), 2.91 (d, *J* = 16.5 Hz, 1H), 2.08 - 1.93 (m, 2H), 1.70 - 1.59 (m, 1H), 1.50 - 1.42 (m, 1H).

A mixture of example **29** (173 mg, 0.31 mmol), $K_4Fe(CN)_6{\cdot}3H_2O$ (168 mg, 0.40 mmol), DBU (240 mg, 1.58 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) in t-BuOH / H_2O (1 / 1, 16 mL) was stirred for 16 h

at 100 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with water (50 mL) and 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 gel chromatography (eluting with MeOH : DCM = 1 : 12, v/v) to give example **30** (117 mg) as a yellow solid. MS: 498 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.37 (d, J = 4.9 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.42 - 7.38 (m, 1H), 7.34 - 7.27 (m, 1H), 7.23 - 7.11 (m, 1H), 6.89 - 6.86, 6.68 - 6.65 (m, 1H), 4.55 - 4.43 (m, 1H), 4.38 - 4.26 (m, 1H), 4.15 - 3.99 (m, 1H), 3.65 (t, J = 6.9 Hz, 1H), 3.25 - 3.12 (m, 2H), 3.02 - 2.91 (m, 1H), 2.13 - 1.81 (m, 2H), 1.65 - 1.59 (m, 1H), 1.50 - 1.42 (m, 1H).

A mixture of example **30** (105 mg, 0.21 mmol) in sulfuric acid (98 %, 5 mL) was stirred for 16 h at 80 °C. After cooling to RT, the reaction mixture was poured into water and the pH value was taken to 10 with $NH_3 \cdot H_2O$ (25 %). The resulting mixture was extracted with EA (2 × 50 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 8, v/v) to give example **31** (30 mg). MS: 516 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.36 (d, J = 4.6 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.36 (dd, J = 8.0, 1.1 Hz, 1H), 7.29 (dd, J = 7.5, 5.2 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.81 (dd, J = 8.0, 1.1 Hz, 1H), 4.07 (s, 1H), 3.99 (d, J = 13.7 Hz, 2H), 3.30 - 3.17 (m, 3H), 2.93 (d, J = 16.5 Hz, 1H), 2.03 - 1.86 (m, 2H), 1.64 - 1.55 (m, 1H), 1.46 - 1.40 (m, 1H).

Example 32



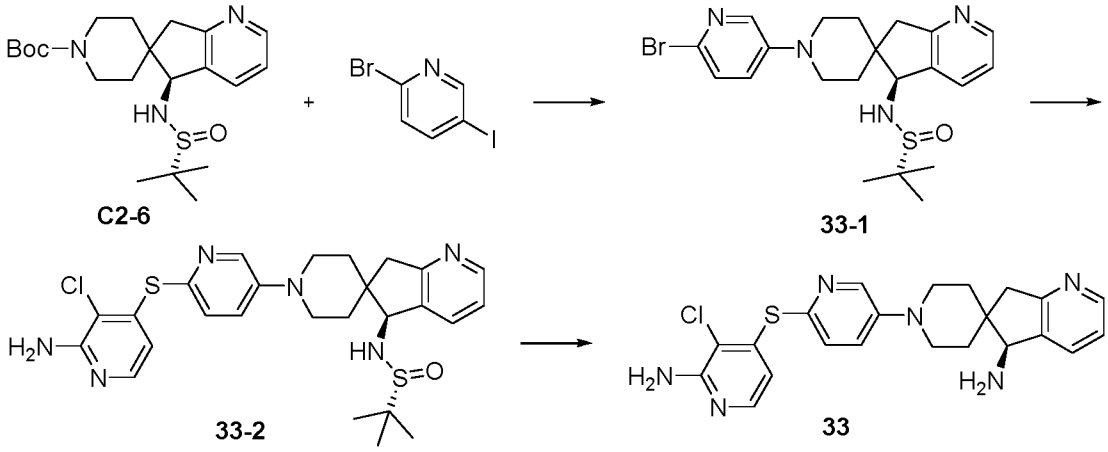
Compound **32-1** was synthesized in the manner of compound **5-1**, except compound **1-3** was replaced with 6-chloro-3-iodopyridin-2-amine.

A mixture of compound **C2-6** (351 mg, 0.86 mmol) and TFA (1 mL) in DCM (20 mL) was stirred for 30 min at RT. The resulting mixture was concentrated under reduced pressure. Compound **32-1** (200 mg, 0.70 mmol), $Pd(OAc)_2$ (33 mg, 0.15 mmol), DavePhos (65 mg, 0.17 mmol), t-BuOK (1.21 g, 10.78 mmol) and toluene (30 mL) was added. The resulting mixture was stirred for 18 h at 100 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with water (100 mL) and extracted with EA (2 × 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **32-2** (0.37 g) as a brown solid. MS: 558 $[M+1]^+$.

A mixture of compound **32-2** (0.37 g, 0.66 mmol) and HCl / EA (4 M, 3.00 mL, 12.00 mmol) in DCM (20 mL) was stirred for 30 min at RT. The resulting mixture was diluted with water (50 mL) and the

pH value was adjusted to 9 with $NH_3 \cdot H_2O$ (25 %). The resulting mixture was extracted with DCM (1 × 50 mL), the organic layer dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 8, v/v) to give example **32** (10 mg). MS: 454 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.43 (dd, J = 13.1, 4.3 Hz, 1H), 7.96 - 7.88 (m, 1H), 7.60 (d, J = 5.2 Hz, 1H), 7.43 - 7.29 (m, 2H), 6.24 (d, J = 8.5 Hz, 1H), 6.01 (d, J = 5.2 Hz, 1H), 4.42 - 4.15 (m, 3H), 3.26 - 3.08 (m, 4H), 1.86 - 1.77 (m, 2H), 1.59 - 1.43 (m, 2H).

Example 33

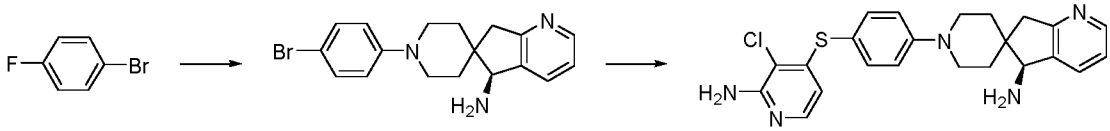


A mixture of compound **C2-6** (552 mg, 1.35 mmol) and TFA (2.50 mL) in DCM (30 mL) was stirred for 1 h at RT. The resulting mixture was concentrated under reduced pressure. 2-Bromo-5-iodopyridine (354 mg, 1.25 mmol), $Pd_2(dba)_3$ (66 mg, 0.072 mmol), BINAP (86 mg, 0.14 mmol), t-BuOK (3204 mg, 28.55 mmol) and toluene (20 mL) was added. The resulting mixture was stirred for 21 h at 100 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with EA (50 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 20, v/v) to give compound **33-1** (392 mg) as a yellow solid. MS: 463 $[M+1]^+$.

A mixture of compound **33-1** (184 mg, 0.40 mmol), intermediate **A1** (80 mg, 0.44 mmol), $Pd_2(dba)_3$ (41 mg, 0.045 mmol), XantPhos (55 mg, 0.095 mmol) and DIPEA (193 mg, 1.49 mmol) in 1,4-dioxane (20 mL) was stirred for 16 h at 110 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 12, v/v) to give compound **33-2** (127 mg). MS: 543 $[M+1]^+$.

A mixture of compound **33-2** (127 mg, 0.23 mmol) and HCl / EA (4 M, 3.00 mL, 12.00 mmol) in DCM (20 mL) was stirred for 1.5 h at RT. The reaction mixture was diluted with water (50 mL) and the pH value was adjusted to 9 with $NH_3 \cdot H_2O$ (25 %). The resulting mixture was extracted with DCM (2 × 50 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 8, v/v) to give example **33** (28 mg). MS: 439 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.45 - 8.34 (m, 2H), 7.87 (d, J = 7.5 Hz, 1H), 7.67 - 7.54 (m, 2H), 7.53 - 7.44 (m, 1H), 7.37 - 7.25 (m, 1H), 5.95 (d, J = 5.5 Hz, 1H), 4.11 (s, 1H), 3.93 - 3.75 (m, 2H), 3.28 - 3.10 (m, 3H), 3.01 - 2.83 (m, 1H), 2.07 - 1.84 (m, 2H), 1.76 - 1.66 (m, 1H), 1.57 - 1.45 (m, 1H).

Example 34

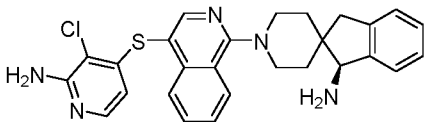


34-1 **34**

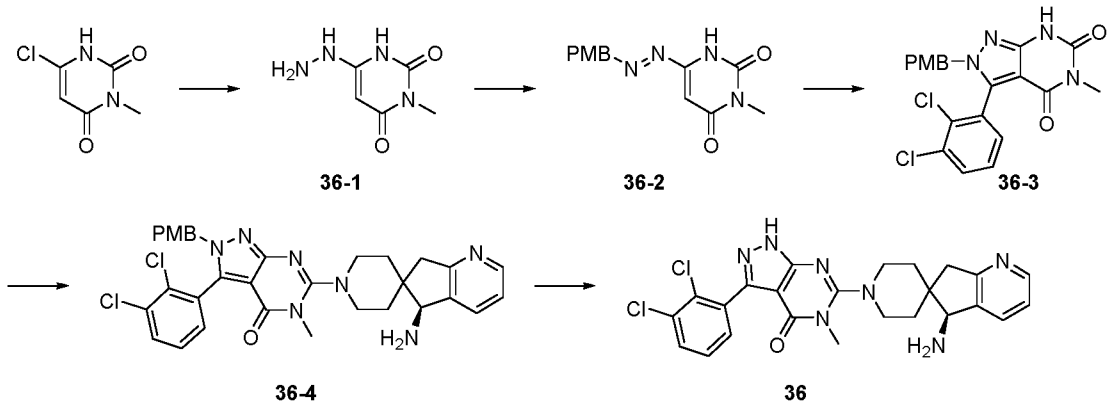
1-Bromo-4-fluorobenzene (3.69 g, 21.09 mmol), intermediate **C2** (0.95 g, 3.04 mmol), K_2CO_3 (5.21 g, 37.70 mmol) and NMP (6 mL) was added to a 15 mL sealed tube. The resulting mixture was stirred for 6.5 h at 140 °C. An additional batch of 1-bromo-4-fluorobenzene (1.22 g, 6.97 mmol) was added and the resulting mixture was stirred for 18 h at 160 °C. After cooling to RT, the reaction mixture was poured into water (50 mL) and 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 gel chromatography (eluting with MeOH : DCM = 1 : 15, v/v) to give compound **34-1** (249 mg) as a brown oil. MS: 358 $[M+1]^+$.

A mixture of compound **34-1** (120 mg, 0.33 mmol), intermediate **A1** (65 mg, 0.36 mmol), $Pd_2(dba)_3$ (61 mg, 0.067 mmol), XantPhos (83 mg, 0.14 mmol) and DIPEA (303 mg, 2.34 mmol) in 1,4-dioxane (10 mL) was stirred for 18 h at 110 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 20, v/v) to give example **34** (47 mg). MS: 438 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.47 (d, J = 4.6 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 5.5 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.39 - 7.33 (m, 1H), 7.13 (d, J = 8.7 Hz, 2H), 5.88 (d, J = 5.5 Hz, 1H), 4.31 (s, 1H), 3.87 - 3.74 (m, 2H), 3.27 - 3.02 (m, 4H), 2.02 - 1.91 (m, 2H), 1.73 - 1.60 (m, 2H).

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

EX No	Chemical Name	Structure	MS & ^{1}HNMR
35	(S)-1'-(4-((2-amino-3-chloropyridin-4-yl)thio)isoquinolin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 488 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.38 (s, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.76 (t, J = 7.2 Hz, 1H), 7.67 (t, J = 7.2 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.47 – 7.32 (m, 5H), 5.63 (d, J = 5.6 Hz, 1H), 4.48 (s, 1H), 4.06 – 3.87 (m, 2H), 3.52 – 3.37 (m, 2H), 3.21 (d, J = 7.5 Hz, 1H), 2.25 – 2.06 (m, 2H), 1.89 – 1.83 (m, 1H), 1.79 – 1.72 (m, 1H).

Example 36



36-1 36-2 36-3

36-4 36

To a solution of 6-chloro-3-methylpyrimidine-2,4(1H,3H)-dione (10.00 g, 62.28 mmol) in EtOH (200 mL) was added hydrazine hydrate (80 %, 52.00 mL) at RT. The resulting mixture was stirred for 4 h at 80 °C. After cooling to RT, the reaction mixture was concentrated to about 100 mL under reduced pressure and filtered. The filtered cake was washed with EtOH (2 × 50 mL). The filtered cake was collected and dried in a high vacuum oven to give compound **36-1** (5.56 g) as a light yellow solid. MS: 157 $[M+1]^+$.

A mixture of compound **36-1** (5.56 g, 35.61 mmol) and 4-methoxybenzaldehyde (7.02 g, 51.56 mmol) in MeOH was stirred for 6 h at 70 °C. After cooling to RT, the reaction mixture was filtered and the filtered cake was washed with MeOH. The filtered cake was collected and dried under high vacuum to give compound **36-2** (5.78 g) as a yellow solid. MS: 275 $[M+1]^+$.

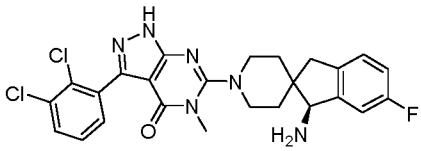
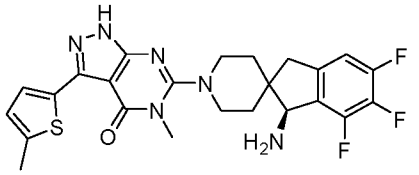
A mixture of compound **36-2** (2.03 g, 7.40 mmol), 2,3-dichlorobenzaldehyde (1.36 g, 7.77 mmol) and piperidine (0.77 g, 9.04 mmol) in DMF / iPrOH (20 mL / 10 mL) was stirred for 18 h at 85 °C. After cooling to RT, the reaction mixture was diluted with EA (200 mL) and washed with brine (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 2, v/v) to give compound **36-3** (2.40 g) as a light yellow solid. MS: 431 $[M+1]^+$.

A mixture of compound **36-3** (197 mg, 0.46 mmol) and BOP (649 mg, 1.47 mmol) in DMF (17 mL) was stirred for 10 min at RT. Then DBU (748 mg, 4.91 mmol) and **C2** (229 mg, 0.73 mmol) was added and stirred for 20 h at RT. The reaction mixture was diluted with EA (100 mL) wad washed with brine (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 8, v/v) to give compound **36-4** (210 mg). MS: 615 $[M+1]^+$.

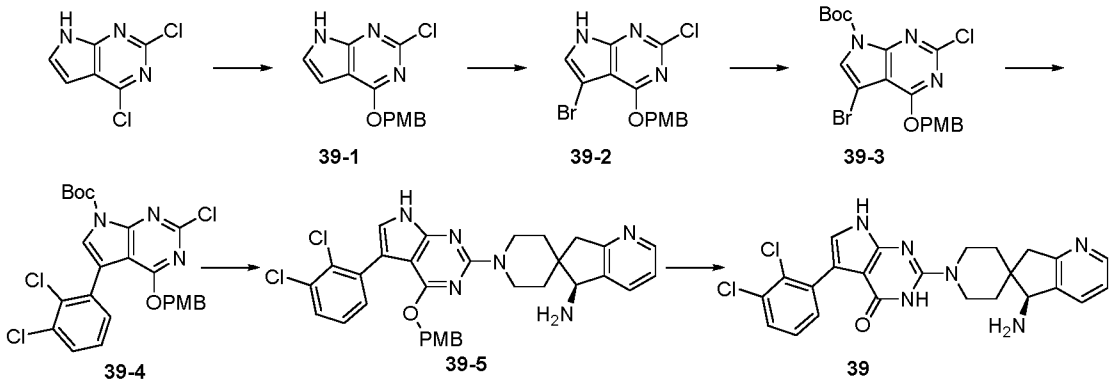
A mixture of compound **36-4** (210 mg, 0.34 mmol) and TFA (15 mL) was stirred for 1.5 h at 100 °C. The reaction mixture was diluted with water (100 mL) and the pH value was taken to 10 with $NH_3 \cdot H_2O$ (25 %). The resulting mixture was extracted with DCM (2 × 50 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 8, v/v) to give example **36** (21 mg). MS: 496 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.38 (d, J = 4.7 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.65 (dd, J = 7.9, 1.5 Hz, 1H), 7.46 (dd, J = 7.6, 1.5 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.31 (dd, J = 7.4, 5.2 Hz, 1H), 4.14 (s, 1H), 3.68 - 3.58 (m, 2H), 3.55 (s, 3H), 3.29 - 3.12 (m, 3H), 3.01 - 2.90 (m, 1H), 2.15 - 1.96 (m, 2H), 1.74 - 1.65 (m, 1H), 1.57 - 1.45 (m, 1H).

The following example was synthesized using the above procedure or modified procedure with the

corresponding starting materials.

EX No	Chemical Name	Structure	MS & ^{1}HNMR
37	(S)-6-(1-amino-6-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(2,3-dichlorophenyl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one		MS: 513 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.65 (dd, J = 7.9, 1.7 Hz, 1H), 7.45 (dd, J = 7.6, 1.7 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.26 (dd, J = 8.2, 5.1 Hz, 1H), 7.16 (dd, J = 8.8, 2.0 Hz, 1H), 7.03 - 6.93 (m, 1H), 4.10 (s, 1H), 3.63 - 3.55 (m, 2H), 3.54 (s, 3H), 3.25 - 3.09 (m, 3H), 2.88 - 2.79 (m, 1H), 2.10 - 1.95 (m, 2H), 1.72 - 1.65 (m, 1H), 1.57 - 1.49 (m, 1H).
38	(S)-6-(1-amino-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-methyl-3-(5-methylthiophen-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one		MS: 501 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.22 (d, J = 3.6 Hz, 1H), 7.10 – 6.99 (m, 1H), 6.81 (d, J = 3.5 Hz, 1H), 4.28 (s, 1H), 3.59 (s, 3H), 3.57 – 3.43 (m, 2H), 3.26 – 3.15 (m, 4H), 2.54 (s, 3H), 1.92 – 1.76 (m, 4H).

Example 39



A mixture of 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (2.53 g, 13.46 mmol), (4-methoxyphenyl)methanol (2.00 mL) and t-BuOK / THF (1 M, 53.00 mL, 53.00 mmol) in 1,4-dioxane (20 mL) was stirred for 2 h at RT. The reaction mixture was quenched with sat.aq.NH_4Cl and extracted with EA (2 × 100 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **39-1** (4.22 g) as a light yellow solid which was used in next step without further purification. MS: 290 $[M+1]^+$.

A mixture of compound **39-1** (4.22 g, 14.57 mmol) and NBS (2.96 g, 16.63 mmol) in DMF (35 mL)

was stirred for 20 min at RT. The reaction mixture was diluted with sat.aq.Na_2SO_3 (200 mL), extracted with EA (2 × 100 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **39-2** (4.76 g) as a brown solid which was used in next step without further purification. MS: 368 $[M+1]^+$.

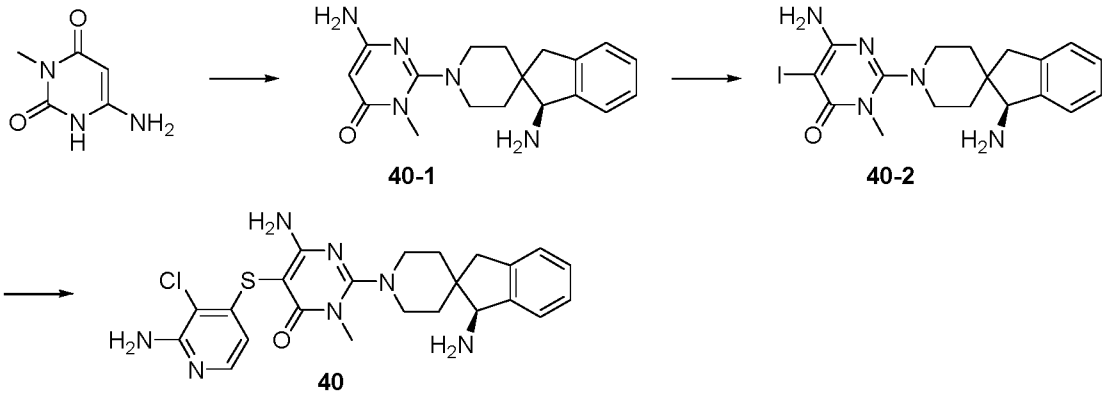
A mixture of compound **39-2** (4.76 g, 12.91 mmol), $(Boc)_2O$ (2.97 g, 13.61 mmol), DIPEA (5.05 g, 39.07 mmol) in DMF (40 mL) was stirred for 16 h at RT. To the mixture was added DMAP (52 mg, 0.43 mmol) and stirred for another 1 h at 40 °C. The reaction mixture purified by silica gel chromatography (eluting with EA : Hex = 1 : 30, v/v) to give compound **39-3** (2.82 g) as a white solid. MS: 468 $[M+1]^+$.

A mixture of compound **39-3** (500 mg, 1.07 mmol), (2,3-dichlorophenyl)boronic acid (215 mg, 1.13 mmol), K_2CO_3 (606 mg, 4.38 mmol) and $Pd(dppf)Cl_2$ (102 mg, 0.14 mmol) in THF / H_2O (5.0 mL / 0.5 mL) was stirred for 3 h at 90 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with brine (50 mL), extracted with EA (2 × 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 10, v/v) to give compound **39-4** (380 mg). MS: 534 $[M+1]^+$.

A mixture of compound **39-4** (241 mg, 0.56 mmol), **C2** (210 mg, 0.67 mmol) and K_2CO_3 (1903 mg, 13.77 mmol) in NMP (15 mL) was stirred for 23 h at 140 °C. After cooling to RT, the reaction mixture was diluted with EA (100 mL) and washed with brine (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 10, v/v) to give compound **39-5** (39 mg) as a brown solid. MS: 601 $[M+1]^+$.

A mixture of compound **39-5** (38 mg, 0.063 mmol) and TFA (2 mL) in DCM (10 mL) was stirred for 1 h at RT. The reaction mixture was diluted with brine (50 mL) and the pH value was taken to 10 with $NH_3 \cdot H_2O$ (25 %). The resulting mixture was extracted with DCM (2 × 30 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 6, v/v) to give example **39** (12 mg). MS: 481 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.43 (d, J = 4.7 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.42 (dd, J = 7.8, 1.5 Hz, 2H), 7.33 (dd, J = 7.5, 5.2 Hz, 1H), 7.28 - 7.21 (m, 1H), 6.87 (s, 1H), 4.28 - 4.18 (m, 2H), 4.16 (s, 1H), 3.31 - 3.20 (m, 3H), 3.05 - 2.94 (m, 1H), 1.98 - 1.82 (m, 2H), 1.65 - 1.58 (m, 1H), 1.51 - 1.45 (m, 1H).

Example 40



40-1 **40-2** **40**

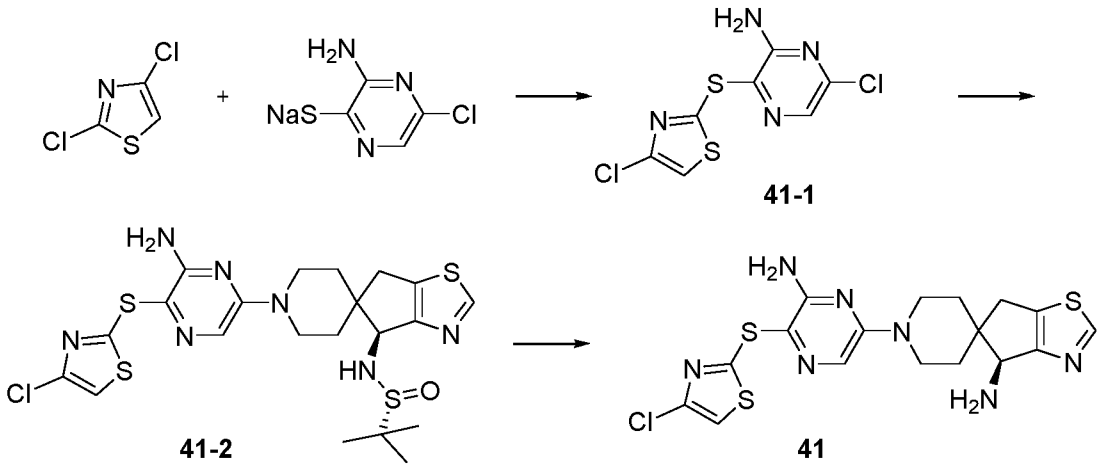
A mixture of 6-amino-3-methylpyrimidine-2,4(1H,3H)-dione (0.50 g, 3.54 mmol) and PyBOP (5.62

g, 10.80 mmol) in DMF (15 mL) was stirred for 10 min at RT. Then DBU (5.62 g, 36.92 mmol) and **C1** (1.39 g, 5.05 mmol) was added and stirred for 3 h at RT. The reaction mixture was diluted with EA (100 mL) wad washed with brine (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 5, v/v) to give compound **40-1** (1135 mg) as a yellow oil. MS: 326 $[M+1]^+$.

A mixture of compound **40-1** (1.13 g, 3.47 mmol) and NIS (859 mg, 3.82 mmol) in DMF (10 mL) was stirred for 17 h at RT. The reaction mixture was diluted with EA (200 mL) and washed sat.aq.Na_2SO_3 with EA (2 × 80 mL) and sat.aq.NH_4Cl (1 × 80 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 8, v/v) to give compound **40-2** (828 mg). MS: 452 $[M+1]^+$.

A mixture of compound **40-2** (103 mg, 0.23 mmol), intermediate **A1** (48 mg, 0.26 mmol), $Pd_2(dba)_3$ (21 mg, 0.023 mmol), XantPhos (25 mg, 0.043 mmol) and DIPEA (103 mg, 0.80 mmol) in 1,4-dioxane (10 mL) was stirred for 15 h at 110 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was filtered through Kieselguhr and the filtrate was concentrated under reduced pressure. The residue was purified by Prep - TLC (eluting with MeOH : DCM = 1 : 10, v/v) to give example **40** (12 mg). MS: 484 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.62 (d, J = 5.5 Hz, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.45 - 7.32 (m, 3H), 6.19 (d, J = 5.5 Hz, 1H), 4.42 (s, 1H), 3.80 - 3.63 (m, 2H), 3.47 (s, 3H), 3.30 - 3.09 (m, 4H), 2.11 - 1.89 (m, 2H), 1.75 (d, J = 12.9 Hz, 1H), 1.66 (d, J = 13.2 Hz, 1H).

Example 41



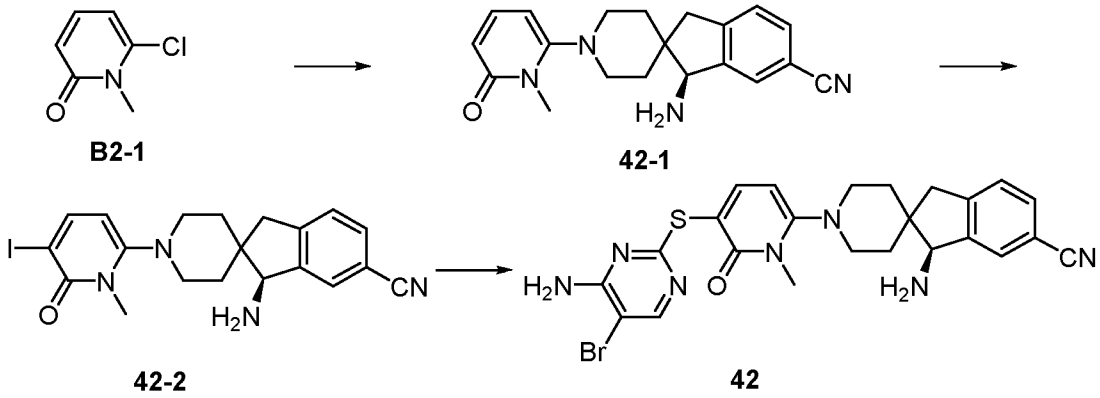
A mixture of 2,4-dichlorothiazole (1.54 g, 10.00 mmol), sodium 3-amino-5-chloropyrazine-2-thiolate -(2.77 g, 15.10 mmol) and K_2CO_3 (2.92 g, 21.10 mmol) in DMF (15 mL) was stirred for 3 h at 75 °C. After cooling to RT, the reaction mixture was diluted with EA (50 mL) and water (50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 5, v/v) to give compound **41-1** (281 mg) as a yellow solid. MS: 279 $[M+1]^+$.

To a solution of intermediate **C3** (288 mg, 0.70 mmol) in DCM (17 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 (5 mL), **41-1** (232 mg, 1.19 mmol) and K_2CO_3 (1.18 g, 8.52 mmol) was added. The

resulting mixture was stirred for 16 h at 95 °C. After cooling to RT, the reaction mixture was diluted with water (30 mL) and EA (30 mL). The aqueous layer was separated and extracted with EA (2 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **41-2** (272 mg) as a red oil. MS: 556 $[M+H]^+$.

A mixture of compound **41-2** (254 mg, 0.43 mmol) and HCl / 1, 4-dioxane (4M, 1 mL) in DCM was stirred for 30 min at RT. The reaction mixture was concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 8, v/v) to give **41** (34 mg) as a yellow solid. MS: 452 $[M+H]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 9.01 (s, 1H), 7.63 (s, 1H), 7.26 (s, 1H), 4.50 - 4.28 (m, 3H), 3.46 - 3.35 (m, 1H), 3.31 - 3.21 (m, 2H), 3.19 - 3.09 (m, 1H), 2.00 - 1.76 (m, 4H).

Example 42

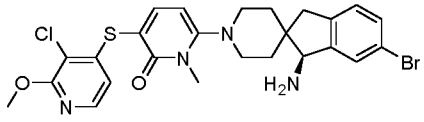


A mixture of compound **B2-1** (192 mg, 1.34 mmol), (S)-1-amino-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile dihydrochloride (406 mg, 1.35 mmol), K_2CO_3 (2132 mg, 15.43 mmol) and NMP (8 mL) was stirred for 1.5 h at 140 °C. After cooling to RT, the reaction mixture was diluted with water (20 mL) and extracted with EA (2 A 50 mL). The combined organic layers were washed with brine (1 b 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 10, v/v) to give compound **42-1** (202 mg) as a brown oil. MS: 335 $[M+1]^+$.

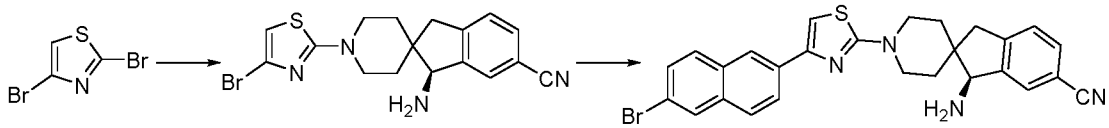
A mixture of compound **42-1** (202 mg, 0.60 mmol), NIS (167 mg, 0.74 mmol) and THF (8 mL) was stirred for 19 h at RT. The reaction mixture was diluted with brine (50 mL) and extracted with EA (2 2 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 20, v/v) to give compound **42-2** (79 mg) as a yellow solid. MS: 461 $[M+1]^+$.

A mixture of compound **42-2** (79 mg, 0.17 mmol), sodium 4-amino-5-bromopyrimidine-2-thiol (57 mg, 0.25 mmol), $Pd_2(dba)_3$ (15 mg, 0.016 mmol), XantPhos (21 mg, 0.036 mmol) and DIPEA (75 mg, 0.58 mmol) in 1,4-dioxane (8 mL) was stirred for 2 h at 90 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 10, v/v) to give example **42** (15 mg) as a yellow solid. MS: 538 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.02 (s, 1H), 7.93 – 7.76 (m, 2H), 7.70 – 7.64 (m, 1H), 7.50 (d, J = 7.5 Hz, 1H), 6.18 (d, J = 8.0 Hz, 1H), 4.29 (s, 1H), 3.62 (s, 3H), 3.46 – 3.36 (m, 2H), 3.30 – 3.15 (m, 4H), 2.06 – 1.90 (m, 2H), 1.77 – 1.67 (m, 2H).

The following compound was synthesized in the similar manner of example **42**.

EX No	Chemical Name	Structure	MS & ^{1}HNMR
43	(S)-6-(1-amino-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-((3-chloro-2-methoxypyridin-4-yl)thio)-1-methylpyridin-2(1H)-one		MS: 561 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.93 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 5.5 Hz, 1H), 7.69 (s, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 6.35 (d, J = 5.5 Hz, 1H), 6.24 (d, J = 8.0 Hz, 1H), 4.39 (s, 1H), 3.98 (s, 3H), 3.62 (s, 3H), 3.21 – 2.90 (m, 6H), 2.10 – 1.95 (m, 2H), 1.79 – 1.64 (m, 2H).

Example 44

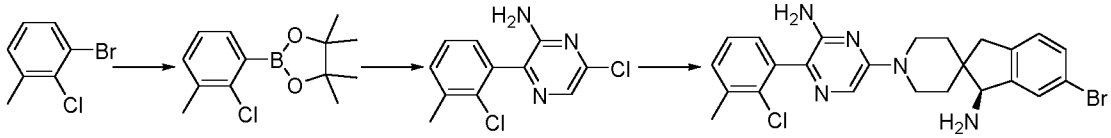


44-1 **44**

Solution of 2,4-dibromothiazole (202 mg, 0.83 mmol), (S)-1-amino-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile dihydrochloride (382 mg, 1.27 mmol) and TEA (1609 mg, 15.90 mmol) in DMF (8 mL) was stirred for 30 h at 90 °C. The reaction mixture was diluted with water (50 mL) and extracted with EA (2 × 50 mL). The combined organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **44-1** (243 mg) as a light yellow solid. MS: 389 $[M+1]^+$.

A mixture of intermediate **A2** (420 mg, 1.67 mmol), compound **44-1** (135 mg, 0.53 mmol), $Pd(PPh_3)_4$ (127 mg, 0.11 mmol), Na_2CO_3 (1120 mg, 10.57 mmol), THF (20 mL) and H_2O (2 mL) was stirred for 16 h at 90 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with brine (100 mL) and extracted with EA (2 × 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 gel chromatography (eluting with MeOH : DCM = 1 : 50, v/v) to give the crude product and was further purified by Prep - TLC (MeOH : DCM = 1 : 40, v/v) to give example **44** (20 mg) as an off - white solid. MS: 515 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.36 (s, 1H), 7.91 – 7.79 (m, 4H), 7.72 – 7.68 (m, 1H), 7.60 – 7.45 (m, 3H), 7.21 – 7.13 (m, 1H), 4.31 (s, 1H), 4.20 – 3.94 (m, 3H), 3.47 – 3.36 (m, 2H), 3.08 (m, 1H), 1.94 – 1.81 (m, 2H), 1.75 – 1.63 (m, 2H).

Example 45



45-1 **45-2** **45**

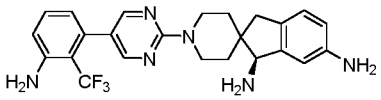
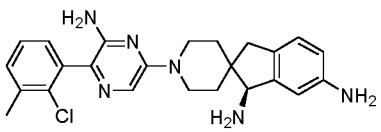
A mixture of 1-bromo-2-chloro-3-methylbenzene (2.89 g, 14.06 mmol),

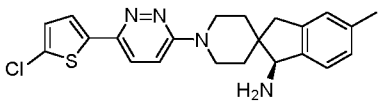
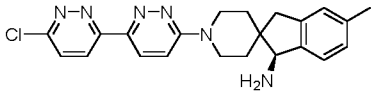
4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.43 g, 21.38 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.21 g, 1.65 mmol), Na_2CO_3 (5.56 g, 52.46 mmol) in 1,4-dioxane (30 mL) was stirred for 22 h at 110 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with EA and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 4, v/v) to give the compound **45-1** (2.17 g).

A mixture of compound **45-1** (1.00 g, 3.96 mmol), 3-bromo-6-chloropyrazin-2-amine (1.03 g, 4.94 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.84 g, 1.15 mmol), K_2CO_3 (2.37 g, 17.15 mmol), CH_3CN (40 mL) and H_2O (4 mL) was stirred for 2 h at 110 °C under nitrogen atmosphere. After cooling to RT, the reaction mixture was diluted with EA and filtered through a pad of Celite. The filtrate was washed with brine, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 15, v/v) to give the compound **45-2** (2.17 g). MS: 254 $[M+1]^+$.

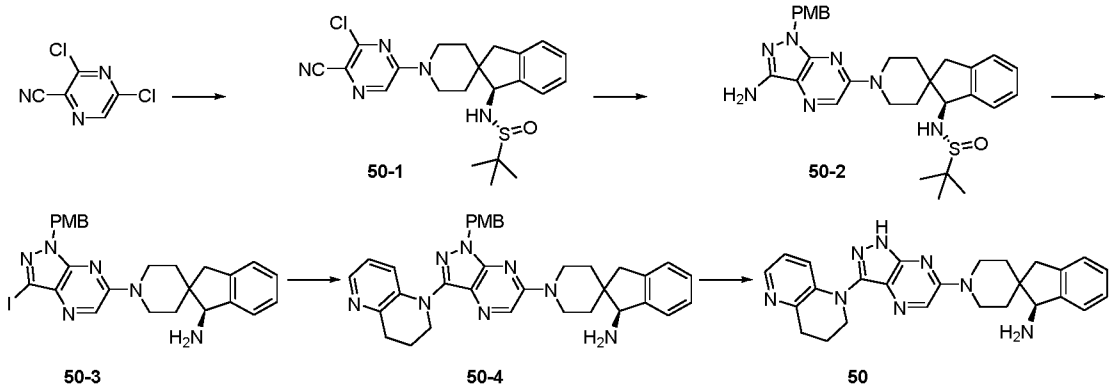
A mixture of compound **45-2** (102 mg, 0.40 mmol), (S)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine dihydrochloride (205 mg, 0.42 mmol), K_2CO_3 (1562 mg, 11.30 mmol) and CH_3CN (20 mL) was stirred for 16 h at 100 °C. After cooling to RT, the reaction mixture was diluted with EA (50 mL) filtered. The filtrate was concentrated under reduced pressure. The residue was purified by Prep - TLC (MeOH : DCM = 1 : 12, v/v) to give example **45** (89 mg) as a yellow solid. MS: 498 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.61 (s, 1H), 7.49 – 7.43 (m, 2H), 7.38 (d, J = 7.0 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.23 (dd, J = 10.8, 7.9 Hz, 2H), 4.24 (t, J = 13.6 Hz, 2H), 4.17 (s, 1H), 3.25 – 3.10 (m, 3H), 2.92 (d, J = 16.2 Hz, 1H), 2.46 (s, 3H), 1.92 – 1.74 (m, 2H), 1.65 – 1.47 (m, 2H).

The following examples were synthesized in the similar manner of example **45**.

EX No	Chemical Name	Structure	MS & ^{1}HNMR
46	(S)-1'-(5-(3-amino-2-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine		MS: 455 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.63 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H) 7.12 (d, J = 8.0 Hz, 2H), 6.89 – 6.72 (m, 3H), 4.68 – 4.53 (m, 2H), 4.23 (s, 1H), 3.44 – 3.37 (m, 2H), 3.09 – 3.03 (m, 2H), 1.76 – 1.61 (m, 4H).
47	(S)-1'-(6-amino-5-(2-chloro-3-methylphenyl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine		MS: 435 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.46 (s, 1H), 7.38 (d, J = 6.8 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 1.7 Hz, 1H), 6.74 (dd, J = 8.0, 2.0 Hz, 1H), 4.35 – 4.07 (m, 3H), 3.28 – 3.09 (m, 2H), 3.07 – 2.90 (m, 2H), 2.45 (s, 3H), 1.88 – 1.73 (m, 2H), 1.70 – 1.56 (m, 2H).

48	(S)-1'-(6-(5-chlorothiophen-2-yl)pyridazin-3-yl)-5-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 411 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 7.83 (d, J = 9.7 Hz, 1H), 7.42 – 7.31 (m, 3H), 7.21 (s, 1H), 7.16 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 4.0 Hz, 1H), 4.45 – 4.36 (m, 1H), 4.33 (s, 1H), 4.26 – 4.15 (m, 1H), 3.45 – 3.34 (m, 2H), 3.17 (s, 2H), 2.38 (s, 3H), 1.95 – 1.84 (m, 1H), 1.83 – 1.70 (m, 2H), 1.68 – 1.56 (m, 1H).
49	(S)-1'-(6'-chloro-[3,3'-bipyridazin]-6-yl)-5-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		MS: 407 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.63 (d, J = 9.1 Hz, 1H), 8.43 (d, J = 9.7 Hz, 1H), 7.92 (d, J = 9.1 Hz, 1H), 7.46 (d, J = 9.7 Hz, 1H), 7.19 (s, 1H), 7.18 – 7.11 (m, 2H), 4.50 (d, J = 13.8 Hz, 1H), 4.40 – 4.35 (m, 1H), 4.28 – 4.25 (m, 1H), 3.48 – 3.43 (m, 2H), 3.18 – 3.11 (m, 2H), 2.37 (s, 3H), 1.94 – 1.78 (m, 4H).

Example 50



A solution of compound **C1-4** (1.90 g, 4.67 mmol) and TFA (6.00 mL) in DCM (20 mL) was stirred for 1 h at RT. The resulting mixture was concentrated under reduced pressure. 3,5-Dichloropyrazine-2-carbonitrile (818 mg, 4.70 mmol), DMSO (8 mL) and DIPEA (6.56 g, 50.76 mmol) was added and stirred for 1 h at 70 °C. The reaction mixture was diluted with water (50 mL) and extracted with EA (2 × 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 gel chromatography (eluting with EA : Hex = 1 : 2, v/v) to give compound **50-1** (1.81 g). MS: 444 $[M+1]^+$.

A mixture of compound **50-1** (1.81 g, 4.08 mmol), (4-methoxybenzyl)hydrazine hydrochloride (0.94 g, 4.98 mmol), TEA (4.60 g, 45.46 mmol) and EtOH (20 mL) was stirred for 18 h at 90 °C. The reaction mixture was concentrated under reduced pressure. The residue was diluted with EA (100 mL), washed with sat.aq.NH_4Cl (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under high vacuum

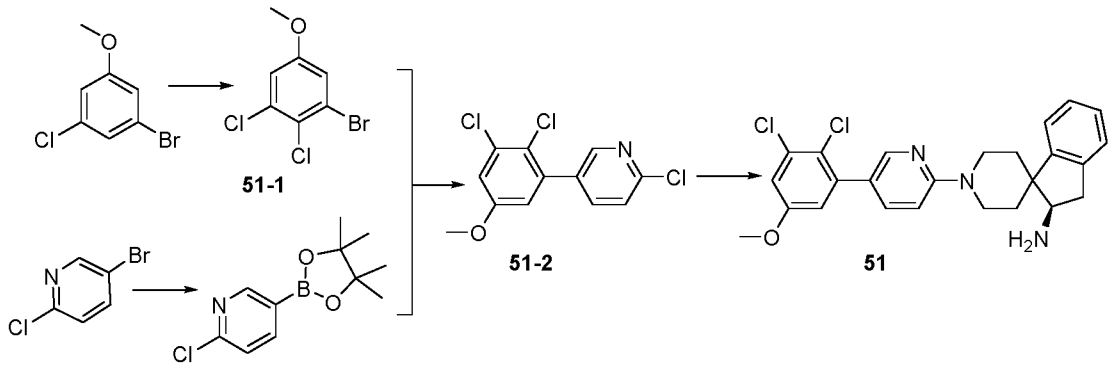
to give compound **50-2** (2.19 g) as a yellow solid. MS: 560 $[M+1]^+$.

A solution of compound **50-2** (1.58 g, 2.82 mmol), tert-butyl nitrite (0.36 g, 3.49 mmol) and CH_2I_2 (1.60 g, 5.97 mmol) in CH_3CN (30 mL) was stirred for 1.5 h at 90 °C. The reaction mixture was diluted with brine (150 mL), MeOH (20 mL) and extracted with EA (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. To the obtained red solid was added EA (20 mL), filtered and the filter cake was collected. The crude **50-3** (1.02 g) was used in next step without further purification. MS: 567 $[M+1]^+$.

A mixture of compound **50-3** (236 mg, 0.42 mmol), 1,2,3,4-tetrahydro-1,5-naphthyridine (62 mg, 0.46 mmol), Pd2(dba)3 (77 mg, 0.084 mmol), BINAP (59 mg, 0.094 mmol) and t-BuONa (121 mg, 1.26 mmol) in toluene (10 mL) was stirred for 16 h at 90 °C under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with MeOH : DCM = 1 : 20, v/v) to give the crude product and was further purified by Prep – TLC (MeOH : DCM = 1 : 20, v/v) to give compound **50-4** (45 mg) as a yellow solid. MS: 573 $[M+1]^+$.

A mixture of compound **50-4** (34 mg, 0.059 mmol), TFA (3.0 mL), H_2SO_4 (98 %, 0.2 mL) and anisole (0.5 mL) was stirred for 4 h at 90 °C. The pH value of the reaction mixture was adjusted to 9 with sat.aq.Na_2CO_3. The resulting mixture was extracted with EA (2 × 20 mL), the organic layers combined, dried over anhydrous Na_2SO_4 and concentrated reduced pressure. The residue was purified by Prep – TLC (MeOH : DCM = 1 : 10, v/v) to give example **50** (3 mg) as a light yellow solid. MS: 453 $[M+1]^+$.

Example 51



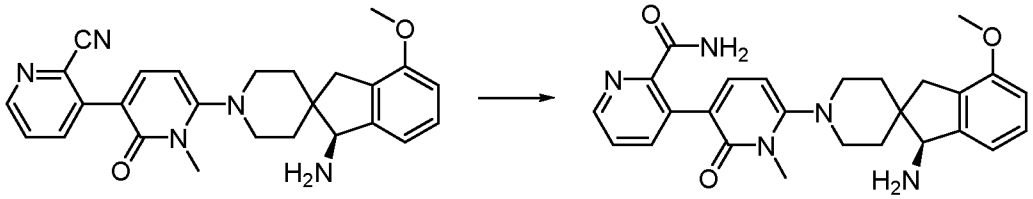
A mixture of 1-bromo-3-chloro-5-methoxybenzene (2.05 g, 9.26 mmol), 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (733 mg, 2.27 mmol) and DMF (15 mL) was stirred for 18 h at 50 °C. The reaction mixture was quenched with water (15 mL) and extracted with EA (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **51-1** (2.60 g) as a white solid.

A mixture of 5-bromo-2-chloropyridine (100 mg, 0.52 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (145 mg, 0.57 mmol), $Pd(dppf)Cl_2$ (19 mg, 0.026 mmol) and CH_3COOK (153 mg, 1.56 mmol) in 1,4-dioxane (10 mL) was stirred for 2.5 h at 90 °C under nitrogen atmosphere. To the resulting mixture was added compound **51-1** (148 mg, 0.58 mmol), $Pd(dppf)Cl_2$ (21 mg, 0.029 mmol), CH_3COOK (154 mg, 1.57 mmol). The resulting mixture was stirred for 16 h at 70 °C. After cooling to RT, the reaction mixture was diluted with water (20 mL) and extracted with EA (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered

and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with EA : Hex = 1 : 10, v/v) to give the compound **51-2** (28 mg). MS: 288 $[M+1]^+$.

Example **51** was synthesized in the similar manner of example **1**, except compound **1-4** was replaced with compound **51-2**. MS: 454 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.16 (d, J = 2.3 Hz, 1H), 7.68 (dd, J = 8.9, 2.5 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.43 – 7.29 (m, 3H), 7.14 (d, J = 2.9 Hz, 1H), 6.97 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 2.9 Hz, 1H), 4.59 (s, 1H), 4.47 – 4.33 (m, 2H), 3.86 (s, J = 7.9 Hz, 3H), 3.26 – 3.06 (m, 3H), 3.00 – 2.89 (m, 1H), 1.93 – 1.72 (m, 4H).

Example 52 & Example 53

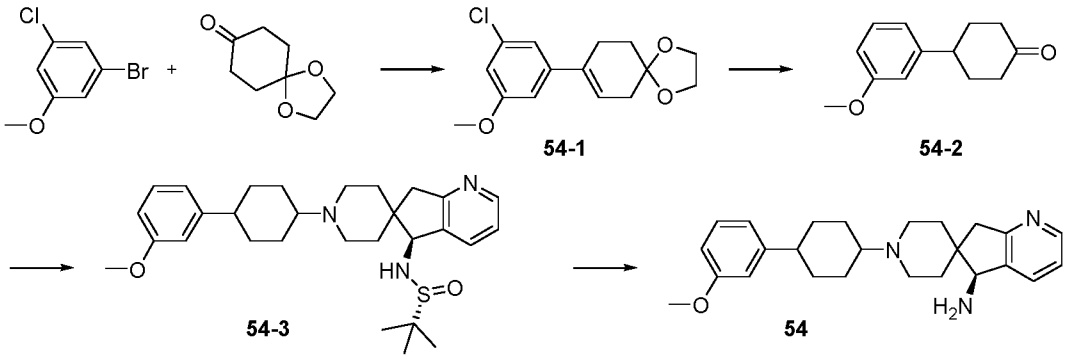


52 **53**

Example **52** was prepared following procedures of **example 51** from intermediate **B2**. MS: 442 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.64 (dd, J = 4.7, 1.4 Hz, 1H), 8.04 (dd, J = 8.1, 1.5 Hz, 1H), 7.79 – 7.66 (m, 2H), 7.28 (t, J = 7.9 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.28 (d, J = 7.9 Hz, 1H), 4.20 (s, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.58 (t, J = 6.0 Hz, 1H), 3.28 – 3.22 (m, 1H), 3.13 – 2.99 (m, 3H), 2.93 – 2.84 (m, 1H), 2.10 – 1.96 (m, 2H), 1.75 – 1.64 (m, 2H).

A solution of example **52** (10 mg, 0.023 mmol), KOH (40 mg, 0.71 mmol) in MeOH (2 mL) and H_2O (2 mL) was stirred for 4 h at 100 °C. The reaction mixture was diluted with water (5 mL), extracted with EA (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the example **53** (7 mg) as a yellow solid. MS: 460 $[M+1]^+$. ^{1}HNMR (400 MHz, methanol - d_4) δ 8.57 (d, J = 4.7 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.75 – 7.68 (m, 1H), 7.66 – 7.54 (m, 2H), 7.47 (d, J = 7.6 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.19 (d, J = 7.7 Hz, 1H), 4.27 (s, 1H), 3.86 (s, 3H), 3.60 (s, 3H), 3.27 – 3.17 (m, 2H), 3.07 – 2.93 (m, 4H), 1.81 – 1.63 (m, 4H).

Example 54



54-1 **54-2** **54-3** **54**

To a - 80 °C solution of 1-bromo-3-chloro-5-methoxybenzene (2.24 g, 10.11 mmol) in THF (50 mL) under nitrogen atmosphere was added n-BuLi (2.5 M, 7.40 mL, 18.50 mmol) dropwise. The resulting mixture was stirred for 40 min at - 80 °C. Then 1,4-dioxaspiro[4.5]decan-8-one (dissolved in 9 mL THF,

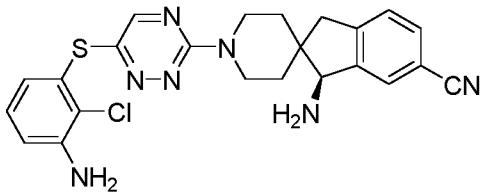
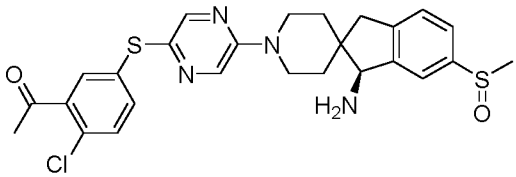
1.62 g, 10.37 mmol) was added dropwise and the resulting mixture was stirred for 40 min. The reaction mixture was quenched with brine (10 mL), diluted with water (100 mL) and extracted with EA (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **54-1** (3.73 g) as a yellow oil.

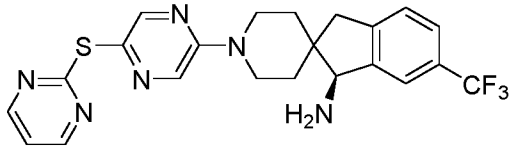
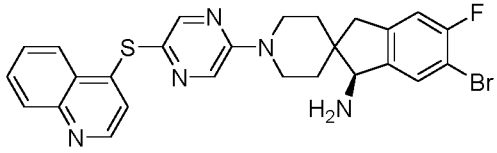
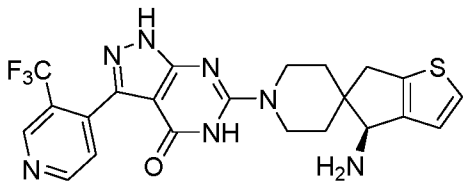
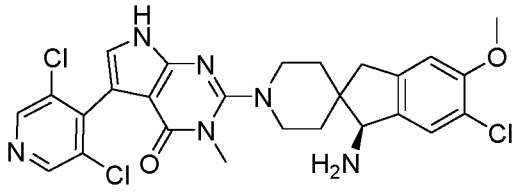
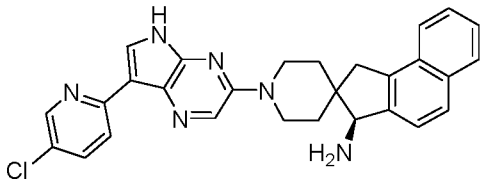
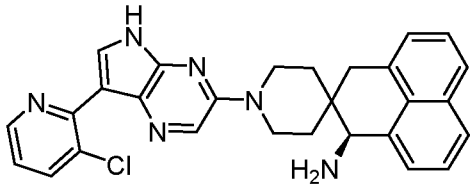
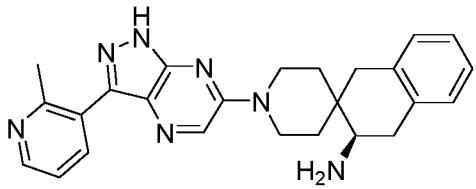
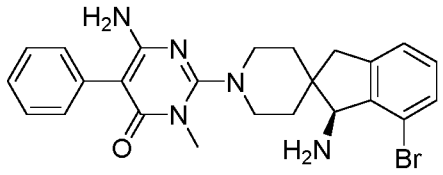
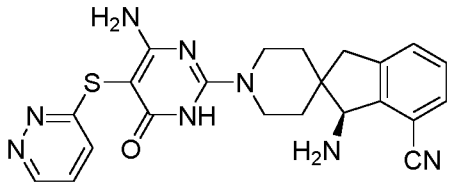
A suspension of compound **54-1** (3.72 g, 13.25 mmol), Pd / C (Pd 10 %, H_2O 54.55 %, 6.07 g) in MeOH (50 mL) was stirred for 2 h at RT under hydrogen atmosphere. The reaction mixture was filtered through a Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in acetone (60 mL) and HCl (aq, 2M, 20 mL) was added. The resulting mixture was stirred for 1 h at 60 °C. The reaction mixture was diluted with water (50 mL) and extracted with EA (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **54-2** (1.82 g) as a white solid. ^{1}H NMR (400 MHz, *d* - DMSO) δ 7.17 (t, *J* = 8.1 Hz, 1H), 6.86 – 6.79 (m, 2H), 6.76 – 6.69 (m, 1H), 3.70 (s, 3H), 3.04 – 2.89 (m, 1H), 2.57 – 2.44 (m, 2H), 2.29 – 2.19 (m, 2H), 2.06 – 1.97 (m, 2H), 1.89 – 1.74 (m, 2H).

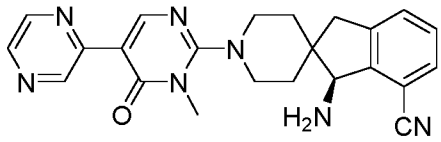
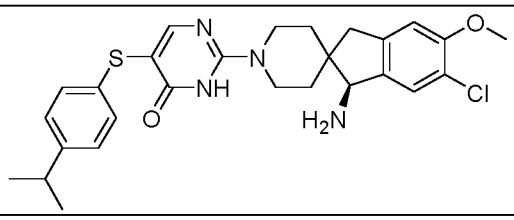
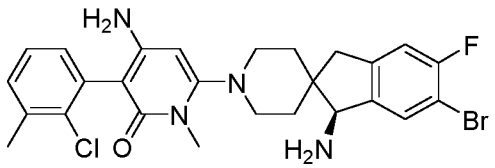
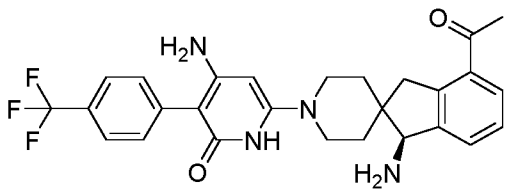
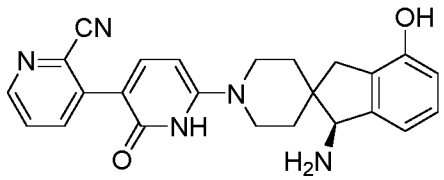
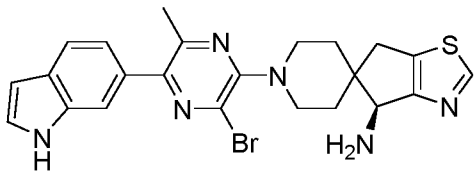
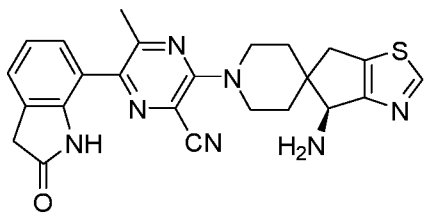
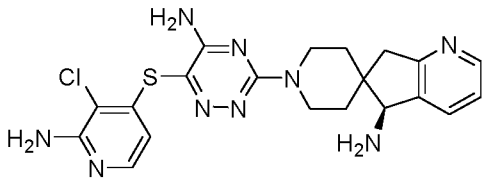
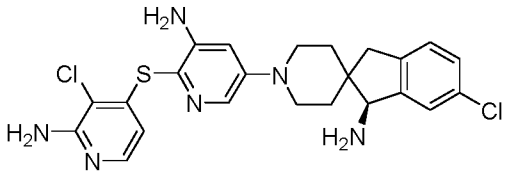
A solution of intermediate **C2-6** (115 mg, 0.28 mmol), TFA (2 mL) and DCM (10 mL) was stirred for 1 h at RT. To the resulting mixture was added compound **54-2** (57 mg, 0.28 mmol), TsOH (5 mg) and $NaBH(OAc)_3$ (120 mg, 0.57 mmol). The resulting mixture was stirred for 3 days at RT. The reaction mixture was diluted with brine (30 mL) and extracted with DCM (2 × 30 mL), the organic layers combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by Prep – TLC (MeOH : DCM = 1 : 15, v/v) to give compound **54-3** (30 mg) as a white solid. MS: 496 $[M+1]^+$.

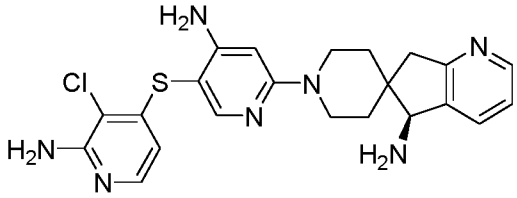
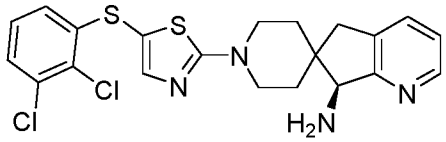
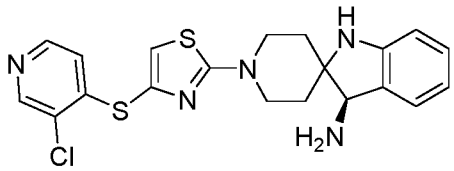
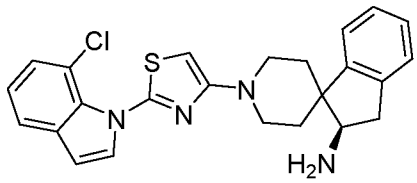
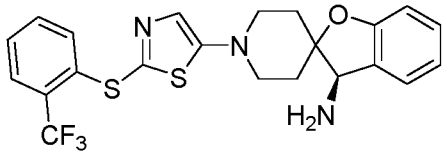
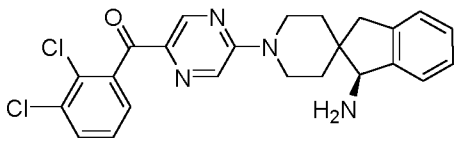
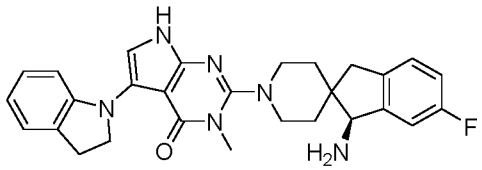
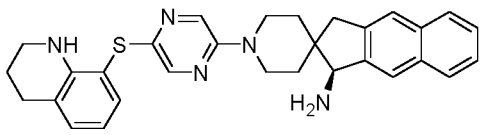
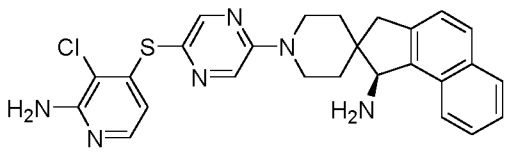
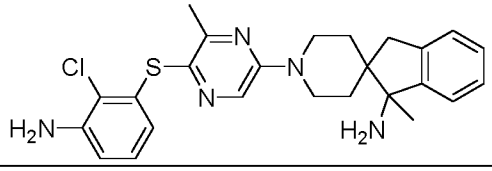
A mixture of compound **54-3** (30 mg, 0.061 mmol) and HCl / EA (4 M, 1.00 mL, 4.00 mmol) in EA (10 mL) was stirred for 2.0 h at RT. The reaction mixture was diluted with water (20 mL) and the pH value was taken to 9 with $NH_3{\cdot}H_2O$ (25 %). The resulting mixture was extracted with EA (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give example **54** (8 mg) as a brown solid. MS: 392 $[M+1]^+$.

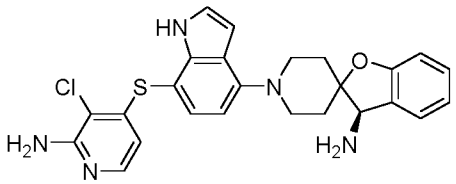
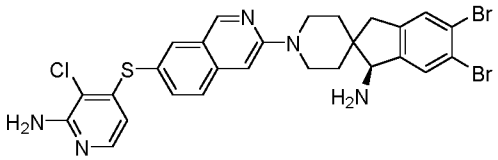
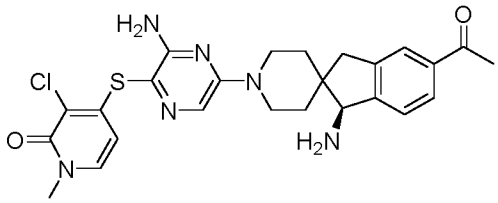
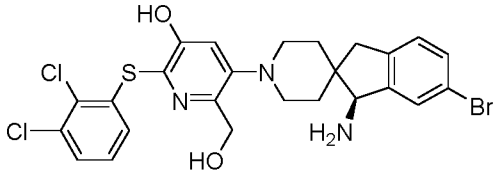
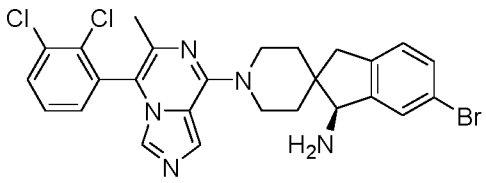
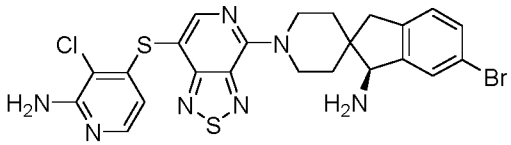
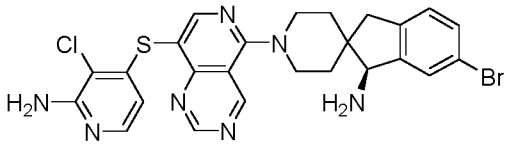
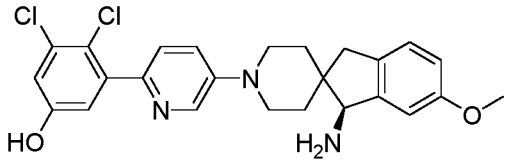
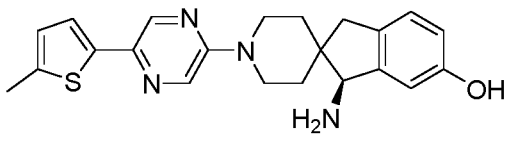
The following compounds were synthesized using the above procedure or modified procedure with the corresponding starting materials.

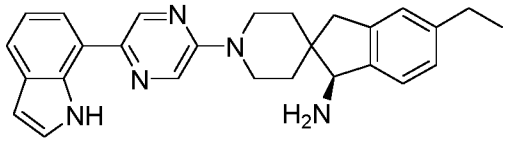
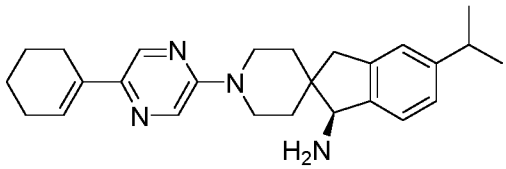
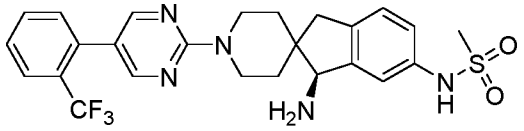
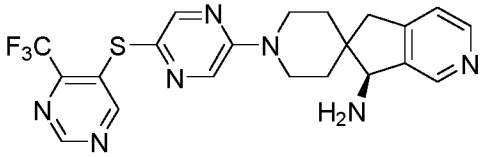
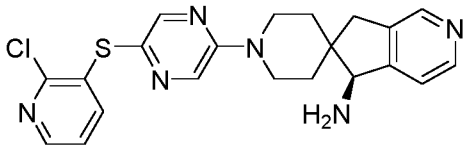
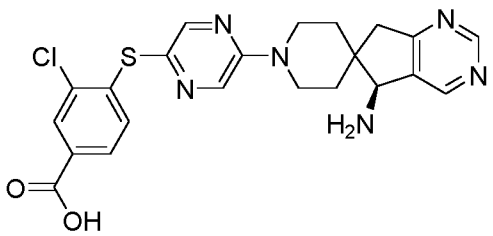
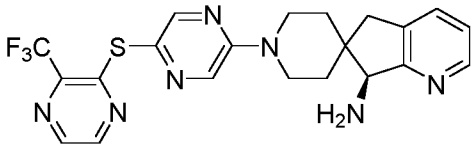
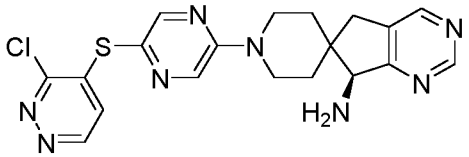
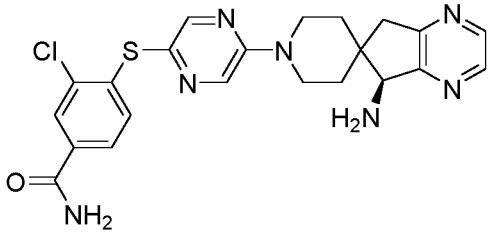
EX	Chemical Name	Structure	MS: $[M+1]^+$
55	(S)-1-amino-1'-(6-((3-amino-2-chlorophenyl)thio)-1,2,4-triazin-3-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile		464
56	1-(5-((5-((1S)-1-amino-6-(methylsulfinyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-2-chlorophenyl)ethan-1-one		527

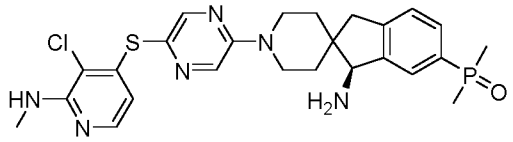
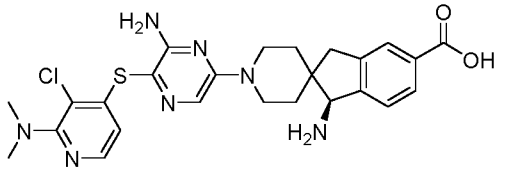
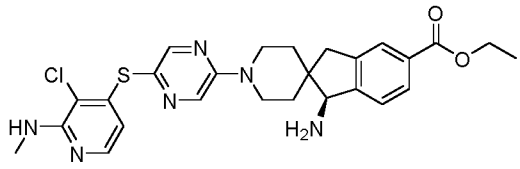
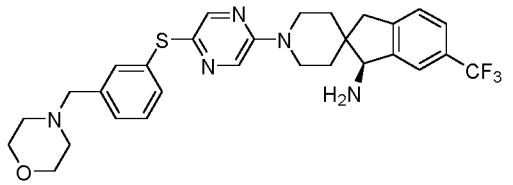
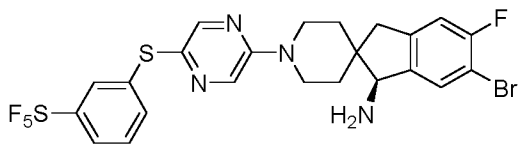
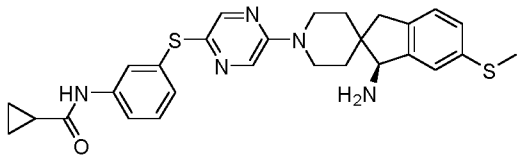
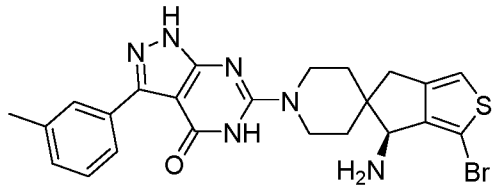
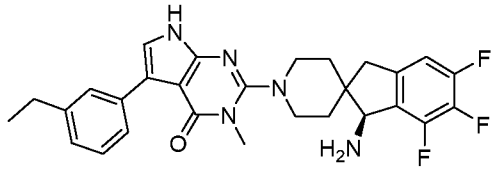
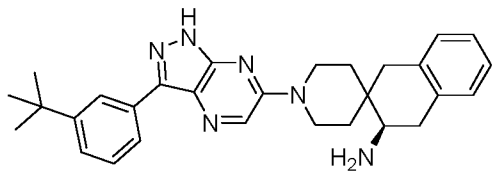
57	(S)-1'-(5-(pyrimidin-2-ylthio)pyrazin-2-yl)-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		459
58	(S)-6-bromo-5-fluoro-1'-(5-(quinolin-4-ylthio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		536
59	(S)-6-(4-amino-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)-3-(3-(trifluoromethyl)pyridin-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one		488
60	(S)-2-(1-amino-6-chloro-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(3,5-dichloropyridin-4-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one		559
61	(S)-1'-(7-(5-chloropyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-3-amine		481
62	(S)-1'-(7-(3-chloropyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-1H,3H-spiro[phenalene-2,4'-piperidin]-1-amine		481
63	(R)-1'-(3-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-3-amine		426
64	(S)-6-amino-2-(1-amino-7-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-phenylpyrimidin-4(3H)-one		480
65	(S)-1-amino-1'-(4-amino-6-oxo-5-(pyridazin-3-ylthio)-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-7-carbonitrile		447

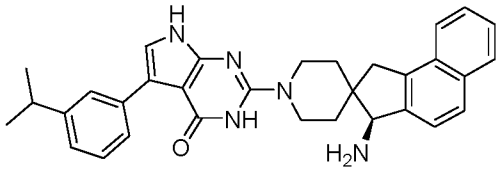
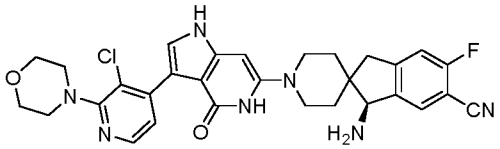
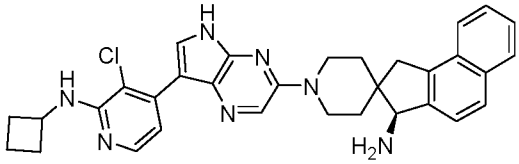
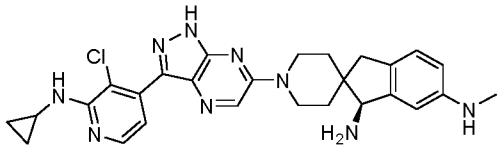
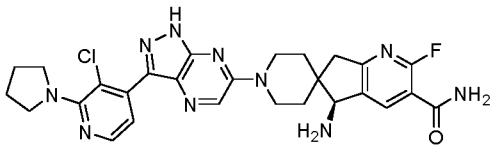
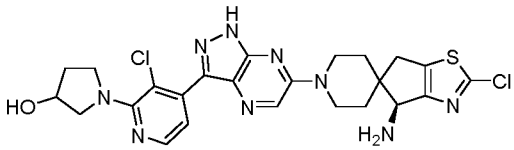
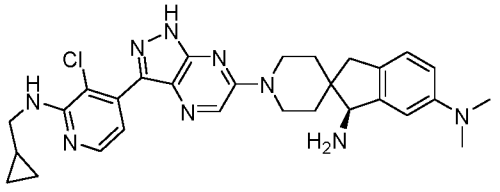
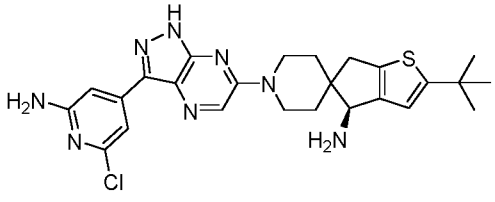
66	(S)-1-amino-1'-(1-methyl-6-oxo-5-(pyrazin-2-yl)-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-7-carbonitrile		414
67	(S)-2-(1-amino-6-chloro-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-((4-isopropylphenyl)thio)pyrimidin-4(3H)-one		511
68	(S)-4-amino-6-(1-amino-6-bromo-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(2-chloro-3-methylphenyl)-1-methylpyridin-2(1H)-one		545
69	(S)-6-(4-acetyl-1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-4-amino-3-(4-(trifluoromethyl)phenyl)pyridin-2(1H)-one		497
70	(S)-6'-(1-amino-4-hydroxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-2'-oxo-1',2'-dihydro-[3,3'-bipyridine]-2-carbonitrile		414
71	(S)-1'-(3-bromo-5-(1H-indol-6-yl)-6-methylpyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		495
72	(S)-3-(4-amino-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-5-methyl-6-(2-oxoindolin-7-yl)pyrazine-2-carbonitrile		458
73	(S)-1'-(5-amino-6-((2-amino-3-chloropyridin-4-yl)thio)-1,2,4-triazin-3-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		456
74	(S)-1'-(5-amino-6-((2-amino-3-chloropyridin-4-yl)thio)pyridin-3-yl)-6-chloro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		487

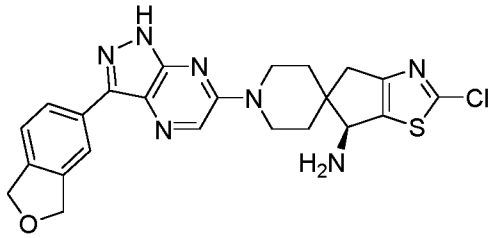
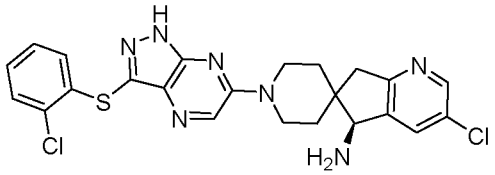
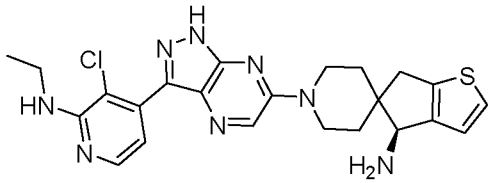
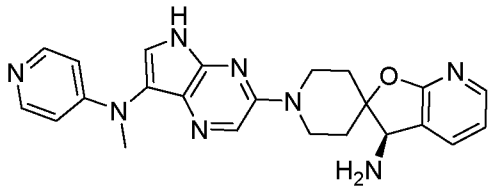
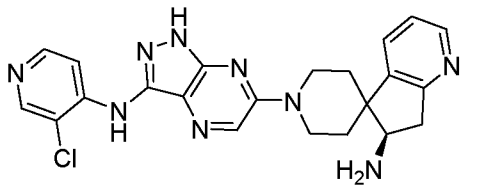
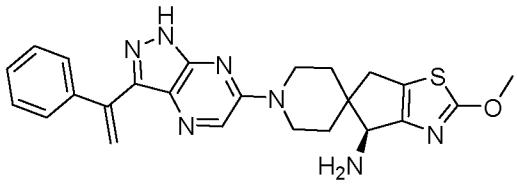
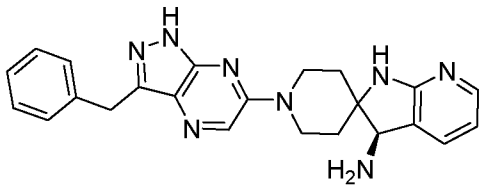
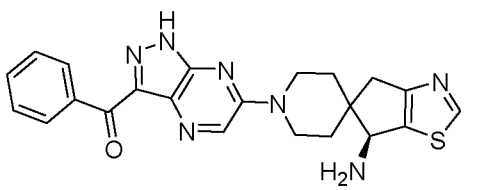
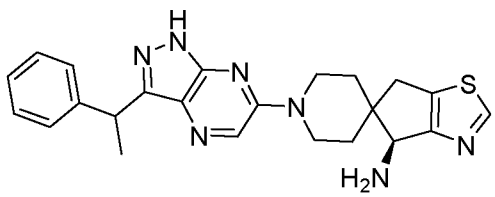
75	(S)-1'-(4-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		454
76	(S)-1'-(5-((2,3-dichlorophenyl)thio)thiazol-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine		463
77	(R)-1'-(4-((3-chloropyridin-4-yl)thio)thiazol-2-yl)spiro[indoline-2,4'-piperidin]-3-amine		430
78	(R)-1'-(2-(7-chloro-1H-indol-1-yl)thiazol-4-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine		435
79	(R)-1'-(2-((2-(trifluoromethyl)phenyl)thio)thiazol-5-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine		464
80	(S)-(5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)(2,3-dichlorophenyl)methanone		453
81	(S)-2-(1-amino-6-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(indolin-1-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one		485
82	(S)-1'-(5-((1,2,3,4-tetrahydroquinolin-8-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[b]naphthalene-2,4'-piperidin]-1-amine		494
83	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-1-amine		489
84	1'-(5-((3-amino-2-chlorophenyl)thio)-6-methylpyrazin-2-yl)-1-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1		466

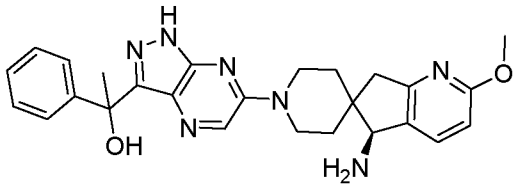
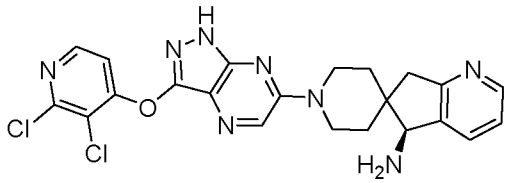
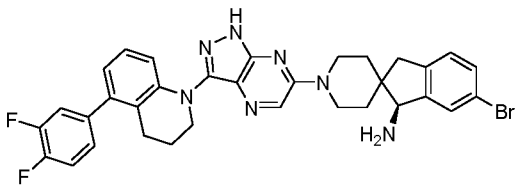
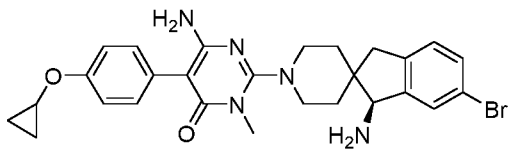
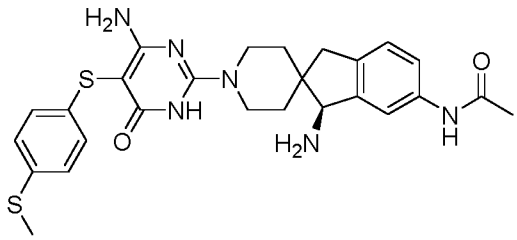
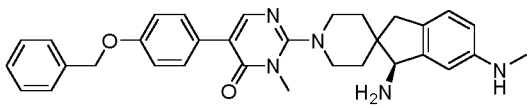
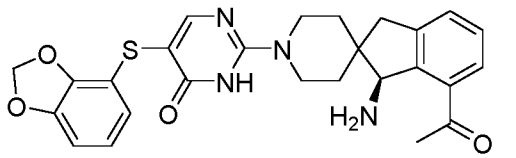
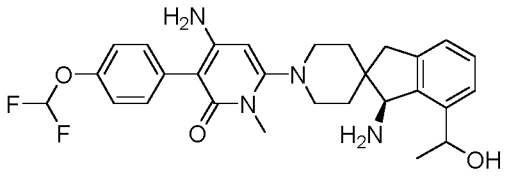
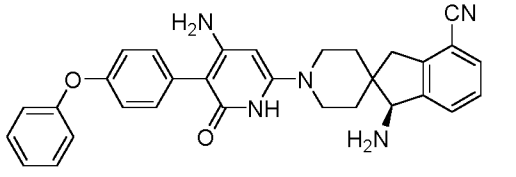
	-amine		
85	(R)-1'-(7-((2-amino-3-chloropyridin-4-yl)thio)-1H-indol-4-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine		478
86	(S)-1'-(7-((2-amino-3-chloropyridin-4-yl)thio)isoquinolin-3-yl)-5,6-dibromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		644
87	(S)-4-((5-(5-acetyl-1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-aminopyrazin-2-yl)thio)-3-chloro-1-methylpyridin-2(1H)-one		511
88	(S)-5-(1-amino-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-2-((2,3-dichlorophenyl)thio)-6-(hydroxymethyl)pyridin-3-ol		480
89	(S)-6-bromo-1'-(5-(2,3-dichlorophenyl)-6-methylimidazo[1,5-a]pyrazin-8-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		556
90	(S)-1'-(7-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,5]thiadiazolo[3,4-c]pyridin-4-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		574
91	(S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)pyrido[4,3-d]pyrimidin-5-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		568
92	(S)-3-(5-(1-amino-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyridin-2-yl)-4,5-dichlorophenol		470
93	(S)-1-amino-1'-(5-(5-methylthiophen-2-yl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol		393

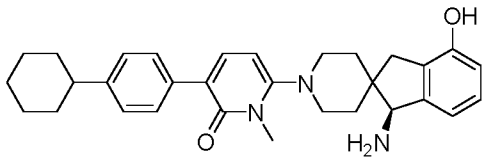
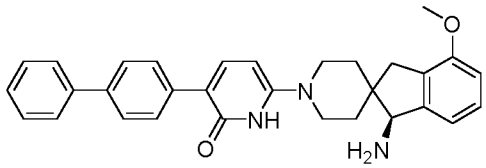
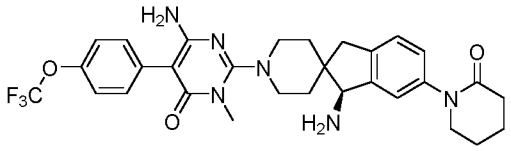
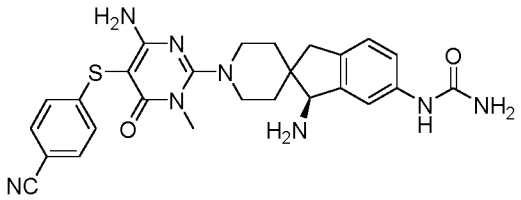
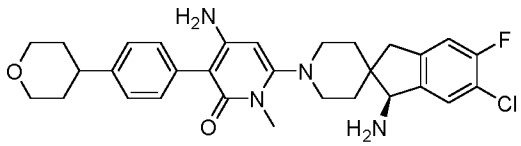
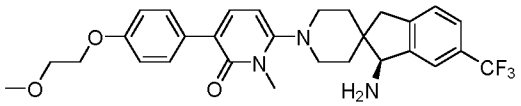
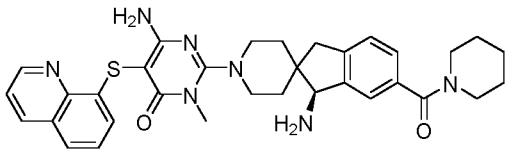
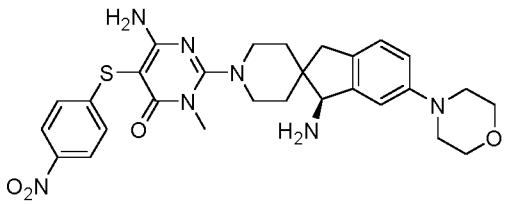
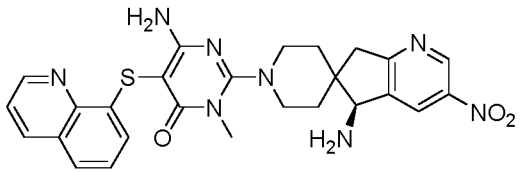
94	(S)-1'-(5-(1H-indol-7-yl)pyrazin-2-yl)-5-ethyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		424
95	(S)-1'-(5-(cyclohex-1-en-1-yl)pyrazin-2-yl)-5-isopropyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		403
96	(S)-N-(1-amino-1'-(5-(2-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)methanesulfonamide		518
97	(S)-1'-(5-((4-(trifluoromethyl)pyrimidin-5-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine		460
98	(S)-1'-(5-((2-chloropyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine		425
99	(S)-4-((5-(5-amino-5,7-dihydrospiro[cyclopenta[d]pyrimidine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chlorobenzoic acid		469
100	(S)-1'-(5-((3-(trifluoromethyl)pyrazin-2-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine		460
101	(S)-1'-(5-((3-chloropyridazin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[d]pyrimidine-6,4'-piperidin]-7-amine		427
102	(S)-4-((5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyrazine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chlorobenzamide		468

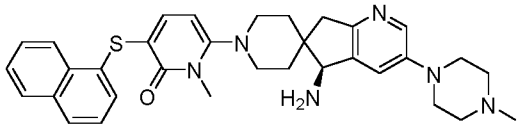
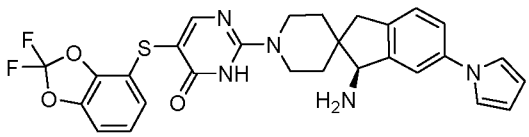
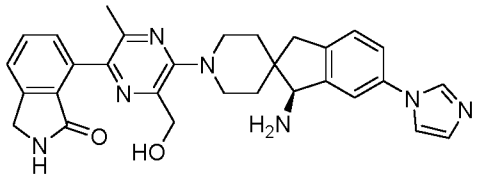
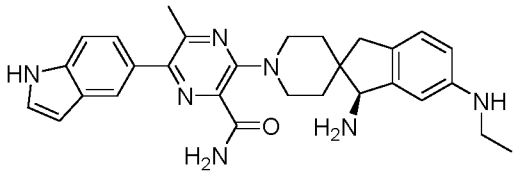
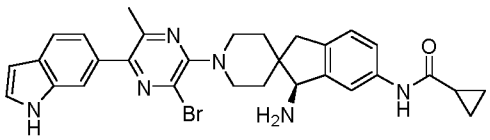
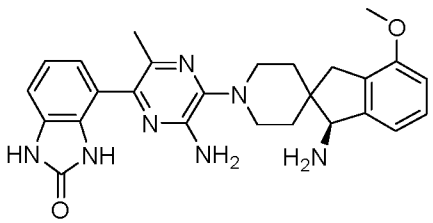
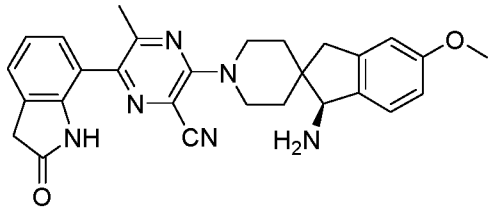
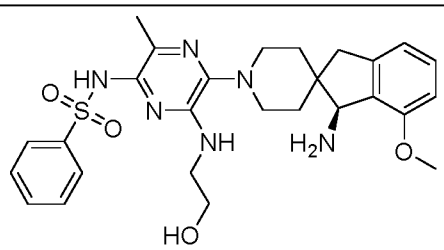
103	(S)-(1-amino-1'-(5-((3-chloro-2-(methylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)dimethylphosphine oxide		529
104	(S)-1-amino-1'-(6-amino-5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-5-carboxylic acid		526
105	ethyl (S)-1-amino-1'-(5-((3-chloro-2-(methylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-5-carboxylate		525
106	(S)-1'-(5-((3-(morpholinomethyl)phenyl)thio)pyrazin-2-yl)-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		556
107	(S)-6-bromo-5-fluoro-1'-(5-((3-(pentafluoro-l6-sulfanyl)phenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		611
108	(S)-N-(3-((5-(1-amino-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)phenyl)cyclopropanecarboxamide		518
109	(S)-6-(6-amino-1-bromo-4H,6H-spiro[cyclopenta[c]thiophene-5,4'-piperidin]-1'-yl)-3-(m-tolyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one		511
110	(S)-2-(1-amino-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(3-ethylphenyl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one		508
111	(R)-1'-(3-(3-(tert-butyl)phenyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-3-amine		467

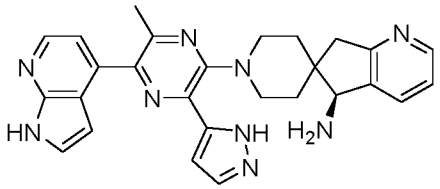
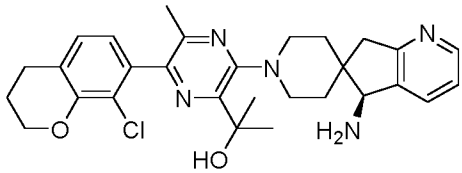
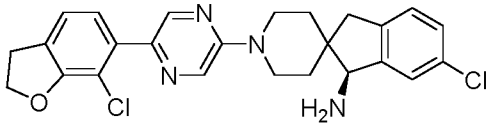
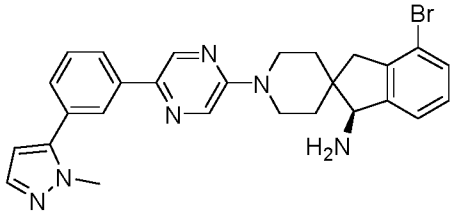
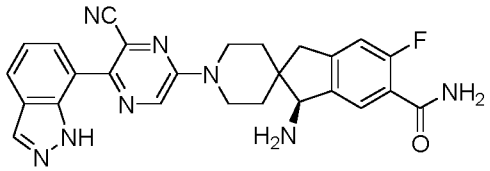
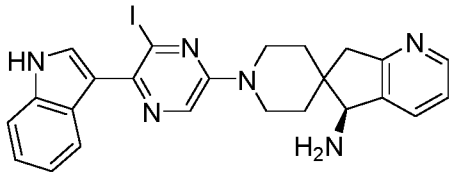
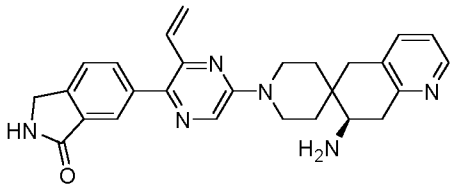
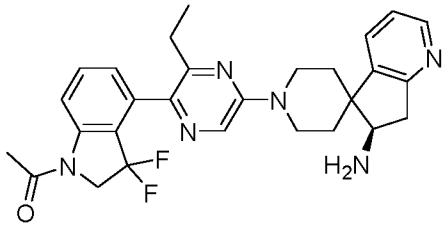
112	(S)-2-(3-amino-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-1'-yl)-5-(3-isopropylphenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one		504
113	(S)-1-amino-1'-(3-(3-chloro-2-morpholinopyridin-4-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridin-6-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile		574
114	(S)-1'-(7-(3-chloro-2-(cyclobutylamino)pyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-3-amine		550
115	(S)-1'-(3-(3-chloro-2-(cyclopropylamino)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-N6-methyl-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine		516
116	(S)-5-amino-1'-(3-(3-chloro-2-(pyrrolidin-1-yl)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-2-fluoro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-3-carboxamide		563
117	1-(4-(6-((S)-4-amino-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-3-chloropyridin-2-yl)pyrrolidin-3-ol		558
118	(S)-1'-(3-(3-chloro-2-((cyclopropylmethyl)amino)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-N6,N6-dimethyl-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine		544
119	(S)-1'-(3-(2-amino-6-chloropyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-2-(tert-butyl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine		509

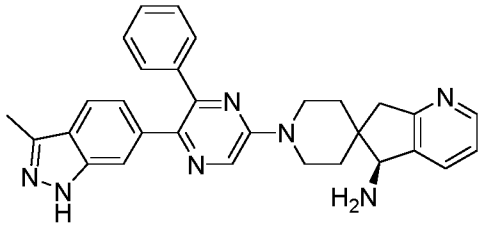
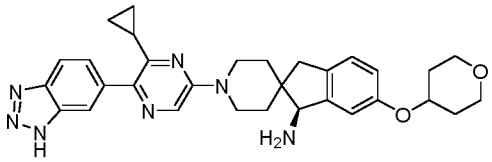
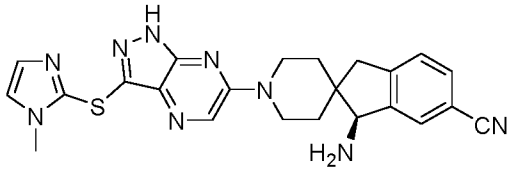
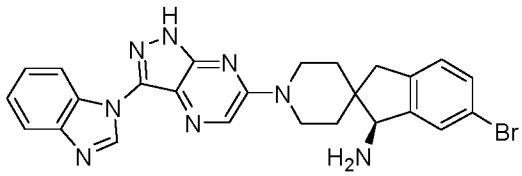
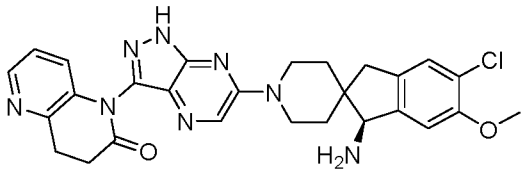
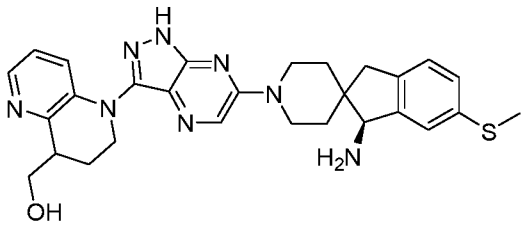
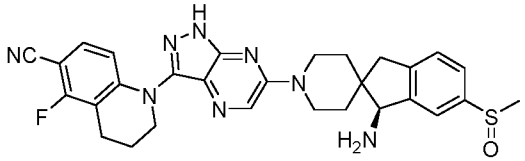
120	(S)-2-chloro-1'-(3-(1,3-dihydroisobenzofuran-5-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine		480
121	(S)-3-chloro-1'-(3-((2-chlorophenyl)thio)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		498
122	(S)-1'-(3-(3-chloro-2-(ethylamino)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine		481
123	(R)-1'-(7-(methyl(pyridin-4-yl)amino)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-3H-spiro[furo[2,3-b]pyridine-2,4'-piperidin]-3-amine		429
124	(R)-1'-(3-((3-chloropyridin-4-yl)amino)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-6-amine		448
125	(S)-2-methoxy-1'-(3-(1-phenylvinyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		460
126	(R)-1-(3-benzyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1',3'-dihydrospiro[piperidine-4,2'-pyrrolo[2,3-b]pyridin]-3'-amine		413
127	(S)-(6-(6-amino-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)(phenyl)methanone		432
128	(4S)-1'-(3-(1-phenylethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine		432

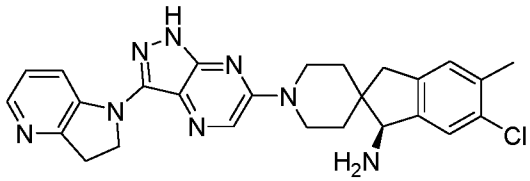
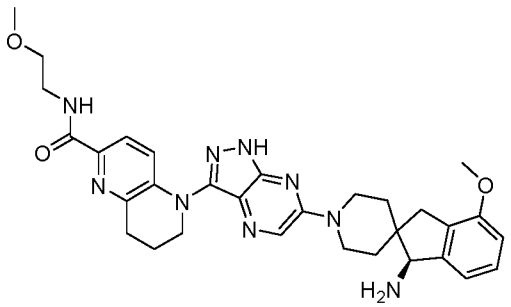
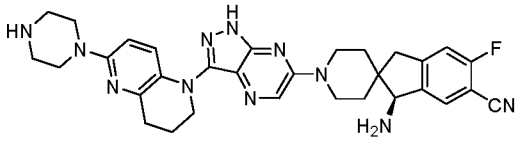
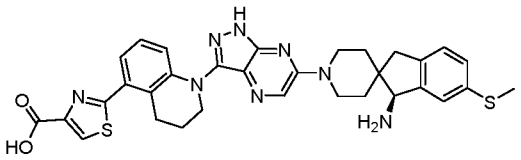
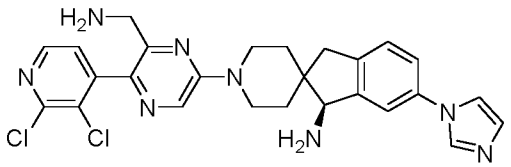
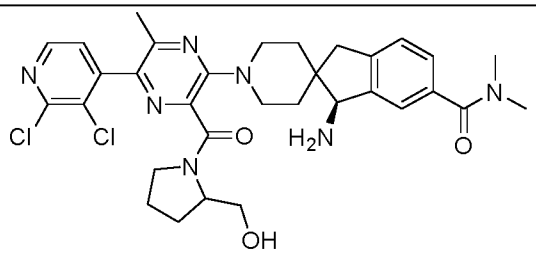
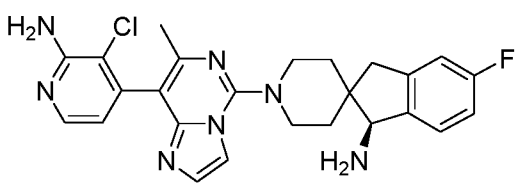
129	1-(6-((S)-5-amino-2-methoxy-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-1-phenylethan-1-ol		472
130	(S)-1'-(3-((2,3-dichloropyridin-4-yl)oxy)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		483
131	(S)-6-bromo-1'-(3-(5-(3,4-difluorophenyl)-3,4-dihydroquinolin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		642
132	(S)-6-amino-2-(1-amino-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(4-cyclopropoxyphenyl)-3-methylpyrimidin-4(3H)-one		536
133	(S)-N-(1-amino-1'-(4-amino-5-((4-(methylthio)phenyl)thio)-6-oxo-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide		523
134	(S)-2-(1-amino-6-(methylamino)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(4-(benzyloxy)phenyl)-3-methylpyrimidin-4(3H)-one		522
135	(S)-2-(7-acetyl-1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(benzo[d][1,3]dioxol-4-ylthio)pyrimidin-4(3H)-one		491
136	4-amino-6-((1S)-1-amino-7-(1-hydroxyethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(4-(difluoromethoxy)phenyl)-1-methylpyridin-2(1H)-one		511
137	(S)-1-amino-1'-(4-amino-6-oxo-5-(4-phenoxyphenyl)-1,6-dihydropyridin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carbonitrile		504

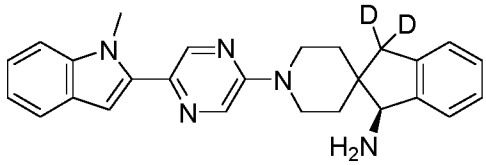
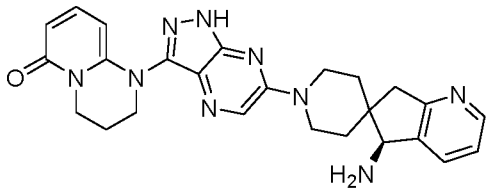
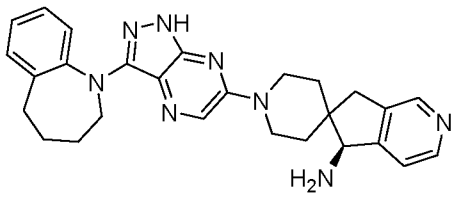
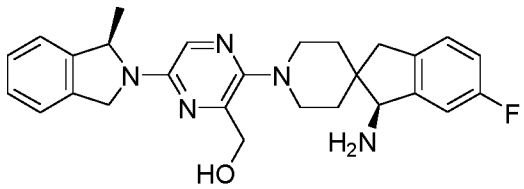
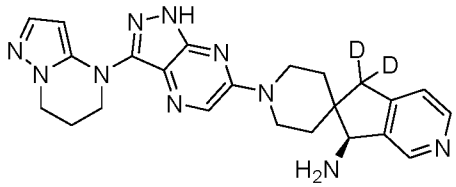
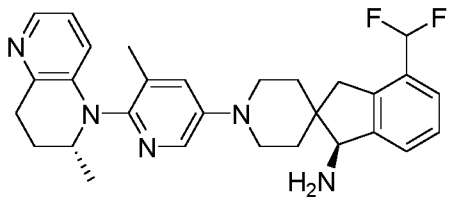
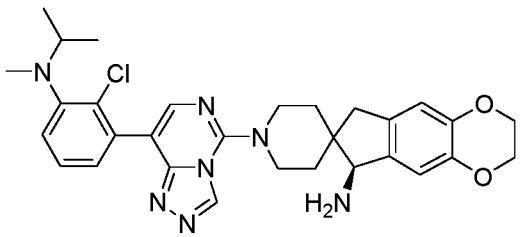
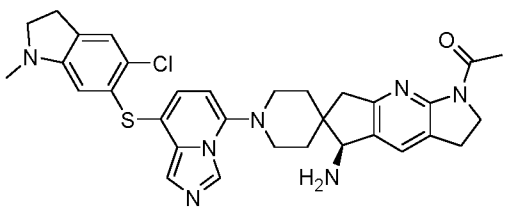
138	(S)-6-(1-amino-4-hydroxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(4-cyclohexylphenyl)-1-methylpyridin-2(1H)-one		484
139	(S)-3-([1,1'-biphenyl]-4-yl)-6-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyridin-2(1H)-one		478
140	(S)-6-amino-2-(1-amino-6-(2-oxopiperidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-(4-(trifluoromethoxy)phenyl)pyrimidin-4(3H)-one		583
141	(S)-1-(1-amino-1'-(4-amino-5-((4-cyanophenyl)thio)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)urea		517
142	(S)-4-amino-6-(1-amino-6-chloro-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1-methyl-3-(4-(tetrahydro-2H-pyran-4-yl)phenyl)pyridin-2(1H)-one		537
143	(S)-6-(1-amino-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(4-(2-methoxyethoxy)phenyl)-1-methylpyridin-2(1H)-one		528
144	(S)-6-amino-2-(1-amino-6-(piperidine-1-carbonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-(quinolin-8-ylthio)pyrimidin-4(3H)-one		596
145	(S)-6-amino-2-(1-amino-6-morpholino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-((4-nitrophenyl)thio)pyrimidin-4(3H)-one		564
146	(S)-6-amino-2-(5-amino-3-nitro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-3-methyl-5-(quinolin-8-ylthio)pyrimidin-4(3H)-one		531

147	(S)-6-(5-amino-3-(4-methylpiperazin-1-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-1-methyl-3-(naphthalen-1-ylthio)pyridin-2(1H)-one		567
148	(S)-2-(1-amino-6-(1H-pyrrol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-((2,2-difluorobenzo[d][1,3]dioxol-4-yl)thio)pyrimidin-4(3H)-one		550
149	(S)-7-(5-(1-amino-6-(1H-imidazol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(hydroxymethyl)-3-methylpyrazin-2-yl)isoindolin-1-one		522
150	(S)-3-(1-amino-6-(ethylamino)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(1H-indol-5-yl)-5-methylpyrazine-2-carboxamide		496
151	(S)-N-(1-amino-1'-(3-bromo-5-(1H-indol-6-yl)-6-methylpyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)cyclopropanecarboxamide		571
152	(S)-4-(6-amino-5-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methylpyrazin-2-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one		472
153	(S)-3-(1-amino-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-methyl-6-(2-oxoindolin-7-yl)pyrazine-2-carbonitrile		481
154	(S)-N-(5-(1-amino-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2-hydroxyethyl)amino)-3-methylpyrazin-2-yl)benzenesulfonamide		539

155	(S)-1'-(6-methyl-3-(1H-pyrazol-5-yl)-5-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		478
156	(S)-2-(3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(8-chlorochroman-7-yl)-5-methylpyrazin-2-yl)propan-2-ol		520
157	(S)-6-chloro-1'-(5-(7-chloro-2,3-dihydrobenzofuran-6-yl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		467
158	(S)-4-bromo-1'-(5-(3-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		515
159	(S)-1-amino-1'-(6-cyano-5-(1H-indazol-7-yl)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide		483
160	(S)-1'-(5-(1H-indol-3-yl)-6-iodopyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		523
161	(R)-6-(5-(7'-amino-7',8'-dihydro-5'H-spiro[piperidine-4,6'-quinolin]-1-yl)-3-vinylpyrazin-2-yl)isoindolin-1-one		453
162	(R)-1-(4-(5-(6-amino-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-1'-yl)-3-ethylpyrazin-2-yl)-3,3-difluoroindolin-1-yl)ethan-1-one		505

163	(S)-1'-(5-(3-methyl-1H-indazol-6-yl)-6-phenylpyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine		488
164	(S)-1'-(5-(1H-benzo[d][1,2,3]triazol-6-yl)-6-cyclopropylpyrazin-2-yl)-6-((tetrahydro-2H-pyran-4-yl)oxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		538
165	(S)-1-amino-1'-(3-((1-methyl-1H-imidazol-2-yl)thio)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile		458
166	(S)-1'-(3-(1H-benzo[d]imidazol-1-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		515
167	(S)-1-(6-(1-amino-5-chloro-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one		531
168	(1-(6-((S)-1-amino-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-1,2,3,4-tetrahydro-1,5-naphthyridin-4-yl)methanol		529
169	1-(6-((1S)-1-amino-6-(methylsulfinyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoro-1,2,3,4-tetrahydroquinoline-6-carbonitrile		557

170	(S)-6-chloro-1'-(3-(2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		487
171	(S)-5-(6-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-N-(2-methoxyethyl)-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carboxamide		584
172	(S)-1-amino-5-fluoro-1'-(3-(6-(piperazin-1-yl)-3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile		580
173	(S)-2-(1-(6-(1-amino-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-1,2,3,4-tetrahydroquinolin-5-yl)thiazole-4-carboxylic acid		625
174	(S)-1'-(6-(aminomethyl)-5-(2,3-dichloropyridin-4-yl)pyrazin-2-yl)-6-(1H-imidazol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		521
175	(1S)-1-amino-1'-(5-(2,3-dichloropyridin-4-yl)-3-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)-6-methylpyrazin-2-yl)-N,N-dimethyl-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide		638
176	(S)-1'-(8-(2-amino-3-chloropyridin-4-yl)-7-methylimidazo[1,2-c]pyrimidin-5-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		478

177	(S)-1'-(5-(1-methyl-1H-indol-2-yl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-3,3-d2-1-amine		410
178	(S)-1-(6-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrimidin-6-one		470
179	(S)-1'-(3-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine		467
180	(3-((S)-1-amino-6-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((R)-1-methylisoindolin-2-yl)pyrazin-2-yl)methanol		460
181	(S)-1'-(3-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5,5-d2-7-amine		443
182	(S)-4-(difluoromethyl)-1'-(5-methyl-6-((R)-2-methyl-3,4-dihydro-1,5-naphthyridin-1(2H)-yl)pyridin-3-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine		470
183	(S)-1'-(8-(2-chloro-3-(isopropyl(methyl)amino)phenyl)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-2,3,6,8-tetrahydrospiro[indeno[5,6-b][1,4]dioxine-7,4'-piperidin]-6-amine		561
184	(S)-1-(5-amino-1'-(8-((5-chloro-1-methylindolin-6-yl)thio)imidazo[1,5-a]pyridin-5-yl)-2,3,5,7-tetrahydro-1H-spiro[cyclopenta[b]pyrrolo[3,2-e]pyridine-6,4'-piperidin]-1-yl)ethan-1-one		601

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 (20nM) 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 1.

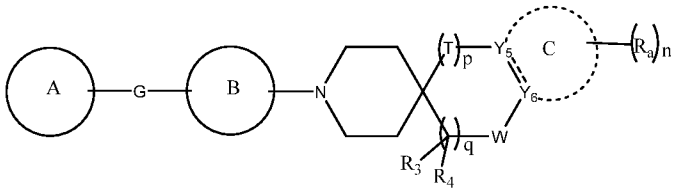
Example	SHP2 inhibition(%)
1@0.02μM	82
2@0.02μM	80
3@0.02μM	81
4@0.02μM	89
5@0.02μM	84
6@0.02μM	89
8@0.02μM	68
15@0.02μM	64
19@0.02μM	61
21@0.02μM	68
23@0.02μM	85
24@0.02μM	87
25@0.02μM	78
26@0.02μM	67
27@0.02μM	79

Example	SHP2 inhibition(%)
28@0.02μM	74
29@0.02μM	68
30@0.02μM	80
31@0.02μM	82
32@0.02μM	75
33@0.02μM	70
36@0.02μM	88
37@0.02μM	68
38@0.02μM	53
39@0.02μM	78
40@0.02μM	68
45@0.02μM	78
47@0.02μM	56
50@0.02μM	86

THE CLAIMS

What is claimed is

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



I

Wherein,

ring A is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$, $-NR_G-SO_2-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$;

each of R_G is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted or unsubstituted;

ring B is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring, a 3-10 membered carbocyclic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

T is absent, O, NR_1 or CR_1R_2;

each of R_1 and R_2 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$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 and R_2 together with the carbon atom to which they are both attached form CO or $C=NR_5$;

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

each of R_3 and R_4 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_3 and R_4 together with the carbon atom to which they are both attached form a 3-12 membered heterocyclic ring or a 5-12 membered heteroaromatic ring or $C=NR_5$, and each of the ring systems is independently optionally substituted or unsubstituted;

each of R_5 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

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

W is absent, O, S or $-C(Rw)_2-$; and each of R_w is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-CO-C_{1-6}$alkyl, $-CO-OC_{1-6}$alkyl, $-C_{1-6}$alkylene-O-C_{1-6}alkoxy, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl;

ring C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or

unsubstituted;

when ring C is absent, Y_5 is $CR_{5a}R_{5b}$, NR_{5a} or O, and Y_6 is $CR_{6a}R_{6b}$, NR_{6a} or O;

when ring C is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring;

i) Y_5 is CR_{5a} or N, and Y_6 is CR_{6a} or N, when the "======" in the term "^{Y_5}======Y_6" represents a single bond; or

ii) Y_5 is C, and Y_6 is C, when the "======" in the term "^{Y_5}======Y_6" represents a double bond;

each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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_a is independently selected from hydrogen, deuterium, halogen, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{3-8}$cycloalkyl,$-C_{1-6}$alkylene-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{a1}, $-C_{1-6}$alkylene-(3-10 membered heterocyclic), $-C_{1-6}$alkylene-(5-10 membered heteroaryl), $-C_{1-6}$alkylene-CO-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-CO-C_{1-6}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, $-C_{3-10}$carbocyclic, -5-10 membered heteroaryl, -3-10 membered heterocyclic, -CO-C_{1-6}alkyl, -COO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-(3-10 membered heterocyclic), -O-C_{1-6}alkylene-CO-OR_{a1}, -O-C_{1-6}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-10}carbocyclic, -O-(3-10 membered heterocyclic), $-NR_{a1}$-CO-C_{1-6}alkyl, $-NR_{a1}$-CO-$NR_{a1}R_{a2}$, $-NR_{a1}$-CO-(5-10 membered heteroaryl), $-NR_{a1}$-CO-C_{3-8}cycloalkyl,$-NR_{a1}$-C_{1-6}alkylene-$NR_{a1}R_{a2}$, $-NR_{a1}$-C_{1-6}alkylene-(3-10 membered heterocyclic), $-NR_{a1}$-C_{1-6}alkylene-(5-10 membered heteroaryl), $-NR_{a1}$-SO_2C_{1-6}alkyl, -S-C_{1-6}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-6}alkyl, -SO_2-C_{1-6}alkyl, -PO(C_{1-6}alkyl)$_2$, -PO(C_{1-6}alkoxy)$_2$, -3-10 membered heterocyclic or -5-10 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6; or

two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted; or

R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, a 3-10 membered heteroaromatic ring or a 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted;

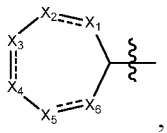
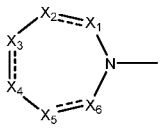
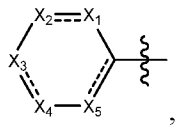
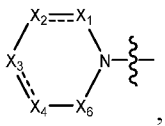
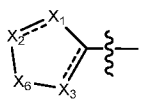
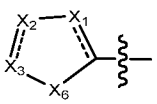
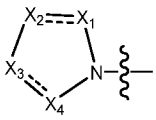
each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

2. The compound or pharmaceutically acceptable salt thereof of claim 1, wherein ring A is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems

is independently optionally substituted or unsubstituted.

3. The compound or pharmaceutically acceptable salt thereof of claim 1 or claim 2, wherein ring A is a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

4. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-3, wherein ring A is a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

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

represents a single bond or a double bond;

X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1};

each of R_{X1} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO;

each of R_{X2} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3};

each of R_{X3} is independently selected from hydrogen, deuterium, halogen, carboxyl, $-NO_2$, $-NH_2$, $-CN$, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl, $-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, $-CN$, $-OH$, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted ;

X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4};

each of R_{X4} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, $-CN$, $-OH$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or a 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, $-CN$, $-OH$, oxo, =O,$-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5};

each of R_{X5} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, $-CN$, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, $-CN$, $-OH$, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$;

each of R_{X6} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, $-CN$, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, $-CN$, $-OH$, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X5} and R_{X6} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted.

6. The compound or pharmaceutically acceptable salt thereof of claim 5, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, $-CN$, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, $-CN$, $-OH$, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

7. The compound or pharmaceutically acceptable salt thereof of claim 5 or claim 6, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

8. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-7, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

9. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-8, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

10. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-9, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

11. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-10, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}\text{alkyl})_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

12. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-11, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}\text{alkyl})_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I,

$-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

13. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-12, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$,CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-4}$alkyl, $-C_{1-3}$alkoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}$alkylene-C_{3-6}cycloalkyl or 3-6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

14. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-13, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxy, ethoxy, propoxy, isopropoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}$alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

15. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-14, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxy, ethoxy, propoxy, isopropoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}$alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

16. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-15, wherein R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

17. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-16, wherein R_{X1} and R_{X2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems

is independently optionally substituted or unsubstituted.

18. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-17, wherein R_{X1} and R_{X2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

19. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-18, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl, $-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

20. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-19, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl,$-O-C_{1-6}$alkylene-C_{1-6}alkyl, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

21. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-20, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl, $-O-C_{1-3}$alkylene-C_{1-3}alkyl, $-O-C_{5-6}$aryl or $-O-C_{1-3}$alkylene-C_{5-6}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

22. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-21, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl, $-O-C_{1-3}$alkylene-C_{1-3}alkyl, $-O-C_{5-6}$aryl or $-O-C_{1-3}$alkylene-C_{5-6}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl,

methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

23. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-22, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl, $-O-C_{1-3}$alkylene-C_{1-3}alkyl, $-O-C_{5-6}$aryl or $-O-C_{1-3}$alkylene-C_{5-6}aryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

24. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-23, wherein R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

25. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-24, wherein R_{X2} and R_{X3} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

26. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-25, wherein R_{X2} and R_{X3} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, an 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

27. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-26, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

28. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-27, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen,

deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, oxo, =O, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

29. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-28, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-3}alkyl, -C_{1-3}alkoxy, -NHCO-(5-10 membered heterocyclyl) or 5-10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, oxo, =O, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

30. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-29, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, oxo, =O, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

31. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-30, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, oxo, =O, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

32. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-31, wherein R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

33. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-32, wherein R_{X3} and R_{X4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

34. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-33, wherein R_{X3} and R_{X4} together with the ring to which they are attached form a 5 membered aromatic

ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

35. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-34, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

36. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-35, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

37. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-36, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

38. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-37, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

39. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-38, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

40. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-39, wherein R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

41. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-40, wherein R_{X4} and R_{X5} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

42. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-41, wherein R_{X4} and R_{X5} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

43. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-42, wherein X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

44. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-43, wherein X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

45. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-44, wherein X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or

-C_{1-3}alkoxy.

46. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-45, wherein X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

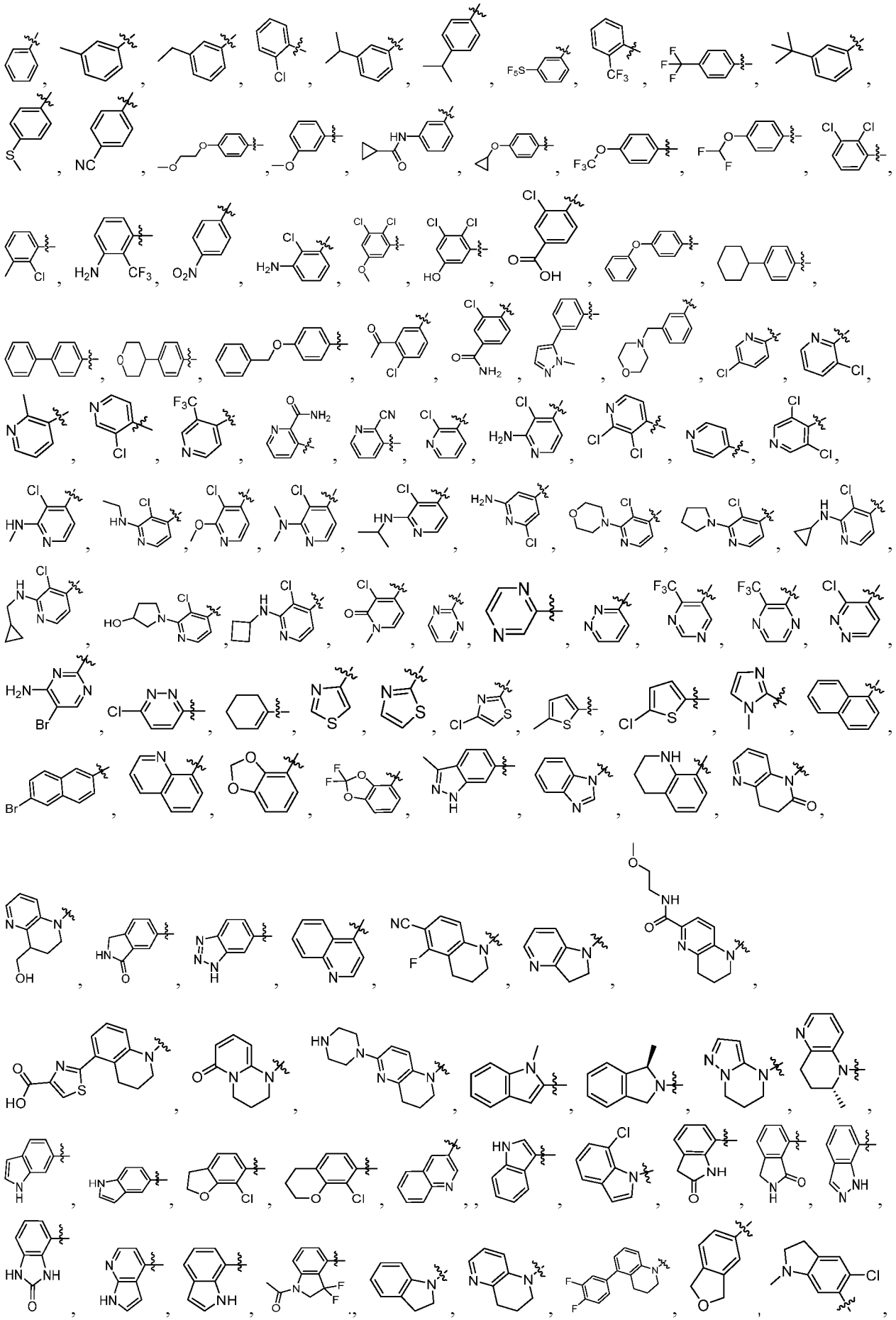
47. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-46, wherein X_6 is O, S, CO or NR_{X6}, or $C(R_{X6})_2$; each of R_{X6} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

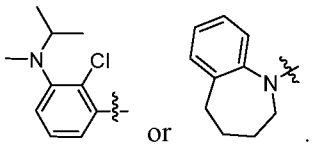
48. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-47, wherein R_{X5} and R_{X6} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

49. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-48, wherein R_{X5} and R_{X6} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

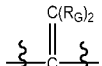
50. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-49, wherein R_{X5} and R_{X6} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

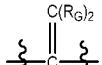
51. The compound or pharmaceutically acceptable salt thereof of any one of claims 5-50, wherein ring A is selected from

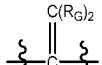




or .

52. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-51, wherein G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$, $-NR_G-SO_2-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted or unsubstituted.

53. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-52, wherein G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$, $-NR_G-SO_2-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted or unsubstituted.

54. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-53, wherein G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$, $-NR_G-SO_2-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted or unsubstituted.

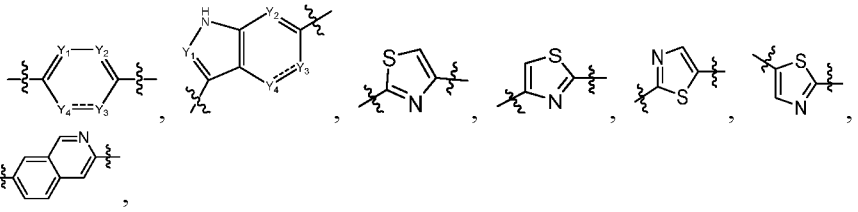
55. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-54, wherein ring B is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring, a 3-10 membered carbocyclic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2,3, 4, 5 or 6 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2, 3, 4, 5 or 6heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

56. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-55, wherein ring B is a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring, a 3-10 membered carbocyclic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2,3, 4, 5 or 6 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2, 3, 4, 5 or 6 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

57. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-56, wherein ring B is a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered

heteroaromatic ring, a 5 membered carbocyclic ring, a 6 membered carbocyclic ring, a 7 membered carbocyclic ring, a 8 membered carbocyclic ring, a 9 membered carbocyclic ring, a 10 membered carbocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, a 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2, 3 or 4 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2, 3 or 4 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

58. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-57,

wherein ring B is 

Y_1 is N or CR_{Y1};

R_{Y1} is selected from hydrogen, deuterium, halogen, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

Y_2 is N or CR_{Y2};

R_{Y2} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

when the "======" in the term "^{Y_3}======^{Y_4}" represents a single bond, Y_3 is NR_{Y3} or $C(R_{Y3})_2$, and Y_4 is CO, $C(R_{Y4})_2$ or NR_{Y4};

when the "======" in the term "^{Y_3}======^{Y_4}" represents a double bond, Y_3 is N or CR_{Y3}, and Y_4 is N or CR_{Y4};

R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, halogen, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH ,$-C_{1-6}$alkylene-OH, $-CO-C_{3-8}$heterocyclic ring, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl, $-C_{1-6}$alkyl substituted with –OH, or $-C_{1-6}$alkoxy; or

R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is

independently optionally substituted or unsubstituted.

59. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-58, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

60. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-59, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

61. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-60, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

62. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-61, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, I, $-NH_2$, -OH, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

63. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-62, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

64. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-63, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

65. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-64, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl,

-C_{1-3}alkoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

66. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-65, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

67. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-66, wherein R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

68. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-67, wherein R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

69. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-68, wherein R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

70. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-69, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, carboxyl, -COO-C_{1-6}alkyl, -NH-C_{1-6}alkylene-OH, -C_{1-6}alkylene-OH, -CO-C_{3-8}heterocyclic ring, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl,

-C_{1-6}alkyl substituted with -OH or -C_{1-6}alkoxy.

71. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-70, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, carboxyl, -COO-C_{1-6}alkyl, -NH-C_{1-6}alkylene-OH, -C_{1-6}alkylene-OH, -CO-C_{3-8}heterocyclic ring, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl, -C_{1-3}alkyl substituted with -OH or -C_{1-3}alkoxy.

72. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-71, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-3}alkyl, carboxyl, -COO-C_{1-3}alkyl, -NH-C_{1-3}alkylene-OH, -C_{1-3}alkylene-OH, -CO-C_{3-8}heterocyclic ring, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl, -C_{1-3}alkyl substituted with -OH or -C_{1-3}alkoxy.

73. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-72, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, methyl, ethyl, propyl, isopropyl, carboxyl, -COO-C_{1-3}alkyl, -NH-C_{1-3}alkylene-OH, -C_{1-3}alkylene-OH, -CO-C_{3-8}heterocyclic ring, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, ethyl substituted with –OH, methoxy, ethoxy, propoxy or isopropoxy.

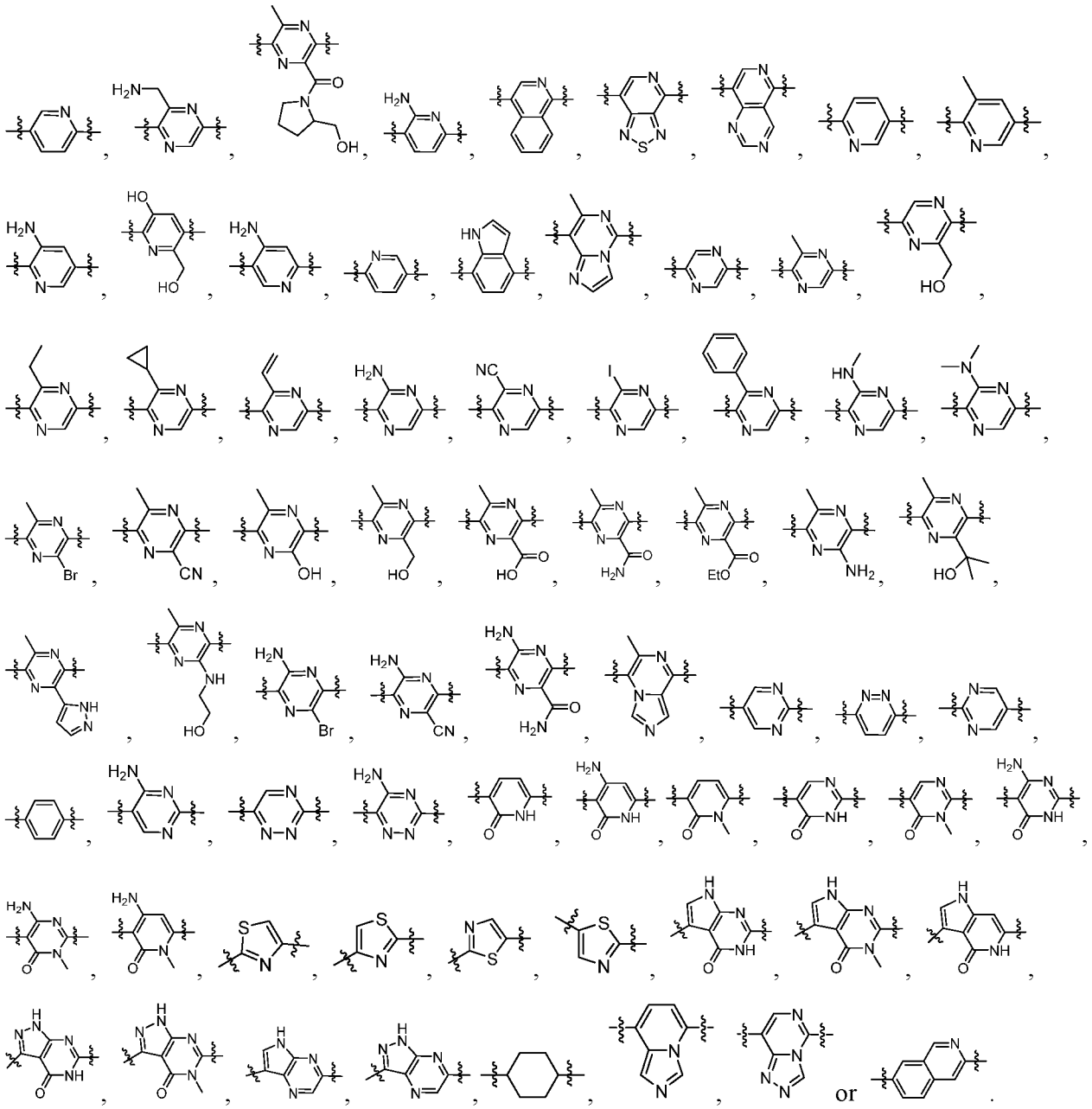
74. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-73, wherein R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

75. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-74, wherein R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

76. The compound or pharmaceutically acceptable salt there of any one of claims 1-75, wherein R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic

ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

77. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-75, wherein ring B is selected from



78. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-77, wherein each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

79. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-78,

wherein each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}alkyl$, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}alkoxy$, or substituted or unsubstituted $-C_{1-3}alkyl$.

80. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-79, wherein each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}alkyl$; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}alkoxy$ substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, $C_{1-3}alkyl$ or $C_{1-3}alkoxy$; methyl; ethyl; propyl; isopropyl; $-C_{1-3}alkyl$ substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, $C_{1-3}alkyl$ or $C_{1-3}alkoxy$.

81. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-80, wherein each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}alkyl$; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}alkoxy$ substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}alkyl$ substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

82. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-81, wherein R_1 and R_2 together with the carbon atom to which they are both attached form CO or $C=NR_5$.

83. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-82, wherein R_1 and R_2 together with the carbon atom to which they are both attached form CO.

84. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-83, wherein R_1 and R_2 together with the carbon atom to which they are both attached form $C=NR_5$.

85. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-84, wherein each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}alkyl$, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}alkoxy$, or substituted or unsubstituted $-C_{1-6}alkyl$.

86. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-85, wherein each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}alkyl$, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}alkoxy$, or substituted or unsubstituted $-C_{1-3}alkyl$.

87. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-86, wherein each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}alkyl$; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}alkoxy$ substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, $C_{1-3}alkyl$ or $C_{1-3}alkoxy$; methyl; ethyl; propyl; isopropyl; $-C_{1-3}alkyl$ substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, $C_{1-3}alkyl$ or $C_{1-3}alkoxy$.

88. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-87, wherein each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}alkyl$; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}alkoxy$ substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl,

methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; -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.

89. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-88, wherein R_3 and R_4 together with the carbon atom to which they are both attached form 3-12 membered heterocyclic ring or 5-12 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

90. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-89, wherein R_3 and R_4 together with the carbon atom to which they are both attached form 3-10 membered heterocyclic ring or 5-10 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

91. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-90, wherein R_3 and R_4 together with the carbon atom to which they are both attached form 3 membered heterocyclic ring, 4 membered heterocyclic ring, 5 membered heterocyclic ring, 6 membered heterocyclic ring, 7 membered heterocyclic ring, 8 membered heterocyclic ring, 9 membered heterocyclic ring, 10 membered heterocyclic ring, 5 membered heteroaromatic ring, 6 membered heteroaromatic ring, 7 membered heteroaromatic ring, 8 membered heteroaromatic ring, 9 membered heteroaromatic ring, 10 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

92. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-91, wherein each of R_5 is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy.

93. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-92, wherein each of R_5 is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy.

94. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-93, wherein each of R_5 is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy

95. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-94, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -CO-C_{1-6}alkyl, -CO-OC_{1-6}alkyl, -C_{1-6}alkylene-O-C_{1-6}alkoxy, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl.

96. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-95,

wherein W is absent, -O, -S or -C(Rw)$_2$-; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, -NH$_2$, -CN, -OH, -NO$_2$, carboxyl, -CO-C$_{1-3}$alkyl, -CO-OC$_{1-3}$alkyl, -C$_{1-3}$alkylene-O-C$_{1-3}$alkoxy, substituted or unsubstituted -C$_{1-3}$alkoxy, or substituted or unsubstituted -C$_{1-3}$alkyl.

97. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-96, wherein W is absent, -O, -S or -C(Rw)$_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH$_2$; -CN;-OH; -NO$_2$; carboxyl; -CO-C$_{1-3}$alkyl; -CO-OC$_{1-3}$alkyl; -C$_{1-3}$alkylene-O-C$_{1-3}$alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -C$_{1-3}$alkoxy substituted with halogen, NH$_2$, CN, OH, NO$_2$, carboxyl, C$_{1-3}$alkyl or C$_{1-3}$alkoxy; methyl; ethyl; propyl; isopropyl; -C$_{1-3}$alkyl substituted with halogen, NH$_2$, CN, OH, NO$_2$, carboxyl, C$_{1-3}$alkyl or C$_{1-3}$alkoxy.

98. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-97, wherein W is absent, -O, -S or -C(Rw)$_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH$_2$; -CN;-OH; -NO$_2$; carboxyl; -CO-C$_{1-3}$alkyl; -CO-OC$_{1-3}$alkyl; -C$_{1-3}$alkylene-O-C$_{1-3}$alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -C$_{1-3}$alkoxy substituted with halogen, NH$_2$, CN, OH, NO$_2$, carboxyl, C$_{1-3}$alkyl or C$_{1-3}$alkoxy; methyl; ethyl; propyl; isopropyl; -C$_{1-3}$alkyl substituted with halogen, NH$_2$, CN, OH, NO$_2$, carboxyl, C$_{1-3}$alkyl or C$_{1-3}$alkoxy.

99. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-98, wherein W is absent, -O, -S or -C(Rw)$_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH$_2$; -CN;-OH; -NO$_2$; carboxyl; -CO-C$_{1-3}$alkyl; -CO-OC$_{1-3}$alkyl; -C$_{1-3}$alkylene-O-C$_{1-3}$alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

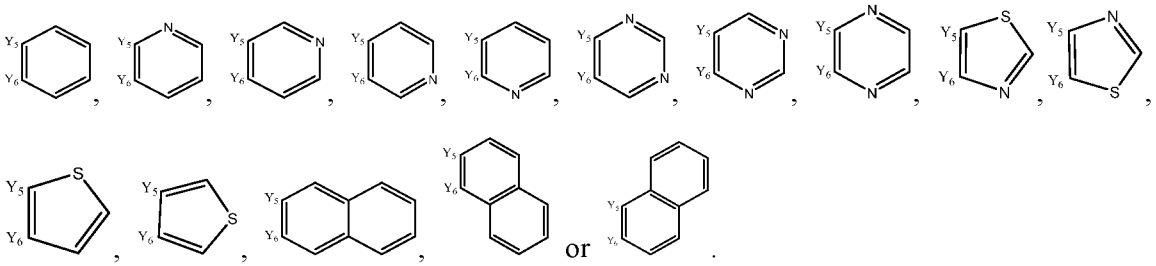
100. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-99, wherein ring C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

101. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-100, wherein ring C is absent, a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

102. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-101, wherein ring C is absent, a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10

membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

103. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-102, wherein ring C is selected from



104. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-103, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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.

105. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-104, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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.

106. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-105, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

107. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-106, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

108. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-107, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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.

109. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-108, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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.

110. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-109, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$;

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

111. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-110, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

112. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-111, wherein each of R_a is independently hydrogen, deuterium, F, Cl, Br, -$NR_{a1}R_{a2}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, -C_{1-3}alkoxy, -C_{1-4}alkyl, -C_{3-6}cycloalkyl,-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-O-C_{1-6}alkyl, -C_{1-3}alkylene-CO-OR_{a1}, -C_{1-3}alkylene-(3-8 membered heterocyclic), -C_{1-3}alkylene-(5-8 membered heteroaryl), -C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, -C_{3-8}carbocyclic, -5-8 membered heteroaryl, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -SO$NR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2-C_{1-3}alkyl, -PO(C_{1-3}alkyl)$_2$, -PO(C_{1-3}alkoxy)$_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

113. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-112, wherein each of R_a is independently hydrogen, deuterium, F, Cl, Br, -$NR_{a1}R_{a2}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, methoxy, ethoxy, propoxy, isopropoxy methyl, ethyl, propyl, isopropyl, butyl, isobutyl, -C_{3-6}cycloalkyl,-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-O-C_{1-6}alkyl, -C_{1-3}alkylene-CO-OR_{a1}, -C_{1-3}alkylene-(3-8 membered heterocyclic), -C_{1-3}alkylene-(5-8 membered heteroaryl), -C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, -C_{3-8}carbocyclic, -5-8 membered heteroaryl, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -SO$NR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2-C_{1-3}alkyl, -PO(C_{1-3}alkyl)$_2$, -PO(C_{1-3}alkoxy)$_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally

substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

114. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-113, wherein two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

115. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-114, wherein two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

116. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-115, wherein two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3 membered heterocyclic ring, a 4 membered heterocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 3 membered carbocyclic ring, a 4 membered carbocyclic ring, a 5 membered carbocyclic ring, a 6 membered carbocyclic ring, wherein each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

117. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-116, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, a 3-10 membered heteroaromatic ring or a 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted with deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

118. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-117, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, a 3-10 membered heteroaromatic ring or a 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

119. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-118, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, a 3-10 membered heteroaromatic ring or a 3-10 membered heterocyclic ring; each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

120. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-116, R_a and R_w with the atom to which they are both attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 5 membered heteroaryl ring, a 6 membered heteroaryl ring, a 5 membered heterocyclic ring or a 6 membered heterocyclic ring; each of the heteroaromatic ring contains 1, 2 or

3 heteroatoms selected from N, O or S; each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

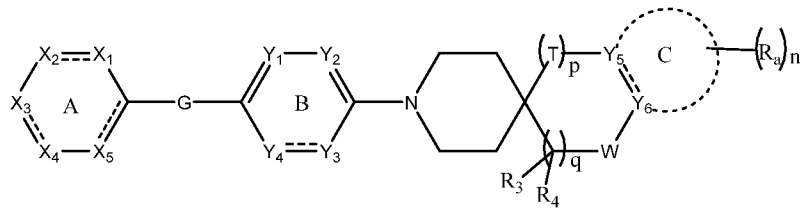
121. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-120, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl.

122. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-121, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, 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.

123. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-122, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

124. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-123, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

125. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-124, wherein the compound is of Formula II:



II

X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1};

each of R_{X1} is independently selected from hydrogen, deuterium, halogen, -NH_2, -$CONH_2$, -CN, -C_{1-6}alkyl or -C_{1-6}alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy;

X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO;

each of R_{X2} is independently selected from hydrogen, deuterium, halogen, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -CO-C_{1-6}alkyl, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -SF_5, -NHCO-C_{3-8}cycloalkyl, -NH-C_{3-8}cycloalkyl, -C_{1-6}alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), -NH-C_{1-6}alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently

optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3};

each of R_{X3} is independently selected from hydrogen, deuterium, halogen, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl, $-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted ;

X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4};

each of R_{X4} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl,$-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

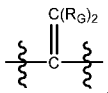
R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5};

each of R_{X5} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

------represents a single bond or a double bond;

G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$, $-NR_G-SO_2-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$;

each of R_G is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted or unsubstituted;

Y_1 is N or CR_{Y1};

R_{Y1} is selected from hydrogen, deuterium, halogen, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

Y_2 is N or CR_{Y2};

R_{Y2} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

when the "======" in the term "Y_3======Y_4" represents a single bond, Y_3 is NR_{Y3} or $C(R_{Y3})_2$, and Y_4 is CO, $C(R_{Y4})_2$ or NR_{Y4};

when the "======" in the term "Y_3======Y_4" represents a double bond, Y_3 is N or CR_{Y3}, and Y_4 is N or CR_{Y4};

R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, halogen, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, carboxyl, $-COO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkylene-OH ,$-C_{1-6}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

T is absent, O, NR_1 or CR_1R_2;

each of R_1 and R_2 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$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 and R_2 together with the carbon atom to which they are both attached form CO or $C=NR_5$;

p is 0, 1, 2 or 3;

each of R_3 and R_4 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl; or

R_3 and R_4 together with the carbon atom to which they are both attached form a 3-12 membered heterocyclic ring or a 5-12 membered heteroaromatic ring or $C=NR_5$, and each of the ring systems is independently optionally substituted or unsubstituted;

each of R_5 is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl

or -C_{1-6}alkoxy;

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

W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen, deuterium, 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 C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

when ring C is absent, Y_5 is $CR_{5a}R_{5b}$, NR_{5a} or O, and Y_6 is $CR_{6a}R_{6b}$, NR_{6a} or O;

when ring C is a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring;

i) Y_5 is CR_{5a} or N, and Y_6 is CR_{6a} or N, when the "------" in the term "^{Y_5}------Y_6" represents a single bond; or

ii) Y_5 is C, and Y_6 is C, when the "------" in the term "^{Y_5}------Y_6" represents a double bond;

each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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_a is independently hydrogen, deuterium, halogen, -$NR_{a1}R_{a2}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, -C_{1-6}alkoxy, -C_{1-6}alkyl, -C_{3-8}cycloalkyl,-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{1-6}alkylene-CO-OR_{a1}, -C_{1-6}alkylene-(3-10 membered heterocyclic), -C_{1-6}alkylene-(5-10 membered heteroaryl), -C_{1-6}alkylene-CO-$NR_{a1}R_{a2}$, -C_{1-6}alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, -C_{1-6}alkylene-NR_{a1}-CO-C_{1-6}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, -C_{3-10}carbocyclic, -5-10 membered heteroaryl, -3-10 membered heterocyclic, -CO-C_{1-6}alkyl, -COO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-(3-10 membered heterocyclic), -O-C_{1-6}alkylene-CO-OR_{a1}, -O-C_{1-6}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-10}carbocyclic, -O-(3-10 membered heterocyclic), -NR_{a1}-CO-C_{1-6}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-10 membered heteroaryl), -NR_{a1}-CO-C_{3-8}cycloalkyl,-NR_{a1}-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-6}alkylene-(3-10 membered heterocyclic), -NR_{a1}-C_{1-6}alkylene-(5-10 membered heteroaryl), -NR_{a1}-SO_2C_{1-6}alkyl, -S-C_{1-6}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-6}alkyl, -SO_2-C_{1-6}alkyl, -PO(C_{1-6}alkyl)$_2$, -PO(C_{1-6}alkoxy)$_2$, -3-10 membered heterocyclic or -5-10 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6; or

two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted;

each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl.

126. The compound or pharmaceutically acceptable salt thereof of claim 125, wherein X_1 is N, S,

NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

127. The compound or pharmaceutically acceptable salt thereof of claim 122 or claim 126, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

128. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-127, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

129. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-128, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

130. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-129, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

131. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-130, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O,$-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

132. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-131, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$,

$-SF_5$, -NHCO-C_{3-8}cycloalkyl, -NH-C_{3-8}cycloalkyl, -C_{1-6}alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), -NH-C_{1-6}alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

133. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-132, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -C_{1-3}alkyl, -C_{1-3}alkoxy, -CO-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, $-SF_5$, -NHCO-C_{3-6}cycloalkyl, -NH-C_{3-6}cycloalkyl, -C_{1-3}alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), -NH-C_{1-3}alkylene-C_{3-6}cycloalkyl or 3-6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

134. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-133, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -CO-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, $-SF_5$, -NHCO-C_{3-6}cycloalkyl, -NH-C_{3-6}cycloalkyl, -C_{1-3}alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), -NH-C_{1-3}alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

135. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-134, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -CO-C_{1-3}alkyl, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, $-SF_5$, -NHCO-C_{3-6}cycloalkyl, -NH-C_{3-6}cycloalkyl, -C_{1-3}alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), -NH-C_{1-3}alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

136. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-135, wherein R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

137. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-137,

wherein R_{X1} and R_{X2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

138. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-137, wherein R_{X1} and R_{X2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

139. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-138, wherein X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl,$-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

140. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-139, wherein X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl, $-O-C_{1-6}$alkylene-C_{1-6}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

141. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-140, wherein X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl, $-O-C_{1-3}$alkylene-C_{1-3}alkoxy, $-O-C_{5-8}$aryl or $-O-C_{1-6}$alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

142. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-141, wherein X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy,

ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, -S-C_{1-3}alkyl, 3-10 membered heterocyclyl, -O-C_{3-6}cycloalkyl or -O-C_{1-3}alkylene-C_{1-3}alkoxy, -O-C_{5-8}aryl or -O-C_{1-3}alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

143. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-142, wherein X_3 is N, S, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, -S-C_{1-3}alkyl, 3-10 membered heterocyclyl, -O-C_{3-6}cycloalkyl or -O-C_{1-3}alkylene-C_{1-3}alkoxy, -O-C_{5-8}aryl or -O-C_{1-3}alkylene-C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

144. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-143, wherein R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

145. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-144, wherein R_{X2} and R_{X3} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

146. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-145, wherein R_{X2} and R_{X3} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

147. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-146, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3,

4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

148. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-147, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

149. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-148, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, -NHCO-(5-10 membered heterocyclyl) or 5-10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

150. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-149, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

151. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-150, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

152. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-151, wherein R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

153. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-152, wherein R_{X3} and R_{X4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the

heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

154. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-153, wherein R_{X3} and R_{X4} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

155. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-154, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

156. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-155, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

157. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-156, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

158. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-157, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

159. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-158, wherein X_5 is N, S, NR_{X5}, $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen,

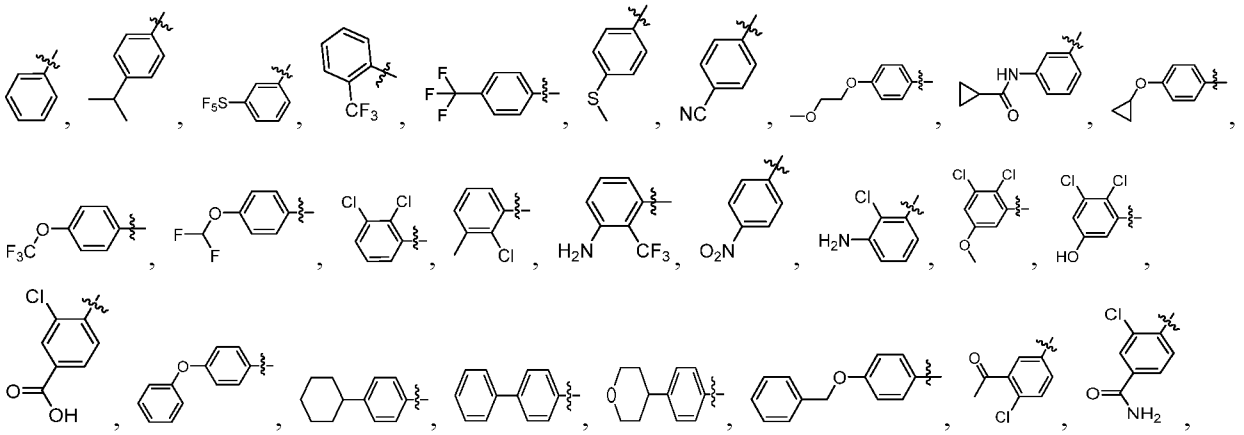
deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

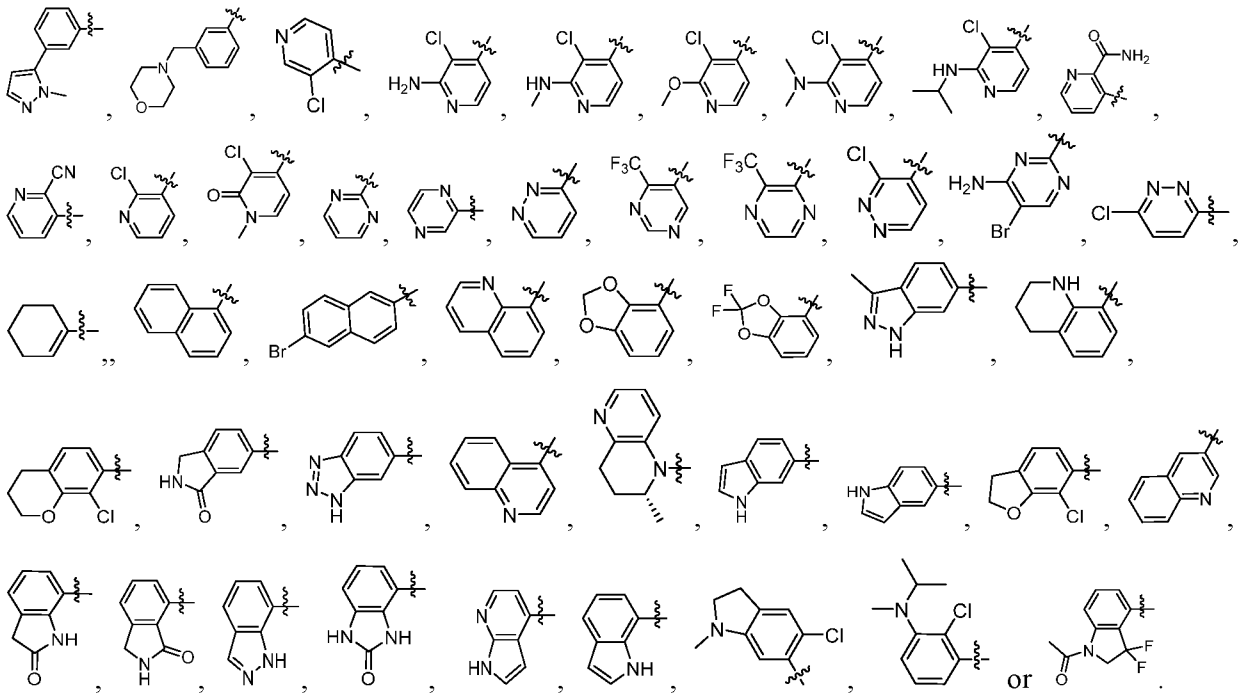
160. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-159, wherein R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

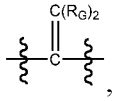
161. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-160, wherein R_{X4} and R_{X5} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

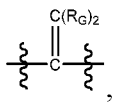
162. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-161, wherein R_{X4} and R_{X5} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

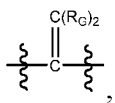
163. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-162, wherein ring A is selected from





164. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-163, wherein G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-, -NR_G-SO_2-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy, and each of which is independently optionally substituted or unsubstituted.

165. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-164, wherein G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-, -NR_G-SO_2-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy, and each of which is independently optionally substituted or unsubstituted.

166. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-165, wherein G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-, -NR_G-SO_2-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted or unsubstituted.

167. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-166, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6}alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

168. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-167, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

169. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-168, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

170. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-169, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

171. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-170, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

172. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-171, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, $-C_{1-6}$ alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

173. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-172, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl, $-C_{1-3}$alkoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, $-C_{1-3}$alkenyl, $-C_{3-6}$cycloalkyl or $-C_{5-8}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

174. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-173, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$,

-C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

175. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-174, R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

176. The compound or pharmaceutically acceptable salt thereof of any one of claims 122-172, R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

177. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-176, R_{Y1} and R_{Y2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

178. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-177, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, carboxyl, -COO-C_{1-6}alkyl, -NH-C_{1-6}alkylene-OH, -C_{1-6}alkylene-OH, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

179. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-178, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, carboxyl, -COO-C_{1-6}alkyl, -NH-C_{1-6}alkylene-OH, -C_{1-6}alkylene-OH, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

180. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-179,

wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, $-C_{1-3}$alkyl, carboxyl, $-COO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkylene-OH, $-C_{1-3}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

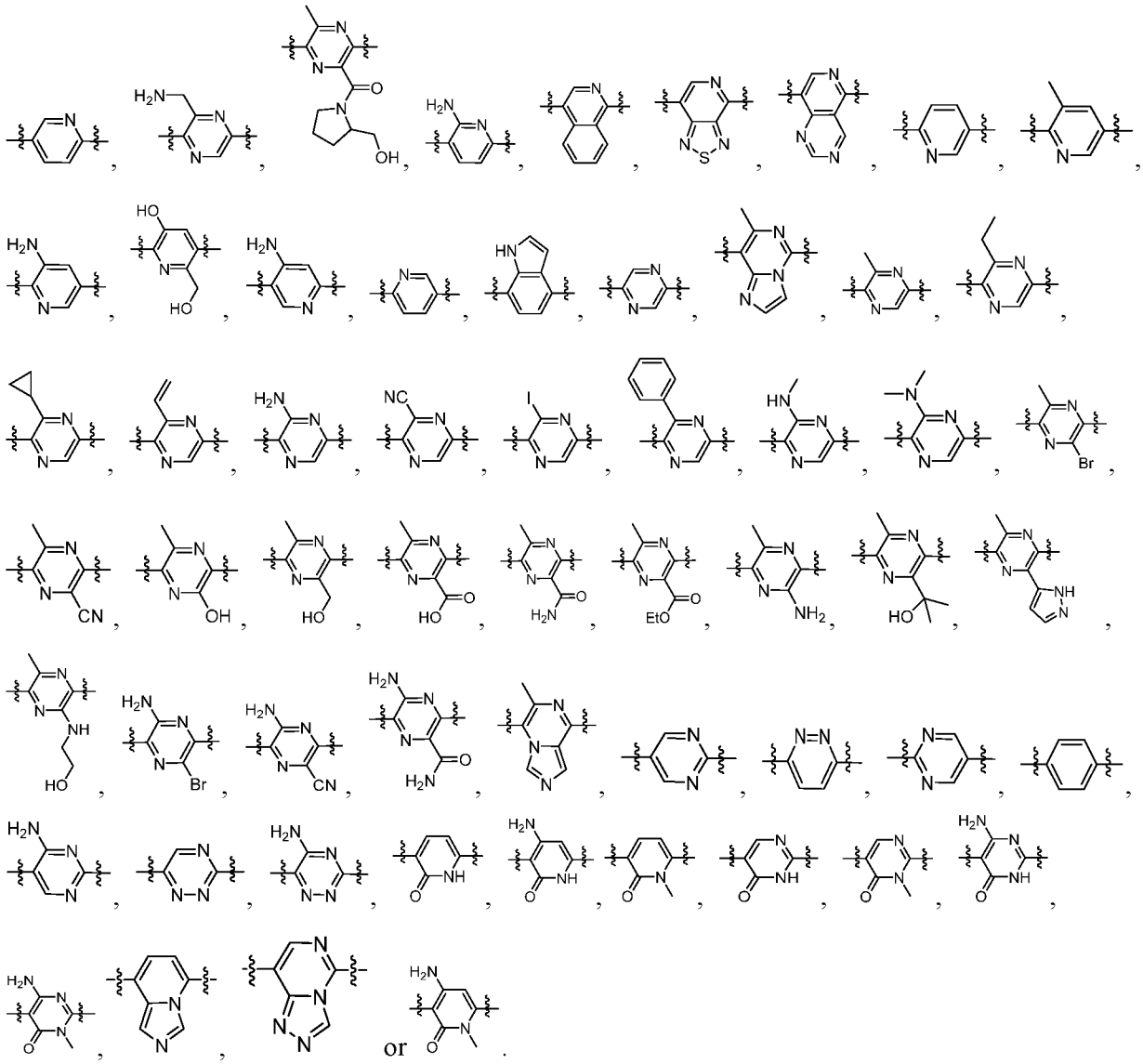
181. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-180, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -OH, -CN, methyl, ethyl, propyl, isopropyl, carboxyl, $-COO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkylene-OH, $-C_{1-3}$alkylene-OH, $-CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

182. The compound or pharmaceutically acceptable salt thereof of any one claims 125-181, wherein R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

183. The compound or pharmaceutically acceptable salt thereof of any one claims 125-182, wherein R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

184. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-183, wherein R_{Y3} and R_{Y4} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

185. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-184, wherein ring B is selected from



186. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-185, wherein each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

187. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-186, wherein each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}$alkyl, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}$alkoxy, or substituted or unsubstituted $-C_{1-3}$alkyl.

188. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-187, wherein each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}$alkyl; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

189. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-188, wherein each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN;

-OH; -NO_2; carboxyl; -NH-C_{1-3}alkyl; -N(C_{1-3}alkyl)$_2$; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

190. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-189, wherein R_1 and R_2 together with the carbon atom to which they are both attached form CO or C=NR_5.

191. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-190, wherein R_1 and R_2 together with the carbon atom to which they are both attached form CO.

192. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-191, wherein R_1 and R_2 together with the carbon atom to which they are both attached form C=NR_5.

193. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-192, wherein each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -NH-C_{1-6}alkyl, -N(C_{1-6}alkyl)$_2$, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl.

194. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-193, wherein each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, substituted or unsubstituted -C_{1-3}alkoxy, or substituted or unsubstituted -C_{1-3}alkyl.

195. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-194, wherein each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; -NH-C_{1-3}alkyl; -N(C_{1-3}alkyl)$_2$; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

196. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-195, wherein each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; -NH-C_{1-3}alkyl; -N(C_{1-3}alkyl)$_2$; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

197. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-196, wherein R_3 and R_4 together with the carbon atom to which they are both attached form a 3-12 membered heterocyclic ring or a 5-12 membered heteroaromatic ring or C=NR_5, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

198. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-197, wherein R_3 and R_4 together with the carbon atom to which they are both attached form a 3-10

membered heterocyclic ring or a 5-10 membered heteroaromatic ring or C=NR_5, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

199. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-198, wherein R_3 and R_4 together with the carbon atom to which they are both attached form a 3 membered heterocyclic ring, a 4 membered heterocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring or C=NR_5, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

200. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-199, wherein each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy.

201. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-200, wherein each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy.

202. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-201, wherein each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy

203. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-202, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, -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.

204. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-203, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -CO-C_{1-3}alkyl, -CO-OC_{1-3}alkyl, -C_{1-3}alkyl-O-C_{1-3}alkoxy, substituted or unsubstituted -C_{1-3}alkoxy, or substituted or unsubstituted -C_{1-3}alkyl.

205. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-204, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN;-OH; -NO_2; carboxyl; -CO-C_{1-3}alkyl; -CO-OC_{1-3}alkyl; -C_{1-3}alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

206. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-205, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen;

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

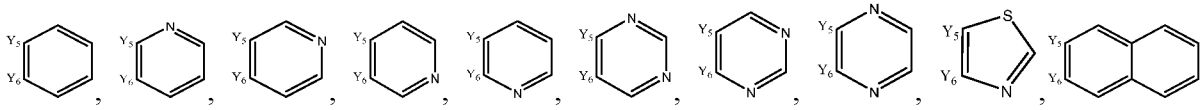
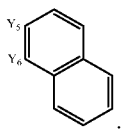
207. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-206, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN;-OH; -NO_2; carboxyl; -CO-C_{1-3}alkyl; -CO-OC_{1-3}alkyl; -C_{1-3}alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

208. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-207, wherein ring C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

209. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-208, wherein ring C is absent, a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

210. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-209, wherein ring C is absent, a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, a 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

211. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-210, wherein ring C is selected from


or

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212. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-211,

wherein each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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.

213. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-212, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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.

214. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-213, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

215. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-214, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -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; -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.

216. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-215, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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.

217. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-216, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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.

218. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-217, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

219. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-218, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

220. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-219, wherein each of R_a is independently selected from hydrogen, deuterium, F, Cl, Br, -$NR_{a1}R_{a2}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, -C_{1-3}alkoxy, -C_{1-3}alkyl, -C_{3-6}cycloalkyl,-C_{1-3}alkylene-$NR_{a1}R_{a2}$,

-C_{1-3}alkylene-O-C_{1-6}alkyl, -C_{1-3}alkylene-CO-OR_{a1}, -C_{1-3}alkylene-(3-8 membered heterocyclic), -C_{1-3}alkylene-(5-8 membered heteroaryl), -C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, -C_{3-8}carbocyclic, -5-10 membered heteroaryl, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -PO(C_{1-3}alkyl)$_2$, -PO(C_{1-3}alkoxy)$_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

221. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-220, wherein each of R_a is independently selected from hydrogen, deuterium, F, Cl, Br, -$NR_{a1}R_{a2}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, methoxy, ethoxy, propoxy, isopropoxy methyl, ethyl, propyl, isopropyl, -C_{3-6}cycloalkyl,-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-O-C_{1-6}alkyl, -C_{1-3}alkylene-CO-OR_{a1}, -C_{1-3}alkylene-(3-8 membered heterocyclic), -C_{1-3}alkylene-(5-8 membered heteroaryl), -C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, -C_{3-8}carbocyclic, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -PO(C_{1-3}alkyl)$_2$, -PO(C_{1-3}alkoxy)$_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

222. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-221, wherein two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

223. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-222, wherein two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

224. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-223,

wherein two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3 membered heterocyclic ring, a 4 membered heterocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 3 membered carbocyclic ring, a 4 membered carbocyclic ring, a 5 membered carbocyclic ring, a 6 membered carbocyclic ring, wherein each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

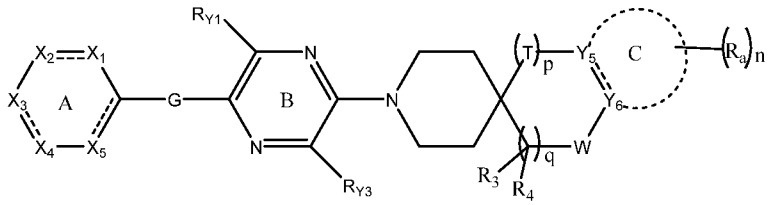
225. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-224, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

226. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-225, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, 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.

227. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-226, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

228. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-227, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

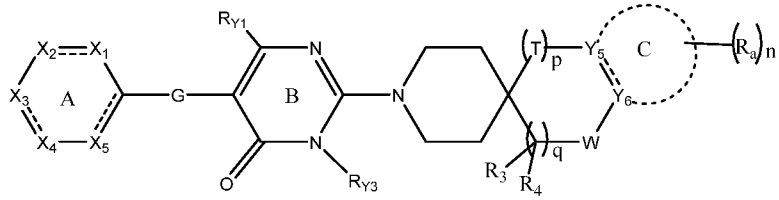
229. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-228, wherein the compound is of Formula II-a:



II-a

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y1}, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined in claims 125-228.

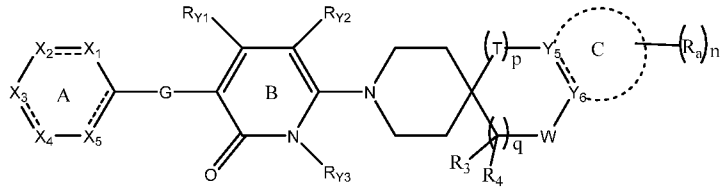
230. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-229, wherein the compound is of Formula II-b



II-b

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y1}, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined in claims 125-228.

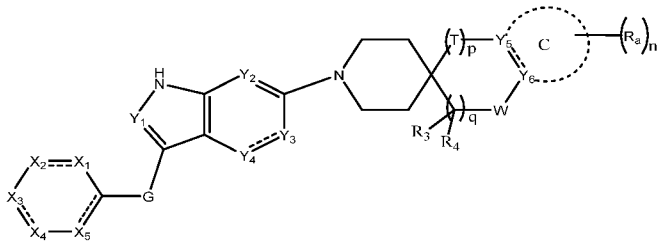
231. The compound or pharmaceutically acceptable salt thereof of any one of claims 125-230, wherein the compound is of Formula II-c



II-c

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y1}, R_{Y2}, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined in claims 125-228.

232. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-124, wherein the compound is of Formula III:



III

X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1};

each of R_{X1} is selected from hydrogen, deuterium, halogen, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO;

each of R_{X2} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3};

each of R_{X3} is independently selected from hydrogen, deuterium, halogen, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl,$-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl or $-O-C_{1-6}$alkylene-C_{1-6}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted ;

X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4};

each of R_{X4} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

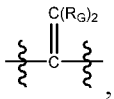
R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

X_5 is N, NR_{X5} $C(R_{X5})_2$ or CR_{X5};

each of R_{X5} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy; or

R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

------represents a single bond or a double bond;

G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$, $-NR_G-SO_2-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$;

each of R_G is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted or unsubstituted;

Y_1 is N or CR_{Y1};

R_{Y1} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}alkyl)_2$, $-C_{1-6}$alkenyl, $-C_{3-8}$cycloalkyl or $-C_{5-10}$aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy;

Y_2 is N or CR_{Y2};

R_{Y2} is selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy,

-NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6} alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy;

when the "======" in the term "^{Y_3}======Y_4" represents a single bond, Y_3 is NR_{Y3}, and Y_4 is CO;

when the "======" in the term "^{Y_3}======Y_4" represents a double bond, Y_3 is N or CR_{Y3}, and Y_4 is N or CR_{Y4};

R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, halogen, -NH_2, -OH, -CN, -C_{1-6}alkyl, carboxyl, -COO-C_{1-6}alkyl, -NH-C_{1-6}alkylene-OH ,-C_{1-6}alkylene-OH, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy;

T is absent, O, NR_1 or CR_1R_2;

each of R_1 and R_2 is independently selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -NH-C_{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 and R_2 together with the carbon atom to which they are both attached form CO or C=NR_5;

p is 0, 1, 2 or 3;

each of R_3 and R_4 is independently selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, -NO_2, carboxyl, -NH-C_{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_3 and R_4 together with the carbon atom to which they are both attached form a 3-12 membered heterocyclic ring or 5-12 membered heteroaromatic ring or C=NR_5, and each of the ring systems is independently optionally substituted or unsubstituted;

each of R_5 is selected from hydrogen, deuterium, halogen, -NH_2, -CN, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy;

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

W is absent, -O, -S or -C(Rw)$_2$-; and each of Rw is independently selected from hydrogen, deuterium, 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 C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the ring systems is independently optionally substituted or unsubstituted;

when ring C is absent, Y_5 is $CR_{5a}R_{5b}$, NR_{5a} or O, and Y_6 is $CR_{6a}R_{6b}$, NR_{6a} or O;

when ring C is 5-12 membered aromatic ring, 5-12 membered heteroaromatic ring or 5-12 membered heterocyclic ring;

i) Y_5 is CR_{5a} or N, and Y_6 is CR_{6a} or N, when the "======" in the term "^{Y_5}======Y_6" represents a single bond; or

ii) Y_5 is C, and Y_6 is C, when the "------" in the term "^{Y_5}------^{Y_6}" represents a double bond;

each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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_a is independently hydrogen, deuterium, halogen, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, $-C_{1-6}$alkoxy, $-C_{1-6}$alkyl, $-C_{3-8}$cycloalkyl,$-C_{1-6}$alkylene-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-O-C_{1-6}alkyl, $-C_{1-6}$alkylene-CO-OR_{a1}, $-C_{1-6}$alkylene-(3-10 membered heterocyclic), $-C_{1-6}$alkylene-(5-10 membered heteroaryl), $-C_{1-6}$alkylene-CO-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, $-C_{1-6}$alkylene-NR_{a1}-CO-C_{1-6}alkyl, -CO-$NR_{a1}R_{a2}$, -COO-C_{1-6}alkyl, -CO-CO-$NR_{a1}R_{a2}$, $-C_{3-10}$carbocyclic, -5-10 membered heteroaryl, -3-10 membered heterocyclic, -CO-C_{1-6}alkyl, -CO-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-NR_{a1}-(3-10 membered heterocyclic), -CO-(3-10 membered heterocyclic), -O-C_{1-6}alkylene-CO-OR_{a1}, -O-C_{1-6}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-6}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-10}carbocyclic, -O-(3-10 membered heterocyclic), $-NR_{a1}$-CO-C_{1-6}alkyl, $-NR_{a1}$-CO-$NR_{a1}R_{a2}$, $-NR_{a1}$-CO-(5-10 membered heteroaryl), $-NR_{a1}$-CO-C_{3-8}cycloalkyl,$-NR_{a1}$-C_{1-6}alkylene-$NR_{a1}R_{a2}$, $-NR_{a1}$-C_{1-6}alkylene-(3-10 membered heterocyclic), $-NR_{a1}$-C_{1-6}alkylene-(5-10 membered heteroaryl), $-NR_{a1}$-SO_2C_{1-6}alkyl, -S-C_{1-6}alkyl, -SO$NR_{a1}R_{a2}$, $-SO_2NR_{a1}R_{a2}$, -SO-C_{1-6}alkyl, $-SO_2C_{1-6}$alkyl, $-PO(C_{1-6}alkyl)_2$, $-PO(C_{1-6}alkoxy)_2$, -3-10 membered heterocyclic or -5-10 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6; or

two adjacent R_a can be joined together to form a 6-membered aryl ring, 5-membered heteroaryl ring, 6-membered heteroaryl ring, -3-6 membered heterocyclic or -3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted; or

R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, 3-10 membered heteroaromatic ring or 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted;

each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, substituted or unsubstituted $-C_{1-6}$alkoxy, or substituted or unsubstituted $-C_{1-6}$alkyl.

233. The compound or pharmaceutically acceptable salt thereof of claim 232, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

234. The compound or pharmaceutically acceptable salt thereof of claim 232 or claim 233, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

235. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-234, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

236. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-235, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

237. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-236, wherein X_1 is N, S, NR_{X1}, $C(R_{X1})_2$, or CR_{X1}; each of R_{X1} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, $-CONH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

238. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-237, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}\text{alkyl})_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

239. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-238 wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, $-CO-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N-(C_{1-6}\text{alkyl})_2$, $-SF_5$, $-NHCO-C_{3-8}$cycloalkyl, $-NH-C_{3-8}$cycloalkyl, $-C_{1-6}$alkylene-(3-8 membered heterocyclyl), -NHCO-(5-12 membered heterocyclyl), $-NH-C_{1-6}$alkylene-C_{3-8}cycloalkyl or 3-8 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

240. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-239, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-4}$alkyl, $-C_{1-3}$alkoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}\text{alkyl})_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}$alkylene-C_{3-6}cycloalkyl or 3-6 membered

heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

241. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-240, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxy, ethoxy, propoxy, isopropoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}$alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

242. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-241, wherein X_2 is N, S, NR_{X2}, $C(R_{X2})_2$, CR_{X2} or CO; each of R_{X2} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxy, ethoxy, propoxy, isopropoxy, $-CO-C_{1-3}$alkyl, $-NH-C_{1-3}$alkyl, $-N-(C_{1-3}alkyl)_2$, $-SF_5$, $-NHCO-C_{3-6}$cycloalkyl, $-NH-C_{3-6}$cycloalkyl, $-C_{1-3}$alkylene-(3-6 membered heterocyclyl), -NHCO-(5-10 membered heterocyclyl), $-NH-C_{1-3}$alkylene-C_{3-6}cycloalkyl, 3 membered heterocyclic, 4 membered heterocyclic, 5 membered heterocyclic or 6 membered heterocyclic, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, -oxo, =O, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

243. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-242, wherein R_{X1} and R_{X2} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

244. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-243, wherein R_{X1} and R_{X2} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

245. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-244, wherein R_{X1} and R_{X2} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic

ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

246. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-245, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl or $-O-C_{1-6}$alkylene-C_{1-6}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

247. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-246, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, C_{3-8}cycloalkyl, C_{5-8}aryl, $-S-C_{1-6}$alkyl, 3-12 membered heterocyclyl, $-O-C_{3-8}$cycloalkyl or $-O-C_{1-6}$alkylene-C_{1-6}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

248. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-247, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, $-C_{1-3}$alkyl,$-C_{1-3}$alkoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl or $-O-C_{1-3}$alkylene-C_{1-3}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

249. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-248, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl or $-O-C_{1-3}$alkylene-C_{1-3}alkyl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

250. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-249, wherein X_3 is N, S, O, NR_{X3}, $C(R_{X3})_2$ or CR_{X3}; each of R_{X3} is independently selected from hydrogen, deuterium, F, Cl, Br, carboxyl, $-NO_2$, $-NH_2$, -CN, $-CONH_2$, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, C_{3-6}cycloalkyl, C_{5-8}aryl, $-S-C_{1-3}$alkyl, 3-10 membered heterocyclyl, $-O-C_{3-6}$cycloalkyl or $-O-C_{1-3}$alkylene-C_{1-3}alkyl, and each of which is independently optionally

substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

251. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-250, wherein R_{X2} and R_{X3} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

252. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-251, wherein R_{X2} and R_{X3} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

253. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-252, wherein R_{X2} and R_{X3} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N or O, and each of the ring systems is independently optionally substituted or unsubstituted.

254. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-253, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl,, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

255. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-254, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl, $-C_{1-6}$alkoxy, -NHCO-(5-12 membered heterocyclyl) or 5-12 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, oxo, =O, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

256. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-255, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen,

deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-3}alkyl,-C_{1-3}alkoxy, -NHCO-(5-10 membered heterocyclyl) or 5-10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, oxo, =O, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

257. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-256, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, oxo, =O, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

258. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-257, wherein X_4 is N, S, NR_{X4}, $C(R_{X4})_2$ or CR_{X4}; each of R_{X4} is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, , -NHCO-(5-10 membered heterocyclyl), 5 membered heteroaryl, 6 membered heteroaryl, 7 membered heteroaryl, 8 membered heteroaryl, 9 membered heteroaryl or 10 membered heteroaryl, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, oxo, =O, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

259. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-258, wherein R_{X3} and R_{X4} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

260. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-259, wherein R_{X3} and R_{X4} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

261. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-260, wherein R_{X3} and R_{X4} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of

the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

262. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-261, wherein X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

263. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-262, wherein X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

264. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-263, wherein X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

265. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-264, wherein X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

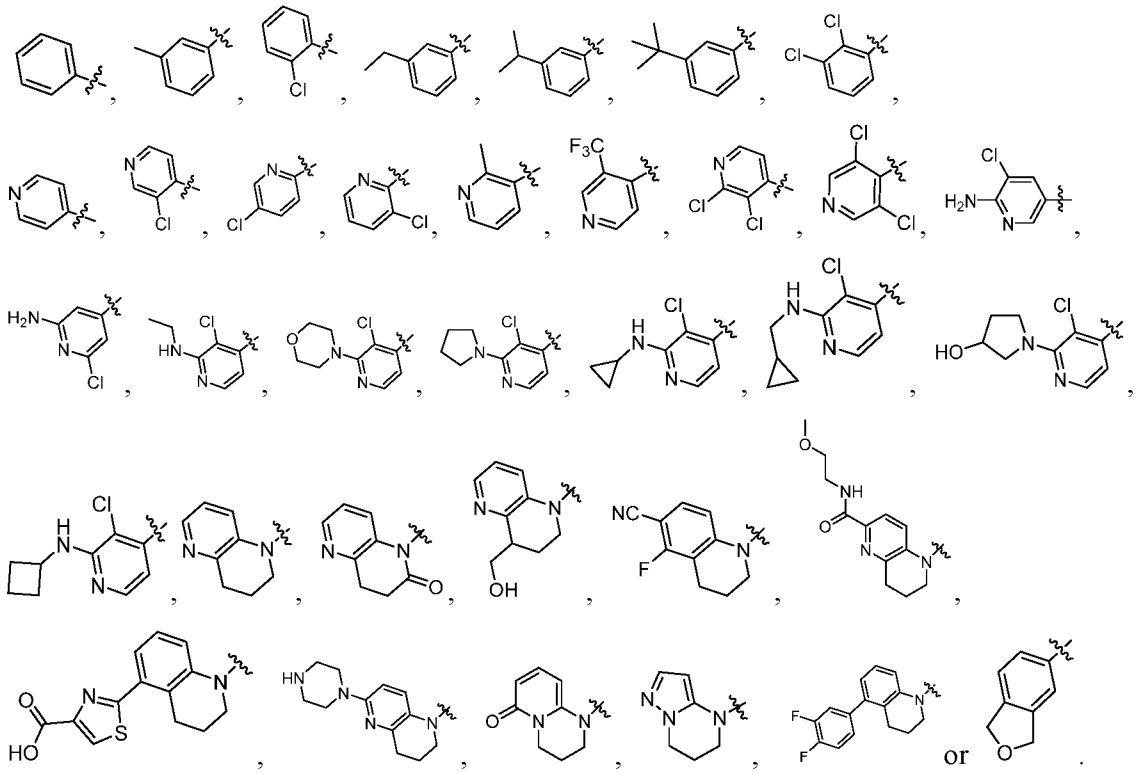
266. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-265, wherein X_5 is N, S, NR_{X5} $C(R_{X5})_2$ or CR_{X5}; each of R_{X5} is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted with 1, 2 or 3 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

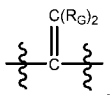
267. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-266, wherein R_{X4} and R_{X5} together with the ring to which they are attached form a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

268. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-267, wherein R_{X4} and R_{X5} together with the ring to which they are attached form a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

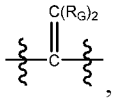
269. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-268, wherein R_{X4} and R_{X5} together with the ring to which they are attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring or a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

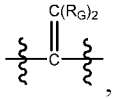
270. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-269, wherein ring A is selected from



271. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-270, wherein G is selected from absent, S, -SO-, $-SO_2-$, O, -CO-, $-NR_G-$,  , $-C(R_G)_2-$ or $-SO_2-NR_G-$; each of R_G is independent selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-C_{1-6}$alkyl

or -C_{1-6}alkoxy, and each of which is independently optionally substituted or unsubstituted.

272. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-271, wherein G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independent selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy, and each of which is independently optionally substituted or unsubstituted.

273. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-272, wherein G is selected from absent, S, -SO-, -SO_2-, O, -CO-, -NR_G-,  , -$C(R_G)_2$- or -SO_2-NR_G-; each of R_G is independent selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy, and each of which is independently optionally substituted or unsubstituted.

274. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-273, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6}alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

275. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-274, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6}alkenyl, -C_{3-8}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

276. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-275, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-3}alkyl, -C_{1-3}alkoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

277. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-276, wherein Y_1 is N or CR_{Y1}; R_{Y1} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

278. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-277, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl,

-C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6} alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

279. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-278, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-6}alkyl, -C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -N-(C_{1-6}alkyl)$_2$, -C_{1-6} alkenyl, -C_{3-8}cycloalkyl or -C_{5-10}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

280. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-279, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -C_{1-3}alkyl, -C_{1-3}alkoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

281. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-280, wherein Y_2 is N or CR_{Y2}; R_{Y2} is selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, -NH-C_{1-3}alkyl, -N-(C_{1-3}alkyl)$_2$, -C_{1-3}alkenyl, -C_{3-6}cycloalkyl or -C_{5-8}aryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

282. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-281, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, carboxyl, -COO-C_{1-6}alkyl, -NH-C_{1-6}alkylene-OH ,-C_{1-6}alkylene-OH, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

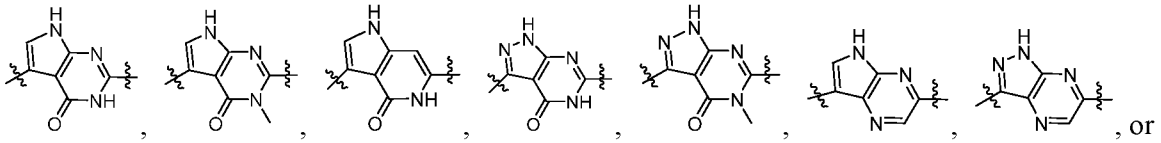
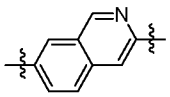
283. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-282, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-6}alkyl, carboxyl, -COO-C_{1-6}alkyl, -NH-C_{1-6}alkylene-OH ,-C_{1-6}alkylene-OH, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

284. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-283, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, -C_{1-3}alkyl, carboxyl, -COO-C_{1-3}alkyl, -NH-C_{1-3}alkylene-OH ,-C_{1-3}alkylene-OH, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I,

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

285. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-284, wherein R_{Y3} and R_{Y4} are independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -OH, -CN, methyl, ethyl, propyl, isopropyl, carboxyl, -COO-C_{1-3}alkyl, -NH-C_{1-3}alkylene-OH ,-C_{1-3}alkylene-OH, -$CONH_2$ or -5-8 membered heteroaryl, and each of which is independently optionally substituted with 1, 2, 3, 4, 5, or 6 substituents, and the said each substituents is independently selected from deuterium, F, Cl, Br, I, -NH_2, -CN, -OH, -NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

286. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-285, wherein ring B is selected from


, or

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287. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-286, wherein each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -NH-C_{1-6}alkyl, -N(C_{1-6}alkyl)$_2$, substituted or unsubstituted -C_{1-6}alkoxy, or substituted or unsubstituted -C_{1-6}alkyl.

288. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-287, wherein each of R_1 and R_2 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, substituted or unsubstituted -C_{1-3}alkoxy, or substituted or unsubstituted -C_{1-3}alkyl.

289. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-288 wherein each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; -NH-C_{1-3}alkyl; -N(C_{1-3}alkyl)$_2$; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

290. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-289, wherein each of R_1 and R_2 is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; -NH-C_{1-3}alkyl; -N(C_{1-3}alkyl)$_2$; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

291. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-290, wherein R_1 and R_2 together with the carbon atom to which they are both attached form CO or C=NR_5.

292. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-291,

wherein R_1 and R_2 together with the carbon atom to which they are both attached form CO.

293. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-292, wherein R_1 and R_2 together with the carbon atom to which they are both attached form $C=NR_5$.

294. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-293, wherein each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-6}alkyl$, $-N(C_{1-6}alkyl)_2$, substituted or unsubstituted $-C_{1-6}alkoxy$, or substituted or unsubstituted $-C_{1-6}alkyl$.

295. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-294, wherein each of R_3 and R_4 is independently selected from hydrogen, deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-NH-C_{1-3}alkyl$, $-N(C_{1-3}alkyl)_2$, substituted or unsubstituted $-C_{1-3}alkoxy$, or substituted or unsubstituted $-C_{1-3}alkyl$.

296. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-295 wherein each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}alkyl$; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}alkoxy$ substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, $C_{1-3}alkyl$ or $C_{1-3}alkoxy$; methyl; ethyl; propyl; isopropyl; $-C_{1-3}alkyl$ substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, $C_{1-3}alkyl$ or $C_{1-3}alkoxy$.

297. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-296, wherein each of R_3 and R_4 is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; $-NH-C_{1-3}alkyl$; $-N(C_{1-3}alkyl)_2$; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}alkoxy$ substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}alkyl$ substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

298. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-297, wherein R_3 and R_4 together with the carbon atom to which they are both attached form 3-12 membered heterocyclic ring or 5-12 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

299. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-298, wherein R_3 and R_4 together with the carbon atom to which they are both attached form 3-10 membered heterocyclic ring or 5-10 membered heteroaromatic ring or $C=NR_5$, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

300. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-299, wherein R_3 and R_4 together with the carbon atom to which they are both attached form 3 membered heterocyclic ring, 4 membered heterocyclic ring, 5 membered heterocyclic ring, 6 membered heterocyclic ring, 7 membered heterocyclic ring, 8 membered heterocyclic ring, 9 membered

heterocyclic ring, 10 membered heterocyclic ring, 5 membered heteroaromatic ring, 6 membered heteroaromatic ring, 7 membered heteroaromatic ring, 8 membered heteroaromatic ring, 9 membered heteroaromatic ring, 10 membered heteroaromatic ring or C=NR_5, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

301. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-300, wherein each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-6}alkyl or -C_{1-6}alkoxy.

302. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-301, wherein each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -C_{1-3}alkyl or -C_{1-3}alkoxy.

303. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-302, wherein each of R_5 is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

304. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-303, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, -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.

305. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-304, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen, deuterium, F, Cl, Br, -NH_2, -CN, -OH, -NO_2, carboxyl, -CO-C_{1-3}alkyl, -CO-OC_{1-3}alkyl, -C_{1-3}alkyl-O-C_{1-3}alkoxy, substituted or unsubstituted -C_{1-3}alkoxy, or substituted or unsubstituted -C_{1-3}alkyl.

306. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-305, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN;-OH; -NO_2; carboxyl; -CO-C_{1-3}alkyl; -CO-OC_{1-3}alkyl; -C_{1-3}alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

307. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-306, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN;-OH; -NO_2; carboxyl; -CO-C_{1-3}alkyl; -CO-OC_{1-3}alkyl; -C_{1-3}alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

308. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-307, wherein W is absent, -O, -S or -$C(Rw)_2$-; and each of Rw is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN;-OH; -NO_2; carboxyl; -CO-C_{1-3}alkyl; -CO-OC_{1-3}alkyl; -C_{1-3}alkyl-O-C_{1-3}alkoxy; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with F, Cl,

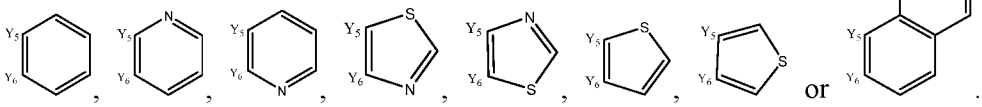
Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

309. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-308, wherein ring C is absent, a 5-12 membered aromatic ring, a 5-12 membered heteroaromatic ring or a 5-12 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

310. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-309, wherein ring C is absent, a 5-10 membered aromatic ring, a 5-10 membered heteroaromatic ring or a 5-10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

311. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-310, wherein ring C is absent, a 5 membered aromatic ring, a 6 membered aromatic ring, a 7 membered aromatic ring, an 8 membered aromatic ring, a 9 membered aromatic ring, a 10 membered aromatic ring, a 5 membered heteroaromatic ring, a 6 membered heteroaromatic ring, a 7 membered heteroaromatic ring, an 8 membered heteroaromatic ring, a 9 membered heteroaromatic ring, a 10 membered heteroaromatic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 7 membered heterocyclic ring, an 8 membered heterocyclic ring, a 9 membered heterocyclic ring, a 10 membered heterocyclic ring, and each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the ring systems is independently optionally substituted or unsubstituted.

312. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-311, wherein ring C is selected from



313. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-312, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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.

314. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-313, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen, deuterium, 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.

315. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-314, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl;

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

316. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-315, wherein each of R_{5a} and R_{5b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -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; -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.

317. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-316, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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.

318. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-317, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen, deuterium, 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.

319. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-318, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -C_{1-3}alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; -C_{1-3}alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

320. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-319, wherein each of R_{6a} and R_{6b} is independently selected from hydrogen; deuterium; F; Cl; Br; -NH_2; -CN; -OH; -NO_2; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; -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; methyl; ethyl; propyl; isopropyl; -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.

321. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-320, wherein each of R_a is independently selected from hydrogen, deuterium, F, Cl, Br, -$NR_{a1}R_{a2}$, -CN, -OH, -NO_2, oxo, =O, carboxyl, -C_{1-3}alkoxy, -C_{1-4}alkyl, -C_{3-6}cycloalkyl,-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-O-C_{1-6}alkyl, -C_{1-3}alkylene-CO-OR_{a1}, -C_{1-3}alkylene-(3-8 membered heterocyclic), -C_{1-3}alkylene-(5-8 membered heteroaryl), -C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, -C_{1-3}alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, -C_{3-8}carbocyclic, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), -NR_{a1}-CO-C_{1-3}alkyl, -NR_{a1}-CO-$NR_{a1}R_{a2}$, -NR_{a1}-CO-(5-8 membered heteroaryl), -NR_{a1}-CO-C_{3-6}cycloalkyl,-NR_{a1}-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -NR_{a1}-C_{1-3}alkylene-(3-8 membered heterocyclic), -NR_{a1}-C_{1-3}alkylene-(5-8 membered heteroaryl), -NR_{a1}-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, -$SONR_{a1}R_{a2}$, -$SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, -SO_2C_{1-3}alkyl, -PO(C_{1-3}alkyl)$_2$, -PO(C_{1-3}alkoxy)$_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally

substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

322. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-321, wherein each of R_a is independently selected from hydrogen, deuterium, F, Cl, Br, $-NR_{a1}R_{a2}$, -CN, -OH, $-NO_2$, oxo, =O, carboxyl, methoxy, ethoxy, propoxy, isopropoxy methyl, ethyl, propyl, isopropyl, butyl, isobutyl, $-C_{3-6}$cycloalkyl,$-C_{1-3}$alkylene-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-O-C_{1-6}alkyl, $-C_{1-3}$alkylene-CO-OR_{a1}, $-C_{1-3}$alkylene-(3-8 membered heterocyclic), $-C_{1-3}$alkylene-(5-8 membered heteroaryl), $-C_{1-3}$alkylene-CO-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-NR_{a1}-CO-$NR_{a1}R_{a2}$, $-C_{1-3}$alkylene-NR_{a1}-CO-C_{1-3}alkyl, -CO-$NR_{a1}R_{a2}$, -CO-CO-$NR_{a1}R_{a2}$, $-C_{3-8}$carbocyclic, -3-8 membered heterocyclic, -CO-C_{1-3}alkyl, -COO-C_{1-3}alkyl, -CO-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-NR_{a1}-(3-8 membered heterocyclic), -CO-(3-8 membered heterocyclic), -O-C_{1-3}alkylene-CO-OR_{a1}, -O-C_{1-3}alkylene-CO-$NR_{a1}R_{a2}$, -O-C_{1-3}alkylene-$NR_{a1}R_{a2}$, -O-C_{3-8}carbocyclic, -O-(3-8 membered heterocyclic), $-NR_{a1}$-CO-C_{1-3}alkyl, $-NR_{a1}$-CO-$NR_{a1}R_{a2}$, $-NR_{a1}$-CO-(5-8 membered heteroaryl), $-NR_{a1}$-CO-C_{3-6}cycloalkyl,$-NR_{a1}$-C_{1-3}alkylene-$NR_{a1}R_{a2}$, $-NR_{a1}$-C_{1-3}alkylene-(3-8 membered heterocyclic), $-NR_{a1}$-C_{1-3}alkylene-(5-8 membered heteroaryl), $-NR_{a1}$-SO_2C_{1-3}alkyl, -S-C_{1-3}alkyl, $-SONR_{a1}R_{a2}$, $-SO_2NR_{a1}R_{a2}$, -SO-C_{1-3}alkyl, $-SO_2C_{1-3}$alkyl, -PO(C_{1-3}alkyl)$_2$, -PO(C_{1-3}alkoxy)$_2$, -3-8 membered heterocyclic or -5-8 membered heteroaryl; each of which is independently optionally substituted; and n is 0, 1, 2, 3, 4, 5 or 6.

323. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-322, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, 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.

324. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-323, wherein two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, -C_{1-6}alkyl or -C_{1-6}alkoxy.

325. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-324, wherein two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3-6 membered heterocyclic ring or a 3-6 membered carbocyclic ring, wherein each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

326. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-325, wherein two adjacent R_a can be joined together to form a 6-membered aromatic ring, a 5-membered heteroaromatic ring, a 6-membered heteroaromatic ring, a 3 membered heterocyclic ring, a 4 membered heterocyclic ring, a 5 membered heterocyclic ring, a 6 membered heterocyclic ring, a 3 membered carbocyclic ring, a 4 membered carbocyclic ring, a 5 membered carbocyclic ring, a 6 membered carbocyclic ring, wherein each of the heteroaryl contains 1, 2 or 3 heteroatoms selected from N, O or S, and each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S, each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, -C_{1-3}alkyl or -C_{1-3}alkoxy.

327. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-326, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, a 3-10 membered heteroaromatic ring or a 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted with deuterium, halogen, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-6}$alkyl or $-C_{1-6}$alkoxy.

328. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-327, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, a 3-10 membered heteroaromatic ring or a 3-10 membered heterocyclic ring; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

329. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-328, R_a and R_w with the atom to which they are both attached form a 3-10 membered aromatic ring, a 3-10 membered heteroaromatic ring or a 3-10 membered heterocyclic ring; each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

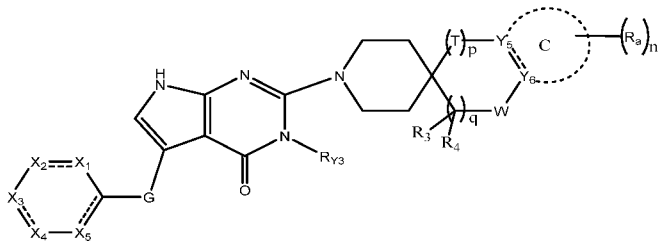
330. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-329, R_a and R_w with the atom to which they are both attached form a 5 membered aromatic ring, a 6 membered aromatic ring, a 5 membered heteroaryl ring, a 6 membered heteroaryl ring, a 5 membered heterocyclic ring or a 6 membered heterocyclic ring; each of the heteroaromatic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; each of the heterocyclic ring contains 1, 2 or 3 heteroatoms selected from N, O or S; and each of the ring systems is independently optionally substituted with deuterium, F, Cl, Br, $-NH_2$, -CN, -OH, $-NO_2$, carboxyl, $-C_{1-3}$alkyl or $-C_{1-3}$alkoxy.

331. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-330, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen, deuterium, 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.

332. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-331, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with halogen, NH_2, CN, OH, NO_2, carboxyl, C_{1-3}alkyl or C_{1-3}alkoxy.

333. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-332, wherein each of R_{a1} and R_{a2} is independently selected from hydrogen; deuterium; F; Cl; Br; $-NH_2$; -CN; -OH; $-NO_2$; carboxyl; methoxy; ethoxy; propoxy; isopropoxy; $-C_{1-3}$alkoxy substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy; methyl; ethyl; propyl; isopropyl; $-C_{1-3}$alkyl substituted with F, Cl, Br, NH_2, CN, OH, NO_2, carboxyl, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy or isopropoxy.

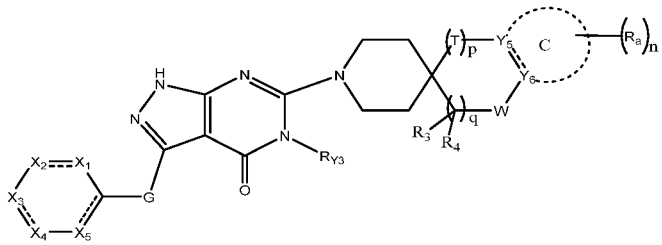
334. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-333, wherein the compound is of Formula III-a:



III-a

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined in claims 232-333.

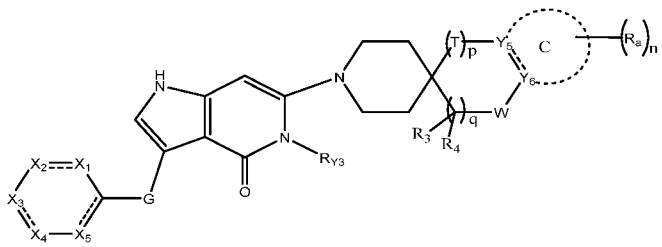
335. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-334, wherein the compound is of Formula III-b:



III-b

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined in claims 232-334.

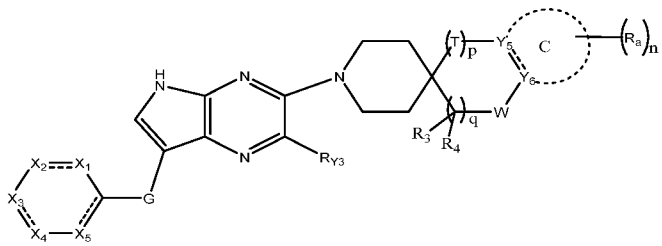
336. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-335, wherein the compound is of Formula III-c:



III-c

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined in claims 232-335.

337. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-336, wherein the compound is of Formula III-d:

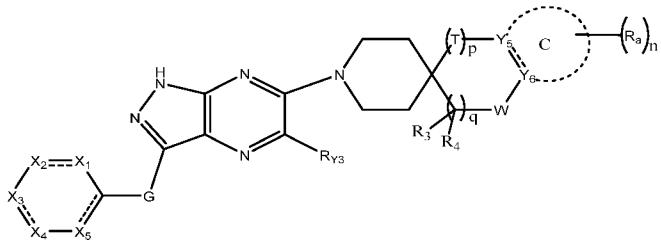


III-d

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined in claims 232-336.

338. The compound or pharmaceutically acceptable salt thereof of any one of claims 232-337,

wherein the compound is of Formula III-e:



III-e

Wherein X_1, X_2, X_3, X_4, X_5, G, R_{Y3}, T, R_3, R_4, W, Y_5, Y_6, R_a, p, q and n are as defined in claims 232-337.

339. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-338, wherein the compound is selected from

1	ethyl (S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5--2-carboxylate
2	(S)-1'-(5-(2,3-dichlorophenyl)-6-methylpyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
3	(S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazine-2-carboxylic acid
4	(S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazine-2-carboxamide
5	ethyl (S)-3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2-amino-3-chloropyridin-4-yl)thio)-5-methylpyrazine-2-carboxylate
6	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)-6-methylpyrazin-2-yl)-1,3-dihydrospiro[indene-2 4'-piperidin]-1-amine
7	(S)-1'-(6-amino-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
8	(S)-1'-(4-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrimidin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
9	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
10	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)-6-(methylamino)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
11	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)-6-(dimethylamino)pyrazin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
12	(S)-1'-(6-amino-5-(thiazol-4-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
13	(S)-1'-(6-amino-5-(thiazol-2-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
14	(S)-1'-(6-amino-5-(quinolin-3-ylthio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine

15	(S)-5-amino-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidine]-3-carbonitrile
16	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-N-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
17	(S)-1'-(5-((3,5-dichloropyridin-4-yl)thio)pyrazin-2-yl)-5,6,7-trifluoro-1,3-dihydrospiro[indene-2, 4'-piperidin]-1-amine
18	(S)-1-amino-1'-(2-((2-cyanopyridin-3-yl)thio)pyrimidin-5-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carbonitrile
19	(S)-1'-(5-((3-chloro-2-methoxypyridin-4-yl)thio)pyrazin-2-yl)-6-(methylthio)-1,3-dihydrospiro [indene-2,4'-piperidin]-1-amine
20	(S)-1-(5-((5-(4-amino-2-(tert-butyl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-2-chlorophenyl)ethan-1-one
21	(S)-1'-(5-((3-chloro-2-(isopropylamino)pyridin-4-yl)thio)pyrazin-2-yl)-6-(methylsulfonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
22	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b] pyridine-6,4'-piperidin]-7,7-d2-5-amine
23	(S)-(3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methyl pyrazin-2-yl)methanol
24	(S)-(3-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2-amino-3-chloropyridin-4-yl)thio)-5-methylpyrazin-2-yl)methanol
25	(S)-1'-(3-bromo-5-(2,3-dichlorophenyl)-6-methylpyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b] pyridine-6,4'-piperidin]-5-amine
26	(S)-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazine-2-carbonitrile
27	(S)-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazine-2-carboxamide
28	(S)-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(2,3-dichlorophenyl)-5-methylpyrazin-2-ol
29	(S)-1'-(6-amino-3-bromo-5-((2,3-dichlorophenyl)thio)pyrazin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
30	(S)-5-amino-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazine-2-carbonitrile
31	(S)-5-amino-3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-((2,3-dichlorophenyl)thio)pyrazine-2-carboxamide
32	(S)-1'-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
33	(S)-1'-(6-((2-amino-3-chloropyridin-4-yl)thio)pyridin-3-yl)-5,7-dihydrospiro[cyclopenta[b] pyridine-6,4'-piperidin]-5-amine
34	(S)-1'-(4-((2-amino-3-chloropyridin-4-yl)thio)phenyl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6, 4'-piperidin]-5-amine

35	(S)-1'-(4-((2-amino-3-chloropyridin-4-yl)thio)isoquinolin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
36	(S)-6-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-3-(2,3-dichlorophenyl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
37	(S)-6-(1-amino-6-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(2,3-dichlorophenyl)-5-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
38	(S)-6-(1-amino-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-methyl-3-(5-methylthiophen-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
39	(S)-2-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-5-(2,3-dichlorophenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
40	(S)-6-amino-2-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-((2-amino-3-chloropyridin-4-yl)thio)-3-methylpyrimidin-4(3H)-one
41	(S)-1'-(6-amino-5-((4-chlorothiazol-2-yl)thio)pyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
42	(S)-1-amino-1'-(5-((4-amino-5-bromopyrimidin-2-yl)thio)-1-methyl-6-oxo-1,6-dihydropyridin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
43	(S)-6-(1-amino-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-((3-chloro-2-methoxypyridin-4-yl)thio)-1-methylpyridin-2(1H)-one
44	(S)-1-amino-1'-(4-(6-bromonaphthalen-2-yl)thiazol-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
45	(S)-1'-(6-amino-5-(2-chloro-3-methylphenyl)pyrazin-2-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
46	(S)-1'-(5-(3-amino-2-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
47	(S)-1'-(6-amino-5-(2-chloro-3-methylphenyl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
48	(S)-1'-(6-(5-chlorothiophen-2-yl)pyridazin-3-yl)-5-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
49	(S)-1'-(6'-chloro-[3,3'-bipyridazin]-6-yl)-5-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
50	(S)-1'-(3-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
51	(R)-1'-(5-(2,3-dichloro-5-methoxyphenyl)pyridin-2-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
52	(S)-6'-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1'-methyl-2'-oxo-1',2'-dihydro-[3,3'-bipyridine]-2-carbonitrile
53	(S)-6'-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1'-methyl-2'-oxo-1',2'-dihydro-[3,3'-bipyridine]-2-carboxamide
54	(S)-1'-(4-(3-methoxyphenyl)cyclohexyl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine

55	(S)-1-amino-1'-(6-((3-amino-2-chlorophenyl)thio)-1,2,4-triazin-3-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
56	1-(5-((5-((1S)-1-amino-6-(methylsulfinyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-2-chlorophenyl)ethan-1-one
57	(S)-1'-(5-(pyrimidin-2-ylthio)pyrazin-2-yl)-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
58	(S)-6-bromo-5-fluoro-1'-(5-(quinolin-4-ylthio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
59	(S)-6-(4-amino-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-1'-yl)-3-(3-(trifluoromethyl)pyridin-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
60	(S)-2-(1-amino-6-chloro-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(3,5-dichloropyridin-4-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
61	(S)-1'-(7-(5-chloropyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-3-amine
62	(S)-1'-(7-(3-chloropyridin-2-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-1H,3H-spiro[phenalene-2,4'-piperidin]-1-amine
63	(R)-1'-(3-(2-methylpyridin-3-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-3-amine
64	(S)-6-amino-2-(1-amino-7-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-phenylpyrimidin-4(3H)-one
65	(S)-1-amino-1'-(4-amino-6-oxo-5-(pyridazin-3-ylthio)-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-7-carbonitrile
66	(S)-1-amino-1'-(1-methyl-6-oxo-5-(pyrazin-2-yl)-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-7-carbonitrile
67	(S)-2-(1-amino-6-chloro-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-((4-isopropylphenyl)thio)pyrimidin-4(3H)-one
68	(S)-4-amino-6-(1-amino-6-bromo-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(2-chloro-3-methylphenyl)-1-methylpyridin-2(1H)-one
69	(S)-6-(4-acetyl-1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-4-amino-3-(4-(trifluoromethyl)phenyl)pyridin-2(1H)-one
70	(S)-6'-(1-amino-4-hydroxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-2'-oxo-1',2'-dihydro-[3,3'-bipyridine]-2-carbonitrile
71	(S)-1'-(3-bromo-5-(1H-indol-6-yl)-6-methylpyrazin-2-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
72	(S)-3-(4-amino-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-5-methyl-6-(2-oxoindolin-7-yl)pyrazine-2-carbonitrile
73	(S)-1'-(5-amino-6-((2-amino-3-chloropyridin-4-yl)thio)-1,2,4-triazin-3-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
74	(S)-1'-(5-amino-6-((2-amino-3-chloropyridin-4-yl)thio)pyridin-3-yl)-6-chloro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

75	(S)-1'-(4-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyridin-2-yl)-5,7-dihydrospiro [cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
76	(S)-1'-(5-((2,3-dichlorophenyl)thio)thiazol-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine
77	(R)-1'-(4-((3-chloropyridin-4-yl)thio)thiazol-2-yl)spiro[indoline-2,4'-piperidin]-3-amine
78	(R)-1'-(2-(7-chloro-1H-indol-1-yl)thiazol-4-yl)-2,3-dihydrospiro[indene-1,4'-piperidin]-2-amine
79	(R)-1'-(2-((2-(trifluoromethyl)phenyl)thio)thiazol-5-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine
80	(S)-(5-(1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)(2,3-dichlorophenyl) methanone
81	(S)-2-(1-amino-6-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(indolin-1-yl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
82	(S)-1'-(5-((1,2,3,4-tetrahydroquinolin-8-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[b] naphthalene-2,4'-piperidin]-1-amine
83	(S)-1'-(5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[cyclopenta[a] naphthalene-2,4'-piperidin]-1-amine
84	1'-(5-((3-amino-2-chlorophenyl)thio)-6-methylpyrazin-2-yl)-1-methyl-1,3-dihydrospiro [indene-2,4'-piperidin]-1-amine
85	(R)-1'-(7-((2-amino-3-chloropyridin-4-yl)thio)-1H-indol-4-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine
86	(S)-1'-(7-((2-amino-3-chloropyridin-4-yl)thio)isoquinolin-3-yl)-5,6-dibromo-1,3-dihydrospiro [indene-2,4'-piperidin]-1-amine
87	(S)-4-((5-(5-acetyl-1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-aminopyrazin-2-yl) thio)-3-chloro-1-methylpyridin-2(1H)-one
88	(S)-5-(1-amino-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-2-((2,3-dichlorophenyl) thio)-6-(hydroxymethyl)pyridin-3-ol
89	(S)-6-bromo-1'-(5-(2,3-dichlorophenyl)-6-methylimidazo[1,5-a]pyrazin-8-yl)-1,3-dihydrospiro [indene-2,4'-piperidin]-1-amine
90	(S)-1'-(7-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,5]thiadiazolo[3,4-c]pyridin-4-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
91	(S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)pyrido[4,3-d]pyrimidin-5-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
92	(S)-3-(5-(1-amino-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyridin-2-yl)-4,5-dichlorophenol
93	(S)-1-amino-1'-(5-(5-methylthiophen-2-yl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-ol
94	(S)-1'-(5-(1H-indol-7-yl)pyrazin-2-yl)-5-ethyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine

95	(S)-1'-(5-(cyclohex-1-en-1-yl)pyrazin-2-yl)-5-isopropyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
96	(S)-N-(1-amino-1'-(5-(2-(trifluoromethyl)phenyl)pyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)methanesulfonamide
97	(S)-1'-(5-((4-(trifluoromethyl)pyrimidin-5-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-7-amine
98	(S)-1'-(5-((2-chloropyridin-3-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
99	(S)-4-((5-(5-amino-5,7-dihydrospiro[cyclopenta[d]pyrimidine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chlorobenzoic acid
100	(S)-1'-(5-((3-(trifluoromethyl)pyrazin-2-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-7-amine
101	(S)-1'-(5-((3-chloropyridazin-4-yl)thio)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[d]pyrimidine-6,4'-piperidin]-7-amine
102	(S)-4-((5-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyrazine-6,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)-3-chlorobenzamide
103	(S)-(1-amino-1'-(5-((3-chloro-2-(methylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)dimethylphosphine oxide
104	(S)-1-amino-1'-(6-amino-5-((3-chloro-2-(dimethylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-5-carboxylic acid
105	ethyl (S)-1-amino-1'-(5-((3-chloro-2-(methylamino)pyridin-4-yl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-5-carboxylate
106	(S)-1'-(5-((3-(morpholinomethyl)phenyl)thio)pyrazin-2-yl)-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
107	(S)-6-bromo-5-fluoro-1'-(5-((3-(pentafluoro-l6-sulfanyl)phenyl)thio)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
108	(S)-N-(3-((5-(1-amino-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyrazin-2-yl)thio)phenyl)cyclopropanecarboxamide
109	(S)-6-(6-amino-1-bromo-4H,6H-spiro[cyclopenta[c]thiophene-5,4'-piperidin]-1'-yl)-3-(m-tolyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one
110	(S)-2-(1-amino-5,6,7-trifluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(3-ethylphenyl)-3-methyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
111	(R)-1'-(3-(3-(tert-butyl)phenyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3,4-dihydro-1H-spiro[naphthalene-2,4'-piperidin]-3-amine
112	(S)-2-(3-amino-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-1'-yl)-5-(3-isopropylphenyl)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one
113	(S)-1-amino-1'-(3-(3-chloro-2-morpholinopyridin-4-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridin-6-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile

114	(S)-1'-(7-(3-chloro-2-(cyclobutylamino)pyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-1,3-dihydrospiro[cyclopenta[a]naphthalene-2,4'-piperidin]-3-amine
115	(S)-1'-(3-(3-chloro-2-(cyclopropylamino)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-N6-methyl-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
116	(S)-5-amino-1'-(3-(3-chloro-2-(pyrrolidin-1-yl)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-2-fluoro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-3-carboxamide
117	1-(4-(6-((S)-4-amino-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-3-chloropyridin-2-yl)pyrrolidin-3-ol
118	(S)-1'-(3-(3-chloro-2-((cyclopropylmethyl)amino)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-N6,N6-dimethyl-1,3-dihydrospiro[indene-2,4'-piperidine]-1,6-diamine
119	(S)-1'-(3-(2-amino-6-chloropyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-2-(tert-butyl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine
120	(S)-2-chloro-1'-(3-(1,3-dihydroisobenzofuran-5-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-6-amine
121	(S)-3-chloro-1'-(3-((2-chlorophenyl)thio)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
122	(S)-1'-(3-(3-chloro-2-(ethylamino)pyridin-4-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[b]thiophene-5,4'-piperidin]-4-amine
123	(R)-1'-(7-(methyl(pyridin-4-yl)amino)-5H-pyrrolo[2,3-b]pyrazin-3-yl)-3H-spiro[furo[2,3-b]pyridine-2,4'-piperidin]-3-amine
124	(R)-1'-(3-((3-chloropyridin-4-yl)amino)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-6-amine
125	(S)-2-methoxy-1'-(3-(1-phenylvinyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
126	(R)-1-(3-benzyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1',3'-dihydrospiro[piperidine-4,2'-pyrrolo[2,3-b]pyridin]-3'-amine
127	(S)-(6-(6-amino-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)(phenyl)methanone
128	(4S)-1'-(3-(1-phenylethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidin]-4-amine
129	1-(6-((S)-5-amino-2-methoxy-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-1-phenylethan-1-ol
130	(S)-1'-(3-((2,3-dichloropyridin-4-yl)oxy)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
131	(S)-6-bromo-1'-(3-(5-(3,4-difluorophenyl)-3,4-dihydroquinolin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
132	(S)-6-amino-2-(1-amino-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(4-cyclopropoxyphenyl)-3-methylpyrimidin-4(3H)-one
133	(S)-N-(1-amino-1'-(4-amino-5-((4-(methylthio)phenyl)thio)-6-oxo-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)acetamide

134	(S)-2-(1-amino-6-(methylamino)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(4-(benzyloxy)phenyl)-3-methylpyrimidin-4(3H)-one
135	(S)-2-(7-acetyl-1-amino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-(benzo[d][1,3]dioxol-4-ylthio)pyrimidin-4(3H)-one
136	4-amino-6-((1S)-1-amino-7-(1-hydroxyethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(4-(difluoromethoxy)phenyl)-1-methylpyridin-2(1H)-one
137	(S)-1-amino-1'-(4-amino-6-oxo-5-(4-phenoxyphenyl)-1,6-dihydropyridin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-4-carbonitrile
138	(S)-6-(1-amino-4-hydroxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(4-cyclohexylphenyl)-1-methylpyridin-2(1H)-one
139	(S)-3-([1,1'-biphenyl]-4-yl)-6-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)pyridin-2(1H)-one
140	(S)-6-amino-2-(1-amino-6-(2-oxopiperidin-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-(4-(trifluoromethoxy)phenyl)pyrimidin-4(3H)-one
141	(S)-1-(1-amino-1'-(4-amino-5-((4-cyanophenyl)thio)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)urea
142	(S)-4-amino-6-(1-amino-6-chloro-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1-methyl-3-(4-(tetrahydro-2H-pyran-4-yl)phenyl)pyridin-2(1H)-one
143	(S)-6-(1-amino-6-(trifluoromethyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-(4-(2-methoxyethoxy)phenyl)-1-methylpyridin-2(1H)-one
144	(S)-6-amino-2-(1-amino-6-(piperidine-1-carbonyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-(quinolin-8-ylthio)pyrimidin-4(3H)-one
145	(S)-6-amino-2-(1-amino-6-morpholino-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methyl-5-((4-nitrophenyl)thio)pyrimidin-4(3H)-one
146	(S)-6-amino-2-(5-amino-3-nitro-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-3-methyl-5-(quinolin-8-ylthio)pyrimidin-4(3H)-one
147	(S)-6-(5-amino-3-(4-methylpiperazin-1-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-1-methyl-3-(naphthalen-1-ylthio)pyridin-2(1H)-one
148	(S)-2-(1-amino-6-(1H-pyrrol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-((2,2-difluorobenzo[d][1,3]dioxol-4-yl)thio)pyrimidin-4(3H)-one
149	(S)-7-(5-(1-amino-6-(1H-imidazol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(hydroxymethyl)-3-methylpyrazin-2-yl)isoindolin-1-one
150	(S)-3-(1-amino-6-(ethylamino)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-(1H-indol-5-yl)-5-methylpyrazine-2-carboxamide
151	(S)-N-(1-amino-1'-(3-bromo-5-(1H-indol-6-yl)-6-methylpyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-6-yl)cyclopropanecarboxamide
152	(S)-4-(6-amino-5-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-3-methylpyrazin-2-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one
153	(S)-3-(1-amino-5-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-5-methyl-6-(2-oxoindolin-7-yl)pyrazine-2-carbonitrile

154	(S)-N-(5-(1-amino-7-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((2-hydroxyethyl)amino)-3-methylpyrazin-2-yl)benzenesulfonamide
155	(S)-1'-(6-methyl-3-(1H-pyrazol-5-yl)-5-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
156	(S)-2-(3-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-6-(8-chlorochroman-7-yl)-5-methylpyrazin-2-yl)propan-2-ol
157	(S)-6-chloro-1'-(5-(7-chloro-2,3-dihydrobenzofuran-6-yl)pyrazin-2-yl)-1,3-dihydrospiro [indene-2,4'-piperidin]-1-amine
158	(S)-4-bromo-1'-(5-(3-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrazin-2-yl)-1,3-dihydrospiro [indene-2,4'-piperidin]-1-amine
159	(S)-1-amino-1'-(6-cyano-5-(1H-indazol-7-yl)pyrazin-2-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
160	(S)-1'-(5-(1H-indol-3-yl)-6-iodopyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-5-amine
161	(R)-6-(5-(7'-amino-7',8'-dihydro-5'H-spiro[piperidine-4,6'-quinolin]-1-yl)-3-vinylpyrazin-2-yl) isoindolin-1-one
162	(R)-1-(4-(5-(6-amino-6,7-dihydrospiro[cyclopenta[b]pyridine-5,4'-piperidin]-1'-yl)-3-ethylpyrazin-2-yl)-3,3-difluoroindolin-1-yl)ethan-1-one
163	(S)-1'-(5-(3-methyl-1H-indazol-6-yl)-6-phenylpyrazin-2-yl)-5,7-dihydrospiro[cyclopenta[b] pyridine-6,4'-piperidin]-5-amine
164	(S)-1'-(5-(1H-benzo[d][1,2,3]triazol-6-yl)-6-cyclopropylpyrazin-2-yl)-6-((tetrahydro-2H-pyran-4-yl)oxy)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
165	(S)-1-amino-1'-(3-((1-methyl-1H-imidazol-2-yl)thio)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
166	(S)-1'-(3-(1H-benzo[d]imidazol-1-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-6-bromo-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
167	(S)-1-(6-(1-amino-5-chloro-6-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-3,4-dihydro-1,5-naphthyridin-2(1H)-one
168	(1-(6-((S)-1-amino-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo [3,4-b]pyrazin-3-yl)-1,2,3,4-tetrahydro-1,5-naphthyridin-4-yl)methanol
169	1-(6-((1S)-1-amino-6-(methylsulfinyl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-5-fluoro-1,2,3,4-tetrahydroquinoline-6-carbonitrile
170	(S)-6-chloro-1'-(3-(2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-1-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl) -5-methyl-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
171	(S)-5-(6-(1-amino-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b] pyrazin-3-yl)-N-(2-methoxyethyl)-5,6,7,8-tetrahydro-1,5-naphthyridine-2-carboxamide
172	(S)-1-amino-5-fluoro-1'-(3-(6-(piperazin-1-yl)-3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carbonitrile
173	(S)-2-(1-(6-(1-amino-6-(methylthio)-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-1H-pyrazolo [3,4-b]pyrazin-3-yl)-1,2,3,4-tetrahydroquinolin-5-yl)thiazole-4-carboxylic acid

174	(S)-1'-(6-(aminomethyl)-5-(2,3-dichloropyridin-4-yl)pyrazin-2-yl)-6-(1H-imidazol-1-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
175	(1S)-1-amino-1'-(5-(2,3-dichloropyridin-4-yl)-3-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)-6-methylpyrazin-2-yl)-N,N-dimethyl-1,3-dihydrospiro[indene-2,4'-piperidine]-6-carboxamide
176	(S)-1'-(8-(2-amino-3-chloropyridin-4-yl)-7-methylimidazo[1,2-c]pyrimidin-5-yl)-5-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
177	(S)-1'-(5-(1-methyl-1H-indol-2-yl)pyrazin-2-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-3,3-d2-1-amine
178	(S)-1-(6-(5-amino-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidin]-1'-yl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]pyrimidin-6-one
179	(S)-1'-(3-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5-amine
180	(3-((S)-1-amino-6-fluoro-1,3-dihydrospiro[indene-2,4'-piperidin]-1'-yl)-6-((R)-1-methylisoindolin-2-yl)pyrazin-2-yl)methanol
181	(S)-1'-(3-(6,7-dihydropyrazolo[1,5-a]pyrimidin-4(5H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidin]-5,5-d2-7-amine
182	(S)-4-(difluoromethyl)-1'-(5-methyl-6-((R)-2-methyl-3,4-dihydro-1,5-naphthyridin-1(2H)-yl)pyridin-3-yl)-1,3-dihydrospiro[indene-2,4'-piperidin]-1-amine
183	(S)-1'-(8-(2-chloro-3-(isopropyl(methyl)amino)phenyl)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-2,3,6,8-tetrahydrospiro[indeno[5,6-b][1,4]dioxine-7,4'-piperidin]-6-amine
184	(S)-1-(5-amino-1'-(8-((5-chloro-1-methylindolin-6-yl)thio)imidazo[1,5-a]pyridin-5-yl)-2,3,5,7-tetrahydro-1H-spiro[cyclopenta[b]pyrrolo[3,2-e]pyridine-6,4'-piperidin]-1-yl)ethan-1-one

340. A pharmaceutical composition comprising at least one compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1-339 and at least one pharmaceutically acceptable excipient.

341. The pharmaceutical composition of claim 340, wherein, the compound in a weight ratio to the said excipient within the range from about 0.0001 to about 10.

342. A combination pharmaceutical product comprising the compound or a pharmaceutically acceptable salt thereof of any of claims 1-339, together with one or more other therapeutically active agents.

343. Use of the compound or a pharmaceutically acceptable salt thereof of any one of claim 1-339, the pharmaceutical composition of claim 340 or 341, or the combination pharmaceutical product of claim 342 for the preparation of a medicament.

344. The use of claim 343, wherein the medicament is used for the treatment or prevention of cancer, cancer metastasis, cardiovascular disease, an immunological disorder or an ocular disorder.

345. Use, in the manufacture of a medicament for use as an inhibitor of SHP2, of at least one compound or a pharmaceutically acceptable salt thereof any one of claims 1-339, the pharmaceutical composition of claim 340 or 341, or the combination pharmaceutical product of claim 342.

346. Use of the compound or a pharmaceutically acceptable salt thereof of any one of claims 1-339, the pharmaceutical composition of claim 340 or 341, or the combination pharmaceutical

product of claim 342 for the preparation of a medicament in the treatment of diseases or conditions mediated by the activity of SHP2.

347. The use of claim 346, wherein the diseases or conditions mediated by the activity of SHP2 is cancer.

348. The use of claim 346, wherein the diseases or conditions mediated by the activity of SHP2 is selected from 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, anaplastic large-cell lymphoma and glioblastoma.

349. A method for preventing or treating a disease, lessening a disease symptoms, delaying the progression or onset of a disease, comprising administering to the patient in need thereof a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof of any one of claims 1-339, the pharmaceutical composition of claims 340or 341, or the combination pharmaceutical product of claim 342, wherein the disease is cancer, cancer metastasis, cardiovascular disease, an immunological disorder or an ocular disorder.

350. A method for inhibiting the activity of SHP2 level, comprising administering to the patient in need thereof a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof of any one of claims 1-339, or the pharmaceutical composition of claims 340 or 341, or the combination pharmaceutical product of claim 342.

351. A method for preventing or treating a disease, lessening a disease symptoms, delaying the progression or onset of a disease, comprising administering to the patient in need thereof a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof of any one of claims 1-339, the pharmaceutical composition of claims 340 or 341, or the combination pharmaceutical product of claim 342, wherein the disease is mediated by the activity of SHP2.

352. The method of claim 351, wherein the disease mediated by the activity of SHP2 is cancer.

353. The method of claim 351, wherein the disease mediated by the activity of SHP2 is selected from 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, anaplastic large-cell lymphoma and glioblastoma.

354. The compound or the pharmaceutically acceptable salt thereof of any one of claims 1-339, the pharmaceutical composition of claims 340 or 341, or the combination pharmaceutical product of claim 342 for use in preventing or treating a disease, lessening a disease symptom, delaying the progression or onset of a disease, wherein the disease is cancer, cancer metastasis, cardiovascular disease, an immunological disorder or an ocular disorder.

355. The compound or the pharmaceutically acceptable slat thereof any one of claims 1-339, the pharmaceutical composition of claims 340 or 341, or the combination pharmaceutical product of claim 339, for use in inhibiting the activity of SHP2.

356. The compound or the pharmaceutically acceptable salt thereof of any one of claims 1-339, the pharmaceutical composition of claims 340 or 341, or the combination pharmaceutical product of

claim 339 for use in preventing or treating a disease, lessening a disease symptom, delaying the progression or onset of a disease, wherein the disease is mediated by the activity of SHP2.

357. The compound or the pharmaceutically acceptable salt thereof, the pharmaceutical composition, or the combination pharmaceutical product of claim 356, wherein the disease mediated by the activity of SHP2 is cancer.

358. The compound or the pharmaceutically acceptable salt thereof, the pharmaceutical composition, or the combination pharmaceutical product of claim 356, wherein the disease mediated by the activity of SHP2 is selected from 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, anaplastic large-cell lymphoma and glioblastoma.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/108181

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/14(2006.01)i; C07D 401/12(2006.01)i; C07D 401/04(2006.01)i; C07D 401/06(2006.01)i; C07D 405/14(2006.01)i; C07D 498/10(2006.01)i; C07D 471/10(2006.01)i; C07D 221/20(2006.01)i; C07D 241/18(2006.01)i; C07D 241/20(2006.01)i; A61K 31/497(2006.01)i; A61P 35/00(2006.01)i; A61P 35/02(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D401/-; C07D 405/-; C07D498/-; C07D471/-; C07D221/-; C07D241/-; A61K31/-; A61P35/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT, CNKI, WPI, EPODOC, ISI Web of Knowledge, Registry, Caplus: JACOBIO, SHP2, inhibitor, src w homology, protein w tyrosine w phosphatase, piperidin+, spiral ring, search the structure in claim 1 REG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 110143949 A (JACOBIO PHARMACEUTICALS CO., LTD.) 20 August 2019 (2019-08-20) see claims 1-51	1-229, 339-358
PX	WO 2018172984 A1 (JACOBIO PHARMACEUTICALS CO., LTD. et al.) 27 September 2018 (2018-09-27) see claims 1-134	1-229, 339-358
X	WO 2018013597 A4 (REVOLUTION MEDICINES INC. et al.) 05 April 2018 (2018-04-05) see abstract, claims 1, 46, 48-58	1-229, 339-358
X	WO 2017211303 A1 (JACOBIO PHARMACEUTICALS CO., LTD.) 14 December 2017 (2017-12-14) see see abstract, examples, claims 1, 72-85	1-229, 339-358
X	WO 2016203405 A1 (NOVARTIS AG et al.) 22 December 2016 (2016-12-22) see abstract, examples, claims 1, 21-22	1-231, 339-358
X	WO 2018057884 A1 (RELAY THERAPEUTICS, INC. et al.) 29 March 2018 (2018-03-29) see abstract, table 1, claims 10-26	1-124, 232-333, 338-358

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
09 December 2019	**06 January 2020**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **LI,Bing** Telephone No. **86-(10)-53962156**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016203404 A1 (NOVARTIS AG et al.) 22 December 2016 (2016-12-22) see abstract, examples, claims 12-14	1-124, 232-358
X	WO 2017156397 A1 (BOARD OF REGENTS THE UNIVERSITY OF TEXAS SYSYTEM) 14 September 2017 (2017-09-14) see abstract, examples, claims 11-24	1-124, 232-358

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/108181

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **349-358**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 349-358 are directed to the methods for treating diseases, but the report is based on the use of the compounds in the manufacture of medicaments for treating the corresponding diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/108181

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	110143949	A	20 August 2019	None			
WO	2018172984	A1	27 September 2018	AU	2018239542	A1	14 November 2019
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				EP	3310779	A1	25 April 2018
				US	2019185475	A1	20 June 2019
WO	2017156397	A1	14 September 2017	None			