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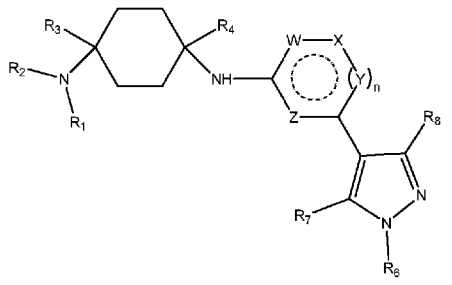
(54) Title: N1 -(4-(5-(CYCLOPROPYLMETHYL)-1 -METHYL-1 H-PYRAZOL-4-YL)PYRIDIN-2-YL)CYCLOHEXANE-1,4-DIAMINE DERIVATIVES AND RELATED COMPOUNDS AS CK1 AND/OR IRAKI INHIBITORS FOR TREATING CANCER



(I)

(57) Abstract: The present invention provides pyrazole derivatives of Formula (I), and in particular N1-(4-(5-(cyclopropylmethyl)-1-methyl-lH-pyrazol-4-yl) pyridin-2-yl)cyclohexane-1,4-diamine derivatives and related compounds as casein kinase 1 (CK1) and/or interleukin 1 receptor associated kinase 1 (IRAKI) inhibitors for treating cancer, inflammatory and immune related disorders.

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N1 -(4-(5-(CYCLOPROPYLMETHYL)-1 -METHYL-1 H-PYRAZOL-4-YL)PYRIDIN-2-YL)CYCLOHEXANE-1 ,4-DIAMINE DERIVATIVES AND RELATED COMPOUNDS AS CK1 AND/OR IRAKI INHIBITORS FORTREATING CANCER

CROSS REFERENCE TO RELATED APPLICATION

This application claims the priority to U.S. Provisional Application No. 62/453,192, filed February 1, 2017; the disclosure of which is incorporated herein by reference in its entirety.

TECHNOLOGICAL FIELD

The present invention provides pyrazole derivatives and uses thereof in methods of treating malignant disease and disorders and methods for treating inflammatory diseases and disorders.

BACKGROUND

The casein kinase 1 family (CK1 or CKI) are serine/threonine kinases with six members (isoforms) in humans: α, γ1, γ2, γ3, δ and ε. They differ in length and sequence of the N-terminal (9–76 amino acids) and especially the C-terminal (24–200 amino acids) non-catalytic domain (Schittek and Sinnberg, *Mol. Cancer* 2014, 13:231).

CK1δ and CK1ε are 98% identical in their kinase domain and 53% identical in their C-terminal regulatory domain (Fish *et al.*, *J. Biol. Chem.* 1995, 270:14875–14883). Whereas, there is some redundancy with respect to CK1 substrate phosphorylation, most CK1 isoforms have distinct biological roles. The wide range of CK1 substrates shows that the CK1 family members are involved in multiple cellular processes, from regulation of membrane trafficking, cytokinesis, vesicular transport, ribosome biogenesis, DNA repair, signal transduction pathways, apoptosis and in the circadian rhythm (Knippschild *et al.*, *Cell. Signal.* 2005, 17:675–689; Cheong and Virshup, *Int. J. Biochem. Cell Biol.* 2011, 43:465–469; Zemp, *et al.*, *J. Cell Sci.* 2014, 127:1242–1253).

CK1α plays a role in the mitotic spindle formation during cell division and in DNA repair mechanisms and participates in RNA metabolism (Knippschild *et al.*, Cell Signal 2005, 17:675–689). It contributes to the activation of mTOR *via* sustained degradation of the endogenous mTOR inhibitor DEPTOR (Duan *et al.*, *Mol. Cell* 2011, 44:317–324).

CK1α has a major role in regulation of the Wnt/β-catenin signaling pathway. The inventors of this application have shown that CK1α is a key component of the β-catenin destruction complex. When the Wnt receptors are not engaged, CK1α phosphorylates β-catenin at serine residue S45, which is necessary for the priming phosphorylation of another kinase, GSK3 (Amit *et al.*, *Genes Dev.* 2002, 16:1066-1076).

β-catenin phosphorylation by GSK3 at residues T41, S37 and S33, generates an ubiquitination degron, recruiting the E3 SCF-β-TrCP, leading to the ubiquitination and degradation of β-catenin (Clevers and Nusse, *Cell* 2012, 149:1192-1205). The inventors have further shown that inducible ablation of CK1α in the mouse gut epithelium triggers a massive epithelial Wnt response, which surprisingly did not alter intestinal homeostasis, with only little enhanced proliferation and no tumorigenesis (Elyada *et al.*, *Nature* 2011, 470:409-413). This is dissimilar to the consequences of acute ablation of other components of the β-catenin destruction complex, such as APC, which results in loss of homeostasis and tumorigenesis (Sansom *et al.*, *Genes Dev.* 2004, 18:1385–1390).

The inventors of the present application have found that the reason for homeostasis maintenance following CK1α ablation is that parallel to Wnt activation, CK1α ablation induces several tumor-suppressor pathways, among which are DNA damage response (DDR), cellular senescence and p53 pathway activation (Elyada *et al.*, *Nature* 2011, 470:409-413; Pribluda *et al.*, *Cancer Cell* 2013, 24:1-5).

Whereas the molecular mechanisms underlying the activation of these anti-neoplastic pathways are still elusive, the inventors have found that that CK1α ablation induces disproportionally minor DNA damage, with no signs of ATM activation, indicating that CK1α-induced DDR and p53 activation likely entail uncommon molecular mechanisms (Burstain *et al.*, unpublished). In addition, the inventors have found that CK1α ablation results in the induction of a new type of an inflammatory response, denoted parainflammation, which is confined to the epithelium, with no common signs of inflammatory response (inflammatory cell infiltration, calor, rubor, tumor, and dolor) (Pribluda *et al.*, *Cancer Cell* 2013, 24:1-5; Lasry and Ben-Neriah, *Trends Immunol.* 2015, 36:217-228). Parainflammation cooperates with WT p53 activation in suppressing tumorigenesis, yet switches to a tumor promoting mechanism in the absence of functional p53 (Pribluda *et al.*, *Cancer Cell* 2013, 24:1-5; Aran *et al.*, *Genome Biol.* 2016, 17:145).

Whereas it is already established that CK1α is a major regulator of p53, the inventors have also found that the combined ablation of CK1δ and CK1ε in the gut epithelium also results in p53 activation, which may synergize with CK1α-induced p53 activation.

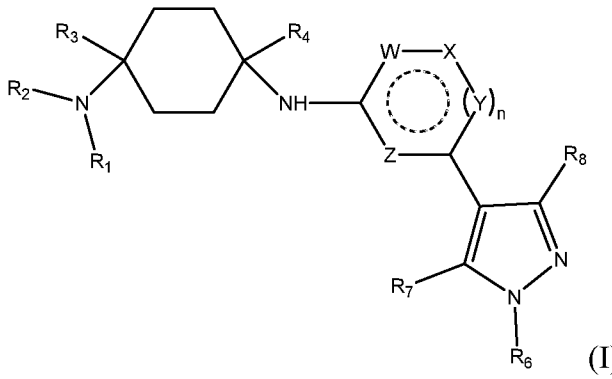
IRAK1 was identified as a therapeutic target for MDS, and certain subsets of AML and triple negative breast cancer (Rhyasen *et al.*, *Cancer Cell* 2013, 24:90–104; Rhyasen *et al.*, *Exp. Hematol.* 2013, 41:1005-7; Wee *et al.*, *Nat. Commun.* 2015, 6:8746). IRAK1 mRNA is over-expressed in ~20-30% of MDS patients and the IRAK1 protein is dramatically over-expressed and is hyperactivated in a majority of MDS marrow sample examined. IRAK1 is a serine/threonine kinase that mediates signals elicited from Toll-like receptor (TLR) and Interleukin-1 Receptor (IL1R). Following receptor activation, IRAK1 becomes phosphorylated which then leads to recruitment of TRAF6, resulting in TRAF6 activation of NF-κB and JNK pathways. The molecular source of IRAK1 overexpression and/ or hyperactivation in MDS (or AML) is not conclusive. It is thought that over-expression of TLR or necessary cofactors in MDS clones may result in chronic IRAK1 activation even in the absence of infection. Small molecule inhibitors targeting IRAK1 (IRAK1/4 Inhibitor, Amgen Inc.) have been originally developed for autoimmune and inflammatory diseases. Given that IRAK1 is hyperactivated (i.e., phosphorylated) in MDS but not normal marrow cells, Starczynowski and colleagues showed that IRAK-Inhibitor treatment (IRAK1/4, Amgen) and the knockdown of IRAK1 resulted in dramatic impairment of MDS cell proliferation, progenitor function, and viability in vitro and in vivo. Yu and colleagues showed that IRAK1 overexpression confers triple negative breast cancer cells (TNBC) growth advantage through NF-κB-related cytokine secretion and metastatic TNBC cells exhibit gain of IRAK1 dependency, resulting in high susceptibility to genetic and pharmacologic inhibition of IRAK1. Paclitaxel treatment of TNBC cells induces strong IRAK1 phosphorylation, an increase in inflammatory cytokine expression, enrichment of cancer stem cells and acquired resistance to paclitaxel treatment. Pharmacologic inhibition of IRAK1 was able to reverse paclitaxel resistance by triggering massive apoptosis. IRAK1 was also found to be a DEK transcriptional target and is essential for head and neck cancer cell survival (Adams *et al.*, *Oncotarget*. 2015, 22; 6:43395-43407) and also as potential target in the treatment of inflammatory- and immune-related disorders (Bahia *et al.*, *Cell. Signal*. 2015, 27:1039-55).

The inventors have thus found that compounds of the invention are able to inhibit

IRAK1, an important upstream regulator of the NF-kB pathway, which plays an important role in hematological malignancies.

GENERAL DESCRIPTION

The present invention provides a compound having Formula (I), or a stereoisomer or salt thereof:



(I)

wherein:

R_1 and R_2 are each independently selected from H; and straight or branched C_1–C_8 alkyl, straight or branched C_1–C_5 alkoxy, straight or branched C_1–C_5 acyl, C_5–C_{15} aryl, and C_3–C_7 heteroaryl, each optionally substituted by at least one of halide, hydroxyl, ester, ether, C_5–C_{15} aryl, C_3–C_7 heteroaryl, and amide; or

R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated, unsaturated, or aromatic ring that may optionally include at least one of N, O, NH, C=N, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, halide, and cyano;

R_3 and R_4 are each independently selected from H and straight or branched C_1–C_8 alkyl optionally substituted by at least one of halide, hydroxyl, alkoxy, C_5–C_{15} aryl, C_3–C_7 heteroaryl, ester, and amide; or

R_1 or R_2 together with R_3 and the carbon and nitrogen atoms they are each connected to form a 4–7 membered saturated, unsaturated, or aromatic ring that may optionally include at least one of N, NH, O, C=N, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, carbonyl, and halide;

W, X, Y, and Z are each independently selected from CH, CR_5, CR_{5c}, NH, N, and S; provided that at least one of W, X, Y and Z is selected from NH, N and S; provided that, when W is N, Z is N, then X is CR_{5c};

n is an integer selected from 0 and 1;

R_5 is selected from OH, NH_2, and halide;

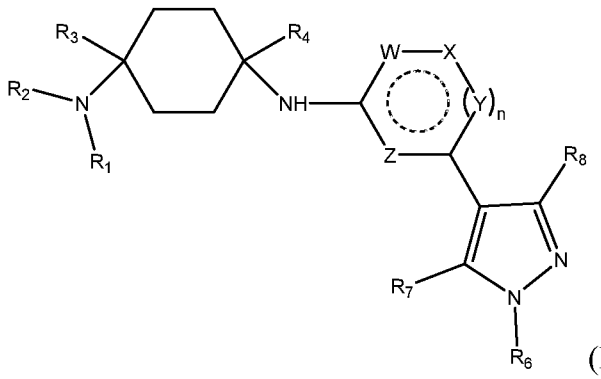
R_{5c} is selected from OH and NH_2;

R_8 is selected from H and halide; and straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, and straight or branched C_2–C_8 alkynyl, each optionally substituted by at least one halide;

R_6 is selected from straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, straight or branched C_2–C_8 alkynyl, C_5–C_{10} cycloalkyl, and saturated or unsaturated 4–6 membered heterocyclyle; each optionally substituted by at least one of straight or branched C_1–C_8 alkyl, C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide; and

R_7 is selected from straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, and straight or branched C_2–C_8 alkynyl; each independently substituted by at least one of C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide.

The present invention provides a compound having Formula (I), or a stereoisomer or salt thereof:



(I)

wherein:

R_1 and R_2 are each independently selected from H; and straight or branched C_1–C_8 alkyl, straight or branched C_1–C_5 alkoxy, straight or branched C_1–C_5 acyl, C_5–C_{15} aryl, and C_3–C_7 heteroaryl, each optionally substituted by at least one of halide, hydroxyl, ester, ether, C_5–C_{15} aryl, C_3–C_7 heteroaryl, and amide; or

R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated, unsaturated, or aromatic ring that may optionally include at least one of N, O, NH, C=N, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, halide, and cyano;

R_3 and R_4 are each independently selected from H and straight or branched C_1–C_8 alkyl optionally substituted by at least one of halide, hydroxyl, alkoxy, C_5–C_{15} aryl, C_3–C_7 heteroaryl, ester, and amide; or

R_1 or R_2 together with R_3 and the carbon and nitrogen atoms they are each connected to form a 4–7 membered saturated, unsaturated, or aromatic ring that may optionally include at least one of N, NH, O, C=N, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, carbonyl, and halide;

W, X, Y, and Z are each selected from CH, CR_5, NH, N, and S; provided that at least one of W, X, Y, and Z is selected from NH, N and S; provided that, when W is N and Z is N, then R_8 is other than H;

n is an integer selected from 0 and 1;

R_5 is selected from OH, NH_2, and halide;

R_8 is selected from H and halide; and straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, and straight or branched C_2–C_8 alkynyl, each optionally substituted by at least one halide;

R_6 is selected from straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, straight or branched C_2–C_8 alkynyl, C_5–C_{10} cycloalkyl, and saturated or unsaturated 4–6 membered heterocyclyle; each optionally substituted by at least one of straight or branched C_1–C_8 alkyl, C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide; and

R_7 is selected from straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, and straight or branched C_2–C_8 alkynyl, each independently substituted by at least one of C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide.

In some embodiments, R_1 and R_2 are each independently selected from H, and straight or branched C_1–C_8 alkyl optionally substituted by at least one of halide, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, ester, ether, and amide.

In other embodiments, R_1 and R_2 are each independently selected from H, and straight or branched C_1–C_5 alkoxy optionally substituted by at least one of halide, hydroxyl, ester, and amide.

In further embodiments, R_1 and R_2 are each independently selected from H, and C_1–C_5 acyl optionally substituted by at least one of halide, hydroxyl, ester, ether, and amide.

In some other embodiments, R_1 and R_2 are each independently selected from H and C_5–C_{15} aryl optionally substituted by at least one of halide, hydroxyl, ester, ether, and amide.

In some embodiments, R_4 is H. In other embodiments, R_3 and R_4 are H.

In other embodiments, R_5 is halide. In some embodiments, R_5 is NH_2. In some embodiments, R_5 is OH.

In other embodiments, R_8 is selected from H, Cl, and straight or branched C_1–C_4 alkyl. In other embodiments, R_8 is H.

In some embodiments, at least one of R_1 and R_2 is H.

In some embodiments, R_6 selected from straight or branched C_1–C_8 alkyl, C_5–C_{10} cycloalkyl, and saturated or unsaturated 4–6 membered heterocyclyle; and R_7 is selected from straight or branched C_1–C_8 alkyl, substituted by at least one of C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide.

In some embodiments, R_6 is selected from straight or branched C_1–C_8 alkyl, C_5–C_{10} cycloalkyl, and 4–6 membered saturated heterocyclyle.

In other embodiments, R_7 is straight or branched C_1–C_8 alkyl substituted by at least one of C_3–C_7 cycloalkyl and hydroxyl.

In some embodiments, R_6 is selected from straight or branched C_1–C_8 alkyl, and saturated, unsaturated, or aromatic 4–6 membered heterocyclyle, each optionally substituted by at least one of straight or branched C_1–C_8 alkyl, C_3–C_7 cycloalkyl, halide, hydroxyl, and CF_3.

In some embodiments, R_7 is straight or branched C_1–C_8 alkyl substituted by at least one C_3–C_7 cycloalkyl.

In other embodiments, R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated ring optionally including at least one of N, O, NH, C=N,

C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, hydroxyl, halide, and cyano.

In some embodiments, R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated ring.

In some embodiments, R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated ring including at least one of N and O.

In further embodiments, R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered aromatic ring optionally including at least one of N and O.

In other embodiments, R_3 and R_4 are H.

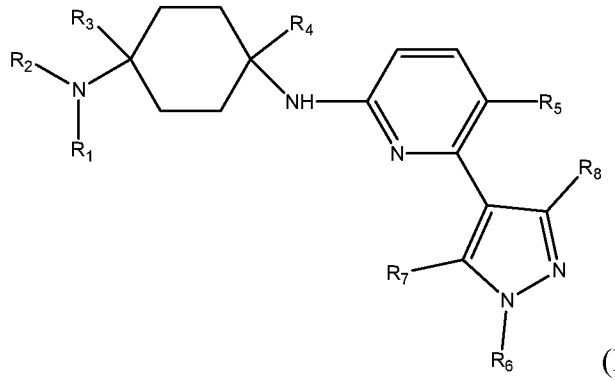
In some embodiments, R_1 or R_2 together with R_3 and the carbon and nitrogen atom they are connected to form a 4–7 membered saturated ring that optionally includes at least one of N, NH, O, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, hydroxyl, carbonyl, and halide.

In some embodiments, R_1 or R_2 together with R_3 and the carbon and nitrogen atom they are connected to form a 4–7 membered saturated ring that includes at least one of NH, O, and C=O.

In other embodiments, n is 1. When n is 1, the ring it relates to is a six membered heteroaromatic ring. In further embodiments, n is 0. When n is 0, the ring it relates to is a five membered heteroaromatic ring. Under this embodiment, when n is 0 and Y is therefore absent, X will be directly connected to the carbon atom on one side and to W on the other side.

In some embodiments, one of W, X, Y and Z is N. In further embodiments, two of W, X, Y and Z is N. In other embodiments, two of W, X, Y and Z are independently selected from NH, N, and S. In some embodiments, X is selected from CH, CR_5, and CR_{5c}. In some embodiments, W is N, Z is N, and X is CR_{5c}.

In some embodiments, a compounds of the invention is selected from the following, wherein R_1–R_8 are as defined herein above:



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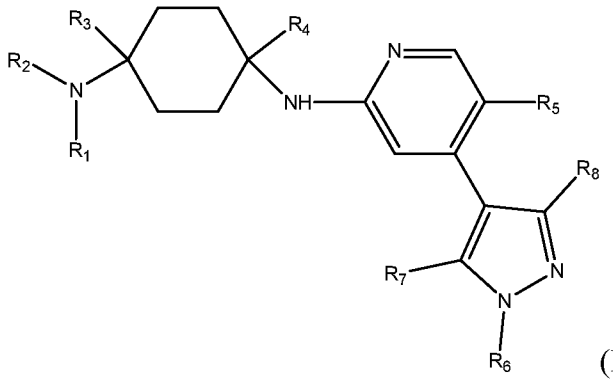

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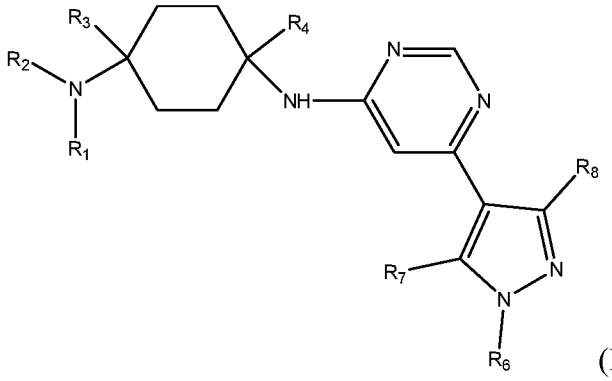

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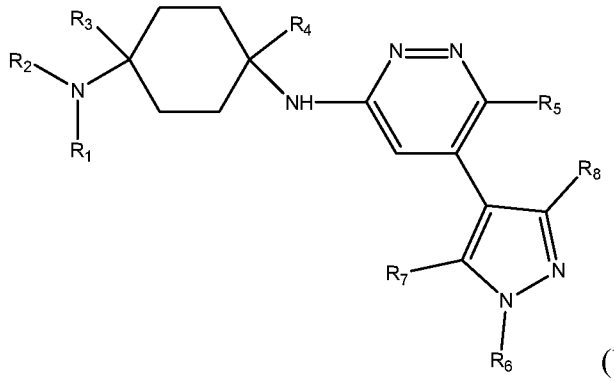

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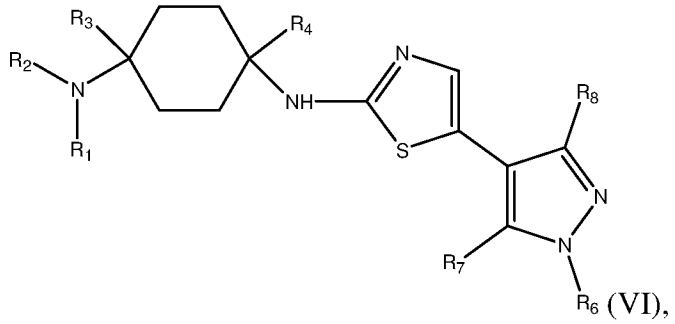

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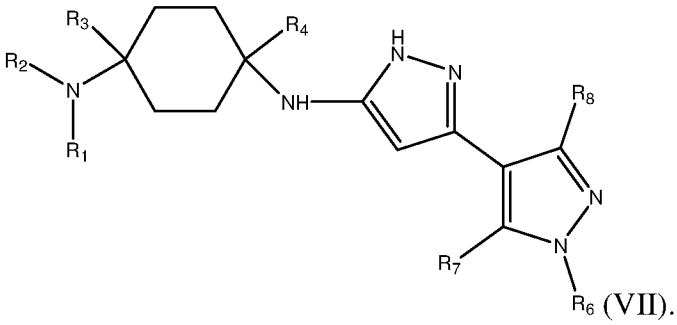
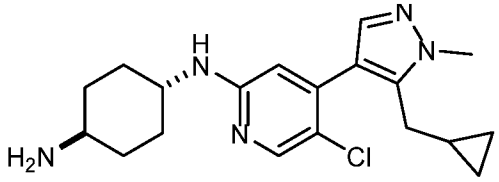


(VII).

In some embodiments, a compound of the invention is selected from the following:



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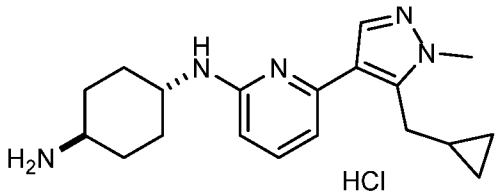

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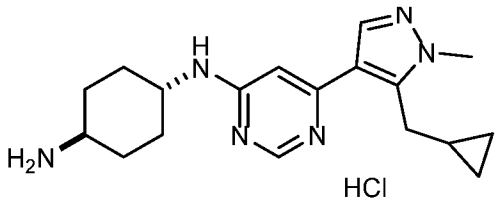

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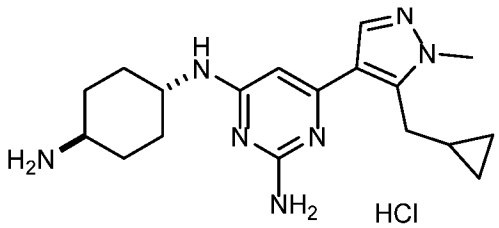

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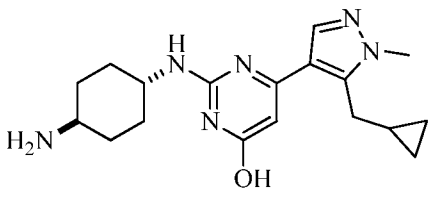
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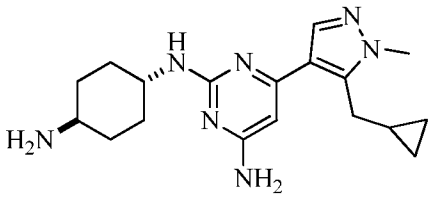
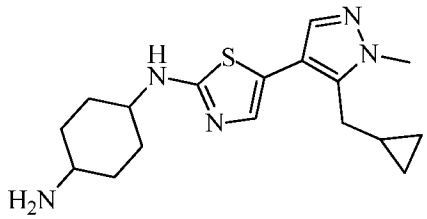

A109,

and


A110.

The term "*straight or branched C_1–C_8 alkyl*" should be understood to encompass a hydrocarbon saturated chain, which can be straight or branched, comprising 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms.

The term "*straight or branched C_2–C_8 alkenyl*" or "*straight or branched C_2–C_5 alkenyl*" should be understood to encompass a hydrocarbon chain having at least one double bond between any two adjacent carbon atoms in the chain, which can be straight or branched, comprising 2, 3, 4, 5, 6, 7, or 8 carbon atoms or 2, 3, 4, 5 carbon atoms, respectively.

The term "*straight or branched C_2–C_8 alkynyl*" should be understood to encompass a hydrocarbon chain having at least one triple bond between any two adjacent carbon atoms in the chain, which can be straight or branched, comprising 2, 3, 4, 5, 6, 7, or 8 carbon atoms.

The term "*straight or branched C_1–C_5 alkoxy*" should be understood to encompass an $-OR_9$ moiety wherein R_9 is straight or branched C_1–C_5 alkyl.

The term "*halide*" should be understood to encompass any halogen radical selected from –F, -Br, -Cl, and -I.

The term "*C_1–C_5 alkyl halide*" should be understood to encompass any straight or branched alkyl chain having between 1 to 5 carbon atoms being substituted by at least one halogen radical selected from –F, -Br, -Cl, and -I, at any point one the straight or branched

chain. In some embodiments, alkyl halide includes one halogen; in other embodiments, alkyl halide includes two halogen atoms (the same or different); in other embodiments, alkyl halide includes three halogen atoms (the same or different).

The term "*hydroxyl*" should be understood to encompass –OH.

The term "*ester*" should be understood to encompass any of $–C(=O)OR_{10}$ or $-OC(=O)R_{10}$, wherein R_{10} is straight or branched $C_1–C_8$ alkyl.

The term "*amide*" should be understood to encompass any of $–C(=O)NR_{11}R_{12}'$, $-NR_{11}C(=O)R_{12}'$, wherein R_{11} and R_{12}' are each independently H, or straight or branched $C_1–C_8$ alkyl.

The term "*ether*" should be understood to encompass any of $–R_{13}OR_{14}'$ or $–OR_{15}'$, wherein R_{13} is selected from straight or branched $C_1–C_8$ alkylene, and R_{14}' and R_{15}' are each independently selected from straight or branched $C_1–C_8$ alkyl.

The term "*straight or branched $C_1–C_5$ acyl*" should be understood to encompass any $–C(=O)R_{16}$, wherein R_{16} is $C_1–C_5$ straight or branched alkyl.

The term "*$C_5–C_{15}$ aryl*" should be understood to encompass any single or fused aromatic ring system comprising 5 to 7 carbon atoms. Examples include, but are not limited to, phenyl, pentalenyl, naphatalenyl, and anthracenyl.

The term "*$C_3–C_7$ heteroaryl*" should be understood to encompass any single or fused aromatic ring system comprising 5 to 7 carbon atoms and at least one heteroatom selected from N, O, and S. Examples include, but are not limited to, furanyl, benzofuranyl, isobenzofuranyl, pyrrolynyl, indolynyl, isoindolinyl, thiophenyl, banzothiophenyl, banzo[c]thiophenyl, imidazolyl, benzimidazolyl, purinyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, thiasolyl, benzothiazolyl, pyridinyl, auinolinyl, isoquinolinyl, pyromodinyl, quinzolinyl, pyridazinyl, and cinnolinyl.

When referring to the embodiment wherein R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated, unsaturated, or aromatic ring, it should be understood to relate to any ring that may be formed having 4, 5, 6, or 7 members including said nitrogen atom. Said ring can be saturated, *i.e.*, having all sigma bonds, unsaturated, *i.e.*, having at least one double or at least one triple bond or any combinations thereof or aromatic,

i.e., a ring system that possess aromatic character, cyclically conjugated molecular ring system with a stability (due to delocalization) significantly greater than that of a hypothetical localized structure (*e.g.*, Kekulé structure).

For example, said ring can be selected from piperidinyl, pyrrolidinyl, and azetidinyl.

When referring to the embodiments wherein R_1 or R_2 together with R_3 and the carbon and nitrogen atom they are connected to form a 4–7 membered saturated, unsaturated or aromatic ring, it should be understood to relate to any ring that may be formed having 4, 5, 6, or 7 members including said nitrogen atom. This ring forms a spiro bi-ring system with the cyclohexyl ring in the backbone of compound of formula I. Said ring can be saturated, *i.e.*, having all sigma bonds, or unsaturated, *i.e.*, having at least one double or at least one triple bond or any combinations thereof. In some embodiments, the ring is an aromatic ring.

The term "*C_5–C_{10} cycloalkyl*" or the term "*C_3–C_7 cycloalkyl*" should be understood to encompass a saturated (*i.e.*, the ring containing only sigma bonds between its members) hydrocarbon ring that comprises 5, 6, 7, 8, 9, or 10 carbon atoms or 3, 4, 5, 6, or 7 carbon atoms, respectively.

The term "*saturated , unsaturated or aromatic 4–6 membered heterocyclyle*" should be understood to encompass a saturated (*i.e.*, the ring containing only sigma bonds between its members), unsaturated or aromatic (*i.e.*, the ring containing at least one double bond or at least one triple bond or any combinations thereof) ring containing 4, 5, or 6 members at least one of which is a heteroatom selected from N, O, S, and P.

The term "*optionally substituted*" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent, the substituents may be the same or different.

Certain of the compounds described herein may contain one or more chiral center, or may otherwise be capable of existing as two enantiomers or several diastereomers. Accordingly, the compounds of this invention include also mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. The compounds of this invention include also mixtures of diastereomers, as well as purified diastereomers or diastereomerically enriched mixtures.

The invention also includes any salt of a compound of formula (I), including any pharmaceutically acceptable salt, wherein a compound of the invention has a net charge (either positive or negative) and at least one counter ion (having a counter negative or positive charge) is added thereto to form said salt. The phrase "*pharmaceutically acceptable salt(s)*" as used herein means those salts of compounds of the invention that are safe and effective for pharmaceutical use in mammals and that possess the desired biological activity. Pharmaceutically acceptable salts include salts of acidic or basic groups present in compounds of the invention. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, *p*-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds of the invention can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. For a review on pharmaceutically acceptable salts, see Berge *et al.*, *J. Pharm. Soc.* 1977, 66:1-19, incorporated herein by reference.

In some embodiments, the compound is a hydrochloride salt. In other embodiments, the compound is a monohydrochloride salt. In other embodiments, is a dihydrochloride salt.

The invention further provides a composition comprising at least one compound as defined in any one of the embodiments herein above.

The present invention also relates to pharmaceutical compositions comprising a compound of the subject invention in admixture with pharmaceutically acceptable auxiliaries, and optionally other therapeutic agents. The auxiliaries must be "*acceptable*" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration or administration

via an implant. The compositions may be prepared by any method well known in the art of pharmacy.

Such methods include the step of bringing in association compounds of the invention or combinations thereof with any auxiliary agent. The auxiliary agent(s), also named accessory ingredient(s), include those conventional in the art, such as carriers, fillers, binders, diluents, disintegrants, lubricants, colorants, flavouring agents, anti-oxidants, and wetting agents.

Pharmaceutical compositions suitable for oral administration may be presented as discrete dosage units such as pills, tablets, dragées or capsules, or as a powder or granules, or as a solution or suspension. The active ingredient may also be presented as a bolus or paste. The compositions can further be processed into a suppository or enema for rectal administration.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material, including instructions for the use of the composition for a use as hereinbefore described.

For parenteral administration, suitable compositions include aqueous and non-aqueous sterile injection. The compositions may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of sterile liquid carrier, for example water, prior to use. For transdermal administration, *e.g.*, gels, patches or sprays can be contemplated. Compositions or formulations suitable for pulmonary administration e.g. by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurized aerosols, nebulisers or insufflators.

The exact dose and regimen of administration of the composition will necessarily be dependent upon the therapeutic or nutritional effect to be achieved and may vary with the particular formula, the route of administration, and the age and condition of the individual subject to whom the composition is to be administered.

The term "*treatment*" or "*therapy*" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the alleviation

or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The patient to be treated is preferably a mammal, in particular a human being.

It should be understood that the dosage ranges set forth above are exemplary only and are not intended to limit the scope of this invention. The therapeutically effective amount for each active compound can vary with factors including but not limited to the activity of the compound used, stability of the active compound in the patient's body, the severity of the conditions to be alleviated, the total weight of the patient treated, the route of administration, the ease of absorption, distribution, and excretion of the active compound by the body, the age and sensitivity of the patient to be treated, and the like, as will be apparent to a skilled artisan. The amount of administration can be adjusted as the various factors change over time.

For oral delivery, the active compounds can be incorporated into a formulation that includes pharmaceutically acceptable carriers such as binders (*e.g.*, gelatin, cellulose, gum tragacanth), excipients (*e.g.*, starch, lactose), lubricants (*e.g.*, magnesium stearate, silicon dioxide), disintegrating agents (*e.g.*, alginate, Primogel, and corn starch), and sweetening or flavoring agents (*e.g.*, glucose, sucrose, saccharin, methyl salicylate, and peppermint). The formulation can be orally delivered in the form of enclosed gelatin capsules or compressed tablets. Capsules and tablets can be prepared in any conventional techniques. The capsules and tablets can also be coated with various coatings known in the art to modify the flavors, tastes, colors, and shapes of the capsules and tablets. In addition, liquid carriers such as fatty oil can also be included in capsules.

Suitable oral formulations can also be in the form of suspension, syrup, chewing gum, wafer, elixir, and the like. If desired, conventional agents for modifying flavors, tastes, colors, and shapes of the special forms can also be included. In addition, for convenient administration by enteral feeding tube in patients unable to swallow, the active compounds can be dissolved in an acceptable lipophilic vegetable oil vehicle such as olive oil, corn oil and safflower oil.

The active compounds can also be administered parenterally in the form of solution or suspension, or in lyophilized form capable of conversion into a solution or suspension form before use. In such formulations, diluents or pharmaceutically acceptable carriers such as

sterile water and physiological saline buffer can be used. Other conventional solvents, pH buffers, stabilizers, anti-bacteria agents, surfactants, and antioxidants can all be included. For example, useful components include sodium chloride, acetates, citrates or phosphates buffers, glycerin, dextrose, fixed oils, methyl parabens, polyethylene glycol, propylene glycol, sodium bisulfate, benzyl alcohol, ascorbic acid, and the like. The parenteral formulations can be stored in any conventional containers such as vials and ampoules.

Routes of topical administration include nasal, bucal, mucosal, rectal, or vaginal applications. For topical administration, the active compounds can be formulated into lotions, creams, ointments, gels, powders, pastes, sprays, suspensions, drops and aerosols. Thus, one or more thickening agents, humectants, and stabilizing agents can be included in the formulations. Examples of such agents include, but are not limited to, polyethylene glycol, sorbitol, xanthan gum, petrolatum, beeswax, or mineral oil, lanolin, squalene, and the like. A special form of topical administration is delivery by a transdermal patch. Methods for preparing transdermal patches are disclosed, *e.g.,* in Brown, *et al.*, *Ann. Rev. Med.* 1988, 39:221-229, which is incorporated herein by reference.

Subcutaneous implantation for sustained release of the active compounds may also be a suitable route of administration. This entails surgical procedures for implanting an active compound in any suitable formulation into a subcutaneous space, *e.g.*, beneath the anterior abdominal wall. *See*, *e.g.*, Wilson *et al.*, *J. Clin. Psych.* 1984, 45:242-247. Hydrogels can be used as a carrier for the sustained release of the active compounds. Hydrogels are generally known in the art. They are typically made by crosslinking high molecular weight biocompatible polymers into a network, which swells in water to form a gel like material. In some instances, hydrogels are biodegradable or biosorbable. For purposes of this invention, hydrogels made of polyethylene glycols, collagen, or poly(glycolic-co-L-lactic acid) may be useful. *See*, *e.g.*, Phillips *et al.*, *J. Pharmaceut. Sci.* 1984, 73:1718-1720.

The invention further provides a compound as defined in any one of the embodiments herein above for use in therapy. The invention further provides a compound as defined in any one of the embodiments herein above for use as a medicament.

The invention provides a compound as defined in any one of the embodiments herein above, for use in the inhibition of and least one of Casein kinase I (CKI) and Interleukin-1 receptor-associated kinase 1 (IRAK1).

The invention provides a compound as defined in any one of the embodiments herein above, for use in the inhibition of Casein kinase I (CKI).

The invention provides a compound as defined in any one of the embodiments herein above, for use in the inhibition of Interleukin-1 receptor-associated kinase 1 (IRAK1).

The invention provides a compound as defined in any one of the embodiments herein above, for use in inducing anti-tumor response. In some embodiments, said anti-tumor response comprises cancer immunotherapy response.

The invention provides a compound as defined in any one of the embodiments herein above, for use in the treatment of a condition, symptom or disease associated with a malignant condition.

In some embodiments, said malignant condition is cancer. In other embodiments, malignant condition is selected from hematological malignancies, multiple myeloma, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), melanoma, ER-negative breast cancer, diffuse large B cell lymphoma (DLBCL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), and head and neck cancer.

In some embodiments, said cancer has WT p53.

The invention provides a compound as defined in any one of the embodiments herein above, for use in the treatment of cancer having WT p53, wherein said WT p53 is a biomarker for the said compound efficacy. In some embodiments, said cancer is selected from Multiple myeloma, leukemia, malignant melanoma, breast cancer, prostate cancer, colorectal cancer and any combinations thereof.

The invention further provides a compound as defined in any one of the embodiments herein above, for use in the induction of cancer immunotherapy response.

The invention provides a compound as defined in any one of the embodiments herein above, for use in the treatment of an inflammatory and immune related disorder including a condition, symptom or disease associated therewith.

The invention provides a method of inhibiting at least one of Casein kinase I (CKI) and Interleukin-1 receptor-associated kinase 1 (IRAK1) in a subject in need thereof

comprising the step of administrating to said subject at least one compound as defined in any one of the embodiments herein above.

The invention further provides a method of inhibiting casein kinase I (CKI) in a subject in need thereof comprising the step of administrating to said subject at least one compound as defined in any one of the embodiments herein above.

The invention provides a method of inhibiting interleukin-1 receptor-associated kinase 1 (IRAK1) in a subject in need thereof comprising the step of administrating to said subject at least one compound as defined in any one of the embodiments herein above.

The invention further provides a method for inducing an immunotherapy response in a subject in need thereof, said method comprising the step of administering to said subject at least one compound as defined in any one of the embodiments herein above.

The invention further provides a method of treating an inflammatory and immune related disorder, including a condition, symptom or disease associated therewith in a subject in need thereof, said method comprising the step of administering to said subject at least one compound as defined in any one of the embodiments herein above.

The term "*Casein kinase 1*" should be understood to encompass a protein kinases family that are serine/threonine-selective enzymes that function as regulators of signal transduction pathways in most eukaryotic cell types. CK1 isoforms are involved in Wnt signaling, circadian rhythms, nucleo-cytoplasmic shuttling of transcription factors, DNA repair, p53 activation and DNA transcription.

The term "*Interleukin-1 receptor-associated kinase 1*" should be understood to encompass an enzyme encoded by the *IRAK1* gene which was found to be an important upstream regulator of the NF-kB pathway involved in disease pathways of hematological malignancies, such as multiple myeloma, MDS, leukemia and lymphoma, breast cancer, head and neck cancer, inflammatory and immune related disorders and others.

When referring to the "*inhibition*" of said enzyme, it should be understood to encompass any qualitative or quantitative decrease in the activity of said enzyme due to direct or indirect binding of at least one compound of the invention to said enzyme.

The term "*induced anti-tumor response*" should be understood to encompass any qualitative or quantitative chemotherapy of cancerous tumors.

The term "*cancer immunotherapy response*" should be understood to encompass any qualitative or quantitative cancer immunotherapy induction of the subject's own immune system to fight the cancerous cells. Typically, immunotherapies can be categorized as active, passive or hybrid (active and passive), and are designed to exploit the fact that cancer cells often have molecules on their surface that can be detected by the immune system of a subject, known as tumour-associated antigens (TAAs); they are often proteins or other macromolecules (*e.g.*, carbohydrates). Active immunotherapy directs the immune system to attack tumor cells by targeting TAAs. Passive immunotherapies enhance existing anti-tumor responses.

When referring to "*inflammatory and immune related disorders*" it should be understood to relate to any type of disorder (including conditions, symptoms and diseases associated therewith) that are treatable with Interleukin-1 receptor associated kinase inhibitors. It has been shown for example that IRAK1 is an indispensable element of IL-Rs and TLR pathways that can regulate the abnormal levels of cytokines, and therefore can be employed to manage immune- and inflammation-related disorders such as for example rheumatoid arthritis, inflammatory bowel disease, psoriasis, gout, asthma and cancer (Bahia *et al.*, *Cell. Signal*. 2015, 27:1039-55).

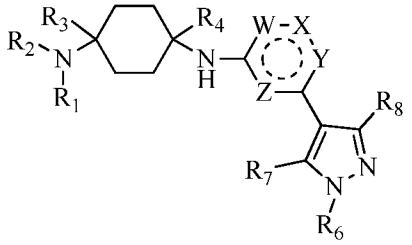
BRIEF DESCRIPTION OF THE DRAWINGS

In order to better understand the subject matter that is disclosed herein and to exemplify how it may be carried out in practice, embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 shows the dose-response analysis in RKO cells. RKO cells were incubated for 16 hours at 37 °C with indicated concentrations of the compounds, or with the vehicle (DMSO) alone (-) and analyzed by Western Blot. Shown are Western Blot signals of β-catenin and p53 stabilization and phosphorylation of H2AX (γH2AX), a marker of DNA damage.

DETAILED DESCRIPTION OF EMBODIMENTS

The invention further provides a compound of Formula I':



(I)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R_1 and R_2 are each independently H, deuterium, C_1–C_8 alkyl, C_2–C_8 alkenyl, C_1–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, C_7–C_{16} aralkyl, heteroaryl, heterocyclyl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; or R_1 and R_2 together with the nitrogen atom to which they are connected form heteroaryl or heterocyclyl;

R_3 and R_4 are each independently H, deuterium, halo, cyano, nitro, C_1–C_8 alkyl, C_2–C_8 alkenyl, C_1–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, C_7–C_{16} aralkyl, heteroaryl, or heterocyclyl; or R_1 and R_3 together with the carbon and nitrogen atoms to which they are connected form heterocyclyl;

W, X, Y, and Z are each independently CR_{5a} or N, provided that, when W and Z are each N, at least one of X and Y is N; or

W, X, and Z are each independently CR_{5a}, NR_{5b}, N, O, or S; and Y is a bond;

each R_{5a} is independently H, deuterium, halo, cyano, nitro, C_1–C_8 alkyl, C_2–C_8 alkenyl, C_1–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, C_7–C_{16} aralkyl, heteroaryl, heterocyclyl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$,

$-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;

each R_{5b} is independently H, deuterium, C_1–C_8 alkyl, C_2–C_8 alkenyl, C_1–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, heteroaryl, heterocyclyl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;

R_6 is H, deuterium, C_1–C_8 alkyl, C_2–C_8 alkenyl, C_1–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, heteroaryl, heterocyclyl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$;

R_7 and R_8 are each independently H, deuterium, halo, cyano, nitro, C_1–C_8 alkyl, C_2–C_8 alkenyl, C_1–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_3–C_{10} cycloalkyl-C_1–C_8 alkyl, C_6–C_{15} aryl, C_7–C_{16} aralkyl, heteroaryl, heterocyclyl, $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; and

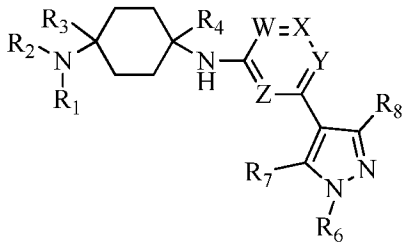
each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently H, deuterium, C_1–C_8 alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, C_7–C_{16} aralkyl, heteroaryl, or heterocyclyl; or R^{1a} and R^{1c} together with the C and N atoms to which they are attached form heterocyclyl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q, where each Q is independently selected from (a) deuterium, cyano, halo, and nitro; (b) C_1–C_8 alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, C_7–C_{16} aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) $-C(O)R^a$, $-C(O)OR^a$, –

$C(O)NR^bR^c$, $-C(NR^a)NR^bR^c$, $-OR^a$, $-OC(O)R^a$, $-OC(O)OR^a$, $-OC(O)NR^bR^c$, $-OC(=NR^a)NR^bR^c$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-OS(O)NR^bR^c$, $-OS(O)_2NR^bR^c$, $-NR^bR^c$, $-NR^aC(O)R^d$, $-NR^aC(O)OR^d$, $-NR^aC(O)NR^bR^c$, $-NR^aC(=NR^d)NR^bR^c$, $-NR^aS(O)R^d$, $-NR^aS(O)_2R^d$, $-NR^aS(O)NR^bR^c$, $-NR^aS(O)_2NR^bR^c$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^bR^c$, and $-S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen or deuterium; (ii) C_1–C_8 alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, C_7–C_{16} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a;

wherein each Q^a is independently selected from the group consisting of (a) deuterium, cyano, halo, and nitro; (b) C_1–C_8 alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, C_7–C_{16} aralkyl, heteroaryl, and heterocyclyl; and (c) $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^fR^g$, $-C(NR^e)NR^fR^g$, $-OR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)NR^fR^g$, $-OC(=NR^e)NR^fR^g$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^fR^g$, $-OS(O)_2NR^fR^g$, $-NR^fR^g$, $-NR^eC(O)R^h$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^fR^g$, $-NR^eC(=NR^h)NR^fR^g$, $-NR^eS(O)R^h$, $-NR^eS(O)_2R^h$, $-NR^eS(O)NR^fR^g$, $-NR^eS(O)_2NR^fR^g$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, $-S(O)NR^fR^g$, and $-S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen or deuterium; (ii) C_1–C_8 alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{10} cycloalkyl, C_6–C_{15} aryl, C_7–C_{16} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

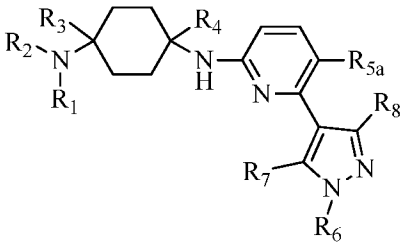
In other embodiments, the compound is a compound of Formula II:



(II)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

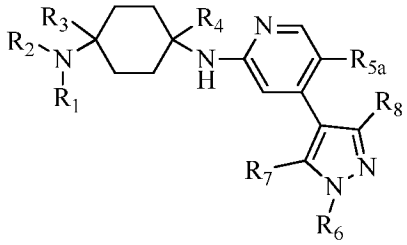
In other embodiments, the compound of the invention has Formula VIII:



(VIII)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

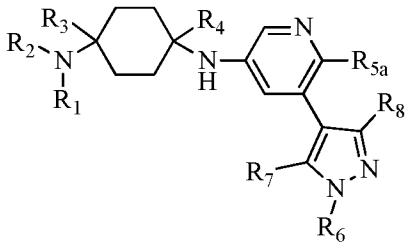
In other embodiments, the compound of the invention has Formula IX:



(IX)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

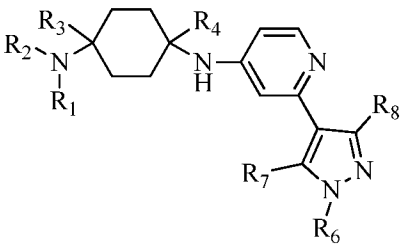
In other embodiments, the compound of the invention has Formula X:



(X)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

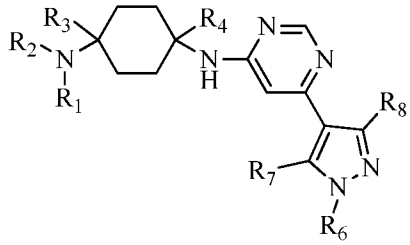
In other embodiments, the compound of the invention has Formula XI:



(XI)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

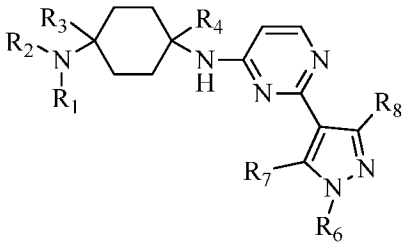
In other embodiments, the compound of the invention has Formula XII:



(XII)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

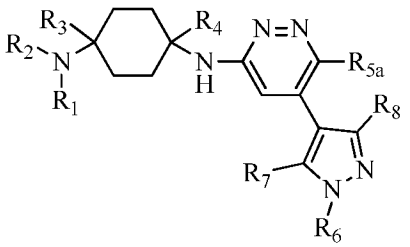
In other embodiments, the compound of the invention has the following general Formula XIII:



(XIII)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

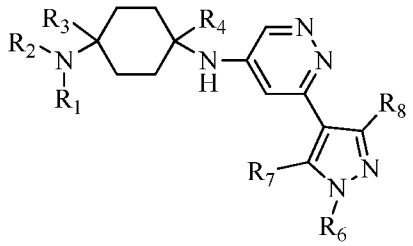
In other embodiments, the compound of the invention has Formula XIV:



(XIV)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

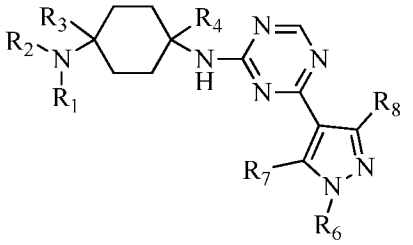
In other embodiments, the compound of the invention has Formula XV:



(XV)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

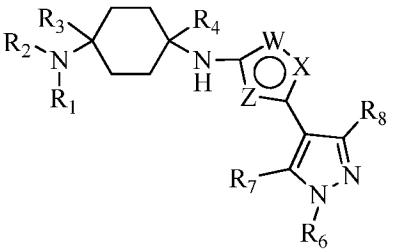
In other embodiments, the compound of the invention has Formula XVI:



(XVI)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

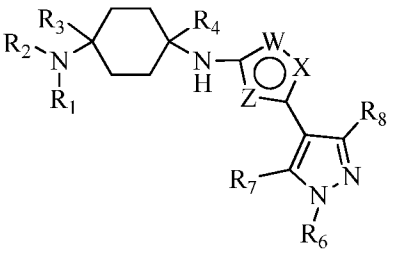
In other embodiments, the compound of the invention has Formula XVIII:



(XVIII)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

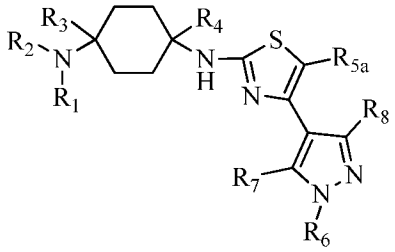
In other embodiments, the compound of the invention has Formula XVIII:



(XVIII)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

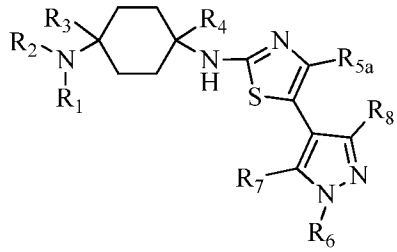
In other embodiments, the compound of the invention has Formula XIX:



(XIX)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

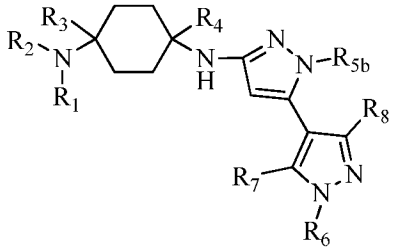
In other embodiments, the compound of the invention has Formula XX:



(XX)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

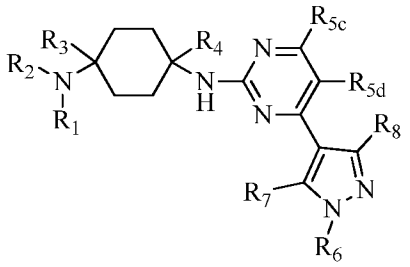
In other embodiments, the compound of the invention has Formula XXI:



(XXI)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In other embodiments, the compound of the invention has Formula XXII:



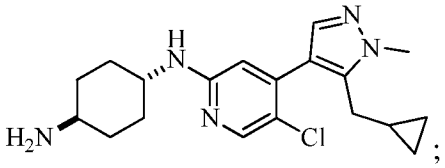
(XXII)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In some embodiments, Y is CR_{5a} or N. In other embodiments, Y is CR_{5a}. In further embodiments, R_{5a} is H, deuterium, or halo. In other embodiments, R_{5a} is H, deuterium, fluoro, or chloro. In other embodiments, Y is N. In other embodiments, W is CR_{5a}. In other embodiments, R_{5a} is H or deuterium. In other embodiments, W is N. In other embodiments, X is CR_{5a}. In other embodiments, R_{5a} is H, deuterium, or amino. In other embodiments, X is N. In other embodiments, Z is CR_{5a}. In other embodiments, R_{5a} is H or deuterium. In other embodiments, Z is N. In some embodiments, Y is a bond. In some embodiments, W is CR_{5a}. In some embodiments, R_{5a} is H or deuterium. In some embodiments, W is NR_{5b}. In some embodiments, R_{5b} is H or deuterium. In some embodiments, W is N. In some embodiments, W is O. In some embodiments, W is S. In some embodiments, X is CR_{5a}. In some embodiments, R_{5a} is H or deuterium. In some embodiments, X is NR_{5b}. In some embodiments, R_{5b} is H or deuterium. In some embodiments, X is N. In some embodiments, X is O. In some embodiments, X is S. In some embodiments, Z is CR_{5a}. In some embodiments, Z is NR_{5b}. In some embodiments, Z is N. In some embodiments, Z is O. In some embodiments, Z is S. In other embodiments, R_1 is H, deuterium, C_1–C_8 alkyl optionally substituted with one or more substituents Q, –C(O)R^{1a}, or –C(O)OR^{1a}. In other embodiments, R_1 is H. In other embodiments, R_2 is H, deuterium, C_1–C_8 alkyl optionally substituted with one or more substituents Q, –C(O)R^{1a}, or –C(O)OR^{1a}. In other embodiments, R_2 is H. In other embodiments, R_3 is H. In other embodiments, R_4 is H. In other embodiments, R_6 is H, deuterium, C_1–C_8 alkyl, C_5–C_{10} cycloalkyl, or heterocyclyl; wherein the alkyl, cycloalkyl, heterocyclyl are each independently and optionally substituted with one or more substitutes Q. In other embodiments, R_6 is C_1–C_8 alkyl, C_5–C_{10} cycloalkyl, or 4–6 membered heterocyclyl; each of which is independently and optionally substituted with one or more substitutes Q. In other embodiments, R_6 is C_1–C_8 alkyl, optionally substituted with one or more substitutes Q. In other embodiments, R_6 is methyl. In other embodiments, R_7 is (i) H or

deuterium; or (ii) C_1–C_8 alkyl, C_3–C_7 cycloalkyl, C_3–C_7 cycloalkyl-C_1–C_8 alkyl, C_6–C_{15} aryl, heteroaryl, or heterocyclyl, each of which is independently and optionally substituted with one or more substitutes Q. In other embodiments, R_7 is C_1–C_8 alkyl optionally substituted with one or more substitutes Q. In other embodiments, R_7 is C_1–C_8 alkyl substituted with one or more of C_3–C_7 cycloalkyl, C_6–C_{15} aryl, heteroaryl, and heterocyclyl. In other embodiments, R_7 is C_3–C_7 cycloalkyl-C_1–C_8 alkyl. In other embodiments, R_7 is cyclopropylmethyl. In other embodiments, R_8 is H.

In other embodiments, a compound of the invention is selected from: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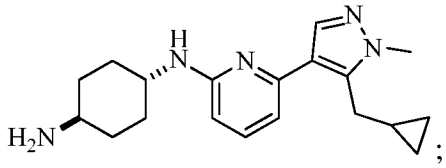
A104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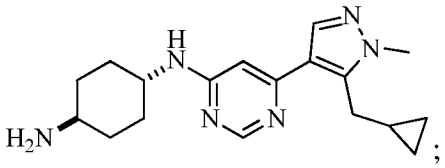
A105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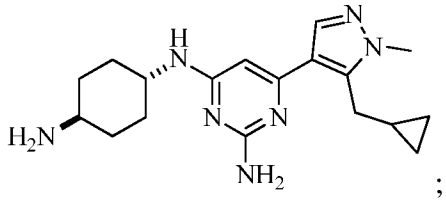
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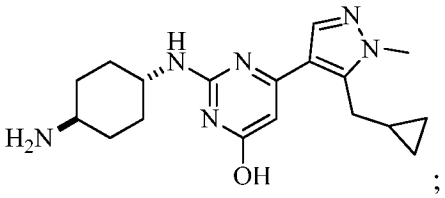
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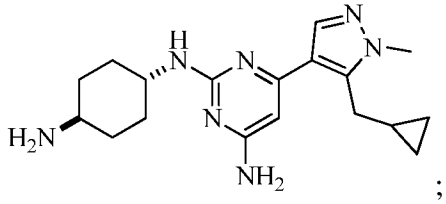
A108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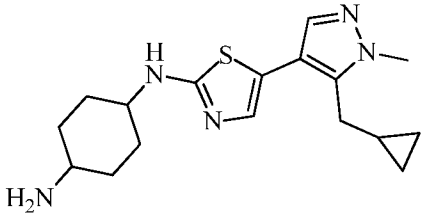
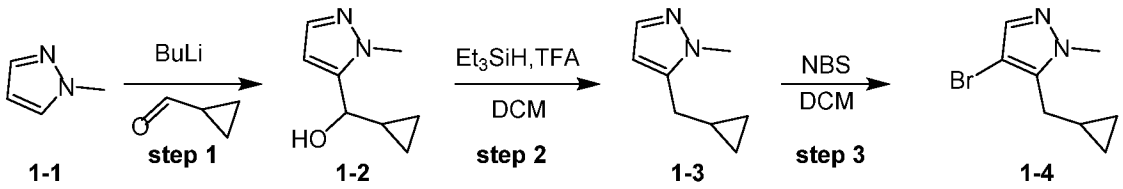
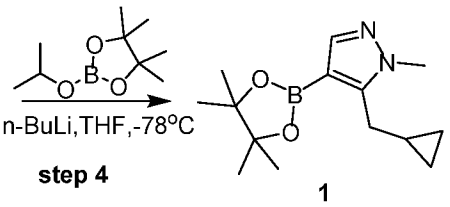


A110

and tautomers, mixtures of two or more tautomers, and isotopic variants thereof; and pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof.

Example 1: Synthesis of 5-(cyclopropylmethyl)-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (**1**)





Step 1: Cyclopropyl(1-methyl-1H-pyrazol-5-yl)methanol (**1-2**)**:** To a solution of compound N-methylpyrazole (**1-1**, 8.00 g, 97.44 mmol, 1.00 *eq*) in THF (160 mL) was added drop-wise n-BuLi (2.5 M, 46.77 mL, 1.20 *eq*) at -78 °C. After 1 h at -78 °C, a solution of cyclopropanecarbaldehyde (8.20 g, 116.93 mmol, 1.20 *eq*) in THF (80 mL) was added drop-wise. The resulting mixture was stirred at 20 °C for 16 h, poured into aqueous NH_4Cl (300 mL) and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (100 mL x 2). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2) to give compound **1-2** (12.00 g, 78.85 mmol, 80.9% yield, 100% purity) as a colorless oil. LCMS: RT = 0.118 min, *m/z* 153.1 $[M+H]^+$.

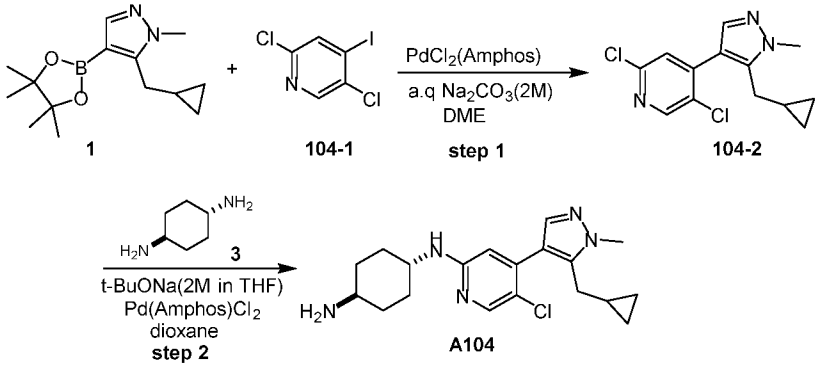
Step 2: 5-(Cyclopropylmethyl)-1-methyl-1H-pyrazole (**1-3**): A mixture of compound **1-2** (9.00 g, 59.14 mmol, 1.00 *eq*), TFA (40.46 g, 354.84 mmol, 26.27 mL, 6.00 *eq*) and Et_3SiH (41.26 g, 354.84 mmol, 56.52 mL, 6.00 *eq*) in DCM (900 mL) was stirred at 40 °C for 36 h. The mixture was adjusted to pH = 8 with aqueous $NaHCO_3$ and separated. The organic layer was concentrated and purified by prep HPLC (basic condition) to give compound **1-3** (2.10 g, 15.42 mmol, 26.1% yield) as a dark brown oil. LCMS: RT = 0.565 min, *m/z* 137.1 $[M+H]^+$.

Step 3: 4-Bromo-5-(cyclopropylmethyl)-1-methyl-1H-pyrazole (**1-4**)**:** To a solution of compound **1-3** (2.10 g, 15.42 mmol, 1.00 *eq*) in DCM (21 mL) was added NBS (3.02 g, 16.96 mmol, 1.10 *eq*) at 0 °C. The mixture was stirred at 20 °C for 2 h, concentrated and purified by column chromatography (SiO_2) to give compound **1-4** (3.00 g, 13.95 mmol,

90.5% yield) as a yellow oil. LCMS: RT = 0.784 min, *m/z* 217.1 $[M+H]^+$ ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 (s, 1 H), 3.87 (s, 3 H), 2.65-2.63 (d, J = 8.8 Hz, 2 H), 0.98-0.94 (m, 1H), 0.55-0.51 (m, 2H), 0.29-0.25 (m, 2H).

Step 4: 5-(Cyclopropylmethyl)-1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (**1**)**:** To a solution of compound **1-4** (3.00 g, 13.95 mmol, 1.00 *eq*) in THF (60 mL) was added n-BuLi (2 M, 10.46 mL, 1.50 *eq*) drop-wise at -78 °C. After 30 min, a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.19 g, 27.90 mmol, 2.00 *eq*) in THF (6 mL) was added. The resulting mixture was warmed to 20 °C and stirred for 0.5h, diluted with saturated NH_4Cl (50 mL) and extracted with EA (100 mL). The organic layer was concentrated and purified by column chromatography (SiO_2) to give compound **1** (3.30 g, 11.40 mmol, 81.7% yield, 90.5% purity) as a colorless oil. LCMS: RT = 0.801 min, *m/z* 263.2 $[M+H]^+$ ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (s, 1 H), 3.85 (s, 3 H), 2.82-2.81 (d, J = 6.8 Hz, 2 H),1.30 (s, 12H), 0.92-0.90 (m, 1H), 0.45-0.42 (m, 2H), 0.29-0.27 (m, 2H).

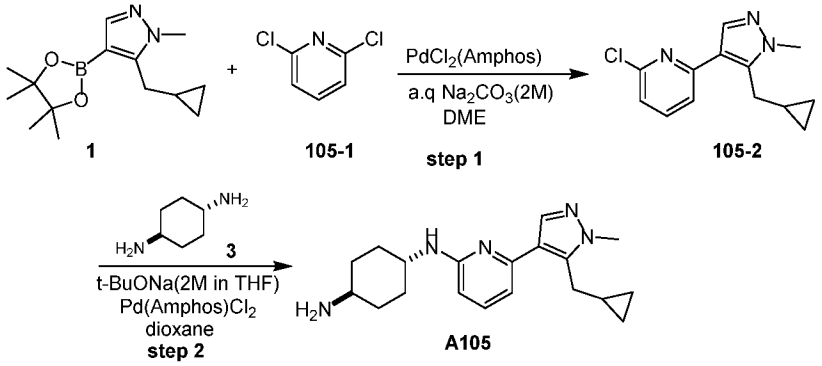
Example 2: Synthesis of (1r,4r)-N1-(5-chloro-4-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)cyclohexane-1,4-diamine (**A104**)



Step 1: 2,5-Dichloro-4-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyridine (**104-2**)**:** To a mixture of 2,5-dichloro-4-iodopyridine (**104-1**, 523.13 mg, 1.91 mmol, 1.00 *eq*) and compound **1** (500.8 mg, 1.91 mmol, 1.0 *eq*) in DME (10 mL) were added Na_2CO_3 (2M, 2.87 mL, 3.00 *eq*) and Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloro palladium (II) (67.62 mg, 95.50 µmol, 67.62 µL, 0.05 *eq*). The resulting mixture was stirred at 80 °C for 2 h under nitrogen, cooled to room temperature, concentrated and purified by column chromatography to give **104-2** (200 mg, 659.3 µmol, 34.5% yield, 93.0% purity) as a yellow oil. LCMS: RT = 0.825 min, *m/z* 282.0 $[M+H]^+$.

Step 2: (1r,4r)-N1-(5-Chloro-4-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)cyclohexane-1,4-diamine (**A104**): To a mixture of **104-2** (180.00 mg, 637.91 µmol, 1.00 *e q*) and (1r,4r)-cyclohexane-1,4-diamine (145.69 mg, 1.28 mmol, 2.00 *eq*) in dioxane (2.70 mL) was added *t*-BuONa (2M, 956.87 µL, 3.00 *eq*) and Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (32.69 mg, 63.79 µmol, 0.10 *eq*). The mixture was stirred at 90 °C for 12 h under nitrogen, cooled to room temperature, filtered, concentrated and purified by prep-HPLC to give **A104** (50 mg, 125.4 µmol, 19.7% yield, 99.4% purity, HCl) as a white solid. LCMS: RT = 2.309 min, *m/z* 360.1 $[M+H]^+$ ^1H NMR (MeOD, 400 MHz): δ 8.07 (s, 1H), 7.83 (s, 1H), 7.06 (s, 1H), 3.99 (s, 3H), 3.79-3.73 (m, 1H), 3.23-3.20 (m, 1H), 2.80-2.78 (d, J = 6.8 Hz, 1H), 2.22-2.14 (m, 4H), 1.68-1.55 (m, 4 H), 0.93-0.90 (m, 1 H), 0.51-0.47 (m, 2H), 0.14-0.12 (m, 2H).

Example 3: Synthesis of (1r,4r)-N1-(6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)cyclohexane-1,4-diamine (**A105**)

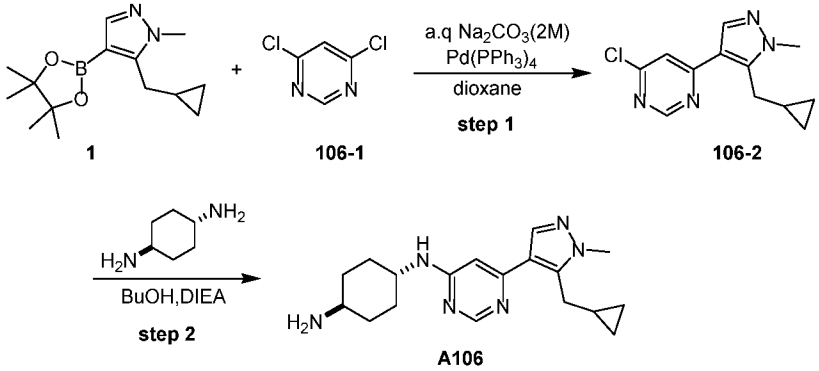


Step 1: 2-Chloro-6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyridine (**105-2**): To a solution of 2, 6-dichloropyridine (562 mg, 3.81 mmol, 1.00 *eq*) and compound **1** (1.00 g, 3.81 mmol, 1.0 *eq*) in DME (20 mL) was added Na_2CO_3 (2M, 5.72 mL, 3.00 *eq*) and Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium (II) (134.89 mg, 190.5 umol, 134.89 uL, 0.05 *eq*). The mixture was stirred at 80 °C for 2 h, cooled to room temperature, concentrated and purified by column chromatography to give **105-2** (500 mg, 1.32 mmol, 34.6% yield, 74.5% purity) as a yellow oil. LCMS: RT = 0.835 min, *m/z* 248.1 $[M+H]^+$.

Step 2: (1r,4r)-N1-(6-(5-(Cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)cyclohexane-1,4-diamine (**A105**): To a solution of 105-2 (400.00 mg, 1.61 mmol, 1.00 *eq*) and (1r,4r)-cyclohexane-1,4-diamine (275.77 mg, 2.42 mmol, 1.50 *eq*) in dioxane (8 mL) was added *t*-BuONa (2M, 2.42 mL, 3.00 *eq*) and Bis(di-*tert*-butyl(4-

dimethylaminophenyl)phosphine)dichloropalladium (II) (82.50 mg, 161.00 µmol, 0.10 *eq*). The mixture was stirred at 90 °C for 12 h, cooled to room temperature, and filtered. The filtrate was concentrated and purified by prep-HPLC to give **A105** (120 mg, 331.25 µmol, 20.6% yield, 99.9% purity, HCl) as a yellow solid. LCMS: RT = 2.164 min, *m/z* 326.2 $[M+H]^+$ ^{1}HNMR (MeOD, 400 MHz): δ 8.01-7.97 (m, 2H), 7.10-7.08 (d, J = 9.2 Hz, 1H), 6.96-6.94 (d, J = 7.2 Hz, 1H), 3.96 (s, 3H), 3.79-3.77 (m, 1H), 3.22-3.17 (m, 1H), 2.92-2.91 (d, J = 6.4 Hz, 1H), 2.21-2.13 (m, 4H), 1.68-1.55 (m, 4H), 0.95-0.93 (m, 1H), 0.52-0.48 (m, 2H), 0.18-0.16 (m, 2H).

Example 4: Synthesis of (1r,4r)-N1-(6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)cyclohexane-1,4-diamine (**A106**)

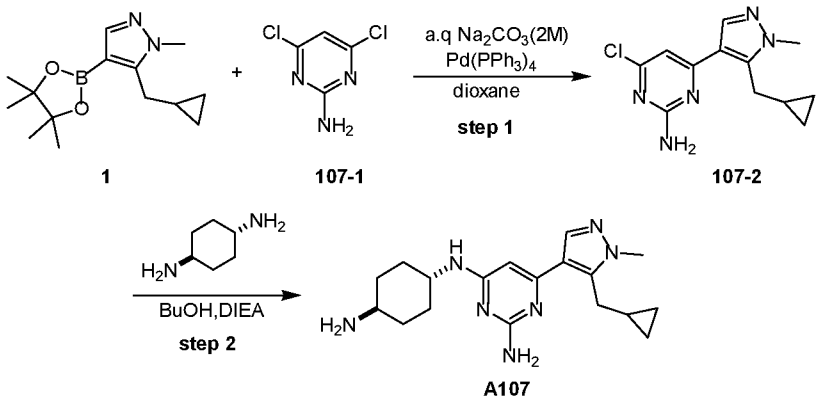


Step 1: 4-Chloro-6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidine (**106-2**): To a solution of 4, 6-dichloropyrimidine (284.5 mg, 1.91 mmol, 1.00 *eq*) and compound **1** (500.0 mg, 1.91 mmol, 1.00 *eq*) in dioxane (10 mL) was added Na_2CO_3 (2 M, 5.73 mL, 6.00 *eq*) and $Pd(PPh_3)_4$ (110.4 mg, 95.5 umol, 0.05 *eq*). The mixture was stirred at 90 °C for 2 h under nitrogen, cooled to room temperature, concentrated and purified by column chromatography to give **106-2** (200.00 mg, 562.9 µmol, 29.5% yield, 70% purity) as a colorless oil. LCMS: RT = 0.784 min, *m/z* 249.0 $[M+H]^+$.

Step 2: (1r,4r)-N1-(6-(5-(Cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)cyclohexane-1,4-diamine (**A106**): To a solution of compound **106-2** (180.0 mg, 723.73 µmol, 1.00 *eq*) in BuOH (1.8 mL) were added (1r,4r)-cyclohexane-1,4-diamine (165.3 mg, 1.45 mmol, 2.00 *eq*) and DIEA (374.1 mg, 505.59 µL, 4.00 eq). The mixture was stirred at 120 °C for 16 h, cooled to room temperature, and filtered. The filtrate was concentrated and purified by prep-HPLC to give **A106** (30.00 mg, 82.67 µmol, 11.4% yield, 100% purity, HCl) as a yellow solid. LCMS: RT = 1.231 min, *m/z* 327.2 $[M+H]^+$ ^{1}HNMR (MeOD, 400 MHz): δ 8.62 (s, 1H), 7.88 (s, 1H), 6.78 (s, 1H), 4.20-4.15 (m, 1H), 3.94 (s, 3H), 3.21-3.17 (m, 1H),

2.20-2.14 (m, 4H), 1.61-1.53 (m, 4H), 1.02-1.00 (m, 1H), 0.59-0.54 (m, 2H), 0.26-0.22 (m, 2H).

Example 5: Synthesis of N4-((1r,4r)-4-aminocyclohexyl)-6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidine-2,4-diamine (**A107**)

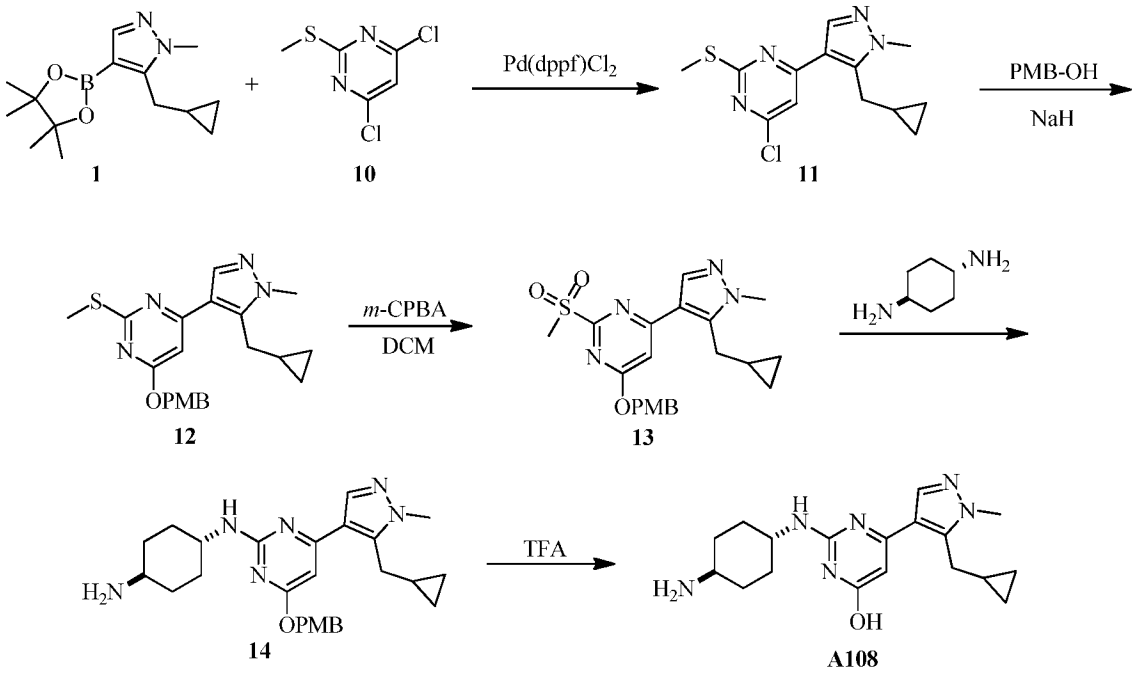


1 107-1 107-2 A107

Step 1: 4-Chloro-6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidin-2-amine (**107-2**): To a solution of 4,6-dichloropyrimidin-2-amine (313.22 mg, 1.91 mmol, 1.00 *eq*) and compound **1** (500.00 mg, 1.91 mmol, 1.00 *eq*) in dioxane (1.0 mL) was added Na_2CO_3 (2M, 5.73 mL, 6.00 *eq*) and $Pd(PPh_3)_4$ (110.36 mg, 95.50 µmol, 0.05 *eq*). The mixture was stirred at 90°C for 2 h under nitrogen, cooled to rt, concentrated and purified by column chromatography to give **107-2** (220.00 mg, 458.8 µmol, 24.0% yield, 55% purity) as a yellow solid. LCMS: RT = 0.724 min, *m/z* 264.0 $[M+H]^+$.

Step 2: N4-((1r,4r)-4-Aminocyclohexyl)-6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidine-2,4-diamine (**A107**): To a solution of compound **5-2** (180.0 mg, 682.52 µmol, 1.00 *eq*) in BuOH (1.8 mL) were added (1r,4r)-cyclohexane-1,4-diamine (155.87 mg, 1.37 mmol, 2.00 *eq*) and DIEA (352.84 mg, 476.80 µL, 4.00 eq). The mixture was stirred at 120 °C for 16 h, cooled to room temperature, and filtered. The filtrate was concentrated and purified by prep-HPLC to give **A107** (40.00 mg, 93.86 µmol, 13.7% yield, 97.2% purity, 2HCl) as a yellow solid. LCMS: RT = 2.140 min, *m/z* 342.2 $[M+H]^+$ ^{1}HNMR (MeOD, 400 MHz) δ 7.81 (s, 1H), 6.14 (s, 1H), 4.07-4.02 (m, 1H), 3.92 (s, 3H), 3.19-3.13 (m, 1H), 2.92-2.90 (d, J = 6.00 Hz, 2H), 2.19-2.12 (m, 4H), 1.60-1.45 (m, 4H), 1.00-0.99 (m, 1H), 0.56-0.53 (m, 2H), 0.24-0.20 (m, 2H).

Example 6: Synthesis of 2-(((1r,4r)-4-aminocyclohexyl)amino)-6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidin-4-ol (**A108**)



1 10 11 12 13 14 A108

Step 1: 4-Chloro-6-(5-(cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-(methylthio)pyrimidine (**11**): To a solution of compound **1** (1.00 g, 3.81 mmol, 1.0 *eq*) in dioxane (20 mL) was added compound **10** (743 mg, 3.81 mmol, 1.0 *eq*), $Pd(dppf)Cl_2$ (139.39 mg, 190 µmol, 0.05 *eq*), and Na_2CO_3 (2M, 3.81 mL, 2.0 *eq*) under nitrogen. The resulting mixture was stirred at 100 °C for 16 hrs under nitrogen. The mixture was filtered and the filtrate was concentrated and purified by silica gel column (PE:EA = 4:1, Rf = 0.4) to give compound **11** (600 mg, 1.49 mmol, 39% yield, 73% purity). LCMS: RT = 0.894 min, *m/z* 295.0 $[M+H]^+$.

Step 2: 4-(5-(Cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)-6-((4-methoxybenzyl)oxy)-2-(methylthio)pyrimidine (**12**): To a solution of PMB-OH (327 mg, 2.36 mmol, 294 µL, 1.2 *eq*) in DMF (6 mL) was added NaH (102 mg, 2.56 mmol, 60% purity, 1.3 *eq*) at 0 °C. After stirred for 1 hr, compound **11** (580 mg, 1.97 mmol, 1.0 *eq*) in THF (1.50 mL) was added drop-wise at 0 °C. The resulting mixture was stirred at 20 °C for 15 hrs. The reaction was quenched with aq. NH_4Cl (50 mL) and extracted with EA (50 mL x 2). The organic layers were concentrated and purified by silica gel column (PE:EA = 10:1~5:1) to give compound **12** (140 mg, 236 µmol, 12% yield, 67% purity). LCMS: RT = 0.984 min, *m/z* 397.0 $[M+H]^+$; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H), 7.40-7.38 (d, J = 2.4 Hz, 2H), 7.30 (m, 1H), 6.93-6.91 (m, 3H), 6.55 (s, 1H), 5.36 (s, 2H), 4.63 (s, 1H), 3.88 (s,

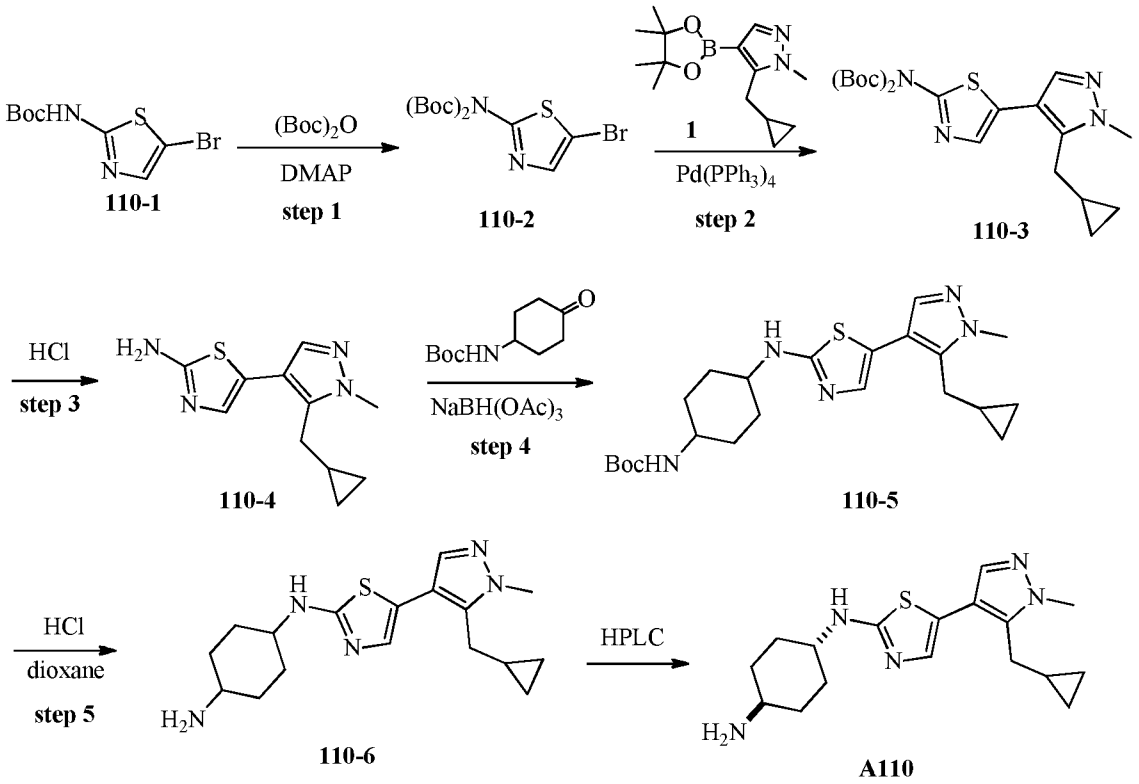
3H), 3.82 (s, 5H), 3.19-3.18 (d, *J* = 6.00 Hz, 2H), 2.60 (s, 3H), 1.09-1.04 (m, 1H), 0.50-0.45 (m, 2H), 0.28-0.25 (m, 2H).

Step 3: 4-(5-(Cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)-6-((4-methoxybenzyl)oxy)-2-(methylsulfonyl)pyrimidine (**13**): To a solution of compound **12** (130 mg, 328 µmol, 1.0 *eq*) in DCM (2.6 mL) was added *m*-CPBA (177 mg, 820 µmol, 80% purity, 2.5 *eq*) at 0 °C. The mixture was stirred at 15 °C for 2 hrs. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were washed with aq. $NaHCO_3$ (10 mL). The organic layer was concentrated and purified by prep-TLC (PE:EA = 1:1, Rf = 0.4) to give compound **13** (80 mg, 170 µmol, 52% yield, 91% purity). LCMS: RT = 0.856 min, *m/z* 429.0 $[M+H]^+$.

Step 4: (1*r*,4*r*)-N^1-(4-(5-(Cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)-6-((4-methoxybenzyl)oxy)pyrimidin-2-yl)cyclohexane-1,4-diamine (**14**): To a solution of compound **13** (80 mg, 187 µmol, 1.0 *eq*) in dioxane (1.2 mL) was added *trans*-cyclohexane-1,4-diamine (85 mg, 747 µmol, 4.0 *eq*). The mixture was stirred at 120 °C for 2 hrs with microwave. The mixture was filtered and concentrated to give compound **14** (100 mg, crude), which was used directly for next step without further purification. LCMS: RT = 0.761 min, *m/z* 463.3 $[M+H]^+$.

Step 5: 2-(((1*r*,4*r*)-4-Aminocyclohexyl)amino)-6-(5-(cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)pyrimidin-4-ol (**A108**): The mixture of compound **14** (100 mg, 216 µmol, 1.0 *eq*) in TFA (2 mL) was stirred at 15 °C for 2 hrs. The mixture was concentrated and purified by prep-HPLC to give compound **A108** (20 mg, 57 µmol, 26% yield, 98% purity). LCMS: RT = 2.668 min, *m/z* 343.2 $[M+H]^+$; ^{1}HNMR (CD_3OD, 400 MHz) δ 7.92 (s, 1H), 3.92 (s, 4H), 3.18-3.17 (m, 1H), 3.00 (s, 2H), 2.23-2.14 (m, 4H), 1.59-1.55 (m, 4H), 1.03(s, 1H), 0.58-0.53 (m, 2H), 0.27-0.23 (m, 2H).

Example 7: Synthesis of (1*r*,4*r*)-N^1-(5-(5-(Cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)thiazol-2-yl)cyclohexane-1,4-diamine (**A110**)



Step 1: *Tert*-butyl (*tert*-butoxycarbonyl)-(5-bromothiazol-2-yl)carbamate (**110-2**): To a solution of *tert*-butyl (5-bromothiazol-2-yl)carbamate (0.5 g, 1.79 mmol, 1.0 *eq*) in THF (20 mL) was added di-*tert*-butyl dicarbonate (0.39 g, 1.79 mmol, 1.0 *eq*) and DMAP (0.1 g, 0.9 mmol 0.5 *eq*). The resulting mixture was stirred at 60 °C for 30 min, cooled to room temperature, diluted with H_2O (25 mL), and extracted with EtOAc (50 mL x 2). The combined organic layers were dried, filtered, concentrated, and purified by prep-TLC to give compound **110-2** (0.35 g, 0.92 mmol, 55% yield). LCMS: RT = 0.944 min, *m/z* 379.0 $[M+H]^+$; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.40 (s, 1H), 1.54 (s, 18H).

Step 2: *N,N*-Bis(*tert*-butoxycarbonyl)- 5-(5-(cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)thiazol-2-amine (**110-3**): To a solution of compound **110-2** (100 mg, 0.26 mmol, 1.0 *eq*) in toluene (10 mL) was added compound **1** (69 mg, 0.26 mmol, 1.0 *eq*) and K_2CO_3 (109 mg, 0.79 mmol, 3.0 *eq*) under N_2, followed by addition of $Pd(PPh_3)_4$ (3.5 mg, 2.64 µmmol, 0.01 *eq*) under N_2. The reaction was heated at 110 °C for 2 hrs and cooled to room temperature. The mixture was poured into water (25 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (10 mL), dried, filtered, concentrated, and purified by prep-TLC to give compound **110-3** (10 mg, 30 µmol, 11% yield). LCMS: RT = 0.922 min, *m/z* 435.3 $[M+H]^+$; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.38 (m,

1H), 7.12 (m, 1H), 3.75 (s, 3H), 2.65-2.63 (m, 2H), 1.34 (s, 18H), 0.82 – 0.80 (m, 1H), 0.37-0.35 (m, 2H), 0.03-0.00 (m, 2H).

Step 3: 5-(5-(Cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)thiazol-2-amine (**110-4**): A mixture of compound **110-3** and HCl is stirred at room temperature for 1 hr and then concentrated to give compound **110-4**.

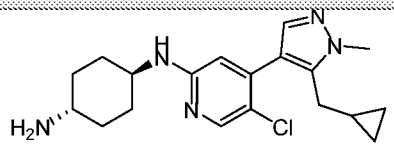
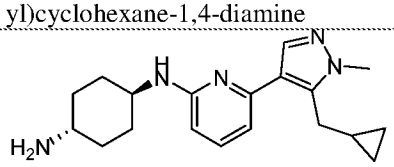
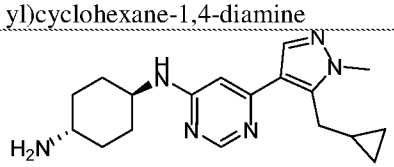
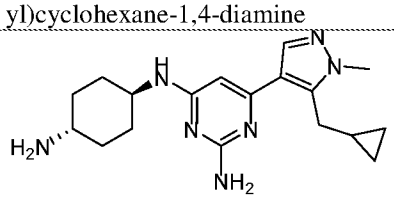
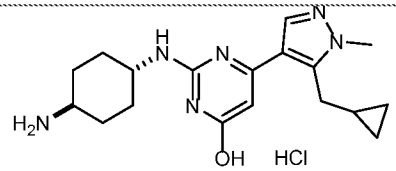
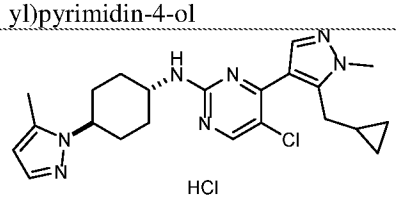
Step 4: *Tert*-butyl (4-((5-(5-(cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)thiazol-2-yl)amino)cyclohexyl)carbamate (**110-5**): To a mixture of compound **110-4** (1.0 *eq*) and *tert*-butyl (4-oxocyclohexyl)carbamate (1.0 *eq*) in DCM are added AcOH (1.0 *eq*) and $NaBH(OAc)_3$ (2.0 *eq*). The resulting mixture is stirred at 20 °C for 2 hrs, and then quenched with H_2O and worked up to give compound **110-5**.

Step 5: N^1-(5-(5-(Cyclopropylmethyl)-1-methyl-1*H*-pyrazol-4-yl)thiazol-2-yl)cyclohexane-1,4-diamine (**110-6**): To a solution of compound **108-5** (1.0 *eq*) in DCM is added TFA at 0 °C. The resulting mixture is stirred at 20 °C for 1 hr and then worked up to give compound **110-6**, which is further purified with HPLC to give compound **A110**.

Example 8: Dose-response compound screen in RKO cells

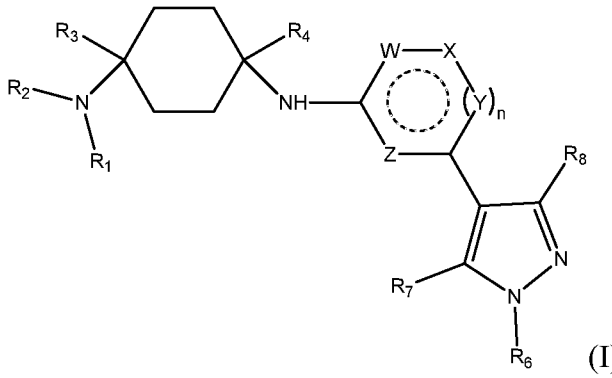
RKO colorectal cells were incubated with serial dilutions of each of the compounds (at a concentration range of 0.167-1.5 μM or 0.11-1 μM in DMSO) for 16 hours at 37 °C. Cells were washed with PBS and cell pellets were incubated with ice cold protein lysis buffer containing protease inhibitor cocktail (1/200; Calbiochem) and phosphatase inhibitors (20 mM p-nitrophenyl phosphate (PNPP), 20 mM β-glycerophosphate and 300 nM okadaic acid). Western blot (WB) analysis was performed by means of standard techniques. Blots were incubated with antibodies detecting β-catenin (1/2,500; BD Transduction), p53 (DO-1&1801 hybridoma mix; dilution of 1:20 of supernatants from each), CKIα (C-19; 1/1,000; Santa Cruz Biotechnology) and phospho-histone H2AX (S139; 1/1,000; Millipore). Secondary antibodies were HRP-linked goat anti-mouse, goat anti-rabbit and rabbit anti-goat antibodies (all 1/10,000; Jackson). Blots were developed using ECL (GE Healthcare). Signal intensities corresponding to β-catenin and p53 stabilization and phosphorylation of H2AX (γH2AX - a marker of DNA damage) -indicators of CKIα inhibition (Elyada *et al.*, *Nature* 1991), were analyzed by the ImageJ software. Relative signal intensities are depicted in Table 1 (see also in Fig. 1), where values of 1 correspond to signals of mock (DMSO)-treated cells.

Table 1 – Activity of Compounds of the Invention

Cmpd.	Structure	Mass ($M+H^+$)	H2AX phosphorylation	p53 stabilization	β-Catenin stabilization
A104	 (1r,4r)-N1-(5-chloro-4-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)cyclohexane-1,4-diamine	Calc'd for $C_{19}H_{27}ClN_5$: 360.2; Found: 360.1	20	20	9
A105	 (1r,4r)-N1-(6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)cyclohexane-1,4-diamine	Calc'd for $C_{19}H_{28}N_5$: 326.2; Found: 326.2	1	2	5
A106	 (1r,4r)-N1-(6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)cyclohexane-1,4-diamine	Calc'd for $C_{19}H_{27}N_6$: 327.2; Found: 327.2	1	1	9
A107	 N4-((1r,4r)-4-aminocyclohexyl)-6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidine-2,4-diamine	Calc'd for $C_{19}H_{28}N_7$: 342.2; Found: 342.2	1	2	4
A108	 2-(((1r,4r)-4-aminocyclohexyl) amino)-6-(5-(cyclopropylmethyl)-1-methyl-1H-pyrazol-4-yl)pyrimidin-4-ol	Calc'd for $C_{18}H_{27}ClN_6O$: 378.9; Found: 378.9	1	1	9
A102		Calc'd for $C_{22}H_{29}Cl_2N_7$: 462.42; Found:462.42	1	1	4

CLAIMS:

1. A compound having Formula (I), or a stereoisomer or salt thereof:



(I)

wherein:

R_1 and R_2 are each independently selected from H; and straight or branched C_1–C_8 alkyl, straight or branched C_1–C_5 alkoxy, straight or branched C_1–C_5 acyl, C_5–C_{15} aryl, and C_3–C_7 heteroaryl, each optionally substituted by at least one of halide, hydroxyl, ester, ether, C_5–C_{15} aryl, C_3–C_7 heteroaryl, and amide; or

R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated, unsaturated, or aromatic ring that may optionally include at least one of N, O, NH, C=N, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, halide, and cyano;

R_3 and R_4 are each independently selected from H, and straight or branched C_1–C_8 alkyl optionally substituted by at least one of halide, hydroxyl, alkoxy, C_5–C_{15} aryl, C_3–C_7 heteroaryl, ester, and amide; or

R_1 or R_2 together with R_3 and the carbon and nitrogen atoms they are each connected to form a 4–7 membered saturated, unsaturated, or aromatic ring that may optionally include at least one of N, NH, O, C=N, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, carbonyl, and halide;

W, X, Y, and Z are each selected from CH, CR_5, CR_{5c}, NH, N, and S; provided that at least one of W, X, Y and Z is selected from NH, N, and S; and provided that, when W is N and Z is N, then X is CR_{5c};

n is an integer selected from 0 and 1;

R_5 is selected from OH, NH_2, and halide; R_{5c} is selected from OH and NH_2;

R_8 is selected from H and halide; and straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, and straight or branched C_2–C_8 alkynyl, each optionally substituted by at least one halide;

R_6 is selected from straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, straight or branched C_2–C_8 alkynyl, C_5–C_{10} cycloalkyl, and saturated or unsaturated 4–6 membered heterocyclyle, each optionally substituted by at least one of straight or branched C_1–C_8 alkyl, C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide;

R_7 is selected from straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, and straight or branched C_2–C_8 alkynyl, each independently substituted by at least one of C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide.

2. The compound according to claim 1, wherein R_1 and R_2 are each independently selected from H, and straight or branched C_1–C_8 alkyl optionally substituted by at least one of halide, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, ester, ether, and amide.

3. The compound according to claim 1, wherein R_1 and R_2 are each independently selected from H, and straight or branched C_1–C_5 alkoxy optionally substituted by at least one of halide, hydroxyl, ester, and amide.

4. The compound according to claim 1, wherein R_1 and R_2 are each independently selected from H, and C_1–C_5 acyl optionally substituted by at least one of halide, hydroxyl, ester, ether, and amide.

5. The compound according to claim 1, wherein R_1 and R_2 are each independently selected from H, and C_5–C_{15} aryl optionally substituted by at least one of halide, hydroxyl, ester, ether, and amide.

6. The compound according to any one of the preceding claims, wherein R_4 is H.

7. The compound according to any one of the preceding claims, wherein R_3 and R_4 are H.

8. The compound according to any one of the preceding claims, wherein R_5 is halide.

9. The compound according to any one of claims 1 to 7, wherein R_5 is NH_2.

10. The compound according to any one of claims 1 to 7, wherein R_5 is OH.

11. The compound according to any one of the preceding claims, wherein R_8 is selected from H, Cl, and straight or branched C_1–C_4 alkyl.

12. The compound according to any one of the preceding claims, wherein R_8 is H.

13. The compound according to any one of the preceding claims, wherein at least one of R_1 and R_2 is H.

14. The compound according to any one of the preceding claims, wherein R_6 selected from straight or branched C_1–C_8 alkyl, C_5–C_{10} cycloalkyl, and saturated or unsaturated 4–6 membered heterocyclyle; and R_7 is selected from straight or branched C_1–C_8 alkyl, substituted by at least one of C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide.

15. The compound according to any one of the preceding claims, wherein R_6 is selected from straight or branched C_1–C_8 alkyl, C_5–C_{10} cycloalkyl, and 4–6 membered saturated heterocyclyle.

16. The compound according to any one of the preceding claims, wherein R_7 is straight or branched C_1–C_8 alkyl substituted by at least one of C_3–C_7 cycloalkyl and hydroxyl.

17. The compound according to any one of the preceding claims, wherein R_6 is selected from straight or branched C_1–C_8 alkyl, saturated , and unsaturated or aromatic 4 –6 membered heterocyclyle, each optionally substituted by at least one of straight or branched C_1–C_8 alkyl, C_3–C_7 cycloalkyl, halide, hydroxyl, and CF_3.

18. The compound according to any one of the preceding claims, wherein R_7 is straight or branched C_1–C_8 alkyl substituted by at least one C_3–C_7 cycloalkyl.

19. The compound according to any one of the preceding claims, wherein R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated ring, optionally including at least one of N, O, NH, C=N, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, hydroxyl, halide, and cyano.

20. The compound according to any one of the preceding claims, wherein R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated ring.

21. The compound according to any one of the preceding claims, wherein R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated ring including at least one of N and O.

22. The compound according to any one of the preceding claims, wherein R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered aromatic ring optionally including at least one of N and O.

23. The compound according to any one of the preceding claims, wherein R_3 and R_4 are H.

24. The compound according to any one of the preceding claims, wherein R_1 or R_2 together with R_3 and the carbon and nitrogen atom they are connected to form a 4–7 membered saturated ring that optionally includes at least one of N, NH, O, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, hydroxyl, carbonyl, and halide.

25. The compound according to any one of the preceding claims, wherein R_1 or R_2 together with R_3 and the carbon and nitrogen atom they are connected to form a 4–7 membered saturated ring that includes at least one of NH, O, and C=O.

26. The compound according to any one of the preceding claims, wherein n is 1.

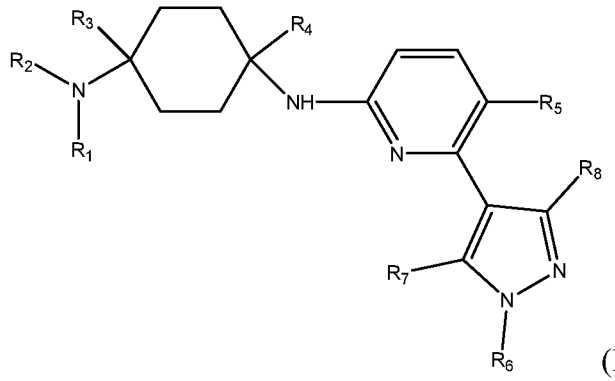
27. The compound according to any one of claims 1 to 25, wherein n is 0.

28. The compound according to any one of the preceding claims, wherein one of W, X, Y, and Z is N.

29. The compound according to any one of claims 1 to 27, wherein two of W, X, Y, and Z is N.

30. The compound according to claim 27, wherein two of W, X, Y, and Z are independently selected from NH, N, and S.

31. The compound according to any one of the preceding claims, selected from the following, wherein R_1–R_8 are as defined herein above:



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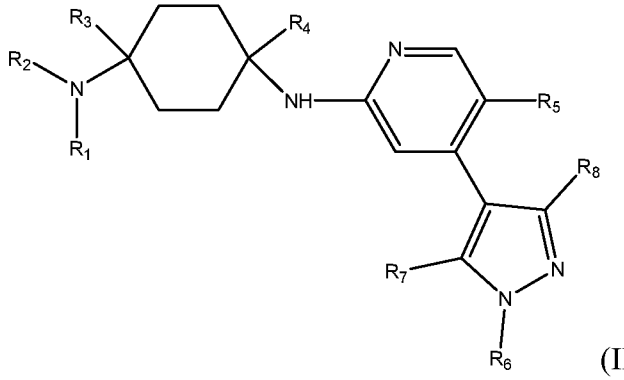
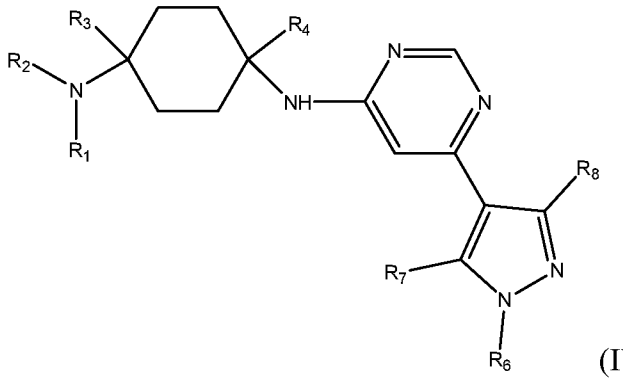
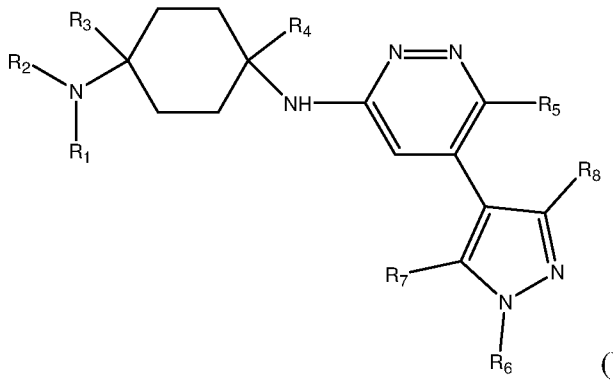


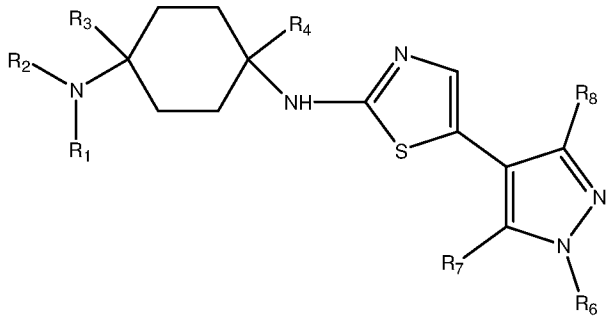
(III),



(IV),

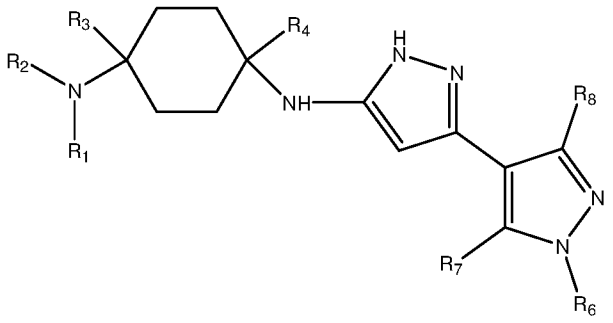


(V),



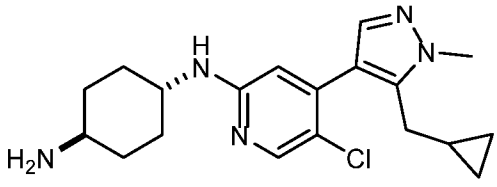
(VI),

and

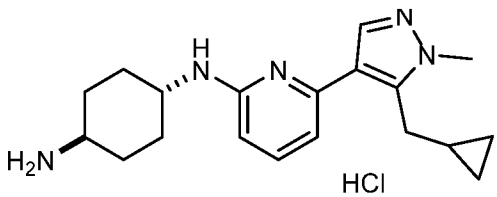


(VII).

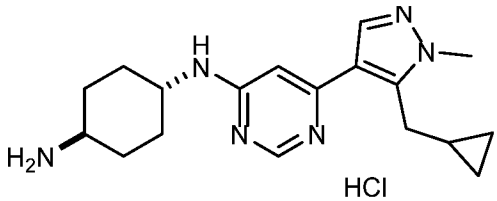
32. The compound according to any one of the preceding claims, selected from the following:



HCl A104,



HCl A105,



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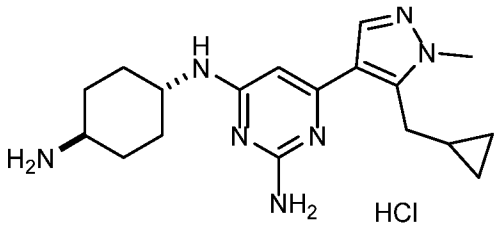
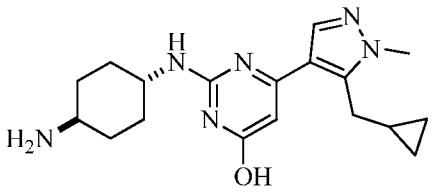
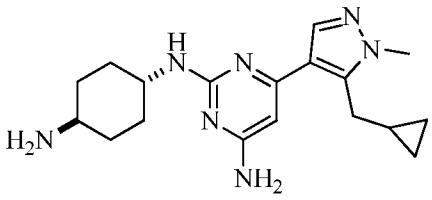


A107,

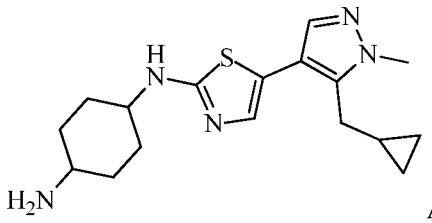


A108,



A109,

and



A110.

33. A pharmaceutical composition comprising at least one compound according to any one of claims 1 to 32.

34. A method of inhibiting at least one of casein kinase I (CKI) and interleukin-1 receptor-associated kinase 1 (IRAK1) in a subject in need thereof, comprising administrating to the subject at least one compound according to any one of claims 1 to 32.

35. A method of inhibiting casein kinase I (CKI) in a subject in need thereof, comprising administrating to the subject at least one compound according to any one of claims 1 to 32.

36. A method of inhibiting interleukin-1 receptor-associated kinase 1 (IRAK1) in a subject in need thereof, comprising administrating to the subject at least one compound according to any one of claims 1 to 32.

37. A method of treating a condition, symptom, or disease associated with a malignant condition in a subject in need thereof, comprising administering to the subject at least one compound according to any one of claims 1 to 32.

38. A method according to claim 37, wherein the malignant condition is cancer.

39. A method according to claim 38, wherein the cancer has WT p53.

40. A method according to claim 39, wherein the WT p53 is a biomarker for the compound efficacy.

41. A method according to claim 38, wherein the cancer is selected from leukemia, multiple myeloma, malignant melanoma, breast cancer, prostate cancer, and colorectal cancer.

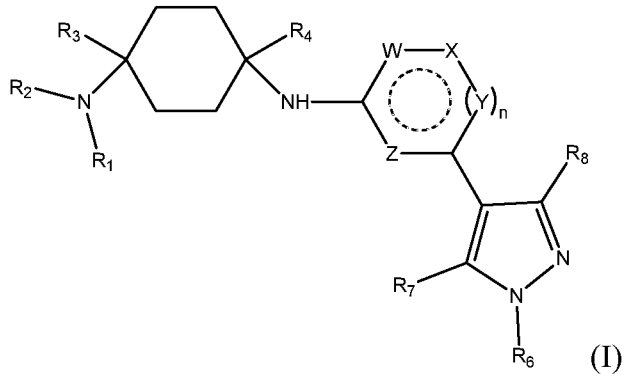
42. A method according to claim 37, wherein the malignant condition is selected from hematological malignancies, multiple myeloma, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), melanoma, ER-negative breast cancer, diffuse large B cell lymphoma (DLBCL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), and head and neck cancer.

43. A method according to any one of claims 34 to 42, further comprising inducing a cancer immunotherapy response in the subject.

44. A method for inducing an immunotherapy response in a subject in need thereof, comprising administering to the subject at least one compound according to any one of claims 1 to 32.

45. A method of treating an inflammatory and immune related disorder in a subject in need thereof, comprising administering to the subject at least one compound according to any one of claims 1 to 32.

46. A compound having Formula (I), or a stereoisomer or salt thereof:



(I)

wherein:

R_1 and R_2 are each independently selected from H; and straight or branched C_1–C_8 alkyl, straight or branched C_1–C_5 alkoxy, straight or branched C_1–C_5 acyl, C_5–C_{15} aryl, and C_3–C_7 heteroaryl, each optionally substituted by at least one of halide, hydroxyl, ester, ether, C_5–C_{15} aryl, C_3–C_7 heteroaryl, and amide; or

R_1 and R_2 together with the nitrogen atom they are connected to form a 4–7 membered saturated, unsaturated, or aromatic ring that may optionally include at least one of N, O, NH, C=N, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, halide, and cyano;

R_3 and R_4 are each independently selected from H, and straight or branched C_1–C_8 alkyl optionally substituted by at least one of halide, hydroxyl, alkoxy, C_5–C_{15} aryl, C_3–C_7 heteroaryl, ester, and amide; or

R_1 or R_2 together with R_3 and the carbon and nitrogen atoms they are each connected to form a 4–7 membered saturated, unsaturated, or aromatic ring that may optionally include at least one of N, NH, O, C=N, C=O, and SO_2, and can optionally be substituted with at least one of straight or branched C_1–C_5 alkyl, C_5–C_{15} aryl, C_3–C_7 heteroaryl, hydroxyl, carbonyl, and halide;

W, X, Y, and Z are each independently selected from CH, CR_5, NH, N, and S; provided that at least one of W, X, Y and Z is selected from NH, N and S; provided that, when W is N and Z is N, then R_8 is other than H;

n is an integer selected from 0 and 1;

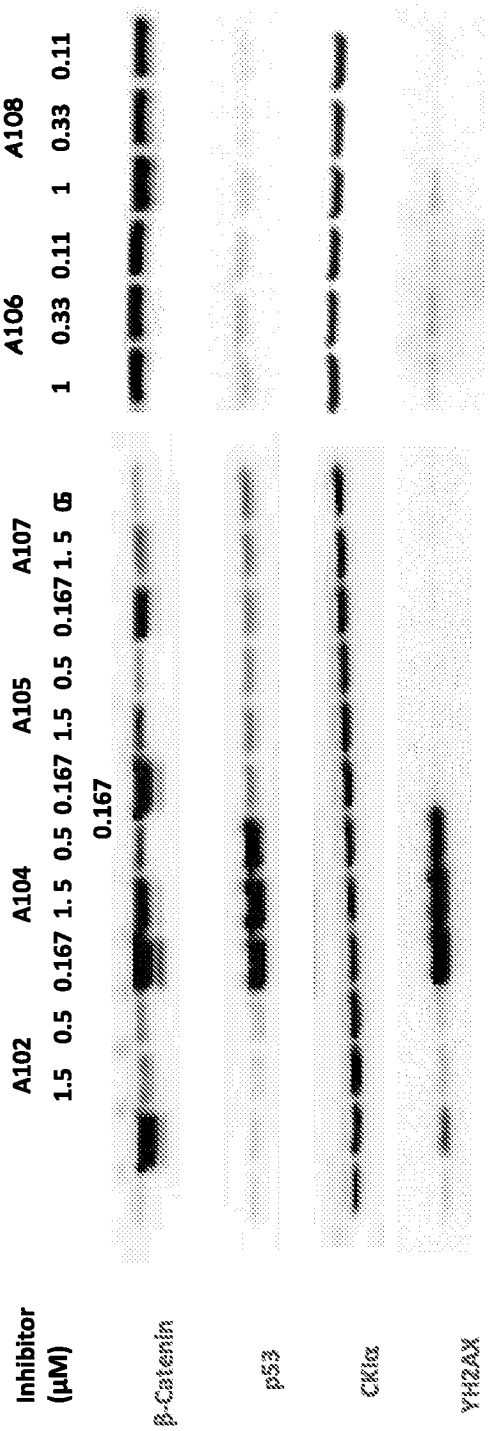
R_5 is selected from OH, NH_2, and halide;

R_8 is selected from H and halide; and straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, and straight or branched C_2–C_8 alkynyl, each optionally substituted by at least one halide;

R_6 is selected from straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, straight or branched C_2–C_8 alkynyl, C_5–C_{10} cycloalkyl, and saturated or unsaturated 4–6 membered heterocyclyle; each optionally substituted by at least one of straight or branched C_1–C_8 alkyl, C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide; and

R_7 is selected from straight or branched C_1–C_8 alkyl, straight or branched C_2–C_8 alkenyl, and straight or branched C_2–C_8 alkynyl; each independently substituted by at least one of C_3–C_7 cycloalkyl, 4–6 membered heterocyclyle, C_5–C_{15} aryl, C_3–C_7 heteroaryl, halide, hydroxyl, and C_1–C_5 alkyl halide.

Figure 1


Inhibitor (μM)
A102
1.5 0.5 0.167
A104
1.5 0.5 0.167
A105
1.5 0.5 0.167
A107
1.5 0.5 0.167
A106
1 0.33 0.11
A108
1 0.33 0.11
β-Catenin
p53
Cklα
γH2AX

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2018/050100

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D403/04 C07D417/04 A61K31/4439 A61K31/506
A61K31/4155 A61K31/427 A61P35/00
ADD.
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)
C07D

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)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/081679 A1 (MERCK PATENT GMBH [DE]) 26 May 2016 (2016-05-26) page 1, paragraph [0002] page 150; compound 44 page 170; compound 111 page 179; compound 143 page 188; compound 182 page 210; compound 263 page 214; compound 276 claims 1, 16, 18	1-46

A	WO 2016/149756 A1 (UNIV MELBOURNE [AU]) 29 September 2016 (2016-09-29) claims 1, 5, 6	1-46

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[X] Further documents are listed in the continuation of Box C.

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6 April 2018	25/04/2018

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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