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(54) Title: SUBSTITUTED INHIBITORS OF MENIN-MLL AND METHODS OF USE

(57) Abstract: The present disclosure provides methods of inhibiting the interaction of menin with MLL1, MLL2 and MLL-fusion oncoproteins. The methods are useful for the treatment of leukemia, solid cancers, diabetes and other diseases dependent on activity of MLL1, MLL2, MLL fusion proteins, and/or menin. Compositions for use in these methods are also provided.

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SUBSTITUTED INHIBITORS OF MENIN-MLL AND METHODS OF USE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/561,089, filed September 20, 2017; U.S. Provisional Application No. 62/577,644, filed October 26, 2017; U.S. Provisional Application No. 62/595,436, filed December 6, 2017; and U.S. Provisional Application No. 62/637,074, filed March 1, 2018, each incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 30, 2018, is named 47535729601_SL.txt and is 15,912 bytes in size.

BACKGROUND OF THE INVENTION

[0003] The mixed-lineage leukemia (MLL) protein is a histone methyltransferase critical for the epigenetic regulation of gene transcription. Many acute leukemias, including acute myeloblastic leukemia (AML), acute lymphoblastic leukemia (ALL) and mixed-lineage leukemia (MLL), are characterized by the presence of chimeric MLL fusion proteins that result from chromosomal translocations of the *MLL* gene located at chromosome 11, band q23 (11q23). Chimeric MLL fusion proteins retain approximately 1,400 amino acids of the N-terminus of MLL, but are fused with one of approximately 80 partner proteins (e.g., AF4, AF9, ENL, AF10, ELL, AF6, AF1p, GAS7). MLL fusion proteins lack the original histone methyltransferase activity of the C-terminus of MLL and gain the ability to regulate transcription of numerous oncogenes, including *HOX* and *MEIS1*, resulting in increased cell proliferation and decreased cell differentiation, ultimately leading to leukemogenesis.

[0004] The menin protein, which is encoded by the Multiple Endocrine Neoplasia (MEN) gene, is a ubiquitously expressed nuclear protein that engages in interactions with DNA processing and repair proteins, chromatin modifying proteins and numerous transcription factors (Agarwal, et al.; *Horm Metab Res*, 2005, 37(6): 369-374). The association of menin with the N-terminus of MLL fusion proteins is necessary for the observed oncogenic activity of MLL fusion proteins. This association has been shown to constitutively up-regulate the expression of *HOX* and *MEIS1* oncogenes and impairs proliferation and differentiation of hematopoietic cells leading to leukemia development. Since menin has been shown to function as a general oncogenic cofactor

in MLL-related leukemias, the interaction between menin and MLL fusion proteins and MLL represents a potential chemotherapeutic target.

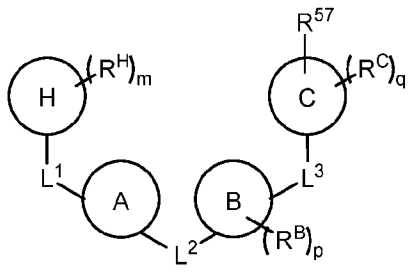
[0005] Patients, especially infants, with leukemias harboring chromosomal translocations of the MLL gene have a dismal prognosis, with less than a 40% five year survival rate (Slany; *Haematologica*, 2009, 94(7): 984-993). A novel therapeutic strategy is urgently needed to treat these leukemias. Small molecule inhibitors that block the menin-MLL interaction are thus valuable targets for treating diseases involving the MLL fusion proteins.

SUMMARY OF THE INVENTION

[0006] The present disclosure addresses a need in the art by providing compositions and methods for inhibiting the protein-protein interaction of menin with MLL1, MLL2 and MLL-fusion oncoproteins. The compositions and methods herein may be useful for treating diseases dependent on the activity of MLL1, MLL2, MLL fusion proteins, and/or menin such as leukemia, solid cancers, and diabetes. In some embodiments, a compound of the disclosure interacts non-covalently with menin and inhibits the interaction of menin with MLL. In some embodiments, a compound of the disclosure covalently binds menin and inhibits the interaction of menin with MLL.

[0007] In some embodiments of a compound provided herein, the compound non-covalently or covalently binds to any one or more isoforms of menin, for example, isoform 1 (SEQ ID NO: 1), isoform 2 (SEQ ID NO: 2) or isoform 3 (SEQ ID NO: 3) of menin. In certain embodiments, the menin protein shares 60% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or 99% or more sequence identity with isoform 1 (SEQ ID NO: 1), isoform 2 (SEQ ID NO: 2) or isoform 3 (SEQ ID NO: 3).

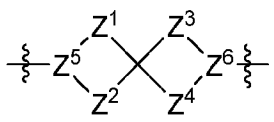
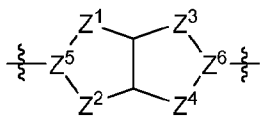
[0008] In one aspect, the present disclosure provides a compound of Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

A is  or  ;

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from -$C(R^{A1})(R^{A2})$-, -$C(R^{A1})(R^{A2})$-$C(R^{A1})(R^{A2})$-, -C(O)-, and -$C(R^{A1})(R^{A2})$-C(O)-, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or -$C(R^{A1})(R^{A2})$-C(O)-;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1, L^2, and L^3 is independently selected from bond, -O-, -S-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -$C(O)N(R^{51})$-, -$C(O)N(R^{51})C(O)$-, -$C(O)N(R^{51})C(O)N(R^{51})$-, -$N(R^{51})C(O)$-, -$N(R^{51})C(O)N(R^{51})$-, -$N(R^{51})C(O)O$-, -$OC(O)N(R^{51})$-, -$C(NR^{51})$-, -$N(R^{51})C(NR^{51})$-, -$C(NR^{51})N(R^{51})$-, -$N(R^{51})C(NR^{51})N(R^{51})$-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)$-, -$S(O)N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, and -$N(R^{51})S(O)N(R^{51})$- or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2, or L^3 can together optionally form a bridge or ring;

R^{50} is, at each occurrence, independently selected from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, -$P(O)(OR^{52})(R^{52})$, -$P(O)(NR^{52})(R^{52})$, -$NR^{52}P(O)(R^{52})$, -$P(O)(NR^{52})(OR^{52})$, -$P(O)(NR^{52})_2$, =O, =S, =$N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, -$P(O)(OR^{52})(R^{52})$, -$P(O)(NR^{52})(R^{52})$, -$NR^{52}P(O)(R^{52})$, -$P(O)(NR^{52})(OR^{52})$, -$P(O)(NR^{52})_2$, =O, =S, =$N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20}

alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

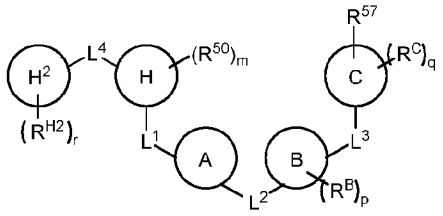
R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

each of R^H and R^B is, at each occurrence, independently selected from R^{50}, or two R^H groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^C is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring; and

each of m, p, and q is independently an integer from 0 to 12.

[0009] In one aspect, the present disclosure provides a compound of Formula (I-G):

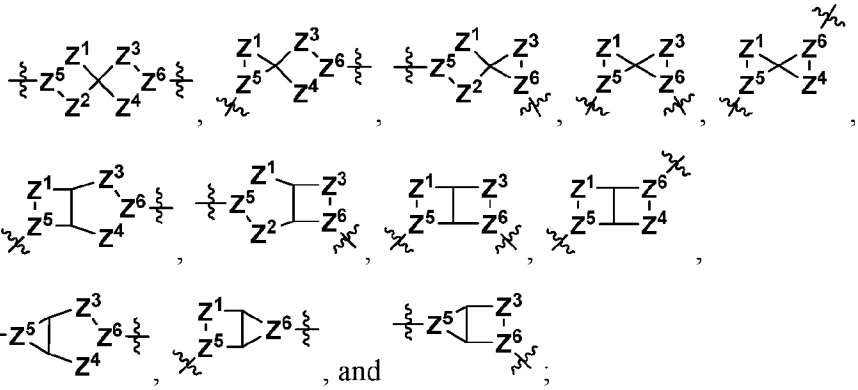


(I-G);

or a pharmaceutically acceptable salt, isotopic form, or prodrug thereof, wherein:

H is selected from C_{5-6} carbocycle and 5- to 6-membered heterocycle;

H^2 is selected from C_{5-6} carbocycle and 5- to 6-membered heterocycle;

A is selected from  ;

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-, -C(O)-, and -C(R^{A1})(R^{A2})-C(O)-, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or -C(R^{A1})(R^{A2})-C(O)-;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1, L^2, L^3 and L^4 is independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2$O-, -N(R^{51})$S(O)_2$-, -$S(O)_2$N(R^{51})-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2$N(R^{51})-, and -N(R^{51})S(O)N(R^{51})- or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2, or L^3 can together optionally form a bridge or ring;

R^{50} is, at each occurrence, independently selected from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2$N(R^{52})$_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, -

$NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, -

$OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

R^{B} is, at each occurrence, independently selected from R^{50}, or two R^{B} groups attached to the same atom or different atoms can together optionally form a bridge or ring;

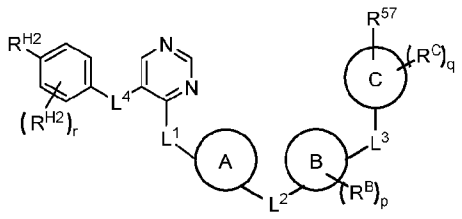
R^{H2} is independently selected at each occurrence from R^{50}, or two R^{H2} groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^{C} is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^{C} groups attached to the same atom or different atoms can together optionally form a bridge or ring;

r is an integer from 1 to 6; and

each of m, p and q is independently an integer from 0 to 12.

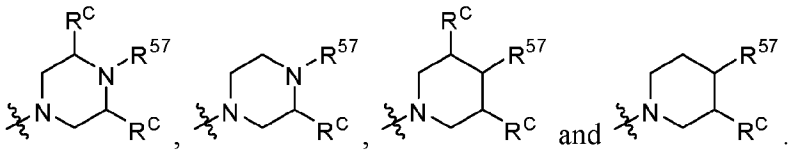
[0010] In some embodiments, the compound of Formula (I-G) is represented by Formula (I-I):



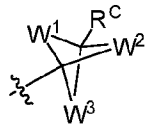
(I-I). In some embodiments, for a compound of Formula (I-G) or (I-I), L^4 is selected from -O-, -S-, -NH- and $-CH_2-$, such as L^4 is selected from -O- and -NH-. In some embodiments, R^{H2} is selected from halo, $-C(O)R^{52}$, and $-C(O)N(R^{52})_2$, optionally wherein R^{52} is selected from hydrogen and C_{1-10} alkyl.

[0011] In some embodiments is a compound of Formula (I), wherein C is a C_{3-12} carbocycle or 3- to 12-membered heterocycle. In some embodiments is a compound of Formula (I), wherein C is a 5- to 12-membered heterocycle, wherein the heterocycle comprises at least one nitrogen atom. In some embodiments is a compound of Formula (I), wherein C is aromatic. In some embodiments is a compound of Formula (I), wherein C is saturated. In some embodiments is a compound of Formula (I), wherein C is selected from piperidinyl, piperazinyl, and morpholinyl.

[0012] In some embodiments is a compound of Formula (I), wherein C is selected from

 . In some embodiments is a compound of Formula (I), wherein R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments is a compound of Formula (I), wherein R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$. In some embodiments is a compound of Formula (I), wherein R^C is selected from C_{1-3} alkyl and C_{1-3} haloalkyl. In some embodiments is a compound of Formula (I), wherein R^C is selected from halogen, $-N(R^{52})_2$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, =O, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, C_{1-3} alkyl, and C_{1-3} haloalkyl, or two R^C groups attached to different atoms can together form a C_{1-3} bridge.

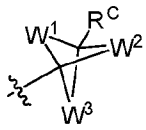
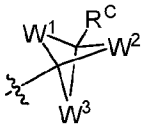
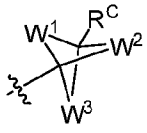
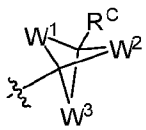
[0013] In some embodiments is a compound of Formula (I), wherein

C is  ;

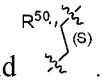
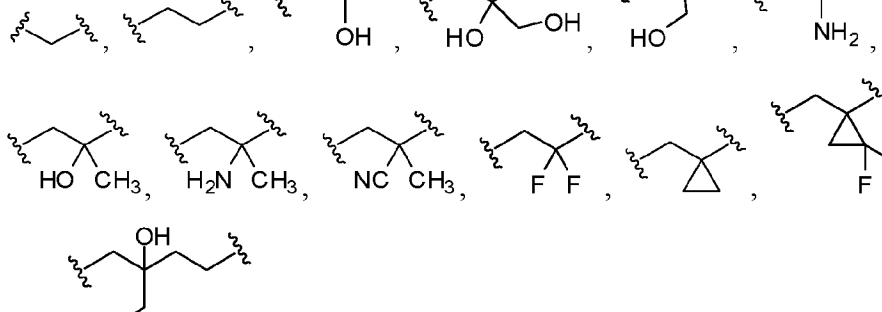
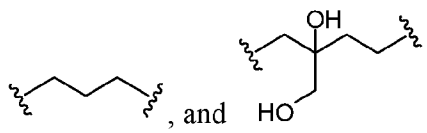
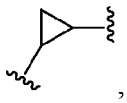
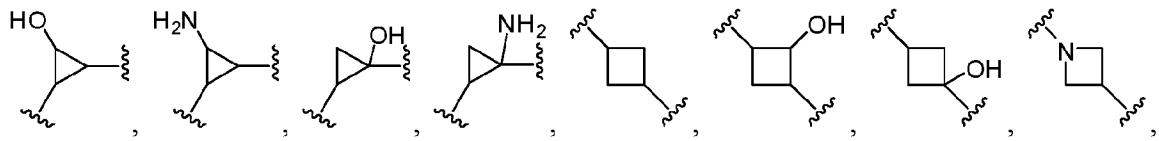
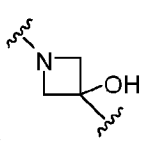
W^1 is C_{1-4} alkylene, optionally substituted with one or more R^{50};

W^2 is selected from a bond; and C_{1-4} alkylene, optionally substituted with one or more R^{50}; and

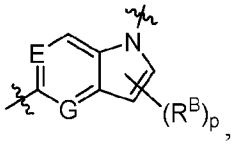
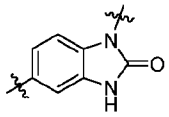
W^3 is selected from absent; and C_{1-4} alkylene, optionally substituted with one or more R^{50}.

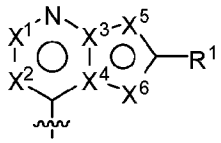
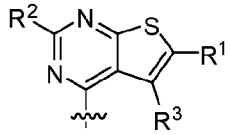
[0014] In some embodiments is a compound of Formula (I), wherein C is  and W^1, W^2, and W^3 are each independently selected from C_{1-4} alkylene, wherein each C_{1-4} alkylene is optionally substituted with one or more R^{50}. In some embodiments is a compound of Formula (I), wherein C is  and W^1, W^2, and W^3 are each C_1 alkylene. In some embodiments is a compound of Formula (I), wherein C is  and W^1 and W^2 are each C_1 alkylene and W^3 is absent. In some embodiments is a compound of Formula (I), wherein C is  and R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, -

$NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, and $-C(O)NR^{53}R^{54}$.

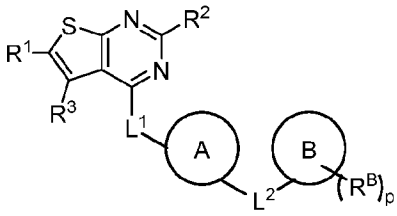
[0015] In some embodiments is a compound of Formula (I), wherein L^3 comprises less than 20 atoms. In some embodiments is a compound of Formula (I), wherein L^3 is not a bond. In some embodiments is a compound of Formula (I), wherein L^3 is C_{1-6} alkylene optionally substituted with one or more R^{50}. In some embodiments is a compound of Formula (I), wherein L^3 is C_2 alkylene substituted with at least one C_{1-3} alkyl or C_{1-3} haloalkyl, and optionally further substituted with one or more R^{50}. In some embodiments is a compound of Formula (I), wherein L^3 is substituted with =O, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-3} alkyl(cyclopropyl), C_{1-3} alkyl($NR^{52}C(O)R^{52}$) or -O(C_{1-6} alkyl). In some embodiments is a compound of Formula (I), wherein L^3 is substituted with $-CH_3$. In some embodiments is a compound of Formula (I), wherein L^3 is selected from  and  . In some embodiments is a compound of Formula (I), wherein R^{50} is methyl. In some embodiments is a compound of Formula (I), wherein L^3 is selected from  , and  , wherein any one of which is optionally substituted with one or more R^{50}. In some embodiments is a compound of Formula (I), wherein R^{50} is methyl. In some embodiments is a compound of Formula (I), wherein L^3 is selected from  ,  , and  , wherein any one of which is optionally substituted with one or more R^{50}.

[0016] In some embodiments is a compound of Formula (I), wherein H is 5- to 12-membered heterocycle and B is 5- to 12-membered heterocycle or C_{4-8} carbocycle. In some embodiments is a compound of Formula (I), wherein B is 6- to 12-membered bicyclic heterocycle. In some embodiments is a compound of Formula (I), wherein B is 6- to 12-membered bicyclic

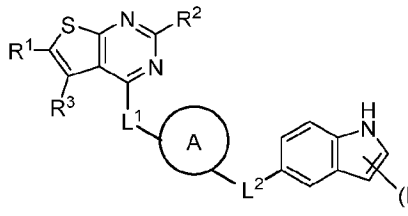
heterocycle and comprises at least one nitrogen atom. In some embodiments is a compound of Formula (I), wherein B is  , wherein each of E and G is independently N or C. In some embodiments is a compound of Formula (I), wherein B is phenylene or  . In some embodiments is a compound of Formula (I), wherein R^B is selected from halogen, methyl, -CN, $-OR^{52}$, and $-N(R^{52})_2$. In some embodiments is a compound of Formula (I), wherein H is 6-membered to 12-membered bicyclic heterocycle.

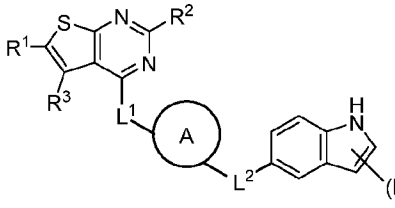
[0017] In some embodiments is a compound of Formula (I), wherein H is  ; X^1 and X^2 are each independently selected from CR^2 and N; X^3 and X^4 are each independently selected from C and N; each of X^5 and X^6 is independently selected from CR^3, N, NR^4, O, and S; R^1, R^2 and R^3 are each independently selected at each occurrence from hydrogen and R^{50}; and R^4 is selected from R^{51}. In some embodiments is a compound of Formula (I), wherein X^3 and X^4 are each C. In some embodiments is a compound of Formula (I), wherein X^6 is CR^3, and R^3 is selected from hydrogen, halogen, $-OR^{52}$, $-N(R^{52})_2$, -CN, $-C(O)OR^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments is a compound of Formula (I), wherein H is  and R^1, R^2 and R^3 are each independently selected at each occurrence from hydrogen and R^{50}. In some embodiments is a compound of Formula (I), wherein R^2 is selected from hydrogen, halogen, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

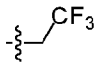
[0018] In some embodiments is a compound of Formula (I) having the structure:

 ; wherein each of R^1, R^2 and R^3 is independently selected at each occurrence from hydrogen and R^{50}.

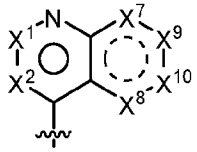
[0019] In some embodiments is a compound of Formula (I) having the structure:

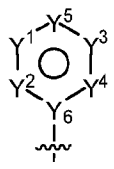

; wherein each of R^1, R^2 and R^3 is independently selected at each occurrence from hydrogen and R^{50}. In some embodiments is a compound of Formula (I) having the structure:


; wherein R^2 is selected from halogen, -OR^{52}, -NH_2, -$N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

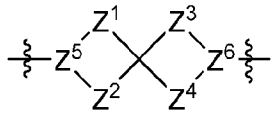
[0020] In some embodiments is a compound of Formula (I), wherein R^3 is selected from hydrogen, halogen, -OR^{52}, -$N(R^{52})_2$, -CN, -C(O)OR^{52}, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments is a compound of Formula (I), wherein R^1 is C_{1-3} haloalkyl. In some embodiments is a compound of Formula (I), wherein R^1 is  .

[0021] In some embodiments is a compound of Formula (I), wherein H is thienopyrimidinyl or thienopyridinyl. In some embodiments is a compound of Formula (I), wherein H is

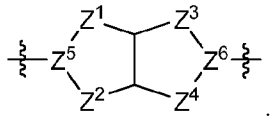

; each of X^1 and X^2 is independently CR^2 or N; each of X^7, X^8, X^9, and X^{10} is independently CR^{16}, $CR^{17}R^{18}$, N, NR^{19}, O, or S; each of R^{16}, R^{17}, and R^{18} is independently selected at each occurrence from hydrogen and R^{50}; and R^{19} is selected from R^{51}. In some embodiments is a compound of Formula (I), wherein X^1 is CR^2, and R^2 is selected from hydrogen, halogen, -OH, -OR^{52}, -NH_2, -$N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments is a compound of Formula (I), wherein X^2 is N. In some embodiments is a compound of Formula (I), wherein H is


; each of Y^1, Y^2, and Y^4 is independently CR^2, N, NR^{21}, O, or S; Y^5 is CR^{20}, N, NR^{21}, O, or S; Y^6 is C or N; Y^3 is a bond, CR^{22}, or N, wherein when Y^3 is CR^{22} or N, then each of Y^1, Y^2, and Y^4 is independently CR^2, N, or NR^{21} and Y^5 is CR^{20}, N, or NR^{21}; each of R^2 and R^{20} is independently selected at each occurrence from hydrogen and R^{50}; and R^{21} is selected from R^{51}.

[0022] In some embodiments is a compound of Formula (I), wherein A is is



. In some embodiments is a compound of Formula (I), wherein A is is

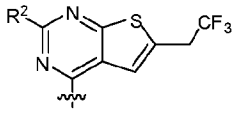


. In some embodiments is a compound of Formula (I), wherein Z^5 and Z^6 are N. In some embodiments is a compound of Formula (I), wherein R^{A2} is, at each occurrence, independently selected from hydrogen, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, -CN, $-NO_2$, and -OH.

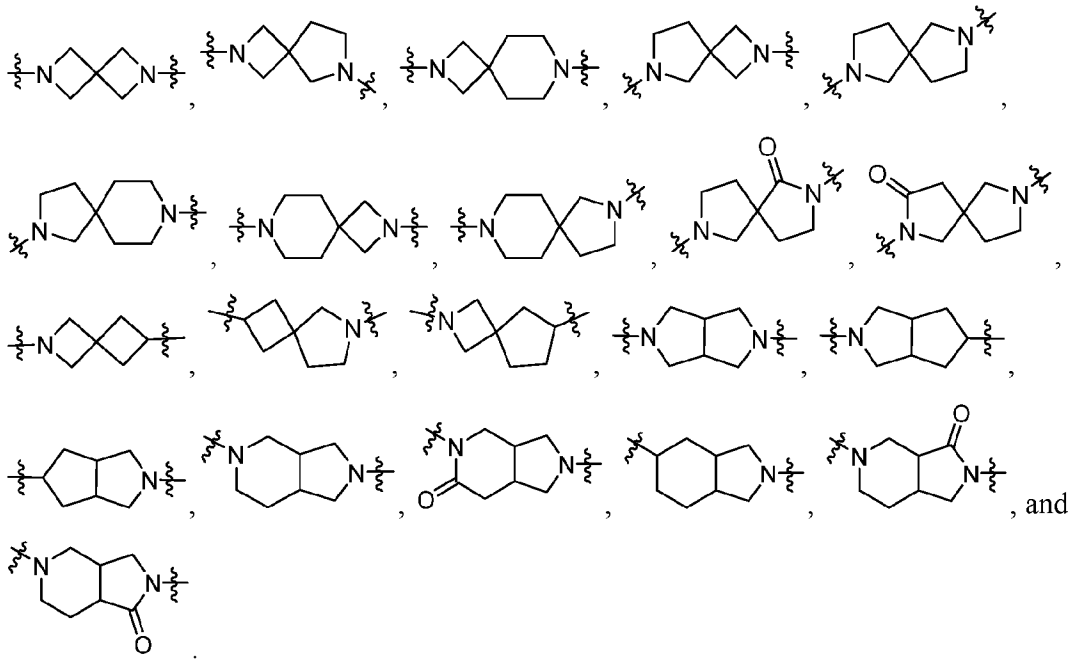
[0023] In some embodiments is a compound of Formula (I), wherein L^1 is a bond or $-N(R^{51})-$. In some embodiments is a compound of Formula (I), wherein L^1 is not a bond. In some embodiments is a compound of Formula (I), wherein L^1 is -NH-. In some embodiments is a compound of Formula (I), wherein L^2 is not a bond. In some embodiments is a compound of Formula (I), wherein L^2 is alkylene or heteroalkylene, each of which is optionally substituted with one or more R^{50}. In some embodiments is a compound of Formula (I), wherein L^2 is C_{1-4} alkylene, optionally substituted with one or more R^{50}. In some embodiments is a compound of Formula (I), wherein L^2 is substituted with =O. In some embodiments is a compound of Formula (I), wherein L^2 is $-CH_2-$, $-N(R^{51})-$, $-N(R^{51})CH_2-$, $-N(R^{51})C(O)-$, and $-N(R^{51})S(O)_2-$. In some embodiments is a compound of Formula (I), wherein L^2 is $-CH_2-$.

[0024] In some embodiments is a compound of Formula (I), wherein H is 5- to 12-membered heterocycle; B is indolylene; and C is 5- to 6-membered heterocycle. In some embodiments is a compound of Formula (I), wherein H is thienopyrimidinyl or thienopyridinyl; B is indolylene; and C is piperidinyl, piperazinyl, or morpholinyl. In some embodiments is a compound of Formula (I), wherein H is thienopyrimidinyl or thienopyridinyl; B is indolylene; and L^1, L^2, and L^3 are not bonds. In some embodiments is a compound of Formula (I), wherein H is thienopyrimidinyl or thienopyridinyl; B is indolylene; and C is piperidinyl, piperazinyl, or morpholinyl. In some embodiments is a compound of Formula (I), wherein H is thienopyrimidinyl or thienopyridinyl; B is 6- to 12-membered bicyclic heterocycle; m is an integer from 0 to 3; and p is an integer from 0 to 3. In some embodiments is a compound of Formula (I), wherein H is thienopyrimidinyl; B is indolylene; L^1 and L^2 are each independently selected from -O-, -S-, -NH-, and $-CH_2-$; L^3 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_{2-}$, -OS(O)-, -

S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)$-, -$S(O)N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, -$N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of L^3 can together optionally form a ring; R^B and R^C are each independently selected at each occurrence from R^{50}, or two R^B groups or two R^C groups attached to the same atom or different atoms can together optionally form a ring; m is an integer from 0 to 3; p is an integer from 0 to 6; and q is an integer from 0 to 6. In some embodiments is a compound of Formula (I), wherein H is thienopyrimidinyl; B is indolylene; L^1 and L^2 are each independently selected from -O-, -S-, -NH-, and -CH_2-; L^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene, each of which is optionally substituted with one or more R^{50}; R^B and R^C are each independently selected at each occurrence from R^{50}, or two R^B groups or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring; m is an integer from 0 to 3; p is an integer from 0 to 3; and q is an integer from 0 to 6.

[0025] In some embodiments is a compound of Formula (I), wherein H is  and R^2 is selected from hydrogen, halogen, -OH, -OR^{52}, -NH_2, -$N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments is a compound of Formula (I), wherein R^2 is selected from -NH_2, -CH_3, and -$NHCH_3$.

[0026] In some embodiments is a compound of Formula (I), wherein A is selected from:



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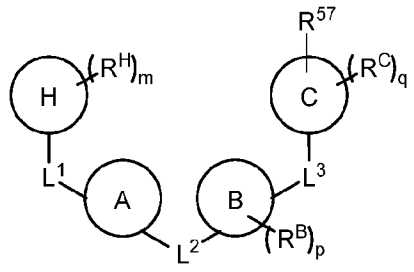
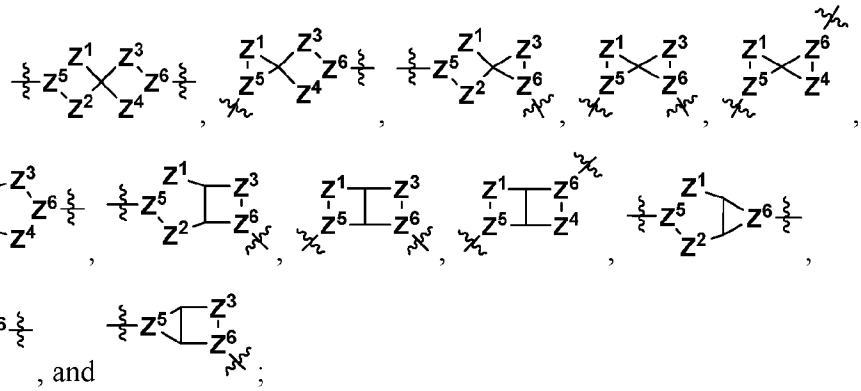
[0027] In one aspect, the present disclosure provides a compound of Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

A is selected from  ;

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-, -C(O)-, and -C(R^{A1})(R^{A2})-C(O)-, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or -C(R^{A1})(R^{A2})-C(O)-;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1, L^2, and L^3 is independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2$O-, -N(R^{51})$S(O)_2$-, -$S(O)_2$N(R^{51})-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2$N(R^{51})-, and -N(R^{51})S(O)N(R^{51})- or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2, or L^3 can together optionally form a bridge or ring;

R^{50} is, at each occurrence, independently selected from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2$N(R^{52})$_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, -

$NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, -

$OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

each of R^H and R^B is, at each occurrence, independently selected from R^{50}, or two R^H groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^C is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring; and

each of m, p, and q is independently an integer from 0 to 12.

[0028] In some embodiments is a compound of Formula (I), wherein the compound is provided as a substantially pure stereoisomer. In some embodiments is a compound of Formula (I), wherein the stereoisomer is provided in at least 90% enantiomeric excess.

[0029] In certain aspects, the present disclosure provides a pharmaceutical composition comprising a compound or salt of Formula (I) and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In some embodiments, the pharmaceutical composition is formulated for injection.

[0030] In certain aspects, the present disclosure provides a method of treating cancer in a subject, comprising administering to the subject in need thereof an effective amount of a compound or salt of Formula (I). In some embodiments, the present disclosure provides a method of treating a hematological cancer, comprising administering to a subject in need thereof an effective amount of a compound or salt of Formula (I). In some embodiments, the present disclosure provides a method of treating a hematological cancer in a subject exhibiting a mutation in the nucleophosmin (NPM1) gene, DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, FMS-like tyrosine kinase-3 (FLT3) gene, isocitrate dehydrogenase 1 (IDH1) gene, isocitrate dehydrogenase 2 (IDH2) gene, or combination thereof, comprising administering to the subject a therapeutically effective amount of a compound or salt of Formula (I). In some embodiments, the present disclosure provides a method of treating a hematological cancer in a

subject in need thereof, comprising: (a) determining the presence or absence of one or more of an NPM1 mutation, DNMT3A mutation, FLT3 mutation, IDH1 mutation, or IDH2 mutation in a biological sample isolated from the subject; and (b) if the one or more of the NPM1 mutation, DNMT3A mutation, FLT3 mutation, IDH1 mutation, or IDH2 mutation is determined to be present in the subject, administering to the subject a therapeutically effective amount of a compound or salt of Formula (I). In some embodiments, the present disclosure provides a method of treating a hematological cancer in a subject, comprising administering to the subject in need thereof an effective amount of a compound or salt of Formula (I) wherein the hematological cancer is leukemia. In some embodiments, the present disclosure provides a method of treating a hematological cancer in a subject, comprising administering to the subject in need thereof an effective amount of a compound or salt of Formula (I) wherein the hematological cancer is lymphoma. In some embodiments, the present disclosure provides a method of treating a hematological cancer in a subject, comprising administering to the subject in need thereof an effective amount of a compound or salt of Formula (I) wherein the hematological cancer is mixed lineage leukemia (MLL), MLL-related leukemia, MLL-associated leukemia, MLL-positive leukemia, MLL-induced leukemia, rearranged mixed lineage leukemia (MLL- r), leukemia associated with a MLL rearrangement or a rearrangement of the MLL gene, acute leukemia, chronic leukemia, indolent leukemia, lymphoblastic leukemia, lymphocytic leukemia, myeloid leukemia, myelogenous leukemia, childhood leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute granulocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myeloproliferative disease (MPD), myeloproliferative neoplasia (MPN), plasma cell neoplasm, multiple myeloma, myelodysplasia, cutaneous T-cell lymphoma, lymphoid neoplasm, AIDS-related lymphoma, thymoma, thymic carcinoma, mycosis fungoides, Alibert-Bazin syndrome, granuloma fungoides, Sezary Syndrome, hairy cell leukemia, T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia, meningeal leukemia, leukemic leptomeningitis, leukemic meningitis, multiple myeloma, Hodgkin's lymphoma, non Hodgkin's lymphoma, or Waldenstrom's macroglobulinemia. In some embodiments, the present disclosure provides a method of treating a hematological cancer in a subject, comprising administering to the subject in need thereof an effective amount of a compound or salt of Formula (I) wherein the hematological cancer is selected from a malignant lymphoma, a leukemia, a mature B cell neoplasm, a mature T cell and natural killer (NK) cell neoplasm, a precursor lymphoid neoplasm, Hodgkin lymphoma (HL), a plasma cell tumor, a mast cell tumor, a neoplasm of histiocytes and accessory lymphoid cells, an immunoproliferative disease, a myeloid leukemia, and a

myelodysplastic syndrome (MDS). In some embodiments, the present disclosure provides a method of treating a hematological cancer in a subject, comprising administering to the subject in need thereof an effective amount of a compound or salt of Formula (I) wherein the hematological cancer is selected from acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, multiple myeloma, mixed lineage leukemia and myelodysplastic syndromes. In some embodiments, the present disclosure provides a method of treating a hematological cancer in a subject, comprising administering to the subject in need thereof an effective amount of a compound or salt of Formula (I) wherein the hematological cancer is selected from acute myeloid leukemia.

[0031] In another aspect, the present disclosure provides a method of treating a subject having acute myeloid leukemia or acute lymphoblastic leukemia, comprising: (a) screening the subject for the presence of an MLL rearrangement, a partial tandem duplication of MLL, or elevated MEIS1 expression levels; and (b) administering a compound or salt of Formula (I) to the subject if one or more of the MLL rearrangement, partial tandem duplication of MLL, or elevated MEIS1 expression levels are determined to be present.

[0032] In certain aspects, the present disclosure provides a method of treating insulin resistance, pre-diabetes, diabetes, or risk of diabetes in a subject, comprising administering to the subject in need thereof an effective amount of a compound or salt of Formula (I). In certain aspects, the present disclosure provides a method of treating hyperglycemia in a subject, comprising administering to the subject in need thereof an effective amount of a compound or salt of Formula (I).

[0033] In certain aspects, the present disclosure provides a method of treating a disease or condition associated with MLL fusion proteins, comprising administering to a subject in need thereof an effective amount of a compound or salt of Formula (I).

[0034] In certain aspects, the present disclosure provides a method of treating a disorder mediated by chromosomal rearrangement on chromosome 11q23 in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound or salt of Formula (I). In certain aspects, the present disclosure provides a method of treating a disorder mediated by an interaction between menin and another protein, comprising administering to a subject in need thereof a therapeutically effective amount of a compound or salt of Formula (I). In some embodiments, the subject is a human.

[0035] In certain aspects, the present disclosure provides a method of promoting proliferation of a pancreatic cell, comprising administering a compound or salt of Formula (I). In some embodiments, the present disclosure provides a method of promoting proliferation of a

pancreatic cell, comprising administering a compound or salt of Formula (I), wherein the pancreatic cell is an islet cell. In some embodiments, the present disclosure provides a method of promoting proliferation of a pancreatic cell, comprising administering a compound or salt of Formula (I), wherein the pancreatic cell is a beta cell. In some embodiments, the present disclosure provides a method of promoting proliferation of a pancreatic cell, comprising administering a compound or salt of Formula (I), wherein the pancreatic cell is a beta cell and beta cell proliferation is evidenced by an increase in beta cell production. In some embodiments, the present disclosure provides a method of promoting proliferation of a pancreatic cell, comprising administering a compound or salt of Formula (I), wherein the pancreatic cell is a beta cell and beta cell proliferation is evidenced by an increase in insulin production. In some embodiments, the present disclosure provides a method of promoting proliferation of a pancreatic cell, comprising administering a compound or salt of Formula (I) to a subject. In some embodiments, the present disclosure provides a method of promoting proliferation of a pancreatic cell, comprising administering a compound or salt of Formula (I) to a subject, wherein the subject is human.

[0036] In certain aspects, the present disclosure provides a method of inhibiting an interaction of menin with one or more of MLL1, MLL2, an MLL fusion protein, and an MLL Partial Tandem Duplication, comprising contacting menin with an effective amount of a compound or salt of Formula (I). In certain aspects, the present disclosure provides a method of inhibiting a menin-MLL interaction, comprising contacting menin with an effective amount of a compound or salt of Formula (I), wherein inhibition of the interaction is evidenced by a reduction in expression of an MLL fusion protein target gene. In certain aspects, the present disclosure provides a method of inhibiting a menin-MLL interaction, comprising contacting menin with an effective amount of a compound or salt of Formula (I), wherein inhibition of the interaction is evidenced by a reduction in expression of an MLL fusion protein target gene and the MLL fusion protein target gene is *HOXA9*, *DLX2*, *PBX3*, or *MEIS1*. In certain aspects, the present disclosure provides a method of stabilizing menin, comprising contacting menin with a compound or salt of Formula (I).

[0037] The contacting may comprise contacting a cell that expresses menin. In some embodiments, the method comprises administering a second therapeutic agent. In some embodiments, the contacting takes place *in vivo*. In some embodiments, the contacting takes place *in vitro*.

[0038] In certain aspects, the present disclosure provides a kit comprising a pharmaceutical composition described herein and instructions for using the composition to treat a subject

suffering from a disease or condition mediated by an interaction between menin and another protein.

INCORPORATION BY REFERENCE

[0039] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0041] **FIG. 1** is an amino acid sequence of human menin, isoform 1 (SEQ ID NO: 1).

[0042] **FIG. 2** is an amino acid sequence of human menin, isoform 2 (SEQ ID NO: 2).

[0043] **FIG. 3** is an amino acid sequence of human menin, isoform 3 (SEQ ID NO: 3).

DETAILED DESCRIPTION OF THE INVENTION

[0044] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0045] "MLL fusion protein" refers to a protein with an N-terminal fragment of MLL fused with a partner protein. Non-limiting examples of a partner protein include 11q23, 11q23.3, 11q24, 1p13.1, 1p32 (EPS15), 21q22, 9p13.3, 9p22 (MLLT3/AF9), ABI1, ABI2, ACACA, ACTN4, AFF1/AF4, AFF3/LAF4, AFF4/AF5, AKAP13, AP2A2, ARHGEF12, ARHGEF17, BCL9L, BTBD18, BUD13, C2CD3, CASC5, CASP8AP2, CBL, CEP164, CEP170B, CREBBP, DCP1A, DCPS, EEFSEC/SELB, ELL, EPS15, FLNA, FNBP1, FOXO3, GAS7, GMPS, KIAA1524, LAMC3, LOC100131626, MAML2, ME2, MLLT1/ENL, MLLT10/AF10, MLLT11/AF1Q, MLLT3/AF9, MLLT4/AF6, MLLT6/AF17, MYH11, MYO1F, NA, NEBL, NRIP3, PDS5A, PICALM, PRPF19, PTD, RUNDC3B, SEPT11, SEPT2, SEPT5, SEPT6, SEPT9, SMAP1, TET1, TNRC18, TOP3A, VAV1, and Xq26.3 (CT45A2). MLL fusion proteins may be created through the joining of a gene that codes for an MLL protein and a gene that codes for a partner protein creating a fusion gene. Translation of this fusion gene may result in a single or multiple polypeptides with functional properties derived from each of the original proteins.

[0046] The term "C_{x-y}" or "C_x-C_y" when used in conjunction with a chemical moiety, such as alkyl, alkenyl, or alkynyl is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y} alkyl" refers to substituted or unsubstituted saturated

hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain. The terms "C_{x-y} alkenyl" and "C_{x-y} alkynyl" refer to substituted or unsubstituted straight-chain or branched-chain unsaturated hydrocarbon groups that contain at least one double or triple bond respectively. Unless stated otherwise specifically in the specification, a C_{x-y} alkyl, C_{x-y} alkenyl, or C_{x-y} alkynyl is optionally substituted by one or more substituents such as those substituents described herein.

[0047] "Carbocycle" refers to a saturated, unsaturated or aromatic ring in which each atom of the ring is a carbon atom. Carbocycle may include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. In some embodiments, the carbocycle is an aryl. In some embodiments, the carbocycle is a cycloalkyl. In some embodiments, the carbocycle is a cycloalkenyl. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, are included in the definition of carbocyclic. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, and naphthyl. Unless stated otherwise specifically in the specification, a carbocycle is optionally substituted by one or more substituents such as those substituents described herein.

[0048] "Heterocycle" refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic heterocycle may be selected from saturated, unsaturated, and aromatic rings. The heterocycle may be attached to the rest of the molecule through any atom of the heterocycle, valence permitting, such as a carbon or nitrogen atom of the heterocycle. In some embodiments, the heterocycle is a heteroaryl. In some embodiments, the heterocycle is a heterocycloalkyl. In an exemplary embodiment, a heterocycle, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene.

[0049] "Heteroaryl" refers to a 3- to 12-membered aromatic ring that comprises at least one heteroatom wherein each heteroatom may be independently selected from N, O, and S. As used herein, the heteroaryl ring may be selected from monocyclic or bicyclic and fused or bridged ring systems rings wherein at least one of the rings in the ring system is aromatic, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The heteroatom(s) in the heteroaryl may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule

through any atom of the heteroaryl, valence permitting, such as a carbon or nitrogen atom of the heteroaryl. Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.* thienyl). Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryls as defined above which are optionally substituted by one or more substituents such as those substituents described herein.

[0050] Compounds of the present disclosure also include crystalline and amorphous forms of those compounds, pharmaceutically acceptable salts, and active metabolites of these compounds having the same type of activity, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[0051] The compounds described herein may exhibit their natural isotopic abundance, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number

predominantly found in nature. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^{1}H (protium), ^{2}H (deuterium), and ^{3}H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increased *in vivo* half-life and/or exposure, or may provide a compound useful for investigating *in vivo* routes of drug elimination and metabolism. Isotopically-enriched compounds may be prepared by conventional techniques well known to those skilled in the art.

[0052] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Enantiomers" are a pair of stereoisomers that are non superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" or "diastereomers" are stereoisomers that have at least two asymmetric atoms but are not mirror images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer, the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) in which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms, the asymmetric centers of which can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible stereoisomers, including racemic mixtures, optically pure forms, mixtures of diastereomers and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. The optical activity of a compound can be analyzed via any suitable method, including but not limited to chiral chromatography and polarimetry, and the degree of predominance of one stereoisomer over the other isomer can be determined.

[0053] Chemical entities having carbon-carbon double bonds or carbon-nitrogen double bonds may exist in *Z*- or *E*- form (or *cis*- or *trans*- form). Furthermore, some chemical entities may exist in various tautomeric forms. Unless otherwise specified, chemical entities described herein are intended to include all *Z*-, *E*- and tautomeric forms as well.

[0054] The term "substituted" refers to moieties having substituents replacing a hydrogen on one

or more carbons or heteroatoms of the structure. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, a carbocycle, a heterocycle, a cycloalkyl, a heterocycloalkyl, an aromatic and heteroaromatic moiety. In some embodiments, substituents may include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazino ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, hydroxy, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); wherein each R^a is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, wherein each R^a, valence permitting, may be optionally substituted with alkyl,

alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and wherein each R^b is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each R^c is a straight or branched alkylene, alkenylene or alkynylene chain.

[0055] It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to a "heteroaryl" group or moiety implicitly includes both substituted and unsubstituted variants.

[0056] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0057] The term "salt" or "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0058] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound described herein that is sufficient to affect the intended application, including but

not limited to disease treatment, as defined below. The therapeutically effective amount may vary depending upon the intended treatment application (in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0059] As used herein, "treatment" or "treating" refers to an approach for obtaining beneficial or desired results with respect to a disease, disorder, or medical condition including but not limited to a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. In certain embodiments, for prophylactic benefit, the compositions are administered to a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0060] A "therapeutic effect," as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0061] The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompass administration of two or more agents to an animal, including humans, so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[0062] The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound having the ability to inhibit a biological function (e.g., activity, expression, binding, protein-protein interaction) of a target protein (e.g., menin, MLL1, MLL2, and/or an MLL fusion protein). Accordingly, the terms "antagonist" and "inhibitor" are defined in the context of the

biological role of the target protein. While preferred antagonists herein specifically interact with (e.g., bind to) the target, compounds that inhibit a biological activity of the target protein by interacting with other members of the signal transduction pathway of which the target protein is a member are also specifically included within this definition. A preferred biological activity inhibited by an antagonist is associated with the development, growth, or spread of a tumor.

[0063] The term "agonist" as used herein refers to a compound having the ability to initiate or enhance a biological function of a target protein, whether by inhibiting the activity or expression of the target protein. Accordingly, the term "agonist" is defined in the context of the biological role of the target polypeptide. While preferred agonists herein specifically interact with (e.g., bind to) the target, compounds that initiate or enhance a biological activity of the target polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

[0064] "Signal transduction" is a process during which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response. A modulator of a signal transduction pathway refers to a compound which modulates the activity of one or more cellular proteins mapped to the same specific signal transduction pathway. A modulator may augment (agonist) or suppress (antagonist) the activity of a signaling molecule.

[0065] An "anti-cancer agent", "anti-tumor agent" or "chemotherapeutic agent" refers to any agent useful in the treatment of a neoplastic condition. One class of anti-cancer agents comprises chemotherapeutic agents. "Chemotherapy" means the administration of one or more chemotherapeutic drugs and/or other agents to a cancer patient by various methods, including intravenous, oral, intramuscular, intraperitoneal, intravesical, subcutaneous, transdermal, buccal, or inhalation or in the form of a suppository.

[0066] "Subject" refers to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics and veterinary applications. In some embodiments, the subject is a mammal, and in some embodiments, the subject is human. "Mammal" includes humans and both domestic animals such as laboratory animals and household pets (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

[0067] "Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein (e.g., compound of Formula (I)). Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some aspects, a prodrug is inactive when administered to a subject but is converted in vivo to an active compound, for example, by hydrolysis. The

prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam); Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," (1987) A.C.S. Symposium Series, Vol. 14; and Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press) each of which is incorporated in full by reference herein. The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound in vivo when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, are typically prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of a hydroxy functional group, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like.

[0068] The term "in vivo" refers to an event that takes place in a subject's body.

[0069] The term "in vitro" refers to an event that takes places outside of a subject's body. For example, an *in vitro* assay encompasses any assay run outside of a subject. *In vitro* assays encompass cell-based assays in which cells alive or dead are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

[0070] "Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl group may or may not be substituted and that the description includes both substituted aryl groups and aryl groups having no substitution.

[0071] "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye, colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

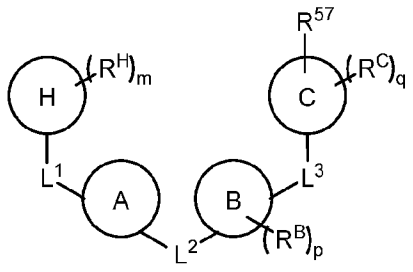
[0072] The present disclosure provides compounds for modulating the interaction of menin with proteins such as MLL1, MLL2 and MLL-fusion oncoproteins. In certain embodiments, the disclosure provides compounds and methods for inhibiting the interaction of menin with its

upstream or downstream signaling molecules including but not limited to MLL1, MLL2 and MLL-fusion oncoproteins. Compounds of the disclosure may be used in methods for the treatment of a wide variety of cancers and other diseases associated with one or more of MLL1, MLL2, MLL fusion proteins, and menin. In certain embodiments, a compound of the disclosure covalently binds menin and inhibits the interaction of menin with MLL. In certain embodiments, a compound of the disclosure interacts non-covalently with menin and inhibits the interaction of menin with MLL.

[0073] Compounds of the disclosure may be used in methods for treating a wide variety of diseases associated with MLL1, MLL2, MLL fusion proteins, and menin. In certain embodiments, a compound of the disclosure interacts non-covalently with menin and inhibits the interaction of menin with MLL. In certain embodiments, a compound of the disclosure covalently binds menin and inhibits the interaction of menin with MLL.

[0074] In some aspects, the present disclosure provides a compound or salt that selectively binds to the menin protein and/or modulates the interaction of menin with an MLL protein (e.g., MLL1, MLL2, or an MLL fusion protein). In certain embodiments, the compound modulates the menin protein by binding to or interacting with one or more amino acids and/or one or more metal ions. Certain compounds may occupy the F9 and/or P13 pocket of menin. The binding of a compound disclosed herein may disrupt menin or MLL (e.g., MLL1, MLL2, or an MLL fusion protein) downstream signaling.

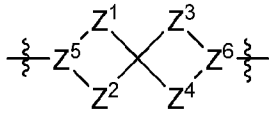
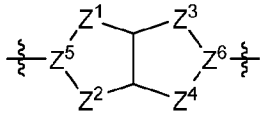
[0075] In certain aspects, the present disclosure provides a compound of Formula (I):



(I);

or a pharmaceutically acceptable salt, isotopic form, or prodrug thereof, wherein:

H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

A is  or  ;

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$, $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$, -C(O)-, and $-C(R^{A1})(R^{A2})-C(O)-$, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or $-C(R^{A1})(R^{A2})-C(O)-$;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1, L^2, and L^3 is independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -N(R^{51})$S(O)_2$-, -$S(O)_2$N(R^{51})-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2$N(R^{51})-, and -N(R^{51})S(O)N(R^{51})- or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2, or L^3 can together optionally form a bridge or ring;

R^{50} is, at each occurrence, independently selected from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -N$R^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2$N(R^{52})$_2$, -$S(=O)_2$N$R^{53}R^{54}$, -N$R^{52}S(=O)_2R^{52}$, -N$R^{52}S(=O)_2$N(R^{52})$_2$, -N$R^{52}S(=O)_2$N$R^{53}R^{54}$, -C(O)R^{52}, -C(O)OR^{52}, -OC(O)R^{52}, -OC(O)OR^{52}, -OC(O)N(R^{52})$_2$, -OC(O)N$R^{53}R^{54}$, -NR^{52}C(O)R^{52}, -NR^{52}C(O)OR^{52}, -NR^{52}C(O)N(R^{52})$_2$, -NR^{52}C(O)N$R^{53}R^{54}$, -C(O)N(R^{52})$_2$, -C(O)N$R^{53}R^{54}$, -P(O)(OR^{52})$_2$, -P(O)(R^{52})$_2$, -P(O)(OR^{52})(R^{52}), -P(O)(NR^{52})(R^{52}), -NR^{52}P(O)(R^{52}), -P(O)(NR^{52})(OR^{52}), -P(O)(NR^{52})$_2$, =O, =S, =N(R^{52});

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -N$R^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2$N(R^{52})$_2$, -$S(=O)_2$N$R^{53}R^{54}$, -N$R^{52}S(=O)_2R^{52}$, -N$R^{52}S(=O)_2$N(R^{52})$_2$, -N$R^{52}S(=O)_2$N$R^{53}R^{54}$, -C(O)R^{52}, -C(O)OR^{52}, -OC(O)R^{52}, -OC(O)OR^{52}, -OC(O)N(R^{52})$_2$, -OC(O)N$R^{53}R^{54}$, -NR^{52}C(O)R^{52}, -NR^{52}C(O)OR^{52}, -NR^{52}C(O)N(R^{52})$_2$, -NR^{52}C(O)N$R^{53}R^{54}$, -C(O)N(R^{52})$_2$, -C(O)N$R^{53}R^{54}$, -P(O)(OR^{52})$_2$, -P(O)(R^{52})$_2$, -P(O)(OR^{52})(R^{52}), -P(O)(NR^{52})(R^{52}), -NR^{52}P(O)(R^{52}), -P(O)(NR^{52})(OR^{52}), -P(O)(NR^{52})$_2$, =O, =S, =N(R^{52}), C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -N$R^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2$N(R^{52})$_2$, -$S(=O)_2$N$R^{53}R^{54}$, -N$R^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form

a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

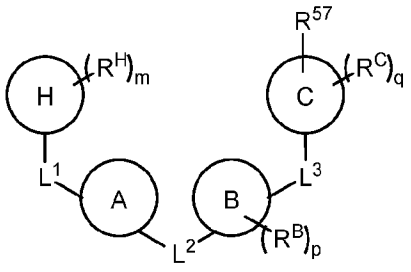
R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

each of R^H and R^B is, at each occurrence, independently selected from R^{50}, or two R^H groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^C is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring; and

each of m, p, and q is independently an integer from 0 to 12.

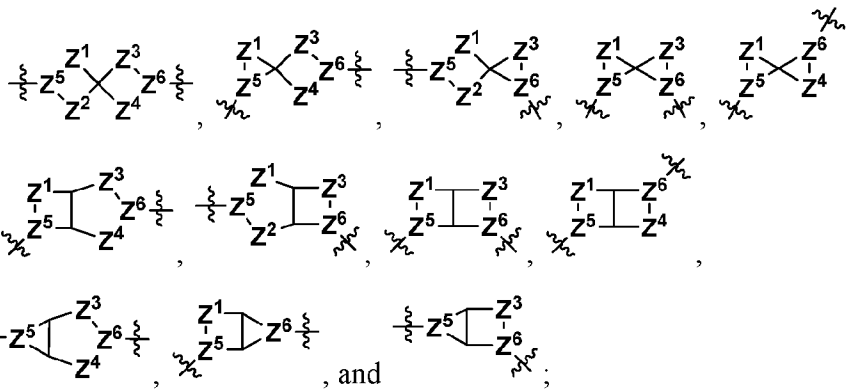
[0076] In certain aspects, the present disclosure provides a compound of Formula (I):



(I);

or a pharmaceutically acceptable salt, isotopic form, or prodrug thereof, wherein:

H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

A is selected from  ;

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-, -C(O)-, and -C(R^{A1})(R^{A2})-C(O)-, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or -C(R^{A1})(R^{A2})-C(O)-;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1, L^2, L^3 and L^4 is independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -N(R^{51})$S(O)_2$-, -$S(O)_2N(R^{51})$-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2N(R^{51})$-, and -N(R^{51})S(O)N(R^{51})- or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2, or L^3 can together optionally form a bridge or ring;

R^{50} is, at each occurrence, independently selected from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, -

$OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, -

$P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, -

$NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

R^B is, at each occurrence, independently selected from R^{50}, or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^H is, at each occurrence, independently selected from R^{50} and $-L^4-H^2-(R^{H2})_r$;

H^2 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

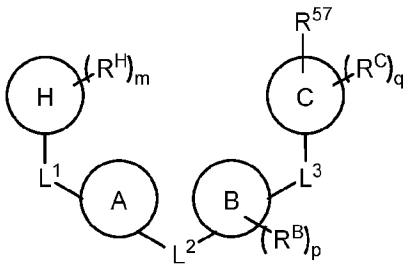
R^{H2} is independently selected at each occurrence from R^{50}, or two R^{H2} groups attached to the same atom or different atoms can together optionally form a bridge or ring;

r is an integer from 1 to 6;

R^C is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring; and

each of m, p, and q is independently an integer from 0 to 12.

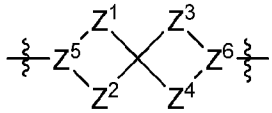
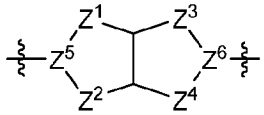
[0077] In certain aspects, the present disclosure provides a compound of Formula (I):



(I);

or a pharmaceutically acceptable salt, isotopic form, or prodrug thereof, wherein:

H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

A is  or  ;

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$, $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$, -C(O)-, and $-C(R^{A1})(R^{A2})-C(O)-$, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or $-C(R^{A1})(R^{A2})-C(O)-$;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1 and L^2 is independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -N(R^{51})$S(O)_2$-, -$S(O)_2$N(R^{51})-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2$N(R^{51})-, and -N(R^{51})S(O)N(R^{51})- or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1 or L^2 can together optionally form a bridge or ring;

L^3 is C_{1-6} alkylene, optionally substituted with one or more R^{50};

R^{50} is, at each occurrence, independently selected from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -N$R^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2$N(R^{52})$_2$, -$S(=O)_2$N$R^{53}R^{54}$, -N$R^{52}S(=O)_2R^{52}$, -N$R^{52}S(=O)_2$N(R^{52})$_2$, -N$R^{52}S(=O)_2$N$R^{53}R^{54}$, -C(O)R^{52}, -C(O)OR^{52}, -OC(O)R^{52}, -OC(O)OR^{52}, -OC(O)N(R^{52})$_2$, -OC(O)N$R^{53}R^{54}$, -NR^{52}C(O)R^{52}, -NR^{52}C(O)OR^{52}, -NR^{52}C(O)N(R^{52})$_2$, -NR^{52}C(O)N$R^{53}R^{54}$, -C(O)N(R^{52})$_2$, -C(O)N$R^{53}R^{54}$, -P(O)(OR^{52})$_2$, -P(O)(R^{52})$_2$, -P(O)(OR^{52})(R^{52}), -P(O)(NR^{52})(R^{52}), -NR^{52}P(O)(R^{52}), -P(O)(NR^{52})(OR^{52}), -P(O)(NR^{52})$_2$, =O, =S, =N(R^{52});

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -N$R^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2$N(R^{52})$_2$, -$S(=O)_2$N$R^{53}R^{54}$, -N$R^{52}S(=O)_2R^{52}$, -N$R^{52}S(=O)_2$N(R^{52})$_2$, -N$R^{52}S(=O)_2$N$R^{53}R^{54}$, -C(O)R^{52}, -C(O)OR^{52}, -OC(O)R^{52}, -OC(O)OR^{52}, -OC(O)N(R^{52})$_2$, -OC(O)N$R^{53}R^{54}$, -NR^{52}C(O)R^{52}, -NR^{52}C(O)OR^{52}, -NR^{52}C(O)N(R^{52})$_2$, -NR^{52}C(O)N$R^{53}R^{54}$, -C(O)N(R^{52})$_2$, -C(O)N$R^{53}R^{54}$, -P(O)(OR^{52})$_2$, -P(O)(R^{52})$_2$, -P(O)(OR^{52})(R^{52}), -P(O)(NR^{52})(R^{52}), -NR^{52}P(O)(R^{52}), -P(O)(NR^{52})(OR^{52}), -P(O)(NR^{52})$_2$, =O, =S, =N(R^{52}), C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -N$R^{53}R^{54}$, -S(=O)R^{52}, -

$S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

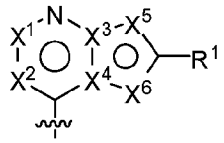
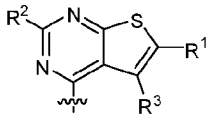
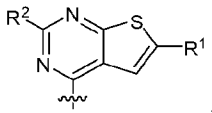
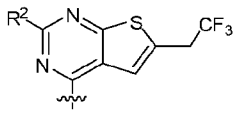
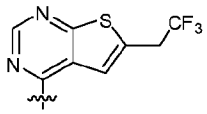
each of R^H and R^B is, at each occurrence, independently selected from R^{50}, or two R^H groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

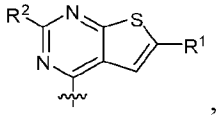
R^C is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring; and

each of m, p, and q is independently an integer from 0 to 12.

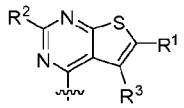
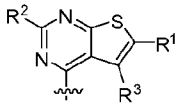
[0078] In some embodiments, for a compound of Formula (I), H is 5- to 12-membered heterocycle, such as 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}. In some embodiments, H contains one or more heteroatoms, such as 1, 2, 3, 4, 5 or 6

ring heteroatoms. In some embodiments, H contains at least 1, 2, 3, 4 or 5 ring nitrogen atoms. In some embodiments, H is thienopyrimidinyl, optionally substituted with one or more R^{50}. In some embodiments, H is substituted with C_{1-4} haloalkyl, such as $-CH_2CF_3$. In some embodiments, H is substituted with one or more R^{50} (e.g., by replacing a hydrogen connected to a ring atom with a bond to R^{50}). H may be substituted with 0, 1, 2, 3, 4, 5, 6 or more R^{50} groups. H may be substituted with 1, 2, 3, 4, 5 or 6 R^{50} groups, such as H substituted with 1 or 2 R^{50} groups. In some embodiments, H is substituted with at least 1, 2, 3, 4, 5 or 6 R^{50} groups. In some embodiments, H is substituted with up to 6, 5, 4, 3, 2 or 1 R^{50} groups.

[0079] In some embodiments, for a compound of Formula (I), H is  , wherein X^1 and X^2 are each independently selected from CR^2 and N; X^3 and X^4 are each independently selected from C and N; X^5 and X^6 are each independently selected from CR^3, N, NR^4, O, and S; R^1, R^2 and R^3 are each independently selected at each occurrence from hydrogen and R^{50}; and R^4 is selected from R^{51}. In some embodiments, X^3 and X^4 are each C. In some embodiments, X^1 is CR^2, and R^2 is selected from hydrogen, halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, and C_{1-2} alkyl. In some embodiments, R^2 is methyl or $-NHCH_3$. In some embodiments, R^2 is H. In some embodiments, X^2 is N. In some embodiments, X^6 is CR^3, and R^3 is selected from hydrogen, halogen, -OH, $-N(R^{52})_2$, -CN, $-C(O)OR^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, X^5 is S. In some embodiments, at least one of X^5 and X^6 is selected from N, NR^4, O and S. In some embodiments, R^1 is C_{1-3} haloalkyl, such as $-CH_2CF_3$. In some embodiments, X^1 is CR^2, X^2 is N, X^3 and X^4 are each C, X^5 is S, X^6 is CR^3, and R^1 is selected from R^{50}. In some embodiments, X^1 is CR^2; X^2 is N; X^3 and X^4 are each C; X^5 is S; X^6 is CH; R^1 is C_{1-3} haloalkyl; and R^2 is selected from hydrogen, halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, H is  . In some embodiments, H is  , such as  or  . In some



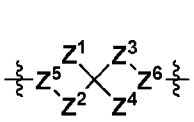
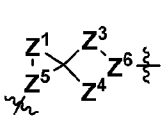
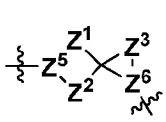
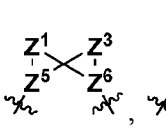
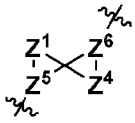
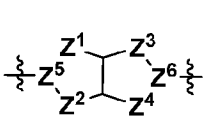
embodiments, H is , and R^2 is selected from hydrogen, halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, R^2 is selected from hydrogen, halogen, -OH, alkoxy (e.g., $-OR^{52}$, $-OCH_3$, $-OCH_2CH_3$), aminoalkyl, alkylamino, $-N(R^{52})_2$ (e.g., $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$), $-N(CH_3)_2$, -CN, C_{1-3} alkyl (e.g., $-CH_3$), cyclopropyl, C_{1-3} alkyl-OR^{52} (e.g., $-CH_2OH$, $-CH_2OC(O)CH_3$), C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

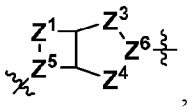
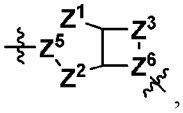
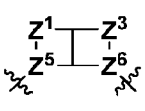
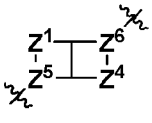
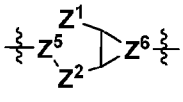
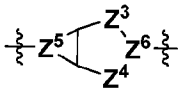
[0080] In some embodiments, for a compound of Formula (I), H is  , wherein R^1 is selected from H, halo, hydroxyl, amino, cyano, dialkylphosphine oxide, oxo, carboxyl, amido, acyl, alkyl, cycloalkyl, heteroalkyl, and haloalkyl; R^2 is selected from hydrogen, halogen, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl; and R^3 is hydrogen or alkyl. In some embodiments, for a compound of Formula (I), H is  , wherein R^1 is cyano; R^2 is selected from $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, and C_{1-3} alkyl; and R^3 is hydrogen.

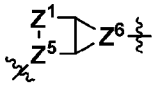
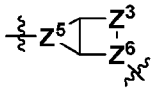
[0081] In some embodiments, for a compound of Formula (I), L^1 is a bond. In some embodiments, for a compound of Formula (I), L^1 is not a bond. In some embodiments, for a compound of Formula (I), L^1 comprises less than 20 atoms, such as less than 10 atoms. In some embodiments, L^1 comprises less than 20, 15, 10, 9, 8, 7, 6, 5, 4, or less than 3 atoms. In some embodiments, L^1 comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15 or at least 20 atoms. In some embodiments, L^1 comprises at least one heteroatom, such as L^1 comprises at least one nitrogen. In some embodiments, L^1 is substituted with one or more R^{50}. In some embodiments, L^1 is unsubstituted. In some embodiments, L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-S(O)_2-$, -S(O)-, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, alkylene, alkenylene, heteroalkylene, and heteroalkenylene. In some embodiments, L^1 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, $-C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-S(O)_2-$, -S(O)-, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, C_{1-6} alkylene and C_{2-6} alkenylene, wherein the C_{1-6} alkylene and C_{2-6} alkenylene are each optionally substituted with one or more R^{50}. In some embodiments, L^1 is $-N(R^{51})-$, such as -NH-. In some embodiments, L^1 is selected from -O-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, $-C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})S(O)_2-$,

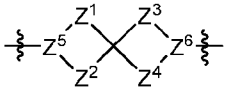
$-S(O)_2N(R^{51})-$, C_{1-4} alkylene, C_{2-4} alkenylene, and C_{1-4} heteroalkylene. In some embodiments, L^1 is $-N(R^{51})-$, wherein R^{51} is selected from hydrogen and alkyl.

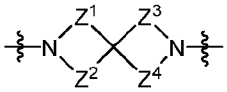
[0082] In some embodiments, for a compound of Formula (I), A is selected from

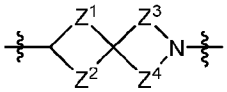
 ,  ,  ,  ,  ,  ,

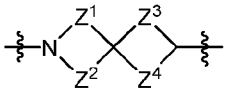
 ,  ,  ,  ,  ,  ,

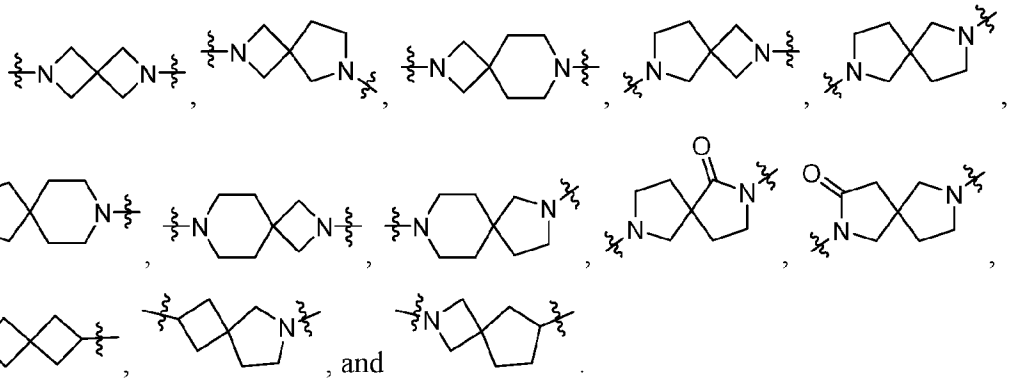
 , and  . In some embodiments, for a compound of Formula (I), A is

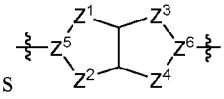
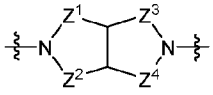
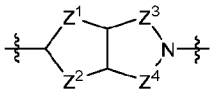
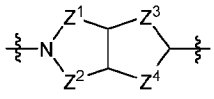
 . In some embodiments, for a compound of Formula (I), A is

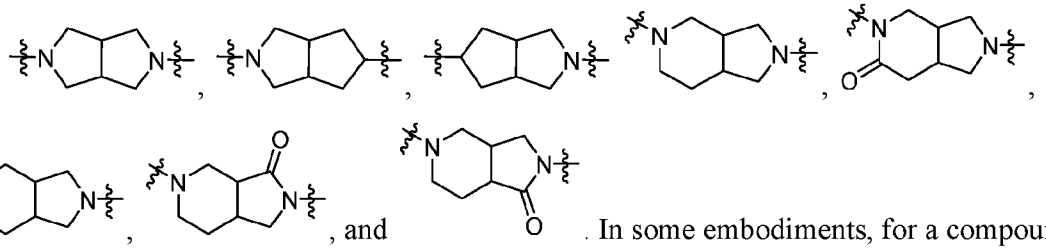
 . In some embodiments, for a compound of Formula (I), A is

 . In some embodiments, for a compound of Formula (I), A is

 . In some embodiments, for a compound of Formula (I), and each of Z^1, Z^2, Z^3, and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$, and $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$. In some embodiments, for a compound of Formula (I), and each of Z^1, Z^2, Z^3, and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$. In some embodiments, for a compound of Formula (I), and Z^1 is $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$ and each of Z^2, Z^3, and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$, and $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$. In some embodiments, for a compound of Formula (I), and each of Z^1 and Z^2 is $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$ and each of Z^3 and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$, and $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$. In some embodiments, for a compound of Formula (I), and Z^3 is $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$ and each of Z^1, Z^2, and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$, and $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$. In some embodiments, for a compound of Formula (I), and each of Z^3 and Z^4 is $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$ and each of Z^1 and Z^2 is independently selected from $-C(R^{A1})(R^{A2})-$, and $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$. In some embodiments, for a compound of Formula (I), Z^1 is $-C(O)-$ and each of Z^2, Z^3, and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$, and $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$. In some embodiments, for a compound of Formula (I), Z^3 is -

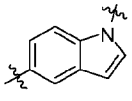
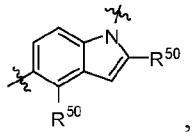
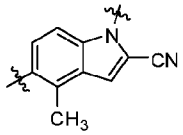
C(O)- and each of Z^1, Z^2, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, and -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-. In some embodiments, for a compound of Formula (I), Z^1 is -C(R^{A1})(R^{A2})-C(O)- and each of Z^2, Z^3, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, and -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-. In some embodiments, for a compound of Formula (I), Z^3 is -C(R^{A1})(R^{A2})-C(O)- and each of Z^1, Z^2, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, and -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-. In some embodiments, for a compound of Formula (I), R^{A1} is, at each occurrence, hydrogen. In some embodiments, for a compound of Formula (I), R^{A2} is, at each occurrence, hydrogen. In some embodiments, for a compound of Formula (I), A is selected from  , and .

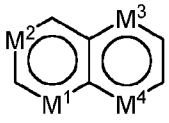
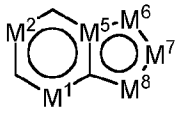
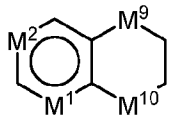
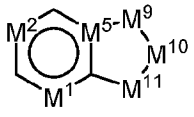
In some embodiments, for a compound of Formula (I), A is  . In some embodiments, for a compound of Formula (I), A is  . In some embodiments, for a compound of Formula (I), A is  . In some embodiments, for a compound of Formula (I), A is  . In some embodiments, for a compound of Formula (I), and each of Z^1, Z^2, Z^3, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, and -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-. In some embodiments, for a compound of Formula (I), and each of Z^1, Z^2, Z^3, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-. In some embodiments, for a compound of Formula (I), and Z^1 is -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})- and each of Z^2, Z^3, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, and -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-. In some embodiments, for a compound of Formula (I), and each of Z^1 and Z^2 is -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})- and each of Z^3 and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, and -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-. In some embodiments, for a compound of Formula (I), and Z^3 is -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})- and each of Z^1, Z^2, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, and -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-. In some embodiments, for a compound of Formula (I), and each of Z^3 and Z^4 is -C(R^{A1})(R^{A2})-

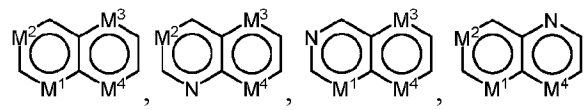
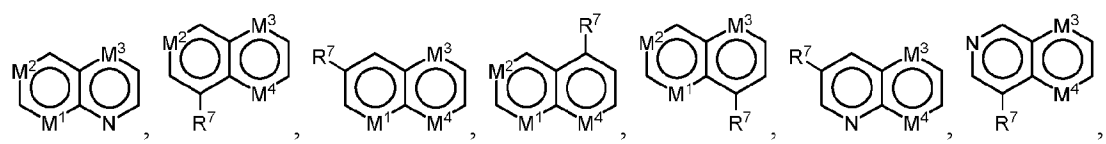
$C(R^{A1})(R^{A2})$- and each of Z^1 and Z^2 is independently selected from -$C(R^{A1})(R^{A2})$-, and -$C(R^{A1})(R^{A2})$-$C(R^{A1})(R^{A2})$-. In some embodiments, for a compound of Formula (I), Z^1 is -C(O)- and each of Z^2, Z^3, and Z^4 is independently selected from -$C(R^{A1})(R^{A2})$-, and -$C(R^{A1})(R^{A2})$-$C(R^{A1})(R^{A2})$-. In some embodiments, for a compound of Formula (I), Z^3 is -C(O)- and each of Z^1, Z^2, and Z^4 is independently selected from -$C(R^{A1})(R^{A2})$-, and -$C(R^{A1})(R^{A2})$-$C(R^{A1})(R^{A2})$-. In some embodiments, for a compound of Formula (I), Z^1 is -$C(R^{A1})(R^{A2})$-C(O)- and each of Z^2, Z^3, and Z^4 is independently selected from -$C(R^{A1})(R^{A2})$-, and -$C(R^{A1})(R^{A2})$-$C(R^{A1})(R^{A2})$-. In some embodiments, for a compound of Formula (I), Z^3 is -$C(R^{A1})(R^{A2})$-C(O)- and each of Z^1, Z^2, and Z^4 is independently selected from -$C(R^{A1})(R^{A2})$-, and -$C(R^{A1})(R^{A2})$-$C(R^{A1})(R^{A2})$-. In some embodiments, for a compound of Formula (I), R^{A1} is, at each occurrence, hydrogen. In some embodiments, for a compound of Formula (I), R^{A2} is, at each occurrence, hydrogen. In some embodiments, for a compound of Formula (I), A is selected from  , and . In some embodiments, for a compound of Formula (I), Z^2 is absent. In some embodiments, Z^3 is absent. In some embodiments, Z^2 and Z^3 are absent.

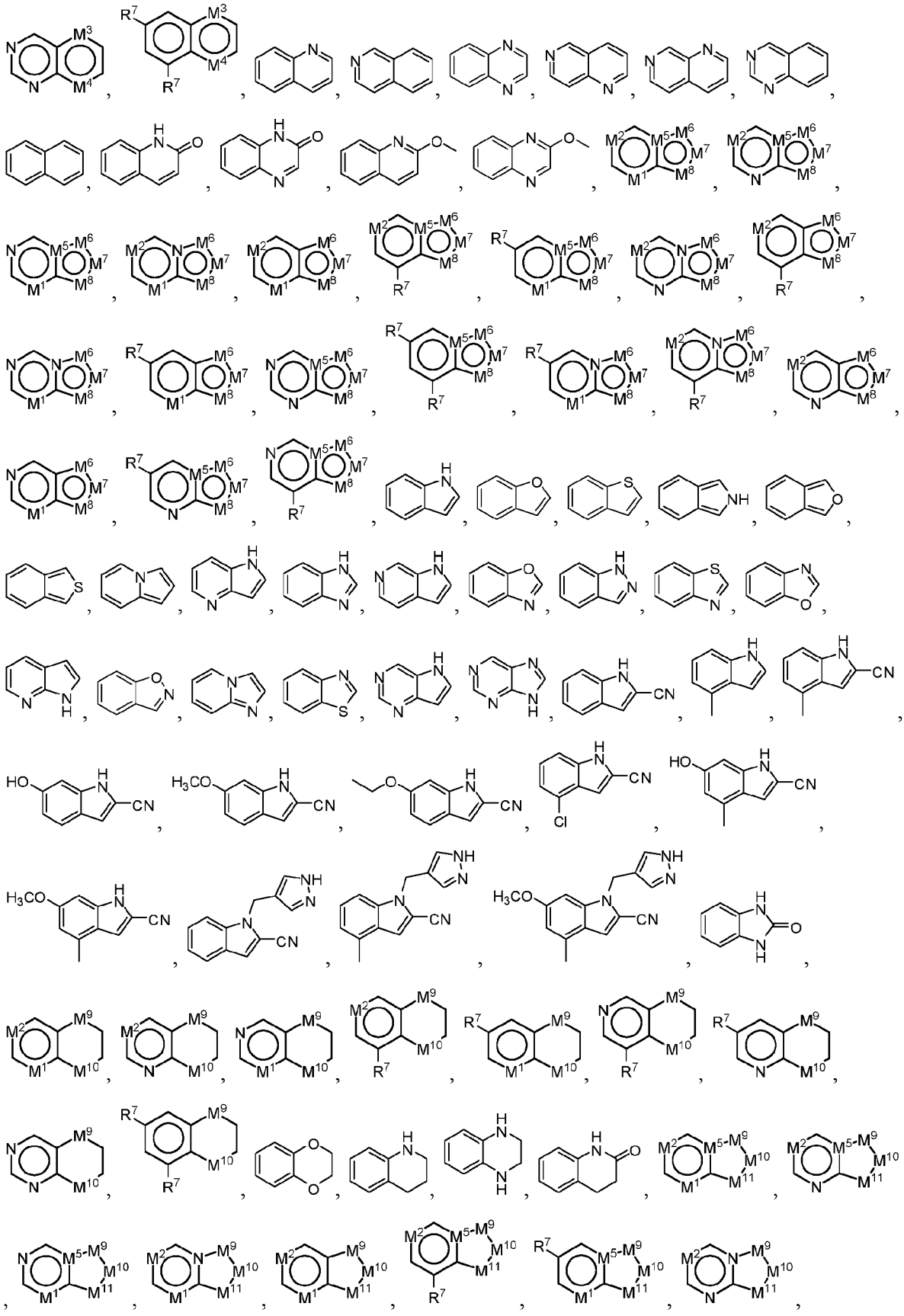
[0083] In some embodiments, for a compound of Formula (I), L^2 is a bond. In some embodiments, for a compound of Formula (I), L^2 is not a bond. In some embodiments, for a compound of Formula (I), L^2 comprises less than 20 atoms, such as less than 10 atoms. In some embodiments, L^2 comprises less than 20, 15, 10, 9, 8, 7, 6, 5, 4, or less than 3 atoms. In some embodiments, L^2 comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15 or at least 20 atoms. In some embodiments, L^2 comprises at least one heteroatom, such as L^2 comprises at least one nitrogen. In some embodiments, L^2 is C_{1-10} alkylene, such as C_{1-4} alkylene, optionally substituted with one or more R^{50}. In some embodiments, L^2 is substituted with one or more R^{50}. In some embodiments, L^2 is unsubstituted. In some embodiments, L^2 is selected from bond, -O-, -S-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)$N(R^{51})$-, -$N(R^{51})$C(O)-, -$N(R^{51})$C(O)$N(R^{51})$-, -$S(O)_2$-, -S(O)-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, alkylene, alkenylene, heteroalkylene, and heteroalkenylene. In some embodiments, L^2 is selected from bond, -O-, -S-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)$N(R^{51})$-, -$N(R^{51})$C(O)-, -$N(R^{51})$C(O)$N(R^{51})$-, -$S(O)_2$-, -S(O)-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, C_{1-6} alkylene and C_{2-6} alkenylene, wherein the C_{1-6} alkylene and C_{2-6}

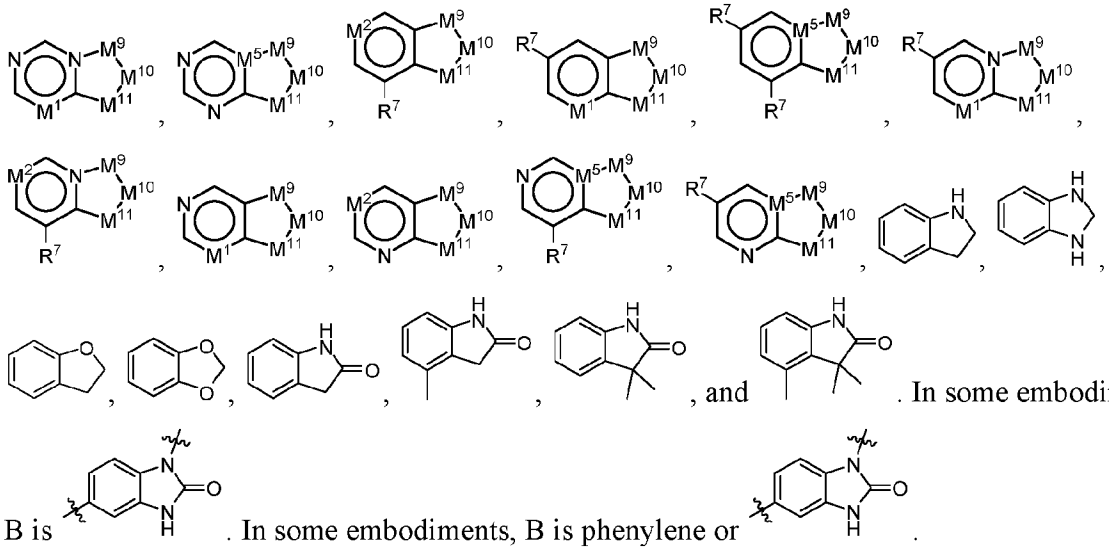
alkenylene are each optionally substituted with one or more R^{50}. In some embodiments, L^2 is selected from -O-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})S(O)$_2$-, -S(O)$_2$N(R^{51})-, C_{1-4} alkylene and C_{1-4} heteroalkylene. In some embodiments, L^2 is selected from -CH_2-, -N(R^{51})-, -N(R^{51})CH_2-, -N(R^{51})C(O)-, and -N(R^{51})S(O)$_2$-. In some embodiments, L^2 is -CH_2-.

[0084] In some embodiments, for a compound of Formula (I), B is 3- to 12-membered heterocycle, such as 6- to 12-membered bicyclic heterocycle. In some embodiments, the heterocycle comprises at least one nitrogen atom. In some embodiments, B is 6- to 12-membered heterocycle, wherein the heterocycle comprises at least 1, 2, 3 or 4 ring heteroatoms selected from N, O and S. In some embodiments, B is a 6,5- or 6,6-bicyclic heterocycle. In some embodiments, B comprises at least one ring nitrogen. In some embodiments, B is indolylene, such as  optionally substituted with one or more R^B. In some embodiments, B is  , such as  .

[0085] In some embodiments, B is selected from  ,  ,  , and  , wherein M^1, M^2, M^3 and M^4 are each independently selected from CR^7, N and NR^9; M^5 is selected from C and N; M^6, M^7 and M^8 are each independently selected from CR^8, N, NR^9, O and S; M^9, M^{10} and M^{11} are each independently selected from CR^{10}, $CR^{11}R^{12}$, NR^{13}, O and S; R^7, R^8, R^{10}, R^{11}, and R^{12} are each independently selected from hydrogen and R^{50}; and R^9 and R^{13} are each independently selected from R^{51}, wherein B may be connected at any ring atom to L^2 or L^3 (e.g., by replacing a hydrogen connected to a ring atom with a bond to L^2 or L^3).

[0086] In some embodiments, B is selected from  ,  .





B is . In some embodiments, B is phenylene or .

[0087] In some embodiments, B is substituted with one or more R^B (e.g., by replacing a hydrogen connected to a ring atom with a bond to R^B). B may be substituted with 0, 1, 2, 3, 4, 5, 6 or more R^B groups. B may be substituted with 1, 2, 3, 4, 5 or 6 R^B groups, such as B substituted with 1 or 2 R^B groups. In some embodiments, B is substituted with at least 1, 2, 3, 4, 5 or 6 R^B groups. In some embodiments, B is substituted with p R^B groups, wherein p is an integer from 0 to 6. In some embodiments, p is 0, 1, 2, 3, 4, 5 or 6. In some embodiments, p is at least 1, 2, 3, 4, 5 or 6. In some embodiments, p is up to 6, 5, 4, 3, 2, or 1. In some embodiments, p is an integer from 1 to 3.

[0088] In some embodiments, R^B is independently selected at each occurrence from halo, hydroxyl, amino, cyano, dialkylphosphine oxide, oxo, carboxyl, amido, acyl, alkyl, cycloalkyl, heteroalkyl, haloalkyl, aminoalkyl, hydroxyalkyl, alkoxy, alkylamino, cycloalkylalkyl, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylamino, cycloalkylalkylamino, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, heterocyclylalkyloxy, heterocyclylamino, heterocyclylalkylamino, aryl, aralkyl, aryloxy, aralkyloxy, arylamino, aralkylamino, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkyloxy, heteroarylamino, and heteroarylalkylamino. In some embodiments, R^B is independently selected at each occurrence from halo, hydroxyl, amino, cyano, dialkylphosphine oxide, oxo, carboxyl, amido, acyl, alkyl, cycloalkyl, heteroalkyl, haloalkyl, aminoalkyl, hydroxyalkyl, alkoxy, alkylamino, heterocyclylalkyl, and heteroarylalkyl. In some embodiments, two R^B groups attached to the same atom or different atoms can together form a ring.

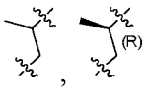
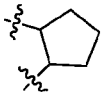
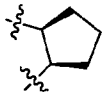
[0089] In some embodiments, for a compound of Formula (I), L^3 is a bond. In some embodiments, for a compound of Formula (I), L^3 is not a bond. In some embodiments, for a compound of Formula (I), L^3 comprises less than 30 atoms, such as less than 20 atoms. In some embodiments, L^3 comprises less than 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, or less than 3 atoms. In

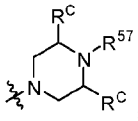
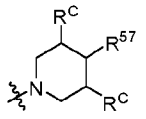
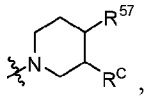
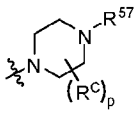
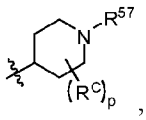
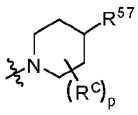
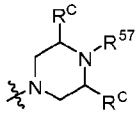
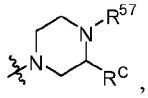
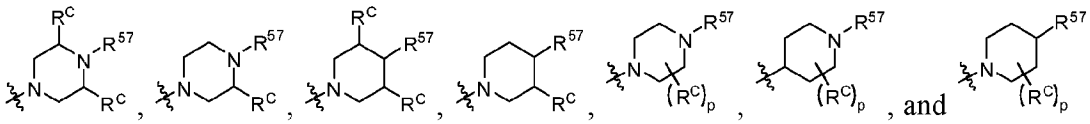
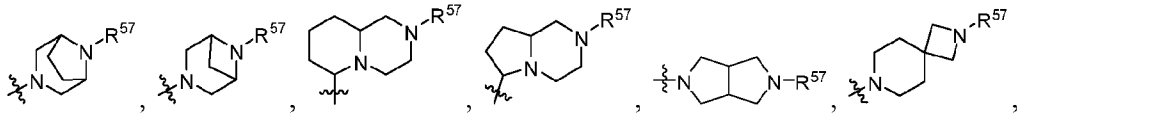
some embodiments, L^3 comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15 or at least 20 atoms. In some embodiments, L^3 comprises at least one heteroatom, such as L^3 comprises at least one nitrogen. In some embodiments, L^3 is C_{1-10} alkylene, such as C_{1-4} alkylene, optionally substituted with one or more R^{50}. In some embodiments, L^3 is substituted with one or more R^{50}. In some embodiments, L^3 is unsubstituted. In some embodiments, L^3 is selected from bond, -O-, -S-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)$N(R^{51})$-, -$N(R^{51})$C(O)-, -$N(R^{51})$C(O)$N(R^{51})$-, -$S(O)_2$-, -S(O)-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, -$N(R^{51})S(O)_2N(R^{51})$-, alkylene, alkenylene, heteroalkylene, and heteroalkenylene. In some embodiments, L^3 is C_{1-6} alkylene, optionally substituted with one or more R^{50}, wherein R^{50} is selected from deuterium, C_{1-4} alkyl, C_{1-4} haloalkyl, and -OR^{52}. In some embodiments, L^3 is-$CH_2CH(R^{50})$-, such as -$CH_2CH(CH_3)$-. In some embodiments, two R^{50} groups attached to the same atom or different atoms of L^3 optionally form a bridge or ring, such as a cyclopropyl ring. In some embodiments, L^3 is substituted with R^{50}, wherein R^{50} forms a bond to ring C. In some embodiments, L^3 is substituted with one or more groups selected from deuterium, C_{1-4} alkyl, C_{1-4} haloalkyl, and -OR^{52}. In some embodiments, L^3 is substituted with -CH_3. In some embodiments, L^3 is C_2 alkylene substituted with at least one C_{1-3} alkyl or C_{1-3} haloalkyl, and optionally further substituted with one or more R^{50}. In some embodiments, L^3 is substituted with =O, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-3} alkyl(cyclopropyl), C_{1-3} alkyl($NR^{52}C(O)R^{52}$) or -O(C_{1-6} alkyl).

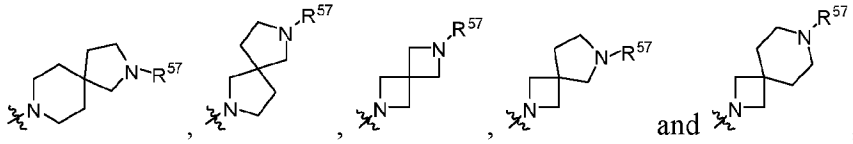
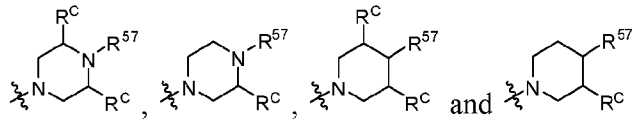
[0090] In some embodiments, for a compound of Formula (I), L^3 is selected from  and  . Optionally, R^{50} is methyl. L^3 may be selected from  and  . In some embodiments, L^3 is  . In some embodiments, L^3 is  . In some embodiments, L^3 comprises a stereocenter. In some embodiments, the stereocenter is in the *R*-configuration. In some embodiments, the stereocenter is in the *S*-configuration. In some embodiments, the *R*-isomer of L^3 is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% excess over the *S*-isomer. In some embodiments, the *S*-isomer of L^3 is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% excess over the *R*-isomer.

[0091] In some embodiments, for a compound of Formula (I), C is azetidinylene, piperidinylene or piperazinylene; R^{57} is -$S(=O)_2R^{58}$, -$S(=O)_2N(R^{52})_2$, or -$NR^{52}S(=O)_2R^{52}$; and L^3 is substituted with one or more R^{50}, wherein L^3 is not -$CH_2CH(OH)$-. In some embodiments, C is azetidinylene, piperidinylene or piperazinylene; R^{57} is -$S(=O)_2R^{58}$, -$S(=O)_2N(R^{52})_2$, or -

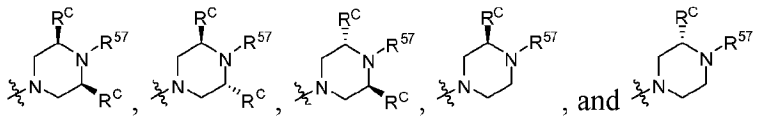
$NR^{52}S(=O)_2R^{52}$; and L^3 is substituted with C_{1-4} alkyl or C_{1-4} haloalkyl.

[0092] In some embodiments, for a compound of Formula (I), L^3 is selected from  , and any combination thereof. In some embodiments, for a compound of Formula (I), L^3 is selected from  and  .

[0093] In some embodiments, for a compound of Formula (I), C is 3- to 12-membered heterocycle, such as 5- to 12-membered heterocycle. In some embodiments, the heterocycle is saturated. In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, 8- to 10-membered fused bicyclic heterocycle, and 7- to 12-membered spirocyclic heterocycle. In some embodiments, the heterocycle comprises at least one nitrogen atom, such as one or two nitrogen atoms. In some embodiments, C comprises at least one ring nitrogen. In some embodiments, C is selected from piperidinyl and piperazinyl, such as  ,  and  , wherein R^{57} is selected from hydrogen and R^{50}. In some embodiments, C is selected from  ,  , and  , wherein R^{57} is selected from hydrogen and R^{50}. In some embodiments, C is selected from  ,  , wherein R^{57} is selected from hydrogen and R^{50}. In some embodiments, C is selected from  , and  .


, optionally substituted with one or more R^C, wherein R^{57} is selected from hydrogen and R^{50}. In some embodiments, C is selected from  , wherein R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$; and C_{1-10} alkyl substituted with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$, such as R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$.

[0094] In some embodiments, for a compound of Formula (I), C is selected from

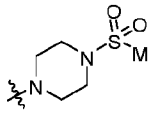
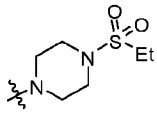
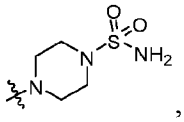
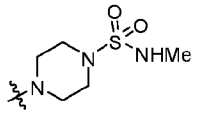
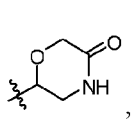
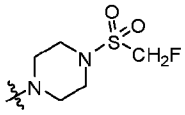
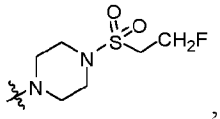
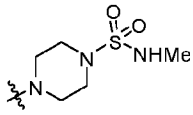
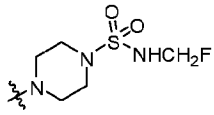
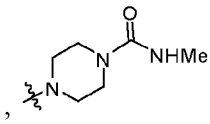
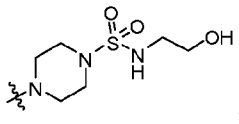
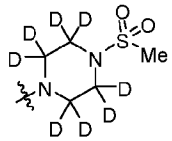
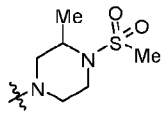
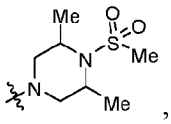
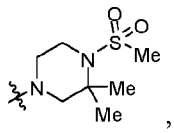
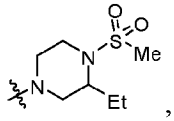
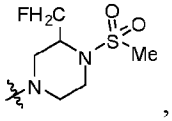
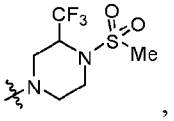
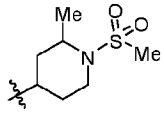
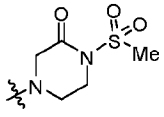

.

[0095] In some embodiments, for a compound of Formula (I), R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$; and C_{1-6} alkyl and C_{2-6} alkenyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, and C_{1-6} alkyl substituted with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$.

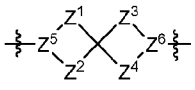
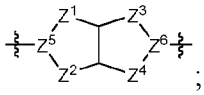
[0096] In some embodiments, for a compound of Formula (I), C is substituted with one or more R^C (e.g., by replacing a hydrogen connected to a ring atom with a bond to R^C). C may be substituted with 0, 1, 2, 3, 4, 5, 6 or more R^C groups. C may be substituted with 1, 2, 3, 4, 5 or 6 R^C groups, such as C substituted with 1 or 2 R^C groups. In some embodiments, C is substituted with at least 1, 2, 3, 4, 5 or 6 R^C groups. In some embodiments, C is unsubstituted. In some embodiments, C is substituted with q R^C groups, wherein q is an integer from 0 to 6. In some embodiments, q is 0, 1, 2, 3, 4, 5 or 6. In some embodiments, q is at least 1, 2, 3, 4, 5 or 6. In

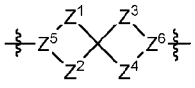
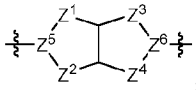
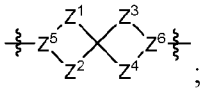
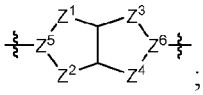
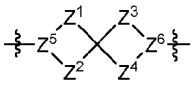
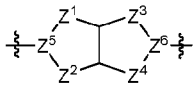
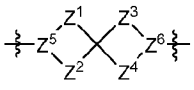
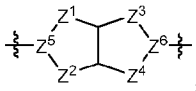
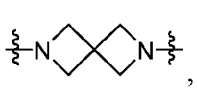
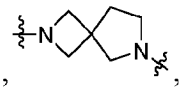
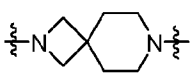
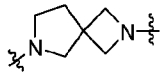
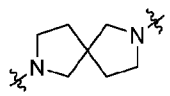
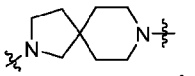
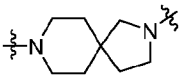
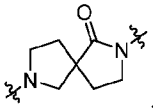
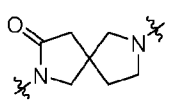
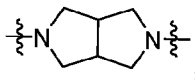
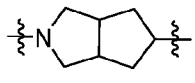
some embodiments, q is up to 6, 5, 4, 3, 2, or 1. In some embodiments, p is 0. In some embodiments, q is 1 or 2. In some embodiments, for a compound of Formula (I), C is azetidinylene, piperidinylene or piperazinylene; R^{57} is $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, or $-NR^{52}S(=O)_2R^{52}$; and p is an integer from 1 to 6.

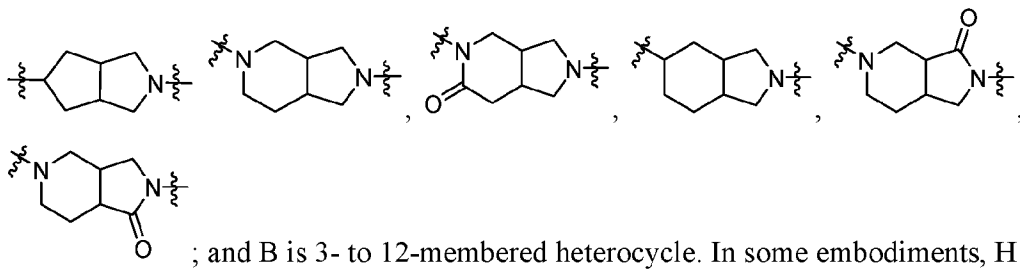
[0097] In some embodiments, for a compound of Formula (I), R^C is selected from $-C(O)R^{52}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, =O, C_{1-3} alkyl, and C_{1-3} haloalkyl, or two R^C groups attached to different atoms can together form a C_{1-3} bridge. In some embodiments, R^C is selected from C_{1-3} alkyl and C_{1-3} haloalkyl, such as $-CH_3$.

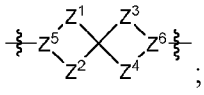
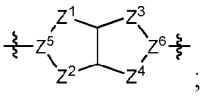
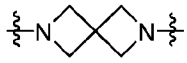
[0098] In some embodiments, C is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

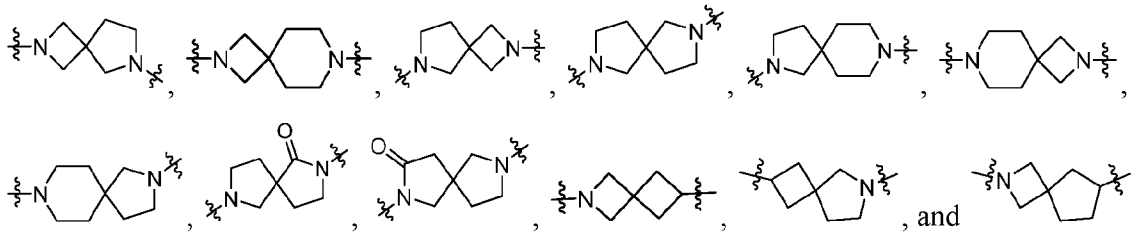
[0099] In some embodiments, for a compound of Formula (I), C is substituted with R^C, wherein R^C comprises a functional group that reacts with one or more residues on menin to form a covalent bond. In some embodiments, R^C reacts with one or more cysteine residues on menin, such as cysteine 329 or cysteine 334, to form a covalent bond. In some embodiments, R^C comprises an α, β-unsaturated carbonyl, an α, β-unsaturated sulfonyl, an epoxide, an aldehyde, a sulfonyl fluoride, a halomethylcarbonyl, a dihalomethylcarbonyl, a trihalomethylcarbonyl or an alkene. In some embodiments, R^C is $-NR^{52}C(O)R^{52}$, wherein R^{52} is independently selected from hydrogen and alkene. In some embodiments, R^C is $-NHC(O)CHCH_2$.

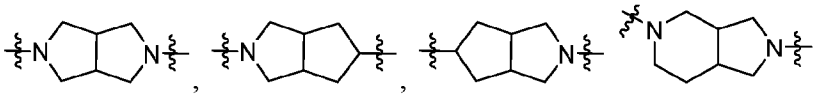
[0100] In some embodiments, for a compound of Formula (I), H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is 3- to 12-membered heterocycle. In some embodiments, for a compound of Formula (I), H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is 3- to 12-membered heterocycle. In some embodiments, H is 6- to 12-membered bicyclic

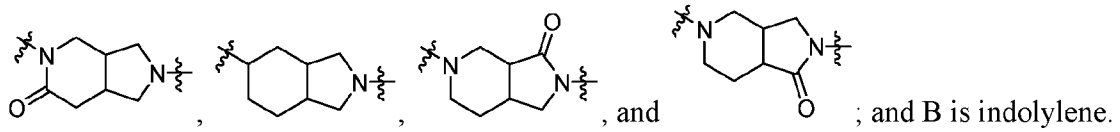
heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is 3- to 12-membered heterocycle. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is 3- to 12-membered heterocycle. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is 6- to 12-membered bicyclic heterocycle. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is 6- to 12-membered bicyclic heterocycle. In some embodiments, H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is 6- to 12-membered bicyclic heterocycle. In some embodiments, H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is 6- to 12-membered bicyclic heterocycle. In some embodiments, H is thienopyrimidinyl, optionally substituted with one or more R^{50}; A is  ; and B is 3- to 12-membered heterocycle. In some embodiments, H is thienopyrimidinyl, optionally substituted with one or more R^{50}; A is  ; and B is 3- to 12-membered heterocycle. In some embodiments, H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; and B is 3- to 12-membered heterocycle. In some embodiments, H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is selected from  ,  ,



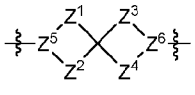
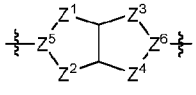
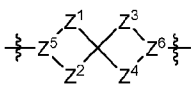
; and B is 3- to 12-membered heterocycle. In some embodiments, H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is indolylene. In some embodiments, H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is  ; and B is indolylene. In some embodiments, H is thienopyrimidinyl substituted with one or more R^{50}; A is selected from  ,

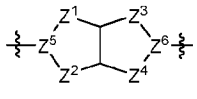
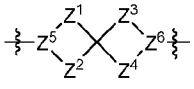
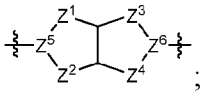
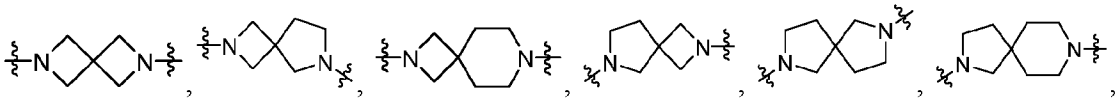
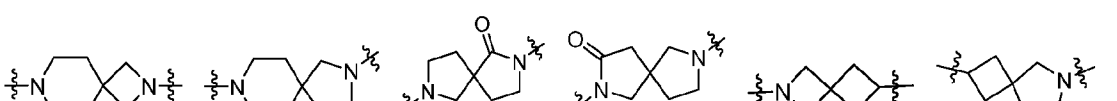
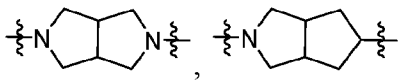
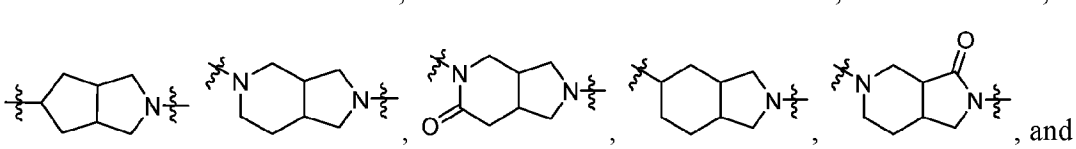
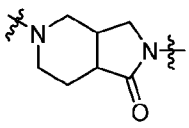
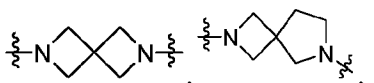


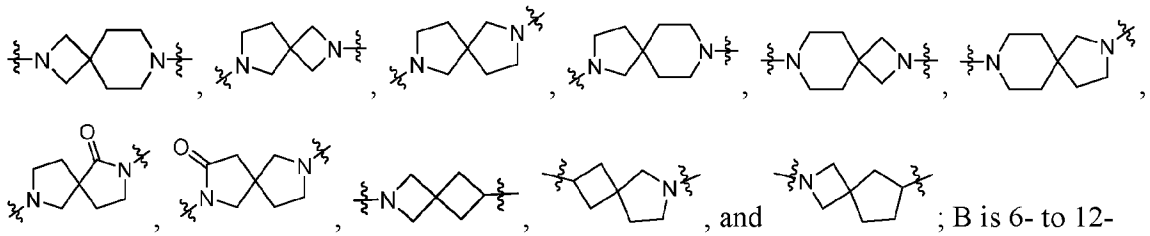
; and B is indolylene. In some embodiments, H is thienopyrimidinyl substituted with one or more R^{50}; A is selected from  ,



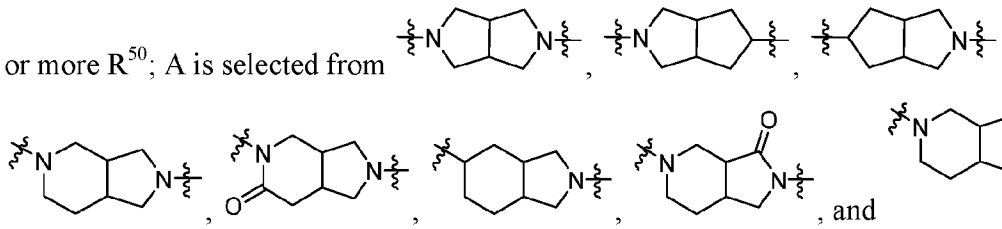
; and B is indolylene.

[0101] In some embodiments, for a compound of Formula (I), H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is  ; B is 3- to 12-membered heterocycle; C is 3- to 12-membered heterocycle; m is an integer from 0 to 3; and p is an integer from 1 to 3. In some embodiments, for a compound of Formula (I), H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is  ; B is 3- to 12-membered heterocycle; C is 3- to 12-membered heterocycle; m is an integer from 0 to 3; and p is an integer from 1 to 3. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is  ; B is 6- to 12-

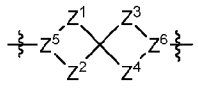
membered bicyclic heterocycle; C is 3- to 12-membered heterocycle; m is an integer from 0 to 3; and p is an integer from 1 to 3. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is  ; B is 6- to 12-membered bicyclic heterocycle; C is 3- to 12-membered heterocycle; m is an integer from 0 to 3; and p is an integer from 1 to 3. In some embodiments, H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50}; A is 3- to 12-membered heterocycle; B is 3- to 12-membered heterocycle; and C is 3- to 12-membered heterocycle. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is  ; B is 6- to 12-membered bicyclic heterocycle; and C is 3- to 12-membered heterocycle. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is  ; B is 6- to 12-membered bicyclic heterocycle; and C is 3- to 12-membered heterocycle. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is selected from  ,  , and  ; B is 6- to 12-membered bicyclic heterocycle; and C is 3- to 12-membered heterocycle. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is selected from  ,  , and  ; B is 6- to 12-membered bicyclic heterocycle; and C is 3- to 12-membered heterocycle. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is selected from  ,



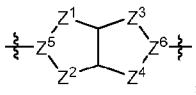
membered bicyclic heterocycle; m is an integer from 0 to 3; and p is an integer from 1 to 3. In some embodiments, H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is selected from



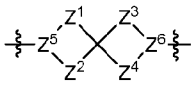
to 12-membered bicyclic heterocycle; m is an integer from 0 to 3; and p is an integer from 1 to 3. In some embodiments, H is thienopyrimidinyl, optionally substituted with one or more R^{50}; A is



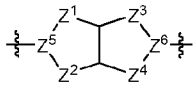
; and B is 6- to 12-membered bicyclic heterocycle. In some embodiments, H is thienopyrimidinyl, optionally substituted with one or more R^{50}; A is



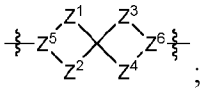
; and B is 6- to 12-membered bicyclic heterocycle. In some embodiments, H is thienopyrimidinyl, optionally substituted with one or more R^{50}; A is



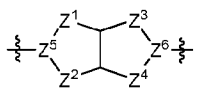
; B is 6- to 12-membered bicyclic heterocycle; m is an integer from 0 to 3; and p is an integer from 1 to 3. In some embodiments, H is thienopyrimidinyl, optionally substituted with one or more R^{50}; A is



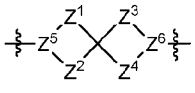
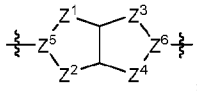
; B is 6- to 12-membered bicyclic heterocycle; m is an integer from 0 to 3; and p is an integer from 1 to 3. In some embodiments, H is 9- to 10-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is



; and B is 9-membered bicyclic heterocycle, wherein each of said heterocycles comprises at least one nitrogen atom. In some embodiments, H is 9- to 10-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is



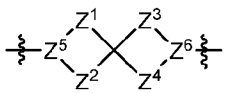
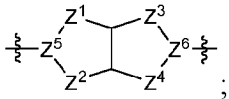
; and B is 9-membered bicyclic heterocycle, wherein each of said heterocycles comprises at least one nitrogen atom. In some embodiments, H is 9- to 10-membered bicyclic

heterocycle, optionally substituted with one or more R^{50}; A is  ; B is 9-membered bicyclic heterocycle; and p is an integer from 1 to 3, wherein each of said heterocycles comprises at least one nitrogen atom. In some embodiments, H is 9- to 10-membered bicyclic heterocycle, optionally substituted with one or more R^{50}; A is  ; B is 9-membered bicyclic heterocycle; and p is an integer from 1 to 3, wherein each of said heterocycles comprises at least one nitrogen atom.

[0102] In some embodiments, for a compound of Formula (I), L^1 comprises less than 10 atoms, L^2 comprises less than 10 atoms, and L^3 comprises less than 20 atoms. In some embodiments, $L^1$is a bond and L^2 and L^3 each comprise at least 1 atom. In some embodiments, L^1 is a bond and L^2 and L^3 each comprise at least 1 atom. In some embodiments, L^2 is a bond and L^1 and L^3 each comprise at least 1 atom. In some embodiments, L^3 is a bond and L^1 and L^2 each comprise at least 1 atom. In some embodiments, L^1, L^2 and L^3 each comprise at least 1 atom, such as at least 2 atoms. In some embodiments, L^1, L^2 and L^3 are each independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -$S(O)_2$-, -S(O)-, -N(R^{51})$S(O)_2$-, -$S(O)_2$N(R^{51})-, -N(R^{51})$S(O)_2$N(R^{51})-, alkylene, alkenylene, heteroalkylene, and heteroalkenylene. In some embodiments, L^1, L^2 and L^3 are each independently selected from -CH_2-, -CH_2CH_2-, -$CH_2CH(CH_3)$-, -N(R^{51})-, -N(R^{51})CH_2-, -N(R^{51})C(O)-, and -N(R^{51})$S(O)_2$-. In some embodiments, L^1 is selected from -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -$S(O)_2$-, -S(O)-, -N(R^{51})$S(O)_2$-, -$S(O)_2$N(R^{51})-, -N(R^{51})$S(O)_2$N(R^{51})-, alkylene, alkenylene, heteroalkylene, and heteroalkenylene; and L^2 and L^3 are independently selected from C_{1-4} alkylene, optionally substituted with one or more R^{50}. In some embodiments, L^1, L^2 and L^3 are each independently selected from -O-, -S-, -N(R^{51})-; C_{1-4} alkylene and 1- to 4-membered heteroalkylene, each of which is optionally substituted with one or more R^{50}. In some embodiments, L^1 is -NH-, L^2 is -CH_2-, and L^3 is C_{1-4} alkylene, optionally substituted with one or more R^{50}.

[0103] In certain aspects, for a compound of Formula (I):

H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50};

A is  or  ;

B and C are each independently selected from 3- to 12-membered heterocycle;

L^1, L^2 and L^3 are each independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-,

-C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -N(R^{51})$S(O)_2$-, -$S(O)_2N(R^{51})$-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2N(R^{51})$-, -N(R^{51})S(O)N(R^{51})-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2 or L^3 can together optionally form a ring;

R^B and R^C are each independently selected at each occurrence from R^{50}, or two R^B groups or two R^C groups attached to the same atom or different atoms can together optionally form a ring;

m is an integer from 0 to 3;

p is an integer from 0 to 6;

R^{50} is independently selected at each occurrence from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -C(O)$R^{52}$, -C(O)$OR^{52}$, -OC(O)$R^{52}$, -OC(O)$OR^{52}$, -OC(O)$N(R^{52})_2$, -OC(O)$NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -C(O)$N(R^{52})_2$, -C(O)$NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =N($R^{52}$);

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -C(O)$R^{52}$, -C(O)$OR^{52}$, -OC(O)$R^{52}$, -OC(O)$OR^{52}$, -OC(O)$N(R^{52})_2$, -OC(O)$NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -C(O)$N(R^{52})_2$, -C(O)$NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =N($R^{52}$), C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

$-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, -

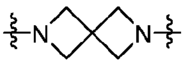
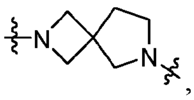
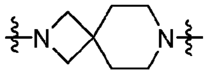
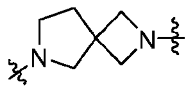
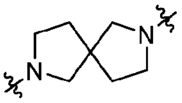
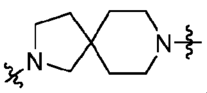
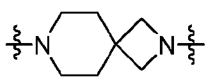
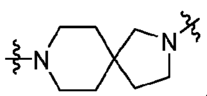
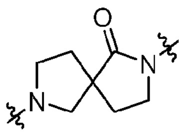
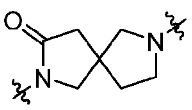
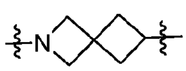
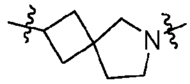
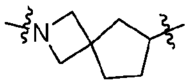
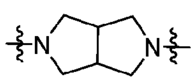
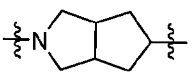
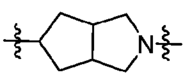
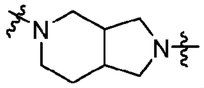
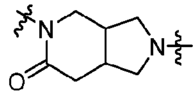
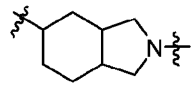
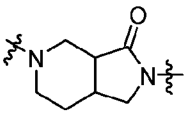
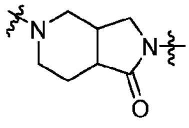
$NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -C(O)NH(C_{1-6} alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -C(O)NH(C_{1-6} alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, and -$P(O)(R^{52})_2$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, -OCH_2CH_3, C_{3-12} carbocycle, or 3- to 6-membered heterocycle.

[0104] In certain aspects, for a compound of Formula (I):

H is thienopyrimidinyl, optionally substituted with one or more R^{50};

A is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

B is indolylene;

L^1 and L^2 are each independently selected from -O-, -S-, -NH-, and $-CH_2-$;

L^3 is selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, -$N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, -$C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, -

$N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of L^3 can together optionally form a ring;

R^B and R^C are each independently selected at each occurrence from R^{50}, or two R^B groups or two R^C groups attached to the same atom or different atoms can together optionally form a ring;

m is an integer from 0 to 3;

p is an integer from 0 to 6;

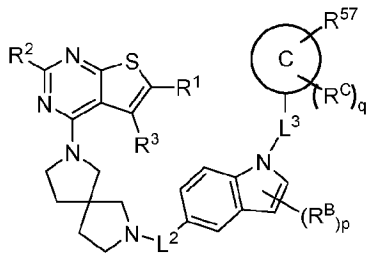
R^{57} is selected from:

$-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1\text{-}6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$; and

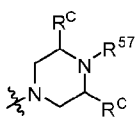
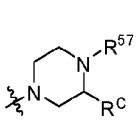
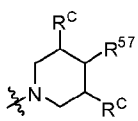
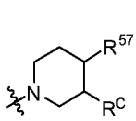
$C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, and $C_{2\text{-}10}$ alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1\text{-}6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, and $-P(O)(R^{52})_2$; and

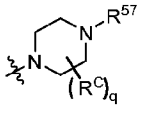
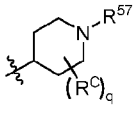
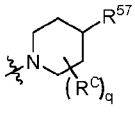
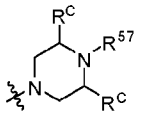
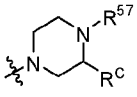
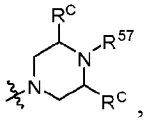
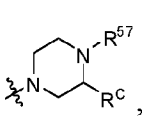
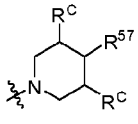
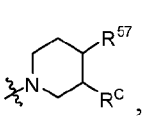
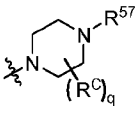
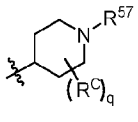
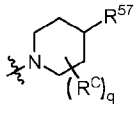
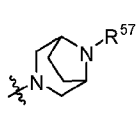
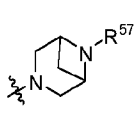
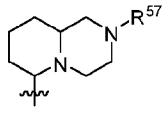
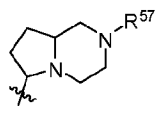
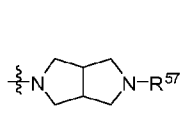
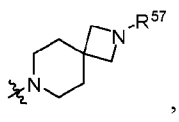
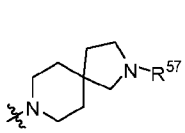
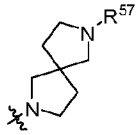
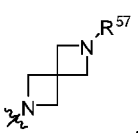
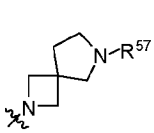
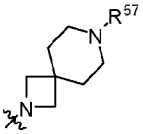
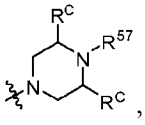
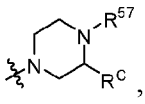
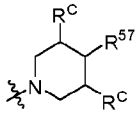
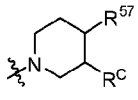
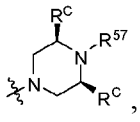
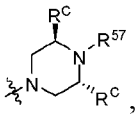
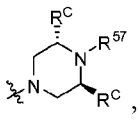
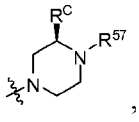
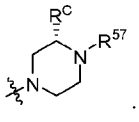
R^{58} is selected from hydrogen; and $C_{1\text{-}20}$ alkyl, $C_{3\text{-}20}$ alkenyl, $C_{2\text{-}20}$ alkynyl, 1- to 6-membered heteroalkyl, $C_{3\text{-}12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, $C_{3\text{-}12}$ carbocycle, or 3- to 6-membered heterocycle.

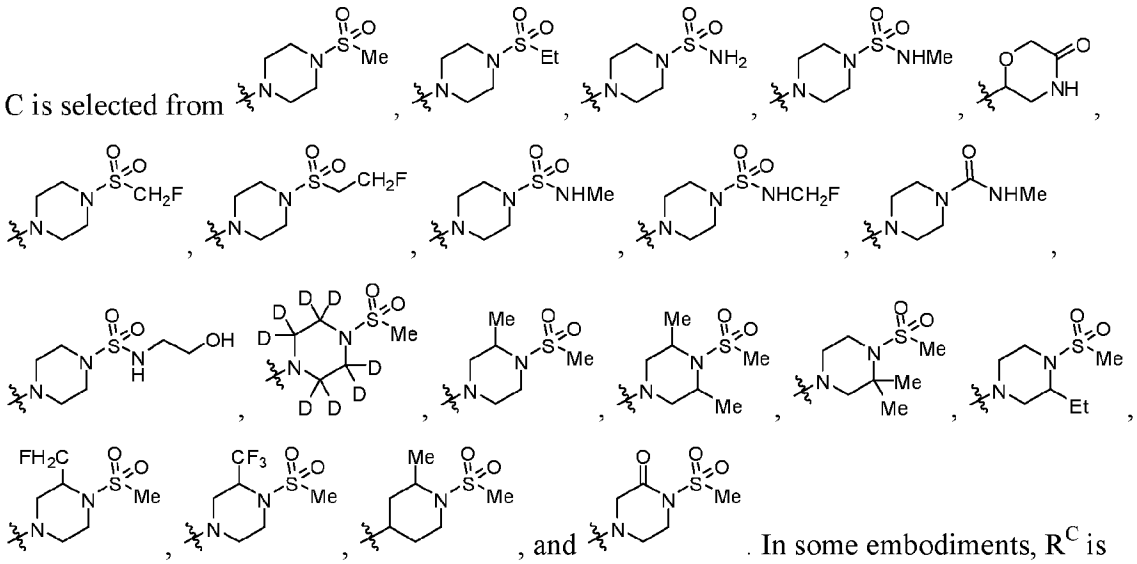
[0105] In certain aspects, a compound of Formula (I) may be represented by:



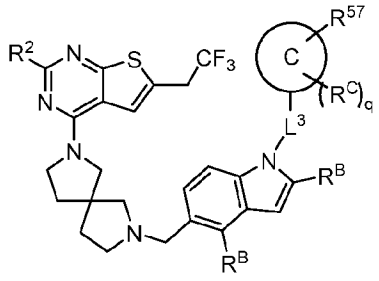
(I-A). In some embodiments, R^1 is selected from R^{50}. In some embodiments, R^1 is $C_{1\text{-}3}$ haloalkyl, such as $-CH_2CF_3$. In some embodiments, R^2 is selected from R^{50}. In some embodiments, R^2 is selected from hydrogen, halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, $C_{1\text{-}3}$ alkyl, $C_{1\text{-}3}$ alkyl-OR^{52}, $C_{1\text{-}3}$ alkyl-$N(R^{52})_2$, $C_{1\text{-}3}$ haloalkyl, $C_{2\text{-}3}$ alkenyl, and $C_{2\text{-}3}$ alkynyl. In some embodiments, R^2 is selected from halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, $C_{1\text{-}3}$ alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, $C_{1\text{-}3}$ alkyl-$N(R^{52})_2$, $C_{1\text{-}3}$ haloalkyl, $C_{2\text{-}3}$ alkenyl, and

C_{2-3} alkynyl, such as R^2 is selected from -OH, -OR^{52}, -NH_2, -$N(R^{52})_2$, -CN, and C_{1-2} alkyl. Optionally, R^2 is selected from -NH_2, -CH_3, -OCH_3, -CH_2OH, and -$NHCH_3$. In some embodiments, R^3 is selected from hydrogen, halogen, -OH, -$N(R^{52})_2$, -CN, -$C(O)OR^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, L^2 is selected from -O-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -$C(O)N(R^{51})$-, -$N(R^{51})C(O)$-, -$N(R^{51})S(O)_2$-, -$S(O)_2N(R^{51})$-, C_{1-4} alkylene and C_{1-4} heteroalkylene. In some embodiments, L^2 is C_{1-4} alkylene, optionally substituted with one or more R^{50}. In some embodiments, L^2 is C_{1-2} alkylene, optionally substituted with one or more R^{50}. In some embodiments, L^2 is selected from -CH_2-, -$N(R^{51})$-, -$N(R^{51})CH_2$-, -$N(R^{51})C(O)$-, and -$N(R^{51})S(O)_2$-. In some embodiments, L^2 is -CH_2-. In some embodiments, R^B is present at one or more positions of the indole, such as at position 2, 3, 4, or 6 of the indole. In some embodiments, R^B is selected from halogen, -CN, -OR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$NR^{52}C(O)R^{52}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, =O, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, and optionally substituted C_{2-10} alkynyl. In some embodiments, R^B is selected from halogen, -CN, -OR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, C_{1-3} alkyl, and optionally substituted C_{1-3} alkyl, such as R^B is selected from halogen, -CN, -OR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, and C_{1-2} alkyl. In some embodiments, p is an integer from 1 to 4, such as an integer from 2 to 3. In some embodiments, p is 2. In some embodiments, L^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene, each of which is substituted with one or more R^{50}. In some embodiments, L^3 is C_{1-6} alkylene, optionally substituted with one or more R^{50}. In some embodiments, L^3 is C_2 alkylene substituted with at least one C_{1-3} alkyl or C_{1-3} haloalkyl, and optionally further substituted with one or more R^{50}. In some embodiments, L^3 is substituted with =O, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-3} alkyl(cyclopropyl), C_{1-3} alkyl($NR^{52}C(O)R^{52}$) or -O(C_{1-6} alkyl). In some embodiments, L^3 is substituted with -CH_3. In some embodiments, L^3 is selected from  and  , where R^{50} is optionally methyl. In some embodiments, C is 3- to 12-membered heterocycle, such as 5- to 12-membered heterocycle. In some embodiments, the heterocycle is saturated. In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, 8- to 10-membered fused bicyclic heterocycle, and 7- to 12-membered spirocyclic heterocycle. In some embodiments, the heterocycle comprises at least one nitrogen atom, such as one or two nitrogen atoms. In some embodiments, C comprises at least one ring nitrogen. In some embodiments, C is selected from piperidinyl and piperazinyl, such as  ,  ,  and  . In some

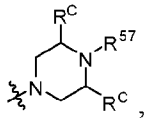
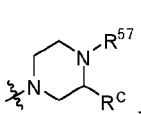
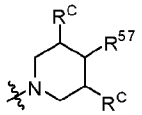
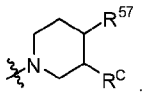
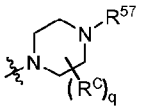
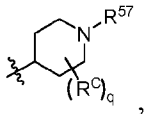
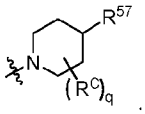
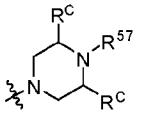
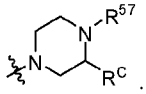
embodiments, C is selected from  ,  , and  . In some embodiments, C is selected from  and  . In some embodiments, C is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and  , optionally substituted with one or more R^C. In some embodiments, C is selected from  ,  ,  and  , wherein R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$; and C_{1-10} alkyl substituted with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$, such as R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$. In some embodiments, C is selected from  ,  ,  ,  , and  . In some embodiments, R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, and $-C(O)NR^{53}R^{54}$. In some embodiments, R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, C_{1-6} alkyl, and C_{1-6} alkyl substituted with $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, or $-C(O)NR^{53}R^{54}$. In some embodiments,

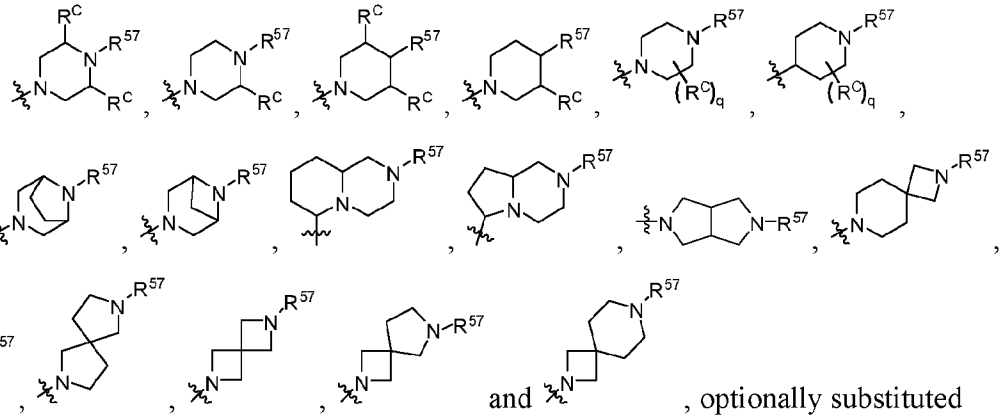
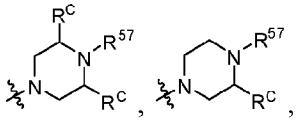
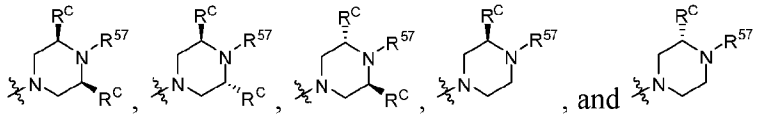
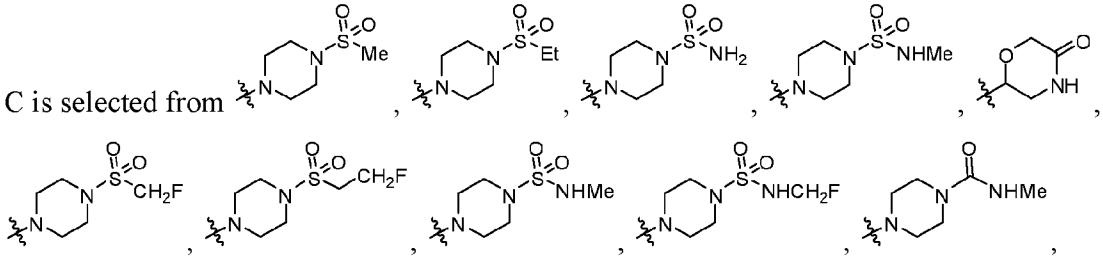
C is selected from  . In some embodiments, R^C is selected from $-C(O)R^{52}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, =O, C_{1-3} alkyl, and C_{1-3} haloalkyl, or two R^C groups attached to different atoms can together form a C_{1-3} bridge. In some embodiments, R^C is selected from C_{1-3} alkyl and C_{1-3} haloalkyl, such as $-CH_3$. In some embodiments, p is selected from an integer 0 to 4, such as p is selected from an integer 0 to 2. In some embodiments, p is 0. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$; and C_{1-6} alkyl and C_{2-6} alkenyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, and C_{1-6} alkyl substituted with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$.

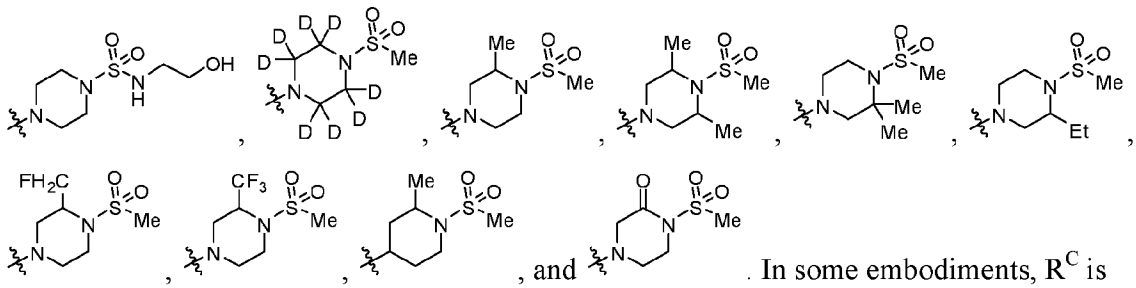
[0106] In certain aspects, a compound of Formula (I) may be represented by:



(I-B). In some embodiments, R^2 is selected from R^{50}. In some

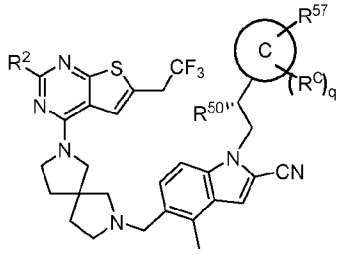
embodiments, R^2 is selected from hydrogen, halogen, -OH, -OR^{52}, -NH_2, -$N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, R^2 is selected from halogen, -OH, -OR^{52}, -NH_2, -$N(R^{52})_2$, -CN, C_{1-3} alkyl, -CH_2OH, -CH_2OR^{52}, -CH_2NH_2, -$CH_2N(R^{52})_2$, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from -OH, -OR^{52}, -NH_2, -$N(R^{52})_2$, -CN, and C_{1-2} alkyl. Optionally, R^2 is selected from -NH_2, -CH_3, -OCH_3, -CH_2OH, and -$NHCH_3$. In some embodiments, R^B is selected from halogen, -CN, -OR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$NR^{52}C(O)R^{52}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, =O, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, and optionally substituted C_{2-10} alkynyl. In some embodiments, R^B is selected from halogen, -CN, -OR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, C_{1-3} alkyl, and optionally substituted C_{1-3} alkyl, such as R^B is selected from halogen, -CN, -OR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, and C_{1-2} alkyl. In some embodiments, L^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene, each of which is substituted with one or more R^{50}. In some embodiments, L^3 is C_{1-6} alkylene, optionally substituted with one or more R^{50}. In some embodiments, L^3 is C_2 alkylene substituted with at least one C_{1-3} alkyl or C_{1-3} haloalkyl, and optionally further substituted with one or more R^{50}. In some embodiments, L^3 is substituted with =O, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-3} alkyl(cyclopropyl), C_{1-3} alkyl($NR^{52}C(O)R^{52}$) or -O(C_{1-6} alkyl). In some embodiments, L^3 is substituted with -CH_3. In some embodiments, L^3 is selected from  and  , where R^{50} is optionally methyl. In some embodiments, C is 3- to 12-membered heterocycle, such as 5- to 12-membered heterocycle. In some embodiments, the heterocycle is saturated. In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, 8- to 10-membered fused bicyclic heterocycle, and 7- to 12-membered spirocyclic heterocycle. In some embodiments, the heterocycle comprises at least one nitrogen atom, such as one or two nitrogen atoms. In some embodiments, C comprises at least one ring nitrogen. In some embodiments, C is selected from piperidinyl and piperazinyl, such as  ,  ,  and  . In some embodiments, C is selected from  ,  , and  . In some embodiments, C is selected from  and  . In some embodiments, C is

selected from  , optionally substituted with one or more R^C. In some embodiments, C is selected from  , wherein R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$; and $C_{1\text{-}10}$ alkyl substituted with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$, such as R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$. In some embodiments, C is selected from  . In some embodiments, R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, and $-C(O)NR^{53}R^{54}$. In some embodiments, R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $C_{1\text{-}6}$ alkyl, and $C_{1\text{-}6}$ alkyl substituted with $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, or $-C(O)NR^{53}R^{54}$. In some embodiments, C is selected from  .

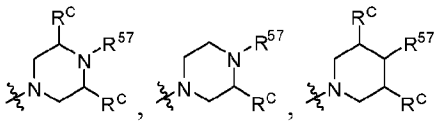
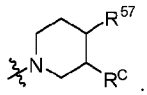
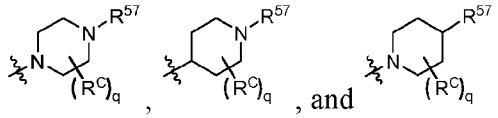
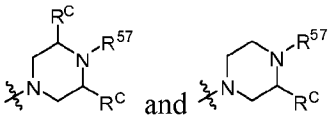
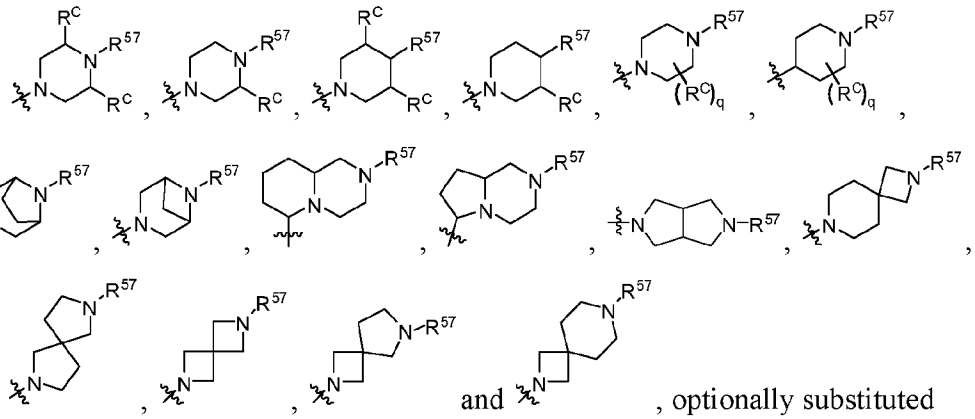
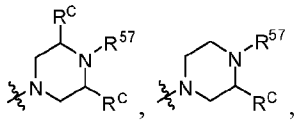


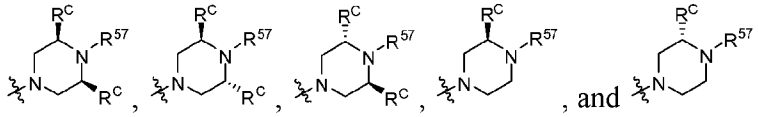
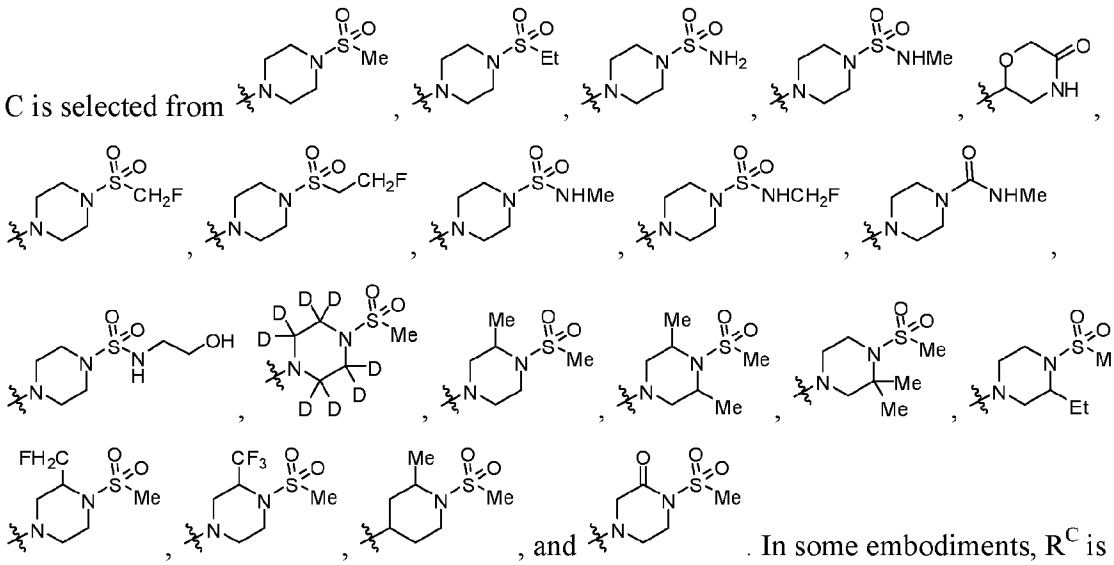
. In some embodiments, R^C is selected from $-C(O)R^{52}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, =O, C_{1-3} alkyl, and C_{1-3} haloalkyl, or two R^C groups attached to different atoms can together form a C_{1-3} bridge. In some embodiments, R^C is selected from C_{1-3} alkyl and C_{1-3} haloalkyl, such as $-CH_3$. In some embodiments, q is selected from an integer 0 to 4, such as q is selected from an integer 0 to 2. In some embodiments, q is 0. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$; and C_{1-6} alkyl and C_{2-6} alkenyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, and C_{1-6} alkyl substituted with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$.

[0107] In certain aspects, a compound of Formula (I) may be represented by:



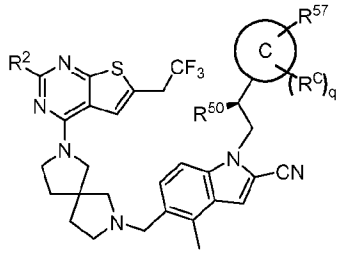
(I-C). In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, such as piperidinyl and piperazinyl. In some embodiments, R^{50} is selected from deuterium, C_{1-4} alkyl, C_{1-4} haloalkyl, and $-OR^{52}$, such as R^{50} is methyl. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$, such as R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$. In some embodiments, R^{57} is $-S(=O)_2CH_3$. In some embodiments, R^{50} is methyl

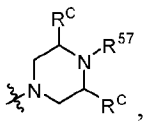
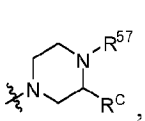
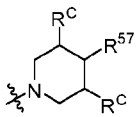
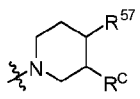
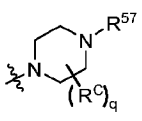
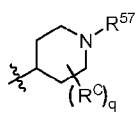
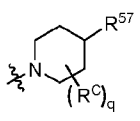
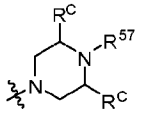
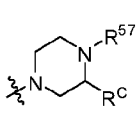
and R^{57} is $-S(=O)_2CH_3$. In some embodiments, R^2 is selected from hydrogen, halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, and C_{1-2} alkyl. In some embodiments, R^2 is methyl or $-NHCH_3$. In some embodiments, R^2 is H. In some embodiments, C is 3- to 12-membered heterocycle, such as 5- to 12-membered heterocycle. In some embodiments, the heterocycle is saturated. In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, 8- to 10-membered fused bicyclic heterocycle, and 7- to 12-membered spirocyclic heterocycle. In some embodiments, the heterocycle comprises at least one nitrogen atom, such as one or two nitrogen atoms. In some embodiments, C comprises at least one ring nitrogen. In some embodiments, C is selected from piperidinyl and piperazinyl, such as  and  . In some embodiments, C is selected from  . In some embodiments, C is selected from  . In some embodiments, C is selected from  , optionally substituted with one or more R^C. In some embodiments, C is selected from  , wherein R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$; and C_{1-10} alkyl substituted with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, -

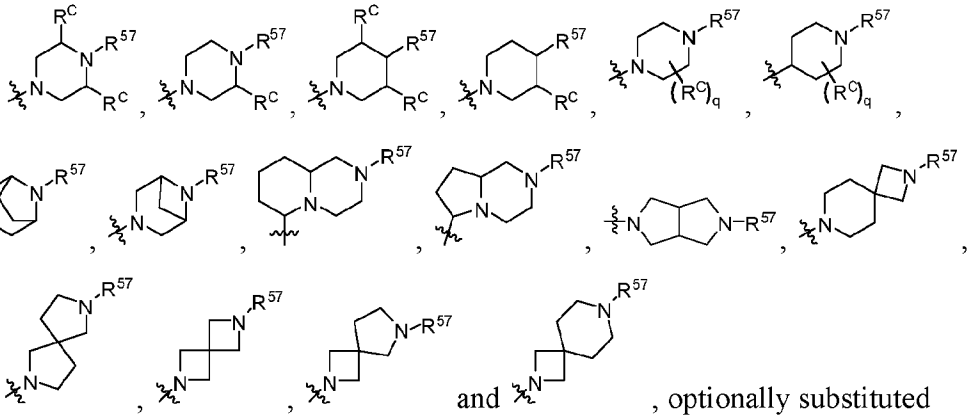
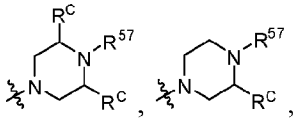
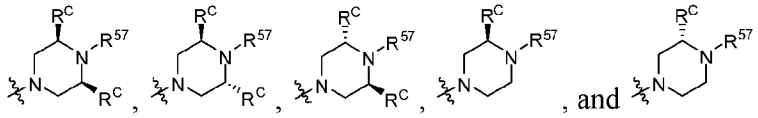
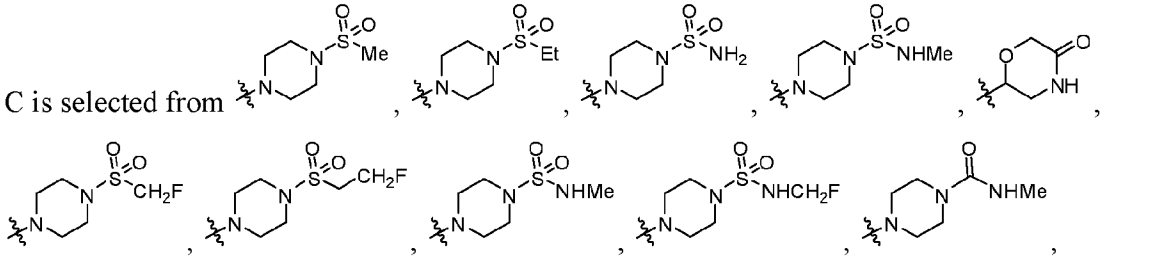
$S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$, such as R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$. In some embodiments, C is selected from  . In some embodiments, R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, and $-C(O)NR^{53}R^{54}$. In some embodiments, R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, C_{1-6} alkyl, and C_{1-6} alkyl substituted with $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, or $-C(O)NR^{53}R^{54}$. In some embodiments, C is selected from  . In some embodiments, R^C is selected from $-C(O)R^{52}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, =O, C_{1-3} alkyl, and C_{1-3} haloalkyl, or two R^C groups attached to different atoms can together form a C_{1-3} bridge. In some embodiments, R^C is selected from C_{1-3} alkyl and C_{1-3} haloalkyl, such as $-CH_3$. In some embodiments, q is selected from an integer 0 to 4, such as q is selected from an integer 0 to 2. In some embodiments, q is 0. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$; and C_{1-6} alkyl and C_{2-6} alkenyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, and C_{1-6} alkyl substituted with one

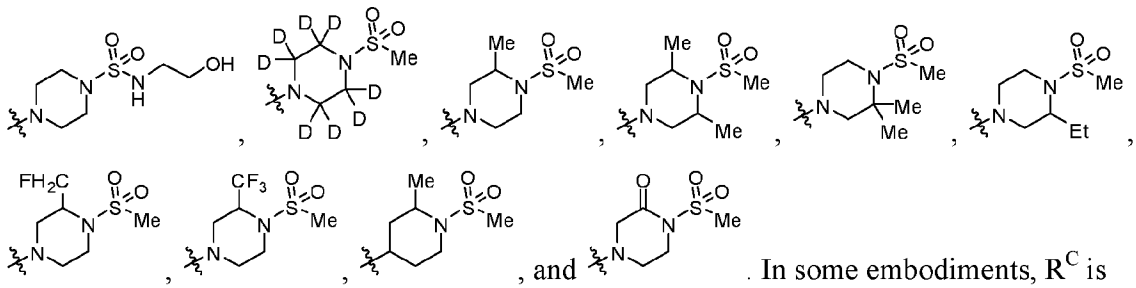
or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$.

[0108] In certain aspects, a compound of Formula (I) may be represented by:



(I-D). In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, such as piperidinyl and piperazinyl. In some embodiments, R^{50} is selected from deuterium, C_{1-4} alkyl, C_{1-4} haloalkyl, and $-OR^{52}$, such as R^{50} is methyl. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$, such as R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$. In some embodiments, R^{57} is $-S(=O)_2CH_3$. In some embodiments, R^{50} is methyl and R^{57} is $-S(=O)_2CH_3$. In some embodiments, R^2 is selected from hydrogen, halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, and C_{1-2} alkyl. In some embodiments, R^2 is methyl or $-NHCH_3$. In some embodiments, R^2 is H. In some embodiments, C is 3- to 12-membered heterocycle, such as 5- to 12-membered heterocycle. In some embodiments, the heterocycle is saturated. In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, 8- to 10-membered fused bicyclic heterocycle, and 7- to 12-membered spirocyclic heterocycle. In some embodiments, the heterocycle comprises at least one nitrogen atom, such as one or two nitrogen atoms. In some embodiments, C comprises at least one ring nitrogen. In some embodiments, C is selected from piperidinyl and piperazinyl, such as  ,  ,  and  . In some embodiments, C is selected from  ,  , and  . In some embodiments, C is selected from  and  . In some embodiments, C

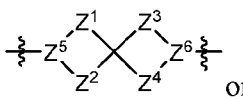
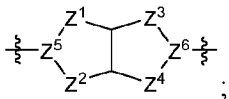
is selected from  , optionally substituted with one or more R^C. In some embodiments, C is selected from  , wherein R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$; and $C_{1\text{-}10}$ alkyl substituted with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$, such as R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$. In some embodiments, C is selected from  . In some embodiments, R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, and $-C(O)NR^{53}R^{54}$. In some embodiments, R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $C_{1\text{-}6}$ alkyl, and $C_{1\text{-}6}$ alkyl substituted with $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, or $-C(O)NR^{53}R^{54}$. In some embodiments, C is selected from  .



. In some embodiments, R^C is selected from $-C(O)R^{52}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, =O, C_{1-3} alkyl, and C_{1-3} haloalkyl, or two R^C groups attached to different atoms can together form a C_{1-3} bridge. In some embodiments, R^C is selected from C_{1-3} alkyl and C_{1-3} haloalkyl, such as $-CH_3$. In some embodiments, q is selected from an integer 0 to 4, such as q is selected from an integer 0 to 2. In some embodiments, q is 0. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$; and C_{1-6} alkyl and C_{2-6} alkenyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, and C_{1-6} alkyl substituted with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$.

[0109] In certain aspects, for a compound of Formula (I):

H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50};

A is  or  ;

B is a C_{3-12} carbocycle;

C is a bond;

L^1, L^2 and L^3 are each independently selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$,

-$N(R^{51})S(O)_2N(R^{51})$-, -$N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2 or L^3 can together optionally form a ring;

R^B is independently selected at each occurrence from R^{50}, or two R^B groups attached to the same atom or different atoms can together optionally form a ring;

p is an integer from 0 to 6;

q is 0;

R^{50} is independently selected at each occurrence from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, =O, =S, =$N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-CN$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, $-OH$, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

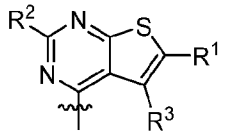
$-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents

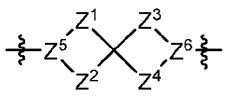
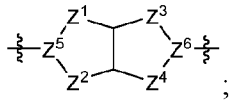
selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1\text{-}6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, and $-P(O)(R^{52})_2$; and

R^{58} is selected from hydrogen; and $C_{1\text{-}20}$ alkyl, $C_{3\text{-}20}$ alkenyl, $C_{2\text{-}20}$ alkynyl, 1- to 6-membered heteroalkyl, $C_{3\text{-}12}$ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, $C_{3\text{-}12}$ carbocycle, or 3- to 6-membered heterocycle.

[0110] In certain aspects, for a compound of Formula (I):

H is  ;

each of R^1, R^2 and R^3 is independently selected at each occurrence from hydrogen and R^{50};

A is  or  ;

B is a $C_{3\text{-}6}$ carbocycle;

C is a bond;

L^1, L^2 and L^3 are each independently selected from bond, -O-, -S-, $-N(R^{51})$-, $-N(R^{51})CH_2$-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})$-, $-C(O)N(R^{51})C(O)$-, $-C(O)N(R^{51})C(O)N(R^{51})$-, $-N(R^{51})C(O)$-, $-N(R^{51})C(O)N(R^{51})$-, $-N(R^{51})C(O)O$-, $-OC(O)N(R^{51})$-, $-C(NR^{51})$-, $-N(R^{51})C(NR^{51})$-, $-C(NR^{51})N(R^{51})$-, $-N(R^{51})C(NR^{51})N(R^{51})$-, $-S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2$-, $-S(O)_2O$-, $-N(R^{51})S(O)_2$-, $-S(O)_2N(R^{51})$-, $-N(R^{51})S(O)$-, $-S(O)N(R^{51})$-, $-N(R^{51})S(O)_2N(R^{51})$-, $-N(R^{51})S(O)N(R^{51})$-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2 or L^3 can together optionally form a ring;

each R^B is selected at each occurrence from R^{50}, or two R^B groups attached to the same atom or different atoms can together optionally form a ring;

p is an integer from 0 to 6;

q is 0;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

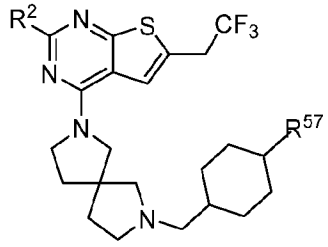
R^{57} is selected from:

$-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, and $-P(O)(R^{52})_2$; and

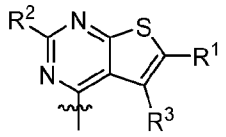
R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle.

[0111] In certain aspects, a compound of Formula (I) may be represented by:

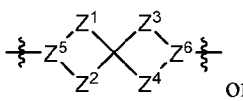
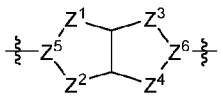


(I-E). In some embodiments, R^2 is selected from R^{50}. In some embodiments, R^2 is selected from hydrogen, halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, R^2 is selected from halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, and C_{1-2} alkyl. Optionally, R^2 is selected from $-NH_2$, $-CH_3$, $-OCH_3$, $-CH_2OH$, and $-NHCH_3$. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$; and C_{1-6} alkyl and C_{2-6} alkenyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, and C_{1-6} alkyl substituted with one or more substituents selected from $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2NR^{53}R^{54}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$.

[0112] In certain aspects, for a compound of Formula (I):

H is  ;

each of R^1, R^2 and R^3 is independently selected at each occurrence from hydrogen and R^{50};

A is  or  ;

B is a 3- to 12- memebered heterocycle;

C is a bond;

L^1, L^2 and L^3 are each independently selected from bond, -O-, -S-, $-N(R^{51})$-, $-N(R^{51})CH_2$-,

-C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -S(O)$_2$-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)$_2$-, -S(O)$_2$O-, -N(R^{51})S(O)$_2$-, -S(O)$_2$N(R^{51})-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})S(O)$_2$N(R^{51})-, -N(R^{51})S(O)N(R^{51})-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2 or L^3 can together optionally form a ring;

each R^B is selected at each occurrence from R^{50}, two R^B groups attached to the same atom or different atoms can together optionally form a ring;

p is an integer from 0 to 6;

q is 0;

R^{50} is independently selected at each occurrence from:

halogen, -NO$_2$, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -NR^{53}R^{54}, -S(=O)R^{52}, -S(=O)$_2$R^{52}, -S(=O)$_2$N(R^{52})$_2$, -S(=O)$_2$NR^{53}R^{54}, -NR^{52}S(=O)$_2$R^{52}, -NR^{52}S(=O)$_2$N(R^{52})$_2$, -NR^{52}S(=O)$_2$NR^{53}R^{54}, -C(O)R^{52}, -C(O)OR^{52}, -OC(O)R^{52}, -OC(O)OR^{52}, -OC(O)N(R^{52})$_2$, -OC(O)NR^{53}R^{54}, -NR^{52}C(O)R^{52}, -NR^{52}C(O)OR^{52}, -NR^{52}C(O)N(R^{52})$_2$, -NR^{52}C(O)NR^{53}R^{54}, -C(O)N(R^{52})$_2$, -C(O)NR^{53}R^{54}, -P(O)(OR^{52})$_2$, -P(O)(R^{52})$_2$, =O, =S, =N(R^{52});

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO$_2$, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -NR^{53}R^{54}, -S(=O)R^{52}, -S(=O)$_2$R^{52}, -S(=O)$_2$N(R^{52})$_2$, -S(=O)$_2$NR^{53}R^{54}, -NR^{52}S(=O)$_2$R^{52}, -NR^{52}S(=O)$_2$N(R^{52})$_2$, -NR^{52}S(=O)$_2$NR^{53}R^{54}, -C(O)R^{52}, -C(O)OR^{52}, -OC(O)R^{52}, -OC(O)OR^{52}, -OC(O)N(R^{52})$_2$, -OC(O)NR^{53}R^{54}, -NR^{52}C(O)R^{52}, -NR^{52}C(O)OR^{52}, -NR^{52}C(O)N(R^{52})$_2$, -NR^{52}C(O)NR^{53}R^{54}, -C(O)N(R^{52})$_2$, -C(O)NR^{53}R^{54}, -P(O)(OR^{52})$_2$, -P(O)(R^{52})$_2$, =O, =S, =N(R^{52}), C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, -NO$_2$, -CN, -OR^{52}, -SR^{52}, -N(R^{52})$_2$, -NR^{53}R^{54}, -S(=O)R^{52}, -S(=O)$_2$R^{52}, -S(=O)$_2$N(R^{52})$_2$, -S(=O)$_2$NR^{53}R^{54}, -NR^{52}S(=O)$_2$R^{52}, -NR^{52}S(=O)$_2$N(R^{52})$_2$, -NR^{52}S(=O)$_2$NR^{53}R^{54}, -C(O)R^{52}, -C(O)OR^{52}, -OC(O)R^{52}, -

$OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

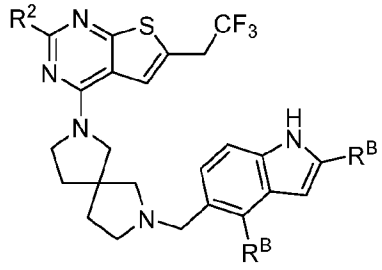
$-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, -

$NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, and $-P(O)(R^{52})_2$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle.

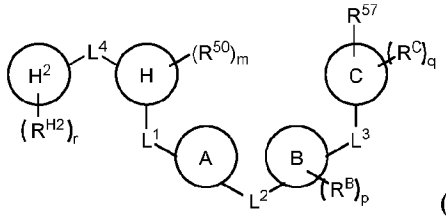
[0113] In certain aspects, a compound of Formula (I) may be represented by:



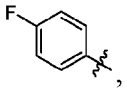
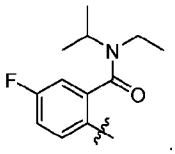
(I-F); wherein R^2 is selected from R^{50} and R^B is selected from halogen, -CN, $-OR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, C_{1-3} alkyl, and optionally substituted C_{1-3} alkyl.

[0114] In some embodiments, R^2 is selected from halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, R^2 is selected from halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, and C_{1-2} alkyl. In some embodiments, R^2 is selected from $-NH_2$, $-CH_3$, $-OCH_3$, $-CH_2OH$, and $-NHCH_3$. In some embodiments, R^B is selected from halogen, -CN, $-OR^{52}$, $-N(R^{52})_2$, and C_{1-2} alkyl.

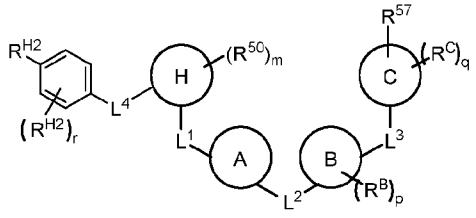
[0115] In certain aspects, a compound of Formula (I) may be represented by:



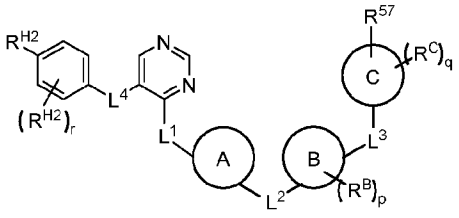
(I-G). In some embodiments, H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, and H^2 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle. In some embodiments, H is selected from C_{5-6} carbocycle and 5- to

6-membered heterocycle, and H^2 is selected from C_{5-6} carbocycle and 5- to 6-membered heterocycle. In some embodiments, H is selected from C_6 carbocycle and 6-membered heterocycle, such as phenyl, pyridyl, or pyrimidinyl. In some embodiments, L^4 is selected form -O-, -S-, -NH- and $-CH_2-$. In some embodiments, H^2 is selected from C_6 carbocycle and 6-membered heterocycle, such as phenyl. In some embodiments, H^2 is substituted with at least one fluoro. In some embodiments, R^{H2} is selected from R^{50}. In some embodiments, R^{H2} is selected from halo, $-C(O)R^{52}$, and $-C(O)N(R^{52})_2$. In some embodiments, R^{H2} is selected from halo, $-C(O)R^{52}$, and $-C(O)N(R^{52})_2$, wherein R^{52} is selected from hydrogen and C_{1-10} alkyl. In some embodiments, H^2 is  , optionally further substituted with one or more R^{H2}. In some embodiments, H^2 is  .

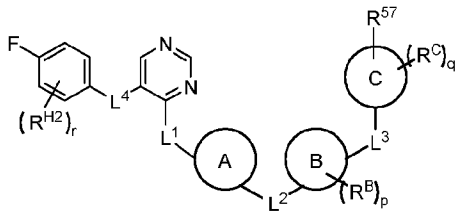
[0116] In certain aspects, a compound of Formula (I) may be represented by:



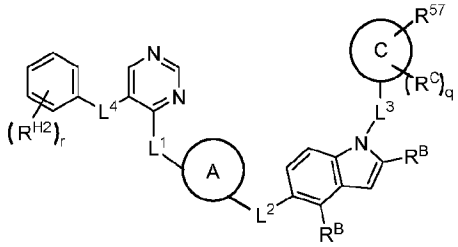
(I-H), such as



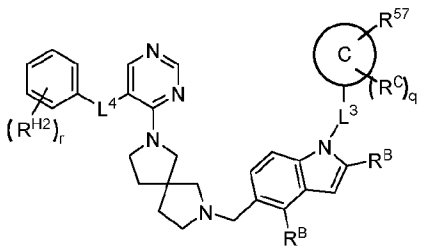
(I-I),



(I-J),

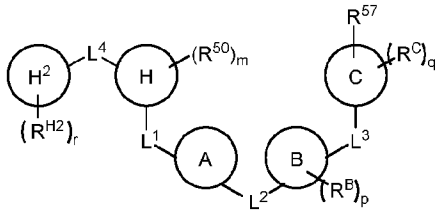


(I-K), or



(I-L). In some embodiments, L^4 is selected from -O- and -NH-.

[0117] In certain aspects, the present disclosure provides a compound of Formula (I-G):

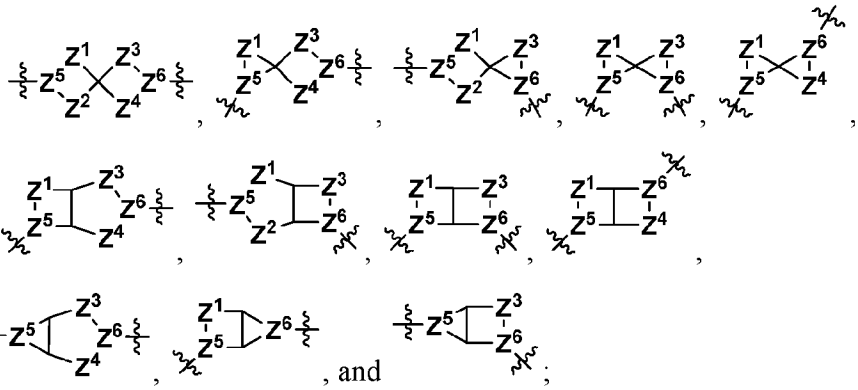


(I-G);

or a pharmaceutically acceptable salt, isotopic form, or prodrug thereof, wherein:

H is selected from C_{5-6} carbocycle and 5- to 6-membered heterocycle;

H^2 is selected from C_{5-6} carbocycle and 5- to 6-membered heterocycle;

A is selected from 

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-, -C(O)-, and -C(R^{A1})(R^{A2})-C(O)-, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or -C(R^{A1})(R^{A2})-C(O)-;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1, L^2, L^3 and L^4 is independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -N(R^{51})$S(O)_2$-, -$S(O)_2N(R^{51})$-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2N(R^{51})$-, and -N(R^{51})S(O)N(R^{51})- or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2, or L^3 can together optionally form a bridge or ring;

R^{50} is, at each occurrence, independently selected from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -

$OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, -

$P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, -

$NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

R^{B} is, at each occurrence, independently selected from R^{50}, or two R^{B} groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^{H2} is independently selected at each occurrence from R^{50}, or two R^{H2} groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^{C} is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^{C} groups attached to the same atom or different atoms can together optionally form a bridge or ring;

r is an integer from 1 to 6; and

each of m, p and q is independently an integer from 0 to 12.

[0118] In certain embodiments, the present disclosure provides a stereoisomer of a compound of Formula (I). In some embodiments, the stereoisomer is in enantiomeric excess. In some embodiments, the stereoisomer is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, enantiomeric excess. In some embodiments, the stereoisomer is in greater than 95% enantiomeric excess, such as greater than 99% enantiomeric excess.

[0119] In certain embodiments, the present disclosure provides a stereoisomer of a compound of Formula (I). In some embodiments, the stereoisomer is in diastereomeric excess. In some embodiments, the stereoisomer is provided in at least 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some embodiments, the stereoisomer is provided in greater than 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9%, diastereomeric excess. In some embodiments, the stereoisomer is in greater than 95% diastereomeric excess, such as greater than

99% diastereomeric excess.

[0120] In certain embodiments, the compound of Formula (I) is preferably used as a non-racemic mixture, wherein one enantiomer is present in excess of its corresponding enantiomer. Typically, such mixture will contain a mixture of the two isomers in a ratio of at least about 9:1, preferably at least 19:1. In some embodiments, the compound is provided in at least 96% enantiomeric excess, meaning the compound has less than 2% of the corresponding enantiomer. In some embodiments, the compound is provided in at least 96% diastereomeric excess, meaning the compound has less than 2% of the corresponding diastereomer.

[0121] In certain embodiments, the compound of Formula (I) is preferably used as a non-racemic mixture wherein the (+)-isomer is the major component of the mixture. Typically, such mixture will contain no more than about 10% of the (–)-isomer, meaning the ratio of (+)- to (–)-isomers is at least about 9:1, and preferably less than 5% of the (–)-isomer, meaning the ratio of (+)- to (–)-isomers is at least about 19:1. In some embodiments, the compound used has less than 2% of the (–)-isomer, meaning it has an enantiomeric excess of at least about 96%. In some embodiments, the compound has an enantiomeric excess of at least 98%. In some embodiments, the compound has an enantiomeric excess of at least 99%.

[0122] In certain embodiments, the compound of Formula (I) is preferably used as a non-racemic mixture wherein the (–)-isomer is the major component of the mixture. Typically, such mixture will contain no more than about 10% of the (+)-isomer, meaning the ratio of (–)- to (+)-isomers is at least about 9:1, and preferably less than 5% of the (+)-isomer, meaning the ratio of (–)- to (+)-isomers is at least about 19:1. In some embodiments, the compound used has less than 2% of the (+)-isomer, meaning it has an enantiomeric excess of at least about 96%. In some embodiments, the compound has an enantiomeric excess of at least 98%. In some embodiments, the compound has an enantiomeric excess of at least 99%.

[0123] In certain aspects, a compound of the disclosure covalently binds to menin and inhibits the interaction of menin with MLL. Such bonding may lead to an increase in the affinity of the compound for menin, which is an advantageous property in many applications, including therapeutic and diagnostic uses. In some embodiments, the compounds of the disclosure comprise electrophilic groups capable of reacting with a nucleophilic group present in a menin protein. Suitable electrophilic groups are described throughout the application, while suitable nucleophilic groups include, for example, cysteine moieties present in the binding domain of a menin protein. Without wishing to be bound by theory, a cysteine residue in the menin binding domain may react with the electrophilic group of a compound of the disclosure, leading to formation of a conjugate product. In some embodiments, the compounds of the disclosure are

capable of covalently bonding to the cysteine residue at position 329 of a menin isoform 2 (SEQ ID NO: 2) or cysteine 334 in menin isoform 1 (SEQ ID NO: 1). In some embodiments, the disclosure provides a conjugate of a compound of the disclosure with a menin protein. For example, the disclosure provides a conjugate of a compound of the disclosure with menin, bound at the cysteine residue 329 of menin isoform 2 (SEQ ID NO: 2) or cysteine 334 in menin isoform 1 (SEQ ID NO: 1).

[0124] In some embodiments, for a compound of Formula (I), one or more of R^B and R^C, when present, comprises a functional group that covalently reacts with one or more residues on menin. In some embodiments, the functional group covalently reacts with one or more cysteine residues on menin. In some embodiments, the functional group covalently reacts with a cysteine on menin at position 329 relative to SEQ ID NO: 2 when optimally aligned or position 334 relative to SEQ ID NO: 1 when optimally aligned. In some embodiments, the functional group covalently reacts with one or more residues on menin selected from cysteine 329, cysteine 241, and/or cysteine 230 on menin relative to SEQ ID NO: 2 when optimally aligned. In some embodiments, the functional group covalently reacts with cysteine 329 relative to SEQ ID NO: 2 when optimally aligned.

[0125] In some embodiments, for a compound of Formula (I), one or more of R^B and R^C, when present, comprises a moiety that covalently reacts with one or more residues on menin. In some embodiments, one or more of R^B and R^C, when present, comprises a moiety that covalently reacts with one or more isoforms of menin, for example, isoform 1 (SEQ ID NO: 1), isoform 2 (SEQ ID NO: 2) or isoform 3 (SEQ ID NO: 3) of menin. In certain embodiments, one or more of R^B and R^C, when present, comprises a moiety that covalently reacts with menin, wherein the menin protein shares 60% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or 99% or more sequence identity with isoform 1 (SEQ ID NO: 1), isoform 2 (SEQ ID NO: 2) or isoform 3 (SEQ ID NO: 3).

[0126] In some embodiments, for a compound of Formula (I), one or more of R^B and R^C, when present, comprises an electrophilic group that is susceptible to nuclephilic attack from a residue on menin. Any suitable electrophilic moiety known to one of skill in the art to bind to nuclephilic residues, for example, any electrophilic moiety known to bind to cysteine residues, is contemplated herein. In some embodiments, one or more of R^B and R^C, when present, comprises a moiety other than an electrophile, wherein the moiety is capable of binding to or covalently reacting with a residue on menin. In some embodiments, a compound or salt of Formula (I) is capable of (a) binding covalently to menin and (b) inhibiting the interation of menin and MLL.

[0127] In some embodiments, for a compound of Formula (I), R^C comprises a functional group

that covalently reacts with one or more residues on menin. In some embodiments, the functional group covalently reacts with one or more cysteine residues on menin. In some embodiments, the functional group covalently reacts with a cysteine on menin at position 329 relative to SEQ ID NO: 2 when optimally aligned or position 334 relative to SEQ ID NO: 1 when optimally aligned.

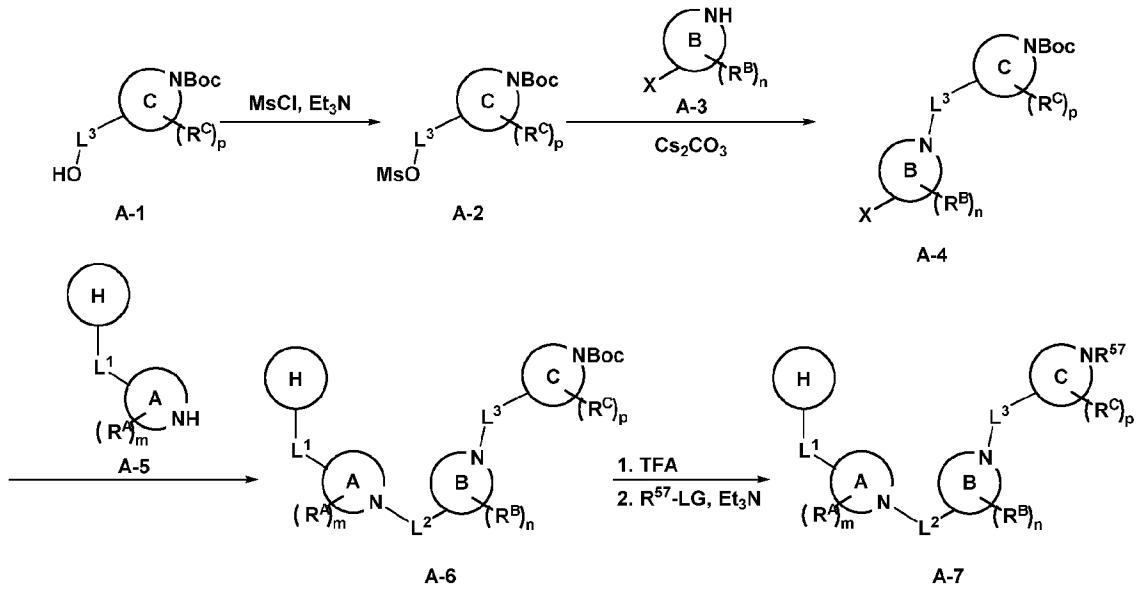
[0128] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof can be chosen to provide stable moieties and compounds.

[0129] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques known in the art. Materials used herein are either commercially available or prepared by synthetic methods generally known in the art. These schemes are not limited to the compounds listed in the examples or by any particular substituents, which are employed for illustrative purposes. Although various steps are described and depicted in **Scheme 1** and **Examples 1-11**, the steps in some cases may be performed in a different order than the order shown in **Scheme 1** and **Examples 1-11**. Various modifications to these synthetic reaction schemes may be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application. Numberings or R groups in each scheme do not necessarily correspond to that of the claims or other schemes or tables herein.

[0130] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10 °C to 200 °C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, e.g., taking place at about atmospheric pressure within a temperature range of about -10 °C to about 110 °C over a period of about 1 to about 24 hours; reactions left to run overnight average a period of about 16 hours.

[0131] In general, compounds of the disclosure may be prepared by the following reaction scheme:

Scheme 1



[0132] In some embodiments, a compound of Formula **A-7** may be prepared according to **Scheme 1**. For example, methanesulfonyl chloride can be added to a solution of alcohol **A-1** and triethylamine to afford mesylate **A-2**. Addition of mesylate **A-2** to a solution of Cs_2CO_3 and amine **A-3** can provide a compound of Formula **A-4**. Coupling of **A-4** to amine **A-5** can proceed according to methods known in the art to give a compound of Formula **A-6**. Addition of TFA can reveal the free amine, which can optionally be reacted with R^{57}-LG, wherein LG is a suitable leaving group, to afford a compound of Formula **A-7**.

[0133] In some embodiments, a compound of the present disclosure, for example, a compound of a formula given in **Table 1**, is synthesized according to one of the general routes outlined in **Scheme 1**, **Examples 1-11**, or by methods generally known in the art. In some embodiments, exemplary compounds may include, but are not limited to, a compound or salt thereof selected from **Table 1**.

Table 1

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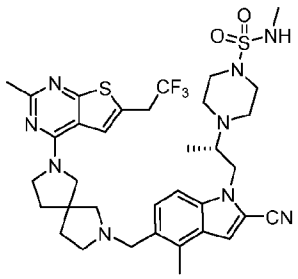
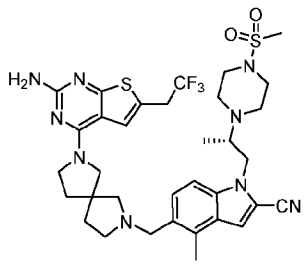
1		2	

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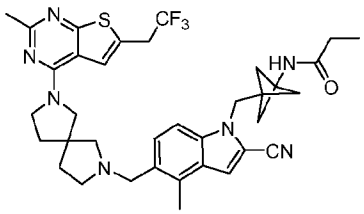
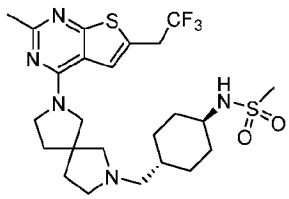
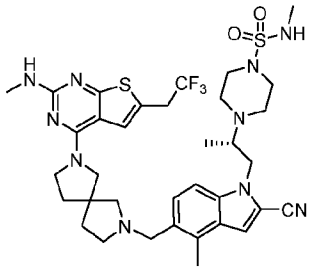
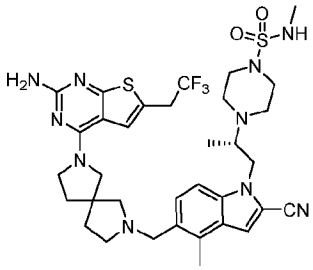
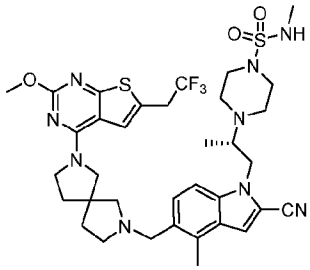
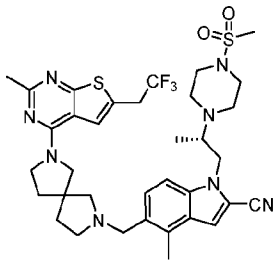
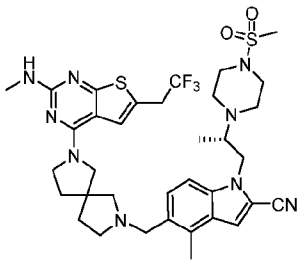
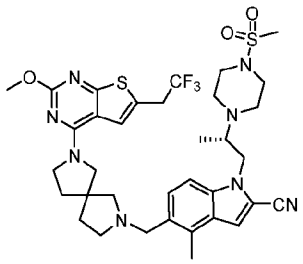
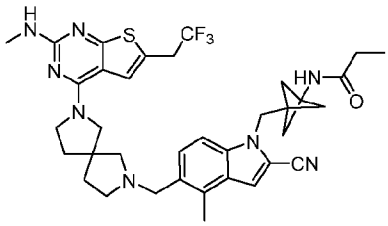
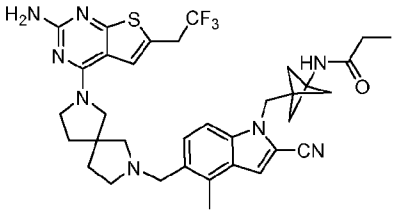
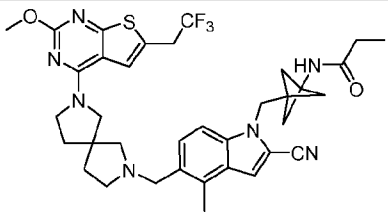
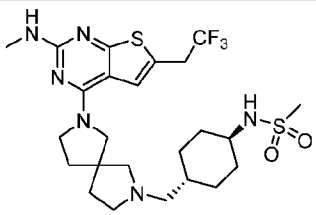
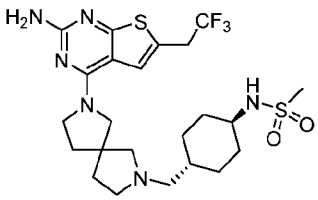
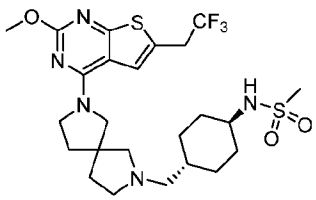
3		4	
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	

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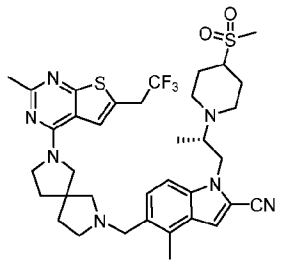
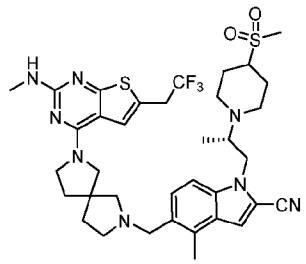
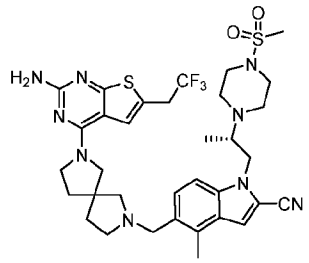
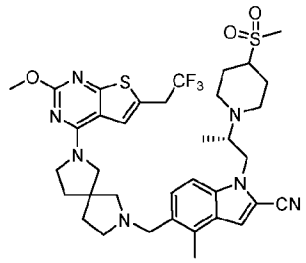
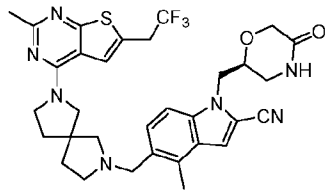
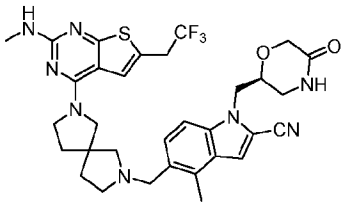
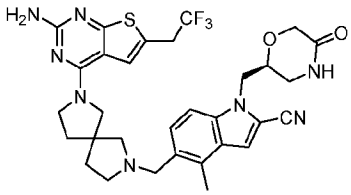
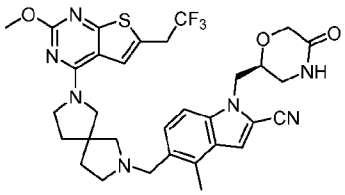
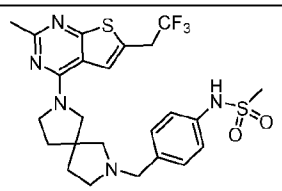
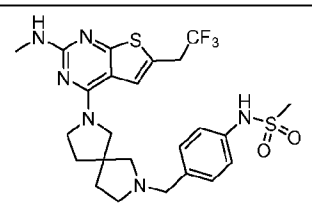
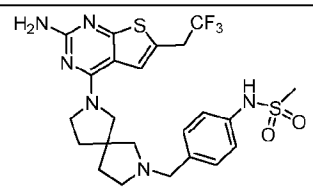
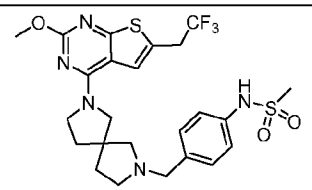
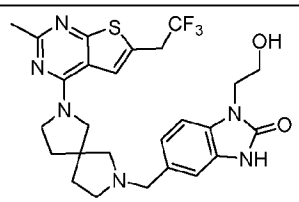
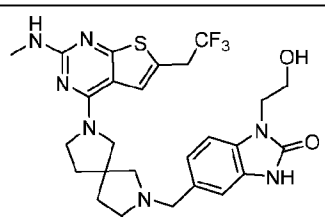
17		18	
19		20	
21		22	
23		24	
25		26	
27		28	
29		30	

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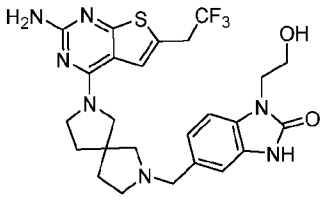
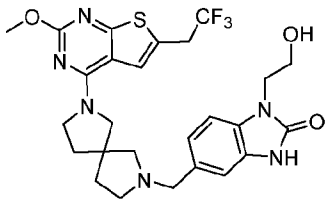
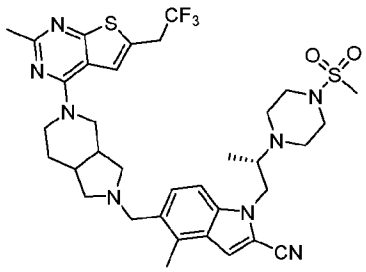
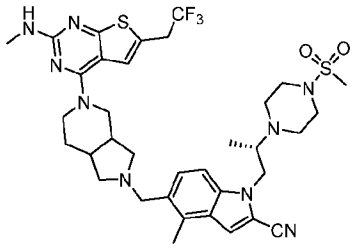
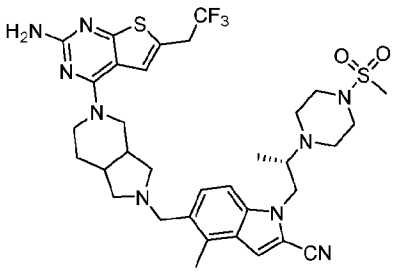
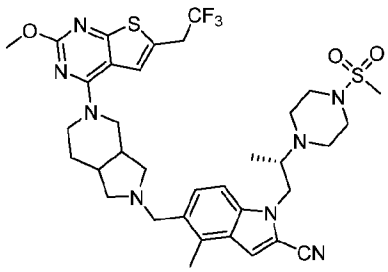
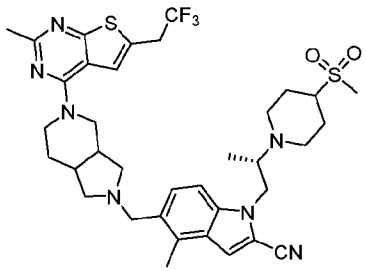
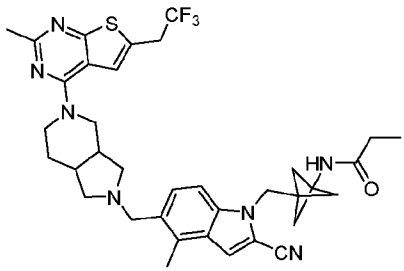
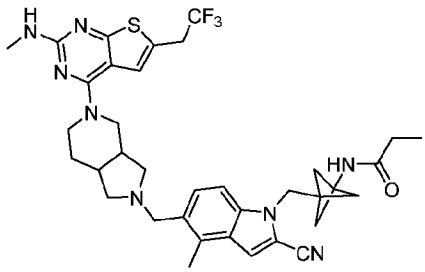
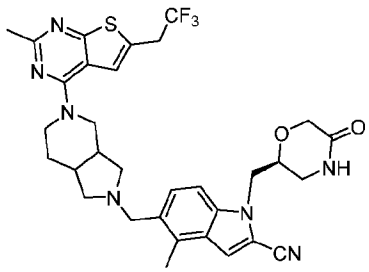
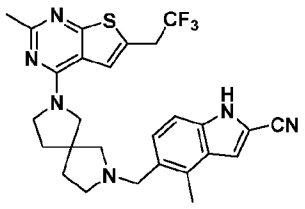
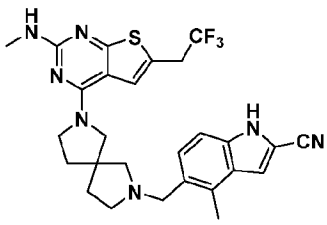
31		32	
33		34	
35		36	
37		38	
39		40	
41		42	

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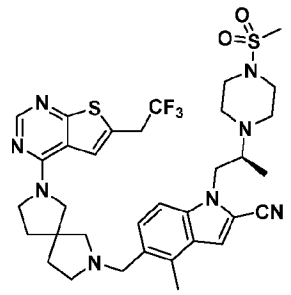
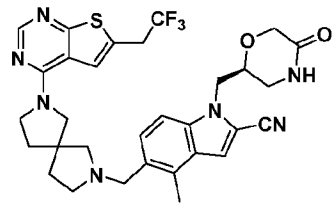
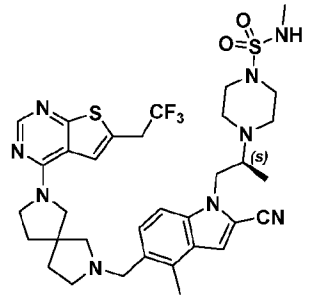
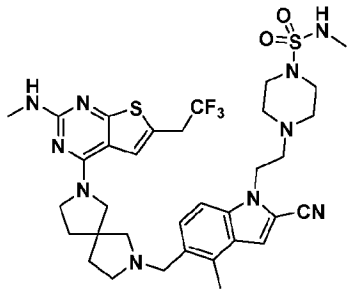
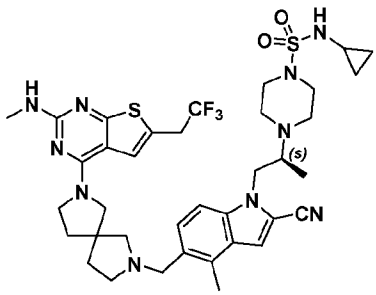
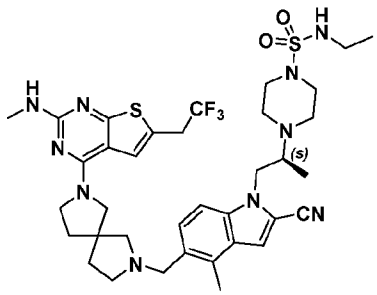
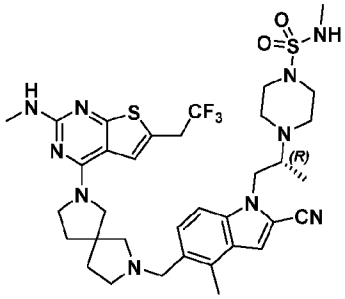
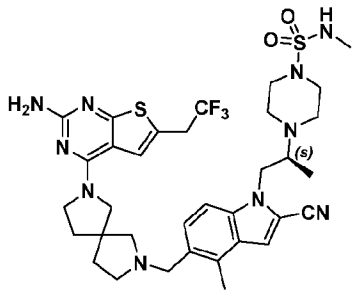
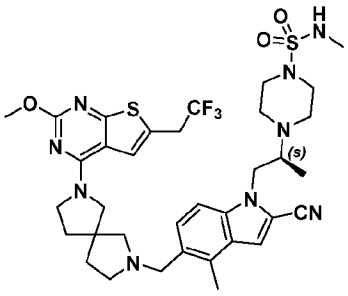
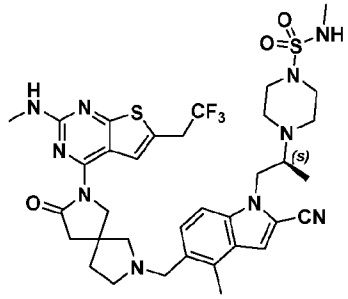
43		44	
45		46	
47		48	
49		50	
51		52	

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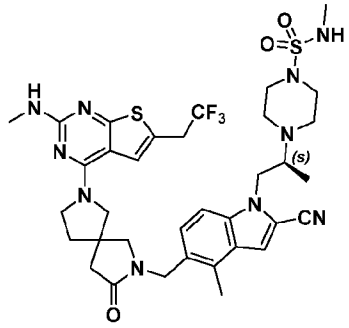
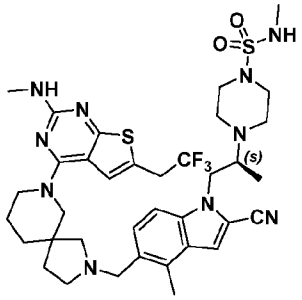
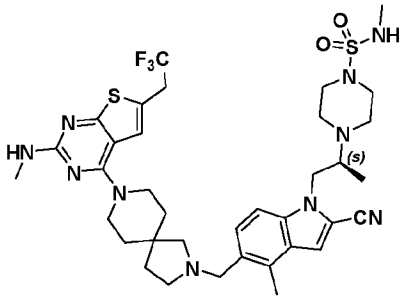
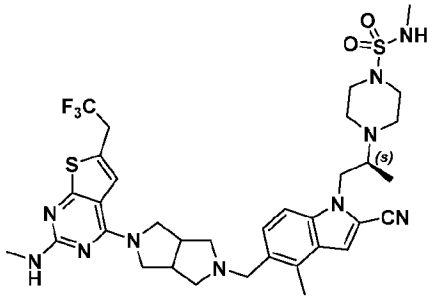
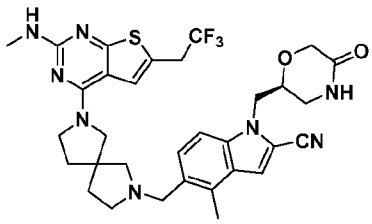
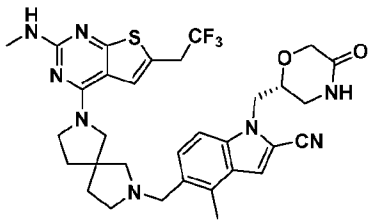
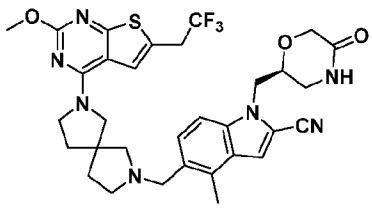
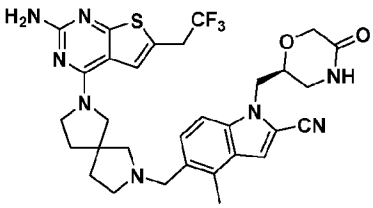
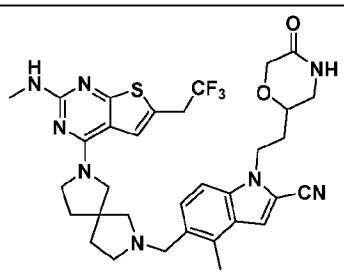
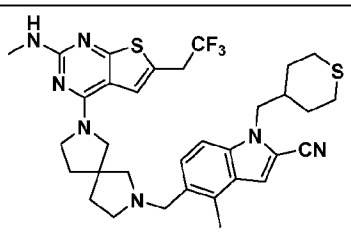
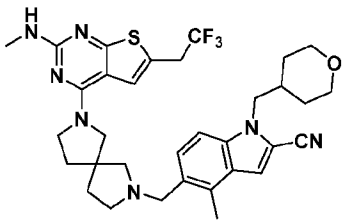
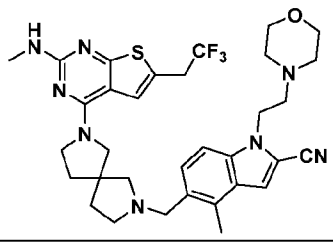
53		54	
55		56	
57		58	
59		60	
61		62	
63		64	

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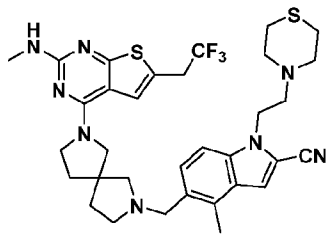
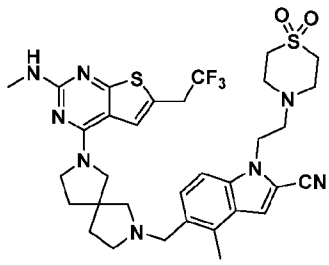
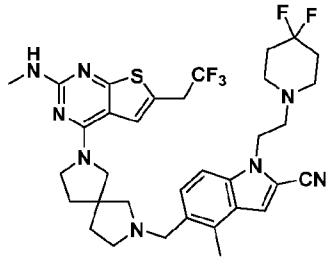
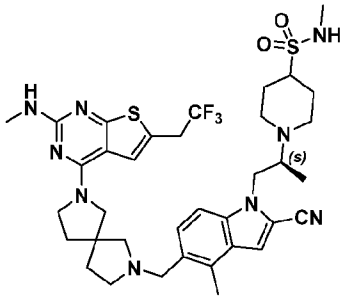
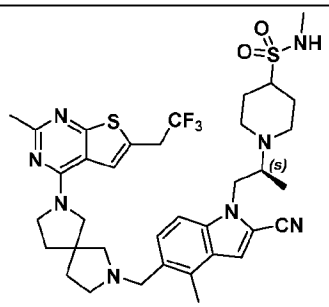
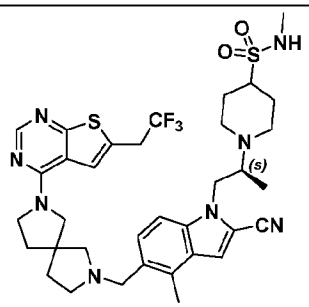
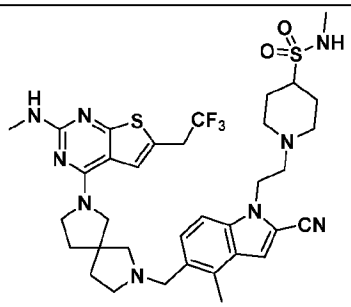
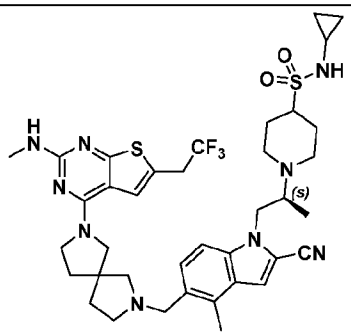
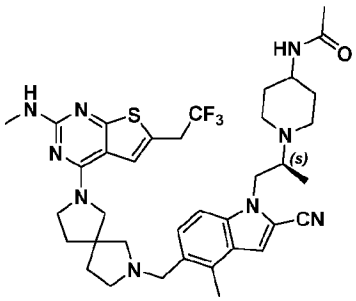
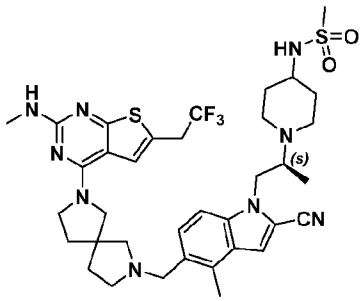
65		66	
67		68	
69		70	
71		72	
73		74	

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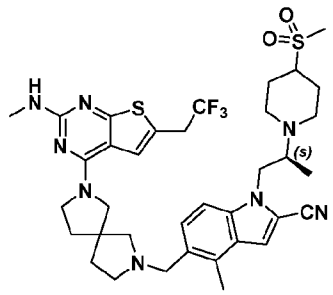
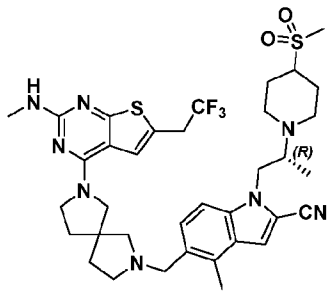
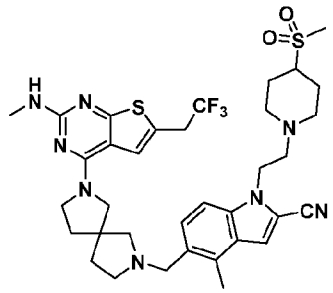
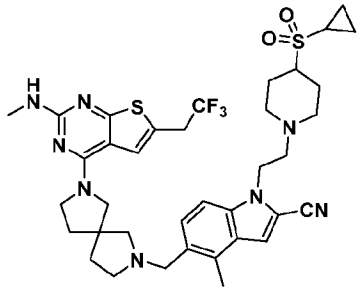
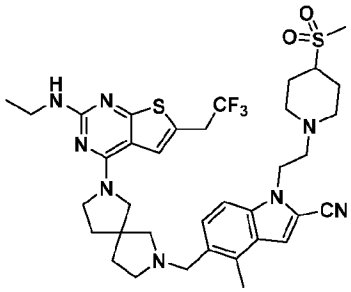
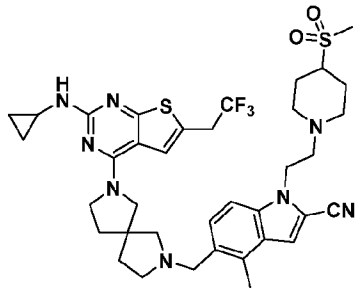
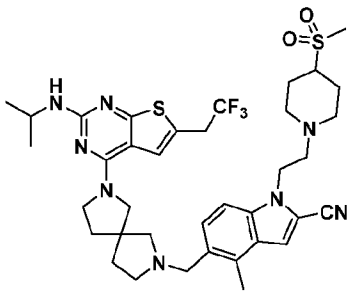
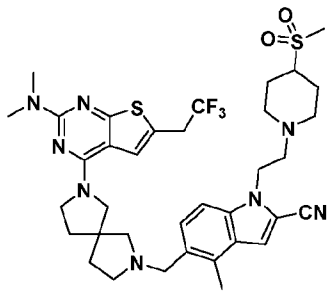
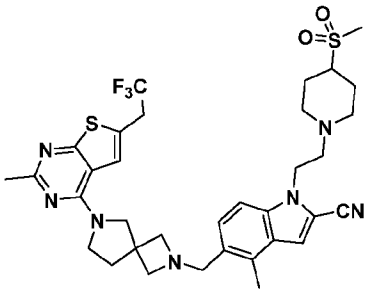
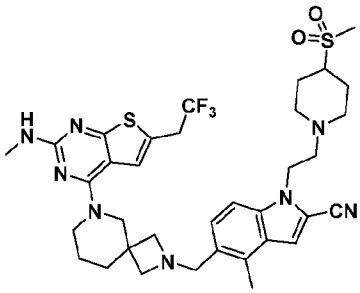
75		76	
77		78	
79		80	
81		82	
83		84	

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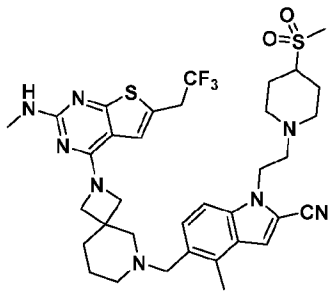
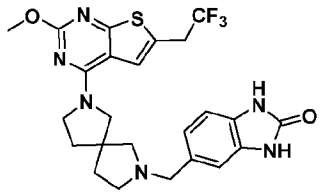
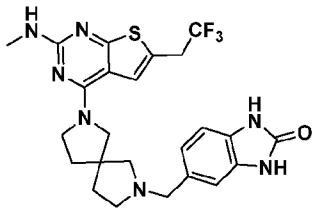
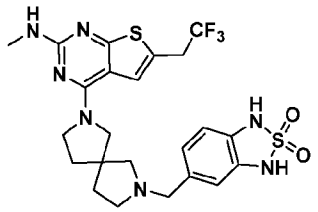
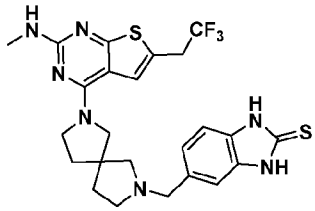
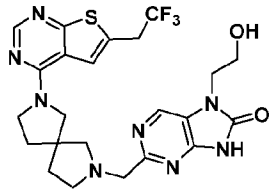
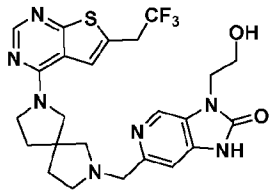
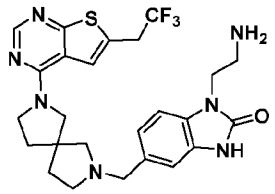
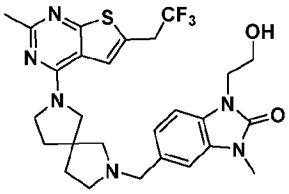
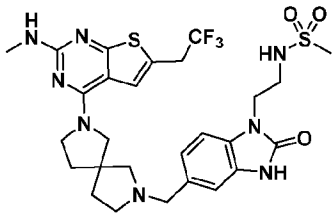
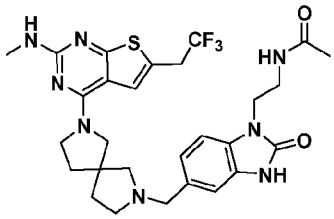
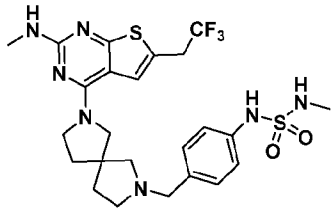
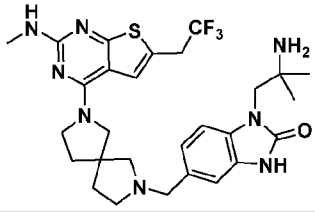
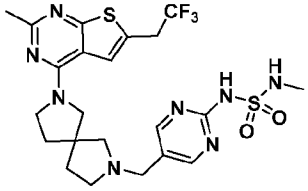
85		86	
87		88	
89		90	
91		92	
93		94	
95		96	
97		98	

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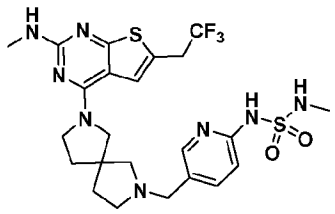
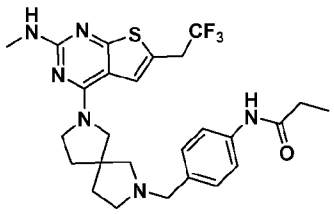
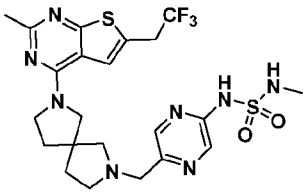
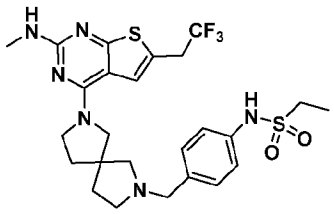
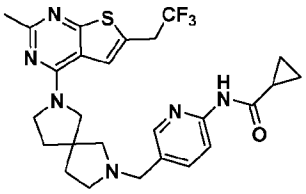
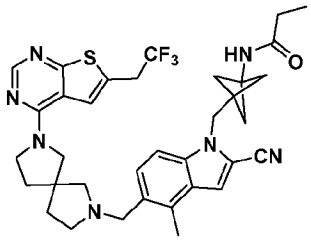
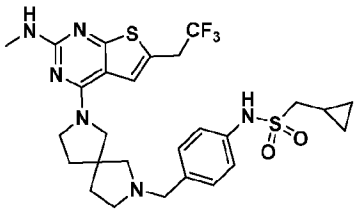
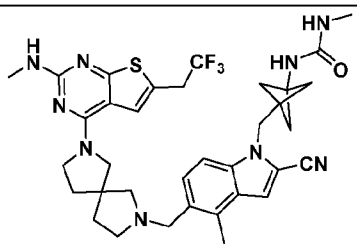
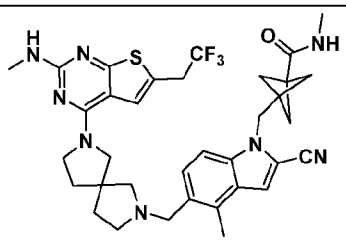
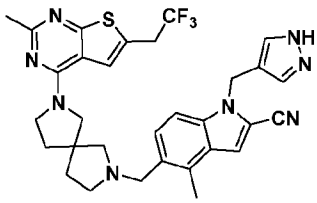
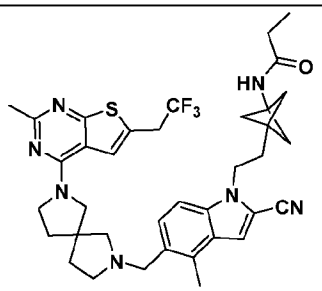
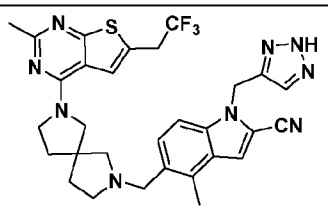
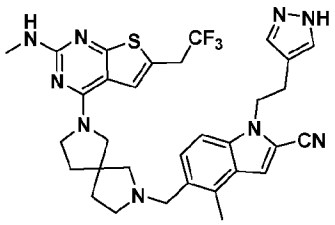
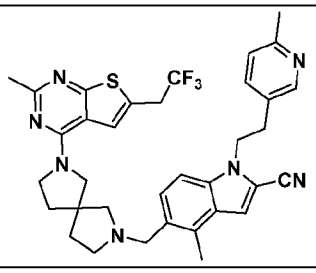
99		100	
101		102	
103		104	
105		106	
107		108	
109		110	
111		112	

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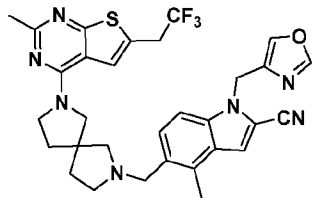
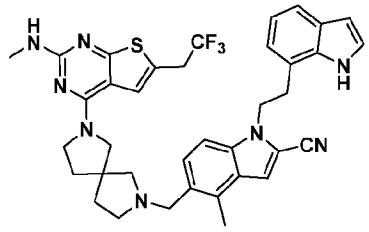
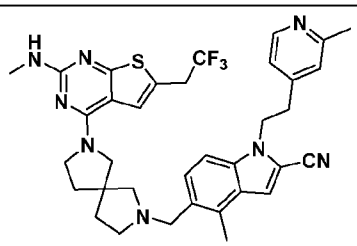
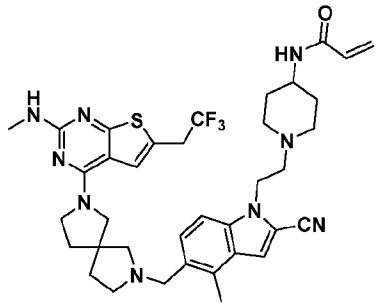
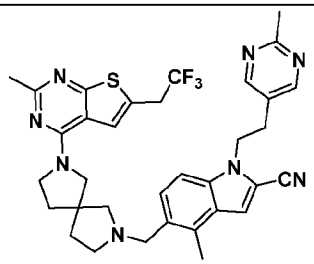
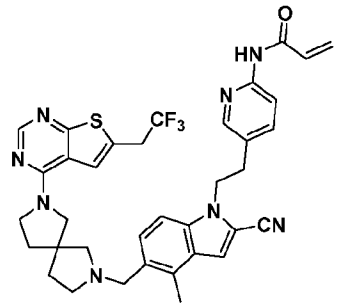
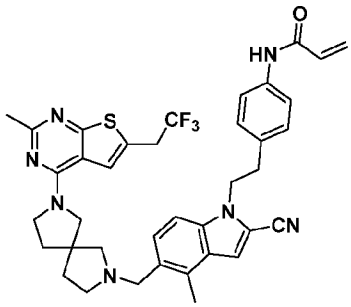
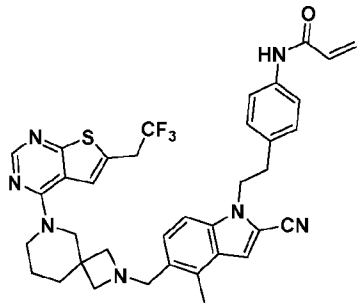
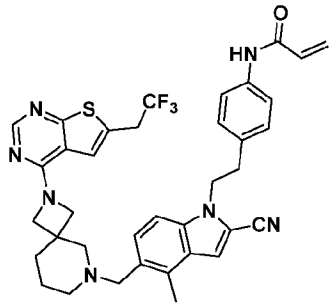
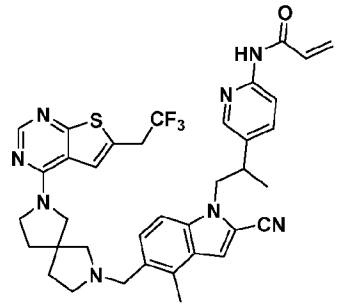
113		114	
115		116	
117		118	
119		120	
121		122	

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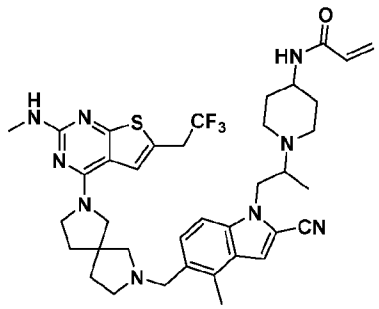
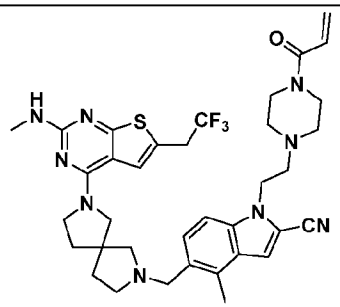
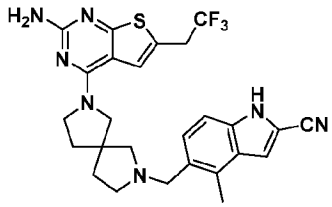
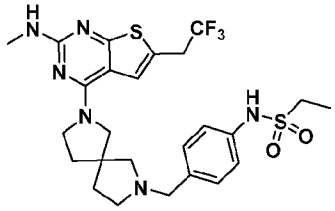
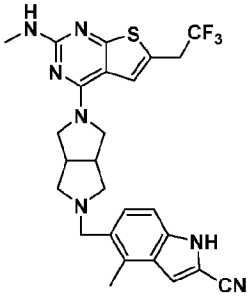
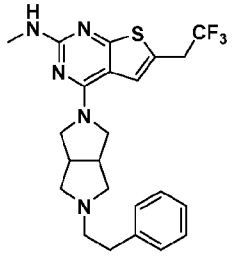
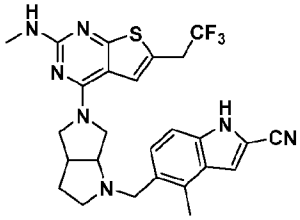
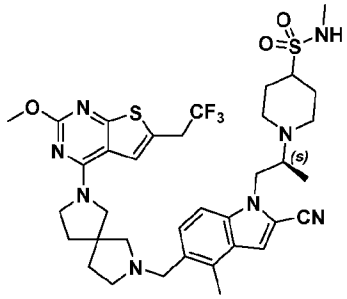
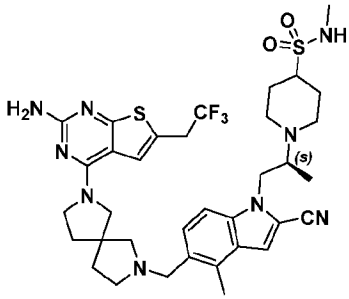
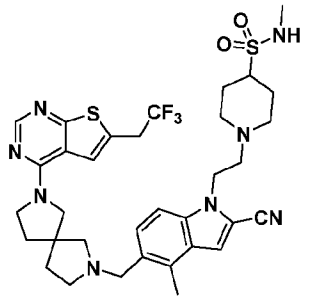
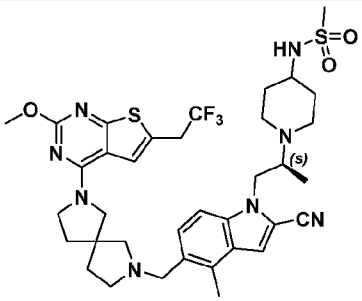
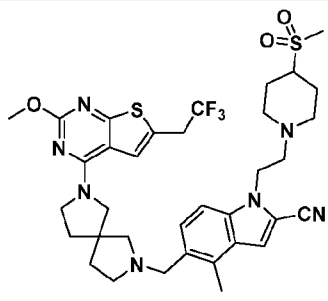
123		124	
125		126	
127		128	
129		130	
131		132	
133		134	

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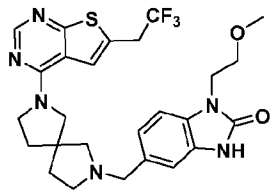
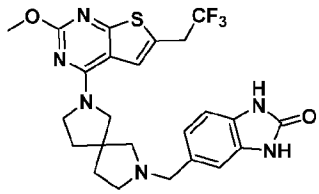
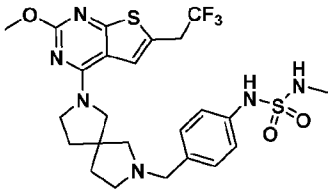
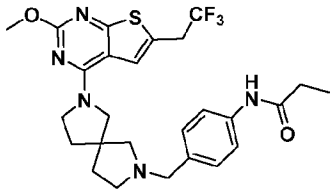
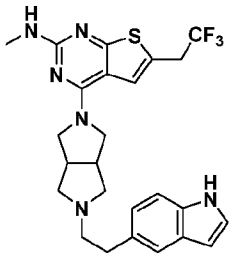
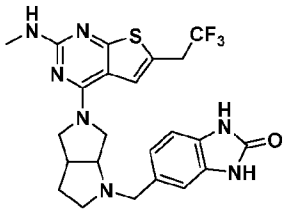
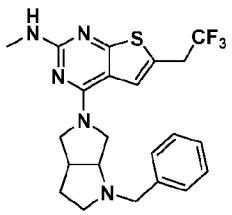
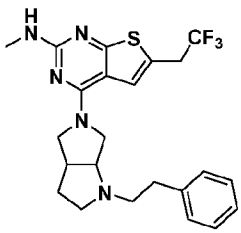
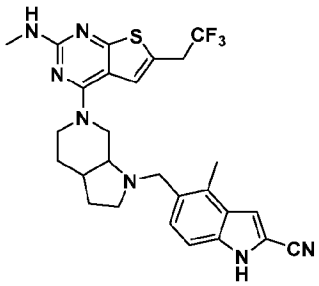
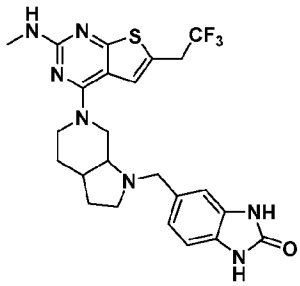
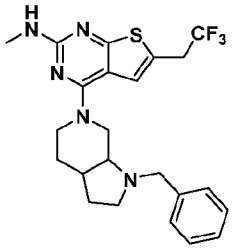
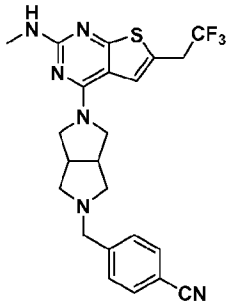
135		136	
137		138	
139		140	
141		142	
143		144	
145		146	

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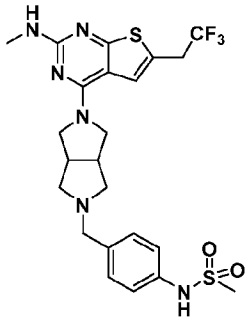
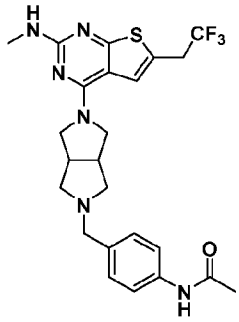
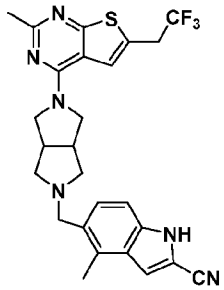
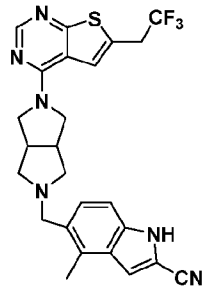
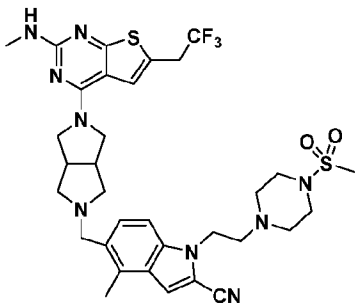
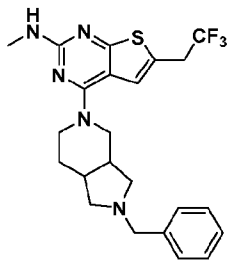
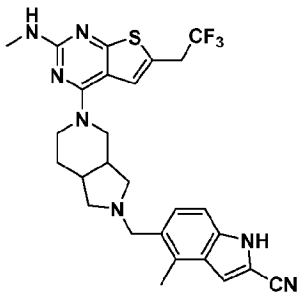
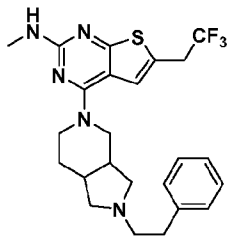
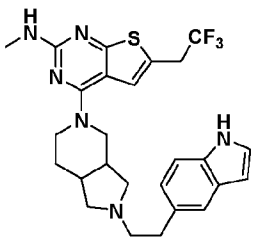
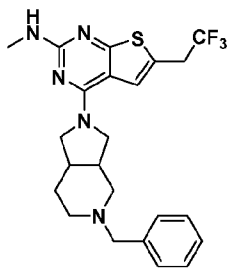
147		148	
149		150	
151		152	
153		154	
155		156	

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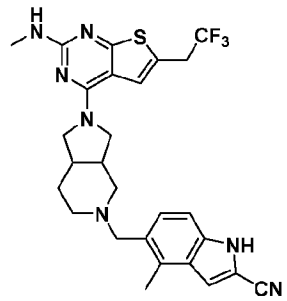
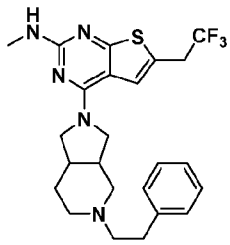
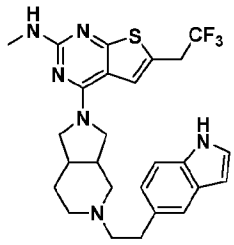
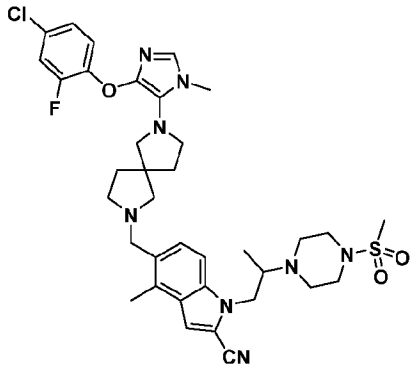
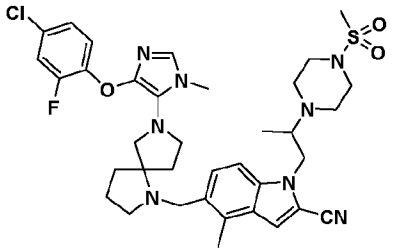
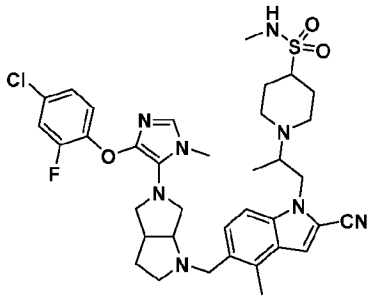
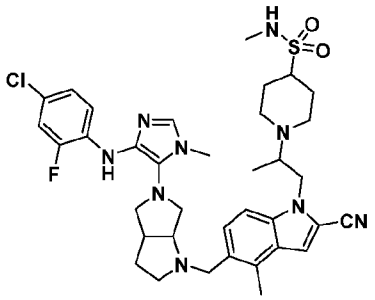
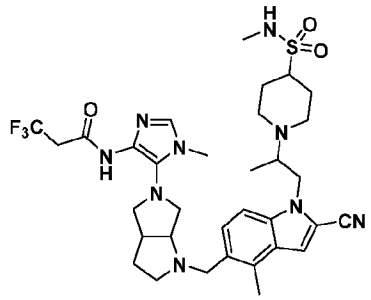
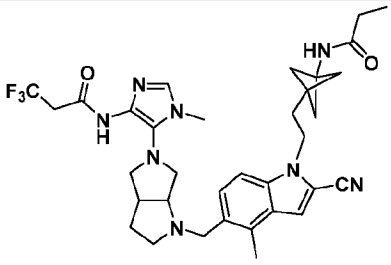
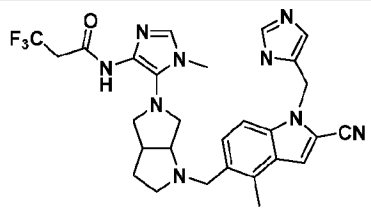
157		158	
159		160	
161		162	
163		164	
165		166	

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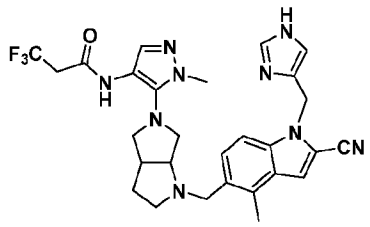
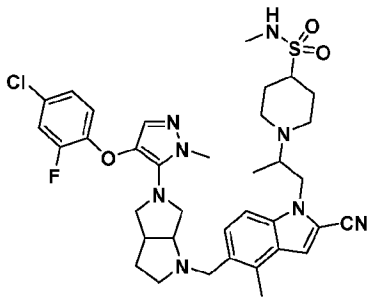
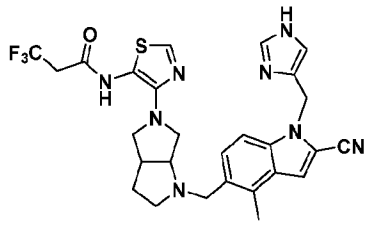
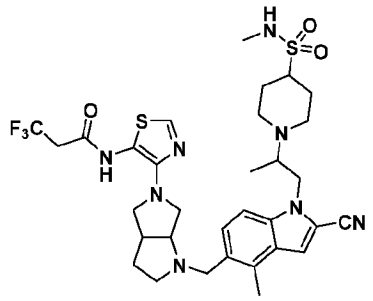
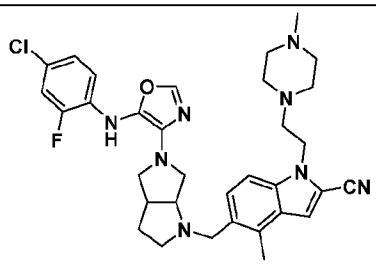
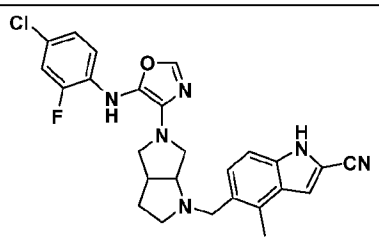
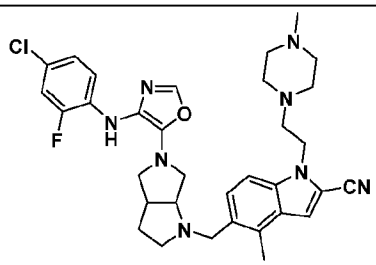
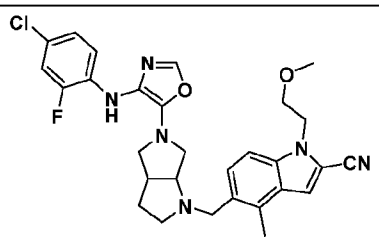
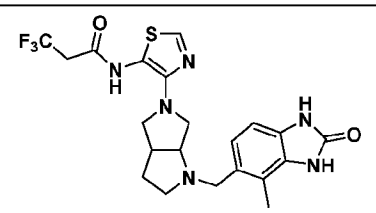
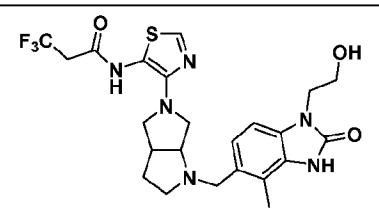
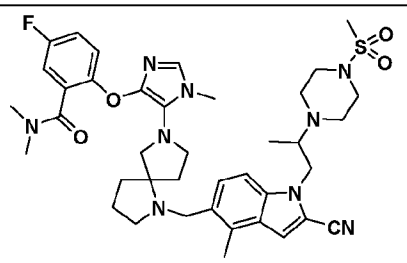
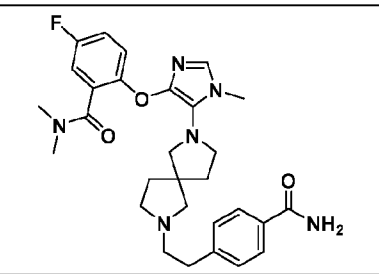
167		168	
169		170	
171		172	
173		174	
175		176	
177		178	

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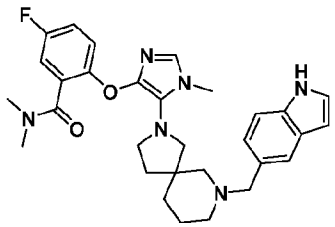
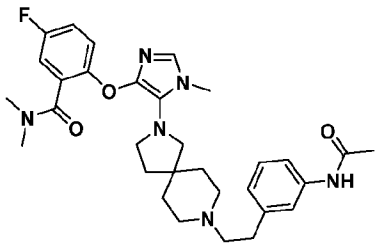
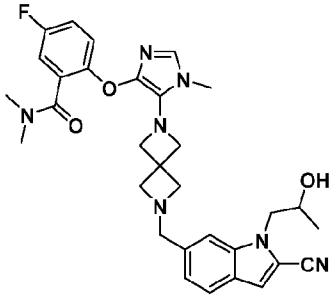
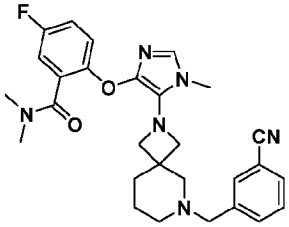
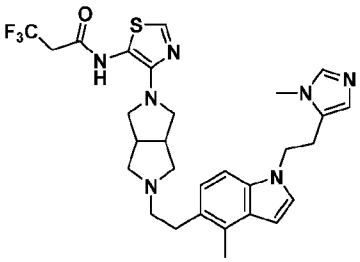
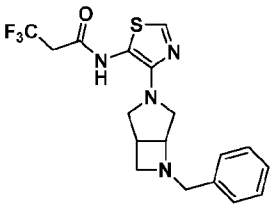
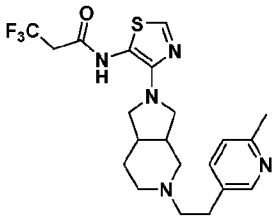
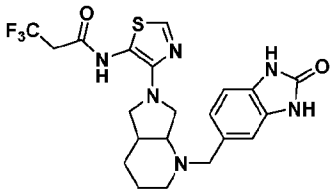
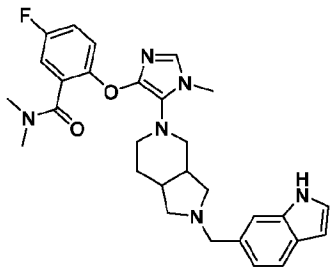
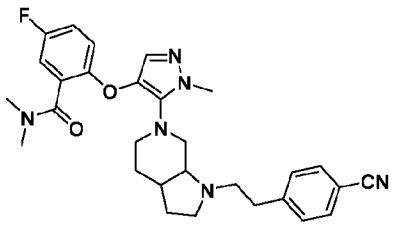
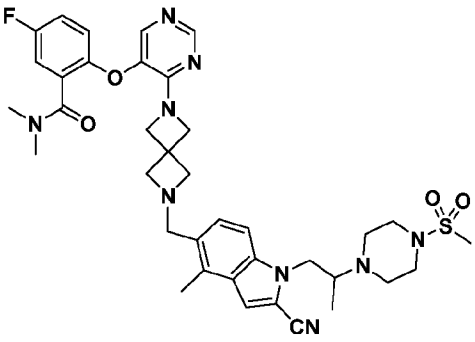
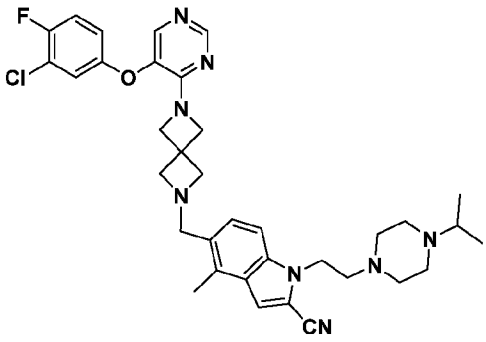
179		180	
181		182	
183		184	
185		186	
187		188	
189		190	

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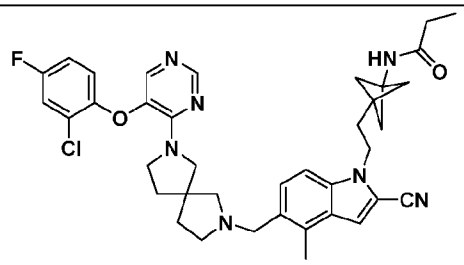
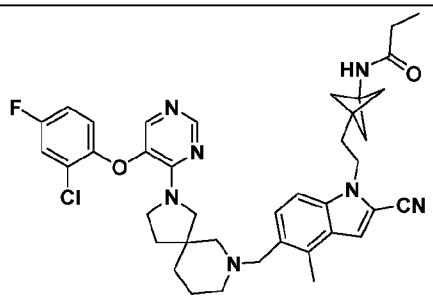
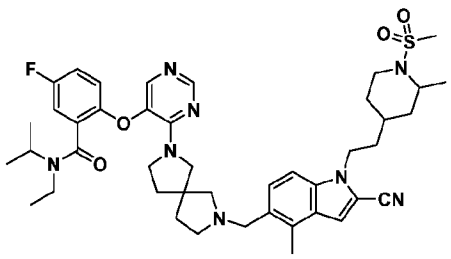
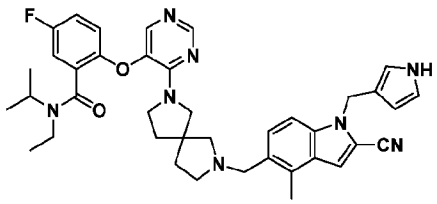
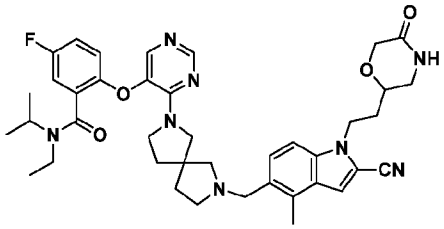
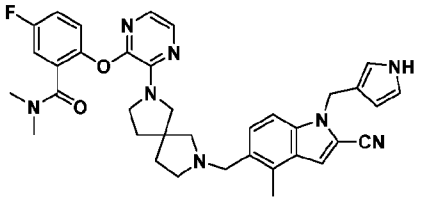
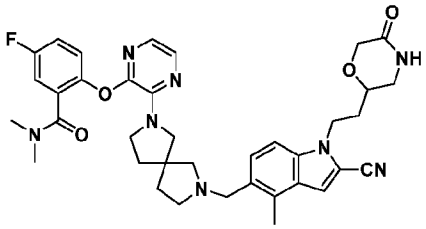
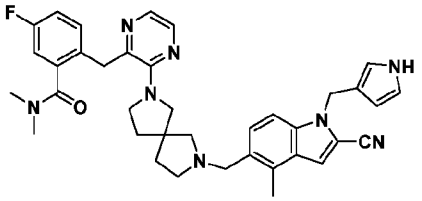
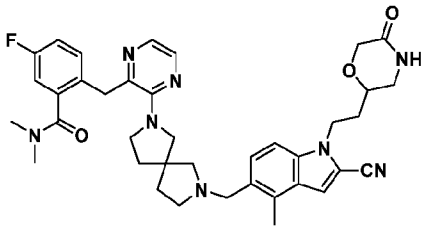
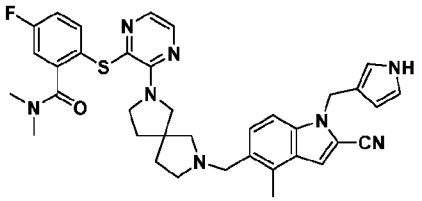
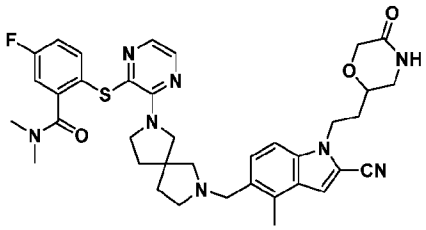
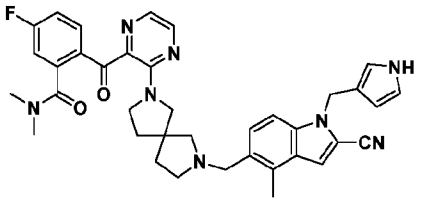
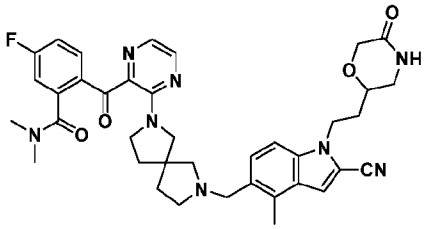
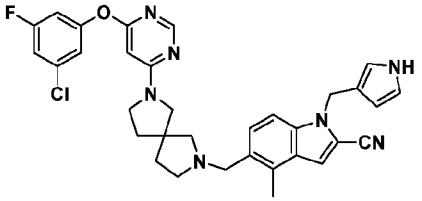
191		192	
193		194	
195		196	
197		198	
199		200	
201		202	
203		204	

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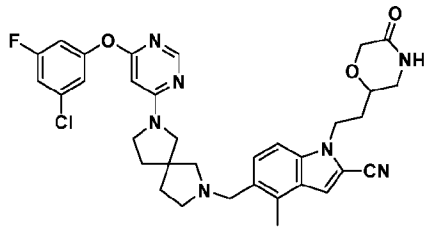
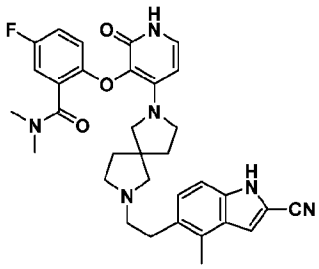
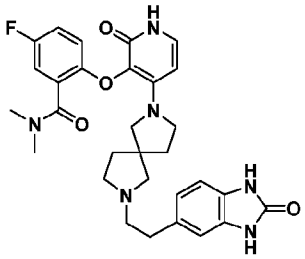
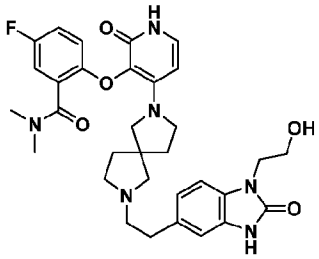
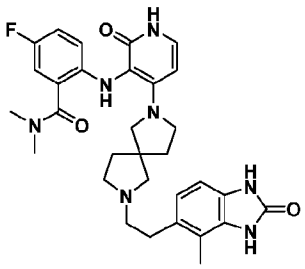
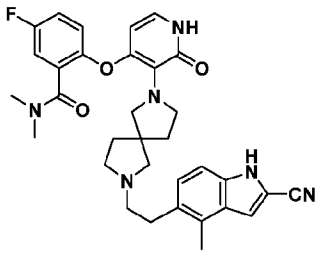
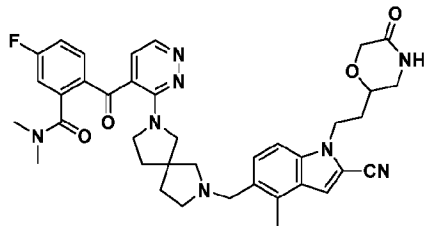
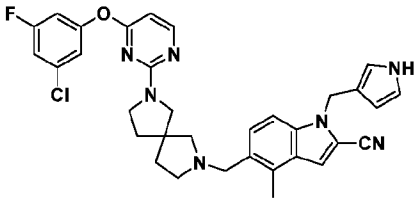
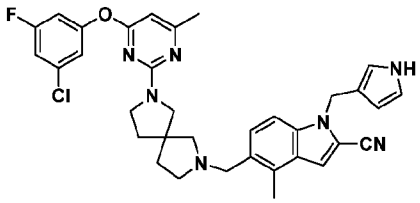
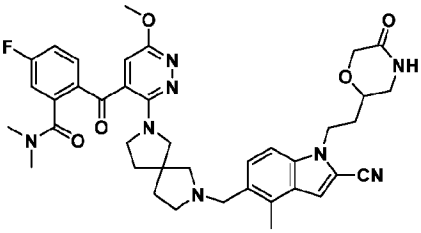
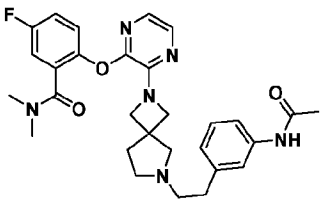
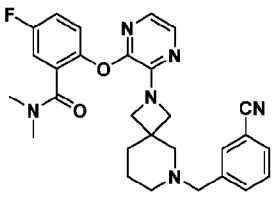
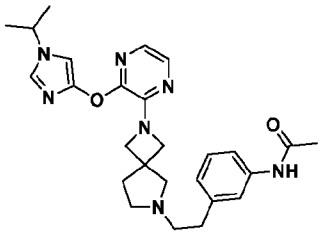
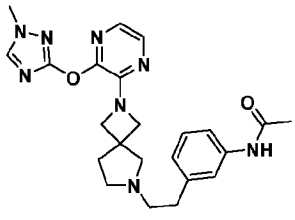
205		206	
207		208	
209		210	
211		212	
213		214	
215		216	
217		218	

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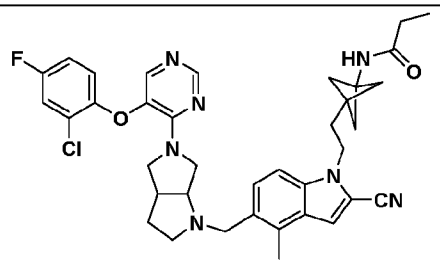
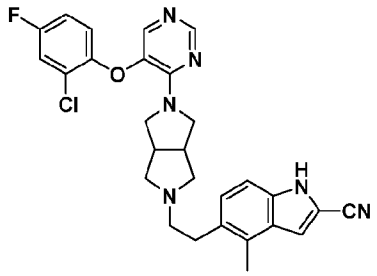
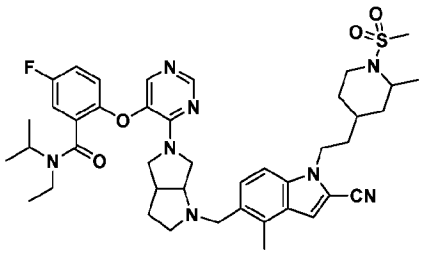
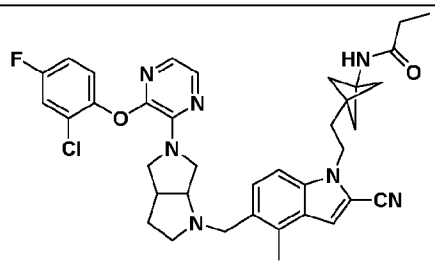
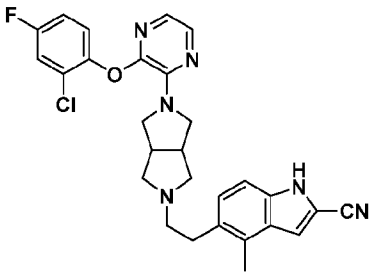
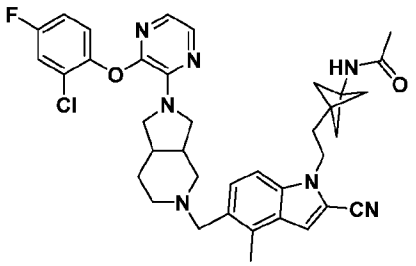
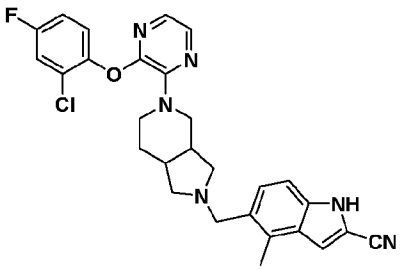
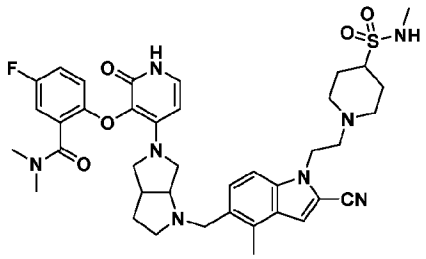
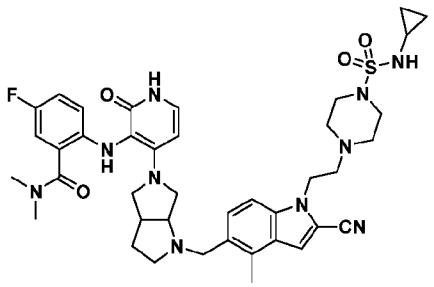
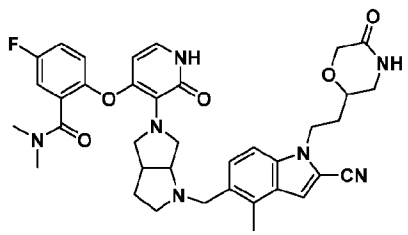
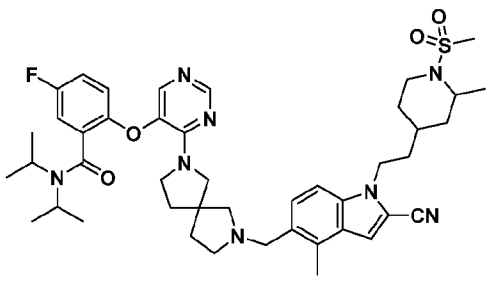
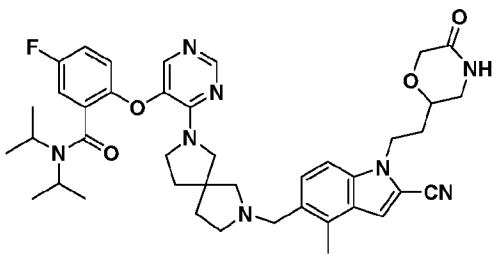
219		220	
221		222	
223		224	
225		226	
227		228	
229		230	

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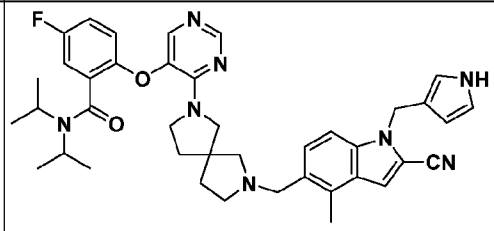
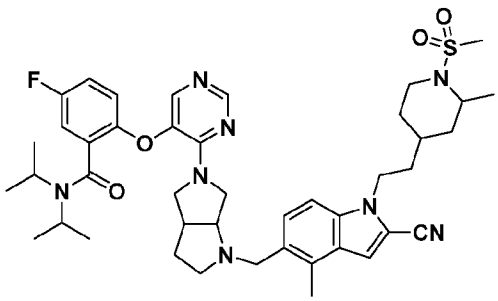
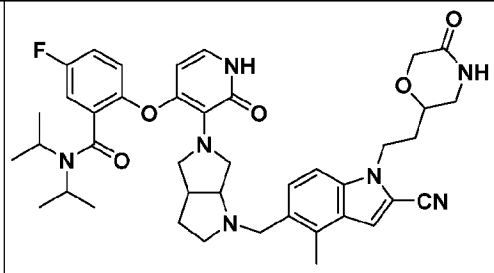
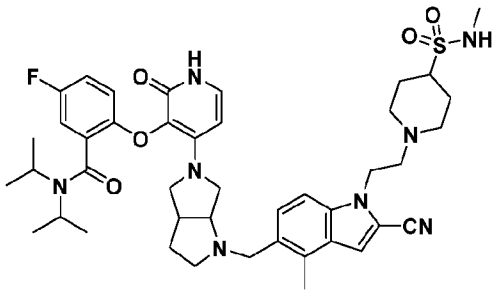
231		232	
233		234	

[0134] Pharmaceutical Compositions

[0135] The compositions and methods of the present disclosure may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound or salt of Formula (I) and a pharmaceutically acceptable carrier.

[0136] In some embodiments, the pharmaceutical composition is formulated for oral administration. In other embodiments, the pharmaceutical composition is formulated for injection. In still more embodiments, the pharmaceutical compositions comprise a compound as disclosed herein and an additional therapeutic agent (e.g., anticancer agent). Non-limiting examples of such therapeutic agents are described herein below.

[0137] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[0138] In certain embodiments, a composition of a compound or salt of Formula (I) is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other

embodiments, a compound or salt of Formula (I) is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the composition is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the composition is administered topically.

[0139] The compound of Formula (I), or a pharmaceutically acceptable salt thereof, may be effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg per day, from 0.5 to 100 mg per day, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used in some embodiments. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[0140] In some embodiments, a compound or salt of Formula (I) is administered in a single dose. Typically, such administration will be by injection, e.g., intravenous injection, in order to introduce the agent quickly. However, other routes are used as appropriate. In some embodiments, a single dose of a compound or salt of Formula (I) is used for treatment of an acute condition.

[0141] In some embodiments, a compound or salt of Formula (I) is administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, or more than six times per day. In other embodiments, dosing is about once a month, once every two weeks, once a week, or once every other day. In another embodiment, a compound or salt of Formula (I) and another agent are administered together about once per day to about 6 times per day. In another embodiment, the administration of a compound or salt of Formula (I) and an agent continues for less than about 7 days. In yet another embodiment, the administration continues for more than about 6 days, more than about 10 days, more than about 14 days, more than about 28 days, more than about two months, more than about six months, or one year or more. In some cases, continuous dosing is achieved and maintained as long as necessary.

[0142] Administration of a compound or salt of Formula (I) may continue as long as necessary. In some embodiments, a compound of the disclosure is administered for more than 1, more than 2, more than 3, more than 4, more than 5, more than 6, more than 7, more than 14, or more than 28 days. In some embodiments, a compound of the disclosure is administered 28 days or less, 14 days or less, 7 days or less, 6 days or less, 5 days or less, 4 days or less, 3 days or less, 2 days or less, or 1 day or a part thereof. In some embodiments, a compound or salt of Formula (I) is

administered chronically on an ongoing basis, e.g., for the treatment of chronic effects.

[0143] In some embodiments, a compound or salt of Formula (I) is administered in dosages. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. Dosing for a compound or salt of Formula (I) may be found by routine experimentation in light of the instant disclosure.

[0144] In some embodiments, a compound or salt of Formula (I) is formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

[0145] Provided herein are pharmaceutical compositions comprising a compound or salt of Formula (I) and a pharmaceutically acceptable diluent(s), excipient(s), or carrier(s). In certain embodiments, the compounds or salts described are administered as pharmaceutical compositions in which a compound or salt of Formula (I) is mixed with other active ingredients, as in combination therapy. Encompassed herein are all combinations of active ingredients set forth in the combination therapies section below and throughout this disclosure. In specific embodiments, the pharmaceutical compositions include one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof.

[0146] A pharmaceutical composition, as used herein, refers to a mixture of a compound or salt of Formula (I) with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, practicing the methods of treatment or use provided herein, therapeutically effective amounts of a compound or salt of Formula (I) are administered in a pharmaceutical composition to a mammal having a disease, disorder or medical condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject,

the potency of the compound used and other factors. A compound or salt of Formula (I) may be used singly or in combination with one or more therapeutic agents as components of mixtures.

[0147] In one embodiment, a compound or salt of Formula (I) is formulated in an aqueous solution. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, a compound or salt of Formula (I) is formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein a compound or salt of Formula (I) is formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

[0148] In another embodiment, a compound or salt of Formula (I) is formulated for oral administration. A compound or salt of Formula (I) may be formulated by combining the active compounds with, e.g., pharmaceutically acceptable carriers or excipients. In various embodiments, a compound or salt of Formula (I) is formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

[0149] In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with a compound or salt of Formula (I), optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0150] In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification

purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

[0151] In certain embodiments, a therapeutically effective amount of a compound or salt of Formula (I) is formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules, contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

[0152] In other embodiments, a therapeutically effective amount of a compound or salt of Formula (I) is formulated for buccal or sublingual administration. Formulations suitable for buccal or sublingual administration include, by way of example only, tablets, lozenges, or gels. In still other embodiments, a compound or salt of Formula (I) is formulated for parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (e.g., in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection as sterile suspensions, solutions or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In additional embodiments, a suspension of a compound or salt of Formula (I) is prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. In certain embodiments, the active agent is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0153] In still other embodiments, a compound or salt of Formula (I) is administered topically. A compound or salt of Formula (I) may be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compositions optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0154] In yet other embodiments, a compound or salt of Formula (I) is formulated for transdermal administration. Transdermal formulations may employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In various embodiments, such patches are constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. In additional embodiments, the transdermal delivery of a compound or salt of Formula (I) is accomplished by means of iontophoretic patches and the like. In certain embodiments, transdermal patches provide controlled delivery of a compound or salt of Formula (I). In specific embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. In alternative embodiments, absorption enhancers are used to increase absorption. Absorption enhancers or carriers include absorbable pharmaceutically acceptable solvents that assist passage through the skin. For example, in one embodiment, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing a compound or salt of Formula (I), optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[0155] In other embodiments, a compound or salt of Formula (I) is formulated for administration by inhalation. Various forms suitable for administration by inhalation include, but are not limited to, aerosols, mists or powders. Pharmaceutical compositions of a compound or salt of Formula (I) are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In specific embodiments, the dosage unit of a pressurized aerosol is determined by providing a valve to deliver a metered amount. In certain embodiments, capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator are formulated containing a powder mix of a compound or salt of Formula (I) and a suitable powder base such as lactose or starch.

[0156] In still other embodiments, a compound or salt of Formula (I) is formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly

suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[0157] In certain embodiments, pharmaceutical compositions are formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients may be optionally used as suitable. Pharmaceutical compositions comprising a compound or salt of Formula (I) are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0158] Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and a compound or salt of Formula (I), sometimes referred to herein as an active agent or ingredient. The active ingredient may be in free-acid or free-base form, or in a pharmaceutically acceptable salt form. Additionally, a compound or salt of Formula (I) may be in unsolvated or solvated forms with pharmaceutically acceptable solvents such as water and ethanol. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

[0159] Methods for the preparation of compositions comprising a compound or salt of Formula (I) include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound or salt of Formula (I). Semi-solid compositions include, but are not limited to, gels, suspensions and creams. The form of the pharmaceutical compositions of a compound or salt of Formula (I) include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[0160] In some embodiments, a pharmaceutical composition comprising a compound or salt of Formula (I) takes the form of a liquid where the agents are present in solution, in suspension or both. Typically when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

[0161] In certain embodiments, aqueous suspensions contain one or more polymers as suspending agents. Polymers include water-soluble polymers such as cellulosic polymers, e.g., hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[0162] Pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of a compound described herein. The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, e.g., polyethylene glycol 400, and glycol ethers.

[0163] Pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[0164] Additionally, useful compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[0165] Pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as

benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[0166] Pharmaceutical compositions may include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

[0167] Pharmaceutical compositions may include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

[0168] In certain embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

[0169] In certain embodiments, delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers useful herein. In certain embodiments, organic solvents such as N-methylpyrrolidone are also employed. In additional embodiments, a compound or salt of Formula (I) is delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials may be used herein. In some embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

[0170] In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

[0171] In some embodiments, the concentration of a compound or salt of Formula (I) provided in a pharmaceutical compositions is less than about:100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%,

0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v or v/v.

[0172] In some embodiments, the concentration of a compound or salt of Formula (I) provided in a pharmaceutical composition is greater than about: 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25%, 19%, 18.75%, 18.50%, 18.25%, 18%, 17.75%, 17.50%, 17.25%, 17%, 16.75%, 16.50%, 16.25%, 16%, 15.75%, 15.50%, 15.25%, 15%, 14.75%, 14.50%, 14.25%, 14%, 13.75%, 13.50%, 13.25%, 13%, 12.75%, 12.50%, 12.25%, 12%, 11.75%, 11.50%, 11.25%, 11%, 10.75%, 10.50%, 10.25%, 10%, 9.75%, 9.50%, 9.25%, 9%, 8.75%, 8.50%, 8.25%, 8%, 7.75%, 7.50%, 7.25%, 7%, 6.75%, 6.50%, 6.25%, 6%, 5.75%, 5.50%, 5.25%, 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 1.25%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v, or v/v.

[0173] In some embodiments, the concentration of a compound or salt of Formula (I) is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v.

[0174] In some embodiments, the concentration of a compound or salt of Formula (I) is in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[0175] In some embodiments, the amount of a compound or salt of Formula (I) is equal to or less

than about: 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

[0176] In some embodiments, the amount of a compound or salt of Formula (I) is more than about: 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5g, 7 g, 7.5g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

[0177] In some embodiments, the amount of one or more compounds of the disclosure is in the range of 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

[0178] For use in the therapeutic applications described herein, kits and articles of manufacture are also provided. In some embodiments, such kits comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers are formed from a variety of materials such as glass or plastic.

[0179] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include those found in, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, the container(s) includes a compound or salt of Formula (I), optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[0180] For example, a kit typically includes one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included. A label is optionally on or associated with the container. For example, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself, a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In addition, a label is used to indicate that the contents are to be used for a specific therapeutic application. In addition, the label indicates directions for use of the contents, such as in the methods described herein. In certain embodiments, the pharmaceutical composition is presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. Or, the pack or dispenser device is accompanied by instructions for administration. Or, the pack or dispenser is accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0181] Methods

[0182] The present disclosure provides a method of inhibiting the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) comprising contacting a cell with an effective amount of a compound or salt of Formula (I). Inhibition of the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) can be assessed and demonstrated by a wide variety of ways known in the art. Non-limiting examples include a showing of (a) a decrease in menin binding to one or more proteins or protein fragments (e.g., MLL1, MLL2, an MLL fusion protein, an MLL Partial Tandem Duplication, or a peptide fragment thereof); (b) a decrease in cell proliferation and/or cell viability; (c) an increase in cell differentiation; (d) a decrease in the levels of downstream targets of MLL1, MLL2, an MLL

fusion protein, and/or an MLL Partial Tandem Duplication (e.g., *Hoxa9*, *DLX2*, *PBX3*, and *Meis1*); and/or (e) decrease in tumor volume and/or tumor volume growth rate. Kits and commercially available assays can be utilized for determining one or more of the above.

[0183] The disclosure also provides methods of using the compounds or pharmaceutical compositions of the present disclosure to treat disease conditions, including but not limited to conditions implicated by menin, MLL, MLL1, MLL2, and/or MLL fusion proteins (*e.g.*, cancer).

[0184] In some embodiments, a method for treatment of cancer is provided, the method comprising administering an effective amount of any of the foregoing pharmaceutical compositions comprising a compound or salt of Formula (I) to a subject in need thereof. In some embodiments, the cancer is mediated by an MLL fusion protein. In other embodiments, the cancer is leukemia, breast cancer, prostate cancer, pancreatic cancer, lung cancer, liver cancer, skin cancer, or a brain tumor. In certain embodiments, the cancer is leukemia. In some embodiments, the cancer comprises a solid tumor.

[0185] In some embodiments, the disclosure provides a method of treating a disorder in a subject in need thereof, wherein the method comprises determining if the subject has an MLL fusion protein and, if the subject is determined to have an MLL fusion protein, administering to the subject a therapeutically effective dose of a compound or salt of Formula (I).

[0186] MLL fusion proteins have also been identified in hematological malignancies (e.g., cancers that affect blood, bone marrow and/or lymph nodes). Accordingly, certain embodiments are directed to administration of a compound or salt of Formula (I) to a patient in need of treatment of a hematological malignancy. Such malignancies include, but are not limited to leukemias and lymphomas. For example, the presently disclosed compounds can be used for treatment of diseases such as Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Chronic myelogenous leukemia (CML), Acute monocytic leukemia (AMoL), hairy cell leukemia, and/or other leukemias. In other embodiments, the compounds are can be used for treatment of lymphomas such as all subtypes of Hodgkins lymphoma or non-Hodgkins lymphoma.

[0187] Determining whether a tumor or cancer comprises an MLL fusion protein can be undertaken by assessing the nucleotide sequence encoding the MLL fusion protein, by assessing the amino acid sequence of the MLL fusion protein, or by assessing the characteristics of a putative MLL fusion protein.

[0188] Methods for detecting an MLL fusion protein nucleotide sequence are known by those of skill in the art. These methods include, but are not limited to, polymerase chain reaction-

restriction fragment length polymorphism (PCR-RFLP) assays, polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) assays, real-time PCR assays, PCR sequencing, mutant allele-specific PCR amplification (MASA) assays, direct sequencing, primer extension reactions, electrophoresis, oligonucleotide ligation assays, hybridization assays, TaqMan assays, SNP genotyping assays, high resolution melting assays and microarray analyses. In some embodiments, the MLL fusion protein is identified using a direct sequencing method of specific regions (e.g., exon 2 and/or exon 3) in the MLL or fusion partner gene, for example. This technique will identify all possible mutations in the region sequenced.

[0189] Methods for detecting an MLL fusion protein are known by those of skill in the art. These methods include, but are not limited to, detection of an MLL fusion protein using a binding agent (e.g., an antibody) specific for the fusion protein, protein electrophoresis and Western blotting, and direct peptide sequencing.

[0190] Methods for determining whether a tumor or cancer comprises an MLL fusion protein can use a variety of samples. In some embodiments, the sample is taken from a subject having a tumor or cancer. In some embodiments, the sample is taken from a subject having a cancer or tumor. In some embodiments, the sample is a fresh tumor/cancer sample. In some embodiments, the sample is a frozen tumor/cancer sample. In some embodiments, the sample is a formalin-fixed paraffin-embedded sample. In some embodiments, the sample is processed to a cell lysate. In some embodiments, the sample is processed to DNA or RNA.

[0191] The disclosure also relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to the mammal a therapeutically effective amount of a compound or salt of Formula (I). In some embodiments, the method relates to the treatment of cancer such as acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS-related cancers (e.g., Lymphoma and Kaposi's Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ

cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or Viral-Induced cancer. In some embodiments, the method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g., benign prostatic hypertrophy (BPH)). In some cases, the method relates to the treatment of leukemia, hematologic malignancy, solid tumor cancer, prostate cancer (e.g., castration-resistant prostate cancer), breast cancer, Ewing's sarcoma, bone sarcoma, primary bone sarcoma, T-cell prolymphocyte leukemia, glioma, glioblastoma, liver cancer (e.g., hepatocellular carcinoma), or diabetes. In some cases, the leukemia comprises AML, ALL, Mixed Lineage Leukemia or leukemias with Partial Tandem Duplications of MLL.

[0192] In certain particular embodiments, the disclosure relates to methods for treatment of lung cancers, the methods comprise administering an effective amount of any of the above described compound (or a pharmaceutical composition comprising the same) to a subject in need thereof. In certain embodiments the lung cancer is a non-small cell lung carcinoma (NSCLC), for example adenocarcinoma, squamous-cell lung carcinoma or large-cell lung carcinoma. In other embodiments, the lung cancer is a small cell lung carcinoma. Other lung cancers treatable with

the disclosed compounds include, but are not limited to, glandular tumors, carcinoid tumors and undifferentiated carcinomas.

[0193] In some embodiments, a method for treatment of a hematological malignancy or Ewing's sarcoma is provided, the method comprising administering an effective amount of any of the foregoing pharmaceutical compositions comprising a compound or salt of Formula (I) to a subject in need thereof.

[0194] The hematological condition may be any condition or disease which primarily affects the blood. Hematological malignancies include, but are not limited to, malignant lymphoma (such as lymphoma NOS, microglioma, non-Hodgkin lymphoma NOS, B cell lymphoma NOS, malignant lymphoma, (non-cleaved cell NOS and diffuse NOS), malignant lymphoma (lymphocytic intermediate differentiation nodular, small cell noncleaved diffuse, undifferentiated cell non-Burkitt, and undifferentiated cell type NOS), lymphosarcoma (NOS and diffuse), reticulum cell sarcoma (NOS and diffuse), reticulosarcoma (NOS and diffuse), composite Hodgkin and non-Hodgkin lymphoma); leukemia (such as acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML)), mixed lineage leukemia (MLL), blast cell leukemia, undifferentiated leukemia, stem cell leukemia, acute leukemia of ambiguous lineage, acute mixed lineage leukemia, acutel bilineal leukemia, chronic lymphocytic leukemia (CLL), chronic myelomonocytic leukemia (CMML), lymphocytic leukemia, lymphatic leukemia); mature B cell neoplasms (such as B-cell chronic lyphocytic leukemia (BCLL)/small cell lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, hairy cell leukemia (HCL), plasma cell myeloma, plasmacytoma, monoclonal immunoglobulin deposition diseases, heavy chain diseases, marginal zone B cell lymphoma, lymphoplasmacytic lymphoma, immunocytoma, malignant lymphoma plasmacytoid, plasmacytic lymphoma, nodal marginal zone B cell lymphoma, follicular lymphoma (grade 1, 2 or 3), primary cutaneous follicle center lymphoma, diffuse large B-cell lymphoma (DLBCL), diffuse large B-cell immunoblastic NOS lymphoma, Epstein-Barr virus-positive DLBCL of the elderly, lymphomatoid granulomatosis, mantle zone lymphoma, primary mediastinal large B-cell lymphoma, intravascular large B-cell lymphoma, plasmablastic lymphoma, primary effusion lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman's disease, and Burkitt lymphoma/leukemia); mature T cell and natural killer (NK) cell neoplasms (such as T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia, aggressive NK cell leukemia, mature T-cell leukemia/lymphoma, extranodal NK/T-cell nasal type lymphoma, intestinal T-cell lymphoma, enteropathy-associated T-cell lymphoma, hepatosplenic T-cell lymphoma, hepatosplenic T-cell ymphoma, blastic NK cell lymphoma,

mycosis fungoides or Sezary syndrome, primary cutaneous CD30-positive T cell lymphoproliferative disorders, anaplastic large cell lymphoma (T-cell and null cell types), peripheral non-specific T-cell lymphoma, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma, cutaneous T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma); precursor lymphoid neoplasms (such as non-specific precursor B-lymphoblastic leukemia/lymphoma, B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities, precursor cell lymphoblastic lymphoma, and precursor T-lymphoblastic leukemia/lymphoma); Hodgkin lymphoma (HL) (such as classical Hodgkin lymphoma, nodular sclerosis form HL, Hodgkin paragranuloma, Hodgkin ranuloma, mixed cellularlity HL, nodular sclerosis cellular phase HL, lymphocyte-rich HL, nodular sclerosis grade 1 HL, nodular sclerosis grade 2 HL lymphocyte depleted HL, lyphocytic-histiocytic predominance HL, miexed cellularity NOS HL, lymphocyte depleted diffuse fibrosis HL, lymphocyte depleted reticular HL, lymphocyte predominance diffuse HL, and nodular lymphocyte-predominant HL); plasma cell tumors (such as plasmacytoma, multiple myeloma (MM), plasma cell leukemia, and plasmacytoma extramedullary); mast cell tumors (such as mastocytoma, mast cell sarcoma, malignant mastocytosis, and mast cell leukemia); neoplasms of histiocytes and accessory lymphoid cells (such as malignant histiocytosis, Langerhans cell histiocytosis (NOS, unifocal, multifocal, or disseminated), histiocytic sarcoma, Langerhans cell sarcoma, dendritic cell sarcoma, and follicular dendritic cell sarcoma); immunoproliferative diseases (such as Waldenstrom macroglobulinemia, heavy chain disease, immunoproliferative small intestinal disease, monoglonal gammopathy of undetermined significance, angiocentric immunoproliferative lesion, angioimmunoblastic lymphadenopathy, T-gamma lymphoproliferative disease, and immunoglobulin deposition disease); myeloid leukemias (such as erythroleukemia, acute myeloid leukemia (NOS, with abnormal marrow eosinophils, minimally differentiated, multilineage dysplasia without maturation, or with maturation), lymphosarcoma cell leukemia, myeloid leukemia NOS, chronic myeloid leukemia NOS, acute promyelocytic leukemia, FAB-M3, acute myelomonocytic leukemia, basophilic leukemia, chronic myelogenous leukemia (BCR/ABL positive, BCR/ABL negative or atypical), acute monoblastic and monocytic leukemia, chloroma or myeloid sarcoma, acute panmyelosis with myelofibrosis); and myelodysplastic syndromes (MDS) (such as polycythemia vera, essential thrombocythemia, myelofibrosis, refractory anemia, (with ringed sideroblasts or excess blasts), and refractory cytopenia with multilineage dysplasia).

[0195] The present disclosure further provides a method of treating a hematological malignancy, such as acute myeloid leukemia, in a subject exhibiting a nucleoporin 98 (NUP98) gene fusion,

mutation in the nucleophosmin (NPM1) gene, mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, mutation in the FMS-like tyrosine kinase-3 (FLT3) gene, mutation in the isocitrate dehydrogenase 1 (IDH1) gene, mutation in the isocitrate dehydrogenase 2 (IDH2) gene, or mixed lineage leukemia (MLL) gene amplification, the method comprising administering to said subject a compound or salt of Formula (I). In some embodiments, the present disclosure provides a method of treating a hematological malignancy, such as acute myeloid leukemia or acute lymphoblastic leukemia, in a subject exhibiting an MLL rearrangement, optionally wherein the subject further exhibits elevated MEIS1 expression levels, the method comprising administering to said subject a compound or salt of Formula (I). In some embodiments, the subject exhibits a partial tandem duplication of MLL (MLL-PTD). In some embodiments, the present disclosure provides a method of treating Ewing's sarcoma, comprising administering to a subject in need thereof a compound or salt of Formula (I).

[0196] In some embodiments, the subject being treated has been tested for the presence of a genetic abnormality or mutation. In some cases, the subject has been tested for the presence of a nucleoporin 98 (NUP98) gene fusion, mutation in the nucleophosmin (NPM1) gene, mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, mutation in the FMS-like tyrosine kinase-3 (FLT3) gene, mutation in the isocitrate dehydrogenase 1 (IDH1) gene, mutation in the isocitrate dehydrogenase 2 (IDH2) gene, or mixed lineage leukemia (MLL) gene amplification. In some cases, the subject has been tested for elevated MEIS1 expression, MLL rearrangement, or partial tandem duplication of MLL. A wide variety of nucleic acid samples and analyses are available for such testing. A nucleic acid sample may be obtained from the subject. In some cases, the nucleic acid sample comprises a nucleic acid selected from genomic DNA, cDNA, circulating tumor DNA, cell-free DNA, RNA, and mRNA. A biological sample may be obtained from the subject. In some cases, the biological sample is a tissue sample (e.g., fixed, paraffin-embedded, fresh, or frozen tissue sample). The tissue sample may be derived from fine needle, core, or other types of biopsy. In some cases, the biological sample is whole blood or plasma.

[0197] In some embodiments, a nucleic acid analysis may be conducted on the biological sample containing nucleic acid. Non-limiting examples of a nucleic acid analysis include PCR, sequencing, hybridization, microarray, SNP, cell-free nucleic acid analysis, and whole genome sequencing.

[0198] The subject may exhibit a nucleoporin 98 (NUP98) gene fusion. In some cases, the nucleoporin 98 (NUP98) gene fusion is a gene fusion of NUP98 and a homeodomain partner gene. In some cases, the nucleoporin 98 (NUP98) gene fusion is a gene fusion of NUP98 and a non-homeodomain partner gene. In some cases, the nucleoporin 98 (NUP98) gene fusion is a

gene fusion of NUP98 and a partner gene selected from HOXA9, HOXA11, HOXA13, HOXC11, HOXC13, HOXD11, HOXD13, PMX1, PMX2, HHEX, PHF23, JARID1A, NSD1, NSD3, MLL, SETBP1, LEDGF, CCDC28, HMGB3, IQCG, RAP1GDS1, ADD3, DDX10, TOP1, TOP2B, LNP1, RARG, ANKRD28, and POU1F1.

[0199] The subject may exhibit a mutation in the nucleophosmin (NPM1) gene. In some cases, the mutation in the nucleophosmin (NPM1) gene is a mutation in exon 12 of the NPM1 gene. In some cases, the mutation in the nucleophosmin (NPM1) gene is a frameshift mutation. In some cases, the mutation in the nucleophosmin (NPM1) gene comprises an insertion of two to nine bases, such as the insertion is of four bases (e.g., TCTG, CATG, CCTG, CGTG, CAGA, CTTG, and TATG). In some cases, the insertion is of nine bases (e.g., CTCTTGCCC and CCCTGGAGA). In some cases, the mutation in the nucleophosmin (NPM1) gene comprises a deletion of nucleotides 965 through 969 (GGAGG).

[0200] The subject may exhibit a mutation in the FLT3 gene. In some cases, the mutation in the FLT3 gene is an internal tandem duplication (FLT3-ITD). In some cases, the mutation in the FLT3 gene is an in-frame, internal tandem duplication mutation of a nucleotide sequence within exon 14. The size of the FLT3-ITD mutation may range from 3 to over 400 bp. In some cases, the FLT3-ITD mutation is near residues 590-600 of the FLT3 amino acid sequence. The FLT3-ITD mutation may be located in exon 14, exon 15 and/or in the intron between exons 14 and 15. The subject may comprise both partial tandem duplication of the MLL gene and a FLT3-ITD mutation. The subject may exhibit a FLT3 activating mutation. In some cases, the mutation in the FLT3 gene is a point mutation involving the tyrosine kinase domain. In some cases, the mutation of the FLT3 gene is a point mutation at aspartate 835 or isoleucine 836.

[0201] The subject may exhibit a mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene. In some cases, the mutation in the DNMT3A gene is a mutation of R882. In some cases, the mutation in the DNMT3A gene is not a mutation of R882. In some cases, the mutation in the DNMT3A gene is a frameshift deletion, missense mutation, nonsense mutation, splice-site substitution, splice-site deletion, or whole-gene deletion.

[0202] The subject may exhibit a mutation in the isocitrate dehydrogenase 1 (IDH1) gene or isocitrate dehydrogenase 2 (IDH2) gene. In some cases, the mutation in the isocitrate dehydrogenase 1 (IDH1) gene is a heterozygous somatic point mutation in codon 132. In some cases, the mutation in the isocitrate dehydrogenase 2 (IDH2) gene is a heterozygous somatic point mutation in codons 172 or 140. In some embodiments, the mutation in the isocitrate dehydrogenase 2 (IDH2) gene is R140Q.

[0203] The subject may exhibit one or more of an NPM1 mutation, FLT3 mutation, IDH1

mutation, IDH2 mutation, and DNMT3A mutation. In some cases, the subject exhibits an NPM1 mutation, a FLT3 mutation, an IDH2 mutation and a DNMT3A mutation. In some cases, the subject exhibits an NPM1 mutation, an IDH1 mutation, a FLT3 mutation and a DNMT3A mutation. In some cases, the subject exhibits an NPM1 mutation, a FLT3 mutation and a DNMT3A mutation. In some cases, the subject exhibits an NPM1 mutation, a FLT3 mutation and an IDH1 mutation. In some cases, the subject exhibits an NPM1 mutation, a FLT3 mutation and an IDH2 mutation. In some cases, the subject exhibits an NPM1 mutation, a DNMT3A mutation and an IDH1 mutation. In some cases, the subject exhibits an NPM1 mutation, a DNMT3A mutation and an IDH2 mutation. In some cases, the subject exhibits an NPM1 mutation and a FLT3 mutation.

[0204] The subject may exhibit a mixed lineage leukemia (MLL) gene amplification. The subject may exhibit a mixed lineage leukemia (MLL) gene rearrangement. The subject may exhibit an 11q23 rearragement. The subject may exhibit MLL partial tandem duplications.

[0205] The subject may exhibit an EWSR1-FLI1 gene fusion, EWSR1-ERG gene fusion, or EWSR1-FEV gene fusion. The subject may exhibit a FUS-NCATc2 gene fusion, CIC-FOXO4 gene fusion, or ETV6-NTRK3 gene fusion. The subject may exhibit a mutation in a STAG2 gene, mutation in a TP53 gene, or CDKN2A deletion.

[0206] The subject may exhibit elevated myeloid ecotropic viral integration site 1 homolog (MEIS1) expression levels ($MEIS1^{high}$). As used herein, "expression" refers to the process by which a polynucleotide is transcribed into mRNA and/or the process by which the transcribed mRNA (also referred to as a "transcript") is subsequently translated into peptides, polypeptides, or proteins. The transcripts and the encoded polypeptides are collectedly referred to as "gene product." If the polynucleotide is derived from genomic DNA, expression may include splicing of the mRNA in a eukaryotic cell. The level of expression (or alternatively, the "expression level") of a MEIS1 gene can be determined, for example, by determining the level of MEIS1 polynucleotides, polypeptides, and/or gene products. "Differentially expressed" or "differential expression" as applied to a nucleotide sequence (*e.g.*, a gene) or polypeptide sequence in a subject, refers to the differential production of the mRNA transcribed and/or translated from the nucleotide sequence or the protein product encoded by the nucleotide sequence. A differentially expressed sequence may be overexpressed or underexpressed as compared to the expression level of a reference sample (i.e., a reference level). As used herein, elevated expression levels refer to an increase in expression, generally at least 1.25 fold, or alternatively, at least 1.5 fold, or alternatively, at least 2 fold, or alternatively, at least 3 fold, or alternatively, at least 4 fold, or alternatively, at least 10 fold expression over that detected in a reference sample. As used herein,

underexpression is a reduction in expression and generally is at least 1.25 fold, or alternatively, at least 1.5 fold, or alternatively, at least 2 fold, or alternatively, at least 3 fold, or alternatively, at least 4 fold, or alternatively, at least 10 fold expression under that detected in a reference sample. Underexpression also encompasses absence of expression of a particular sequence as evidenced by the absence of detectable expression in a test subject when compared to a reference sample.

[0207] Determining whether a tumor or cancer comprises a nucleoporin 98 (NUP98) gene fusion, mutation in the nucleophosmin (NPM1) gene, mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, mutation in the FMS-like tyrosine kinase-3 (FLT3) gene, mutation in the isocitrate dehydrogenase 1 (IDH1) gene, mutation in the isocitrate dehydrogenase 2 (IDH2) gene, or mixed lineage leukemia (MLL) gene amplification can be undertaken by assessing the nucleotide sequence encoding the protein, by assessing the amino acid sequence of the protein, or by assessing the characteristics of a putative protein.

[0208] Determining whether a tumor or cancer comprises an MLL rearrangement or partial tandem duplication of MLL (MLL-PTD) can be undertaken by assessing the nucleotide sequence encoding the protein, by assessing the amino acid sequence of the protein, or by assessing the characteristics of a putative protein.

[0209] Determining whether a tumor or cancer comprises elevated MEIS1 expression levels can be assessed by any appropriate method. The expression level of a gene, such as MEIS1, may be assessed by detecting a level of mRNA transcribed from the gene, by detecting a level of cDNA produced from reverse transcription of mRNA transcribed from the gene, by detecting a level of polypeptide encoded by the gene, or by a nucleic acid amplification assay, a hybridization assay, sequencing, or a combination thereof. Regulation of a target gene or gene transcript can also be determined indirectly, such as by measuring the effect on a phenotypic indicator of the gene or gene transcript activity, such as by cellular assay. Methods of detecting gene expression products are known in the art. These methods can be performed on a sample by sample basis or modified for high throughput analysis, for example, using Affymetrix™ U133 microarray chips.

[0210] Methods for detecting a nucleotide sequence of a nucleoporin 98 (NUP98) gene fusion, mutation in the nucleophosmin (NPM1) gene, mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, mutation in the FMS-like tyrosine kinase-3 (FLT3) gene, mutation in the isocitrate dehydrogenase 1 (IDH1) gene, mutation in the isocitrate dehydrogenase 2 (IDH2) gene, or mixed lineage leukemia (MLL) gene amplification are known by those of skill in the art. Similarly, methods for detecting an MLL rearrangement, elevated MEIS1 expression levels, or partial tandem duplication of MLL (MLL-PTD) are known by those of skill in the art. These methods include, but are not limited to, polymerase chain reaction-

restriction fragment length polymorphism (PCR-RFLP) assays, polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) assays, real-time PCR assays, PCR sequencing, mutant allele-specific PCR amplification (MASA) assays, direct sequencing, primer extension reactions, electrophoresis, oligonucleotide ligation assays, hybridization assays, TaqMan assays, SNP genotyping assays, high resolution melting assays and microarray analyses. In some embodiments, the NUP98 fusion protein is identified using a direct sequencing method of specific regions in the NUP98 or fusion partner gene, for example. In some embodiments, the mutation in the nucleophosmin (NPM1) gene, mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, mutation in the FMS-like tyrosine kinase-3 (FLT3) gene, mutation in the isocitrate dehydrogenase 1 (IDH1) gene, mutation in the isocitrate dehydrogenase 2 (IDH2) gene, or mixed lineage leukemia (MLL) gene amplification is identified using a direct sequencing method of specific regions in the gene, for example. This technique can identify all possible mutations in the region sequenced.

[0211] Methods for detecting an NUP98 fusion protein, mutant nucleophosmin (NPM1) protein, mutant FMS-like tyrosine kinase-3 (FLT3) protein, mutant isocitrate dehydrogenase 1 (IDH1) protein, mutant isocitrate dehydrogenase 2 (IDH2) protein, or mutant DNA (cytosine-5)-methyltransferase 3A (DNMT3A) protein are known by those of skill in the art. These methods include, but are not limited to, detection of a mutant protein or fusion protein, such as an NUP98 fusion protein, using a binding agent (e.g., an antibody) specific for the mutant protein or fusion protein, protein electrophoresis and Western blotting, and direct peptide sequencing.

[0212] Subjects that can be treated with a compound of the disclosure, or a pharmaceutically acceptable salt, ester, prodrug, solvate, tautomer, stereoisomer, isotopologue, hydrate or derivative of the compound, according to the methods of this disclosure include, for example, subjects that have been diagnosed as having acute myeloid leukemia, acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS-related cancers (e.g., Lymphoma and Kaposi's Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell

tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, viral-induced cancer, leukemia, hematologic malignancy, solid tumor cancer, prostate cancer, castration-resistant prostate cancer, breast cancer, Ewing's sarcoma, bone sarcoma, primary bone sarcoma, T-cell prolymphocyte leukemia, glioma, glioblastoma, hepatocellular carcinoma, liver cancer, or diabetes. In some embodiments subjects that are treated with the compounds of the disclosure include subjects that have been diagnosed as having a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g., benign prostatic hypertrophy (BPH)).

[0213] The disclosure further provides methods of modulating the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) by contacting the menin with an effective amount of a compound or salt of Formula (I). Modulation can be inhibiting or activating protein activity of menin, one or more of its binding partners, and/or one or more of the downstream targets of menin or one or more of its binding partners. In some embodiments, the disclosure provides methods of inhibiting the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an

MLL Partial Tandem Duplication) by contacting menin with an effective amount of a compound or salt of Formula (I). In some embodiments, the disclosure provides methods of inhibiting the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) by contacting a cell, tissue, or organ that expresses menin, MLL1, MLL2, an MLL fusion protein, and/or an MLL Partial Tandem Duplication. In some embodiments, the disclosure provides methods of inhibiting protein activity in subject including but not limited to rodents and mammal (e.g., human) by administering to the subject an effective amount of a compound or salt of Formula (I). In some embodiments, the percentage modulation exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%. In some embodiments, the percentage of inhibiting exceeds 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

[0214] In some embodiments, the disclosure provides methods of inhibiting the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in a cell by contacting the cell with an amount of a compound of the disclosure sufficient to inhibit the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in the cell. In some embodiments, the disclosure provides methods of inhibiting the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in a tissue by contacting the tissue with an amount of a compound or salt of Formula (I) sufficient to inhibit the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in the tissue. In some embodiments, the disclosure provides methods of inhibiting the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in an organism by contacting the organism with an amount of a compound or salt of Formula (I) sufficient to inhibit the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in the organism. In some embodiments, the disclosure provides methods of inhibiting the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in an animal by contacting the animal with an amount of a compound of the disclosure sufficient to inhibit the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in the animal. In some embodiments, the disclosure provides methods of inhibiting the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in a mammal by contacting the mammal with an amount of a compound of the disclosure sufficient to inhibit the interaction of menin and one or more proteins (e.g., MLL1,

MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in the mammal. In some embodiments, the disclosure provides methods of inhibiting the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in a human by contacting the human with an amount of a compound of the disclosure sufficient to inhibit the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in the human. The present disclosure provides methods of treating a disease mediated by the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) in a subject in need of such treatment.

[0215] The disclosure also provides methods of treating a disorder mediated by menin interaction with one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication) by administering to a subject in need thereof a therapeutically effective amount of a compound or salt of Formula (I).

[0216] The disclosure further provides methods of treating a disorder mediated by chromosomal rearrangement on chromosome 11q23 in a subject in need thereof by administering to the subject a therapeutically effective amount of a compound or salt of Formula (I).

[0217] The disclosure also provides methods for the treatment of a disease or condition by administering an effective amount of a compound or salt of Formula (I) to a subject suffering from the disease or condition.

[0218] The disclosure further provides methods for the treatment of a disease or condition by administering a compound or salt of Formula (I) to a subject suffering from the disease or condition, wherein the compound binds to menin and inhibits the interaction of menin with one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein, or an MLL Partial Tandem Duplication).

[0219] The disclosure further provides methods of stabilizing menin, comprising contacting menin with a compound or salt of Formula (I). In some embodiments, the contacting step comprises contacting menin with an amount of the compound sufficient to stabilize menin. In some embodiments, the contacting step takes place *in vivo*. In some embodiments, the contacting step takes place *in vitro*. In some embodiments, the contacting step takes place in a cell.

[0220] The present disclosure also provides methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound or salt of Formula (I). In one aspect, such therapy includes but is not limited to the combination of one or more compounds of the disclosure with chemotherapeutic agents, therapeutic antibodies, and radiation

treatment, to provide a synergistic or additive therapeutic effect.

[0221] Where desired, a compound or pharmaceutical composition of the present disclosure can be used in combination with Notch inhibitors and/or c-Myb inhibitors. Where desired, a compound or pharmaceutical composition of the present disclosure can be used in combination with MLL-WDR5 inhibitors and/or Dot11 inhibitors. Where desired, a compound or pharmaceutical composition of the present disclosure can be used in combination with FLT3 inhibitors and/or Dot1L inhibitors. In some embodiments, a compound or pharmaceutical composition of the present disclosure is administered in combination with a second therapeutic that is effective in treating subjects that exhibit a FLT3 mutation, such as FLT3-ITD, or who otherwise exhibit oncogenic FLT3. In some embodiments, a compound or pharmaceutical composition of the present disclosure is administered in combination with a FLT3 inhibitor, such as quizartinib. Exemplary FLT3 inhibitors include quizartinib (AC220), crenolanib besylate (CP-868596-26), gilteritinib (ASP2215), lestaurtinib (CEP-701), midostaurin (Rydapt®, PKC412), pexidartinib (PLX3397), ponatinib (AP24534), SKLB1028, sorafenib (Nexavar®), sunitinib (Sutent®, SU11248), and XL999. In some embodiments, a compound or pharmaceutical composition of the present disclosure is administered in combination with as IDH2 inhibitor such as enasidenib.

[0222] Many chemotherapeutics are presently known in the art and can be used in combination with a compound of the disclosure. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

[0223] Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec® (Imatinib Mesylate), Velcade® (bortezomib), Casodex (bicalutamide), Iressa® (gefitinib), and Adriamycin as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXANTM); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin,

authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, CasodexTM, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.RTM.; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g., paclitaxel (TAXOLTM, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERETM, Rhone-Poulenc Rorer, Antony, France); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, (NolvadexTM), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO). Where desired, the compounds or pharmaceutical composition of the present disclosure can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 17-N-

Allylamino-17-demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell-cycle nonspecific antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitrucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126 or Zosuquidar.

[0224] This disclosure further relates to a method for using a compound or salt of Formula (I) or a pharmaceutical composition provided herein, in combination with radiation therapy for inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the disclosure in this combination therapy can be determined as described herein.

[0225] Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (e.g., At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner of the present disclosure include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or

radioactive micro spheres.

[0226] The compounds or pharmaceutical compositions of the disclosure can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, antiproliferative agents, glycolysis inhibitors, or autophagy inhibitors.

[0227] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound of the disclosure and pharmaceutical compositions described herein. Anti-angiogenesis agents include, for example, rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include CELEBREXTM (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24,1996), WO 96/27583 (published March 7,1996), European Patent Application No. 97304971.1 (filed July 8,1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26,1998), WO 98/03516 (published January 29,1998), WO 98/34918 (published August 13,1998), WO 98/34915 (published August 13,1998), WO 98/33768 (published August 6,1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13,1994), European Patent Publication 931, 788 (published July 28,1999), WO 90/05719 (published May 31,1990), WO 99/52910 (published October 21,1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17,1999), PCT International Application No. PCT/IB98/01113 (filed July 21,1998), European Patent Application No. 99302232.1 (filed March 25,1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12,1999), United States Patent 5,863, 949 (issued January 26,1999), United States Patent 5,861, 510 (issued January 19,1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (e.g., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-ll, MMP-12, andMMP-13). Some specific examples of MMP inhibitors useful in the disclosure are AG-3340, RO 32-3555, and RS 13-0830.

[0228] Autophagy inhibitors include, but are not limited to chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases

of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy), may also be used.

[0229] In some embodiments, the compounds described herein are formulated or administered in conjunction with liquid or solid tissue barriers also known as lubricants. Examples of tissue barriers include, but are not limited to, polysaccharides, polyglycans, seprafilm, interceed and hyaluronic acid.

[0230] In some embodiments, medicaments which are administered in conjunction with the compounds described herein include any suitable drugs usefully delivered by inhalation for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate, ketotifen or nedocromil; anti-infectives, e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatories, e.g., beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, e.g., noscapine; bronchodilators, e.g., ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, e.g., amiloride; anticholinergics e.g., ipratropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g., insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments are used in the form of salts (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimize the activity and/or stability of the medicament.

[0231] Other exemplary therapeutic agents useful for a combination therapy include but are not limited to agents as described above, radiation therapy, hormone antagonists, hormones and their releasing factors, thyroid and antithyroid drugs, estrogens and progestins, androgens, adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones, insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas, agents affecting calcification and bone turnover: calcium, phosphate, parathyroid hormone, vitamin D, calcitonin, vitamins such as water-soluble vitamins, vitamin B complex, ascorbic acid, fat-soluble vitamins, vitamins A, K, and E, growth

factors, cytokines, chemokines, muscarinic receptor agonists and antagonists; anticholinesterase agents; agents acting at the neuromuscular junction and/or autonomic ganglia; catecholamines, sympathomimetic drugs, and adrenergic receptor agonists or antagonists; and 5-hydroxytryptamine (5-HT, serotonin) receptor agonists and antagonists.

[0232] Therapeutic agents can also include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids, prostaglandins, thromboxanes, leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-antipyretic agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β-adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

[0233] Additional therapeutic agents contemplated herein include diuretics, vasopressin, agents affecting the renal conservation of water, rennin, angiotensin, agents useful in the treatment of myocardial ischemia, anti-hypertensive agents, angiotensin converting enzyme inhibitors, β-adrenergic receptor antagonists, agents for the treatment of hypercholesterolemia, and agents for the treatment of dyslipidemia.

[0234] Other therapeutic agents contemplated include drugs used for control of gastric acidity, agents for the treatment of peptic ulcers, agents for the treatment of gastroesophageal reflux disease, prokinetic agents, antiemetics, agents used in irritable bowel syndrome, agents used for diarrhea, agents used for constipation, agents used for inflammatory bowel disease, agents used for biliary disease, agents used for pancreatic disease. Therapeutic agents used to treat protozoan infections, drugs used to treat Malaria, Amebiasis, Giardiasis, Trichomoniasis, Trypanosomiasis, and/or Leishmaniasis, and/or drugs used in the chemotherapy of helminthiasis. Other therapeutic agents include antimicrobial agents, sulfonamides, trimethoprim-sulfamethoxazole quinolones, and agents for urinary tract infections, penicillins, cephalosporins, and other, β-lactam antibiotics, an agent comprising an aminoglycoside, protein synthesis inhibitors, drugs used in the chemotherapy of tuberculosis, mycobacterium avium complex disease, and leprosy, antifungal agents, antiviral agents including nonretroviral agents and antiretroviral agents.

[0235] Examples of therapeutic antibodies that can be combined with a compound of the disclosure include but are not limited to anti-receptor tyrosine kinase antibodies (cetuximab,

panitumumab, trastuzumab), anti CD20 antibodies (rituximab, tositumomab), and other antibodies such as alemtuzumab, bevacizumab, and gemtuzumab.

[0236] Moreover, therapeutic agents used for immunomodulation, such as immunomodulators, immunosuppressive agents, tolerogens, and immunostimulants are contemplated by the methods herein. In addition, therapeutic agents acting on the blood and the blood-forming organs, hematopoietic agents, growth factors, minerals, and vitamins, anticoagulant, thrombolytic, and antiplatelet drugs.

[0237] For treating renal carcinoma, one may combine a compound of the present disclosure with sorafenib and/or avastin. For treating an endometrial disorder, one may combine a compound of the present disclosure with doxorubincin, taxotere (taxol), and/or cisplatin (carboplatin). For treating ovarian cancer, one may combine a compound of the present disclosure with cisplatin (carboplatin), taxotere, doxorubincin, topotecan, and/or tamoxifen. For treating breast cancer, one may combine a compound of the present disclosure with taxotere (taxol), gemcitabine (capecitabine), tamoxifen, letrozole, tarceva, lapatinib, PD0325901, avastin, herceptin, OSI-906, and/or OSI-930. For treating lung cancer, one may combine a compound of the present disclosure with taxotere (taxol), gemcitabine, cisplatin, pemetrexed, Tarceva, PD0325901, and/or avastin.

[0238] Further therapeutic agents that can be combined with a compound of the disclosure are found in Goodman and Gilman's "The Pharmacological Basis of Therapeutics" Tenth Edition edited by Hardman, Limbird and Gilman or the Physician's Desk Reference, both of which are incorporated herein by reference in their entirety.

[0239] The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the one or more compounds of the disclosure will be co-administered with other agents as described above. When used in combination therapy, the compounds described herein are administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the disclosure and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present disclosure can be administered just followed by and any of the agents described above, or vice versa. In some embodiments of the separate administration protocol, a compound of the

disclosure and any of the agents described above are administered a few minutes apart, or a few hours apart, or a few days apart.

[0240] The present disclosure provides a method of promoting beta cell proliferation. In some embodiments, the method comprises contacting menin with an effective amount of a compound of Formula (I). Optionally, the compound inhibits the interaction of menin and MLL. Inhibition of the menin/MLL interaction can be assessed by a wide variety of techniques known in the art. Non-limiting examples include a showing of (a) a decrease in menin binding to MLL, or a peptide fragment thereof; (b) a decrease in $p27^{Kip1}$ and/or $p18^{INK4C}$ mRNA levels; (c) a decrease in $p27^{Kip1}$ and/or $p18^{INK4C}$ protein levels; (d) a decrease in the levels of downstream targets of MLL; (e) an increase in beta cells; and/or (f) an increase in pancreatic islet cell proliferation. Kits and commercially available assays can be utilized for determining one or more of the above. In some embodiments, the promoted beta cell proliferation is evidenced by an increase in insulin production. Optionally, contacting menin comprises contacting a cell that expresses menin. The contacting step may take place *in vivo* or *in vitro*. The promoted beta cell proliferation may be evidenced by an increase in beta cell production. In some embodiments, the number of beta cells in a treated islet increases by at least 1.1-fold, at least 1.2-fold, at least 1.3-fold, at least 1.4-fold, at least 1.5-fold, at least 1.6-fold, at least 1.7-fold, at least 1.8-fold, at least 1.9-fold, at least 2-fold, at least 2.5-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 7.5-fold, or at least 10-fold relative to the number of beta cells in an islet treated with vehicle only. In some embodiments, the increase in the number of beta cells in a treated islet is compared to a number of beta cells in an islet prior to treatment. Beta cell proliferation may be assessed using methods known in the art. For example, beta cell proliferation can be assessed using quantitative-stereological methods or by immunohistochemistry imaging methods, either using manual or automated image processing. Non-limiting examples of suitable methods are described in Noorafshan, A.; et al. *J. Pancreas* **2012**, *13*, 427-432; Chen, H.; et al. *Frontiers in Physiology* **2013**, *3*, 1-9; and Kilimnik, G.; et al. *Islets* **2012**, *4*, 167-172.

[0241] In certain embodiments, the present disclosure provides a method of increasing the size of a pancreatic islet, comprising administering an effective amount of a compound described herein to a subject in need thereof. In some embodiments, the average size of treated pancreatic islets increases by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, or at least 60% relative to the average size of pancreatic islets treated with vehicle only. The size of pancreatic islets may be expressed in any unit commonly used in the art, such as area (e.g., mm^2) or volume (e.g., mm^3), and can be assessed using methods known in the art. For example, pancreatic islet size can

be assessed using quantitative-stereological methods or by immunohistochemistry imaging methods, either using manual or automated image processing. Non-limiting examples of suitable methods are described in Noorafshan, A.; et al. *J. Pancreas* **2012**, *13*, 427-432; Chen, H.; et al. *Frontiers in Physiology* **2013**, *3*, 1-9; and Kilimnik, G.; et al. *Islets* **2012**, *4*, 167-172.

[0242] In certain embodiments, the present disclosure provides a method of increasing the average beta cell number per islet, comprising administering an effective amount of a compound described herein to a subject in need thereof. In some embodiments, the average beta cell number per islet of treated islets increases by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, or at least 40% relative to the average beta cell number per islet of islets treated with vehicle only. The average beta cell number per islet can be assessed using methods known in the art. For example, average beta cell number per islet can be assessed using quantitative-stereological methods or by immunohistochemistry imaging methods, either using manual or automated image processing. Non-limiting examples of suitable methods are described in Noorafshan, A.; et al. *J. Pancreas* **2012**, *13*, 427-432; Chen, H.; et al. *Frontiers in Physiology* **2013**, *3*, 1-9; and Kilimnik, G.; et al. *Islets* **2012**, *4*, 167-172.

[0243] In certain embodiments, the present disclosure provides a method of improving islet transplantation, comprising contacting an islet cell with an effective amount of a compound described herein. In some embodiments, the contacting takes place prior to transplantation of the islet into a recipient. In some embodiments, the contacting takes place after transplantation of the islet into a recipient. The contacting may take place *in vivo*, *ex vivo* or *in vitro*.

[0244] In certain embodiments, the present disclosure provides a method of treating a disease or condition in a subject having impaired beta cell production, comprising administering to the subject an effective amount of a compound of Formula (I). The disease or condition may comprise diabetes, such as type 1 diabetes or type 2 diabetes. In some embodiments, the disease or condition is characterized by impaired glucose metabolism and/or hyperglycemia. The treated subject may exhibit decreased plasma glucose levels. For example, plasma glucose levels may be reduced by at least 10 mg/dL, 20 mg/dL, 30 mg/dL, 40 mg/dL, 50 mg/dL, 60 mg/dL, 70 mg/dL, 80 mg/dL, 90 mg/dL, or at least 100 mg/dL relative to plasma glucose levels measured before the administering the effective amount of the compound of Formula (I). A fasting plasma glucose level of the treated subject may be less than 150 mg/dL, such as less than 140 mg/dL, 130 mg/dL, 120 mg/dL, 110 mg/dL, 100 mg/dL, 90 mg/dL, or less than 80 mg/dL.

[0245] In certain embodiments, the present disclosure provides a method of treating impaired glucose metabolism, comprising administering an effective amount of a compound or salt of Formula (I) to a subject in need thereof.

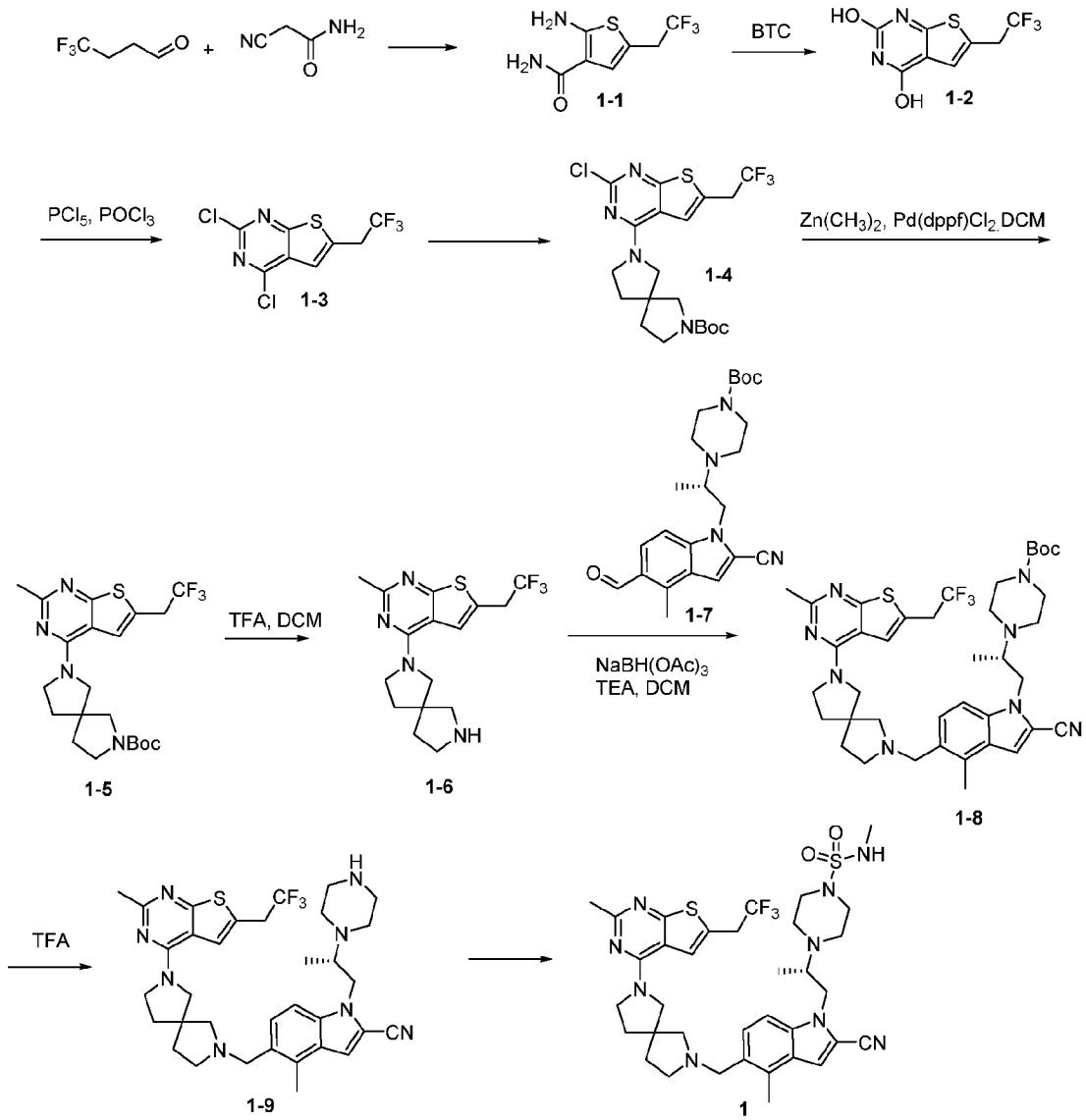
[0246] Subjects that can be treated according the subject methods include, for example, subjects that have been diagnosed as having impaired glucose tolerance, hyperglycemia, impaired glucose metabolism, diabetes, type 1 diabetes, or type 2 diabetes, or subjects suffering from a disease associated with reduced beta cell number and/or impaired beta-cell function, for example but not limited to one of the diseases for which a pro-proliferative effect on pancreatic beta cells and/or an anti-apoptotic/pro-survival effect on pancreatic beta cells and/or a beta cell neogenesis-promoting effect would be beneficial: Type I diabetes: new onset, established, prevention in high-risk patients (identified e.g. via screening for multiple autoantibodies); LADA: new onset and established; Type II diabetes: when loss of beta cell mass occurs; MODY (Maturity Onset Diabetes of the Young, all forms); Gestational diabetes; Islet+duct cell transplantation-treatment of recipients before or after transplantation; Treatment of islets before transplantation/during pre-transplantation culture; and Pancreatitis-associated beta cell loss.

[0247] The methods described herein may be used to treat diabetes type I, LADA or prognosed diabetes type II, but also used preventively on subjects at risk to develop complete beta-cell degeneration, like for example but not limited to patients suffering from diabetes type II or LADA and type I diabetes in early stages, or other types of diseases as indicated above. The methods may also be used to prevent or ameliorate diabetes in patients at risk for type I diabetes or LADA (identified e.g. by screening for autoantibodies, genetic predisposition, impaired glucose tolerance or combinations thereof.

[0248] The following examples are given for the purpose of illustrating various embodiments of the disclosure and are not meant to limit the present disclosure in any fashion. The present examples, along with the methods and compositions described herein, are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the disclosure. Changes therein and other uses which are encompassed within the spirit of the disclosure as defined by the scope of the claims will occur to those skilled in the art.

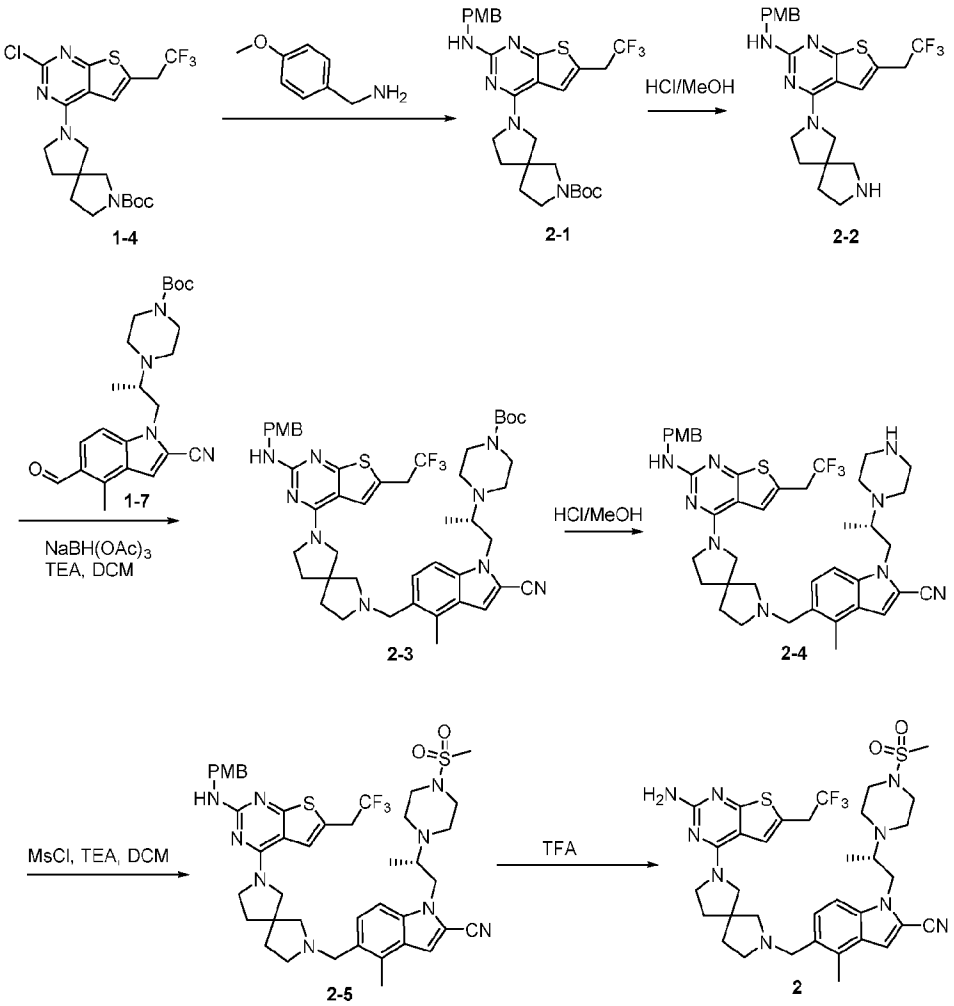
EXAMPLES

[0249] Example 1: Synthesis of 4-((2S)-1-(2-cyano-4-methyl-5-((7-(2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)methyl)-1H-indol-1-yl)propan-2-yl)-N-methylpiperazine-1-sulfonamide (**1**).



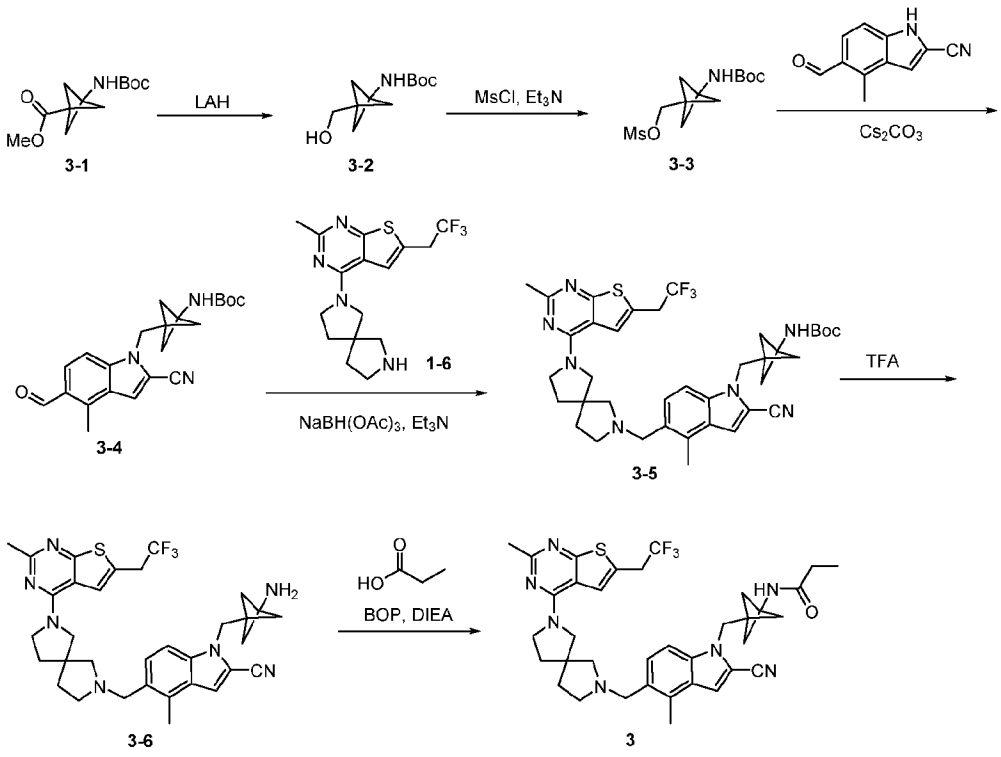
[0250] 4-((2S)-1-(2-cyano-4-methyl-5-((7-(2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)methyl)-1H-indol-1-yl)propan-2-yl)-N-methylpiperazine-1-sulfonamide (**1**) is synthesized in nine steps starting from 4,4,4-trifluorobutanal and 2-cyanoacetamide.

[0251] Example 2: Synthesis of 5-((7-(2-amino-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)methyl)-4-methyl-1-((S)-2-(4-(methylsulfonyl)piperazin-1-yl)propyl)-1H-indole-2-carbonitrile (**2**).



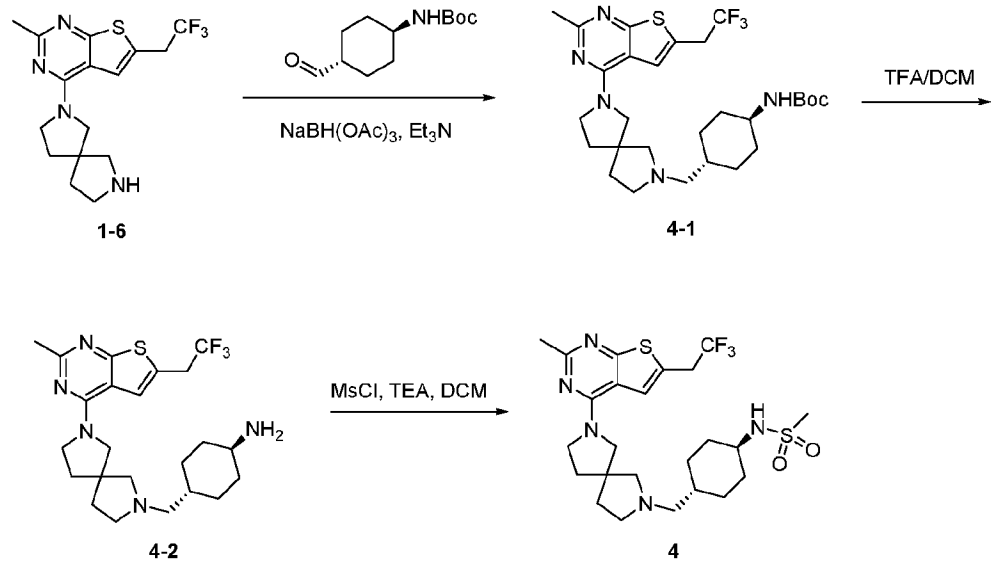
[0252] 5-((7-(2-amino-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)methyl)-4-methyl-1-((S)-2-(4-(methylsulfonyl)piperazin-1-yl)propyl)-1H-indole-2-carbonitrile (**2**) is synthesized in six steps starting from tert-butyl 7-(2-chloro-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (**1-4**) from Example 1.

[0253] Example 3: Synthesis of N-(3-((2-cyano-4-methyl-5-((7-(2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)methyl)-1H-indol-1-yl)methyl)bicyclo[1.1.1]pentan-1-yl)propionamide (**3**).



[0254] N-(3-((2-cyano-4-methyl-5-((7-(2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)methyl)-1H-indol-1-yl)methyl)bicyclo[1.1.1]pentan-1-yl)propionamide (**3**) is synthesized in six steps starting from methyl 3-((tert-butoxycarbonyl)amino)bicyclo[1.1.1]pentane-1-carboxylate (**3-1**).

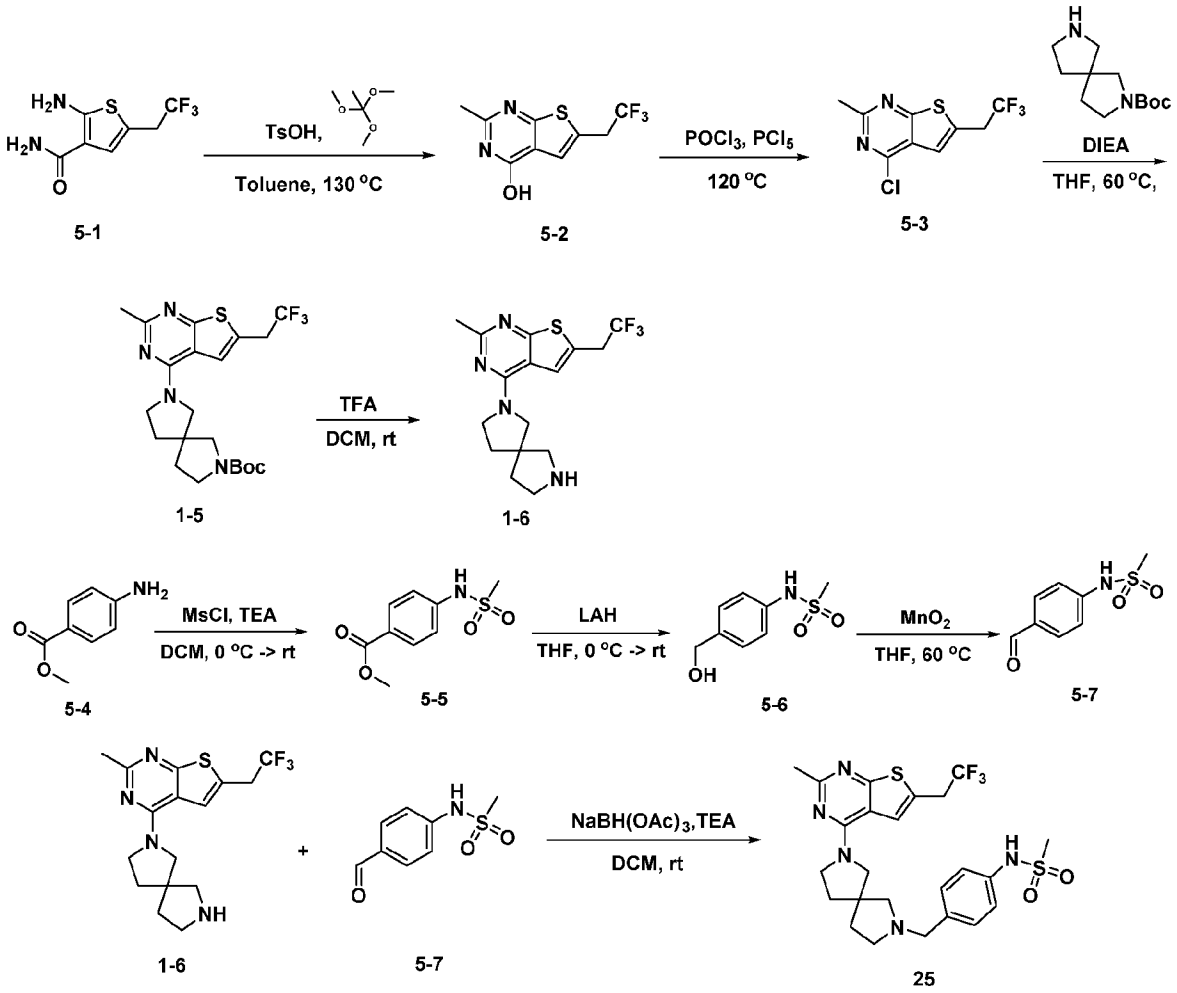
[0255] Example 4: Synthesis of N-((1r,4r)-4-((7-(2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)methyl)cyclohexyl)methanesulfonamide (**4**).



[0256] N-((1r,4r)-4-((7-(2-methyl-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonan-2-yl)methyl)cyclohexyl)methanesulfonamide (**4**) is synthesized in three

steps starting from 2-methyl-4-(2,7-diazaspiro[4.4]nonan-2-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidine (**1-6**).

[0257] **Example 5**: Synthesis of Compound **25**.



[0258] Step A: To a solution of compound **5-1** (2.2 g, 10.0 mmol) and 1,1,1-trimethoxyethane (6 mL, 50.0 mmol) in 15 mL of toluene was added 200 mg of TsOH. The reaction was stirred at 130 °C overnight. Solvent was removed to give the crude product, which was purified by silica gel column chromatography (eluent: DCM/MeOH = 40:1) to give compound **5-2** as a brown solid (2.2 g, yield: 98%).

[0259] Step B: To a mixture of compound **5-2** (500 mg, 2.2 mmol) in 10 mL of $POCl_3$ was added PCl_5 (937 mg. 4.5 mmol), and the reaction was stirred at 120 °C for 10 hours. Solvent was removed and the residue was diluted with DCM. The organic solution was washed with $NaHCO_3$, H_2O, brine and dried over Na_2SO_4. The solution was filtered and concentrated. The residue was purified by silica gel column chromatography (eluent: PE/EA = 5:1) to give compound **5-3** as a brown oil (500 mg, yield: 98%).

[0260] Step C: A mixture of compound **5-3** (1.6 g, 6 mmol), tert-butyl 2,7-

diazaspiro[4.4]nonane-2-carboxylate (1.3 g, 6 mmol) and DIEA (1.56 g, 12 mmol) in 30 mL of THF was stirred at 60 °C for 10 hours. Solvent was removed and the residue was diluted with EA. The organic solution was washed with $NaHCO_3$, H_2O, brine and dried over Na_2SO_4. The solution was filtered and concentrated. The residue was purified by silica gel column chromatography (eluent: PE/EA = 5:1~3:1) to give compound **1-5** (1.6 g, yield: 59%). ESI-MS *m/z*: 457.40 (M+H) ^{1}HNMR (400MHz, $CDCl_3$) δ:7.28 (s, 1H), 3.92~3.96 (m, 2H), 3.34~3.80 (m, 8H), 2.57 (s, 3H), 1.91~2.10 (m, 4H), 1.48 (s, 9H).

[0261] Step D: To a solution of compound **1-5** (180 mg, 0.27 mmol) in 4 mL of DCM was added 3 mL of TFA and the reaction mixture was stirred at room temperature for 3 hours. Solvent was removed and 10 mL of 7N NH_3 in MeOH solution was added. Solvent was removed and the residue was purified by silica gel column chromatography (eluent: 10% MeOH in DCM) to give compound **1-6** as a yellow solid (1.3 g, yield: 100%). ESI-MS *m/z*: 357.35 (M+H).

[0262] Step E: To a mixture of compound **5-4** (1.5 g, 10 mmol) and Et_3N (2.0 g, 20 mmol) in 10 mL of DCM was add slowly MsCl (1.4 g, 12 mmol) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 18h before it was diluted with DCM. The organic solvent was washed with $NaHCO_3$, H_2O, brine and dried over Na_2SO_4. The solution was filtered and concentrated. The residue was purified by silica gel column chromatography (eluent: PE/EA = 1:1) to give compound **5-5** as a white solid (500 mg, yield: 20%).

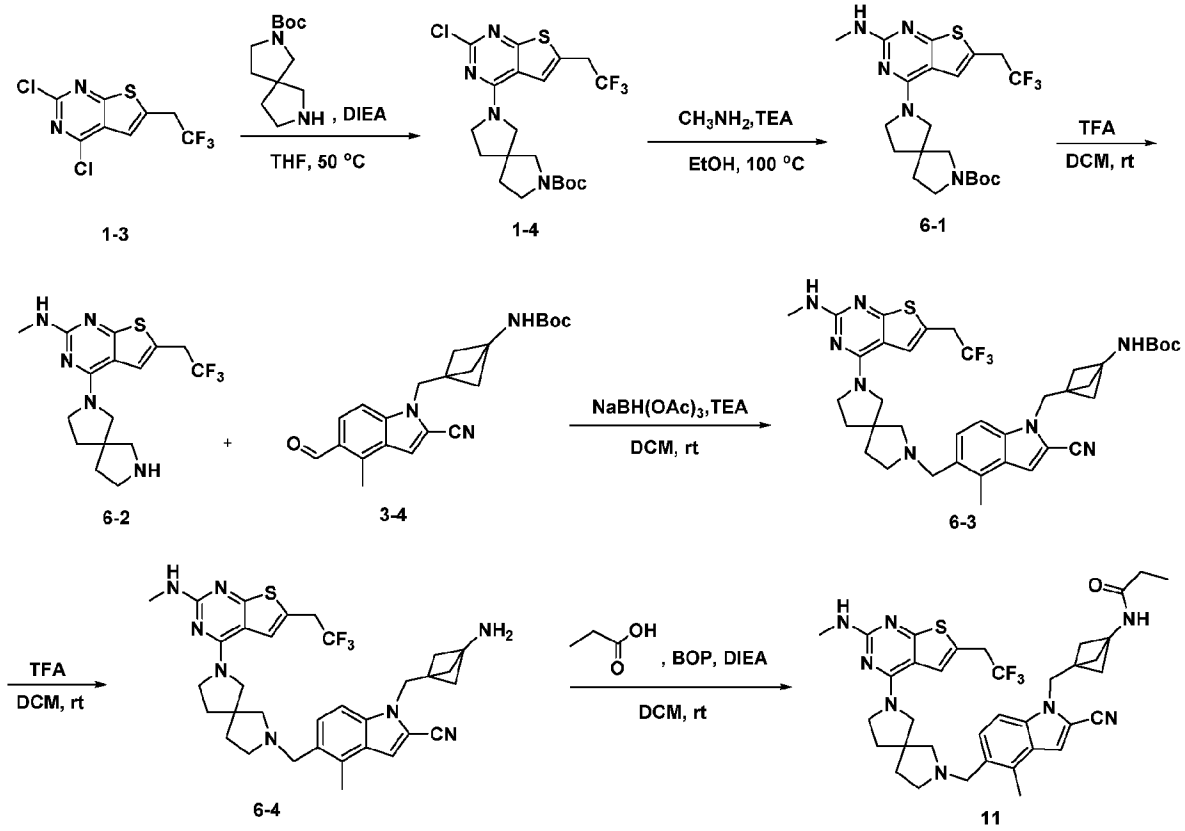
[0263] Step F: To a mixture of compound **5-5** (500 mg, 2.0 mmol) in 10 mL of THF was add slowly LAH (80 mg, 2.0 mmol) at 0 °C under N_2. The mixture was stirred at room temperature for 1h, and additional LAH (80 mg, 2.0 mmol) was added at 0 °C. The reaction was quenched with EA, H_2O, and 1N HCl. Solid was filtered and the organic solvent was concentrated. The residue was purified by silica gel column chromatography (eluent: DCM/MeOH = 20:1) to give compound **5-6** as a white solid (230 mg, yield: 55%).

[0264] Step G: To a solution of compound **5-6** (230 mg, 1.1 mmol) and in 10 mL of THF was add slowly MnO_2 (200 mg, 2.2 mmol). The mixture was stirred at 60 °C under N_2 for 8h. The mixture was filtered and the organic solvent was concentrated. Compound **5-7** was obtained after silica gel column chromatography (eluent: PE/EA = 5:1) as a brown solid (200 mg, yield: 90%).

[0265] Step H: A solution of compound **5-7** (60 mg, 0.27 mmol), compound **1-6** (90 mg, 0.25 mmol) and TEA (150 mg, 1.5 mmol) in 15 mL of DCM was stirred at room temperature for 2 hours before $NaBH(OAc)_3$ (320 mg, 1.5 mmol) was added. The mixture reaction was stirred at room temperature overnight. The reaction was partitioned between DCM and $NaHCO_3$ (sat.), and the organic layer was washed by brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by Prep-TLC (DCM/MeOH = 20:1) to give

compound **25** as a solid (60 mg, yield: 40%). ESI-MS *m/z*: 540.12 (M+H). ^{1}HNMR (400MHz, DMSO): 9.66 (s, 1H), 7.63(s, 1H), 7.19~7.30 (dd, 4H, *J* = 8.8 Hz), 4.04 (q, *J* = 10.4 Hz, 2H), 3.50~3.95 (m, 6H), 2.96 (s, 3H), 2.40~2.65 (m, 4H), 2.42 (s, 3H), 1.78~2.05 (m, 4H).

[0266] Example 6: Synthesis of Compound **11**.



[0267] Step A: A solution of compound **1-3** (3.20 g, 11.15 mmol), tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (2.52 g, 11.15 mmol) and DIEA (2.88 g, 22.3 mmol) in 80 mL of THF was stirred at 50 °C overnight. Solvent was removed under vacuum and the residue was dissolved in ethyl acetate. The solution was washed with saturated $NaHCO_3$ aqueous solution and brine, dried with anhydrous sodium sulfate and purified by silica gel column chromatography (PE/EA: 3/1) to give compound **1-4** as a solid (4.5 g, yield: 85%). ESI-MS *m/z*: 476 (M+H).

[0268] Step B: A mixture of compound **1-4** (1.24 g, 2.6mmol), TEA (1.6 g, 13mmol) and CH_3NH_2 alcohol solution (1.78 g, 13 mmol) was added to a seal tube and stirred at 100 °C overnight. Solvent was removed and the residue was purified by silica gel column chromatography (PE/EA: 3/1~1:1) to give compound **6-1** as a solid (1.21 g, 98%). ESI-MS *m/z*: 472 (M+H).

[0269] Step C: To a solution of compound **6-1** (0.5 g, 1.06 mmol) in 8 mL of DCM was added 2 mL of TFA. The mixture was stirred at room temperature for 3h. DCM and TFA were removed

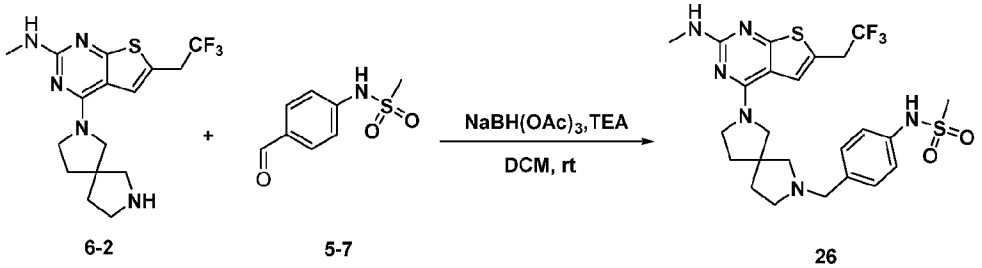
under vacuum and the residue was dissolved in MeOH and 7N MeOH·NH_3 was added. Then MeOH was removed under vacuum and the residue was purified by silica gel column chromatography (DCM/MeOH: 10/1) to give compound **6-2** as a solid (0.37 g, 94%). ESI-MS *m/z*: 372.2 (M+H).

[0270] Step D: A solution of compound **6-2** (73 mg, 0.197 mmol), compound **3-4** (75 mg 0.197 mmol) and TEA (119.2 mg, 1.18 mmol) in 10 mL of DCM was stirred at room temperature for 2 h before $NaBH(OAc)_3$ (250 mg, 1.18 mmol) was added slowly and stirred overnight. The reaction solution was washed with saturated $NaHCO_3$ aqueous solution, brine, and dried with anhydrous sodium sulfate. Solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH: 30/1) to give compound **6-3** as a solid (130 mg, 89%). ESI-MS *m/z*: 368.45 (M+H).

[0271] Step E: To a solution of compound **6-3** (130 mg, 0.177 mmol) in 3 mL of DCM, was added 3 mL of TFA. The mixture was stirred at room temperature for 3h. DCM and TFA were removed under vacuum and the residue was dissolved in MeOH and MeOH·NH_3 was added to neutralize the TFA residue. Then MeOH was removed under vacuum and residue was purified by silica gel column chromatography (DCM/MeOH: 30/1) to give compound **6-4** as a solid (86 mg, 76%). ESI-MS *m/z*: 635.25 (M+H).

[0272] Step F: A mixture of compound **6-4** (86 mg, 0.136 mmol), propionic acid (21 mg, 0.272mmol), and BOP (115 mg, 0.272 mmol) was dissolved in 15 mL DCM and stirred for 20 minutes before DIEA (53 mg, 0.41 mmol) was added and stirred overnight. The reaction solution was washed with water, saturated $NaHCO_3$ aqueous solution, dried with anhydrous sodium sulfate and purified with silica gel column chromatography (10% MeOH in dichloromethane) to give final product **11** as a solid (40 mg, 42%). ESI-MS *m/z*: 691.30 (M+H). ^{1}HNMR (400MHz, DMSO): 8.22 (s, 1H), 7.55 (m, 1H), 7.3~7.42 (m, 2H), 6.5 (s, 1H), 4.49 (s, 2H), 3.85 (m, 3H), 3.50~3.80 (m, 6H), 2.78 (m, 3H), 2.5~2.7 (m, 8H), 1.89~2.06 (m, 5H), 1.70 (m, 6H) , 0.85~0.95 (m, 3H).

[0273] **Example** 7: Synthesis of Compound **26**.

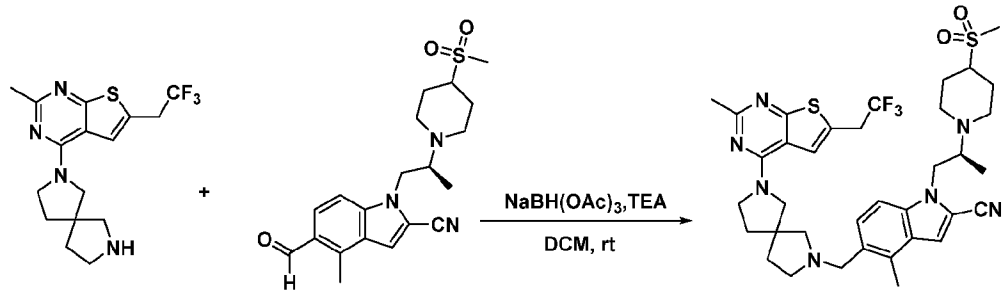


6-2 5-7 26

[0274] A solution of compound **5-7** (40 mg, 0.2 mmol), compound **6-2** (75 mg, 0.2 mmol) and TEA (120 mg, 1.2 mmol) in 15 mL of DCM was stirred at room temperature for 2 hours before

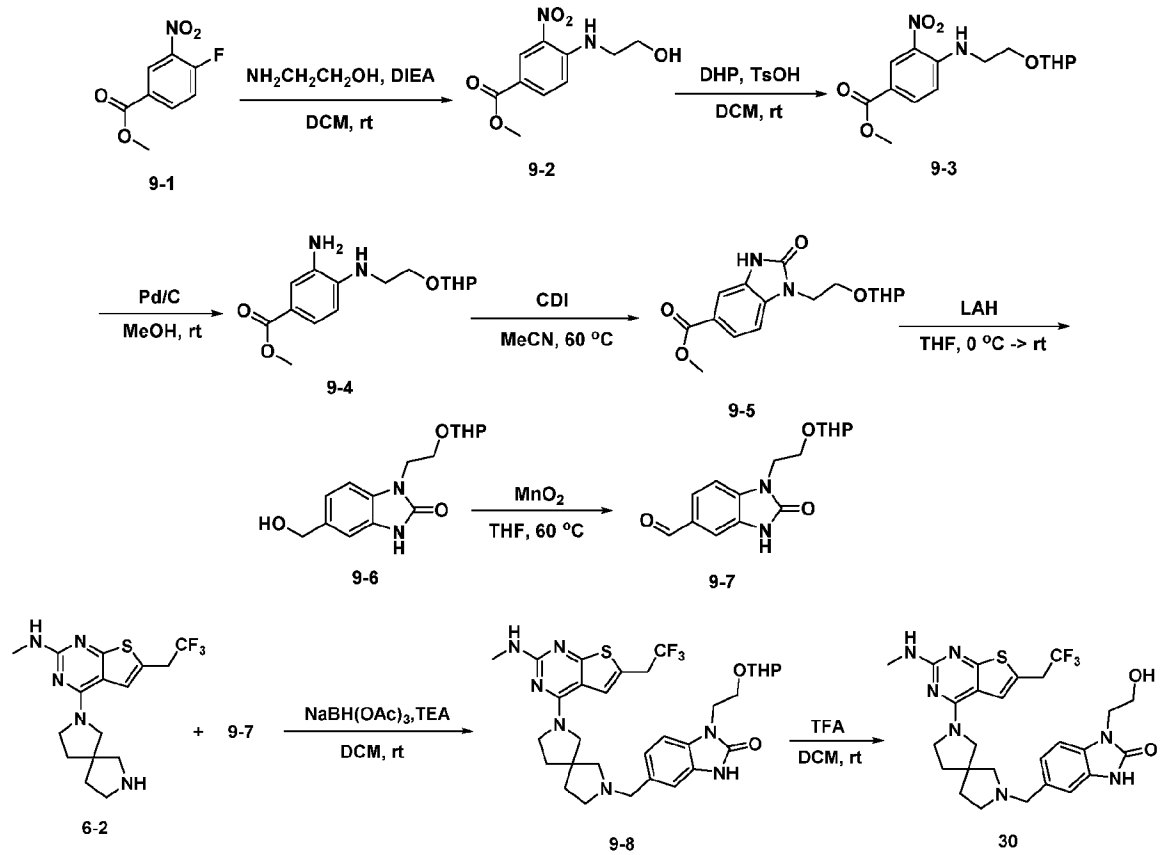
$NaBH(OAc)_3$ (255 mg, 1.2 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and $NaHCO_3$ (sat.), and the organic layer was washed by brine and dried over Na_2SO_4. Solvent was removed under vacuum to get a residue, which was purified by Prep-TLC(DCM/MeOH=15:1) to give **26** as a solid (40 mg, yield: 36%). ESI-MS *m/z*: 555.18 (M+H). ^{1}HNMR (400MHz, DMSO): 9.72 (br, 1H), 7.16~7.40 (m, 5H), 4.86 (d, *J* = 4.8 Hz, 1H), 3.86 (q, *J* = 10.8 Hz, 2H), 3.14~3.72 (m, 8H), 2.98 (s, 3H), 2.78 (d, *J* = 4.4 Hz, 3H), 2.50-2.70 (m, 2H),1.68~2.00 (m, 4H).

[0275] Example 8: Synthesis of Compound **17**.



[0276] A solution of compound **8-1** (104 mg, 0.28 mmol), compound **1-6** (100 mg, 0.28 mmol) and TEA (170 mg, 1.7 mmol) in 15 mL of DCM was stirred at room temperature for 2 hours before $NaBH(OAc)_3$ (360 mg, 1.7 mmol) was added. The mixture reaction was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and $NaHCO_3$ (sat.), and the organic layer was washed by brine and dried over Na_2SO_4. The solvent was removed under vacuum to get a residue, which was purified by silica gel column chromatography (eluent: DCM/MeOH = 20:1) plus a second purification by Prep-HPLC to give **17** as a solid (80 mg, yield: 30%). ESI-MS m/z: 728.1 (M+H), 364.5 (1/2 M+H). ^{1}HNMR (400MHz, DMSO): 7.61 (s, 1H), 7.47(m, 1H), 7.30-7.36 (m, 2H), 3.97~4.30 (m, 4H), 3.60~3.72 (m, 6H), 2.97~3.15 (m, 3H), 2.88 (s, 3H), 2.50~2.67 (m, 3H),2.34~2.46 (m, 5H), 1.58~2.16 (m, 8H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.80~0.88 (m, 3H).

[0277] Example 9: Synthesis of Compound **30**.



[0278] Step A: To a solution of compound **9-1** (2.0 g, 10.0 mmol) in 15 mL of DCM was added 2-aminoethanol (3 ml, 30 mmol) at room temperature. The reaction was stirred overnight. Solvent was removed to give the crude product, which was purified by silica gel column chromatography (eluent: DCM/MeOH = 40:1) to give compound **9-2** as a yellow solid (2.3 g, yield: 98%).

[0279] Step B: A mixture of compound **9-2** (2.3 g, 10 mmol) in DCM was added DHP (1.26 g, 15 mmol), followed by TsOH (172 mg, 1 mmol). The reaction mixture was stirred at room temperature for 10 hours, and diluted with DCM. The organic solvent was washed with $NaHCO_3$ (sat.), H_2O, brine and dried over Na_2SO_4. The solution was filtered and concentrated and the residue was purified by silica gel column chromatography (eluted PE/EA = 1:1) to give compound **9-3** as a yellow soild (3.5 g, yield: 98%).

[0280] Step C: To a solution of compound **9-3** (3.5 g, 10 mmol) in 35 mL of MeOH was added 300 mg of Pd/C. The reaction was stirred at room temperature under H_2 for 10 hours. The suspension was filtered and concentrated to give compound **9-4** as a brown solid (2.5 g, yield: 85%).

[0281] Step D: To a mixture of compound **9-4** (2.5 g, 8.5 mmol) and DIEA (3.4 g, 27 mmol) in 30 mL of MeCN was added CDI (2.1 g, 13 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 8h, then diluted with ethyl acetate. The organic solution was washed with

H_2O, brine and dried over Na_2SO_4. The solution was filtered and concentrated. The residue was purified by silica gel column chromatography (eluted PE/EA=1:1) to give compound **9-5** as a white solid (2.6 g, yield: 90%).

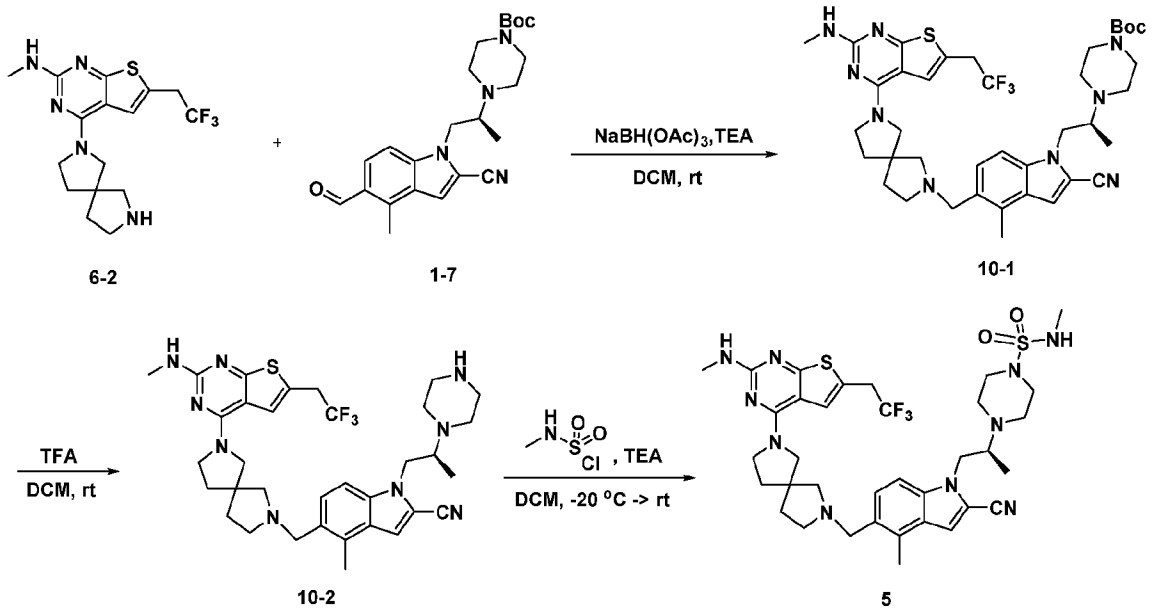
[0282] Step E: To a mixture of compound **9-5** (2.5 g, 7.8 mmol) in THF (30 mL) was added slowly LAH (1.2 g, 31 mmol) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 4h. The reaction was quenched with ethyl acetate, H_2O, and 2N NaOH. Solid was filtered and the organic solvent was concentrated. The residue was purified by silica gel column chromatography (eluent: DCM/MeOH = 20:1) to give compound **9-6** as a brown solid (1.7 g, yield: 75%).

[0283] Step F: To a solution of compound **9-6** (1.7 g, 5.8 mmol) in 30 mL of THF was added slowly MnO_2 (1.1 g, 11.7 mmol). The reaction mixture was stirred at 60 °C under N_2 for 8h. The mixture was filtered and the organic solvent was concentrated. The product compound **9-7** was obtained after flash column chromatography (eluent: DCM/MeOH = 50:1) purification as a brown solid (1.5 g, yield: 90%).

[0284] Step G: A solution of compound **9-7** (60 mg, 0.2 mmol), compound **6-2** (75 mg, 0.2 mmol) and TEA (120 mg, 1.2 mmol) in 15 mL of DCM was stirred at room temperature for 2 hours before $NaBH(OAc)_3$ (255 mg, 1.2 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and $NaHCO_3$ (sat.), and the organic layer was washed by brine and dried over Na_2SO_4. The solvent was removed under vacuum to get the residue, which was purified by Prep-TLC (DCM/MeOH = 20:1) to give compound **9-8** as a solid (100 mg, yield: 75%). ESI-MS *m/z*: 646.12 (M+H).

[0285] Step H: To a solution of compound **9-8** (100 mg, 0.27 mmol) in 4 mL of DCM was added 3 mL of TFA and the reaction mixture was stirred at room temperature for 3 hours. Solvent was removed and a solution of 7N NH_3 in MeOH (10 ml) was added. Solvent was removed and the residue was purified by Prep-TLC (eluted DCM/ MeOH=12:1) to give **30** as a solid (50 mg, yield: 45%). ESI-MS *m/z*: 562.3 (M+H) ^{1}HNMR (400MHz, DMSO): 10.80 (br, 1H), 7.38(s, 1H), 6.95~7.08 (m, 3H), 6.50 (m, 1H), 4.86 (t, J = 5.6 Hz, 1H), 3.55~4.10 (m, 12H), 3.05~3.30 (m, 2H), 2.78 (d, J = 4.8 Hz, 3H), 2.54~2.72 (m, 2H), 1.70~2.10 (m, 4H).

[0286] Example 10: Synthesis of Compound **5**.



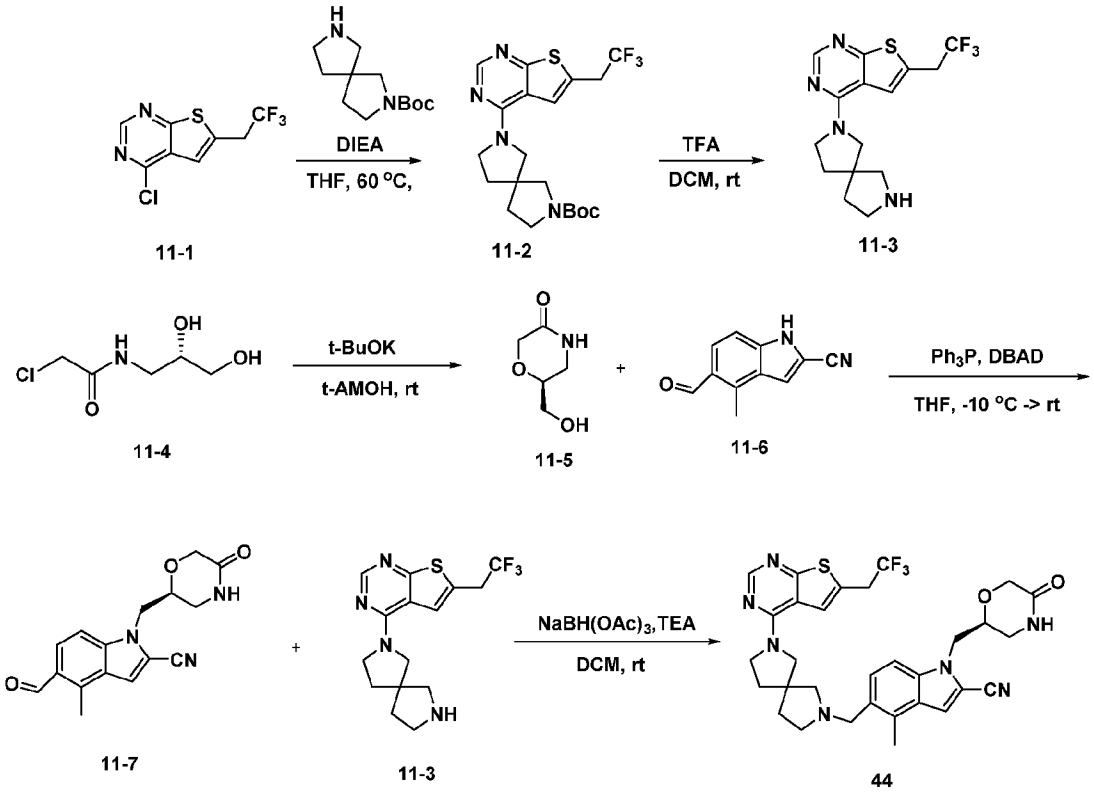
6-2 1-7 10-1 10-2 5

[0287] Step A: A solution of compound **6-2** (70 mg, 0.189 mmol), compound **1-7** (66 mg 0.160 mmol) and TEA (114 mg, 1.13mmol) in 10 mL of DCM was stirred for 2 h before $NaBH(OAc)_3$ (240 mg, 1.13 mmol) was added slowly and stirred overnight. Then the reaction solution was washed with saturated $NaHCO_3$ aqueous solution, brine, and dried with anhydrous sodium sulfate. Solvent was removed and the residue was purified by silica gel column chromatography (DCM/MeOH: 30/1) to give compound **10-1** as a solid (128 mg, 88%). ESI-MS *m/z*: 384, 766.5(M+H).

[0288] Step B: To a solution of compound **10-1** (128 mg, 0.167 mmol) in 3 mL of DCM was added 3 mL of TFA. The mixture was stirred at room temperature for 3h. DCM and TFA were removed under vacuum and the residue was dissolved in MeOH before $MeOH{\cdot}NH_3$ was added to neutralize the TFA residue. MeOH was removed under vacuum to give crude compound **10-2** as a solid (120 mg). ESI-MS *m/z*: 666 (M+H).

[0289] Step C: To a solution of compound **10-2** (110 mg, 0.167 mmol) and TEA (33 mg, 0.25 mmol) in DCM (10 mL) at -10 °C was added methylsulfamoyl chloride (33 mg, 0.25 mmol) over 20 mins and stirred at room temperature for 1 h. Then 1 mL water was added to quench the reaction, and the solution was washed with water, saturated $NaHCO_3$ aqueous solution and brine and dried with anhydrous sodium sulfate. Solvent was removed and residue was purified by silica gel column chromatography (DCM/MeOH: 10/1) to give the final product **5** as a solid. ESI-MS *m/z*: 380.7, 759.3 (M+H). ^{1}HNMR (400MHz, DMSO): 8.22 (d, J = 1.6Hz, 1H), 7.33~7.40 (m, 3H), 8.22 (q, J = 4.8Hz, 1H), 6.51 (d, J = 4.4Hz, 1H), 4.13~4.30 (m, 2H), 3.50~3.95 (m, 8H), 2.87~3.15 (m, 6H), 2.50~2.80 (m, 8H),2.45~2.50 (m, 3H), 2.30~2.34 (m, 2H), 1.78~2.10 (m, 5H), 0.98 (d, J = 6.4 Hz, 3H), 0.80~0.86 (m, 2H).

[0290] **Example 11**: Synthesis of Compound **44**.



[0291] Step A: A mixture of compound **11-1** (0.5 g, 2 mmol), tert-butyl 2,7-diazaspiro[4.4]nonane-2-carboxylate (450 mg, 2 mmol) and DIEA (516 mg, 4mmol) in 10 mL of THF was stirred at 60 °C for 10 hours. Solvent was removed by vacuum and the residue was diluted with ethyl acetate. The solution was filtered and concentrated. The residue was purified by silica gel column chromatography (eluent: PE/EA=5:1~3:1) to give compound **11-2** as a yellow solid (800 mg, yield: 90%). ESI-MS *m/z*: 443.40 (M+H).

[0292] Step B: To a solution of compound **11-2** (500 mg, 1.1 mmol) in 4 mL of DCM was added 2 mL of TFA and the reaction solution was stirred at room temperature for 3 hours. Solvent was removed and a solution of 7N NH_3 in MeOH (10 ml) was added. Solvent was evaporated and the residue purified by silica gel column chromatography (eluent: 10% MeOH in dichloromethane) to give compound **11-3** as a yellow solid (400 mg, yield: 100%).

[0293] Step C: To a suspension of t-BuOK (10 g, 89.5 mmol) in 70 mL of t-AmOH was added compound **11-4** (6 g, 35.8 mmol) in 150 mL of t-AmOH dropwise at room temperature over 2 h. The reaction mixture was stirred for another 1 h before MeOH (50 mL) and water (5 mL) were added and stirred for 30 mins. The mixture was concentrated under vacuum to dryness and the residue was purified by silica gel column chromatography (EA/MeOH: 20/1) to give compound **11-5** as a solid (0.85g, 18%). ^{1}H NMR (400 MHz, DMSO) δ:7.95 (s, 1H), 4.86 (t, 1H), 4.01 (m, 2H), 3.65 (m, 1H), 3.37~3.55 (m, 2H), 3.03~3.23 (m, 2H). ESI-MS *m/z*: 345. 3 (M+H).

[0294] Step D: Compound **11-5** (600 mg, 2.28 mmol) and compound **11-6** (840 mg, 2.28 mmol) were dissolved in 100 mL of THF and stirred for 20 mins. The reaction solution cooled below -10 °C before Ph_3P (1.57 mg, 3.42 mmol) in 15 mL of THF was added dropwise over 40 mins and stirred for 20 mins. Then DBAD (1.79 g, 3.42 mmol) in 15 mL of THF was added dropwise over 30 mins and the resulting mixture was stirred at room temperature overnight. Solvent was removed and the residue and purified by silica gel column chromatography (PE/EA 1:1~0:1) to give compound **11-7** as a solid (300 mg, 44.3%). ESI-MS *m/z*: 298.50 (M+H). ^{1}H NMR (400 MHz, DMSO) δ: 10.38 (m, 1H), 8.0~8.13 (m, 1H), 7.40~7.88 (m, 2H), 7.67~7.76 (m, 1H), 4.6~4.7 (m, 1H), 4.4~4.5 (m, 1H), 4.0~4.13 (m, 2H), 3.88~4.0 (m, 1H), 3.38~3.47 (m, 1), 3.12~3.22 (t, 1H), 2.8~2.9 (m, 3H).

[0295] Step E: A solution of compound **11-7** (30 mg, 0.101 mmol), compound **11-3** (43 mg 0.119mmol) and TEA (72 mg, 0.713mmol) in 16 mL of DCM was stirred for 2 h before $NaBH(OAc)_3$ (151 mg, 0.713 mmol) was added slowly and stirred overnight. Then the reaction solution was washed with saturated $NaHCO_3$ aqueous solution, brine, and dried with anhydrous sodium sulfate. Solvent was removed and residue was purified by silica gel column chromatography (DCM/MeOH: 10/1) to give **44** as a solid (30 mg, 46%). ESI-MS *m/z*: 623.25 (M+H). ^{1}HNMR (400MHz, DMSO): 8.26(s, 1H), 8.05 (d, 1H), 7.60~7.70 (s, 2H), 7.40~7.58 (m, 1H), 7.20~7.40 (s, 1H), 4.55 (m, 1H), 4.40 (m, 1H), 3.95~4.18 (m, 5H), 3.55~3.74 (m, 4H), 3.10~3.30(m, 2H), 2.52~2.80 (m, 5H), 2.30~2.51 (m, 3H), 1.70~2.25 (m, 5H).

[0296] **Example 12**: *Fluorescence polarization assay.* This example illustrates an assay effective in monitoring the binding of MLL to menin. Fluorescence polarization (FP) competition experiments were performed to determine the effectiveness with which a compound inhibits the menin-MLL interaction, reported as an IC_{50} value. A fluorescein-labeled peptide containing the high affinity menin binding motif found in MLL was produced according to Yokoyama et al. (*Cell*, **2005**, 123(2): 207-218), herein incorporated by reference in its entirety. Binding of the labeled peptide (1.7 kDa) to the much larger menin (~67 kDa) is accompanied by a significant change in the rotational correlation time of the fluorophore, resulting in a substantial increase in the fluorescence polarization and fluorescence anisotropy (excitation at 500 nm, emission at 525 nm). The effectiveness with which a compound inhibits the menin-MLL interaction was measured in an FP competition experiment, wherein a decrease in fluorescence anisotropy correlates with inhibition of the interaction and was used as a read-out for IC_{50} determination.

[0297] **Table 2** shows biological activities of selected compounds in a fluorescence polarization assay. Compound numbers correspond to the numbers and structures provided in **Table 1** and **Examples 1-11**.

Table 2

	Less than 50 nM (++++)	50 nM to less than 250 nM (+++)	250 nM to 1000 nM (++)	Greater than 1000 nM (+)
Menin MLL 4-43 IC_{50} (nM)	5, 14, 17, 21, 22, 30, 43, 44, 45, 68, 69, 70, 75, 77	1, 8, 9, 11, 26, 46, 126, 127	3, 25, 29, 42, 139, 152, 155	41, 96, 125, 128, 129, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 153, 154, 156, 157, 158, 159

[0298] Example 13: *Homogenous time-resolve fluorescence (HTRF) assay.* A homogeneous time-resolve fluorescence (HTRF) assay is utilized as a secondary assay to confirm the results of the FP assay. In some embodiments, the HTRF assay is the primary assay and the FP assay is used as a secondary assay to confirm results. HTRF is based on the non-radiative energy transfer of the long-lived emission from the Europium cryptate (Eu^{3+}-cryptate) donor to the allophycocyanin (XL665) acceptor, combined with time-resolved detection. An Eu^{3+}-cryptate donor is conjugated with mouse anti-6His monoclonal antibody (which binds His-tagged menin) and XL665-acceptor is conjugate to streptavidin (which binds biotinylated MLL peptide). When these two fluorophores are brought together by the interaction of menin with the MLL peptide, energy transfer to the acceptor results in an increase in fluorescence emission at 665 nm and increased HTRF ratio (emission intensity at 665 nm/emission intensity at 620 nm). Inhibition of the menin-MLL interaction separates the donor from the acceptor, resulting in a decrease in emission at 665 nm and decreased HTRF ratio.

[0299] Example 14: *Cell proliferation assay.* The ability of a compound of the present disclosure to inhibit the growth of cells, such as human leukemia cell, acute myeloid leukemia cell, cells with an MLL fusion, control cells without an MLL fusion, VCaP, LNCaP, 22RV1, DU145, LNCaP-AR, MV4;11, KOPN-8, ML-2, MOLM-13, RS4;11, SEM, bone marrow cells (BMCs), MLL-AF9, MLL-AF4, MLL-ENL, MLL-CBP, MLL-GAS7, MLL-AF1p, MLL-AF6, HM-2, E2A-HLF, REH, U937, K562, KG-1, HL-60 and NB4 cells, is tested using a cell viability assay, such as the Promega CellTiter-Glo® Luminescent Cell Viability Assay (Promega Technical Bulletin, **2015**, "CellTiter-Glo® Luminescent Cell Viability Assay": 1-15, herein incorporated by reference in its entirety). Cells are plated at relevant concentrations, for example about $1x10^5 - 2x10^5$ cells per well in a 96-well plate. A compound of the present disclosure is added at a concentration up to about 2 μM with eight, 2-fold serial dilutions for each compound. Cells are incubated at 37 °C for a period of time, for example, 72 hours, then cells in the control wells are counted. Media is changed to restore viable cell numbers to the original concentration, and compounds are re-supplied. Proliferation is measured about 72 hours later using Promega

CellTiter-Glo® reagents, as per kit instructions.

[0300] Example 15: *RT-PCR analysis of MLL fusion protein downstream targets.* The effect of a compound of the present disclosure on expression of one or more MLL fusion protein downstream targets is assessed by RT-PCR. Cells, such as human leukemia cell, acute myeloid leukemia cell, cells with an MLL fusion, control cells without an MLL fusion, VCaP, LNCaP, 22RV1, DU145, LNCaP-AR, MV4;11, KOPN-8, ML-2, MOLM-13, RS4;11, SEM, bone marrow cells (BMCs), MLL-AF9, MLL-AF4, MLL-ENL, MLL-CBP, MLL-GAS7, MLL-AF1p, MLL-AF6, HM-2, E2A-HLF, REH, U937, K562, KG-1, HL-60 and NB4 cells, are treated with an effective concentration of a compound disclosed herein for about 7 days or less, then total RNA is extracted from cells using any available kit such as an RNeasy mini kit (QIAGEN) according to the manufacturer's instructions. Total RNA is reverse transcribed using a High Capacity cDNA Reverse Transcription Kit (Applied Biosystems), and relative quantification of relevant gene transcripts (e.g., *Hoxa9*, *DLX2*, *PBX3*, and *Meis1*) is determined by real-time PCR. Effective inhibition of the menin-MLL interaction is expected to result in the downregulation of downstream targets of MLL, including *Hoxa9*, *DLX2*, *PBX3*, and *Meis1*.

[0301] Example 16: *Pharmacokinetic studies in mice*. The pharmacokinetics of menin-MLL inhibitors are determined in female C57BL/6 mice following intravenous (iv) dosing at 15 mg/kg and oral dosing (po) at 30 mg/kg. Compounds are dissolved in the vehicle containing 25% (v/v) DMSO, 25% (v/v) PEG-400 and 50% (v/v) PBS. Serial blood samples (50 μL) are collected over 24 h, centrifuged at 15,000 rpm for 10 min and saved for analysis. Plasma concentrations of the compounds are determined by the LC-MS/MS method developed and validated for this study. The LC-MS/MS method consists of an Agilent 1200 HPLC system and chromatographic separation of tested compound is achieved using an Agilent Zorbax Extend-C18 column (5 cm x 2.1 mm, 3.5 μm; Waters). An AB Sciex QTrap 3200 mass spectrometer equipped with an electrospray ionization source (ABI-Sciex, Toronto, Canada) in the positive-ion multiple reaction monitoring (MRM) mode is used for detection. All pharmacokinetic parameters are calculated by noncompartmental methods using WinNonlin® version 3.2 (Pharsight Corporation, Mountain View, CA, USA).

[0302] Example 17: *Efficacy study in mouse xenograft tumor model.* Immunodeficient mice, such as 8-10 week-old female nude (nu/nu) mice, are used for *in vivo* efficacy studies in accordance with the guidelines approved by IACUC. Leukemia cells, such as human MV4-11 leukemia cells available from ATCC, are implanted subcutaneously via needle into female nude mice (5×10^6 cells/mouse). When the tumor reaches a size of approximately 150 to 250 mm^3 in mice, the tumor-bearing mice are randomly assigned to a vehicle control or compound treatment

group (8 animals per group). Animals are treated with a compound of the present disclosure by oral gavage or intraperitoneal injection in an appropriate amount and frequency as can be determined by the skilled artisan without undue experimentation. Subcutaneous tumor volume in nude mice and mice body weight are measured twice weekly. Tumor volumes are calculated by measuring two perpendicular diameters with calipers ($V = (\text{length} \times \text{width}^2)/2$). Percentage tumor growth inhibition (%TGI = 1 – [change of tumor volume in treatment group/change of tumor volume in control group]*100) is used to evaluate anti-tumor efficacy. Statistical significance is evaluated using a one-tailed, two sample *t* test. $P<0.05$ is considered statistically significant.

[0303] Example 18: *Efficacy study in prostate tumor xenograft model.* Immunodeficient mice, such as 4-6 week-old male CB17 severe combined immunodeficiency (SCID) mice, are used for *in vivo* efficacy studies in accordance with the guidelines approved by IACUC. Parental prostate cancer cells, such as VCaP or LNCaP-AR cells, are implanted subcutaneously into male CB.17.SCID mice (3-4 x 10^6 cells in 50% Matrigel). When the tumor reaches a palpable size of approximately 80 mm^3, the tumor-bearing mice are randomly assigned to a vehicle control or compound treatment group (6 or more animals per group). Animals are treated with a compound of the present disclosure by intraperitoneal injection in an appropriate amount and frequency as can be determined by the skilled artisan without undue experimentation. In one example, mice are treated with 40 mg/kg of a compound of the present disclosure daily by i.p. injection for two weeks, then 5 days per week thereafter. Subcutaneous tumor volume and mice body weight are measured twice weekly. Tumor volumes are calculated by measuring two perpendicular diameters with calipers ($V = (\text{length} \times \text{width}^2)/2$).

[0304] Example 19: *Efficacy study in castration-resistant prostate tumor xenograft model (VCaP).* Immunodeficient mice, such as 4-6 week-old male CB17 severe combined immunodeficiency (SCID) mice, are used for *in vivo* efficacy studies in accordance with the guidelines approved by IACUC. Parental prostate cancer cells, such as VCaP cells, are implanted subcutaneously into male CB.17.SCID mice (3-4 x 10^6 cells in 50% Matrigel). When the tumor reaches a size of approximately 200-300 mm^3, the tumor-bearing mice are physically castrated and tumors observed for regression and regrowth to approximately 150 mm^3. The tumor-bearing mice are randomly assigned to a vehicle control or compound treatment group (6 or more animals per group). Animals are treated with a compound of the present disclosure by intraperitoneal injection in an appropriate amount and frequency as can be determined by the skilled artisan without undue experimentation. In one example, mice are treated with 40 mg/kg of a compound of the present disclosure daily by i.p. injection. Subcutaneous tumor volume and mice body weight are measured twice weekly. Tumor volumes are calculated by measuring two

perpendicular diameters with calipers (V = (length x width^2)/2).

[0305] Example 20: *Efficacy study in castration-resistant prostate tumor xenograft model (LNCaP-AR).* Immunodeficient mice, such as 4-6 week-old male CB17 severe combined immunodeficiency (SCID) mice, are used for *in vivo* efficacy studies in accordance with the guidelines approved by IACUC. CB.17.SCID mice are surgically castrated and allowed to recover for 2-3 weeks before implanting parental prostate cancer cells, such as LNCaP-AR cells, subcutaneously into (3-4 x 10^6 cells in 50% Matrigel). When the tumor reaches a size of approximately 80-100 mm^3, the tumor-bearing mice are randomly assigned to a vehicle control or compound treatment group (6 or more animals per group). Animals are treated with a compound of the present disclosure by intraperitoneal injection in an appropriate amount and frequency as can be determined by the skilled artisan without undue experimentation. In one example, mice are treated with 60 mg/kg of a compound of the present disclosure daily by i.p. injection for 27 days. Subcutaneous tumor volume and mice body weight are measured twice weekly. Tumor volumes are calculated by measuring two perpendicular diameters with calipers (V = (length x width^2)/2).

[0306] Example 21: *Cellular Thermal Shift Assay (CETSA).* For the cell lysate CETSA experiments, cultured cells from cell lines (e.g., HEK293, bone marrow samples) are harvested and washed with PBS. The cells are diluted in kinase buffer (KB) (25 mM Tris(hydroxymethyl)-aminomethane hydrochloride (Tris-HCl, pH 7.5), 5 mM beta-glycerophosphate, 2 mM dithiothreitol (DTT), 0.1 mM sodium vanadium oxide, 10 mM magnesium chloride) or in phosphate-buffered saline (PBS) (10 mM phosphate buffer (pH 7.4), 2.7 mM potassium chloride and 137 mM sodium chloride). All buffers are supplemented with Complete protease inhibitor cocktail. The cell suspensions are freeze-thawed three times using liquid nitrogen. The soluble fraction (lysate) is separated from the cell debris by centrifugation at 20000 x g for 20 minutes at 4°C. The cell lysates are diluted with appropriate buffer and divided into two aliquots, with one aliquot being treated with drug and the other aliquot with the diluent of the inhibitor (control). After 10-30 minute incubation at room temperature the respective lysates are divided into smaller (50µL) aliquots and heated individually at different temperatures for 3 minutes followed by cooling for 3 minutes at room temperature. The appropriate temperatures are determined in preliminary CETSA experiments. The heated lysates are centrifuged at 20000 x g for 20 minutes at 4°C in order to separate the soluble fractions from precipitates. The supernatants are transferred to new microtubes and analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) followed by western blot analysis.

[0307] For the intact cell experiments the drug-treated cells from the in vitro experiments above

are heated as previously described followed by addition of KB (30μL) and lysed using 2 cycles of freeze-thawing with liquid nitrogen. The soluble fractions are isolated and analyzed by western blot.

[0308] For the in vivo mice experiments, lysates of frozen tissues are used. The frozen organs (e.g., liver or kidney) are thawed on ice and briefly rinsed with PBS. The organs are homogenized in cold PBS using tissue grinders followed by 3 cycles of freeze-thawing using liquid nitrogen. Tissue lysates are separated from the cellular debris and lipids. The tissue lysates are diluted with PBS containing protease inhibitors, divided into 50μL aliquots and heated at different temperatures. Soluble fractions are isolated and analyzed by western blot.

[0309] It is expected that the aliquots treated with one or more of the compounds disclosed herein exhibit increased thermal stabilization of menin compared to the control aliquots.

[0310] Example 22: *CETSA-like dot-blot experiments on purified proteins.* Purified protein (0.5 μg) is added to the wells of a PCR plate and the volume adjusted to 50 μL by addition of buffer or cell lysates and ligands depending on the experimental setup. The samples are heated for the designated time and temperature in a thermocycler. After heating, the samples are immediately centrifuged for 15 min at 3000 x g and filtered using a 0.65μm Multiscreen HTS 96 well filter plate. 3 μL of each filtrate are blotted onto a nitrocellulose membrane. Primary antibody and secondary conjugate are used for immunoblotting. All membranes are blocked with blocking buffer; standard transfer and western blot protocols recommended by the manufacturers are used. All antibodies are diluted in blocking buffer. The dot-blot is developed. Chemiluminescence intensities are detected and imaged. Raw dot blot images are processed. The background is subtracted and intensities are quantified. Graphs are plotted and fitted using sigmoidal dose-response (variable slope).

[0311] Example 23: *Cell proliferation assays.* The ability of a compound of the present disclosure to inhibit the growth of cells is tested in both MLL leukemia cell lines (e.g., MV4;11, MOLM13 and/or KOPN8) and control cell lines (e.g., K562, REH, U937, KG-1, and/or HL-60) using the MTT cell proliferation assay (ATCC® 30-1010K). Cells are plated at about $1x10^5$ cells per well in a 96-well plate. A compound of the present disclosure is added at a concentration up to about 2 μM with seven, 2-fold serial dilutions for each compound. Cells are incubated at 37 °C for 72 hours, then cells in the control wells were counted. Media is changed to restore viable cell numbers to the original concentration, and compounds are re-supplied. Proliferation is measured 96 hours later using MTT reagents, as per kit instructions.

[0312] Example 24: *Efficacy study in mouse xenograft tumor model.* Immunocompromised 8-10 week-old female nude (nu/nu) mice are used for *in vivo* efficacy studies in accordance with

IACUC guidelines. Human MV4;11 leukemia cells available from ATCC are implanted subcutaneously into female nude mice (5 x 10^6 cells/mouse). When the tumor reach a size of approximately 150 to 250 mm^3, the tumor-bearing mice are randomly assigned to a vehicle control or a compound treatment group (8 mice per group). Mice in each treatment group are administered a compound of the present disclosure by oral gavage at the dosage indicated (50 mg/kg, bid; 50 gm/kg, qd; 100 mg/kg, bid; 100 mg/kg, qd; 200 mg/kg, qd.; or 200 mg/kg, bid). Subcutaneous tumor volume and mouse body weight are measured twice weekly. Tumor volumes are calculated by measuring two perpendicular diameters with calipers (V = (length x $width^2$)/2).

[0313] Example 25: *Efficacy study in xenotransplantation mouse model of MLL leukemia.* Immunocompromised 8-10 week-old female NSG mice are used for *in vivo* efficacy studies in accordance with IACUC guidelines. Luciferase expressing human MV4;11 leukemia cells (MV4;11-luc) are engrafted intravenously via tail vein injection (1 x 10^7 cells/animal). When the mean luminescence of the cells reach approximately 1.5x10^6, the tumor-bearing mice are randomly assigned to a vehicle control or a compound treatment group (5 animals per group). Animals in each of the treatment groups are administered a different compound of the present disclosure by oral gavage (120 mg/kg b.i.d, 150 mg/kg b.i.d., 200 mg/kg b.i.d., or 200 mg/kg q.d.). Body weight is measured daily, while mean luminescence is measured 6 days after initiating the treatment with compound or vehicle.

[0314] Animals are sacrificed on Day 7 of treatment and bone marrow samples collected and prepared for gene expression analysis. Expression levels of MLL fusion protein target genes *HOXA9*, *DLX2*, *PBX3*, and/or *MEIS1* are measured by qRT-PCR.

[0315] Example 26: *Survival study in xenotransplantation mouse model of MLL leukemia.* For survival studies in the xenotransplantation MV4;11 xenograft model, 6 to 8-week old female NSG mice are intravenously injected with 1 x 10^7 luciferase-expressing MV4;11 cells harboring MLL-AF4 translocation. At day 12 after transplantation, treatment is initiated with a compound disclosed herein and is continued for 22 consecutive days.

[0316] For survival studies in the xenotransplantation MOLM13 xenograft model, 6 to 8-week old female NSG mice are intravenously injected with 0.5 x 10^6 MOLM13 cells harboring MLL-AF9 translocation. At day 4 after transplantation, treatment is initiated with a compound disclosed herein and is continued for 16 consecutive days in the compound treated mice or until terminal leukemia developed in the vehicle-treated mice.

[0317] Example 27: *Cell culture and islet isolation.* Islet cells can be isolated from a variety of species according to methods known in the art. For example, rat islets are isolated by the

standard collagenase digestion method from the pancreata of adult Sprague–Dawley rats (200–250 g) and cultured in RPMI medium (Invitrogen) with 10% FBS (Thermo Scientific). In brief, approximately 9 mL of ice-cold Collagenase V (Sigma) solution is injected into the pancreas via the common bile duct. After dissection, the pancreas is incubated for approximately 35 min at about 37°C and then further dissociated by repeated pipetting by using a 10-mL pipette. Islets are purified by Histopaque 1.077 (Sigma) density gradient centrifugation and manually picked by using a stereomicroscope. Islets are allowed to recover from the isolation procedure for an approximate duration of 1-2 days in RPMI medium containing approximately 10% fetal bovine serum in non-tissue culture-treated petri dishes to prevent attachment.

[0318] Example 28: *Rat primary dispersed islet cell proliferation assay*. Rested islets, such as rat islets, are trypsinized to single-cell suspensions and plated in 384-well clear bottom plates and cultured in the presence or absence of a subject compound disclosed herein for approximately 4 days in growth medium containing approximately 2 μM EdU (Invitrogen). Cells are fixed in 4% paraformaldehyde solution (Electron Microscopy Sciences) and stained by standard immunofluorescence techniques for insulin (polyclonal guinea pig antiinsulin, DAKO) and nuclear DNA is stained with Hoechst. EdU incorporation is measured by click reaction with AlexaFluor-647-azide (Invitrogen). Plates are imaged on ImageXpress Ultra (Molecular Devices). Imaging data are analyzed by MetaXpress (Molecular Devices). Total insulin positive cells and EdU/insulin-double positive cells are counted and reported as percentage of insulin positive cells containing EdU. Fold change can be calculated by normalizing percent EdU-positive β cells to DMSO-treated wells.

[0319] Example 29: *Human islet proliferation assay*. Freshly-isolated explants of non-diabetic, human pancreatic islets are cultured in the presence of DMSO or a compound disclosed herein for 120 hours in growth medium containing 10 μM EdU (1000 islet equivalents per sample). Islets are fixed and stained by immunofluorescence for insulin and EdU. Beta cell proliferation, islet area, and average beta cell number per islet are assessed in accordance with methods described herein. Treatment with a compound disclosed herein induces beta cell proliferation, as evidenced by an increase in the size of human islets and/or an increase in the average beta cell number per islet.

[0320] Example 30: *Human islet isolation*. Human islet isolations are conducted using standard procedures in the art, for example, as described in Qi, M. et al. *Transplantation Direct* **2015**, 1-9 (doi: 10.1097/TXD.0000000000000522). In short, a donor pancreas is cleaned and cannulated, then subjected to automated perfusion using a perfusion apparatus. Liberase HI, collagenase NB1 with NP, or liberase MTF C/T is infused, then the distended pancreas is cut into pieces and

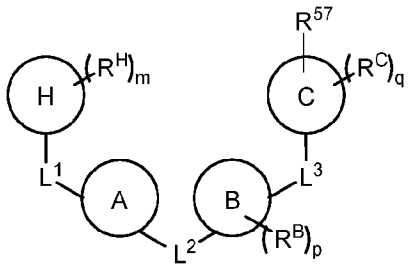
loaded into a digestion chamber for digestion at 37 °C. Once 50% or more of the islets are free from acinar tissues, the enzyme digestion is terminated by adding surplus media for enzyme dilution. Tissue is collected, centrifuged and combined with human serum albumin. The combined tissue is purified using a cell processor and continuous density gradients. After isolations, islets are cultured in Connaught Medical Research Laboratories 1066 medium (pH 7.4) with 0.5% human serum albumin and 0.1 μg/mL insulin-like growth factor-1 at 37 °C under 5% CO_2 for up to 72 hours.

[0321] While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

What is claimed is:

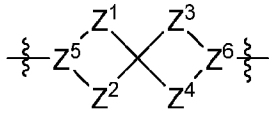
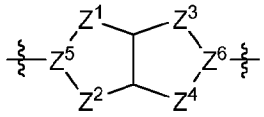
1. A compound of Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

A is  or  ;

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$, $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$, -C(O)-, and $-C(R^{A1})(R^{A2})-C(O)-$, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or $-C(R^{A1})(R^{A2})-C(O)-$;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1, L^2, and L^3 is independently selected from bond, -O-, -S-, $-N(R^{51})-$, $-N(R^{51})CH_2-$, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, -OS(O)-, -S(O)O-, -S(O)-, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, and $-N(R^{51})S(O)N(R^{51})-$ or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2, or L^3 can together optionally form a bridge or ring;

R^{50} is, at each occurrence, independently selected from:

halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, -

$P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-

membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, -

$P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

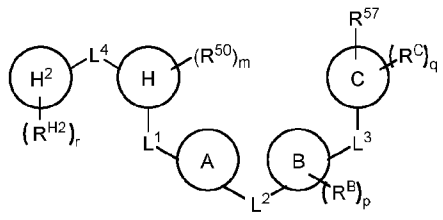
R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

each of R^H and R^B is, at each occurrence, independently selected from R^{50}, or two R^H groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^C is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring; and

each of m, p, and q is independently an integer from 0 to 12.

2. A compound of Formula (I-G):

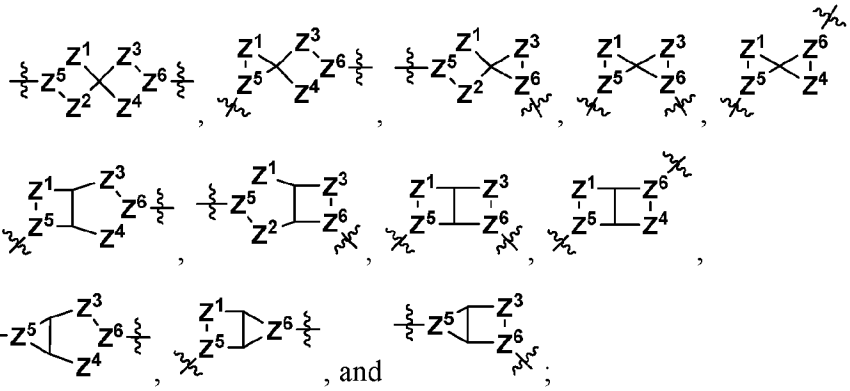


(I-G);

or a pharmaceutically acceptable salt, isotopic form, or prodrug thereof, wherein:

H is selected from C_{5-6} carbocycle and 5- to 6-membered heterocycle;

H^2 is selected from C_{5-6} carbocycle and 5- to 6-membered heterocycle;

A is selected from  ;

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from $-C(R^{A1})(R^{A2})-$, $-C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-$, -C(O)-, and $-C(R^{A1})(R^{A2})-C(O)-$, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or $-C(R^{A1})(R^{A2})-C(O)-$;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1, L^2, L^3 and L^4 is independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -N(R^{51})$S(O)_2$-, -$S(O)_2N(R^{51})$-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2N(R^{51})$-, and -N(R^{51})S(O)N(R^{51})- or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2, or L^3 can together optionally form a bridge or ring;

R^{50} is, at each occurrence, independently selected from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -C(O)$R^{52}$, -C(O)$OR^{52}$, -OC(O)$R^{52}$, -OC(O)$OR^{52}$, -OC(O)$N(R^{52})_2$, -OC(O)$NR^{53}R^{54}$, -$NR^{52}$C(O)$R^{52}$, -$NR^{52}$C(O)$OR^{52}$, -$NR^{52}$C(O)$N(R^{52})_2$, -$NR^{52}$C(O)$NR^{53}R^{54}$, -C(O)$N(R^{52})_2$, -C(O)$NR^{53}R^{54}$, -P(O)$(OR^{52})_2$, -P(O)$(R^{52})_2$, -P(O)$(OR^{52})(R^{52})$, -P(O)$(NR^{52})(R^{52})$, -$NR^{52}$P(O)$(R^{52})$, -P(O)$(NR^{52})(OR^{52})$, -P(O)$(NR^{52})_2$, =O, =S, =N($R^{52}$);

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -C(O)$R^{52}$, -C(O)$OR^{52}$, -OC(O)$R^{52}$, -OC(O)$OR^{52}$, -OC(O)$N(R^{52})_2$, -OC(O)$NR^{53}R^{54}$, -$NR^{52}$C(O)$R^{52}$, -$NR^{52}$C(O)$OR^{52}$, -$NR^{52}$C(O)$N(R^{52})_2$, -$NR^{52}$C(O)$NR^{53}R^{54}$, -C(O)$N(R^{52})_2$, -C(O)$NR^{53}R^{54}$, -P(O)$(OR^{52})_2$, -P(O)$(R^{52})_2$, -P(O)$(OR^{52})(R^{52})$, -P(O)$(NR^{52})(R^{52})$, -$NR^{52}$P(O)$(R^{52})$, -P(O)$(NR^{52})(OR^{52})$, -P(O)$(NR^{52})_2$, =O, =S, =N($R^{52}$), C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -S(=O)R^{52}, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -C(O)$R^{52}$, -C(O)$OR^{52}$, -OC(O)$R^{52}$, -

$OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

R^B is, at each occurrence, independently selected from R^{50}, or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

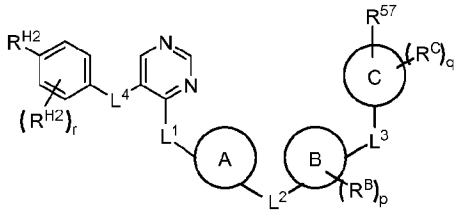
R^{H2} is independently selected at each occurrence from R^{50}, or two R^{H2} groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^C is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring;

r is an integer from 1 to 6; and

each of m, p and q is independently an integer from 0 to 12.

3. The compound of claim 2, wherein the compound of Formula (I-G) is represented by Formula (I-I):



(I-I).

4. The compound of claim 2 or 3, wherein L^4 is selected from -O-, -S-, -NH- and -CH_2-.

5. The compound of claim 4, wherein L^4 is selected from -O- and -NH-.

6. The compound of any one of claims 2-5, wherein R^{H2} is selected from halo, -$C(O)R^{52}$, and –$C(O)N(R^{52})_2$.

7. The compound of claim 6, wherein R^{52} is selected from hydrogen and C_{1-10} alkyl.

8. The compound of any one of the preceding claims, wherein C is C_{3-12} carbocycle or 3- to 12-membered heterocycle.

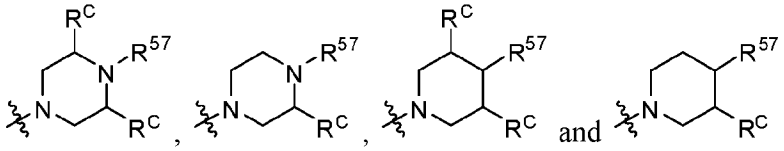
9. The compound of claim 8, wherein C is 5- to 12-membered heterocycle, wherein the heterocycle comprises at least one nitrogen atom.

10. The compound of claim 9, wherein C is aromatic.

11. The compound of claim 9, wherein C is saturated.

12. The compound of claim 11, wherein C is selected from piperidinyl, piperazinyl, and morpholinyl.

13. The compound of claim 12, wherein C is selected from:



and

.

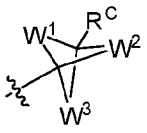
14. The compound of claim 1 or 13, wherein R^{57} is selected from -$S(=O)R^{52}$, -$S(=O)_2R^{58}$, -$S(=O)_2N(R^{52})_2$, and -$NR^{52}S(=O)_2R^{52}$.

15. The compound of any one of claims 1 or 14, wherein R^{57} is selected from -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$NHS(=O)_2CH_3$, and -$S(=O)_2NHCH_3$.

16. The compound of any one of claims 1-15, wherein R^C is selected from C_{1-3} alkyl and C_{1-3} haloalkyl.

17. The compound of any one of claims 1-12, wherein q is at least 1, and wherein R^C is selected from halogen, -$N(R^{52})_2$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, =O, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$C(O)N(R^{52})_2$, C_{1-3} alkyl, and C_{1-3} haloalkyl, or two R^C groups attached to different atoms can together form a C_{1-3} bridge.

18. The compound of any one of claims 1 to 8, wherein:

C is  ;

W^1 is C_{1-4} alkylene, optionally substituted with one or more R^{50};

W^2 is selected from a bond; and C_{1-4} alkylene, optionally substituted with one or more R^{50}; and

W^3 is selected from absent; and C_{1-4} alkylene, optionally substituted with one or more R^{50}.

19. The compound of claim 18, wherein W^1, W^2 and W^3 are each independently selected from C_{1-4} alkylene, wherein each C_{1-4} alkylene is optionally substituted with one or more R^{50}.

20. The compound of claim 19, wherein W^1, W^2 and W^3 are each C_1 alkylene.

21. The compound of claim 20, wherein W^1 and W^2 are each C_1 alkylene and W^3 is absent.

22. The compound of any one of claims 18-21, wherein R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, and $-C(O)NR^{53}R^{54}$.

23. The compound of any one of claims 1-22, wherein L^3 comprises less than 20 atoms.

24. The compound of any one of claims 1-23, wherein L^3 is not a bond.

25. The compound of any one of claims 1-24, wherein L^3 is C_{1-6} alkylene, optionally substituted with one or more R^{50}.

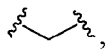
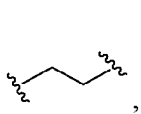
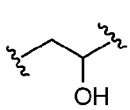
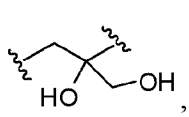
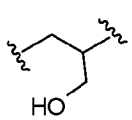
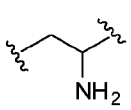
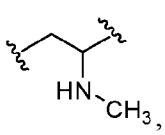
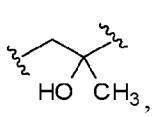
26. The compound of claim 24, wherein L^3 is C_2 alkylene substituted with at least one C_{1-3} alkyl or C_{1-3} haloalkyl, and optionally further substituted with one or more R^{50}.

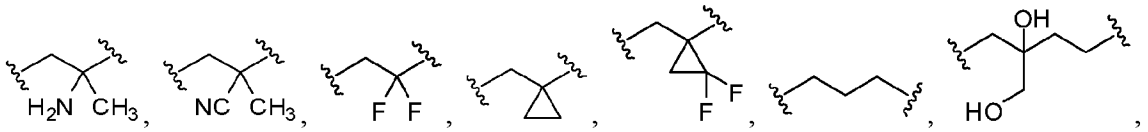
27. The compound of any one of claims 1-26, wherein L^3 is substituted with =O, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-3} alkyl(cyclopropyl), C_{1-3} alkyl($NR^{52}C(O)R^{52}$) or -O(C_{1-6} alkyl).

28. The compound of claim 27, wherein L^3 is substituted with $-CH_3$.

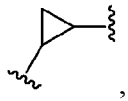
29. The compound of any one of claims 1 to 26, wherein L^3 is selected from  and  .

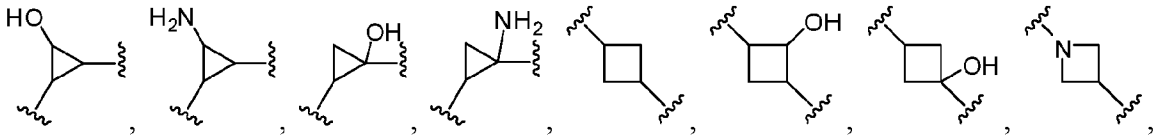
30. The compound of claim 29, wherein R^{50} is methyl.

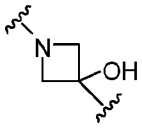
31. The compound of any one of claims 1 to 25, wherein L^3 is selected from  ,  ,  ,  ,  ,  ,  ,  ,



wherein any one of which is optionally substituted with one or more R^{50}.

32. The compound of any one of claims 1 to 24, wherein L^3 is selected from  ,



and  , wherein any one of which is optionally substituted with one or more R^{50}.

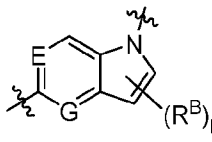
33. The compound of any one of claims 1 or 8-32, wherein:

H is 5- to 12-membered heterocycle; and

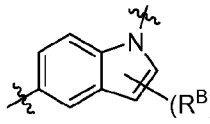
B is 5- to 12-membered heterocycle or C_{4-8} carbocycle.

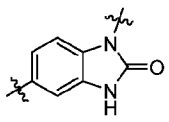
34. The compound of any one of claims 1-33, wherein B is 6- to 12-membered bicyclic heterocycle.

35. The compound of claim 34, wherein B comprises at least one nitrogen atom.

36. The compound of claim 35, wherein B is  , wherein each of E and G is independently N or C.

37. The compound of claim 35, wherein B is indolylene.

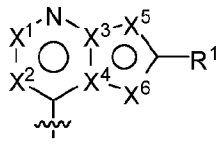
38. The compound of claim 37, wherein B is  .

39. The compound of any one of claims 1-33, wherein B is phenylene or  .

40. The compound of any one of claims 1-39, wherein R^B is selected from halogen, methyl, -CN, $-OR^{52}$, and $-N(R^{52})_2$.

41. The compound of any one of claims 1 or 8-40, wherein H is 6-membered to 12-membered bicyclic heterocycle.

42. The compound of any one of claims 1 or 8-41, wherein:

H is  ;

each of X^1 and X^2 is independently selected from CR^2 and N;

each of X^3 and X^4 is independently selected from C and N;

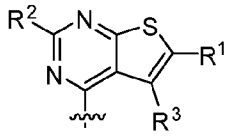
each of X^5 and X^6 is independently selected from CR^3, N, NR^4, O, and S;

each of R^1, R^2 and R^3 is independently selected at each occurrence from hydrogen and R^{50}; and

R^4 is selected from R^{51}.

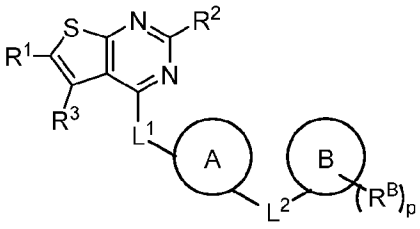
43. The compound of claim 42, wherein X^3 and X^4 are each C.

44. The compound of claim 42 or 43, wherein X^6 is CR^3, and R^3 is selected from hydrogen, halogen, $-OR^{52}$, $-N(R^{52})_2$, -CN, $-C(O)OR^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl.

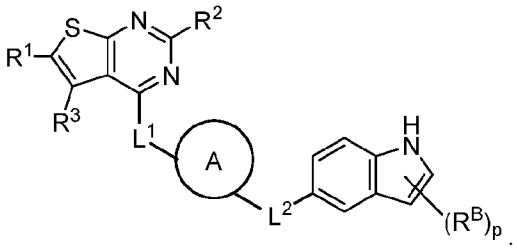
45. The compound of claim 42, wherein H is  .

46. The compound of claim 45, wherein R^2 is selected from hydrogen, halogen, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

47. The compound of claim 1, having the structure:

 ; wherein each of R^1, R^2 and R^3 is independently selected at each occurrence from hydrogen and R^{50}.

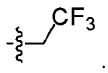
48. The compound of claim 47, having the structure:

 .

49. The compound of claim 48, wherein R^2 is selected from halogen, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

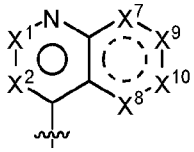
50. The compound of any one of claims 45-49, wherein R^3 is selected from hydrogen, halogen, $-OR^{52}$, $-N(R^{52})_2$, -CN, $-C(O)OR^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl.

51. The compound of any one of claims 42-50, wherein R^1 is C_{1-3} haloalkyl.

52. The compound of claim 51, wherein R^1 is  .

53. The compound of any one of claims 1 or 8-41, wherein H is thienopyrimidinyl or thienopyridinyl.

54. The compound of any one of claims 1 or 8-41, wherein:

H is  ;

each of X^1 and X^2 is independently CR^2 or N;

each of X^7, X^8, X^9, and X^{10} is independently CR^{16}, $CR^{17}R^{18}$, N, NR^{19}, O, or S;

each of R^{16}, R^{17}, and R^{18} is independently selected at each occurrence from hydrogen and R^{50}; and

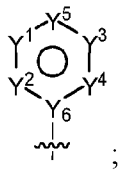
R^{19} is selected from R^{51}.

55. The compound of any one of claims 42-44 or 54, wherein X^1 is CR^2, and R^2 is selected from hydrogen, halogen, -OH, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

56. The compound of any one of claims 42-44, 54, or 55, wherein X^2 is N.

57. The compound of any one of claims 1 or 8-40, wherein H is 5- or 6-membered monocyclic heterocycle.

58. The compound of claim 57, wherein:

H is  ;

each of Y^1, Y^2, and Y^4 is independently CR^2, N, NR^{21}, O, or S;

Y^5 is CR^{20}, N, NR^{21}, O, or S;

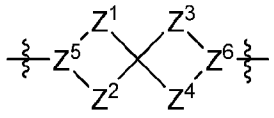
Y^6 is C or N;

Y^3 is a bond, CR^{22}, or N, wherein when Y^3 is CR^{22} or N, then each of Y^1, Y^2, and Y^4 is independently CR^2, N, or NR^{21} and Y^5 is CR^{20}, N, or NR^{21};

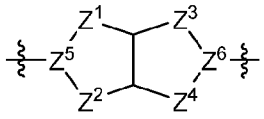
each of R^2 and R^{20} is independently selected at each occurrence from hydrogen and R^{50}; and

R^{21} is selected from R^{51}.

59. The compound of any one of claims 1-58, wherein:

A is  .

60. The compound of any one of claims 1-58, wherein:

A is  .

61. The compound of claim 59 or 60, wherein Z^5 and Z^6 are N.

62. The compound of any one of claims 59-61, wherein R^{A1} is, at each occurrence, independently selected from hydrogen, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, -CN, $-NO_2$, and -OH.

63. The compound of any one of claims 59-62, wherein R^{A2} is, at each occurrence, independently selected from hydrogen, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, -CN, $-NO_2$, and -OH.

64. The compound of any one of claims 1-63, wherein L^1 is a bond or $-N(R^{51})-$.

65. The compound of any one of claims 1-63, wherein L^1 is not a bond.

66. The compound of any one of claims 1-63, wherein L^1 is -NH-.

67. The compound of any one of claims 1-66, wherein L^2 is not a bond.

68. The compound of any one of claims 1-67, wherein L^2 is alkylene or heteroalkylene, each of which is optionally substituted with one or more R^{50}.

69. The compound of any one of claims 1-68, wherein L^2 is C_{1-4} alkylene, optionally substituted with one or more R^{50}.

70. The compound of claim 69, wherein L^2 is substituted with =O.

71. The compound of any one of claims 1-67, wherein L^2 is selected from $-CH_2-$, $-N(R^{51})-$, $-N(R^{51})CH_2-$, $-N(R^{51})C(O)-$, and $-N(R^{51})S(O)_2-$.

72. The compound of claim 71, wherein L^2 is $-CH_2-$.

73. The compound of claim 1, wherein:

H is 5- to 12-membered heterocycle;

B is indolylene; and

C is 5- to 6-membered heterocycle.

74. The compound of claim 1, wherein:

H is thienopyrimidinyl or thienopyridinyl;

B is indolylene; and

C is piperidinyl, piperazinyl, or morpholinyl.

75. The compound of claim 1, wherein:

H is thienopyrimidinyl or thienopyridinyl;

B is indolylene; and

L^1, L^2, and L^3 are not bonds.

76. The compound of claim 1, wherein:

H is thienopyrimidinyl;

B is 6- to 12-membered bicyclic heterocycle;

m is an integer from 0 to 3; and

p is an integer from 0 to 3.

77. The compound of claim 1, wherein:

H is thienopyrimidinyl;

B is indolylene;

L^1 and L^2 are each independently selected from -O-, -S-, -NH-, and -CH_2-;

L^3 is selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -N(R^{51})$S(O)_2$-, -$S(O)_2$N(R^{51})-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2$N(R^{51})-, -N(R^{51})S(O)N(R^{51})-; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of L^3 can together optionally form a ring;

R^B and R^C are each independently selected at each occurrence from R^{50}, or two R^B groups or two R^C groups attached to the same atom or different atoms can together optionally form a ring;

m is an integer from 0 to 3;

p is an integer from 0 to 6; and

q is an integer from 0 to 6.

78. The compound of claim 1, wherein:

H is thienopyrimidinyl;

B is indolylene;

L^1 and L^2 are each independently selected from -O-, -S-, -NH-, and -CH_2-;

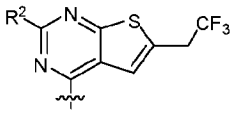
L^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, and C_{2-6} alkynylene, each of which is optionally substituted with one or more R^{50};

R^B and R^C are each independently selected at each occurrence from R^{50}, or two R^B groups or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring;

m is an integer from 0 to 3;

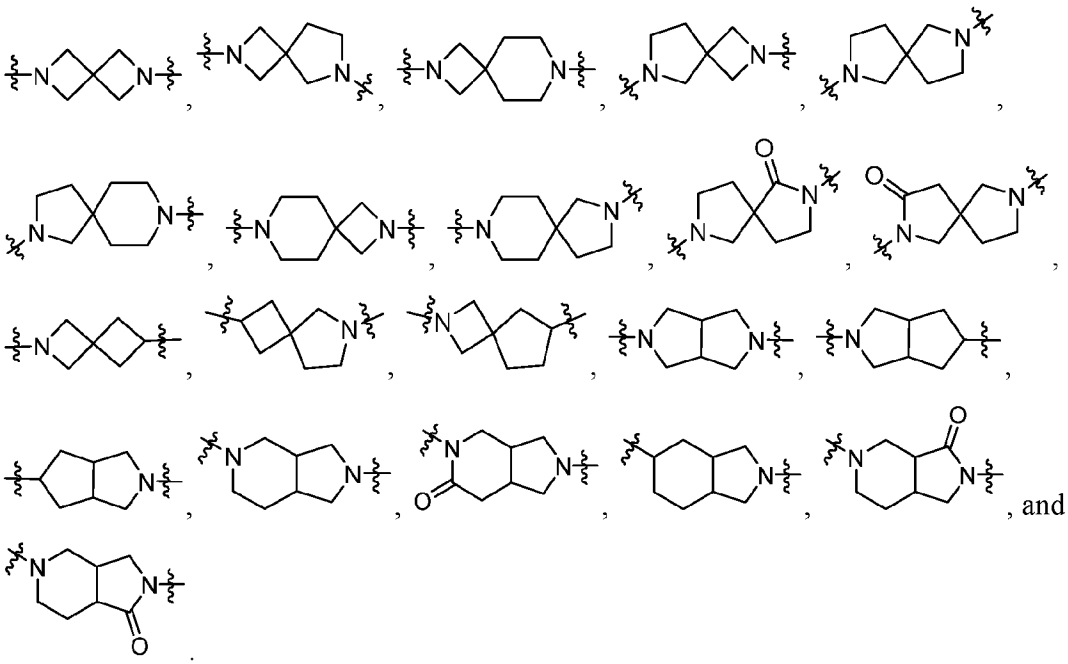
p is an integer from 0 to 3; and

q is an integer from 0 to 6.

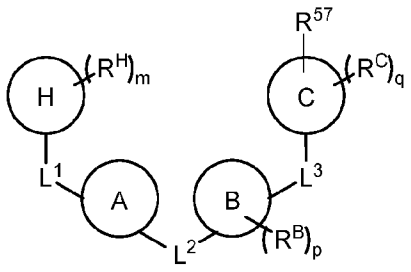
79. The compound of any one of claims 76-78, wherein H is  and R^2 is selected from hydrogen, halogen, -OH, -OR^{52}, -NH_2, -$N(R^{52})_2$, -CN, C_{1-3} alkyl, C_{1-3} alkyl-OR^{52}, C_{1-3} alkyl-$N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

80. The compound of claim 79, wherein R^2 is selected from -NH_2, -CH_3, and -$NHCH_3$.

81. The compound of any one of claims 1-80, wherein A is selected from:



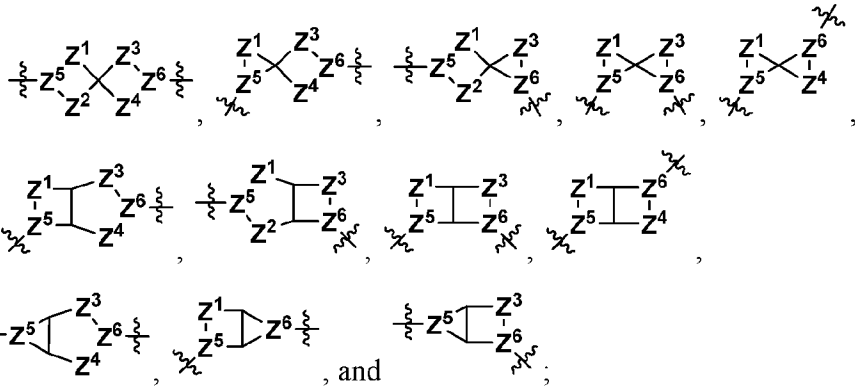
82. A compound of Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

A is selected from  ;

each of Z^1, Z^2, Z^3, and Z^4 is independently selected from -C(R^{A1})(R^{A2})-, -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-, -C(O)-, and -C(R^{A1})(R^{A2})-C(O)-, wherein no more than one of Z^1, Z^2, Z^3, and Z^4 is -C(O)- or -C(R^{A1})(R^{A2})-C(O)-;

Z^5 and Z^6 is independently selected from -C(H)- and -N-;

B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

C is selected from bond, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

each of L^1, L^2, and L^3 is independently selected from bond, -O-, -S-, -N(R^{51})-, -N(R^{51})CH_2-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R^{51})-, -C(O)N(R^{51})C(O)-, -C(O)N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)-, -N(R^{51})C(O)N(R^{51})-, -N(R^{51})C(O)O-, -OC(O)N(R^{51})-, -C(NR^{51})-, -N(R^{51})C(NR^{51})-, -C(NR^{51})N(R^{51})-, -N(R^{51})C(NR^{51})N(R^{51})-, -$S(O)_2$-, -OS(O)-, -S(O)O-, -S(O)-, -$OS(O)_2$-, -$S(O)_2O$-, -N(R^{51})$S(O)_2$-, -$S(O)_2N(R^{51})$-, -N(R^{51})S(O)-, -S(O)N(R^{51})-, -N(R^{51})$S(O)_2N(R^{51})$-, and -N(R^{51})S(O)N(R^{51})- or from alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50}, wherein two R^{50} groups attached to the same atom or different atoms of any one of L^1, L^2, or L^3 can together optionally form a bridge or ring;

R^{50} is, at each occurrence, independently selected from:

halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -$NR^{52}S(=O)_2N(R^{52})_2$, -$NR^{52}S(=O)_2NR^{53}R^{54}$, -$C(O)R^{52}$, -$C(O)OR^{52}$, -$OC(O)R^{52}$, -$OC(O)OR^{52}$, -$OC(O)N(R^{52})_2$, -$OC(O)NR^{53}R^{54}$, -$NR^{52}C(O)R^{52}$, -$NR^{52}C(O)OR^{52}$, -$NR^{52}C(O)N(R^{52})_2$, -$NR^{52}C(O)NR^{53}R^{54}$, -$C(O)N(R^{52})_2$, -$C(O)NR^{53}R^{54}$, -$P(O)(OR^{52})_2$, -$P(O)(R^{52})_2$, -$P(O)(OR^{52})(R^{52})$, -$P(O)(NR^{52})(R^{52})$, -$NR^{52}P(O)(R^{52})$, -$P(O)(NR^{52})(OR^{52})$, -$P(O)(NR^{52})_2$, =O, =S, =N($R^{52}$);

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO_2, -CN, -OR^{52}, -SR^{52}, -$N(R^{52})_2$, -$NR^{53}R^{54}$, -$S(=O)R^{52}$, -$S(=O)_2R^{52}$, -$S(=O)_2N(R^{52})_2$, -$S(=O)_2NR^{53}R^{54}$, -$NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle,

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, -CN, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, -

$NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =O, =S, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50};

R^{57} is selected from:

hydrogen, halogen, $-NO_2$, -CN, $-SR^{52}$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{58}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NH(C_{1-6}$ alkyl), $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, $=N(R^{52})$; and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from $-NO_2$, -CN, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, =S, and $=N(R^{52})$; and

R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, =O, -OH, $-OCH_3$, $-OCH_2CH_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50};

R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50};

each of R^H and R^B is, at each occurrence, independently selected from R^{50}, or two R^H groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

R^C is, at each occurrence, independently selected from hydrogen or R^{50}, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring; and

each of m, p, and q is independently an integer from 0 to 12.

83. The compound of any one of claims 1-82, wherein the compound is provided as a substantially pure stereoisomer.

84. The compound of claim 83, wherein the stereoisomer is provided in at least 90% enantiomeric excess.

85. The compound of any one of claims 1-84, wherein the compound is isotopically enriched.

86. A pharmaceutical composition comprising a compound of any one of claims 1-85, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

87. The pharmaceutical composition of claim 86, wherein the pharmaceutical composition is formulated for oral administration.

88. The pharmaceutical composition of claim 86, wherein the pharmaceutical composition is formulated for injection.

89. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-85, or a pharmaceutically acceptable salt thereof.

90. A method of treating a hematological cancer in a subject exhibiting a mutation in the nucleophosmin (NPM1) gene, DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, FMS-like tyrosine kinase-3 (FLT3) gene, isocitrate dehydrogenase 1 (IDH1) gene, isocitrate dehydrogenase 2 (IDH2) gene, or combination thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-85, or a pharmaceutically acceptable salt thereof.

91. A method of treating a hematological cancer in a subject in need thereof, comprising:

a. determining the presence or absence of one or more of an NPM1 mutation, DNMT3A mutation, FLT3 mutation, IDH1 mutation, or IDH2 mutation in a biological sample isolated from the subject; and

b. if the one or more of the NPM1 mutation, DNMT3A mutation, FLT3

mutation, IDH1 mutation, or IDH2 mutation is determined to be present in the subject, administering to the subject a therapeutically effective amount of a compound of any one of claims 1-85, or a pharmaceutically acceptable salt thereof.

92. The method of any one of claims 89-91, wherein the cancer is a hematological cancer.

93. The method of claim 92, wherein the cancer is leukemia.

94. The method of claim 92, wherein the cancer is lymphoma.

95. The method of claim 92, wherein the cancer is mixed lineage leukemia (MLL), MLL-related leukemia, MLL-associated leukemia, MLL-positive leukemia, MLL-induced leukemia, rearranged mixed lineage leukemia (MLL-r), leukemia associated with a MLL rearrangement or a rearrangement of the MLL gene, acute leukemia, chronic leukemia, indolent leukemia, lymphoblastic leukemia, lymphocytic leukemia, myeloid leukemia, myelogenous leukemia, childhood leukemia, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute granulocytic leukemia, acute nonlymphocytic leukemia, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myeloproliferative disease (MPD), myeloproliferative neoplasia (MPN), plasma cell neoplasm, multiple myeloma, myelodysplasia, cutaneous T-cell lymphoma, lymphoid neoplasm, AIDS-related lymphoma, thymoma, thymic carcinoma, mycosis fungoides, Alibert-Bazin syndrome, granuloma fungoides, Sezary Syndrome, hairy cell leukemia, T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia, meningeal leukemia, leukemic leptomeningitis, leukemic meningitis, multiple myeloma, Hodgkin's lymphoma, non Hodgkin's lymphoma, or Waldenstrom's macroglobulinemia.

96. The method of claim 92, wherein the cancer is selected from a malignant lymphoma, a leukemia, a mature B cell neoplasm, a mature T cell and natural killer (NK) cell neoplasm, a precursor lymphoid neoplasm, Hodgkin lymphoma (HL), a plasma cell tumor, a mast cell tumor, a neoplasm of histiocytes and accessory lymphoid cells, an immunoproliferative disease, a myeloid leukemia, and a myelodysplastic syndrome (MDS).

97. The method of claim 92, wherein the cancer is selected from acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, multiple myeloma, mixed lineage leukemia and myelodysplastic syndromes.

98. The method of claim 97, wherein the cancer is acute myeloid leukemia.

99. A method of treating a subject having acute myeloid leukemia or acute lymphoblastic leukemia, comprising:

a. screening the subject for the presence of an MLL rearrangement, a partial tandem duplication of MLL, or elevated MEIS1 expression levels; and

b. administering a compound or salt of any one of claims 1-85 to the subject if one or more of the MLL rearrangement, partial tandem duplication of MLL, or elevated MEIS1 expression levels are determined to be present.

100. A method of treating insulin resistance, pre-diabetes, diabetes, or risk of diabetes in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-85, or a pharmaceutically acceptable salt thereof.

101. A method of treating hyperglycemia in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-85, or a pharmaceutically acceptable salt thereof.

102. A method of treating a disease or condition associated with MLL fusion proteins, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-85.

103. A method of treating a disorder mediated by chromosomal rearrangement on chromosome 11q23 in a subject in need thereof, the method comprising: administering to the subject a therapeutically effective amount of a compound of any one of claims 1-85.

104. A method of treating a disorder mediated by an interaction between menin and another protein, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-85.

105. The method of any one of claims 89-104, wherein the subject is a human.

106. A method of promoting proliferation of a pancreatic cell, comprising administering a compound of any one of claims 1-85, or a pharmaceutically acceptable salt thereof.

107. The method of claim 106, wherein the pancreatic cell is an islet cell.

108. The method of claim 106, wherein the pancreatic cell is a beta cell.

109. The method of claim 108, wherein the beta cell proliferation is evidenced by an increase in beta cell production.

110. The method of claim 108, wherein the beta cell proliferation is evidenced by an increase in insulin production.

111. The method of any one of claims 106-110, further comprising administering the compound to a subject.

112. The method of claim 111, wherein the subject suffers from diabetes.

113. The method of claim 112, wherein the diabetes is type 1 diabetes.

114. The method of claim 112, wherein the diabetes is type 2 diabetes.

115. The method of claim 111, wherein the subject suffers from prediabetes.

116. The method of claim 111, wherein the subject suffers from impaired beta cell production.

117. The method of claim 111, wherein the subject is human.

118. A method of inhibiting an interaction of menin with one or more of MLL1, MLL2, a MLL fusion protein, and a MLL Partial Tandem Duplication, comprising contacting menin with an effective amount of a compound of any one of claims 1-85.

119. A method of inhibiting a menin-MLL interaction, comprising contacting menin with an effective amount of a compound of any one of claims 1-85, wherein inhibition of the interaction is evidenced by a reduction in expression of a MLL fusion protein target gene.

120. The method of claim 119, wherein the MLL fusion protein target gene is *HOXA9*, *DLX2*, *PBX3*, or *MEIS1*.

121. A method of stabilizing menin, comprising contacting menin with a compound of any one of claims 1-85.

122. The method of any one of claims 118-121, wherein the contacting comprises contacting a cell that expresses menin.

123. The method of any one of claims 118-121, comprising administering a second therapeutic agent.

124. The method of any one of claims 118-121, wherein the contacting takes place *in vivo*.

125. The method of any one of claims 118-121, wherein the contacting takes place *in vitro*.

126. A kit comprising a pharmaceutical composition of claim 86 and instructions for using the composition to treat a subject suffering from a disease or condition mediated by an interaction between menin and another protein.

FIG. 1

Amino acid sequence of human menin, isoform 1 (SEQ ID NO: 1):

MGLKAAQKTLFPLRSIDDVVRLFAAELGREEPDLVLLSLVLGFVEHFLAVNRVIPTNVPE
LTFQPSPAPDPPGGLTYFPVADLSIIAALYARFTAQIRGAVDLSLYPREGGVSSRELVKK
VSDVIWNSLSRSYFKDRAHIQSLFSFITGWSPVGTKLDSSGVAFAVVGACQALGLRDVHL
ALSEDHAWVVFGPNGEQTAEVTWHGKGNEDRRGQTVNAGVAERSWLYLKGSYMRCDRKME
VAFMVCAINPSIDLHTDSLELLQLQQKLLWLLYDLGHLERYPMALGNLADLEELEPTPGR
PDPLTLYHKGIASAKTYYRDEHIYPYMYLAGYHCRNRNVREALQAWADTATVIQDYNYCR
EDEEIYKEFFEVANDVIPNLLKEAASLLEAGEERPGEQSQGTQSQGSALQDPECFAHLLR
FYDGICKWEEGSPTPVLHVGWATFLVQSLGRFEGQVRQKVRIVSREAEAAEAEEPWGEEA
REGRRRGPRRESKPEEPPPPKKPALDKGLGTGQGAVSGPPRKPPGTVAGTARGPEGGSTA
QVPAPTASPPPEGPVLTFQSEKMKGMKELLVATKINSSAIKLQLTAQSQVQMKKQKVSTP
SDYTLSFLKRQRKGL

FIG. 2

Amino acid sequence of human menin, isoform 2 (SEQ ID NO: 2):

MGLKAAQKTLFPLRSIDDVVRLFAAELGREEPDLVLLSLVLGFVEHFLAVNRVIPTNVPE
LTFQPSPAPDPPGGLTYFPVADLSIIAALYARFTAQIRGAVDLSLYPREGGVSSRELVKK
VSDVIWNSLSRSYFKDRAHIQSLFSFITGTKLDSSGVAFAVVGACQALGLRDVHLALSED
HAWVVFGPNGEQTAEVTWHGKGNEDRRGQTVNAGVAERSWLYLKGSYMRCDRKMEVAFMV
CAINPSIDLHTDSLELLQLQQKLLWLLYDLGHLERYPMALGNLADLEELEPTPGRPDPLT
LYHKGIASAKTYYRDEHIYPYMYLAGYHCRNRNVREALQAWADTATVIQDYNYCREDEEI
YKEFFEVANDVIPNLLKEAASLLEAGEERPGEQSQGTQSQGSALQDPECFAHLLRFYDGI
CKWEEGSPTPVLHVGWATFLVQSLGRFEGQVRQKVRIVSREAEAAEAEEPWGEEAREGRR
RGPRRESKPEEPPPPKKPALDKGLGTGQGAVSGPPRKPPGTVAGTARGPEGGSTAQVPAP
TASPPPEGPVLTFQSEKMKGMKELLVATKINSSAIKLQLTAQSQVQMKKQKVSTPSDYTL
SFLKRQRKGL

FIG. 3

Amino acid sequence of human menin, isoform 3 (SEQ ID NO: 3):

MGLKAAQKTLFPLRSIDDVVRLFAAELGREEPDLVLLSLVLGFVEHFLAVNRVIPTNVPE
LTFQPSPAPDPPGGLTYFPVADLSIIAALYARFTAQIRGAVDLSLYPREGGVSSRELVKK
VSDVIWNSLSRSYFKDRAHIQSLFSFITGTKLDSSGVAFAVVGACQALGLRDVHLALSED
HAWSWLYLKGSYMRCDRKMEVAFMVCAINPSIDLHTDSLELLQLQQKLLWLLYDLGHLER
YPMALGNLADLEELEPTPGRPDPLTLYHKGIASAKTYYRDEHIYPYMYLAGYHCRNRNVR
EALQAWADTATVIQDYNYCREDEEIYKEFFEVANDVIPNLLKEAASLLEAGEERPGEQSQ
GTQSQGSALQDPECFAHLLRFYDGICKWEEGSPTPVLHVGWATFLVQSLGRFEGQVRQKV
RIVSREAEAAEAEEPWGEEAREGRRRGPRRESKPEEPPPPKKPALDKGLGTGQGAVSGPP
RKPPGTVAGTARGPEGGSTAQVPAPTASPPPEGPVLTFQSEKMKGMKELLVATKINSSAI
KLQLTAQSQVQMKKQKVSTPSDYTLSFLKRQRKGL

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/445; C07C 43/225; C09K 19/32 (2018.01)
CPC - A61K 31/445; C07C 43/225; C09K 19/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PUBCHEM. CID 10614048. 25 October 2006, pp. 1-9. Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/compound/10614048>; page 3, formula	1, 82
A	WO 2016/197027 A1 (KURA ONCOLOGY, INC., et al.) 08 December 2016; paragraph [0007]	1, 82
A	US 7,744,968 B2 (REIFFENRATH, V et al.) 29 June 2010; column 3, lines 5-50	1, 82
A	US 5,445,764 A (POETSCH, E et al.) 29 August 1995; column 1, lines 10-45; column 2, lines 1-2	1, 82
A	WO 2016/195776 A1 (KURA ONCOLOGY, INC., et al.) 08 December 2016; paragraph [0007]	1, 82
P, X	WO 2017/161002 A1 (KURA ONCOLOGY, INC., et al.) 21 September 2017; entire document	1, 82

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 October 2018 (24.10.2018)	20 DEC 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US18/51666

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-46, 50-72, 81, 83-126
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***-Please See Within the Next Supplemental Box-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 82

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

-***-Continued from Box No. III Observations where unity of invention is lacking -***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-5 (in-part), 47-49 (in-part), 73-80 (in-part), 82 (in-part); compound of Formula (I), wherein H is C3-12 carbocycle; A is first shown moiety wherein each of Z1, Z2, Z3, and Z4 is –C(RA1)(RA2)- and RA1 and RA2 are each hydrogen; each of Z5 and Z6 is –C(H)-; B is C3-12 carbocycle; each of L1, L2, and L3 is independently a bond; R57 is hydrogen; and each of m, p, and q is independently 0 (first exemplary compound structure).

The compound, compositions and methods will be searched to the extent the compound encompasses a compound of Formula (I), wherein H is C3-12 carbocycle; A is first shown moiety wherein each of Z1, Z2, Z3, and Z4 is –C(RA1)(RA2)- and RA1 and RA2 are each hydrogen; each of Z5 and Z6 is –C(H)-; B is C3-12 carbocycle; each of L1, L2, and L3 is independently a bond; R57 is hydrogen; and each of m, p, and q is independently 0 (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure (e.g. no optional or variable atoms or substituents) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part) and 82 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula (I), wherein H is C3-12 carbocycle; A is first shown moiety wherein each of Z1, Z2, Z3, and Z4 is –C(RA1)(RA2)- and RA1 and RA2 are each hydrogen; each of Z5 and Z6 is –C(H)-; B is C3-12 carbocycle; each of L1, L2, and L3 is independently a bond; R57 is hydrogen; and each of m, p, and q is independently 0 (first exemplary compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula (I), wherein H is C3-12 carbocycle; A is first shown moiety wherein each of Z1, Z2, Z3, and Z4 is –C(RA1)(RA2)- and RA1 and RA2 are each hydrogen; each of Z5 and Z6 is –C(H)-; B is a 3- to 12-membered heterocycle; each of L1, L2, and L3 is independently a bond; R57 is hydrogen; and each of m, p, and q is independently 0 (first exemplary elected compound structure).

Groups I+ share the technical features including: a compound of Formula (I), wherein H is C3-12 carbocycle wherein m is 2 and each RH is R50 wherein R50 is –OR52 wherein R52 is hydrogen; A is second shown moiety wherein each of Z1, Z2, Z3, and Z4 is –C(RA1)(RA2)- and RA1 and RA2 are each hydrogen; each of Z5 and Z6 is –C(H)-; B is C3-12 carbocycle wherein p is 2 and each RB is R50 wherein R50 is –OR52 wherein R52 is hydrogen; each of L1, L2, and L3 is independently a bond; R57 is hydrogen; and q is 0.

However, these shared technical features are previously disclosed by US 2012/0058998 A1 to Sanders, et al. (hereinafter 'Sanders').

Sanders discloses a compound of Formula (I), wherein H is C3-12 carbocycle wherein m is 2 and each RH is R50 wherein R50 is –OR52 wherein R52 is hydrogen; A is second shown moiety wherein each of Z1, Z2, Z3, and Z4 is –C(RA1)(RA2)- and RA1 and RA2 are each hydrogen; each of Z5 and Z6 is –C(H)-; B is C3-12 carbocycle wherein p is 2 and each RB is R50 wherein R50 is –OR52 wherein R52 is hydrogen; each of L1, L2, and L3 is independently a bond; R57 is hydrogen; and q is 0 (compound 39 of formula 2,5-bis (3,4-dihydroxybenzoyl)bicyclo [3.3.0](-)octane, as shown; paragraphs [0115]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Sanders reference, unity of invention is lacking.