



(12) **DEMANDE DE BREVET CANADIEN**
CANADIAN PATENT APPLICATION

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2021/05/14
(87) Date publication PCT/PCT Publication Date: 2021/11/25
(85) Entrée phase nationale/National Entry: 2022/11/10
(86) N° demande PCT/PCT Application No.: CN 2021/093857
(87) N° publication PCT/PCT Publication No.: 2021/233227
(30) Priorités/Priorities: 2020/05/16 (US63/026,021);
2020/06/26 (US63/044,962); 2021/01/15 (US63/137,733)

(51) Cl.Int./Int.Cl. *C07D 473/34* (2006.01),
A61K 31/52 (2006.01), *C07D 513/04* (2006.01)

(71) Demandeur/Applicant:
FOCHON BIOSCIENCES, LTD., CN

(72) Inventeurs/Inventors:
ZHOU, ZUWEN, CN;
TAN, RUI, CN;
XU, HUA, CN;
LIU, QIHONG, CN;
ZHANG, HUAJIE, CN;
LIU, BIN, CN;

...

(74) Agent: LAVERY, DE BILLY, LLP

(54) Titre : COMPOSES UTILES EN TANT QU'INHIBITEURS DE PROTEINE KINASE

(54) Title: COMPOUNDS AS PROTEIN KINASE INHIBITORS

(57) Abrégé/Abstract:

Provided are certain PI3K inhibitors, pharmaceutical compositions thereof, and methods of use thereof.



(72) **Inventeurs(suite)/Inventors(continued)**: ZHANG, WEIPENG, CN; LI, ZHIFU, CN; LIU, YANXIN, CN; LIN, SHU, US;
ZHAO, XINGDONG, CN; WANG, WEIBO, US

Date Submitted: 2022/11/10

CA App. No.: 3178569

Abstract:

Provided are certain PI3K inhibitors, pharmaceutical compositions thereof, and methods of use thereof.

COMPOUNDS AS PROTEIN KINASE INHIBITORS

[001] This application claims the priority to the U.S. provisional application No. 63/026,021, 63/044,962 and 63/137,733, each of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[002] Provided are certain compounds or pharmaceutically acceptable salts thereof which can inhibit kinase activity of PI3K and may be useful for the treatment of hyper-proliferative diseases like cancer and inflammation, or immune and autoimmune diseases.

BACKGROUND OF THE INVENTION

[003] Phosphoinositide 3-kinase (PI3K) belongs to a large family of lipid signaling kinase that plays key role in cellular processes, including cell growth, differentiation, migration and apoptosis. PI3K family is divided to three classes, I, II and III, based on sequence homology and lipid substrate specificity. Among them, Class I PI3K, which includes PI3K α , PI3K β , PI3K γ , and PI3K δ , is mostly studied.

[004] Class I PI3K is a heterodimer formed by two subunits, a catalytic subunit (p110) and a regulatory subunit (p85). The catalytic subunit, p110, has four isotypes, α , β , γ , and δ . The p110 α has a role in insulin-dependent signaling, p110 β in platelet aggregation, thrombosis and insulin signaling, and p110 γ and p110 δ are expressed mainly in leukocytes and have roles in lymphocyte activation, mast cell degranulation, and chemotaxis. The catalytic p110 subunit associates with p85 regulatory subunit. Upon reception of upstream activation signals, the p85 regulatory subunit releases its inhibition of p110, such that p110 can interact with the lipid membranes to phosphorylate phosphatidylinositol-4,5-bisphosphate (PIP2) at the 3'-OH position of the inositol ring to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3), which then activates downstream signals, resulting in dysregulation of metabolism and protein synthesis, and cell growth, proliferation and survival.

[005] All four class I catalytic PI3K isoforms show a characteristic expression pattern in vivo. p110 α and p110 β are expressed ubiquitously in mammalian tissue, while p110 γ and p110 δ appear to be more selectively expressed in leukocyte, endothelial cells and smooth muscle cells. Deletion of the p110 α or p110 β induces embryonic lethality. p110 γ -deficient mice develop and reproduce normally, although they have suboptimal immune responses because of defects in T-cell activation as well as in neutrophil and macrophage migration. The loss of p110 δ mice are also viable and fertile but exhibit significant defects in T, B cell activation.

[006] The PI3K pathway is commonly deregulated in cancer cells. The expression of PI3K δ is generally restricted to hematopoietic cell types. The p110 δ isoform is constitutively activated in B cell tumors, and inactivation of it have demonstrated its important role for treatment of B cell malignancy. It's demonstrated that the PI3K δ plays a critical role in the signaling pathways of various types of leukemia. Hence, it has become an attractive target for pharmacotherapy. Preclinical data on acute myeloid leukemia and chronic lymphocytic leukemia has identified the PI3K δ as predominant isoform in these diseases. Therefore, a

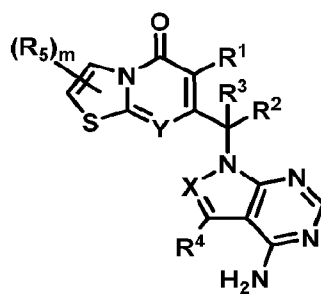
compound having an inhibitory activity on PI3K will be useful for the prevention and treatment of cancer.

[007] Therefore, a compound having an inhibitory activity on PI3K will be useful for the prevention or treatment of cancer. Although PI3K inhibitors were disclosed in the arts, e.g. WO 2012146666, WO 2003035075 and US 20110015212, many suffer from short half-life or toxicity. Therefore, there is a need for new PI3K inhibitors that have at least one advantageous property selected from solubility, drug-drug interactions, potency, stability, selectivity, toxicity, drug resistance, pharmacokinetics and pharmacodynamics properties as an alternative for the treatment of hyper-proliferative diseases. In this regard, a novel class of PI3K inhibitors is provided herein.

DISCLOSURE OF THE INVENTION

[008] Disclosed herein are certain novel compounds, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, and their use as pharmaceuticals.

[009] In one aspect, disclosed herein is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,
wherein:

X is selected from CR⁶ and N;

Y is selected from CR⁷ and N;

R¹ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A1}R^{B1}, -OR^{A1}, -C(O)R^{A1}, -C(=NR^{E1})R^{A1}, -C(=N-OR^{B1})R^{A1}, -C(O)OR^{A1}, -OC(O)R^{A1}, -C(O)NR^{A1}R^{B1}, -NR^{A1}C(O)R^{B1}, -C(=NR^{E1})NR^{A1}R^{B1}, -NR^{A1}C(=NR^{E1})R^{B1}, -OC(O)NR^{A1}R^{B1}, -NR^{A1}C(O)OR^{B1}, -NR^{A1}C(O)NR^{A1}R^{B1}, -NR^{A1}C(S)NR^{A1}R^{B1}, -NR^{A1}C(=NR^{E1})NR^{A1}R^{B1}, -S(O)_tR^{A1}, -S(O)(=NR^{E1})R^{B1}, -N=S(O)R^{A1}R^{B1}, -S(O)₂OR^{A1}, -OS(O)₂R^{A1}, -NR^{A1}S(O)_tR^{B1}, -NR^{A1}S(O)(=NR^{E1})R^{B1}, -S(O)_tNR^{A1}R^{B1}, -S(O)(=NR^{E1})NR^{A1}R^{B1}, -NR^{A1}S(O)₂NR^{A1}R^{B1}, -NR^{A1}S(O)(=NR^{E1})NR^{A1}R^{B1}, -P(O)R^{A1}R^{B1} and -P(O)(OR^{A1})(OR^{B1}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

R² is selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

R³ is selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl,

C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X3};

or R² and R³ together with the atoms to which they are attached form a C₃₋₁₀ cycloalkyl or heterocyclic ring of 4 to 12 members containing 1, 2 or 3 heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X2} groups;

R⁴ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A4}R^{B4}, -OR^{A4}, -C(O)R^{A4}, -C(=NR^{E4})R^{A4}, -C(=N-OR^{B4})R^{A4}, -C(O)OR^{A4}, -OC(O)R^{A4}, -C(O)NR^{A4}R^{B4}, -NR^{A4}C(O)R^{B4}, -C(=NR^{E4})NR^{A4}R^{B4}, -NR^{A4}C(=NR^{E4})R^{B4}, -OC(O)NR^{A4}R^{B4}, -NR^{A4}C(O)OR^{B4}, -NR^{A4}C(O)NR^{A4}R^{B4}, -NR^{A4}C(S)NR^{A4}R^{B4}, -NR^{A4}C(=NR^{E4})NR^{A4}R^{B4}, -S(O)_rR^{A4}, -S(O)(=NR^{E4})R^{B4}, -N=S(O)R^{A4}R^{B4}, -S(O)₂OR^{A4}, -OS(O)₂R^{A4}, -NR^{A4}S(O)_rR^{B4}, -NR^{A4}S(O)(=NR^{E4})R^{B4}, -S(O)_rNR^{A4}R^{B4}, -S(O)(=NR^{E4})NR^{A4}R^{B4}, -NR^{A4}S(O)₂NR^{A4}R^{B4}, -NR^{A4}S(O)(=NR^{E4})NR^{A4}R^{B4}, -P(O)R^{A4}R^{B4} and -P(O)(OR^{A4})(OR^{B4}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X4};

each R⁵ is independently selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A5}R^{B5}, -OR^{A5}, -C(O)R^{A5}, -C(=NR^{E5})R^{A5}, -C(=N-OR^{B5})R^{A5}, -C(O)OR^{A5}, -OC(O)R^{A5}, -C(O)NR^{A5}R^{B5}, -NR^{A5}C(O)R^{B5}, -C(=NR^{E5})NR^{A5}R^{B5}, -NR^{A5}C(=NR^{E5})R^{B5}, -OC(O)NR^{A5}R^{B5}, -NR^{A5}C(O)OR^{B5}, -NR^{A5}C(O)NR^{A5}R^{B5}, -NR^{A5}C(S)NR^{A5}R^{B5}, -NR^{A5}C(=NR^{E5})NR^{A5}R^{B5}, -S(O)_rR^{A5}, -S(O)(=NR^{E5})R^{B5}, -N=S(O)R^{A5}R^{B5}, -S(O)₂OR^{A5}, -OS(O)₂R^{A5}, -NR^{A5}S(O)_rR^{B5}, -NR^{A5}S(O)(=NR^{E5})R^{B5}, -S(O)_rNR^{A5}R^{B5}, -S(O)(=NR^{E5})NR^{A5}R^{B5}, -NR^{A5}S(O)₂NR^{A5}R^{B5}, -NR^{A5}S(O)(=NR^{E5})NR^{A5}R^{B5}, -P(O)R^{A5}R^{B5} and -P(O)(OR^{A5})(OR^{B5}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X5};

R⁶ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A6}R^{B6}, -OR^{A6}, -C(O)R^{A6}, -C(=NR^{E6})R^{A6}, -C(=N-OR^{B6})R^{A6}, -C(O)OR^{A6}, -OC(O)R^{A6}, -C(O)NR^{A6}R^{B6}, -NR^{A6}C(O)R^{B6}, -C(=NR^{E6})NR^{A6}R^{B6}, -NR^{A6}C(=NR^{E6})R^{B6}, -OC(O)NR^{A6}R^{B6}, -NR^{A6}C(O)OR^{B6}, -NR^{A6}C(O)NR^{A6}R^{B6}, -NR^{A6}C(S)NR^{A6}R^{B6}, -NR^{A6}C(=NR^{E6})NR^{A6}R^{B6}, -S(O)_rR^{A6}, -S(O)(=NR^{E6})R^{B6}, -N=S(O)R^{A6}R^{B6}, -S(O)₂OR^{A6}, -OS(O)₂R^{A6}, -NR^{A6}S(O)_rR^{B6}, -NR^{A6}S(O)(=NR^{E6})R^{B6}, -S(O)_rNR^{A6}R^{B6}, -S(O)(=NR^{E6})NR^{A6}R^{B6}, -NR^{A6}S(O)₂NR^{A6}R^{B6}, -NR^{A6}S(O)(=NR^{E6})NR^{A6}R^{B6}, -P(O)R^{A6}R^{B6} and -P(O)(OR^{A6})(OR^{B6}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X6};

R⁷ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A7}R^{B7}, -OR^{A7}, -C(O)R^{A7}, -C(=NR^{E7})R^{A7}, -C(=N-OR^{B7})R^{A7}, -C(O)OR^{A7}, -OC(O)R^{A7}, -C(O)NR^{A7}R^{B7}, -NR^{A7}C(O)R^{B7}, -C(=NR^{E7})NR^{A7}R^{B7}, -NR^{A7}C(=NR^{E7})R^{B7}, -OC(O)NR^{A7}R^{B7}, -NR^{A7}C(O)OR^{B7}, -NR^{A7}C(O)NR^{A7}R^{B7}, -NR^{A7}C(S)NR^{A7}R^{B7}, -NR^{A7}C(=NR^{E7})NR^{A7}R^{B7}, -S(O)_rR^{A7}, -S(O)(=NR^{E7})R^{B7}, -N=S(O)R^{A7}R^{B7}, -S(O)₂OR^{A7}, -OS(O)₂R^{A7}, -NR^{A7}S(O)_rR^{B7}, -NR^{A7}S(O)(=NR^{E7})R^{B7}, -S(O)_rNR^{A7}R^{B7}, -S(O)(=NR^{E7})NR^{A7}R^{B7}, -NR^{A7}S(O)₂NR^{A7}R^{B7}, -NR^{A7}S(O)(=NR^{E7})NR^{A7}R^{B7}, -P(O)R^{A7}R^{B7} and -P(O)(OR^{A7})(OR^{B7}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X7};

$-\text{NR}^{\text{A}7}\text{S}(\text{O})(=\text{NR}^{\text{E}7})\text{NR}^{\text{A}7}\text{R}^{\text{B}7}$, $-\text{P}(\text{O})\text{R}^{\text{A}7}\text{R}^{\text{B}7}$ and $-\text{P}(\text{O})(\text{OR}^{\text{A}7})(\text{OR}^{\text{B}7})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}7}$;

each $\text{R}^{\text{A}1}$ and $\text{R}^{\text{B}1}$ are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}1}$;

or " $\text{R}^{\text{A}1}$ and $\text{R}^{\text{B}1}$ " together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 $\text{R}^{\text{X}1}$ groups;

each $\text{R}^{\text{A}4}$ and $\text{R}^{\text{B}4}$ are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}4}$;

or " $\text{R}^{\text{A}4}$ and $\text{R}^{\text{B}4}$ " together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 $\text{R}^{\text{X}4}$ groups;

each $\text{R}^{\text{A}5}$ and $\text{R}^{\text{B}5}$ are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}5}$;

or " $\text{R}^{\text{A}5}$ and $\text{R}^{\text{B}5}$ " together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 $\text{R}^{\text{X}5}$ groups;

each $\text{R}^{\text{A}6}$ and $\text{R}^{\text{B}6}$ are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}6}$;

or " $\text{R}^{\text{A}6}$ and $\text{R}^{\text{B}6}$ " together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 $\text{R}^{\text{X}6}$ groups;

each $\text{R}^{\text{A}7}$ and $\text{R}^{\text{B}7}$ are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}7}$;

or " $\text{R}^{\text{A}7}$ and $\text{R}^{\text{B}7}$ " together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally

substituted with 1, 2 or 3 R^{X7} groups;

each R^{E1} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{al}$, $-SR^{al}$, $-S(O)_rR^{al}$, $-C(O)R^{al}$, $-C(O)OR^{al}$, $-C(O)NR^{al}R^{b1}$ and $-S(O)_rNR^{al}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X1} ;

each R^{E4} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{al}$, $-SR^{al}$, $-S(O)_rR^{al}$, $-C(O)R^{al}$, $-C(O)OR^{al}$, $-C(O)NR^{al}R^{b1}$ and $-S(O)_rNR^{al}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X4} ;

each R^{E5} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{al}$, $-SR^{al}$, $-S(O)_rR^{al}$, $-C(O)R^{al}$, $-C(O)OR^{al}$, $-C(O)NR^{al}R^{b1}$ and $-S(O)_rNR^{al}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X5} ;

each R^{E6} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{al}$, $-SR^{al}$, $-S(O)_rR^{al}$, $-C(O)R^{al}$, $-C(O)OR^{al}$, $-C(O)NR^{al}R^{b1}$ and $-S(O)_rNR^{al}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X6} ;

each R^{E7} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{al}$, $-SR^{al}$, $-S(O)_rR^{al}$, $-C(O)R^{al}$, $-C(O)OR^{al}$, $-C(O)NR^{al}R^{b1}$ and $-S(O)_rNR^{al}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X7} ;

each R^{X1} , R^{X2} , R^{X3} , R^{X4} , R^{X5} , R^{X6} and R^{X7} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{cl}R^{dl})_tNR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tOR^{b1}$, $-(CR^{cl}R^{dl})_tC(O)R^{al}$, $-(CR^{cl}R^{dl})_tC(=NR^{el})R^{al}$, $-(CR^{cl}R^{dl})_tC(=N-OR^{b1})R^{al}$, $-(CR^{cl}R^{dl})_tC(O)OR^{b1}$, $-(CR^{cl}R^{dl})_tOC(O)R^{b1}$, $-(CR^{cl}R^{dl})_tC(O)NR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}C(O)R^{b1}$, $-(CR^{cl}R^{dl})_tC(=NR^{el})NR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}C(=NR^{el})R^{b1}$, $-(CR^{cl}R^{dl})_tOC(O)NR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}C(O)OR^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}C(O)NR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}C(S)NR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}C(=NR^{el})NR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tS(O)_rR^{b1}$, $-(CR^{cl}R^{dl})_tS(O)(=NR^{el})R^{b1}$, $-(CR^{cl}R^{dl})_tN=S(O)R^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tS(O)_2OR^{b1}$, $-(CR^{cl}R^{dl})_tOS(O)_2R^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}S(O)_rR^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}S(O)(=NR^{el})R^{b1}$, $-(CR^{cl}R^{dl})_tS(O)(=NR^{el})NR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}S(O)_2NR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tNR^{al}S(O)(=NR^{el})NR^{al}R^{b1}$, $-(CR^{cl}R^{dl})_tP(O)R^{al}R^{b1}$ and $-(CR^{cl}R^{dl})_tP(O)(OR^{al})(OR^{b1})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

each R^{a1} and each R^{b1} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

or R^{a1} and R^{b1} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{c1} and each R^{d1} are independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

or R^{c1} and R^{d1} together with the carbon atom(s) to which they are attached form a ring

of 3 to 12 members containing 0, 1, or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{e1} is independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, CN, NO_2 , $-OR^{a2}$, $-SR^{a2}$, $-S(O)_tR^{a2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$, $-S(O)_tNR^{a2}R^{b2}$ and $-C(O)NR^{a2}R^{b2}$;

each R^Y is independently selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N-OR^{a2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$ and $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from OH, CN, amino, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{a2} and each R^{b2} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

or R^{a2} and R^{b2} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{c2} and each R^{d2} are independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

or R^{e2} and R^{d2} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

each R^{e2} is independently selected from hydrogen, CN, NO₂, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, -C(O)C₁₋₄ alkyl, -C(O)C₃₋₁₀ cycloalkyl, -C(O)OC₁₋₄ alkyl, -C(O)OC₃₋₁₀ cycloalkyl, -C(O)N(C₁₋₄ alkyl)₂, -C(O)N(C₃₋₁₀ cycloalkyl)₂, -S(O)₂C₁₋₄ alkyl, -S(O)₂C₃₋₁₀ cycloalkyl, -S(O)₂N(C₁₋₄ alkyl)₂ and -S(O)₂N(C₃₋₁₀ cycloalkyl)₂;

m is selected from 0, 1 and 2;

each r is independently selected from 0, 1 and 2;

each t is independently selected from 0, 1, 2, 3 and 4.

[010] In yet another aspect, the present disclosure provides pharmaceutical compositions comprising a compound of formula (I) or at least one pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[011] In yet another aspect, the disclosure provides methods for modulating PI3K, comprising administering to a system or a subject in need thereof, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or pharmaceutical compositions thereof, thereby modulating said PI3K.

[012] In yet another aspect, disclosed is a method to treat, ameliorate or prevent a condition which responds to inhibition of PI3K comprising administering to a system or subject in need of such treatment an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or pharmaceutical compositions thereof, and optionally in combination with a second therapeutic agent, thereby treating said condition.

[013] Alternatively, the present disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a condition mediated by PI3K. In particular embodiments, the compounds of the disclosure may be used alone or in combination with a second therapeutic agent to treat a condition mediated by PI3K.

[014] Alternatively, disclosed is a compound of formula (I) or a pharmaceutically acceptable salt thereof for treating a condition mediated by PI3K.

[015] Specifically, the condition herein includes but not limited to, an autoimmune disease, a heteroimmune disease, an infectious disease or a cell proliferative disorder.

[016] Furthermore, the disclosure provides methods for treating a cell proliferative disorder, comprising administering to a system or subject in need of such treatment an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or pharmaceutical compositions thereof, and optionally in combination with a second therapeutic agent, thereby treating said condition.

[017] Specifically, the condition herein includes but not limited to, is an autoimmune disease, a heteroimmune disease, an allergic disease, an inflammatory disease or a cell proliferative disorder.

[018] In certain embodiments, the cell-proliferative disorder is includes but not limited to, breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, testicular cancer, lung cancer (including NSCLC, SCLC, squamous cell carcinoma or

adenocarcinoma), esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer (including RCC), liver cancer (including HCC), pancreatic cancer, stomach (i.e., gastric) cancer, thyroid cancer, chronic lymphocytic leukemia (CLL), lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia and myeloma.

[019] In certain embodiments, the condition is cell proliferative disorder. In one embodiment, the cell proliferative disorder is B-cell proliferative disorder, which includes but not limited to, B-cell malignancies, B-cell chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, multiple sclerosis, small lymphocytic lymphoma, mantle cell lymphoma, B-cell non-Hodgkin's lymphoma, activated B-cell like diffuse large B-cell lymphoma, multiple myeloma, diffuse large B-cell lymphoma, follicular lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, and plasmacytoma.

[020] In certain embodiments, the condition is autoimmune disease, which includes but not limited to, rheumatoid arthritis, psoriatic arthritis, psoriasis, osteoarthritis, juvenile arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, myasthenia gravis, Hashimoto's thyroiditis, multiple sclerosis, acute disseminated encephalomyelitis, Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, scleroderma, primary biliary cirrhosis, Reiter's syndrome, psoriasis, dysautonomia, neuromyotonia, interstitial cystitis, lupus, systemic lupus erythematosus, and lupus nephritis.

[021] In certain embodiments, the condition is heteroimmune disease, which includes but not limited to, graft versus host disease, transplantation, transfusion, anaphylaxis, allergy, type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[022] In certain embodiments, the condition is inflammatory disease, which includes but not limited to, athma, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritic, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, endonitis, tonsillitis, uveitis, vaginitis, vasculitis, and vulvitis.

[023] In the above methods for using the compounds of the disclosure, a compound of formula (I) or a pharmaceutically acceptable salt thereof may be administered to a system comprising cells or tissues, or to a subject including a mammalian subject such as a human or animal subject.

Certain Terminology

[024] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. All patents, patent applications, published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there is a plurality of definitions for terms herein, those in this section prevail.

[025] It is to be understood that the foregoing general description and the following detailed description are explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be

noted that, as used in the specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the context clearly dictates otherwise. It should also be noted that use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include”, “includes”, and “included” is not limiting. Likewise, use of the term “comprising” as well as other forms, such as “comprise”, “comprises”, and “comprised” is not limiting.

[026] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, IR and UV/Vis spectroscopy and pharmacology, within the skill of the art are employed. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

[027] Where substituent groups are specified by their conventional chemical formulas, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left. As a non-limiting example, CH_2O is equivalent to OCH_2 .

[028] The term “substituted” means that a hydrogen atom is replaced by a substituent. It is to be understood that substitution at a given atom is limited by valency.

[029] The term “ C_{i-j} ” or “i-j membered” used herein means that the moiety has i-j carbon atoms or i-j atoms. For example, “ C_{1-6} alkyl” means said alkyl has 1-6 carbon atoms. Likewise, C_{3-10} cycloalkyl means said cycloalkyl has 3-10 carbon atoms.

[030] When any variable (e.g. R) occurs at the structure of a compound over one time, it is defined independently at each case. Therefore, for example, if a group is substituted by 0-2 R, the group may be optionally substituted by at most two R and R has independent option at each case. Additionally, a combination of substituents and/or the variants thereof are allowed only if such a combination will result in a stable compound.

[031] The expression “one or more” or “at least one” refers to one, two, three, four, five, six, seven, eight, nine or more.

[032] Unless stated otherwise, the term “hetero” means heteroatom or heteroatom radical (i.e. a radical containing heteroatom), i.e. the atoms beyond carbon and hydrogen atoms or the radical containing such atoms. Preferably, the heteroatom(s) is independently selected from the group consisting of O, N, S, P and the like. In an embodiment wherein two or more heteroatoms are involved, the two or more heteroatoms may be the same, or part or all of the two or more heteroatoms may be different.

[033] The term “alkyl”, employed alone or in combination with other terms, refers to branched or straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Unless otherwise specified, “alkyl” refers to C_{1-10} alkyl. For example, C_{1-6} , as in “ C_{1-6} alkyl” is defined to include groups having 1, 2, 3, 4, 5, or 6 carbons in a linear or branched arrangement. For example, “ C_{1-8} alkyl” includes but is not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl, pentyl, hexyl, heptyl, and octyl.

[034] The term “cycloalkyl”, employed alone or in combination with other terms, refers to a saturated monocyclic or multicyclic (e.g. bicyclic or tricyclic) hydrocarbon ring system, usually with 3 to 16 ring atoms. The ring atoms of cycloalkyl are all carbon and the cycloalkyl contains zero heteroatoms and zero double bonds. In a multicyclic cycloalkyl, two or more rings can be fused or bridged or spiro together. Examples of monocyclic ring systems include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The bridged cycloalkyl is a polycyclic ring system containing 3-10 carbon atoms, which contains one or two alkylene bridges, each alkylene bridge consisting of one, two, or three carbon atoms, each linking two non-adjacent carbon atoms of the ring system. Cycloalkyl can be fused with aryl or heteroaryl group. In some embodiments, cycloalkyl is benzocondensed. Representative examples of such bridged cycloalkyl ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, bicyclo[4.2.1]nonane, tricyclo[3.3.1.0^{3,7}]nonane and tricyclo[3.3.1.1^{3,7}]decane (adamantane). The monocyclic or bridged cycloalkyl can be attached to the parent molecular moiety through any substitutable atom contained within the ring system.

[035] The term “alkenyl”, employed alone or in combination with other terms, refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing 2-10 carbon atoms and at least one carbon to carbon double bond. In some embodiments, the cyclic refers to monocyclic or multicyclic. In a multicyclic alkenyl, two or more rings can be fused or bridged or spiro together. In some embodiments, one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, “C₂₋₆ alkenyl” means an alkenyl radical having 2-6 carbon atoms. Alkenyl groups include but are not limited to ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

[036] The term “alkynyl”, employed alone or in combination with other terms, refers to a hydrocarbon radical, straight, branched or cyclic, containing 2-10 carbon atoms and at least one carbon to carbon triple bond. In some embodiments, up to three carbon-carbon triple bonds may be present. Thus, “C₂₋₆ alkynyl” means an alkynyl radical having 2-6 carbon atoms. Alkynyl groups include but are not limited to ethynyl, propynyl, butynyl, and 3-methylbutynyl. The straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

[037] The term “halogen” (or “halo”) refers to fluorine, chlorine, bromine and iodine.

[038] The term “alkoxy”, employed alone or in combination with other terms, refers to an alkyl as defined above, which is single bonded to an oxygen atom. The attachment point of an alkoxy radical to a molecule is through the oxygen atom. An alkoxy radical may be depicted as -O-alkyl. The term “C₁₋₁₀ alkoxy” refers to an alkoxy radical containing 1-10 carbon atoms, having straight or branched moieties. Alkoxy group includes but is not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, and the like.

[039] The term “cycloalkoxy”, employed alone or in combination with other terms, refers to cycloalkyl as defined above, which is single bonded to an oxygen atom. The attachment point of a cycloalkoxy radical to a molecule is through the oxygen atom. A cycloalkoxy radical may be depicted as -O-cycloalkyl. “C₃₋₁₀ cycloalkoxy” refers to a cycloalkoxy radical containing 3-10 carbon atoms. Cycloalkoxy can be fused with aryl or heteroaryl group. In some embodiments, cycloalkoxy is benzocondensed. Cycloalkoxy group includes but is not limited to, cyclopropoxy, cyclobutoxy, cyclopentyloxy, cyclohexyloxy, and the like.

[040] The term “alkylthio”, employed alone or in combination with other terms, refers to an alkyl radical as defined above, which is single bonded to a sulfur atom. The attachment point of an alkylthio radical to a molecule is through the sulfur atom. An alkylthio radical may be depicted as -S-alkyl. The term “C₁₋₁₀ alkylthio” refers to an alkylthio radical containing 1-10 carbon atoms, having straight or branched moieties. Alkylthio group includes but is not limited to, methylthio, ethylthio, propylthio, isopropylthio, butylthio, hexylthio, and the like.

[041] The term “cycloalkylthio”, employed alone or in combination with other terms, refers to cycloalkyl as defined above, which is single bonded to a sulfur atom. The attachment point of a cycloalkylthio radical to a molecule is through the sulfur atom. A cycloalkylthio radical may be depicted as -S-cycloalkyl. “C₃₋₁₀ cycloalkylthio” refers to a cycloalkylthio radical containing 3-10 carbon atoms. Cycloalkylthio can be fused with aryl or heteroaryl group. In some embodiments, cycloalkylthio is benzocondensed. Cycloalkylthio group includes but is not limited to, cyclopropylthio, cyclobutylthio, cyclohexylthio, and the like.

[042] The term “alkylamino”, employed alone or in combination with other terms, refers to an alkyl as defined above, which is single bonded to a nitrogen atom. The attachment point of an alkylamino radical to a molecule is through the nitrogen atom. An alkylamino radical may be depicted as -NH(alkyl). The term “C₁₋₁₀ alkylamino” refers to an alkylamino radical containing 1-10 carbon atoms, having straight or branched moieties. Alkylamino group includes but is not limited to, methylamino, ethylamino, propylamino, isopropylamino, butylamino, hexylamino, and the like.

[043] The term “cycloalkylamino”, employed alone or in combination with other terms, refers to cycloalkyl as defined above, which is single bonded to a nitrogen atom. The attachment point of a cycloalkylamino radical to a molecule is through the nitrogen atom. A cycloalkylamino radical may be depicted as -NH(cycloalkyl). “C₃₋₁₀ cycloalkylamino” refers to a cycloalkylamino radical containing 3-10 carbon atoms. Cycloalkylamino can be fused with aryl or heteroaryl group. In some embodiments, cycloalkylamino is benzocondensed. Cycloalkylamino group includes but is not limited to, cyclopropylamino, cyclobutylamino, cyclohexylamino, and the like.

[044] The term “di(alkyl)amino”, employed alone or in combination with other terms, refers to two alkyl as defined above, which are single bonded to a nitrogen atom. The attachment point of a di(alkyl)amino radical to a molecule is through the nitrogen atom. A di(alkyl)amino radical may be depicted as -N(alkyl)₂. The term “di(C₁₋₁₀ alkyl)amino” refers to a di(C₁₋₁₀ alkyl)amino radical wherein the alkyl radicals each independently contains 1-10 carbon atoms, having straight or branched moieties.

[045] The term “aryl”, employed alone or in combination with other terms, refers to a monovalent, monocyclic-, bicyclic- or tricyclic aromatic hydrocarbon ring system having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms (a “C₆₋₁₄ aryl” group), particularly a ring having 6 carbon atoms (a “C₆ aryl” group), e.g. a phenyl group; or a ring having 10 carbon atoms (a “C₁₀ aryl” group), e.g. a naphthyl group; or a ring having 14 carbon atoms, (a “C₁₄ aryl” group), e.g. an anthranyl group. Aryl can be fused with cycloalkyl or heterocycle group.

[046] Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in “-yl” by removal of one hydrogen atom from the carbon atom with the free valence are named by removing “-yl” and adding “-idene” to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene.

[047] The term “heteroaryl”, employed alone or in combination with other terms, refers to a monovalent, monocyclic-, bicyclic- or tricyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a “5- to 14-membered heteroaryl” group), particularly 5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom selected from N, O and S. Heteroaryl can be fused with cycloalkyl or heterocycle group. In some embodiments, “heteroaryl” refers to

a 5- to 8-membered monocyclic aromatic ring containing one or more, for example, from 1 to 4, or, in some embodiments, from 1 to 3, heteroatoms selected from N, O and S, with the remaining ring atoms being carbon; or

a 8- to 12-membered bicyclic aromatic ring system containing one or more, for example, from 1 to 6, or, in some embodiments, from 1 to 4, or, in some embodiments, from 1 to 3, heteroatoms selected from N, O and S, with the remaining ring atoms being carbon; or

a 11- to 14-membered tricyclic aromatic ring system containing one or more, for example, from 1 to 8, or, in some embodiments, from 1 to 6, or, in some embodiments, from 1 to 4, or in some embodiments, from 1 to 3, heteroatoms selected from N, O and S, with the remaining ring atoms being carbon.

[048] When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1.

[049] Examples of heteroaryl groups include, but are not limited to, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, pyridazinyl, triazinyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl, tetrazolyl, thienyl, furyl.

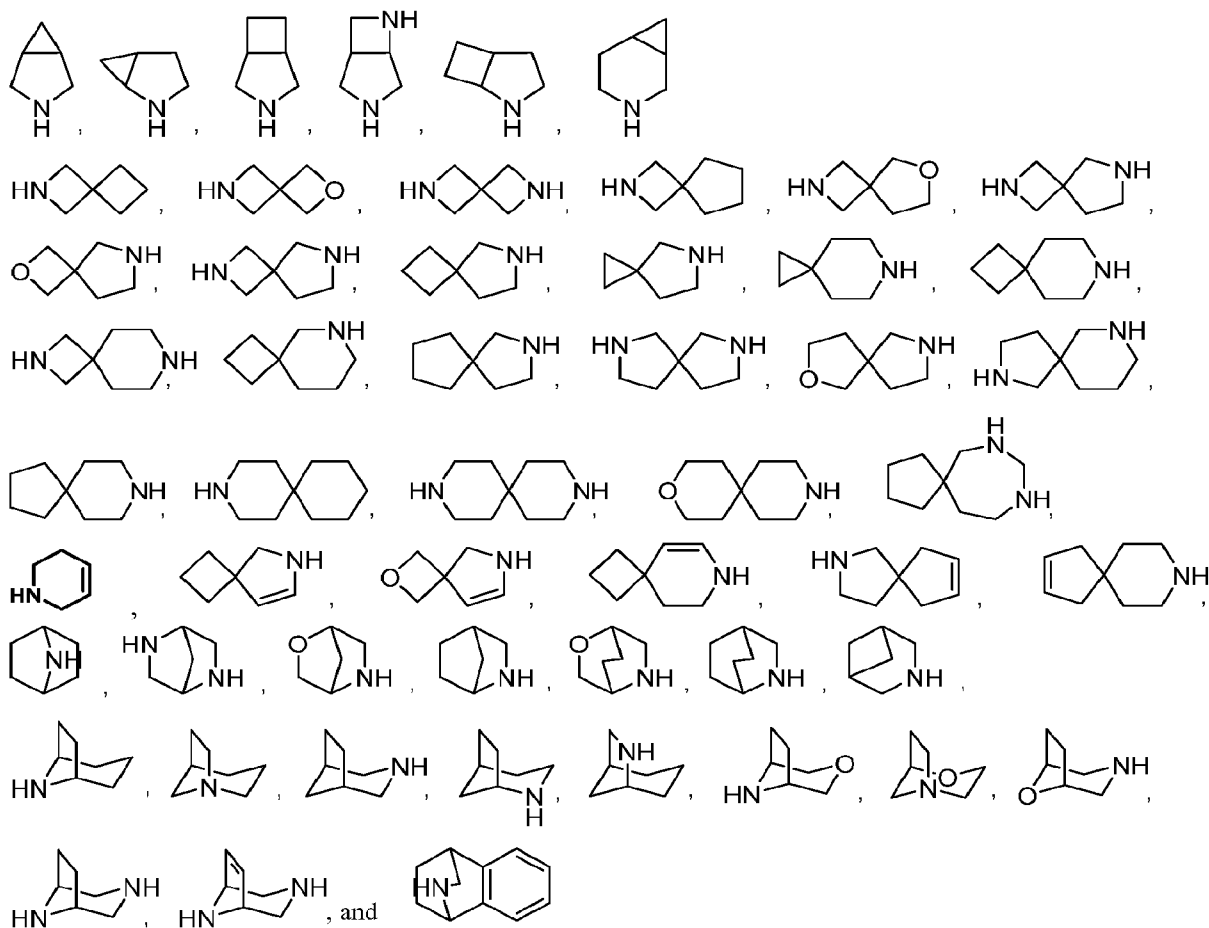
[050] Further heteroaryl groups include but are not limited to indolyl, benzothieryl, benzofuryl, benzoimidazolyl, benzotriazolyl, quinoxaliny, quinoliny, and isoquinoliny. “Heteroaryl” is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl.

[051] Bivalent radicals derived from univalent heteroaryl radicals whose names end in “-yl” by removal of one hydrogen atom from the atom with the free valence are named by adding “-idene” to the name of the corresponding univalent radical, e.g., a pyridyl group with two points of attachment is a pyridylidene.

[052] The term “heterocycle”, employed alone or in combination with other terms, (and variations thereof such as “heterocyclic”, or “heterocyclyl”) broadly refers to a saturated or unsaturated mono- or multicyclic (e.g. bicyclic) aliphatic ring system, usually with 3 to 12 ring atoms, wherein at least one (e.g. 2, 3 or 4) ring atom is heteroatom independently selected from O, S, N and P (preferably O, S, N). In a multicyclic heterocycle, two or more rings can be fused or bridged or spiro together. Heterocycle can be fused with aryl or heteroaryl group. In some embodiments, heterocycle is benzocondensed. Heterocycle also includes ring systems substituted with one or more oxo or imino moieties. In some embodiments, the C, N, S and P atoms in the heterocycle ring are optionally substituted by oxo. In some embodiments, the C, S and P atoms in the heterocycle ring are optionally substituted by imino, and imino can be unsubstituted or substituted. The point of the attachment may be carbon atom or heteroatom in the heterocyclic ring, provided that attachment results in the creation of a stable structure. When the heterocyclic ring has

substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure result.

[053] Suitable heterocycles include, for example, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-3-yl, imidazolidin-4-yl, imidazolidin-5-yl, pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl, pyrazolidin-5-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, hexahydropyridazin-1-yl, hexahydropyridazin-3-yl and hexahydropyridazin-4-yl. Morpholinyl groups are also contemplated, such as morpholin-1-yl, morpholin-2-yl, morpholin-3-yl and morpholin-4-yl. Examples of heterocycle with one or more oxo moieties include but are not limited to, piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-thiomorpholinyl and 1,1-dioxo-thiomorpholinyl. Bicyclic heterocycles include, for example:



[054] As used herein, “aryl-alkyl” refers to an alkyl moiety as defined above substituted by an aryl group as defined above. Exemplary aryl-alkyl groups include but are not limited to benzyl, phenethyl and naphthylmethyl groups. In some embodiments, aryl-alkyl groups have 7-20 or 7-11 carbon atoms. When used in the phrase “aryl-C₁₋₄ alkyl”, the term “C₁₋₄” refers to the alkyl portion of the moiety and does not describe the number of atoms in the aryl portion of the moiety.

[055] As used herein, “heterocycl-alkyl” refers to alkyl as defined above substituted by heterocycl-alkyl as defined above. When used in the phrase “heterocycl-alkyl-C₁₋₄”,

alkyl”, the term “C₁₋₄” refers to the alkyl portion of the moiety and does not describe the number of atoms in the heterocyclyl portion of the moiety.

[056] As used herein, “cycloalkyl-alkyl” refers to alkyl as defined above substituted by cycloalkyl as defined above. When used in the phrase “C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl”, the term “C₃₋₁₀” refers to the cycloalkyl portion of the moiety and does not describe the number of atoms in the alkyl portion of the moiety, and the term “C₁₋₄” refers to the alkyl portion of the moiety and does not describe the number of atoms in the cycloalkyl portion of the moiety.

[057] As used herein, “heteroaryl-alkyl” refers to alkyl as defined above substituted by heteroaryl as defined above. When used in the phrase “heteroaryl-C₁₋₄ alkyl”, the term “C₁₋₄” refers to the alkyl portion of the moiety and does not describe the number of atoms in the heteroaryl portion of the moiety.

[058] For avoidance of doubt, reference, for example, to substitution of alkyl, cycloalkyl, heterocyclyl, aryl and/or heteroaryl refers to substitution of each of those groups individually as well as to substitutions of combinations of those groups. That is, if R is aryl-C₁₋₄ alkyl and may be unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituents, independently selected from R^X, it should be understood that the aryl portion may be unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituents, independently selected from R^X and the alkyl portion may also be unsubstituted or substituted with at least one substituent, such as one, two, three, or four substituents, independently selected from R^X.

[059] The term “pharmaceutically acceptable salts” refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases may be selected, for example, from aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium and zinc salts. Further, for example, the pharmaceutically acceptable salts derived from inorganic bases may be selected from ammonium, calcium, magnesium, potassium and sodium salts. Salts in the solid form may exist in one or more crystalline forms, or polymorphs, and may also be in the form of solvates, such as hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases may be selected, for example, from salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine and tripropylamine, tromethamine.

[060] When the compound disclosed herein is basic, salts may be prepared using at least one pharmaceutically acceptable non-toxic acid, selected from inorganic and organic acids. Such acid may be selected, for example, from acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric and p-toluenesulfonic acids. In some embodiments, such acid may be selected, for example, from citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric and tartaric acids.

[061] The terms “administration of” and or “administering” a compound or a pharmaceutically acceptable salt should be understood to mean providing a compound or a pharmaceutically acceptable salt thereof to the individual in recognized need of treatment.

[062] The term “effective amount” means the amount of the a compound or a pharmaceutically acceptable salt that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[063] The term “composition” as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to a pharmaceutical composition is intended to encompass a product comprising the active ingredient (s) and the inert ingredient (s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.

[064] The term “pharmaceutically acceptable” it is meant compatible with the other ingredients of the formulation and not unacceptably deleterious to the recipient thereof.

[065] The term “subject” as used herein in reference to individuals suffering from a disorder, a condition, and the like, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non- mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[066] The terms “treat,” “treating” or “treatment,” and other grammatical equivalents as used herein, include alleviating, abating or ameliorating a disease or condition, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition, and are intended to include prophylaxis. The terms further include achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[067] The term “protecting group” or “Pg” refers to a substituent that can be commonly employed to block or protect a certain functionality while reacting other functional groups on the compound. For example, an “amino-protecting group” is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include but are not limited to acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a “hydroxy-protecting group” refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include but are not limited to acetyl and silyl. A “carboxy-protecting group” refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-\text{CH}_2\text{CH}_2\text{SO}_2\text{Ph}$, cyanoethyl, 2-(trimethylsilyl)ethyl,

2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfonyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 1991.

[068] The term “NH protecting group” as used herein includes, but not limited to, trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, para-nitrobenzyloxycarbonyl, ortho-bromobenzyloxycarbonyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, phenylacetyl, formyl, acetyl, benzoyl, tert-amylloxycarbonyl, tert-butoxycarbonyl, para-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyl-oxycarbonyl, 4-(phenylazo)-benzyloxycarbonyl, 2-furfuryloxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxy-carbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantylloxycarbonyl, 8-quinolyloxycarbonyl, benzyl, diphenylmethyl, triphenylmethyl, 2-nitrophenylthio, methanesulfonyl, para-toluenesulfonyl, *N,N*-dimethylaminomethylene, benzylidene, 2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthylmethylene, 3-hydroxy-4-pyridylmethylene, cyclohexylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxycyclo-hexylidene, diphenylphosphoryl, dibenzylphosphoryl, 5-methyl-2-oxo-2*H*-1,3-dioxol-4-yl-methyl, trimethylsilyl, triethylsilyl and triphenylsilyl.

[069] The term “C(O)OH protecting group” as used herein includes, but not limited to, methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, n-butyl, tert-butyl, phenyl, naphthyl, benzyl, diphenylmethyl, triphenylmethyl, para-nitrobenzyl, para-methoxybenzyl, bis(para-methoxyphenyl)methyl, acetylmethyl, benzoylmethyl, para-nitrobenzoylmethyl, para-bromobenzoylmethyl, para-methanesulfonylbenzoylmethyl, 2-tetrahydropyranyl, 2-tetrahydrofuranyl, 2,2,2-trichloro-ethyl, 2-(trimethylsilyl)ethyl, acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl, phthalimidomethyl, succinimidomethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, methylthiomethyl, 2-methylthioethyl, phenylthiomethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyl dimethylsilyl, tert-butyl diphenylsilyl, diphenylmethylsilyl and tert-butylmethoxyphenylsilyl.

[070] The term “OH or SH protecting group” as used herein includes, but not limited to, benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-(phenylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantylloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, 4-ethoxy-1-naphthylloxycarbonyl, 8-quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, pivaloyl, benzoyl, methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl (phenylmethyl), para-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, triphenylmethyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloro-ethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyl dimethylsilyl, tert-butyl diphenylsilyl, diphenylmethylsilyl and tert-butylmethoxyphenylsilyl.

[071] Geometric isomers may exist in the present compounds. Compounds of this invention may contain carbon-carbon double bonds or carbon-nitrogen double bonds in the E or Z configuration, wherein the term "E" represents higher order substituents on opposite sides of the carbon-carbon or carbon-nitrogen double bond and the term "Z" represents higher order substituents on the same side of the carbon-carbon or carbon-nitrogen double bond as determined by the Cahn-Ingold-Prelog Priority Rules. The compounds of this invention may also exist as a mixture of "E" and "Z" isomers. Substituents around a cycloalkyl or heterocycloalkyl are designated as being of cis or trans configuration. Furthermore, the invention contemplates the various isomers and mixtures thereof resulting from the disposal of substituents around an adamantane ring system. Two substituents around a single ring within an adamantane ring system are designated as being of Z or E relative configuration. For examples, see C. D. Jones, M. Kaselj, R. N. Salvatore, W. J. le Noble J. Org. Chem. 1998, 63, 2758-2760.

[072] Compounds of this invention may contain asymmetrically substituted carbon atoms in the R or S configuration, in which the terms "R" and "S" are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those carbon atoms. Atoms with an excess of one configuration over the other are assigned the configuration present in the higher amount, preferably an excess of about 85-90%, more preferably an excess of about 95-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

Isotope Enriched or Labeled Compounds.

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

[074] In another embodiment, the isotope-labeled compounds contain deuterium (^2H), tritium (^3H) or ^{14}C isotopes. Isotope-labeled compounds of this invention can be prepared by the general methods well known to persons having ordinary skill in the art. Such isotope-labeled compounds can be conveniently prepared by carrying out the procedures disclosed in the Examples disclosed herein and Schemes by substituting a readily available isotope-labeled reagent for a non-labeled reagent. In some instances, compounds may be treated with isotope-labeled reagents to exchange a normal atom with its isotope, for example, hydrogen for deuterium can be exchanged by the action of a deuterated acid such as $\text{D}_2\text{SO}_4/\text{D}_2\text{O}$.

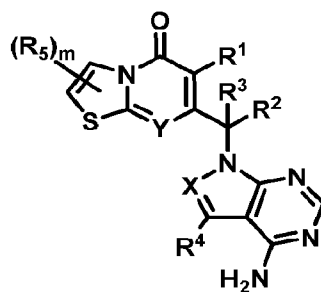
[075] The isotope-labeled compounds of the invention may be used as standards to determine the effectiveness of PI3K inhibitors in binding assays. Isotope containing compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the nonisotope-labeled parent compound (Blake et al. J. Pharm. Sci. 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the in vivo active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., Advances in Drug Research Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al, J. Labelled

Compounds. Radiopharmaceuticals., 36(10), 927-932 (1995); Kushner et al., Can. J. Physiol. Pharmacology, 77, 79-88 (1999).

[076] In addition, non-radioactive isotope containing drugs, such as deuterated drugs called "heavy drugs" can be used for the treatment of diseases and conditions related to PI3K activity. Increasing the amount of an isotope present in a compound above its natural abundance is called enrichment. Examples of the amount of enrichment include but are not limited to from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %.

[077] Stable isotope labeling of a drug can alter its physico-chemical properties such as pKa and lipid solubility. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. Accordingly, the incorporation of an isotope at a site of metabolism or enzymatic transformation will slow said reactions potentially altering the pharmacokinetic profile or efficacy relative to the non-isotopic compound.

[078] In an Embodiment (1), this invention provides to a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

X is selected from CR^6 and N;

Y is selected from CR^7 and N;

R^1 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, CN, NO_2 , $-NR^{A1}R^{B1}$, $-OR^{A1}$, $-C(O)R^{A1}$, $-C(=NR^{E1})R^{A1}$, $-C(=N-OR^{B1})R^{A1}$, $-C(O)OR^{A1}$, $-OC(O)R^{A1}$, $-C(O)NR^{A1}R^{B1}$, $-NR^{A1}C(O)R^{B1}$, $-C(-NR^{E1})NR^{A1}R^{B1}$, $-NR^{A1}C(-NR^{E1})R^{B1}$, $-OC(O)NR^{A1}R^{B1}$, $-NR^{A1}C(O)OR^{B1}$, $-NR^{A1}C(O)NR^{A1}R^{B1}$, $-NR^{A1}C(S)NR^{A1}R^{B1}$, $-NR^{A1}C(=NR^{E1})NR^{A1}R^{B1}$, $-S(O)_rR^{A1}$, $-S(O)(=NR^{E1})R^{B1}$, $-N=S(O)R^{A1}R^{B1}$, $-S(O)_2OR^{A1}$, $-OS(O)_2R^{A1}$, $-NR^{A1}S(O)_rR^{B1}$, $-NR^{A1}S(O)(=NR^{E1})R^{B1}$, $-S(O)_rNR^{A1}R^{B1}$, $-S(O)(=NR^{E1})NR^{A1}R^{B1}$, $-NR^{A1}S(O)_2NR^{A1}R^{B1}$, $-NR^{A1}S(O)(=NR^{E1})NR^{A1}R^{B1}$, $-P(O)R^{A1}R^{B1}$ and $-P(O)(OR^{A1})(OR^{B1})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1} ;

R^2 is selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl,

C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2};

R³ is selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X3};

or R² and R³ together with the atoms to which they are attached form a C₃₋₁₀ cycloalkyl or heterocyclic ring of 4 to 12 members containing 1, 2 or 3 heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X2} groups;

R⁴ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A4}R^{B4}, -OR^{A4}, -C(O)R^{A4}, -C(=NR^{E4})R^{A4}, -C(=N-OR^{B4})R^{A4}, -C(O)OR^{A4}, -OC(O)R^{A4}, -C(O)NR^{A4}R^{B4}, -NR^{A4}C(O)R^{B4}, -C(=NR^{E4})NR^{A4}R^{B4}, -NR^{A4}C(=NR^{E4})R^{B4}, -OC(O)NR^{A4}R^{B4}, -NR^{A4}C(O)OR^{B4}, -NR^{A4}C(O)NR^{A4}R^{B4}, -NR^{A4}C(S)NR^{A4}R^{B4}, -NR^{A4}C(=NR^{E4})NR^{A4}R^{B4}, -S(O)_rR^{A4}, -S(O)(=NR^{E4})R^{B4}, -N=S(O)R^{A4}R^{B4}, -S(O)₂OR^{A4}, -OS(O)₂R^{A4}, -NR^{A4}S(O)_rR^{B4}, -NR^{A4}S(O)(=NR^{E4})R^{B4}, -S(O)_rNR^{A4}R^{B4}, -S(O)(=NR^{E4})NR^{A4}R^{B4}, -NR^{A4}S(O)₂NR^{A4}R^{B4}, -NR^{A4}S(O)(=NR^{E4})NR^{A4}R^{B4}, -P(O)R^{A4}R^{B4} and -P(O)(OR^{A4})(OR^{B4}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X4};

each R⁵ is independently selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A5}R^{B5}, -OR^{A5}, -C(O)R^{A5}, -C(=NR^{E5})R^{A5}, -C(=N-OR^{B5})R^{A5}, -C(O)OR^{A5}, -OC(O)R^{A5}, -C(O)NR^{A5}R^{B5}, -NR^{A5}C(O)R^{B5}, -C(=NR^{E5})NR^{A5}R^{B5}, -NR^{A5}C(=NR^{E5})R^{B5}, -OC(O)NR^{A5}R^{B5}, -NR^{A5}C(O)OR^{B5}, -NR^{A5}C(O)NR^{A5}R^{B5}, -NR^{A5}C(S)NR^{A5}R^{B5}, -NR^{A5}C(=NR^{E5})NR^{A5}R^{B5}, -S(O)_rR^{A5}, -S(O)(=NR^{E5})R^{B5}, -N=S(O)R^{A5}R^{B5}, -S(O)₂OR^{A5}, -OS(O)₂R^{A5}, -NR^{A5}S(O)_rR^{B5}, -NR^{A5}S(O)(=NR^{E5})R^{B5}, -S(O)_rNR^{A5}R^{B5}, -S(O)(=NR^{E5})NR^{A5}R^{B5}, -NR^{A5}S(O)₂NR^{A5}R^{B5}, -NR^{A5}S(O)(=NR^{E5})NR^{A5}R^{B5}, -P(O)R^{A5}R^{B5} and -P(O)(OR^{A5})(OR^{B5}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X5};

R⁶ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A6}R^{B6}, -OR^{A6}, -C(O)R^{A6}, -C(=NR^{E6})R^{A6}, -C(=N-OR^{B6})R^{A6}, -C(O)OR^{A6}, -OC(O)R^{A6}, -C(O)NR^{A6}R^{B6}, -NR^{A6}C(O)R^{B6}, -C(=NR^{E6})NR^{A6}R^{B6}, -NR^{A6}C(=NR^{E6})R^{B6}, -OC(O)NR^{A6}R^{B6}, -NR^{A6}C(O)OR^{B6}, -NR^{A6}C(O)NR^{A6}R^{B6}, -NR^{A6}C(S)NR^{A6}R^{B6}, -NR^{A6}C(=NR^{E6})NR^{A6}R^{B6}, -S(O)_rR^{A6}, -S(O)(=NR^{E6})R^{B6}, -N=S(O)R^{A6}R^{B6}, -S(O)₂OR^{A6}, -OS(O)₂R^{A6}, -NR^{A6}S(O)_rR^{B6}, -NR^{A6}S(O)(=NR^{E6})R^{B6}, -S(O)_rNR^{A6}R^{B6}, -S(O)(=NR^{E6})NR^{A6}R^{B6}, -NR^{A6}S(O)₂NR^{A6}R^{B6}, -NR^{A6}S(O)(=NR^{E6})NR^{A6}R^{B6}, -P(O)R^{A6}R^{B6} and -P(O)(OR^{A6})(OR^{B6}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X6};

R⁷ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄

alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A7}R^{B7}, -OR^{A7}, -C(O)R^{A7}, -C(=NR^{E7})R^{A7}, -C(=N-OR^{B7})R^{A7}, -C(O)OR^{A7}, -OC(O)R^{A7}, -C(O)NR^{A7}R^{B7}, -NR^{A7}C(O)R^{B7}, -C(=NR^{E7})NR^{A7}R^{B7}, -NR^{A7}C(=NR^{E7})R^{B7}, -OC(O)NR^{A7}R^{B7}, -NR^{A7}C(O)OR^{A7}, -NR^{A7}C(O)NR^{A7}R^{B7}, -NR^{A7}C(S)NR^{A7}R^{B7}, -NR^{A7}C(=NR^{E7})NR^{A7}R^{B7}, -S(O)_rR^{A7}, -S(O)(=NR^{E7})R^{B7}, -N=S(O)R^{A7}R^{B7}, -S(O)₂OR^{A7}, -OS(O)₂R^{A7}, -NR^{A7}S(O)_rR^{B7}, -NR^{A7}S(O)(=NR^{E7})R^{B7}, -S(O)_rNR^{A7}R^{B7}, -S(O)(=NR^{E7})NR^{A7}R^{B7}, -NR^{A7}S(O)₂NR^{A7}R^{B7}, -NR^{A7}S(O)(=NR^{E7})NR^{A7}R^{B7}, -P(O)R^{A7}R^{B7} and -P(O)(OR^{A7})(OR^{B7}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X7};

each R^{A1} and R^{B1} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

or “R^{A1} and R^{B1}” together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X1} groups;

each R^{A4} and R^{B4} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X4};

or “R^{A4} and R^{B4}” together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X4} groups;

each R^{A5} and R^{B5} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X5};

or “R^{A5} and R^{B5}” together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X5} groups;

each R^{A6} and R^{B6} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X6};

or “R^{A6} and R^{B6}” together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X6} groups;

each R^{A7} and R^{B7} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄

alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X7};

or “R^{A7} and R^{B7}” together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X7} groups;

each R^{E1} is independently selected from hydrogen, C₁₋₁₀ alkyl, CN, NO₂, -OR^{a1}, -SR^{a1}, -S(O)_rR^{a1}, -C(O)R^{a1}, -C(O)OR^{a1}, -C(O)NR^{a1}R^{b1} and -S(O)_rNR^{a1}R^{b1}, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X1};

each R^{E4} is independently selected from hydrogen, C₁₋₁₀ alkyl, CN, NO₂, -OR^{a1}, -SR^{a1}, -S(O)_rR^{a1}, -C(O)R^{a1}, -C(O)OR^{a1}, -C(O)NR^{a1}R^{b1} and -S(O)_rNR^{a1}R^{b1}, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X4};

each R^{E5} is independently selected from hydrogen, C₁₋₁₀ alkyl, CN, NO₂, -OR^{a1}, -SR^{a1}, -S(O)_rR^{a1}, -C(O)R^{a1}, -C(O)OR^{a1}, -C(O)NR^{a1}R^{b1} and -S(O)_rNR^{a1}R^{b1}, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X5};

each R^{E6} is independently selected from hydrogen, C₁₋₁₀ alkyl, CN, NO₂, -OR^{a1}, -SR^{a1}, -S(O)_rR^{a1}, -C(O)R^{a1}, -C(O)OR^{a1}, -C(O)NR^{a1}R^{b1} and -S(O)_rNR^{a1}R^{b1}, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X6};

each R^{E7} is independently selected from hydrogen, C₁₋₁₀ alkyl, CN, NO₂, -OR^{a1}, -SR^{a1}, -S(O)_rR^{a1}, -C(O)R^{a1}, -C(O)OR^{a1}, -C(O)NR^{a1}R^{b1} and -S(O)_rNR^{a1}R^{b1}, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X7};

each R^{X1}, R^{X2}, R^{X3}, R^{X4}, R^{X5}, R^{X6} and R^{X7} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, halogen, CN, NO₂, -(CR^{cl}R^{dl})_tNR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tOR^{b1}, -(CR^{cl}R^{dl})_tC(O)R^{a1}, -(CR^{cl}R^{dl})_tC(=NR^{e1})R^{a1}, -(CR^{cl}R^{dl})_tC(=N-OR^{b1})R^{a1}, -(CR^{cl}R^{dl})_tC(O)OR^{b1}, -(CR^{cl}R^{dl})_tOC(O)R^{b1}, -(CR^{cl}R^{dl})_tC(O)NR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}C(O)R^{b1}, -(CR^{cl}R^{dl})_tC(=NR^{e1})NR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}C(=NR^{e1})R^{b1}, -(CR^{cl}R^{dl})_tOC(O)NR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}C(O)OR^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}C(O)NR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}C(S)NR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}C(=NR^{e1})NR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tS(O)_rR^{b1}, -(CR^{cl}R^{dl})_tS(O)(=NR^{e1})R^{b1}, -(CR^{cl}R^{dl})_tN=S(O)R^{a1}R^{b1}, -(CR^{cl}R^{dl})_tS(O)₂OR^{b1}, -(CR^{cl}R^{dl})_tOS(O)₂R^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}S(O)_rR^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}S(O)(=NR^{e1})R^{b1}, -(CR^{cl}R^{dl})_tS(O)_rNR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}S(O)₂NR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tS(O)(=NR^{e1})NR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tNR^{a1}S(O)(=NR^{e1})NR^{a1}R^{b1}, -(CR^{cl}R^{dl})_tP(O)R^{a1}R^{b1} and -(CR^{cl}R^{dl})_tP(O)(OR^{a1})(OR^{b1}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

each R^{a1} and each R^{b1} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y;

or R^{a1} and R^{b1} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{c1} and each R^{d1} are independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

or R^{c1} and R^{d1} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1, or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{e1} is independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, CN, NO_2 , $-OR^{a2}$, $-SR^{a2}$, $-S(O)_tR^{a2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$, $-S(O)_tNR^{a2}R^{b2}$ and $-C(O)NR^{a2}R^{b2}$;

each R^Y is independently selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N-OR^{b2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_tR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_tR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$ and $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from OH, CN, amino, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{a2} and each R^{b2} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

or R^{a2} and R^{b2} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{c2} and each R^{d2} are independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl and

heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

or R^{c2} and R^{d2} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

each R^{e2} is independently selected from hydrogen, CN, NO₂, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, -C(O)C₁₋₄ alkyl, -C(O)C₃₋₁₀ cycloalkyl, -C(O)OC₁₋₄ alkyl, -C(O)OC₃₋₁₀ cycloalkyl, -C(O)N(C₁₋₄ alkyl)₂, -C(O)N(C₃₋₁₀ cycloalkyl)₂, -S(O)₂C₁₋₄ alkyl, -S(O)₂C₃₋₁₀ cycloalkyl, -S(O)₂N(C₁₋₄ alkyl)₂ and -S(O)₂N(C₃₋₁₀ cycloalkyl)₂;

m is selected from 0, 1 and 2;

each r is independently selected from 0, 1 and 2;

each t is independently selected from 0, 1, 2, 3 and 4.

[079] In another Embodiment (2), the invention provides a compound of Embodiment (1) or a pharmaceutically acceptable salt thereof, wherein X is N.

[080] In another Embodiment (3), the invention provides a compound of Embodiment (1) or a pharmaceutically acceptable salt thereof, wherein X is CR⁶.

[081] In another Embodiment (4), the invention provides a compound of Embodiment (3) or a pharmaceutically acceptable salt thereof, wherein R⁶ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl and C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X6}.

[082] In another Embodiment (5), the invention provides a compound of Embodiment (4) or a pharmaceutically acceptable salt thereof, wherein R⁶ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, methyl, ethyl, isopropyl and cyclopropyl, wherein methyl, ethyl, isopropyl and cyclopropyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X6}. In another Embodiment, wherein each R^{X6} is independently selected from deuterium and F.

[083] In another Embodiment (6), the invention provides a compound of any one of Embodiments (1)-(5) or a pharmaceutically acceptable salt thereof, wherein Y is N.

[084] In another Embodiment (7), the invention provides a compound of any one of Embodiments (1)-(5) or a pharmaceutically acceptable salt thereof, wherein Y is CR⁷.

[085] In another Embodiment (8), the invention provides a compound of Embodiment (7) or a pharmaceutically acceptable salt thereof, wherein R⁷ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy and C₃₋₁₀ cycloalkoxy, wherein alkyl, alkenyl, cycloalkyl, alkoxy and cycloalkoxy are each unsubstituted or substituted with at least one substituent, independently selected from R^{X7}.

[086] In another Embodiment (9), the invention provides a compound of Embodiment (8) or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from hydrogen, halogen, OH, CN, NH_2 , NO_2 , methyl, ethyl, isopropyl and cyclopropyl, wherein methyl, ethyl, isopropyl and cyclopropyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X7} , preferably, R^7 is hydrogen.

[087] In another Embodiment (10), the invention provides a compound of any one of Embodiments (1)-(9) or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, cycloalkyl, alkoxy, cycloalkoxy, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1} .

[088] In another Embodiment (11), the invention provides a compound of Embodiment (10) or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1} .

[089] In another Embodiment (12), the invention provides a compound of Embodiment (11) or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from phenyl, pyridinyl and pyrimidinyl, which is unsubstituted or substituted with halogen, OH, CN, NH_2 , NO_2 , C_{1-10} alkyl and C_{3-10} cycloalkyl.

[090] In another Embodiment (13), the invention provides a compound of Embodiment (12) or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl or 3-fluorophenyl.

[091] In another Embodiment (14), the invention provides a compound of any one of Embodiments (1)-(13) or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl and heteroaryl, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2} and R^{X3} .

[092] In another Embodiment (15), the invention provides a compound of Embodiment (14) or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl and C_{3-10} cycloalkyl- C_{1-4} alkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2} and R^{X3} .

[093] In another Embodiment (16), the invention provides a compound of Embodiment (15) or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, methyl, ethyl and cyclopropyl.

[094] In another Embodiment (17), the invention provides a compound of any one of Embodiments (1)-(16) or a pharmaceutically acceptable salt thereof, wherein m is 1.

[095] In another Embodiment (18), the invention provides a compound of any one of Embodiments (1)-(17) or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, CN, NO_2 , $-NR^{A5}R^{B5}$, $-OR^{A5}$, $-C(O)R^{A5}$, $-C(O)OR^{A5}$, $-OC(O)R^{A5}$, $-C(O)NR^{A5}R^{B5}$, $-NR^{A5}C(O)R^{B5}$, $-S(O)_rR^{A5}$, $-S(O)_2OR^{A5}$ and $-S(O)_rNR^{A5}R^{B5}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X5} .

[096] In another Embodiment (19), the invention provides a compound of Embodiment (18) or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, CN, NO_2 , $-NR^{A5}R^{B5}$, $-OR^{A5}$, $-C(O)R^{A5}$,

$-\text{NR}^{\text{A}5}\text{C}(\text{O})\text{R}^{\text{B}5}$, $-\text{S}(\text{O})_r\text{R}^{\text{A}5}$ and $-\text{S}(\text{O})_r\text{NR}^{\text{A}5}\text{R}^{\text{B}5}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}5}$.

[097] In another Embodiment (20), the invention provides a compound of Embodiment (19) or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, F, Cl, methyl, ethyl, isopropyl and cyclopropyl.

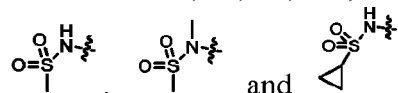
[098] In another Embodiment (21), the invention provides a compound of any one of Embodiments (1)-(20) or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from C_{1-10} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}4}$.

[099] In another Embodiment (22), the invention provides a compound of Embodiment (21) or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}4}$.

[100] In another Embodiment (23), the invention provides a compound of Embodiment (22) or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from phenyl, pyridinyl, pyrimidinyl and thiazolyl, wherein phenyl, pyridinyl, pyrimidinyl and thiazolyl are each unsubstituted or substituted with at least one substituent, independently selected from $\text{R}^{\text{X}4}$.

[101] In another Embodiment (24), the invention provides a compound of any one of Embodiments (1)-(23) or a pharmaceutically acceptable salt thereof, wherein each $\text{R}^{\text{X}4}$ is independently selected from C_{1-10} alkyl, C_{3-10} cycloalkyl, halogen, CN, NO_2 , $-(\text{CR}^{\text{cl}}\text{R}^{\text{dl}})_i\text{NR}^{\text{al}}\text{R}^{\text{bl}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{dl}})_i\text{OR}^{\text{bl}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{dl}})_i\text{C}(\text{O})\text{R}^{\text{al}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{dl}})_i\text{NR}^{\text{al}}\text{C}(\text{O})\text{R}^{\text{bl}}$ and $-(\text{CR}^{\text{cl}}\text{R}^{\text{dl}})_i\text{NR}^{\text{al}}\text{S}(\text{O})_r\text{R}^{\text{bl}}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{Y} .

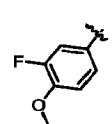
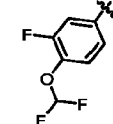
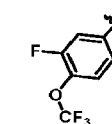
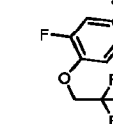
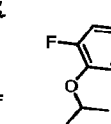
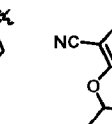
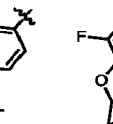
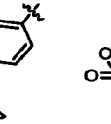
[102] In another Embodiment (25), the invention provides a compound of Embodiment (24) or a pharmaceutically acceptable salt thereof, wherein each $\text{R}^{\text{X}4}$ is independently selected from F, Cl, Br, CN, $-\text{NH}_2$, methyl, ethyl, methoxy, ethoxy, isopropoxy, cyclopropoxy,

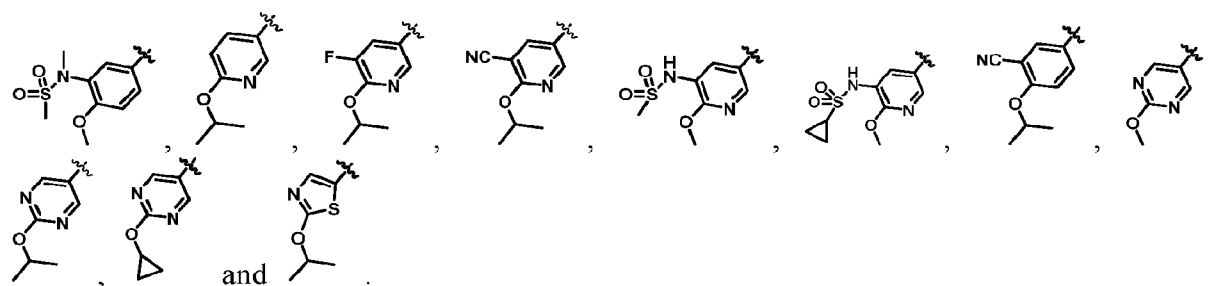
, wherein methyl, ethyl, methoxy, ethoxy, isopropoxy and cyclopropoxy are each unsubstituted or substituted with at least one substituent, independently selected from halogen.

[103] In another Embodiment (26), the invention provides a compound of Embodiment (25) or a pharmaceutically acceptable salt thereof, wherein each $\text{R}^{\text{X}4}$ is

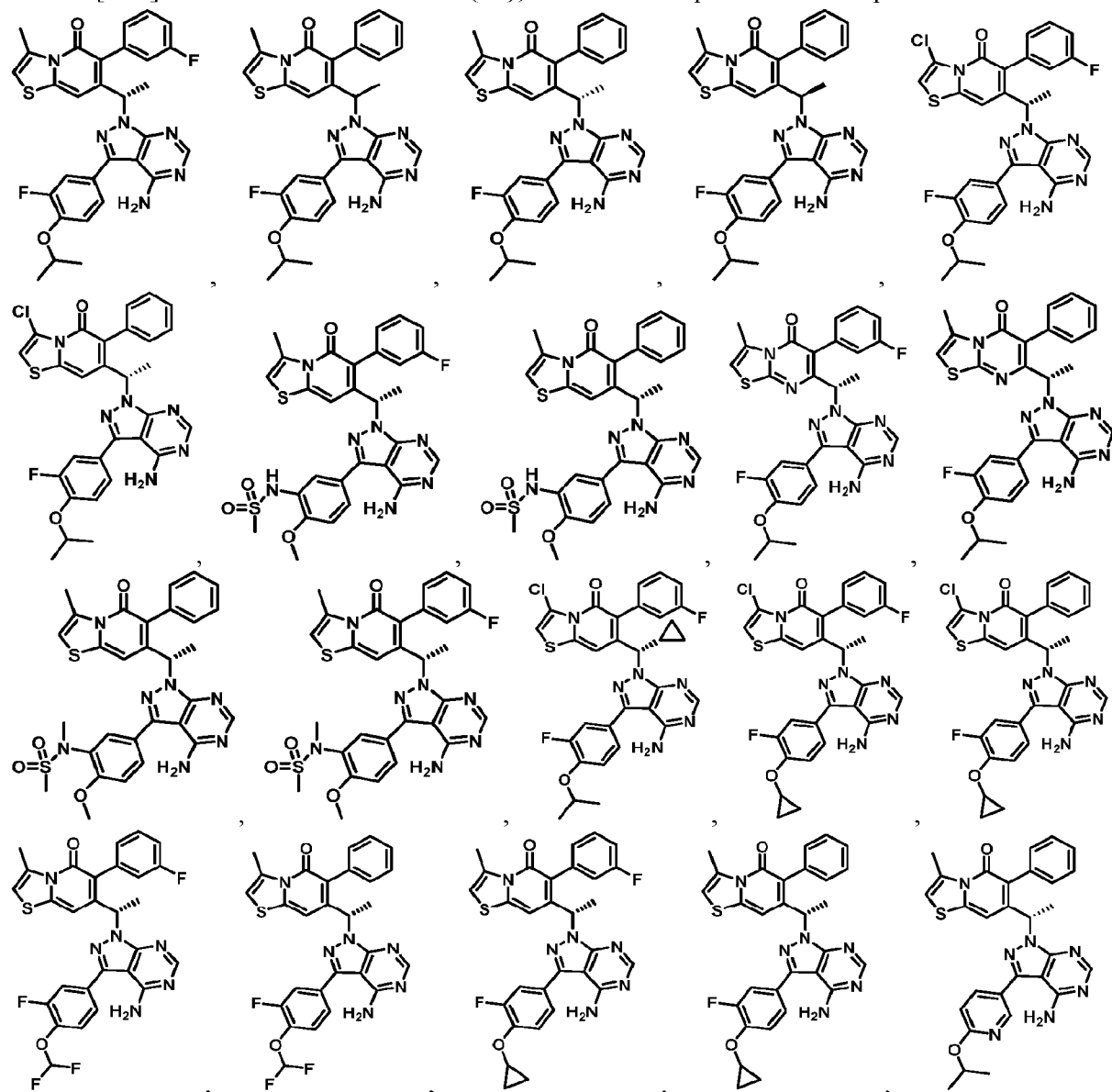
independently selected from F, CN, methoxy, ethoxy, isopropoxy, cyclopropoxy, , , , , , and .

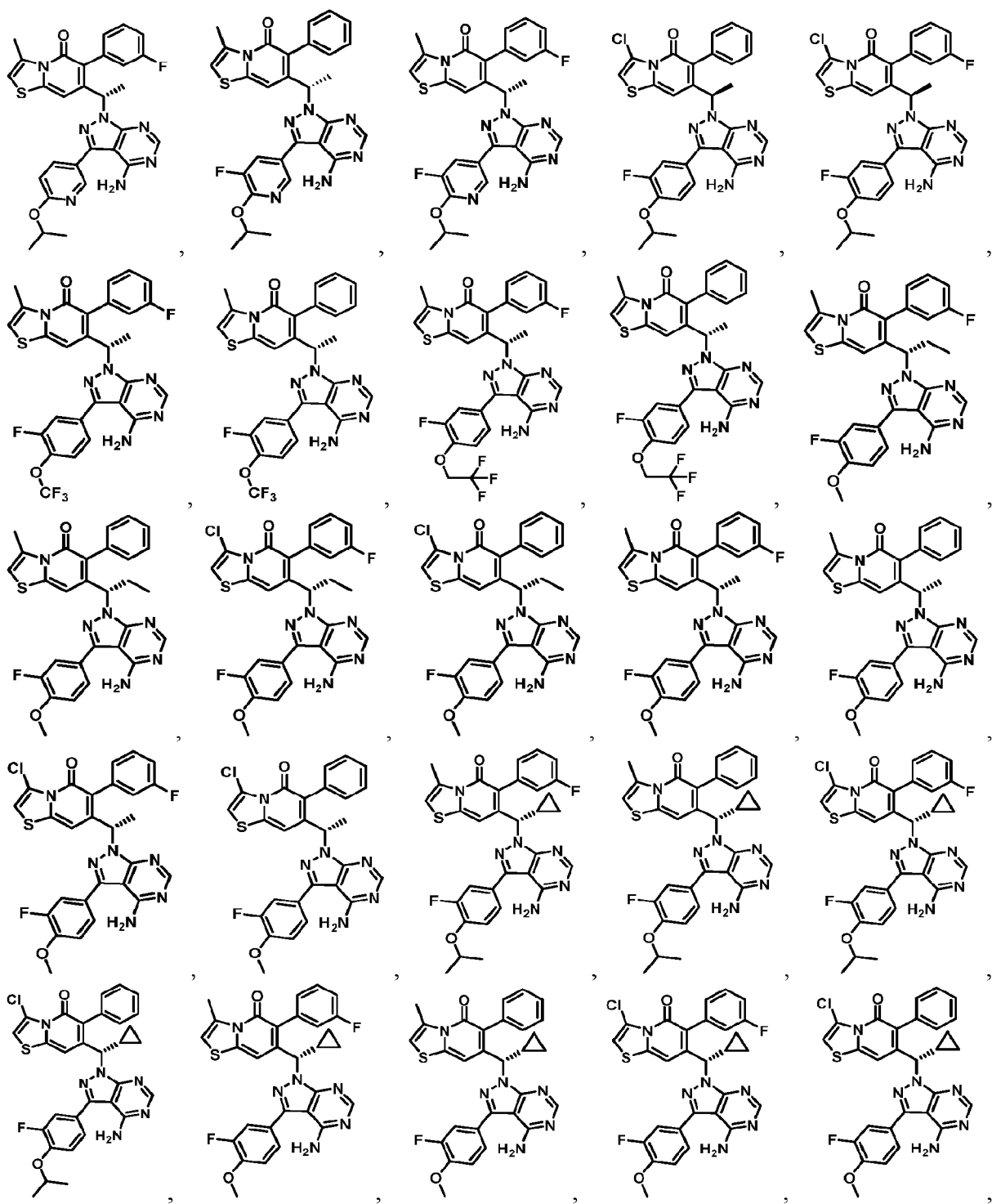
[104] In another Embodiment (27), the invention provides a compound of any one of Embodiments (1)-(26) or a pharmaceutically acceptable salt thereof, wherein R^4 is selected

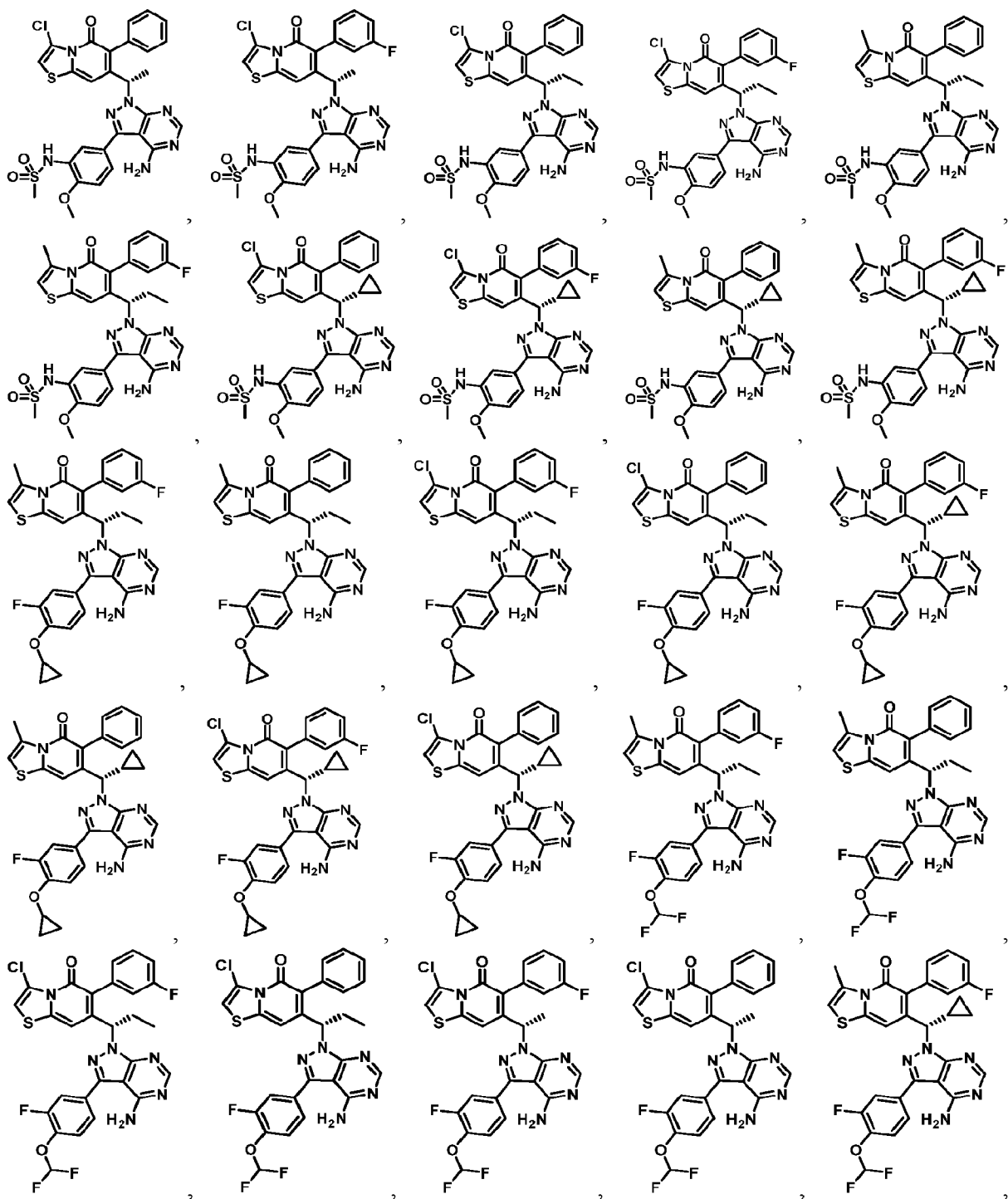
from , , , , , , , and .

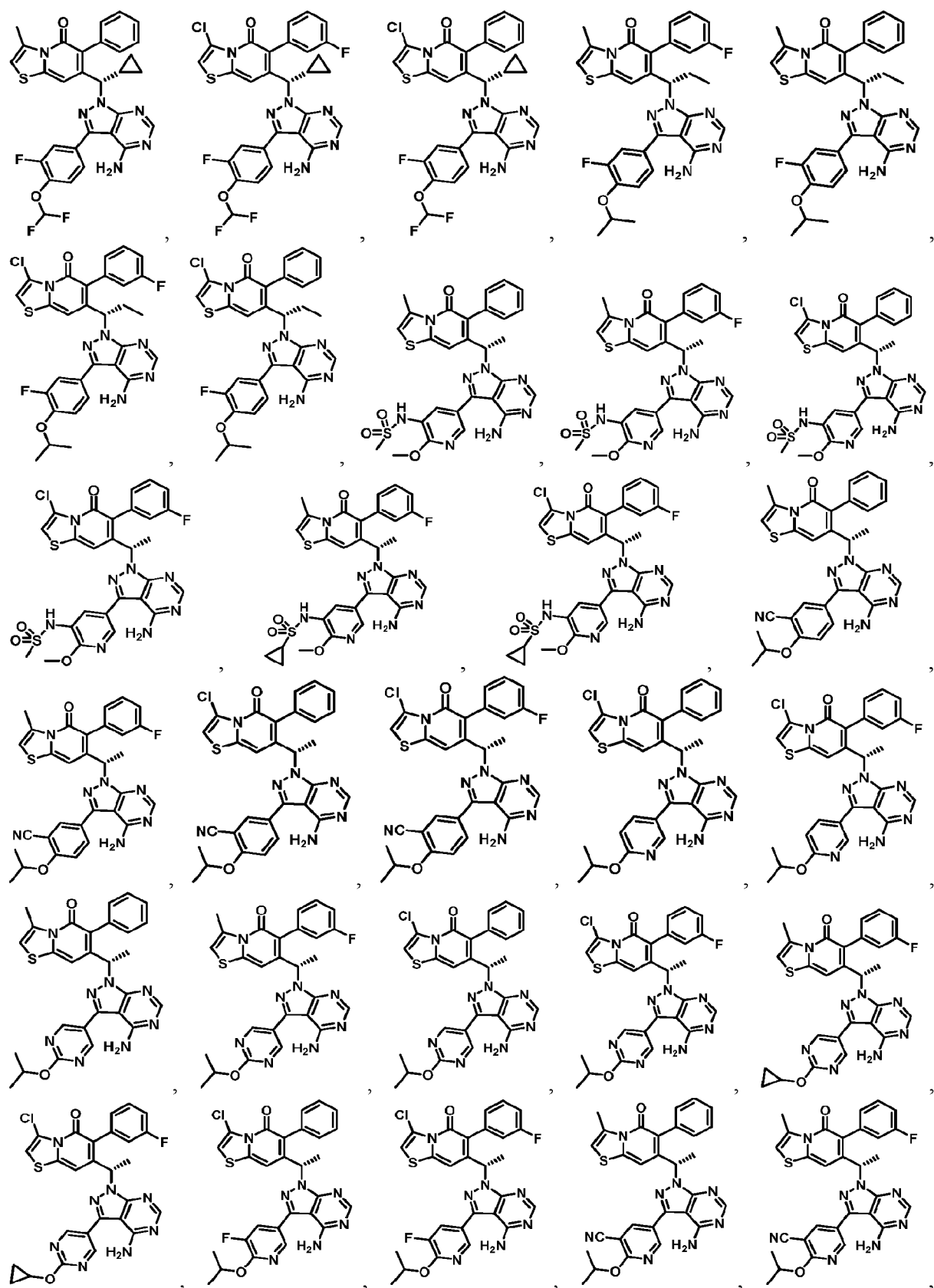


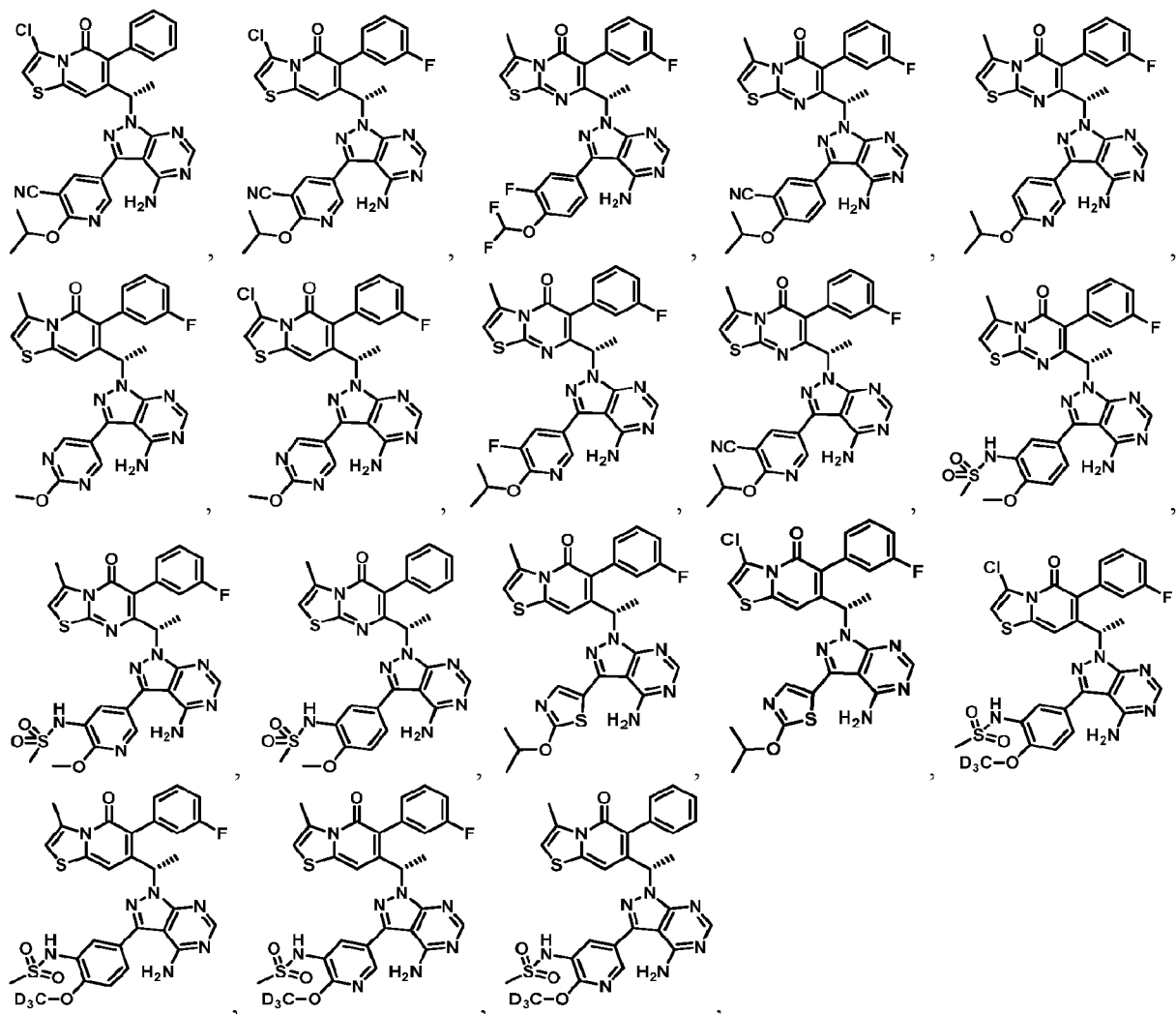
[105] In another Embodiment (28), the invention provides a compound selected from











and pharmaceutically acceptable salts thereof.

[106] In another Embodiment (29), the invention provides a pharmaceutical composition comprising a compound of any one of Embodiments (1)-(28) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

[107] In another Embodiment (30), the invention provides a method of treating, ameliorating or preventing a condition, which responds to inhibition of PI3K, comprising administering to a subject in need of such treatment an effective amount of a compound of any one of Embodiments (1)-(28), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent.

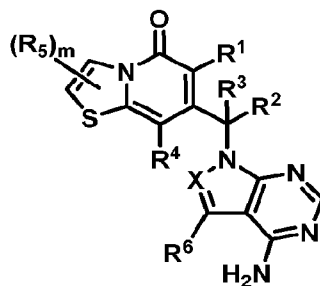
[108] In another Embodiment (31), the invention provides a use of a compound of any one of Embodiments (1)-(28) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a cell-proliferative disorder.

[109] In another Embodiment (32), the invention provides a compound of Embodiment (31) or a pharmaceutically acceptable salt thereof, wherein the cell-proliferative disorder includes but not limited to, breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, testicular cancer, lung cancer (including NSCLC, SCLC, squamous

cell carcinoma or adenocarcinoma), esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer (including RCC), liver cancer (including HCC), pancreatic cancer, stomach (i.e., gastric) cancer, thyroid cancer, chronic lymphocytic leukemia (CLL), lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia and myeloma.

[110] Some embodiments can also be described as follows:

[111] In another Embodiment <1>, the invention provides a compound of formula <I'>



<I'>

or a pharmaceutically acceptable salt thereof,
wherein:

X is selected from CR⁷ and N;

R¹ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X;

R² and R³ are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X;

R⁴ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X;

each R⁵ is independently selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A1}R^{B1}, -OR^{A1}, -C(O)R^{A1}, -C(=NR^{E1})R^{A1}, -C(=N-OR^{B1})R^{A1}, -C(O)OR^{A1}, -OC(O)R^{A1}, -C(O)NR^{A1}R^{B1}, -NR^{A1}C(O)R^{B1}, -C(=NR^{E1})NR^{A1}R^{B1}, -NR^{A1}C(=NR^{E1})R^{B1}, -OC(O)NR^{A1}R^{B1}, -NR^{A1}C(O)OR^{B1}, -NR^{A1}C(O)NR^{A1}R^{B1}, -NR^{A1}C(S)NR^{A1}R^{B1}, -NR^{A1}C(=NR^{E1})NR^{A1}R^{B1}, -S(O)₂R^{A1}, -S(O)(=NR^{E1})R^{B1}, -N=S(O)R^{A1}R^{B1}, -S(O)₂OR^{A1}, -OS(O)₂R^{A1}, -NR^{A1}S(O)₂R^{B1}, -NR^{A1}S(O)(=NR^{E1})R^{B1}, -S(O)₂NR^{A1}R^{B1}, -S(O)(=NR^{E1})NR^{A1}R^{B1}, -NR^{A1}S(O)₂NR^{A1}R^{B1},

$-\text{NR}^{\text{A1}}\text{S}(\text{O})(=\text{NR}^{\text{E1}})\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-\text{P}(\text{O})\text{R}^{\text{A1}}\text{R}^{\text{B1}}$ and $-\text{P}(\text{O})(\text{OR}^{\text{A1}})(\text{OR}^{\text{B1}})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X} ;

R^6 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, CN, NO_2 , $-\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{OR}^{\text{A2}}$, $-\text{C}(\text{O})\text{R}^{\text{A2}}$, $-\text{C}(=\text{NR}^{\text{E2}})\text{R}^{\text{A2}}$, $-\text{C}(=\text{N}-\text{OR}^{\text{B2}})\text{R}^{\text{A2}}$, $-\text{C}(\text{O})\text{OR}^{\text{A2}}$, $-\text{OC}(\text{O})\text{R}^{\text{A2}}$, $-\text{C}(\text{O})\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{NR}^{\text{A2}}\text{C}(\text{O})\text{R}^{\text{B2}}$, $-\text{C}(=\text{NR}^{\text{E2}})\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{NR}^{\text{A2}}\text{C}(=\text{NR}^{\text{E2}})\text{R}^{\text{B2}}$, $-\text{OC}(\text{O})\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{NR}^{\text{A2}}\text{C}(\text{O})\text{OR}^{\text{B2}}$, $-\text{NR}^{\text{A2}}\text{C}(\text{O})\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{NR}^{\text{A2}}\text{C}(\text{S})\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{NR}^{\text{A2}}\text{C}(=\text{NR}^{\text{E2}})\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{S}(\text{O})_2\text{R}^{\text{A2}}$, $-\text{S}(\text{O})(=\text{NR}^{\text{E2}})\text{R}^{\text{B2}}$, $-\text{N}=\text{S}(\text{O})\text{R}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{S}(\text{O})_2\text{OR}^{\text{A2}}$, $-\text{OS}(\text{O})_2\text{R}^{\text{A2}}$, $-\text{NR}^{\text{A2}}\text{S}(\text{O})_2\text{R}^{\text{B2}}$, $-\text{NR}^{\text{A2}}\text{S}(\text{O})(=\text{NR}^{\text{E2}})\text{R}^{\text{B2}}$, $-\text{S}(\text{O})_2\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{S}(\text{O})(=\text{NR}^{\text{E2}})\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{NR}^{\text{A2}}\text{S}(\text{O})_2\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{NR}^{\text{A2}}\text{S}(\text{O})(=\text{NR}^{\text{E2}})\text{NR}^{\text{A2}}\text{R}^{\text{B2}}$, $-\text{P}(\text{O})\text{R}^{\text{A2}}\text{R}^{\text{B2}}$ and $-\text{P}(\text{O})(\text{OR}^{\text{A2}})(\text{OR}^{\text{B2}})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X} ;

R^7 is selected from hydrogen, halogen, OH, CN, NH_2 , NO_2 , C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X} ;

each R^{A1} , R^{A2} , R^{B1} and R^{B2} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X} ;

or each " R^{A1} and R^{B1} ," or " R^{A2} and R^{B2} ," and together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^{X} groups;

each R^{E1} and R^{E2} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , OR^{A1} , SR^{A1} , $-\text{S}(\text{O})_2\text{R}^{\text{A1}}$, $-\text{C}(\text{O})\text{R}^{\text{A1}}$, $-\text{S}(\text{O})_2\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, and $-\text{C}(\text{O})\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$;

each R^{X} is independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{OR}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{C}(\text{O})\text{R}^{\text{A1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{C}(=\text{NR}^{\text{E1}})\text{R}^{\text{A1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{C}(=\text{N}-\text{OR}^{\text{B1}})\text{R}^{\text{A1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{C}(\text{O})\text{OR}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{OC}(\text{O})\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{C}(\text{O})\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{C}(\text{O})\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{C}(=\text{NR}^{\text{E1}})\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{C}(=\text{NR}^{\text{E1}})\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{OC}(\text{O})\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{C}(\text{O})\text{OR}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{C}(\text{O})\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{C}(\text{S})\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{C}(=\text{NR}^{\text{E1}})\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{S}(\text{O})_2\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{S}(\text{O})(=\text{NR}^{\text{E1}})\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{N}=\text{S}(\text{O})\text{R}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{S}(\text{O})_2\text{OR}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{OS}(\text{O})_2\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{S}(\text{O})_2\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{S}(\text{O})(=\text{NR}^{\text{E1}})\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{S}(\text{O})_2\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{S}(\text{O})_2\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{NR}^{\text{A1}}\text{S}(\text{O})(=\text{NR}^{\text{E1}})\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{P}(\text{O})\text{R}^{\text{A1}}\text{R}^{\text{B1}}$ and $-(\text{CR}^{\text{cl}}\text{R}^{\text{d1}})_t\text{P}(\text{O})(\text{OR}^{\text{A1}})(\text{OR}^{\text{B1}})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{Y} ;

each R^{A1} and each R^{B1} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein

alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

or R^{a1} and R^{b1} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{c1} and each R^{d1} are independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

or R^{c1} and R^{d1} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1, or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{e1} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , OR^{a2} , SR^{a2} , $-S(O)_tR^{a2}$, $-C(O)R^{a2}$, $-S(O)_tNR^{a2}R^{b2}$, and $-C(O)NR^{a2}R^{b2}$;

each R^Y is independently selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N-OR^{b2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(-NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(-NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_tR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_tR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$ and $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from OH, CN, amino, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{a2} and each R^{b2} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

or R^{a2} and R^{b2} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{c2} and each R^{d2} are independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, C_{1-10} alkylamino, C_{3-10} cycloalkylamino, di(C_{1-10} alkyl)amino, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

or R^{c2} and R^{d2} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, OH, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, C_{1-10} alkylthio, C_{3-10} cycloalkylthio, amino, C_{1-10} alkylamino, C_{3-10} cycloalkylamino and di(C_{1-10} alkyl)amino;

each R^{e2} is independently selected from hydrogen, C_{1-10} alkyl, CN and NO_2 ;

m is selected from 0, 1, 2 and 3;

each r is independently selected from 0, 1 and 2;

each t is independently selected from 0, 1, 2, 3 and 4.

[112] In another Embodiment <2>, the invention provides a compound of Embodiment <1> or a pharmaceutically acceptable salt thereof, wherein X is N.

[113] In another Embodiment <3>, the invention provides a compound of Embodiment <1> or a pharmaceutically acceptable salt thereof, wherein X is CR^7 .

[114] In another Embodiment <4>, the invention provides a compound of Embodiment <3> or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from hydrogen, halogen, OH, CN, NH_2 , NO_2 , C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[115] In another Embodiment <5>, the invention provides a compound of Embodiment <4> or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from hydrogen, halogen, OH, CN, NH_2 , NO_2 , C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, wherein alkyl, cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[116] In another Embodiment <6>, the invention provides a compound of any one of Embodiments <1>-<5> or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from hydrogen, halogen, OH, CN, NH_2 , NO_2 , C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, cycloalkyl, alkoxy, cycloalkoxy, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[117] In another Embodiment <7>, the invention provides a compound of Embodiment <6> or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[118] In another Embodiment <8>, the invention provides a compound of Embodiment <7> or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl, which is unsubstituted or substituted with halogen.

[119] In another Embodiment <9>, the invention provides a compound of Embodiment <8> or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl or 3-fluorophenyl.

[120] In another Embodiment <10>, the invention provides a compound of any one of Embodiments <1>-<9> or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl and heteroaryl, wherein alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[121] In another Embodiment <11>, the invention provides a compound of Embodiment <10> or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl and C_{3-10} cycloalkyl- C_{1-4} alkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[122] In another Embodiment <12>, the invention provides a compound of Embodiment <11> or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, methyl, ethyl and cyclopropyl.

[123] In another Embodiment <13>, the invention provides a compound of any one of Embodiments <1>-<12> or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen, halogen, OH, CN, NH_2 , NO_2 , C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkoxy, heterocyclyl, aryl and heteroaryl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[124] In another Embodiment <14>, the invention provides a compound of Embodiment <13> or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen, halogen, OH, CN, NO_2 , C_{1-10} alkyl and C_{3-10} cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[125] In another Embodiment <15>, the invention provides a compound of Embodiment <14> or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

[126] In another Embodiment <16>, the invention provides a compound of any one of Embodiments <1>-<15> or a pharmaceutically acceptable salt thereof, wherein m is selected from 0, 1 and 2.

[127] In another Embodiment <17>, the invention provides a compound of Embodiment <16> or a pharmaceutically acceptable salt thereof, wherein m is 1.

[128] In another Embodiment <18>, the invention provides a compound of any one of Embodiments <1>-<17> or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, CN, NO_2 , $-NR^{A1}R^{B1}$, $-OR^{A1}$, $-C(O)R^{A1}$, $-C(O)OR^{A1}$, $-OC(O)R^{A1}$, $-C(O)NR^{A1}R^{B1}$, $-NR^{A1}C(O)R^{B1}$, $-S(O)_rR^{A1}$, $-S(O)_2OR^{A1}$ and $-S(O)_rNR^{A1}R^{B1}$, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[129] In another Embodiment <19>, the invention provides a compound of Embodiment <18> or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, CN, NO_2 , $-NR^{A1}R^{B1}$, $-OR^{A1}$, $-C(O)R^{A1}$, $-NR^{A1}C(O)R^{B1}$, $-S(O)_rR^{A1}$ and $-S(O)_rNR^{A1}R^{B1}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[130] In another Embodiment <20>, the invention provides a compound of Embodiment <19> or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, F, Cl, methyl and ethyl.

[131] In another Embodiment <21>, the invention provides a compound of any one of Embodiments <1>- <20> or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, CN, NO_2 , $-NR^{A2}R^{B2}$, $-OR^{A2}$, $-C(O)R^{A2}$, $-C(O)OR^{A2}$, $-OC(O)R^{A2}$, $-C(O)NR^{A2}R^{B2}$, $-NR^{A2}C(O)R^{B2}$, $-S(O)_rR^{A2}$, $-S(O)_2OR^{A2}$ and $-S(O)_rNR^{A2}R^{B2}$, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[132] In another Embodiment <22>, the invention provides a compound of Embodiment <21> or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[133] In another Embodiment <23>, the invention provides a compound of Embodiment <22> or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from aryl, wherein aryl is unsubstituted or substituted with at least one substituent, independently selected from R^X .

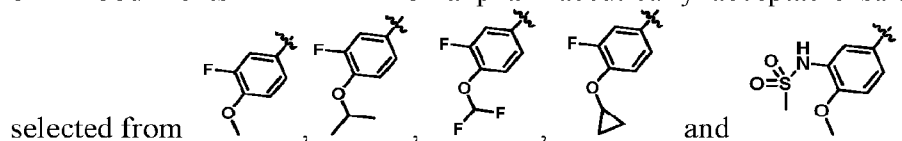
[134] In another Embodiment <24>, the invention provides a compound of Embodiment <23> or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl, wherein phenyl is unsubstituted or substituted with at least one substituent, independently selected from R^X .

[135] In another Embodiment <25>, the invention provides a compound of any one of Embodiments <1>- <24> or a pharmaceutically acceptable salt thereof, wherein the substituent R^X of R^6 is independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tOR^{b1}$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$, $-(CR^{c1}R^{d1})_tC(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_2OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_rR^{b1}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y .

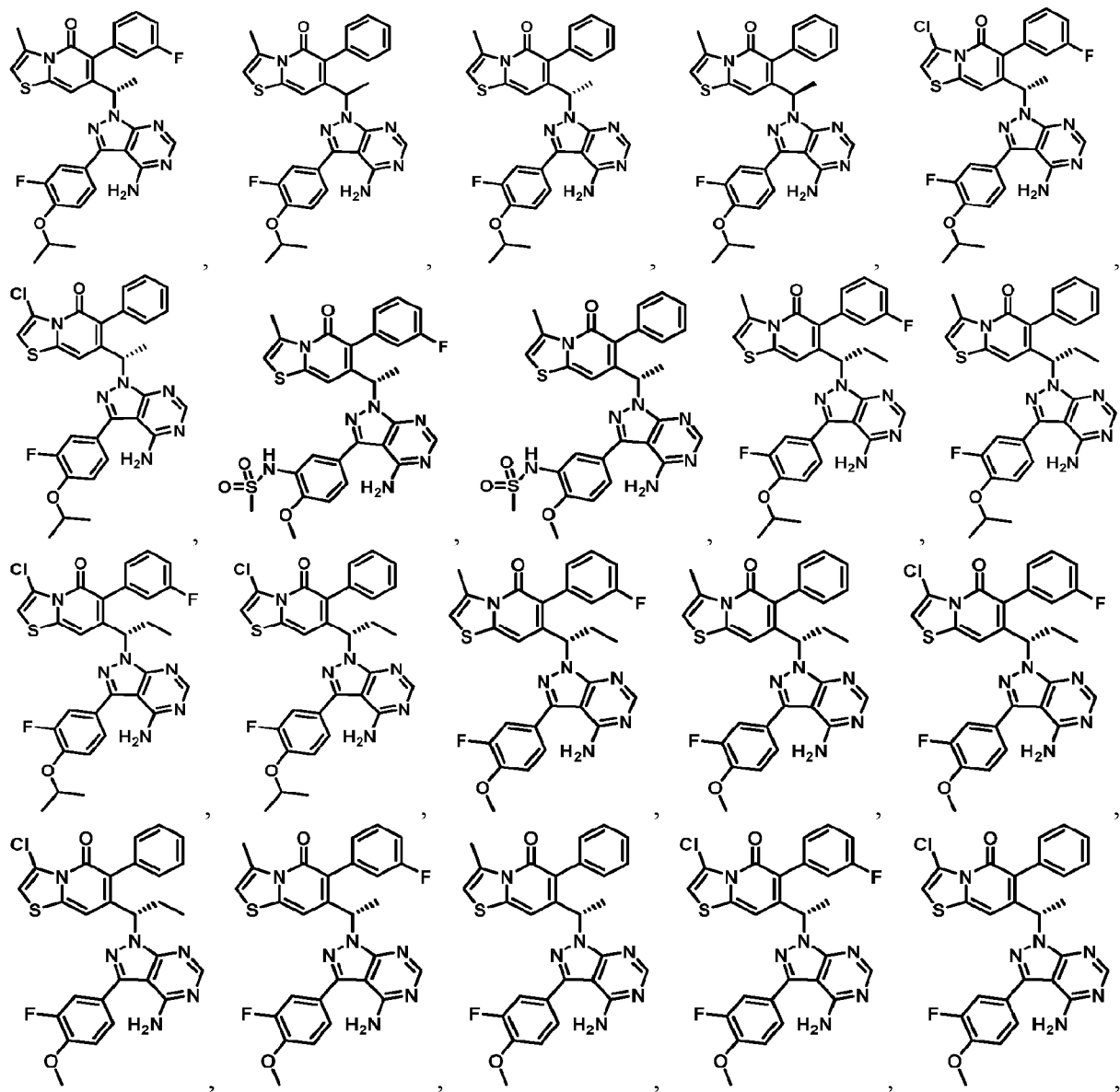
[136] In another Embodiment <26>, the invention provides a compound of Embodiment <25> or a pharmaceutically acceptable salt thereof, wherein the substituent R^X of R^6 is independently selected from C_{1-10} alkyl, C_{3-10} cycloalkyl, halogen, CN, NO_2 , $-(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tOR^{b1}$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$ and $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y .

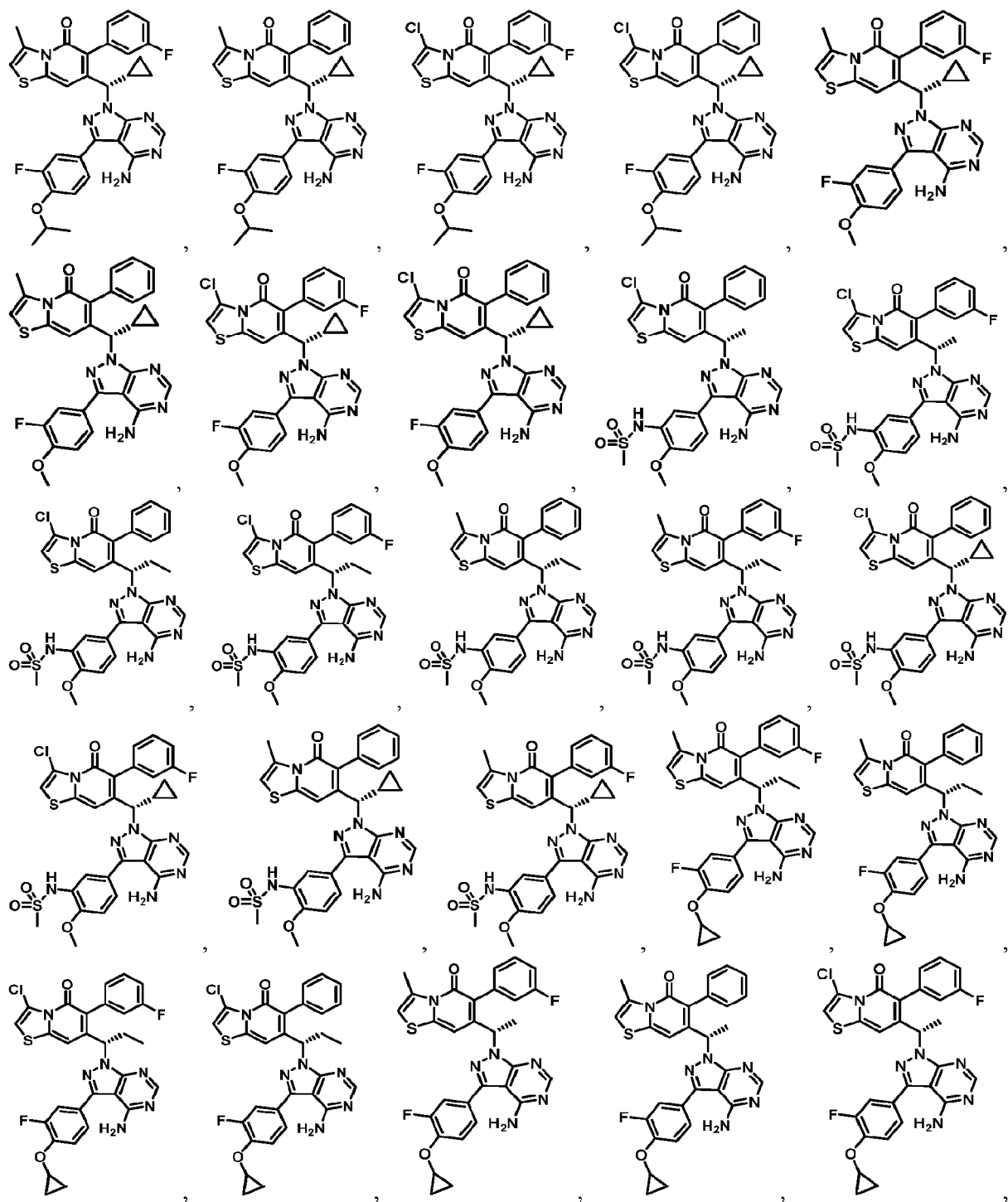
[137] In another Embodiment <27>, the invention provides a compound of Embodiment <26> or a pharmaceutically acceptable salt thereof, wherein the substituent R^X of R^6 is independently selected from F, Cl, Br, methoxy, ethoxy, isopropoxy, cyclopropyloxy and $-NHSO_2CH_3$, wherein methoxy, ethoxy, isopropoxy and cyclopropyloxy are each unsubstituted or substituted with at least one substituent, independently selected from R^Y .

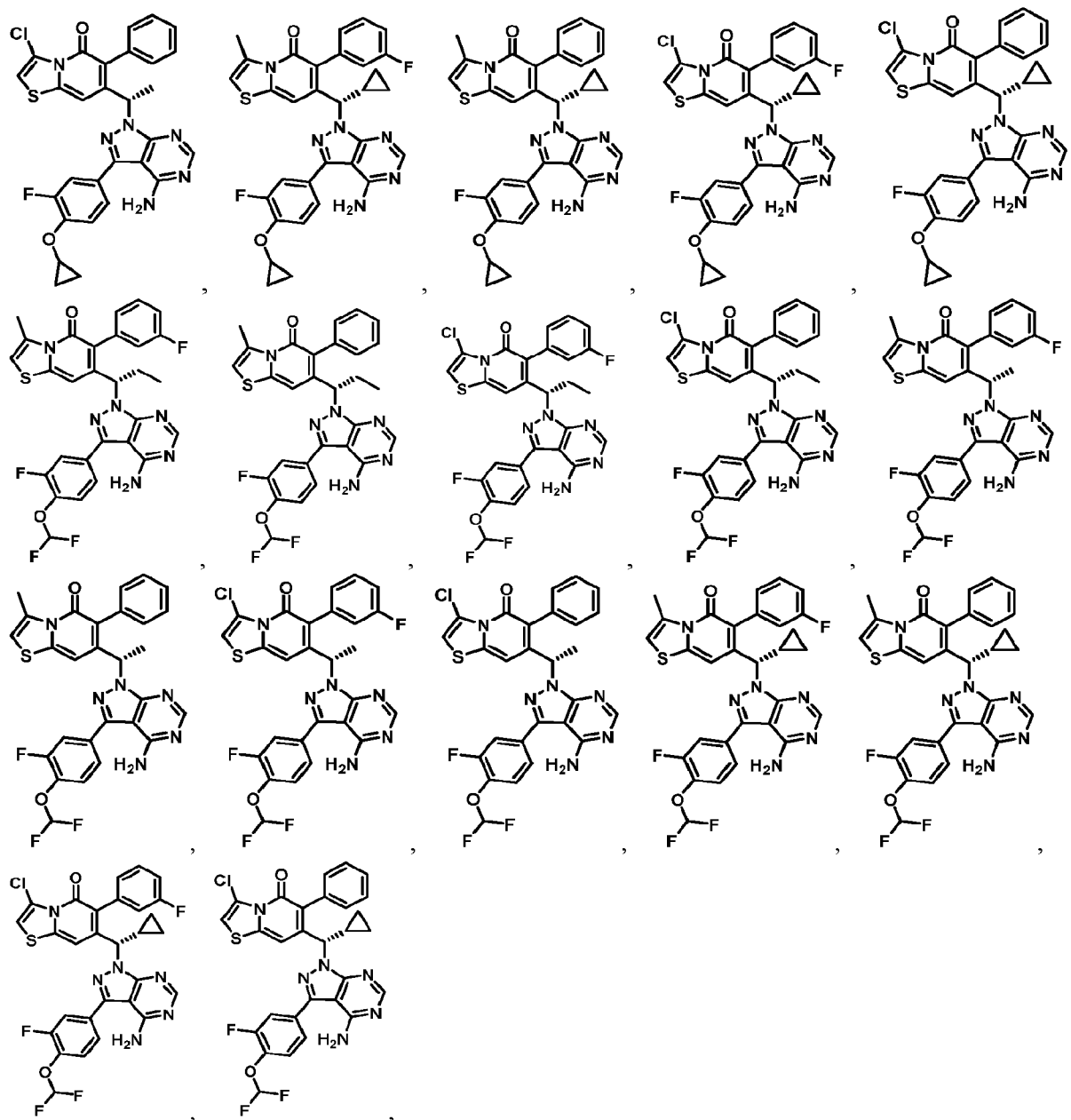
[138] In another Embodiment <28>, the invention provides a compound of any one of Embodiments <1>- <27> or a pharmaceutically acceptable salt thereof, wherein R⁶ is



[139] In another Embodiment <29>, the invention provides a compound selected from







and pharmaceutically acceptable salts thereof.

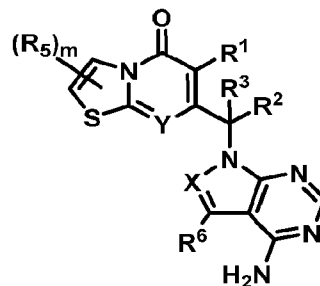
[140] In another Embodiment <30>, the invention provides a pharmaceutical composition comprising a compound of any one of Embodiments <1>- <29> or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

[141] In another Embodiment <31>, the invention provides a method of treating, ameliorating or preventing a condition, which responds to inhibition of PI3K, comprising administering to a subject in need of such treatment an effective amount of a compound of any one of Embodiments <1>-<29>, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent.

[142] In another Embodiment <32>, the invention provides a use of a compound of any one of Embodiments <1>-<29> or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a cell-proliferative disorder.

[143] Some embodiments can also be described as follows:

[144] In another Embodiment [1], this invention provides to a compound of formula [I']



[I']

or a pharmaceutically acceptable salt thereof,
wherein:

X is selected from CR⁷ and N;

Y is selected from CR⁴ and N;

R¹ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A1}R^{B1}, -OR^{A1}, -C(O)R^{A1}, -C(=NR^{E1})R^{A1}, -C(=N-OR^{B1})R^{A1}, -C(O)OR^{A1}, -OC(O)R^{A1}, -C(O)NR^{A1}R^{B1}, -NR^{A1}C(O)R^{B1}, -C(=NR^{E1})NR^{A1}R^{B1}, -NR^{A1}C(=NR^{E1})R^{B1}, -OC(O)NR^{A1}R^{B1}, -NR^{A1}C(O)OR^{B1}, -NR^{A1}C(O)NR^{A1}R^{B1}, -NR^{A1}C(S)NR^{A1}R^{B1}, -NR^{A1}C(=NR^{E1})NR^{A1}R^{B1}, -S(O)_rR^{A1}, -S(O)(=NR^{E1})R^{B1}, -N=S(O)R^{A1}R^{B1}, -S(O)₂OR^{A1}, -OS(O)₂R^{A1}, -NR^{A1}S(O)_rR^{B1}, -NR^{A1}S(O)(=NR^{E1})R^{B1}, -S(O)_rNR^{A1}R^{B1}, -S(O)(=NR^{E1})NR^{A1}R^{B1}, -NR^{A1}S(O)₂NR^{A1}R^{B1}, -NR^{A1}S(O)(=NR^{E1})NR^{A1}R^{B1}, -P(O)R^{A1}R^{B1} and -P(O)(OR^{A1})(OR^{B1}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X,

R² and R³ are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X,

or R² and R³ together with the atoms to which they are attached form a C₃₋₁₀ cycloalkyl or heterocyclic ring of 4 to 12 members containing 1, 2 or 3 heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^X groups;

R⁴ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A2}R^{B2}, -OR^{A2}, -C(O)R^{A2}, -C(=NR^{E2})R^{A2}, -C(=N-OR^{B2})R^{A2}, -C(O)OR^{A2}, -OC(O)R^{A2}, -C(O)NR^{A2}R^{B2}, -NR^{A2}C(O)R^{B2}, -C(=NR^{E2})NR^{A2}R^{B2}, -NR^{A2}C(=NR^{E2})R^{B2}, -OC(O)NR^{A2}R^{B2}, -NR^{A2}C(O)OR^{B2}, -NR^{A2}C(O)NR^{A2}R^{B2}, -NR^{A2}C(S)NR^{A2}R^{B2}, -NR^{A2}C(=NR^{E2})NR^{A2}R^{B2}, -S(O)_rR^{A2},

-S(O)(=NR^{E2})R^{B2}, -N=S(O)R^{A2}R^{B2}, -S(O)₂OR^{A2}, -OS(O)₂R^{A2}, -NR^{A2}S(O)_rR^{B2}, -NR^{A2}S(O)(=NR^{E2})R^{B2}, -S(O)_rNR^{A2}R^{B2}, -S(O)(=NR^{E2})NR^{A2}R^{B2}, -NR^{A2}S(O)₂NR^{A2}R^{B2}, -NR^{A2}S(O)(=NR^{E2})NR^{A2}R^{B2}, -P(O)R^{A2}R^{B2} and -P(O)(OR^{A2})(OR^{B2}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X,

each R⁵ is independently selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A3}R^{B3}, -OR^{A3}, -C(O)R^{A3}, -C(=NR^{E3})R^{A3}, -C(=N-OR^{B3})R^{A3}, -C(O)OR^{A3}, -OC(O)R^{A3}, -C(O)NR^{A3}R^{B3}, -NR^{A3}C(O)R^{B3}, -C(=NR^{E3})NR^{A3}R^{B3}, -NR^{A3}C(=NR^{E3})R^{B3}, -OC(O)NR^{A3}R^{B3}, -NR^{A3}C(O)OR^{B3}, -NR^{A3}C(O)NR^{A3}R^{B3}, -NR^{A3}C(S)NR^{A3}R^{B3}, -NR^{A3}C(=NR^{E3})NR^{A3}R^{B3}, -S(O)_rR^{A3}, -S(O)(=NR^{E3})R^{B3}, -N=S(O)R^{A3}R^{B3}, -S(O)₂OR^{A3}, -OS(O)₂R^{A3}, -NR^{A3}S(O)_rR^{B3}, -NR^{A3}S(O)(=NR^{E3})R^{B3}, -S(O)_rNR^{A3}R^{B3}, -S(O)(=NR^{E3})NR^{A3}R^{B3}, -NR^{A3}S(O)₂NR^{A3}R^{B3}, -NR^{A3}S(O)(=NR^{E3})NR^{A3}R^{B3}, -P(O)R^{A3}R^{B3} and -P(O)(OR^{A3})(OR^{B3}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X,

R⁶ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A4}R^{B4}, -OR^{A4}, -C(O)R^{A4}, -C(=NR^{E4})R^{A4}, -C(=N-OR^{B4})R^{A4}, -C(O)OR^{A4}, -OC(O)R^{A4}, -C(O)NR^{A4}R^{B4}, -NR^{A4}C(O)R^{B4}, -C(=NR^{E4})NR^{A4}R^{B4}, -NR^{A4}C(=NR^{E4})R^{B4}, -OC(O)NR^{A4}R^{B4}, -NR^{A4}C(O)OR^{B4}, -NR^{A4}C(O)NR^{A4}R^{B4}, -NR^{A4}C(S)NR^{A4}R^{B4}, -NR^{A4}C(=NR^{E4})NR^{A4}R^{B4}, -S(O)_rR^{A4}, -S(O)(=NR^{E4})R^{B4}, -N=S(O)R^{A4}R^{B4}, -S(O)₂OR^{A4}, -OS(O)₂R^{A4}, -NR^{A4}S(O)_rR^{B4}, -NR^{A4}S(O)(=NR^{E4})R^{B4}, -S(O)_rNR^{A4}R^{B4}, -S(O)(=NR^{E4})NR^{A4}R^{B4}, -NR^{A4}S(O)₂NR^{A4}R^{B4}, -NR^{A4}S(O)(=NR^{E4})NR^{A4}R^{B4}, -P(O)R^{A4}R^{B4} and -P(O)(OR^{A4})(OR^{B4}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X,

R⁷ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A5}R^{B5}, -OR^{A5}, -C(O)R^{A5}, -C(=NR^{E5})R^{A5}, -C(=N-OR^{B5})R^{A5}, -C(O)OR^{A5}, -OC(O)R^{A5}, -C(O)NR^{A5}R^{B5}, -NR^{A5}C(O)R^{B5}, -C(=NR^{E5})NR^{A5}R^{B5}, -NR^{A5}C(=NR^{E5})R^{B5}, -OC(O)NR^{A5}R^{B5}, -NR^{A5}C(O)OR^{B5}, -NR^{A5}C(O)NR^{A5}R^{B5}, -NR^{A5}C(S)NR^{A5}R^{B5}, -NR^{A5}C(=NR^{E5})NR^{A5}R^{B5}, -S(O)_rR^{A5}, -S(O)(=NR^{E5})R^{B5}, -N=S(O)R^{A5}R^{B5}, -S(O)₂OR^{A5}, -OS(O)₂R^{A5}, -NR^{A5}S(O)_rR^{B5}, -NR^{A5}S(O)(=NR^{E5})R^{B5}, -S(O)_rNR^{A5}R^{B5}, -S(O)(=NR^{E5})NR^{A5}R^{B5}, -NR^{A5}S(O)₂NR^{A5}R^{B5}, -NR^{A5}S(O)(=NR^{E5})NR^{A5}R^{B5}, -P(O)R^{A5}R^{B5} and -P(O)(OR^{A5})(OR^{B5}), wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X,

each R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{B1}, R^{B2}, R^{B3}, R^{B4} and R^{B5} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X,

or "R^{A1} and R^{B1}" or "R^{A2} and R^{B2}" or "R^{A3} and R^{B3}" or "R^{A4} and R^{B4}" or "R^{A5} and R^{B5}", and together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^X groups;

each R^{E1} , R^{E2} , R^{E3} , R^{E4} and R^{E5} are independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{a1}$, $-SR^{a1}$, $-S(O)_tR^{a1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$, $-C(O)NR^{a1}R^{b1}$ and $-S(O)_tNR^{a1}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^X ,

each R^X is independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tOR^{b1}$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=N-OR^{b1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(S)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_tR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tN=S(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_2OR^{b1}$, $-(CR^{c1}R^{d1})_tOS(O)_2R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_tR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_2NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tP(O)R^{a1}R^{b1}$ and $-(CR^{c1}R^{d1})_tP(O)(OR^{a1})(OR^{b1})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

each R^{a1} and each R^{b1} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

or R^{a1} and R^{b1} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{c1} and each R^{d1} are independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

or R^{c1} and R^{d1} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1, or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{e1} is independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, CN, NO_2 , $-OR^{a2}$, $-SR^{a2}$, $-S(O)_tR^{a2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$, $-S(O)_tNR^{a2}R^{b2}$ and $-C(O)NR^{a2}R^{b2}$;

each R^Y is independently selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N-OR^{b2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(S)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_tR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2OR^{b2}$,

$-(\text{CR}^{\text{c}2}\text{R}^{\text{d}2})_i\text{OS}(\text{O})_2\text{R}^{\text{b}2}$, $-(\text{CR}^{\text{c}2}\text{R}^{\text{d}2})_i\text{NR}^{\text{a}2}\text{S}(\text{O})_2\text{R}^{\text{b}2}$, $-(\text{CR}^{\text{c}2}\text{R}^{\text{d}2})_i\text{NR}^{\text{a}2}\text{S}(\text{O})(=\text{NR}^{\text{e}2})\text{R}^{\text{b}2}$,
 $-(\text{CR}^{\text{c}2}\text{R}^{\text{d}2})_i\text{S}(\text{O})_2\text{NR}^{\text{a}2}\text{R}^{\text{b}2}$, $-(\text{CR}^{\text{c}2}\text{R}^{\text{d}2})_i\text{S}(\text{O})(=\text{NR}^{\text{e}2})\text{NR}^{\text{a}2}\text{R}^{\text{b}2}$, $-(\text{CR}^{\text{c}2}\text{R}^{\text{d}2})_i\text{NR}^{\text{a}2}\text{S}(\text{O})_2\text{NR}^{\text{a}2}\text{R}^{\text{b}2}$,
 $-(\text{CR}^{\text{c}2}\text{R}^{\text{d}2})_i\text{NR}^{\text{a}2}\text{S}(\text{O})(=\text{NR}^{\text{e}2})\text{NR}^{\text{a}2}\text{R}^{\text{b}2}$, $-(\text{CR}^{\text{c}2}\text{R}^{\text{d}2})_i\text{P}(\text{O})\text{R}^{\text{a}2}\text{R}^{\text{b}2}$ and
 $-(\text{CR}^{\text{c}2}\text{R}^{\text{d}2})_i\text{P}(\text{O})(\text{OR}^{\text{a}2})(\text{OR}^{\text{b}2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl
 and heteroaryl are each unsubstituted or substituted with at least one substituent,
 independently selected from OH, CN, amino, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,
 C₃₋₁₀ cycloalkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, C₁₋₁₀
 alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

each R^{a2} and each R^{b2} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀
 alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀
 cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino,
 di(C₁₋₁₀ alkyl)amino, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl and
 heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy,
 alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are
 each unsubstituted or substituted with at least one substituent, independently selected from
 halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀
 cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀
 cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

or R^{a2} and R^{b2} together with the atom(s) to which they are attached form a heterocyclic
 ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected
 from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1 or 2
 substituents, independently selected from halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,
 C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio,
 amino, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

each R^{c2} and each R^{d2} are independently selected from hydrogen, halogen, C₁₋₁₀ alkyl,
 C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀
 cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino,
 di(C₁₋₁₀ alkyl)amino, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl and
 heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy,
 alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are
 each unsubstituted or substituted with at least one substituent, independently selected from
 halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀
 cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀
 cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

or R^{c2} and R^{d2} together with the carbon atom(s) to which they are attached form a ring
 of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen,
 sulfur and nitrogen, and optionally substituted with 1 or 2 substituents, independently selected
 from halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy,
 C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀
 cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

each R^{e2} is independently selected from hydrogen, CN, NO₂, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl,
 C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, -C(O)C₁₋₄ alkyl, -C(O)C₃₋₁₀
 cycloalkyl, -C(O)OC₁₋₄ alkyl, -C(O)OC₃₋₁₀ cycloalkyl, -C(O)N(C₁₋₄ alkyl)₂, -C(O)N(C₃₋₁₀
 cycloalkyl)₂, -S(O)₂C₁₋₄ alkyl, -S(O)₂C₃₋₁₀ cycloalkyl, -S(O)₂N(C₁₋₄ alkyl)₂ and -S(O)₂N(C₃₋₁₀
 cycloalkyl)₂;

m is selected from 0, 1, 2 and 3;

each r is independently selected from 0, 1 and 2;

each t is independently selected from 0, 1, 2, 3 and 4.

[145] In another Embodiment [2], the invention provides a compound of Embodiment [1] or a pharmaceutically acceptable salt thereof, wherein X is N.

[146] In another Embodiment [3], the invention provides a compound of Embodiment [1] or a pharmaceutically acceptable salt thereof, wherein X is CR⁷.

[147] In another Embodiment [4], the invention provides a compound of Embodiment [3] or a pharmaceutically acceptable salt thereof, wherein R⁷ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X.

[148] In another Embodiment [5], the invention provides a compound of Embodiment [4] or a pharmaceutically acceptable salt thereof, wherein R⁷ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, wherein alkyl, cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^X.

[149] In another Embodiment [6], the invention provides a compound of Embodiment [1] or a pharmaceutically acceptable salt thereof, wherein Y is N.

[150] In another Embodiment [7], the invention provides a compound of Embodiment [1] or a pharmaceutically acceptable salt thereof, wherein Y is CR⁴.

[151] In another Embodiment [8], the invention provides a compound of Embodiment [7] or a pharmaceutically acceptable salt thereof, wherein R⁴ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, heterocyclyl, aryl and heteroaryl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X.

[152] In another Embodiment [9], the invention provides a compound of Embodiment [8] or a pharmaceutically acceptable salt thereof, wherein R⁴ is selected from hydrogen, halogen, OH, CN, NO₂, C₁₋₁₀ alkyl and C₃₋₁₀ cycloalkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^X.

[153] In another Embodiment [10], the invention provides a compound of Embodiment [9] or a pharmaceutically acceptable salt thereof, wherein R⁴ is hydrogen.

[154] In another Embodiment [11], the invention provides a compound of any one of Embodiments [1]- [10] or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, cycloalkyl, alkoxy, cycloalkoxy, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X.

[155] In another Embodiment [12], the invention provides a compound of Embodiment [11] or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X.

[156] In another Embodiment [13], the invention provides a compound of Embodiment [12] or a pharmaceutically acceptable salt thereof, wherein R¹ is phenyl, which is unsubstituted or substituted with halogen.

[157] In another Embodiment [14], the invention provides a compound of Embodiment [13] or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl or 3-fluorophenyl.

[158] In another Embodiment [15], the invention provides a compound of any one of Embodiments [1]- [14] or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl and heteroaryl, wherein alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[159] In another Embodiment [16], the invention provides a compound of Embodiment [15] or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl and C_{3-10} cycloalkyl- C_{1-4} alkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[160] In another Embodiment [17], the invention provides a compound of Embodiment [16] or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, methyl, ethyl and cyclopropyl.

[161] In another Embodiment [18], the invention provides a compound of any one of Embodiments [1]- [17] or a pharmaceutically acceptable salt thereof, wherein m is selected from 0, 1 and 2.

[162] In another Embodiment [19], the invention provides a compound of Embodiment [18] or a pharmaceutically acceptable salt thereof, wherein m is 1.

[163] In another Embodiment [20], the invention provides a compound of any one of Embodiments [1]- [19] or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, CN, NO_2 , $-NR^{A1}R^{B1}$, $-OR^{A1}$, $-C(O)R^{A1}$, $-C(O)OR^{A1}$, $-OC(O)R^{A1}$, $-C(O)NR^{A1}R^{B1}$, $-NR^{A1}C(O)R^{B1}$, $-S(O)_rR^{A1}$, $-S(O)_2OR^{A1}$ and $-S(O)_rNR^{A1}R^{B1}$, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[164] In another Embodiment [21], the invention provides a compound of Embodiment [20] or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, CN, NO_2 , $-NR^{A1}R^{B1}$, $-OR^{A1}$, $-C(O)R^{A1}$, $-NR^{A1}C(O)R^{B1}$, $-S(O)_rR^{A1}$ and $-S(O)_rNR^{A1}R^{B1}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[165] In another Embodiment [22], the invention provides a compound of Embodiment [21] or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, F, Cl, methyl and ethyl.

[166] In another Embodiment [23], the invention provides a compound of any one of Embodiments [1]- [22] or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, CN, NO_2 , $-NR^{A2}R^{B2}$, $-OR^{A2}$, $-C(O)R^{A2}$, $-C(O)OR^{A2}$, $-OC(O)R^{A2}$, $-C(O)NR^{A2}R^{B2}$, $-NR^{A2}C(O)R^{B2}$, $-S(O)_rR^{A2}$, $-S(O)_2OR^{A2}$ and $-S(O)_rNR^{A2}R^{B2}$, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[167] In another Embodiment [24], the invention provides a compound of Embodiment [23] or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from C_{1-10} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

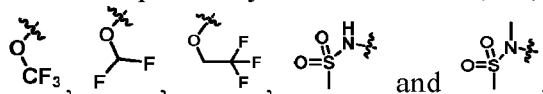
[168] In another Embodiment [25], the invention provides a compound of Embodiment [24] or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

[169] In another Embodiment [26], the invention provides a compound of Embodiment [25] or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from phenyl and pyridinyl, wherein phenyl and pyridinyl are each unsubstituted or substituted with at least one substituent, independently selected from R^X .

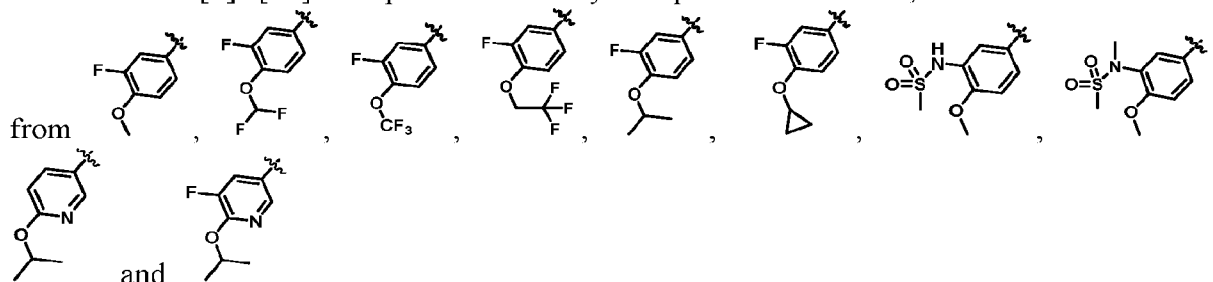
[170] In another Embodiment [27], the invention provides a compound of any one of Embodiments [1]- [26] or a pharmaceutically acceptable salt thereof, wherein the substituent R^X of R^6 is independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{cl}R^{dl})_tNR^{al}R^{bl}$, $-(CR^{cl}R^{dl})_tOR^{bl}$, $-(CR^{cl}R^{dl})_tC(O)R^{al}$, $-(CR^{cl}R^{dl})_tC(O)OR^{bl}$, $-(CR^{cl}R^{dl})_tNR^{al}C(O)R^{bl}$, $-(CR^{cl}R^{dl})_tS(O)_rR^{bl}$, $-(CR^{cl}R^{dl})_tS(O)_2OR^{bl}$, $-(CR^{cl}R^{dl})_tNR^{al}S(O)_rR^{bl}$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y .

[171] In another Embodiment [28], the invention provides a compound of Embodiment [27] or a pharmaceutically acceptable salt thereof, wherein the substituent R^X of R^6 is independently selected from C_{1-10} alkyl, C_{3-10} cycloalkyl, halogen, CN, NO_2 , $-(CR^{cl}R^{dl})_tNR^{al}R^{bl}$, $-(CR^{cl}R^{dl})_tOR^{bl}$, $-(CR^{cl}R^{dl})_tC(O)R^{al}$, $-(CR^{cl}R^{dl})_tNR^{al}C(O)R^{bl}$ and $-(CR^{cl}R^{dl})_tNR^{al}S(O)_rR^{bl}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y .

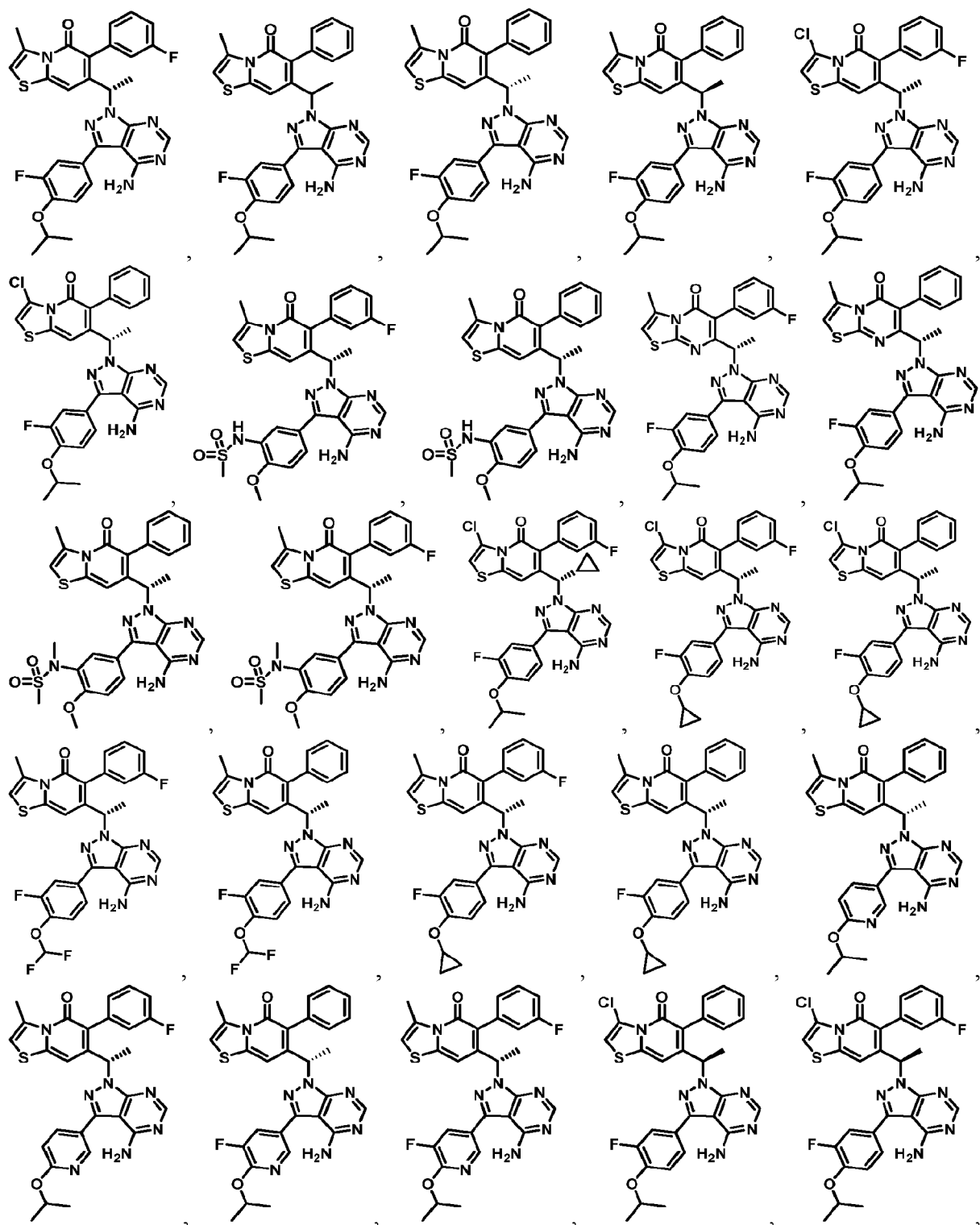
[172] In another Embodiment [29], the invention provides a compound of Embodiment [28] or a pharmaceutically acceptable salt thereof, wherein the substituent R^X of R^6 is independently selected from F, Cl, Br, methoxy, ethoxy, isopropoxy, cyclopropyloxy,

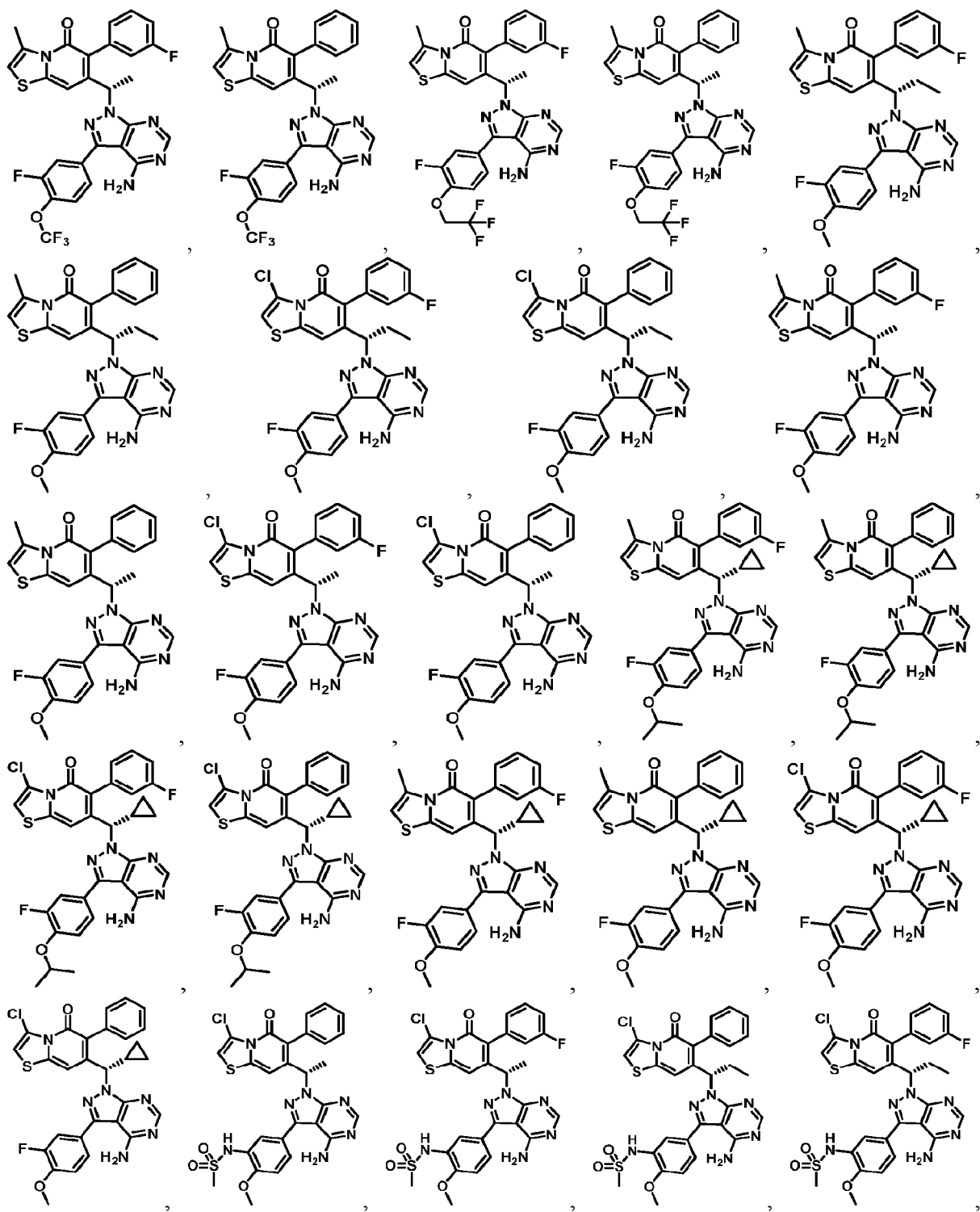


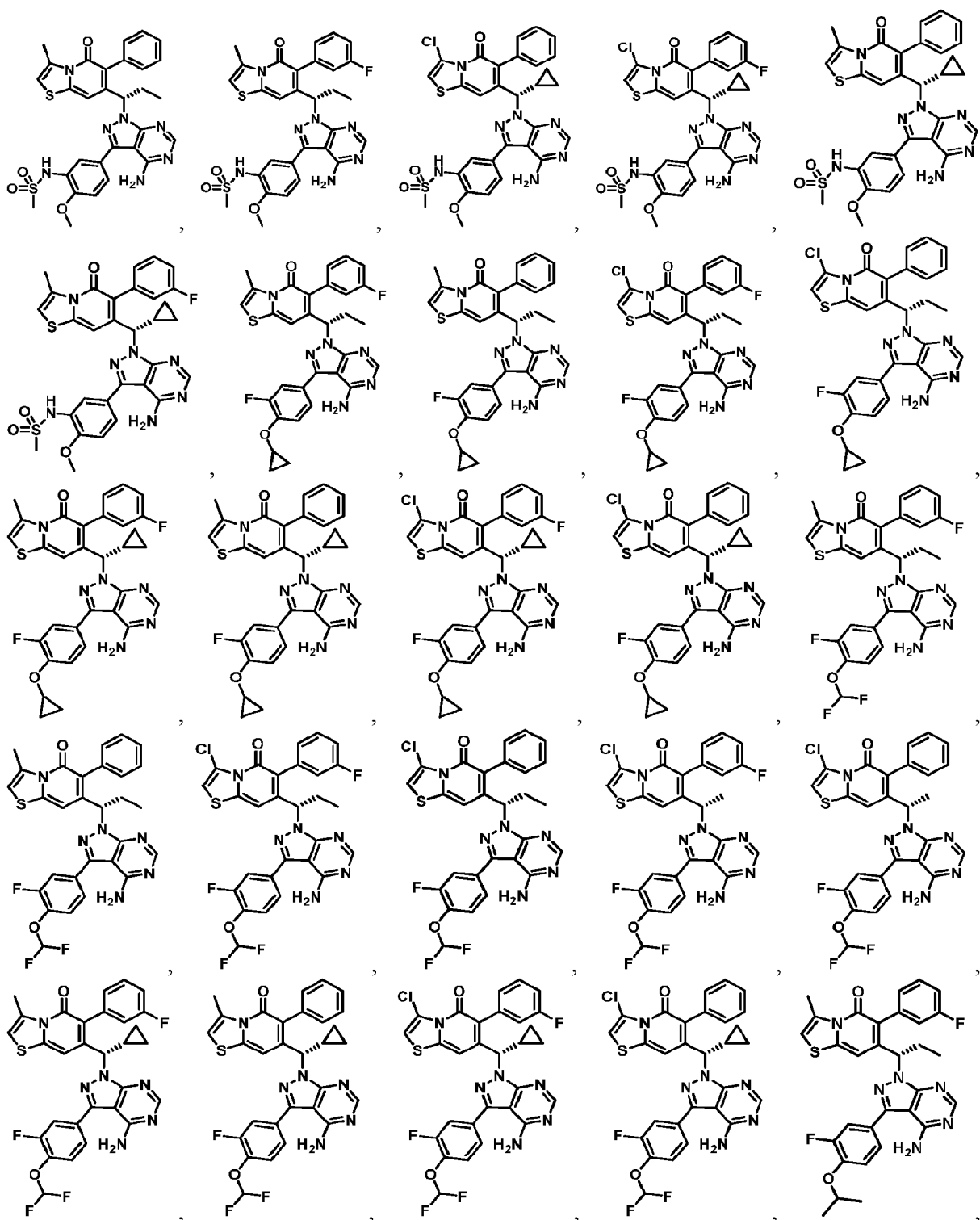
[173] In another Embodiment [30], the invention provides a compound of any one of Embodiments [1]- [29] or a pharmaceutically acceptable salt thereof, wherein R^6 is selected

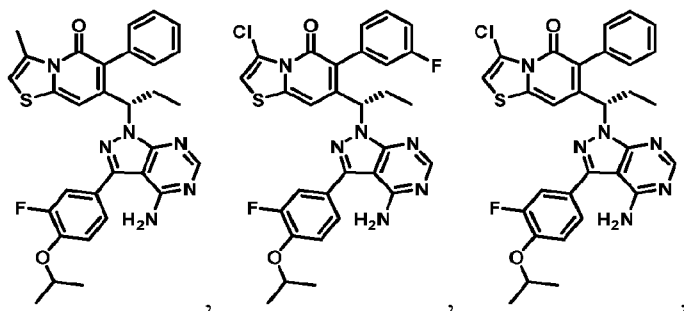


[174] In another Embodiment [31], the invention provides a compound selected from









and pharmaceutically acceptable salts thereof.

[175] In another Embodiment [32], the invention provides a pharmaceutical composition comprising a compound of any one of Embodiments [1]- [31] or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

[176] In another Embodiment [33], the invention provides a method of treating, ameliorating or preventing a condition, which responds to inhibition of PI3K, comprising administering to a subject in need of such treatment an effective amount of a compound of any one of Embodiments [1]-[31], or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent.

[177] In another Embodiment [34], the invention provides a use of a compound of any one of Embodiments [1]- [31] or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a cell-proliferative disorder.

[178] In another Embodiment [35], the invention provides a compound of Embodiment [34] or a pharmaceutically acceptable salt thereof, wherein the cell-proliferative disorder includes but not limited to lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor.

[179] In another Embodiment [36], the invention provides a compound of Embodiment [34] or a pharmaceutically acceptable salt thereof, wherein the cell-proliferative disorder is B-cell proliferative disorder.

[180] In another Embodiment [37], the invention provides a compound of Embodiment [36] or a pharmaceutically acceptable salt thereof, wherein B-cell proliferative disorder includes but not limited to, B-cell malignancies, B-cell chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, multiple sclerosis, small lymphocytic lymphoma, mantle cell lymphoma, B-cell non-Hodgkin's lymphoma, activated B-cell like diffuse large B-cell lymphoma, multiple myeloma, diffuse large B-cell lymphoma, follicular lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, and plasmacytoma.

[181] In yet another of its aspects, there is provided a kit comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof; and instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the composition is to be administered, storage information for the composition, dosing information and instructions regarding how to administer the

composition. In one particular variation, the kit comprises the compound in a multiple dose form.

[182] In still another of its aspects, there is provided an article of manufacture comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof; and packaging materials. In one variation, the packaging material comprises a container for housing the compound. In one particular variation, the container comprises a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the compound. In another variation, the article of manufacture comprises the compound in a multiple dose form.

[183] In a further of its aspects, there is provided a therapeutic method comprising administering a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

[184] In another of its aspects, there is provided a method of inhibiting a PI3K comprising contacting the PI3K with a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

[185] In yet another of its aspects, there is provided a method of inhibiting a PI3K comprising causing a compound disclosed herein, or a pharmaceutically acceptable salt thereof to be present in a subject in order to inhibit the PI3K *in vivo*.

[186] In a further of its aspects, there is provided a method of inhibiting PI3K comprising administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits the PI3K *in vivo*, the second compound being a compound according to any one of the above embodiments and variations.

[187] In another of its aspects, there is provided a method of treating a disease state for which a PI3K possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising causing a compound disclosed herein, or a pharmaceutically acceptable salt thereof to be present in a subject in a therapeutically effective amount for the disease state.

[188] In a further of its aspects, there is provided a method of treating a disease state for which a PI3K possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits the PI3K *in vivo*. It is noted that the compounds of the present invention may be the first or second compounds.

[189] In one variation of each of the above methods the disease state is selected from the group consisting of cancerous hyperproliferative disorders (e.g., brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, epidermoid, esophageal, testicular, gynecological or thyroid cancer); non-cancerous hyperproliferative disorders (e.g., benign hyperplasia of the skin (e.g., psoriasis), restenosis, and benign prostatic hypertrophy (BPH)); pancreatitis; kidney disease; pain; preventing blastocyte implantation; treating diseases related to vasculogenesis or angiogenesis (e.g., tumor angiogenesis, acute and chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer); asthma; neutrophil chemotaxis (e.g., reperfusion injury in myocardial infarction and stroke and inflammatory arthritis); septic shock; T-cell mediated diseases where immune suppression would be of value (e.g., the prevention of organ transplant rejection, graft versus host disease, lupus

erythematosus, multiple sclerosis, and rheumatoid arthritis); atherosclerosis; inhibition of keratinocyte responses to growth factor cocktails; chronic obstructive pulmonary disease (COPD) and other diseases.

[190] In another of its aspects, there is provided a method of treating a disease state for which a mutation in the *PI3K* gene contributes to the pathology and/or symptomology of the disease state including, for example, melanomas, lung cancer, colon cancer and other tumor types.

[191] In still another of its aspects, the present invention relates to the use of a compound of any of the above embodiments and variations as a medicament. In yet another of its aspects, the present invention relates to the use of a compound according to any one of the above embodiments and variations in the manufacture of a medicament for inhibiting a PI3K.

[192] In a further of its aspects, the present invention relates to the use of a compound according to any one of the above embodiments and variations in the manufacture of a medicament for treating a disease state for which a PI3K possesses activity that contributes to the pathology and/or symptomology of the disease state.

Administration and Pharmaceutical Compositions

[193] In general, compounds of the disclosure will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors known to those of ordinary skill in the art. For example, for the treatment of neoplastic diseases and immune system disorders, the required dosage will also vary depending on the mode of administration, the particular condition to be treated and the effect desired.

[194] In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.001 to about 100 mg/kg per body weight, or particularly, from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, may be in the range from about 0.5 mg to about 2000 mg, or more particularly, from about 0.5 mg to about 1000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50 mg active ingredient.

[195] Compounds of the disclosure may be administered as pharmaceutical compositions by any conventional route; for example, enterally, e.g., orally, e.g., in the form of tablets or capsules; parenterally, e.g., in the form of injectable solutions or suspensions; or topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form.

[196] Pharmaceutical compositions comprising a compound of the present disclosure in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent may be manufactured in a conventional manner by mixing, granulating, coating, dissolving or lyophilizing processes. For example, pharmaceutical compositions comprising a compound of the disclosure in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms for oral administration contain, for example, from about 0.1 mg to about 500 mg of active substance.

[197] In one embodiment, the pharmaceutical compositions are solutions of the active ingredient, including suspensions or dispersions, such as isotonic aqueous solutions. In the case of lyophilized compositions comprising the active ingredient alone or together with a carrier such as mannitol, dispersions or suspensions can be made up before use. The pharmaceutical compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. Suitable preservatives include but are not limited to antioxidants such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid. The solutions or suspensions may further comprise viscosity-increasing agents, including but not limited to, sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, gelatins, or solubilizers, e.g. Tween 80 (polyoxyethylene (20) sorbitan monooleate).

[198] Suspensions in oil may comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. Examples include but are not limited to liquid fatty acid esters that contain as the acid component a long-chained fatty acid having 8-22 carbon atoms, or in some embodiments, 12-22 carbon atoms. Suitable liquid fatty acid esters include but are not limited to lauric acid, tridecyl acid, myristic acid, pentadecyl acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid and linoleic acid, and if desired, may contain antioxidants, for example vitamin E, 3-carotene or 3,5-di-tert-butyl-hydroxytoluene. The alcohol component of these fatty acid esters may have six carbon atoms and may be monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol. Suitable alcohol components include but are not limited to methanol, ethanol, propanol, butanol or pentanol or isomers thereof; glycol and glycerol.

[199] Other suitable fatty acid esters include but are not limited ethyl-oleate, isopropyl myristate, isopropyl palmitate, LABRAFIL® M 2375, (polyoxyethylene glycerol), LABRAFIL® M 1944 CS (unsaturated polyglycolized glycerides prepared by alcoholysis of apricot kernel oil and comprising glycerides and polyethylene glycol ester), LABRASOL™ (saturated polyglycolized glycerides prepared by alcoholysis of TCM and comprising glycerides and polyethylene glycol ester; all available from GaKefosse, France), and/or MIGLYOL® 812 (triglyceride of saturated fatty acids of chain length C8 to C12 from Hüls AG, Germany), and vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil, or groundnut oil.

[200] Pharmaceutical compositions for oral administration may be obtained, for example, by combining the active ingredient with one or more solid carriers, and if desired, granulating a resulting mixture, and processing the mixture or granules by the inclusion of additional excipients, to form tablets or tablet cores.

[201] Suitable carriers include but are not limited to fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients include but are not limited to flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

[202] Tablet cores may be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arable, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions

in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

[203] Pharmaceutical compositions for oral administration may also include hard capsules comprising gelatin or soft-sealed capsules comprising gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient may be dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

[204] Pharmaceutical compositions suitable for rectal administration are, for example, suppositories comprising a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

[205] Pharmaceutical compositions suitable for parenteral administration may comprise aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents. Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions. The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

[206] The disclosure also provides for a pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a compound of the disclosure as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

Combination therapies

[207] The compounds or pharmaceutical acceptable salts of the disclosure may be administered as the sole therapy, or together with other therapeutic agent or agents.

[208] For example, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e. by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the individual is enhanced). Or, by way of example only, the benefit experienced by an individual may be increased by administering one of the compounds described herein with another therapeutic agent that also has therapeutic benefit. By way of example only, in a treatment for gout involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the individual with another therapeutic agent for gout. Or, by way of example only, if one of the side effects experienced by an individual upon receiving one of the compounds described herein is nausea, then it may be appropriate to administer an anti-nausea agent in combination with the compound. Or, the additional therapy or therapies include, but are not limited to

physiotherapy, psychotherapy, radiation therapy, application of compresses to a diseased area, rest, altered diet, and the like. Regardless of the disease, disorder or condition being treated, the overall benefit experienced by the individual may be additive of the two therapies or the individual may experience a synergistic benefit.

[209] In the instances where the compounds described herein are administered in combination with other therapeutic agents, the compounds described herein may be administered in the same pharmaceutical composition as other therapeutic agents, or because of different physical and chemical characteristics, be administered by a different route. For example, the compounds described herein may be administered orally to generate and maintain good blood levels thereof, while the other therapeutic agent may be administered intravenously. Thus the compounds described herein may be administered concurrently, sequentially or dosed separately to other therapeutic agents.

EXAMPLES

[210] Various methods may be developed for synthesizing a compound of formula (I) or a pharmaceutically acceptable salt thereof. Representative methods for synthesizing a compound of formula (I) or a pharmaceutically acceptable salt thereof are provided in the Examples. It is noted, however, that a compound of formula (I) or a pharmaceutically acceptable salt thereof may also be synthesized by other synthetic routes that others may devise.

[211] It will be readily recognized that certain compounds of formula (I) have atoms with linkages to other atoms that confer a particular stereochemistry to the compound (e.g., chiral centers). It is recognized that synthesis of a compound of formula (I) or a pharmaceutically acceptable salt thereof may result in the creation of mixtures of different stereoisomers (enantiomers, diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

[212] A compound of formula (I) can also be prepared as a pharmaceutically acceptable acid addition salt by, for example, reacting the free base form of the at least one compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of the at least one compound of formula (I) can be prepared by, for example, reacting the free acid form of the at least one compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of formula (I) are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of formula (I) can be prepared using salts of the starting materials or intermediates.

[213] The free acid or free base forms of the compounds of formula (I) can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of formula (I) in an acid addition salt form can be converted to the corresponding free base thereof by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of formula (I) in a base addition salt form can be converted to the corresponding free acid thereof by, for example, treating with a suitable acid (e.g., hydrochloric acid, etc).

[214] The N-oxides of a compound of formula (I) or a pharmaceutically acceptable salt thereof can be prepared by methods known to those of ordinary skill in the art. For example, N-oxides can be prepared by treating an unoxidized form of the compound of formula (I) with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, meta-chloroperoxybenzoic acid, or the like) in a suitable inert organic

solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0 to 80°C. Alternatively, the N-oxides of the compounds of formula (I) can be prepared from the N-oxide of an appropriate starting material.

[215] Compounds of formula (I) in an unoxidized form can be prepared from N-oxides of compounds of formula (I) by, for example, treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, and the like) in a suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, and the like) at 0 to 80°C.

[216] Protected derivatives of the compounds of formula (I) can be made by methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

[217] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. For example, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); L (liters); mL (milliliters); μ L (microliters); psi (pounds per square inch); M (molar); mM (millimolar); i.v. (intravenous); Hz (Hertz); MHz (megahertz); mol (moles); mmol (millimoles); RT (room temperature); min (minutes); h (hours); mp (melting point); TLC (thin layer chromatography); Rt (retention time); RP (reverse phase); MeOH (methanol); i-PrOH (isopropanol); TEA (triethylamine); TFA (trifluoroacetic acid); TFAA (trifluoroacetic anhydride); THF (tetrahydrofuran); DMSO (dimethyl sulfoxide); EtOAc (ethyl acetate); DME (1,2-dimethoxyethane); DCM (dichloromethane); DCE (dichloroethane); DMF (N,N-dimethylformamide); DMPU (N,N'-dimethylpropyleneurea); CDI (1,1-carbonyldiimidazole); IBCF (isobutyl chloroformate); HOAc (acetic acid); HOSu (N-hydroxysuccinimide); HOBt (1-hydroxybenzotriazole); Et₂O (diethyl ether); EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride); BOC (tert-butyloxycarbonyl); Fmoc (9-fluorenylmethoxycarbonyl); DCC (dicyclohexylcarbodiimide); CBZ (benzyloxycarbonyl); Ac (acetyl); atm (atmosphere); TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl); TIPS (triisopropylsilyl); TBS (t-butyldimethylsilyl); DMAP (4-dimethylaminopyridine); Me (methyl); OMe (methoxy); Et (ethyl); tBu (tert-butyl); HPLC (high pressure liquid chromatography); BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride); TBAF (tetra-n-butylammonium fluoride); m-CPBA (meta-chloroperbenzoic acid).

For example, the following abbreviations in table 1 may be used in the examples and throughout the specification.

[218] References to ether or Et₂O are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions were conducted under an inert atmosphere at RT unless otherwise noted.

[219] ¹H NMR spectra were recorded on a Varian Mercury Plus 400. Chemical shifts are expressed in parts per million (ppm). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad).

[220] Low-resolution mass spectra (MS) and compound purity data were acquired on a Shimadzu LC/MS single quadrupole system equipped with electrospray ionization (ESI) source, UV detector (220 and 254 nm), and evaporative light scattering detector (ELSD). Thin-layer chromatography was performed on 0.25 mm Superchemgroup silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid, ninhydrin, or p-anisaldehyde solution. Flash column chromatography was performed on silica gel (200-300 mesh, Branch of Qingdao Haiyang Chemical Co., Ltd).

Synthetic Schemes

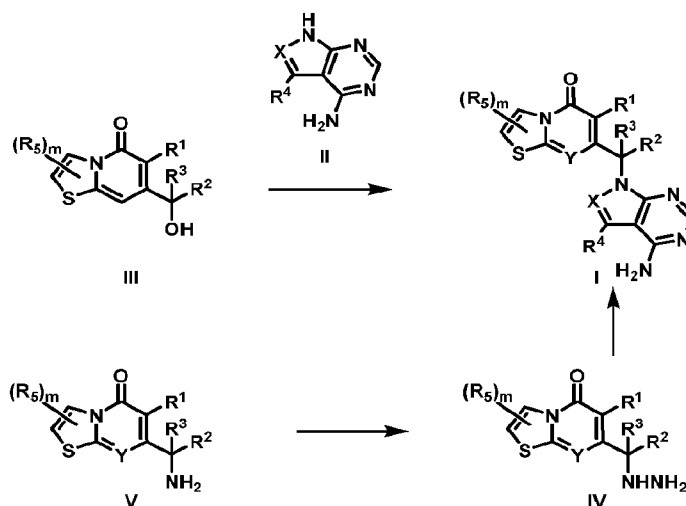
[221] A compound of formula I and/or a pharmaceutically acceptable salt thereof may be synthesized according to a variety of reaction schemes. Some illustrative schemes are provided below and in the examples. Other reaction schemes could be readily devised by those skilled in the art in view of the present disclosure.

[222] In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxyl, amino, imino, thio or carboxyl groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991

[223] Synthetic methods for preparing the compounds of the present invention are illustrated in the following Schemes and Examples. Starting materials are commercially available or may be made according to procedures known in the art or as illustrated herein.

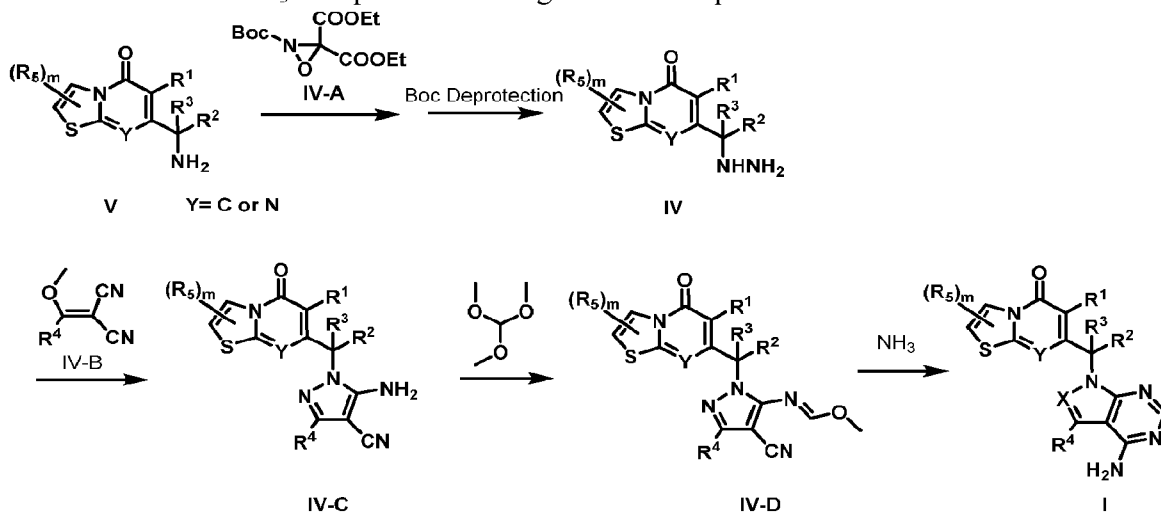
[224] The intermediates shown in the following schemes are either known in the literature or may be prepared by a variety of methods familiar to those skilled in the art.

[225] As an illustration, two synthetic approaches of compounds of formula I of the present disclosure are shown in Scheme 1. As show in the scheme, the compounds of formula I can be disassembled into intermediates III or V, which are either commercially available or known in the literature. Amination of the amino group of intermediates of formula V and subsequent necessary derivatization reaction gives compounds of formula IV which can be further converted to compounds of formula I via a sequence of cyclization, condensation and cyclization. Alternatively, compounds of formula I can be obtained through the coupling of intermediates of formula III with intermediates of formula II using Mitsunobu reaction known in the literature.



Scheme 1

[226] As a further illustration of the preparation of compounds of formula I, one of the synthetic approach of the compounds of formula I is outlined in Scheme 2. As shown in the scheme, starting from amine V, which is either commercially available or known in the literature, Compounds of formula IV can be prepared through conversion of the amino group of intermediates of formula V into a hydrazine group. Reaction of hydrazine IV with intermediates IV-B in the presence of such a base as TEA leads to compounds of formula IV-C which can be further transformed to compounds of formula IV-D through condensation reaction with such a reagent as trimethoxymethane. Ensuing cyclization of compounds of formula IV-D with NH₃ in a protic solvent gives the compounds of formula I.

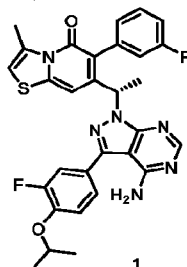


Scheme 2

[227] In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

Example 1

[228] (S)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one (1)



[229] 4-Methylthiazole-2-carbaldehyde (1a)

[230] 4-Methylthiazole-2-carbaldehyde (**1a**) was prepared according to the method described in *WO201113875*.

[231] Dimethyl 2-(diethoxyphosphoryl)succinate (1b)

[232] Dimethyl 2-(diethoxyphosphoryl)succinate (**1b**) was prepared according to the method described in *Eur. J. Med. Chem.* 2010, 45: 4403.

[233] Dimethyl 2-((4-methylthiazol-2-yl)methylene)succinate (1c)

[234] To a solution of dimethyl 2-(diethoxyphosphoryl)succinate (**1b**) (0.56 g, 2.0 mmol) in THF (10 mL) was added NaH (60%, 0.092 g, 2.4 mmol) at 0°C, and the mixture was stirred at 0-5°C for 1 h. A solution of 4-methylthiazole-2-carbaldehyde (**1a**) (0.25 g, 2.0 mmol) in THF (2 mL) was added. The mixture was stirred at r.t. for 3 h. The reaction was quenched by saturated NH₄Cl aqueous solution (20 mL) and extracted with EtOAc (2 × 30 mL). The extracts were washed with saturated brine (30 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel eluting with PE / EtOAc (10:1) to give the title compound dimethyl 2-((4-methylthiazol-2-yl)methylene)succinate (**1c**). MS-ESI (m/z): 256 [M + 1]⁺.

[235] Methyl 3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylate (1d)

[236] A mixture of dimethyl 2-((4-methylthiazol-2-yl)methylene)succinate (**1c**) (3.77 g, 14.7 mmol) and PPA (50.0 g) was stirred at 80°C overnight. The reaction mixture was poured into 250 g ice and adjusted with Na₂CO₃ to pH = 9~10. The mixture was extracted with DCM (3 × 100 mL). The extracts were washed with saturated brine (100 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel eluting with PE / EtOAc (10:1~2:1) to give the title compound methyl 3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylate (**1d**). MS-ESI (m/z): 224 [M + 1]⁺.

[237] Methyl 6-iodo-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylate (1e)

[238] To a solution of methyl 3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylate (**1d**) (1.5 g, 6.7 mmol) in DCM (50 mL) was added NIS (0.9 g, 4 mmol). The mixture was stirred at r.t. for 3 h. Another portion of NIS (0.9 g, 4 mmol) was added and stirred at r.t. for 3 h. Then the final portion of NIS (0.2 g, 0.88 mmol) was added. The mixture was stirred at r.t. for another 1 h and diluted with DCM (50 mL), washed with saturated Na₂S₂O₃ aqueous solution (50 mL), saturated NaHCO₃ aqueous solution (50 mL) and saturated brine (50 mL), dried over Na₂SO₄ and concentrated. the residue was purified by column chromatography on silica gel eluting with PE/EtOAc (10:1~5:1) to give title compound methyl 6-iodo-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylate (**1e**). MS-ESI (m/z): 350 [M + 1]⁺.

[239] Methyl 6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylate (1f)

[240] A mixture of methyl 6-iodo-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylate (**1e**) (1.0 g, 3.0 mmol), commercial available (4-fluorophenyl)boronic acid (0.93 g, 6.0 mmol) and Cs₂CO₃ (2.6 g, 10 mmol) in dioxane (15 mL) was degassed, and Pd(PPh₃)₂Cl₂ (0.24 g, 0.3 mmol) was added, and then degassed again. The mixture was stirred at 85°C for 5 h under N₂ atmosphere. The mixture was cooled to r.t. and concentrated. The residue was purified by column chromatography on silica gel eluting with PE/EtOAc (10:1~4:1) to give the title compound methyl 6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylate (**1f**). MS-ESI (m/z): 318 [M + 1]⁺.

[241] 6-(3-Fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylic acid (1g)

[242] To a mixture of methyl 6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylate (**1f**) (1.6 g, 5.0 mmol) in THF (16 mL) and H₂O (16 mL) was added LiOH·H₂O (0.64 g, 15 mmol) at r.t.. The mixture was stirred for 7 h at r.t.. The reaction mixture was poured into 25 g ice and adjusted with 1 N HCl to pH = 2. The mixture was extracted with EA (3 × 100 mL). The extracts were washed with saturated brine (100 mL), dried over Na₂SO₄ and concentrated to give 6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylic acid (**1g**). MS-ESI (m/z): 304 [M + 1]⁺.

[243] 6-(3-Fluorophenyl)-N-methoxy-N,3-dimethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxamide (1h)

[244] A mixture of 6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxylic acid (**1g**) (1.0 g, 3.3 mmol), *N,O*-dimethylhydroxylamine hydrochloride (0.5 g, 4.9 mmol), EDCI (1.3 g, 6.6 mmol), HOBt (0.9 g, 6.6 mmol) and DIPEA (1.7 g, 13 mmol) in DMF (15 mL) was stirred at r.t. for 12 h, diluted with water (50 mL), and extracted with EA (50 mL × 2). The organic phase was washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄, and concentrated to give 6-(3-fluorophenyl)-*N*-methoxy-*N*,3-dimethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxamide (**1h**). MS-ESI (m/z): 347 [M + 1]⁺.

[245] 7-Acetyl-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one (1i)

[246] To a solution of 6-(3-fluorophenyl)-*N*-methoxy-*N*,3-dimethyl-5-oxo-5H-thiazolo[3,2-a]pyridine-7-carboxamide (**1h**) (0.5 g, 1.5 mmol) in THF (11 mL) was added MeMgBr (0.7 mL, 2.0 mmol) at 0°C. The mixture was warmed to r.t. slowly and stirred at r.t. for 1 h. The reaction was quenched by saturated NH₄Cl aqueous solution (15 mL) at 0°C and extracted by EtOAc (2 × 50 mL). The extracts were washed with brine (50 mL), dried over Na₂SO₄, and evaporated. The residue was purified by column chromatography on silica gel eluting with PE/EtOAc (4/1 ~ 3/1) to give title compound 7-acetyl-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one (**1i**). MS-ESI (m/z): 302 [M + 1]⁺.

[247] (S)-6-(3-fluorophenyl)-7-(1-hydroxyethyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one (1j)

[248] To a solution of 7-acetyl-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one (**1i**) (0.17 g, 0.56 mmol) in THF (5 mL) was added (*S*)-CBS (0.56 mL, 0.56 mmol) at -20°C. Then BH₃·Me₂S was added dropwise to the mixture at -20°C. The mixture was warmed to r.t. slowly and stirred at r.t. for 12 h. The reaction was quenched by MeOH (3 mL) at 0°C, poured into saturated NaHCO₃ aqueous solution (15 mL) and extracted with EtOAc (2 × 50 mL). The extracts were washed with brine (50 mL), dried over Na₂SO₄, and evaporated. The residue was purified by column chromatography on silica gel eluting with

PE/EtOAc (5/1 ~ 1/1) to give title compound (*S*)-6-(3-fluorophenyl)-7-(1-hydroxyethyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**1j**). MS-ESI (*m/z*): 304 [*M* + 1]⁺.

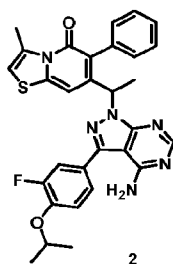
[249] *(S)*-7-(1-(4-Amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (1)

[250] A mixture of (*S*)-6-(3-fluorophenyl)-7-(1-hydroxyethyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**1j**) (20 mg, 0.066 mmol), 3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (prepared according to the method described in WO2012151525.) (19 mg, 0.066 mmol) and PPh₃ (35 mg, 0.13 mmol) in toluene (2 mL) was stirred at 50°C for 0.5 h, and then DIAD (27 mg, 0.13 mmol) was added. It was stirred at 50°C for 2 h, diluted with water (50 mL), and extracted with EA (50 mL × 2). The extracts were washed with brine (50 mL), dried over Na₂SO₄, and evaporated. The residue was purified by column chromatography on silica gel eluting with PE/EtOAc (2/3) to give the title compound

(*S*)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**1**). MS-ESI (*m/z*): 573 [*M* + 1]⁺.

Example 2

[251] *7*-(1-(4-Amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (2)



[252] *7*-acetyl-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (2a)

[253] The title compound 7-acetyl-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**2a**) was prepared according to the synthetic method of **1i** by replacing (4-fluorophenyl)boronic acid with phenylboronic acid. MS-ESI (*m/z*): 284 [*M* + 1]⁺.

[254] *7*-(1-hydroxyethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (2b)

[255] To a solution of 7-acetyl-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**2a**) (0.11 g, 0.38 mmol) in THF/MeOH (2.5 / 0.5 mL) was added NaBH₄ (24 mg, 1.19 mmol). The mixture was warmed to r.t. slowly and stirred at r.t. for overnight. The mixture was concentrated and diluted with EtOAc. The mixture was adjusted with 1 N HCl to pH = 7 ~ 8, the aqueous phase was extracted with EtOAc. The extracts were washed with brine, dried over Na₂SO₄, and concentrated to give 7-(1-hydroxyethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**2b**). MS-ESI (*m/z*): 286 [*M* + 1]⁺.

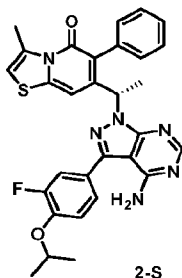
[256] *7*-(1-(4-Amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (2)

[257] The title compound 7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**2**) was prepared according to the synthetic method of **1** by replacing (*S*)-6-(3-fluorophenyl)-

7-(1-hydroxyethyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**1j**) with 7-(1-hydroxyethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**2b**). MS-ESI (*m/z*): 555 [*M* + 1]⁺.

Example 2-S

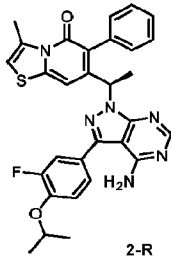
[258] (*S*)-7-(1-(4-Amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (2-S)



[259] The title compound (*S*)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**2-S**) was prepared according to the synthetic method of **1** by replacing (4-fluorophenyl)boronic acid with phenylboronic acid. MS-ESI (*m/z*): 555 [*M* + 1]⁺.

Example 2-R

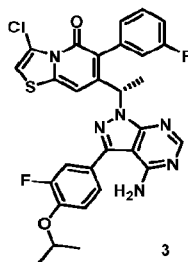
[260] (*R*)-7-(1-(4-Amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (2-R)



[261] The title compound (*R*)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**2-R**) was prepared according to the synthetic method of **1** by replacing (4-fluorophenyl)boronic acid and (*S*)-CBS with phenylboronic acid and (*R*)-CBS. MS-ESI (*m/z*): 555 [*M* + 1]⁺.

Example 3

[262] (*S*)-7-(1-(4-Amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5*H*-thiazolo[3,2-*a*]pyridin-5-one (3)



[263] (4-Chlorothiazol-2-yl)methanol (3a)

[264] (4-Chlorothiazol-2-yl)methanol (**3a**) was prepared according to the method described in WO2013149362.

[265] 4-Chlorothiazole-2-carbaldehyde (3b)

[266] To a solution of (4-chlorothiazol-2-yl)methanol (**3a**) (1.93 g, 12.95 mmol) in DCM (20 mL) was added DMP (6.04 g, 14.25 mol) at 0-5°C, stirred for 2-4 h at the same temperature. The mixture was diluted with DCM (50 mL), washed with saturated NaHCO₃ aqueous solution (50 mL), dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on silica gel eluting with PE/EtOAc (20:1) to give 4-chlorothiazole-2-carbaldehyde (**3b**). MS-ESI (m/z): 148, 150 [M + 1]⁺

[267] 7-Acetyl-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one (3c)

[268] The title compound 7-acetyl-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one (**3c**) was prepared according to the synthetic method of **1i** by replacing 4-methylthiazole-2-carbaldehyde (**1a**) with 4-chlorothiazole-2-carbaldehyde (**3b**). MS-ESI (m/z): 322 [M + 1]⁺.

[269] (S)-3-Chloro-6-(3-fluorophenyl)-7-(1-hydroxyethyl)-5H-thiazolo[3,2-a]pyridin-5-one (3d)

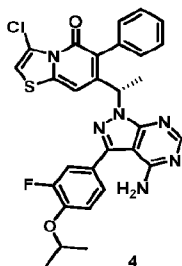
[270] To a solution of 7-acetyl-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one (**3c**) (0.06 g, 0.18 mmol) in THF (10 mL) was added (+)-Dip-Cl (2.2 mL, 3.7 mmol) at -20°C. The mixture was warmed to r.t. slowly and stirred at r.t. for 12 h. The reaction was quenched by MeOH (3 mL) at 0°C, poured into saturated NaHCO₃ aqueous solution (15 mL) and extracted by EtOAc (2 × 50 mL). The extracts were washed with brine (50 mL), dried over Na₂SO₄, and evaporated. The residue was purified by column chromatography on silica gel eluting with PE/EtOAc (2/1) to give title compound (S)-3-chloro-6-(3-fluorophenyl)-7-(1-hydroxyethyl)-5H-thiazolo[3,2-a]pyridin-5-one (**3d**). MS-ESI (m/z): 324 [M + 1]⁺.

[271] (S)-7-(1-(4-Amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one (3)

[272] The title compound (S)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one (**3**) was prepared according to the synthetic method of **1** by replacing 6-(3-fluorophenyl)-7-(1-hydroxyethyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one (**1g**) with 3-chloro-6-(3-fluorophenyl)-7-(1-hydroxyethyl)-5H-thiazolo[3,2-a]pyridin-5-one (**3d**). MS-ESI (m/z): 593 [M + 1]⁺.

Example 4

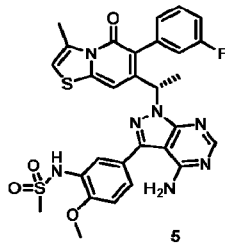
[273] (S)-7-(1-(4-Amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one (4)



[274] The title compound (*S*)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-chloro-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**4**) was prepared according to the synthetic method of **3** by replacing (4-fluorophenyl)boronic acid with phenylboronic acid. MS-ESI (*m/z*): 575 [*M* + 1]⁺.

Example 5

[275] (*S*)-*N*-(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridin-7-yl)ethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide (**5**)



[276] (*S*)-1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridin-7-yl)ethyl methanesulfonate (**5a**)

[277] A mixture of (*S*)-6-(3-fluorophenyl)-7-(1-hydroxyethyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**1j**) (0.03 g, 0.1 mmol), MsCl (0.017 g, 0.15 mmol), TEA (0.031 g, 0.3 mmol) in DCM (2 mL) was stirred at 0°C for 0.5 h. The reaction was quenched by ice water (10 mL) and extracted by DCM (20 mL), the DCM phase was washed with brine (20 mL), dried over Na₂SO₄, and evaporated. The residue was used directly for next step. MS-ESI (*m/z*): 382 [*M* + 1]⁺.

[278] (*S*)-7-(1-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**5b**)

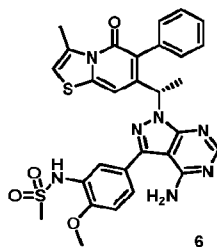
[279] A mixture of (*S*)-1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridin-7-yl)ethyl methanesulfonate (**5a**) (0.038 g, 0.1 mmol), 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (prepared according to the method described in WO2012151525.) (0.052 g, 0.2 mmol), K₂CO₃ (0.034g, 0.25 mmol) in DMF (2 mL) was stirred at 50°C for 12 h. The reaction was quenched by water (20 mL) and extracted by EtOAc (20 mL). The EtOAc phase was washed with brine (20 mL), dried over Na₂SO₄, and evaporated. The residue was purified by PTLC EtOAc/PE (3:1) to give (*S*)-7-(1-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**5b**). MS-ESI (*m/z*): 547 [*M* + 1]⁺.

[280] (*S*)-*N*-(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridin-7-yl)ethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide (**5**)

[281] A mixture of (*S*)-7-(1-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**5b**) (0.028g, 0.05 mmol), *N*-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-methanesulfonamide (prepared according to the method described in *WO2015198289*.) (0.032 g, 0.1 mmol), Na₂CO₃ (0.016g, 0.15 mmol) and Pd(PPh₃)₄ (0.020 g, 0.017 mmol) in DMF (2 mL) was stirred at 90°C for 2 h. The reaction was quenched by water (20 mL) and extracted by EtOAc (20 mL), the EtOAc phase was washed with brine (20 mL), dried over Na₂SO₄, and evaporated. The residue was purified by PTLC DCM/MeOH (20:1) to give (*S*)-*N*-(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyridin-7-yl)ethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide (**5**). MS-ESI (*m/z*): 620 [*M* + 1]⁺.

Example 6

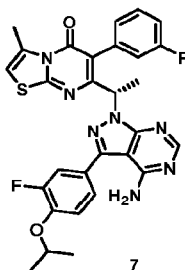
[282] (*S*)-*N*-(5-(4-amino-1-(1-(3-methyl-5-oxo-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-7-yl)ethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide (**6**)



[283] The title compound (*S*)-*N*-(5-(4-amino-1-(1-(3-methyl-5-oxo-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-7-yl)ethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide (**6**) was prepared according to the synthetic method of **5** by replacing 7-(1-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one (**5b**) with 7-(1-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5*H*-thiazolo[3,2-*a*]pyridin-5-one. MS-ESI (*m/z*): 602 [*M* + 1]⁺.

Example 7

[284] (*S*)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**7**)



[285] (*S*)-7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**7a**)

[286] The title compound (*S*)-7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**7a**) was prepared according to the method described in *WO2012125629*. MS-ESI (*m/z*): 304 [*M* + 1]⁺.

[287] (S)-tert-butyl 2-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)hydrazinecarboxylate (7b)

[288] To a solution of (S)-7-(1-aminoethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (**7a**) (340 mg, 1.12 mmol) in THF (5 mL) and sat. aq. NaHCO₃ (5 mL) was added 2-(tert-butyl) 3,3-diethyl 1,2-oxaziridine-2,3,3-tricarboxylate (324 mg, 1.12 mmol) at RT. The mixture was stirred at RT for 1 h. The reaction mixture was diluted with water, extracted with EtOAc. The extracts were dried over Na₂SO₄ and concentrated to give the title compound (S)-tert-butyl 2-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)hydrazinecarboxylate (**7b**). MS-ESI (m/z): 419 [M + 1]⁺.

[289] (S)-6-(3-fluorophenyl)-7-(1-hydrazinylethyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (7c)

[290] To a solution of (S)-tert-butyl 2-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)-hydrazinecarboxylate (**7b**) (400 mg, 0.95 mmol) in DCM (10 mL) and anisole (5 mL) was added TFA (5 mL). The mixture was stirred at RT for 2 h. The solvent was removed in vacuo. The residue was diluted with MTBE and water, the aqueous layer was separated and adjusted to pH 9 ~ 10 with solid Na₂CO₃. Extracted with DCM, the extracts were dried over Na₂SO₄ and concentrated to give the title compound (S)-6-(3-fluorophenyl)-7-(1-hydrazinylethyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (**7c**). MS-ESI (m/z): 319 [M + 1]⁺.

[291] (S)-5-amino-3-(3-fluoro-4-isopropoxyphenyl)-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)-1H-pyrazole-4-carbonitrile (7d)

[292] To a solution of (S)-6-(3-fluorophenyl)-7-(1-hydrazinylethyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (**7c**) (83 mg, 0.26 mmol) in anhydrous EtOH (5 mL) was added Et₃N (0.18 mL, 1.29 mmol) and 2-((3-fluoro-4-isopropoxyphenyl)(methoxy)methylene)malononitrile (70 mg, 0.27 mmol), the mixture was stirred at RT for 2 h and then heated to reflux for 1 h. The mixture was concentrated. The residue was purified by column chromatography on silica gel eluting with DCM/EtOAc (10:0 ~ 10:1) to give the title compound (S)-5-amino-3-(3-fluoro-4-isopropoxyphenyl)-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)-1H-pyrazole-4-carbonitrile (**7d**). MS-ESI (m/z): 547 [M + 1]⁺.

[293] (S)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (7)

[294] To a solvent of thrimethyl orthoformate (10 mL) was added (S)-5-amino-3-(3-fluoro-4-isopropoxyphenyl)-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)-1H-pyrazole-4-carbonitrile (**7d**) (100 mg, 0.18 mmol), the mixture was heated to reflux for 48 h. The mixture was cooled to RT and concentrated. The residue was added NH₃ in MeOH (7.0 N, 5 mL) and stirred at RT for 1 h, then stirred at 60°C for another 3 h. The mixture was diluted with water and extracted with DCM. The extracts were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel eluting with DCM/EtOAc (10:1 ~ 3:1) to give the title compound (S)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one (**7**). MS-ESI (m/z): 574 [M + 1]⁺.

[295] Following essentially the same procedures described for **Examples 1-7**, **Examples 8-115** listed in Table 1 were prepared from the appropriate starting materials which are commercially available or known in the literature. The structures and names of **Examples 8-115** are given in Table 1.

Table 1

Example	Structure	Name	DATA
8		(S)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyrimidin-5-one	MS-ESI (m/z): 556 [M + 1] ⁺
9		(S)-N-(5-(4-amino-1-(1-(3-methyl-5-oxo-6-phenyl-5H-thiazolo[3,2-a]pyridin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-N-methylmethanesulfonamide	MS-ESI (m/z): 616 [M + 1] ⁺
10		(S)-N-(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)-N-methylmethanesulfonamide	MS-ESI (m/z): 634 [M + 1] ⁺
11		(S)-7-((4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z): 619 [M + 1] ⁺
12		(S)-7-(1-(4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z): 591 [M + 1] ⁺

Example	Structure	Name	DATA
13		(S)-7-(1-(4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):573 [M + 1] ⁺
14		(S)-7-(1-(4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):581 [M + 1] ⁺
15		(S)-7-(1-(4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):563 [M + 1] ⁺
16		(S)-7-(1-(4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):571 [M + 1] ⁺
17		(S)-7-(1-(4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):553 [M + 1] ⁺
18		(S)-7-(1-(4-amino-3-(6-isopropoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):538 [M + 1] ⁺

Example	Structure	Name	DATA
19		(S)-7-(1-(4-amino-3-(6-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):556 [M + 1] ⁺
20		(S)-7-(1-(4-amino-3-(5-fluoro-6-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):556 [M + 1] ⁺
21		(S)-7-(1-(4-amino-3-(5-fluoro-6-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):574 [M + 1] ⁺
22		(R)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):575 [M + 1] ⁺
23		(R)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):593 [M + 1] ⁺

Example	Structure	Name	DATA
24		(S)-7-(1-(4-amino-3-(3-fluoro-4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):599 [M + 1] ⁺
25		(S)-7-(1-(4-amino-3-(3-fluoro-4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):581 [M + 1] ⁺
26		(S)-7-(1-(4-amino-3-(3-fluoro-4-(2,2,2-trifluoroethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):613 [M + 1] ⁺
27		(S)-7-(1-(4-amino-3-(3-fluoro-4-(2,2,2-trifluoroethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):595 [M + 1] ⁺
28		(S)-7-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):559 [M + 1] ⁺
29		(S)-7-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):541 [M + 1] ⁺

Example	Structure	Name	DATA
30		(<i>S</i>)-7-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)propyl)-3-chloro-6-(3-fluorophenyl)-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):579 [<i>M</i> + 1] ⁺
31		(<i>S</i>)-7-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)propyl)-3-chloro-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):561 [<i>M</i> + 1] ⁺
32		(<i>S</i>)-7-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):545 [<i>M</i> + 1] ⁺
33		(<i>S</i>)-7-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):527 [<i>M</i> + 1] ⁺
34		(<i>S</i>)-7-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):565 [<i>M</i> + 1] ⁺
35		(<i>S</i>)-7-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-3-chloro-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):547 [<i>M</i> + 1] ⁺

Example	Structure	Name	DATA
36		(S)-7-((4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):599 [M + 1] ⁺
37		(S)-7-((4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):581 [M + 1] ⁺
38		(S)-7-((4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):619 [M + 1] ⁺
39		(S)-7-((4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):601 [M + 1] ⁺
40		(S)-7-((4-amino-3-(3-fluoro-4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):571 [M + 1] ⁺
41		(S)-7-((4-amino-3-(3-fluoro-4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):553 [M + 1] ⁺

Example	Structure	Name	DATA
42		(<i>S</i>)-7-((4-amino-3-(3-fluoro-4-methoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)(cyclopropyl)methyl)-3-chloro-6-(3-fluorophenyl)-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):591 [<i>M</i> + 1] ⁺
43		(<i>S</i>)-7-((4-amino-3-(3-fluoro-4-methoxyphenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)(cyclopropyl)methyl)-3-chloro-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):573 [<i>M</i> + 1] ⁺
44		(<i>S</i>)- <i>N</i> -(5-(4-amino-1-(1-(3-chloro-5-oxo-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (<i>m/z</i>):622 [<i>M</i> + 1] ⁺
45		(<i>S</i>)- <i>N</i> -(5-(4-amino-1-(1-(3-chloro-6-(3-fluorophenyl)-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (<i>m/z</i>):640 [<i>M</i> + 1] ⁺
46		(<i>S</i>)- <i>N</i> -(5-(4-amino-1-(1-(3-chloro-5-oxo-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)propyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (<i>m/z</i>):636 [<i>M</i> + 1] ⁺
47		(<i>S</i>)- <i>N</i> -(5-(4-amino-1-(1-(3-chloro-6-(3-fluorophenyl)-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)propyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (<i>m/z</i>):654 [<i>M</i> + 1] ⁺

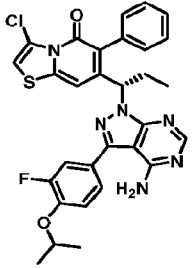
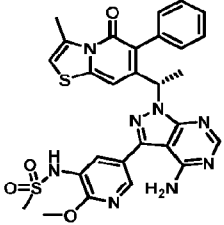
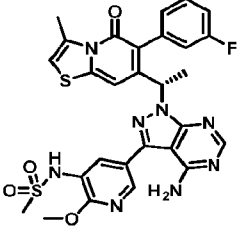
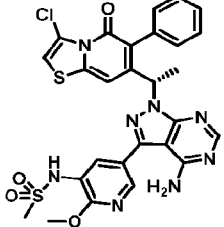
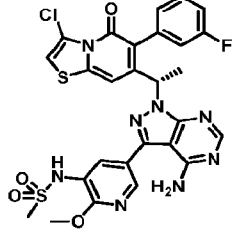
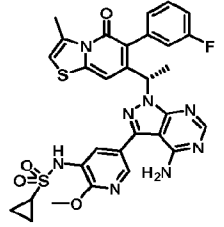
Example	Structure	Name	DATA
48		(S)-N-(5-(4-amino-1-(1-(3-methyl-5-oxo-6-phenyl-5H-thiazolo[3,2-a]pyridin-7-yl)propyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (m/z):616 [M + 1] ⁺
49		(S)-N-(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridin-7-yl)propyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (m/z):634 [M + 1] ⁺
50		(S)-N-(5-(4-amino-1-(1-(3-chloro-5-oxo-6-phenyl-5H-thiazolo[3,2-a]pyridin-7-yl)(cyclopropyl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (m/z):648 [M + 1] ⁺
51		(S)-N-(5-(4-amino-1-(1-(3-chloro-6-(3-fluorophenyl)-5-oxo-5H-thiazolo[3,2-a]pyridin-7-yl)(cyclopropyl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (m/z):666 [M + 1] ⁺
52		(S)-N-(5-(4-amino-1-(1-(cyclopropyl(3-methyl-5-oxo-6-phenyl-5H-thiazolo[3,2-a]pyridin-7-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (m/z):628 [M + 1] ⁺
53		(S)-N-(5-(4-amino-1-(1-(cyclopropyl(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridin-7-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (m/z):646 [M + 1] ⁺

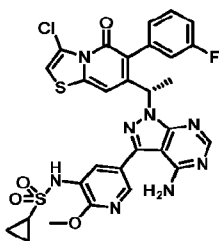
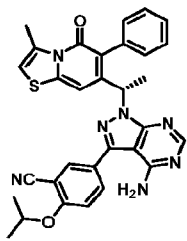
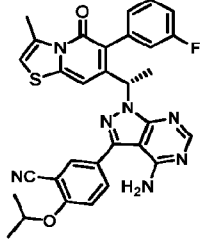
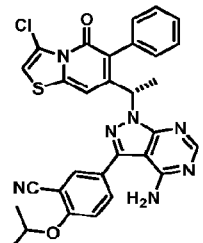
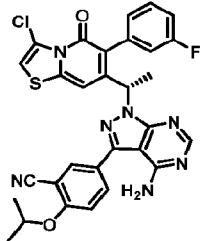
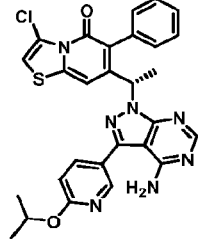
Example	Structure	Name	DATA
54		(S)-7-(1-(4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):585 [M + 1] ⁺
55		(S)-7-(1-(4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):567 [M + 1] ⁺
56		(S)-7-(1-(4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):605 [M + 1] ⁺
57		(S)-7-(1-(4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):587 [M + 1] ⁺
58		(S)-7-((4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):597 [M + 1] ⁺

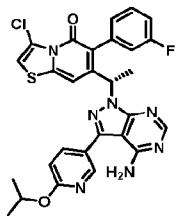
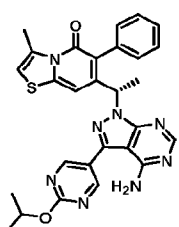
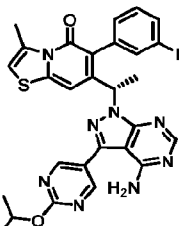
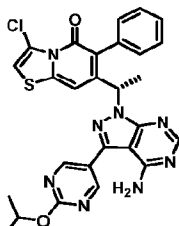
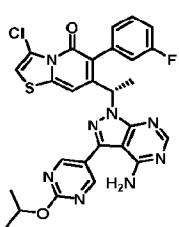
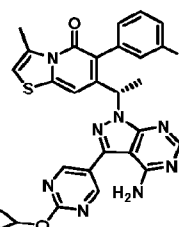
Example	Structure	Name	DATA
59		(S)-7-((4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):579 [M + 1] ⁺
60		(S)-7-((4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):617 [M + 1] ⁺
61		(S)-7-((4-amino-3-(4-cyclopropoxy-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):599 [M + 1] ⁺
62		(S)-7-(1-(4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):595 [M + 1] ⁺
63		(S)-7-(1-(4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):577 [M + 1] ⁺

Example	Structure	Name	DATA
64		(S)-7-(1-(4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):615 [M + 1] ⁺
65		(S)-7-(1-(4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):597 [M + 1] ⁺
66		(S)-7-(1-(4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):601 [M + 1] ⁺
67		(S)-7-(1-(4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):583 [M + 1] ⁺
68		(S)-7-((4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):607 [M + 1] ⁺

Example	Structure	Name	DATA
69		(S)-7-((4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):589 [M + 1] ⁺
70		(S)-7-((4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):627 [M + 1] ⁺
71		(S)-7-((4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)(cyclopropyl)methyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):609 [M + 1] ⁺
72		(S)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z): 587 [M + 1] ⁺
73		(S)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):569 [M + 1] ⁺
74		(S)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):607 [M + 1] ⁺

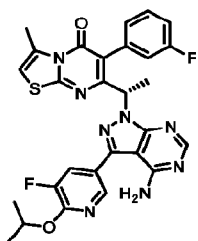
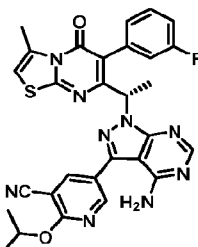
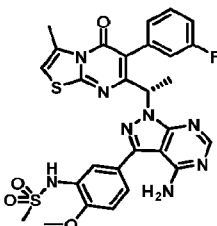
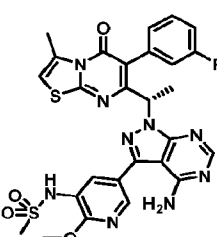
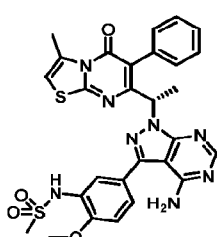
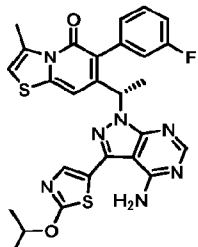
Example	Structure	Name	DATA
75		(S)-7-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):589 [M + 1] ⁺
76		(S)-N-(5-(4-amino-1-(1-(3-methyl-5-oxo-6-phenyl-5H-thiazolo[3,2-a]pyridin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxypyridin-3-yl)methanesulfonamide	MS-ESI (m/z):603 [M + 1] ⁺
77		(S)-N-(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxypyridin-3-yl)methanesulfonamide	MS-ESI (m/z):621 [M + 1] ⁺
78		(S)-N-(5-(4-amino-1-(1-(3-chloro-5-oxo-6-phenyl-5H-thiazolo[3,2-a]pyridin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxypyridin-3-yl)methanesulfonamide	MS-ESI (m/z):623 [M + 1] ⁺
79		(S)-N-(5-(4-amino-1-(1-(3-chloro-6-(3-fluorophenyl)-5-oxo-5H-thiazolo[3,2-a]pyridin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxypyridin-3-yl)methanesulfonamide	MS-ESI (m/z):641 [M + 1] ⁺
80		(S)-N-(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyridin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide	MS-ESI (m/z):647 [M + 1] ⁺

Example	Structure	Name	DATA
81		(<i>S</i>)- <i>N</i> -(5-(4-amino-1-(1-(3-chloro-6-(3-fluorophenyl)-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-methoxypyridin-3-yl)cyclopropanesulfonamide	MS-ESI (<i>m/z</i>):667 [<i>M</i> + 1] ⁺
82		(<i>S</i>)-5-(4-amino-1-(1-(3-methyl-5-oxo-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-isopropoxybenzonitrile	MS-ESI (<i>m/z</i>):562 [<i>M</i> + 1] ⁺
83		(<i>S</i>)-5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-isopropoxybenzonitrile	MS-ESI (<i>m/z</i>):580 [<i>M</i> + 1] ⁺
84		(<i>S</i>)-5-(4-amino-1-(1-(3-chloro-5-oxo-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-isopropoxybenzonitrile	MS-ESI (<i>m/z</i>):582 [<i>M</i> + 1] ⁺
85		(<i>S</i>)-5-(4-amino-1-(1-(3-chloro-6-(3-fluorophenyl)-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-isopropoxybenzonitrile	MS-ESI (<i>m/z</i>):600 [<i>M</i> + 1] ⁺
86		(<i>S</i>)-7-(1-(4-amino-3-(6-isopropoxy-pyridin-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-3-chloro-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):558 [<i>M</i> + 1] ⁺

Example	Structure	Name	DATA
87		(S)-7-(1-(4-amino-3-(6-isopropoxy-pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):576 [M + 1] ⁺
88		(S)-7-(1-(4-amino-3-(2-isopropoxy-pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-methyl-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):539 [M + 1] ⁺
89		(S)-7-(1-(4-amino-3-(2-isopropoxy-pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):557 [M + 1] ⁺
90		(S)-7-(1-(4-amino-3-(2-isopropoxy-pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-phenyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):559 [M + 1] ⁺
91		(S)-7-(1-(4-amino-3-(2-isopropoxy-pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):577 [M + 1] ⁺
92		(S)-7-(1-(4-amino-3-(2-cyclopropoxy-pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):555 [M + 1] ⁺

Example	Structure	Name	DATA
93		(<i>S</i>)-7-(1-(4-amino-3-(2-cyclopropoxypyrimidin-5-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):575 [<i>M</i> + 1] ⁺
94		(<i>S</i>)-7-(1-(4-amino-3-(5-fluoro-6-isopropoxypyridin-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-3-chloro-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):576 [<i>M</i> + 1] ⁺
95		(<i>S</i>)-7-(1-(4-amino-3-(5-fluoro-6-isopropoxypyridin-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (<i>m/z</i>):594 [<i>M</i> + 1] ⁺
96		(<i>S</i>)-5-(4-amino-1-(1-(3-methyl-5-oxo-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-isopropoxynicotinonitrile	MS-ESI (<i>m/z</i>):563 [<i>M</i> + 1] ⁺
97		(<i>S</i>)-5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-isopropoxynicotinonitrile	MS-ESI (<i>m/z</i>):581 [<i>M</i> + 1] ⁺
98		(<i>S</i>)-5-(4-amino-1-(1-(3-chloro-5-oxo-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-isopropoxynicotinonitrile	MS-ESI (<i>m/z</i>):583 [<i>M</i> + 1] ⁺

Example	Structure	Name	DATA
99		(<i>S</i>)-5-(4-amino-1-(1-(3-chloro-6-(3-fluorophenyl)-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-isopropoxynicotinonitrile	MS-ESI (<i>m/z</i>):601 [<i>M</i> + 1] ⁺
100		(<i>S</i>)-7-(1-(4-amino-3-(4-(difluoromethoxy)-3-fluorophenyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyrimidin-5-one	MS-ESI (<i>m/z</i>):582 [<i>M</i> + 1] ⁺
101		(<i>S</i>)-5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyrimidin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-isopropoxybenzonitrile	MS-ESI (<i>m/z</i>):581 [<i>M</i> + 1] ⁺
102		(<i>S</i>)-7-(1-(4-amino-3-(6-isopropoxypyrimidin-3-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyrimidin-5-one	MS-ESI (<i>m/z</i>):557 [<i>M</i> + 1] ⁺
103		(<i>S</i>)-7-(1-(4-amino-3-(2-methoxypyrimidin-5-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyrimidin-5-one	MS-ESI (<i>m/z</i>):529 [<i>M</i> + 1] ⁺
104		(<i>S</i>)-7-(1-(4-amino-3-(2-methoxypyrimidin-5-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyrimidin-5-one	MS-ESI (<i>m/z</i>):549 [<i>M</i> + 1] ⁺

Example	Structure	Name	DATA
105		(S)-7-(1-(4-amino-3-(5-fluoro-6-isopropoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one	MS-ESI (m/z):575 [M + 1] ⁺
106		(S)-5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-isopropoxynitrile	MS-ESI (m/z):582 [M + 1] ⁺
107		(S)-N-(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (m/z):621 [M + 1] ⁺
108		(S)-N-(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxypyridin-3-yl)methanesulfonamide	MS-ESI (m/z):622 [M + 1] ⁺
109		(S)-N-(5-(4-amino-1-(1-(3-methyl-5-oxo-6-phenyl-5H-thiazolo[3,2-a]pyrimidin-7-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl)methanesulfonamide	MS-ESI (m/z):603 [M + 1] ⁺
110		(S)-7-(1-(4-amino-3-(2-isopropoxythiazol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-(3-fluorophenyl)-3-methyl-5H-thiazolo[3,2-a]pyridin-5-one	MS-ESI (m/z):562 [M + 1] ⁺

Example	Structure	Name	DATA
111		(<i>S</i>)-7-(1-(4-amino-3-(2-isopropoxythiazol-5-yl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-1-yl)ethyl)-3-chloro-6-(3-fluorophenyl)-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-5-one	MS-ESI (m/z):582 [M + 1] ⁺
112		(<i>S</i>)- <i>N</i> -(5-(4-amino-1-(1-(3-chloro-6-(3-fluorophenyl)-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-(methoxy- <i>d</i> ₃)phenyl)methanesulfonamide	MS-ESI (m/z):643 [M + 1] ⁺
113		(<i>S</i>)- <i>N</i> -(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-(methoxy- <i>d</i> ₃)phenyl)methanesulfonamide	MS-ESI (m/z):623 [M + 1] ⁺
114		(<i>S</i>)- <i>N</i> -(5-(4-amino-1-(1-(6-(3-fluorophenyl)-3-methyl-5-oxo-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-(methoxy- <i>d</i> ₃)pyridin-3-yl)methanesulfonamide	MS-ESI (m/z):624 [M + 1] ⁺
115		(<i>S</i>)- <i>N</i> -(5-(4-amino-1-(1-(3-methyl-5-oxo-6-phenyl-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyridin-7-yl)ethyl)-1 <i>H</i> -pyrazolo[3,4- <i>d</i>]pyrimidin-3-yl)-2-(methoxy- <i>d</i> ₃)pyridin-3-yl)methanesulfonamide	MS-ESI (m/z):606 [M + 1] ⁺

Cell Proliferation Assays

OCI-LY10 cells

[296] MTS testing kit was purchased from Promega (Madison, WI, USA). The RPMI-1640, Fetal bovine serum and Penicillin-Streptomycin were purchased from BI (Biological Industries, Beit Haemek, Israel). Dimethyl sulfoxide (DMSO) was purchased

from Sigma (St. Louis., MO, USA). OCI-LY10 cells were cultured in RPMI1640 supplemented with Penicillin-Streptomycin and 10% FBS.

[297] To investigate whether a compound is able to inhibit the activity of PI3K δ in cells, a mechanism-based assay using OCI-LY10 (PI3K δ dependent) cells was developed. In this assay, inhibition of PI3K δ was detected by the inhibition of OCI-LY10 cells proliferation. Cells were plated into 96-well plates at a density of 10000 cells/well. Plates were incubated at 37 °C, with 5 % CO₂ for 4 h. Compounds were serially diluted and added to the plates with the final compound concentrations as 10000, 3333.3, 1111.1, 270.4, 123.5, 41.2, 13.7, 4.6 and 1.5 nM. Plates were incubated at 37 °C, with 5 % CO₂ for 72 h. 20 μ l MTS was added into each well and the plates were incubated at 37 °C, with 5 % CO₂ for exactly 2 h. The absorbance was measured by a microplate reader at 490 nm. IC₅₀ was calculated using GraphPad Prism 5.0 software.

WSU-DHL cells

[298] MTS testing kit was purchased from Promega. The DMEM, Fetal bovine serum and Penicillin-Streptomycin were purchased from Gibco. Dimethyl sulfoxide (DMSO) was purchased from Sigma.

[299] To investigate whether a compound is able to inhibit the activity of PI3K in cells, a mechanism-based assay using WSU-DHL cell was developed. In this assay, inhibition of PI3K was detected by the inhibition of WSU-DHL cells proliferation. WSU-DHL cells were cultured in culture flasks to 40-80% confluence in DMEM plus 10% fetal bovine serum. Cells were collected and plated onto 96-well plates at desired cell density (10000 cells/well). Plates were incubated overnight at 37°C, with 5% CO₂ to adhere. Compounds were added to the plates, the final compound concentrations were 10000, 3333, 1111, 270, 123.5, 41.2, 13.7, 4.6 and 1.5 nM. Place plates at 37°C, with 5% CO₂ for 48 h. After removing the medium, 20 μ l MTS / 100 μ l medium mixture solution were added to each well and incubate the plates for exactly 2 hours. Stop the reaction by adding 25 μ l 10% SDS per well. Measure absorbance at 490 nm and 650 nm (reference wavelength). IC₅₀ was calculated using GraphPad Prism 5.0.

TMD-8 cells

[300] Alarm blue was purchased from Sigma - Aldrich (St. Louis., MO, USA, Cat. # R7017). The RPMI-1640 supplemented with Penicillin-Streptomycin were purchased from Hyclone (South Logan, Utah, USA, Cat. # SV30010). Fetal bovine serum was purchased from Gibco (Carlsbad, CA, USA, Cat. # 10099141C). Dimethyl sulfoxide (DMSO) was purchased from Sigma (St. Louis., MO, USA, Cat. # D2650). The TMD-8 cell was obtained from Zhen Shanghai and Shanghai Industrial Co., Ltd. TMD-8 cells were cultured in RPMI1640 supplemented with Penicillin-Streptomycin and 10% FBS.

[301] To investigate whether a compound is able to inhibit the activity of PI3K δ in cells, a mechanism-based assay using TMD-8 (PI3K δ dependent) cells was developed. In this assay, inhibition of PI3K δ was detected by the inhibition of TMD-8 cells proliferation. Cells were plated into 96-well plates at a density of 5000 cells/well. Compounds were serially diluted and added to the plates with the final compound concentrations as 5000, 833.33, 138.89, 23.15, 3.858, 0.643, 0.107 and 0.018 nM. Plates were incubated at 37°C, with 5% CO₂ for TMD-8 cells 4 days. Alarm blue (22 μ L of 1mM) was added into each well and the plates were incubated at 37°C, with 5% CO₂ for 1 ~ 4 h. The fluorescence was measured by a microplate reader (Bio-Tek Instruments, Model. Synergy HT) at an excitation wavelength of 530 nm and an emission of wavelength of 590nm. IC₅₀ was calculated using GraphPad Prism 7.0 software. The IC₅₀ for each compound was calculated by fitting the data with a non-linear regression equation: $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{Log IC}_{50} - X) * \text{HillSlope}))}$, where X is the log of compound concentration and Y is percent inhibition.

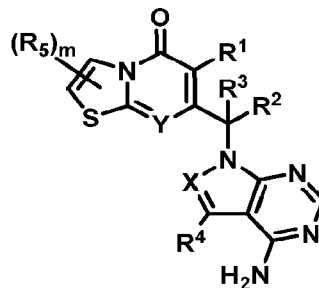
[302] Select compounds prepared as described above were assayed according to the biological procedures described herein. The results are given in Table 2.

Table 2

Example	OCI-LY10 IC ₅₀ (nM)	Example	OCI-LY10 IC ₅₀ (nM)
1	1	76	1
2	2	77	1
2-S	1	78	3
3	1	79	2
4	1	82	1
5	1	83	1
6	1	84	1
7	4	85	8
8	6	86	2
11	1	87	64
12	18	88	34
13	15	89	73
14	1	90	7
15	1	94	30
16	26	96	21
17	65	97	44
18	1	98	8
19	1	99	8
20	1	100	1
21	1	101	18
44	40	102	70
45	41	103	22
66	5	104	64
67	1	105	70
/	/	106	43

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,
wherein:

X is selected from CR^6 and N;

Y is selected from CR^7 and N;

R^1 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, CN, NO_2 , $-NR^{A1}R^{B1}$, $-OR^{A1}$, $-C(O)R^{A1}$, $-C(=NR^{E1})R^{A1}$, $-C(=N-OR^{B1})R^{A1}$, $-C(O)OR^{A1}$, $-OC(O)R^{A1}$, $-C(O)NR^{A1}R^{B1}$, $-NR^{A1}C(O)R^{B1}$, $-C(=NR^{E1})NR^{A1}R^{B1}$, $-NR^{A1}C(=NR^{E1})R^{B1}$, $-OC(O)NR^{A1}R^{B1}$, $-NR^{A1}C(O)OR^{B1}$, $-NR^{A1}C(O)NR^{A1}R^{B1}$, $-NR^{A1}C(S)NR^{A1}R^{B1}$, $-NR^{A1}C(=NR^{E1})NR^{A1}R^{B1}$, $-S(O)_2R^{A1}$, $-S(O)(=NR^{E1})R^{B1}$, $-N=S(O)R^{A1}R^{B1}$, $-S(O)_2OR^{A1}$, $-OS(O)_2R^{A1}$, $-NR^{A1}S(O)_2R^{B1}$, $-NR^{A1}S(O)(=NR^{E1})R^{B1}$, $-S(O)_2NR^{A1}R^{B1}$, $-S(O)(=NR^{E1})NR^{A1}R^{B1}$, $-NR^{A1}S(O)_2NR^{A1}R^{B1}$, $-NR^{A1}S(O)(=NR^{E1})NR^{A1}R^{B1}$, $-P(O)R^{A1}R^{B1}$ and $-P(O)(OR^{A1})(OR^{B1})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1} ;

R^2 is selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2} ;

R^3 is selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X3} ;

or R^2 and R^3 together with the atoms to which they are attached form a C_{3-10} cycloalkyl or heterocyclic ring of 4 to 12 members containing 1, 2 or 3 heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X2} groups;

R^4 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, CN, NO_2 , $-NR^{A4}R^{B4}$, $-OR^{A4}$, $-C(O)R^{A4}$, $-C(=NR^{E4})R^{A4}$, $-C(=N-OR^{B4})R^{A4}$, $-C(O)OR^{A4}$, $-OC(O)R^{A4}$, $-C(O)NR^{A4}R^{B4}$, $-NR^{A4}C(O)R^{B4}$,

-C(=NR^{E4})NR^{A4}R^{B4}, -NR^{A4}C(=NR^{E4})R^{B4}, -OC(O)NR^{A4}R^{B4}, -NR^{A4}C(O)OR^{B4},
 -NR^{A4}C(O)NR^{A4}R^{B4}, -NR^{A4}C(S)NR^{A4}R^{B4}, -NR^{A4}C(=NR^{E4})NR^{A4}R^{B4}, -S(O)_rR^{A4},
 -S(O)(=NR^{E4})R^{B4}, -N=S(O)R^{A4}R^{B4}, -S(O)₂OR^{A4}, -OS(O)₂R^{A4}, -NR^{A4}S(O)_rR^{B4},
 -NR^{A4}S(O)(=NR^{E4})R^{B4}, -S(O)_rNR^{A4}R^{B4}, -S(O)(=NR^{E4})NR^{A4}R^{B4}, -NR^{A4}S(O)₂NR^{A4}R^{B4},
 -NR^{A4}S(O)(=NR^{E4})NR^{A4}R^{B4}, -P(O)R^{A4}R^{B4} and -P(O)(OR^{A4})(OR^{B4}), wherein alkyl, alkenyl,
 alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted
 with at least one substituent, independently selected from R^{X4};

each R⁵ is independently selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl,
 C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄
 alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A5}R^{B5}, -OR^{A5},
 -C(O)R^{A5}, -C(=NR^{E5})R^{B5}, -C(=N-OR^{B5})R^{A5}, -C(O)OR^{A5}, -OC(O)R^{A5}, -C(O)NR^{A5}R^{B5},
 -NR^{A5}C(O)R^{B5}, -C(=NR^{E5})NR^{A5}R^{B5}, -NR^{A5}C(=NR^{E5})R^{B5}, -OC(O)NR^{A5}R^{B5}, -NR^{A5}C(O)OR^{B5},
 -NR^{A5}C(O)NR^{A5}R^{B5}, -NR^{A5}C(S)NR^{A5}R^{B5}, -NR^{A5}C(=NR^{E5})NR^{A5}R^{B5}, -S(O)_rR^{A5},
 -S(O)(=NR^{E5})R^{B5}, -N=S(O)R^{A5}R^{B5}, -S(O)₂OR^{A5}, -OS(O)₂R^{A5}, -NR^{A5}S(O)_rR^{B5},
 -NR^{A5}S(O)(=NR^{E5})R^{B5}, -S(O)_rNR^{A5}R^{B5}, -S(O)(=NR^{E5})NR^{A5}R^{B5}, -NR^{A5}S(O)₂NR^{A5}R^{B5},
 -NR^{A5}S(O)(=NR^{E5})NR^{A5}R^{B5}, -P(O)R^{A5}R^{B5} and -P(O)(OR^{A5})(OR^{B5}), wherein alkyl, alkenyl,
 alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted
 with at least one substituent, independently selected from R^{X5};

R⁶ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀
 cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄
 alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A6}R^{B6}, -OR^{A6}, -C(O)R^{A6}, -C(=NR^{E6})R^{B6},
 -C(=N-OR^{B6})R^{A6}, -C(O)OR^{A6}, -OC(O)R^{A6}, -C(O)NR^{A6}R^{B6}, -NR^{A6}C(O)R^{B6},
 -C(=NR^{E6})NR^{A6}R^{B6}, -NR^{A6}C(=NR^{E6})R^{B6}, -OC(O)NR^{A6}R^{B6}, -NR^{A6}C(O)OR^{B6},
 -NR^{A6}C(O)NR^{A6}R^{B6}, -NR^{A6}C(S)NR^{A6}R^{B6}, -NR^{A6}C(=NR^{E6})NR^{A6}R^{B6}, -S(O)_rR^{A6},
 -S(O)(=NR^{E6})R^{B6}, -N=S(O)R^{A6}R^{B6}, -S(O)₂OR^{A6}, -OS(O)₂R^{A6}, -NR^{A6}S(O)_rR^{B6},
 -NR^{A6}S(O)(=NR^{E6})R^{B6}, -S(O)_rNR^{A6}R^{B6}, -S(O)(=NR^{E6})NR^{A6}R^{B6}, -NR^{A6}S(O)₂NR^{A6}R^{B6},
 -NR^{A6}S(O)(=NR^{E6})NR^{A6}R^{B6}, -P(O)R^{A6}R^{B6} and -P(O)(OR^{A6})(OR^{B6}), wherein alkyl, alkenyl,
 alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted
 with at least one substituent, independently selected from R^{X6};

R⁷ is selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀
 cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄
 alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, CN, NO₂, -NR^{A7}R^{B7}, -OR^{A7}, -C(O)R^{A7}, -C(=NR^{E7})R^{B7},
 -C(=N-OR^{B7})R^{A7}, -C(O)OR^{A7}, -OC(O)R^{A7}, -C(O)NR^{A7}R^{B7}, -NR^{A7}C(O)R^{B7},
 -C(=NR^{E7})NR^{A7}R^{B7}, -NR^{A7}C(=NR^{E7})R^{B7}, -OC(O)NR^{A7}R^{B7}, -NR^{A7}C(O)OR^{B7},
 -NR^{A7}C(O)NR^{A7}R^{B7}, -NR^{A7}C(S)NR^{A7}R^{B7}, -NR^{A7}C(=NR^{E7})NR^{A7}R^{B7}, -S(O)_rR^{A7},
 -S(O)(=NR^{E7})R^{B7}, -N=S(O)R^{A7}R^{B7}, -S(O)₂OR^{A7}, -OS(O)₂R^{A7}, -NR^{A7}S(O)_rR^{B7},
 -NR^{A7}S(O)(=NR^{E7})R^{B7}, -S(O)_rNR^{A7}R^{B7}, -S(O)(=NR^{E7})NR^{A7}R^{B7}, -NR^{A7}S(O)₂NR^{A7}R^{B7},
 -NR^{A7}S(O)(=NR^{E7})NR^{A7}R^{B7}, -P(O)R^{A7}R^{B7} and -P(O)(OR^{A7})(OR^{B7}), wherein alkyl, alkenyl,
 alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted
 with at least one substituent, independently selected from R^{X7};

each R^{A1} and R^{B1} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl,
 C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄
 alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl,
 alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted
 with at least one substituent, independently selected from R^{X1};

or "R^{A1} and R^{B1}" together with the atom(s) to which they are attached form a
 heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms
 independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally
 substituted with 1, 2 or 3 R^{X1} groups;

each R^{A4} and R^{B4} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X4} ;

or " R^{A4} and R^{B4} " together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X4} groups;

each R^{A5} and R^{B5} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X5} ;

or " R^{A5} and R^{B5} " together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X5} groups;

each R^{A6} and R^{B6} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X6} ;

or " R^{A6} and R^{B6} " together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X6} groups;

each R^{A7} and R^{B7} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X7} ;

or " R^{A7} and R^{B7} " together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^{X7} groups;

each R^{E1} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{a1}$, $-SR^{a1}$, $-S(O)_rR^{a1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$, $-C(O)NR^{a1}R^{b1}$ and $-S(O)_rNR^{a1}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X1} ;

each R^{E4} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{a1}$, $-SR^{a1}$, $-S(O)_rR^{a1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$, $-C(O)NR^{a1}R^{b1}$ and $-S(O)_rNR^{a1}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X4} ;

each R^{E5} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{a1}$, $-SR^{a1}$, $-S(O)_rR^{a1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$, $-C(O)NR^{a1}R^{b1}$ and $-S(O)_rNR^{a1}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X5} ;

each R^{E6} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{a1}$, $-SR^{a1}$, $-S(O)_rR^{a1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$, $-C(O)NR^{a1}R^{b1}$ and $-S(O)_rNR^{a1}R^{b1}$, wherein alkyl is

unsubstituted or substituted with at least one substituent, independently selected from R^{X6} ;

each R^{E7} is independently selected from hydrogen, C_{1-10} alkyl, CN, NO_2 , $-OR^{a1}$, $-SR^{a1}$, $-S(O)_rR^{a1}$, $-C(O)R^{a1}$, $-C(O)OR^{a1}$, $-C(O)NR^{a1}R^{b1}$ and $-S(O)_rNR^{a1}R^{b1}$, wherein alkyl is unsubstituted or substituted with at least one substituent, independently selected from R^{X7} ;

each R^{X1} , R^{X2} , R^{X3} , R^{X4} , R^{X5} , R^{X6} and R^{X7} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{c1}R^{d1})_tNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tOR^{b1}$, $-(CR^{c1}R^{d1})_tC(O)R^{a1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(=N-OR^{e1})R^{a1}$, $-(CR^{c1}R^{d1})_tC(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)R^{b1}$, $-(CR^{c1}R^{d1})_tC(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tOC(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)OR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(O)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(S)NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}C(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tS(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tN=S(O)R^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_2OR^{b1}$, $-(CR^{c1}R^{d1})_tOS(O)_2R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_rR^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})R^{b1}$, $-(CR^{c1}R^{d1})_tS(O)_rNR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)(=NR^{e1})NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tNR^{a1}S(O)_2NR^{a1}R^{b1}$, $-(CR^{c1}R^{d1})_tP(O)R^{a1}R^{b1}$ and $-(CR^{c1}R^{d1})_tP(O)(OR^{a1})(OR^{b1})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

each R^{a1} and each R^{b1} are independently selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

or R^{a1} and R^{b1} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1, or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{c1} and each R^{d1} are independently selected from hydrogen, halogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, and heteroaryl- C_{1-4} alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

or R^{c1} and R^{d1} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1, or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1, 2 or 3 R^Y groups;

each R^{e1} is independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, CN, NO_2 , $-OR^{a2}$, $-SR^{a2}$, $-S(O)_rR^{a2}$, $-C(O)R^{a2}$, $-C(O)OR^{a2}$, $-S(O)_rNR^{a2}R^{b2}$ and $-C(O)NR^{a2}R^{b2}$;

each R^Y is independently selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, heterocyclyl, heterocyclyl- C_{1-4} alkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, halogen, CN, NO_2 , $-(CR^{c2}R^{d2})_tNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tOR^{b2}$, $-(CR^{c2}R^{d2})_tC(O)R^{a2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(=N-OR^{e2})R^{a2}$, $-(CR^{c2}R^{d2})_tC(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)R^{b2}$, $-(CR^{c2}R^{d2})_tC(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tOC(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)OR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(O)NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}C(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tS(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tN=S(O)R^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tOS(O)_2R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_rR^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})R^{b2}$, $-(CR^{c2}R^{d2})_tS(O)_rNR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)(=NR^{e2})NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tNR^{a2}S(O)_2NR^{a2}R^{b2}$, $-(CR^{c2}R^{d2})_tP(O)R^{a2}R^{b2}$ and $-(CR^{c2}R^{d2})_tP(O)(OR^{a2})(OR^{b2})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y ;

$-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{S}(\text{O})(=\text{NR}^{\text{e2}})\text{R}^{\text{b2}}$, $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{N}=\text{S}(\text{O})\text{R}^{\text{a2}}\text{R}^{\text{b2}}$, $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{S}(\text{O})_2\text{OR}^{\text{b2}}$,
 $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{OS}(\text{O})_2\text{R}^{\text{b2}}$, $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{NR}^{\text{a2}}\text{S}(\text{O})\text{R}^{\text{b2}}$, $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{NR}^{\text{a2}}\text{S}(\text{O})(=\text{NR}^{\text{e2}})\text{R}^{\text{b2}}$,
 $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{S}(\text{O})\text{NR}^{\text{a2}}\text{R}^{\text{b2}}$, $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{S}(\text{O})(=\text{NR}^{\text{e2}})\text{NR}^{\text{a2}}\text{R}^{\text{b2}}$, $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{NR}^{\text{a2}}\text{S}(\text{O})_2\text{NR}^{\text{a2}}\text{R}^{\text{b2}}$,
 $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{NR}^{\text{a2}}\text{S}(\text{O})(=\text{NR}^{\text{e2}})\text{NR}^{\text{a2}}\text{R}^{\text{b2}}$, $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{P}(\text{O})\text{R}^{\text{a2}}\text{R}^{\text{b2}}$ and
 $-(\text{CR}^{\text{c2}}\text{R}^{\text{d2}})_i\text{P}(\text{O})(\text{OR}^{\text{a2}})(\text{OR}^{\text{b2}})$, wherein alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from OH, CN, amino, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

each R^{a2} and each R^{b2} are independently selected from hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino, di(C₁₋₁₀ alkyl)amino, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

or R^{a2} and R^{b2} together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 12 members containing 0, 1 or 2 additional heteroatoms independently selected from oxygen, sulfur, nitrogen and phosphorus, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

each R^{c2} and each R^{d2} are independently selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino, di(C₁₋₁₀ alkyl)amino, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl and heteroaryl-C₁₋₄ alkyl, wherein alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, alkylamino, cycloalkylamino, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

or R^{c2} and R^{d2} together with the carbon atom(s) to which they are attached form a ring of 3 to 12 members containing 0, 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 or 2 substituents, independently selected from halogen, CN, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ cycloalkyl, OH, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, C₁₋₁₀ alkylthio, C₃₋₁₀ cycloalkylthio, amino, C₁₋₁₀ alkylamino, C₃₋₁₀ cycloalkylamino and di(C₁₋₁₀ alkyl)amino;

each R^{e2} is independently selected from hydrogen, CN, NO₂, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, -C(O)C₁₋₄ alkyl, -C(O)C₃₋₁₀ cycloalkyl, -C(O)OC₁₋₄ alkyl, -C(O)OC₃₋₁₀ cycloalkyl, -C(O)N(C₁₋₄ alkyl)₂, -C(O)N(C₃₋₁₀ cycloalkyl)₂, -S(O)₂C₁₋₄ alkyl, -S(O)₂C₃₋₁₀ cycloalkyl, -S(O)₂N(C₁₋₄ alkyl)₂ and -S(O)₂N(C₃₋₁₀ cycloalkyl)₂;

m is selected from 0, 1 and 2;

each r is independently selected from 0, 1 and 2;

- each t is independently selected from 0, 1, 2, 3 and 4.
2. A compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein X is N.
 3. A compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein X is CR⁶.
 4. A compound of claim 3 or a pharmaceutically acceptable salt thereof, wherein R⁶ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl and C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X6}.
 5. A compound of claim 4 or a pharmaceutically acceptable salt thereof, wherein R⁶ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, methyl, ethyl, isopropyl and cyclopropyl, wherein methyl, ethyl, isopropyl and cyclopropyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X6}.
 6. A compound of any one of claims 1-5 or a pharmaceutically acceptable salt thereof, wherein Y is N.
 7. A compound of any one of claims 1-5 or a pharmaceutically acceptable salt thereof, wherein Y is CR⁷.
 8. A compound of claim 7 or a pharmaceutically acceptable salt thereof, wherein R⁷ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy and C₃₋₁₀ cycloalkoxy, wherein alkyl, alkenyl, cycloalkyl, alkoxy and cycloalkoxy are each unsubstituted or substituted with at least one substituent, independently selected from R^{X7}.
 9. A compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein R⁷ is selected from hydrogen, halogen, OH, CN, NH₂, NO₂, methyl, ethyl, isopropyl and cyclopropyl, wherein methyl, ethyl, isopropyl and cyclopropyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X7}.
 10. A compound of any one of claims 1-9 or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkoxy, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, and heteroaryl-C₁₋₄ alkyl, wherein alkyl, cycloalkyl, alkoxy, cycloalkoxy, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.
 11. A compound of claim 10 or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X1}.
 12. A compound of claim 11 or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from phenyl, pyridinyl and pyrimidinyl, which is unsubstituted or substituted with halogen, OH, CN, NH₂, NO₂, C₁₋₁₀ alkyl and C₃₋₁₀ cycloalkyl.
 13. A compound of claim 12 or a pharmaceutically acceptable salt thereof, wherein R¹ is phenyl or 3-fluorophenyl.
 14. A compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof, wherein R² and R³ are independently selected from hydrogen, C₁₋₁₀ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, heterocyclyl, heterocyclyl-C₁₋₄ alkyl, aryl and heteroaryl, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2} and R^{X3}.

15. A compound of claim 14 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, C_{1-10} alkyl, C_{3-10} cycloalkyl and C_{3-10} cycloalkyl- C_{1-4} alkyl, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X2} and R^{X3} .

16. A compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, methyl, ethyl and cyclopropyl.

17. A compound of any one of claims 1-16 or a pharmaceutically acceptable salt thereof, wherein m is 1.

18. A compound of any one of claims 1-17 or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, CN, NO_2 , $-NR^{A5}R^{B5}$, $-OR^{A5}$, $-C(O)R^{A5}$, $-C(O)OR^{A5}$, $-OC(O)R^{A5}$, $-C(O)NR^{A5}R^{B5}$, $-NR^{A5}C(O)R^{B5}$, $-S(O)_rR^{A5}$, $-S(O)_2OR^{A5}$ and $-S(O)_rNR^{A5}R^{B5}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X5} .

19. A compound of claim 18 or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, halogen, C_{1-10} alkyl, C_{3-10} cycloalkyl, CN, NO_2 , $-NR^{A5}R^{B5}$, $-OR^{A5}$, $-C(O)R^{A5}$, $-NR^{A5}C(O)R^{B5}$, $-S(O)_rR^{A5}$ and $-S(O)_rNR^{A5}R^{B5}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X5} .

20. A compound of claim 19 or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from hydrogen, F, Cl, methyl, ethyl, isopropyl and cyclopropyl.

21. A compound of any one of claims 1-20 or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from C_{1-10} alkyl, C_{3-10} cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X4} .

22. A compound of claim 21 or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from aryl and heteroaryl, wherein aryl and heteroaryl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X4} .

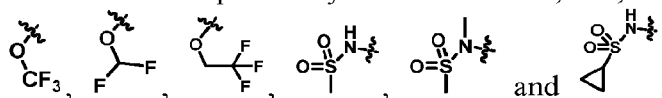
23. A compound of claim 22 or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from phenyl, pyridinyl, pyrimidinyl and thiazolyl, wherein phenyl, pyridinyl, pyrimidinyl and thiazolyl are each unsubstituted or substituted with at least one substituent, independently selected from R^{X4} .

24. A compound of any one of claims 1-23 or a pharmaceutically acceptable salt thereof, wherein each R^{X4} is independently selected from C_{1-10} alkyl, C_{3-10} cycloalkyl, halogen, CN, NO_2 , $-(CR^{C1}R^{D1})_tNR^{A1}R^{B1}$, $-(CR^{C1}R^{D1})_tOR^{B1}$, $-(CR^{C1}R^{D1})_tC(O)R^{A1}$, $-(CR^{C1}R^{D1})_tNR^{A1}C(O)R^{B1}$ and $-(CR^{C1}R^{D1})_tNR^{A1}S(O)_rR^{B1}$, wherein alkyl and cycloalkyl are each unsubstituted or substituted with at least one substituent, independently selected from R^Y .

25. A compound of claim 24 or a pharmaceutically acceptable salt thereof, wherein each R^{X4} is independently selected from F, Cl, Br, CN, $-NH_2$, methyl, ethyl, methoxy, ethoxy,

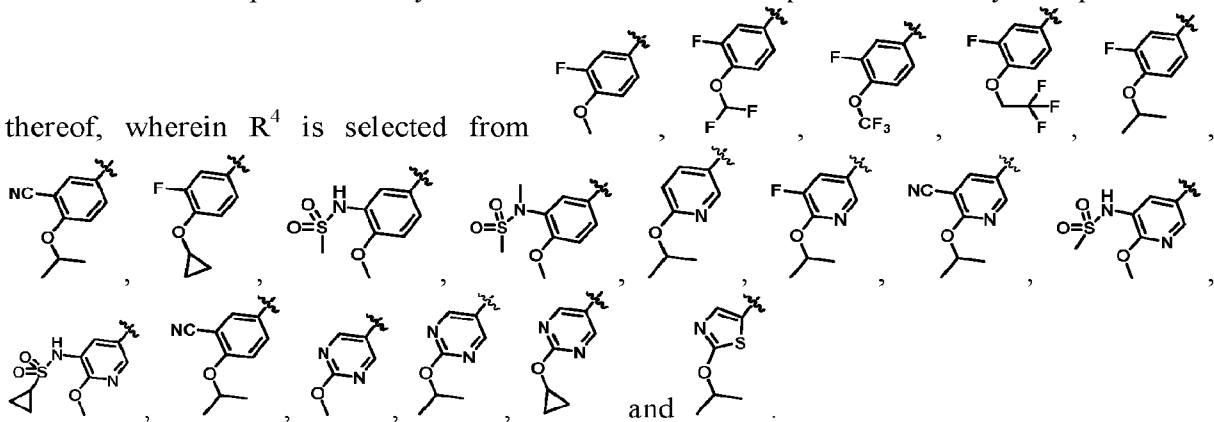
isopropoxy, cyclopropoxy, ,  and , wherein methyl, ethyl, methoxy, ethoxy, isopropoxy and cyclopropoxy are each unsubstituted or substituted with at least one substituent, independently selected from halogen.

26. A compound of claim 25 or a pharmaceutically acceptable salt thereof, wherein each R^{X4} is independently selected from F, CN, methoxy, ethoxy, isopropoxy, cyclopropoxy,

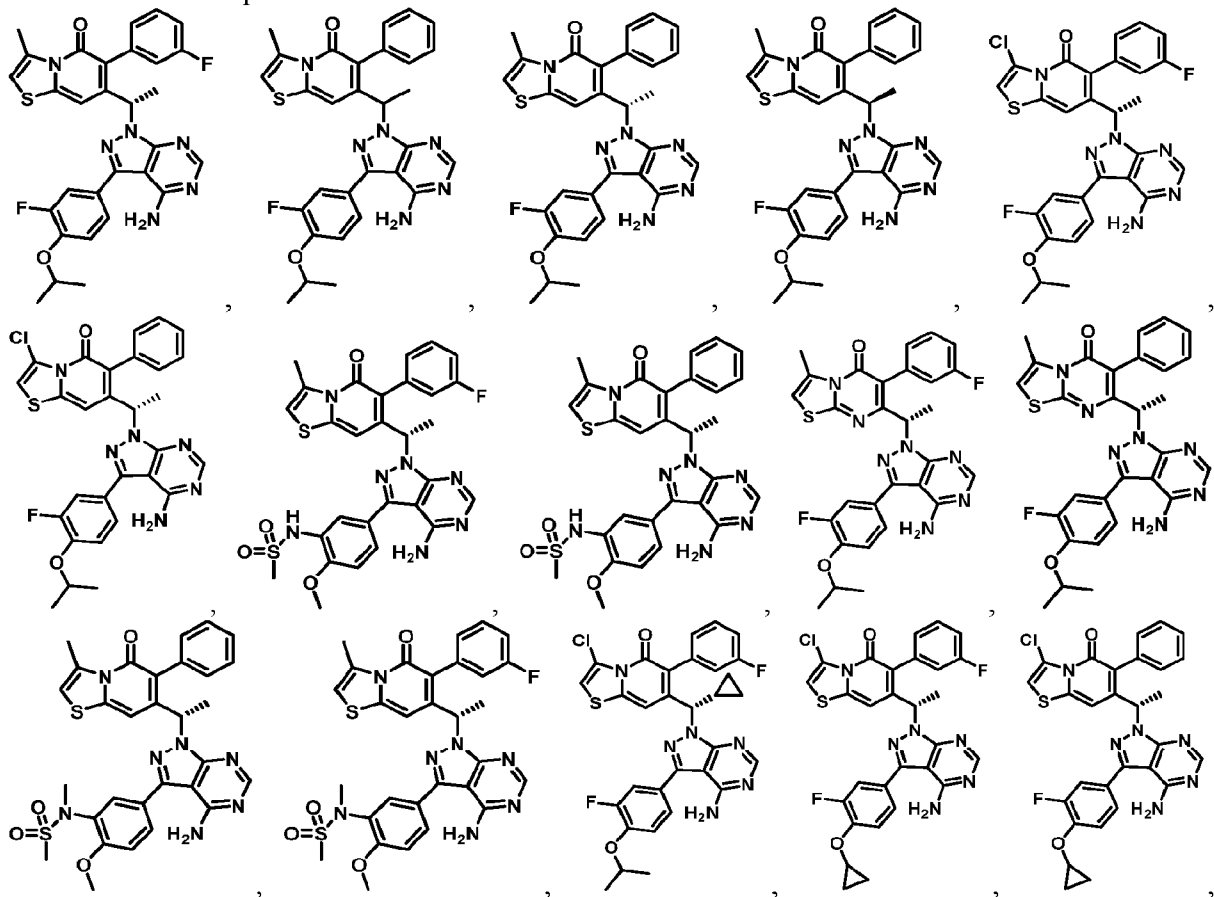


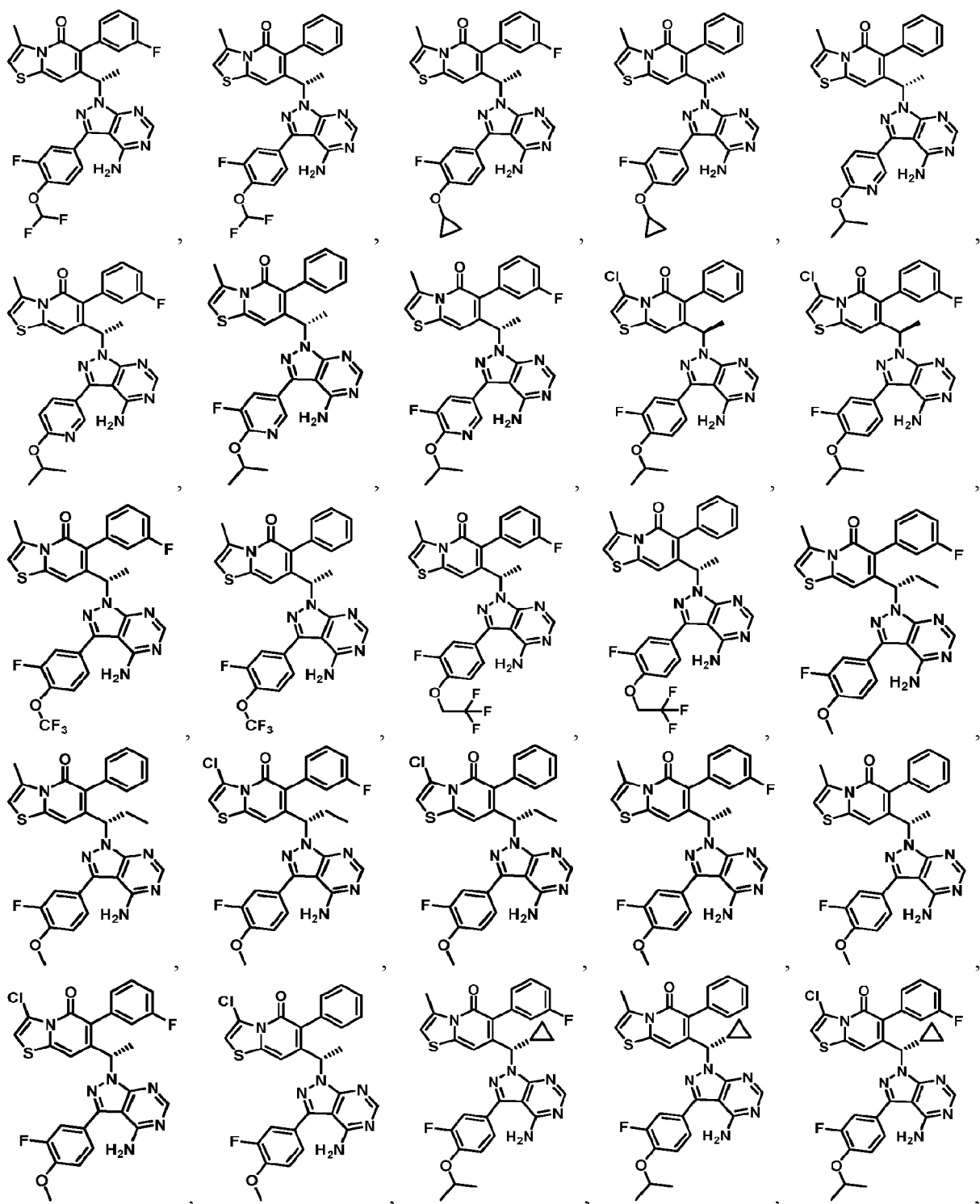
27. A compound of any one of claims 1-26 or a pharmaceutically acceptable salt

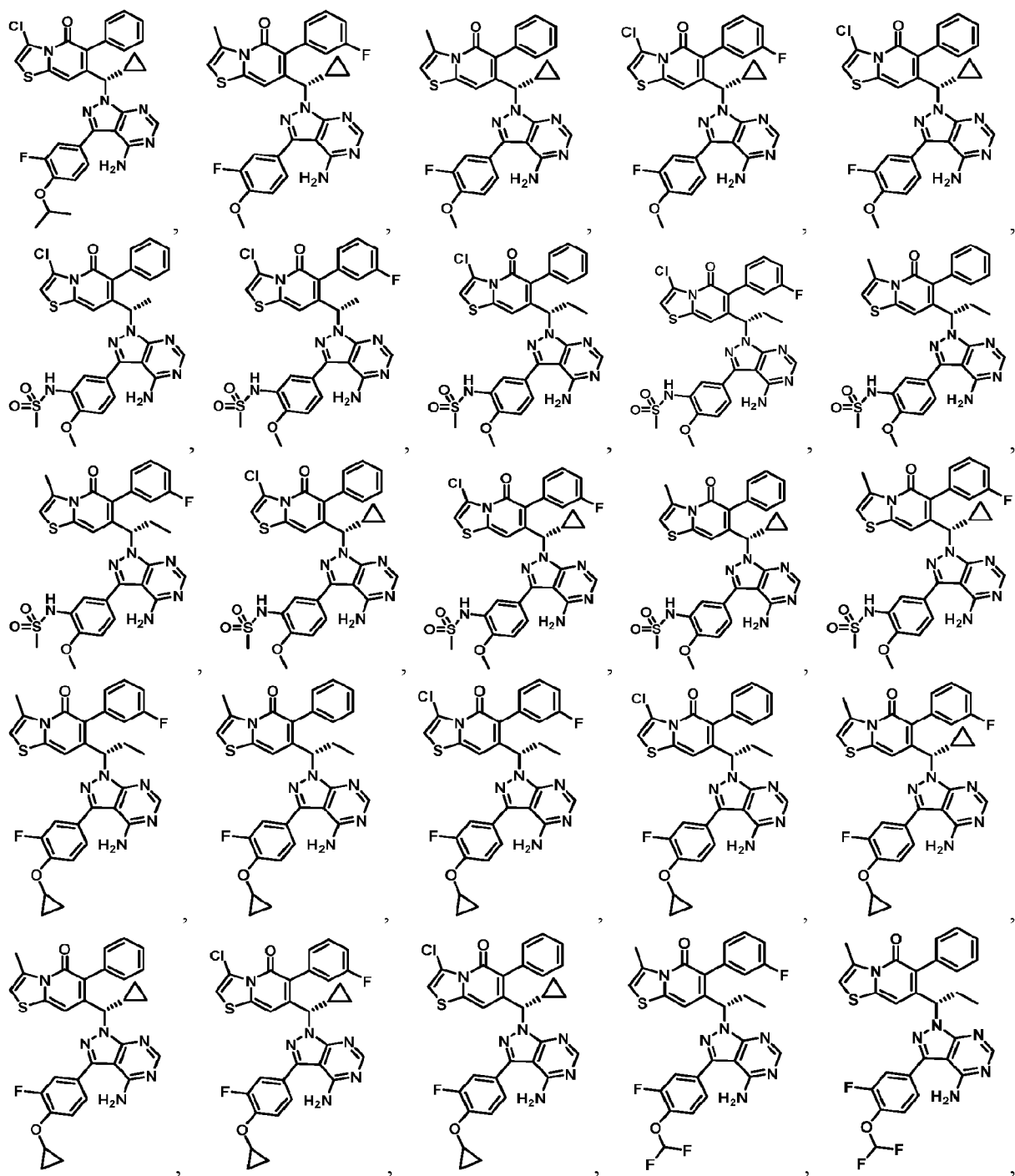
thereof, wherein R^4 is selected from

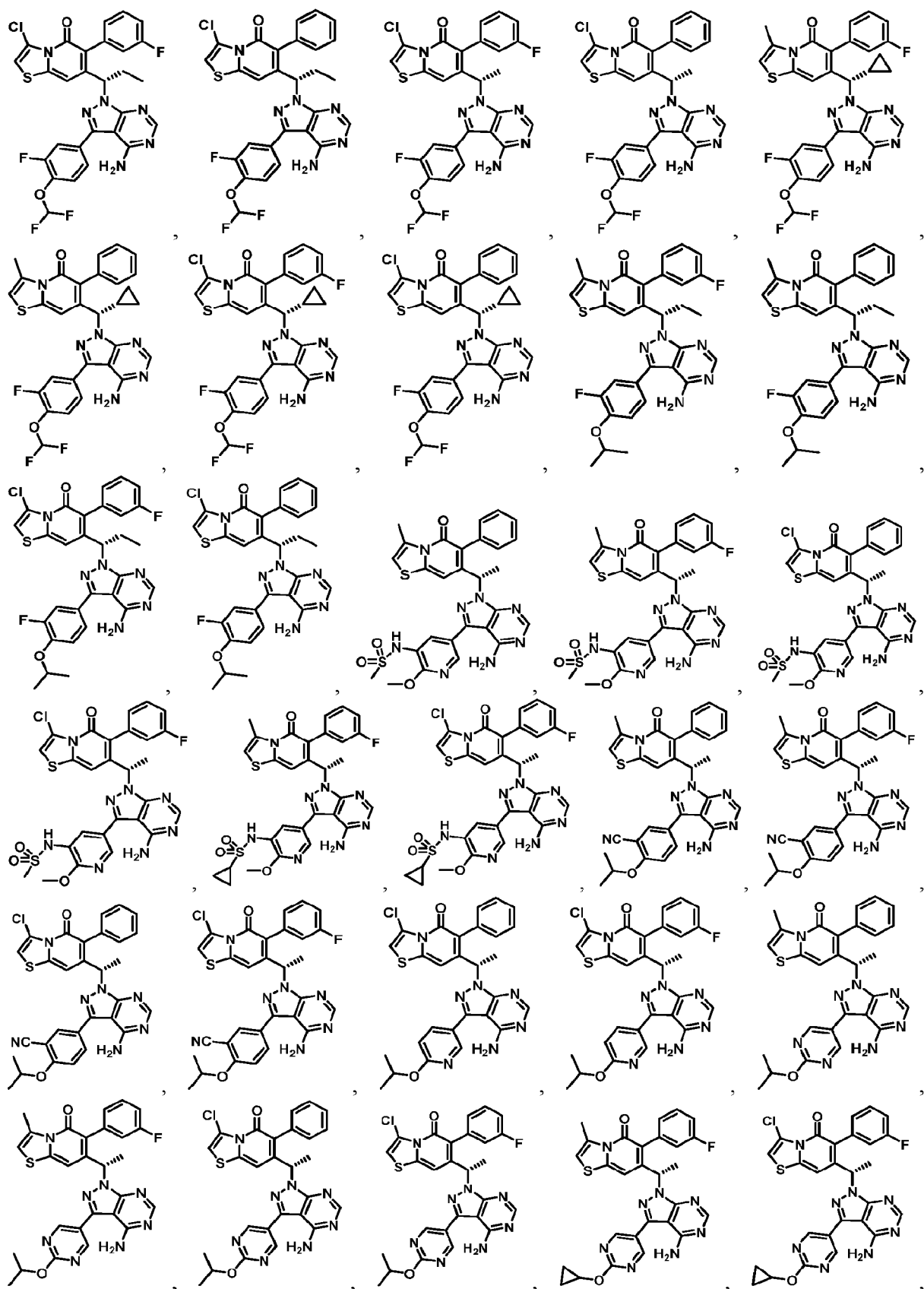


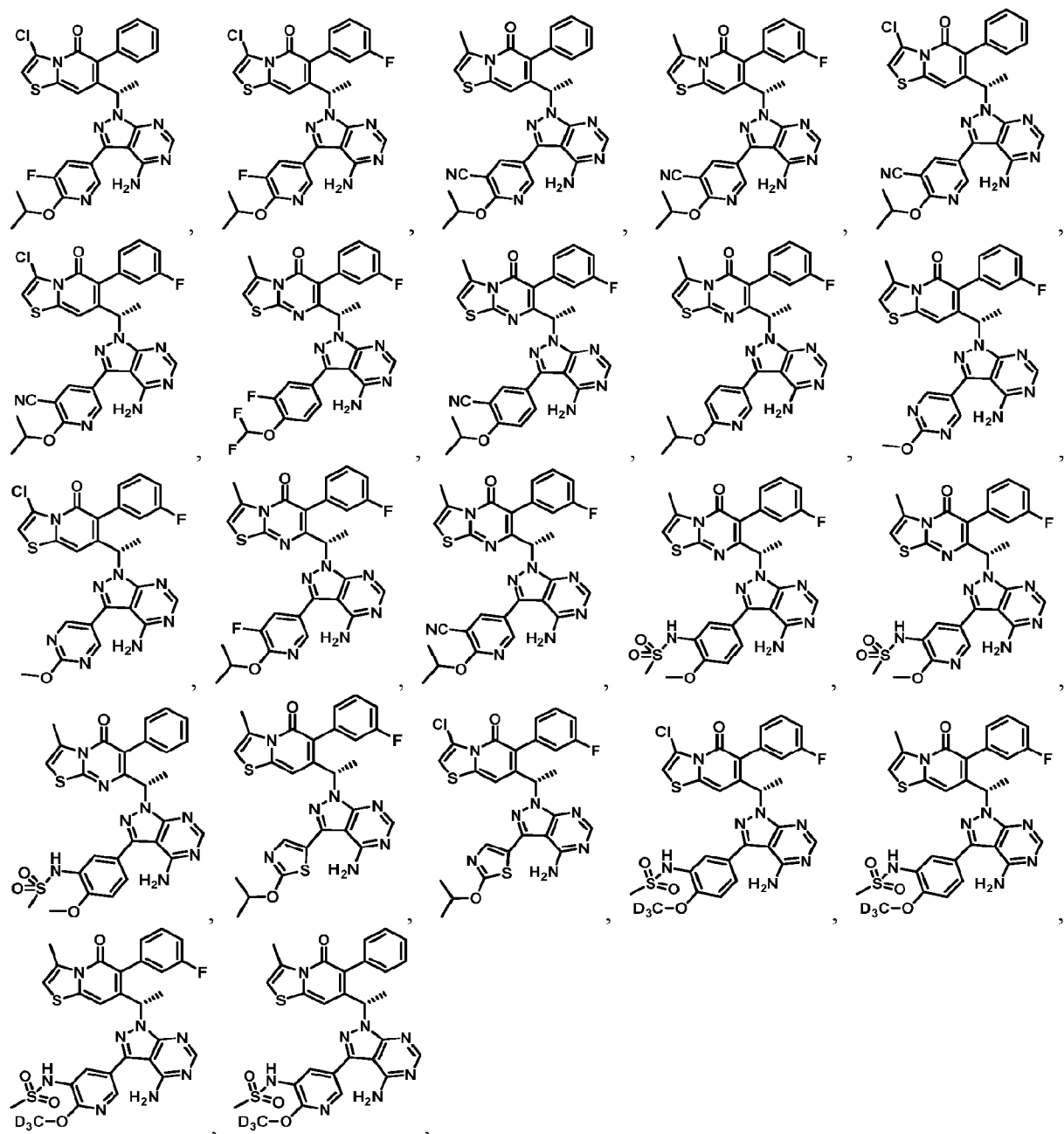
28. A compound selected from











and pharmaceutically acceptable salts thereof.

29. A pharmaceutical composition, comprising a compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

30. A method of treating, ameliorating or preventing a condition, which responds to inhibition of PI3K, comprising administering to a subject in need of such treatment an effective amount of a compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, and optionally in combination with a second therapeutic agent.

31. Use of a compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a cell-proliferative disorder.

32. The use of a compound of claims 31 or a pharmaceutically acceptable salt thereof, wherein the cell-proliferative disorder is includes but not limited to, breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, testicular cancer, lung cancer (including NSCLC, SCLC, squamous cell carcinoma or adenocarcinoma), esophageal cancer, head and neck cancer, colorectal cancer, kidney cancer (including RCC), liver cancer (including HCC), pancreatic cancer, stomach (i.e., gastric) cancer, thyroid cancer, chronic lymphocytic leukemia (CLL), lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia and myeloma.