[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).

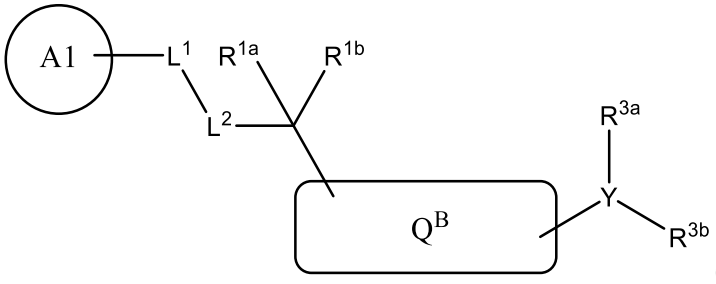
[0016] In the setting of cancer with mutated PI3Kα, one way to overcome the problem of compensatory production of insulin and/or glucose upon systemic inhibition caused by inhibition of the patient's wild-type PI3K would be to develop inhibitors with enhanced selectivity for mutant over wild-type. This 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 mutated, 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

[0019] One example of the present disclosure includes a compound of Formula (A):

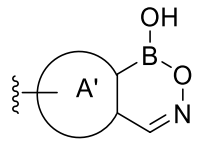


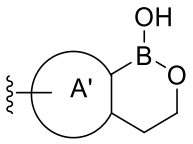
(A),

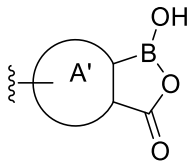
or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof,

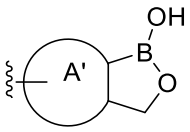
wherein

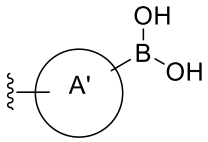
A1 is selected from the group consisting of:



,


,


,


, and


;

 each represents the point of attachment to the depicted L^1;

each depicted A' independently is selected from cycloalkyl, heterocyclyl, aryl, and heteroaryl;

wherein each of heterocyclyl and heteroaryl may contain one or more heteroatoms selected from N, O, and S;

each A1 is optionally substituted;

L^1 is selected from the group consisting of (i) a direct bond, (ii) optionally substituted arylene, and (iii) 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 H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

Q^B an optionally substituted 8- to 14-membered fused ring system optionally containing one or more heteroatoms selected from the group consisting of O, N, and S; and

Y is H, CR^{3c}, N, O, or S;

when Y is H, each of R^{3a} and R^{3b} is absent;

when Y is 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, 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, and S, and wherein the ring or ring system is optionally substituted;

when Y is CR^{3c}

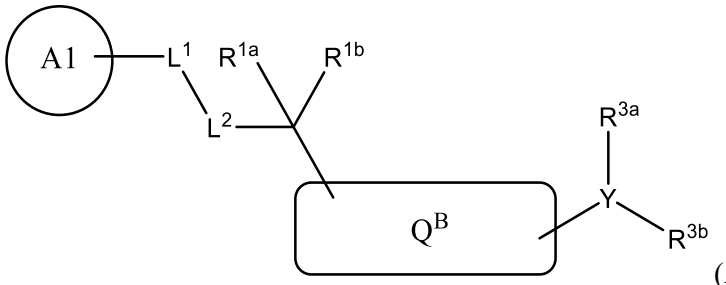
R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

each of R^{3a} and R^{3b} independently is selected from the group consisting of H, 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; 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, and S, and wherein the Y-containing ring or ring system is optionally substituted; or

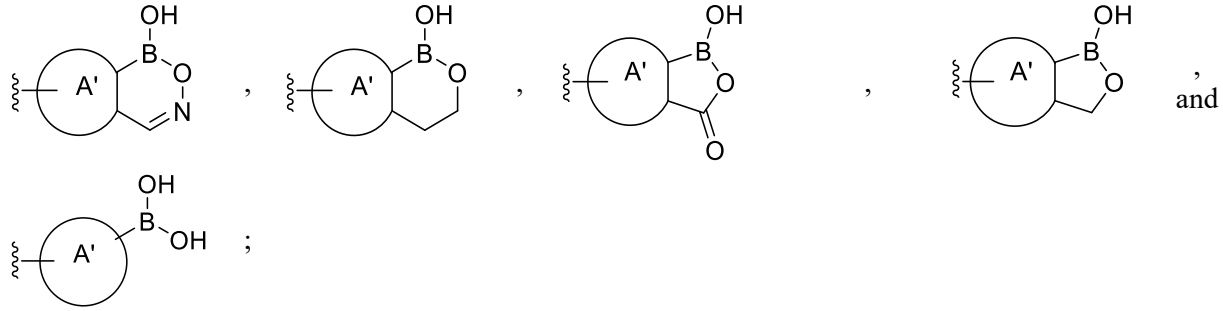
when Y is O or S, R^{3a} is absent and R^{3b} is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl.

[0019a] In one aspect, the present disclosure refers to a compound of Formula (A):



(A),

or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, wherein A1 is selected from the group consisting of:



;

each ≀ represents the point of attachment to the depicted L^1;

each depicted A' independently is selected from cycloalkyl, heterocyclyl, aryl, and heteroaryl;

wherein each of heterocyclyl and heteroaryl may contain one or more heteroatoms selected from N, O, and S;

each A1 is optionally substituted;

L^1 is selected from the group consisting of (i) a direct bond, (ii) optionally substituted arylene, and (iii) 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 H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

Q^B an optionally substituted 8- to 14-membered fused ring system optionally containing one or more heteroatoms selected from the group consisting of O, N, and S; and

Y is H, CR^{3c}, N, O, or S;

a) when Y is H, each of R^{3a} and R^{3b} is absent;

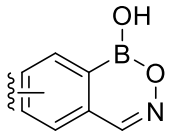
b) when Y is N,

c) each of R^{3a} and R^{3b} independently is selected from the group consisting of H, 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; 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, and S, and wherein the ring or ring system is optionally substituted;

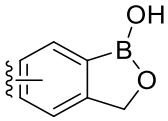
d) when Y is CR^{3c}
R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;
each of R^{3a} and R^{3b} independently is selected from the group consisting of H, 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; 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, and S, and wherein the Y-containing ring or ring system is optionally substituted; or

e) when Y is O or 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.

[0001] One example of the present disclosure includes wherein A1 is selected from:



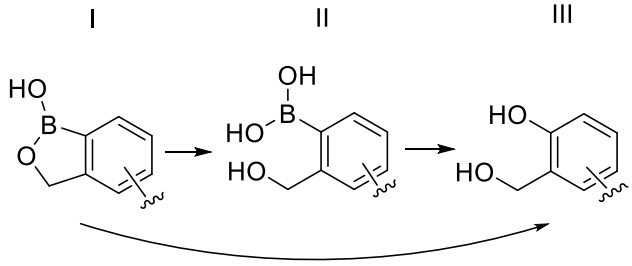
and



, wherein

each A1 is optionally substituted from either depicted ring.

[0020] As provided in more detail herein and as appreciated by those skilled in the art, examples of the present disclosure 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:



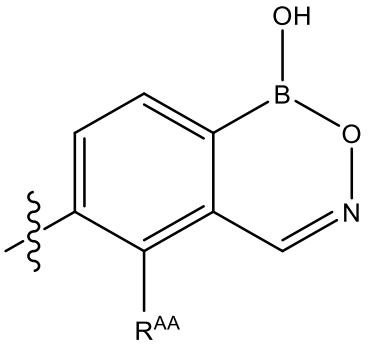
[0021] As provided in more detail herein and as appreciated by those skilled in the art, examples of the present disclosure may include an isotopomer or isotopic isomer, wherein one or more atom of a compound of the present disclosure is replaced with an isotope, such as deuterium for hydrogen or ^{13}C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

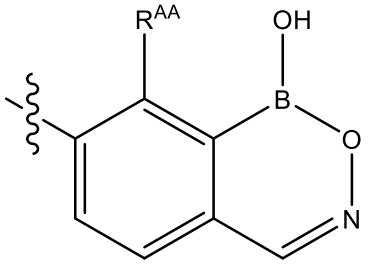
[0022] One example of the present disclosure includes wherein each R^{A1} independently is selected from halogen, OH, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, $(CH_2)_{0-6}CN$, $(CH_2)_{1-6}OH$, $(CH_2)_{0-6}O$-C_{1-6} alkyl, $(CH_2)_{0-6}O$-C_{2-6} alkenyl, $(CH_2)_{0-6}O$-C_{2-6} alkynyl, $(CH_2)_{0-}$

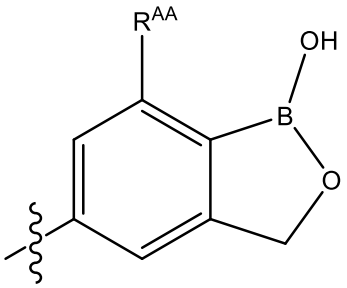
$_6$C(O)H, $(CH_2)_{0-6}$C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_{0-6}$C(O)OH, $(CH_2)_{0-6}$C(O)O(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}NH_2$, $(CH_2)_{0-6}$NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}$N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}$C(O)NH_2, $(CH_2)_{0-6}$C(O)NH(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}$C(O)N(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}$NHC(O)H, $(CH_2)_{0-6}$NHC(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), and $(CH_2)_{0-6}$N(C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl)C(O)(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), or an isotopic form of R^{A1}.

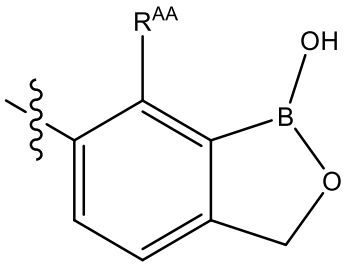
[0023] The recited substituent may be substituted from either depicted ring of A1, and the concept is extended to the more specific recited groups identified in a comparable position, where an optional substituent may be substituted as available throughout the ring or ring system.

[0024] One example of the present disclosure includes wherein A1 is selected from the group consisting of:



,


,


, and


and

each A1 is optionally further substituted.

[0025] One example of the present disclosure includes wherein each R^{AA} is independently 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, OH, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, and O-C_{2-6} alkynyl.

[0026] For clarity, when R^{AA} is hydrogen, the depicted R^{AA} is absent and A1 is not further substituted.

[0027] One example of the present disclosure includes wherein one or more atom is an isotopic form.

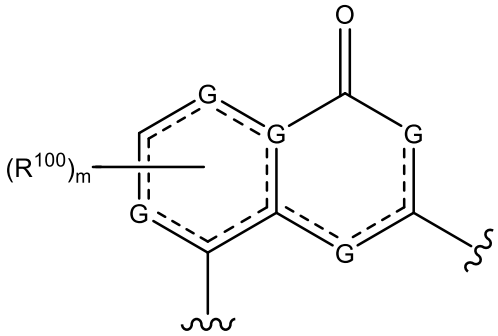
[0028] One example of the present disclosure includes wherein the isotope is deuterium.

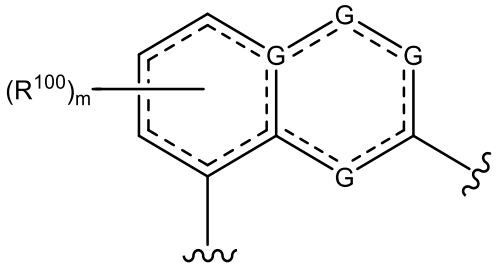
[0029] One example of the present disclosure includes wherein R^{AA} is deuterated.

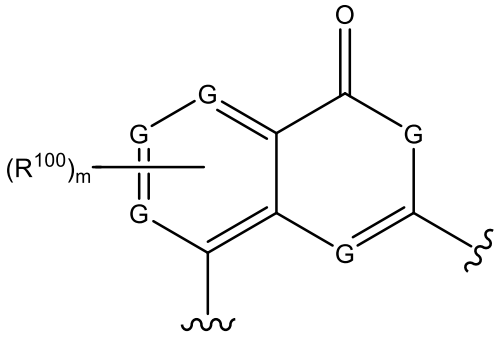
[0030] One example of the present disclosure includes wherein R^{AA} is selected from the group consisting of C_{1-6} alkyl, O-C_{1-6} alkyl, C_{1-6} haloalkyl, deuterated C_{1-6} alkyl, deuterated O-C_{1-6} alkyl, deuterated C_{1-6} haloalkyl, halogen, and CN.

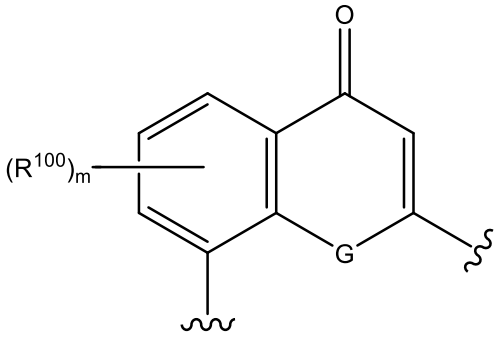
[0031] One example of the present disclosure includes wherein R^{AA} is F, Cl, CH_3, OCH_3, or CD_3.

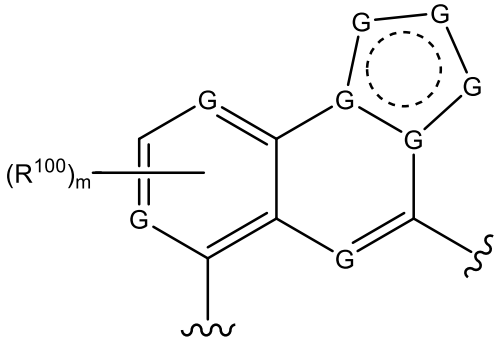
[0032] One example of the present disclosure includes wherein Q^B is selected from the group consisting of:

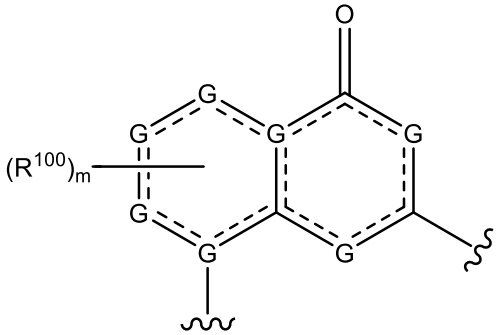


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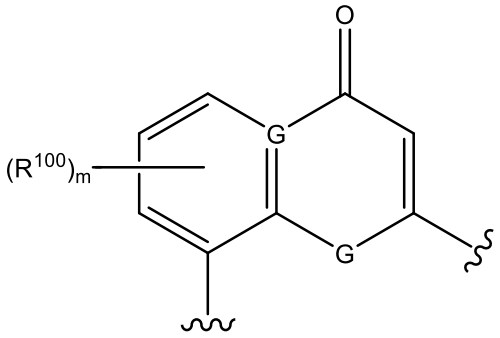
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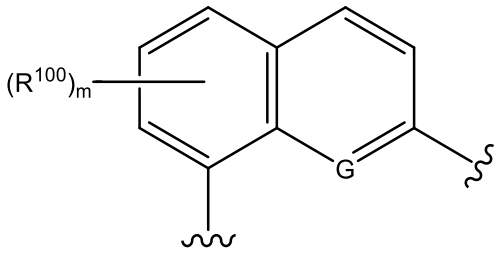
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wherein

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;

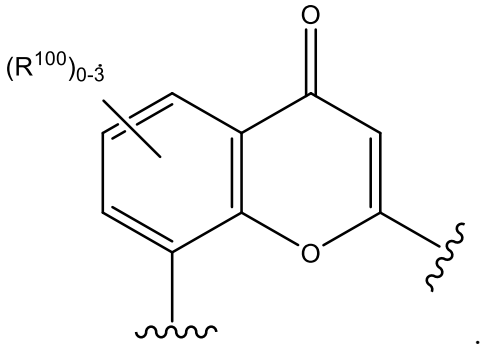
when m is not 0, each R^{100} may be substituted from any depicted ring; and

when present, each R^{100} 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), $(CH_2)_q$-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}, $(CH_2)_q$-NH-$(CH_2)_r$-OR^{140}, 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;

R^{140} is an E3 ligase binding ligand; and

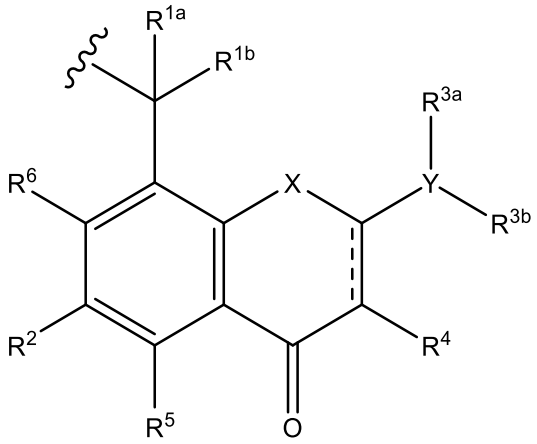
each of q and r, independently is, at each occurrence, selected from 0, 1, 2, 3, 4, 5, and 6.

[0033] One example of the present disclosure includes wherein Q^B is selected from the group consisting of:



.

[0034] One example of the present disclosure includes wherein Q^B 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, $(CH_2)_{0-6}$-R^{QB1}, $(CH_2)_{0-6}$-OR^{QB1}, $(CH_2)_{0-6}$-$N(R^{QB1})_2$, $(CH_2)_{0-6}$-$C(O)R^{QB1}$, $(CH_2)_{0-6}$-$C(O)OR^{QB1}$, $(CH_2)_{0-6}$-$C(O)N(R^{QB1})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-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, $(CH_2)_{0-6}$-R^{QB1}, $(CH_2)_{0-6}$-OR^{QB1}, $(CH_2)_{0-6}$-$N(R^{QB1})_2$, $(CH_2)_{0-6}$-$C(O)R^{QB1}$, $(CH_2)_{0-6}$-$C(O)OR^{QB1}$, $(CH_2)_{0-6}$-$C(O)N(R^{QB1})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-heteroaryl;

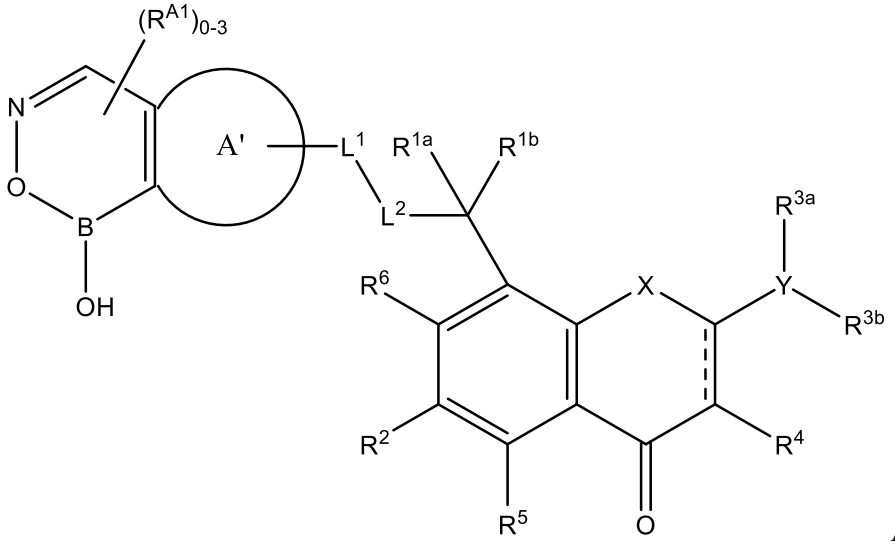
R^5 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_{0-6}$-R^{QB1}, $(CH_2)_{0-6}$-OR^{QB1}, $(CH_2)_{0-6}$-

$N(R^{QB1})_2$, $(CH_2)_{0-6}$-$C(O)R^{QB1}$, $(CH_2)_{0-6}$-$C(O)OR^{QB1}$, $(CH_2)_{0-6}$-$C(O)N(R^{QB1})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-heteroaryl;

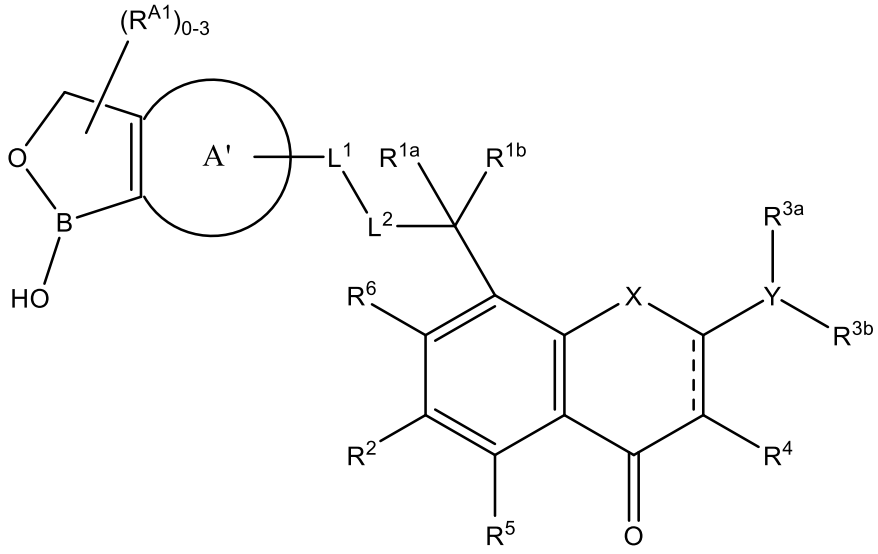
R^6 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_{0-6}$-R^{QB1}, $(CH_2)_{0-6}$-OR^{QB1}, $(CH_2)_{0-6}$-$N(R^{QB1})_2$, $(CH_2)_{0-6}$-$C(O)R^{QB1}$, $(CH_2)_{0-6}$-$C(O)OR^{QB1}$, $(CH_2)_{0-6}$-$C(O)N(R^{QB1})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-heteroaryl; and

each R^{QB1} 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.

[0035] One example of the present disclosure includes wherein the compound is a compound of Formula A(Ia) or A(Ib):



A(Ia), or



A(Ib),

[0036] One example of the present disclosure includes wherein A' is fused aryl or heteroaryl.

[0037] One example of the present disclosure includes wherein A' is selected from optionally substituted phenyl.

[0038] One example of the present disclosure includes wherein A' is substituted phenyl.

[0039] One example of the present disclosure includes wherein L^1 is selected from the group consisting of a direct bond, optionally substituted heteroarylene, or optionally substituted arylene.

[0040] One example of the present disclosure includes wherein optionally substituted arylene is optionally substituted phenylene.

[0041] One example of the present disclosure includes wherein optionally substituted heteroaylene is optionally substituted pyridylene.

[0042] One example of the present disclosure includes wherein each of optionally substituted arylene and optionally substituted heteroarylene is unsubstituted.

[0043] One example of the present disclosure includes wherein each of optionally substituted arylene and optionally substituted heteroarylene is substituted with one or two substitutents selected from the group consisting of halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_2-C_3 alkenyl, C_2-C_3 haloalkenyl, C_2-C_3 alkynyl, C_2-C_3 haloalkynyl, OH, O-(C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl), NH_2, NH(C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl), N(C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl)$_2$, C_3 cycloalkyl, and C_3 halocycloalkyl.

[0044] The compound of claim 22, wherein each of optionally substituted arylene and optionally substituted heteroarylene is substituted with one or two substitutents selected from the group consisting of halogen and C_1-C_3 alkyl.

[0045] One example of the present disclosure includes wherein L^2 is NH.

[0046] One example of the present disclosure includes wherein each of R^{1a} and R^{1b} independently is selected from the group consisting of H, halogen, CN, C_{1-3} haloalkyl, and C_{1-3} alkyl.

[0047] One example of the present disclosure includes wherein each of R^{1a} and R^{1b} independently is selected from the group consisting of H and CH_3.

[0048] One example of the present disclosure includes wherein the depicted dashed bond is a double bond.

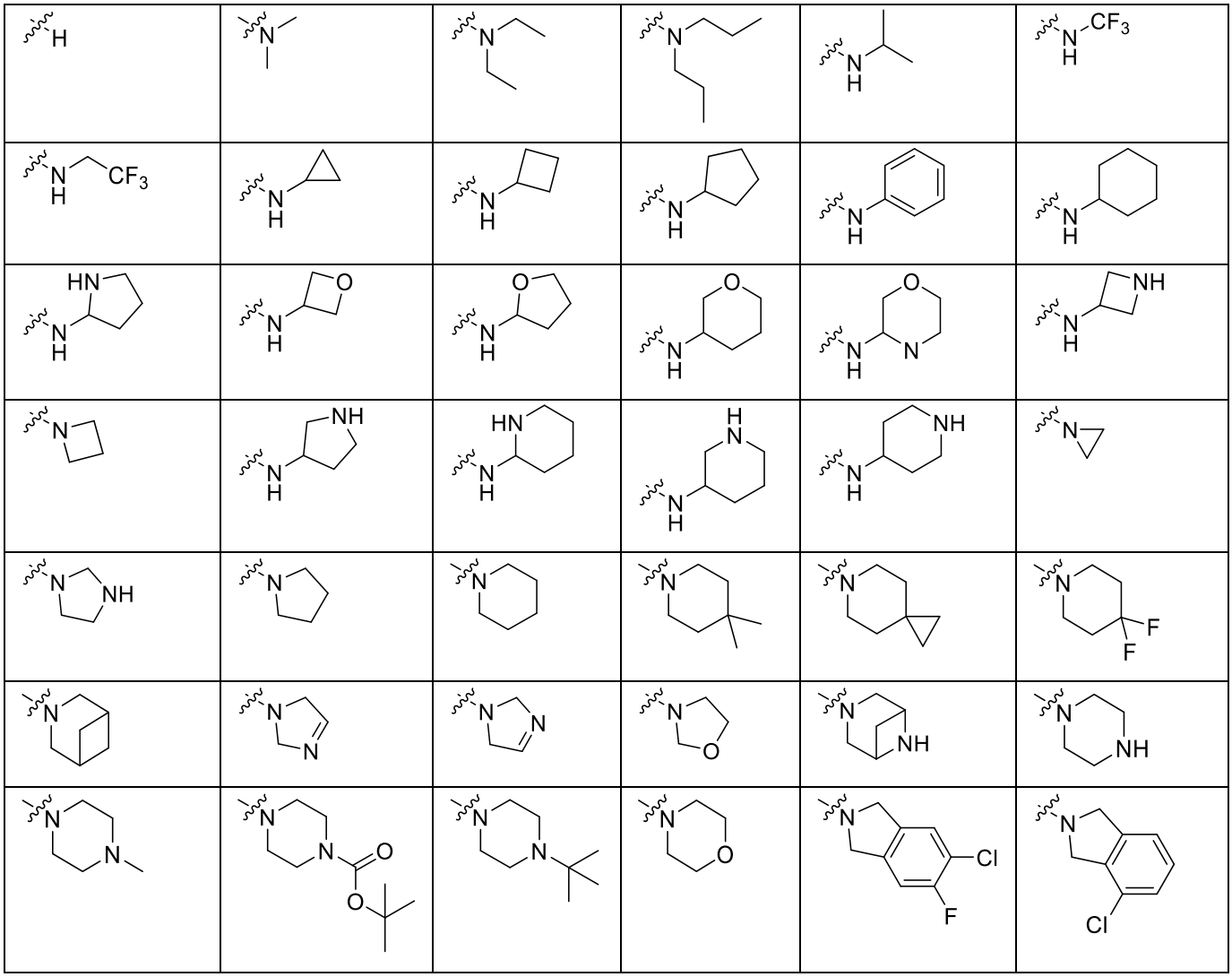
[0049] Portions of one or more examples of the present disclosure may be incorporated as disclosed herein to create a compound of the present disclosure. Reference is hereby made to the synthetic teaching and examples disclosed of one or more of the following patent publications: WO 2024/026423, WO 2024/008122, 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 examples, a portion, Q^B, may be

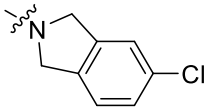
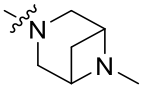
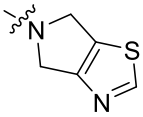
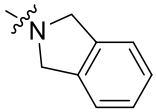
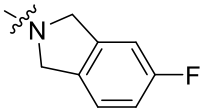
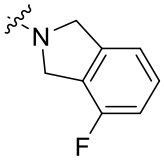
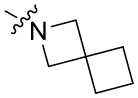
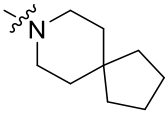
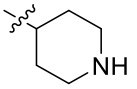
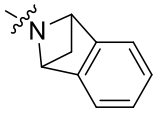
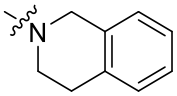
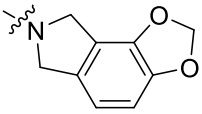
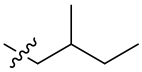
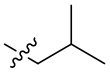
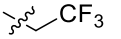
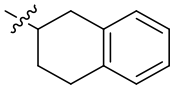
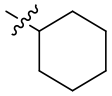
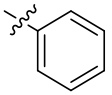
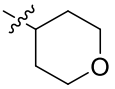
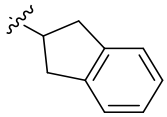
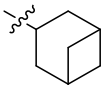
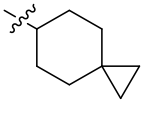
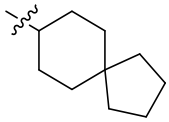
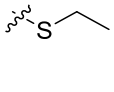
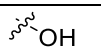
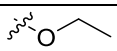
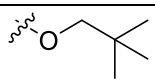
selected from the noted publications. In certain examples, a portion, Y^T, may be selected from the noted publications. For example, a portion, of the depicted $Y(R^{3a})(R^{3b})$, may be selected from the noted publications.

[0050] As provided in more detail herein and as appreciated by those skilled in the art, Y^T may be selected and a compound of the present disclosure may be prepared to enhance molecular properties (e.g., molecular weight, dipole moment, polarizability, van der Waals volume, and surface area) or bulk properties (e.g., acidic or basic character in solution, octanol/water partition coefficient, solubility). Moreover, Y^T may be selected to enhance hydrogen-bonding capacity and, thereby improved selectivity for a target.

[0051] One example of the present disclosure includes wherein Y is N or CR^3.

[0052] One example of the present disclosure includes wherein Y is selected from the group consisting of substituted or unsubstituted:



					
					
					
					
					
			and		

[0053] One example of the present disclosure includes wherein Y is CR^{3c} 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.

[0054] One example of the present disclosure includes wherein each of R^{3a} and R^{3b} is independently selected from the group consisting of H, 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.

[0055] One example of the present disclosure includes 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.

[0056] One example of the present disclosure includes wherein R^4 is H or CH_3.

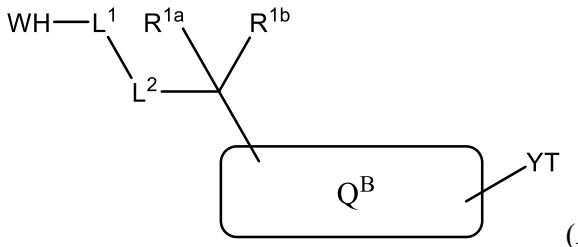
[0057] One example of the present disclosure includes wherein R^2 is H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[0058] One example of the present disclosure includes wherein R^4 is CH_3.

[0059] One example of the present disclosure includes wherein R^5 is H.

[0060] One example of the present disclosure includes wherein R^6 is H.

[0061] One aspect of the present disclosure includes a compound of Formula (AWH):



(AWH),

or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, wherein

WH is a warhead moiety;

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 $(CH_2)_{1-6}$, O, C(O), S, and NH;

each of R^{1a} 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;

or L^2-$C(R^{1a})(R^{1b})$ combines to form NHC(S), C(S)NH, NHC(O), C(O)NH, $NHS(O)_2$, $S(O)_2NH$, NHC(NH), or C(NH)NH;

Q^B an optionally substituted 8- to 14-membered spiro or fused ring system optionally containing one or more heteroatoms selected from the group consisting of O, N, and S;

YT is any moiety that provides desired physicochemical properties; and

an optional E3 ligase binding ligand.

[0062] One example of the present disclosure includes wherein the optional E3 ligase binding ligand is connected via a linker.

[0063] One example of the present disclosure includes wherein WH is a ring system:

Q1-Q2,

wherein:

the ring system is attached to the depicted L^1 through either the Q1 or Q2 portion; and

Q1 is an optionally substituted 5- or 6-membered ring, having one or more degrees of unsaturation, and optionally having one or more heteroatom selected from B, N, O, or S; and

Q2 is fused to Q1 and is an optionally substituted 5- or 6-membered ring, having one or more degrees of unsaturation, and optionally having one or more heteroatom selected from B, N, O, or S;

or

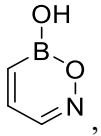
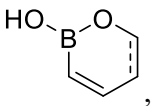
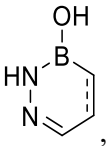
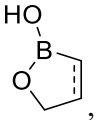
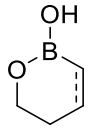
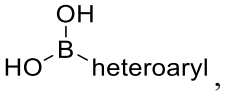
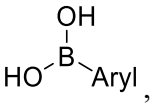
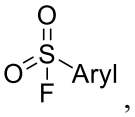
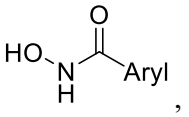
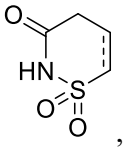
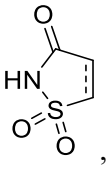
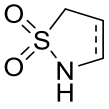
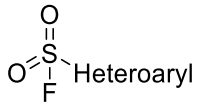
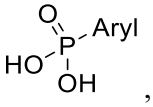
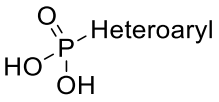
Q1 does not exist; and

Q2 is an optionally substituted 5- or 6-membered ring, having one or more degrees of unsaturation, and optionally having one or more heteroatom selected from B, N, O, or S;

[0064] One example of the present disclosure includes wherein WH is selected from an optionally substituted:

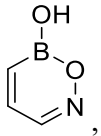
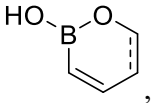
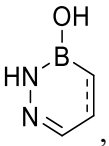
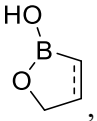
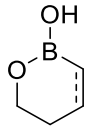
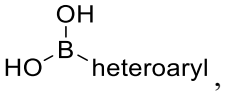
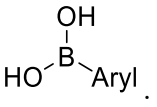
Group (a): a cyclohexenone derivative, an alkyl halide derivative, a sulfonyl derivative, an α-cyanoenone derivative, and an epoxide or spiro-epoxide derivative;

Group (b)


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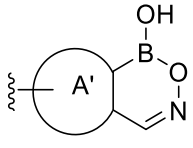
Group (c):


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and

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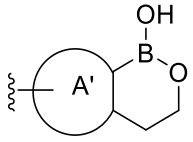
[0065] One example of the present disclosure includes wherein optionally substituted is substituted with one or more substitutents selected from the group consisting of: deuterium, halogen, haloalkyl, R', OR', OH, SH, SR', NO_2, CN, C(O)R', NH_2, C(O)OR', OC(O)R', $CON(R')_2$, $OC(O)N(R')_2$, NH_2, NHR', $N(R')_2$, 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', $SO_2N(R')_2$, $NHS(O)_2H$, $NR'S(O)_2H$, $NHS(O)_2R'$,

$NR'S(O)_2R'$, $Si(R')_3$, =O, =S, =NNHR', $=NNH_2$, $=NN(R')_2$, =N-OR', =N-OH, =NNHCOR', =NNHCOH, $=NNHCO_2R'$, $=NNHCO_2H$, $=NNHSO_2R'$, $=NNHSO_2H$, =N-CN, =NH, =NR', where each of the preceding may be linked through a divalent alkylene linker, $(CH_2)_x$, where x is 1, 2, or 3, and where 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.

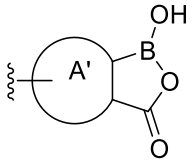
[0066] One example of the present disclosure includes wherein Q1-Q2 is selected from:



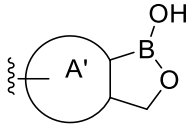
(I^{X1})



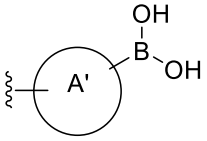
(I^{X2})



(I^{X3});



(I^{X4});



(I^{X5});

where each  represents the point of attachment to the depicted L^1;

each depicted A' is a cycloalkyl, heterocyclyl, aryl, or heteroaryl, mono-ring;

wherein each of the heterocyclyl or heteroaryl rings contain one or more heteroatoms selected from N, O, and S; and

each is optionally substituted with one or more R^{A1}, where each R^{A1} independently is selected from 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, $(CH_2)_{0-6}CN$, $(CH_2)_{1-6}OH$, $(CH_2)_{0-6}O$-C_{1-6} alkyl, $(CH_2)_{0-6}O$-C_{2-6} alkenyl, $(CH_2)_{0-6}O$-C_{2-6} alkynyl, $(CH_2)_{0-6}C(O)H$, $(CH_2)_{0-6}C(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_{0-6}C(O)OH$, $(CH_2)_{0-6}C(O)O$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}NH_2$, $(CH_2)_{0-6}NH$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl),

$(CH_2)_{0-6}N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}C(O)NH_2$, $(CH_2)_{0-6}C(O)NH(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}C(O)N(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}NHC(O)H$, $(CH_2)_{0-6}NHC(O)(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), and $(CH_2)_{0-6}N(C_{1-6}$ alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl)$C(O)(C_{1-6}$ alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), or an isotopic form of R^A.

[0067] One example of the present disclosure includes wherein A' is aryl.

[0068] One example of the present disclosure includes wherein A' is phenyl.

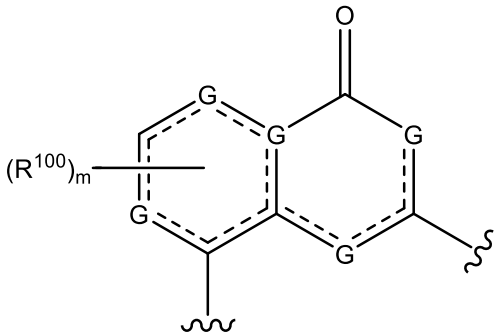
[0069] One example of the present disclosure includes wherein A' is heterocyclyl.

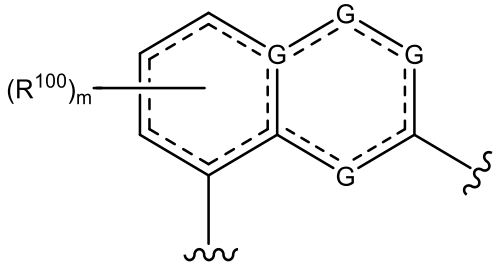
[0070] One example of the present disclosure includes wherein A' is heteroaryl.

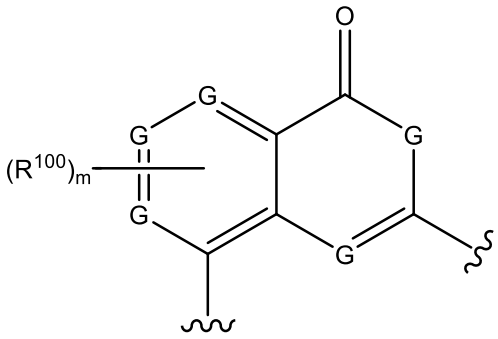
[0071] One example of the present disclosure includes wherein heteroaryl is a 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from N, O, and S.

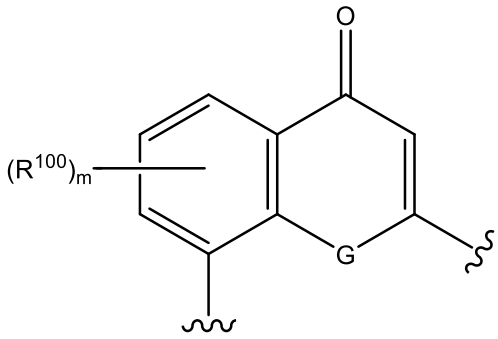
[0072] One example of the present disclosure includes wherein Q^B is an oxo-substituted 6,6 fused ring containing one or more heteroatom selected from O, N, or S.

[0073] One example of the present disclosure includes wherein Q^B is selected from:

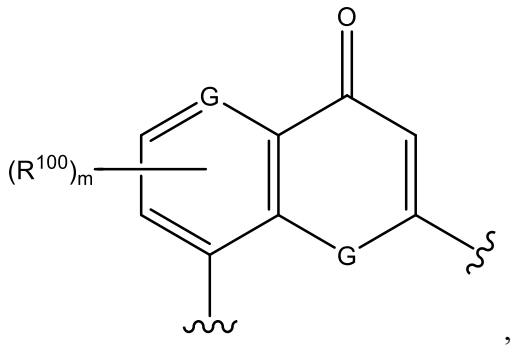
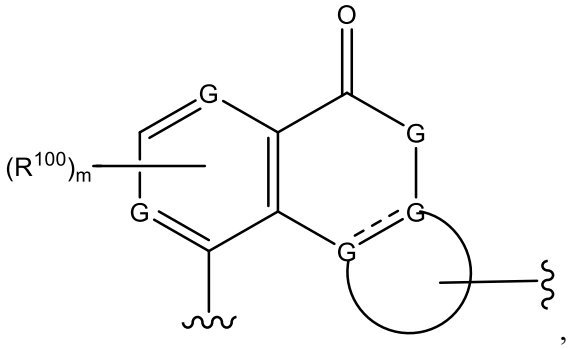
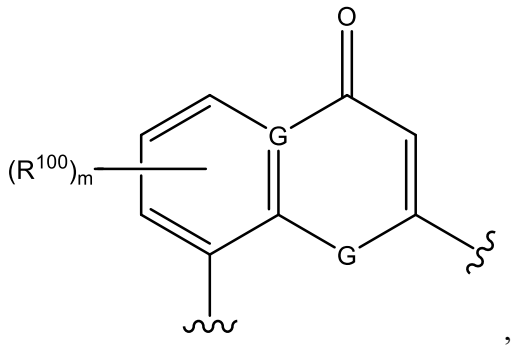
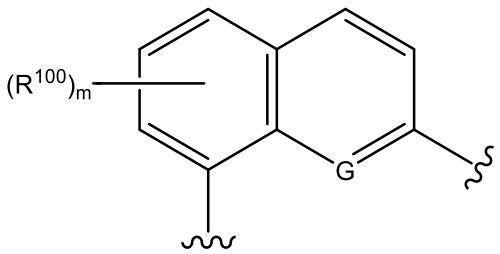


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wherein

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

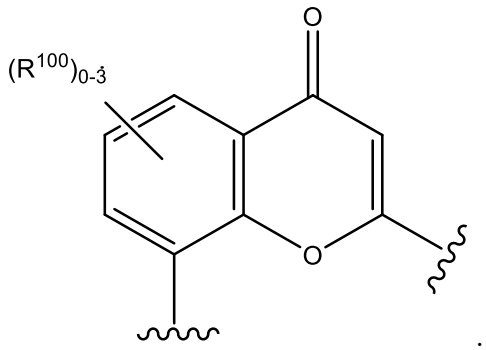
each m is, at each occurrence, independently selected from 0, 1, 2, 3, 4, 5, and 6; and

each R^{100} 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_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_q$-N(H or C_{1-6}alkyl), $(CH_2)_q$-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}, $(CH_2)_q$-NH-$(CH_2)_r$-OR^{140}, 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;

R^{140} is an E3 ligase binding ligand; and

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

[0074] One example of the present disclosure includes wherein Q^B is selected from:



[0075] One example of the present disclosure includes wherein at least one R^{100} is substituted from a depicted N in Q^B.

[0076] One example of the present disclosure includes wherein Y^T is $YR^{3a}R^{3b}$; and

Y is H, CR^{3c}, N, O, or S;

when Y is H, each of R^{3a} and R^{3b} is absent;

when Y is 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, 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, and S, and wherein the ring or ring system is optionally substituted;

when Y is CR^{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} independently is selected from the group consisting of H, 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; or

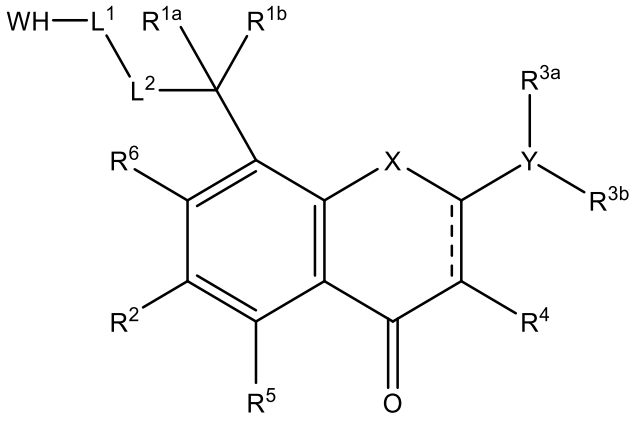
Y, as an C atom, combines with R^{3a} and R^{3b} to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more heteroatoms selected from the group consisting of N, O, and S, and wherein the Y-containing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

when Y is O or 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.

[0077] One example of the present disclosure includes wherein when $YR^{3a}R^{3b}$ forms a ring, the ring is optionally substituted with one or more substitutents selected from the group consisting of: 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', $SO_2N(R')_2$, $NHS(O)_2H$, $NR'S(O)_2H$, $NHS(O)_2R'$, $NR'S(O)_2R'$, $Si(R')_3$, =O, =S, =NNHR', $=NNH_2$, $=NN(R')_2$, =N-OR', =N-OH, =NNHCOR', =NNHCOH, $=NNHCO_2R'$, $=NNHCO_2H$, $=NNHSO_2R'$, $=NNHSO_2H$, =N-CN, =NH, =NR', where each of the preceding may be linked through a divalent alkylene linker, $(CH_2)_x$, where x is 1, 2, or 3, and where 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.

[0078] One example of the present disclosure includes wherein the compound is a compound of (AWH2):



(AWH2),

or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, 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_{1-6} alkoxy, $(CH_2)_{0-6}$-R^{AWH2}, $(CH_2)_{0-6}$-OR^{AWH2}, $(CH_2)_{0-6}$-$N(R^{AWH2})_2$, $(CH_2)_{0-6}$-$C(O)R^{AWH2}$, $(CH_2)_{0-6}$-$C(O)OR^{AWH2}$, $(CH_2)_{0-6}$-$C(O)N(R^{AWH2})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-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_{1-6} alkoxy, $(CH_2)_{0-6}$-R^{AWH2}, $(CH_2)_{0-6}$-OR^{AWH2}, $(CH_2)_{0-6}$-$N(R^{AWH2})_2$, $(CH_2)_{0-6}$-$C(O)R^{AWH2}$, $(CH_2)_{0-6}$-$C(O)OR^{AWH2}$, $(CH_2)_{0-6}$-$C(O)N(R^{AWH2})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-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_{1-6} alkoxy, $(CH_2)_{0-6}$-R^{AWH2}, $(CH_2)_{0-6}$-OR^{AWH2}, $(CH_2)_{0-6}$-$N(R^{AWH2})_2$, $(CH_2)_{0-6}$-$C(O)R^{AWH2}$, $(CH_2)_{0-6}$-$C(O)OR^{AWH2}$, $(CH_2)_{0-6}$-$C(O)N(R^{AWH2})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-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_{1-6} alkoxy, $(CH_2)_{0-6}$-R^{AWH2}, $(CH_2)_{0-6}$-OR^{AWH2}, $(CH_2)_{0-6}$-$N(R^{AWH2})_2$, $(CH_2)_{0-6}$-$C(O)R^{AWH2}$, $(CH_2)_{0-6}$-$C(O)OR^{AWH2}$, $(CH_2)_{0-6}$-$C(O)N(R^{AWH2})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-heteroaryl; and

each R^{AWH2} 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.

[0079] One example of the present disclosure includes wherein Y is N or CR^{3c}.

[0080] One example of the present disclosure includes wherein Y combines with R^{3a} and R^{3b} to form:

cycloalkyl substituted with $B(OH)_2$;

aryl substituted with $B(OH)_2$;

heterocyclyl, either

containing a B atom in the ring or ring system,

ii) substituted with $B(OH)_2$, or

iii) substituted with an optionally substituted 4- to 6-membered ring containing a B atom, one or more additional heteroatoms selected from O, N, or S, and one or more degrees of unsaturation; or

heteroaryl, either

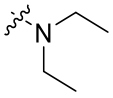
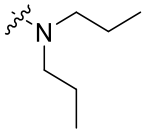
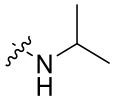
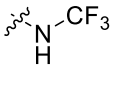
containing a B atom in the ring or ring system, or

substituted with $B(OH)_2$, or

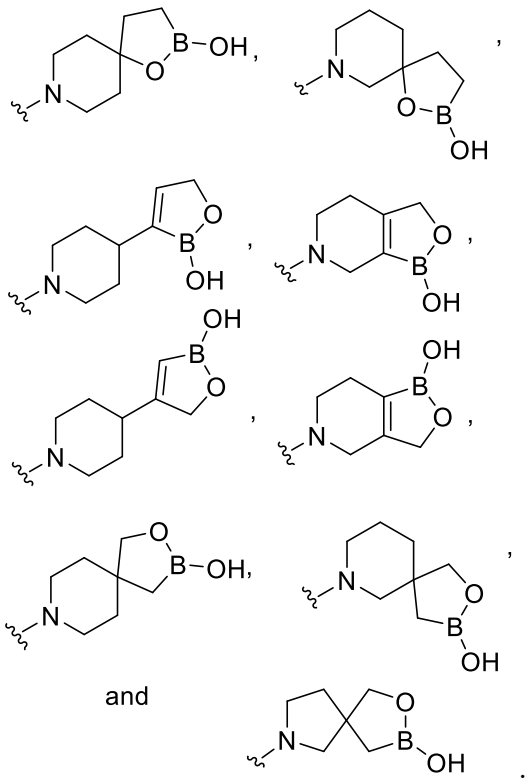
substituted with an optionally substituted 4- to 6-membered ring containing a B atom, one or more additional heteroatoms selected from O, N, or S, and one or more degrees of unsaturation; and

wherein each Y-ring or ring system is optionally substituted.

[0081] One example of the present disclosure includes wherein Y^T is selected from the group consisting of substituted or unsubstituted:

[0082] One example of the present disclosure includes wherein Y^T is selected from the group consisting of:



[0083] One example of the present disclosure includes wherein Y is CR^{3c}, R^{3c} is absent or H, and each of R^{3a} and R^{3b} is independently selected from the group consisting of H, 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.

[0084] As provided in more detail herein and as appreciated by those skilled in the art, examples of the present disclosure may be defined in terms of a warhead, which is intended to describe a functional group that offers chemical capture of a targeted amino acid residue on a target protein, including formation of covalent or hydrogen bonds with one or more targeted amino acids. As one example of warhead interaction, the burial of hydrophobic amino acids in the protein core is a driving force in protein folding. The extent to which an amino acid interacts with the solvent and the protein core is naturally proportional to the surface area exposed to the solvent environment. The accessible surface area (ASA) or solvent-accessible surface area (SASA) is the surface area of a biomolecule that is accessible to a solvent. The SASA is the surface characterized around a protein by a hypothetical center of a solvent sphere. As provided in more detail herein and as appreciated by those skilled in the art, the present disclosure references chemical capture, namely chemical bonds or other interactions that allow atoms to be more stable by, for example, by filling their valence shell of electrons. Chemical capture, and

therefore warhead interaction with a targeted amino acid, includes covalent bonds, hydrogen bonds, ionic bonds, and van der Waals interactions.

[0085] One example of the present disclosure includes wherein WH provides chemical capture of a solvent accessible surface area of a protein.

[0086] One example of the present disclosure includes wherein the chemical capture is a binding interaction.

[0087] One example of the present disclosure includes wherein the binding interaction is covalent binding.

[0088] One example of the present disclosure includes wherein the binding interaction is hydrogen binding.

[0089] One example of the present disclosure includes wherein the solvent accessible surface area of a protein is an accessible amino acid.

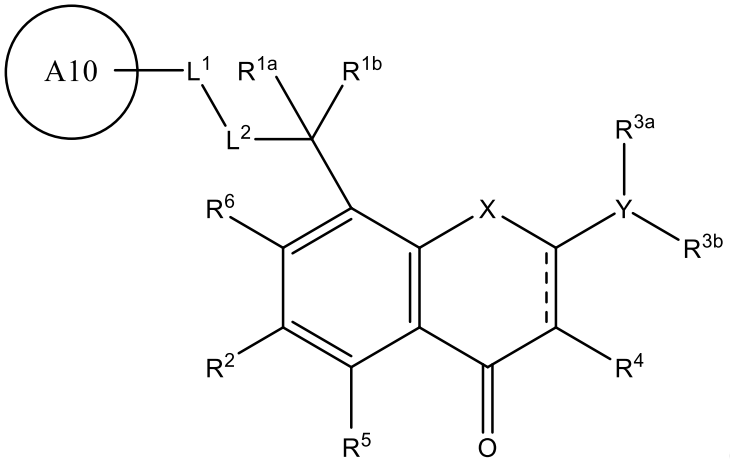
[0090] One example of the present disclosure includes wherein the amino acid is arginine, histidine, lysine, glutamic acid, serine, threonine, or glutamine.

[0091] One example of the present disclosure includes wherein the amino acid is histidine.

[0092] One example of the present disclosure includes wherein WH is a boron-containing warhead.

[0093] One example of the present disclosure includes wherein WH is a non-boron-containing warhead.

[0094] One example of the present disclosure includes a compound of Formula (AX):



(AX)

or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, wherein

A10 is a 5- to 14-membered mono- or fused-ring system comprising one or more of cycloalkyl, heterocyclyl, aryl, and heteroaryl,

each of heterocyclyl or heteroaryl rings may contain one or more heteroatoms selected from N, O, S, and B;

A10 is optionally substituted with one or more R^{A10};

each R^{A10} independently is selected from 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, oxo, $(CH_2)_{0-6}CN$, $(CH_2)_{1-6}OH$, $(CH_2)_{0-6}O$-C_{1-6} alkyl, $(CH_2)_{0-6}O$-C_{2-6} alkenyl, $(CH_2)_{0-6}O$-C_{2-6} alkynyl, $(CH_2)_{0-6}C(O)H$, $(CH_2)_{0-6}C(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_{0-6}C(O)OH$, $(CH_2)_{0-6}C(O)O$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}NH_2$, $(CH_2)_{0-6}NH$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}N$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}C(O)NH_2$, $(CH_2)_{0-6}C(O)NH$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}C(O)N$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}NHC(O)H$, $(CH_2)_{0-6}NHC(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}N$(C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl)$C(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $B(OH)_2$, SO_2-halogen, and O-SO_2-halogen;

L^1 is selected from the group consisting of a direct bond, 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 H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

or L^2-$C(R^{1a})(R^{1b})$ combines to form NHC(O), C(O)NH, $NHS(O)_2$, $S(O)_2NH$, or $C(NH)NH_2$;

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;

Y is H, CR^{3c}, N, O, or S;

when Y is H, each of R^{3a} and R^{3b} is absent;

when Y is 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, 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, and S, and wherein the ring or ring system is optionally substituted;

when Y is CR^{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} independently is selected from the group consisting of H, 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; 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, and S, and wherein the Y-containing ring or ring system is optionally substituted; or

when Y is O or 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;

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, $(CH_2)_{0-6}$-R^{AX}, $(CH_2)_{0-6}$-OR^{AX}, $(CH_2)_{0-6}$-$N(R^{AX})_2$, $(CH_2)_{0-6}$-$C(O)R^{AX}$, $(CH_2)_{0-6}$-$C(O)OR^{AX}$, $(CH_2)_{0-6}$-$C(O)N(R^{AX})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-heteroaryl;

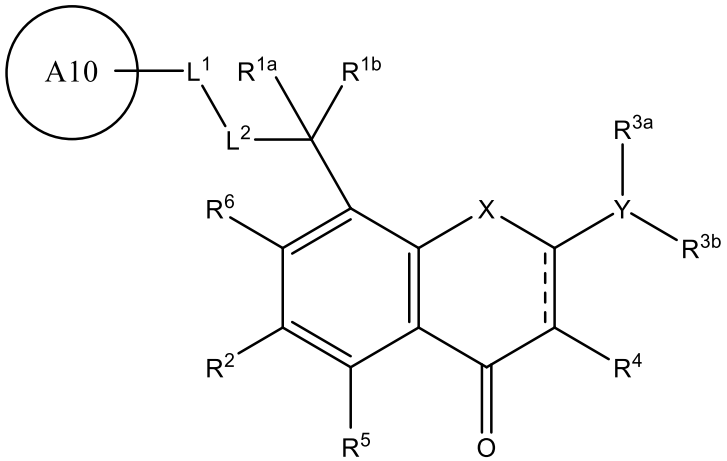
R^4 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_{0-6}$-R^{AX}, $(CH_2)_{0-6}$-OR^{AX}, $(CH_2)_{0-6}$-$N(R^{AX})_2$, $(CH_2)_{0-6}$-$C(O)R^{AX}$, $(CH_2)_{0-6}$-$C(O)OR^{AX}$, $(CH_2)_{0-6}$-$C(O)N(R^{AX})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-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, $(CH_2)_{0-6}$-R^{AX}, $(CH_2)_{0-6}$-OR^{AX}, $(CH_2)_{0-6}$-$N(R^{AX})_2$, $(CH_2)_{0-6}$-$C(O)R^{AX}$, $(CH_2)_{0-6}$-$C(O)OR^{AX}$, $(CH_2)_{0-6}$-$C(O)N(R^{AX})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-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, $(CH_2)_{0-6}$-R^{AX}, $(CH_2)_{0-6}$-OR^{AX}, $(CH_2)_{0-6}$-$N(R^{AX})_2$, $(CH_2)_{0-6}$-$C(O)R^{AX}$, $(CH_2)_{0-6}$-$C(O)OR^{AX}$, $(CH_2)_{0-6}$-$C(O)N(R^{AX})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-heteroaryl; and

each R^{AX} 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.

[0094a] In one aspect, the present disclosure refers to a compound of Formula (AX):



(AX)

or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, wherein A10 is a 5- to 14-membered mono- or fused-ring system comprising one or more of cycloalkyl, heterocyclyl, aryl, and heteroaryl,

each of heterocyclyl or heteroaryl rings may contain one or more heteroatoms selected from N, O, S, and B;

A10 is optionally substituted with one or more R^{A10};

each R^{A10} independently is selected from 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, oxo, $(CH_2)_{0-6}CN$, $(CH_2)_{1-6}OH$, $(CH_2)_{0-6}O$-C_{1-6} alkyl, $(CH_2)_{0-6}O$-C_{2-6} alkenyl, $(CH_2)_{0-6}O$-C_{2-6} alkynyl, $(CH_2)_{0-6}C(O)H$, $(CH_2)_{0-6}C(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_{0-6}C(O)OH$, $(CH_2)_{0-6}C(O)O$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}NH_2$, $(CH_2)_{0-6}NH$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}N$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}C(O)NH_2$, $(CH_2)_{0-6}C(O)NH$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}C(O)N$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}NHC(O)H$, $(CH_2)_{0-6}NHC(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}N$(C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl)$C(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $B(OH)_2$, SO_2-halogen, and O-SO_2-halogen;

L^1 is selected from the group consisting of a direct bond, 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 H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

or L^2-$C(R^{1a})(R^{1b})$ combines to form NHC(O), C(O)NH, $NHS(O)_2$, $S(O)_2NH$, or $C(NH)NH_2$;

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;

Y is H, CR^{3c}, N, O, or S;

a) when Y is H, each of R^{3a} and R^{3b} is absent;

b) when Y is 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, 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, and S, and wherein the ring or ring system is optionally substituted;

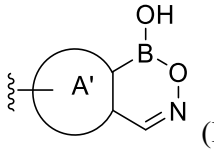
c) when Y is CR^{3c}
R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;
each of R^{3a} and R^{3b} independently is selected from the group consisting of H, 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; 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, and S, and wherein the Y-containing ring or ring system is optionally substituted; or

d) when Y is O or 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;

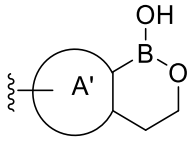
R^2 is selected from the group consisting of H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, C_{1-6} alkoxy, $(CH_2)_{0-6}$-R^{AX}, $(CH_2)_{0-6}$-OR^{AX}, $(CH_2)_{0-6}$-$N(R^{AX})_2$, $(CH_2)_{0-6}$-$C(O)R^{AX}$, $(CH_2)_{0-6}$-$C(O)OR^{AX}$, $(CH_2)_{0-6}$-$C(O)N(R^{AX})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-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, $(CH_2)_{0-6}$-R^{AX}, $(CH_2)_{0-6}$-OR^{AX}, $(CH_2)_{0-6}$-$N(R^{AX})_2$, $(CH_2)_{0-6}$-$C(O)R^{AX}$, $(CH_2)_{0-6}$-$C(O)OR^{AX}$, $(CH_2)_{0-6}$-$C(O)N(R^{AX})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-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, $(CH_2)_{0-6}$-R^{AX}, $(CH_2)_{0-6}$-OR^{AX}, $(CH_2)_{0-6}$-$N(R^{AX})_2$, $(CH_2)_{0-6}$-$C(O)R^{AX}$, $(CH_2)_{0-6}$-$C(O)OR^{AX}$, $(CH_2)_{0-6}$-$C(O)N(R^{AX})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-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, $(CH_2)_{0-6}$-R^{AX}, $(CH_2)_{0-6}$-OR^{AX}, $(CH_2)_{0-6}$-$N(R^{AX})_2$, $(CH_2)_{0-6}$-$C(O)R^{AX}$, $(CH_2)_{0-6}$-$C(O)OR^{AX}$, $(CH_2)_{0-6}$-$C(O)N(R^{AX})_2$, $(CH_2)_{0-6}$-C_{3-10} cycloalkyl, $(CH_2)_{0-6}$-aryl, $(CH_2)_{0-6}$-heterocycle, and $(CH_2)_{0-6}$-heteroaryl; and
each R^{AX} 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,
optionally, wherein the depicted dashed bond is a double bond.

[0095] One example of the present disclosure includes wherein at least one of A10 or $Y(R^{3a})(R^{3b})$ has one or more of: (a) a B atom in the defined ring or ring sytem; (b) is substituted with a $B(OH)_2$; or carries a ring or ring system substituent that contains a B atom in the ring or ring system.

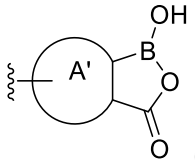
[0096] One example of the present disclosure includes wherein A10 is selected from the group consisting of:



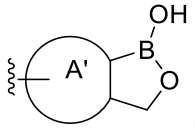
(I^{X1})



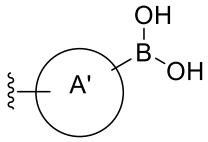
(I^{X2})



(I^{X3});



(I^{X4});



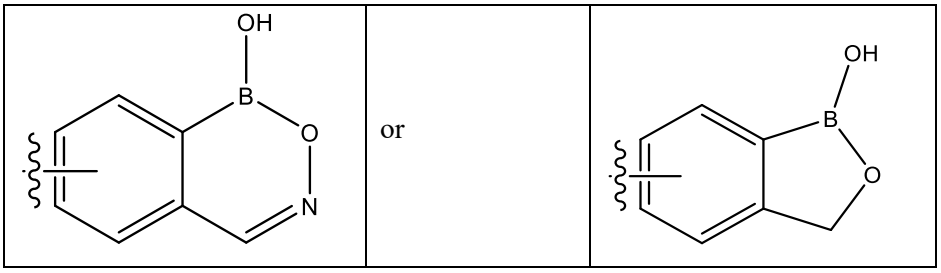
(I^{X5});

where each  represents the point of attachment to the depicted L^1;

each depicted A' independently is a cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

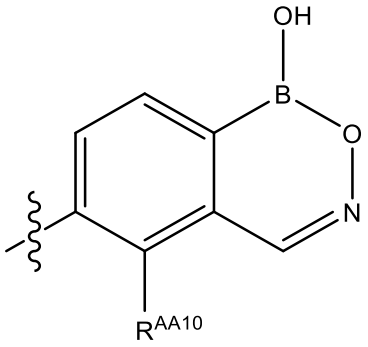
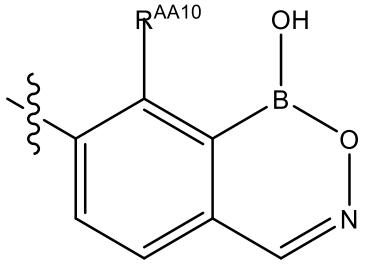
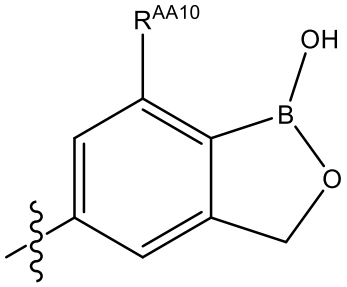
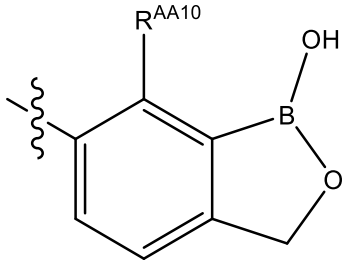
each A10 is optionally substituted with one or more R^{A10} on either depicted ring.

[0097] One example of the present disclosure includes wherein A10 is:



each optionally substituted with one or more R^{A10} on either depcited ring.

[0098] One example of the present disclosure includes wherein A10 is selected from the group consisting of:

	,		,
	, and		; and

each R^{AA10} is independently selected from the group consisting of: halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6 cycloalkyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, OH, O-C_3-C_6 cycloalkyl, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, O-C_{2-6} alkynyl, and CN or a deuterated form thereof; and

each A10 may be further substituted with one or more R^{A10}.

[0099] One example of the present disclosure includes wherein R^{AA10} is F, Cl, CH_3, OCH_3, or CD_3.

[00100] One example of the present disclosure includes wherein A10 is not further substituted.

[00101] One example of the present disclosure includes wherein A10 is further substituted with one or more R^{A10}, each independently selected from the group consisting of: halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_3-C_6 cycloalkyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, OH, O-C_{1-6} alkyl, O-C_{2-6} alkenyl, and O-C_{2-6} alkynyl.

[00102] One example of the present disclosure includes wherein L^1 is:

substituted or unsubstituted arylene; or

substituted or unsubstituted heteroarylene.

The compound of any one of claims 69 to 77, wherein L^1 is

substituted or unsubstituted phenylene; or

substituted or unsubstituted 5- to 10-membered heteroarylene having one or more heteroatoms selected from N, O, and S.

[00103] One example of the present disclosure includes wherein L^1 is substituted or unsubstituted phenylene; or substituted or unsubstituted pyridinylene.

[00104] One example of the present disclosure includes wherein L^1 is substituted with one or more halogen, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_2-C_3 alkenyl, C_2-C_3 haloalkenyl, C_2-C_3 alkynyl, C_2-C_3 haloalkynyl, OH, O-(C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl), NH_2, NH(C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl), N(C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl)$_2$, C_3 cycloalkyl, and C_3 halocycloalkyl.

[0001] One example of the present disclosure includes wherein L^1 is substituted with one or more halogen or C_1-C_3 alkyl.

[00105] One example of the present disclosure includes wherein X is oxygen.

[00106] One example of the present disclosure includes wherein Y is N or CR^{3c}.

[00107] One example of the present disclosure includes wherein Y is CR^{3c}; R^{3c} is H and each of R^{3a} and R^{3b} independently is selected from the group consisting of H, 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.

[00108] One example of the present disclosure includes wherein Y combines with R^{3a} and R^{3b} to form:

cycloalkyl substituted with $B(OH)_2$;

aryl substituted with $B(OH)_2$;

heterocyclyl, either

containing a B atom in the ring or ring system,

ii) substituted with $B(OH)_2$, or

iii) substituted with an optionally substituted 4- to 6-membered ring containing a B atom, one or more additional heteroatoms selected from O, N, or S, and one or more degrees of unsaturation; or

heteroaryl, either

containing a B atom in the ring or ring system, or

substituted with $B(OH)_2$, or

substituted with an optionally substituted 4- to 6-membered ring containing a B atom, one or more additional heteroatoms selected from O, N, or S, and one or more degrees of unsaturation; and

wherein each Y-ring or ring system is optionally substituted.

[00109] One example of the present disclosure includes wherein Y is nitrogen.

[00110] One example of the present disclosure includes wherein R^{1a} is CH_3.

[00111] One example of the present disclosure includes wherein R^{1b} is H.

[00112] One example of the present disclosure includes 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.

[00113] One example of the present disclosure includes wherein R^2 is CH_3.

[00114] One example of the present disclosure includes wherein R^4 is H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

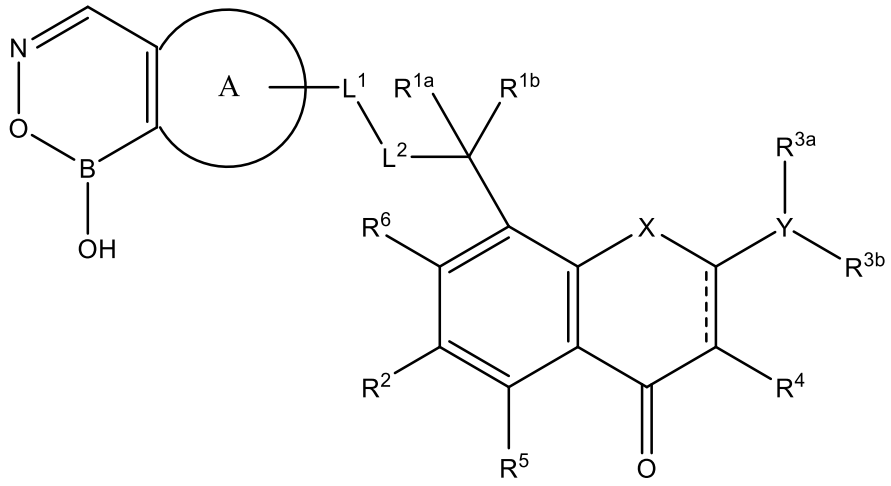
[00115] One example of the present disclosure includes wherein R^4 is H or CH_3.

[00116] One example of the present disclosure includes wherein R^5 is H.

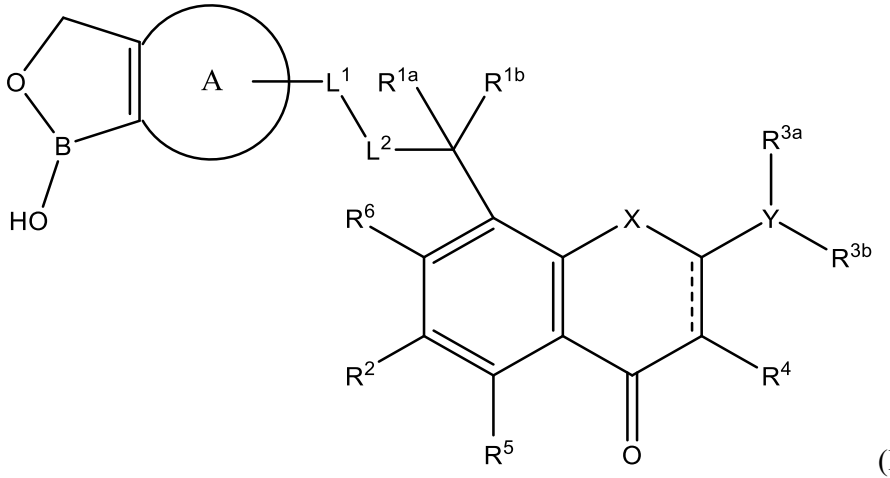
[00117] One example of the present disclosure includes wherein R^6 is H.

[00118] One example of the present disclosure includes wherein the depicted dashed bond is a double bond.

[00119] One example of the present disclosure includes a compound of Formula Ia or Ib:



(Ia),



(Ib)

or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof,

A is an aryl or heteroaryl ring, and together with the depicted boron ring, creates a fused ring system that includes the depicted boron-containing ring, and which system is optionally substituted with one or more R^A;

each R^A independently is selected from 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, $(CH_2)_{0-6}CN$, $(CH_2)_{1-6}OH$, $(CH_2)_{0-6}O$-C_{1-6} alkyl, $(CH_2)_{0-6}O$-C_{2-6} alkenyl,

$(CH_2)_{0-6}O$-C_{2-6} alkynyl, $(CH_2)_{0-6}C(O)H$, $(CH_2)_{0-6}C(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_{0-6}C(O)OH$, $(CH_2)_{0-6}C(O)O$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}NH_2$, $(CH_2)_{0-6}NH$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}N$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}C(O)NH_2$, $(CH_2)_{0-6}C(O)NH$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}C(O)N$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}NHC(O)H$, $(CH_2)_{0-6}NHC(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), and $(CH_2)_{0-6}N$(C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl)$C(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl) or a deuterated form thereof;

L^1 is selected from the group consisting of a direct bond, 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 H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;

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;

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; and

Y is N or CR^{3a}; and

when Y is 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, 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

R^{3a} and R^{3b} combine with the N atom 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, and S, and wherein the ring or ring system is optionally substituted;

when Y is CR^{3c},

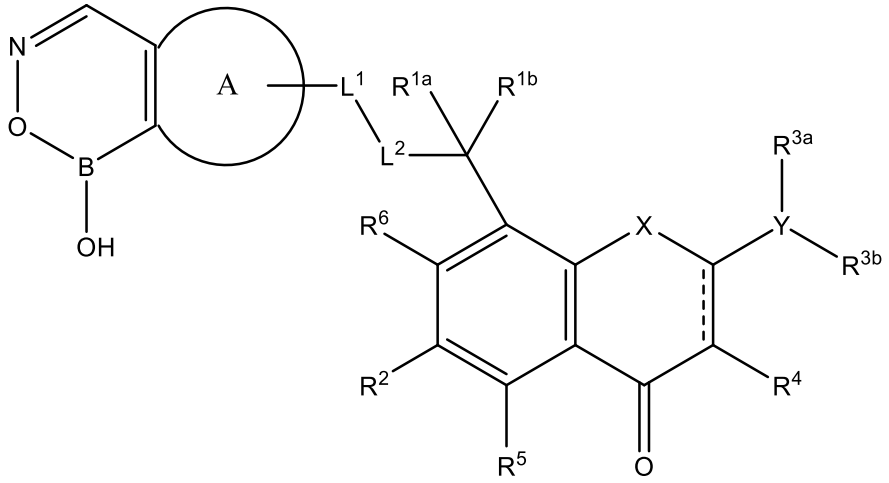
R^{3c} is absent or is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl;

each of R^{3a} and R^{3b} independently is selected from the group consisting of H, 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; or

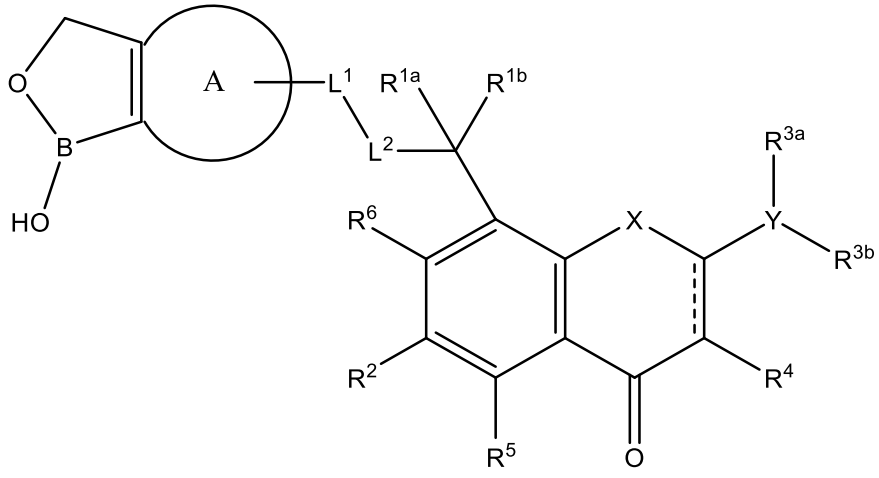
R^{3a} and R^{3b} combine with the C atom to form a cycloalkyl, aryl, heterocyclic, or heteroaromatic mono ring or spiro or fused ring system, where the heterocyclic and heteroaromatic rings contain one or more

heteroatoms selected from the group consisting of N, O, and S, and wherein the Y-containing ring or ring system is optionally substituted.

[00119a] In one aspect, the present disclosure refers to a compound of Formula Ia or Ib:



(Ia),



(Ib)

or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof,

A is an aryl or heteroaryl ring, and together with the depicted boron ring, creates a fused ring system that includes the depicted boron-containing ring, and which system is optionally substituted with one or more R^A;

each R^A independently is selected from 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, $(CH_2)_{0-6}CN$, $(CH_2)_{1-6}OH$, $(CH_2)_{0-6}O$-C_{1-6} alkyl, $(CH_2)_{0-6}O$-C_{2-6} alkenyl, $(CH_2)_{0-6}O$-C_{2-6} alkynyl, $(CH_2)_{0-6}C(O)H$, $(CH_2)_{0-6}C(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{1-6} alkynyl), $(CH_2)_{0-6}C(O)OH$, $(CH_2)_{0-6}C(O)O$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}NH_2$, $(CH_2)_{0-6}NH$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}N$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}C(O)NH_2$, $(CH_2)_{0-6}C(O)NH$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), $(CH_2)_{0-6}C(O)N$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl)$_2$, $(CH_2)_{0-6}NHC(O)H$, $(CH_2)_{0-6}NHC(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl), and $(CH_2)_{0-6}N$(C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl)$C(O)$(C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl) or a deuterated form thereof;

L^1 is selected from the group consisting of a direct bond, 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 H, halogen, CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy;
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;
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; and
Y is N or CR^{3a}; and

a) when Y is 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, 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
R^{3a} and R^{3b} combine with the N atom 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, and S, and wherein the ring or ring system is optionally substituted;

b) when Y is CR^{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} independently is selected from the group consisting of H, 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; or
R^{3a} and R^{3b} combine with the C atom 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, and S, and wherein the Y-containing ring or ring system is optionally substituted,

optionally, wherein the depicted dashed bond is a double bond.

[00120] In the event of any open valency in one or more sompound of the present disclosure, such open valency may be considered to he hydrogen or an optional substitutent as herein defined.

[00121] One example of the present disclosure includes wherein A is a phenyl ring.

[00122] One example of the present disclosure includes wherein R^A is absent.

[00123] One example of the present disclosure includes wherein the fused ring system is substituted with one R^A.

[00124] One example of the present disclosure includes wherein the fused ring system is substituted with two R^A.

[00125] One example of the present disclosure includes wherein each R^A is independently selected from the group consisting of C_{1-6} alkyl, O-C_{1-6} alkyl, C_{1-6} haloalkyl, and halogen, or a deuterated form thereof.

[00126] One example of the present disclosure includes wherein each R^A is independently selected from the group consisting of halogen, CD_3, CH_3, OCH_3,and CF_3.

[00127] One example of the present disclosure includes wherein L^1 is optionally substituted phenylene.

[00128] One example of the present disclosure includes wherein L^1 is phenylene substituted with one or more halogen or $C_{1\text{-}6}$alkyl.

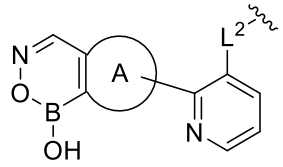
[00129] One example of the present disclosure includes wherein L^1 is optionally substituted heteroarylene.

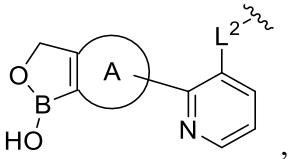
[00130] One example of the present disclosure includes wherein L^1 is optionally substituted pyridinylene.

[00131] One example of the present disclosure includes wherein L^1 is pyridinylene substituted with one or more halogen or $C_{1\text{-}6}$alkyl.

[00132] One example of the present disclosure includes wherein L^1 is substituted with one or two halogen.

[00133] One example of the present disclosure includes wherein the pyridinylene is attached as:

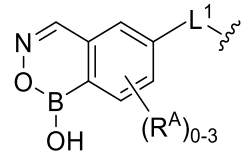


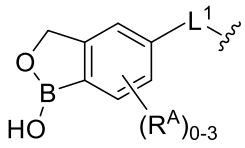
or


,

in either instance the depicted fused ring is optionally substituted with one or more R^A.

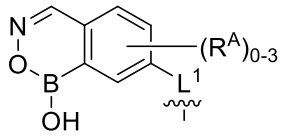
[00134] One example of the present disclosure includes wherein the depicted L^1 moiety is substituted *para* to the depicted B atom in the fused ring system:

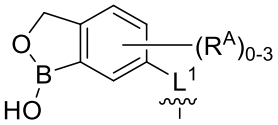


or


.

[00135] One example of the present disclosure includes wherein the depicted L^1 moiety is substituted *meta* to the depicted B atom in the fused ring system.



or


.

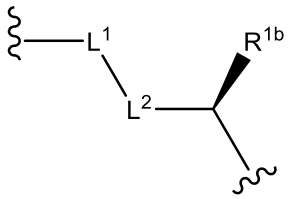
[00136] One example of the present disclosure includes wherein L^2 is NH.

[00137] One example of the present disclosure includes 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.

[00138] One example of the present disclosure includes wherein R^{1b} is C_{1-6} alkyl.

[00139] One example of the present disclosure includes wherein R^{1b} is methyl.

[00140] One example of the present disclosure includes wherein the chiral center is in the R configuration, as depicted by:



[00141] One example of the present disclosure includes wherein X is O.

[00142] One example of the present disclosure includes wherein

Y is CH and each of R^{3a} and R^{3b} is selected from the group consisting of 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; or

Y is CH and combines with R^{3a} and R^{3b} to form a cycloalkyl or heterocyclic mono ring system comprising one heteroatom selected from N and O.

[00143] One example of the present disclosure includes wherein Y is CH and each of R^{3a} and R^{3b} is C_{1-3}alkyl.

[00144] One example of the present disclosure includes wherein each of R^{3a} and R^{3b} is CH_3.

[00145] One example of the present disclosure includes wherein R^2 is CH_3.

[00146] One example of the present disclosure includes wherein R^4 is H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

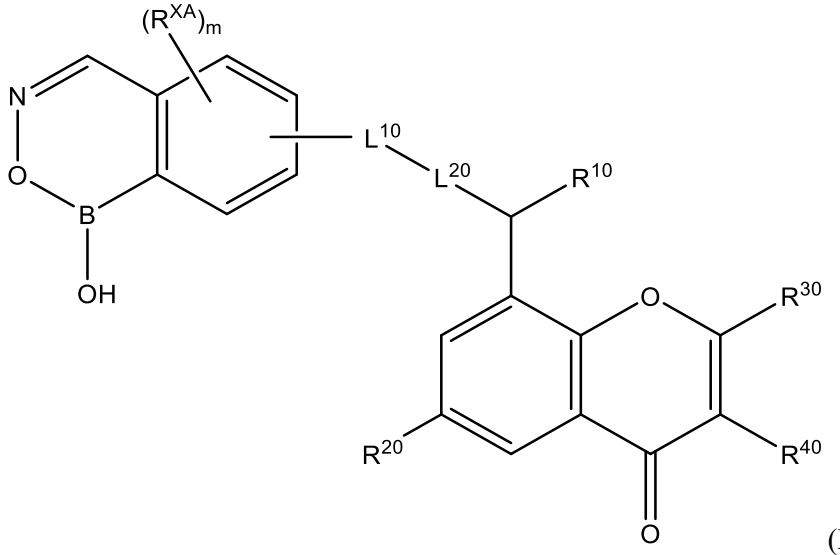
[00147] One example of the present disclosure includes wherein R^4 is H or CH_3.

[00148] One example of the present disclosure includes wherein R^5 is H.

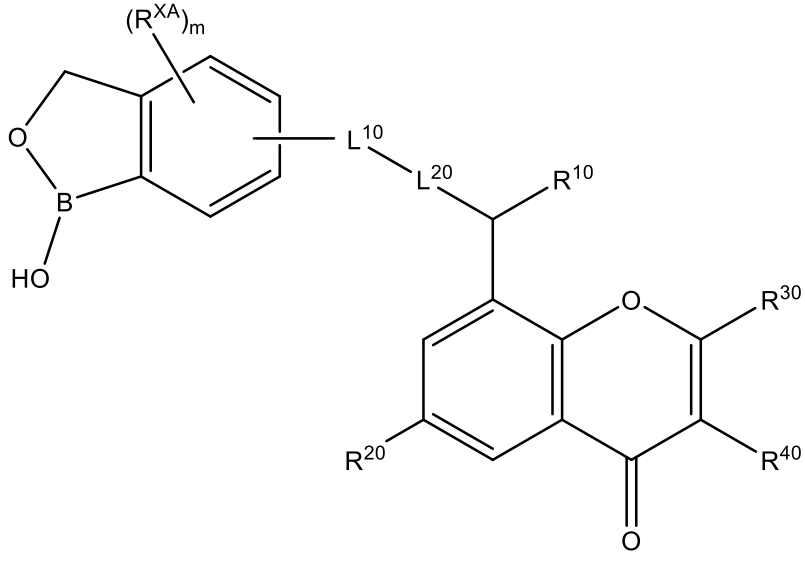
[00149] One example of the present disclosure includes wherein R^6 is H.

[00150] The One example of the present disclosure includes wherein the depicted dashed bond is a double bond.

[00151] One aspect of the present disclosure includes a compound of Formula Xa or Xb:



(Xa), or



(Xb),

or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, wherein

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

each R^{XA} independently is selected from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl, or a deuterated form thereof;

L^{10} is selected from the group consisting of a direct bond, optionally substituted arylene, or optionally susbstituted heteroarylene;

L^{20} is selected from the group consisting of O and NH;

R^{10} is selected from the group consisting of H and C_{1-6} alkyl;

R^{20} is selected from the group consisting of H, halogen, C_1-C_6 haloalkyl, and C_{1-6} alkyl;

R^{30} is selected from the group consisting of H or optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, N(C_1-C_6 alkyl), 6-membered aryl, 5- or 6-membered heteroaryl, or 3- to 10-membered heterocyclyl; and

R^{40} is selected from the group consisting of H and C_{1-6} alkyl.

[00152] One example of the present disclosure includes wherein L^{10} is an optionally substituted phenylene.

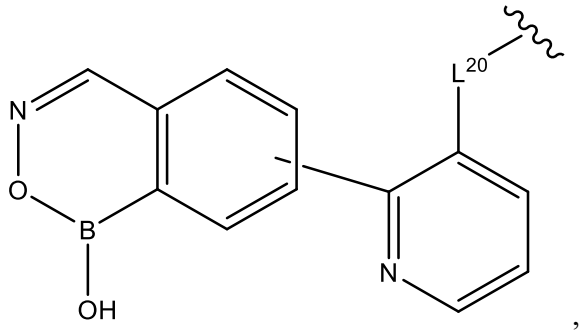
[00153] One example of the present disclosure includes wherein L^{10} is phenylene substituted with one or more halogen.

[00154] One example of the present disclosure includes wherein L^{10} is optionally substituted heteroarylene.

[00155] One example of the present disclosure includes wherein L^{10} is optionally substituted pyridinylene.

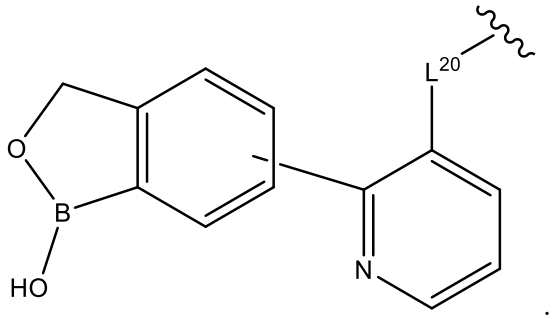
[00156] One example of the present disclosure includes wherein L^{10} is pyridinylene substituted with one or more halogen.

[00157] One example of the present disclosure includes wherein a compound, as optionally substituted:



,

or



.

[00158] One example of the present disclosure includes wherein L^{20} is NH.

[00159] One example of the present disclosure includes wherein R^{10} is C_{1-6} alkyl.

[00160] One example of the present disclosure includes wherein R^{10} is CH_3.

[00161] One example of the present disclosure includes wherein R^{20} is C_{1-6} alkyl.

[00162] One example of the present disclosure includes wherein R^{20} is CH_3.

[00163] One example of the present disclosure includes wherein R^{40} is C_{1-6} alkyl.

[00164] One example of the present disclosure includes wherein R^{40} is CH_3.

[00165] One example of the present disclosure includes wherein R^{30} is optionally substituted aryl, heteroaryl, or heterocyclyl.

[00166] One example of the present disclosure includes wherein the optionally substituted heterocyclyl comprises 3- to 6- ring atoms, with 1 or 2 of the ring atoms being independently selected from the group consisting of nitrogen and oxygen.

[00167] One example of the present disclosure includes wherein the optionally substituted heterocyclyl is optionally substituted piperidinyl.

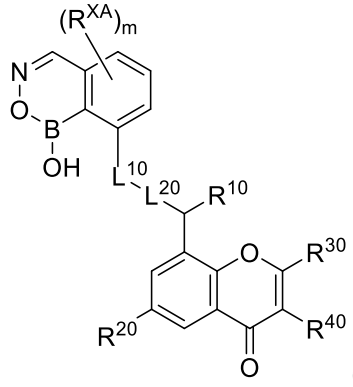
[00168] One example of the present disclosure includes wherein the optionally substituted piperidinyl is piperidinyl substituted with gem di-methyl.

[00169] One example of the present disclosure includes wherein the optionally substituted heterocyclyl is optionally substituted morpholinyl.

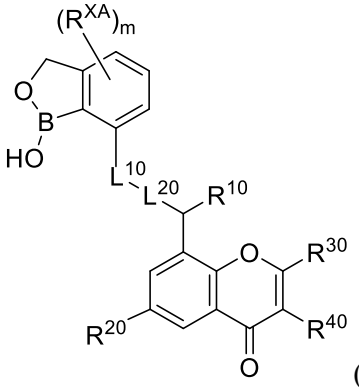
[00170] One example of the present disclosure includes wherein the optionally substituted heterocyclyl comprises three to six ring atoms, wherein one atom is oxygen.

[00171] One example of the present disclosure includes wherein R^{30} is optionally substituted: C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[00172] One example of the present disclosure includes wherein the compound is of formula XI:

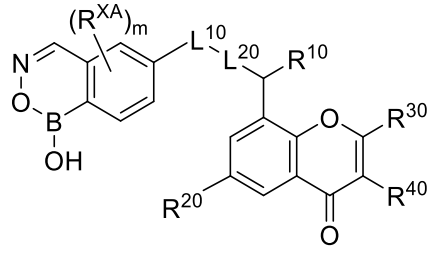


(XIa) or

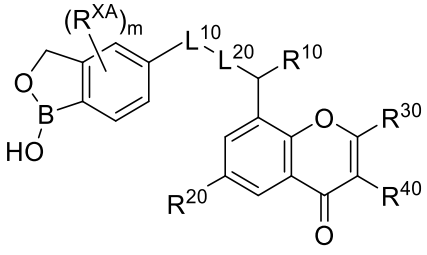


(XIb).

[00173] One example of the present disclosure includes wherein the compound is of formula XII:

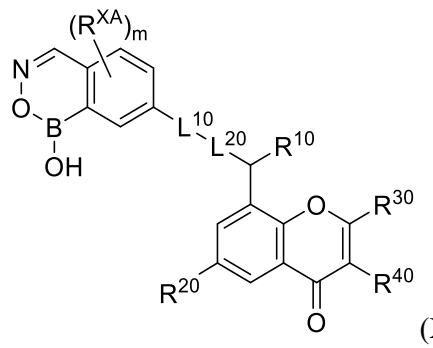


(XIIa) or

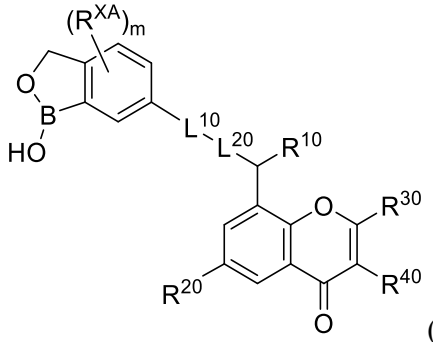


(XIIb).

[00174] One example of the present disclosure includes wherein the compound is of formula XIII:

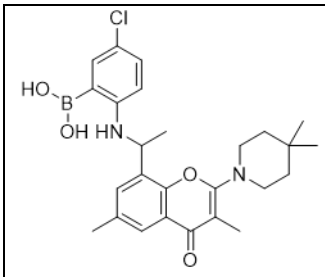
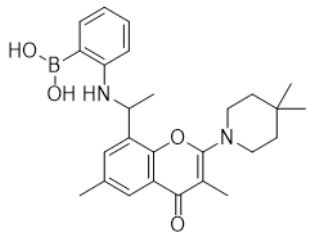
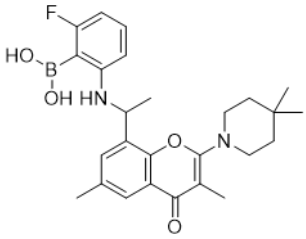
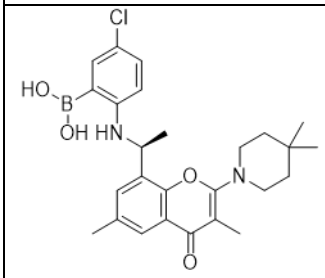
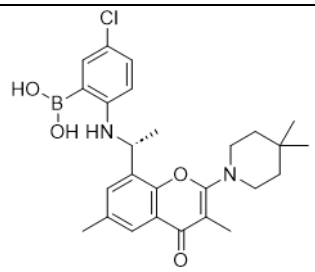
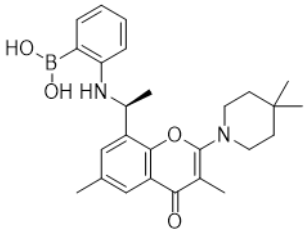
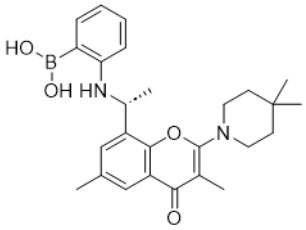
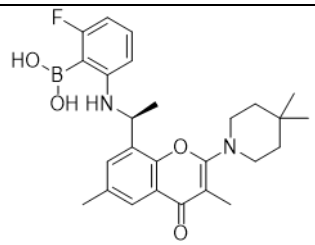
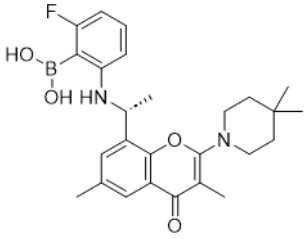
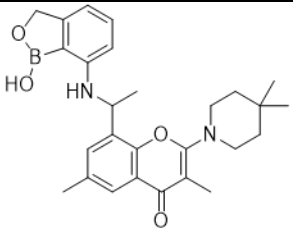
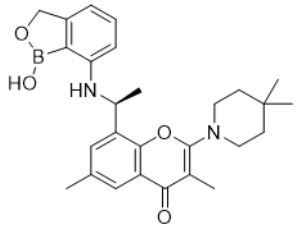
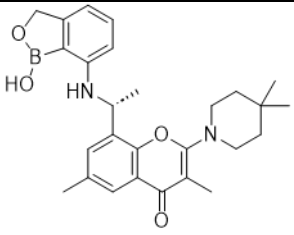


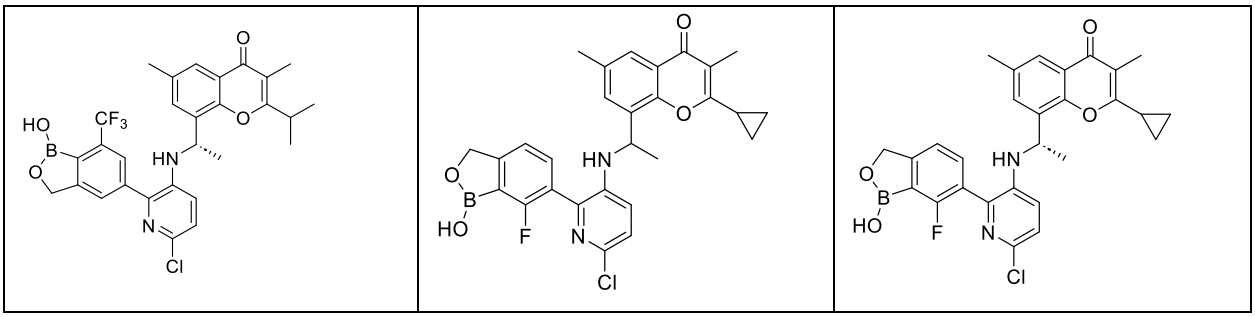
(XIIIa) or



(XIIIb).

[00175] One aspect of the present disclosure includes a compound selected from the group consisting of:



or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof.

[00176] One example of the present disclosure includes wherein the compound is a racemate.

[00177] One example of the present disclosure includes wherein the compound is a single stereoisomer substantially free of any alternative forms.

[00178] One example of the present disclosure includes wherein the stereoisomeric form is R.

[00179] One example of the present disclosure includes wherein the compound is a tautomeric form of a preferred equilibria.

[00180] One aspect 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.

[00181] One aspect 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.

[00182] One example 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.

[0182a] In one aspect, the present disclosure refers to use of the compound as disclosed herein in the manufacture of a medicament for the treatment of cancer or a PI3K-mediated disease or disorder in a patient in need thereof.

[00183] One example 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.

[00184] One example 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.

[00184a] In one aspect, the present disclosure refers to use of the compound as disclosed herein in the manufacture of a medicament for the treatment of a disease or disorder mediated by one or more PIK3CA genes, wherein the treatment comprises modulating one or more of wild type or one or more mutations of the one or more PIK3CA genes, optionally, comprising modulating one mutation; or optionally, comprising modulating two or more mutations; or optionally, comprising modulating wild type, optionally, wherein the modulation is inhibition, or optionally, wherein the modulation is selective inhibition for one or more mutations over wild-type.

[00185] One example includes modulating one mutation.

[00186] One example includes modulating two or more mutations.

[00187] One example includes modulating wild type.

[00188] One example includes wherein the PIK3CA is a PIK3CA mutant.

[00189] One example includes wherein the PIK3CA mediates a cancer.

[00190] One example includes wherein the PIK3CA regulates cancer initiation, progression, or metasasis.

[00191] One example includes wherein wherein the one or more mutations are any p110 mutation.

[00192] One example 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.

[00193] One example includes wherein the one or more mutations are selected from one or more mutations of H1047, E545, and E542.

[00194] One example includes wherein modulation is inhibition.

[00195] One example includes wherein modulation is selective inhibiton for one or more mutations over wild-type.

[00196] One example includes wherein the mutations are selected from H1047X, E545X, and E542X.

[00197] One example includes wherein the mutation is H1047X.

[00198] One example includes wherein the mutation is H1047L

[00199] One example includes wherein the mutation is H1047R.

[00200] One example includes wherein a mutation is E545X.

[00201] One example includes wherein the mutation is E545K.

[00202] One example includes wherein a mutation is E542X.

[00203] One example includes wherein the mutation is E542K.

[00204] One example includes wherein the method further comprises the compound chemically capturing a solvent accessible surface area of a protein.

[00205] One example includes wherein the solvent accessible surface area comprises one or more amino acid residue.

[00206] One example includes wherein the amino acid residue is selected from one or more of arginine, histidine, lysine, glutamic acid, serine, threonine, or glutamine.

[00207] One example includes wherein the amino acid residue is histidine.

[00208] One example includes wherein the histidine is HIS1048.

[00209] One example includes wherein chemical capture is interacting.

[00210] One example includes wherein interacting is binding.

[00211] One example includes wherein binding is covalent binding.

[00212] One example includes wherein binding is hydrogen bonding.

[00213] One example includes wherein the method further comprises administering a compound of the present disclosure.

[00214] One example of the present disclosure includes a method for inhibiting PI3K activity in a cell, comprising modulating a solvent accessible surface area of a protein with a compound of the present disclosure.

[00214a] In one aspect, the present disclosure refers to use of the compound as disclosed herein in the manufacture of a medicament for inhibiting PI3K activity in a cell, wherein a solvent accessible surface area of a protein is to be modulated with the medicament, optionally, wherein the modulating is in vitro, or optionally, wherein the modulating is in vivo, optionally, wherein the PI3K targeted gene is PIK3CA,optionally, wherein the PI3K is PI3Kα, optionally, wherein the PI3Kα is a PI3Kα mutant, optionally, wherein the PI3Kα is a PI3Kα wild type, optionally, wherein the PI3K mediates a cancer, optionally, wherein the PI3K regulates cancer initiation, progression, or metastasis,optionally, wherein modulation is inhibition, or optionally, wherein modulation is selective inhibition over wild-type, providing preferential inhibition at a multiple level of: greater than 1, between about 1.5 to about 20 or greater, between about 1.5 and 100 or greater.

[00215] One example includes wherein the modulating is in vitro.
[00216] One example includes wherein the modulating is in vivo.
[00217] One example includes wherein the PI3K targeted gene is PIK3CA.
[00218] One example includes wherein the PI3K is PI3Kα .
[00219] One example includes wherein the PI3Kα is a PI3Kα mutant.
[00220] One example includes wherein the PI3Kα is a PI3Kα wild type.
[00221] One example includes wherein the PI3K mediates a cancer.
[00222] One example includes wherein the PI3K regulates cancer initiation, progression, or metastasis.
[00223] One example 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.
[00224] One example includes wherein the one or more mutations are selected from one or more mutations of of H1047, E545, and E542.
[00225] One example includes wherein modulation is inhibition.
[00226] One example includes wherein modulation is selective inhibition over wild-type, providing preferential inhibition at a multiple level of: greater than 1, between about 1.5 to about 20 or greater, between about 1.5 and 100 or greater.
[00227] One example includes wherein the mutations are selected from H1047X, E545X, and E542X.
[00228] One example includes wherein a mutation is H1047X.
[00229] One example includes wherein the mutation is H1047L
[00230] One example includes wherein the mutation is H1047R.
[00231] One example includes wherein the mutation is GLU545X.
[00232] One example includes wherein the mutation is E545K.
[00233] One example includes wherein the mutation is GLU542X.
[00234] One example includes wherein the mutation is E542K.
[00235] One example includes further comprising the compound chemically capturing a solvent accessible surface area of the protein.
[00236] One example includes wherein the solvent accessible surface area comprises one or more amino acid residue.
[00237] One example includes wherein the amino acid residue is selected from one or more of arginine, histidine, lysine, glutamic acid, serine, threonine, or glutamine.
[00238] One example includes wherein the amino acid residue is histidine.
[00239] One example includes wherein the histidine is H1048.
[00240] One example includes wherein chemical capture is interacting.

[00241] One example includes wherein interacting is binding.
[00242] One example includes wherein binding is covalent binding.
[00243] One example includes wherein binding is hydrogen bonding.
[00244] One example of the present disclosure includes a method of inhibiting PI3K comprising chemically capturing a solvent accessible surface area and modulating a p110 mutated protein subunit.
[00244a] In one aspect, the present disclosure refers to use of the compound as disclosed herein in the manufacture of a medicament for the inhibition of PI3K wherein the inhibition comprises chemically capturing a solvent accessible surface area and modulating a p110 mutated protein subunit, optionally, wherein the solvent accessible surface area comprises one or more amino acid residue, optionally, wherein the amino acid residue is selected from one or more of arginine, histidine, lysine, glutamic acid, serine, threonine, or glutamine, optionally, wherein the amino acid residue is histidine, optionally, wherein the histidine is H1048.
[00245] One example includes wherein the solvent accessible surface area comprises one or more amino acid residue.
[00246] One example includes wherein the amino acid residue is selected from one or more of arginine, histidine, lysine, glutamic acid, serine, threonine, or glutamine.
[00247] One example includes wherein the amino acid residue is histidine.
[00248] One example includes wherein the histidine is H1048.
[00249] One example includes wherein chemical capture is interacting.
[00250] One example includes wherein interacting is binding.
[00251] One example includes wherein binding is covalent binding.
[00252] One example includes wherein binding is hydrogen bonding.
[00253] One example includes wherein the p110 mutated protein subunit comprises at least one amino acid mutation compared to the wild type p110 protein subunit.
[00254] One example 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.
[00255] One example includes wherein the one or more mutations are selected from one or more of H1047, E545, and E542.
[00256] One example includes comprising administering a compound of the present disclosure.
[00257] One example of the present diclsoure includes a method of treating a disease or disorder mediated by PI3Kα, comprising chemically capturing a solvent accessible amino acid residue and modulating one or more of H1047X, E545X, and E542X.
[00257a] In one aspect, the present disclosure refers to use of a compound of as disclosed herein in the manufacture of a medicament for the treatment of a disease or disorder mediated by PI3Kα, wherein the treatment comprises chemically capturing a solvent accessible amino acid residue and modulating one or more of H1047X, E545X, and E542X, optionally, wherein the amino acid residue is selected from one or more of arginine, histidine, lysine, glutamic acid, serine, threonine, or glutamine, optionally, wherein the amino acid residue is histidine, optionally, wherein the histidine is HIS1048.
[00258] One example includes wherein the amino acid residue is selected from one or more of arginine, histidine, lysine, glutamic acid, serine, threonine, or glutamine.
[00259] One example includes wherein the amino acid residue is histidine.
[00260] One example includes wherein the histidine is HIS1048.
[00261] One example includes wherein chemical capture is interacting.
[00262] One example includes wherein interacting is binding.
[00263] One example includes wherein binding is covalent binding.
[00264] One example includes wherein binding is hydrogen bonding.

[00265] One example includes modulating one or more of H1047L and H1047R.
[00266] One example includes modulating GLU545K.
[00267] One example includes modulating GLU542K.
[00268] One example includes administering a compound of the present disclosure
[00269] One example 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.
[00269a] In one aspect, the present disclosure refers to use of the compound as disclosed herein in the manufacture of a medicament for the inhibition of a PIK3CA gene target protein (PI3K) or treatment of a disease or disorder mediated by PIK3CA, wherein the inhibition or treatment comprises 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, optionally, wherein the two or more mutant variants are selected from mutations of H1047, E545, and E542.
[00270] One example includes wherein the two or more mutant varients are selected from mutations of H1047, E545, and E542
[00271] One example 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.
[00272] One example includes wherein the two or more mutant varients are selected from mutations of H1047, E545, and E542.
[00273] One example includes administering a compound of the present disclosure.
[00274] One example 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.
[00275] [00274a] In one aspect, the present disclosure refers to use of the compound as disclosed herein in the manufacture of a medicament for modulating a PI3K to treat a disease or disorder by interacting the compound with at least two mutant variants, optionally, wherein the PI3K gene target is PIK3CA, optionally, wherein the PI3K mediates a cancer, or optionally, wherein the PI3K regulates cancer initiation, progression, or metastasis, optionally, wherein modulation is inhibition, or optionally, wherein modulation is selective inhibition over wild-type. One example includes wherein the PI3K gene target is PIK3CA.
[00276] One example includes wherein the PI3K mediates a cancer.
[00277] One example includes wherein the PI3K regulates cancer initiation, progression, or metastasis.
[00278] One example 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.
[00279] One example includes wherein the mutant variants are selected from mutations of one or more of H1047, E545, and E542.
[00280] One example includes wherein modulation is inhibition.
[00281] One example includes wherein modulation is selective inhibiton over wild-type.
[00282] One example includes wherein the mutation is H1047X.
[00283] One example includes wherein the mutation is H1047L.
[00284] One example includes wherein the mutation is H1047R.
[00285] One example includes wherein the mutation is E545X.
[00286] One example includes wherein the mutation is E545K.
[00287] One example includes wherein the mutation is E542.

[00288] One example includes wherein the mutation is E542K.

[00289] One example includes administering a compound of the present disclosure and capturing a solvent accessible surface area of a protein.

[00290] One example includes wherein the solvent accessible surface area comprises one or more amino acid residue.

[00291] One example includes wherein the amino acid residue is selected from one or more of arginine, histidine, lysine, glutamic acid, serine, threonine, or glutamine.

[00292] One example includes wherein the amino acid residue is histidine.

[00293] One example includes wherein the histidine is HIS1048.

[00294] One example includes wherein chemical capture is interacting.

[00295] One example includes wherein interacting is binding.

[00296] One example includes wherein binding is covalent binding.

[00297] One example includes wherein binding is hydrogen binding.

[00298] In one example, the present disclosure includes a method of any one of claims 156 to 273, wherein the disease or disorder is cancer.

[00299] One example includes wherein the disease or disorder is PROS: PIK3CA-Related Overgrowth Spectrum.

[00300] One example 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.

[00301] One example includes wherein the disease or disorder is breast cancer.

[00302] In one example, the present disclosure includes a method comprising administration of one or more additional therapeutic agent.

[00303] One example includes wherein administration is of two or more additional therapeutic agents.

[00304] One example 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.

[00305] One example includes wherein the additional therapeutic agents are selected from fulvestrant, vepdegestrant, palazestrant, imlunestrant, elacestrant, giredestrant, camizestrant, palbociclib, ribociclib, abemaciclib, anastronzole, exemestane, and letrozole.

[00306] One example includes wherein each agent is provided in a separate dosage form.

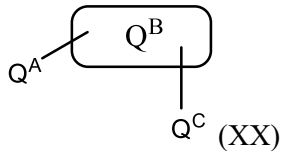
[00307] One example includes wherein one or more agent is provided in a combined dosage form.

[00308] In one example, 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.
[00308a] In one aspect, the present disclosure refers to use of the compound as disclosed herein in the manufacture of a medicament for the modulation of one or more PI3K enzymes to regulate one or more of disease initiation and progression, wherein the modulation comprises interaction with at least one histidine and modulation of at least one surface accessible amino acid or residue, optionally, wherein one or more PI3K is inhibited, optionally, wherein the PI3K is PI3Kα, optionally, wherein the PI3Kα is a mutated variant thereof.
[00309] One example includes wherein one or more PI3K is inhibited.
[00310] One example includes wherein the PI3K is PI3Kα.
[00311] One example includes wherein the PI3Kα is a mutated variant thereof.
[00312] In one example, the present disclosure includes a method for treating cancer in a patient in need thereof, comprising:
[00313] determining that the cancer is associated with a PI3K wild-type or one or more PI3K mutations; and
[00314] administering to the patient a therapeutically effective amount of a compound of the present disclosure
[00314a] In one aspect, the present disclosure refers to use of the compound as disclosed herein in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein the treatment comprises determining that the cancer is associated with a PI3K wild-type or one or more PI3K mutations, optionally, wherein the PI3K is a mutated variant thereof.
[00315] One example includes wherein the PI3K is a mutated variant thereof.
[00316] In one aspect, the present disclosure includes a compound of the present disclosure, for use in therapy.
[00317] In one example, the present disclosure includes a compound of the present disclosure, for use in the treatment of cancer.
[00317a] In one aspect, the present disclosure refers to use of a compound as disclosed herein, in the manufacture of a medicament for: (i) the treatment of cancer, (ii) the inhibition of activity of PI3K, (iii) the treatment of a PI3K-mediated disease or disorder, optionally, wherein the PI3K is PI3Kα, optionally, wherein the PI3Kα is wild type, optionally, wherein the PI3Kα is a mutated variant thereof.
[00318] In one example, the present disclosure includes a compound of the present disclosure, for use in the inhibition of PI3K.
[00319] In one example, the PI3K is PI3Kα.
[00320] In one example, the PI3Kα is wild type.
[00321] In one example, the PI3Kα is a mutated variant thereof.
[00322] In one example, the present disclosure includes a use of a compound of the present disclosure, in the manufacture of a medicament for the treatment of cancer.
[00323] In one example, 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.
[00324] In one example, 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.
[00325] In one example, the PI3K is PI3Kα.
[00326] In one example, the PI3Kα is wild type.
[00327] In one example, the PI3Kα is a mutated variant thereof.
[00328] One aspect of the present disclosure includes a process for preparing a compound of the present disclosure.

[00329] One example of the present disclosure includes a compound obtained by a process of the present disclosure.

[00330] One example of the present disclosure includes an adduct comprising a compound having a warhead capable of chemical capture of a solvent accessible surface area (SASA) of a protein. In one example, the SASA comprises a residue of one or more of an available arginine, histidine, lysine, glutamic acid, serine, threonine, and glutamine. In one example, the SASA comprises a histidine residue. In one example, the chemical capture is interaction. In one example, the interaction is binding. In one example, the binding is covalent binding. In one example, the binding is hydrogen bonding. In one example, the warhead comprises at least one boron heteroatom. In one example, the warhead comprises a ring or ring system having at least one boron atom incorporated therein. In one example, the warhead comprises at least one $B(OH)_2$ group as a substituent. In one example, the warhead does not include a boron heteroatom. In one example, the warhead is selected from: a cyclohexenone derivative, an alkyl halide derivative, a sulfonyl derivative, an α-cyanoenone derivative, and an epoxide or spiro-epoxide derivative.

[00331] In one example, the present disclosure includes a compound of formula XX:



(XX)

or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, wherein

Q^B comprises an optionally substituted 8- to 14-membered spiro or fused ring system optionally containing one or more heteroatoms selected from the group consisting of O, N, or S;

Q^A is $^{XX}A1$-$^{XX}L^1$-$^{XX}L^2$-C($^{XX}R^{1a}$-$^{XX}R^{1b}$), wherein:

$^{XX}A1$ is a warhead moiety that provides chemical capture of an available solvent accessible surface area of a protein;

$^{XX}L^1$ is selected from the group consisting of a direct bond, optionally substituted arylene, and optionally substituted heteroarylene;

$^{XX}L^2$ is selected from the group consisting of O and NH; and

each of $^{XX}R^{1a}$ and $^{XX}R^{1b}$ 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;

or $^{XX}L^2$-C($^{XX}R^{1a}$)($^{XX}R^{1b}$) combines to form NHC(O), C(O)NH, $NHS(O)_2$, $S(O)_2NH$, or $C(NH)NH_2$;

Q^C is ^{XX}Y($^{XX}R^{3a}$-$^{XX}R^{3b}$) wherein:

^{XX}Y is H, $C^{XX}R^{3c}$, N, O, or S;

when ^{XX}Y is H, each of $^{XX}R^{3a}$ and $^{XX}R^{3b}$ is absent;

when ^{XX}Y is N,

each of $^{XX}R^{3a}$ and $^{XX}R^{3b}$ independently is selected from the group consisting of H, 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; or

Y, as an N atom, combines with $^{XX}R^{3a}$ and $^{XX}R^{3b}$ 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, and S, and wherein the ring or ring system is optionally substituted;

when Y is $C^{XX}R^{3c}$

$^{XX}R^{3c}$ 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;

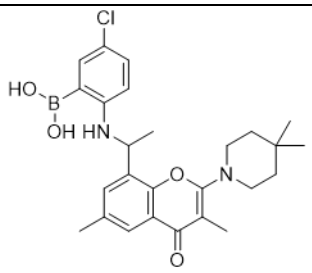
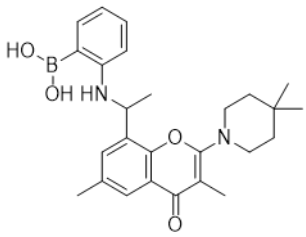
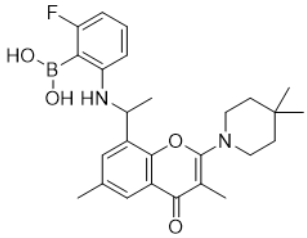
each of $^{XX}R^{3a}$ and $^{XX}R^{3b}$ independently is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, aryl, C_{3-6} cycloalkyl, and 3 to 6 membered heterocyclyl; or

^{XX}Y, as an C atom, combines with $^{XX}R^{3a}$ and $^{XX}R^{3b}$ 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, and S, and wherein the ^{XX}Y-containing ring or ring system is optionally substituted; or

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

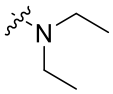
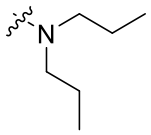
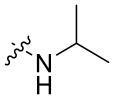
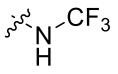
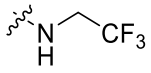
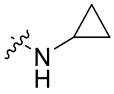
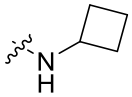
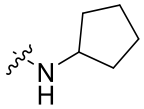
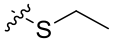
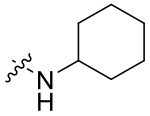
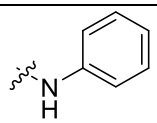
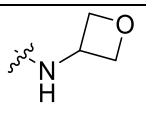
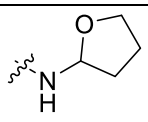
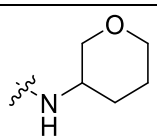
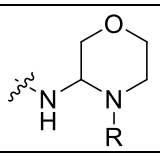
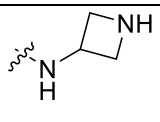
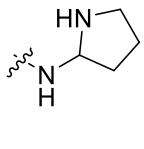
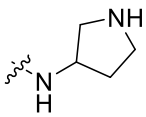
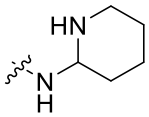
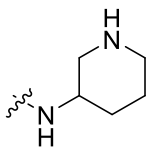
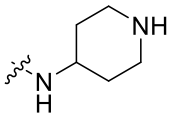
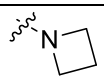
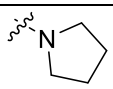
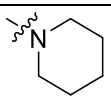
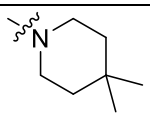
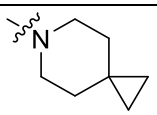
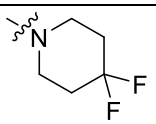
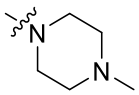
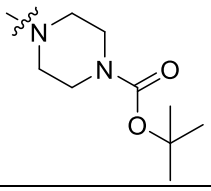
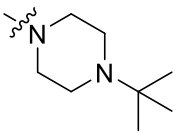
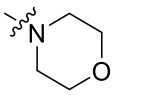
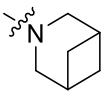
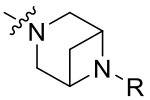
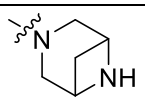
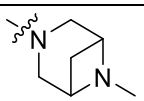
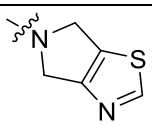
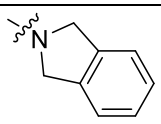
[00332] One example of the present disclosure includes a compound of Table 1, or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof.

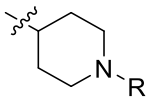
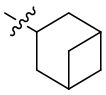
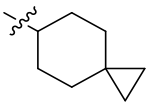
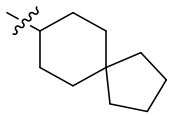
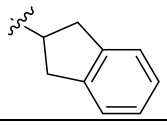
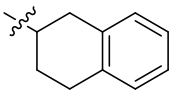
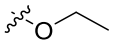
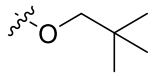
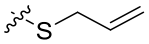
[00333] Table 1: Compounds of the present disclosure

[00334] One example of the present disclosure includes a compound of the present disclosure, or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, wherein the Y^T group, as well as the more specific recited groups identified in a comparable position to Y^T, is selected from Table 2.

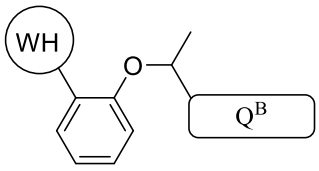
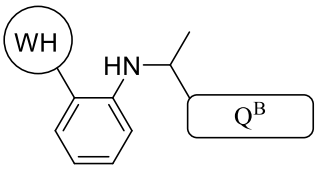
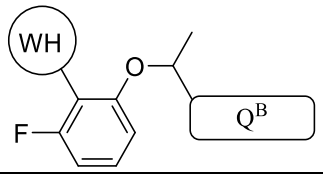
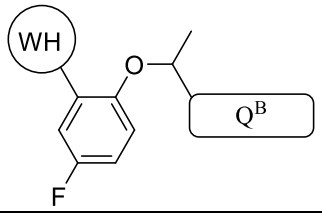
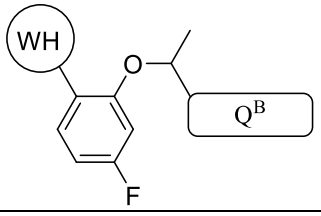
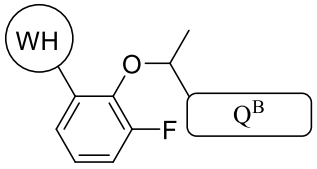
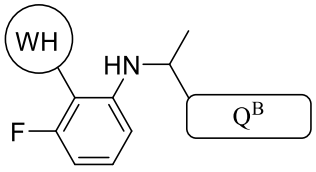
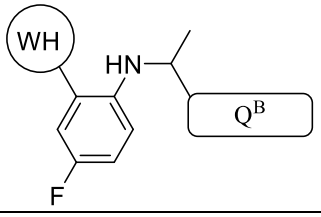
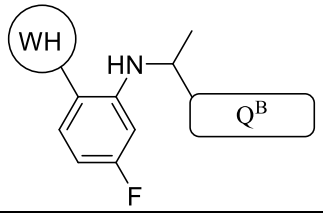
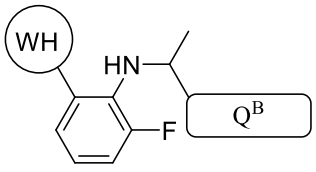
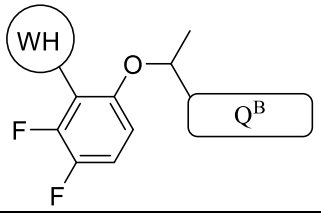
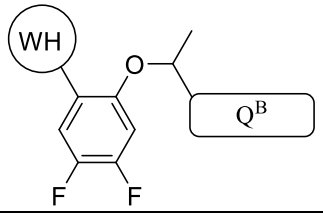
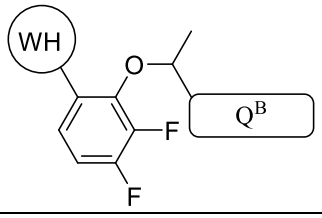
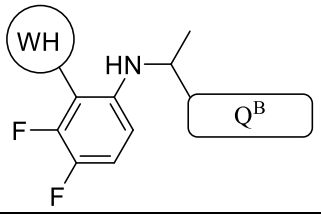
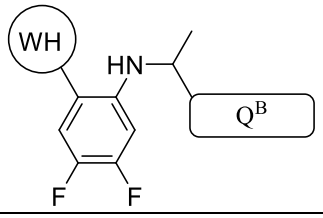
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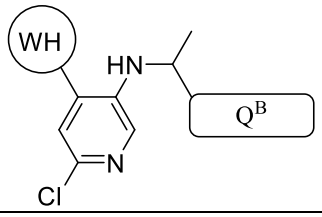
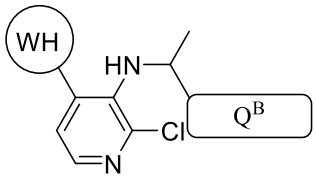
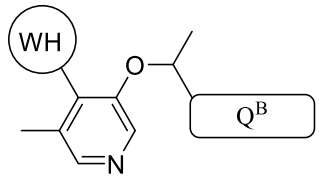
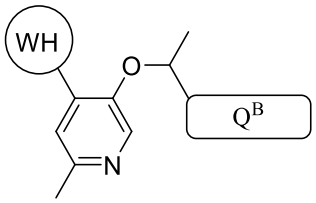
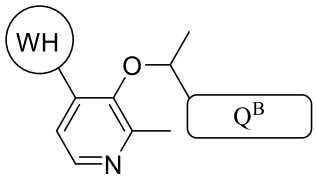
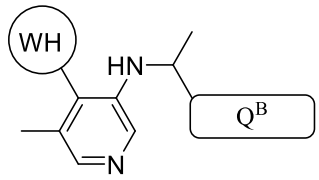
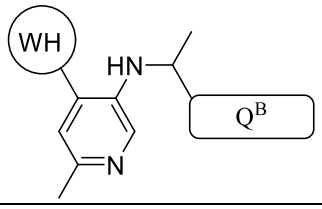
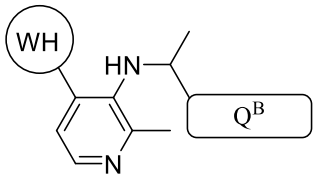
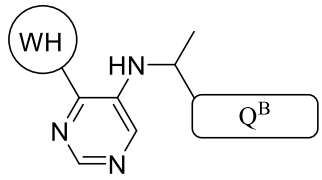
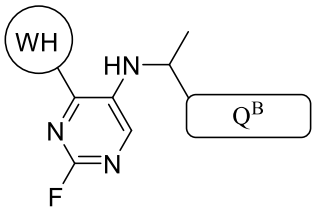
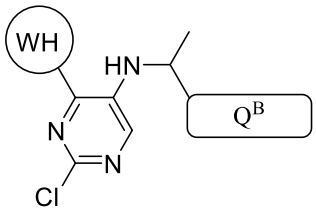
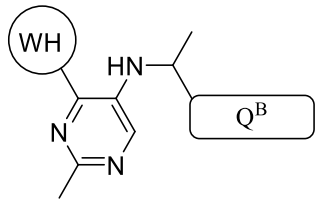
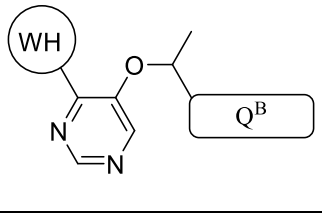
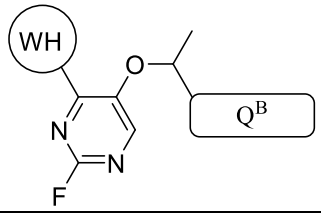
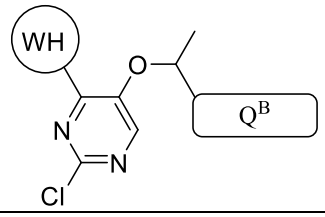
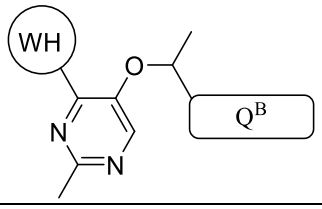
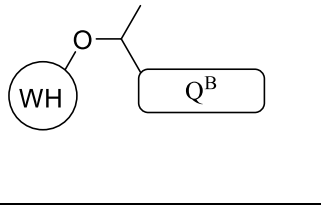
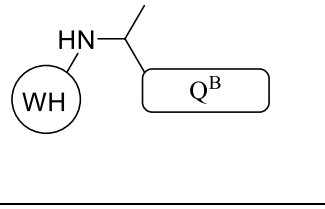
					
					
					
					
					
					
					

					
				and	

[00336] One example of the present disclosure includes a compound of the present disclosure, or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, wherein the linker group, as well as the more specific recited groups identified in a comparable position to L^1-L^2, is selected from Table 3.

[00337] Table 3:

[00338] One example of the present disclosure includes a compound of the present disclosure, or a tautomer, enantiomer, diastereomer, mixture, salt, hydrate, solvate, or deuterated form thereof, wherein the Q^B group, as well as the more specific recited groups identified in a comparable position to Q^B, is selected from Table 4.

[00339] Table 4:

[00340] One or more aspects and examples may be incorporated in a different example although not specifically described. That is, all aspects and examples may be combined in any way or combination.

Brief Description of the Drawings

[00341] Figure 1 provides tabulated biological data for compounds of the present disclosure.

Detailed Description

Definitions

[00342] 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.

[00343] 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.

[00344] As used herein "halogen" or "halo" refers to a halogen. In some embodiments, the halogen is preferably Br, Cl, or F.

[00345] 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. 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.

[00346] The term "haloalkyloxy" refers to O-haloalkyl.

[00347] As used herein, "alkoxy" refers to an O-alkyl group having the specified number of carbon atoms.

[00348] 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.