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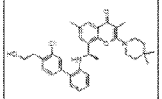
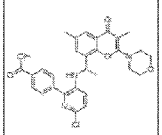
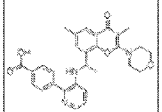
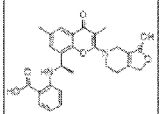
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Structure	In-Cell HTRF IC50 (nM) pAKT_S473 SKBR3 6.0h 10.0%FBS Avg	In-Cell HTRF IC50 (nM) pAKT_S473 T-47D 6.0h 10.0%FBS Avg	In-Cell HTRF IC50 (nM) pAKT_S473 MCF7 6.0h 10.0%FBS Avg	ADP-Glo DR IC50 (nM) PI3K wt 4.0h pre-inc Avg	ADP-Glo DR IC50 (nM) PI3K H1047R 4.0h pre-inc Avg
	C	A	B	C	B
	C	C	C	C	C
	C	C	C	C	C
	C	B	C	C	A

(57) Abstract: The present disclosure provides novel chemical compounds or their salts, compositions containing them, and their medical uses. The compounds are active as PI3K inhibitors, including PI3K mutants, and are useful in the treatment or control of diseases or disorders mediated by PI3K and its mutants.

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[Continued on next page]

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CHEMICAL COMPOUNDS

Cross-Reference to Related Applications

[0001] The present application claims the benefit of United States Provisional Application Numbers 63/524518 filed 30 June 2023 and 63/512406 filed 07 July 2023, each of which is incorporated herein in its entirety.

Field of the Invention

[0002] The present disclosure provides novel boron compounds or their salts, compositions containing them, and their medical uses. The compounds are active as kinase inhibitors.

Background of the Invention

[0003] The activity of cells may be regulated by external signals that stimulate or inhibit intracellular events. The process by which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response is referred to as signal transduction. Over the past decades, cascades of signal transduction events have been elucidated and found to play a central role in a variety of biological responses. Defects in various components of signal transduction pathways have been found to account for a vast number of diseases, including numerous forms of cancer, inflammatory disorders, metabolic disorders, vascular and neuronal diseases (Gaestel et al. Current Medicinal Chemistry (2007) 14:2214-2234).

[0004] Kinases represent a class of important signaling molecules. Kinases may generally be classified into protein kinases and lipid kinases, and certain kinases exhibit dual specificities.

[0005] Protein kinases are enzymes that phosphorylate other proteins and/or themselves (i.e., autophosphorylation). Protein kinases can be generally classified into three major groups based upon their substrate utilization: tyrosine kinases which predominantly phosphorylate substrates on tyrosine residues (e.g., erb2, PDGF receptor, EGF receptor, VEGF receptor, src, abl), serine/threonine kinases which predominantly phosphorylate substrates on serine and/or threonine residues (e.g., mTorCl, mTorC2, ATM, ATR, DNA-PK, Akt), and dual-specificity kinases which phosphorylate substrates on tyrosine, serine and/or threonine residues.

[0006] Lipid kinases are enzymes that catalyze the phosphorylation of lipids within cells. These enzymes, and the resulting phosphorylated lipids and lipid-derived biologically active organic molecules, play a role in many different physiological processes, including cell proliferation, migration, adhesion, and differentiation. A particular group of lipid kinases comprises membrane lipid kinases, i.e., kinases that catalyze the phosphorylation of lipids contained in or associated with cell membranes. Examples of such enzymes include phosphinositide(s) kinases (such as PB-kinases, PI4-Kinases), diacylglycerol kinases, and sphingosine kinases.

[0007] The PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene provides instructions for making the p110 alpha (p110α) protein, which is one piece (subunit) of an enzyme called phosphatidylinositol 3-kinase (PI3K). The p110α protein is called the catalytic subunit because it performs the action of PI3K, while the other subunit (produced by a different gene) regulates the enzyme's activity.

[0008] Phosphatidylinositol 3 kinase (PI3K) is a key molecule in the initiation of signal transduction pathways after the binding of extracellular signals to cell surface receptors. An intracellular kinase, PI3K activates multiple intracellular signaling pathways that affect cell growth, proliferation, migration, secretion, differentiation, transcription and translation. Dysregulation of PI3K activity, and aberrant PI3K signaling, lead to a broad range of human diseases, such as cancer, immune disorders, diabetes, and cardiovascular diseases. The PI3K signaling pathway is one of the most highly mutated systems in human cancers.

[0009] PI3K signaling is involved in many other disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

[0010] PI3K is a member of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3 '-OH group on phosphatidylinositols or phosphoinositides. The class I PI3Ks are typically activated by tyrosine kinases or G-protein coupled receptors, and phosphorylate PIP2 to generate PIP3, which engages downstream effectors such as those in the pathways of Akt/PDKl, mTOR, the Tee family kinases, and the Rho family GTPases. The class II and III play a key role in intracellular trafficking through the synthesis of P1(3)P and P1(3,4)P2.

[0011] PI3Ks phosphorylate the 3';-hydroxyl group of phosphatidylinositides (PtdIns). They are divided into three classes based on their structures and substrate specificities. In mammals, class I PI3Ks are further divided into subclasses IA and IB based on their modes of regulation. Class IA PI3Ks are heterodimers of a p110 catalytic subunit and a p85 regulatory subunit. The genes ***PIK3CA,*** ***PIK3CB,*** and ***PIK3CD*** respectively encode three highly homologous class IA catalytic isoforms: p110α, p110β, and p110δ. These isoforms associate with any of five regulatory isoforms, p85α (and its splicing variants p55α and p50α, encoded by ***PIK3R1***), p85β (***PIK3R2***), and p55γ (***PIK3R3***), collectively called p85 type regulatory subunits. Class IB PI3Ks are heterodimers of a p110γ catalytic subunit (encoded by ***PIK3CG***) coupled with regulatory isoforms p101 (***PIK3R5***) or p87 (p84 or $p87^{PIKAP}$, encoded by ***PIK3R6***). While p110α and p110β are ubiquitously expressed, p110δ and p110γ expression is largely restricted to leukocytes. Initial PI3K-directed drug discovery consisted largely of non-isoform-selective pan-PI3K inhibitors. More recent studies, however, have demonstrated that different PI3K isoforms play

divergent roles in cellular signaling and cancer, suggesting that inhibitors targeting individual isoforms may be able to achieve greater therapeutic efficacy. Isoform-selective inhibitors are now emerging. See. Thorpe et al., PI3K in Cancer: Divergent Roles of Isoforms, Modes of Activation, and Therapeutic Targeting, Nat. Rev. Cancer, 2015, 15(1): 7-24.

[0012] Overactivation of the PI3K pathway is one of the most frequent events in human cancers. *PIK3CA* mutation has been established as causative in many cancer types. Mutations in the gene coding for an isoform are point mutations clustered within several hotspots in helical and kinase domains. Missense mutations occur in all domains of p110α, but the majority cluster in two hotspots, the most common being E542K and E545K in the helical domain and H1047R in the kinase domain. Cell-based analyses confirmed that these hotspot mutations confer transformation via constitutive activation of p110α. Because of the high rate of mutations, targeting of this pathway may provide valuable therapeutic opportunities.

[0013] Genetic alterations in gene signaling are believed to be involved in a range of cancers such as endometrial cancer, breast cancer, esophageal squamous-cell cancer. cervical squamous-cell carcinoma, cervical adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, glioblastoma, ovarian cancer, non-small-cell lung cancer, esophagogastric cancer, nerve-sheath tumor, head and neck squamous-cell carcinoma, melanoma, esophagogastric adenocarcinoma, soft-tissue sarcoma, prostate cancer, fibrolamellar carcinoma, hepatocellular carcinoma, diffuse glioma, colorectal cancer, pancreatic cancer, cholangiocarcinoma, B-cell lymphoma, mesothelioma, adrenocortical carcinoma, renal non-clear-cell carcinoma, renal clear-cell carcinoma, germ-cell carcinoma, thymic tumor, pheochromocytoma, miscellaneous neuroepithelial tumor, thyroid cancer, leukemia, and encapsulated glioma (Goncalves MD, Hopkins BD, Cantley LC. Phosphatidylinositol 3-Kinase, Grm.vth Disorders, and Cancer. N Engl J Med.2018 Nov 22;379(21):2052-2062).

[0014] The alpha isoform has been implicated, for example, in a variety of human cancers. Angiogenesis has been shown to selectively require the alpha isoform in the control of endothelial cell migration. (Graupera et al, Nature 2008; 453; 662-6). Mutations in the gene coding for PI3Ka or mutations which lead to hyperactivation of PI3Ka are believed to occur in many human cancers such as lung, stomach, endometrial, ovarian, bladder, breast, colon, brain, prostate, and skin cancers. Mutations in the gene coding are point mutations clustered within several hotspots in kinase and helical domains, such as H1047R, E545K and E542K. Many of these mutations have been shown to be oncogenic gain-of-function mutations. Because of the high rate of mutations, targeting of this protein may provide valuable therapeutic opportunities including cancer. While other isoforms are expressed primarily in hematopoietic cells, PI3Ka is expressed constitutively.

[0015] Due to the central role of PI3K in regulating organismal glucose homeostasis, inhibition in patients often gives rise to hyperglycemia and/or hyperinsulinemia (Busaidy NL, et al, *Management of metabolic effects associated with anticancer agents targeting the PBK-Akt-mTOR pathway*. J Clin Oneal 2012;30:2919-28). High levels of circulating insulin could potentially be mitogenic and/or antiapoptotic for cancer cells and thus negate the antiproliferative effects of inhibitors (Blouin M-J, et al, Abstract 4615: the hyperinsulinemia caused by inhibitors attenuates their antineoplastic efficacy, but can be minimized by co-administration of metformin. Cancer Res 2013; 73 :4615).

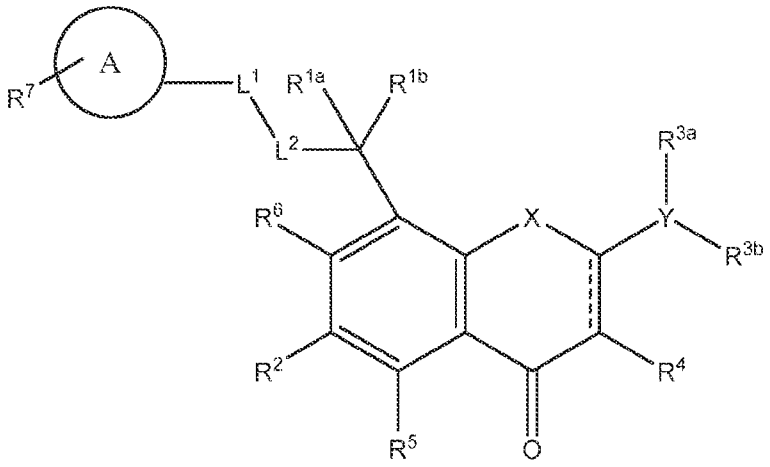
[0016] In the setting of cancer with mutated PI3Kα, one way to overcome the problem of compensatory production of insulin and/or glucose upon systemic inhibition caused by inhibition of the patient's wild-type PI3K would be to develop inhibitors with enhanced selectivity for mutant over wild-type. This would create an increased window for drug dosing to selectively inhibit the pathologic signaling of mutant varients in the cancer cells without affecting the wild-type in the host tissues that control systemic metabolism (Okkenhaug K, Graupera M, Vanhaesebroeck B. *Targeting PBK in Cancer: Impact on Tumor Cells, Their Protective Strama, Angiogenesis, and Immunotherapy*. Cancer Discov. 2016 Oct;6(10): 1090-1105), thus limiting toxicities and permitting higher doses and more complete inhibition of the drug target (Ariella B. Hanker, et al, *Challenges for the clinical development of PBK inhibitors: Strategies to improve their impact in solid tumors*. Cancer Discov. 2019 Apr; 9(4): 482-491).

[0017] Currently, PI3K inhibitors are nearly equipotent to wild-type and mutant, such as PI3Kα. Mutant selective PI3Kα inhibitors have been elusive due to the PI3Kα mutations location distal to the active site. As such, inhibitors which target a second, peripheral, binding pocket, with potential differential activity for mutant over wild-type (e.g., H1047R) may provide a route to selective PI3Kα inhibition. Thus, targeting a, peripheral binding pocket of PI3Ka, may in turn provide a valuable therapeutic target for drug development.

[0018] As such, kinases, for example lipid kinases such as PI3Ks, are prime targets for drug development. The present disclosure provides a new class of kinase inhibitors.

Summary of the Invention

[0019] One embodiment of the present disclosure includes a compound of Formula (I):



(I)

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof, wherein

A is selected from the group consisting of

a. C_{1-6} alkyl,

b. C_{2-6} alkenyl,

c. C_{2-6} alkynyl, and

d. 3- to 14- membered mono-ring or fused ring system, which may have one or more degrees of unsaturation, and which may contain one or more heteroatoms selected from O, N, or S,

e. each of which A may be further substituted with one or more R^A;

R^7 is selected from the group consisting of: CHO, OH, oxo, C_1-C_6 alkyl(OH), C_2-C_6 alkenyl(OH), C_2-C_6 alkynyl(OH), C_1-C_6 alkyl(NH_2), C_2-C_6 alkenyl(NH_2), C_2-C_6 alkynyl(NH_2), C_1-C_6 alkyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkenyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkynyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_1-C_6 alkyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkenyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkynyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C(O)NH_2, C(O)NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), C(O)N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, S(O)$_2NH_2$, S(O)$_2$NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), S(O)$_2$(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, C(O)OC_1-C_6 alkyl, C(O)OC_1-C_6 alkenyl, and C(O)OC_1-C_6 alkynyl, and C(O)OH;

L^1 is selected from the group consisting of an optionally substituted cycloalkylene, optionally substituted heterocyclylene, optionally substituted arylene, and optionally substituted heteroarylene;

L^2 is selected from the group consisting of O and NH;

each of R^{1a} and R^{1b} is the same or different and is independently is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, and O-C_{2-6} alkynyl;

X is C(R^x)$_2$, O, NR^x, or S;

each R^X is the same or different and is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

Y is selected from:

a) H, where each of R^{3a} and R^{3b} are absent;

b) C-R^{3c}, wherein

i) R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

ii) each of R^{3a} and R^{3b} is the same or different and independently is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

as noted hereinabove, the value for each of alkenyl and alkynyl includes a C1, with the intention that when Y is C, then Y may be bound through a double or triple bond to a C atom;

or

iii) Y, as an C atom, combines with R^{3a} and R^{3b} to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more heteroatoms selected from the group consisting of N, O, S, and B, and wherein the Y-containing ring or ring system is optionally substituted with one or more R^Y;

c) N, wherein

i) each of R^{3a} and R^{3b} independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

[0001] Y, as an N atom, combines with R^{3a} and R^{3b} to form a 3- to 14-membered mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms selected from the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^Y;

d) O, wherein R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

and

e) S, wherein R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^2 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$,

$(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^4 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^5 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^6 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

when present, each of R^A, R^Y, and R^{100} independently is selected from the group consisting of: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-C(O)OH, $(CH_2)_q$-C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-$N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl$)_2$, $(CH_2)_q$-$C(O)NH_2$, $(CH_2)_q$-C(O)NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-$C(O)N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl$)_2$, $(CH_2)_q$-NHC(O)H, $(CH_2)_q$-NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-$N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-$N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl;

each of m and q independently is, at each occurrence, selected from 0, 1, 2, 3, 4, 5, and 6;

and

wherein for each occurrence of cycloalkyl, heterocycle, aryl, and heteroaryl as one or more of R^A, R^Y, and R^{100}, is optionally substituted with one or more of C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

[0020] In one aspect, when Y is incorporated into or includes any ring or ring system:

the Y ring or ring system contains a B atom in the Y ring or ring system;

the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is $B(OH)_2$;

the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

the Y ring or ring system is further substituted with one or more R^Y, which at least one R^Y is $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, where each of said cycloalkyl, heterocycle, aryl, or heteroaryl is substituted with $B(OH)_2$.

[0021] In one aspect, L^1 is optionally substituted phenylene.

[0022] In one aspect, L^1 is phenylene substituted with one or more halogen.

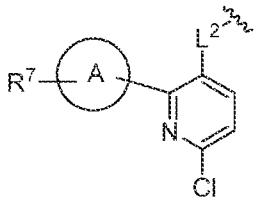
[0023] In one aspect, L^1 is optionally substituted heteroarylene.

[0024] In one aspect, L^1 is optionally substituted pyridinylene.

[0025] In one aspect, L^1 is pyridinylene substituted with at least one or more halogen.

[0026] In one aspect, L^1 is substituted with at least one or more halogen or C_{1-6}alkyl.

[0027] In one aspect, L^1 is optionally substituted pyridinylene, and the pyridinylene is attached as:



[0028] In one aspect, R^7 is COOH or C_1-C_6 alkyl(OH).

[0029] In one aspect, A is selected from the group consisting of phenyl and 5-6 membered heteroaryl.

[0030] In one aspect, A is phenyl.

[0031] In one aspect, A is substituted with one or two R^A that may be the same or different.

[0032] In one aspect, each R^A is selected from the group consisting of: C_{1-6} alkyl, halogen, and C_{1-6} haloalkyl.

[0033] In one aspect, A is substituted with one or two R^A and at least one R^A is a halogen.

[0034] In one aspect, halogen is fluorine or chlorine.

[0035] In one aspect: R^{1a} is H; and R^{1b} independently is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy.

[0036] In one aspect, R^{1b} is C_{1-6} alkyl.

[0037] In one aspect, R^{1b} is methyl.

[0038] In one aspect, R^{1b} is methyl and R^{1a} is hydrogen.

[0039] In one aspect, L^2 is O.

[0040] In one aspect, L^2 is NH.

[0041] In one aspect, X is O.

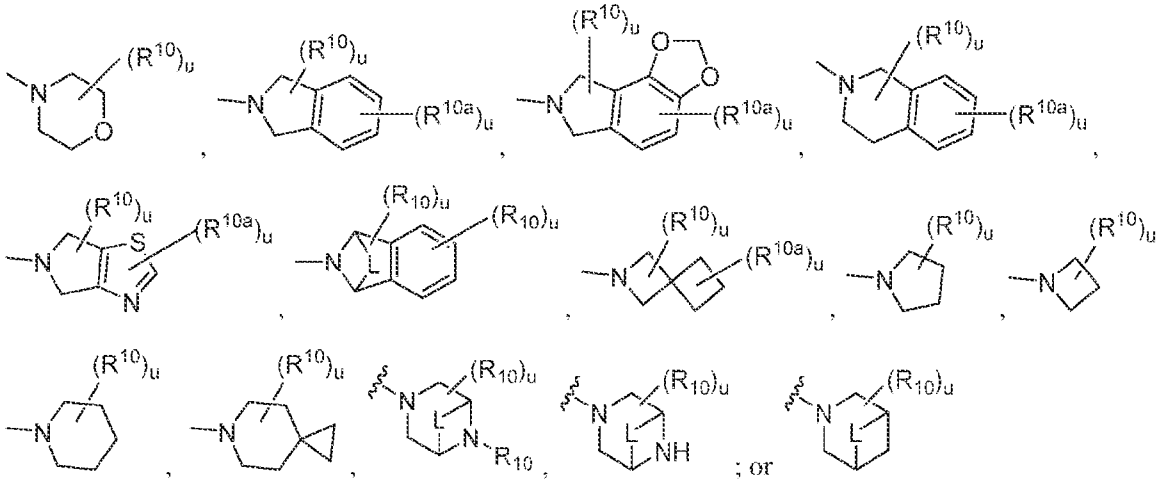
[0042] In one aspect, Y is an N, which combines with R^{3a} and R^{3b} to form a 3- to 14-membered mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms selected from

the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^Y.

[0043] In one aspect, Y is an N, which combines with R^{3a} and R^{3b} to form an isoindolene that is optionally substituted with one or more R^Y.

[0044] In one aspect, Y is an N, which combines with R^{3a} and R^{3b} to form a piperidine that is optionally substituted with one or more R^Y.

[0045] In one aspect, Y is an N, which combines with R^{3a} and R^{3b} to form:



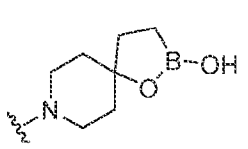
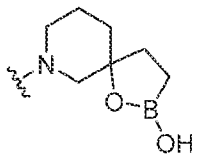
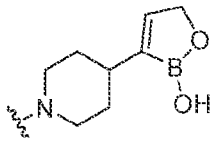
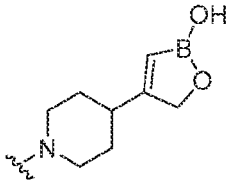
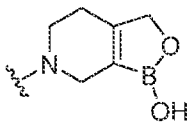
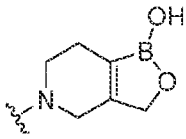
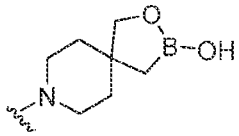
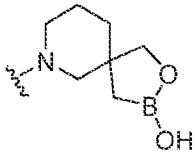
wherein

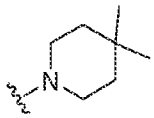
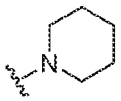
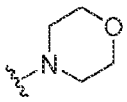
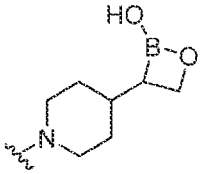
each R^{10} and R^{10a} is the same or different and is individually selected from an R^Y;

each u is 0, 1, 2, 3, 4, 5, or 6; and

each L is absent, (CH_2), $(CH_2)_2$, or $(CH_2)_3$.

[0046] In one aspect, Y is an N, which combines with R^{3a} and R^{3b} to form one of:


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or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof.

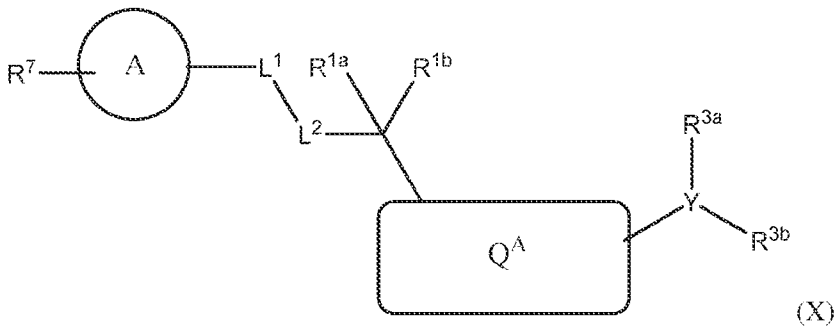
[0047] In one aspect, each of R^2, R^4, R^5, and R^6 independently is H, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6 cycloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, or C_{1-6} haloalkyl.

[0048] In one aspect, R^2 is H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; R^5 is H; and R^6 is H.

[0049] In one aspect, R^2 is methyl.

[0050] In one aspect, R^4 is selected from the group consisting of CH_3.

[0051] One embodiment of the present disclosure includes a compound of Formula X:



(X)

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof, wherein

Q^A is an optionally substituted 8- to 14-membered ring system, which may have one or more degrees of unsaturation, which may contain one or more heteroatoms selected from O, N, or S, and which may be further substituted with one or more R^Q;

A is selected from the group consisting of

a. C_{1-6} alkyl,

b. C_{2-6} alkenyl,

c. C_{2-6} alkynyl, and

d. 3- to 14- membered mono-ring or fused ring system, which may have one or more degrees of unsaturation, and which may contain one or more heteroatoms selected from O, N, or S,

e. each of which A may be further substituted with one or more R^A;

L^1 is selected from the group consisting of a direct bond, optionally substituted cycloalkylene, optionally substituted heterocyclylene, optionally substituted arylene, and optionally substituted heteroarylene;

L^2 is selected from the group consisting of consisting of a direct bond, $(CR^R_2)_{1-6}$, O, C(O), S, and NR^R;

each of R^R, R^{1a}, and R^{1b} is the same or different and is independently is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, and O-C_{2-6} alkynyl;

or

L^2-$C(R^{1a})(R^{1b})$ combines to form $NR^RC(S)$, $C(S)NR^R$, $NR^RC(O)$, $C(O)NR^R$, $NR^RS(O)_2$, $S(O)_2NR^R$, $NR^RC(NR^R)$, or $C(NR^R)NR^R$;

Y is selected from:

a. H, where each of R^{3a} and R^{3b} are absent;

b. C-R^{3c}, wherein

i. R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

ii. each of R^{3a} and R^{3b} is the same or different and independently is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;
as noted hereinabove, the value for each of alkenyl and alkynyl includes a C1, with the intention that when Y is C, then Y may be bound through a double or triple bond to a C atom;
or

iii. Y, as an C atom, combines with R^{3a} and R^{3b} to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more heteroatoms selected from the group consisting of N,

O, S, and B, and wherein the Y-containing ring or ring system is optionally substituted with one or more R^Y;

c. N, wherein

i. each of R^{3a} and R^{3b} independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

ii. Y, as an N atom, combines with R^{3a} and R^{3b} to form a 3- to 14-membered mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms selected from the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^Y;

d. O, wherein R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

and

e. S, wherein R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^7 is selected from the group consisting of: H, CHO, OH, oxo, C_1-C_6 alkyl(OH), C_2-C_6 alkenyl(OH), C_2-C_6 alkynyl(OH), C_1-C_6 alkyl(NH_2), C_2-C_6 alkenyl(NH_2), C_2-C_6 alkynyl(NH_2), C_1-C_6 alkyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkenyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkynyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_1-C_6 alkyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkenyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkynyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), C(O)N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, $S(O)_2NH_2$, $S(O)_2$NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), $S(O)_2$(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, C(O)OC_1-C_6 alkyl, C(O)OC_1-C_6 alkenyl, and C(O)OC_1-C_6 alkynyl, and C(O)OH;

when present, each instance of R^A, R^Q, and R^Y, is the same or different and independently is selected from the group consisting of:

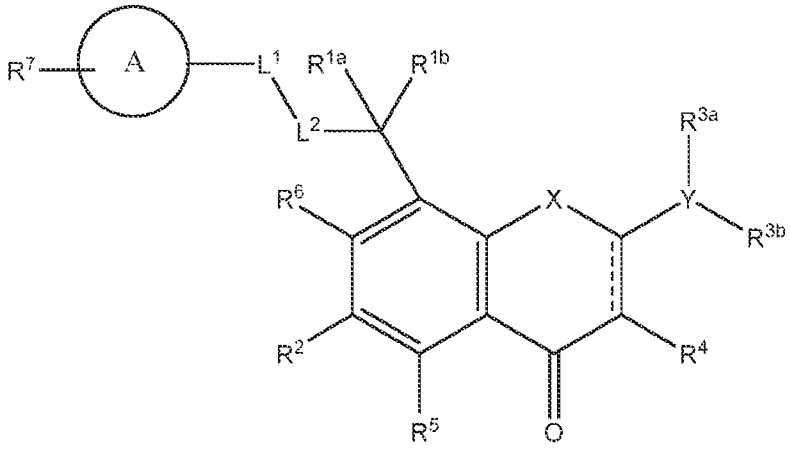
H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-C(O)OH, $(CH_2)_q$-C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-$C(O)NH_2$, $(CH_2)_q$-C(O)NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C(O)N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-NHC(O)H, $(CH_2)_q$-NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl,

and

$(CH_2)_q$-O-C(O)-$(CH_2)_r$-R^{140}, $(CH_2)_q$-NH-C(O)-$(CH_2)_r$-R^{140}, $(CH_2)_q$-O-C(O)-$(CH_2)_r$-OR^{140}, $(CH_2)_q$-NH-C(O)-$(CH_2)_r$-OR^{140}, $(CH_2)_q$-O-$(CH_2)_r$-R^{140}, $(CH_2)_q$-NH-$(CH_2)_r$-R^{140}, $(CH_2)_q$-O-$(CH_2)_r$-OR^{140}, and $(CH_2)_q$-NH-$(CH_2)_r$-OR^{140}, where R^{140} is an E3 ligase binding ligand,

wherein each occurrence of R^A, R^Q, and R^Y, as cycloalkyl, heterocycle, aryl, or heteroaryl is optionally substituted with one or more of C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, OH, $B(OH)_2$, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

[0052] In one embodiment, the compound is of Formula X1:



(X1),

wherein

X is $C(R^x)_2$, O, NR^x, or S;

each R^x is the same or different and is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^2 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-C(O)R^{100}, $(CH_2)_m$-C(O)OR^{100}, $(CH_2)_m$-C(O)$N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^4 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-C(O)R^{100}, $(CH_2)_m$-C(O)OR^{100}, $(CH_2)_m$-C(O)$N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^5 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-C(O)R^{100}, $(CH_2)_m$-C(O)OR^{100}, $(CH_2)_m$-C(O)$N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^6 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

each R^{100} is the same or different and is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-C(O)OH, $(CH_2)_q$-C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-$C(O)NH_2$, $(CH_2)_q$-C(O)NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C(O)N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-NHC(O)H, $(CH_2)_q$-NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl,

and

$(CH_2)_q$-O-C(O)-$(CH_2)_r$-R^{140}, $(CH_2)_q$-NH-C(O)-$(CH_2)_r$-R^{140}, $(CH_2)_q$-O-C(O)-$(CH_2)_r$-OR^{140}, $(CH_2)_q$-NH-C(O)-$(CH_2)_r$-OR^{140}, $(CH_2)_q$-O-$(CH_2)_r$-R^{140}, $(CH_2)_q$-NH-$(CH_2)_r$-R^{140}, $(CH_2)_q$-O-$(CH_2)_r$-OR^{140}, and $(CH_2)_q$-NH-$(CH_2)_r$-OR^{140}, where R^{140} is an E3 ligase binding ligand,

each of m, q, and r, independently is, at each occurrence, selected from 0, 1, 2, 3, 4, 5, and 6.

[0053] In one aspect, Y comprises a B atom.

[0054] In one aspect, Y is incorporated into or includes any ring or ring system:

the Y ring or ring system contains a B atom in the Y ring or ring system;

the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is $B(OH)_2$;

the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

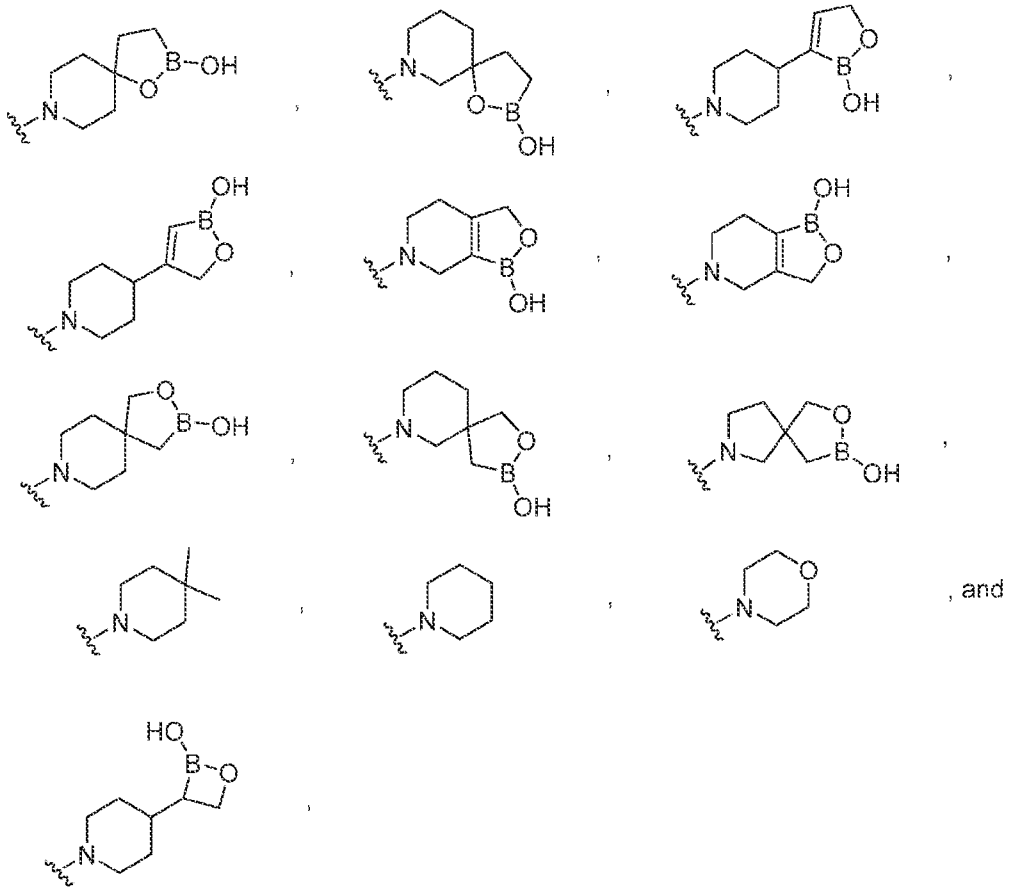
the Y ring or ring system is further substituted with one or more R^Y, which at least one R^Y is $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, where each of said cycloalkyl, heterocycle, aryl, or heteroaryl is substituted with $B(OH)_2$.

[0055] In one aspect, Y is a ring or ring system wherein:

the Y ring or ring system contains a B atom in the Y ring or ring system;

the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

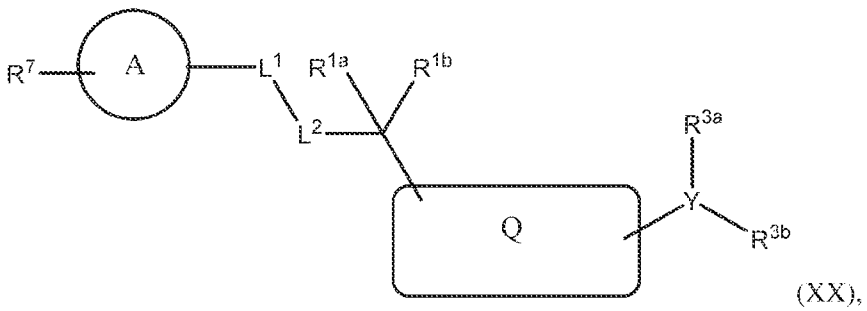
$Y(R^{3a})(R^{3b})$ is selected from:



, and

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof.

[0056] One embodiment of the present disclosure includes a compound of Formula XX:



(XX),

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof, wherein

A is selected from the group consisting of

C_{1-6} alkyl,

C_{2-6} alkenyl,

C_{2-6} alkynyl, and

3- to 14- membered mono-ring or fused ring system, which may have one or more degrees of unsaturation, and which may contain one or more heteroatoms selected from O, N, or S,

each of which A may be further substituted with one or more R^A;

R^7 is selected from the group consisting of: CHO, OH, oxo, C_1-C_6 alkyl(OH), C_2-C_6 alkenyl(OH), C_2-C_6 alkynyl(OH), C_1-C_6 alkyl(NH_2), C_2-C_6 alkenyl(NH_2), C_2-C_6 alkynyl(NH_2), C_1-C_6 alkyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkenyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkynyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_1-C_6 alkyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkenyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkynyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C(O)NH_2, C(O)NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), C(O)N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, S(O)$_2NH_2$, S(O)$_2$NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), S(O)$_2$(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, C(O)OC_1-C_6 alkyl, C(O)OC_1-C_6 alkenyl, and C(O)OC_1-C_6 alkynyl, and C(O)OH;

L^1 is selected from the group consisting of a direct bond, optionally substituted cycloalkylene, optionally substituted heterocyclylene, optionally substituted arylene, and optionally substituted heteroarylene;

L^2 is selected from the group consisting of O and NH;

each of R^{1a} and R^{1b} independently is selected from the group consisting of hydrogen, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, C_{2-6} alkenyloxy, and C_{2-6} alkynyloxy;

Q is a 8- to 14- membered fused ring system, which may have one or more degrees of unsaturation, which may contain one or more heteroatoms selected from O, N, or S, and which may be further substituted with one or more R^Q;

Y is selected from:

a. H, where each of R^{3a} and R^{3b} are absent;

b. C-R^{3c}, wherein

i. R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

ii. each of R^{3a} and R^{3b} is the same or different and independently is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; as noted hereinabove, the value for each of alkenyl and alkynyl includes a C1, with the intention that when Y is C, then Y may be bound through a double or triple bond to a C atom; or

iii. Y, as an C atom, combines with R^{3a} and R^{3b} to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more

heteroatoms selected from the group consisting of N, O, S, and B, and wherein the Y-containing ring or ring system is optionally substituted with one or more R^Y;

c. N, wherein

i. each of R^{3a} and R^{3b} independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

ii. Y, as an N atom, combines with R^{3a} and R^{3b} to form a 3- to 14-membered mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms selected from the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^Y;

d. O, wherein R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

and

e. S, wherein R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

provided that at least one of the following applies:

a) the Y ring or ring system contains a B atom in the Y ring or ring system;

b) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is $B(OH)_2$;

c) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

d) the Y ring or ring system is further substituted with one or more R^Y, which at least one R^Y is $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, where each of said cycloalkyl, heterocycle, aryl, or heteroaryl is substituted with $B(OH)_2$,

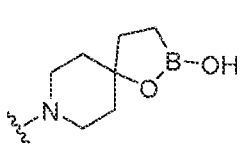
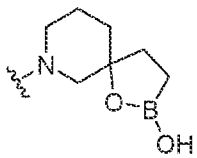
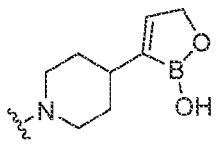
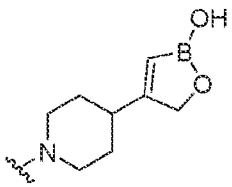
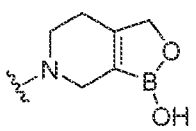
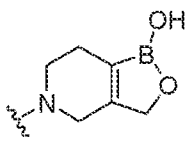
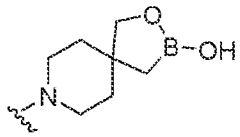
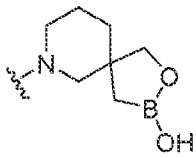
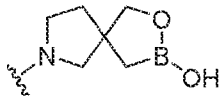
when present, each of R^A, R^Q, and R^Y is the same or different and independently is selected from the group consisting of: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-C(O)OH, $(CH_2)_q$-C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-C(O)NH_2, $(CH_2)_q$-C(O)NH(C_{1-6}

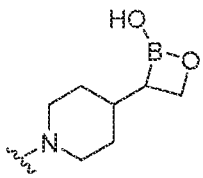
alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C(O)N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-NHC(O)H, $(CH_2)_q$-NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, $(CH_2)_q$-heteroaryl,
wherein for each occurrence of cycloalkyl, heterocycle, aryl, and heteroaryl as one or more of R^A, R^Y, and R^Q, is optionally substituted with one or more of C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, OH, C_{1-6} alkoxy, and C_{1-6} baloalkoxy; and
each q independently is 0, 1, 2, 3, 4, 5, or 6.

[0057] In one aspect, the Y ring or ring system contains a B atom in the ring or ring system.

[0058] In one aspect, the Y ring or ring system is substituted with a 4-, 5-, or 6-membered ring, which contains a B atom in the ring.

[0059] In one aspect, when Y is incorporated in or is substituted with a ring or ring system that is selected from:


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and

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or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof.

[0060] In one aspect, L^1 is a direct bond.

[0061] In one aspect, A is a 5- or 6-membered heteroaryl or phenyl

[0062] In one aspect, A is phenyl.

[0063] In one aspect, R^7 is COOH.

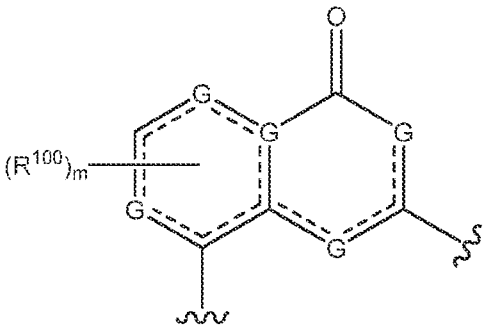
[0064] In one aspect, L^2 is O.

[0065] In one aspect, L^2 is NH.

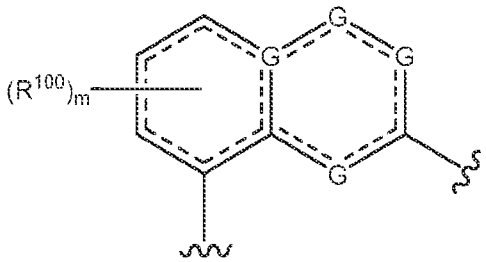
[0066] In one aspect, R^{1a} is H or CH_3.

[0067] In one aspect, R^{1b} is H or CH_3.

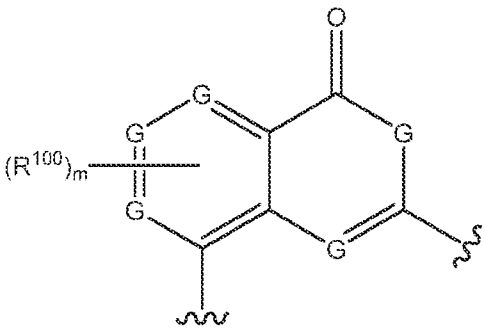
[0068] In one aspect, Q is selected from the group consisting of:



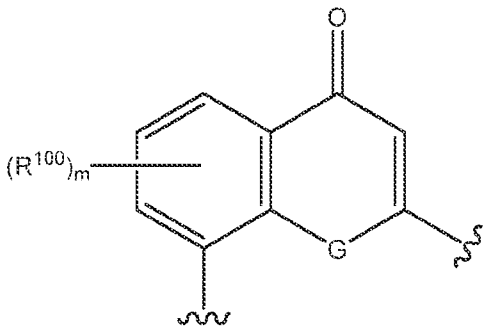
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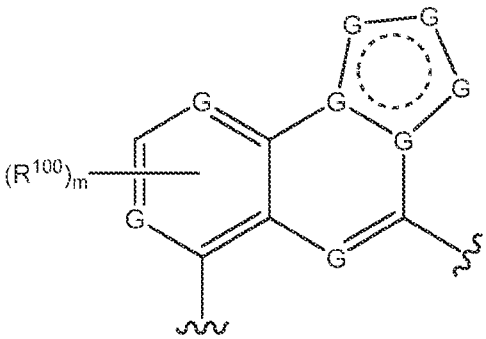
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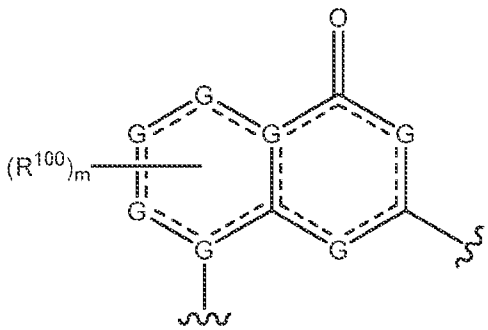
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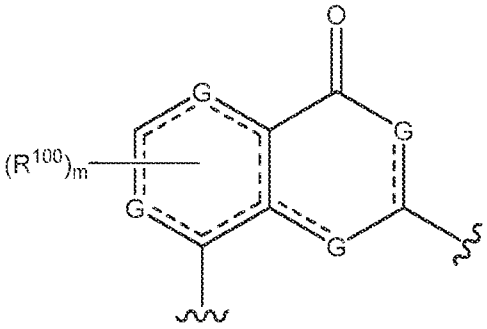
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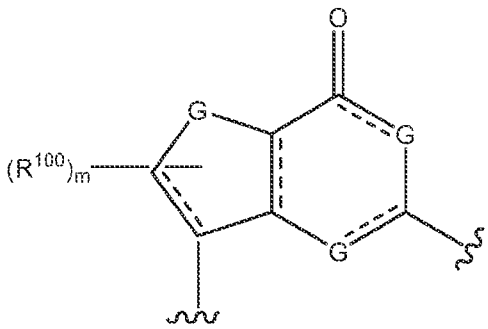


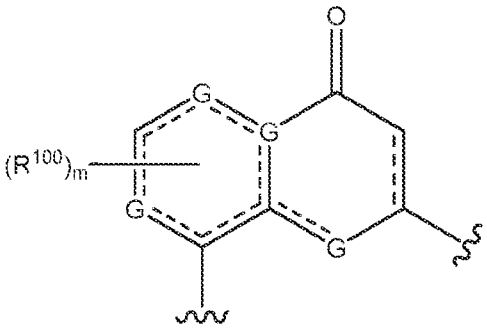
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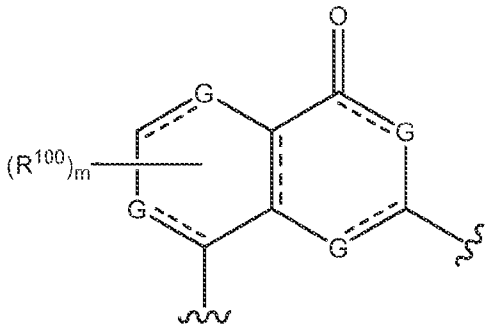


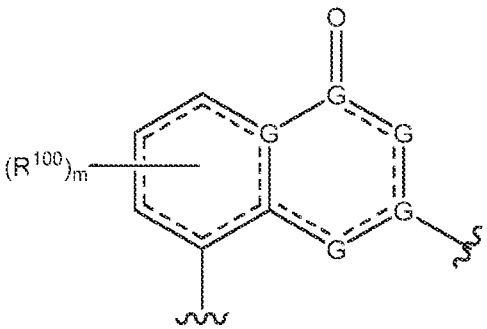
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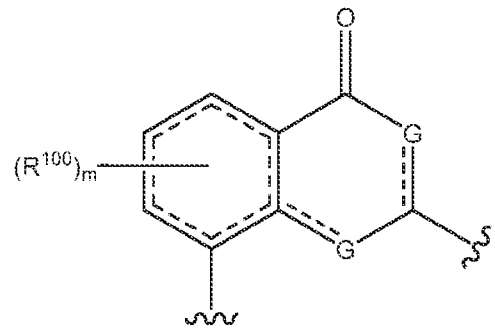


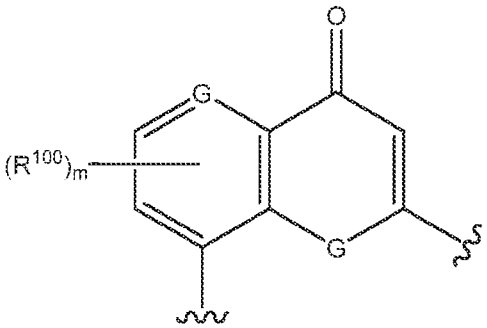


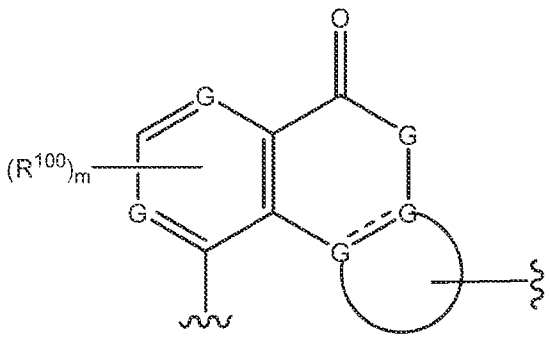


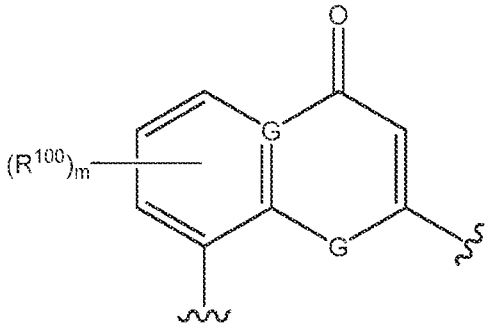




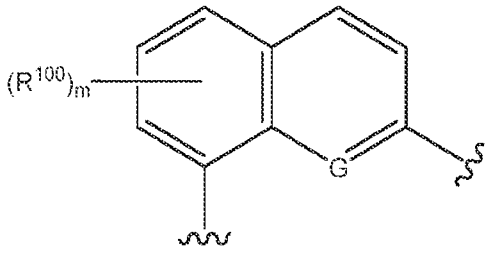








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wherein

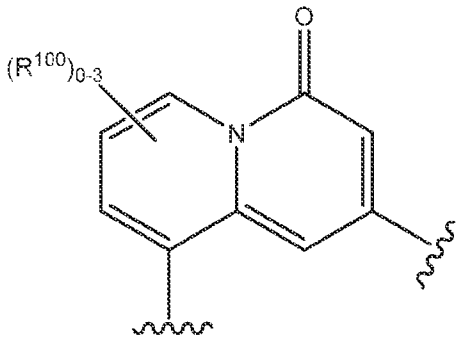
each G is, at each occurrence, independently selected from carbon or a heteroatom selected from O, N, or S;

each m is, at each occurrence, independently selected from 0, 1, 2, 3, 4, 5, and 6;

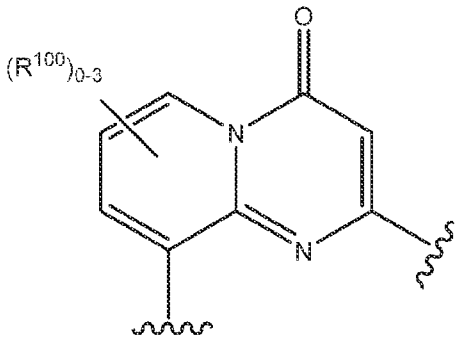
when m is not 0, each R^{100} may be substituted from any depicted ring; and

when present, each R^{100} is the same or different and independently is selected from the group consisting of halogen, OH, oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $(CH_2)_q$-N(H or C_{1-6}alkyl), C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl, wherein each of the cycloalkyl, heterocycle, aryl, and heteroaryl is optionally substituted with one or more halogen, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

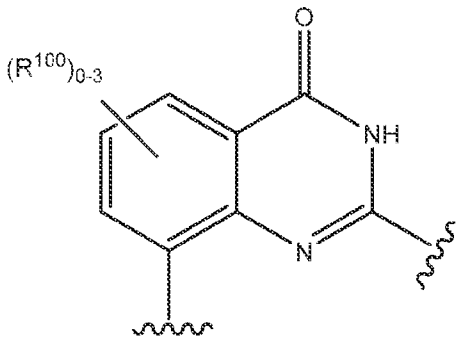
[0069] In one aspect, Q is selected from the group consisting of:



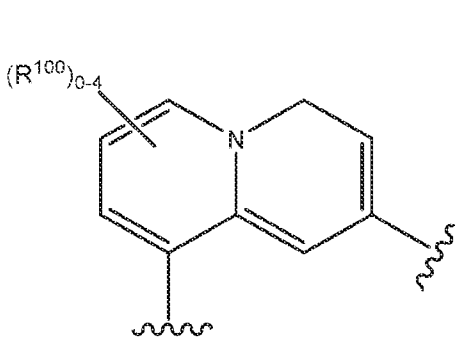
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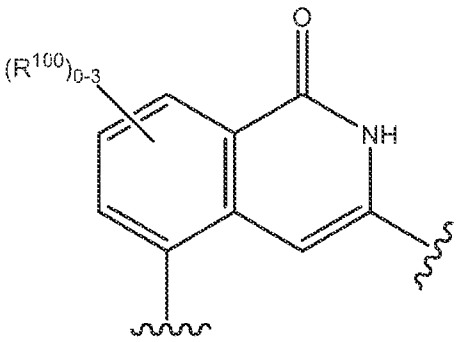
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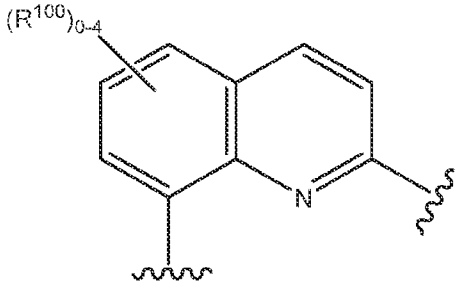
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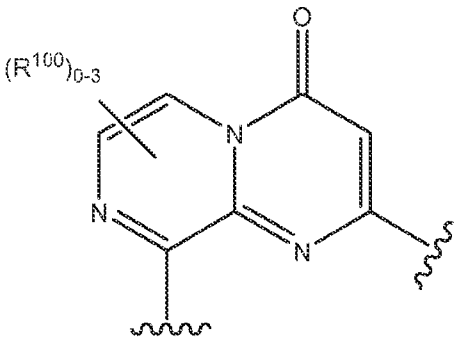
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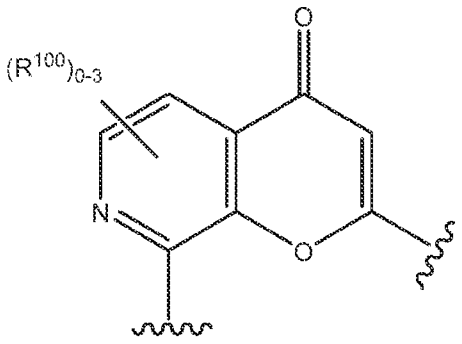
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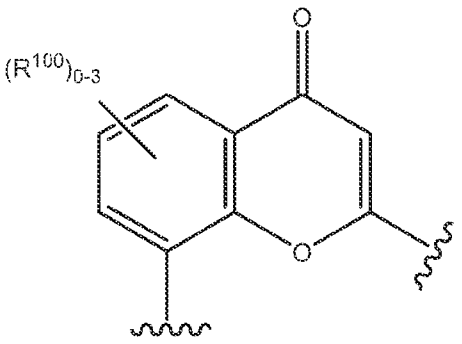
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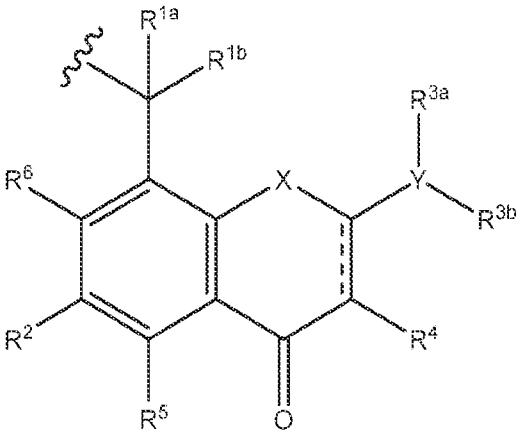


, and



.

[0070] In one embodiment, Q is:



(Q^B1),

wherein

X is $C(R^x)_2$, O, NR^x, or S;

each R^x independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^2 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^4 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^5 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

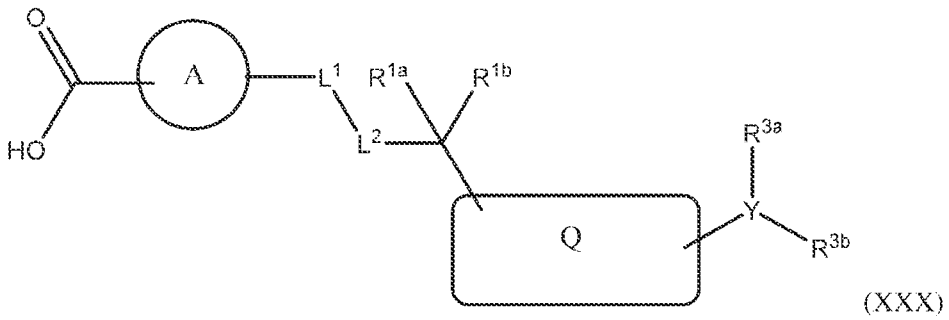
R^6 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

and

each R^{100} is independently H, halogen, OH, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, C_{2-6} alkynoxy, C_{1-6} haloalkoxy, C_{2-6} haloalkenoxy, and C_{2-6} alkynoxy.

[0071] In one aspect, X is O.

[0072] One embodiment of the present disclosure includes a compound of Formula XXX:



(XXX)

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof, wherein

A is selected from the group consisting of

C_{1-6} alkyl,

C_{2-6} alkenyl,

C_{2-6} alkynyl, and

3- to 14- membered mono-ring or fused ring system, which may have one or more degrees of unsaturation, and which may contain one or more heteroatoms selected from O, N, or S,

each of which A may be further substituted with one or more R^A;

Q is a 8- to 14- membered fused ring system, which may have one or more degrees of unsaturation, which may contain one or more heteroatoms selected from O, N, or S, and which may be further substituted with one or more R^Q;

L^1 is selected from the group consisting of a direct bond, optionally substituted cycloalkylene, optionally substituted heterocyclylene, optionally substituted arylene, and optionally substituted heteroarylene;

L^2 is selected from the group consisting of O and NH;

each of R^{1a} and R^{1b} is the same or different and is independently is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, and O-C_{2-6} alkynyl;

Y is selected from:

H, where each of R^{3a} and R^{3b} are absent;

C-R^{3c}, R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

each of R^{3a} and R^{3b} is the same or different and independently is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; as noted hereinabove, the value for each of alkenyl and alkynyl includes a C1, with the intention that when Y is C, then Y may be bound through a double or triple bond to a C atom;

or

Y, as an C atom, combines with R^{3a} R^{3b} to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more heteroatoms selected from the group consisting of N, O, S, and B, and wherein the Y-containing ring or ring system is optionally substituted with one or more R^Y;

N, each of R^{3a} and R^{3b} independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

Y, as an N atom, combines with R^{3a} and R^{3b} to form a heterocyclic or heteroaromatic mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms selected from the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^Y;

O, when Y is O, R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

S, when Y is S, R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

provided that at least one of the following applies:

a) the Y ring or ring system contains a B atom in the Y ring or ring system;

b) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is $B(OH)_2$;

c) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

d) the Y ring or ring system is further substituted with one or more R^Y, which at least one R^Y is $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, where each of said cycloalkyl, heterocycle, aryl, or heteroaryl is substituted with $B(OH)_2$;

when present, each of R^A, R^Y, and R^Q which may be the same or different any independently is selected from the group consisting of: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-C(O)OH, $(CH_2)_q$-C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-C(O)NH_2, $(CH_2)_q$-C(O)NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C(O)N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-NHC(O)H, $(CH_2)_q$-NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl, $(CH_2)_q$-O-C(O)-$(CH_2)_r$-R^{140}, $(CH_2)_q$-NH-C(O)-$(CH_2)_r$-R^{140}, $(CH_2)_q$-O-C(O)-$(CH_2)_r$-OR^{140}, $(CH_2)_q$-NH-C(O)-$(CH_2)_r$-OR^{140}, $(CH_2)_q$-O-$(CH_2)_r$-R^{140}, $(CH_2)_q$-NH-$(CH_2)_r$-R^{140}, $(CH_2)_q$-O-$(CH_2)_r$-OR^{140}, and $(CH_2)_q$-NH-$(CH_2)_r$-OR^{140}, where R^{140} is an E3 ligase binding ligand,

each of q and r, independently is, at each occurrence, selected from 0, 1, 2, 3, 4, 5, and 6; and

wherein for each occurrence of cycloalkyl, heterocycle, aryl, and heteroaryl, as one or more of R^A, R^Y, and R^Q, is optionally substituted with one or more of C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

[0073] In one aspect, L^1 is a direct bond.

[0074] In one aspect, A is 5- or 6-membered heteroaryl or phenyl.

[0075] In one aspect, A is phenyl.

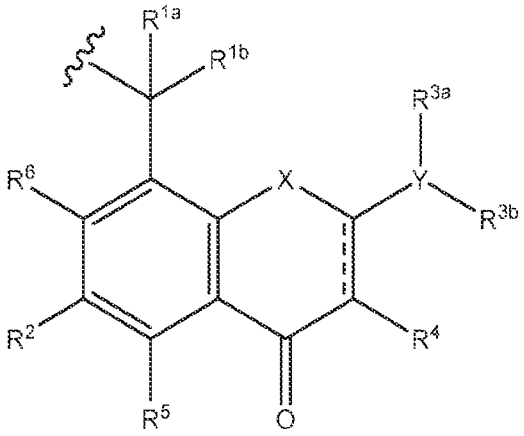
[0076] In one aspect, L^2 is O.

[0077] In one aspect, L^2 is NH.

[0078] In one aspect, R^{1a} is H or CH_3.

[0079] In one aspect, R^{1b} is H or CH_3.

[0080] In one aspect, Q is:



(Q^B1),

wherein

X is $C(R^x)_2$, O, NR^x, or S;

each R^x independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^2 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^4 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^5 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^6 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$,

$(CH_2)_m$-C(O)R^{100}, $(CH_2)_m$-C(O)OR^{100}, $(CH_2)_m$-C(O)N(R^{100})$_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

each m independently is 0, 1, 2, 3, 4, 5, or 6;

and

each R^{100} is independently H, halogen, OH, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, C_{2-6} alkynoxy, C_{1-6} haloalkoxy, C_{2-6} haloalkenoxy, and C_{2-6} alkynoxy.

[0081] In one aspect, X is O.

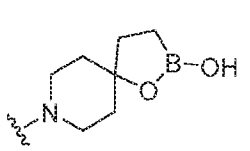
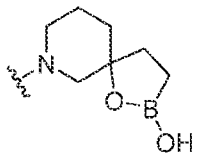
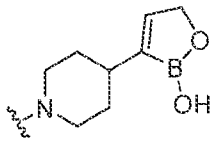
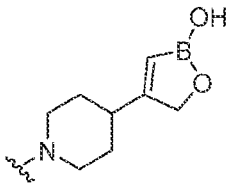
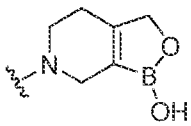
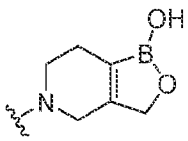
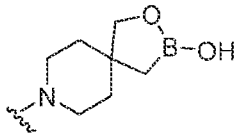
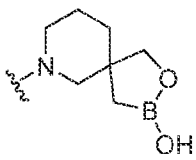
[0082] In one aspect, each of R^2, R^4, R^5, and R^6 independently is H, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6 cycloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, or C_{1-6} haloalkyl.

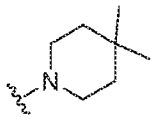
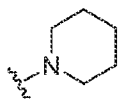
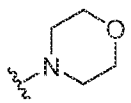
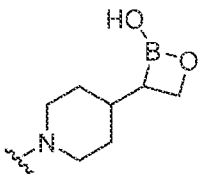
[0083] In one aspect, R^2 is H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; R^5 is H; and R^6 is H.

[0084] In one aspect, R^2 is methyl.

[0085] In one aspect, R^4 is methyl.

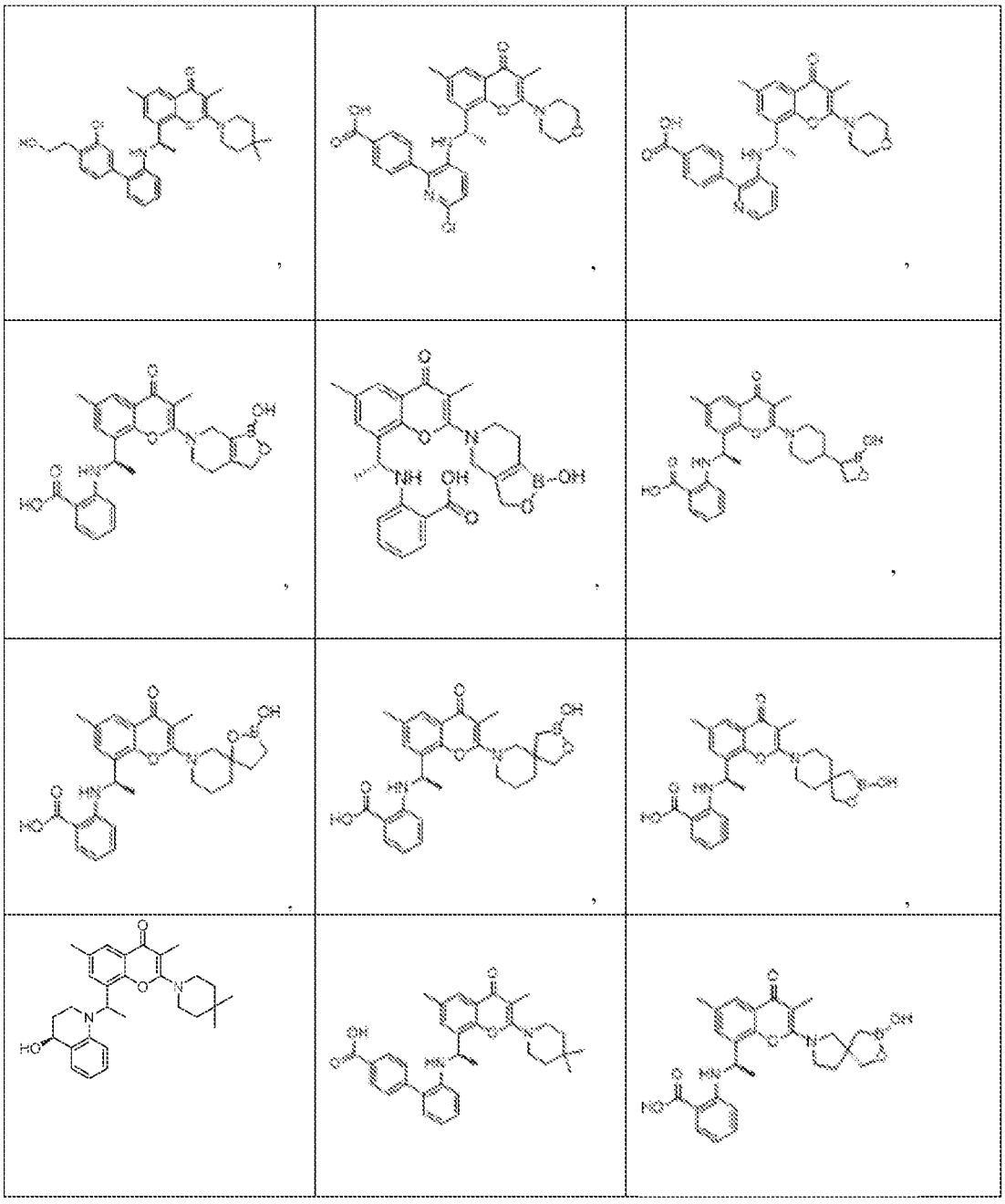
[0086] In one aspect, Y is incorporated in or is substituted with a ring or ring system that is selected from:

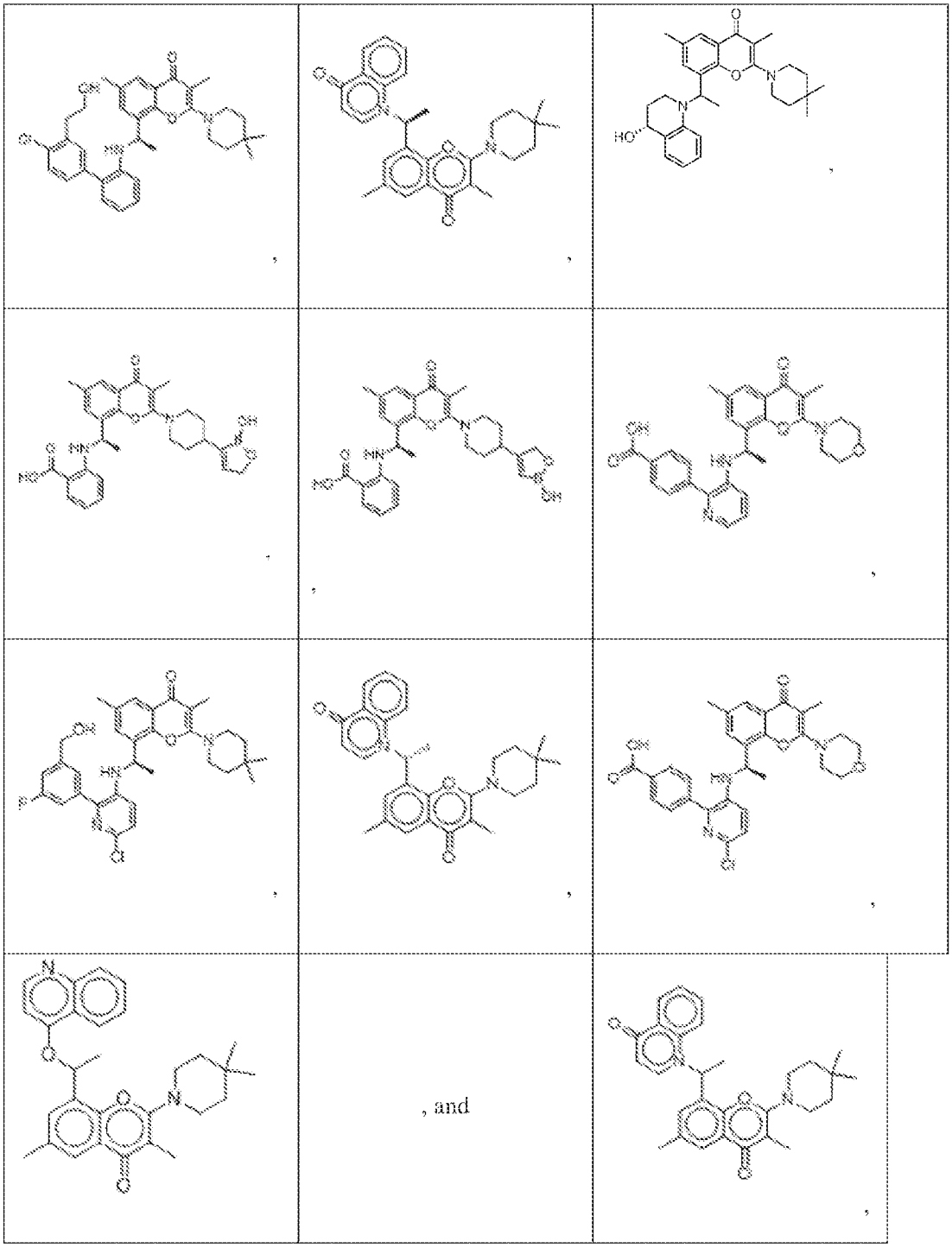

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or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof.

[0087] One embodiment of the present disclosure includes a compound selected from the group consisting of:



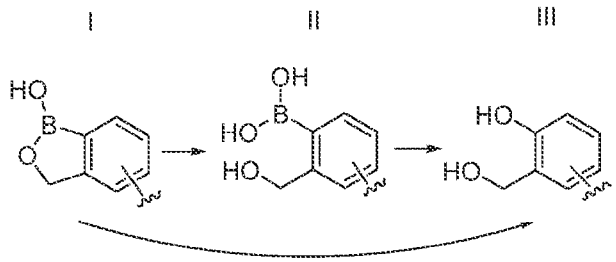


, and

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof.

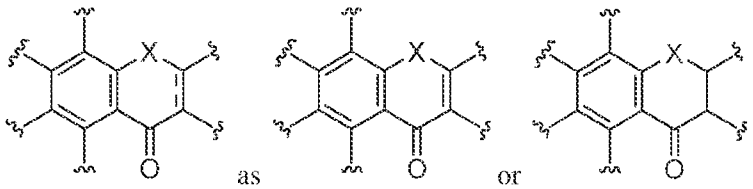
[0020] As provided in more detail herein and as appreciated by those skilled in the art, embodiments of the present invention may include a boron atom incorporated into a ring. Metabolic oxidation or hydrolysis may form alternative products (II) or (III). Species (II) may be in equilibrium with the parent

compound (I). The scope of the present disclosure is intended to capture all forms. A representative example is shown below:



[0021] As provided in more detail herein and as appreciated by those skilled in the art, embodiments of the present invention may include an isotopomer or isotopic isomer, wherein one or more atom of a compound of the present disclosure is replaced with an isotope, such as deuterium for hydrogen or ^{13}C for carbon. The scope of the present disclosure is intended to capture isotopic forms of the compounds.

[0022] One aspect of the present disclosure includes a depicted dashed bond. In a preferred embodiment, the depicted dashed bond is a pi bond. An additional aspect of the present disclosure includes where the depicted dashed bond indicates a pi bond is absent, wherein the octet is filled by hydrogen atoms.



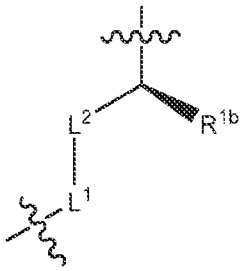
[0023] Portions of one or more embodiments of the present disclosure may be incorporated as disclosed herein to create a compound of the present disclosure. Reference is hereby made to the synthetic teaching and examples disclosed of one or more of the following patent publications: WO 2024/026423, WO 2024/008122, WO 2024/000401, WO 2023/239710, WO 2023/230262, WO 2023/207881, WO 2023/205680, WO 2023/192416, WO 2023/159155, WO 2023/081209, WO 2023/078401, WO 2023/060262, WO 2024/026419, WO 2024/026424, and WO 2021/202964, each of which is incorporated herein with regard to the synthetic teaching. In certain embodiments, a portion, Q, may be selected from the noted publications. In certain embodiments, a portion, Y, may be selected from the noted publications. For example, a portion, of the depicted $Y(R^{3a})(R^{3b})$, may be selected from the noted publications.

[0024] One aspect of the present disclosure includes wherein the compound is a racemate.

[0025] One aspect of the present disclosure includes wherein the compound is a single stereoisomer substantially free of any alternative forms.

[0026] One aspect of the present disclosure includes wherein the stereoisomeric form is R.

[0027] In once aspect, a chiral center is in the R configuration, as depicted by:



[0028] One aspect of the present disclosure includes wherein the compound is a tautomeric form of a preferred equilibria.

[0029] One embodiment of the present disclosure includes a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present disclosure and a pharmaceutically acceptable excipient.

[0030] One embodiment of the present disclosure includes a method of inhibiting cell proliferation comprising contacting a cell with an effective amount of a compound of the present disclosure.

[0031] One embodiment of the present disclosure includes a method for treating cancer in a patient comprising administering a therapeutically effective amount of a compound of the present disclosure to a patient in need thereof.

[0032] One embodiment of the present disclosure includes a method of treating a PI3K-mediated disease or disorder in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of the present disclosure.

[0033] One aspect includes a method of treating a disease or disorder mediated by one or more PIK3CA genes comprising modulating one or more of wild type or one or more mutations of the one or more PIK3CA genes. The scope of the present disclosure includes all other isoforms.

[0034] One aspect includes modulating one mutation.

[0035] One aspect includes modulating two or more mutations.

[0036] One aspect includes modulating wild type.

[0037] One aspect includes wherein the PIK3CA is a PIK3CA mutant.

[0038] One aspect includes wherein the PIK3CA mediates a cancer.

[0039] One aspect includes wherein the PIK3CA regulates cancer initiation, progression, or metasasis.

[0040] One aspect includes wherein wherein the one or more mutations are any p110 mutation.

[0041] One aspect includes wherein the one or more mutations are selected from one or more mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

[0042] One aspect includes wherein the one or more mutations are selected from one or more mutations of H1047, E545, and E542.

[0043] One aspect includes wherein modulation is inhibition.

[0044] One aspect includes wherein modulation is selective inhibiton for one or more mutations over wild-type.

[0045] One aspect includes wherein the mutations are selected from H1047X, E545X, and E542X.

[0046] One aspect includes wherein the mutation is H1047X.

[0047] One aspect includes wherein the mutation is H1047L

[0048] One aspect includes wherein the mutation is H1047R.

[0049] One aspect includes wherein a mutation is E545X.

[0050] One aspect includes wherein the mutation is E545K.

[0051] One aspect includes wherein a mutation is E542X.

[0052] One aspect includes wherein the mutation is E542K.

[0053] One aspect includes wherein the method further comprises administering a compound of the present disclosure.

[0054] One aspect includes wherein modulation is selective inhibition over wild-type, providing preferential inhibition at a multiple level of: greater than 1,

[0055] One aspect includes wherein the mutations are selected from H1047X, E545X, and E542X.

[0056] One aspect includes wherein a mutation is H1047X.

[0057] One aspect includes wherein the mutation is H1047L

[0058] One aspect includes wherein the mutation is H1047R.

[0059] One aspect includes wherein the mutation is GLU545X.

[0060] One aspect includes wherein the mutation is E545K.

[0061] One aspect includes wherein the mutation is GLU542X.

[0062] One aspect includes wherein the mutation is E542K.

[0063] One aspect includes wherein the p110 mutated protein subunit comprises at least one amino acid mutation compared to the wild type p110 protein subunit.

[0064] One aspect includes wherein the at least one amino acid mutation are selected from one or more mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

[0065] One aspect includes wherein the one or more mutations are selected from one or more of H1047, E545, and E542.

[0066] One aspect includes comprising administering a compound of the present disclosure.

[0067] One aspect includes modulating one or more of H1047L and H1047R.

[0068] One aspect includes modulating GLU545K.

[0069] One aspect includes modulating GLU542K.

[0070] One aspect includes administering a compound of the present disclosure

[0071] One embodiment of the present disclosure includes a method of inhibiting a PIK3CA gene target protein (PI3K) comprising modulating two or more mutant variants selected from mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

[0072] One aspect includes wherein the two or more mutant varients are selected from mutations of H1047, E545, and E542

[0073] One embodiment of the present disclosure includes a method of treating a disease or disorder mediated by PIK3CA, comprising modulating two or more mutant variants selected from mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

[0074] One aspect includes wherein the two or more mutant varients are selected from mutations of H1047, E545, and E542.

[0075] One aspect includes administering a compound of the present disclosure.

[0076] One embodiment of the present disclosure includes a method of modulating a PI3K to treat a disease or disorder by interacting a compound of the present disclosure with at least two mutant variants.

[0077] One aspect includes wherein the PI3K gene target is PIK3CA.

[0078] One aspect includes wherein the PI3K mediates a cancer.

[0079] One aspect includes wherein the PI3K regulates cancer initiation, progression, or metastasis.

[0080] One aspect includes wherein the mutant variants are selected from mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

[0081] One aspect includes wherein the mutant variants are selected from mutations of one or more of H1047, E545, and E542.

[0082] One aspect includes wherein modulation is inhibition.

[0083] One aspect includes wherein modulation is selective inhibiton over wild-type.

[0084] One aspect includes wherein the mutation is H1047X.

[0085] One aspect includes wherein the mutation is H1047L.

[0086] One aspect includes wherein the mutation is H1047R.

[0087] One aspect includes wherein the mutation is E545X.

[0088] One aspect includes wherein the mutation is E545K.

[0089] One aspect includes wherein the mutation is E542.

[0090] One aspect includes wherein the mutation is E542K.

[0091] In one embodiment, the present disclosure includes a method of the present disclosure, wherein the disease or disorder is cancer.

[0092] One aspect includes wherein the disease or disorder is PROS: PIK3CA-Related Overgrowth Spectrum.

[0093] One aspect includes wherein the disease or disorder is breast cancer, colorectal cancer, uterine cancer, bladder cancer, lung cancer, giloma, head and neck cancer, or other solid tumors.

[0094] One aspect includes wherein the disease or disorder is breast cancer.

[0095] In one embodiment, the present disclosure includes a method comprising administration of one or more additional therapeutic agent.

[0096] One aspect includes wherein administration is of two or more additional therapeutic agents.

[0097] One aspect includes wherein the additional therapeutic agents are selected from selective estrogen receptor degraders, Protac-mediated estrogen receptor inhibitors, complete estrogen receptor antagonists, sarcoplasmic reticulum calcium ATPase inhibitors, CDK2/4/6 inhibitors, CDK4/6 inhibitors, and aromatase inhibitors.

[0098] One aspect includes wherein the additional therapeutic agents are selected from fulvestrant, vepdegestrant, palazestrant, imlunestrant, elacestrant, giredestrant, camizestrant, palbociclib, ribociclib, abemaciclib, anastronzole, exemestane, and letrozole.

[0099] One aspect includes wherein each agent is provided in a separate dosage form.

[00100] One aspect includes wherein one or more agent is provided in a combined dosage form.

[00101] In one embodiment, the present disclosure includes a method to modulate one or more PI3K enzymes to regulate one or more of disease initiation and progression comprising interaction with at least one histidine and modulation of at least one surface accessible amino acid or residue.

[00102] One aspect includes wherein one or more PI3K is inhibited.

[00103] One aspect includes wherein the PI3K is PI3Kα.

[00104] One aspect includes wherein the PI3Kα is a mutated variant thereof.

[00105] In one embodiment, the present disclosure includes a method for treating cancer in a patient in need thereof, comprising:

determining that the cancer is associated with a PI3K wild-type or one or more PI3K mutations; and administering to the patient a therapeutically effective amount of a compound of the present disclosure

[00106] One aspect includes wherein the PI3K is a mutated variant thereof.

[00107] In one embodiment, the present disclosure includes a compound of the present disclosure, for use in therapy.

[00108] In one embodiment, the present disclosure includes a compound of the present disclosure, for use in the treatment of cancer.

[00109] In one embodiment, the present disclosure includes a compound of the present disclosure, for use in the inhibition of PI3K.

[00110] In one aspect, the PI3K is PI3Kα.

[00111] In one aspect, the PI3Kα is wild type.

[00112] In one aspect, the PI3Kα is a mutated variant thereof.

[00113] In one embodiment, the present disclosure includes a use of a compound of the present disclosure, in the manufacture of a medicament for the treatment of cancer.

[00114] In one embodiment, the present disclosure includes a use of a compound of the present disclosure, in the manufacture of a medicament for the inhibition of activity of PI3K.

[00115] In one embodiment, the present disclosure includes a use of a compound of the present disclosure in the manufacture of a medicament for the treatment of a PI3K-mediated disease or disorder.

[00116] In one aspect, the PI3K is PI3Kα.

[00117] In one aspect, the PI3Kα is wild type.

[00118] In one aspect, the PI3Kα is a mutated variant thereof.

[00119] One embodiment of the present disclosure includes a process for preparing a compound of the present disclosure.

[00120] One embodiment of the present disclosure includes a compound obtained by a process of the present disclosure.

[00121] One or more aspects and embodiments may be incorporated in a different embodiment although not specifically described. That is, all aspects and embodiments may be combined in any way or combination.

Brief Description of the Drawings

[00122] Figure 1 provides tabulated biological data for compounds of the present disclosure.

Detailed Description

Definitions

[00123] When referring to the compounds disclosed herein, the following terms have the following meanings unless indicated otherwise. The following definitions are meant to clarify, but not limit, the terms defined. If a particular term used herein is not specifically defined, such term should not be considered indefinite. Rather, terms are used within their accepted meanings.

[00124] As used herein, "alkyl" refers to monovalent saturated aliphatic hydrocarbon groups having from 1 to 20 carbon atoms, preferably 1-8 carbon atoms, more preferably 1-6 carbon atoms. The hydrocarbon chain may be either straight-chained or branched. Illustrative alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, and *tert*-butyl. Similarly, an "alkenyl" group refers to an alkyl

group having one or more double bonds present in the chain, and an "alkynyl" group refers to an alkyl group having one or more triple bonds present in the chain.

[00125] Certain labels relevant to the present disclosure include reference to an alpha designation, such as an isotype. As used herein, "a," "alpha," and "α," may be used interchangeably.

[00126]

[00127] As used herein "halogen" or "halo" refers to a halogen. In some embodiments, the halogen is preferably Br, Cl, or F.

[00128] As used herein, "haloalkyl" refers to monovalent saturated aliphatic hydrocarbon groups having from 1 to 20 carbon atoms, preferably 1-8 carbon atoms, more preferably 1-6 carbon atoms, wherein at least one hydrogen atom is substituted by a halogen, including but not limited to perhalo groups where all hydrogen atoms are replaced with halogen atoms. The haloalkyl chain can be either straight-chained or branched. Illustrative alkyl groups include trifluoromethyl, trifluoroethyl, trifluoropropyl, trifluorobutyl, and pentafluoroethyl. Similarly, a "haloalkenyl" group refers to a haloalkyl group having one or more double bonds present in the chain, and a "haloalkynyl" group refers to a haloalkyl group having one or more triple bonds present in the chain.

[00129] The term "haloalkyloxy" refers to O-haloalkyl.

[00130] As used herein, "alkoxy" refers to an O-alkyl group having the specified number of carbon atoms. Alkenoxy and alkynoxy are used similarly to refer to groups with one or more double or triple bonds, respectively. Such groups may be depicted as O-alkyl, O-alkenyl, and O-alkynyl, and should be considered an alternative but equivalent recitations.

[00131] An "alkylene," group is an alkyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Exemplary alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Moreover, an "alkylene" linker group refers to a divalent alkyl group, namely $(CH_2)_x$, where x is 1 to 20, preferably 1 to 8, preferably 1 to 6, and more preferably 1 to 3.

[00132]

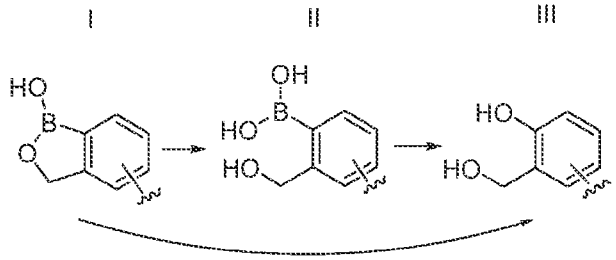
[00133] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteroatom selected from the group consisting of O, S, and N.

[00134] As used herein, "hydroxyalkyl" refers to an alkyl group as herein defined substituted with one or more –OH group. Similarly, a "hydroxyalkenyl" group refers to a hydroxyalkyl group having one or more double bonds present in the chain, and a "hydroxyalkynyl" group refers to a hydroxyalkyl group having one or more triple bonds present in the chain. Likewise, a "dihydroxyalkyl" group provides two –OH substituents.

[00135] As used herein, "aryl" refers to a substituted or unsubstituted carbocyclic aromatic ring system, either pendent or fused, such as phenyl, naphthyl, anthracenyl, phenanthryl, tetrahydronaphthyl, or indane. A preferred aryl group is phenyl.

[00136] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group as defined herein above, either of which may independently be optionally substituted or unsubstituted. An example of an aralkyl group is $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl. An example of a substituted aralkyl is wherein the alkyl group is substituted with hydroxyalkyl.

[00137] As appreciated by those skilled in the art, boron is able to form dative bonds with, for example, oxygen or nitrogen under some circumstances. Dative bonds are usually weaker than covalent bonds. In situations where a boron is covalently bonded to at least one oxygen or nitrogen, and is at the same time datively bonded to an oxygen or nitrogen, respectively, the dative bond and covalent bond between the boron and the two identical heteroatoms can interconvert or be in the form of a resonance hybrid. Additionally, the dative bond may be reversible depending on the chemical structure of the parent compound and the biological environement. For example, reversible dative bonds formed via a boron atom may lead to the formation of hydrolysis products (II) or metabolic oxidation products (III). Hydrolysis products (II) may be in equilbrium with the parent compound (I). The scope of the present disclosure is intended to capture all forms. A representative example is shown below:



[00138] There is potential uncertainty surrounding the exact nature and extent of electron sharing in these situations. The structures supplied are intended to include any and all possible bonding scenarios between boron and the atom to which it is bound.

[00139]

[00140] As used herein, "cycloalkyl" refers to a saturated, an unsaturated or a partially saturated hydrocarbon ring, containing from 3 to 15 ring atoms. Illustrative cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, as well as partially saturated versions thereof, such as cyclohexenyl, and cyclohexadienyl. Moreover, bridged rings, such as adamantane, are included within the definition of "cycloalkyl."

[00141] As used herein, the term "heterocyclyl" refers to an unsaturated or partially saturated hydrocarbon ring, containing from 3 to 15 ring atoms, wherein one or more carbon atom is replaced with a heteroatom selected from B, O, N, S, or Si, where each N, S, or Si may be oxidized, and where each N may be quarternized. A heterocyclyl group may be attached to the remainder of the molecule through a heteroatom. Heterocyclyl does not include heteroaryl. Examples include, but are not limited to, aziridine, oxirane, thiirance, azetidine, oxetane, thietane, pyrrolidine, pyrazolidine, imidazolidine, tetrahydrofuran, tetrahydrothiophene, piperidine, piperazine, tetrahydropyran, thiane, morpholine, thiomorpholine, pyrrolizidine, indoline, decahydroquinoline, tetrahydroquinoline, and azaadamantane.

[00142] The term "heterocyclylalkyl" refers to a heterocyclyl group as defined herein covalently linked to an alkyl group as defined hereinabove wherein the radical is on the alkyl group, wherein the alkyl group of the heterocyclylalkyl may be optionally substituted.

[00143] As used herein, the term "heteroaryl" or "heteroaromatic" refers to aromatic ring groups having 5 to 14 ring atoms selected from carbon and at least one (typically 1-4, more typically 1 or 2) heteroatom (e.g., boron, oxygen, nitrogen, sulfur, or silicon). They include monocyclic rings and polycyclic rings in which a monocyclic heteroaromatic ring is fused to one or more other carbocyclic aromatic or heteroaromatic rings. Examples of monocyclic heteroaryl groups include, but are not limited to, furanyl (e.g., 2-furanyl, 3-furanyl), imidazolyl (e.g., N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 2-oxadiazolyl, 5-oxadiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), pyrazolyl (e.g., 3-pyrazolyl, 4-pyrazolyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), triazolyl (e.g., 2-triazolyl, 5-triazolyl), tetrazolyl (e.g., tetrazolyl) and thienyl (e.g., 2-thienyl, 3-thienyl. Examples of monocyclic six-membered nitrogen-containing heteroaryl groups include pyrimidinyl, pyridinyl and pyridazinyl. Examples of polycyclic aromatic heteroaryl groups include carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, indolyl, acridinyl, or benzisoxazolyl.

[00144] The terms "arylalkyl," "heteroarylalkyl," and "heterocyclylalkyl" refers to those radicals in which an aryl, heteroaryl, or heterocyclyl group is linked through an alkyl group. Examples includes benzyl, phenethyl, pyridylmethyl, and the like. The terms also include alkyl linking groups in which a carbon atom, for example, a methylene group, has been replaced by, for example, an oxygen atom. Examples include phenoxymethyl, pyrid-2-yloxymethyl, 3-(naphth-1-yloxy)propyl, and the like. Similarly, the term "benzyl" as used herein is a radical in which a phenyl group is attached to a CH_2 group, thus, a CH_2Ph group. Benzyl groups may be substituted or unsubstituted. The term substituted benzyl refers to radicals

in which the phenyl group or CH_2 contains one or more substituents. In one embodiment, the phenyl group may have 1 to 5 substituents, or in another embodiment 2 to 3 substituents.

[00145] A "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, wherein the radical is on the alkyl group, either of which is independently optionally substituted or unsubstituted. Examples of heteroarylalkyl groups include a heteroaryl group having 5, 6, 9, or 10 ring atoms bonded to a C1-C6 alkyl group. Examples of heteroarylalkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, thiazolylethyl, benzimidazolylmethyl, benzimidazolylethyl quinazolinylmethyl, quinolinylmethyl, quinolinylethyl, benzofuranylmethyl, isoquinolinylmethyl, cinnolinylmethyl, and benzothiophenylethyl. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[00146] As used herein "optionally substituted" refers to a substitution of a hydrogen atom, which would otherwise be present for the substituent. When discussing ring systems, the optional substitution is typically with 1, 2, or 3 substituents replacing the normally-present hydrogen. When referencing straight and branched moieties, however, the number of substitutions may be more, occurring wherever hydrogen is present. The substitutions may be the same or different.

[00147] Illustrative substituents, which with multiple substituents can be the same or different, include deuterium, halogen, haloalkyl, R', OR', OH, SH, SR', NO_2, CN, C(O)R', NH_2, C(O)OR', OC(O)R', $CON(R')_2$, $OC(O)N(R')_2$, NH_2, NHR', $N(R')_2$, NHCOR', NHCOH, $NHCONH_2$, NHCONHR', $NHCON(R')_2$, NRCOR', NRCOH, $NHCO_2H$, $NHCO_2R'$, $NHC(S)NH_2$, NHC(S)NHR', $NHC(S)N(R')_2$, CO_2R', CO_2H, CHO, $CONH_2$, CONHR', $CON(R')_2$, $S(O)_2H$, $S(O)_2R'$, SO_2NH_2, S(O)H, S(O)R', SO_2NHR', $SO_2N(R')_2$, $NHS(O)_2H$, $NR'S(O)_2H$, $NHS(O)_2R'$, $NR'S(O)_2R'$, $Si(R')_3$, where each of the preceding may be linked through a divalent alkylene linker, $(CH_2)_x$, where x is 1, 2, or 3. In embodiments where a saturated carbon atom is optionally substituted with one or more substituent groups, the substituents may be the same or different and also include =O, =S, =NNHR', $=NNH_2$, $=NN(R')_2$, =N-OR', =N-OH, =NNHCOR', $=NNHCO_2R'$, $=NNHCO_2H$, $=NNHSO_2R'$, $=NNHSO_2H$, =N-CN, =NH, or =NR'. For each of the preceding, each may be linked through an alkylene linker, $(CH_2)_x$, where x is 1, 2, or 3, Each occurrence of R' is the same or different and represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, or when two R' are each attached to a nitrogen atom, they may form a saturated or unsaturated heterocyclic ring containing from 4 to 6 ring atoms.

[00148] In some embodiments of the present disclosure, a heteroatom may be a boron (B) atom.

[00149] The scope of the present disclosure includes isotopic versions of the compounds herein disclosed. As an example, one strategy to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites includes an attempt to replace one or more hydrogen atoms with deuterium

atoms. Deuterium is a safe, stable, non-radioactive isotope of hydrogen. Compared to hydrogen, deuterium forms stronger bonds with carbon. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability. At the same time, because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

[00150] Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, M I et al, J Pharm Sci, 1975, 64:367-91; Foster, A B, Adv Drug Res 1985, 14:1-40 ("Foster"); Kushner, D J et al, Can J Physiol Pharmacol 1999, 79-88; Fisher, M B et al, Curr Opin Drug Discov Devel, 2006, 9:101-09 ("Fisher")). The results have been variable and unpredictable. For some compounds deuteration caused decreased metabolic clearance in vivo. For others, there was no change in metabolism. Still others demonstrated increased metabolic clearance. The variability in deuterium effects has also led experts to question or dismiss deuterium modification as a viable drug design strategy for inhibiting adverse metabolism (see Foster at p. 35 and Fisher at p. 101).

[00151] The effects of deuterium modification on a drug's metabolic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. Only by actually preparing and testing a deuterated drug can one determine if and how the rate of metabolism will differ from that of its non-deuterated counterpart. See, for example, Fukuto et al. (J. Med. Chem. 1991, 34, 2871-76). Many drugs have multiple sites where metabolism is possible. The site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug.

[00152] In the compounds of this disclosure, any atom designated specifically as "H" or "hydrogen", that position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, that position may be designated specifically as "D" or "deuterium", where the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

[00153] The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

[00154] In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium

incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[00155] A compound represented by a particular chemical structure containing one or more deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the potential deuterium positions. The relative amount of such isotopologues in a compound of this disclosure will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. As set forth above, the relative amount of such isotopologues will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues in toto will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

[00156] As used herein, "an effective amount" of a compound is an amount that is sufficient to negatively modulate or inhibit the activity of PI3K or a mutant thereof. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[00157] As used herein, a "therapeutically effective amount" of a compound is an amount that is sufficient to ameliorate, or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of PI3K or a mutant thereof. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[00158] As used herein, treatment means any manner in which the symptoms or pathology of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein.

[00159] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

[00160] As used herein, the term "about" when used to modify a numerically defined parameter (e.g., the dose of the PI3K inhibitor detailed herein or a pharmaceutically acceptable salt thereof, or the length of treatment time described herein) means that the parameter may vary by as much as 10% below or above the stated numerical value for that parameter. For example, a dose of about 5 mg/kg may vary between 4.5 mg/kg and 5.5 mg/kg. "About" when used at the beginning of a listing of parameters is meant to modify each parameter. For example, about 0.5 mg, 0.75 mg or 1.0 mg means about 0.5 mg, about 0.75 mg or about 1.0 mg. Likewise, about 5% or more, 10% or more, 15% or more, 20% or more, and 25% or more means about 5% or more, about 10% or more, about 15% or more, about 20% or more, and about 25% or more.

[00161] As used herein, a salt refers to any salt of a compound disclosed herein which retains its biological properties and which is not toxic or otherwise undesirable for pharmaceutical use.

[00162] Such salts may be derived from a variety of organic and inorganic counter-ions known in the art. Such salts include acid addition salts formed with organic or inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, sulfamic, acetic, trifluoroacetic, trichloroacetic, propionic, hexanoic, cyclopentylpropionic, glycolic, glutaric, pyruvic, lactic, malonic, succinic, sorbic, ascorbic, malic, maleic, fumaric, tartaric, citric, benzoic, 3-(4-hydroxybenzoyl)benzoic, picric, cinnamic, mandelic, phthalic, lauric, methanesulfonic, ethanesulfonic, 1,2-ethane-disulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, 4-chlorobenzenesulfonic, 2-naphthalenesulfonic, 4-toluenesulfonic, camphoric, camphorsulfonic, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic, glucoheptonic, 3-phenylpropionic, trimethylacetic, *tert*-butylacetic, lauryl sulfuric, gluconic, benzoic, glutamic, hydroxynaphthoic, salicylic, stearic, cyclohexylsulfamic, quinic, muconic acid, and like acids.

[00163] Salts further include, by way of example only, salts of non-toxic organic or inorganic acids, such as halides, such as, chloride and bromide, sulfate, phosphate, sulfamate, nitrate, acetate, trifluoroacetate, trichloroacetate, propionate, hexanoate, cyclopentylpropionate, glycolate, glutarate, pyruvate, lactate, malonate, succinate, sorbate, ascorbate, malate, maleate, fumarate, tartarate, citrate, benzoate, 3-(4-hydroxybenzoyl)benzoate, picrate, cinnamate, mandelate, phthalate, laurate, methanesulfonate (mesylate), ethanesulfonate, 1,2-ethane-disulfonate, 2-hydroxyethanesulfonate, benzenesulfonate (besylate), 4-chlorobenzenesulfonate, 2-naphthalenesulfonate, 4-toluenesulfonate, camphorate, camphorsulfonate, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylate, glucoheptonate, 3-phenylpropionate, trimethylacetate, *tert*-butylacetate, lauryl sulfate, gluconate, benzoate, glutamate, hydroxynaphthoate, salicylate, stearate, cyclohexylsulfamate, quinate, muconate, and the like.

[00164] Examples of inorganic bases that may be used to form base addition salts include, but are not limited to, metal hydroxides, such as lithium hydroxide, sodium hydroxide, and potassium hydroxide; metal amides, such as lithium amide and sodium amide; metal carbonates, such as lithium carbonate, sodium carbonate, and potassium carbonate; and ammonium bases such as ammonium hydroxide and ammonium carbonate.

[00165] Examples of organic bases that may be used to form base addition salts include, but are not limited to, metal alkoxides, such as lithium, sodium, and potassium alkoxides including lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, and potassium tert-butoxide; quaternary ammonium hydroxides, such as choline hydroxide; and amines including, but not limited to, aliphatic amines (i.e., alkylamines, alkenylamines, alkynylamines, and alicyclic amines), heterocyclic amines, arylamines, heteroarylamines, basic amino acids, amino

sugars, and polyamines. In some embodiments, salt forms may include lithium, sodium, potassium, and amine salts.

[00166] The base may be a quaternary ammonium hydroxide, wherein one or more of the alkyl groups of the quaternary ammonium ion are optionally substituted with one or more suitable substituents. Preferably, at least one alkyl group is substituted with one or more hydroxyl groups. Non-limiting examples of quaternary ammonium hydroxides that may be used in accordance with the present disclosure include choline hydroxide, trimethylethylammonium hydroxide, tetramethylammonium hydroxide, and is preferably choline hydroxide. An alkylamine base may be substituted or unsubstituted. Non-limiting examples of unsubstituted alkylamine bases that may be used in accordance with the present disclosure include methylamine, ethylamine, diethylamine, and triethylamine. A substituted alkylamine base may be substituted with one or more hydroxyl groups, and preferably one to three hydroxyl groups. Non-limiting examples of substituted alkylamine bases that may be used in accordance with the present disclosure include 2-(diethylamino)ethanol, N,N-dimethylethanolamine (deanol), tromethamine, ethanolamine, and diolamine.

[00167] "Salt counterion", as used herein, refers to positively charged ions that associate with a compound of the invention when the boron is fully negatively or partially negatively charged. Examples of salt counterions include H^+, H_3O^+, ammonium, lithium, potassium, calcium, magnesium and sodium. The compounds comprising a boron bonded to a carbon and three heteroatoms (such as three oxygens described in this section) can optionally contain a fully negatively charged boron or partially negatively charged boron, due to the nature of the dative bond between the boron and one of the oxygens. Due to the negative charge, a positively charged counterion may associate with this compound, thus forming a salt. Examples of positively charged counterions include H^+, H_3O^+, calcium, lithium, sodium, ammonium, potassium, magnesium. The salts of these compounds are implicitly contained in descriptions of these compounds. The present invention also encompasses compounds that are poly- or multi-valent species, including, for example, species such as dimers, trimers, tetramers and higher homologs of the compounds of use in the invention or reactive analogues thereof.

[00168] In certain cases, the depicted substituents may contribute to optical isomers and/or stereoisomerism. Compounds having the same molecular formula but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example when it is bonded to four different groups, a pair of enantiomers is possible. A molecule with at least one stereocenter may be characterized by the absolute configuration of its asymmetric center and is

designated (*R*) or (*S*) according to the rules of Cahn and Prelog (Cahn *et al.*, 1966, *Angew. Chem.* 78: 413-447, *Angew. Chem., Int. Ed. Engl.* 5: 385-414 (errata: *Angew. Chem., Int. Ed. Engl.* 5:511); Prelog and Helmchen, 1982, *Angew. Chem.* 94: 614-631, *Angew. Chem. Internat. Ed. Eng.* 21: 567-583; Mata and Lobo, 1993, *Tetrahedron: Asymmetry* 4: 657-668) or may be characterized by the manner in which the molecule rotates the plane of polarized light and is designated dextrorotatory or levorotatory (namely, as (+)- or (-)-isomers, respectively). A chiral compound may exist as either an individual enantiomer or as a mixture thereof. A mixture containing equal proportions of enantiomers is called a "racemic mixture".

[00169] In certain embodiments, the compounds disclosed herein may possess one or more asymmetric centers, and such compounds may therefore be produced as a racemic mixture, an enantiomerically enriched mixture, or as an individual enantiomer. Unless indicated otherwise, for example by designation of stereochemistry at any position of a formula, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Methods for determination of stereochemistry and separation of stereoisomers are well-known in the art.

[00170] In certain embodiments, the compounds disclosed herein are "stereochemically pure". A stereochemically pure compound has a level of stereochemical purity that would be recognized as "pure" by those of skill in the art. Of course, this level of purity may be less than 100%. In certain embodiments, "stereochemically pure" designates a compound that is substantially free, i.e. at least about 85% or more, of alternate isomers. In particular embodiments, the compound is at least about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5% or about 99.9% free of other isomers.

[00171] All isomeric forms (especially all regio- and stereoisomeric forms, e.g. all chiral, enantiomeric, diastereomeric, racemic forms, tautomeric and all geometric isomeric forms, as well as atropisomers, (including interconverting atropisomerism) of a compound of the present description are intended within this invention, unless the specific isomer form is specifically indicated. Obviously, the isomer which is pharmacologically most effective and most free from side effects is preferred.

[00172] As used herein, the terms "subject" and "patient" may be used interchangeably herein. In one embodiment, the subject is a human. In one embodiment, the subject is a companion animal such as a dog or cat. In a further embodiment, the subject is an animal such as a sheep, cow, horse, goat, fish, pig, or domestic fowl (e.g., chicken, turkey, duck, or goose). In another embodiment, the subject is a primate such as a monkey such as a cynomolgous monkey or a chimpanzee.

[00173] In addition, a pharmaceutically acceptable prodrug of the compound represented by the formulae is also included in the present disclosure. The pharmaceutically acceptable prodrug refers to a compound having a group which may be converted into an amino group, a hydroxyl group, a carboxyl group, or the

like, by solvolysis or under a physiological condition. Examples of the groups forming the prodrug include those as described in Prog. Med., 5, 2157-2161 (1985) or "Pharmaceutical Research and Development" (Hirokawa Publishing Company, 1990), vol. 7, Drug Design, 163-198. The term prodrug is used throughout the specification to describe any pharmaceutically acceptable form of a compound which, upon administration to a patient, provides the active compound. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present disclosure. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that may be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound.

[00174] The present disclosure includes all pharmaceutically acceptable isotopically-labelled compounds of the disclosure wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the disclosure include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, boron, such as ^{10}B and ^{11}B, , fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S. Certain isotopically-labelled compounds of the disclosure, such as those incorporating a radioactive isotope, may be useful in drug or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{10}B, ^{18}F, ^{15}O and ^{13}N, may be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Reference is made to BNCT or boron neutron capture therapy. Isotopically-labeled compounds of the disclosure may generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Compositions and Methods of Administration

[00175] The compounds of the present disclosure used in the methods disclosed herein may be administered in certain embodiments using pharmaceutical compositions including at least one compound, if appropriate in the salt form, either used alone or in the form of a combination with one or

more compatible and pharmaceutically acceptable carriers, such as diluents or adjuvants, or with another agent. There are provided compositions which comprise a derivative of a compound of the present disclosure or a salt thereof, and an acceptable excipient, carrier or diluent. The composition may also be in a variety of forms which include, but are not limited to, oral formulations, injectable formulations, and topical, dermal or subdermal formulations.

[00176] The composition may be in a form suitable for oral use, for example, as dietary supplements, troches, lozenges, chewables, tablets, hard or soft capsules, emulsions, aqueous or oily suspensions, aqueous or oily solutions, dispersible powders or granules, syrups, or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, bittering agents, flavoring agents, coloring agents and preserving agents in order to provide elegant and palatable preparations.

[00177] Lozenges are solid compositions containing one or more active ingredients intended to dissolve or disintegrate slowly in the oral cavity by passive incubation in the oral cavity, or actively by sucking or chewing. They may be used for systemic effect if the drug is absorbed through the buccal or esophageal lining or is swallowed. In particular, soft lozenges may be chewed or allowed to dissolve slowly in the mouth. These dosage forms have the advantage of being flavored and thus easy to administer to both human and animal patients; have formulas that are easy to change and may be patient specific; may deliver accurate amounts of the active ingredient to the oral cavity and digestive system; and allow for the drug to remain in contact with the oral or esophageal cavity for an extended period of time.

[00178] Tablets may contain the active ingredient in admixture with non-toxic, pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

[00179] Formulations for oral use may be hard gelatin capsules, wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. Capsules may also be soft gelatin capsules, wherein the active ingredient is mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[00180] The compositions may also be in the form of oil-in-water or water-in-oil emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening agents, bittering agents, flavoring agents, and preservatives.

[00181] In one embodiment of the formulation, the composition is in the form of a microemulsion. Microemulsions are well suited as the liquid carrier vehicle. Microemulsions are quaternary systems comprising an aqueous phase, an oily phase, a surfactant and a cosurfactant. They are translucent and isotropic liquids. Microemulsions are composed of stable dispersions of microdroplets of the aqueous phase in the oily phase or conversely of microdroplets of the oily phase in the aqueous phase. The size of these microdroplets is less than 200 nm (1000 to 100,000 nm for emulsions). The interfacial film is composed of an alternation of surface-active (SA) and co-surface-active (Co-SA) molecules which, by lowering the interfacial tension, allows the microemulsion to be formed spontaneously. In one embodiment of the oily phase, the oily phase may be formed from mineral or vegetable oils, from unsaturated polyglycosylated glycerides or from triglycerides, or alternatively from mixtures of such compounds. In one embodiment of the oily phase, the oily phase comprises of triglycerides; in another embodiment of the oily phase, the triglycerides are medium-chain triglycerides, for example, C_8-C_{10} caprylic/capric triglyceride. In another embodiment, the oily phase will represent a % v/v range selected from the group consisting of about 2 to about 15%; about 7 to about 10%; and about 8 to about 9% v/v of the microemulsion. The aqueous phase includes, for example, water or glycol derivatives, such as propylene glycol, glycol ethers, polyethylene glycols or glycerol. In one embodiment of the glycol derivatives, the glycol is selected from the group consisting of propylene glycol, diethylene glycol monoethyl ether, dipropylene glycol monoethyl ether and mixtures thereof. Generally, the aqueous phase will represent a proportion from about 1 to about 4% v/v in the microemulsion. Surfactants for the microemulsion include diethylene glycol monoethyl ether, dipropylene glycol monomethyl ether, polyglycolyzed C_8-C_{10} glycerides or polyglyceryl-6 dioleate. In addition to these surfactants, the cosurfactants include short-chain alcohols, such as ethanol and propanol. Some compounds are common to the three components discussed above, for example, aqueous phase, surfactant and cosurfactant. However, it is well within the skill level of the practitioner to use different compounds for each component of the same formulation. In one embodiment, for example, for the amount of surfactant/cosurfactant, the cosurfactant to surfactant ratio may be from about 1/10 to about 1/2. In

another embodiment for the amount of cosurfactant, there will be from about 25 to about 75% v/v of surfactant and from about 10 to about 55% v/v of cosurfactant in the microemulsion.

[00182] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, atachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as sucrose, saccharin or aspartame, bittering agents, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid, or other known preservatives.

[00183] Aqueous suspensions may contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occuring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide, with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents and/or bittering agents, such as those set forth herein.

[00184] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, bittering, flavoring and coloring agents, may also be present.

[00185] As used herein, the term "dispersion" refers to a disperse system in which one substance, the dispersed phase, is distributed, in discrete units, throughout a second substance (the continuous phase or vehicle). The size of the dispersed phase can vary considerably (e.g. colloidal particles of nanometer dimension, to multiple microns in size). In general, the dispersed phases can be solids, liquids, or gases. In the case of a solid dispersion, the dispersed and continuous phases are both solids. In pharmaceutical applications, a solid dispersion can include a crystalline drug (dispersed phase) in an amorphous polymer (continuous phase); or alternatively, an amorphous drug (dispersed phase) in an amorphous polymer (continuous phase). In some embodiments, a solid dispersion includes the polymer constituting the

dispersed phase, and the drug constitute the continuous phase. In other embodiments, a solid dispersion includes the drug constituting the dispersed phase, and the polymer constituting the continuous phase. An amorphous solid dispersion (ASD) refers to an amorphous active pharmaceutical ingredient stabilized by a polymer matrix to provide enhanced characteristics, including stability, to a solid material having no long range order in the position of its molecules. The moledules in an amorphous solid are generally arranged in a random manner with no well-defined arrangement. Amorphous solids are generally isotropic, i.e. exhibit similar properties in all directions and do not have definite melting points. Amorphous solid dispersions (ASDs) may be used for poorly soluble pharmaceutical compounds. In an ASD, the solubility of the drug substance is improved by disarranging its crystalline lattice to produce a higher energy state of amorphous form (See, Duarte et al., 2015; Elgindy et al., 2011).

[00186] Spray drying converts a liquid feed to a dried particulate form. Spray drying generally involves bringing into contact a highly dispersed liquid suspension or solution and a sufficient volume of hot air to promote drying of the liquid droplets. For example, a liquid solution containing a compound of the present disclosure, or a salt thereof and at least one polymer can be sprayed into a current of warm filtered gas that evaporates the solvent and conveys the dried product to a collector. Evaporated solvent and spent gas are removed from the collector and can be sent to a condenser to capture the solvent. For example, commercial spray dryers are manufactured by Buchi Ltd. and Niro (e.g., the PSD line of spray driers manufactured by Niro) (see. US 2004/0105820, US 2003/0144257). Techniques and methods for spray drying may be found in Perry's Chemical Engineering Handbook, 6th Ed., R. H. Perry, D. W. Green & J. O. Maloney, eds.), McGraw-Hill book co. (1984); and Marshall "Atomization and Spray-Drying" 50, Chem. Eng. Prog. Monogr. Series 2 (1954). All three references are incorporated herein in their entirety by reference. Accordingly, compositions comprising compounds of the present disclosure may prepared as spray dry dispersions.

[00187] Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring agent(s) and coloring agent(s).

[00188] The compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. Preservatives, such as phenol or benzyl alcohol, may be used.

[00189] In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00190] Topical, dermal and subdermal formulations may include emulsions, creams, ointments, gels or pastes.

[00191] Organic solvents that may be used in the disclosure include but are not limited to: acetyltributyl citrate, fatty acid esters such as the dimethyl ester, diisobutyl adipate, acetone, acetonitrile, benzyl alcohol, butyl diglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, monomethylacetamide, dipropylene glycol monomethyl ether, liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone (e.g. N-methylpyrrolidone), diethylene glycol monoethyl ether, ethylene glycol and diethyl phthalate, or a mixture of at least two of these solvents.

[00192] As vehicle or diluent, compositions of the present disclosure may include plant oils such as, but not limited to soybean oil, groundnut oil, castor oil, corn oil, cotton oil, olive oil, grape seed oil, sunflower oil, etc.; mineral oils such as, but not limited to, petrolatum, paraffin, silicone, etc.; aliphatic or cyclic hydrocarbons or alternatively, for example, medium-chain (such as C_8-C_{12}) triglycerides.

[00193] Dosage forms may contain from about 0.5 mg to about 5 g of an active agent.

[00194] In one embodiment of the disclosure, the active agent is present in the formulation at a concentration of about 0.05 to 10% weight/volume.

[00195] A compound of the present disclosure may be employed as such or in the form of their preparations or formulations as combinations.

[00196] These one or more additional active agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

[00197] The pharmaceutical preparation comprising the compounds of the present disclosure for delivery to a human or other mammal, is preferably in unit dosage form, in which the preparation is subdivided into unit doses containing an appropriate quantity of the active component. The unit dosage form may be a packaged preparation containing discrete quantities of the preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form may be a capsule, tablet or lozenge itself, or it may be an appropriate number of any of these in packaged form.

[00198] The quantity of active component in a unit dose preparation may be varied or adjusted from about 0.1 mg to about 2000 mg, according to the particular application and the potency of the active component. The composition may, if desired, also contain other compatible therapeutic agents.

[00199] In therapeutic use for the treatment or alleviation of one or more symptoms for one or more diseases or disorders, such as cancer, in a human or other mammal, the compounds utilized in the method of treatment are administered at an initial dosage of about 0.1 mg/kg to about 2,000 mg/kg per interval, about 0.1 mg/kg to about 1,900 mg/kg per interval, about 0.1 mg/kg to about 1,800 mg/kg per interval, about 0.1 mg/kg to about 1,700 mg/kg per interval, about 0.1 mg/kg to about 1,600 mg/kg per interval, about 0.1 mg/kg to about 1,500 mg/kg per interval, about 0.1 mg/kg to about 1,400 mg/kg per interval, about 0.1 mg/kg to about 1,300 mg/kg per interval, about 0.1 mg/kg to about 1,200 mg/kg per interval, about 0.1 mg/kg to about 1,100 mg/kg per interval, about 0.1 mg/kg to about 1,000 mg/kg per interval, about 0.1 mg/kg to about 500 mg/kg per interval, about 0.1 mg/kg to about 100 mg/kg per interval, about 0.1 mg/kg to about 50.0 mg/kg per interval, about 0.1 mg/kg to about 10.0 mg/kg per interval, about 0.1 mg/kg to about 5.0 mg/kg per interval, about 0.1 mg/kg to about 2.5 mg/kg per interval, about 0.1 mg/kg to about 2.0 mg/kg per interval, about 0.1 mg/kg to about 1.0 mg/kg per interval, about 0.4 mg/kg to about 1.0 mg/kg per interval, or about 0.4 mg/kg to about 0.6 mg/kg per interval. Preferred intervals may be daily, twice-daily, thrice-daily, weekly, bi-weekly, monthly, quarterly, semi-annually, or annually. The dosages may be varied depending on the requirements of the patient, for example, the size of the human or mammal being treated, the severity of the condition being treated, the route of administration, and the potency of the compound(s) being used. Determination of the proper dosage and route of administration for a particular situation is within the skill of the practitioner. Generally, the treatment will be initiated with smaller dosages, which are less than the optimum dose of the compound, which may be increased in small increments until the optimum effect under the particular circumstances of the condition is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

[00200] In therapeutic use, the compounds of the present disIcosure are useful in manufacture of a medicament for a method of the treating any indication where inhibition of PI3K or a mutant variant thereof would be desirable.

[00201] One embodiment of the present disclosure provides the compounds of the present disclosure incorporated in a proteolysis targeting chimera (PROTAC), namely a heterobifunctional molecule comprising two active domains and a linker. A PROTAC may include an E3 ubiquitin ligase targeting moiety and a compound of the present disclosure, namely a targeting warhead to bind a target protein meant for degradation.

[00202] In yet another aspect, the disclosure provides for methods for inhibiting PI3K, including PI3Ka, or a mutant thereof, activity in a cell, comprising contacting the cell in which inhibition of PI3K, including PI3Ka, or a mutant thereof, activity is desired with an effective amount of a compound of the present disclosure, pharmaceutically acceptable salts thereof, or pharmaceutical compositions containing

the compound or pharmaceutically acceptable salt thereof. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo.

[00203] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" a PI3K, including PI3Kα, or a mutant thereof, with a compound provided herein includes the administration of a compound provided herein to an individual or patient, such as a human, having PI3K, including PI3Kα, or a mutant thereof, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing the PI3K, including PI3Kα, or a mutant thereof.

[00204] In one embodiment, a cell in which inhibition of PI3K, or a mutant thereof, activity is desired is contacted with an effective amount of a compound of the present disclosure to negatively modulate the activity. In other embodiments, a therapeutically effective amount of pharmaceutically acceptable salt or pharmaceutical compositions containing the compound of the present disclosure may be used.

[00205] By negatively modulating the activity of PI3K, or a mutant thereof, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced PI3K, or a mutant thereof, activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to effect the desired negative modulation of PI3K, or a mutant thereof. The degree of modulation of PI3K, or a mutant thereof, may be monitored in vitro using well known methods, including those described below. In addition, the inhibitory activity of exemplary compounds in cells may be monitored, for example, by measuring the inhibition of PI3K, or a mutant thereof, to assess the effectiveness of treatment and dosages may be adjusted accordingly by the attending medical practitioner.

[00206] In another aspect, methods of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of the present disclosure, pharmaceutically acceptable salts thereof or pharmaceutical compositions comprising the compound or pharmaceutically acceptable salts thereof are provided.

[00207] The compositions and methods provided herein may be used for the treatment of a PI3K-associated cancer (or mutant variant thereof) in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of the present disclosure, pharmaceutically acceptable salts thereof or pharmaceutical compositions comprising the compound or pharmaceutically acceptable salts thereof are provided. In one embodiment, the PI3K-associated, or mutant variant thereof, is cancer.

[00208] The compositions and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as lung, prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the disclosure include, but are not limited, to tumor types such as astrocytic, breast, cervical, colorectal,

endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More specifically, these compounds can be used to treat: cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi,

lipoma, angioma, dermatofibroma, keloids, psoriasis; and adrenal glands: neuroblastoma. In certain embodiments, the cancer is selected from breast cancer, colorectal cancer, uterine cancer, bladder cancer, lung cancer, giloma, head and neck cancer, and other solid tumors. In some embodiments, the cancer is breast cancer.

[00209] The concentration and route of administration to the patient will vary depending on the cancer to be treated. The compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions comprising such compounds and salts also may be co-administered with other anti-neoplastic compounds, e.g., chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively.

[00210] In another aspect the disease/condition/cancer to be treated/prevented as herein (above and below) defined is selected from the group consisting of pancreatic cancer, colorectal cancer, lung cancer, multiple myeloma, melanoma, uterine cancer, endometrial cancer, thyroid cancer, acute myeloid leukemia, bladder cancer, urothelial cancer, gastric cancer, cervical cancer, head and neck squamous cell carcinoma, diffuse large B cell lymphoma, esophageal cancer, chronic lymphocytic leukemia, hepatocellular cancer, breast cancer, ovarian cancer, prostate cancer, glioblastoma, renal cancer and sarcomas, salivary gland cancers and urinary tract cancers.

[00211] The compounds of the disclosure may be used on their own or in combination with one or several other pharmacologically active substances such as state-of-the-art or standard-of-care compounds, such as, e.g., cell proliferation inhibitors, anti-angiogenic substances, steroids or immune modulators/checkpoint inhibitors, and the like.

[00212] Pharmacologically active substances which may be administered in combination with the compounds according to the disclosure, include, without being restricted thereto, hormones, hormone analogues and antihormones (e.g. tamoxifen, toremifene, raloxifene, fulvestrant, megestrol acetate, flutamide, nilutamide, bicalutamide, aminoglutethimide, cyproterone acetate, finasteride, buserelin acetate, fludrocortisone, fluoxymesterone, medroxyprogesterone, octreotide), aromatase inhibitors (e.g. anastrozole, letrozole, liarozole, vorozole, exemestane, atamestane), LHRH agonists and antagonists (e.g. goserelin acetate, luprolide), inhibitors of growth factors and/or of their corresponding receptors (growth factors such as for example platelet derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insuline-like growth factors (IGF), human epidermal growth factor (HER, e.g. HER2, HER3, HER4), and hepatocyte growth factor (HGF) and/or their corresponding receptors), inhibitors are for example (anti-)growth factor antibodies, (anti) growth factor receptor antibodies and tyrosine kinase inhibitors, such as for example cetuximab, gefitinib, afatinib, nintedanib, imatinib, lapatinib, bosutinib, bevacizumab and trastuzumab); antimetabolites (e.g. antifolates such as methotrexate, raltitrexed, pyrimidine analogues such as 5-

fluorouracil (5-FU), ribonucleoside and deoxyribonucleoside analogues, capecitabine and gemcitabine, purine and adenosine analogues such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine (ara C), fludarabine); antitumour antibiotics (e.g. anthracyclins such as doxorubicin, doxil (pegylated liposomal doxorubicin hydrochloride, myocet (non-pegylated liposomal doxorubicin), daunorubicin, epirubicin and idarubicin, mitomycin-C, bleomycin, dactinomycin, plicamycin, streptozocin); platinum derivatives (e.g. cisplatin, oxaliplatin, carboplatin); alkylation agents (e.g. estramustin, meclorethamine, melphalan, chlorambucil, busulphan, dacarbazin, cyclophosphamide, ifosfamide, temozolomide, nitrosoureas such as for example carmustin and lomustin, thiotepa); antimitotic agents (e.g. Vinca alkaloids such as for example vinblastine, vindesin, vinorelbin and vincristine; and taxanes such as paclitaxel, docetaxel); angiogenesis inhibitors (e.g. tasquinimod), tubuline inhibitors; DNA synthesis inhibitors, PARP inhibitors, topoisomerase inhibitors (e.g. epipodophyllotoxins such as for example etoposide and etopophos, teniposide, amsacrin, topotecan, irinotecan, mitoxantrone), serine/threonine kinase inhibitors (e.g. PDK 1 inhibitors, Raf inhibitors, A-Raf inhibitors, B-Raf inhibitors, CRaf inhibitors, mTOR inhibitors, mTORC1/2 inhibitors, PI3K inhibitors, PI3Ka inhibitors, dual mTOR/PI3K inhibitors, STK 33 inhibitors, AKT inhibitors, PLK 1 inhibitors, inhibitors of CDKs, Aurora kinase inhibitors), tyrosine kinase inhibitors (e.g. PTK2/FAK inhibitors), protein protein interaction inhibitors (e.g. IAP activator, Mcl-1 , MDM2/MDMX), MEK inhibitors, ERK inhibitors, FLT3 inhibitors, BRD4 inhibitors, IGF-1 R inhibitors, TRAILR2 agonists, Bcl-xL inhibitors, Bcl-2 inhibitors, Bcl-2/Bcl-xL inhibitors, ErbB receptor inhibitors, BCR-ABL inhibitors, ABL inhibitors, Src inhibitors, SHP2 inhibitors, rapamycin analogs (e.g. everolimus, temsirolimus, ridaforolimus, sirolimus), androgen synthesis inhibitors, androgen receptor inhibitors, DNMT inhibitors, HDAC inhibitors, ANG1/2 inhibitors, CYP17 inhibitors, radiopharmaceuticals, proteasome inhibitors, immunotherapeutic agents such as immune checkpoint inhibitors (e.g. CTLA4, PD1, PD-L1, PD-L2, LAG3, and TIM3 binding molecules/immunoglobulins, such as e.g. ipilimumab, nivolumab, pembrolizumab), ADCC (antibody-dependent cell-mediated cytotoxicity) enhancers (e.g. anti-CD33 antibodies, anti-CD37 antibodies, anti-CD20 antibodies), t-cell engagers (e.g. bi-specific T-cell engagers (BiTEs®) like e.g. CD3 x BCMA, CD3 x CD33, CD3 x CD1 9), PSMA x CD3), tumor vaccines and various chemotherapeutic agents such as amifostin, anagrelid, clodronat, filgrastin, interferon, interferon alpha, leucovorin, procarbazine, levamisole, mesna, mitotane, pamidronate and porfimer. As an example, an SHP2 (Src homology-2 domain-containing protein tyrosine phosphatase-2) is a non-receptor protein tyrosine phosphatase that removes tyrosine phosphorylation. Functionally, SHP2 serves as an important hub to connect several intracellular oncogenic signaling pathways, such as Jak/STAT, PI3K/AKT, RAS/Raf/MAPK, and PD-1/PD-L1 pathways. Mutations and/or overexpression of SHP2 has been associated with genetic developmental diseases and cancers.

[00213] In certain embodiments, a compound of the present disclosure may be combined with one or more additional therapeutic agent. In other embodiments, a compound of the present invention may be combined with two or more additional therapeutic agents. In one aspect, the additional therapeutic agents are selected from selective estrogen receptor degraders, Protac-mediated estrogen receptor inhibitors, complete estrogen receptor antagonists, sarcoplasmic reticulum calcium ATPase inhibitors, CDK2 inhibitors, CDK2/4/6 inhibitors, CDK4/6 inhibitors, aromatase inhibitors, KRAS inhibitors, RAF, MEK, or ERK inhibitors, AKT inhibitors, mTOR inhibitors, tyrosine kinase inhibitors, DNA Synthesis inhibitors, SHP2 inhibitors, BCL-2 family inhibitors, immune checkpoint inhibitors, and SRC inhibitors. In another aspect, the additional therapeutic agents are selected from palbociclib, abemaciclib, ribociclib, letrozole, fulvestrant, palazestrant, camizestrant, elacestrant, imlunestrant exernestane, anastrozole, LSZ102, cetuximab, trastuzumab, pertuzumab, nab-paclitaxel, tucatinib, vinorelbine, evexomostat, eribulin, capecitabine, gedatolisib, tamoxifen, zotatifin, neratinib, giredestrant, talazoparib, pembroluzimab, metformin, AMG-510, trametinib, dabrafenib, LY 3214996, PF-07104091, everolimus, and capivasertib. In one asepct, each agent is provided in a separate dosage form. In one aspect, one or more agent is provided in a combined dosage form.

[00214] Also provided herein is a compound of the present disclosure, or a salt thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

[00215] Also provided herein is a compound of the present disclosure, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of cancer.

[00216] Also provided herein is a compound of the present disclosure, or a pharmaceutically acceptable salt or solvate thereof for use in the inhibition of PI3K or a mutant variant thereof.

[00217] In some embodiments the mutant varient thereof may be a PI3Kα mutation of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110. In other embodiments, the mutant varient thereof may be a PI3Kα mutation of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, E110, R88, I391, R108H, Y1021, R93W, T1025A, R93, V344, R38, P539, E418, and E970

[00218] Also provided herein is a compound of the present disclosure, or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein, for use in the treatment of a PI3K-associated, or mutant variant, disease or disorder.

[00219] Also provided herein is the use of a compound of the present disclosure, or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of cancer.

[00220] Also provided herein is a use of a compound of the present disclosure or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for the inhibition of activity of PI3K or a mutant variant.

[00221] Also provided herein is the use of a compound of the present disclosure, or a pharmaceutically acceptable salt or solvate thereof, as defined herein, in the manufacture of a medicament for the treatment of a PI3K-associated disease or disorder.

[00222] Also provided herein is a method for treating cancer in a patient in need thereof, the method comprising (a) determining that cancer is associated with a PI3K mutation (e.g., as determined using an approved assay or kit); and (b) administering to the patient a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[00223] One skilled in the art will recognize that, both in vivo and in vitro trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

[00224] One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

[00225] The present disclosure explicitly encompasses those compounds presented below, including salt forms thereof. The present disclosure also encompasses those compounds presented below, including stereoisomers thereof. A composition comprising a therapeutically acceptable amount of any of these compounds is also within the scope of the disclosure. The composition may further comprise a pharmaceutically acceptable excipient, diluent, carrier, or mixture thereof. Such a composition may be administered to a subject in need thereof to treat or control a disease or disorder mediated, in whole or in part, directly or indirectly, by PI3K or a mutant form thereof. The composition may further comprise an additional active agent, as described herein.

[00226] **SYNTHETIC EXAMPLES**

[00227] Compounds of the present disclosure may be synthesized following the teachings of the schemes and specification. The following examples provide a more detailed description of the process conditions for preparing compounds of the present disclosure. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following schemes or modes of preparation. The compounds of the present disclosure may be prepared from commercially available reagents using the synthetic methods and reaction schemes described herein, or using other reagents and conventional methods well known to those skilled in the art, making appropriate modifications as would be appreciated by those of skill in the art.

[00228] Certain abbreviations may be used in describing the examples of the present disclosure. The abbreviations are believed to be used consistently within commonly accepted use of those skilled in the art.

[00229] As will be apparent, certain compounds of the present disclosure may not only represent a final product having the desired biological effect, but also capable of serving as a synthetic intermediate to yet an alternative final product compound of the present disclosure.

[00230] For compounds of the present disclosure that contain one or more chiral center, examples may be presented as racemic mixtures or may be characterized as having a particular stereochemical orientation. Stereochemical configuration herein has been labeled based on information from prior art regarding a preferential biology of one enantiomer over the other. Absolute configuration has not been characterized. All steriosomers for the depicted compounds are aspects of the invention. Moreover, although the following examples recite characterizing data for particular isomers, the order is random and does not necessarily provide any indication regarding the order of the recited compound names or depictions.

[00231] In the following schemes, general substituent groups are represented with assignments that may not align with the formulae of the present disclosure. The following schemes provide a key for such substituent groups that should be followed for the schemes and not applied to the formulae of the present disclosure.

[00232] Synthetic support for referenced portions of one or more embodiments of the present disclosure is hereby made to the synthetic teaching and examples disclosed of one or more of the following patent publications: WO 2024/026423, WO 2024/008122, WO 2024/000401, WO 2023/239710, WO 2023/230262, WO 2023/207881, WO 2023/205680, WO 2023/192416, WO 2023/159155, WO 2023/081209, WO 2023/078401, WO 2023/060262, WO 2024/026419, WO 2024/026424, and WO 2021/202964.

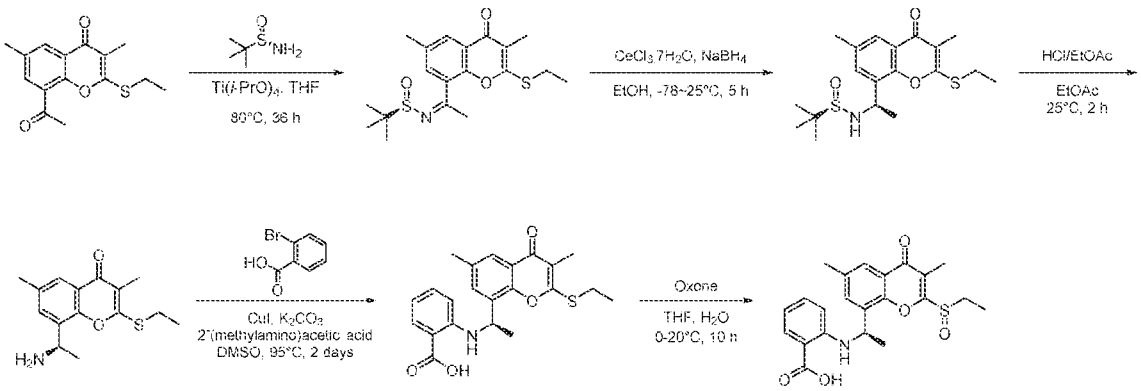
EXAMPLES

Experimental Procedures:

[00233] Reference is made to the disclosure of PCT/US2024/020036, which is hereby incorporated in its entirety, with particular reference to the synthetic teaching and incorporation of all schemes and examples.

[00234] Example 1

[00235] *Synthetic Scheme:*



[00236] *Experimental: Preparation of (R,Z)-N-[1-(2-ethylsulfanyl-3,6-dimethyl-4-oxo-chromen-8-yl) ethylidene]-2-methyl-propane-2-sulfinamide*

[00237] To a solution of 8-acetyl-2-ethylsulfanyl-3,6-dimethyl-chromen-4-one (19.00 g, 68.75 mmol, 1 *eq*) and (R)-2-methylpropane-2-sulfinamide (16.67 g, 137.51 mmol, 2 *eq*) in THF (400 mL) was added $Ti(i\text{-}PrO)_4$ (78.16 g, 275.01 mmol, 81.17 mL, 4 *eq*) at 25°C in one portion, the resulting reaction mixture was warmed to 80°C and stirred at 80°C for 36 h. The reaction mixture was cooled to 25°C, added water (1000 mL) and then filtered through a pad of celite. The filter cake was washed with EtOAc (500 mL x 3) and then the filtrate was extracted with EtOAc (300 mL x 5). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give the title compound. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.07, 8.02 (s, 1H), 7.45, 7.23 (s, 1H), 3.17-3.14 (m, 2H), 2.83, 2.47 (s, 3H), 2.47 (s, 3H), 2.10, 2.07 (s, 3H), 1.41 (t, J = 7.6 Hz, 3H), 1.32, 1.23 (s, 9H).

[00238] *Preparation of (R)-N-[(1R)-1-(2-ethylsulfanyl-3,6-dimethyl-4-oxo-chromen-8-yl)ethyl] -2-methyl-propane-2-sulfinamide*

[00239] To a mixture of (*R,Z*)-N-[1-(2-ethylsulfanyl-3.6-dimethyl-4-oxo-chromen-8-yl)ethylidene]-2-methyl-propane-2-sulfinamide (17.30 g, 45.58 mmol, 1 eq) and $CeCl_3.7H_2O$ (8.49 g, 22.79 mmol, 2.17 mL, 0.5 eq) in EtOH (300 mL) was added $NaBH_4$ (4.14 g, 109.40 mmol, 2.4 eq) at -78°C in portions under N_2. Then the resulting reaction mixture was warmed to 25°C slowly and stirred at 25°C for 5 h. The reaction mixture was cooled to 0°C and quenched by addition H_2O (200 mL) at 0 °C. Then the mixture was adjusted to pH = 7 with HCl (2 N) and extracted with EtOAc (150 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give the title compound (10.70 g, 28.04 mmol, 61.52% yield) as a light yellow solid. ^1H NMR ($CDCl_3$, 400 MHz) δ

7.94 (s, 1H), 7.48 (s, 1H), 5.16-5.12 (m, 1H), 3.50 (d, *J* = 3.2 Hz, 1H), 3.30-3.24 (m, 2H), 2.46 (s, 3H), 2.08 (s, 3H), 1.60 (d, *J* = 6.4 Hz, 3H), 1.47 (t, *J* = 7.2 Hz, 3H), 1.26 (s, 9H).

[00240] *Preparation of 8-[(1R)-1-aminoethyl]-2-ethylsulfanyl-3,6-dimethyl-chromen-4-one*

[00241] To a solution of (R)-N-[(1R)-1-(2-ethylsulfanyl-3,6-dimethyl-4-oxo-chromen-8-yl)ethyl]-2-methyl-propane-2-sulfinamide (10.70 g, 28.04 mmol, 1 *eq*) in EtOAc (100 mL) was added HCl/EtOAc (4 M, 100 mL) dropwise at 25°C, the resulting reaction mixture was stirred at 25°C for 2 h. The resulting suspension was directly filtered. The filter cake was dissolved in H_2O (150 mL), adjusted pH = 9 with $NH_3.H_2O$ and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (7.60 g, 24.22 mmol, 86.35% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.75 (s, 1H), 7.66 (s, 1H), 4.56 (q, *J* = 6.4 Hz, 1H), 3.27 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 2.03 (s, 2H), 1.93 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.31 (d, *J* = 6.4 Hz, 3H).

[00242] *Preparation of 2-[[(1R)-1-(2-ethylsulfanyl-3,6-dimethyl-4-oxo-chromen-8-yl)ethyl] amino]benzoic acid*

[00243] This reaction was carried out by 3.8 g x 2 batches in parallel. A mixture of 8-[(1R)-1-aminoethyl]-2-ethylsulfanyl-3,6-dimethyl-chromen-4-one (3.80 g, 13.70 mmol, 1 *eq*), 2-iodobenzoic acid (10.19 g, 41.10 mmol, 3 *eq*), CuI (521.82 mg, 2.74 mmol, 0.2 *eq*), K_2CO_3 (4.73 g, 34.25 mmol, 2.5 *eq*) and 2-(methylamino)acetic acid (244.11 mg, 2.74 mmol, 0.2 *eq*) in DMSO (50 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 95°C for 2 days under N_2 atmosphere. 2 parallel reactions were combined for work up. The reaction mixture was cooled to 25°C and directly filtered. The filtrate was diluted with H_2O (100 mL) and extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give the title compound (3.80 g, 9.56 mmol, 34.89% yield) as a light yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.81 (s, 1H), 8.35 (d, J = 6.0 Hz, 1H), 7.81 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.71 (s, 1H), 7.46 (s, 1H), 7.25-7.21 (m, 1H), 5.15-5.12 (m, 1H), 6.56 (t, J = 7.2 Hz, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 2.15-5.12 (m, 1H), 3.29 (q, *J* = 3.6 Hz, 2H), 2.33 (s, 3H), 1.96 (s, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.38 (t, *J* = 7.6 Hz, 3H).

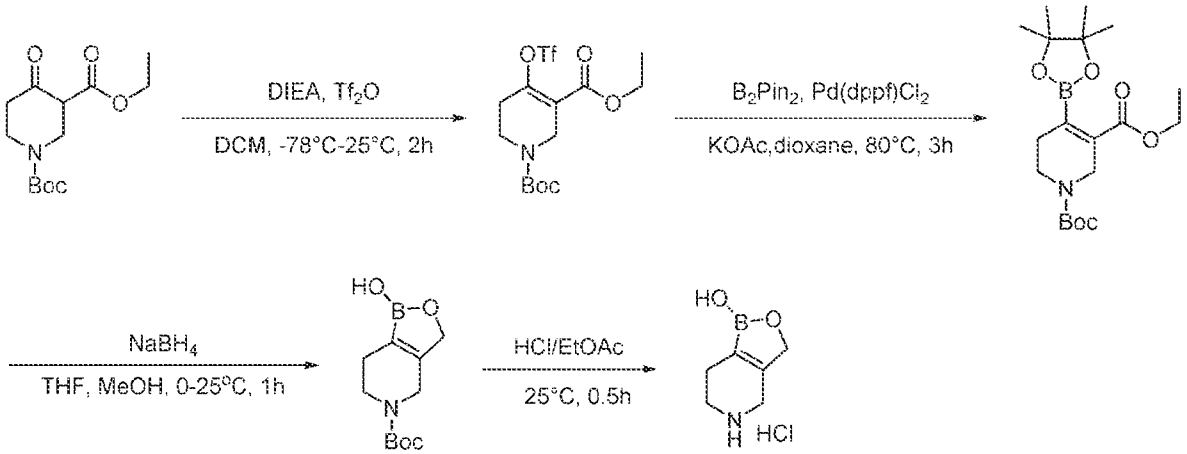
[00244] *Preparation of 2-[[(1R)-1-(2-ethylsulfinyl-3,6-dimethyl-4-oxo-chromen-8-yl)ethyl] amino]benzoic acid*

[00245] To a solution of 2-[[(1R)-1-(2-ethylsulfanyl-3,6-dimethyl-4-oxo-chromen-8-yl)ethyl]amino] benzoic acid (1.90 g, 4.78 mmol, 1 eq) in THF (30 mL) \H_2O (20 mL) was added oxone (2.41 g, 3.90 mmol, 0.82 eq) in portions at 0°C. Then the reaction mixture was warmed to 20°C and stirred at 20°C for

10 h. The reaction mixture was quenched by addition aq. $Na_2S_2O_8$ (30 mL) at 0°C, diluted with H_2O (25 mL) and the aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 60 mL/min) to give 2-[[(1R)-1-(2-ethylsulfinyl-3,6-dimethyl-4-oxo-chromen-8-yl)ethyl]amino]benzoic acid (1.20 g, crude) as a light yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.40-8.34 (m, 1H), 7.83-7.76 (m, 2H), 7.61-7.55 (m, 1H), 7.22-7.18 (m, 1H), 6.59-6.52 (m, 1H), 6.44-6.42 (m, 1H), 5.20-5.14 (m, 1H), 3.28-3.25 (m, 2H), 2.37-2.35 (m, 3H), 2.13-2.12 (m, 3H), 1.64-1.59 (m, 3H), 1.25 (t, *J* = 7.6 Hz, 3H).

[00246] Example 2: Synthesis of representative intermediates

[00247] *Synthetic Scheme*



[00248] *Preparation of 1-(tert-butyl) 3-ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1,3(2H)-dicarboxylate*

[00249] To a solution of O1-tert-butyl O3-ethyl 4-oxopiperidine-1,3-dicarboxylate (20.0 g, 73.72 mmol, 1 *eq*) and DIEA (47.64 g, 368.58 mmol, 64.20 mL, 5 *eq*) in DCM (300 mL) was added Tf_2O (24.96 g, 88.46 mmol, 14.60 mL, 1.2 eq) dropwise at -78°C, then the resulting reaction mixture was stirred at 25°C for 2 h. The reaction mixture was quenched by addition H_2O (150 mL) at 0°C, diluted with H_2O (150 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethylacetate/Petroleum ether gradient @ 200 mL/min) to give the title compound (23.0 g, 57.02mmol, 77.35% yield) as yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.33-4.30 (m, 2H), 4.28 (s, 2H), 3.62 (t, *J* = 4.0 Hz, 2H), 2.23-2.49 (m, 2H), 1.48 (s, 9H), 1.34 (t, *J* = 8.0 Hz, 3H)

[00250] *Preparation of 1-(tert-butyl) 3-ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1,3(2H)-dicarboxylate*

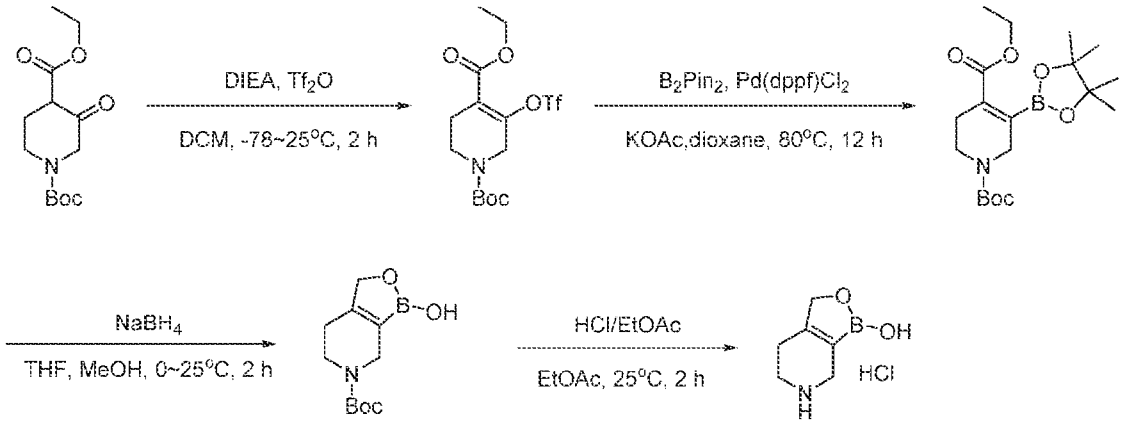
[00251] To a mixture of 1-(tert-butyl) 3-ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1,3(2H)-dicarboxylate (1.00 g, 2.48 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (181.40 mg, 247.91 umol, 0.1 *eq*), B_2Pin_2 (1.26 g, 4.96 mmol, 2 *eq*) and KOAc (486.61 mg, 4.96 mmol, 2 *eq*) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 80°C for 3 h under N_2 atmosphere. The reaction mixture was quenched by addition H_2O (10 mL) at 0°C, diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ethergradient @ 36 mL/min) to give the title compound (0.750 g, 1.97 mmol, 79.35% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.24 (d, J = 6.4, 2H), 4.13-4.08 (m, 2H), 3.48-3.43 (m, 2H), 2.32 (s, 2H), 1.34 (s, 12H), 1.27-1.24 (m, 12H).

[00252] *Preparation of tert-butyl 1-hydroxy-1,4,6,7-tetrahydro-[1,2]oxaborolo[4,3-c]pyridine-5(3H)-carboxylate*

[00253] To a solution of *1-(tert-butyl) 3-ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1,3(2H)-dicarboxylate* (3.00 g, 7.87 mmol, 1 eq) in THF (30 mL)\MeOH (3 mL) was added $NaBH_4$ (893 mg, 23.61 mmol, 3 eq) in portions at 0°C. The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was quenched by addition H_2O (50 mL) at 0°C, adjusted pH=5 with 2N HCl and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethylacetate/Petroleum ether gradient @ 50 mL/min) to give the title compound (1.70 g, 7.11 mmol, 90.37% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (s, 1H), 4.37 (s, 2H), 4.00 (s, 2H), 3.38 (t, J = 5.6 Hz, 2H), 2.11 (s, 2H), 1.39 (s, 9H). MS (ESI): mass calcd. For $C_{11}H_{18}BNO_4$ 239.13, m/z found 184.2 $[M-56+H]^+$. HPLC: 94.39% (220 nm), 100.00% (254 nm).

[00254] *Preparation of 4,5,6,7-tetrahydro-[1,2]oxaborolo[4,3-c]pyridin-1(3H)-ol*

[00255] To a solution of tert-butyl 1-hydroxy-3,4,6,7-tetrahydrooxaborolo[4,3-c]pyridine-5-carboxylate (0.600 g, 2.51 mmol, 1 *eq*) in EtOAc (6 mL) was added HCl/EtOAc (4 N 3.14 mL, 5 *eq*) dropwise at 25°C, the reaction mixture was stirred at 25°C for 0.5 h. The reaction mixture was directly filtered, the filter cake was washed with EtOAc (5 mL x 2) and dried in vacuo to give the title compound (0.150 g, 855.09 umol, 34.07% yield, HCl) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.43 (s, 2H), 8.86 (s, 1H), 4.39 (s, 2H), 3.76 (s, 2H), 3.09 (d, J = 4.8 Hz, 2H), 2.34 (s, 2H). MS (ESI): mass calcd. For $C_6H_{11}BNO_2Cl$ 139.08, m/z found 140.2 $[M+H]^+$. HPLC: 100.00% (220 nm), 100.00% (254 nm).



[00256] *Preparation of 1-(tert-butyl) 4-ethyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,4(2H)-dicarboxylate*

[00257] To a solution of 1-(tert-butyl) 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (23.00 g, 84.77 mmol, 1 *eq*) and DIEA (13.15 g, 101.73 mmol, 17.72 mL, 1.2 *eq*) in DCM (230 mL) was added dropwise Tf_2O (26.31 g, 93.25 mmol, 15.39 mL, 1.1 *eq*) at -78°C. The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H_2O (200 mL) at 0 °C, and then extracted with DCM (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ethergradient @ 50 mL/min) to give the title compound (32.60 g, 80.82 mmol, 95.33% yield) as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.33-4.28 (m, 2H), 4.13-4.10 (m, 2H) , 3.54 (t, J = 11.2 Hz, 2H), 2.61-2.58 (m, 2H),1.48 (s, 9H), 1.36-1.33 (m, 3H).

[00258] *Preparation of 1-(tert-butyl) 4-ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1,4(2H)-dicarboxylate*

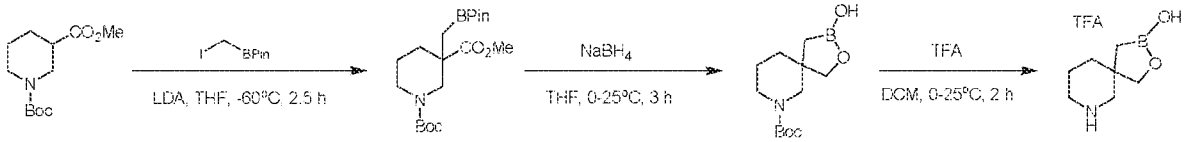
[00259] To a solution of B_2Pin_2 (1.26 g, 4.96 mmol, 2 *eq*) and 1-(tert-butyl) 4-ethyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,4(2H)-dicarboxylate (1.00 g, 2.48 mmol, 1 *eq*) in dioxane (30 mL) were added $Pd(dppf)Cl_2$ (181.40 mg, 247.91 umol, 0.1 *eq*) and KOAc (486.60 mg, 4.96 mmol, 2 *eq*) in portions at 20°C. The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered and the filtrate was directly concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give the title compound (2.87 g, crude) as yellow oil, which was used directly for next step without further purification.

[00260] *Preparation of tert-butyl 1-hydroxy-3,4,5,7-tetrahydro-[1,2]oxaborolo[3,4-c]pyridine-6(1H)-carboxylate*

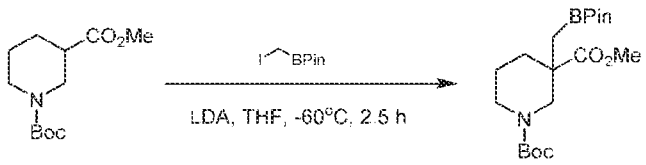
[00261] To a solution of 1-(tert-butyl) 4-ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1,4(2H)-dicarboxylate (2.8 g, 7.34 mmol, 1 eq) in THF (30 mL)\MeOH (3 mL) was added $NaBH_4$ (833.5 mg, 22.03 mmol, 3 *eq*) in portions at 0°C. The resulting reaction mixture was stirred at 25°C for 2 h. The reaction mixture was quenched by addition H_2O (50mL) at 0°C, adjusted pH=5 with 2N HCl and then extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 25%-55%,10min) to give the title compound (1.00 g, 4.18 mmol, 56.96% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.64 (s, 1H), 4.33 (s, 2H), 3.92 (s, 2H), 3.46-3.43 (m, 2H), 2.20 (s, 2H),1.40 (s, 9H). MS (ESI): mass calcd. For C11H18BNO4 239.13, m/z found 184.1 [M+H-^{t}Bu]$^+$.

[00262] *Preparation of 4,5,6,7-tetrahydro-[1,2]oxaborolo[3,4-c]pyridin-1(3H)-ol*

[00263] To a solution of tert-butyl 1-hydroxy-3,4,5,7-tetrahydro-[1,2]oxaborolo[3,4-c]pyridine-6(1H)-carboxylate (1.00 g, 4.18 mmol, 1 eq) in EtOAc (20 mL) was added HCl/EtOAc (4 N, 10.46 mL, 10 eq) dropwise at 25°C, the resulting reaction mixture was stirred at 25 °C for 2 h. The reaction suspension was directly filtered and the filter cake was triturated with MeCN to give the title compound (181 mg, 1.30 mmol, 31.14% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.99 (s, 2H), 8.87 (s, 1H), 4.40 (s, 2H), 3.66 (s, 2H), 3.20-3.19 (m, 2H), 2.49-2.45 (m, 2H). MS (ESI): mass calcd. For C6H10BNO2 139.08, m/z found 140.1. HPLC: 90.59% purity (220 nm).



[00264] *Preparation of 1-(tert-butyl) 3-methyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)piperidine-1,3-dicarboxylate*



[00265] To a solution of 1-(tert-butyl) 3-methyl piperidine-1,3-dicarboxylate (700 mg, 2.88 mmol, 1 eq) in THF (10 mL) was added LDA (2 M, 1.73 mL, 1.2 eq) dropwise at -60°C, the reaction mixture was stirred at -60°C for 0.5 h. Then a solution of 2-(iodomethyl) -4,4,5,5-tetramethyl-1,3,2-dioxaborolane (924 mg, 3.45 mmol, 1.2 eq) in THF (3 mL) was added to the above mixture dropwise at -60°C and the resulting mixture was stirred at -60 °C for additional 2 h. The reaction mixture was quenched by sat aq

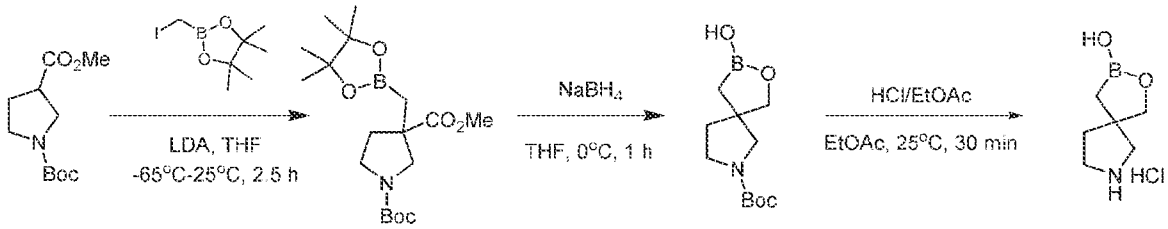
NH_4Cl (30 mL) and then extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ethergradient @ 60 mL/min) to give the title compound (1.00 g, 2.60 mmol, 90.21% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95-3.93 (m, 1H), 3.66 (s, 3H), 3.50-3.45 (m, 1H), 3.22-3.15 (m, 2H), 2.10-2.04 (m, 1H), 1.63-1.55 (m, 3H), 1.45 (s, 9H), 1.23 (d, J = 1.6 Hz, 12H), 1.03-1.01 (m, 1H), 0.90 - 0.83 (m, 1H)

[00266] *Preparation of tert-butyl 3-hydroxy-2-oxa-7-aza-3-boraspiro[4.5]decane-7-carboxylate*

[00267] This reaction was carried out by 750 mg x 2 batches in parallel. To a solution of 1-(tert-butyl) 3-methyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)piperidine-1,3-dicarboxylate (750 mg, 1.95 mmol, 1 eq) in THF (8 mL) was added $NaBH_4$ (368 mg, 9.73 mmol, 5 eq) in portions at 0°C, the reaction mixture was stirred at 25°C for 3 h. 2 parallel reactions were combined for work up. The reaction mixture was diluted with H_2O (50 mL), adjusted to pH = 5 with 2N HCl and then extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ethergradient @ 60 mL/min) to give the title compound (1 g, crude) as a white oil. The crude product (300 mg) was further purified by prep-HPLC (column: Phenomenex C18 80 x 40mm x 3um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 10%-40%,8min) to give the title compound (130 mg, 43.33% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.53 (s, 1H), 3.62 (d, J = 9.2 Hz, 1H), 3.54 (d, J = 9.2 Hz, 1H), 3.19 (s, 2H), 3.11 (s, 2H), 1.51-1.45 (m, 2H), 1.44-1.42 (m, 2H), 1.38 (s, 9H), 0.79-0.71 (m, 1H), 0.60-0.58 (m, 1H). MS (ESI): mass calcd. For $C_{12}H_{22}BNO_4$ 255.16, m/z found 200.3 $[M+H-56]^+$.

[00268] *Preparation of 2-oxa-7-aza-3-boraspiro[4.5]decan-3-ol*

[00269] To a solution of tert-butyl 3-hydroxy-2-oxa-7-aza-3-boraspiro[4.5]decane-7-carboxylate (110 mg, 431 μmol, 1 eq) in DCM (7 mL) was added TFA (245 mg, 2.16 mmol, 159 μL, 5 eq) in one portion at 0°C, the reaction mixture was stirred at 25°C for 2 h. The reaction mixture was directly concentrated under reduced pressure to give the title compound (115 mg, 99.1% yield, TFA) as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.53 (s, 1H), 8.39 (s, 1H), 3.76 (d, J = 9.6 Hz, 1H), 3.65 (d, J = 10.0 Hz, 1H), 3.04-2.87 (m, 4H), 1.71-1.58 (m, 2H), 1.55-1.41 (m, 2H), 0.99-0.88 (m, 1H), 0.83-0.71 (m, 1H). MS (ESI): mass calcd. For $C_9H_{15}BF_3NO_4$ 253.11, m/z found 156.3 $[M+H]^+$.



[00270] *Preparation of 1-(tert-butyl) 3-methyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pyrrolidine-1,3-dicarboxylate*

[00271] To a solution of 1-(tert-butyl) 3-methyl pyrrolidine-1,3-dicarboxylate (10.0 g, 43.6 mmol, 1 *eq*) in THF (100 mL) was added dropwise LDA (2 M, 26.1 mL, 1.2 *eq*) at -65°C, the reaction mixture was stirred at -65°C for 0.5 h. Then 2-(iodomethyl)-4,4,5,5-tetramethyl -1.3,2-dioxaborolane (14.0 g, 52.3 mmol, 1.2 *eq*) was added dropwise to the mixture at -65°C and the resulting reaction mixture was warmed up to 25°C and stirred for 2 h. The reaction mixture was poured into sat.aq.NH_4Cl (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 3/1) to give the title compound (13.5 g, 83.82% yield) as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.88-3.85 (m, 1H), 3.68 (s, 3H), 3.42 (s, 2H), 3.25 (d, J = 11.2 Hz, 1H), 2.36-2.32 (m, 1H), 2.05-1.86 (m, 1H), 1.46 (s, 9H), 1.26 (s, 12H), 1.18 (s, 2H).

[00272] *Preparation of tert-butyl 3-hydroxy-2-oxa-7-aza-3-boraspiro[4.4]nonane-7-carboxylate*

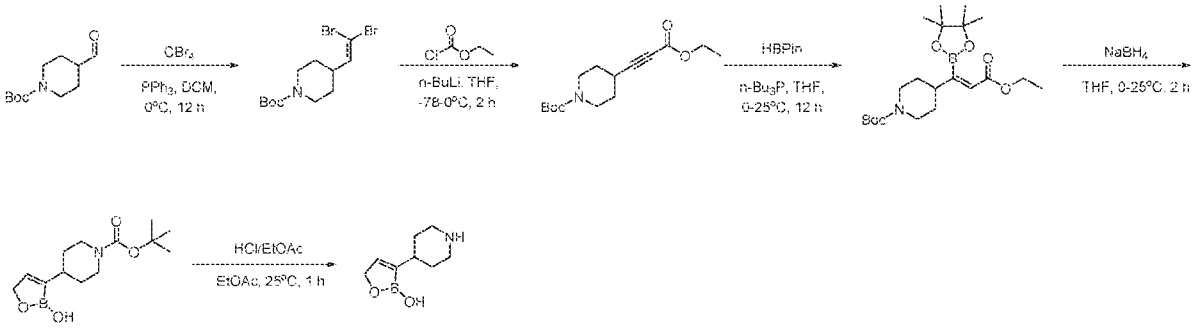
[00273] To a solution of 1-(tert-butyl) 3-methyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pyrrolidine-1,3-dicarboxylate (2.0 g, 5.4 mmol, 1 *eq*) in THF (20 mL)\MeOH (0.5 mL) was added $NaBH_4$ (615 mg, 16.2 mmol, 3 *eq*) in portions at 0°C, the reaction mixture was stirred at 0°C for 1 h. The reaction mixture was poured into H_2O (20 mL), adjusted pH = 5 with 2N HCl and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/1 to 0/1) to give the title compound (240 mg, 15.32% yield) as a white solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.62 (s, 1H), 3.75 (s, 2H), 3.35-3.20 (m, 2H), 3.18-3.08 (m, 2H), 1.76-1.66 (m, 2H), 1.40 (s, 9H), 0.95-0.80 (m, 2H). MS (ESI): mass calcd. For $C_{11}H_{20}BNO_4$ 241.15, m/z found 240.1 [M-H]$^-$. HPLC: n/a (220 nm), n/a (254 nm). LCMS: 98.7% purity (ELSD)

[00274] *Preparation of* 2-oxa-7-aza-3-boraspiro[4.4]nonan-3-ol

[00275] To a solution of tert-butyl 3-hydroxy-2-oxa-7-aza-3-boraspiro[4.4]nonane-7-carboxylate (200 mg, 829.56 umol, 1 *eq*) in EtOAc (5 mL) was added HCl/EtOAc (4 N, 4.0 mL, 20 *eq*) at 25°C, the reaction mixture was stirred at 25°C for 0.5 h. The reaction mixture was concentrated under reduced

pressure to give the title compound (100 mg, 22.65% yield, HCl) as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.26 (s, 2H), 8.72 (s, 1H), 3.87-3.77 (m, 2H), 3.22-3.18 (m, 2H), 3.01 (s, 2H), 1.86-1.76 (m, 2H), 1.07-0.89 (m, 2H). MS (ESI): mass calcd. For $C_6H_{13}ClBNO_2$ 141.10, m/z found 142.3 $[M+H]^+$. HPLC: n/a% (220 nm), n/a% (254 nm). LCMS: 100% (ELSD).

[00276] *Scheme*



[00277] *Preparation of tert-butyl 4-(2,2-dibromovinyl)piperidine-1-carboxylate*

[00278] To a solution of CBr_4 (23.32 g, 70.33 mmol, 1.5 eq) and PPh_3 (36.89 g, 140.66 mmol, 3 eq) in DCM (1200 mL) was added tert-butyl 4-formylpiperidine-1-carboxylate (10.0 g, 46.89 mmol, 1 eq) in portions at 0°C, the reaction mixture was stirred at 0°C for 12 h. The reaction mixture was quenched by addition H_2O (300 mL) at 0°C, diluted with H_2O (100 mL) and extracted with EtOAc (150 mL x 2). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 5/1) to give tert-butyl 4-(2,2-dibromovinyl)piperidine-1-carboxylate (100.00 g, 270.94 mmol, 57.78% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.25 (d, J = 8.8 Hz, 1H), 4.06 (q, J = 4.8 Hz, 2H), 2.78 (t, J = 10.8 Hz, 2H), 2.48-2.40 (m, 1H), 1.72 (d, J = 13.6 Hz, 2H), 1.46 (s, 9H), 1.37-1.30 (m, 2H).

[00279] *Preparation of tert-butyl 4-(3-ethoxy-3-oxo-prop-1-ynyl)piperidine-1-carboxylate*

[00280] To a solution of tert-butyl 4-(2,2-dibromovinyl)piperidine-1-carboxylate (25.0 g, 67.73 mmol, 1 eq) in THF (300 mL) was added dropwise n-BuLi (2.5 M, 54.19 mL, 2 eq) at -78°C. After addition, the reaction mixture was stirred at -78°C for 1 h, and then ethyl carbonochloridate (11.03 g, 101.60 mmol, 9.67 mL, 1.5 eq) was added dropwise at -78°C, the resulting reaction mixture was stirred at 0°C for 1 h. The reaction mixture was quenched by addition H_2O (800 mL) at 0°C, adjusted pH = 4 with 2N HCl and then extracted with EtOAc (250 mL x 2). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 10/1) to give the title compound (70.0 g, 248.80 mmol, 91.83% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.22 (q,

J = 14.4 Hz, 2H), 3.74-3.30 (m, 2H), 3.20-3.14 (m, 2H), 2.71-2.70 (m, 1H), 1.83-1.80 (m, 2H), 1.67-1.63 (m, 2H), 1.45 (s, 9H), 1.31 (q, *J* = 4.0 Hz, 3H).

[00281] *Preparation of tert-butyl 4-[(E)-3-ethoxy-3-oxo-1-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)prop-1-enyl]piperidine-1-carboxylate*

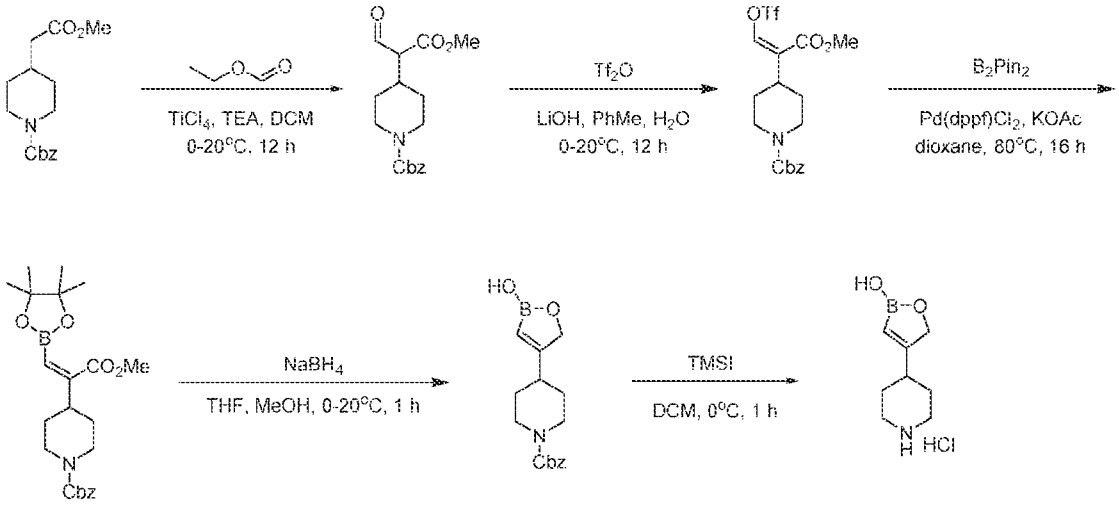
[00282] To a mixture of tert-butyl 4-(3-ethoxy-3-oxo-prop-1-ynyl)piperidine-1-carboxylate (17.8 g, 63.27 mmol, 1 eq) and tributylphosphine (2.56 g, 12.65 mmol, 3.12 mL, 0.2 eq) in THF (200 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (16.19 g, 126.53 mmol, 18.36 mL, 2 eq) dropwise at 0°C, the resulting reaction mixture was stirred at 25°C for 12 h under N_2 atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 240 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 200 mL/min) to give the title compound (20.0 g, crude) as white oil, which was used directly for next step without further purification.

[00283] *Preparation of tert-butyl 4-(2-hydroxy-2,5-dihydro-1,2-oxaborol-3-yl)piperidine-1-carboxylate*

[00284] To a solution of tert-butyl (E)-4-(3-ethoxy-3-oxo-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)piperidine-1-carboxylate (2.00 g, 5.06 mmol, 1 eq) in THF (30 mL) was added dropwise $NaBH_4$ (382.8 mg, 10.12 mmol, 2 eq) in portions at 0°C. The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H_2O (50 mL) at 0°C, adjusted pH=5 with 2N HCl and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C_{18} 100*30mm*10um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 30%-60%, 10min) to give the title compound (0.9 g, 3.37 mmol, 66.59% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.53 (s, 1H), 6.86 (s, 1H), 4.37 (s, 2H), 3.98 (d, *J* = 12.0 Hz, 2H), 2.72 (s, 2H), 2.27 (t, *J* = 10.4 Hz, 1H), 1.72 (d, *J* = 11.2 Hz, 2H), 1.40 (s, 9H), 1.27-1.20 (m, 2H). MS (ESI): mass calcd. For $C_{13}H_{22}BNO_4$ 267.16, m/z found 212.1 $[M-56+H]^+$. HPLC: 99.01% (220 nm), 91.01% (254 nm).

[00285] *Preparation of 3-(piperidin-4-yl)-1,2-oxaborol-2(5H)-ol*

[00286] To a solution of tert-butyl 4-(2-hydroxy-2,5-dihydro-1,2-oxaborol-3-yl)piperidine-1-carboxylate (800 mg, 2.99 mmol, 1 eq) in EtOAc (5 mL) was added HCl/EtOAc (4N, 5 mL) dropwise at 25°C, the reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was triturated with CH_3CN (4 mL x 3) to give the title compound (200 mg, 982.93 umol, 32.82% yield, HCl) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.91 (s, 2H), 8.65 (s, 1H), 6.90 (s, 1H), 4.40 (s, 2H), 3.26 (d, *J* = 12.8 Hz, 2H), 2.90-2.84 (m, 2H), 2.50 (t, *J* = 1.60 Hz, 1H), 1.92 (d, *J* = 12.4 Hz, 2H), 1.63-1.56 (m, 2H). MS (ESI): mass calcd. For $C_8H_{14}BNO_2$ 167.11, m/z found 168.1 $[M+H]^+$. HPLC: 99.00% (220 nm).



[00287] *Preparation of benzyl 4-(1-formyl-2-methoxy-2-oxo-ethyl)piperidine-1-carboxylate*

[00288] This reaction was carried out 5 g x 2 batches in parallel. To a mixture of benzyl 4-(2-methoxy-2-oxo-ethyl)piperidine-1-carboxylate (5.00 g, 17.16 mmol, 1 eq) and ethyl formate (3.81 g, 51.49 mmol, 4.14 mL, 3 eq) in DCM (50 mL) was added dropwise tetrachlorotitanium (4.88 g, 25.74 mmol, 4.88 mL, 1.5 eq) at 0°C under N_2, then TEA (4.34 g, 42.90 mmol, 5.97 mL, 2.5 eq) was added dropwise to the reaction mixture at 0°C. The reaction mixture was stirred at 20°C for 12 h. The reaction mixture was poured into ice-H_2O (100 mL) and the aqueous phase was extracted with DCM (100 mL x 3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ethergradient @ 100 mL/min) to give the title compound (8.00 g, crude) as yellow oil, which was a mixture of enol form and aldehyde form. 1H NMR ($CDCl_3$, 400 MHz) δ 11.65 (d, J = 12.4 Hz, 1 H), 9.72 (d, J = 3.2 Hz, 0.5 H), 7.38-7.32 (m, 8 H), 7.04-7.01 (m, 1 H), 5.14-5.13 (m, 3 H), 4.26 (br s, 3 H), 3.80 (s, 3 H), 3.78 (s, 1 H), 2.79-2.76 (m, 4 H), 2.43-2.35 (m, 1 H), 2.35-2.27 (m, 0.5 H), 1.75-1.67 (m, 3 H), 1.47 -1.35 (m, 4 H).

[00289] *Preparation of benzyl 4-[(Z)-1-methoxycarbonyl-2-(trifluoromethylsulfonyloxy) vinyl]piperidine-1-carboxylate*

[00290] This reaction were carried out 3.5 g x 2 batches in parallel.

[00291] To a mixture of benzyl 4-(1-formyl-2-methoxy-2-oxo-ethyl)piperidine-1-carboxylate (3.50 g, 10.96 mmol, 1 eq) in toluene (35 mL) was added dropwise aq. $LiOH.H_2O$ (5 M, 6.58 mL, 3 eq) at 0°C under N_2. Then Tf_2O (3.71 g, 13.15 mmol, 2.17 mL, 1.2 eq) was added dropwise to the reaction mixture at 0°C and stirred for 12 h at 20°C. The combined reaction mixture was poured into sat.aq.NH_4Cl (100 mL) and the aqueous phase was extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (60 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The

residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 150 mL/min) to give the title compound (6.00 g, crude, containing 30% E-isomer) as yellow oil, which was a mixture of Z/E isomers. 1H NMR ($CDCl_3$, 400 MHz) δ 7.61 (s, 0.5 H), 7.39-7.32 (m, 9 H), 6.66 (s, 1 H), 5.14 (br s, 3 H), 4.29 (br s, 4 H), 3.84 (s, 3 H), 3.79 (s, 1 H), 2.89-2.76 (m, 4 H), 2.62-2.56 (m, 1 H), 2.01-1.94 (m, 1 H), 1.79 (br d, J = 12.0 Hz, 2 H), 1.57 (br d, J = 13.6 Hz, 1 H), 1.51-1.39 (m, 3 H).

[00292] *Preparation of benzyl 4-[(Z)-1-methoxycarbonyl-2-(4,4,5,5-tetramethyl-1,3,2 -dioxaborolan-2-yl)vinyl] piperidine-1 –carboxylate*

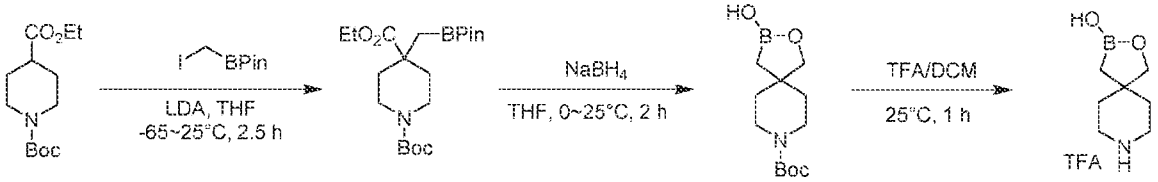
[00293] To a mixture of benzyl 4-[(Z)-1-methoxycarbonyl-2-(trifluoromethylsulfonyloxy)vinyl] piperidine-1-carboxylate (6.00 g, 13.29 mmol, 1 eq) and B_2Pin_2 (13.50 g, 53.17 mmol, 4 eq) in dioxane (50 mL) was added KOAc (3.26 g, 33.23 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (486 mg, 664.58 umol, 0.05 eq) in one portion at 20°C under N_2. The reaction mixture was stirred at 80°C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 120g SepaFlash® Silica Flash Column, Eluent of 10% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give the title compound (6.00 g, crude containing 30% E-isomer) as yellow oil, which was a mixture of Z/E isomers.1H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.30 (m, 8 H), 6.40 (s, 0.5 H), 5.88 (s, 1 H), 5.14-5.13 (m, 3 H), 4.26 (br s, 3 H), 3.78 (s, 3 H), 3.73 (s, 1 H), 3.12-3.04 (m, 0.5 H), 2.84-2.71 (m, 4 H), 2.62-2.55 (m, 1 H), 2.01-1.86 (m, 1 H), 1.77 (br d, J = 12.4 Hz, 2 H), 1.58 (br d, J = 12.0 Hz, 1 H), 1.33 (s, 12 H).

[00294] *Preparation of benzyl 4-(2-hydroxy-2,5-dihydro-1,2- oxaborol-4-yl)piperidine -1-carboxylate*

[00295] To a mixture of benzyl 4-[(Z)-1-methoxycarbonyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan -2-yl)vinyl]piperidine-1-carboxylate (6.00 g, 13.98 mmol, 1 eq) in THF (100 mL)\MeOH (10 mL) was added $NaBH_4$ (2.16 g, 57.10 mmol, 4.09 eq) in portions at 0°C under N_2. The reaction mixture was stirred at 20°C for 1 h. The reaction mixture was poured into H_2O (20 mL), adjusted to pH = 5 by adding HCl (2N) and extracted with EtOAc (20 mL x 3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Luna 80 x 30mm x 3um;mobile phase: [water(HCl)-MEOH];B%: 40%-65%, 8min and column: Phenomenex Luna 80 x 30mm x 3um;mobile phase: [water(HCl)-MEOH];B%: 45%-60%, 8min) to give benzyl 4-(2-hydroxy-2,5-dihydro-1,2-oxaborol-4-yl)piperidine-1-carboxylate (0.80 g, 2.66 mmol, 19.01% yield) as a white solid. 1H NMR (DMSO-d_6, 400 MHz) δ 8.42 (s, 1 H), 7.39-7.31 (m, 5 H), 5.40 (s, 1 H), 5.07 (s, 2 H), 4.41 (s, 2 H), 4.04 (d, J = 13.2 Hz, 2 H), 2.86-2.85 (m, 2 H), 2.40 (t, J = 11.6 Hz, 1 H), 1.77 (d, J = 12. 0 Hz, 2 H), 1.36-1.27 (m, 2 H). MS (ESI): mass calcd. For $C_{16}H_{20}BNO_4$, 301.15, m/z found 302.1 $[M+H]^+$. HPLC: 99.51% (220 nm), 95.45% (254 nm).

[00296] *Preparation of 4-(piperidin-4-yl)-1,2-oxaborol-2(5H)-ol*

[00297] To a mixture of benzyl 4-(2-hydroxy-2,5-dihydro-1,2-oxaborol-4-yl)piperidine-1-carboxylate (150 mg, 498.10 umol, 1 eq) in DCM (2 mL) was added dropwise TMSI (299 mg, 1.49 mmol, 204 uL, 3 eq) at 0°C, the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into HCl (2N, 5 mL) and the aqueous phase was extracted with DCM (10 mL x 3). The organic phase was discarded, and the aqueous phase was directly freeze-dried to give 4-(piperidin-4-yl)-1,2-oxaborol-2(5H)-ol (180 mg, 884.64 umol, 88.80% yield, HCl) as a white solid. 1H NMR (DMSO-d_6, 400 MHz) δ 8.45 (br s, 2 H), 8.18 (br s, 1 H), 5.43 (d, J = 1.2 Hz, 1 H), 4.43 (d, J = 1.6 Hz, 2 H), 3.30 (d, J = 12.4 Hz, 2 H), 2.98-2.89 (m, 2 H), 2.52-2.51 (m, 1 H), 1.94 (d, J = 13.2 Hz, 2 H), 1.61-1.51 (m, 2 H). MS (ESI): mass calcd. For C8H14BNO2, 167.11, m/z found 168.2 $[M+H]^+$. HPLC: 92.93% (220 nm), 98.27% (254 nm).



[00298] *Preparation of 1-tert-butyl 4-ethyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methyl)piperidine-1,4-dicarboxylate*

[00299] To a solution of 1-tert-butyl 4-ethyl piperidine-1,4-dicarboxylate (2.00 g, 7.77 mmol, 1 *eq*) in THF (20 mL) was added LDA (2 M, 4.66 mL, 1.2 *eq*) dropwise at -65°C. The reaction mixture was stirred at -65°C for 0.5 h. Then 2-(iodomethyl)-4,4,5,5-tetramethyl -1,3,2-dioxaborolane (2.50 g, 9.33 mmol, 1.2 *eq*) was added into the reaction mixture at -65°C dropwise. The reaction mixture was warmed up to 25°C and stirred for 2 h. The reaction mixture was quenched by addition sat.aq. NH_4Cl (20 mL) at 0 °C, and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 1/1) to give 1-tert-butyl 4-ethyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)piperidine -1,4-dicarboxylate (2.40 g, 4.83 mmol, 62.18% yield, 80% purity) as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.06-4.02 (m, 2H), 3.62-3.59 (m, 2H), 3.00-2.94 (m, 2H), 1.97 (d, J = 13.6 Hz, 2H), 1.43-1.39 (m, 2H), 1.36 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H), 1.23 (s, 12H), 0.99 (s, 2H). MS (ESI): mass calcd. For $C_{20}H_{36}BNO_6$ 397.26, m/z found 298.3 $[M-Boc+1]^+$.

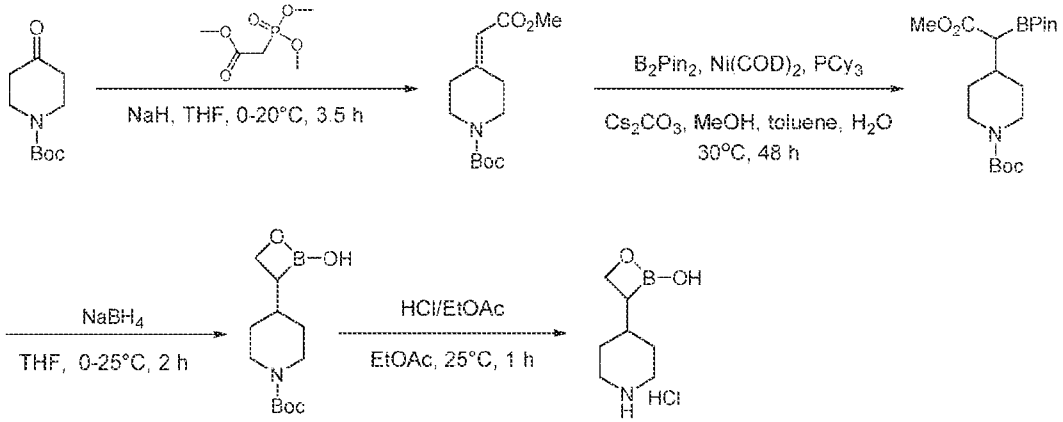
[00300] *Preparation of tert-butyl 3-hydroxy-2-oxa-8-aza-3-boraspiro[4.5]decane-8-carboxylate*

[00301] To a solution of 1-tert-butyl 4-ethyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl) piperidine-1,4-dicarboxylate (2.00 g, 5.03 mmol, 1 *eq*) in THF (25 mL) was added $NaBH_4$ (550 mg, 14.54 mmol, 2.89 *eq*) in portions at 0°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was poured into sat.aq. NH_4Cl (100 mL) at 0°C under N_2 atmosphere, and then extracted with EtOAc (100 mL x 3). The combined organic layers were washed dried over Na_2SO_4, filtered and

concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 1/1) to give tert-butyl 3-hydroxy-2-oxa-8-aza-3-boraspiro[4.5]decane-8-carboxylate (0.7 g, 2.69 mmol, 53.49% yield, 98.129% purity) as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.52 (s, 1H), 3.64 (s, 2H), 3.46-3.40 (m, 2H), 3.14-3.10 (m, 2H), 1.36 (s, 9H), 1.34 (t, J = 5.2 Hz, 4H), 0.76 (m, 2H). MS (ESI): mass calcd. For $C_{12}H_{22}BNO_4$ 255.16, m/z found 254.1 $[M-H]^-$. HPLC: 99.67% (220 nm), n/a (254 nm).

[00302] *Preparation of 2-oxa-8-aza-3-boraspiro[4.5]decan-3-ol*

[00303] To a solution of tert-butyl 3-hydroxy-2-oxa-8-aza-3-boraspiro[4.5]decane-8-carboxylate (560 mg, 2.20 mmol, 1 *eq*) in DCM (5 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL, 6.15 *eq*) dropwise at 25°C, the reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30mm *5um;mobile phase: [water(TFA)-ACN];B%: 99%-85%,10min) to give 3-hydroxy-2- oxa-8-aza-3-boraspiro[4.5]decane (440 mg, 1.64 mmol, 74.51% yield, TFA) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.62 (s, 1H), 8.48 (s, 2H), 3.69 (s, 2H), 3.11-3.97 (m, 4H), 1.63-1.52 (m, 4H), 0.82 (s, 2H). MS (ESI): mass calcd. For $C_7H_{14}BNO_2$ 155.11, m/z found 156.3 $[M+H]^+$. HPLC: 97.91% (220 nm), n/a % (254 nm).



[00304] *Preparation of tert-butyl 4-(2-methoxy-2-oxo-ethylidene)piperidine-1-carboxylate*

[00305] To a mixture of NaH (2.61 g, 65.25 mmol, 60% purity, 1.3 eq) in THF (200 mL) was added methyl 2-(dimethoxyphosphoryl)acetate (13.19 g, 62.74 mmol, 9.07 mL, 1.25 eq) dropwise at 0°C under N_2, the reaction mixture was stirred at 0°C for 30 min. Then a solution of tert-butyl 4-oxopiperidine-1-carboxylate (10.00 g, 50.19 mmol, 1 eq) in THF (50 mL) was added to the mixture dropwise. The reaction mixture was warmed to 20°C and stirred for 3 h. The reaction mixture was poured into sat.aq.NH_4Cl (250 mL) and extracted with EtOAc (80 mL x 3). The combined organic phase was washed with brine (80 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=5/1 to 4/1) to

give tert-butyl 4-(2-methoxy-2-oxo-ethylidene)piperidine-1-carboxylate (3.40 g, 13.32 mmol, 26.53% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.53 (s, 1H), 3.89 (s, 2H), 3.68 (s, 3H), 3.50 (t, *J* = 5.6 Hz, 2H), 3.03 (s, 2H), 2.13 (s, 2H), 1.46 (s, 9H).

[00306] *Preparation of tert-butyl 4-(2-methoxy-2-oxo-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)piperidine-1-carboxylate*

[00307] This reaction was carried out by 1.00 g x 3 batches in parallel. A mixture of $Ni(COD)_2$ (54 mg, 196 umol, 0.05 eq), Cs_2CO_3 (1.91 g, 5.88 mmol, 1.5 eq) and PCy_3 (110 mg, 392 umol, 127 uL, 0.1 eq) in toluene (35 mL) was stirred at 0°C for 20 min. Then a solution of tert-butyl 4-(2-methoxy-2-oxo-ethylidene) piperidine-1-carboxylate (1.00 g, 3.92 mmol, 1 eq) and B_2Pin_2 (1.49 g, 5.88 mmol, 1.5 eq) in toluene (35 mL) was added dropwise to the reaction mixture at 0 °C. Finally MeOH (1 mL) and H_2O (0.2 mL) were added in one portion and the reaction mixture was stirred at 30°C for 48 h. 3 parallel reaction were combined for work-up. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250 x 70mm,15 um);mobile phase: [water(FA)-ACN];B%: 70%-100%,20min) to give the title compound (1.00 g, 2.60 mmol, 22.09% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.69 (d, *J* = 13.2 Hz, 2H), 3.56 (s, 3H), 2.91 (s, 2H), 2.29 (s, 2H), 1.68 (d, *J* = 13.2 Hz, 2H), 1.37 (s, 9H), 1.19 (s, 12H), 1.12-1.03 (m, 2H).

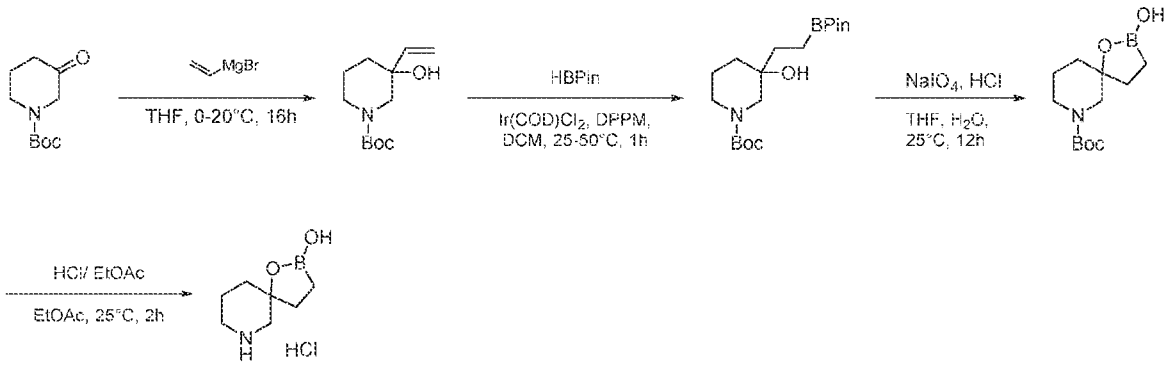
[00308] *Preparation of tert-butyl 4-(2-hydroxy-1,2-oxaboretan-3-yl)piperidine-1-carboxylate*

[00309] To a solution of *tert-butyl 4-(2-methoxy-2-oxo-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)piperidine-1-carboxylate* (1.00 g, 2.60 mmol, 1 eq) in THF (5 mL) was added $NaBH_4$ (0.30 g, 7.93 mmol, 3 eq) in portions at 0°C, the mixture was stirred at 25°C for 2 h. The reaction mixture was quenched by addition H_2O (8 mL) at 0°C, adjusted pH = 5 with 2N HCl and then extracted with EtOAc (4 mL x 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 4-(2-hydroxy-1,2-oxaboretan-3-yl)piperidine-1-carboxylate (0.50 g, 1.96 mmol, 75.51% yield) as white oil, which was used directly for next step without further purification.

[00310] *Preparation of 3-(piperidin-4-yl)-1,2-oxaboretan-2-ol*

[00311] To a solution of *tert-butyl 4-(2-hydroxy-1,2-oxaboretan-3-yl)piperidine-1-carboxylate* (0.40 g, 1.57 mmol, 1 eq) in EtOAc (4 mL) was added HCl/EtOAc (4 N, 3.92 mL, 10 eq) at 25°C, the reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was triturated with MeCN (5 mL) at 25°C to give 3-(piperidin-4-yl)-1,2-oxaboretan-2-ol (0.15 g, 967.73 umol, 61.72% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.75 (s, 1H), 8.57 (s, 1H), 8.09 (s, 1H), 4.00-3.96 (m, 1H), 3.93-3.85 (m, 1H), 3.31 (s, 1H), 3.25 (d, *J* = 12.8 Hz, 1H), 2.79 (s, 2H), 1.73 (dd, *J* = 2.4, 12.4 Hz, 1H), 1.65-1.59 (m, 2H), 1.42-1.38 (m, 1H),

1.36-1.28 (m, 1H), 0.94-0.88 (m, 1H). MS (ESI): mass calcd. For $C_7H_{15}BClNO_2$ 155.11, m/z found 156.3 $[M+H]^+$. HPLC: 92.52% (220 nm), 100.00% (254 nm).



[00312] *Preparation of tert-butyl 3-hydroxy-3-vinylpiperidine-1-carboxylate*

[00313] To a single round-bottom flask equipped with a magnetic stir bar was added bromo(vinyl)magnesium (1 M, 150 mL, 3 *eq*) at 0°C, then a solution of tert-butyl 3-oxopiperidine-1-carboxylate (10.0 g, 50.19 mmol, 1 *eq*) in THF (100 mL) was added slowly at 0°C during a period of 20 min. The reaction mixture was stirred at 20°C for 16 h. The reaction mixture was quenched with H_2O (200 mL) at 0°C, and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~30% EtOAc/PE gradient @ 60 mL/min) to give tert-butyl 3-hydroxy-3-vinylpiperidine-1- carboxylate (8.0 g, 35.20 mmol, 70.13% yield) as an off white oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.95-5.88 (m, 1H), 5.38 (d, J = 17.2 Hz, 1H), 5.15 (d, J = 11.6 Hz, 1H), 3.81-3.58 (m, 2H), 3.05-2.96 (m, 2H), 2.04-1.80 (m, 2H), 1.72-1.62 (m, 2H), 1.46 (s, 9H).

[00314] *Preparation of tert-butyl 3-hydroxy-3-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) ethyl)piperidine-1-carboxylate*

[00315] A mixture of tert-butyl 3-hydroxy-3-vinyl-piperidine-1-carboxylate (500 mg, 2.20 mmol, 1 *eq*), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (563 mg, 4.40 mmol, 638 µL, 2 *eq*), DPPM (85 mg, 220 µmol, 0.1 *eq*) and chloroiridium;(1Z,5Z)-cycloocta-1,5-diene (74 mg, 109.99 µmol, 0.05 *eq*) in DCM (10 mL) at 25°C was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 50°C for 1 h under N_2 atmosphere. The reaction mixture was cooled to 25°C, quenched with H_2O (20 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/PE gradient @ 40 mL/min) to give the title compound (370 mg, crude) as colorless oil, which was used directly for next step without further purification.

[00316] *Preparation of tert-butyl 2-hydroxy-1-oxa-7-aza-2-boraspiro[4.5]decane-7-carboxylate*

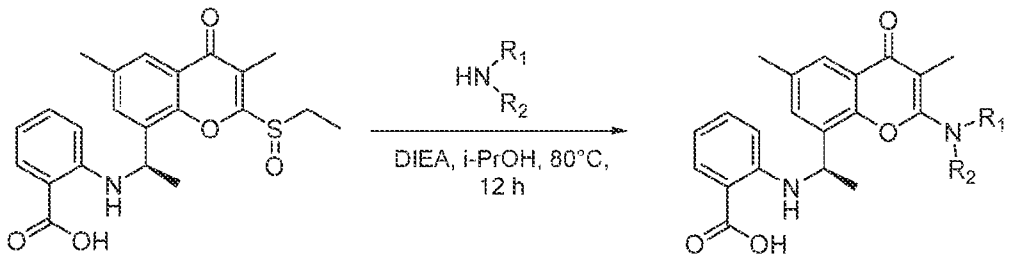
[00317] To a solution of tert-butyl 3-hydroxy-3-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl] piperidine-1-carboxylate (3.20 g, 9.01 mmol, 1 eq) in THF (100 mL)\H_2O (25 mL)\HCl (2 M, 3.15 mL, 0.7 eq) was added $NaIO_4$ (5.78 g, 27.02 mmol, 1.50 mL, 3 eq) in portions at 25°C. The reaction mixture was stirred at 25°C for 12 h. The reaction mixture was diluted with H_2O (100 mL) at 0°C and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Titank C18 Bulk 250*70mm 10u;mobile phase: [H2O(0.2%FA)-ACN];gradient:30%-60% B over 20.0 min) to give the title compound (550 mg, 2.16 mmol, 23.94% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.46 (s, 1H), 3.28-3.13 (m, 4H), 1.66-1.53 (m, 6H), 1.38 (s, 9H), 0.85-0.81 (m, 2H).

[00318] *Preparation of 1-oxa-7-aza-2-boraspiro[4.5]decan-2-ol*

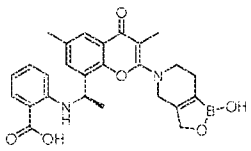
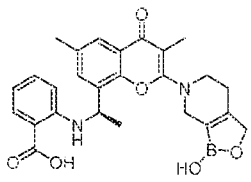
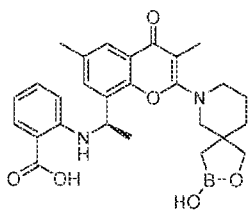
[00319] To a solution of tert-butyl 2-hydroxy-1-oxa-9-aza-2-boraspiro[4.5]decane-9-carboxylate (250 mg, 979.94 μmol, 1 eq) in EtOAc (2 mL) was added HCl/EtOAc (4 N, 2 mL) dropwise at 25°C. The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give the title compound (150 mg, crude, HCl salt) as brown oil, which was used directly for next step without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.42-9.40 (m, 1H), 8.42-8.40 (m, 1H), 3.07-2.83 (m, 4H), 1.75-7.59 (m, 6H), 0.93-0.89 (m, 2H).

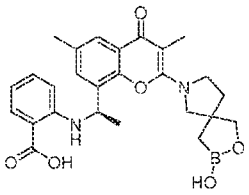
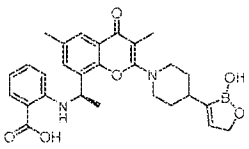
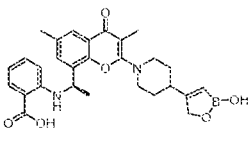
[00320] Example 3:

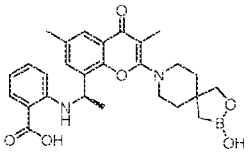
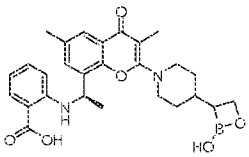
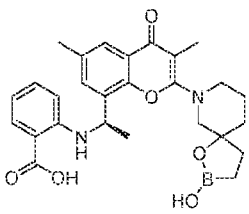
[00321] *General procedure for synthesis of target compounds:*



[00322] To a solution of 2-(((1R)-1-(2-(ethylsulfinyl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino)benzoic acid (1 eq) and amine (3 eq) in i-PrOH (for each 0.1 g of benzoic acid, 1 mL of i-PrOH was used) was added DIEA (25 eq) in one portion at 25°C, then the resulting mixture was heated to 80°C and stirred at 80°C for 12 h. The reaction mixture was cooled to 25°C, directly filtered and the filtrate was concentrated under reduced pressure. Then the residue was further purified by Prep-HPLC to give the desired product.

Structure	IUPAC Name	Exact Mass $[M+H]^+$	1H NMR (DMSO-d_6, 400 MHz)
	(R)-2-((1-(2-(1-hydroxy-1,4,6,7-tetrahydro-[1,2]oxaborolo[4,3-c]pyridin-5(3H)-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino) benzoic acid	Calc'd 475.3 Found 475.3	8.69 (s, 1H), 7.80 (dd, J = 1.6, 8.0 Hz, 1H), 7.64 (s, 1H), 7.39 (s, 1H), 7.21-7.18 (m, 1H), 6.55-6.51 (m, 1H), 6.44-6.41 (m, 1H), 5.09-5.06 (m, 1H), 4.41 (s, 2H), 4.23-4.22 (m, 2H), 3.52 (t, J = 5.2 Hz, 2H), 2.36-2.33 (m, 2H), 2.31 (s, 3H), 1.96 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H)
	(R)-2-((1-(2-(1-hydroxy-3,4,5,7-tetrahydro-[1,2]oxaborolo[3,4-c]pyridin-6(1H)-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino) benzoic acid	Calc'd 473.3$[M-H]^-$ Found 473.1$[M-H]^-$	12.55 (s, 1H), 9.24 (s, 1H), 8.46 (s, 1H),7.80 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H), 7.38 (s, 1H), 7.18 (t, J = 6.8 Hz, 1H), 6.52 (t, J = 7.6 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 5.09-5.03 (s, 1H), 4.38 (s, 2H), 4.20-4.11 (m, 2H), 3.60-3.55 (m, 2H), 2.50-2.45 (m, 2H), 2.31 (s, 3H), 1.99 (s, 3H), 1.26 (d, J = 7.2 Hz, 3H).
	2-(((1R)-1-(2-(3-hydroxy-2-oxa-7-aza-3-boraspiro[4.5]decan-7-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino) benzoic acid	Calc'd 489.2$[M-H]^-$ Found 489.1$[M-H]^-$	12.78 (s, 1H), 8.55 (s, 1H), 8.35 (d, J = 6.0Hz, 1H), 7.82-7.79 (m, 1H), 7.63 (s, 1H), 7.38 (s, 1H), 7.24-7.20 (m, 1H), 6.54 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 5.11-5.07 (m, 1H), 3.85-3.80 (m, 1H), 7.67-7.65 (m, 1H), 3.36-3.34 (m, 2H), 3.14-3.13 (m, 2H), 2.30 (s, 3H), 1.92 (s,

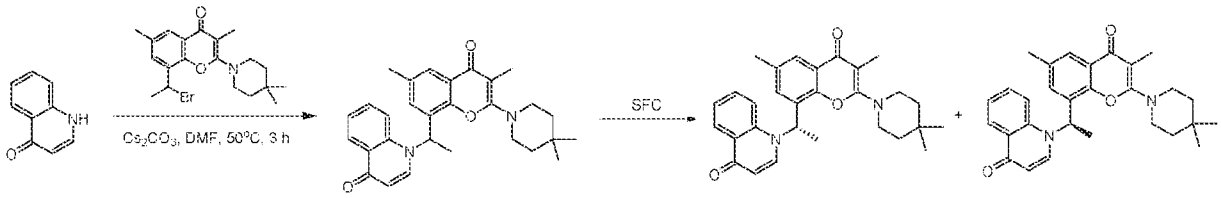
Structure	IUPAC Name	Exact Mass $[M+H]^+$	1H NMR (DMSO-d_6, 400 MHz)
			3H), 1.62-1.57 (m, 7H), 0.84-0.69 (m, 2H)
	2-(((1R)-1-(2-(3-hydroxy-2-oxa-7-aza-3-boraspiro[4.4]nonan-7-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino) benzoic acid	Calc'd 477.2 Found 477.3	8.73 (s, 1H), 7.80-7.78 (m, 1H), 7.60 (s, 1H), 7.32 (s, 1H), 7.15-7.12 (m, 1H), 6.49 (t, J = 6.8 Hz, 1H), 6.37 (3, J = 8.4 Hz, 1H), 5.03-5.02 (m, 1H), 3.89-3.82 (m, 4H), 3.66-3.62 (m, 2H), 2.29 (s, 3H), 2.07 (s, 3H), 1.87-1.82 (m, 2H), 1.54 (d, J = 6.4Hz, 3H), 1.00-0.90 (m, 2H)
	(R)-2-((1-(2-(4-(2-hydroxy-2,5-dihydro-1,2-oxaborol-3-yl)piperidin-1-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino) benzoic acid	Calc'd 503.2 Found 503.3	8.54 (s, 1H), 7.79 (d, J = 6.4 Hz, 1H), 7.63 (s, 1H), 7.40 (s, 1H), 7.19 (t, J = 7.2 Hz, 1H), 6.89 (s, 1H), 6.52 (t, J = 6.8 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 5.08-5.07 (m, 1H), 4.38 (s, 2H), 3.83-3.78 (m, 2H), 3.32-3.12 (m, 2H), 2.40-2.37 (m, 1H), 2.31 (s, 3H), 1.93 (s, 3H), 1.88-1.85 (m, 2H), 1.60-1.54 (m, 5H)
	(R)-2-((1-(2-(4-(2-hydroxy-2,5-dihydro-1,2-oxaborol-4-yl)piperidin-1-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-	Calc'd 503.2 Found 503.3	8.81 (s, 1H), 8.44 (s, 1H), 8.80-8.78 (s, 1H), 7.63 (s, 1H), 7.40 (s, 1H), 7.19 (t, J = 7.6 Hz, 1H), 6.50-6.46 (m, 1H), 6.40-6.39 (m, 1H), 5.44 (s, 1H), 5.06-5.05 (m, 1H), 4.44 (s, 2H), 3.80-3.77 (m, 2H), 3.20-3.12 (m, 2H), 2.50-

Structure	IUPAC Name	Exact Mass $[M+H]^+$	1H NMR (DMSO-d_6, 400 MHz)
	yl)ethyl)amino) benzoic acid		2.47 (m, 1H), 2.32 (s, 3H), 1.90-1.88 (m, 5H), 1.63-1.54 (m, 5H)
	(R)-2-((1-(2-(3-hydroxy-2-oxa-8-aza-3-boraspiro[4.5]decan-8-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino) benzoic acid	Calc'd 491.2 Found 491.2	8.76 (s, 1H), 8.56 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.62 (s, 1H), 7.40 (s, 1H), 7.15 (t, J = 8.4 Hz, 1H), 6.51-6.47 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 5.09-5.01 (m, 1H), 3.71 (s, 2H), 3.48-3.35 (m, 4H), 2.30 (s, 3H), 1.91 (s, 3H), 1.65-1.60 (m, 7H), 0.84 (s, 2H)
	2-(((1R)-1-(2-(4-(2-hydroxy-1,2-oxaboretan-3-yl)piperidin-1-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino) benzoic acid	Calc'd 491.2 Found 491.2	9.89 (s, 1H), 7.77-7.75 (m, 1H), 7.60 (s, 1H), 7.40 (s, 1H), 6.93-6.89 (m, 1H), 6.35 (t, J = 6.8 Hz, 1H), 6.17 (d, J = 8.4 Hz, 1H), 4.97-4.93 (m, 1H), 3.54-3.51 (m, 2H), 3.44-3.99 (m, 2H), 2.29 (s, 3H), 1.93 (s, 3H), 1.74-7.70 (m, 6H), 1.52 (d, J = 6.8 Hz, 3H), 0.89-0.85 (m, 2H)
	2-(((1R)-1-(2-(2-hydroxy-1-oxa-7-aza-2-boraspiro[4.5]decan-7-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino) benzoic acid	Calc'd 491.2 Found 491.4	8.64 (s, 1H), 8.49 (s, 1H), 7.81-7.79 (m, 1H), 7.62 (s, 1H), 7.38 (s, 1H), 7.18-7.16 (m, 1H), 6.53-6.49 (m, 1H), 6.43-6.38 (m, 1H), 5.07 (s, 1H), 3.55-3.52 (m, 2H), 3.36-3.24 (m, 2H), 2.30 (s, 3H), 1.93 (s, 3H), 1.66-163 (m,

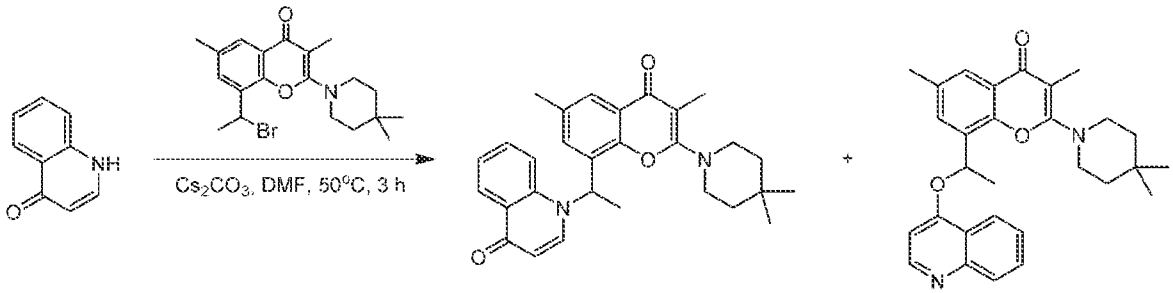
Structure	IUPAC Name	Exact Mass $[M+H]^+$	1H NMR (DMSO-d_6, 400 MHz)
			4H), 1.59-1.57 (m, 5H), 0.86-0.82 (m, 2H)

[00323] Example 4

[00324] *Synthetic Scheme:*



[00325] *Preparation of 1-[1-[2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-4-oxo-chromen-8-yl] ethyl]quinolin-4-one and 2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-8- [1-(4-quinolyloxy) ethyl]chromen-4-one*



[00326] To a mixture of 8-(1-bromoethyl)-2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-chromen-4-one (200 mg, 509.78 μmol, 1 eq) and Cs_2CO_3 (332 mg, 1.02 mmol, 2 eq) in DMF (4 mL) was added 1H-quinolin-4-one (74 mg, 509.78 μmol, 1 eq) in one portion at 20°C, the reaction mixture was heated to 50°C and stirred for 3 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was directly concentrated in vacuo. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 x 30 mm x 10 um; mobile phase: [H_2O(10mM NH_4HCO_3)-ACN]; gradient: 45%-75% B over 8.0 min) to give 1-[1-[2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]quinolin-4-one (34.0 mg, 74.5 μmol, 14.61% yield, 100.00% purity) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.22 (d, J = 8.0 Hz, 1H), 8.04-8.02 (m, 1H), 7.81 (s, 1H), 7.78-7.77 (m, 1H), 7.66 (s, 1H), 7.61-7.59 (m, 1H), 7.44-7.42 (m, 1H), 6.53-6.51 (m, 1H), 6.00 (d, J = 8.0 Hz, 1H), 2.94-2.91 (m, 2H), 2.76-2.73 (m, 2H), 2.49 (s, 3H), 1.87-1.86 (m, 3H), 1.83 (s, 3H), 1.06 (s, 4H), 0.77(s, 6H). MS (ESI): mass calcd. For $C_{29}H_{32}N_2O_3$ 456.24, m/z found 457.2 $[M+H]^+$. HPLC: 100.00% (220 nm), 100.00% (254 nm). 2-(4,4-

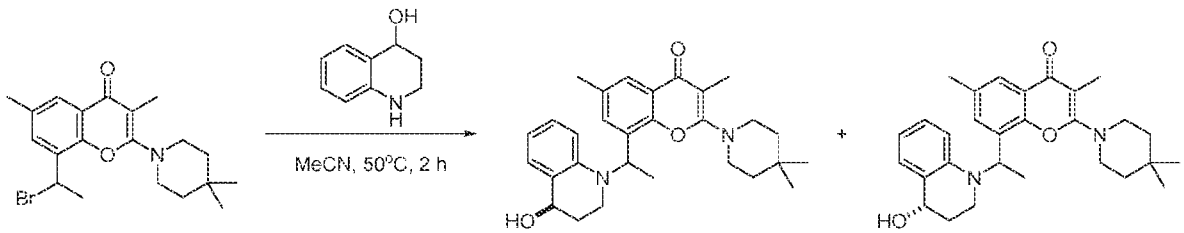
dimethyl-1-piperidyl)-3,6-dimethyl-8-[1-(4-quinolyloxy)ethyl]chromen-4-one was also obtained as a white solid (166 mg, 356 μmol, 69.86% yield, 98.54% purity). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.63 (d, J = 5.2 Hz, 1H), 8.27 (d, J = 0.8 Hz, 1H), 7.95-7.93 (m, 1H), 7.76-7.76 (m, 1H), 7.75-7.72 (m, 1H), 7.61 (s, 2H), 6.91 (d, J = 5.2 Hz, 1H), 6.18 (q, J = 6.4 Hz, 1H), 3.37-3.34 (m, 4H), 2.34 (s, 3H), 1.91 (s, 3H), 1.85 (d, J = 6.4 Hz, 3H), 1.41-1.38 (m, 4H), 0.94 (s, 6H). MS (ESI): mass calcd. For $C_{29}H_{32}N_2O_3$ 456.24, m/z found 457.2 $[M+H]^+$. HPLC: 98.54% (220 nm), 94.79% (254 nm).

[00327] *Preparation of (S)-1-(1-(2-(4,4-dimethylpiperidin-1-yl)-3,6-dimethyl-4-oxo -4H-chromen-8-yl)ethyl)quinolin-4(1H)-one and (R)-1-(1-(2-(4,4-dimethylpiperidin-1-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)quinolin-4(1H)-one*

[00328] 1-(1-(2-(4,4-dimethylpiperidin-1-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)quinolin-4(1H)-one was separated by SFC (column: REGIS (s,s) WHELK-O1 (250 mm x 30 mm, 5 um); mobile phase: [CO_2-EtOH]; B%: 50%, isocratic elution mode) to give (S)-1-(1-(2-(4,4-dimethylpiperidin-1-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)quinolin-4(1H)-one (31.3 mg, 60.7 μmol, 31.30% yield, 99.57% purity) and (R)-1-(1-(2-(4,4-dimethylpiperidin-1-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)quinolin-4(1H)-one (29.0 mg, 56.3 μmol, 29.00% yield, 100.00% purity) as white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.22 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.82 (t, J = 4.0 Hz, 2H), 7.77 (s, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.52 (t, J = 76.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 6.00 (d, J = 8.0 Hz, 1H), 2.93 (t, J = 20.0 Hz, 2H), 2.75 (t, J = 8.0 Hz, 2H), 2.45 (s, 3H), 1.87-1.83 (m, 6H), 1.06 (t, J = 12.0 Hz, 4H), 0.77 (s, 6H). MS (ESI): mass calcd. For $C_{29}H_{32}N_2O_3$ 456.24, m/z found 457.2 $[M+H]^+$. HPLC: 99.57% (220 nm), 100.00% (254 nm). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.23 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.82 (t, J = 4.0 Hz, 2H), 7.77 (s, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.52 (t, J = 76.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 6.00 (d, J = 8.0 Hz, 1H), 2.93 (t, J = 20.0 Hz, 2H), 2.75 (t, J = 8.0 Hz, 2H), 2.45 (s, 3H), 1.87-1.83 (m, 6H), 1.06 (t, J = 12.0 Hz, 4H), 0.77 (s, 6H). MS (ESI): mass calcd. For $C_{29}H_{32}N_2O_3$ 456.24, m/z found 457.3 $[M+H]^+$. HPLC: 99.32% (220 nm), 100.00% (254 nm).

[00329] Example 5

[00330] *Synthetic Scheme:*

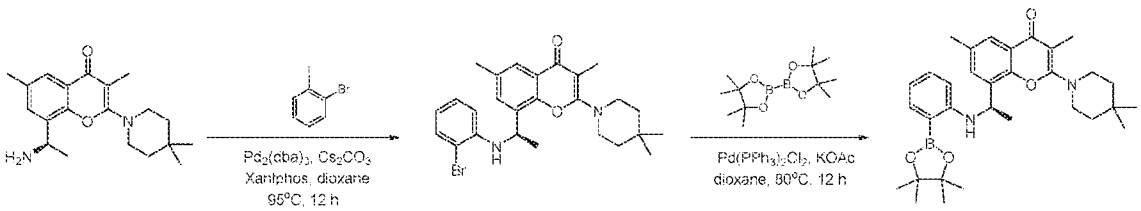
[00331] 

[00332] *Preparation of 2-(4,4-dimethylpiperidin-1-yl)-8-(1-((R)-4-hydroxy-3,4-dihydroquinolin-1(2H)-yl)ethyl)-3,6-dimethyl-4H-chromen-4-one and 2-(4,4-dimethylpiperidin-1-yl)-8-(1-((S)-4-hydroxy-3,4-dihydroquinolin-1(2H)-yl)ethyl)-3,6-dimethyl-4H-chromen-4-one*

[00333] A mixture of 1,2,3,4-tetrahydroquinolin-4-ol (260.0 mg, 1.74 mmol, 1 eq) and 8-(1-bromoethyl)-2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-chromen-4-one (683.7 mg, 1.74 mmol, 1 eq) in MeCN (3 mL) was stirred at 50 °C for 2 h. The reaction suspension was cooled to 25°C and directly filtered. The filter cake was further purified by Prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [H2O(10mM NH4HCO3)-ACN];gradient:40%-70% B over 8.0 min) to give 2-(4,4-dimethylpiperidin-1-yl)-8-(1-((R)-4-hydroxy-3,4-dihydroquinolin-1(2H)-yl)ethyl)-3,6-dimethyl-4H-chromen-4-one (11.8 mg, 25.62 µmol, 1.47% yield) as a white solid and 2-(4,4-dimethylpiperidin-1-yl)-8-(1-((S)-4-hydroxy-3,4-dihydroquinolin-1(2H)-yl)ethyl)-3,6-dimethyl-4H-chromen-4-one (18.5 mg, 40.16 µmol, 2.30% yield) as a white solid. ^{1}H NMR (DMSO-d_6,400 MHz) δ 7.70 (s, 1H), 7.53 (s, 1H), 7.14 (d, J = 6.8Hz, 1H), 7.07-7.03 (m, 1H), 6.80 (d, J = 8.4Hz, 1H), 6.55 (d, J = 7.2Hz, 1H), 5.53-5.52 (m, 1H), 5.02 (s, 1H), 4.41 (s, 1H), 3.17-3.02 (m, 6H), 2.41 (s, 3H), 1.86 (s, 3H), 1.70-1.53 (m, 5H), 1.20-1.16 (m, 4H), 0.83 (s, 6H). MS (ESI): mass calcd. For C29H36N2O3 460.27, m/z found 459.2 [M-H]$^-$. HPLC: 93.57% (220 nm), 97.38% (254 nm). ^{1}H NMR (DMSO-d_6,400 MHz) δ 7.68 (s, 1H), 7.48 (s, 1H), 7.14 (d, J = 6.4Hz, 1H), 6.99 (t, J = 7.2Hz, 1H), 6.66(d, J = 8.4Hz, 1H), 6.50 (d, J = 7.2Hz, 1H), 5.47-5.42 (m, 1H), 5.00 (s, 1H), 4.55-4.53 (m, 1H), 3.21-2.94 (m, 6H), 2.38 (s, 3H), 1.87 (s, 3H), 1.76-1.73(m, 2H), 1.57 (d, J = 6.8Hz, 3H), 1.27-1.23 (m, 4H), 0.83 (s, 6H). MS (ESI): mass calcd. For C29H36N2O3 460.27, m/z found 459.2 [M-H]$^-$. HPLC: 97.67% (220 nm), 98.34 (254 nm).

[00334] Example 6

[00335] *Synthetic Scheme:*



[00336] *Preparation of 8-[(1R)-1-(2-bromoanilino)ethyl]-2-(4,4-dimethyl-1-piperidyl)-3,6 -dimethyl-chromen-4-one*

[00337] The reaction was carried out by 9.00 g x 3 batches in parallel. A mixture of 8-[(1R)-1-aminoethyl]-2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-chromen-4-one (9.00 g, 27.4 mmol, 1eq), 1-bromo-2-iodo-benzene (15.5 g, 54.8 mmol, 7.04 mL, 2 eq), Cs_2CO_3 (26.8 g, 82.2 mmol, 3 eq), Xantphos (4.76 g, 8.22 mmol, 0.3 eq) and $Pd_2(dba)_3$ (2.01 g, 2.19 mmol, 0.08 eq) in dioxane (500 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was heated to 95°C and stirred at 95 °C for 12 h under N_2 atmosphere. 3 reactions were combined for work up. The reaction mixture was cooled to 25°C, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to5/1) to give

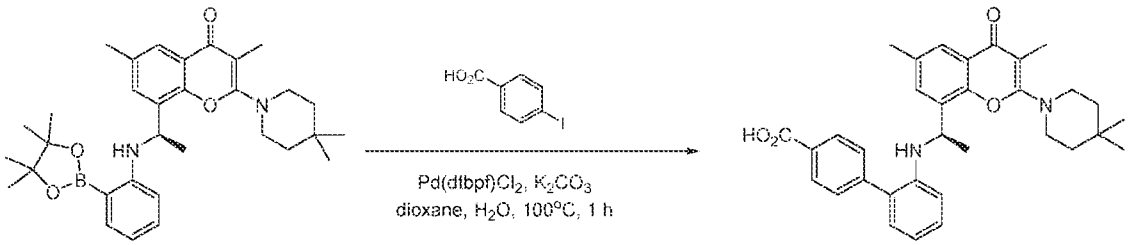
the title compound (33.0 g, 68.26mmol, 83.04% yield) as light yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.63 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 6.8 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.51 (t, J = 7.8 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 5.28 (d, J = 6.8 Hz, 1H), 5.06-5.02 (m, 1H), 3.43-3.32 (m, 4H), 2.32 (s, 3H), 1.92 (s, 3H), 1.62 (d, J = 6.4 Hz, 3H), 1.46 (d, J = 5.6 Hz, 4H), 0.99 (s, 6H).

[00338] *Preparation of 2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-8-[(1R)-1-[2-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]ethyl]chromen-4-one*

[00339] A mixture of 8-[(1R)-1-(2-bromoanilino)ethyl]-2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-chromen -4-one (33.0 g, 68.3 mmol, 1 eq), B_2Pin_2 (52.0 g, 204 mmol, 3 eq), KOAc (13.4 g, 136 mmol, 2 eq) and $Pd(PPh_3)_2Cl_2$ (4.79g, 6.83 mmol, 0.1 eq) in dioxane (800 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was heated to 80°C and stirred at 80 °C for 12 h under N_2 atmosphere. The reaction mixture was cooled to 25°C, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 5/1) to give the title compound (38.0 g, 57.30 mmol, 83.95% yield, 80% purity) as light yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.63 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.52 (t, J = 7.2 Hz, 1H), 6.32 (t, J = 8.0 Hz, 2H), 5.04-5.00 (m, 1H), 3.41-3.33 (m, 4H), 2.31 (s, 3H), 1.91 (s, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.45 (d, J = 6.8 Hz, 4H), 1.32 (s, 12 H), 0.98 (s, 6H).

[00340] Example 7

[00341] *Synthetic Scheme:*



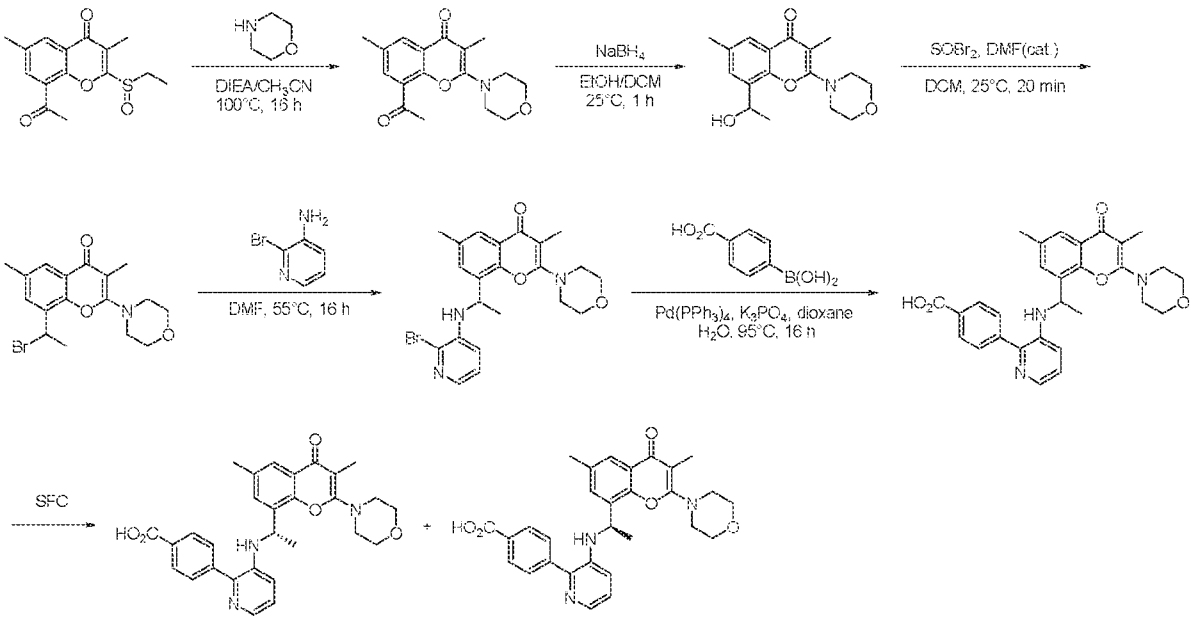
[00342] *Preparation of 4-[2-[[(1R)-1-[2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-4-oxo-chromen-8-yl]ethyl]amino]phenyl]benzoic acid*

[00343] To a mixture of 2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-8-[(1R)-1-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]ethyl]chromen-4-one (200 mg, 377 μmol, 1 eq) and 4-iodobenzoic acid (112 mg, 452 μmol, 1.2 eq) in dioxane (2 mL)\H_2O (0.3 mL) were added K_2CO_3 (156 mg, 1.13 mmol, 3 eq) and $Pd(dtbpf)Cl_2$ (25 mg, 37.7 μmol, 0.1 eq) in portions at 20°C, the resulting reaction mixture was degassed, purged with N_2 for 3 times, and then stirred at 100°C for 1 h under N_2 atmosphere. The reaction mixture was cooled to 25°C, filtered and the filtrate was directly purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40mm x 10um; mobile phase: [H2O(10mM NH4HCO3)-ACN];gradient:35%-65% B over 8.0 min) to give the title compound (73.2 mg, 139 μmol, 37.0% yield)

as a white solid. ^{1}H NMR (DMSO-d_6,400 MHz) δ 8.01 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.46 (s, 1H), 7.10-6.98 (m, 2H), 6.68 (t, J = 7.2 Hz, 1H), 6.49 (d, J = 7.6 Hz, 1H), 5.01-4.90 (m, 1H), 4.87 (d, J = 6.0 Hz, 1H), 3.30-3.17 (m, 4H), 2.32 (s, 3H), 1.91 (s, 3H), 1.46 (d, J = 6.4 Hz, 3H), 1.44-1.36 (m, 4H), 0.97 (s, 6H). MS (ESI): mass calcd. For $C_{33}H_{36}N_2O_4$ 524.27, m/z found 525.3 $[M+H]^+$. HPLC: 99.35% (220 nm), 98.94% (254 nm). Chiral purity: 100 ee%

[00344] Example 8

[00345] *Synthetic Scheme:*



[00346] *Preparation of 8-acetyl-3,6-dimethyl-2-morpholino-chromen-4-one*

[00347] To a solution of 8-acetyl-2-ethylsulfinyl-3,6-dimethyl-chromen-4-one (10.00 g, 34.21 mmol, 1 *eq*) and morpholine (17.88 g, 205.23 mmol, 18.06 mL, 6 *eq*) in MeCN (200 mL) was added DIEA (22.10 g, 171.03 mmol, 29.79 mL, 5 *eq*) dropwise at 25°C. The reaction mixture was heated to 100°C and stirred at 100°C for 16 h. The reaction mixture was cooled to 0°C and the suspension was filtered. The filter cake was washed with MTBE (20 mL x 2) and dried in vacuum to give 8-acetyl-3,6-dimethyl-2-morpholino-chromen-4-one (7.30 g, 24.23 mmol, 70.82% yield) as off-white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.98 (s, 1H), 7.90 (s, 1H), 3.75-3.72 (m, 4H), 3.45-3.43 (m, 4H), 2.70 (s, 3H), 2.43 (s, 3H), 1.94 (s, 3H).

[00348] *Preparation of 8-(1-hydroxyethyl)-3,6-dimethyl-2-morpholino-chromen-4-one*

[00349] To a solution of 8-acetyl-3,6-dimethyl-2-morpholino-chromen-4-one (7.30 g, 24.23 mmol, 1 *eq*) in EtOH (70 mL)\DCM (70 mL) was added $NaBH_4$ (2.18 g, 57.62 mmol, 2.38 *eq*) in portions at 0°C under N_2, the reaction mixture was warmed to 25°C stirred at 25°C for 1 h. To the reaction mixture was added H_2O (100 mL) dropwise until no gas released, adjusted pH to 6 with 3N HCl and then extracted

with DCM (100 mL x 3). The combined organic phase was washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with (Petroleum ether: Ethyl acetate, 50 ml, v/v=5:1) at 25 C for 30 min, and then filtered. The filter cake was dried in vacuo to give the title compound (6.40 g, 21.10 mmol, 87.09% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.63 (s, 1H), 7.60 (s, 1H), 5.32 (d, J = 4.0 Hz, 1H), 5.51 (q, J = 6.0 Hz, 1H), 3.75-3.73 (m, 4H), 3.44-3.35 (m, 4H), 2.39 (s, 3H), 1.91 (s, 3H), 1.41 (d, J = 6.0 Hz, 3H).

[00350] *Preparation of 8-(1-bromoethyl)-3,6-dimethyl-2-morpholino-chromen-4-one*

[00351] To a solution of 8-(1-hydroxyethyl)-3,6-dimethyl-2-morpholino-chromen-4-one (6.4 g, 21.10 mmol, 1 *eq*) in DCM (70 mL) / DMF (77.11 mg, 1.05 mmol, 81.16 µL, 0.05 *eq*) was added $SOBr_2$ (5.70 g, 27.43 mmol, 2.12 mL, 1.3 *eq*) dropwise at 0°C, the resulting reaction mixture was warmed to 25°C and stirred for 20 min. The reaction mixture was poured into ice\water (100 mL) at 0°C, and then extracted with DCM (100 mL x 3). The combined organic layers were washed with sat.aq $NaHCO_3$ until pH = 8, then the combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give 8-(1-bromoethyl)-3,6-dimethyl-2-morpholino-chromen-4-one (4.5 g, 12.29 mmol, 58.24% yield) as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, J = 1.2 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 5.64 (q, J = 6.8 Hz, 1H), 3.90-3.87 (m, 4H), 3.52-3.49 (m, 4H), 2.45 (s, 3H), 2.16 (d, J = 7.2 Hz, 3H), 2.06 (s, 3H).

[00352] *Preparation of 8-[1-[(2-bromo-3-pyridyl)amino]ethyl]-3,6-dimethyl-2-morpholino-chromen-4-one*

[00353] To a solution of 8-(1-bromoethyl)-3,6-dimethyl-2-morpholino-chromen-4-one (3.20 g, 8.74 mmol, 1 *eq*) in DMF (30 mL) was added 2-bromopyridin-3-amine (3.33 g, 19.22 mmol, 2.2 *eq*) in one portion at 25°C, the resulting reaction mixture was warmed to 55°C and stirred at 55°C for 16 h. The reaction mixture was cooled to 25°C, poured into ice-water (90 mL) and the resulting suspension was directly filtered. The filter cake was washed with H_2O (10 mL x 2) and dried in vacuo to give the residue. The residue was further triturated with Petroleum ether : Ethyl acetate (50 mL, v/v=3:1) to give the title compound (3.00 g, 6.55 mmol, 74.91% yield) as an off-white solid. 1H NMR (DMSO-d_6, 400 MHz) δ 7.65 (s, 1H), 7.59 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 4.8, 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 5.58 (d, J = 7.2 Hz, 1H), 5.04 (q, J = 6.8 Hz, 1H), 3.75-3.73 (m, 4H), 3.45-3.42 (m, 4H), 2.32 (s, 3H), 1.93 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H).

[00354] *Preparation of 4-[3-[1-(3,6-dimethyl-2-morpholino-4-oxo-chromen-8-yl)ethylamino]-2-pyridyl]benzoic acid*

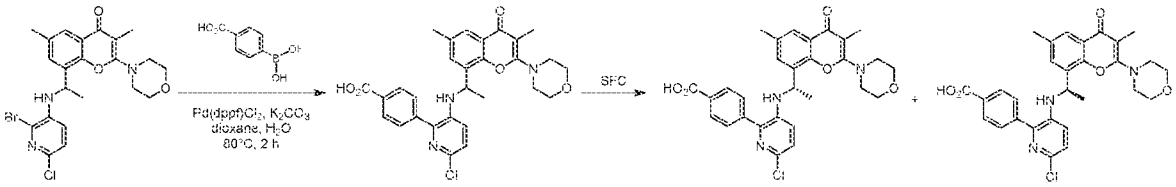
[00355] A mixture of 8-[1-[(2-bromo-3-pyridyl)amino]ethyl]-3,6-dimethyl-2-morpholino-chromen-4-one (500.0 mg, 1.09 mmol, 1 *eq*), 4-boronobenzoic acid (271.5 mg, 1.64 mmol, 1.5 *eq*), K_3PO_4 (810.4 mg, 3.82 mmol, 3.5 *eq*) and $Pd(PPh_3)_4$ (126.1 mg, 109.09 μmol, 0.1 *eq*) in dioxane (10 mL)\H_2O (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was heated to 95°C and stirred at 95°C for 16 h under N_2 atmosphere. The reaction mixture was cooled to 25°C, and then directly concentrated under reduced pressure to give a residue. The residue was further purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 10%-40% B over 8.0 min) to give the title compound (250 mg, 463.91 μmol, 42.53% yield, 92.70% purity) as a white solid. 1H NMR (DMSO-d_6, 400 MHz) δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 1.2 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.05 (dd, *J* = 4.8, 8.4 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.39 (d, *J* = 6.8 Hz, 1H), 4.96 (q, *J* = 6.8 Hz, 1H), 3.71-3.68 (m, 4H), 3.33-3.32 (m, 4H), 2.31 (s, 3H), 1.92 (s, 3H), 1.50 (d, *J* = 6.8 Hz, 3H).

[00356] *Preparation of 4-[3-[[(1S)-1-(3,6-dimethyl-2-morpholino-4-oxo-chromen-8-yl)ethyl]amino]-2-pyridyl] benzoic acid and 4-[3-[[(1R)-1-(3,6-dimethyl-2-morpholino-4-oxo-chromen-8-yl)ethyl]amino]-2-pyridyl] benzoic acid*

[00357] 4-[3-[1-(3,6-dimethyl-2-morpholino-4-oxo-chromen-8-yl)ethylamino]-2-pyridyl]benzoic acid (250 mg, 92.70% purity) was separated by SFC (column: DAICEL CHIRALPAK IG (250mm*30mm, 10um); mobile phase: [CO_2-IPA]; B%:50%, isocratic elution mode) to give 4-[3-[[(1S)-1-(3,6-dimethyl-2-morpholino-4-oxo-chromen-8-yl)ethyl]amino]-2-pyridyl]benzoic acid (99.4 mg, 197.72 μmol, 42.62% yield, 99.37% purity) as an off-white solid and 4-[3-[[(1R)-1-(3,6-dimethyl-2-morpholino-4-oxo-chromen-8-yl)ethyl]amino]-2-pyridyl]benzoic acid (93.3 mg, 197.72 μmol, 40.17% yield, 99.78% purity) as an off-white solid. 1H NMR (DMSO-d_6,400 MHz) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 4.0 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 1H), 7.50 (d, *J* = 1.6 Hz, 1H), 7.07 (dd, *J* = 4.8, 8.4 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.44 (d, *J* = 6.8 Hz, 1H), 4.96 (q, *J* = 6.8 Hz, 1H), 3.71-3.68 (m, 4H), 3.32-3.27 (m, 4H), 2.32 (s, 3H), 1.92 (s, 3H), 1.51 (d, *J* = 6.8 Hz, 3H). MS (ESI): mass calcd. For $C_{29}H_{29}N_3O_5$ 499.21, m/z found 500.3 $[M+H]^+$. HPLC: 99.37% (220 nm), 99.67% (254 nm). Chiral purity: 100 % ee. 1H NMR (DMSO-d_6,400 MHz) δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 4.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 1H), 7.50 (d, *J* = 1.6 Hz, 1H), 7.06 (dd, *J* = 4.4, 8.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.43 (d, *J* = 6.8 Hz, 1H), 4.96 (q, *J* = 6.8 Hz, 1H), 3.71-3.68 (m, 4H), 3.35-3.28 (m, 4H), 2.32 (s, 3H), 1.92 (s, 3H), 1.51 (d, *J* = 6.4 Hz, 3H). MS (ESI): mass calcd. For $C_{29}H_{29}N_3O_5$ 499.21, m/z found 500.2 $[M+H]^+$. HPLC: 99.78% (220 nm), 99.91% (254 nm). Chiral purity: 100 % ee.

[00358] Example 9

[00359] *Synthetic Scheme:*



[00360] *Preparation of 4-[6-chloro-3-[1-(3,6-dimethyl-2-morpholino-4-oxo-chromen-8-yl) ethylamino]-2-pyridyl]benzoic acid*

[00361] To a mixture of 8-[1-[(2-bromo-6-chloro-3-pyridyl)amino]ethyl]-3,6-dimethyl-2-morpholino-chromen-4-one (250 mg, 507 μmol, 1 eq), 4-boronobenzoic acid (126 mg, 760 μmol, 1.5 eq) in dioxane (2.5 mL) / H_2O (0.5 mL) were added K_2CO_3 (140 mg, 1.01 mmol, 2 eq) and $Pd(dppf)Cl_2$ (37 mg, 50.7 μmol, 0.1 eq). The reaction mixture was stirred at 80°C for 2 h under N_2. The reaction mixture was cooled to 25°C, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40mm x 10um;mobile phase: [H2O(10mM NH4HCO3)-ACN];gradient:15%-45% B over 8.0 min) to give the title compound (64 mg, 119 μmol, 23.6% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.05 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 1.6 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 5.65 (d, J = 6.4 Hz, 1H), 4.98-4.91 (m, 1H), 3.70 (t, J = 4.8 Hz, 4H), 3.29-3.27 (m, 4H), 2.32 (s, 3H), 1.92 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H).

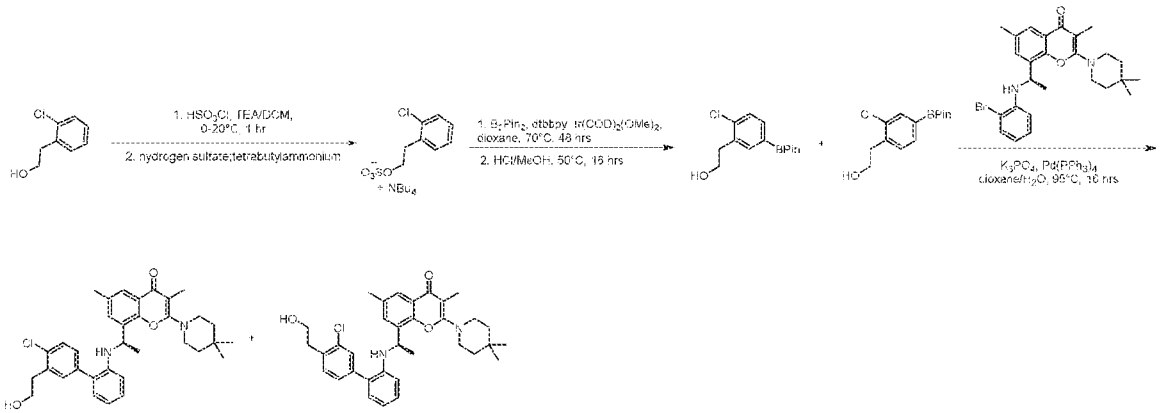
[00362] *Preparation of (S)-4-(6-chloro-3-((1-(3,6-dimethyl-2-morpholino-4-oxo-4H-chromen-8-yl)ethyl)amino)pyridin-2-yl)benzoic acid and (R)-4-(6-chloro-3-((1-(3,6-dimethyl-2-morpholino-4-oxo-4H-chromen-8-yl)ethyl)amino)pyridin-2-yl)benzoic acid*

[00363] 4-[6-chloro-3-[1-(3,6-dimethyl-2-morpholino-4-oxo-chromen-8-yl)ethylamino]-2-pyridyl]benzoic acid (0.09 g, 168 μmol, 1 eq) was separated by SFC (column: DAICEL CHIRALPAK IG (250mm*30mm,10um);mobile phase: [CO2-IPA(0.1% □H3H2O)];B%:50%, isocratic elution mode) to give (S)-4-(6-chloro-3-((1-(3,6-dimethyl-2-morpholino-4-oxo-4H-chromen-8-yl)ethyl)amino)pyridin-2-yl)benzoic acid (29.6 mg, 55.4 μmol, 32.8% yield) as a white solid and (R)-4-(6-chloro-3-((1-(3,6-dimethyl-2-morpholino-4-oxo-4H-chromen-8-yl)ethyl)amino)pyridin-2-yl)benzoic acid (32.2 mg, 60.3 μmol, 35.7% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.04 (s, 1H), 8.06 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 1.2 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 5.71 (d, J = 7.2 Hz, 1H), 5.02-4.83 (m, 1H), 3.70 (t, J = 4.8 Hz, 4H), 3.37-3.33 (m, 4H), 2.32 (s, 3H), 1.92 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H). MS (ESI): mass calcd. For $C_{29}H_{28}ClN_3O_5$ 533.17, m/z found 534.1 $[M+H]^+$. HPLC: 100.00% (220 nm), 100.00% (254 nm). Chiral purity: 100.00 ee%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.04 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 1.2 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 5.71 (d, J = 7.2 Hz, 1H), 5.02-4.86 (m, 1H), 3.70 (t, J = 4.8 Hz, 4H), 3.37-3.33 (m, 4H), 2.32 (s, 3H), 1.92 (s,

3H), 1.51 (d, J = 6.8 Hz, 3H). MS (ESI): mass calcd. For $C_{29}H_{28}ClN_3O_5$ 533.17, m/z found 534.1 $[M+H]^+$. HPLC: 100.00% (220 nm), 100.00% (254 nm). Chiral purity: 99.46 ee%

[00364] Example 10

[00365] *Synthetic Scheme:*



[00366] *Preparation of 2-(2-chlorophenyl)ethyl sulfate;tetrabutylammonium*

[00367] To a solution of 2-(2-chlorophenyl)ethanol (5.00 g, 31.93 mmol, 1 eq) and TEA (12.92 g, 127.71 mmol, 17.78 mL, 4 eq) in DCM (50 mL) was added sulfurochloridic acid (3.72 g, 31.93 mmol, 2.12 mL, 1 eq) at 0°C under N_2, the resulting reaction mixture was allowed to warm to 25°C and stirred at 25°C for 1 h. The reaction mixture quenched by addition 10% aq.NaOH (50 mL) and extracted with DCM (80 mL x 3). To the aqueous layer was added hydrogen sulfate;tetrabutylammonium (8.67 g, 25.54 mmol, 0.8 eq) and then extracted with DCM (50 mL x 3) again. The combined organic layers were washed with H_2O (50 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2-(2-chlorophenyl)ethyl sulfate;tetrabutylammonium (11.00 g, 23.01 mmol, 72.06% yield) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, J = 1.6Hz, 1H), 7.29-7.27 (m, 1H), 7.16-7.11 (m, 2H), 4.25 (t, J = 7.2 Hz, 2H), 3.26-3.22 (m, 8H), 3.14 (t, J = 7.2 Hz, 2H), 1.66-1.60 (m, 8H), 1.44-1.39 (m, 8H), 0.98 (t, J = 7.2 Hz, 12H).

[00368] *Preparation of 2-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) ethan-1-ol and 2-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-ol*

[00369] This reaction was carried out by 3 g x 2 batches in parallel.

[00370] To a mixture of 2-(2-chlorophenyl)ethyl sulfate;tetrabutylammonium (3.00 g, 6.27 mmol, 1 eq) and B_2Pin_2 (2.39 g, 9.41 mmol, 1.5 eq) in dioxane (30 mL) was added $Ir(COD)_2(OMe)_2$ (416 mg, 627.45 μmol, 0.1 eq) at 25°C, the reaction mixture was bubbled with N_2 for 2 min. Then 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (337 mg, 1.25 mmol, 0.2 eq) was added in one portion under N_2 in glovebox . The resulting mixture was heated to 70°C and stirred at 70 °C for 48 h under N_2 atmosphere. Two parallel reaction mixtures were combined, concentrated under reduced pressure and dissolved in HCl (1

M in MeOH, 60 mL, 9.56 eq). Then the reaction mixture was heated to 50°C and stirred at 50°C for 16 h. The reaction mixture was cooled to 25°C, quenched by addition H_2O (50 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were washed brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient @ 150 mL/min) to give Part 1: a mixture of [4-chloro-3-(2-hydroxyethyl)phenyl]boronic acid and [3-chloro-4-(2-hydroxyethyl)phenyl]boronic acid (1.67 g, 8.33 mmol, 66.40% yield) as colorless oil. Part 2: a mixture of 2-(2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-ol and 2-(2-chloro-4-(4,4,5.5-tetramethyl-1.3,2-dioxaborolan-2-yl)phenyl) ethan-1-ol (0.6 g, 2.12 mmol, 16.92% yield) as light yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.80 (s, 0.5 H), 7.70 (d, J = 1.2 Hz, 0.5 H), 7.63-7.59 (m, 1H), 7.36 (d, J = 8.0 Hz, 0.5 H), 7.28 (d, J = 6.4 Hz, 0.5H), 3.90-3.86 (m, 2H), 3.04 (t, J = 6.8 Hz, 2H), 1.34 (s, 12H).

[00371] *Preparation of 8-[(1R)-1-[2-[4-chloro-3-(2-hydroxyethyl)phenyl]anilino]ethyl]-2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-chromen-4-one and 8-[(1R)-1-[2-[3-chloro-4-(2-hydroxyethyl)phenyl]anilino]ethyl]-2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-chromen-4-one*

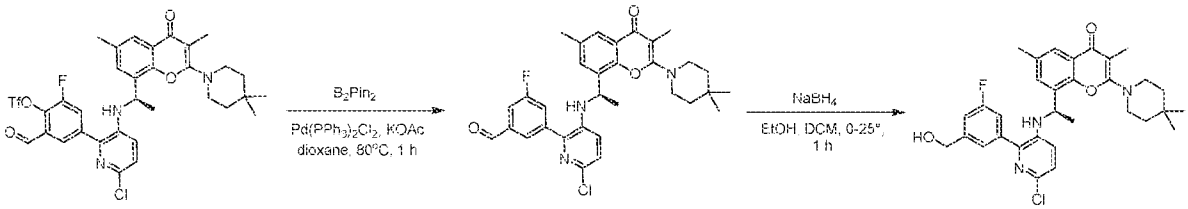
[00372] To a mixture of 2-[2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanol and 2-[2-chloro-4-(4,4,5.5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanol (262 mg, 930 µmol, 0.75 eq), 8-[(1R)-1-(2-bromoanilino)ethyl]-2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-chromen-4-one (300 mg, 620.55 µmol, 1 eq) and K_3PO_4 (263 mg, 1.24 mmol, 2 eq) in dioxane (5 mL)\ H_2O (1 mL) was added $Pd(PPh_3)_4$ (72 mg, 62.06 µmol, 0.1 eq) in one portion under N_2. Then the reaction mixture was degassed and purged with N_2 for 3 times, heated to 95°C and stirred at 95 °C for 16 h under N_2 atmosphere. The reaction mixture was cooled to 20°C, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [H_2O(10mM NH_4HCO_3)-ACN];gradient:70%-95% B over 8.0 min) to give 8-[(1R)-1-[2-[4-chloro-3-(2-hydroxyethyl)phenyl] anilino]ethyl]-2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-chromen-4-one (0.15 g, 255.10 µmol, 41.11% yield, 95.09% purity) as a white solid and 8-[(1R)-1-[2-[3-chloro-4-(2-hydroxyethyl)phenyl]anilino]ethyl]-2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-chromen-4-one (0.3 g, 536.54 µmol, 86.46% yield, 100% purity) as a white solid. 1H NMR (DMSO-d_6, 400 MHz) δ 7.62 (s, 1H), 7.50 (d, J = 6.0 Hz, 1H), 7.49-7.46 (m, 2H), 7.33 (d, J = 2.0 Hz, 1H), 7.04-7.02 (m, 2H), 6.68 (t, J = 7.2 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H), 4.99-4.93 (m, 2H), 4.75 (t, J = 5.2 Hz, 1H), 3.70-3.66 (m, 2H), 3.40-3.34 (m, 4H), 2.89 (t, J = 6.8 Hz, 2H), 2.51 (s, 3H), 1.92 (s, 3H), 1.48 (d, J = 6.0 Hz, 3H), 1.44 (s, 4H), 0.99 (s, 6H).

[00373] MS (ESI): mass calcd. For $C_{34}H_{39}ClN_2O_3$ 558.26, m/z found 559.2 $[M+H]^+$. HPLC: 95.09% (220 nm), 95.56% (254 nm). 1H NMR (DMSO-d_6, 400 MHz) δ 7.61 (s, 1H), 7.46-7.44 (m, 3H), 7.43-7.39 (m,

1H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 1.2 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 6.49 (t, *J* = 8.4 Hz, 1H), 4.95 (t, *J* = 6.8 Hz, 1H), 4.91 (t, *J* = 6.8 Hz, 1H), 3.69-3.64 (m, 2H), 3.36-3.33 (m, 4H), 2.89 (t, *J* = 6.8 Hz, 2H), 2.32 (s, 3H), 1.91 (s, 3H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.42 (t, *J* = 5.2 Hz, 4H), 0.97 (s, 6H). MS (ESI): mass calcd. For $C_{34}H_{39}ClN_2O_3$ 558.26, m/z found 559.1 $[M+H]^+$. HPLC: 100.00% (220 nm), 100.00% (254 nm).

[00374] Example 11

[00375] *Synthetic Scheme:*



[00376] *Preparation of (R)-3-(6-chloro-3-((1-(2-(4,4-dimethylpiperidin-1-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino)pyridin-2-yl)-5-fluorobenzaldehyde*

[00377] To a solution of [4-[6-chloro-3-[[(1R)-1-[2-(4,4-dimethyl-1-piperidyl)-3,6-dimethyl-4-oxo -chromen-8-yl]ethyl]amino]-2-pyridyl]-2-fluoro-6-formyl-phenyl]trifluoromethanesulfonate (300 mg, 422.46 μmol, 1 eq) and B_2Pin_2 (107 mg, 422.46 μmol, 1 eq) in dioxane (10 mL) were added KOAc (124 mg, 1.27 mmol, 3 eq) and $Pd(PPh_3)_2Cl_2$ (29 mg, 42.25 μmol, 0.1 eq) in portions. The resulting reaction mixture was stirred at 80 °C for 1 h. LCMS showed the De-OTf byproduct formed as major. After cooling to 25°C, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [H2O(10mM NH4HCO3)-ACN];gradient:58%-88% B over 8.0 min) to give the title compound (60 mg, 106.74 μmol, 24% yield) as a white solid. MS (ESI): mass calcd. For C32H33ClFN3O3 561.22, m/z found 562.2 $[M+H]^+$.

[00378] *Preparation of (R)-8-(1-((6-chloro-2-(3-fluoro-5-(hydroxymethyl)phenyl) pyridin-3-yl) amino)ethyl)-2-(4,4-dimethylpiperidin-1-yl)-3,6-dimethyl-4H-chromen-4-one*

[00379] To a solution of (R)-3-(6-chloro-3-((1-(2-(4,4-dimethylpiperidin-1-yl)-3,6-dimethyl-4-oxo-4H-chromen-8-yl)ethyl)amino)pyridin-2-yl)-5-fluorobenzaldehyde (60.0 mg, 106.75 μmol, 1 eq) in DCM (1 mL)\EtOH (1 mL) was added $NaBH_4$ (8.9 mg, 234.85 μmol, 2.2 eq) in one portion at 0°C, the reaction mixture was stirred at 25°C for 1 h. The reaction mixture was quenched with ice-water (10 mL), adjusted to pH=5 with 2N HCl and extracted with EtOAc (8 mL x 3). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with MeCN (1 mL) at 25°C for 30 min to give the title compound (33.0 mg, 58.50 μmol, 54.80% yield) as a white solid. ^1H NMR (DMSO-d_6 400MHz) δ 7.62 (s, 1H), 7.47-7.44

(m, 2H), 7.36 (d, J = 9.6 Hz, 1H), 7.19 (d, J = 9.6 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 5.63 (d, J = 7.2 Hz, 1H), 5.40 (t, J = 5.6 Hz, 1H), 4.96-4.93 (m, 1H), 4.56 (t, J = 6.0 Hz, 1H), 3.33-3.31 (m, 4H), 2.31 (s, 3H), 1.91 (s, 3H), 1.51 (d, J = 6.4 Hz, 3H), 1.44-1.41 (m, 3H), 0.97 (s, 6H). MS (ESI): mass calcd. For $C_{32}H_{35}ClFN_3O_3$563.2, m/z found 564.2 $[M+H]^+$. HPLC: 96.97% (220 nm), 96.69% (254 nm). Chiral purity: 98.34 ee%.

[00380] **BIOLOGICAL EXAMPLES**

[00381] The compounds of the present disclosure may be tested in multiple assays.

[00382] **pAKT**

[00383] Compounds were tested in cancer cell lines with or without PI3Kα mutations including SKBR3 (wt), MCF7 (E545K), and T-47D (H1047R) cancer cell lines purchased from ATCC. pAKT1/2/3 (Ser473) HTRF kits were purchased from Revvity. In brief, the assay utilizes a plate-based assay format to detect endogenous AKT rapidly and directly in cells when Ser473 is phosphorylated. Adherent cells are lysed, then subjected to an Eu^{3+}-Cryptate (donor) and d2 (acceptor) antibodies. Emission from the donor antibody triggers a Fluorescence Resonance Energy Transfer (FRET) at the acceptor antibody. The signal directly corresponds to pAKT at Ser473.

[00384] Cells were treated with compounds in dose response titration for 6 hours at 37°C with 5% CO_2 in 96-well tissue culture treated plates. Cells were assayed in media containing 10% FBS and penicillin-streptomyocin. After compound treatment, cells were lysed with 20-25 µL of 1X supplemented lysis buffer for 30 minutes. During cellular lysis, antibodies were prepared according to manufacturer's instructions. Briefly, antibodies were diluted in detection buffer and pre-mixed at a 1:1 volume of pAKT Eu antibody and pAKT d2 antibody. Ten µL of lysate was transferred to a 384-well plate where the lysates were incubated at room temperature with 2 µL of pre-mixed pAKT antibodies overnight. Plates were read on a Cytation 5 plate reader (BioTek) where 620 and 665 nm wavelength emissions were measured. The ratio between 665 nm and 620 nm was used to generate the IC_{50} for tested compounds, where ratios were normalized to DMSO control and background signal.

[00385] **ADP-Glo**

[00386] Compound activity was determined biochemically via the ADP-Glo Kinase Assay purchased from Promega in conjunction with PIP_2:PS lipid kinase substrate from ThermoFisher Scientific and (p110a/p85a) and (p110a [H1047R]/p85a) enzymes from Viva. The assay was performed according to the manufacturer's instructions with compounds pre-incubated with 1nM of enzyme and 2.5nM of pY2-peptide derived from PDGFRb for 4 hours. The reaction proceeded by addition of 1mM ATP and either 200mM, 50mM, or 25mM of lipid substrate. Ideal enzyme and substrate concentrations were determined empirically through enzyme titration to represent 5% product formation as recommended by the manufacturer. The kinase reaction was allowed to proceed for one hour prior to measurement of

bioluminescent light output on a Cytation 5 plate reader with a 0.5 second integration time. Compounds were tested in seven point dose response and IC_{50} were determined by normalization to DMSO and no enzyme controls.

[00387] Tested compounds are reported as: (A) less than or equal to 500 nM; (B) greater than 500 nM to less than or equal to 1,000 nM; (C) greater than 1,000 nM.

[00388] Figure 1 provides tabulated biological data for compounds of the present disclosure according to the testing protocols described herein. One embodiment of the present disclosure includes all exemplified compounds. One embodiment of the present disclosure includes all compounds reported A, B, or C, in one or more assay. One embodiment of the present disclosure includes all compounds reported A or B in one or more assay. One embodiment of the present disclosure includes all compounds reported A, in one or more assay.

[00389] All publications, patents, and patent applications cited in this specification are incorporated herein by reference for the teaching to which such citation is used.

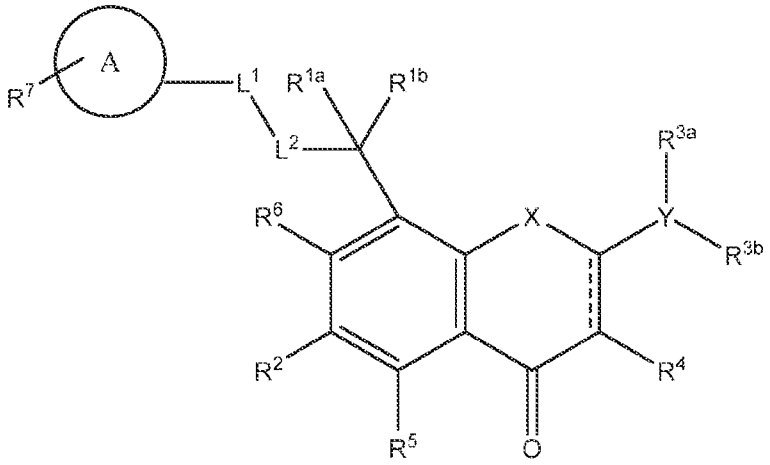
[00390] Test compounds for the experiments described herein were employed in free or salt form.

[00391] The specific responses observed may vary according to and depending on the particular active compound selected or whether there are present carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present disclosure.

[00392] Although specific embodiments of the present disclosure are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present disclosure and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

That which is claimed is:

1. A compound of Formula (I):



(I)

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof, wherein

A is selected from the group consisting of

$C_{1\text{-}6}$ alkyl,

$C_{2\text{-}6}$ alkenyl,

$C_{2\text{-}6}$ alkynyl, and

3- to 14- membered mono-ring or fused ring system, which may have one or more degrees of unsaturation, and which may contain one or more heteroatoms selected from O, N, or S,

each of which A may be further substituted with one or more R^A;

R^7 is selected from the group consisting of: CHO, OH, oxo, C_1-C_6 alkyl(OH), C_2-C_6 alkenyl(OH), C_2-C_6 alkynyl(OH), C_1-C_6 alkyl(NH_2), C_2-C_6 alkenyl(NH_2), C_2-C_6 alkynyl(NH_2), C_1-C_6 alkyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkenyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkynyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_1-C_6 alkyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkenyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkynyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C(O)NH_2, C(O)NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), C(O)N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, S(O)$_2NH_2$, S(O)$_2$NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), S(O)$_2$(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, C(O)OC_1-C_6 alkyl, C(O)OC_1-C_6 alkenyl, and C(O)OC_1-C_6 alkynyl, and C(O)OH;

L^1 is selected from the group consisting of an optionally substituted cycloalkylene, optionally substituted heterocyclylene, optionally substituted arylene, and optionally substituted heteroarylene;

L^2 is selected from the group consisting of O and NH;

each of R^{1a} and R^{1b} is the same or different and is independently is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, and O-C_{2-6} alkynyl;

X is $C(R^x)_2$, O, NR^x, or S;
each R^x is the same or different and is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

Y is selected from:

a) H, where each of R^{3a} and R^{3b} are absent;

b) C-R^{3c}, wherein

R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

each of R^{3a} and R^{3b} is the same or different and independently is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

Y, as an C atom, combines with R^{3a} and R^{3b} to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more heteroatoms selected from the group consisting of N, O, S, and B, and wherein the Y-containing ring or ring system is optionally substituted with one or more R^Y;

c) N, wherein

each of R^{3a} and R^{3b} independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

Y, as an N atom, combines with R^{3a} and R^{3b} to form a 3- to 14-membered mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms

selected from the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^Y;

d) O, wherein

R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

and

e) S, wherein

R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^2 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^4 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^5 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^6 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

when present, each of R^A, R^Y, and R^{100} independently is selected from the group consisting of: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-$C(O)OH$, $(CH_2)_q$-$C(O)O(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-$NH(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-

$N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-$C(O)NH_2$, $(CH_2)_q$-$C(O)NH(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-$C(O)N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-NHC(O)H, $(CH_2)_q$-$NHC(O)(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-$N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-$N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$C(O)(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl;

each of m, and q independently is, at each occurrence, selected from 0, 1, 2, 3, 4, 5, and 6;

and

wherein for each occurrence of cycloalkyl, heterocycle, aryl, and heteroaryl as one or more of R^A, R^Y, and R^{100}, is optionally substituted with one or more of C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

2. The compound of claim 1, wherein when Y is incorporated into or includes any ring or ring system:

i) the Y ring or ring system contains a B atom in the Y ring or ring system;

ii) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is $B(OH)_2$;

iii) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

iv) the Y ring or ring system is further substituted with one or more R^Y, which at least one R^Y is $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, where each of said cycloalkyl, heterocycle, aryl, or heteroaryl is substituted with $B(OH)_2$.

3. The compound of claim 1 or 2, wherein L^1 is optionally substituted phenylene.

4. The compound of claim 3, wherein L^1 is phenylene substituted with one or more halogen.

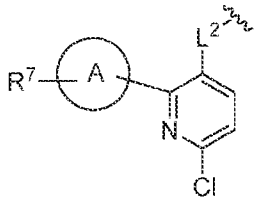
5. The compound of claim 1 or 2, wherein L^1 is optionally substituted heteroarylene.

6. The compound of claim 5, wherein L^1 is optionally substituted pyridinylene.

7. The compound of claim 6, wherein L^1 is pyridinylene substituted with at least one or more halogen.

8. The compound of any one of claims 1 to 7, wherein L^1 is substituted with at least one or more halogen or C_{1-6}alkyl.

9. The compound of any one of claims 1 to 8, wherein L^1 is optionally substituted pyridinylene, and the pyridinylene is attached as:



10. The compound of any one of claims 1 to 8, wherein R^7 is COOH or C_1-C_6 alkyl(OH).

11. The compound of any one of claims 1 to 10, wherein A is selected from the group consisting of phenyl and 5-6 membered heteroaryl.

12. The compound of claim 11, wherein A is phenyl.

13. The compound of any one of claims 1 to 12, wherein A is substituted with one or two R^A that may be the same or different.

14. The compound of any one of claims 1 to 13, wherein each R^A is selected from the group consisting of: C_{1-6} alkyl, halogen, and C_{1-6} haloalkyl.

15. The compound of claim 14, wherein A is substituted with one or two R^A and at least one R^A is a halogen.

16. The compound of claim 14 or 15, wherein halogen is fluorine or chlorine.

17. The compound of any one of claims 1 to 16, wherein

R^{1a} is H; and

R^{1b} independently is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy.

18. The compound of claim 17, wherein R^{1b} is C_{1-6} alkyl.

19. The compound of claim 18, wherein R^{1b} is methyl.

20. The compound of claim 19, wherein R^{1b} is methyl and R^{1a} is hydrogen.

21. The compound of any one of claims 1 to 20, wherein L^2 is O.

22. The compound of any one of claims 1 to 20, wherein L^2 is NH.

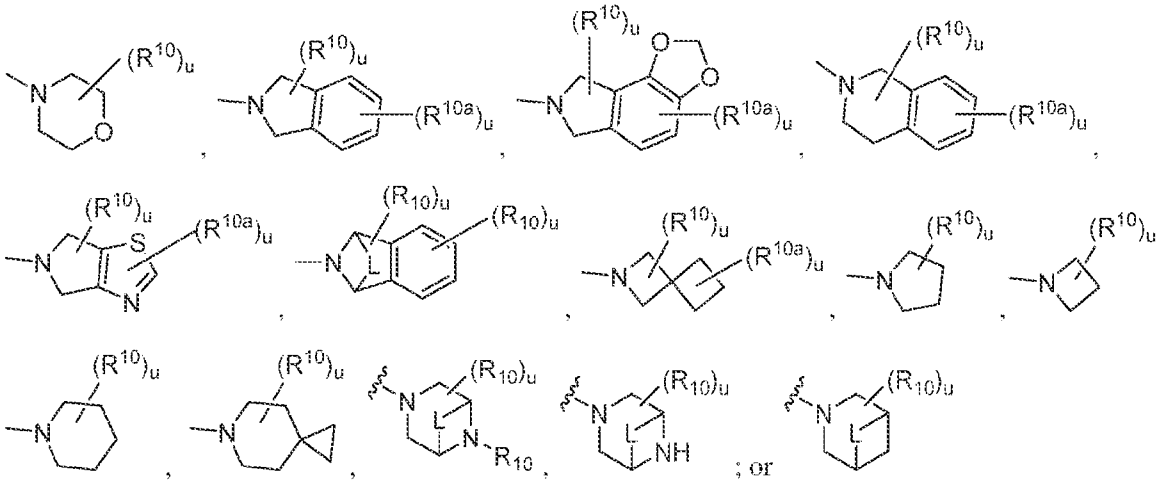
23. The compound of any one of claims 1 to 22, wherein X is O.

24. The compound of any one of claims 1 or 3 to 23, wherein Y is an N, which combines with R^{3a} and R^{3b} to form a 3- to 14-membered mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms selected from the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^{Y}.

25. The compound of claim 24, wherein Y is an N, which combines with R^{3a} and R^{3b} to form an isoindolene that is optionally substituted with one or more R^{Y}.

26. The compound of claim 24, wherein Y is an N, which combines with R^{3a} and R^{3b} to form a piperidine that is optionally substituted with one or more R^{Y}.

27. The compound of claim 24, wherein Y is an N, which combines with R^{3a} and R^{3b} to form:



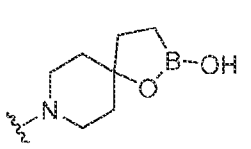
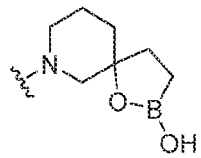
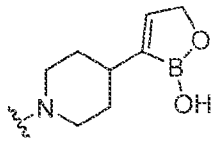
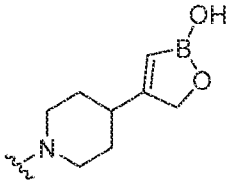
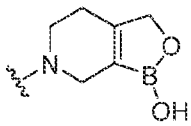
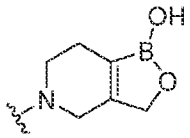
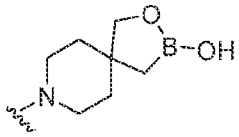
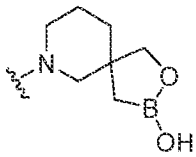
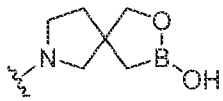
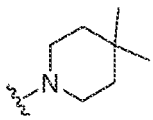
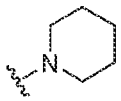
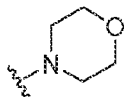
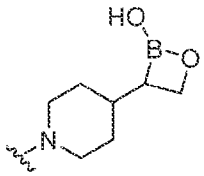
wherein

each R^{10} and R^{10a} is the same or different and is individually selected from an R^{Y};

each u is 0, 1, 2, 3, 4, 5, or 6; and

each L is absent, (CH_2), $(CH_2)_2$, or $(CH_2)_3$.

28. The compound of claim 24, wherein Y is an N, which combines with R^{3a} and R^{3b} to form one of:













, and

.

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof.

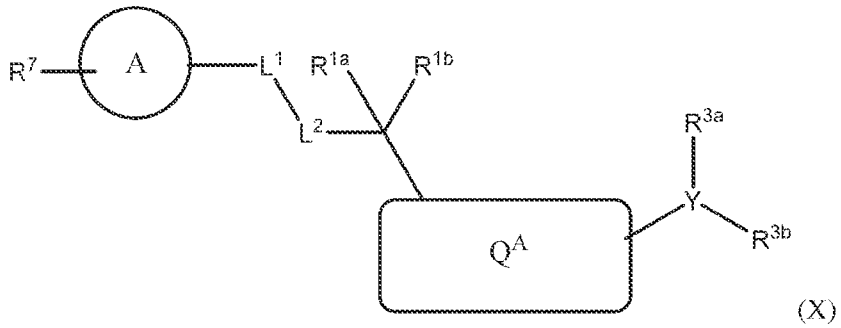
29. The compound of any one of claims 1 to 28, wherein each of R^2, R^4, R^5, and R^6 independently is H, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6 cycloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, or C_{1-6} haloalkyl.

30. The compound of any one of claims 1 to 29, wherein R^2 is H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; R^5 is H; and R^6 is H.

31. The compound of claim 30, wherein R^2 is methyl.

32. The compound of any one of claims 1 to 31, wherein R^4 is selected from the group consisting of CH_3.

33. A compound of Formula X:



(X)

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof, wherein

Q^A is an optionally substituted 8- to 14-membered ring system, which may have one or more degrees of unsaturation, which may contain one or more heteroatoms selected from O, N, or S, and which may be further substituted with one or more R^Q;

A is selected from the group consisting of

C_{1-6} alkyl,

C_{2-6} alkenyl,

C_{2-6} alkynyl, and

3- to 14- membered mono-ring or fused ring system, which may have one or more degrees of unsaturation, and which may contain one or more heteroatoms selected from O, N, or S,

each of which A may be further substituted with one or more R^A;

L^1 is selected from the group consisting of a direct bond, optionally substituted cycloalkylene, optionally substituted heterocyclylene, optionally substituted arylene, and optionally substituted heteroarylene;

L^2 is selected from the group consisting of consisting of a direct bond, $(CR^R_2)_{1-6}$, O, C(O), S, and NR^R;

each of R^R, R^{1a}, and R^{1b} is the same or different and is independently is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, and O-C_{2-6} alkynyl;

or

L^2-$C(R^{1a})(R^{1b})$ combines to form $NR^RC(S)$, $C(S)NR^R$, $NR^RC(O)$, $C(O)NR^R$, $NR^RS(O)_2$, $S(O)_2NR^R$, $NR^RC(NR^R)$, or $C(NR^R)NR^R$;

Y is selected from:

a) H, where each of R^{3a} and R^{3b} are absent;

b) C-R^{3c}, wherein

R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

each of R^{3a} and R^{3b} is the same or different and independently is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

Y, as an C atom, combines with R^{3a} and R^{3b} to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more heteroatoms selected from the group consisting of N, O, S, and B, and wherein the Y-containing ring or ring system is optionally substituted with one or more R^{Y};

c) N, wherein

each of R^{3a} and R^{3b} independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

Y, as an N atom, combines with R^{3a} and R^{3b} to form a 3- to 14-membered mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms selected from the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^{Y};

d) O, wherein

R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

and

e) S, wherein

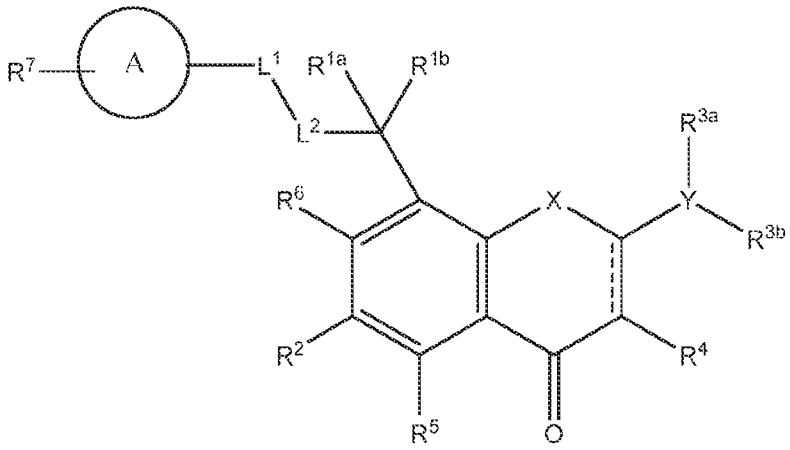
R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{7} is selected from the group consisting of: H, CHO, OH, oxo, C_1-C_6 alkyl(OH), C_2-C_6 alkenyl(OH), C_2-C_6 alkynyl(OH), C_1-C_6 alkyl(NH_2), C_2-C_6 alkenyl(NH_2), C_2-C_6 alkynyl(NH_2), C_1-C_6 alkyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkenyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)),

C_2-C_6 alkynyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_1-C_6 alkyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkenyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkynyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), $C(O)N(C_1$-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, $S(O)_2NH_2$, $S(O)_2NH(C_1$-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), $S(O)_2(C_1$-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, $C(O)OC_1$-C_6 alkyl, $C(O)OC_1$-C_6 alkenyl, and $C(O)OC_1$-C_6 alkynyl, and C(O)OH;

when present, each instance of R^A, R^Q, and R^Y, is the same or different and independently is selected from the group consisting of:
H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-C(O)OH, $(CH_2)_q$-C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-$C(O)NH_2$, $(CH_2)_q$-C(O)NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C(O)N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-NHC(O)H, $(CH_2)_q$-NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl,
and
wherein each occurrence of R^A, R^Q, and R^Y, as cycloalkyl, heterocycle, aryl, or heteroaryl is optionally substituted with one or more of C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, OH, $B(OH)_2$, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

34. The compound of claim 33, of Formula X1



(X1),

wherein

X is $C(R^x)_2$, O, NR^x, or S;

each R^x is the same or different and is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^2 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^4 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^5 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^6 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$,

$(CH_2)_m$-C(O)R^{100}, $(CH_2)_m$-C(O)OR^{100}, $(CH_2)_m$-C(O)N$(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

each R^{100} is the same or different and is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-C(O)OH, $(CH_2)_q$-C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-C(O)NH_2, $(CH_2)_q$-C(O)NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C(O)N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-NHC(O)H, $(CH_2)_q$-NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl,

and

each of m and q independently is, at each occurrence, selected from 0, 1, 2, 3, 4, 5, and 6.

35. The compound of claim 33 or 34, wherein Y comprises a B atom.

36. The compound of any one of claims 33 to 35, wherein when Y is incorporated into or includes any ring or ring system:

i) the Y ring or ring system contains a B atom in the Y ring or ring system;

ii) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is $B(OH)_2$;

iii) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

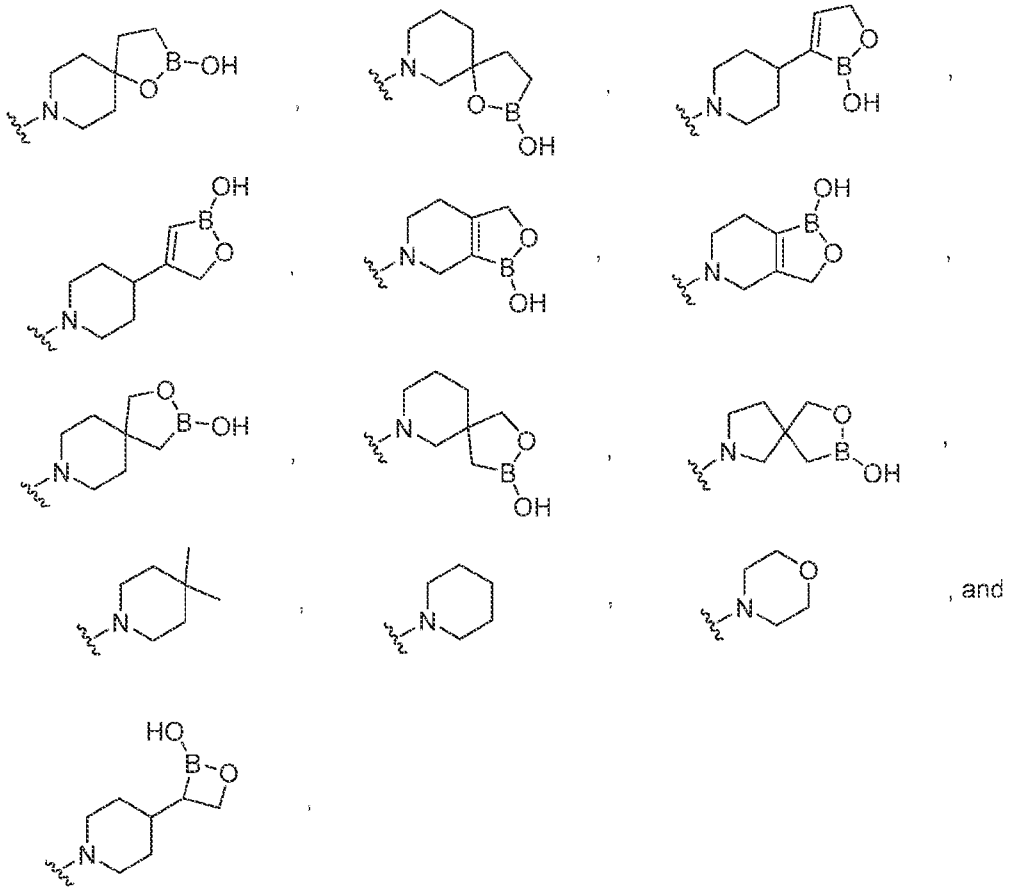
iv) the Y ring or ring system is further substituted with one or more R^Y, which at least one R^Y is $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, where each of said cycloalkyl, heterocycle, aryl, or heteroaryl is substituted with $B(OH)_2$.

37. The compound of any one of claims 33 to 36, wherein Y is a ring or ring system wherein:

a) the Y ring or ring system contains a B atom in the Y ring or ring system;

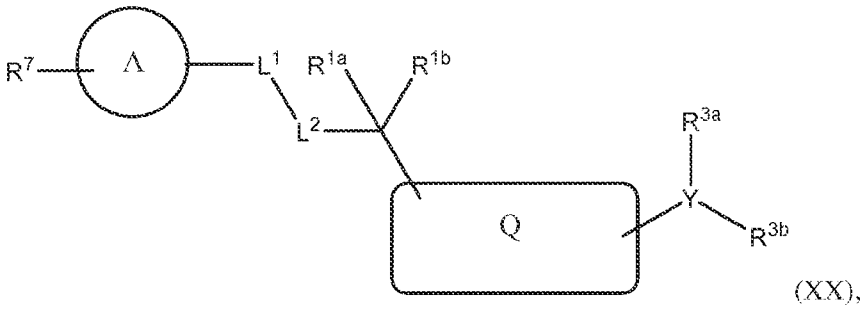
b) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

c) $Y(R^{3a})(R^{3b})$ is selected from:



or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof.

38. A compound of Formula XX:



(XX),

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof, wherein

A is selected from the group consisting of

C_{1-6} alkyl,

C_{2-6} alkenyl,

C_{2-6} alkynyl, and

3- to 14- membered mono-ring or fused ring system, which may have one or more degrees of unsaturation, and which may contain one or more heteroatoms selected from O, N, or S,

each of which A may be further substituted with one or more R^A;

R^7 is selected from the group consisting of: CHO, OH, oxo, C_1-C_6 alkyl(OH), C_2-C_6 alkenyl(OH), C_2-C_6 alkynyl(OH), C_1-C_6 alkyl(NH_2), C_2-C_6 alkenyl(NH_2), C_2-C_6 alkynyl(NH_2), C_1-C_6 alkyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkenyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_2-C_6 alkynyl(NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)), C_1-C_6 alkyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkenyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C_2-C_6 alkynyl(N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$), C(O)NH_2, C(O)NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), C(O)N(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, S(O)$_2NH_2$, S(O)$_2$NH(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl), S(O)$_2$(C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl)$_2$, C(O)OC_1-C_6 alkyl, C(O)OC_1-C_6 alkenyl, and C(O)OC_1-C_6 alkynyl, and C(O)OH;

L^1 is selected from the group consisting of a direct bond, optionally substituted cycloalkylene, optionally substituted heterocyclylene, optionally substituted arylene, and optionally substituted heteroarylene;

L^2 is selected from the group consisting of O and NH;

each of R^{1a} and R^{1b} independently is selected from the group consisting of hydrogen, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, C_{2-6} alkenyloxy, and C_{2-6} alkynyloxy;

Q is a 8- to 14- membered fused ring system, which may have one or more degrees of unsaturation, which may contain one or more heteroatoms selected from O, N, or S, and which may be further substituted with one or more R^Q;

Y is selected from:

a) H, where each of R^{3a} and R^{3b} are absent;

b) C-R^{3c}, wherein

R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

each of R^{3a} and R^{3b} is the same or different and independently is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

Y, as an C atom, combines with R^{3a} and R^{3b} to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more heteroatoms selected from the group consisting of N, O, S, and B, and wherein the Y-containing ring or ring system is optionally substituted with one or more R^Y;

c) N, wherein

each of R^{3a} and R^{3b} independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

Y, as an N atom, combines with R^{3a} and R^{3b} to form a 3- to 14-membered mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms selected from the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^Y;

d) O, wherein

R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

and

e) S, wherein

R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

provided that at least one of the following applies:

a) the Y ring or ring system contains a B atom in the Y ring or ring system;

b) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is $B(OH)_2$;

c) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

d) the Y ring or ring system is further substituted with one or more R^Y, which at least one R^Y is $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, where each of said cycloalkyl, heterocycle, aryl, or heteroaryl is substituted with $B(OH)_2$.

when present, each of R^A, R^Q, and R^Y is the same or different and independently is selected from the group consisting of: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-C(O)OH, $(CH_2)_q$-C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-C(O)NH_2, $(CH_2)_q$-C(O)NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C(O)N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-NHC(O)H, $(CH_2)_q$-NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, $(CH_2)_q$-heteroaryl,

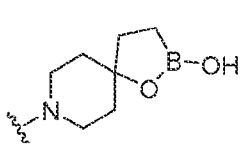
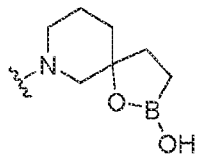
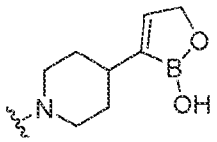
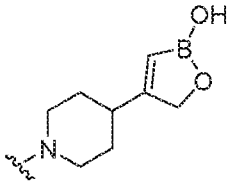
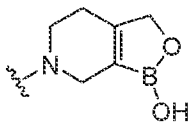
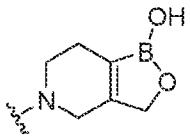
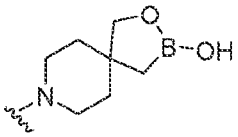
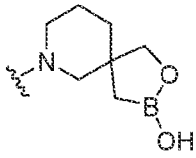
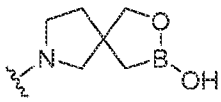
wherein for each occurrence of cycloalkyl, heterocycle, aryl, and heteroaryl as one or more of R^A, R^Y, and R^Q, is optionally substituted with one or more of C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

each q independently is 0, 1, 2, 3, 4, 5, or 6.

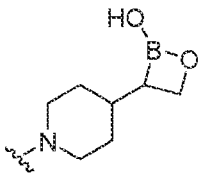
39. The compound of claim 38, wherein the Y ring or ring system contains a B atom in the ring or ring system.

40. The compound of claim 38, wherein the Y ring or ring system is substituted with a 4-, 5-, or 6-membered ring, which contains a B atom in the ring.

41. The compound of any one of claims 38 to 40, wherein Y is incorporated in or is substituted with a ring or ring system that is selected from:

and



or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof.

42. The compound of any one of claims 38 to 41, wherein L^1 is a direct bond.

43. The compound of any one of claims 38 to 42, wherein A is a 5- or 6-membered heteroaryl or phenyl

44. The compound of claim 43, wherein A is phenyl.

45. The compound of any one of claims 38 to 44, wherein R^7 is COOH.

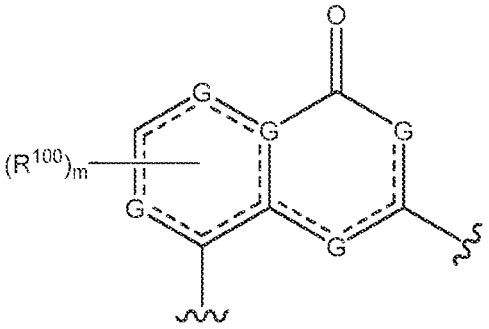
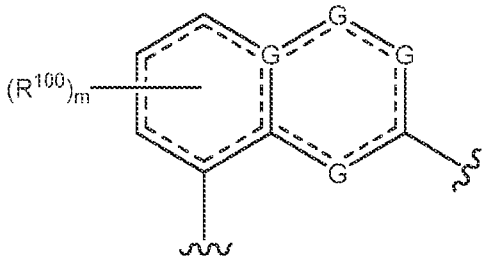
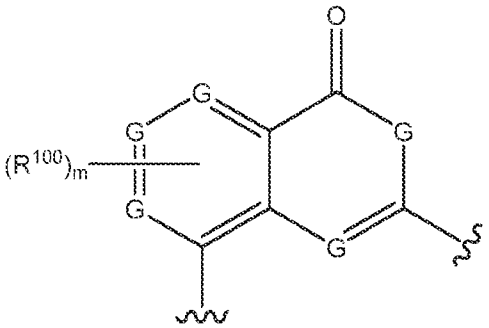
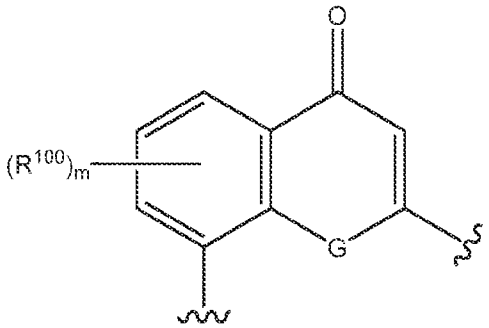
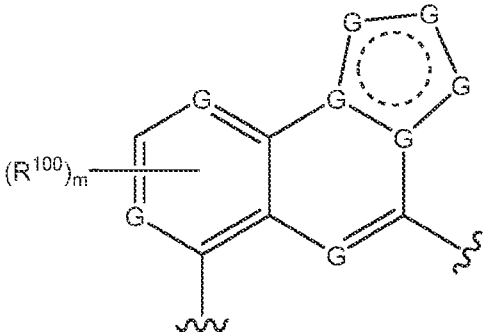
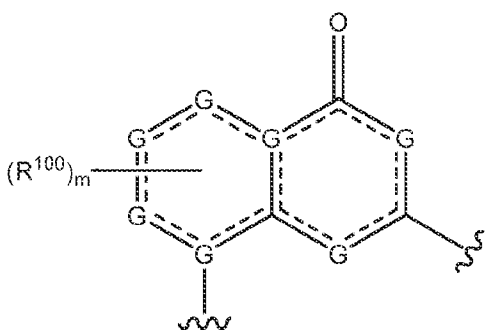
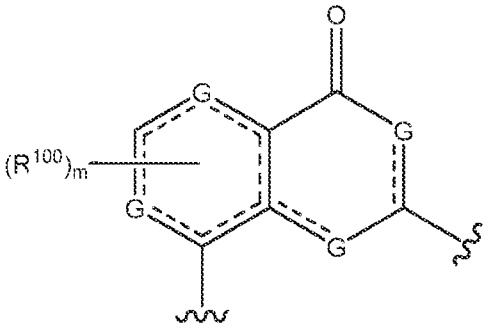
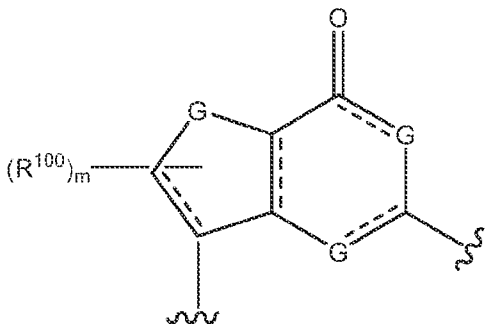
46. The compound of any one of claims 38 to 45, wherein L^2 is O.

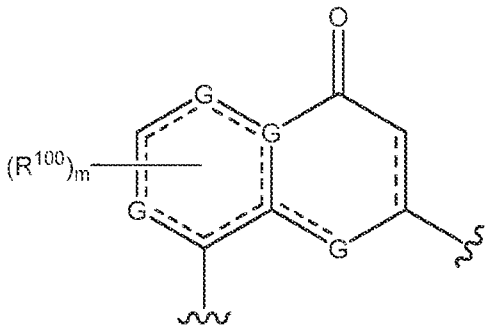
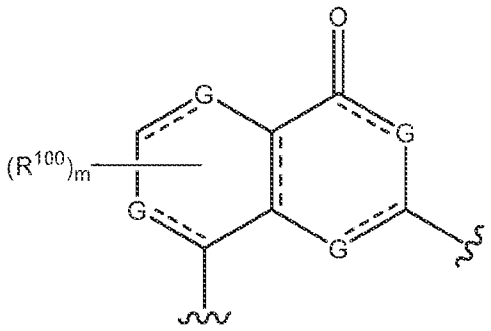
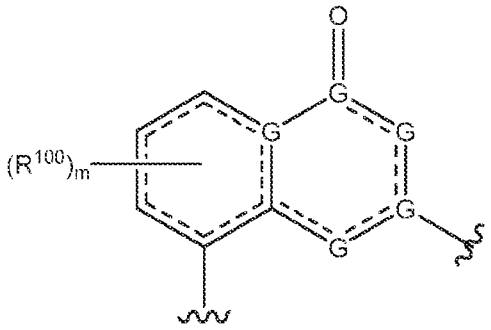
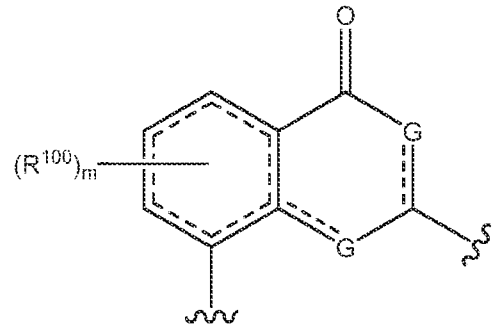
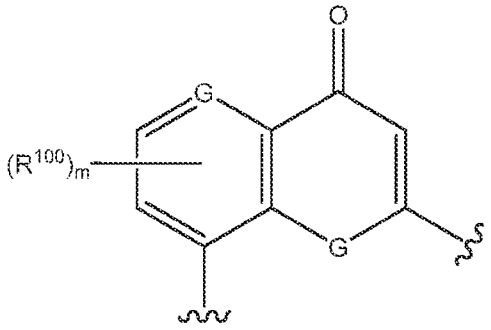
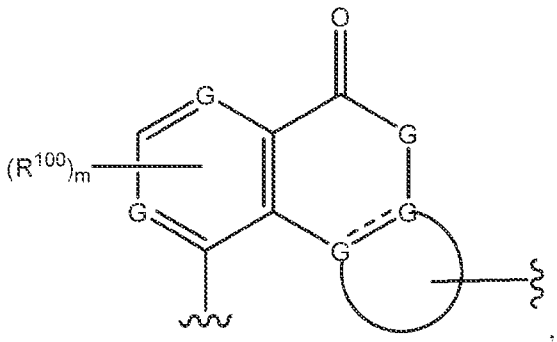
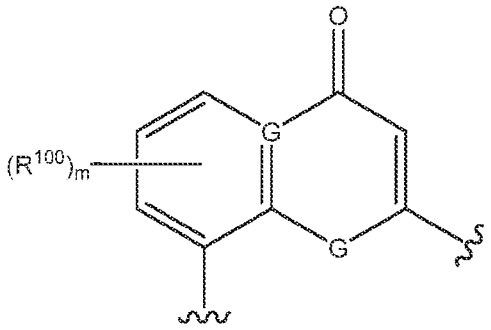
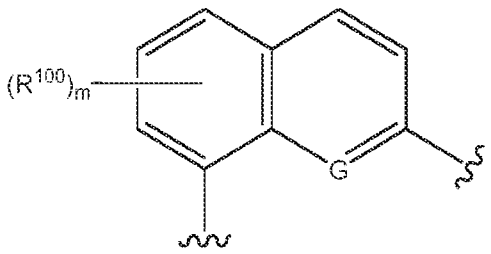
47. The compound of any one of claims 38 to 45, wherein L^2 is NH.

48. The compound of any one of claims 38 to 47, wherein R^{1a} is H or CH_3.

49. The compound of any one of claims 38 to 48, wherein R^{1b} is H or CH_3.

50. The compound of any one of claims 38 to 49, wherein Q is selected from the group consisting of:








, and

,

wherein

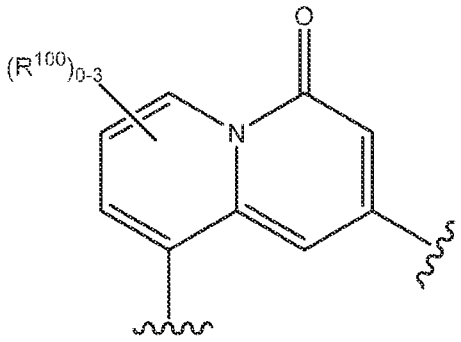
each G is, at each occurrence, independently selected from carbon or a heteroatom selected from O, N, or S;

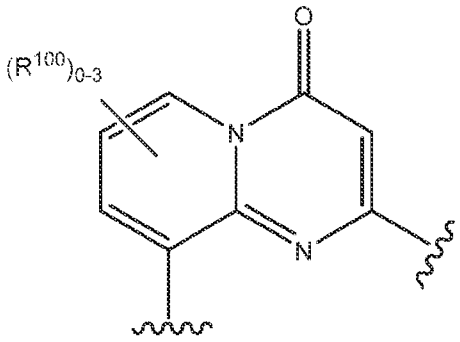
each m is, at each occurrence, independently selected from 0, 1, 2, 3, 4, 5, and 6;

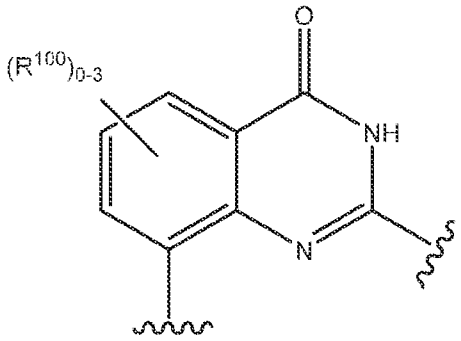
when m is not 0, each R^{100} may be substituted from any depicted ring; and

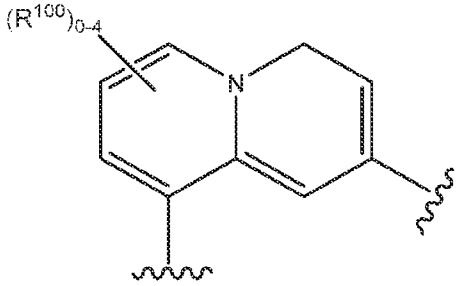
when present, each R^{100} is the same or different and independently is selected from the group consisting of halogen, OH, oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $(CH_2)_q$-N(H or C_{1-6}alkyl), C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl, wherein each of the cycloalkyl, heterocycle, aryl, and heteroaryl is optionally substituted with one or more halogen, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

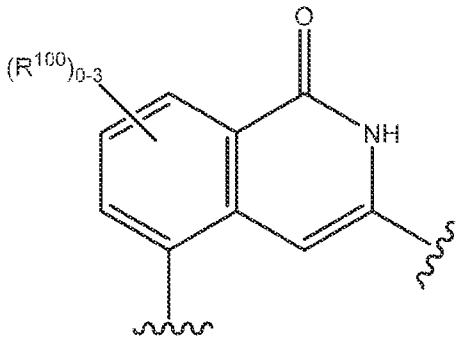
51. The compound of any one of claims 38 to 50, wherein Q is selected from the group consisting of:

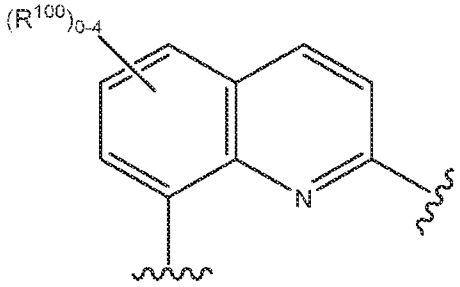


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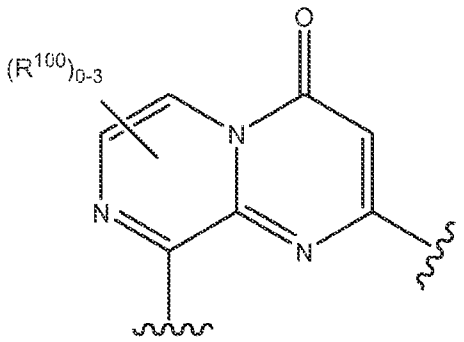
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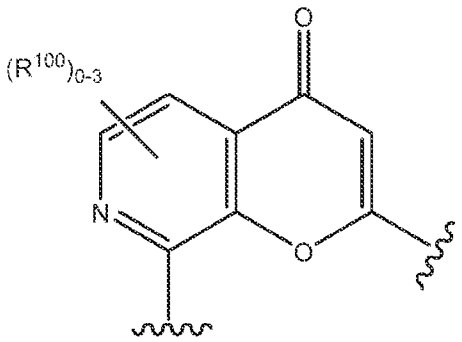
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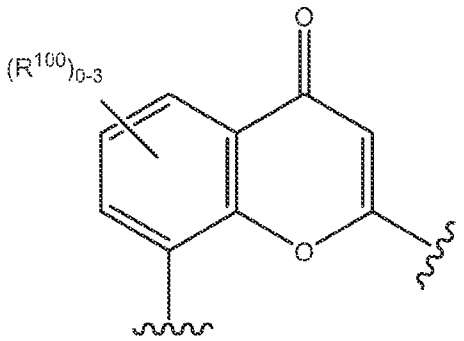
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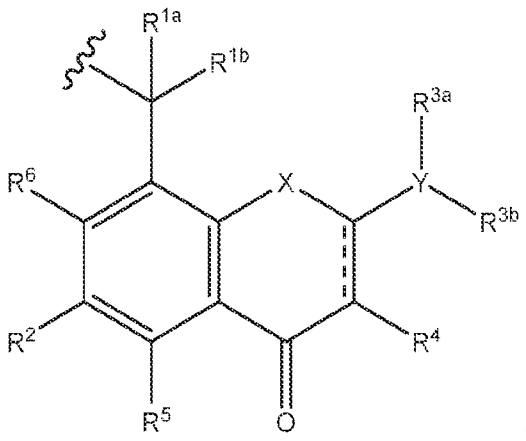


, and



.

52. The compound of any one of claims 38 to 51, wherein Q is:



(Q^B1),

wherein

X is $C(R^x)_2$, O, NR^x, or S;

each R^x independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^2 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^4 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^5 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

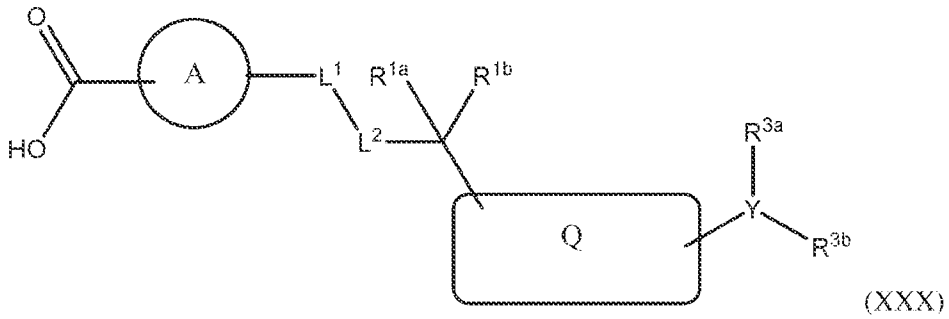
R^6 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

and

each R^{100} is independently H, halogen, OH, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, C_{2-6} alkynoxy, C_{1-6} haloalkoxy, C_{2-6} haloalkenoxy, and C_{2-6} alkynoxy.

53. The compound of any one of claims 38 to 52, wherein X is O.

54. A compound of Formula XXX:



(XXX)

or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof, wherein

A is selected from the group consisting of

C_{1-6} alkyl,

C_{2-6} alkenyl,

C_{2-6} alkynyl, and

3- to 14- membered mono-ring or fused ring system, which may have one or more degrees of unsaturation, and which may contain one or more heteroatoms selected from O, N, or S,

each of which A may be further substituted with one or more R^A;

Q is a 8- to 14- membered fused ring system, which may have one or more degrees of unsaturation, which may contain one or more heteroatoms selected from O, N, or S, and which may be further substituted with one or more R^Q;

L^1 is selected from the group consisting of a direct bond, optionally substituted cycloalkylene, optionally substituted heterocyclylene, optionally substituted arylene, and optionally substituted heteroarylene;

L^2 is selected from the group consisting of O and NH;

each of R^{1a} and R^{1b} is the same or different and is independently is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, and O-C_{2-6} alkynyl;

or

Y is selected from:

a) H, where each of R^{3a} and R^{3b} are absent;

b) C-R^{3c},

R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

each of R^{3a} and R^{3b} is the same or different and independently is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

Y, as an C atom, combines with R^{3a} R^{3b} to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more heteroatoms selected from the group consisting of N, O, S, and B, and wherein the Y-containing ring or ring system is optionally substituted with one or more R^Y;

c) N,

each of R^{3a} and R^{3b} independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

Y, as an N atom, combines with R^{3a} and R^{3b} to form a heterocyclic or heteroaromatic mono ring or spiro or fused ring system, which may contain one or more additional heteroatoms selected from the group consisting of N, O, S, and B, and wherein the ring or ring system is optionally substituted with one or more R^Y;

d) O,

when Y is O, R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

and

e) S,

when Y is S, R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

provided that at least one of the following applies:

i) the Y ring or ring system contains a B atom in the Y ring or ring system;

ii) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is $B(OH)_2$;

iii) the Y ring or ring system is substituted with one or more R^Y, which at least one R^Y is either $(CH_2)_q$-heterocycle or $(CH_2)_q$-heteroaryl, where each of said heterocycle or heteroaryl comprises at least one B atom; or

iv) the Y ring or ring system is further substituted with one or more R^Y, which at least one R^Y is $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, or $(CH_2)_q$-heteroaryl, where each of said cycloalkyl, heterocycle, aryl, or heteroaryl is substituted with $B(OH)_2$.

when present, each of R^A, R^Y, and R^Q which may be the same or different any independently is selected from the group consisting of: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $B(OH)_2$, OH, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, $(CH_2)_q$-C(O)OH, $(CH_2)_q$-C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-NH_2, $(CH_2)_q$-NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$, $(CH_2)_q$-$C(O)NH_2$, $(CH_2)_q$-C(O)NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C(O)N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)$_2$,

$(CH_2)_q$-NHC(O)H, $(CH_2)_q$-NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)H, $(CH_2)_q$-N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_q$-C_{3-10} cycloalkyl, $(CH_2)_q$-heterocycle, $(CH_2)_q$-aryl, and $(CH_2)_q$-heteroaryl,

each q independently is, at each occurrence, selected from 0, 1, 2, 3, 4, 5, and 6;

and

wherein for each occurrence of cycloalkyl, heterocycle, aryl, and heteroaryl, as one or more of R^A, R^Y, and R^Q, is optionally substituted with one or more of C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, OH, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

55. The compound of claim 54, wherein L^1 is a direct bond.

56. The compound of claim 54 or 55, wherein A is 5- or 6-membered heteroaryl or phenyl.

57. The compound of claim 56, wherein A is phenyl.

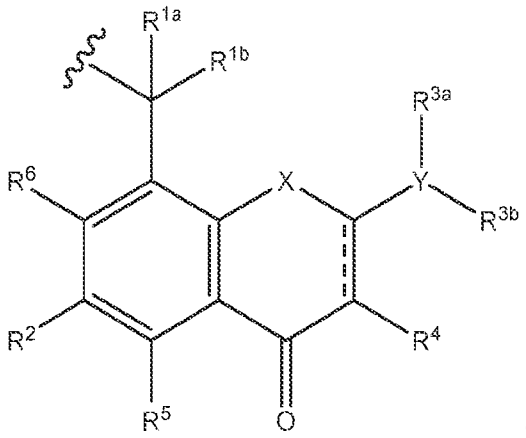
58. The compound of any one of claims 54 to 57, wherein L^2 is O.

59. The compound of any one of claims 54 to 57, wherein L^2 is NH.

60. The compound of any one of claims 54 to 59, wherein R^{1a} is H or CH_3.

61. The compound of any one of claims 54 to 60, wherein R^{1b} is H or CH_3.

62. The compound of any one of claims 54 to 61,wherein Q is:



(Q^61),

wherein

X is $C(R^x)_2$, O, NR^x, or S;

each R^x independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^2 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^4 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^5 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

R^6 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_m$-R^{100}, $(CH_2)_m$-OR^{100}, $(CH_2)_m$-$N(R^{100})_2$, $(CH_2)_m$-$C(O)R^{100}$, $(CH_2)_m$-$C(O)OR^{100}$, $(CH_2)_m$-$C(O)N(R^{100})_2$, $(CH_2)_m$-C_{3-10} cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heterocycle, and $(CH_2)_m$-heteroaryl;

each m independently is 0, 1, 2, 3, 4, 5, or 6;

and

each R^{100} is independently H, halogen, OH, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, C_{2-6} alkynoxy, C_{1-6} haloalkoxy, C_{2-6} haloalkenoxy, and C_{2-6} alkynoxy.

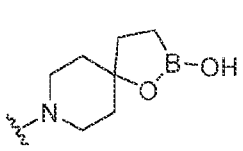
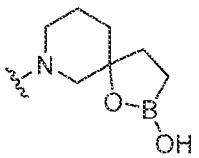
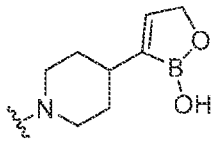
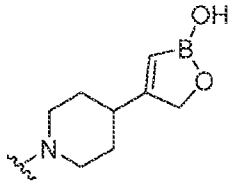
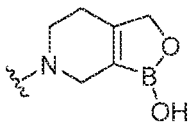
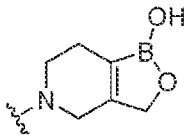
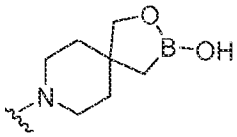
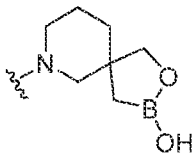
63. The compound of any claim 62, wherein X is O.

64. The compound of claim 62 or 63, wherein each of R^2, R^4, R^5, and R^6 independently is H, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6 cycloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, or C_{1-6} haloalkyl.

65. The compound of any one of claims 62 to 64, wherein R^2 is H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; R^5 is H; and R^6 is H.

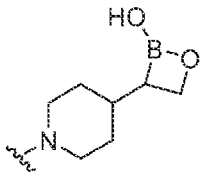
66. The compound of claim 65, wherein each of R^2 and R^4 is methyl.

67. The compound of any one of claims 54 to 66, wherein Y is incorporated in or is substituted with a ring or ring system that is selected from:


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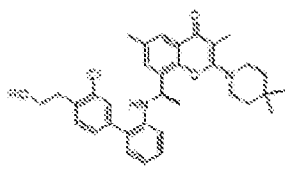
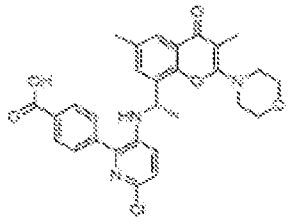
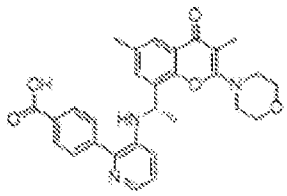
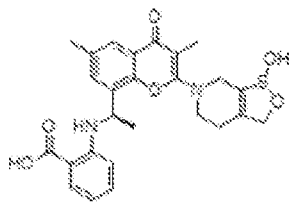
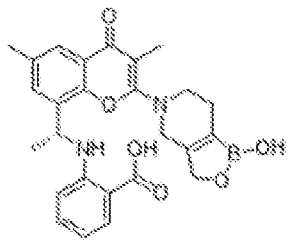
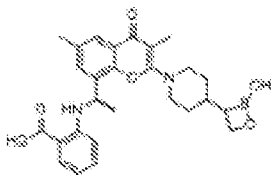
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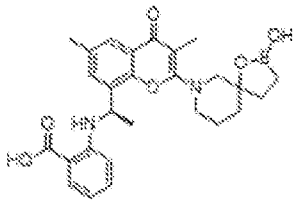
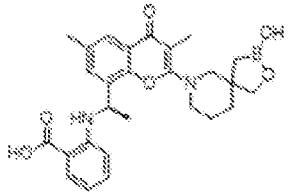
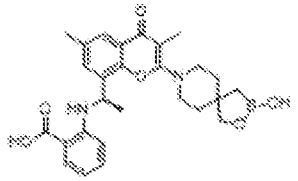
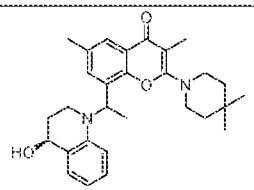
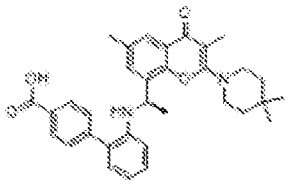
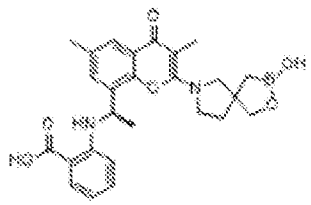
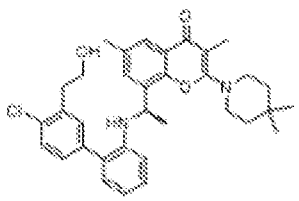
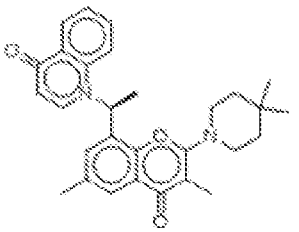
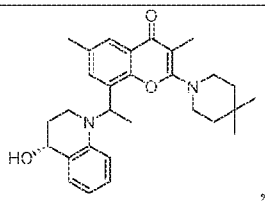
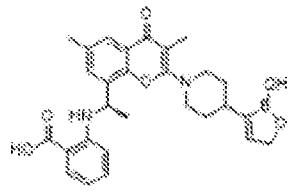
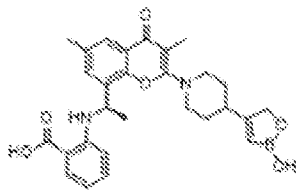
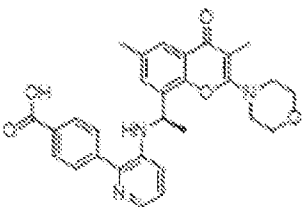
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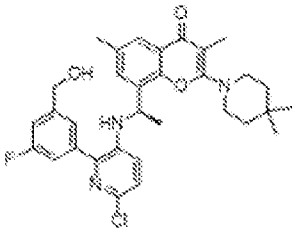

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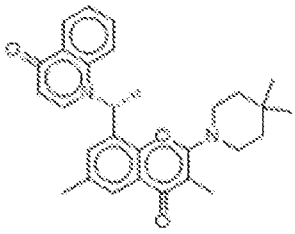
68. A compound selected from the group consisting of:

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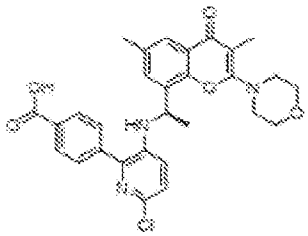
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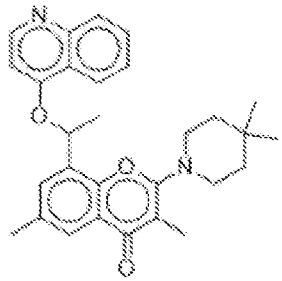
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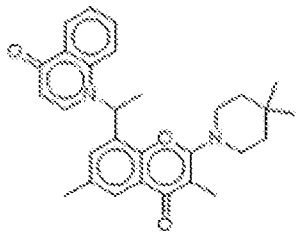
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or a tautomer, enantiomer, diastereomer, isotopomer, mixture, or salt thereof.

69. A compound of any one of claims 1 to 68 as a racemate.

70. The compound of any one of claims 1 to 68, as a single stereoisomer substantially free of any alternative forms.

71. The compound of claim 70, wherein the stereoisomeric form is R.

72. The compound of any one of claims 1 to 71, as a tautomeric form of a preferred equilibria.

73. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 72 and a pharmaceutically acceptable excipient.

74. A method of inhibiting cell proliferation comprising contacting a cell with an effective amount of a compound of any one of claims 1 to 72.

75. A method for treating cancer in a patient comprising administering a therapeutically effective amount of a compound of any one of claims 1 to 72 to a patient in need thereof.

76. A method of treating a PI3K-mediated disease or disorder in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 72.

77. A method of treating a disease or disorder mediated by one or more PIK3CA genes comprising modulating one or more of wild type and one or more mutations of the one or more PIK3CA genes.

78. The method of claim 77, comprising modulating one mutation.

79. The method of claim 77, comprising modulating two or more mutations.

80. The method of any one of claims 77 to 79, comprising modulating wild type.

81. The method of any one of claims 77 to 80, wherein the PIK3CA is a PIK3CA mutant.

82. The method of any one of claims 77 to 81, wherein the PIK3CA mediates a cancer.

83. The method of any one of claims 77 to 82, wherein the PIK3CA regulates cancer initiation, progression, or metasasis.

84. The method of any one of claims 77 to 83, wherein the one or more mutations are any p110a mutation.

85. The method of any one of claims 77 to 84, wherein the one or more mutations are selected from one or more mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

86. The method of any one of claims 77 to 85, wherien the one or more mutations are selected from one or more mutations of H1047, E545, and E542.

87. The method of any one of claims 77 to 86, wherein modulation is inhibition.

88. The method of any one of claims 77 to 87, wherein modulation is selective inhibiton for one or more mutations over wild-type.

89. The method of any one of claims 77 to 88, wherein the mutations are selected from H1047X, E545X, and E542X.

90. The method of any one of claims 77 to 89, wherein the mutation is H1047X.

91. The method of claim 90, wherein the mutation is H1047L

92. The method of claim 90, wherein the mutation is H1047R.

93. The method of any one of claims 77 to 92, wherein the mutation is E545X.

94. The method of claim 93, wherein the mutation is E545K.

95. The method of any one of claims 77 to 94, wherein the mutation is E542X.

96. The method of claim 95, wherein the mutation is E542K.

97. The method of any one of claims 77 to 96, comprising administering a compound of any one of claims 1 to 72.

98. The method of claim 98, wherein the PI3K is PI3Kα.

99. The method of claim 99, wherein the PI3Kα is a PI3Kα mutant.

100. The method of claim 99, wherein the PI3Kα is a PI3Kα wild type.

101. The method of any one of claims 98 to 100, wherein the PI3K is a PI3Ka and mediates a cancer.

102. The method of any one of claims 98 to 101, wherein the PI3K is a PI3Ka and regulates cancer initiation, progression, or metastasis.

103. The method of any one of claims 98 to 102, wherein the one or more mutations are selected from one or more mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

104. The method of any one of claims 98 to 103, wherien the one or more mutations are selected from one or more mutations of of H1047, E545, and E542.

105. The method of any one of claims 98 to 105, wherein modulation is inhibition.

106. The method of any one of claims 98 to 106, wherein modulation is selective inhibition over wild-type, providing preferential inhibition at a multiple level of greater than 1.

107. The method of any one of claims 98 to 107, wherein the mutations are selected from H1047X, E545X, and E542X.

108. The method of any one of claims 98 to 108, wherein a mutation is H1047X.

109. The method of claim 109, wherein the mutation is H1047L

110. The method of claim 109, wherein the mutation is H1047R.

111. The method of any one of claims 98 to 111, wherein the mutation is GLU545X.

112. The method of claim 112, wherein the mutation is E545K.

113. The method of any one of claims 98 to 113, wherein the mutation is GLU542X.

114. The method of claim 114, wherein the mutation is E542K.

115. The method of any one of claims 98 to 114, wherein the at least one amino acid mutation are selected from one or more mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

116. The method of claim 115, wherien the one or more mutations are selected from one or more of H1047, E545, and E542.

117. The method of claim 116 to 118, comprising administering a compound of any one of claims 1 to 72.

118. The method of any one of claims 116 to 119, comprising administering a compound of any one of claims 1 to 72.

119. A method of inhibiting a PIK3CA gene target protein (PI3K) comprising modulating one or more mutant variants selected from mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

120. The method of claim 121, wherien the one or more mutant varients are selected from mutations of H1047, E545, and E542

121. A method of treating a disease or disorder mediated by PIK3CA, comprising modulating two or more mutant variants selected from mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

122. The method of claim 124, wherien the one or more mutant varients are selected from mutations of H1047, E545, and E542.

123. The method of any one of claims 122 to 124, comprising administering a compound of any one of claims 1 to 72.

124. A method of modulating a PI3K to treat a disease or disorder by interacting a compound of any one of claims 1 to 72 with at least one mutant variants.

125. The method of claim 126, wherein the PI3K gene target is PIK3CA.

126. The method of claim 126 or 127, wherein the PI3K mediates a cancer.

127. The method of any one of claims 126 to 128, wherein the PI3K regulates cancer initiation, progression, or metastasis.

128. The method of any one of claims 126 to 129, wherein the mutant variants are selected from mutations of H1047, E545, E542, N345, E726, C420, Q546, G118, E453, Q546, G1049, M1043, K111, E81, N1044, and E110.

129. The method of claim 130, wherien the mutant variants are selected from mutations of one or more of H1047, E545, and E542.

130. The method of any one of claims 126 to 131, wherein modulation is inhibition.

131. The method of claim 132, wherein modulation is selective inhibiton over wild-type.

132. The method of any one of claims 126 to 133, wherein the mutation is H1047X.

133. The method of claim 134, wherein the mutation is H1047L.

134. The method of claim 134, wherein the mutation is H1047R.

135. The method of any one of claims 126 to 136, wherein the mutation is E545X.

136. The method of claim 137, wherein the mutation is E545K.

137. The method of any one of claims 126 to 138, wherein the mutation is E542.

138. The method of claim 139, wherein the mutation is E542K.

139. A method of any one of claims 74 to 140, wherein the disease or disorder is cancer.

140. A method of any one of claims 74 to 141, wherein the disease or disorder is PROS: PIK3CA-Related Overgrowth Spectrum.

141. A method of any one of claims 74 to 142, wherein the disease or disorder is breast cancer, colorectal cancer, uterine cancer, bladder cancer, lung cancer, glioma, head and neck cancer, or other solid tumors.

142. The method of claim 143, wherein the disease or disorder is breast cancer.

143. A method of any one of claims 74 to 144 further comprising administration of one or more additional therapeutic agent.

144. The method of claim 145, further comprising administration of two or more additional therapeutic agents.

145. The method of claim 145 or 146, wherein the additional therapeutic agents are selected from selective estrogen receptor degraders, Protac-mediated estrogen receptor inhibitors, complete estrogen receptor antagonists, sarcoplasmic reticulum calcium ATPase inhibitors, CDK2/4/6 inhibitors, CDK4/6 inhibitors, and aromatase inhibitors.

146. The method of any one of claims 145 to 147, wherein the additional therapeutic agents are selected from fulvestrant, vepdegestrant, palazestrant, imlunestrant, elacestrant, giredestrant, camizestrant, palbociclib, ribociclib, abemaciclib, anastronzole, exemestane, and letrozole.

147. The method of any one of claims 145 to 148, wherein each agent is provided in a separate dosage form.

148. The method of any one of claims 145 to 149, wherein one or more agent is provided in a combined dosage form.

149. The method of claim 151, wherein one or more PI3K is inhibited.

150. The method of claim 152, wherein the PI3K is PI3Kα.

151. The method of claim 153, wherein the PI3Kα is a mutated variant thereof.

152. The method of claim 151 to 154, comprising administering a compound of any one of claims 1 to 72.

153. A method for treating cancer in a patient in need thereof, comprising:

(a) determining that the cancer is associated with a PI3K wild-type or one or more PI3K mutations; and

(b) administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 72.

154. The method of claim 156, wherein the PI3K is a mutated variant thereof.

155. A compound of any one of claims 1 to 72, for use in therapy.

156. A compound of any one of claims 1 to 72, for use in the treatment of cancer.

157. A compound of any one of claims 1 to 72, for use in the inhibition of PI3K.

158. The compound of claim 161, wherein the PI3K is PI3Kα.

159. The compound of claim 161, wherein the PI3Kα is wild type.

160. The compound of claim 161, wherein the PI3Kα is a mutated variant thereof.

161. Use of a compound of any one of claims 1 to 72, in the manufacture of a medicament for the treatment of cancer.

162. Use of a compound of any one of claims 1 to 72, in the manufacture of a medicament for the inhibition of activity of PI3K.

163. Use of a compound of any one of claims 1 to 72, in the manufacture of a medicament for the treatment of a PI3K-mediated disease or disorder.

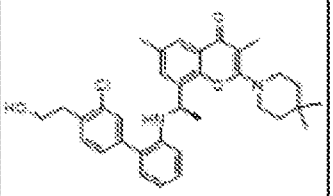
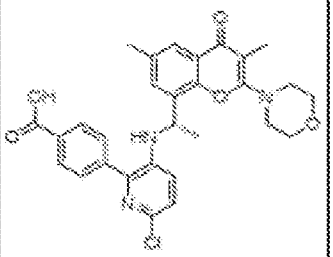
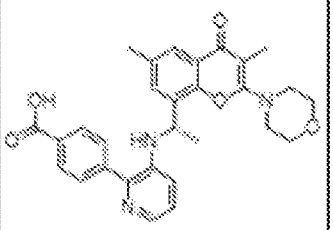
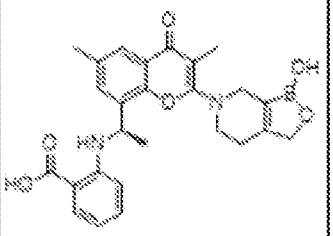
164. The use of claim 165 or 166, wherein the PI3K is PI3Kα.

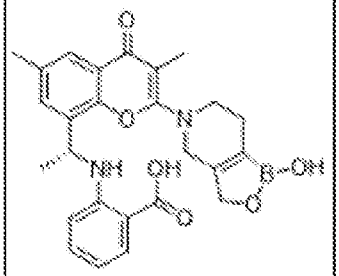
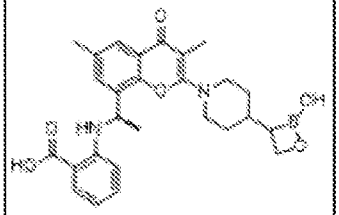
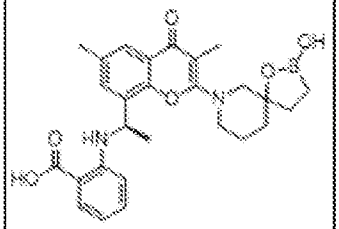
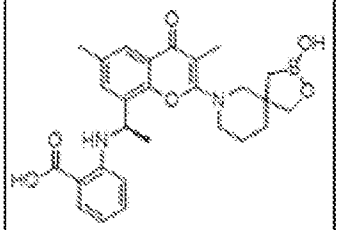
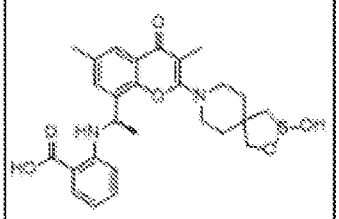
165. The use of claim 167, wherein the PI3Kα is wild type.

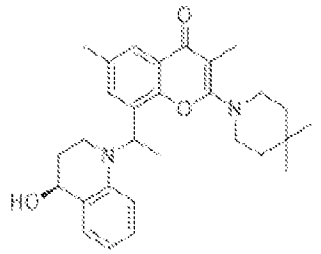
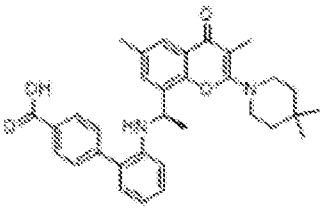
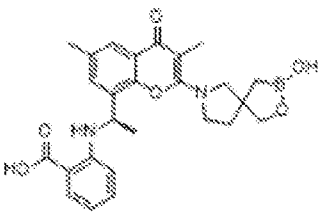
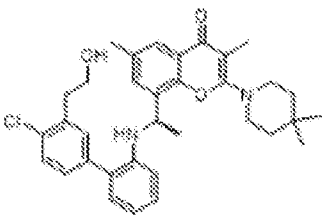
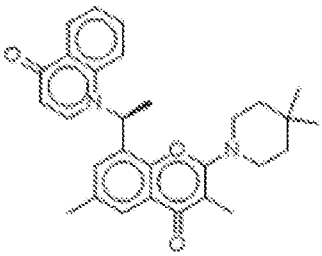
166. The use of claim 167, wherein the PI3Kα is a mutated variant thereof.

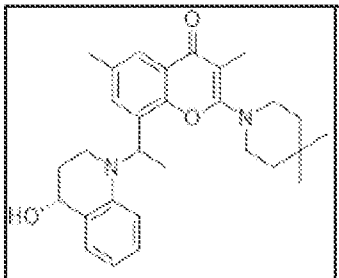
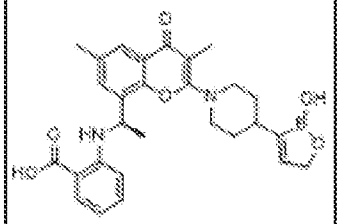
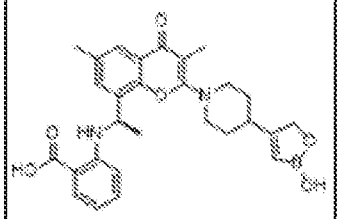
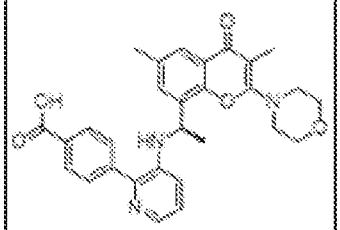
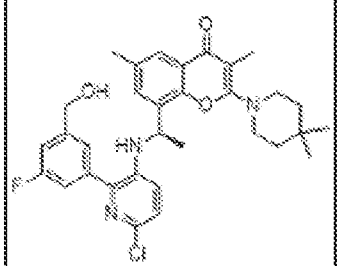
167. A process for preparing a compound of any one of claims 1 to 72.

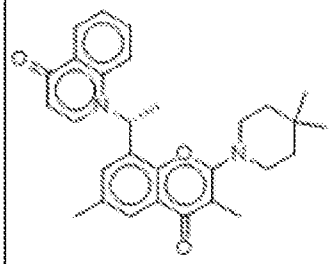
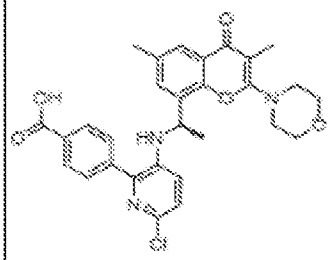
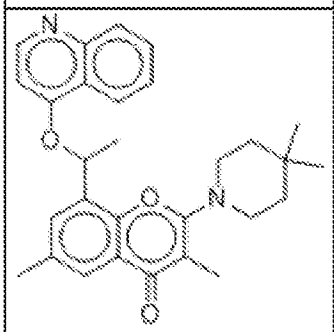
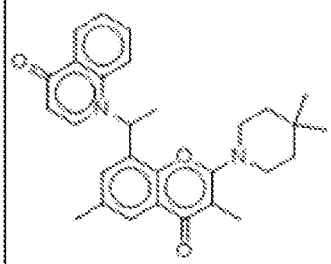
168. A compound of any one of claims 1 to 72, obtained by a process of claim 167.

Structure	In-Cell HTRF IC50 (nM) pAKT_S473 SKBR3 6.0h 10.0%FBS Avg	In-Cell HTRF IC50 (nM) pAKT_S473 T-47D 6.0h 10.0%FBS Avg	In-Cell HTRF IC50 (nM) pAKT_S473 MCF7 6.0h 10.0%FBS Avg	ADP-Glo DR IC50 (nM) PI3K wt 4.0h pre-inc Avg	ADP-Glo DR IC50 (nM) PI3K H1047R 4.0h pre-inc Avg
	C	A	B	C	B
	C	C	C	C	C
	C	C	C	C	C
	C	B	C	C	A

	C	B	C	C	A
	C	A	C	C	A
	C	B	C	C	A
	C	C	C	C	A
	C	C	C	C	A

	C	C	C	C	B
	C	A	B	B	A
	C	C	C	C	A
	C	B	C	C	A
	C	C	C	C	C

	C	C	C	C	B
	C	A	B	C	A
	C	A	C	C	A
	C	C	C	C	A
	C	A	A	C	A

	C	B	C	C	C
	C	A	C	A	A
	C	C	C	C	C
	C	C	C	C	C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/036277

A. CLASSIFICATION OF SUBJECT MATTER

C07D 405/04(2006.01)i; **C07F 5/02**(2006.01)i; **C07D 405/12**(2006.01)i; **C07D 405/14**(2006.01)i; **A61K 31/453**(2006.01)i; **A61K 31/69**(2006.01)i; **A61K 31/4709**(2006.01)i; **A61K 31/5377**(2006.01)i; **A61P 35/00**(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 405/04(2006.01); A61K 31/4709(2006.01); A61K 31/4985(2006.01); A61K 31/519(2006.01); A61P 3/00(2006.01); A61P 35/00(2006.01); C07D 471/04(2006.01); C07D 519/00(2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN(registry, caplus) & Keywords: boron, benzopyranone, phosphatidylinositol 3 kinase(PI3K), inhibitor, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021-202964 A1 (PETRA PHARMA CORPORATION) 07 October 2021 (2021-10-07) claims 1, 18-23; paragraphs [0002], [0010]-[0014], [0981]; pages 175, 179, 185; table 2	1,3-7,33,34,119
A		2,35,38-41,54-57,68
A	CN 113072551 A (SHANGHAI HANSOH BIOMEDICAL CO., LTD. et al.) 06 July 2021 (2021-07-06) paragraph [1005]	1-7,33-35,38-41,54-57,68,119
A	US 7872011 B2 (JACKSON, S. P. et al.) 18 January 2011 (2011-01-18) claim 1	1-7,33-35,38-41,54-57,68,119
A	WO 2023-288242 A1 (RELAY THERAPEUTICS, INC.) 19 January 2023 (2023-01-19) claim 1	1-7,33-35,38-41,54-57,68,119

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 2024	**27 October 2024**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office **189 Cheongsa-ro, Seo-gu, Daejeon** **35208, Republic of Korea**	**HEO, Joo Hyung**
Facsimile No. **+82-42-481-8578**	Telephone No. **+82-42-481-5373**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/036277

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017-090002 A2 (GVK BIOSCIENCES PRIVATE LIMITED) 01 June 2017 (2017-06-01) claim 1	1-7,33-35,38-41 ,54-57,68,119

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/036277

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **74-118, 120-153**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 74-118 and 120-153 pertain to methods for treatment of the human body by surgery or therapy, as well as diagnostic methods (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. ☑ Claims Nos.: **12,15,18-20,25-28,31,44,63,66,71,91,92,94,96,98-118,122-123,125-152,154,158-160,165,166**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- Claims 12, 15, 18-20, 25-28, 31, 44, 63, 66, 71, 91, 92, 94, 96, 116, 122, 125, 129, 131, 136, 138, 142, 144, 149-151, 154, 158-160, 165 and 166 are unclear, because they refer to multiple dependent claims which do not comply with PCT Rule 6.4(a).

- Claims 98, 99, 105-109, 111-114, 117, 118, 123, 126-128, 130, 132, 134, 135, 137, 139-141, 143, 145-148 and 152 refer to claims 98, 99, 105-109, 111-114, 117, 118, 123, 126-128, 130, 132, 134, 135, 137, 139-141, 143, 145-148 and 152 themselves, and claims 100-108, 110, 111, 113, 115-118, 125-133, 135-148 and 150 depend on any one of claims 98, 99, 105-109, 111-114, 117, 118, 123, 126-128, 130, 132, 134, 135, 137, 139-141, 143, 145-148 and 152.

Therefore, claims 98-118, 123, 125-148, 150 and 152 do not comply with PCT Article 6.

3. ☑ Claims Nos.: **8-11,13,14,16,17,21-24,29,30,32,36,37,42,43,45-53,58-62,64,65,67,69,70,72-76,81-90,93, 95,97,102-108, 111,113,115,117,118,123,124,126-128,130,132,135,137,139-141,143,145-148,152,153,155-157,161-164,167,168**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2024/036277

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		EP 4126851 A1	08 February 2023
		JP 2023-521321 A	24 May 2023
		JP 7505023 B2	24 June 2024
		KR 10-2022-0163462 A	09 December 2022
		TW 202200567 A	01 January 2022
		TW I794780 B	01 March 2023
		US 11649227 B2	16 May 2023
		US 2022-0372023 A1	24 November 2022
		US 2023-0286960 A1	14 September 2023
CN 113072551 A	06 July 2021	CN 113072551 B	13 August 2024
		CN 113348170 A	03 September 2021
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		EP 4086253 A1	09 November 2022
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		EP 1537102 A4	08 December 2010
		JP 2006-500361 A	05 January 2006
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		US 2006-0276470 A1	07 December 2006
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		WO 2004-016607 A1	26 February 2004
		WO 2004-016607 A8	24 March 2005
		WO 2004-016607 B1	15 April 2004
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		EP 4370124 A1	22 May 2024
		TW 202317579 A	01 May 2023
WO 2017-090002 A2	01 June 2017	WO 2017-090002 A3	15 February 2018
		WO 2017-090002 A4	19 April 2018