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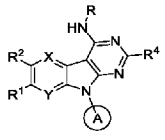
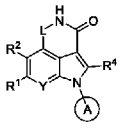
(54) Title: TRICYCLIC HETEROCYCLIC DERIVATIVES, COMPOSITIONS AND USES THEREOF



(IA) and



(IB).

(57) Abstract: Provided tricyclic heterocyclic derivatives as shown in Formulas (IA) and (IB), pharmaceutical compositions comprising them, a process for their preparation, and their use as therapeutic agents.

TRICYCLIC HETEROCYCLIC DERIVATIVES, COMPOSITIONS AND USES THEREOF

TECHNICAL FIELD

The present disclosure relates to tricyclic heterocyclic derivatives as inhibitor of PKMYT1. The present disclosure also relates to methods for preparing the tricyclic heterocyclic derivatives, pharmaceutical compositions, and their uses in the treatment of diseases related to the activity of PKMYT1 including, *e.g.,* cancers and other diseases.

BACKGROUND

Cell cycle is the essential way for cell division and growth regardless of either healthy cells or tumor cells. Generally, the cell cycle can be divided into four phases: pre-DNA synthesis (G1 phase), DNA synthesis (S phase), post-DNA synthesis (G2 phase), and mitosis (M phase). The progressions of cells from G1-phase into S-phase and G2-phase into M-phase (the mitotic phase) are very important stages for the repair of DNA damage as well as complex and active changes of various substances in cell. Cells set a series of cell-cycle checkpoints during the four phases to ensure the integrity of DNA replication and the completion of damage repair (Kevin J. Barnum, 2014). For some reason, if cells enter mitosis with compromised genomic material, it may happen for cells with cell cycle disorder, apoptosis, cancer and other malignant results. Additionally, because cancers also utilize cell cycle for tumor cell division, long-term accumulation of DNA damage unrepaired in the period of G1 to S-phase and G2 to M-phase will lead to mitotic catastrophe and tumor cell death.

The Protein Kinase, Membrane Associated Tyrosine/Threonine 1 (PKMYT1) is a cell cycle regulating protein which belongs to WEE family of kinases. PKMYT1 blocks the progression of cells from G2-phase into M-phase of the cell cycle through negatively regulating CDK1-Cyclin B complex. In the process of DNA damage repair, PKMYT1 phosphorylates CDK1 protein at amino acid sites of Tyr15 and Thr14 to maintain CDK1-Cyclin B complex in an inactive state in G2-phase and finally prevent cells entry into mitosis (Dongjun Jeong, 2018), which provides enough time for DNA damage repair. At the same time, Wee1 also involve in the CDK1 phosphorylation at amino acid site of Tyr15. PKMYT1 knockdown or inhibition can prompt cells to enter mitosis prematurely without completing DNA damage repair, leading to cell death.

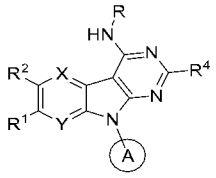
On the other hand, CCNE1 amplification can disrupt the regulation of cell entry into S phase, trigger DNA replication stress, and cause genome instability. CCNE1 amplification is prevalent in multiple tumor types, particularly in high-grade serous ovarian cancer, uterine tumor and gastro-oesophageal cancers, ranging in frequency from 5-40%. Cyclin E1, encoded by the CCNE1 gene,

promotes the transition of the cell cycle from G1-phase to S-phase by binding and activating cyclin-dependent protein kinase 2 (CDK2). In a genome screening study based on CRISPR technology, it was found that the high expression/amplification of CCNE1 and the inhibition of PKMYT1 have a high degree of synthetic lethal effect (David Gallo, 2022), that is excessively accelerated cycle transition make the cells lose the opportunity for adequate DNA damage repair and cause cell death. During normal cell cycles, Cyclin E1 levels are tightly regulated, accumulating at the G1/S transition and being completely degraded by the end of S phase. The Cyclin E1 degradation can be mediated by FBXW7, which is an E3 ubiquitin ligase (Chien-Hung Yeh, 2018). The loss-of-function mutation of FBXW7 will lead to the loss of its ubiquitination function to Cyclin E, such that Cyclin E cannot be degraded and thus overexpressed.

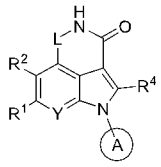
Therefore, PKMYT1 inhibitors can be used to treat tumors with certain genetic alterations using a synthetic lethality therapeutic strategy. The invention provides compounds, pharmaceutical compositions containing the same, methods of preparing the compounds, and methods of use. Compounds of the invention may be used to inhibit PKMYT1 in a cell with CCNE1 amplification, FBXW7 loss-of-function mutations or other genetic alterations driving DNA replication stress and genome instability in G1 to S phase progression. The subject may be in need of a treatment for a disease or condition, e.g., a disease or condition having a symptom of cell hyperproliferation, e.g., a cancer. The PKMYT1 inhibitory activity of the compounds disclosed herein is useful for treating a subject in need of a treatment for cancer.

SUMMARY

The present disclosure relates to, *inter alia*, compounds of Formula (IA) and (IB),



(IA) and



(IB);

or a pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, Isotopic variants or prodrugs thereof; wherein the variables are as defined below.

In another aspect, provided herein is a pharmaceutical composition comprising a compound of formula (IA) and (IB), or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, Isotopic variants or prodrugs thereof and at least one pharmaceutically acceptable carrier.

In another aspect, provided herein is a method of inhibiting PKMYT1 comprising:

contacting a PKMYT1 with a compound of formula (IA) and (IB), or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, Isotopic variants or prodrugs thereof.

In another aspect, provided herein is a method of treating cancers and other diseases comprising administering to a patient a therapeutically effective amount of a compound of formula (IA) and (IB), or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, Isotopic variants or prodrugs thereof.

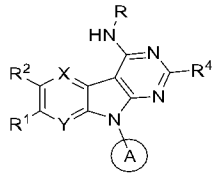
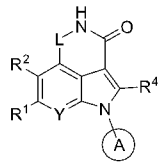
The details of one or more embodiments are set forth in the description below. Other features, objects, and advantages will be apparent from the description and from the claims.

DETAILED DESCRIPTION

The present disclosure may be more fully appreciated by reference to the following description, including the following definitions and examples. Certain features of the disclosed compositions and methods which are described herein in the context of separate aspects, may also be provided in combination in a single aspect. Alternatively, various features of the disclosed compositions and methods that are, for brevity, described in the context of a single aspect, may also be provided separately or in any sub-combination.

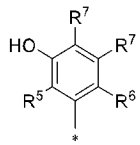
Before the present invention is further described, it is to be understood that the invention is not limited to the particular embodiments set forth herein, and it is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

The present disclosure provides, *inter alia,* a compound of formula (IA) and (IB):


(IA) and

(IB);

or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variants or prodrugs thereof, wherein:

ring A is selected from: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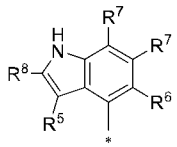
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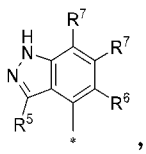
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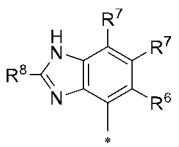
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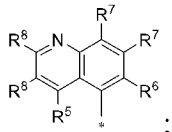

;

X is N or CR^3;

Y is N or CR^9;

L is $(CR^{10}R^{11})_n$, $NR^{12}(CH_2CH_2)_m$, or $O(CH_2CH_2)_m$;

n is 1, 2 or 3; m is 0 or 1;

R is selected from H, D or C_1-C_6 alkyl optionally substituted with F, OH or CN;

R^1, R^2 and R^3 are each independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

or R^1 and R^2 together with the carbon atoms to which they are attached form a C_3-C_7 cycloalkyl, or 4-7 membered heterocycloalkyl, wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

or R^2 and R^3 together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl, or 4-7 membered heterocycloalkyl, wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

each R^4 is independently selected from H, D, NH_2, CN, C_1-C_3 alkyl optionally substituted with D, halogen or CN;

each R^5 is independently selected from H, D, halo, CN, C_1-C_6 alkyl optionally substituted with D, halogen or CN;

each R^6 is independently selected from H, D, halo, CN, OR^B, SF_5, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl is optionally substituted with D, halo, CN, NH_2, OH, -O-C_1-C_6 alkyl, -OC_1-C_6 haloalkyl;

each R^7 is independently selected from H, D, halogen, Me, CF_3, OH, OMe, OCF_3;

each R^8 is independently selected from H, D, CN, SF_5, C_1-C_6 alkyl optionally substituted with D, halogen or CN;

R^9 is selected from H, D, CN, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_3-C_5 cycloalkyl;

R^{10} and R^{11} are each independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, CN, halo, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $NR^cS(O)_2R^b$, or $NR^cS(O)_2NR^cR^d$;

or R^{10} and R^{11} together with the carbon atom(s) to which they are attached form a C_3-C_7 cycloalkyl, or 4-7 membered heterocycloalkyl, wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, or $NR^cS(O)_2NR^cR^d$;

R^{12} is H, D, C_1-C_3 alkyl optionally substituted with D, OH, halogen, CN;

each R^A is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^e)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

each R^B is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $C(O)R^b$,

$OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$;

R^C and R^D are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$;

or R^C and R^D together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, oxo, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, or C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, or OC_1-C_4 haloalkyl;

each R^a is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

each R^b is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl;

R^c and R^d are each independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10}

aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-5-10 membered heteroaryl, C_6-C_{10} aryl-C_6-C_{10} aryl, 5-10 membered heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C_6-C_{10} aryl, or 5-10 membered heteroaryl-5-10 membered heteroaryl; wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10} aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-5-10 membered heteroaryl, C_6-C_{10} aryl-C_6-C_{10} aryl, 5-10 membered heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C_6-C_{10} aryl, or 5-10 membered heteroaryl-5-10 membered heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C(O)OR^{a1}, C(O)R^{b1}, S(O)$_2$$R^{b1}$, C_1-C_4 alkyl-O-C_1-C_4 alkyl, and C_1-C_4 alkyl-O-C_1-C_4 alkyl-O-;

or R^c and R^d together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C(O)OR^{a1}, C(O)R^{b1}, S(O)$_2$$R^{b1}$, C_1-C_4 alkoxy-C_1-C_4 alkyl, and C_1-C_4 alkoxy-C_1-C_4 alkoxy;

each R^e is independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, (C_1-C_4 alkoxy)-C_1-C_4 alkyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkyl, C_3-C_{10} cycloalkyl-C_1-C_4 alkyl, 5-10 membered heteroaryl-C_1-C_4 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_4 alkyl;

each R^f is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, or 4-10 membered heterocycloalkyl;

each R^{a1} is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

each R^{b1} is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alky; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10

membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alky is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl.

In some embodiments, R is selected from H, D or C_1-C_6 alkyl optionally substituted with F, OH or CN. In some embodiments, R is H. In some embodiments, R is D. In some embodiments, R is C_1-C_6 alkyl optionally substituted with F, OH or CN. In some embodiments, R is Me.

In some embodiments, X is N.

In some embodiments, X is CR^3.

In some embodiments, R^3 is independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, for example, but not limited to, R^3 is independently selected from H, D, halo, CN, SF_5, NH_2, OH, OCH_3, OCH_2CH_3, $NHCH_3$, $NHCH_2CH_3$, $N(CH_3)_2$, CH_3, CH_2CH_3, CF_3, CH_2CF_3, $C(O)R^B$, or $C(O)NR^CR^D$.

In some embodiments, Y is N.

In some embodiments, Y is CR^9, and R^9 is selected from H, D, CN, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_3-C_5 cycloalkyl.

In some embodiments, R^9 is H. In some embodiments, R^9 is D. In some embodiments, R^9 is CN. In some embodiments, R^9 is halogen (such as F, Cl, Br, I). In some embodiments, R^9 is C_1-C_4 alkyl. In some embodiments, R^9 is C_1-C_4 haloalkyl. In some embodiments, R^9 is OC_1-C_4 alkyl. In some embodiments, R^9 is OC_1-C_4 haloalkyl. In some embodiments, R^9 is C_3-C_5 cycloalkyl.

In some embodiments, R^1 is independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, L is $(CR^{10}R^{11})_n$, $NR^{12}(CH_2CH_2)_m$, or $O(CH_2CH_2)_m$.

In some embodiments, L is $(CR^{10}R^{11})_n$. In some embodiments, L is $CR^{10}R^{11}$. In some embodiments, L is $(CR^{10}R^{11})_2$. In some embodiments, L is $(CR^{10}R^{11})_3$.

In some embodiments, L is $NR^{12}(CH_2CH_2)_m$. In some embodiments, L is NR^{12}. In some embodiments, L is $NR^{12}CH_2CH_2$.

In some embodiments, L is $O(CH_2CH_2)_m$. In some embodiments, L is O. In some embodiments, L is OCH_2CH_2.

In some embodiments, R^1 is independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^1 is independently selected from H, D, halo, CN, SF_5, OH, NH_2, OCH_3, OCH_2CH_3, $NHCH_3$, $NHCH_2CH_3$, $N(CH_3)_2$, CH_3, CH_2CH_3, CF_3, CH_2CF_3, $C(O)R^B$, $C(O)NR^CR^D$. In some embodiments, R^2 is independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl or 4-10 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_{10} cycloalkyl or 4-10 membered heterocycloalkyl is optionally substituted with 1, 2, or 3

substituents independently selected from D, OH, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^2 is independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, for example, but not limited to, R^2 is independently selected from H, D, halo, CN, SF_5, OH, NH_2, OCH_3, OCH_2CH_3, $NHCH_3$, $NHCH_2CH_3$, $N(CH_3)_2$, CH_3, CH_2CH_3, CF_3, CH_2CF_3, $C(O)R^B$, $C(O)NR^CR^D$.

In some embodiments, R^1 and R^2 together with the carbon atoms to which they are attached form a C_3-C_7 cycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^1 and R^2 together with the carbon atoms to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^2 and R^3 together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^2 and R^3 together with the carbon atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently

selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^cR^f$, $P(O)OR^cOR^f$, $OP(O)OR^cOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, each R^4 is independently selected from H, D, NH_2, or CN. In some embodiments, R^4 is H. In some embodiments, R^4 is D. In some embodiments, R^4 is NH_2. In some embodiments, R^4 is CN.

In some embodiments, R^4 is C_1-C_3 alkyl optionally substituted with D, halogen or CN. In some embodiments, R^4 is Me. In some embodiments, R^4 is CD_3. In some embodiments, R^4 is CF_3.

In some embodiments, each R^5 is independently selected from H, D, halo, CN or C_1-C_6 alkyl optionally substituted with D, halogen or CN.

In some embodiments, R^5 is H. In some embodiments, R^5 is D. In some embodiments, R^5 is halo (such as F, Cl, Br, I). In some embodiments, R^5 is CN. In some embodiments, R^5 is C_1-C_6 alkyl optionally substituted with D, halogen or CN.

In some embodiments, for example, but not limited to, each R^5 is independently selected from H, D, halo, CN, CH_3, CD_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CH_2OH, CH_2CH_2OH.

In some embodiments, each R^6 is independently selected from H, D, halo, CN, SF_5, OR^B, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl optionally substituted with D, halo, CN, NH_2, OH, -O-C_1-C_6 alkyl, -OC_1-C_6 haloalkyl.

In some embodiments, for example, but not limited to, R^6 is H, D, halo, CN, CH_3, CD_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CH_2OH, CH_2CH_2OH or cyclopropyl.

In some embodiments, each R^7 is independently selected from H, D, halogen, Me, CF_3, OH, OMe, OCF_3.

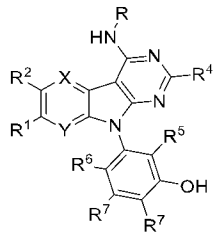
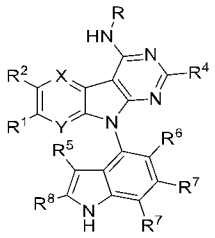
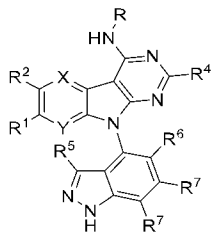
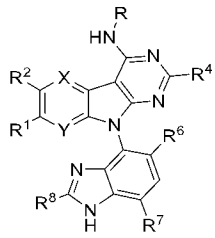
In some embodiments, R^7 is H. In some embodiments, R^7 is D. In some embodiments, R^7 is halogen (such as F, Cl, Br or I). In some embodiments, R^7 is OH. In some embodiments, R^7 is OMe.

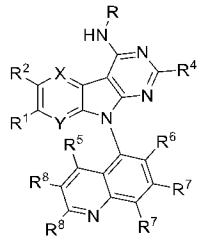
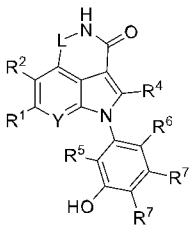
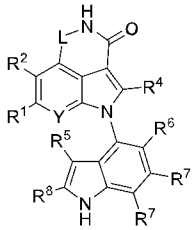
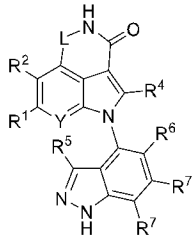
In some embodiments, each R^8 is independently selected from H, D, CN, SF_5, C_1-C_6 alkyl optionally substituted with D, halogen or CN.

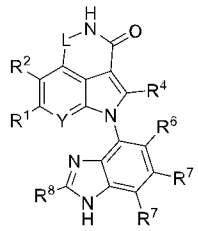
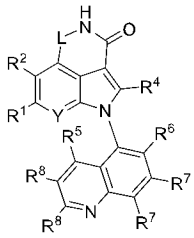
In some embodiments, R^8 is H. In some embodiments, R^8 is D. In some embodiments, R^8 is CN. In some embodiments, R^8 is SF_5.

In some embodiments, R^8 is C_1-C_6 alkyl optionally substituted with D, halogen or CN. In some embodiments, for example, but not limited to, R^8 is CH_3, CD_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3.

In some embodiments, the compound of formula (IA) and (IB) is represented by the compound of formula (IAa), (IAb), (IAc), (IAd), (IAe), (IBa), (IBb), (IBc), (IBd), or (IBe):

 (IAa),  (IAb),  (IAc),  (IAd),

 (IAe),  (IBa),  (IBb),  (IBc),

 (IBd), or  (IBe);

or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variants or prodrugs thereof; wherein X, Y, L, R, R^1, R^2, R^4, R^5, R^6, R^7, R^8 are defined with respect to Formula (IA) and (IB).

In some embodiments, L is $(CR^{10}R^{11})_n$, $NR^{12}(CH_2CH_2)_m$, or $O(CH_2CH_2)_m$.

In some embodiments, L is $(CR^{10}R^{11})_n$. In some embodiments, L is $CR^{10}R^{11}$. In some embodiments, L is $(CR^{10}R^{11})_2$. In some embodiments, L is $(CR^{10}R^{11})_3$.

In some embodiments, L is $NR^{12}(CH_2CH_2)_m$. In some embodiments, L is NR^{12}. In some embodiments, L is $NR^{12}CH_2CH_2$.

In some embodiments, L is $O(CH_2CH_2)_m$. In some embodiments, L is O. In some embodiments, L is OCH_2CH_2.

In some embodiments, R is selected from H, D or C_1-C_6 alkyl optionally substituted with F, OH or CN. In some embodiments, R is H. In some embodiments, R is D. In some embodiments, R is Me.

In some embodiments, R^4 is selected from H, D, NH_2, or CN. In some embodiments, R^4 is H. In some embodiments, R^4 is D. In some embodiments, R^4 is NH_2. In some embodiments, R^4 is CN.

In some embodiments, R^4 is C_1-C_3 alkyl optionally substituted with D, halogen or CN. In some embodiments, R^4 is Me. In some embodiments, R^4 is CD_3. In some embodiments, R^4 is CF_3.

In some embodiments, R^5 is selected from H, D, halo, or CN. In some embodiments, R^5 is H. In some embodiments, R^5 is D. In some embodiments, R^5 is CN. In some embodiments, R^5 is F. In some embodiments, R^5 is Cl.

In some embodiments, R^5 is C_1-C_6 alkyl optionally substituted with D, halogen or CN. In some embodiments, R^5 is Me. In some embodiments, R^5 is CD_3. In some embodiments, R^5 is CF_3.

In some embodiments, R^6 is selected from H, D, halo, CN, SF_5, OR^B. In some embodiments, R^6 is H. In some embodiments, R^6 is D. In some embodiments, R^6 is CN. In some embodiments, R^6 is F. In some embodiments, R^6 is Cl. In some embodiments, R^6 is Br. In some embodiments, R^6 is SF_5.

In some embodiments, R^6 is C_1-C_6 alkyl optionally substituted with D, halo, CN, NH_2, OH, -O-C_1-C_6 alkyl, -OC_1-C_6 haloalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 4-7 membered heterocycloalkyl. In some embodiments, R^6 is Me. In some embodiments, R^6 is CD_3. In some embodiments, R^6 is CF_3. In some embodiments, R^6 is cyclopropyl.

In some embodiments, R^7 is H. In some embodiments, R^7 is D.

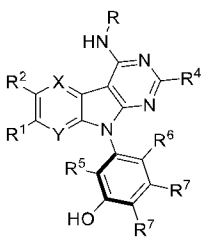
In some embodiments, R^7 is halogen. In some embodiments, R^7 is F. In some embodiments, R^7 is Cl.

In some embodiments, R^7 is OH. In some embodiments, R^7 is OMe.

In some embodiments, R^8 is selected from H, D, CN, SF_5. In some embodiments, R^8 is H. In some embodiments, R^8 is D. In some embodiments, R^8 is CN. In some embodiments, R^8 is SF_5.

In some embodiments, R^8 is C_1-C_6 alkyl optionally substituted with D, halogen or CN. In some embodiments, R^8 is Me. In some embodiments, R^8 is CD_3. In some embodiments, R^8 is CF_3.

In some embodiments, the compound of formula (IA) and (IB) is represented by the compound of formula (IIAa), (IIAb), (IIAc), (IIAd), (IIAe), (IIBa), (IIBb), (IIBc), (IIBd), or (IIBe):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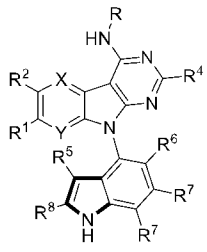
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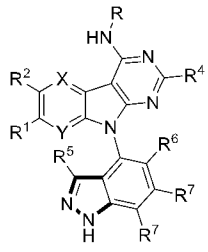
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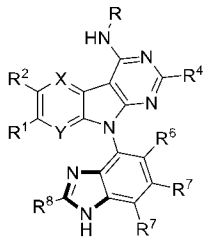
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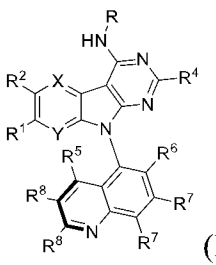
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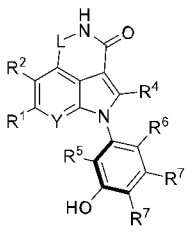
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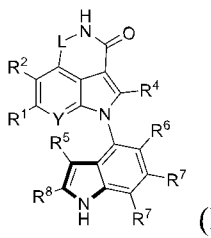
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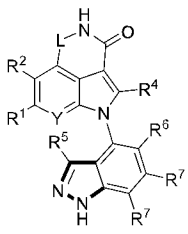
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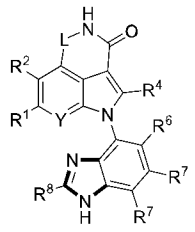
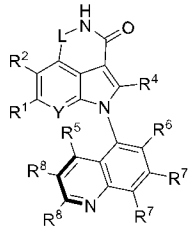
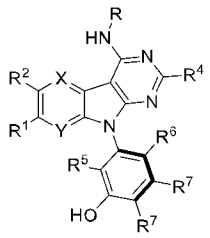
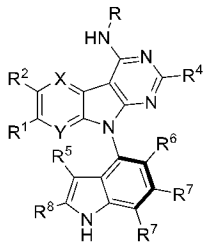
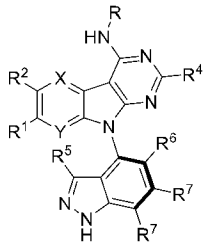
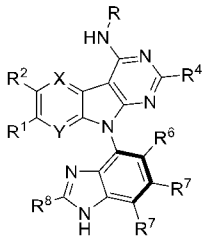
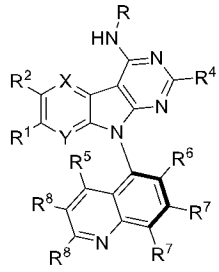
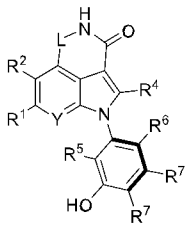
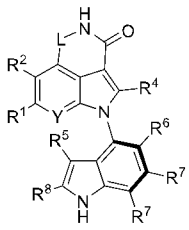
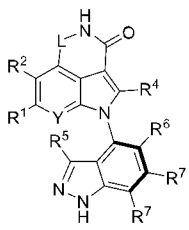
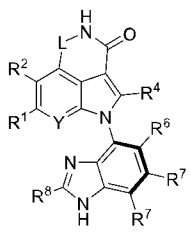
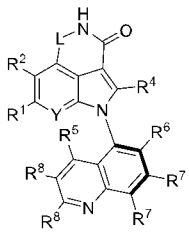
 (IIBd), or  (IIBe);

or pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, isotopic variants or prodrugs thereof; wherein X, Y, L, R, R^1, R^2, R^4, R^5, R^6, R^7, R^8 are defined with respect to Formula (IA) and (IB).

In some embodiments, the compound of formula (IA) and (IB) is represented by the compound of formula (IIIAa), (IIIAb), (IIIAc), (IIIAd), (IIIAe), (IIIBa), (IIIBb), (IIIBc), (IIIBd), or (IIIBe):

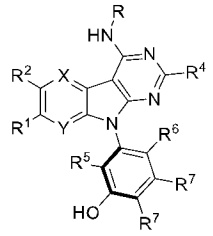
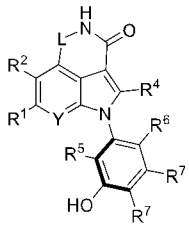
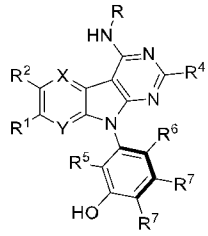
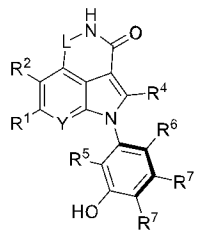
 (IIIAa),  (IIIAb),  (IIIAc),  (IIIAd),

 (IIIAe),  (IIIBa),  (IIIBb),  (IIIBc),

 (IIIBd), or  (IIIBe);

or pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, Isotopic variants or prodrugs thereof; wherein X, Y, L, R, R^1, R^2, R^4, R^5, R^6, R^7, R^8 are defined with respect to Formula (IA) and (IB).

In some embodiments, the compound of formula (IA) and (IB) is represented by the compound of formula (IIAa), (IIBa), (IIIAa), (IIIBa):


(IIAa),

(IIBa),

(IIIAa),

(IIIBa);

or pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, isotopic variants or prodrugs thereof; wherein X, Y, L, R, R^1, R^2, R^4, R^5, R^6, R^7 are defined with respect to Formula (IA) and (IB).

In some embodiments, L is $(CR^{10}R^{11})_n$, $NR^{12}(CH_2CH_2)_m$, or $O(CH_2CH_2)_m$.

In some embodiments, L is $(CR^{10}R^{11})_n$. In some embodiments, L is $CR^{10}R^{11}$. In some embodiments, L is $(CR^{10}R^{11})_2$. In some embodiments, L is $(CR^{10}R^{11})_3$.

In some embodiments, L is $NR^{12}(CH_2CH_2)_m$. In some embodiments, L is NR^{12}. In some embodiments, L is $NR^{12}CH_2CH_2$.

In some embodiments, L is $O(CH_2CH_2)_m$. In some embodiments, L is O. In some embodiments, L is OCH_2CH_2.

In some embodiments, R is selected from H, D or C_1-C_6 alkyl optionally substituted with F, OH or CN. In some embodiments, R is H. In some embodiments, R is D. In some embodiments, R is Me.

In some embodiments, R^4 is selected from H, D, NH_2, or CN. In some embodiments, R^4 is H. In some embodiments, R^4 is D. In some embodiments, R^4 is NH_2. In some embodiments, R^4 is CN.

In some embodiments, R^4 is C_1-C_3 alkyl optionally substituted with D, halogen or CN. In some embodiments, R^4 is Me. In some embodiments, R^4 is CD_3. In some embodiments, R^4 is CF_3.

In some embodiments, R^5 is selected from H, D, halo, or CN. In some embodiments, R^5 is H. In some embodiments, R^5 is D. In some embodiments, R^5 is CN. In some embodiments, R^5 is F. In some embodiments, R^5 is Cl.

In some embodiments, R^5 is C_1-C_6 alkyl optionally substituted with D, halogen or CN. In some embodiments, R^5 is Me. In some embodiments, R^5 is CD_3. In some embodiments, R^5 is CF_3.

In some embodiments, R^6 is selected from H, D, halo, CN, SF_5, OR^B. In some embodiments, R^6 is H. In some embodiments, R^6 is D. In some embodiments, R^6 is CN. In some embodiments, R^6 is F. In some embodiments, R^6 is Cl. In some embodiments, R^6 is Br. In some embodiments, R^6 is SF_5.

In some embodiments, R^6 is C_1-C_6 alkyl optionally substituted with at least one of D, halo, CN, NH_2, OH, -O-C_1-C_6 alkyl, -OC_1-C_6 haloalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted 4-7 membered heterocycloalkyl. In some embodiments, R^6 is Me. In some embodiments, R^6 is CD_3. In some embodiments, R^6 is CF_3. In some embodiments, R^6 is cyclopropyl.

In some embodiments, R^7 is H. In some embodiments, R^7 is D.

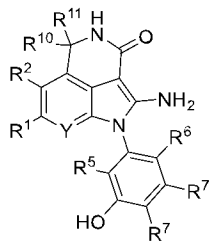
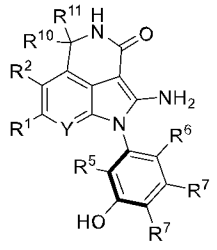
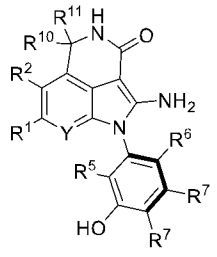
In some embodiments, R^7 is halogen. In some embodiments, F. In some embodiments, Cl.

In some embodiments, R^7 is OH. In some embodiments, R^7 is OMe.

In some embodiments, R^8 is selected from H, D, CN, SF_5. In some embodiments, R^8 is H. In some embodiments, R^8 is D. In some embodiments, R^8 is CN. In some embodiments, R^8 is SF_5.

In some embodiments, R^8 is C_1-C_6 alkyl optionally substituted with D, halogen or CN. In some embodiments, R^8 is Me. In some embodiments, R^8 is CD_3. In some embodiments, R^8 is CF_3.

In some embodiments, the compound of formula (IB) is represented by the compound of formula (IVBa), (IVBb), or (IVBc):


(IVBa),

(IVBb), or

(IVBc);

or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variant or prodrugs thereof; wherein Y, R^1, R^2, R^5, R^6, R^7, R^{10}, R^{11} are defined with respect to Formula (IB).

In compounds of Formula (IA) and (IB), each R^A is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^A is independently selected from H. In some embodiments, R^A is independently selected from D.

In some embodiments, R^A is independently selected from C_1-C_6 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl, wherein the C_1-C_6 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$.

In other embodiments, R^A is independently selected from C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^cOR^f$, $OP(O)OR^cOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$.

In compounds of Formula (IA) and (IB), each R^B is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, R^B is independently selected from H. In some embodiments, R^B is independently selected from D.

In some embodiments, R^B is C_1-C_6 alkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$. In some embodiments, R^B is C_1-C_6 alkyl.

In some embodiments, R^B is isopropyl, isobutyl, tert-butyl; each is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl. In some embodiments, R^B is isopropyl. In some embodiments, R^B is isobutyl. In some embodiments, R^B is tert-butyl.

In some embodiments, R^B is C_2-C_6 alkynyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, R^B is C_2-C_6 alkenyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, R^B is C_3-C_{10} cycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, R^B is cyclopropyl, cyclobutyl, cycylopentyl, cyclohexanyl; each is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl.

In other embodiments, R^B is 4-10 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, R^B is azetidinyl, pyrrolidinyl, piperidinyl or azepanyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In other embodiments, R^B is C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $C(O)R^b$,

$OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, each R^C is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, each R^C is independently selected from H. In some embodiments, each R^C is independently selected from D.

In some embodiments, each R^C is independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; each is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, each R^C is independently selected from C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; each is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, each R^D is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $OC(O)NR^cR^d$,

NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, each R^D is independently selected from H. In some embodiments, each R^D is independently selected from D.

In some embodiments, each R^D is independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; each is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, each R^D is independently selected from C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; each is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In other embodiments, R^C and R^D together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, oxo, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, or OC_1-C_4 haloalkyl.

In some embodiments, each R^a is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy.

In some embodiments, each R^b is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl.

In some embodiments, R^c and R^d are each independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10} aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-5-10 membered heteroaryl, C_6-C_{10} aryl-C_6-C_{10} aryl, 5-10 membered heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C_6-C_{10} aryl, or 5-10 membered heteroaryl-5-10 membered heteroaryl; wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10} aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-5-10 membered heteroaryl, C_6-C_{10} aryl-C_6-C_{10} aryl, 5-10 membered heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C_6-C_{10} aryl, or 5-10 membered heteroaryl-5-10 membered heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, $C(O)OR^{a1}$, $C(O)R^{b1}$, $S(O)_2R^{b1}$, C_1-C_4 alkyl-O-C_1-C_4 alkyl, and C_1-C_4 alkyl-O-C_1-C_4 alkyl-O-.

In some embodiments, R^c and R^d together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, $C(O)OR^{a1}$, $C(O)R^{b1}$, $S(O)_2R^{b1}$, C_1-C_4 alkoxy-C_1-C_4 alkyl, and C_1-C_4 alkoxy-C_1-C_4 alkoxy.

In some embodiments, each R^e is each independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, (C_1-C_4 alkoxy)-C_1-C_4 alkyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkyl, C_3-C_{10} cycloalkyl-C_1-C_4 alkyl, 5-10 membered heteroaryl-C_1-C_4 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_4 alkyl.

In some embodiments, each R^f is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl.

In some embodiments, each R^{a1} is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents

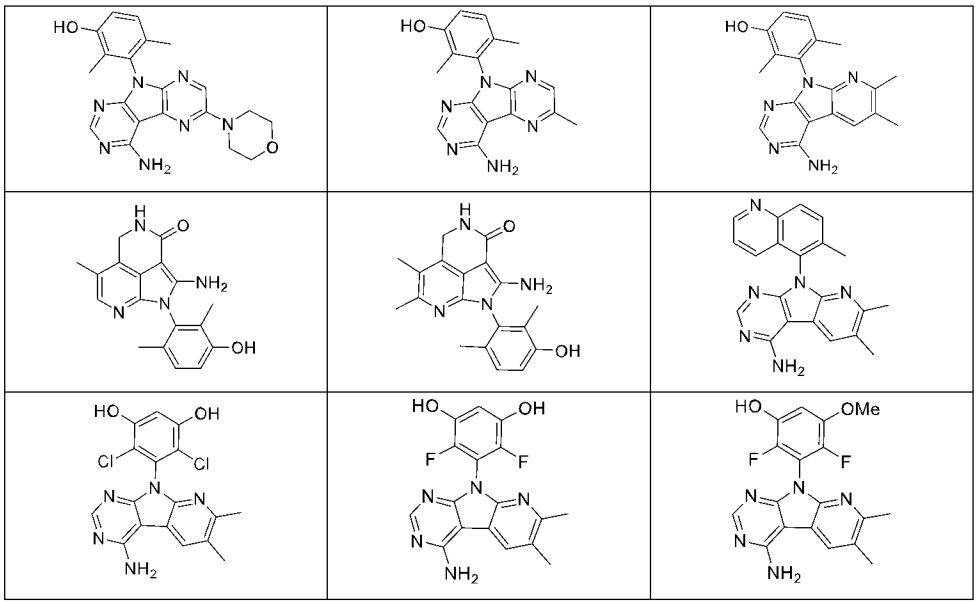
independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy.

In some embodiments, each R^{b1} is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alky; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alky is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl.

In some embodiments, the compounds of Formula (IA) and (IB) are the pharmaceutically acceptable salts. In some embodiments, the compounds of Formula (IA) and (IB) are stereoisomers. In some embodiments, the compounds of Formula (IA) and (IB) are solvates. In some embodiments, the compounds of Formula (IA) and (IB) are N-oxides of the compounds of Formula (IA) and (IB).

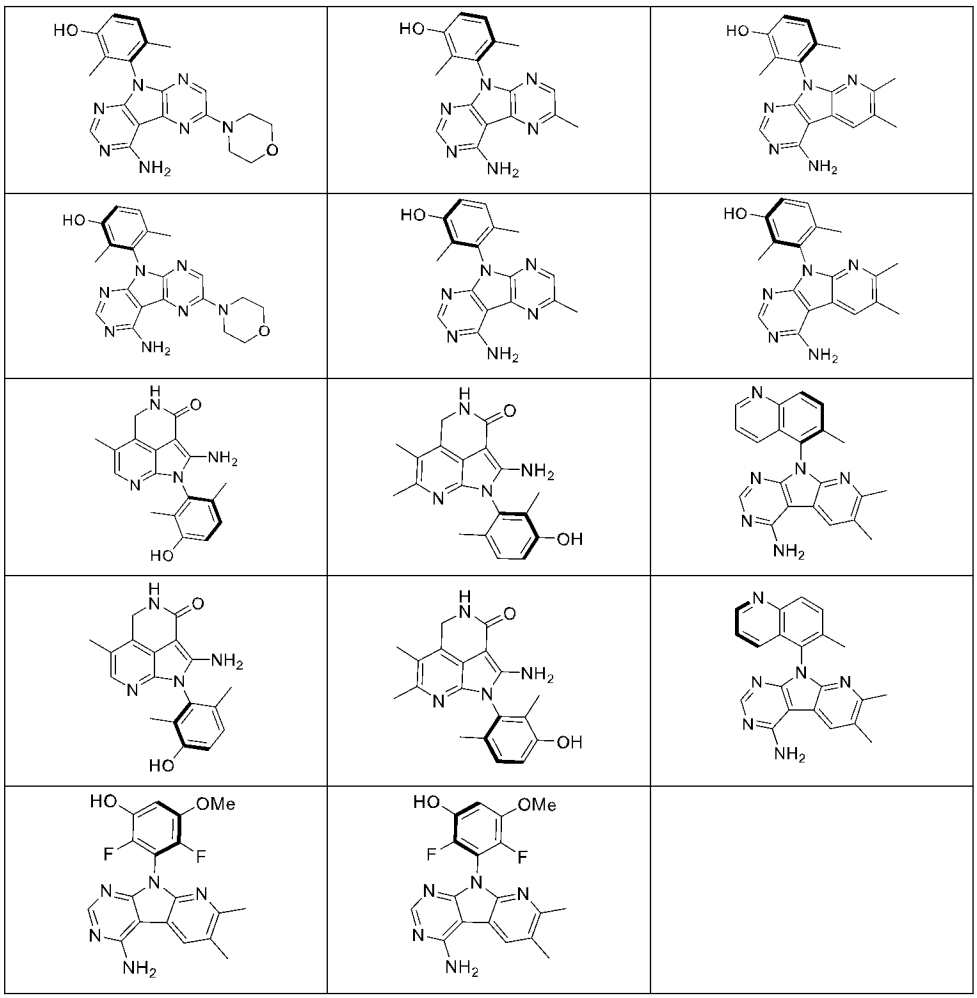
Stereoisomers of the compounds of Formula (IA) and (IB), and the pharmaceutical salts and solvates thereof, are also contemplated, described, and encompassed herein. Methods of using compounds of Formula (IA) and (IB) are described, as well as pharmaceutical compositions including the compounds of Formula (IA) and (IB).

In some embodiments, the compound of Formula (IA) and (IB) is:



or a pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variants or prodrugs thereof.

In some embodiments, the compound of Formula (IA) and (IB) is:



or a pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variants or prodrugs thereof.

It will be apparent that the compounds of Formula (IA) and (IB), including all subgenera described herein, may have multiple stereogenic centers. As a result, there exist multiple stereoisomers (enantiomers and diastereomers) of the compounds of Formula (IA) and (IB) (and subgenera described herein). The present disclosure contemplates and encompasses each stereoisomer of any compound of Formula (IA) and (IB) (and subgenera described herein), as well as mixtures of said stereoisomers.

Pharmaceutically acceptable salts and solvates of the compounds of Formula (IA) and (IB) (including all subgenera described herein) are also within the scope of the disclosure.

Isotopic variants of the compounds of Formula (IA) and (IB) (including all subgenera described herein) are also contemplated by the present disclosure.

The present disclosure further provides compounds described herein, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein. The present disclosure further

provides uses of a compound described herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in any of the methods described herein.

The present disclosure further provides pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention provides a method of inhibiting PKMYT1 in a cell expressing PKMYT1, the method comprising contacting the cell with the compound disclosed herein.

In some embodiments, the cell is associated with CCNE1 amplification, FBXW7 loss-of-function mutations or other genetic alterations which depend on PKMYT1. In some embodiments, the cell is in a subject.

The invention provides a method of treating a subject in need thereof comprising administering to the subject the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein.

In some embodiments, the subject is suffering from, and is in need of a treatment for, a disease or condition having the symptom of cell hyperproliferation. In some embodiments, the disease or condition is a cancer. In some embodiments, the cancer is a cancer with CCNE1 amplification, FBXW7 loss-of-function mutations or other genetic alterations which depend on PKMYT1.

Routs of administration for the compounds in the present disclosure include, but not limited to oral, injection, topical and inhalation.

Definitions

Unless other indicated, the following terms are intended to have the meaning set forth below. Other terms are defined elsewhere throughout the specification.

As used herein, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology such as "solely", "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

At various places in the present specification, variables defining divalent linking groups are described. It is specifically intended that each linking substituent include both the forward and backward forms of the linking substituent. For example, -NR(CR'R")- includes both -NR(CR'R")- and -(CR'R")NR- and is intended to disclose each of the forms individually. Where the structure requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable lists "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted", unless otherwise indicated, refers to any level of substitution, *e.g.,* mono-, di-, tri-, tetra- or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. The phrase "optionally substituted" means unsubstituted or substituted. The term "substituted" means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.,* oxo, can replace two hydrogen atoms.

The term "Cn-Cm" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. For example, the term "C_1-C_6 alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl. "C_0 alkyl" refers to a covalent bond.

It is further intended that the compounds of the invention are stable. As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable sub-combination.

As used herein, unless otherwise indicated, the term "alkyl", by itself or as part of another substituent, is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms. Similary, $C_{1\text{-}8}$, as in $C_{1\text{-}8}$ alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms in a linear or branched arrangement. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, neopentyl), and the like.

As used herein, unless otherwise indicated, "alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds. Example alkenyl groups include, but are not limited to, ethenyl, propenyl, and the like.

As used herein, unless otherwise indicated, "alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds. Example alkynyl groups include, but are not limited to, ethynyl, propynyl, and the like.

As used herein, unless otherwise indicated, "haloalkyl" refers to an alkyl group having one or more halogen substituents. Example haloalkyl groups include, but are not limited to, CF_3, C_2F_5, CHF_2, CH_2F, CCl_3, $CHCl_2$, C_2Cl_5, and the like.

As used herein, unless otherwise indicated, "aryl" refers to an unsubstituted or substituted monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons. In some embodiments, aryl groups have from 6 to about 20 carbon atoms. In some embodiments, aryl groups have from 6 to about 14 carbon atoms. In some embodiments, aryl groups have from 6 to about 10 carbon atoms. Example aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like.

As used herein, unless otherwise indicated, "cycloalkyl" refers to an unsubstituted or substituted non-aromatic carbocycles including cyclized alkyl, alkenyl, and alkynyl groups. Cycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) ring systems, including fused rings, spirocyclic rings, and bridged rings (*e.g.*, a bridged bicycloalkyl group). In some embodiments, cycloalkyl groups can have from 3 to about 20 carbon atoms, 3 to about 14 carbon atoms, 3 to about 10 carbon atoms, or 3 to 7 carbon atoms. Cycloalkyl groups can further have 0, 1, 2, or 3 double bonds and/or 0, 1, or 2 triple bonds. Cycloalkyl groups can be optionally substituted by oxo or sulfido (e.g., -C(O)- or -C(S)-). Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of pentane, pentene, hexane, and the like. A cycloalkyl group having one or more fused aromatic rings can be attached though either the aromatic or non-aromatic portion. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized, for example, having an oxo or sulfido substituent. In some embodiments, the cycloalkyl is a C_3-C_7 monocyclic cycloalkyl. In some embodiments, the cycloalkyl is a C_4-C_{10} spirocycle or bridged cycloalkyl. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, cubane, adamantane, bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[2.2.2]octanyl, spiro[3.3]heptanyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, cycloalkyl are cyclic-containing, non-aromatic hydrocarbon groups having from 3 to 12 carbon atoms ("C_3-C_{12}"), preferably from 3 to 6 carbon atoms ("C_3-C_6"). Examples of cycloalkyl groups include, for example, cyclopropyl (C_3; 3-membered), cyclobutyl (C_4; 4-membered), cyclopropylmethyl (C_4), cyclopentyl (C_5), cyclohexyl (C_6), 1-methylcyclopropyl (C_4), 2-methylcyclopentyl (C_4), adamantanyl (C_{10}), and the like.

The term "spirocycloalkyl" when used alone or as part of a substituent group refers to a non-aromatic hydrocarbon group containing two cycloalkyl rings, and wherein the two cycloalyl rings share a single carbon atom in common.

As used herein, unless otherwise indicated, a "heteroaryl" group refers to an unsubstituted or substituted aromatic heterocycle having at least one heteroatom ring member such as boron, sulfur, oxygen, or nitrogen. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused

rings) systems. Any ring-forming N atom in a heteroaryl group can also be oxidized to form an N-oxo moiety. Examples of heteroaryl groups include without limitation, pyridyl, N-oxopyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, unless otherwise indicated, "heterocycloalkyl" refers to an unsubstituted or substituted monocyclic (saturated or partially unsaturated ring) or polycyclic heterocycles having at least one non-aromatic ring (saturated or partially unsaturated ring), wherein one or more of the ring-forming carbon atoms of the heterocycloalkyl is replaced by a heteroatom selected from N, O, S and B, and wherein the ring-forming carbon atoms and heteroatoms of the heterocycloalkyl group can be optionally substituted by one or more oxo or sulfido (e.g., C(O), S(O), C(S), or $S(O)_2$, etc.). Heterocycloalkyl groups include monocyclic and polycyclic (e.g., having 2 fused rings) systems. Included in heterocycloalkyl are monocyclic and polycyclic 3-10, 4-10, 3-7, 4-7, and 5-6 membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles and bridged rings (e.g., a 5-10 membered bridged biheterocycloalkyl ring having one or more of the ring-forming carbon atoms replaced by a heteroatom independently selected from N, O, S and B). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds.

Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the non-aromatic heterocyclic ring, for example, benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring- forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl group contains 3 to 10 ring-forming atoms, 4 to 10 ring- forming atoms, 3 to 7 ring-forming atoms, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to 4 heteroatoms, 1 to 3 heteroatoms, 1 to 2 heteroatoms or 1 heteroatom. In some embodiments, the heterocycloalkyl is a monocyclic 4-6 membered heterocycloalkyl having 1 or 2 heteroatoms independently selected from N, O, S and B and having one or more oxidized ring members.

Example heterocycloalkyl groups include, but are not limited to, pyrrolidin-2-one, 1,3-isoxazolidin-2-one, pyranyl, tetrahydropyran, oxetanyl, azetidinyl, morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl,

isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl, benzazapene, 1,2,3,4-tetrahydroisoquinoline, azabicyclo[3.1.0]hexanyl, diazabicyclo[3.1.0]hexanyl, oxabicyclo[2.1.1]hexanyl, azabicyclo[2.2.1]heptanyl, diazabicyclo[2.2.1]heptanyl, azabicyclo[3.1.1]heptanyl, diazabicyclo[3.1.1]heptanyl, azabicyclo[3.2.1]octanyl, diazabicyclo[3.2.1]octanyl, oxabicyclo[2.2.2]octanyl, azabicyclo[2.2.2]octanyl, diazabicyclo[2.2.2]octanyl, azaadamantanyl, diazaadamantanyl, oxa-adamantanyl, azaspiro[3.3]heptanyl, diazaspiro[3.3]heptanyl, oxa-azaspiro[3.3]heptanyl, azaspiro[3.4]octanyl, diazaspiro[3.4]octanyl, oxa-azaspiro[3.4]octanyl, oxa-azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, diazaspiro[2.5]octanyl, azaspiro[4.4]nonanyl, diazaspiro[4.4]nonanyl, oxa-azaspiro[4.4]nonanyl, azaspiro[4.5]decanyl, diazaspiro[4.5]decanyl, diazaspiro[4.4]nonanyl, oxa-diazaspiro[4.4]nonanyl, octahydropyrrolo[3,4-c]pyrrolyl and the like.

In some embodiments, heterocycloalkyl refers to any three to ten membered monocyclic or bicyclic, saturated ring structure containing at least one heteroatom selected from the group consisting of O, N and S. The heterocycloalkyl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure. Examples of suitable heterocycloalkyl groups include, but are not limited to, azepanyl, aziridinyl, azetidinyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, pyrazolidinyl, piperazinyl, piperidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, oxazepanyl, oxiranyl, oxetanyl, quinuclidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperazinyl, and the like.

In some embodiments, the term "spiroheterocycloalkyl" when used alone or as part of a substituent group refers to a non-aromatic group containing two rings, at least one of which is a heterocycloalkyl ring, and wherein the two rings share a single carbon atom in common.

As used herein, unless otherwise indicated, "arylcycloalkyl" refers to cycloalkyl group substituted by an aryl group.

As used herein, unless otherwise indicated, "arylheterocycloalkyl" refers to a heterocycloalkyl group substituted by an aryl group.

As used herein, unless otherwise indicated, "arylheteroaryl" refers to a heteroaryl group substituted by an aryl group.

As used herein, unless otherwise indicated, "biaryl" refers to an aryl group substituted by another aryl group.

As used herein, unless otherwise indicated, "heteroarylcycloalkyl" refers to a cycloalkyl group substituted by a heteroaryl group.

As used herein, unless otherwise indicated, "heteroarylheterocycloalkyl" refers to a heterocycloalkyl group substituted by a heteroaryl group.

As used herein, unless otherwise indicated, "heteroarylaryl" refers to an aryl group substituted by a heteroaryl group.

As used herein, unless otherwise indicated, "biheteroaryl" refers to a heteroaryl group substituted by another heteroaryl group.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

As used herein, unless otherwise indicated, "alkoxy" refers to an –O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), t-butoxy, and the like.

As used herein, unless otherwise indicated, "hydroxylalkyl" refers to an alkyl group substituted by OH.

As used herein, unless otherwise indicated, "cyanoalkyl" refers to an alkyl group substituted by CN.

As used herein, unless otherwise indicated, "alkoxyalkyl" refers to an alkyl group substituted by an alkoxy group.

As used herein, unless otherwise indicated, "alkoxyalkoxy" refers to an alkoxy group substituted by alkoxy.

As used herein, unless otherwise indicated, "haloalkoxy" refers to an –O-(haloalkyl) group.

As used herein, unless otherwise indicated, "arylalkyl" refers to alkyl substituted by aryl and "cycloalkylalkyl" refers to alkyl substituted by cycloalkyl. An example arylalkyl group is benzyl.

As used herein, unless otherwise indicated, "heteroarylalkyl" refers to alkyl substituted by heteroaryl and "heterocycloalkylalkyl" refers to alkyl substituted by heterocycloalkyl.

As used herein, unless otherwise indicated, "oxo" refers to an oxygen substituent that is connected by a double bond (i.e., =O).

As used herein, unless otherwise indicated, the phrase "optionally substituted" means unsubstituted or substituted.

As used herein, unless otherwise indicated, the term "substituted" refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s). Typical substituents include, but are not limited to, D, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl-$NR^{c1}R^{d1}$, -$(CH_2CH_2O)_oC_1$-C_6 alkyl wherein o is 1-10; C_{2-6} alkenyl-$NR^{c1}R^{d1}$, C_{2-6} alkynyl-$NR^{c1}R^{d1}$, OC_{2-6} alkyl-$NR^{c1}R^{d1}$, CN, NO_2, N_3, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, -$CH_2C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, -$NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{g1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{g1})NR^{c1}R^{d1}$, $P(R^{f1})_2$, $P(OR^{e1})_2$, $P(O)R^{e1}R^{f1}$, $P(O)OR^{e1}OR^{f1}$, $S(O)R^{b1}$, -$SO(=NR^{b1})$; $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$, aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, or heterocycloalkyl are optionally substituted with D, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl-$NR^{c1}R^{d1}$, C_{2-6} alkenyl-$NR^{c1}R^{d1}$, C_{2-6} alkynyl-$NR^{c1}R^{d1}$, OC_{2-6} alkyl-$NR^{c1}R^{d1}$, CN, NO_2, N_3, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, -$CH_2C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$,

$OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $-NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $C(=NR^{g1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{g1})NR^{c1}R^{d1}$, $P(R^{f1})_2$, $P(OR^{c1})_2$, $P(O)R^{c1}R^{f1}$, $P(O)OR^{c1}OR^{f1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$;

wherein, R^{a1} is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{b1} is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl;

R^{c1} and R^{d1} are each independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl; wherein the C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, and C_{1-4} haloalkoxy;

each R^{e1} is each independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, (C_1-C_4 alkoxy)-C_1-C_4 alkyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkyl, C_3-C_{10} cycloalkyl-C_1-C_4 alkyl, 5-10 membered heteroaryl-C_1-C_4 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_4alkyl;

R^{f1} is independently selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl;

R^{g1} is independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl; wherein the C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone–enol pairs, amide-imidic acid pairs, lactam–lactim pairs, amide-imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

In some cases, the compounds of the present disclosure may exist as rotational isomers. Descriptions of a compound of the invention that do not indicate a particular rotational isomer are intended to encompass any individual rotational isomers, as well as mixtures of rotational isomers in any proportion. Depiction of a particular rotational isomer is meant to refer to the depicted rotational isomer, substantially free of other rotational isomers.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

In some embodiments, the compounds of the invention, and salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially

separated from the environment in which was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of an agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

A "solvate" refers to a physical association of a compound of Formula (IA) and (IB) with one or more solvent molecules.

"Subject" includes humans. The terms "human", "patient" and "subject" are used interchangeably herein.

"Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

"Compounds of the present disclosure," and equivalent expressions, are meant to embrace compounds of Formula (IA) and (IB) as described herein, as well as its subgenera, which expression includes the stereoisomers (e.g., entaniomers, diastereomers) and constitutional isomers (e.g., tautomers) of compounds of Formula (IA) and (IB) as well as the pharmaceutically acceptable salts, where the context so permits.

As used herein, the term "isotopic variant" refers to a compound that contains proportions of isotopes at one or more of the atoms that constitute such compound that is greater than natural abundance. For example, an "isotopic variant" of a compound can be radiolabeled, that is, contain one or more radioactive isotopes, or can be labeled with non-radioactive isotopes such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art.

It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers", for example, diastereomers, enantiomers, and atropisomers. The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (*R*)-or (*S*)-stereoisomers at each asymmetric center, or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include all stereoisomers and mixtures, racemic or otherwise, thereof. Where one chiral center exists in a structure, but no specific stereochemistry is shown for that center, both enantiomers, individually or as a mixture of enantiomers, are encompassed by that structure. Where more than one chiral center exists in a structure, but no specific stereochemistry is shown for the centers, all enantiomers and diastereomers, individually or as a mixture, are encompassed by that structure. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

Pharmaceutical Compositions

Also provided are pharmaceutical compositions comprising compounds of Formula (IA) and (IB), or a pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, Isotopic variants or prodrugs thereof, and a pharmaceutically acceptable carrier.

The compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for injection use (for example as aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

The compositions may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

An effective amount of a compound of Formula (IA) and (IB) or a pharmaceutically salt thereof for use in therapy is an amount sufficient to treat or prevent a proliferative condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the individual treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.1 mg to 1000 mg of Formula (IA) and (IB) or a pharmaceutically salt thereof with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (IA) and (IB) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

Methods of Administration

The compounds of Formula (IA) and (IB) or a pharmaceutically salt thereof or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrastemal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

Methods of Use

The method typically comprises administering to a subject a therapeutically effective amount of a compound of the invention. The therapeutically effective amount of the subject combination of compounds may vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of proliferation or downregulation of activity of a target protein. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

As used herein, the term "IC_{50}" refers to the half maximal inhibitory concentration of an inhibitor in inhibiting biological or biochemical function. This quantitative measure indicates how much of a particular inhibitor is needed to inhibit a given biological process (or component of a process, i.e. an enzyme, cell, cell receptor or microorganism) by half. In other words, it is the half maximal (50%) inhibitory concentration (IC) of a substance (50% IC, or IC_{50}).

In some embodiments, the subject methods utilize a PKMYT1 inhibitor with an IC_{50} value of about or less than a predetermined value, as ascertained in an in vitro assay. In some embodiments, the PKMYT1 inhibitor inhibits PKMYT1 with an IC_{50} value of about 1 nM or less, 2 nM or less, 5 nM or less, 7 nM or less, 10 nM or less, 20 nM or less, 30 nM or less, 40 nM or less, 50 nM or less, 60 nM or less, 70 nM or less, 80 nM or less, 90 nM or less, 100 nM or less, 120 nM or less, 140 nM or less, 150 nM or less, 160 nM or less, 170 nM or less, 180 nM or less, 190 nM or less, 200 nM or less, 225 nM or less, 250 nM or less, 275 nM or less, 300 nM or less, 325 nM or less, 350 nM or less,

375 nM or less, 400 nM or less, 425 nM or less, 450 nM or less, 475 nM or less, 500 nM or less, 550 nM or less, 600 nM or less, 650 nM or less, 700 nM or less, 750 nM or less, 800 nM or less, 850 nM or less, 900 nM or less, 950 nM or less, 1 μM or less, 1.1 μM or less, 1.2 μM or less, 1.3 μM or less, 1.4 μM or less, 1.5 μM or less, 1.6 μM or less, 1.7 μM or less, 1.8 μM or less, 1.9 μM or less, 2 μM or less, 5 μM or less, 10 μM or less, 15 μM or less, 20 μM or less, 25 μM or less, 30 μM or less, 40 μM or less, 50 μM, 60 μM, 70 μM, 80 μM, 90 μM, 100 μM, 200 μM, 300 μM, 400 μM, or 500 μM, or less, (or a number in the range defined by and including any two numbers above).

PKMYT1 is a synthetic lethal target in the cancers with certain genetic alterations, e.g., CCNE1 amplification or FBXW7 loss-of-function mutations, which may have the symptom of cell hyperproliferation. The subject methods are useful for treating disease conditions associated with CCNE1 amplification, FBXW7 loss-of-function mutations or other genetic alterations which depend on PKMYT1.

Non-limiting examples of such disease conditions include but are not limited to breast cancer, invasive ductal carcinoma, invasive lobular carcinoma, Paget's disease of the breast, hereditary breast-ovarian cancer syndrome, medullary breast cancer, mucinous breast cancer, inflammatory breast cancer, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, gastric cancer, gastric lymphoma, gastrointestinal cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gastrointestinal stromal tumor, prostate cancer, acinar adenocarcinoma of prostate, prostatic ductal adenocarcinoma, prostate sarcoma, small cell prostate cancer, squamous cell prostate cancer, pancreatic cancer, exocrine pancreatic cancer, neuroendocrine pancreatic cancer, uterine cancer, uterine sarcoma, uterine corpus sarcoma, cervical cancer, squamous cell cervical cancer, cervical adenocarcinoma, cervical adenosquamous carcinoma, small cell cervical cancer, cervical mucinous tumor, clear cell cervical cancer, cervical lymphoma, cervical sarcoma, endometrial cancer, endometrial uterine cancer, endometrioid tumor, lung cancer, non-small cell lung cancer, small cell lung cancer, brain stem glioma, brain cancer, cerebellar astrocytoma, cerebral astrocytoma, head and neck cancer, glioblastoma multiforme, glioma, gliomatosis cerebri, ganglioglioma, ganglioneuroma, paraganglioma, primitive neuroectodermal tumor, supratentorial primitive neuroectodermal tumor, visual pathway glioma, neurinoma, neuroblastoma, neuroblastoma, neurofibroma, neuroma, esthesioneuroblastoma, extrahepatic bile duct cancer, Bellini duct carcinoma, cholangiocarcinoma, acute eosinophilic leukemia, acute lymphoblastic leukemia, acute lymphocytic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute myeloblasts leukemia with maturation, acute myeloid dendritic cell leukemia, acute myeloid leukemia, acute myelogenous leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aggressive NK-cell leukemia, chronic lymphocytic leukemia, chronic monocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorder, chronic neutrophilic leukemia, erythroleukemia, hairy Cell leukemia, leukemia, lymphoid leukemia, lymphoma, macroglobulinemia, mast cell leukemia, monocytic

leukemia, myeloid leukemia, T-cell acute lymphoblastic leukemia, T-cell large granular lymphocyte leukemia, T-cell leukemia, T-cell prolymphocytic leukemia, AIDS-related lymphoma, angioimmunoblastic T-cell lymphoma, B-cell leukemia, B-cell lymphoma, cutaneous T-cell lymphoma, diffuse large B cell lymphoma, enteropathy-associated T-cell lymphoma, follicular lymphoma, hepatosplenic T-cell lymphoma, Hodgkin lymphoma, Hodgkin's lymphoma, lymphangioma, lymphangiosarcoma, lymphoepithelioma, MALT lymphoma, mantle cell lymphoma, non-Hodgkin lymphoma, non-Hodgkin lymphoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, small cell lymphoma, T-cell lymphoma, terminal lymphatic cancer.

The term "CCNE1 amplification" refers to the increased CCNE1 genes which leads to the increased expression of cyclin E protein in a diseased cell e.g., cancer cell, relative to expression of cyclin E protein in a control cell (e.g., non-diseased cell of the same type). The amount of cyclin E expression can be at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 10-fold, at least 20-fold, at least 50-fold, relative to cyclin E expression in a control cell. Examples of CCNE1 amplification cancers include, but are not limited to, uterine Carcinosarcoma, ovarian epithelial tumor, endometrial cancer, esophagogastric cancer, sarcoma, bladder cancer, adrenocortical carcinoma, non-small cell lung cancer, pancreatic cancer, pleural mesothelioma, breast cancer, head and neck cancer, mature B-cell neoplasms, cervical cancer, ovarian cancer, hepatobiliary cancer, glioblastoma, colorectal cancer, melanoma, pheochromocytoma, glioma, prostate cancer, uterine cancer, sarcoma, stomach cancer, lung cancer, esophageal cancer, endometrial cancer, osteosarcoma, leukemia, lymphoma, and biliary tract carcinoma.

Examples of FBXW7 loss-of-function mutations cancers include, but are not limited to, uterine cancer, endometrial cancer, colorectal cancer, cervical cancer, esophagogastric cancer, bladder cancer, head and neck cancer, melanoma, non-small cell lung cancer, pancreatic cancer, sarcoma, breast cancer, stomach cancer, ovarian epithelial tumor, glioma, hepatobiliary cancer, ocular melanoma, glioblastoma, thyroid cancer, renal clear cell carcinoma, renal non-clear cell carcinoma, ovarian cancer, lung cancer, and esophageal cancer.

In some embodiments, said method is for use in the treatment or prevention of lymphoma, soft tissue, rhabdoid, multiple myeloma, uterus, gastric, peripheral nervous system, rhabdomyosarcoma, bone, colorectal, mesothelioma, breast, ovarian, lung, fibroblast, central nervous system, urinary tract, upper aerodigestive, leukemia, kidney, skin, esophagus, and pancreas (data from large scale drop out screens in cancer cell lines indicate that some cell lines from the above cancers are dependent on polymerase theta for proliferation see https://depmap.org/portal/).

In other embodiments, said method is for treating a disease selected from breast cancer, lung cancer, pancreatic cancer, prostate cancer, colon cancer, ovarian cancer, uterine cancer, or cervical cancer.

In other embodiments, said method is for treating a disease selected from the cancers with poor chemotherapy response or chemotherapy resistance, e.g., Epithelial Ovarian Cancer.

In other embodiments, said method is for treating a disease selected from the cancers with P53 or ATM mutations, e.g., head and neck cancer, non-small cell lung cancer, ovarian epithelial tumor, esophagogastric cancer, pancreatic cancer, colorectal cancer, bladder cancer, glioma, sarcoma, endometrial cancer, breast cancer, hepatobiliary cancer, glioblastoma, adrenocortical carcinoma, melanoma, pleural Mesothelioma, prostate cancer, cholangiocarcinoma, mature B-cell neoplasms, cervical cancer, leukemia, renal non-clear cell carcinoma, thymic epithelial tumor, renal clear cell carcinoma, seminoma, pheochromocytoma, thyroid cancer, and non-seminomatous germ cell tumor.

In other embodiments, said method is for treating a disease selected from leukemia such as acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, myeloproliferative disorders, chronic myelogenous leukemia (CML), mastocytosis, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), myelodysplastic syndrome (MDS) or epidermoid cancer.

Compounds of the disclosure, as well as pharmaceutical compositions comprising them, can be administered to treat any of the described diseases, alone or in combination with a medical therapy. Medical therapies include, for example, surgery and radiotherapy (*e.g.,* gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, systemic radioactive isotopes).

In other methods, compounds of the disclosure, as well as pharmaceutical compositions comprising them, can be administered to treat any of the described diseases, alone or in combination with one or more other agents.

In other methods, the compounds of the disclosure, as well as pharmaceutical compositions comprising them, can be administered in combination with agonists of nuclear receptors agents.

In other methods, the compounds of the disclosure, as well as pharmaceutical compositions comprising them, can be administered in combination with antagonists of nuclear receptors agents.

Combination Therapies

The compounds of the present invention may be used as a single agent or combined with other treatments. Such treatment may include one or more of the following categories of cancer therapies: such as surgery, chemotherapies, radiation therapies, targeted therapy (for example growth factor inhibitors, kinase inhibitors, cyclin dependent kinase inhibitors and so on), other DDR modulators (for example PARP inhibitor, DNA-PK inhibitor, ATM inhibitor, ATR inhibitor, CHK1 inhibitor, LIG4 inhibitor, HIF-1 inhibitor, HDAC inhibitor, RAD51 inhibitor, WRN inhibitor, PRMT5 inhibitor, MAT2A inhibitor and PolQ inhibitor and so on), immunotherapies, and gene and cell therapy approaches.

For treating cancers and other proliferative diseases, the compounds of the invention can be used in combination with a medical therapy such as surgery, radiotherapy or chemotherapy. Examples of radiotherapies include gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes. Examples of suitable chemotherapeutic agents include one or more of the following categories of anti-tumor agents: other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimi dines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumor antibiotics (for example anthracyclines like bleomycin, doxorubicin, daunomycin, epimbicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and antineoplastic drugs like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin); cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5a-reductase (for example finasteride); anti-invasion agents such as c-Src kinase family inhibitors (for example AZD0530, dasatinib and bosutinib), and metalloproteinase inhibitors (for example marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to heparanase).

For treating cancer and other proliferative diseases, the compounds of the invention can be used in combination with targeted therapies, including inhibitors of growth factor function (for example the anti-erbB2 antibody trastuzumab, the anti-EGFR antibody panitumumab, the anti-erbB antibody cetuximab and any growth factor or growth factor receptor antibodies disclosed by Stem et al. (Critical reviews in oncology/haematology, 2005, Vol. 54, ppl 1-29); such inhibitors also include tyrosine kinase inhibitors (for example inhibitors of the EGFR family tyrosine kinase inhibitors such as gefitinib, erlotinib and Cl 1033), erbB2 tyrosine kinase inhibitors such as lapatinib; inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib; inhibitors of serine/threonine kinases (for example Ras/Raf inhibitors such as sorafenib, tipifamib and lonafamib); inhibitors of cell proliferation through MEK and/or AKT kinases; c-kit inhibitors; abl kinase inhibitors; PI3 kinase inhibitors; Flt3 kinase inhibitors, CSF-IR kinase inhibitors and aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 and AX39459);

antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib, vatalanib, sunitinib, axitinib, pazopanib, AZD2171; compounds such as those disclosed in International Patent Applications WO97/22596, WO97/30035, WO97/32856 and WO98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin)); vascular damaging agents such as combretastatin A4 and compounds disclosed in International Patent Applications WO99/02166, WO00/40529, WO00/41669, WO01/92224, WO02/04434 and WO02/08213; an endothelin receptor antagonist, for example zibotentan or atrasentan; PARP inhibitors such as olaparib, rucaparib, niraparib, talazoparib, veliparib, and pamiparib; PARP1 selective inhibitors such as AZD9547, AZD5305, AG-14361 and NMS-P118; other DNA damage repair modulator such as DNA-PK inhibitor (for example LY294002, NU7026, NU7441, IC86621, IC87102, IC87361, OK-1035, SU11752, vanillin, NK314, IC486241, BVAN08, M3814, AZD7648, VX-984, Doxycycline), ATM inhibitor (for example caffeine, wortmannin, CP-466722, KU-55933, KU-60019, and KU-559403), ATR inhibitor (for example schisandrin B, NU6027, NVP-BEZ235, VE-821, VE-822, AZ20, Elimusertib, RP-3500 and AZD6738), CHK1 inhibitor (for example LY2606368, PF-00477736, SRA737, SCH900776, MK8776, CCT244747 and AZD6738), DNA LIG4 inhibitor (for example SCR7), HIF-1 inhibitor (for example LW6 and PX-478), HDAC inhibitor (for example short-chain fatty acids, benzamides, hydroxamic acids, and cyclic tetrapeptides, suberoylanilide hydroxamic acid (SAHA), trichostatin A), RAD51 inhibitor (for example CYT-0851, SCR-6992, SAT-93/101, CAM833, JKYN-1 (IBR120-series, B02-iso)), WRN (for example NCGC00029283), antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense; gene therapy approaches, including for example approaches to produce aberrant genes such as aberrant p53, CCNE1 amplification or FBXW7 loss-of-function mutations; GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumor cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumor cell lines and approaches using anti-idiotypic antibodies, approaches using immune checkpoint inhibitors such as CTLA-4, PD-1, PD-L1, BTLA, TIM3, LAG3, 0X40, 41BB, VISTA, CD96, TGF, CD73, CD39, A2AR, A2BR, IDOl, TD02, Arginase, B7-H3, B7-H4; approaches using inhibitors of the aforementioned immune-checkpoint receptors and ligands, for

example ipilimumab, abatacept, nivolumab, pembrolizumab, atezolizumab, nivolumab, and durvalumab..

Synthesis

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates or products at the temperatures at which the reactions are carried out, *e.g.,* temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups is described, *e.g.,* in Kocienski, *Protecting Groups,* (Thieme, 2007); Robertson, *Protecting Group Chemistry,* (Oxford University Press, 2000); Smith *el ah, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* 6th Ed. (Wiley, 2007); Peturssion *et al,* "Protecting Groups in Carbohydrate Chemistry," *J Chem. Educ.,* 1997, *74(*11), 1297; and Wuts *et al., Protective Groups in Organic Synthesis,* 4th Ed., (Wiley, 2006).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The expressions, "ambient temperature", "room temperature", and "r.t." as used herein, are understood in the art, and refer generally to a temperature, e.g. a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

Compounds of the invention can be prepared according to numerous preparatory routes known in the literature. The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare

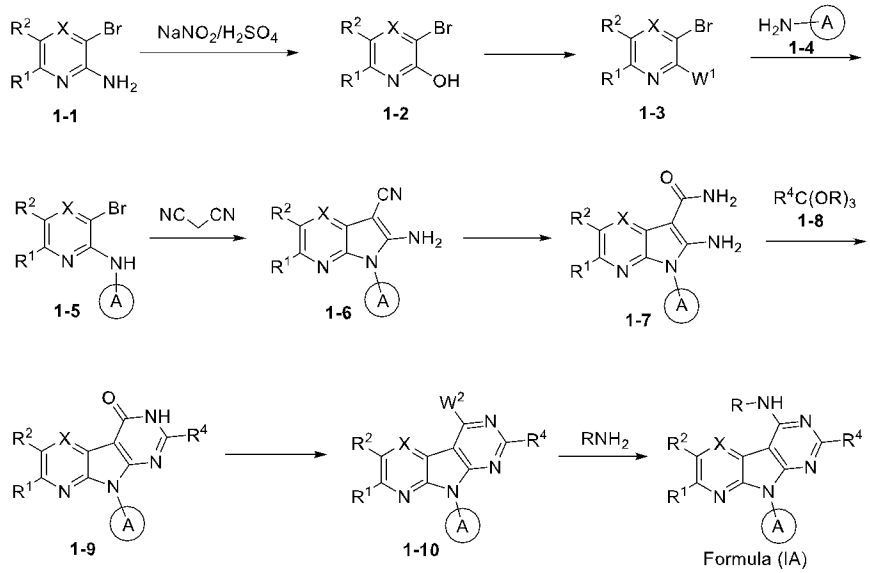
various compounds of the invention. Example synthetic methods for preparing compounds of the invention are provided in the Schemes below.

The following Examples are provided to illustrate some of the concepts described within this disclosure. While the Examples are considered to provide an embodiment, it should not be considered to limit the more general embodiments described herein.

General Synthetic Procedures

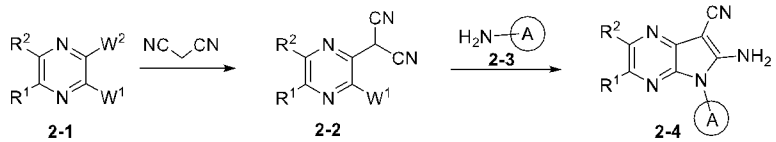
A series of tricyclic derivatives of formula (IA) can be prepared as the methods described in Scheme 1. The 2-amino derivatives **1-1** can be converted to the 2-hydroxy derivatives **1-2**, which can be transformed into the corresponding derivatives **1-3** where W^1 is halogen (e.g., Cl, or Br) or pseudohalogen (e.g., OTf or OMs) either by reaction with a halogenation reagent such as $SOCl_2$, $POCl_3$ or $POBr_3$ with or without the catalytic of DMF (where W^1 is Cl or Br) or reaction with TfCl or MsCl (where W^1 is OTf or OMs) in the presence of a base such as Hunig's base. Coupling of compounds **1-3** with aromatic amines **1-4** under Buchwald coupling conditions (e.g., in the presence of a palladium catalyst, such as BrettPhos Pd G3, t-BuXphos Pd G3, RuPhos Pd G3 or XantPhos Pd G3 and a base, such as t-BuOK, t-BuONa, Cs_2CO_3, or K_2CO_3) can afford aromatic amine derivatives **1-5**. Reaction of the amine derivatives **1-5** with malononitrile to produce aminopyrroles **1-6** can be achieved under palladium-mediated conditions (e.g., in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2/PPh_3$, and a base, such as t-BuOK or t-BuONa). Hydrolysis of the nitrile in **1-6** can be conducted under acidic or basic conditions to yield pyrrole-amide derivatives **1-7** which can be transformed into indole-pyrimidone **1-9** by treatment of with trialkyl orthoformate **1-8** (where R is methyl or ethyl) in the presence of an acid such as p-TsOH, or HCl. The indole-pyrimidone **1-9** can be converted into intermediates **1-10** where W^2 is halogen (e.g., Cl, or Br) or pseudohalogen (e.g., OTf or OMs) either by reaction with a halogenation reagent such as $SOCl_2$, $POCl_3$ or $POBr_3$ with or without the catalytic of DMF (where W^2 is Cl or Br) or reaction with TfCl or MsCl (where W^2 is OTf or OMs) in the presence of a base such as Hunig's base. Reaction of the intermediates **1-10** with ammonia or amine derivatives can afford the desired tricyclic derivatives of formula (IA).

Scheme 1



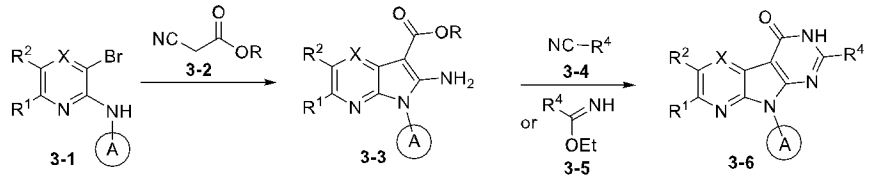
A series of intermediates **2-4** for preparations of tricyclic derivatives of formula (IA) can be prepared as the methods described in Scheme 2. Substitution of compounds **2-1** (W^1 and W^2 are halogen e.g., Cl, or Br) with malononitrile can form malononitrile derivatives **2-2** under palladium-mediated conditions (e.g., in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2/PPh_3$, and a base, such as t-BuOK or t-BuONa). Coupling of malononitrile derivatives **2-2** with aromatic amines **2-3** under Buchwald coupling conditions (e.g., in the presence of a palladium catalyst, such as BrettPhos Pd G3, t-BuXphos Pd G3, RuPhos Pd G3 or XantPhos Pd G3 and a base, such as t-BuOK, t-BuONa, Cs_2CO_3, or K_2CO_3) can afford aminopyrrole derivatives **2-4**.

Scheme 2



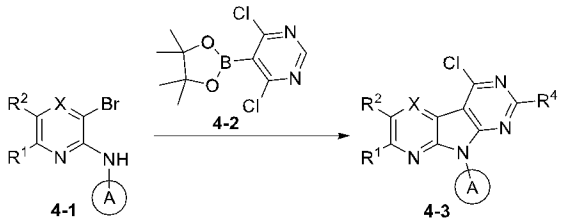
A series of intermediates **3-6** for preparations of tricyclic derivatives of formula (IA) can be prepared as the methods described in Scheme 3. Reaction of the aromatic amines **3-1** with alkyl 2-cyanoacetate **3-2** (where, R is Me or Et) to yield aminopyrrole ester **3-3** can be achieved under palladium-mediated conditions (e.g., in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2/PPh_3$, and a base, such as t-BuOK or t-BuONa). Tricyclic derivatives **3-6** can be prepared by reactions of the aminopyrrole ester **3-3** with cyano derivatives 2-4 in the presence of an acid, such as dry HCl, TsOH or H_2SO_4) or ethyl alkyl-carbimidate **3-5**.

Scheme 3



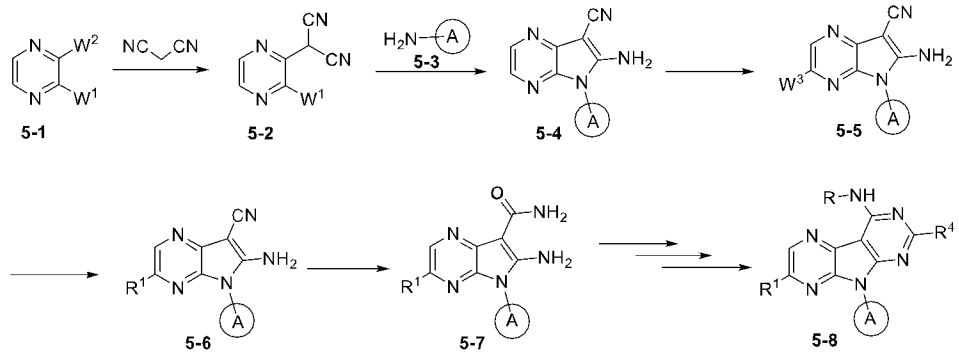
A series of intermediates **4-3** for preparations of tricyclic derivatives of formula (IA) can be prepared as the methods described in Scheme 4. Suzuki coupling of compounds **4-1** with boronate ester **4-2** can afford the intermediates **4-3** under standard Suzuki conditions (e.g., in the presence of a palladium catalyst, such as [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and a base, such as K_3PO_4).

Scheme 4



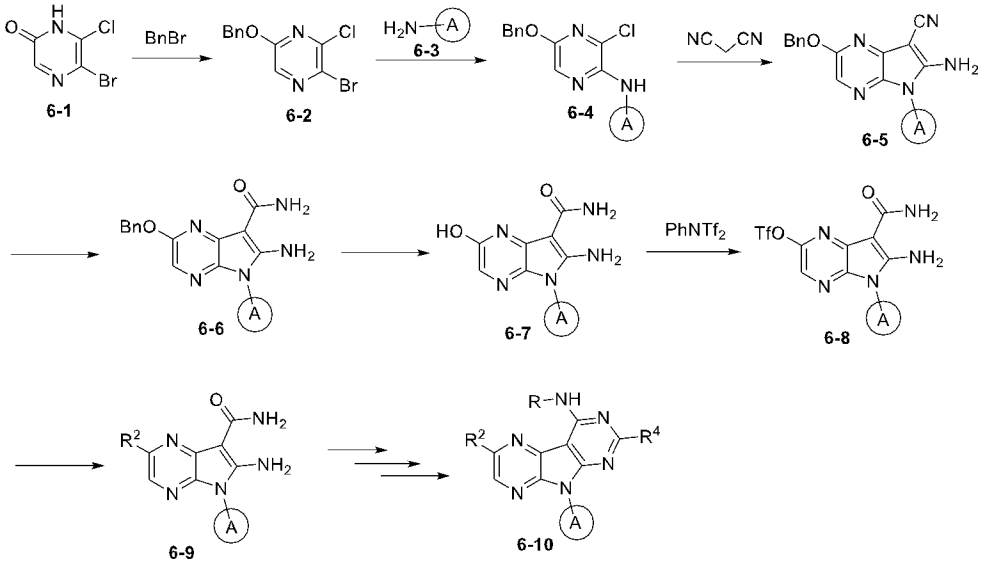
A series of tricyclic derivatives of formula **5-8** can be prepared as the methods described in Scheme 5. Compounds **5-1** where W^2 is halogen (e.g., Cl, Br, or I) and W^1 is halogen (e.g., Br, or Cl) can be transformed into aminopyrrole derivatives **5-4** either by consequently reactions with malononitrile and Buchwald's amination with aromatic amines **5-3** as described in the scheme 2 or Buchwald's amination with aromatic amines **5-3** first and then reactions with malononitrile under palladium-mediated conditions for transformations of compounds **1-3** to aminopyrroles **1-6** as described in scheme 1 (e.g., in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2/PPh_3$, and a base, such as t-BuOK or t-BuONa). The aminopyrrole derivatives **5-4** can be halogenated with suitable reagents, such as N-chlorosuccimide (NCS), N-bromosuccimide (NBS) or N-iodosuccimide (NIS) to provide compounds **5-5** where W^3 is a halogen (e.g., Cl, Br, or I) in which a suitable group R^1 can be installed in the presence of a metal-mediated coupling such as standard Suzuki conditions (e.g., in the presence of a palladium catalyst, such as [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and a base, such as K_3PO_4), or standard Negishi conditions (e.g., in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)), or standard Stille conditions (e.g., in the presence of a palladium(0) catalyst, such as tetrakis(triphenyl-phosphine)palladium(0)) to afford compounds **5-6**. Compounds **5-6** can be further converted to the desired tricyclic derivatives of formula **5-8** as those described for compounds **1-6** to formula (IA) and (IB) in scheme 1.

Scheme 5



Alternatively, a series of tricyclic derivatives of formula **6-10** can be prepared as the methods described in Scheme 6. O-alkylation of pyrazin-2(1H)-one **6-1** with benzyl bromide or benzyl chloride in the presence of a base such as NaH, or K_2CO_3 can afford pyrazine **6-2** which can be transformed into aminopyrrole amide **6-6** by consequently reactions with aromatic amines **6-3** and malononitrile, and hydrolysis as those described for the transformations of compounds **1-3** to **1-7** in scheme 1. Hydrogenation of compounds **6-6** can produce the corresponding compounds **6-7** in the presence of a palladium catalyst such as Pd/C or $Pd(OH)_2/C$. The hydroxyl group in compounds **6-7** can be converted to the corresponding triflate derivatives **6-8** by treatment with a triflation reagent such as $PhNTf_2$ or Tf_2O in the presence of a base such as Et_3N or Hunig's base. The triflate derivatives **6-8** can be transformed into desired compounds **6-9** which can lead to the final tricyclic derivatives **6-10** as those described in scheme 1.

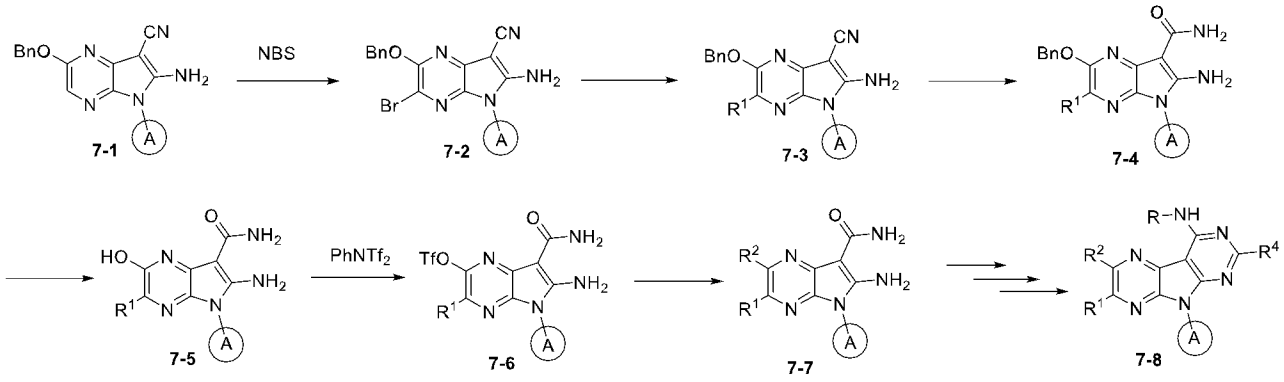
Scheme 6



Alternatively, a series of tricyclic derivatives of formula **7-8** can be prepared as the methods described in the scheme 7. The compounds **7-3** can be prepared by halogenation with N-chlorosuccimide (NCS), N-bromosuccimide (NBS) or N-iodosuccimide (NIS) and a metal-mediated coupling to install R^1 group under Suzuki conditions, Negishi conditions or Stille conditions as

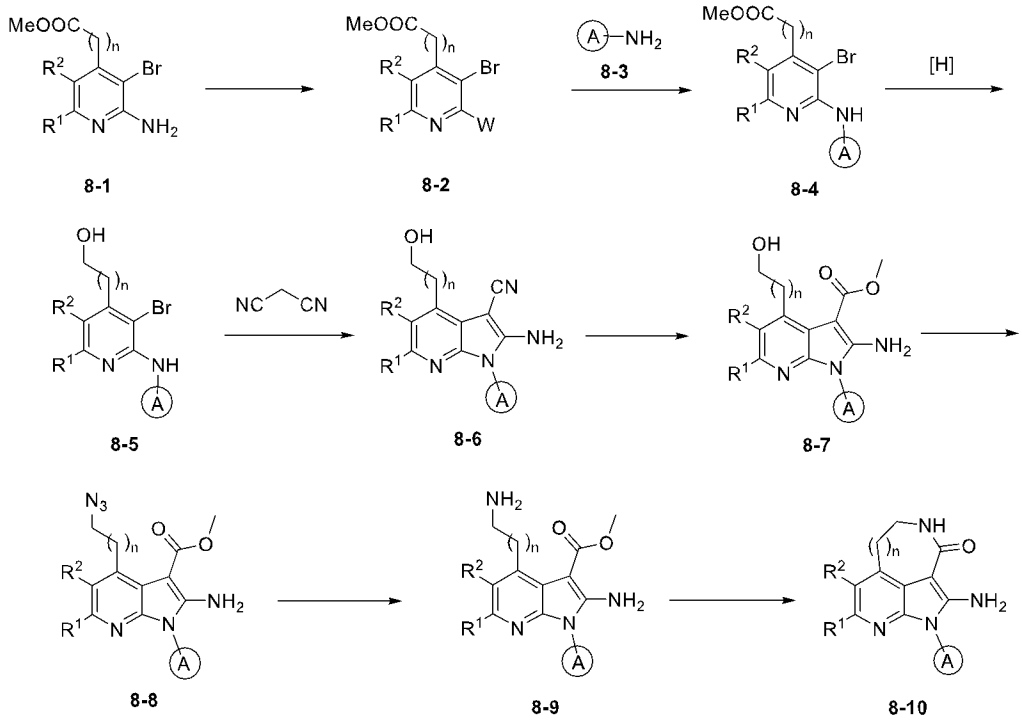
described in scheme 5. Compounds **7-3** can be converted to the desired tricyclic derivatives **7-8** as those described in scheme 6.

Scheme 7



A series of tricyclic derivatives of formula **8-10** can be prepared as the methods described in Scheme 8. The 2-amino bromo derivatives **8-1** (n is 0, 1 or 2) can be transformed into the corresponding derivatives **8-2** where W is halogen (e.g., Cl, Br or I) by treatment with $NaNO_2$ in the presence of an acid such as HCl, or HBr and following reaction with a halogenation reagent such as CuCl, CuBr or CuI. Coupling of compounds **8-2** with a suitable aromatic amine **8-3** under Buchwald coupling conditions (e.g., in the presence of a palladium catalyst, such as BrettPhos Pd G3, t-BuXphos Pd G3, RuPhos Pd G3 or XantPhos Pd G3 and a base, such as t-BuOK, t-BuONa, Cs_2CO_3, or K_2CO_3) can afford aromatic amine derivatives **8-4**. The carboxylate group in **8-4** can be reduced to the corresponding alcohol **8-5** by using a reducing reagent such as $LiBH_4$ or $NaBH_4$. Substitution of the 3-Br in aromatic amines **8-5** with malononitrile to produce aminopyrroles **8-6** can be achieved under copper-mediated coupling conditions (e.g., CuI in the presence of diamine-based ligands, such as N^1,N^2-dimethylethane-1,2-diamine, N^1,N^2-dimethylcyclohexane-1,2-diamine or cyclohexane-1,2-diamine) or under palladium-mediated conditions (e.g., in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2/PPh_3$, and a base, such as t-BuOK or t-BuONa). Hydrolysis of the nitrile in **8-6** can be done under acidic or basic conditions to yield pyrrole-amide derivatives **8-7** which can be transformed into compounds **8-8** by treatment of with DPPA (diphenyl phosphorazidate) and DBU or by Mitsunobo reaction with azide or sodium azide and DEAD or DIAD. Reduction of the azide group in compounds **8-8** to the corresponding amines **8-9** can be achieved by treatment with triphenylphosphine or by hydrogenation in the presence of a palladium catalyst such as Pd/C. Intramolecular amide formation can afford the desired tricyclic derivatives of formula **8-10**.

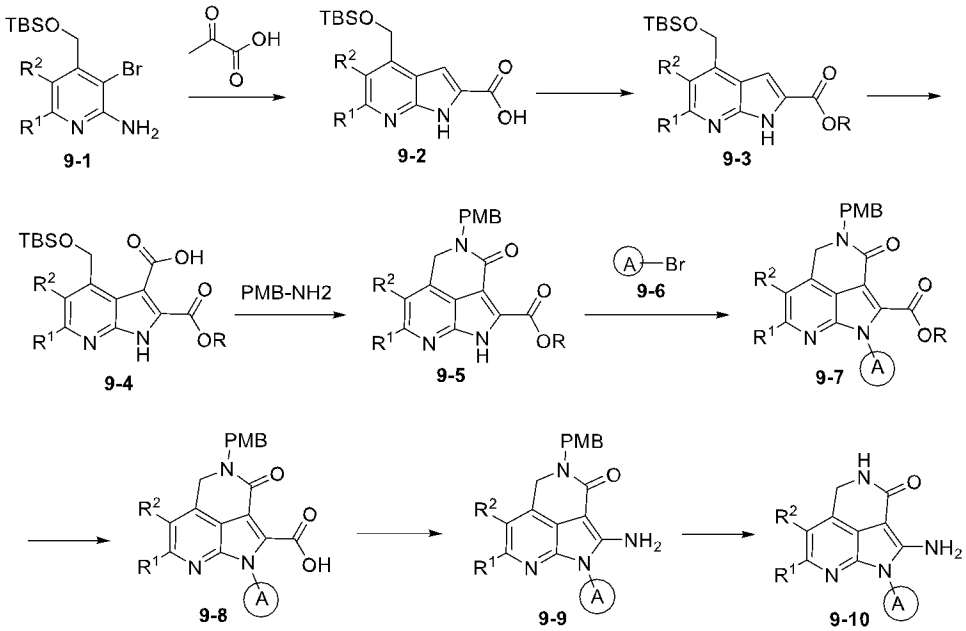
Scheme 8



Alternatively, a series of tricyclic lactam derivatives of formula **9-10** can be prepared as the methods described in Scheme 9. Condensation of 3-bromopyridin-2-amines **9-1** with pyruvic acid can give azaindole acids **9-2** in the presence of a palladium catalyst such as bis(tri-tert-butylphosphine)palladium(0), and a base such as potassium phosphate. The azaindole acids **9-2** can be conveniently transformed into the corresponding azaindole ester **9-3** (where R is Me or Et) by treatment with diazomethane (where R is Me) or treatment with oxalyl chloride following by alcohol ROH. Azaindole derivatives **9-4** can be prepared from the azaindole ester **9-3** in various ways: 1) treatment **9-3** with $POCl_3$ in a catalytic amount of DMF, and following by treatment with an oxidative reagent such as Ag_2O) treatment **9-3** with anhydrous trifluoroacetic acid following with NaOH; 3) treatment **9-3** with 2,2,2-trichloroacetyl chloride following with NaOH. The indole derivatives **9-4** can be transformed into azaindole lactams **9-5** by treatment with a protected amine such as p-methoxybenzylamine PMB-NH_2 in the presence of an amide coupling reagent such BOP, ByBOP, HATU or HBTU, and a base such as Et_3N or Hunig's base. Coupling of the indole lactams **9-5** with aromatic iodide or bromides **9-6** under Buchwald coupling conditions (e.g., in the presence of a palladium catalyst, such as BrettPhos Pd G3, t-BuXphos Pd G3, RuPhos Pd G3 or XantPhos Pd G3 and a base, such as t-BuOK, t-BuONa, Cs_2CO_3, or K_2CO_3) can afford aza-indole derivatives **9-7** which then can be transformed into amino-azaindole derivatives **9-9** by Curtius rearrangement of the products of the reactions of azaindole acids **9-8** with DPPA (diphenylphosphoryl azide). Removal of the protecting group PMB in **9-9** to give the final tricyclic lactam derivatives **9-10** can be achieved by hydrogenation in the presence of a palladium catalyst such as Pd/C or Pd(OH)2/C or under acid

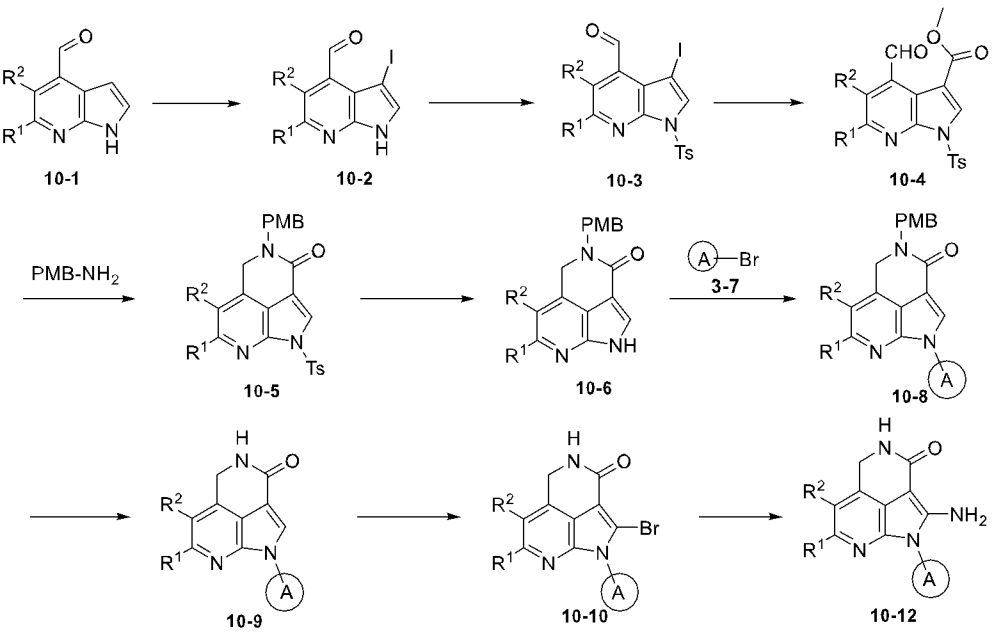
conditions such as TFA.

Scheme 9



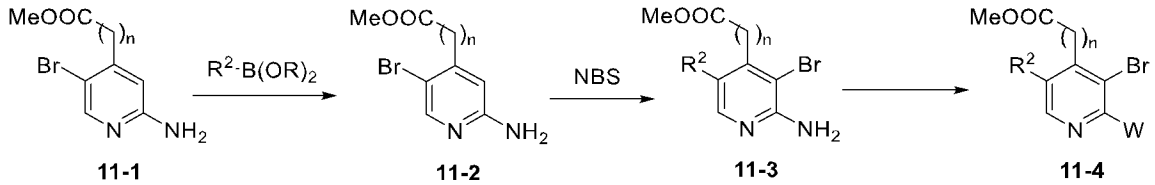
A series of intermediates **10-6** for preparations of tricyclic derivatives of formula (IB) can be prepared as the methods described in Scheme 10. Substitution of the 3-bromo in aromatic amines **10-1** with alkyl 2-cyanoacetate **10-2** (R = Me or Et) to yield aminopyrrole ester **10-3** can be achieved under palladium-mediated conditions (e.g., in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2/PPh_3$, and a base, such as t-BuOK or t-BuONa). Tricyclic derivatives **10-6** can be prepared by reactions of the aminopyrrole ester **10-3** with cyano derivatives **10-4** in the presence of an acid, such as dry HCl, TsOH or H_2SO_4) or ethyl alkyl-carbimidate **10-5**.

Scheme 10



A series of intermediates **11-3** for preparations of tricyclic derivatives of formula (IB) can be prepared as the methods described in Scheme 11. Suzuki coupling of compounds **4-1** with boronate ester **11-2** can afford the intermediates **11-3** under standard Suzuki conditions (e.g., in the presence of a palladium catalyst, such as [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and a base, such as K_3PO_4).

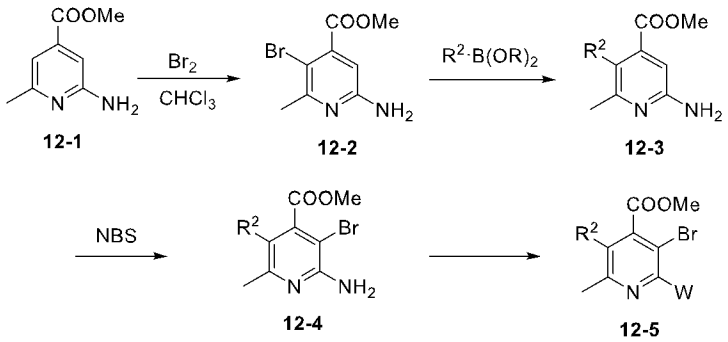
Scheme 11



A series of tricyclic derivatives of formula **12-8** can be prepared as the methods described in Scheme 12. Compounds **12-1** where W^2 is halogen (e.g., Cl, Br, or I) and W^1 is halogen (e.g., Br, or Cl) can be transformed into aminopyrrole derivatives **12-4** either by consequently reactions with malononitrile and Buchwald's amination with aromatic amines **12-3** as described in the scheme 9 or Buchwald's amination with aromatic amines **12-3** first and then reactions with malononitrile under palladium-mediated conditions for transformations of compounds **8-3** to aminopyrroles **8-6** as described in scheme 8. (e.g., in the presence of a palladium catalyst, such as $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2/PPh_3$, and a base, such as t-BuOK or t-BuONa). The aminopyrrole derivatives **12-4** can be halogenated with suitable reagents, such as N-chlorosuccimide (NCS), N-bromosuccimide (NBS) or N-iodosuccimide (NIS) to provide compounds **12-5** where W^3 is a halogen (e.g., Cl, Br, or I) in which a suitable group R^1 can be installed in the presence of a metal-mediated coupling such as standard Suzuki conditions (e.g., in the presence of a palladium catalyst, such as [1,1′-

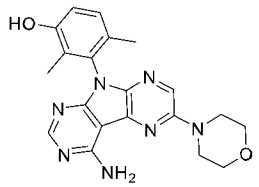
bis(diphenylphosphino)ferrocene]dichloropalladium(II) and a base, such as K_3PO_4), or standard Negishi conditions (e.g., in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0) or [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)), or standard Stille conditions (e.g., in the presence of a palladium(0) catalyst, such as tetrakis(triphenyl-phosphine)palladium(0)) to afford compounds **12-6**. Compounds **12-6** can be further converted to the desired tricyclic derivatives of formula **12-8** as those described for compounds **8-6** to formula (IA) and (IB) in scheme 8.

Scheme 12

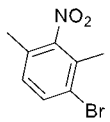


Examples

Example 1: 3-(4-Amino-6-morpholino-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol

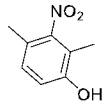


Step 1: 1-bromo-2,4-dimethyl-3-nitrobenzene



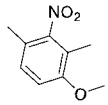
To a suspension of 1,3-dimethyl-2-nitrobenzene (20.0 g, 132 mmol) and Fe (2.96 g, 52.9 mmol) in $CHCl_3$ (200 mL) was added a solution of Br_2 (22.2 g, 139 mmol) in $CHCl_3$ (100 mL). The reaction mixture was stirred at 15 ℃ for 12 h., and then diluted with water (500 mL). The mixture was extracted with DCM (2 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude title compound (26.0 g) as a light brown solid, which was used in next step without purification. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.4, 1H), 7.01 (d, J = 8.4, 1H), 2.35 (s, 3H), 2.26 (s, 3H).

Step 2: 2,4-dimethyl-3-nitrophenol



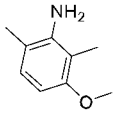
A mixture of 1-bromo-2,4-dimethyl-3-nitrobenzene (20.0 g, 86.9 mmol), KOH (14.6 g, 261 mmol), 2'-di-tert-butylphosphino-2,4,6-triisopropylbiphenyl (7.38 g, 17.4 mmol) and bis(dibenzylideneacetone)palladium (7.96 g, 8.69 mmol) in dioxane (200 mL) and H_2O (200 mL) was degassed and recharged with N_2 for 3 cycles, and stirred at 90 ℃ for 12 h under N_2 atmosphere. After cooling to r.t., the reaction mixture was diluted with water (600 mL), adjusted with 1M HCl aq. to pH ~3 and extracted with EtOAc (250 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (2-20%) to afford the title compound (10.0 g, crude) as a light brown solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.95 (d, J = 8.4, 1H), 6.78 (d, J = 8.4, 1H), 2.22 (s, 3H), 2.17 (s, 3H).

Step 3: 1-methoxy-2,4-dimethyl-3-nitrobenzene



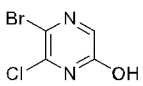
To a solution of 2,4-dimethyl-3-nitrophenol (12.0 g, 71.8 mmol) in acetone (84.0 mL) was added cesium carbonate (46.8 g, 144 mmol) and CH_3I (15.3 g, 108 mmol). The reaction mixture was stirred at 15 ℃ for 12 h. The mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (2-20%) to afford crude title compound (10 g) as a light-yellow solid.

Step 4: 3-methoxy-2,6-dimethylaniline



To a solution of 1-methoxy-2,4-dimethyl-3-nitrobenzene (7 g, 38.6 mmol) in EtOH (35.0 mL) and H_2O (35.0 mL) was added Fe (21.6 g, 386 mmol) and NH_4Cl (20.7 g, 386 mmol). The reaction mixture was stirred at 80 ℃ for 2 h. The solid was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (2-20%) to afford the title compound (5.00 g) as a light-yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.90 (d, J = 12, 1H), 6.32 (d, J = 8.0, 1H), 3.80 (s, 3H), 3.62 (brs, 2H), 2.15 (s, 3H), 2.09 (s, 3H).

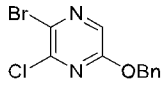
Step 5: 5-bromo-6-chloropyrazin-2-ol



To a solution of 5-bromo-6-chloropyrazin-2-amine (20.0 g, 96.0 mmol) in conc. H_2SO_4 (98%, 140 mL) was carefully added $NaNO_2$ (7.28 g, 106 mmol) in small portions at 0℃. The reaction mixture

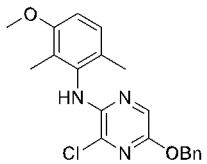
was stirred at 0 ℃ for 1 h., and poured into ice-water. The solid crashed out was collected by filtration, dried under vacuum to afford the title compound (20.0 g) as a light brown solid, which was used in next step without further purification.

Step 6: 5-(benzyloxy)-2-bromo-3-chloropyrazine



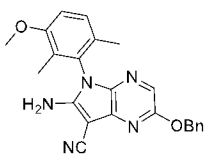
To a solution of 5-bromo-6-chloropyrazin-2-ol (8.00 g, 38.2 mmol) in toluene (140 mL) was added (bromomethyl)benzene (7.19 g, 42.0 mmol) and Ag_2CO_3 (21.1 g, 76.4 mmol). The reaction mixture was stirred at 15 ℃ for 3 h. The solid was removed by filtration and the filtrate was collected and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel. column eluting with EtOAc/PE (10-50%) to afford the title compound (6.90 g, 60.3% yield) as a brown solid.^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.39-7.47 (m, 5H), 5.38 (s, 2H).

Step 7: 5-(benzyloxy)-3-chloro-N-(3-methoxy-2,6-dimethylphenyl)pyrazin-2-amine



To a solution of 5-(benzyloxy)-2-bromo-3-chloropyrazine (3.19 g, 10.6 mmol) in toluene (15.0 mL) was added potassium tert-butoxide (1.59 g, 14.2 mmol), 3-methoxy-2,6-dimethylaniline (1.61 g, 10.6 mmol), bis(dibenzylideneacetone)palladium (487 mg, 0.53 mmol) and Xantphos (616 mg, 1.06 mmol) at r.t. The reaction mixture was degassed and recharged with nitrogen 3 cycles and stirred at 80 ℃ for 1 h. The reaction mixture was cooled to r.t, and concentrated under reduced pressure to afford crude product, which was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (0.25–2%) to afford the title compound (2.40 g, 60.9% yield) as light-yellow oil. ^{1}H NMR: (400 MHz, CDCl3) δ 7.75 (s, 1H), 7.27-7.65 (m, 5H), 7.08 (d, J = 8.4, 1H), 6.77 (d, J = 8.4, 1H), 6.06 (s, 1H), 5.30 (s, 2H), 3.84 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H).

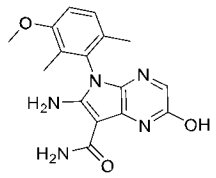
Step 8: 6-amino-2-(benzyloxy)-5-(3-methoxy-2,6-dimethylphenyl)-5H-pyrrolo[2,3-b]pyrazine-7-carbonitrile



To a solution of propanedinitrile (1.04 g, 15.8 mmol) in dimethyl ether (73.0 mL) was added sodium hydride (632 mg, 15.8 mmol) at r.t. The reaction mixture was stirred at r.t for 30 mins, followed by addition of a solution of 5-(benzyloxy)-3-chloro-N-(3-methoxy-2,6-dimethylphenyl)pyrazin-2-amine (1.46 g, 3.95 mmol) in 1,2-dimethoxyethane (7.30 mL) and tetrakis(triphenylphosphine)palladium (2.28 g, 1.97 mmol) at r.t.. The reaction mixture was degassed

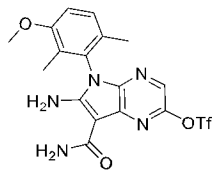
and recharged with nitrogen for three cycles, and stirred at 80 ~ 85 ℃ for 2 h. After cooling, the mixture was quenched with H_2O (100 mL) at 0 ℃, and extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with MeOH/DCM (1-50%) to afford the title compound (1.90 g, 78.7% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.23-7.53 (m, 6H), 6.97 (d, J = 8.4, 1H), 5.49 (s, 2H), 4.85 (s, 2H), 3.87 (s, 3H), 1.93 (s, 3H), 1.86 (s, 3H).

Step 9: 6-amino-2-hydroxy-5-(3-methoxy-2,6-dimethylphenyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide



A solution of 6-Amino-2-(benzyloxy)-5-(3-methoxy-2,6-dimethylphenyl)-5H-pyrrolo[2,3-b]pyrazine-7-carbonitrile (1.90 g, 4.76 mmol) in conc. H_2SO_4 (98%, 10 mL) was stirred at 15 ℃ for 2 h, and quenched by adding the reaction mixture into ice (~50 g) below 10 ℃. The mixture was adjusted with $NH_3.H_2O$ (25-30%, ~40 mL) to pH ~8, extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (1.30 g) as brown oil which was used directly in next step without purification. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.21 (d, J = 8.4, 1H), 6.95 (d, J = 8.4, 1H), 6.05 (brs, 2H), 3.87 (s, 3H), 1.95 (s, 3H), 1.88 (s, 3H). LCMS calc. for $C_{16}H_{18}N_5O_3$ $[M+H]^+$: m/z = 328.1; found: 327.9.

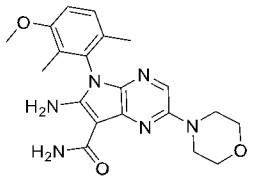
Step 10: 6-amino-7-carbamoyl-5-(3-methoxy-2,6-dimethylphenyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl trifluoromethanesulfonate



To a solution of 6-amino-2-hydroxy-5-(3-methoxy-2,6-dimethylphenyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (1.30 g, 3.97 mmol) in DMF (6.00 mL) was added cesium carbonate (2.85 g, 8.74 mmol) at r.t., followed by addition of N-phenyl-bis(trifluoromethanesulfonimide) (1.56 g, 4.37 mmol) at 0 ~5 ℃. The reaction mixture was stirred at 0 ~ 5 ℃ for 0.5 h, quenched with water (20.0 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine (5mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (10-50%) to afford the title

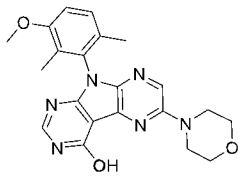
compound (0.64 g, 35.1% yield) as a light brown oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.16 (s, 1H), 6.92 (d, J = 8.4, 1H), 3.81 (s, 3H), 1.86 (s, 3H), 1.79 (s, 3H).

Step 11: 6-amino-5-(3-methoxy-2,6-dimethylphenyl)-2-morpholino-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide



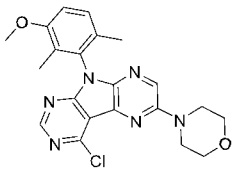
To a solution of 6-amino-7-carbamoyl-5-(3-methoxy-2,6-dimethylphenyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl trifluoromethanesulfonate (0.64 g, 1.39 mmol) in DMSO (2.0 mL) was added morpholine (3.0 g, 34.4 mmol). The reaction mixture was stirred at 135 ℃ for 2 h. The reaction mixture was cooled to r.t., quenched with water (6.00 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (10-50%) to afford the title compound (0.34 g, 0.86 mmol) as a light brown foam. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.70 (brs, 1H), 7.44 (s, 1H), 7.21 (d, J = 8.4, 1H), 6.95 (d, J = 8.4, 1H), 6.02 (brs, 2H), 3.89-3.92 (m, 4H), 3.87 (s, 3H), 3.48-3.50 (m, 4H), 1.95 (s, 3H), 1.88 (s, 3H).

Step 12: 9-(3-methoxy-2,6-dimethylphenyl)-6-morpholino-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-4-ol



A mixture of 6-amino-5-(3-methoxy-2,6-dimethylphenyl)-2-morpholino-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (0.2 g, 0.5 mmol) and trimethyl orthoformate (4 mL) was added TsOH.H_2O (9.60 mg, 0.05 mmol). The reaction mixture was stirred at 40 ℃ for 1 h., and concentrated under reduced pressure to afford crude title compound (0.2 g) as brown oil which was used directly in next step without purification. LCMS calc. for $C_{21}H_{23}N_6O_3$ $[M+H]^+$: m/z = 407.2; found: 407.1.

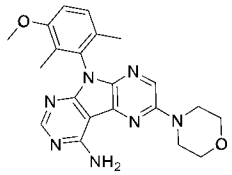
Step 13: 4-(4-chloro-9-(3-methoxy-2,6-dimethylphenyl)-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-6-yl)morpholine



A mixture of 9-(3-methoxy-2,6-dimethylphenyl)-6-morpholino-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-4-ol (0.20 g, 0.49 mmol) and $POCl_3$ (7.55 g, 49.2 mmol)

was stirred at 100 ℃ for 1 h. The reaction mixture was concentrated under reduced pressure, diluted with water (1 mL), adjusted with saturated $NaHCO_3$ (1 mL) to pH ~8, and extracted with EtOAc (2 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude title compound (0.2 g) as a light brown oil which was used directly in next step without purification. LCMS calc. for $C_{21}H_{22}ClN_6O_2$ $[M+H]^+$: m/z = 425.1; found: 425.0.

Step 14: 9-(3-methoxy-2,6-dimethylphenyl)-6-morpholino-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-4-amine



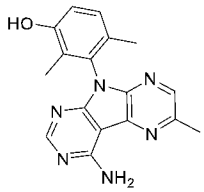
To a solution of 4-(4-chloro-9-(3-methoxy-2,6-dimethylphenyl)-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-6-yl)morpholine (0.2 g, 0.47 mmol) in MeOH (1.0 mL) was added NH_3/MeOH (6 M, 20.0 mL) in a sealed tube. The reaction mixture was stirred at 80 ℃ overnight, and concentrated under reduced pressure to afford crude title compound (0.2 g) as a light brown oil, which was used directly in next step without purification. ^{1}H NMR: (400 MHz, MeOD) δ 8.25 (s, 1H), 7.99 (s, 1H), 7.23 (d, *J* = 8.4, 1H), 7.08 (d, *J* = 8.4, 1H), 3.87-3.90 (m, 7H), 3.64-3.66 (m, 4H), 1.80-1.81 (m, 2H), 1.72-1.73 (m, 2H). LCMS calc. for $C_{21}H_{24}N_7O_2$ $[M+H]^+$: m/z = 406.2; found: 406.3.

Step 15: 3-(4-amino-6-morpholino-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol

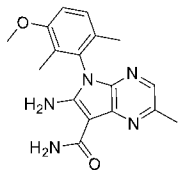
A mixture of 9-(3-methoxy-2,6-dimethylphenyl)-6-morpholino-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-4-amine (0.2 g, 0.49 mmol) in HBr (40%) (4.47 g, 22.1 mmol, 3 mL) was stirred at 80 ℃ for 1 h. The reaction mixture was poured into ice-water, adjusted with $NH_3.H_2O$ (25-30%) to pH 7~8 at 0 ℃, and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by Prep-HPLC on a C18 column eluting with MeCN/water (30-60% with 1% NH_4HCO_3) to afford the desired compound (0.048 g, 24.5% yield) as a light-yellow solid. ^{1}H NMR: (400 MHz, MeOD) δ 8.25 (s, 1H), 7.99 (s, 1H), 7.08 (d, *J* = 8.4, 1H), 6.91 (d, *J* = 8.4, 1H), 3.87-3.90 (m, 4H), 3.64-3.66 (m, 4H), 1.78 (s, 3H), 1.72 (s, 3H). LCMS calc. for $C_{20}H_{22}N_7O_2$ $[M+H]^+$: m/z = 392.2; found: 392.1.

This compound is a mixture of *(3Ra)*-(4-Amino-6-morpholino-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol and its enantiomer *(3Sa)*-(4-Amino-6-morpholino-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol.

Example 2: 3-(4-Amino-6-methyl-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol

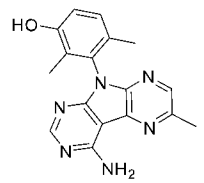


Step 1: 6-amino-5-(3-methoxy-2,6-dimethylphenyl)-2-methyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide



A mixture of 6-amino-7-carbamoyl-5-(3-methoxy-2,6-dimethylphenyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl trifluoromethanesulfonate (1.00 g, 2.18 mmol, Example 1 Step 10), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (601 mg, 2.39 mmol, 0.67 mL, 50% purity), tetrakis(triphenylphosphine)palladium (252 mg, 0.22 mmol) and potassium carbonate (902 mg, 6.53 mmol) in dioxane (10.0 mL) was degassed and recharged with N_2 for 3 cycles, and stirred at 140 ℃ for 2 h under N_2 atmosphere. After cooling to 15 ℃, the reaction mixture was diluted with H_2O (50 mL), and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel. column eluting with EtOAc/PE (10-50%) to afford the title compound (0.40 g, 56.5% yield) as a light brown foam. LCMS calc. for $C_{17}H_{20}N_5O_2$ $[M+H]^+$: m/z = 326.2; found: 325.9

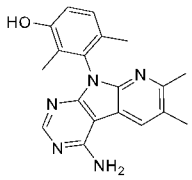
Step 2: 3-(4-amino-6-methyl-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol



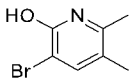
This compound was prepared using procedures analogous to those described for Example 1 Step 12-15 using 6-amino-5-(3-methoxy-2,6-dimethylphenyl)-2-methyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide in Step 12. ^1H NMR: (400 MHz, MeOD) δ 8.34 (s, 1H), 8.25 (s, 1H), 7.05 (d, J = 8.4, 1H), 6.92 (d, J = 8.4, 1H), 2.67 (s, 3H), 1.68 (s, 3H), 1.58 (s, 3H). LCMS calc. for $C_{17}H_{17}N_6O$ $[M+H]^+$: m/z = 321.1; found: 321.1.

This compound is a mixture of *(3Ra)*-(4-Amino-6-methyl-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol and its enantiomer *(3Sa)*-(4-Amino-6-methyl-9H-pyrazino[2',3':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol.

Example 3: 3-(4-Amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol

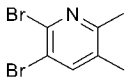


Step 1: 3-bromo-5,6-dimethylpyridin-2-ol



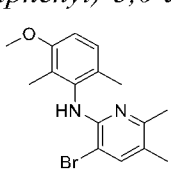
This compound was prepared using procedures analogous to those described for Example 1 Step 5 using 3-bromo-5,6-dimethylpyridin-2-amine to replace 5-bromo-6-chloropyrazin-2-amine. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 11.96 (brs, 1H), 7.73 (s, 1H), 2.11 (s, 3H), 1.96 (s, 3H). LCMS calc. for C_7H_9BrNO $[M+H]^+$: m/z = 201.9; found: 201.8.

Step 2: 2,3-dibromo-5,6-dimethylpyridine



To a solution of 3-bromo-5,6-dimethylpyridin-2-ol (12.3 g, 60.9 mmol) in DMF (37.0 mL) and toluene (62.0 mL) was added dropwise a solution of $POBr_3$ (26.2 g, 91.3 mmol, 9.28 mL) in xylene (30.0 mL) at 90 ℃ under nitrogen. The reaction mixture was stirred at 90 ℃ for 12 h. After cooling to r.t., the mixture was slowly poured into water (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed sequentially with NaOH aq. (0.5 N, 30 mL), water (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (5-20%) to afford the title compound (12.0 g, 74.4% yield) as a white solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 2.45 (s, 3H), 2.24 (s, 3H). LCMS calc. for $C_7H_8Br_2N$ $[M+H]^+$: m/z = 263.8; found: 263.8.

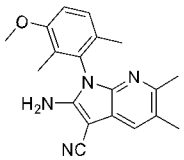
Step 3: 3-bromo-N-(3-methoxy-2,6-dimethylphenyl)-5,6-dimethylpyridin-2-amine



This compound was prepared using procedures analogous to those described for Example 1 Step 7 using 2,3-dibromo-5,6-dimethylpyridine to replace 5-(benzyloxy)-2-bromo-3-chloropyrazine, and

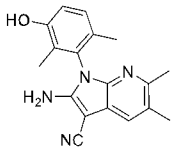
cesium carbonate to replace potassium tert-butoxide. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.20 (s, 1H), 3.85 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H). LCMS calc. for $C_{16}H_{20}BrN_2O$ $[M+H]^+$: m/z = 335.1; found: 335.0.

Step 4: 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



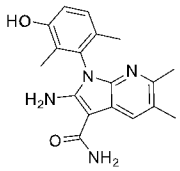
To a solution of propanedinitrile (1.97 g, 29.8 mmol) in 1,2-dimethoxyethane (35.0 mL) was added sodium tert-butoxide (2.87 g, 29.8 mmol) under N_2 atmosphere. The mixture was stirred at 15 ℃ for 30 min, followed by addition of 3-bromo-N-(3-methoxy-2,6-dimethylphenyl)-5,6-dimethylpyridin-2-amine (5.00 g, 14.9 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (1.22 g, 1.49 mmol). The reaction mixture was degassed and recharged with nitrogen for 3 cycles, stirred at 85 ℃ for 12 h under N_2 atmosphere. After cooling to r.t., the mixture was diluted with water (40.0 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (10-50%) to afford the title compound (4.30 g, 90.0% yield) as a light brown solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 4.50 (brs, 1H), 3.88 (s, 3H), 2.38 (s, 3H), 2.33 (s, 3H), 1.92 (s, 3H), 1.85 (s, 3H). LCMS calc. for $C_{19}H_{21}N_4O$ $[M+H]^+$: m/z = 321.2; found: 321.0.

Step 5: 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



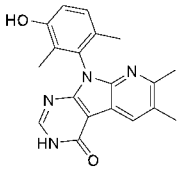
To a solution of 2-amino-1-(3-methoxy-2,6-dimethylphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (4.00 g, 12.5 mmol) in DCM (40.0 mL) was added dropwise BBr_3 (6.26 g, 25.0 mmol, 2.41 mL) at 0 ℃. The mixture was stirred at 25 ℃ for 1 h. The reaction mixture was quenched with water (100 mL) at 0 ℃, and extracted with 2-methyltetrahydrofuran (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude title compound (2.00 g) as a light-yellow solid, which was used directly in next step without purification. ^{1}H NMR: (400 MHz, DMSO-*d*$_6$) δ 9.50 (s, 1H), 7.37 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 6.4 Hz, 1H), 6.72 (s, 2H), 2.25 (s, 3H), 2.24 (s, 3H), 1.74 (s, 3H), 1.65 (s, 3H). LCMS calc. for $C_{18}H_{19}N_4O$ $[M+H]^+$: m/z = 307.1; found: 307.1.

Step 6: 2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide



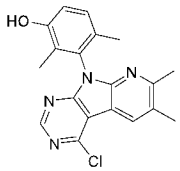
This compound was prepared using procedures analogous to those described for Example 1 Step 9. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.82 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.71 (s, 2H), 6.63 (s, 2H), 2.26 (s, 3H), 2.24 (s, 3H), 1.73 (s, 3H), 1.65 (s, 3H). LCMS calc. for $C_{18}H_{21}N_4O_2$ $[M+H]^+$: m/z = 325.2; found: 325.2.

Step 7: 9-(3-hydroxy-2,6-dimethylphenyl)-6,7-dimethyl-3,9-dihydro-4H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-4-one



This compound was prepared using procedures analogous to those described for Example 1 Step 12. ^{1}H NMR: (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 9.49 (s, 1H), 8.16 (s, 1H), 8.09 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 1.67 (s, 3H), 1.57 (s, 3H). LCMS calc. for $C_{19}H_{19}N_4O_2$ $[M+H]^+$: m/z = 335.1; found: 335.1.

Step 8: 3-(4-chloro-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol



This compound was prepared using procedures analogous to those described for Example 1 Step 13. ^{1}H NMR: (400 MHz, MeOD) δ 8.69 (s, 1H), 8.54 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 2.59 (s, 3H), 2.53 (s, 3H), 1.74 (s, 3H), 1.68 (s, 3H). LCMS calc. for $C_{19}H_{18}ClN_4O$ $[M+H]^+$: m/z = 353.1; found: 353.2.

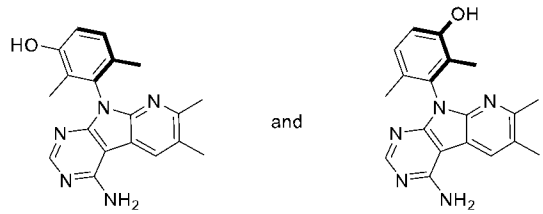
Step 9: 3-(4-amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol

This compound was prepared using procedures analogous to those described for Example 1 Step 14. ^{1}H NMR: (400 MHz, DMSO-d6) δ 9.52 (brs, 1H), 8.72 (s, 1H), 8.37 (s, 1H), 8.17 (brs, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H), 1.66 (s, 3H), 1.56 (s, 3H). LCMS calc. for $C_{19}H_{20}N_5O$ $[M+H]^+$: m/z = 334.2; found: 334.1.

This compound is a mixture of *(3Ra)*-(4-Amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol and its enantiomer *(3Sa)*-(4-Amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol.

Example 4: (3*R*a)-3-(4-Amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol and

Example 5: (3*S*a)-3-(4-amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-dimethylphenol



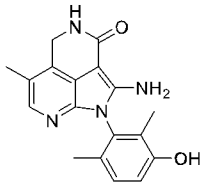
Example 4 Example 5

The Example 3 (204 mg) was separated by Chiral-HPLC to give P1 (the earlier eluted product, 49.8 mg, Retention time = 2.478 min. in chiral analytic HPLC) and P2 (the latter eluted product, 62.9 mg, Retention time = 2.783 min. in chiral analytic HPLC). Chiral HPLC separation conditions: Instrument: Waters-SFC80; Column: DAICEL CHIRALCEL OJ (250 mm×30 mm, 10 μm); Mobile phase A: Supercritical CO_2, Mobile phase B: MeOH (0.1%IPAM), Gradient: B% = 33% isocratic elution mode; Flow rate: 60 g/min; Sample preparation: methanol; Injection Volume: 2.0 mL; Detector Wavelength: 220 nm; Column temperature: 40 °C; Back pressure: 100 bar. The separated products were determined by chiral analytic HPLC. Chiral HPLC conditions: Column: Chiralcel OJ-3, 150×4.6 mm I.D., 3 μm; Mobile phase A: CO_2, Mobile phase B: MeOH (0.1% IPAm); Flow rate: 2.5 ml/min and Run time: 5 min; Detector Wavelength: 220 nm.

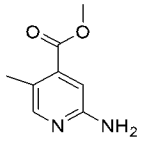
P1 was assigned Example 4. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.59 (s, 1H), 8.19 (s, 1H), 7.34 (s, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 1.65 (s, 3H), 1.55 (s, 3H). LCMS calc. for $C_{19}H_{20}N_5O$ $[M+H]^+$: m/z = 334.2; Found: 334.1.

P2 was assigned Example 5. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.59 (s, 1H), 8.19 (s, 1H), 7.34 (s, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 1.65 (s, 3H), 1.55 (s, 3H). LCMS calc. for $C_{19}H_{20}N_5O$ $[M+H]^+$: m/z = 334.2; Found: 334.1.

Example 6: 2-Amino-1-(3-hydroxy-2,6-dimethylphenyl)-6-methyl-4,5-dihydropyrrolo[4,3,2-de][2,6]naphthyridin-3(1H)-one

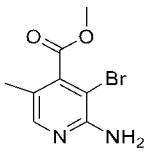


Step 1: methyl 2-amino-5-methylpyridine-4-carboxylate



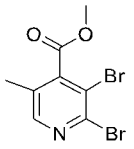
To a solution of methyl 2-amino-5-bromopyridine-4-carboxylate (10.0 g, 43.2 mmol) in 1,4-dioxane (100 mL) was added trimethyl-1,3,5,2,4,6-trioxatriborinane (27.1 g, 216 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (3.17 g, 4.32 mmol) and potassium carbonate (17.9 g, 129 mmol). The reaction mixture was degassed and recharged with nitrogen for 3 cycles, and stirred at 100℃ for 5 h. The solid was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (0 - 40%) to afford the title compound (7.00 g, 97% yield) as a yellow solid. LCMS calc. for $C_8H_{11}N_2O_2$ $[M+H]^+$: m/z = 167.1; found: 167.1.

Step 2: methyl 2-amino-3-bromo-5-methylpyridine-4-carboxylate



To a solution of methyl 2-amino-5-methylpyridine-4-carboxylate (7.00 g, 42.1 mmol) in acetonitrile (50 mL) was added N-bromosuccinimide (7.50 g, 42.1 mmol). The reaction mixture was stirred at r.t. overnight, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (0 - 50%) to afford the title compound (8.20 g, 79% yield) as a white solid. LCMS calc. for $C_8H_{10}BrN_2O_2$ $[M+H]^+$: m/z = 245.0; found: 245.0.

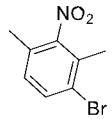
Step 3: methyl 2,3-dibromo-5-methylpyridine-4-carboxylate



To a mixture of methyl 2-amino-3-bromo-5-methylpyridine-4-carboxylate (2.00 g, 8.16 mmol) and HBr (10 mL, 40% aq.) was added dropwise a solution of $NaNO_2$ (0.56 g, 8.16 mmol) in H_2O (2 mL) at -10 ℃. The reaction mixture was stirred at -10 ℃ for 30 mins, followed by addition of CuBr (1.40 g, 9.75 mmol), and stirred at -5 ℃ for an additional 2 h. The reaction mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash

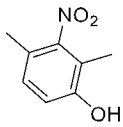
chromatography on a silica gel column eluting with EtOAc/ PE (0 - 30%) to afford the title compound (800 mg, 31% yield) as a light-yellow solid. LCMS calc. for $C_8H_8Br_2NO_2$ $[M+H]^+$: m/z = 307.9; found: 307.9.

Step 4: 1-bromo-2,4-dimethyl-3-nitrobenzene



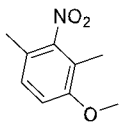
To a suspension of 1,3-dimethyl-2-nitrobenzene (20.0 g, 132 mmol) and Fe (2.96 g, 52.9 mmol) in $CHCl_3$ (200 mL) was added a solution of Br_2 (22.2 g, 139 mmol) in $CHCl_3$ (100 mL). The reaction mixture was stirred at 15 ℃ for 12 h, and then diluted with water (500 mL). The mixture was extracted with DCM (2 x 250 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude title compound (26.0 g) as a light brown solid which was used in next step without purification. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4, 1H), 7.01 (d, *J* = 8.4, 1H), 2.35 (s, 3H), 2.26 (s, 3H).

Step 5: 2,4-dimethyl-3-nitrophenol



A mixture of 1-bromo-2,4-dimethyl-3-nitrobenzene (20.0 g, 86.9 mmol), KOH (14.6 g, 261 mmol), 2'-di-tert-butylphosphino-2,4,6-triisopropylbiphenyl (7.38 g, 17.4 mmol) and bis(dibenzylideneacetone)palladium (7.96 g, 8.69 mmol) in dioxane (200 mL) and H_2O (200 mL) was degassed and recharged with N_2 for 3 cycles, and stirred at 90 ℃ for 12 h. under N_2 atmosphere. After cooling to r.t., the reaction mixture was diluted with water (600 mL), adjusted with 1M HCl aq. to pH ~3 and extracted with EtOAc (250 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (2-20%) to afford the title compound (10.0 g, crude) as a light brown solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.4, 1H), 6.78 (d, *J* = 8.4, 1H), 2.22 (s, 3H), 2.17 (s, 3H).

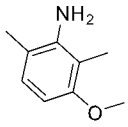
Step 6: 1-methoxy-2,4-dimethyl-3-nitrobenzene



To a solution of 2,4-dimethyl-3-nitrophenol (12.0 g, 71.8 mmol) in acetone (84.0 mL) was added cesium carbonate (46.8 g, 144 mmol) and CH_3I (15.3 g, 108 mmol). The reaction mixture was stirred at 15 ℃ for 12 h. The mixture was filtered. The filtrate was concentrated under reduced pressure. The

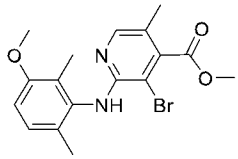
residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (2-20%) to afford crude title compound (10 g) as a light-yellow solid.

Step 7: 3-methoxy-2,6-dimethylaniline



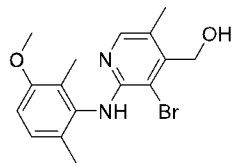
To a solution of 1-methoxy-2,4-dimethyl-3-nitrobenzene (7 g, 38.6 mmol) in EtOH (35.0 mL) and H_2O (35.0 mL) was added Fe (21.6 g, 386 mmol) and NH_4Cl (20.7 g, 386 mmol). The reaction mixture was stirred at 80 ℃ for 2 h. The solid was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (2-20%) to afford the title compound (5.00 g) as a light-yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.90 (d, J = 12, 1H), 6.32 (d, J = 8.0, 1H), 3.80 (s, 3H), 3.62 (brs, 2H), 2.15 (s, 3H), 2.09 (s, 3H).

Step 8: methyl 3-bromo-2-[(3-methoxy-2,6-dimethylphenyl)amino]-5-methylpyridine-4-carboxylate



A mixture of methyl 2,3-dibromo-5-methylpyridine-4-carboxylate (100 mg, 0.324 mmol), 3-methoxy-2,6-dimethylaniline (58.7 mg, 0.389 mmol), bis(dibenzylideneacetone)palladium (29.6 mg, 0.032 mmol), XantPhos (37.4 mg, 0.065 mmol) and potassium t-butoxide (108 mg, 0.972 mmol) in toluene (5 mL) was degassed and recharged with nitrogen for 3 cycles, stirred at 80℃ overnight under nitrogen atmosphere. After cooling to r.t., the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc /PE(0 - 50%) to afford the title compound (45.0 mg, 36% yield) as a yellow solid. LCMS calc. for $C_{17}H_{20}BrN_2O_3$ $[M+H]^+$: m/z = 379.1; found: 379.1.

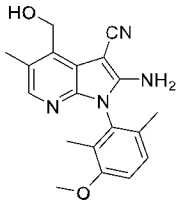
Step 9: {3-bromo-2-[(3-methoxy-2,6-dimethylphenyl)amino]-5-methylpyridin-4-yl}methanol



To a solution of methyl 3-bromo-2-[(3-methoxy-2,6-dimethylphenyl)amino]-5-methylpyridine-4-carboxylate (1.15 g, 3.03) in tetrahydrofuran (25 mL) was added dropwise a solution of lithium borohydride in tetrahydrofuran (2 M, 7.6 mL, 15.2 mmol) at 0℃. The reaction mixture was stirred at 60℃ overnight before quenched with water (150 mL). The mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography

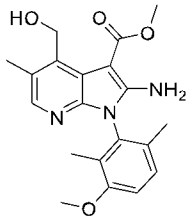
on a silica gel column eluting with EtOAc / PE (0-50%) to afford the title compound (640 mg, 60% yield) as an off-white solid. LCMS calc. for $C_{16}H_{20}BrN_2O_2$ $[M+H+2]^+$: m/z =353.1; Found: 353.0.

Step 10: 2-amino-4-(hydroxymethyl)-1-(3-methoxy-2,6-dimethylphenyl)-5-methylpyrrolo[2,3-b]pyridine-3-carbonitrile



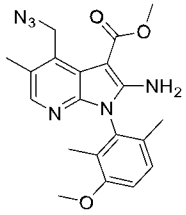
A mixture of {3-bromo-2-[(3-methoxy-2,6-dimethylphenyl)amino]-5-methylpyridin-4-yl}methanol (540 mg, 1.54 mmol), malononitrile (203 mg, 3.07 mmol), N^1,N^2-dimethylethane-1,2-diamine (54.2 mg, 0.615 mmol), CuI (58.6 mg, 0.307 mmol) and potassium carbonate (637 mg, 4.61 mmol) in DMSO (5 mL) was degassed and recharged with nitrogen for 3 cycles. The reaction mixture was irradiated with microwave radiation at 130℃ for 1 h before quenched with water (80 mL). The mixture was extracted with EtOAc (3 x 120 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (EtOAc/PE, 1:1) to afford the title compound (198 mg, 38% yield) as a yellow solid. LCMS calc. for $C_{19}H_{21}N_4O_2$ $[M+H]^+$: m/z = 337.2; Found: 337.1.

Step 11: methyl 2-amino-4-(hydroxymethyl)-1-(3-methoxy-2,6-dimethylphenyl)-5-methylpyrrolo[2,3-b]pyridine-3-carboxylate



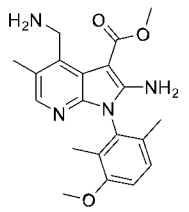
A mixture of 2-amino-4-(hydroxymethyl)-1-(3-methoxy-2,6-dimethylphenyl)-5-methylpyrrolo[2,3-b]pyridine-3-carbonitrile (198 mg, 0.589 mmol) and HCl(g) in MeOH (4M, 5 mL) was stirred at 60 ℃ for 8 h. The reaction mixture was concentrated under reduced pressure, the residue was purified by Prep-TLC (EtOAc/ PE, 1:1) to afford the title compound (121 mg, 56% yield) as a yellow solid. LCMS calc. for $C_{20}H_{24}N_3O_4$ $[M+H]^+$: m/z = 370.2 found: 370.1.

Step 12: methyl 2-amino-4-(azidomethyl)-1-(3-methoxy-2,6-dimethylphenyl)-5-methylpyrrolo[2,3-b]pyridine-3-carboxylate



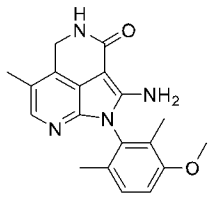
A mixture of methyl 2-amino-4-(hydroxymethyl)-1-(3-methoxy-2,6-dimethylphenyl)-5-methylpyrrolo[2,3-b]pyridine-3-carboxylate (121 mg, 0.328 mmol), diphenylphosphoryl azide (450 mg, 1.64 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (249 mg, 1.64 mmol) in tetrahydrofuran (10 mL) was stirred at 60℃ for 6 h before quenched with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc/PE, 1/1) to afford the title compound (77 mg, 60% yield) as a yellow solid. LCMS calc. for $C_{20}H_{23}N_6O_3$ $[M+H]^+$: m/z = 395.2; Found: 395.2.

Step 13: methyl 2-amino-4-(aminomethyl)-1-(3-methoxy-2,6-dimethylphenyl)-5-methylpyrrolo[2,3-b]pyridine-3-carboxylate



A mixture of methyl 2-amino-4-(azidomethyl)-1-(3-methoxy-2,6-dimethylphenyl)-5-methylpyrrolo[2,3-b]pyridine-3-carboxylate (77.0 mg, 0.195 mmol) and triphenylphosphine (102 mg, 0.39 mmol) in water (2 mL) and tetrahydrofuran (10 mL) was stirred at r.t. overnight under nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (MeOH / DCM, 1/10) to afford the title compound (56 mg, 78% yield) as an off-white solid. LCMS calc. for $C_{20}H_{25}N_4O_3$ $[M+H]^+$: m/z =369.2; Found: 369.1.

Step 14: 3-amino-2-(3-methoxy-2,6-dimethylphenyl)-9-methyl-2,6,11-triazatricyclo[6.3.1.0^{4,12}]dodeca-1(11),3,8(12),9-tetraen-5-one



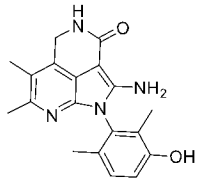
A mixture of methyl 2-amino-4-(aminomethyl)-1-(3-methoxy-2,6-dimethylphenyl)-5-methylpyrrolo[2,3-b]pyridine-3-carboxylate (56 mg, 0.152 mmol) and potassium carbonate (63.02 mg, 0.456 mmol) in methanol (4 mL) was stirred at 80 ℃ overnight before quenching with water (50 mL). The mixture was extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc/ PE, 1/9) to afford the title compound (46 mg, 90% yield) as a yellow solid. LCMS calc. for $C_{19}H_{21}N_4O_2$ $[M+H]^+$: m/z =337.2; Found: 337.1.

Step 15: 3-amino-2-(3-hydroxy-2,6-dimethylphenyl)-9-methyl-2,6,11-triazatricyclo[6.3.1.0^{4,12}]dodeca-1(11),3,8(12),9-tetraen-5-one

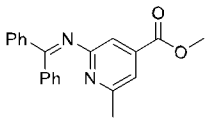
A solution of 3-amino-2-(3-methoxy-2,6-dimethylphenyl)-9-methyl-2,6,11-triazatricyclo[6.3.1.0^{4,12}]dodeca-1(11),3,8(12),9-tetraen-5-one (50.0 mg, 0.149 mmol) in dichloromethane (3 mL) was added dropwise to a solution of BBr_3 (0.447 mL, 1M in DCM, 0.447 mmol) in dichloromethane (5 mL) at -78℃. The reaction mixture was stirred at r.t. for 1 h and concentrated under reduced pressure. The residue was dissolved in a mix-solvents of water and methanol (H_2O/MeOH=1:5, 5 ml) and stirred at r.t. for 1 h, which was purified directly by Prep-HPLC eluting with MeCN/H_2O (20% to 50% with 0.1% FA) to afford the desired product (16.8 mg, 35% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 7.55 (s, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.79 (s, 1H), 5.99 (s, 2H), 4.75 (s, 2H), 2.13 (s, 3H), 1.78 (s, 3H), 1.69 (s, 3H). LCMS calc. for $C_{18}H_{19}N_4O_2$ $[M+H]^+$: m/z =323.2; Found: 323.1.

The desired compound for Example 1 step 15 was a mixture of 2-Amino-(1*Ra*)-(3-hydroxy-2,6-dimethylphenyl)-6-methyl-4,5-dihydropyrrolo[4,3,2-de][2,6]naphthyridin-3(1H)-one and its enantiomer 2-Amino-(1*Sa*)-(3-hydroxy-2,6-dimethylphenyl)-6-methyl-4,5-dihydropyrrolo[4,3,2-de][2,6]naphthyridin-3(1H)-one.

Example 7: 2-Amino-1-(3-hydroxy-2, 6-dimethylphenyl)-6, 7-dimethyl-4, 5-dihydropyrrolo [4, 3, 2-de] [2, 6] naphthyridin-3(1H)-one



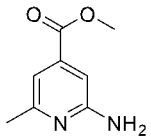
Step 1: methyl 2-((diphenylmethylene) amino)-6-methylisonicotinate



A mixture of methyl 2-bromo-6-methylisonicotinate (83 g, 361 mmol), benzophenone imine (71.9 g, 399 mmol), Cs_2CO_3 (353 g, 108 mmol) and Xantphos (20.9 g, 36.1 mmol) in dioxane (581 mL) was degassed and purged with N_2 for 3 cycles, $Pd_2(dba)_3$ (16.5 g, 18.0 mmol) was added to the mixture. The mixture was degassed and purged with N_2 for 3 cycles and then the mixture was stirred at 80 ℃ overnight under N_2 atmosphere. After cooled to r.t., the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with ethyl acetate/petroleum ether (0.5~3.3%) to afford the title compound (160 g, 44.7% yield) as light yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.73–7.74 (m, 2H), 7.62–7.64 (m, 3H), 7.42–7.43

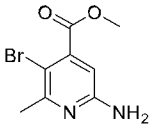
(m, 4H), 7.11–7.19 (m, 2H), 6.82 (s, 1H), 3.77 (s, 3H), 2.42 (s, 3H). LCMS calc. for $C_{21}H_{19}N_2O_2$ $[M+H]^+$: m/z = 331.1; Found: 331.2.

Step 2: methyl 2-amino-6-methylisonicotinate



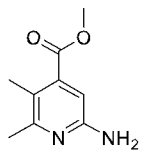
To a solution of methyl 2-((diphenylmethylene) amino)-6-methylisonicotinate (51.6 g, 156 mmol) in THF (50 mL) was added HCl (6 M, 104 mL). The mixture was stirred at 20 ℃ for 2 h. The reaction mixture was diluted with H_2O (200 mL), adjusted pH value to 8~9 with $NH_3.H_2O$ (30 mL), extracted with EA (150 mL x 3). The combined organic layers were washed with brine (150 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with MTBE (180 mL) at 20°C for 2 h to afford the title compound (60 g, 77.0% yield) as a light yellow solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 6.76 (s, 2H), 6.20 (s, 2H), 3.82 (s, 3H), 2.28 (s, 3H). LCMS calc. for $C_8H_{11}N_2O_2$ $[M+H]^+$: m/z = 167.1; Found: 167.2.

Step 3: methyl 6-amino-3-bromo-2-methylisonicotinate



To a solution of methyl 2-amino-6-methylisonicotinate (18.3 g, 110 mmol) in ACN (112 mL) was added NBS (19.6 g, 110 mmol). The mixture was stirred at 20 ℃ for 0.5 h. The reaction mixture was diluted with H_2O (200 mL), extracted with EA (100 mL x 3). The combined organic layers were washed with brine (200 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with MTBE (150 mL) at 20 °C for 1 h to afford the title compound (49 g, 60.5% yield) as a yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.53 (s, 1H), 4.58 (s, 2H), 3.93 (s, 3H), 2.55 (s, 3H). LCMS calc. for $C_8H_{10}BrN_2O_2$ $[M+H]^+$: m/z = 244.9; Found: 244.9.

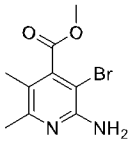
Step 4: methyl 6-amino-2,3-dimethylisonicotinate



A mixture of methyl 6-amino-3-bromo-2-methylisonicotinate (11 g, 44.9 mmol), methylboronic acid (8.06 g, 135 mmol), and K_2CO_3 (24.8 g, 180 mmol) in dioxane (77 mL) was degassed and purged with N_2 for 3 cycles. Pd(dppf)Cl_2 (3.28 g, 4.49 mmol) was added to the mixture and was degassed and purged with N_2 for 3 cycles. Then the mixture was stirred at 80 ℃ for overnight under N_2 atmosphere. The reaction mixture was diluted with H_2O (200 mL), extracted with EA (150 mL x 4). The combined organic layers were washed with brine (500 mL x 2), dried over Na_2SO_4, filtered and concentrated

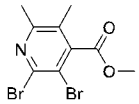
under reduced pressure to give a residue. The residue was triturated with MTBE: EA (15/1, 84 mL) at 20 ℃ for 1 h, filtered and the cake was triturated with ACN (40 mL) at 20 ℃ for 1 h to afford the title compound (28 g, 86.5% yield) as a yellow solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 6.51 (s, 1H), 5.85 (s, 2H), 3.80 (s, 3H), 2.27 (s, 3H), 2.13 (s, 3H). LCMS calc. for $C_9H_{13}N_2O_2$ $[M+H]^+$: m/z = 181.1; Found: 180.9.

Step 5: methyl 2-amino-3-bromo-5, 6-dimethylisonicotinate



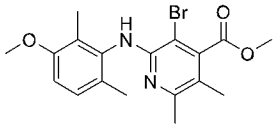
This compound was prepared using procedures analogous to those described for Example 6 Step 2 using methyl 6-amino-2,3-dimethylisonicotinate to replace methyl 2-amino-5-methylpyridine-4-carboxylate to afford the title product as a yellow solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 6.13 (s, 1H), 3.87 (s, 3H), 2.24 (s, 3H), 1.98 (s, 3H). LCMS calc. for $C_9H_{12}BrN_2O_2$ $[M+H]^+$: m/z = 259.0; Found: 258.9.

Step 6: methyl 2, 3-dibromo-5,6-dimethylisonicotinate



To a solution of methyl 2-amino-3-bromo-5,6-dimethylisonicotinate (9.5 g, 36.7 mmol) in dibromomethane (67 mL) was added benzyltriethylammonium bromide (44.9 g, 165 mmol) and tert-butyl nitrite (37.8 g, 367 mmol). The mixture was stirred at 20 ℃ for 3 h., diluted with H_2O (80 mL), and extracted with DCM (150 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EA/PE (0.5~35%) to afford the title compound (16 g, 67.5% yield) as a colorless oil. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 3.98 (s, 3H), 2.44 (s, 3H), 2.19 (s, 3H). LCMS calc. for $C_9H_{10}Br_2NO_2$ $[M+H]^+$: m/z = 323.9; Found: 323.9.

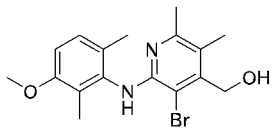
Step 7: methyl 3-bromo-2-((3-methoxy-2,6-dimethylphenyl)amino)-5,6-dimethylisonicotinate



A mixture of methyl 2,3-dibromo-5,6-dimethylisonicotinate (5.0 g, 15.5 mmol), 3-methoxy-2,6-dimethyl-aniline (2.34 g, 15.5 mmol,), Cs_2CO_3 (12.6 g, 38.7 mmol) and Xantphos (896 mg, 1.55 mmol), $Pd_2(dba)_3$ (709 mg, 0.774 mmol) in DME (35 mL) was degassed and purged with N_2 for 3 times, then the mixture was stirred at 80 ℃ overnight under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica

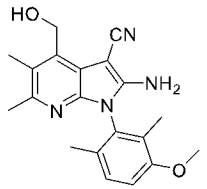
gel column eluting with EA/PA (0.5~35%) to afford the title compound (8.0 g, 65.7% yield) as a black brown solid. LCMS calc. for $C_{18}H_{22}BrN_2O_3$ $[M+H]^+$: m/z = 393.1; Found: 393.1.

Step 8: (3-bromo-2-((3-methoxy-2, 6-dimethylphenyl) amino) -5, 6-dimethylpyridin-4-yl) methanol



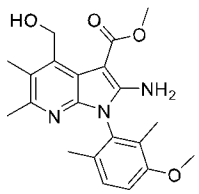
To a solution of methyl 3-bromo-2-((3-methoxy-2, 6-dimethylphenyl) amino)-5, 6-dimethylisonicotinate (3 g, 7.63 mmol) in DCM (21 mL) was added DIBAL-H (1 M, 21 mL). The mixture was stirred at -70 ℃ for 2 h., then quenched by addition H_2O (200 mL) at 0 ℃ in N_2, and extracted with DCM (150 mL x 3). The combined organic layers were washed with brine (80 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EA/PE (0-5%) to afford the title compound (3.0 g, 53.8% yield) as a yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.36 (s, 1H), 4.85 (d, *J* = 6.4 Hz, 2H), 3.85 (s, 3H), 2.27 (s, 3H). 2.25 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H). LCMS calc. for $C_{17}H_{22}BrN_2O_2$ $[M+H]^+$: m/z = 365.1; Found: 365.1.

Step 9: 2-amino-4-(hydroxymethyl)-1-(3-methoxy-2, 6-dimethylphenyl)-5, 6-dimethyl-1H-pyr rolo [2, 3-b] pyridine-3-carbonitrile



This compound was prepared using procedures analogous to those described for Example 6 Step 10 using (3-bromo-2-((3-methoxy-2, 6-dimethylphenyl) amino)-5, 6-dimethylpyridin-4-yl) methanol and malononitrile to afford the title product as a yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.06 (s, 2H), 4.47 (s, 3H), 3.81 (s, 3H), 2.32 (d, *J* = 14 Hz, 6H), 1.84 (s, 3H),1.77 (s, 3H). LCMS calc. for $C_{20}H_{23}N_4O_2$ $[M+H]^+$: m/z = 351.2; Found: 351.2.

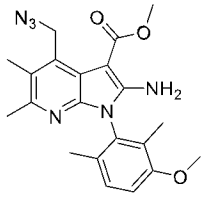
Step 10: methyl 2-amino-4-(hydroxymethyl)-1-(3-methoxy-2, 6-dimethylphenyl)-5, 6-dimethyl -1H-pyrrolo [2, 3-b] pyridine-3-carboxylate



This compound was prepared using procedures analogous to those described for Example 6 Step 11 using 2-amino-4-(hydroxymethyl)-1-(3-methoxy-2, 6-dimethylphenyl)-5, 6-dimethyl-1H-

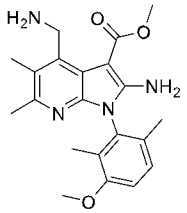
pyrrolo [2, 3-b] pyridine-3-carbonitrile to afford the title product as a yellow solid. LCMS calc. for $C_{21}H_{26}N_3O_4$ $[M+H]^+$: m/z = 384.2; Found: 384.2.

Step 11: methyl 2-amino-4-(azidomethyl)-1-(3-methoxy-2, 6-dimethylphenyl)-5, 6-dimethyl-1H-pyrrolo [2, 3-b] pyridine-3-carboxylate



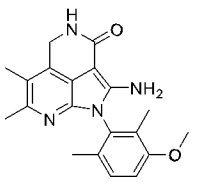
This compound was prepared using procedures analogous to those described for Example 6 Step 12 using methyl 2-amino-4-(hydroxymethyl)-1-(3-methoxy-2, 6-dimethylphenyl)-5, 6-dimethyl-1H-pyrrolo [2, 3-b] pyridine-3-carboxylate and DPPA to afford the title product as a yellow solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.25 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.78 (s, 2H), 5.05-5.14 (m, 2H), 3.83 (d, J = 14.8 Hz, 6H), 2.29 (s, 3H), 2.25 (s, 3H), 1.77 (s, 3H),1.69 (s, 3H). LCMS calc. for $C_{21}H_{25}N_6O_3$ $[M+H]^+$: m/z = 409.2; Found: 409.2.

Step 12: methyl 2-amino-4-(aminomethyl)-1-(3-methoxy-2, 6-dimethylphenyl)-5, 6-dimethy l-1H-pyrrolo [2, 3-b] pyridine-3-carboxylate



This compound was prepared using procedures analogous to those described for Example 6 Step 13 using methyl 2-amino-4-(azidomethyl)-1-(3-methoxy-2, 6-dimethylphenyl)-5, 6-dimethyl-1H-pyrrolo [2, 3-b] pyridine-3-carboxylate and PPh_3 to afford the title product as a white solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.28 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.68 (s, 2H), 4.20 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.27 (d, J = 4.0 Hz, 6H), 1.78 (s, 3H), 1.68 (s, 3H). LCMS calc. for $C_{21}H_{27}N_4O_3$ $[M+H]^+$: m/z = 383.2; Found: 383.2.

Step 13: 2-amino-1-(3-methoxy-2, 6-dimethylphenyl)-6, 7-dimethyl-4, 5-dihydropyrrolo [4, 3, 2-de] [2, 6] naphthyridin-3(1H)-one



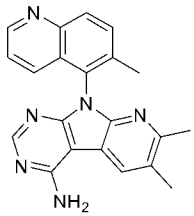
This compound was prepared using procedures analogous to those described for Example 6 Step 14 using methyl 2-amino-4-(aminomethyl)-1-(3-methoxy-2, 6-dimethylphenyl)-5, 6-dimethyl-1H-pyrrolo [2, 3-b] pyridine-3-carboxylate to afford the title product as a white solid. ^{1}H NMR:

(400 MHz, DMSO-d_6) δ 7.23 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H), 5.84 (s, 2H), 4.75 (s, 2H), 3.85 (s, 3H), 2.28 (s, 3H), 2.06 (s, 3H), 1.84 (s, 3H), 1.73 (s, 3H). LCMS calc. for $C_{20}H_{23}N_4O_2$ $[M+H]^+$: m/z = 351.2; Found: 351.1.

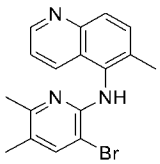
Step 14: 2-amino-1-(3-hydroxy-2, 6-dimethylphenyl)-6, 7-dimethyl-4, 5-dihydropyrrolo [4, 3, 2-de] [2, 6] naphthyridin-3(1H)-one

This compound was prepared using procedures analogous to those described for Example 6 Step 15 using 2-amino-1-(3-methoxy-2, 6-dimethylphenyl)-6, 7-dimethyl-4, 5-dihydropyr rolo [4, 3, 2-de] [2, 6] naphthyridin-3(1H)-one to afford the title product as a white solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.75 (s, 1H), 5.78 (s, 2H), 4.75 (s, 2H), 2.29 (s, 3H), 2.06 (s, 3H), 1.79 (s, 3H), 1.69 (s, 3H). LCMS calc. for $C_{19}H_{21}N_4O_2$ $[M+H]^+$: m/z = 337.2; Found: 337.1.

Example 8: 6,7-Dimethyl-9-(6-methylquinolin-5-yl)-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-4-amine

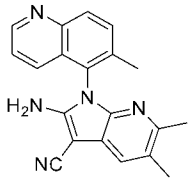


Step 1: N-(3-bromo-5,6-dimethylpyridin-2-yl)-6-methylquinolin-5-amine



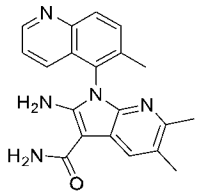
A mixture of 2,3-dibromo-5,6-dimethylpyridine (10.0 g, 37.7 mmol, Example 3 Step 2), 6-methylquinolin-5-amine (5.97 g, 37.7 mmol), Xantphos (2.18 g, 3.77 mmol), Cs_2CO_3 (30.7 g, 94.4 mmol) and $Pd_2(dba)_3$ (1.73 g, 1.89 mmol) in DME (60 mL) was degassed and purged with N_2 for 3 cycles, and then stirred at 80 ℃ overnight under N_2 atmosphere. The reaction mixture was cooled to r.t., diluted with water (250 mL), extracted with EA (50 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EA/PE (0~5%) to afford the title compound (7.50 g, 58.1% yield) as a yellow solid. ^{1}H NMR : (400 MHz, MeOD) δ 8.75 (dd, J = 4.4, 1.6 Hz, 1H), 8.33 (dd, J = 8.4, 0.4 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.61 (s, 1H), 7.45 (dd, J = 8.4, 4.4 Hz, 1H) , 2.37 (s, 3H) , 2.13 (s, 3H), 2.01 (d, J = 3.2 Hz, 3H). LCMS calc. for $C_{17}H_{17}BrN_3$ $[M+H]^+$: m/z = 342.1; Found: 342.1.

Step 2: 2-amino-5,6-dimethyl-1-(6-methylquinolin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



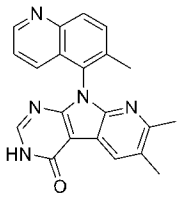
To a solution of propanedinitrile (2.89 g, 43.8 mmol) in DME (45 mL) was added *t*-BuONa (4.2 g, 43.8 mmol) under N_2 atmosphere and the mixture was stirred at 25 ℃ for 0.5 h. Then *N*-(3-bromo-5,6-dimethylpyridin-2-yl)-6-methylquinolin-5-amine (7.5 g, 21.9 mmol) was added at 25 ℃, followed by the addition of $Pd(dppf)Cl_2.CH_2Cl_2$ (1.79 g, 2.19 mmol). The resulting mixture was stirred at 85 ℃ overnight under N_2 atmosphere. The reaction mixture was quenched with water (50 mL) dropwise, extracted with EA (50 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was triturated with DCM (22 mL). The solid was collected by filtration to afford the title compound (3.5 g, 50% yield) as a yellow solid. LCMS calc. for $C_{20}H_{18}N_5$ $[M+H]^+$: m/z = 328.2; Found: 328.2.

Step 3: 2-amino-5,6-dimethyl-1-(6-methylquinolin-5-yl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide



This compound was prepared using procedures analogous to those described for Example 1 Step 9 using 2-amino-5,6-dimethyl-1-(6-methylquinolin-5-yl)-1H-pyrrolo[2,3-b] pyridine -3-carbonitrile to afford the title product as a yellow solid. ^{1}H NMR : (400 MHz, DMSO-d_6) δ 8.90 (d, J = 2.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.87-7.92 (m, 2H), 7.46 (dd, J = 8.4, 4.0 Hz, 1H), 7.36-7.38 (m, 1H), 6.90 (s, 2H), 6.74 (s, 2H), 2.27 (s, 3H), 2.14 (d, J = 4.0 Hz, 6H). LCMS calc. for $C_{20}H_{20}N_5O$ $[M+H]^+$: m/z = 346.2; Found: 346.2.

Step 4: 6,7-dimethyl-9-(6-methylquinolin-5-yl)-3,9-dihydro-4H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-4-one



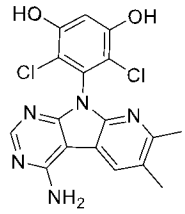
This compound was prepared using procedures analogous to those described for Example 1 Step 12 using 2-amino-5,6-dimethyl-1-(6-methylquinolin-5-yl)-1H-pyrrolo [2,3-b] pyridine-3-carboxamide and trimethoxymethane to afford the title product as a yellow solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 12.6 (br s, 1H), 8.90 (t, J = 4.0 Hz, 1H), 8.25 (s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 8.06 (s,

1H), 7.90 (d, J = 8.8 Hz, 1H), 7.35-7.40 (m, 2H), 2.40 (s, 3H), 2.33 (s, 3H), 2.05 (s, 3H). LCMS calc. for $C_{21}H_{18}N_5O$ $[M+H]^+$: m/z = 356.1; Found: 356.2.

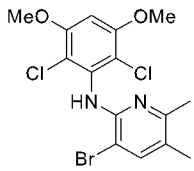
Step 5: 6,7-dimethyl-9-(6-methylquinolin-5-yl)-9H-pyrido[3',2':4,5]pyrrolo[2,3-d] pyrimidin-4-amine

This compound was prepared using procedures analogous to those described for Example 1 Step 13-14 using 6,7-dimethyl-9-(6-methylquinolin-5-yl)-3,9-dihydro-4H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-4-one in Step 13 to afford the title product as a white solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.19 (d, J = 4.0 Hz, 1H), 8.63 (d, J = 8.8 Hz, 1H), 8.30-8.31 (m, 2H), 8.05 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.60-7.63 (m, 1H), 2.53 (s, 3H), 2.49 (s, 3H), 2.22 (s, 3H). LCMS calc. for $C_{21}H_{19}N_6$ $[M+H]^+$: m/z = 355.2; Found: 355.1.

Example 9: 5-(4-Amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-4,6-dichlorobenzene-1,3-diol

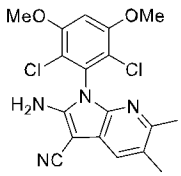


Step 1: 3-bromo-N-(2,6-dichloro-3,5-dimethoxyphenyl)-5,6-dimethylpyridin-2-amine



This compound was prepared using procedures analogous to those described for Example 8 Step 1 using 2,3-dibromo-5,6-dimethylpyridine (Example 3 Step 2) and 2,6-difluoro-3,5-dimethoxyaniline to afford the title product as a white solid. LCMS calc. for $C_{15}H_{16}BrCl_2N_2O_2$ [M+H]: m/z = 407.2; Found: 407.2.

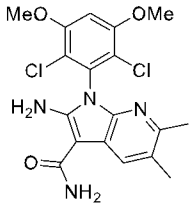
Step 2: 2-amino-1-(2,6-dichloro-3,5-dimethoxyphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



This compound was prepared using procedures analogous to those described for Example 8 Step 2 using propanedinitrile and 3-bromo-N-(2,6-dichloro-3,5-dimethoxyphenyl)-5,6-

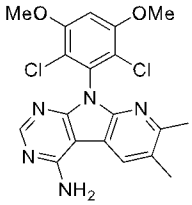
dimethylpyridin-2-amine to afford the title product as a brown solid. LCMS calc. for $C_{18}H_{17}Cl_2N_4O_2$ $[M+H]^+$: m/z = 391.1; Found: 391.1.

Step 3: 2-amino-1-(2,6-dichloro-3,5-dimethoxyphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide



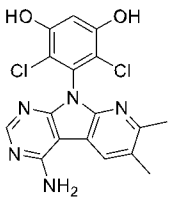
This compound was prepared using procedures analogous to those described for Example 1 Step 9 using 2-amino-1-(2,6-dichloro-3,5-dimethoxyphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile to afford the title product. LCMS calc. for $C_{18}H_{19}Cl_2N_4O_3$ $[M+H]^+$: m/z = 409.2; Found: 409.2.

Step 4: 9-(2,6-dichloro-3,5-dimethoxyphenyl)-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-4-amine



This compound was prepared using procedures analogous to those described for Example 1 Step 12-14 using 2-amino-1-(2,6-dichloro-3,5-dimethoxyphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide and trimethoxymethane in Step 12 to afford the title product. LCMS calc. for $C_{19}H_{18}Cl_2N_5O_2$ $[M+H]^+$: m/z = 418.1; Found: 418.1.

Step 5: 5-(4-amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-4,6-dichlorobenzene-1,3-diol

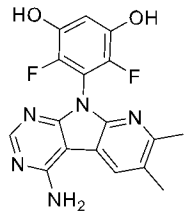


To a solution of 9-(2,6-dichloro-3,5-dimethoxyphenyl)-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-4-amine (50 mg, 0.12 mmol) in DCM (5 mL) was added BBr_3 (0.06 g, 0.24 mmol) dropwise at 0 ℃. The mixture was stirred at r.t. for 1 h., quenched with H_2O (10 mL) and extracted with 2-MeTHF (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by Prep-HPLC eluting with MeCN/water (10-95% with 0.1% NH_4HCO_3) to afford the title

product (2.7 mg, yield:5.8%). ^{1}H NMR (400 MHz,) δ 10.60 (s, 2H), 8.57 (s, 1H), 8.20 (s, 1H), 7.38 (s, 2H), 6.92 (s, 1H), 2.43 (s, 3H), 2.38 (s, 3H). LCMS calc. for $C_{17}H_{14}Cl_2N_5O_2$ $[M+H]^+$: m/z = 390.2; Found: 390.2.

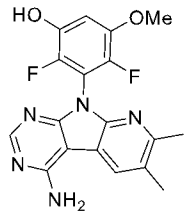
Example 10: 5-(4-Amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-4,6-difluorobenzene-1,3-diol and

Example 11: 3-(4-Amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-difluoro-5-methoxyphenol



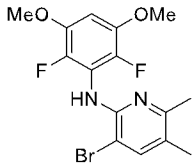
Example 10

and



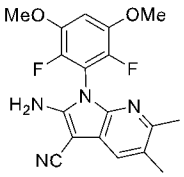
Example 11

Step 1: 3-bromo-N-(2,6-difluoro-3,5-dimethoxyphenyl)-5,6-dimethylpyridin-2-amine



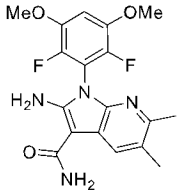
This compound was prepared using procedures analogous to those described for Example 8 Step 1 using 2,3-dibromo-5,6-dimethylpyridine (Example 3 Step 2) and 2,6-difluoro-3,5-dimethoxyaniline to afford the title product as a white solid. LCMS calc. for $C_{15}H_{16}BrF_2N_2O_2$ [M+H]: m/z = 373.2; Found: 373.2.

Step 2: 2-amino-1-(2,6-difluoro-3,5-dimethoxyphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile



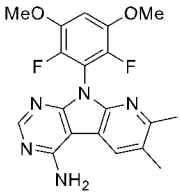
This compound was prepared using procedures analogous to those described for Example 8 Step 2 using 2 3-bromo-N-(2,6-difluoro-3,5-dimethoxyphenyl)-5,6-dimethylpyridin-2-amine to afford the title product as a brown solid. LCMS calc. for $C_{18}H_{17}F_2N_4O_2$ $[M+H]^+$: m/z = 359.2; Found: 359.2.

Step 3: 2-amino-1-(2,6-difluoro-3,5-dimethoxyphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide



This compound was prepared using procedures analogous to those described for Example 1 Step 9 using 2-amino-1-(2,6-difluoro-3,5-dimethoxyphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile to afford the title product. LCMS calc. for $C_{18}H_{19}F_2N_4O_3$ $[M+H]^+$: m/z = 377.2; Found: 377.2.

Step 4: 9-(2,6-difluoro-3,5-dimethoxyphenyl)-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-4-amine



This compound was prepared using procedures analogous to those described for Example 1 Step 12-14 using 2-amino-1-(2,6-difluoro-3,5-dimethoxyphenyl)-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide and trimethoxymethane in Step 12 to afford the title product. LCMS calc. for $C_{19}H_{17}F_2N_4O_3$ $[M+H]^+$: m/z = 387.2; Found: 387.2.

Step 5: 5-(4-amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-4,6-difluorobenzene-1,3-diol (Example 10) and 3-(4-amino-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-9-yl)-2,4-difluoro-5-methoxyphenol (Example 11)

To a solution of 9-(2,6-difluoro-3,5-dimethoxyphenyl)-6,7-dimethyl-9H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-4-amine (90 mg, 0.23 mmol) in DCM (10 mL) was added BBr_3 (0.115 g, 0.46 mmol) dropwise at 0 ℃. The mixture was stirred at r.t. for 1 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with 2-MeTHF (10 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure and purified by Prep-HPLC eluting with MeCN/water (10-95% with 0.1% NH_4HCO_3) to afford two products: P1 (the earlier eluted fraction: 5.46 mg, yield:6.5%) and P2 (the latter eluted fraction: 3.35 mg, yield:3.8%). P1 was assigned to Example 10. ^{1}H NMR (400 MHz, DMSO) δ 9.87 (s, 2H), 8.60 (s, 1H), 8.24 (s, 1H), 7.44 (s, 2H), 6.80 (t, J = 8.6 Hz, 1H), 2.46 (s, 3H), 2.39 (s, 3H). LCMS calc. for $C_{17}H_{14}F_2N_5O_2$ $[M+H]^+$: m/z = 358.0; Found: 358.0. And P2 was assigned to Example 11. ^{1}H NMR (400 MHz, DMSO) δ 10.18 (s, 1H), 8.61 (s, 1H), 8.24 (s, 1H), 7.45 (s, 2H), 6.97 (t, J = 8.3 Hz, 1H), 3.87 (s, 3H), 2.45 (s, 3H), 2.39 (s, 3H). LCMS calc. for $C_{18}H_{16}F_2N_5O_2$ $[M+H]^+$: m/z = 372.0; Found: 372.0.

Example A: PKMYT1 kinase assay

PKMYT1 kinase assay was initiated for evaluating potential inhibitory effect of candidate compounds. PKMYT1 was ordered from Carna, 05-176 and stored at -80°C in aliquots. ADP quantity produced from ATP hydrolysis by PKMYT1 catalytic reaction was measured using a commercially available ADP-Glo Assay (ADP-Glo™ Kinase Assay from Promega, 10 000 assays, #V9102). Briefly, Compounds dissolved in DMSO (Sigma, D8418) were plated into a 384-well assay plate (Greiner, 784075) in duplicate using a dispenser (Labcyte, Echo 665), and tested on a 10-point 3-fold serial dilution. Assay measurements were performed with 1×buffer comprising 1x kinase Buffer with 50uM DTT. Add 2.5 μl 2X PKMYT1 mix into the assay plates. After centrifuging at 1000g for 30s, the plates were covered and left to incubate for 10 minutes at RT before the addition of 2.5 μl 2X substrate mix [Unactive CDK1 (SignalChem, C22-14G-20) and ATP (Promega, V910B)] to initiate reaction. The final PKMYT1 enzyme concentration was 2.5ng/ul; the final ATP concentration was 200uM and the final unactive CDK1 concentration was 0.01ug/ul. After incubating 2 hours at RT, 4 μL of ADP-Glo reagent was added and the plate was spun briefly and sealed and incubated in the dark for 40 minutes at RT. Following this, 8 μL of kinase detection reagent was added and the plate was spun briefly, sealed and incubated for 40 minutes at RT in the dark. Read on a multimode plate reader (Perkin Elmer, Envision 2104) in Luminescence mode. Average luminescence signal of high control (Wells with 1% DMSO) was calculated as High Control (HC). Average luminescence signal of low control (Wells with 10000nM PD0166285) was calculated as Low control (LC).

$\%inhibition = 100 - 100*(Signal_{cmpd} - Signal_{Ave\_LC})/(Signal_{Ave\_HC} - Signal_{Ave\_LC})$.

IC_{50} values were determined by fitting the data to the standard 4 parameters with Hill Slope using GraphPad Prism software. IC_{50} data is proved below in Table 1. +++<=0.1 μM, 0.1 μM< ++<=1 μM, +>1 μM.

Example B: Cell viability assay

Cell viability studies were conducted in HCC1569 cell line. Cells were cultured in RPMI 1640 (Hyclone, SH3080901B) with 10% FBS (AusGeneX, FBS500-S) and 1% penicillin-streptomycin (Gibco, 15140122). Cells were seeded in 96-well cell culture plates (PerkinElmer, 6005680) at a density of 1500 cells/well. Compounds dissolved in DMSO were plated in duplicate using a multichannel pipette, and tested on a 9-point 3-fold serial dilution. DMSO final concentration was 0.2% for all wells. Cells were incubated for 7 days in a 37 ℃ active humidified incubator at 5% CO_2. Cell viability was measured using the Cell Titer-Glo reagent (Promega, Catalog#: G7573) as manufacturer's instructions. Luminescence signal was measured with a multimode plate reader (Perkin Elmer, Envision 2105 or BMG, ClarioStar Plus). Average values of 0.2% DMSO treated wells in a plate was calculated as high control (HC). Average values of only medium in a plate was calculated as low control (LC).

%inhibition=100 - 100*($Signal_{cmpd}$ - $Signal_{Ave\_LC}$)/($Signal_{Ave\_HC}$ - $Signal_{Ave\_LC}$).

IC_{50} values were determined by fitting the data to the standard 4 parameters with Hill Slope using GraphPad Prism software. IC_{50} data is proved below in Table 2.

+++<=5 μM, 5 μM< ++<=50 μM, + >50 μM, ND: not determine.

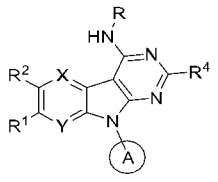
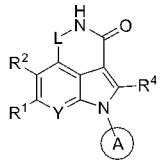
Table 1

Example No.	PKMYT1 kinase assay (IC_{50})	Cell viability assay (IC_{50})
1	+++	+++
2	+++	++
3	+++	+++
4	+++	+++
5	++	++
6	+++	++
7	+++	++
8	+	++
9	++	ND
10	+++	++
11	++	++

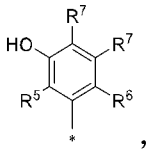
Although the present disclosure has been comprehensively described through its embodiments, it is worth noting that various changes and modifications are obvious to those skilled in the art. Such changes and modifications should be included in the scope of the appended claims of the present disclosure.

What is Claimed:

1. A compound of formula (IA) and (IB), or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variants or prodrugs thereof, wherein:


(IA) and

(IB);

ring A is selected from: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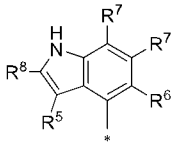
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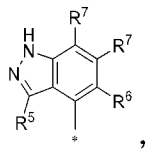
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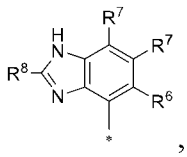
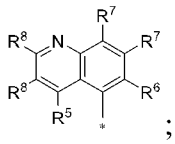

, or

;

X is N or CR^3;

Y is N or CR^9;

L is $(CR^{10}R^{11})_n$, $NR^{12}(CH_2CH_2)_m$, or $O(CH_2CH_2)_m$;

n is 1, 2 or 3; m is 0 or 1;

R is selected from H, D or C_1-C_6 alkyl optionally substituted with F, OH or CN;

R^1, R^2 and R^3 are each independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

or R^1 and R^2 together with the carbon atoms to which they are attached form a C_3-C_7 cycloalkyl, or 4-7 membered heterocycloalkyl, wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

or R^2 and R^3 together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl, or 4-7 membered heterocycloalkyl, wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^cR^f$, $P(O)OR^cOR^f$, $OP(O)OR^cOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

each R^4 is independently selected from H, D, NH_2, CN, C_1-C_3 alkyl optionally substituted with D, halogen or CN;

each R^5 is independently selected from H, D, halo, CN, C_1-C_6 alkyl optionally substituted with D, halogen or CN;

each R^6 is independently selected from H, D, halo, CN, OR^B, SF_5, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl is optionally substituted with D, halo, CN, NH_2, OH, -O-C_1-C_6 alkyl, -OC_1-C_6 haloalkyl;

each R^7 is independently selected from H, D, halogen, Me, CF_3, OH, OMe, OCF_3;

each R^8 is independently selected from H, D, CN, SF_5, C_1-C_6 alkyl optionally substituted with D, halogen or CN;

each R^9 is independently selected from H, D, CN, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_3-C_5 cycloalkyl;

R^{10} and R^{11} are each independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, CN, halo, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $NR^cS(O)_2R^b$, or $NR^cS(O)_2NR^cR^d$;

or R^{10} and R^{11} together with the carbon atom(s) to which they are attached form a C_3-C_7 cycloalkyl, or 4-7 membered heterocycloalkyl, wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, or $NR^cS(O)_2NR^cR^d$;

R^{12} is H, D, C_1-C_3 alkyl optionally substituted with D, OH, halogen, CN;

each R^A is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-

C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^cOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

each R^B is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$;

R^C and R^D are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, OC_1-C_4 haloalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$;

or R^C and R^D together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, oxo, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, or C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, or OC_1-C_4 haloalkyl;

each R^a is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently

selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

each R^b is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl;

R^c and R^d are each independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10} aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-5-10 membered heteroaryl, C_6-C_{10} aryl-C_6-C_{10} aryl, 5-10 membered heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C_6-C_{10} aryl, or 5-10 membered heteroaryl-5-10 membered heteroaryl; wherein the C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10} aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-5-10 membered heteroaryl, C_6-C_{10} aryl-C_6-C_{10} aryl, 5-10 membered heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C_6-C_{10} aryl, or 5-10 membered heteroaryl-5-10 membered heteroaryl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C(O)OR^{a1}, C(O)R^{b1}, S(O)$_2$$R^{b1}$, C_1-C_4 alkyl-O-C_1-C_4 alkyl, and C_1-C_4 alkyl-O-C_1-C_4 alkyl-O-;

or R^c and R^d together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C(O)OR^{a1}, C(O)R^{b1}, S(O)$_2$$R^{b1}$, C_1-C_4 alkoxy-C_1-C_4 alkyl, and C_1-C_4 alkoxy-C_1-C_4 alkoxy;

each R^e is independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, (C_1-C_4 alkoxy)-C_1-C_4 alkyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkyl, C_3-C_{10} cycloalkyl-C_1-C_4 alkyl, 5-10 membered heteroaryl-C_1-C_4 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_4 alkyl;

each R^f is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, or 4-10 membered heterocycloalkyl;

each R^{a1} is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, or C_1-C_4 haloalkoxy;

each R^{b1} is independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alky; wherein the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alky is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl.

2. The compound of claim 1, wherein, X is N.

3. The compound of claim 1, wherein, X is CR^3.

4. The compound of claim 3, wherein, R^3 is independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

5. The compound of claim 3, wherein, R^3 is independently selected from H, D, halo, CN, SF_5, NH_2, OH, NH_2, OCH_3, OCH_2CH_3, $NHCH_3$, $NHCH_2CH_3$, $NH(CH_3)_2$, CH_3, CH_2CH_3, CF_3, CH_2CF_3, $C(O)R^B$, or $C(O)NR^CR^D$.

6. The compound of anyone of claim 1-5, wherein, R is selected from H, D or C_1-C_6 alkyl optionally substituted with F, OH or CN.

7. The compound of anyone of claim 1-6, wherein, R^1 is independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$; preferably, R^1 is independently selected from H, D, halo, CN, SF_5, OH, NH_2, OCH_3, OCH_2CH_3, $NHCH_3$, $NHCH_2CH_3$, $NH(CH_3)_2$, CH_3, CH_2CH_3, CF_3, CH_2CF_3, $C(O)R^B$, $C(O)NR^CR^D$.

8. The compound of anyone of claim 1-7, wherein, R^2 is independently selected from H, D, halo, CN, SF_5, NR^CR^D, OR^A, $C(O)R^B$, $C(O)NR^CR^D$, C_1-C_6 alkyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents independently selected from D, OH, CN, halo, C_1-C_4 alkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$; preferably, R^2 is independently selected from H, D, halo, CN, SF_5, OH, NH_2, OCH_3, OCH_2CH_3, $NHCH_3$, $NHCH_2CH_3$, $NH(CH_3)_2$, CH_3, CH_2CH_3, CF_3, CH_2CF_3, $C(O)R^B$, $C(O)NR^CR^D$.

9. The compound of anyone of claim 1-6, wherein, R^1 and R^2 together with the carbon atoms to which they are attached form a C_3-C_7 cycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

10. The compound of anyone of claim 1-6, wherein, R^1 and R^2 together with the carbon atoms to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

11. The compound of anyone of claim 1-3, wherein, R^2 and R^3 together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^e)(OR^d)$, $C(=NR^e)NR^cR^d$, $NR^dC(=NR^e)NR^cR^d$, $NR^dC(=NR^e)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

12. The compound of anyone of claim 1-3, wherein, R^2 and R^3 together with the carbon atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from D, halo, CN, NO_2, oxo, OR^a, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^e)(OR^d)$, $C(=NR^e)NR^cR^d$, $NR^dC(=NR^e)NR^cR^d$, $NR^dC(=NR^e)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

13. The compound of anyone of claim 1-12, wherein, R^4 is selected from H, D, NH_2, or CN, Me, CD_3 or CF_3.

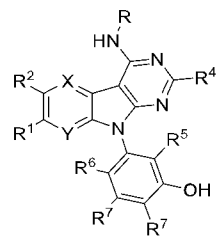
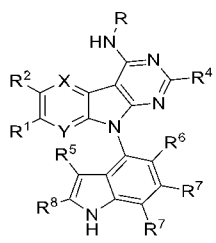
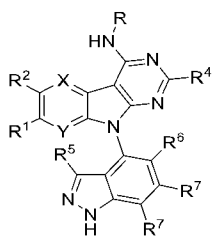
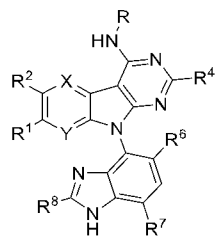
14. The compound of anyone of claim 1-13, wherein, R^5 is selected from H, D, halo, CN, CH_3, CD_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CH_2OH, CH_2CH_2OH.

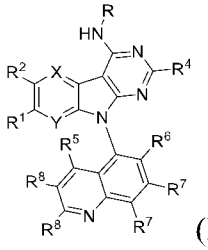
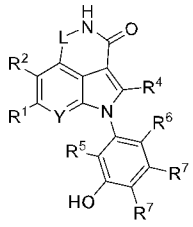
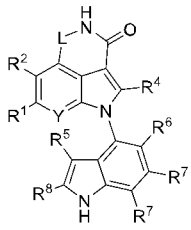
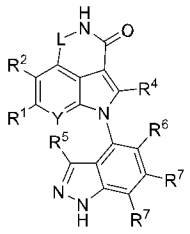
15. The compound of anyone of claim 1-15, wherein, R^6 is selected from H, D, halo, CN, CH_3, CD_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CH_2OH, CH_2CH_2OH.

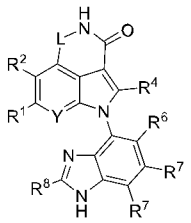
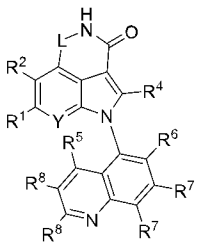
16. The compound of anyone of claim 1-15, wherein, R^7 is H, D, F, Cl, Me, CF_3, OH, OMe.

17. The compound of anyone of claim 1-16, wherein, R^8 is selected from H, D, CN, SF_5, CH_3, CD_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3.

18. The compound of anyone of claim 1-17, wherein, the compound of formula (IA) and (IB) is represented by the compound of formula (IAa), (IAb), (IAc), (IAd), (IAe), (IBa), (IBb), (IBc), (IBd), or (IBe):

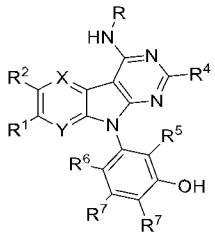
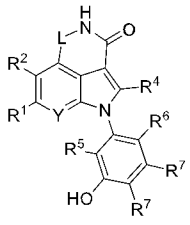

(IAa),

(IAb),

(IAc),

(IAd),

 (IAe),  (IBa),  (IBb),  (IBc),

 (IBd), or  (IBe);

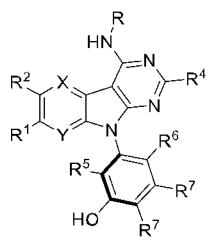
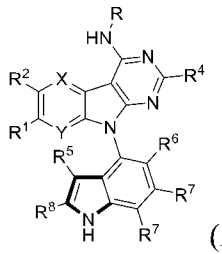
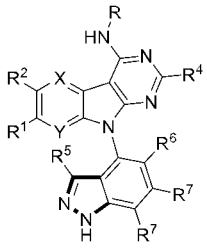
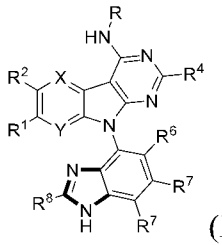
or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variants or prodrugs thereof; wherein X, Y, L, R, R^1, R^2, R^4, R^5, R^6, R^7, R^8 are defined with respect to Formula (IA) and (IB).

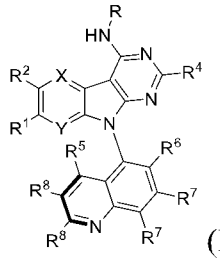
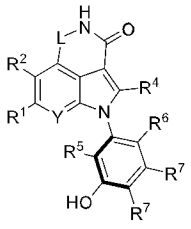
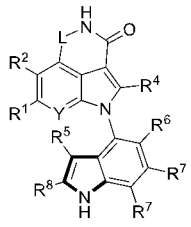
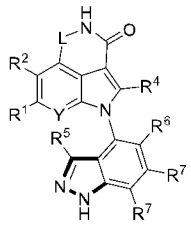
19. The compound of claim 18, wherein, the compound of formula (IA) and (IB) is represented by the compound of formula (IAa), (IBa):

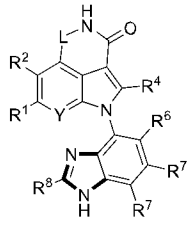
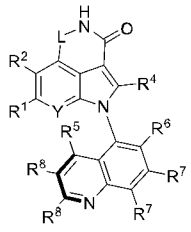
 (IAa),  (IBa);

or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variants or prodrugs thereof; wherein X, Y, L, R, R^1, R^2, R^4, R^5, R^6 and R^7 are defined with respect to Formula (IA) and (IB).

20. The compound of anyone of claim 1-19, wherein, the compound of formula (IA) and (IB) is represented by the compound of formula (IIAa), (IIAb), (IIAc), (IIAd), (IIAe), (IIBa), (IIBb), (IIBc), (IIBd), or (IIBe):

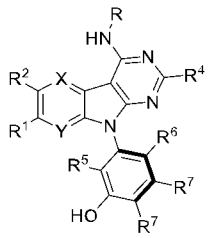
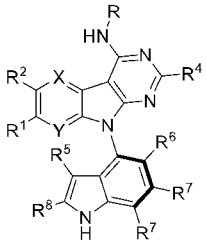
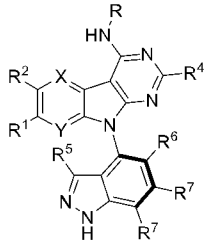
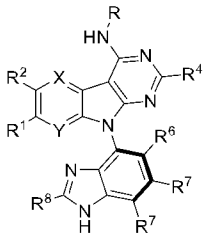
 (IIAa),  (IIAb),  (IIAc),  (IIAd),

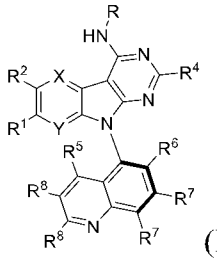
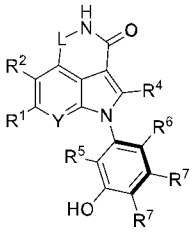
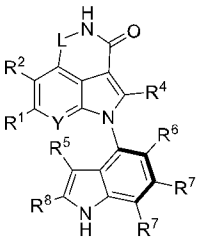
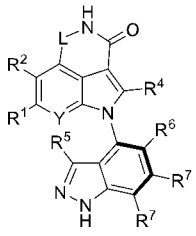
 (IIAe),  (IIBa),  (IIBb),  (IIBc),

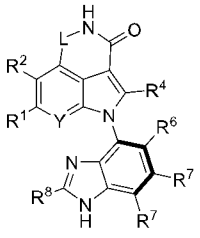
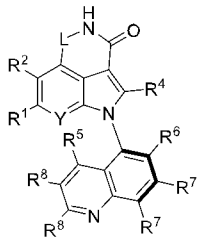
 (IIBd), or  (IIBe);

or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, Isotopic variants or prodrugs thereof; wherein X, Y, L, R, R^1, R^2, R^4, R^5, R^6, R^7, R^8 are defined with respect to Formula (IA) and (IB).

21. The compound of anyone of claim 1-20, wherein, the compound of formula (IA) and (IB) is represented by the compound of formula (IIIAa), (IIIAb), (IIIAc), (IIIAd), (IIIAe), (IIIBa), (IIIBb), (IIIBc), (IIIBd), or (IIIBe):

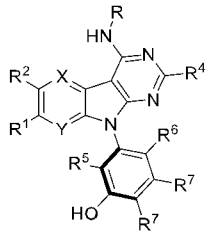
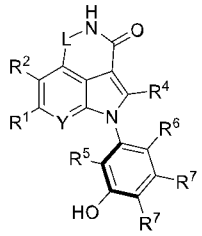
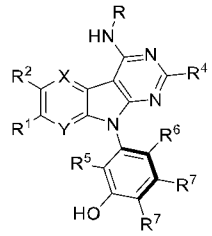
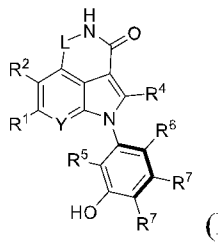
 (IIIAa),  (IIIAb),  (IIIAc),  (IIIAd),

 (IIIAe),  (IIIBa),  (IIIBb),  (IIIBc),

 (IIIBd), or  (IIIBe);

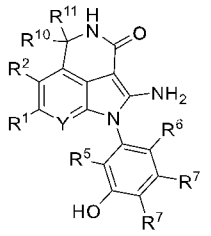
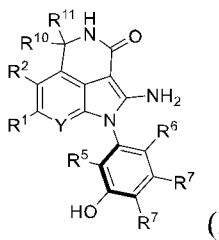
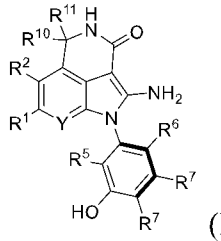
or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, Isotopic variants or prodrugs thereof; wherein X, Y, L, R, R^1, R^2, R^4, R^5, R^6, R^7, R^8 are defined with respect to Formula (IA) and (IB).

22. The compound of anyone of claim 1-21, wherein, the compound of formula (IA) and (IB) is represented by the compound of formula (IIAa), (IIBa), (IIIAa), (IIIBa):


(IIAa),

(IIBa),

(IIIAa),

(IIIBa);

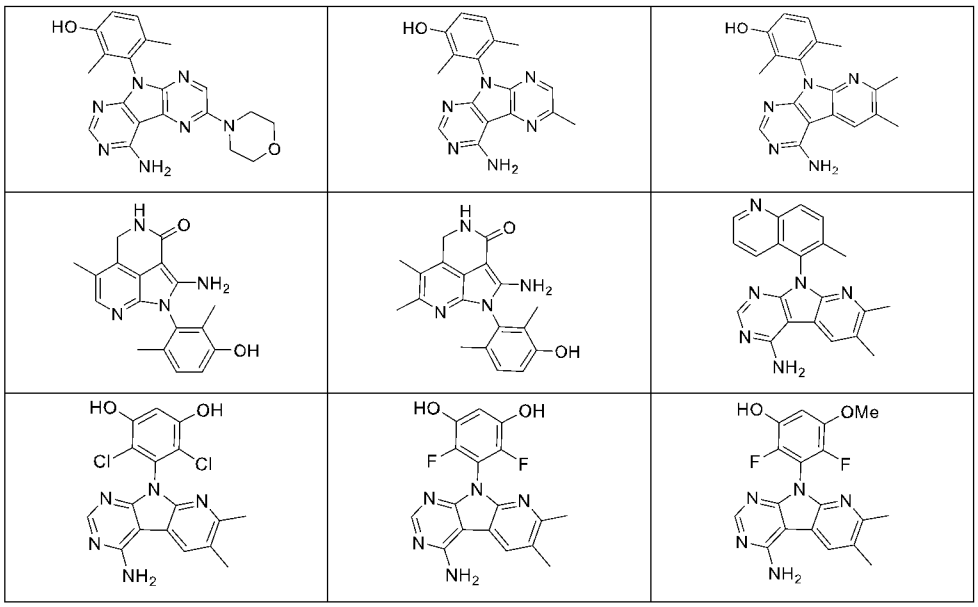
or pharmaceutically acceptable salt, stereoisomer, solvate, N-oxide, isotopic variants or prodrugs thereof; wherein X, Y, L, R, R^1, R^2, R^4, R^5, R^6, R^7 are defined with respect to Formula (IA) and (IB).

23. The compound of anyone of claim 1-22, wherein, the compound of formula (IB) is represented by the compound of formula (IVBa), (IVBb), or (IVBc):


(IVBa),

(IVBb), or

(IVBc);

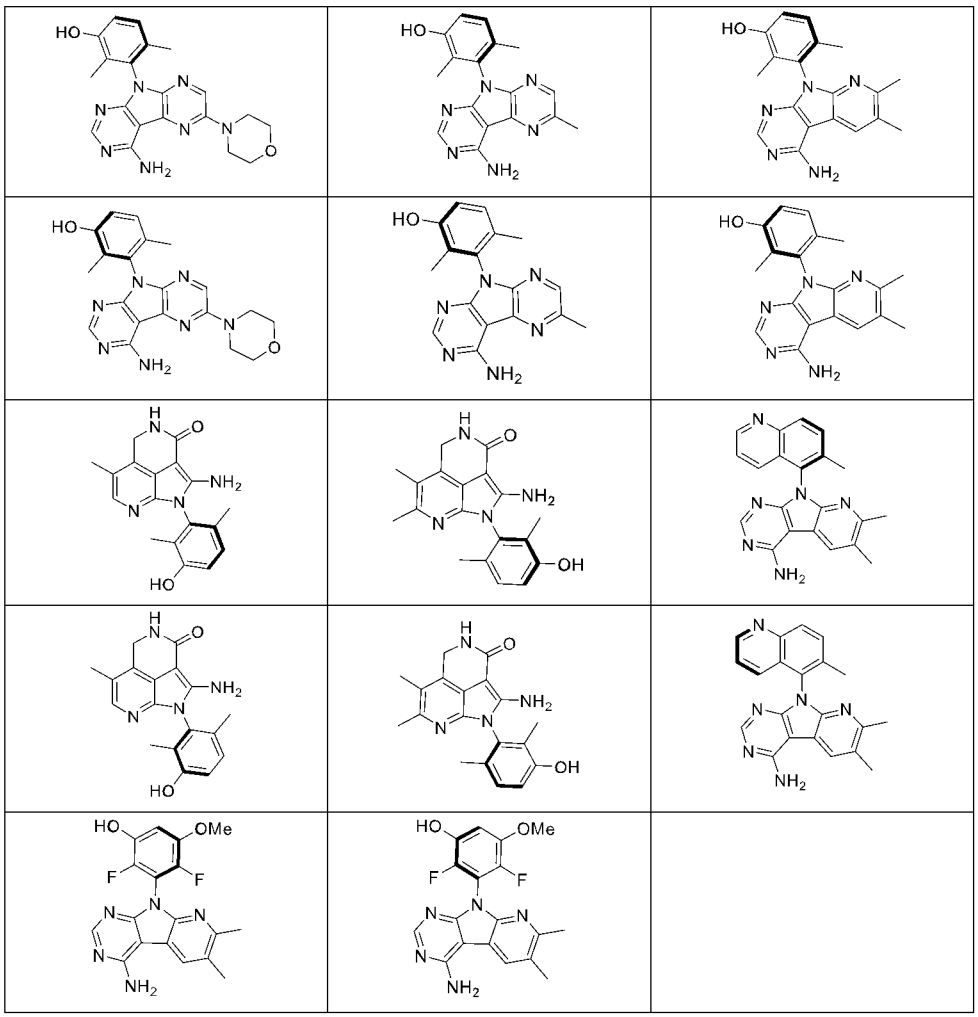
or pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variant or prodrugs thereof; wherein Y, R^1, R^2, R^5, R^6, R^7, R^8, R^{10}, R^{11} are defined with respect to Formula (IB).

24. The compound of anyone of claim 1-23, wherein, the compound of Formula (IA) and (IB) is:



or a pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variants or prodrugs thereof.

25. The compound of claim 24, wherein, the compound is:



or a pharmaceutically acceptable salt, stereoisomer, atropisomer, solvate, N-oxide, isotopic variants or prodrugs thereof.

26. A pharmaceutical composition comprising a compound of anyone of claim 1-25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

27. A method of treating a subject in need thereof comprising administering to the subject the compound of anyone of claim 1-25, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 26.

28. The method of claim 27, wherein, the subject is suffering from, and is in need of a treatment for, a disease or condition having the symptom of cell hyperproliferation.

29. The method of claim 28, wherein, the disease or condition is a cancer.

30. The method of claim 29, wherein, the cancer is a cancer with CCNE1 amplification, FBXW7 loss-of-function mutations or other genetic alterations which depend on PKMYT1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2023/113479

A. CLASSIFICATION OF SUBJECT MATTER

C07D471/16(2006.01)i; A61K31/395(2006.01)i; A61P35/00(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)

IPC: C07D; A61K; A61P

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)

CNTXT, DWPI, WPABS, CNKI, ISI Web of Science, STN(CAPLUS), STN(REGISTRY), STN(MARPAT), structure search, tricyclic heterocyclic, cancer?, tumo?r, cell hyperproliferation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2023155892 A1 (INSILICO MEDICINE IP LTD.) 24 August 2023 (2023-08-24) description, pages 25-27,	1, 7-8, 13-16, 18-19, 26-30
E	WO 2023198199 A1 (SIMCERE ZAIMING PHARMACEUTICAL CO., LTD.) 19 October 2023 (2023-10-19) description, pages 1-2 and 15	1, 7-8, 13-16, 18-19, 26-30
A	WO 2022094354 A1 (LENGO THERAPEUTICS, INC.) 05 May 2022 (2022-05-05) claims 1, 68-70; description, pages 232-233	1-30
A	WO 2014164596 A1 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN) 09 October 2014 (2014-10-09) claims 1, 13-14, 17 and 21; description, pages 2-4, 142	1-30
A	WO 9702266 A1 (CIBA-GEIGY AG et al.) 23 January 1997 (1997-01-23) claims 1-18; description, page 64	1-30
A	WO 2008079965 A1 (INCYTE CORPORATION et al.) 03 July 2008 (2008-07-03) claims 1-102; description, page 77	1-30

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2023	**04 December 2023**

Name and mailing address of the ISA/CN	Authorized officer
CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**GAN,Yu** Telephone No. **(+86) 010-53962246**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020020385 A1 (SHANGHAI HANSOH BIOMEDICAL CO., LTD. et al.) 30 January 2020 (2020-01-30) claims 1-26	1-30
A	WO 2021195781 A1 (REPARE THERAPEUTICS INC.) 07 October 2021 (2021-10-07) claims 1-53	1-30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2023/113479

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.: **27-30**
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claims 27-30 includes the method for treatment of human body by therapy as defined in PCT Rule 39.1(iv). This search has been carried out on the basis of the subject matter of the use of the claimed compound for preparation of a medicament for treating 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/CN2023/113479

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2023155892	A1	24 August 2023	None			
WO	2023198199	A1	19 October 2023	None			
WO	2022094354	A1	05 May 2022	CO	2023006748	A2	18 August 2023
				AU	2021372535	A1	08 June 2023
				TW	202233603	A	01 September 2022
				IL	302457	A	01 June 2023
				EP	4237418	A1	06 September 2023
				KR	20230116795	A	04 August 2023
				ECSP	23039172	A	31 August 2023
				CA	3196676	A1	05 May 2022
WO	2014164596	A1	09 October 2014	AU	2014249192	A1	10 September 2015
				AU	2014249192	B2	21 December 2017
				CA	2903463	A1	09 October 2014
				EP	2970312	A1	20 January 2016
				EP	2970312	A4	10 August 2016
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				US	9675697	B2	13 June 2017
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				JP	6401773	B2	10 October 2018
WO	9702266	A1	23 January 1997	CY	2365	B1	04 June 2004
				EP	0836605	A1	22 April 1998
				EP	0836605	B1	06 February 2002
				DK	0836605	T3	13 May 2002
				TR	199800012	T1	21 April 1998
				SK	398	A3	08 July 1998
				MX	9800215	A	31 March 1998
				PL	324285	A1	11 May 1998
				PL	188959	B1	31 May 2005
				KR	19990028756	A	15 April 1999
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				NO	975956	D0	18 December 1997
				NO	975956	L	10 February 1998
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				ES	2172670	T3	01 October 2002
				NZ	312665	A	30 August 1999
				ATE	212993	T1	15 February 2002
				CZ	1598	A3	15 April 1998
				HK	1008222	A1	07 May 1999
				PT	836605	E	31 July 2002
				JPH	11508570	A	27 July 1999
				JP	4146514	B2	10 September 2008
				HU	9900330	A2	28 May 1999
				HU	9900330	A3	28 August 2001
				IL	122855	A0	16 August 1998
				IL	122855	A	31 August 2004

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2023/113479

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
				AU	6414896	A	05 February 1997
				AU	707626	B2	15 July 1999
				CA	2224435	A1	23 January 1997
				CA	2224435	C	05 August 2008
				SI	9620103	A	31 October 1998
				EA	199800116	A1	29 October 1998
				EA	001428	B1	26 February 2001
				BR	9609617	A	25 May 1999
				BR	9609617	B1	27 July 2010
				DE	69619114	D1	21 March 2002
				DE	69619114	T2	02 October 2002
WO	2008079965	A1	03 July 2008	US	2013274257	A1	17 October 2013
				US	8841318	B2	23 September 2014
				EP	2121692	A1	25 November 2009
				EP	2121692	B1	10 April 2013
				JP	2010514690	A	06 May 2010
				JP	5492565	B2	14 May 2014
				US	2008188500	A1	07 August 2008
				US	8513270	B2	20 August 2013
				CA	2673038	A1	03 July 2008
				CA	2673038	C	15 December 2015
				ES	2415863	T3	29 July 2013
WO	2020020385	A1	30 January 2020	None			
WO	2021195781	A1	07 October 2021	IL	296934	A	01 December 2022
				EP	4126879	A1	08 February 2023
				CO	2022015638	A2	18 November 2022
				CA	3177200	A1	07 October 2021
				BR	112022019611	A2	29 November 2022
				CR	20220558	A	12 December 2022
				KR	20230011279	A	20 January 2023
				AU	2021250744	A1	17 November 2022
				JP	2023521633	A	25 May 2023
				ECSP	22083904	A	30 November 2022
				US	2023151014	A1	18 May 2023