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BURROWS et al. (43) Pub. Date: Aug. 14, 2025(54) METHODS FOR TREATING
HEMATOLOGICAL MALIGNANCIES AND
EWING'S SARCOMA(71) Applicant: KURA ONCOLOGY, INC., San
Diego, CA (US)(72) Inventors: Francis BURROWS, San Diego, CA
(US); Linda V. KESSLER, San Diego,
CA (US); Liansheng LI, San Diego,
CA (US); Pingda REN, San Diego, CA
(US); Yi WANG, San Diego, CA (US);
Tao WU, San Diego, CA (US);
Jingchuan ZHANG, San Diego, CA
(US)

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A61P 35/02 (2018.01)

ABSTRACT

The present disclosure provides methods for treating hematological malignancies and Ewing's sarcoma using menin inhibitors. Compositions for use in these methods are also provided.

Specification includes a Sequence Listing.

Antitumor efficacy in OCI-AML3 model

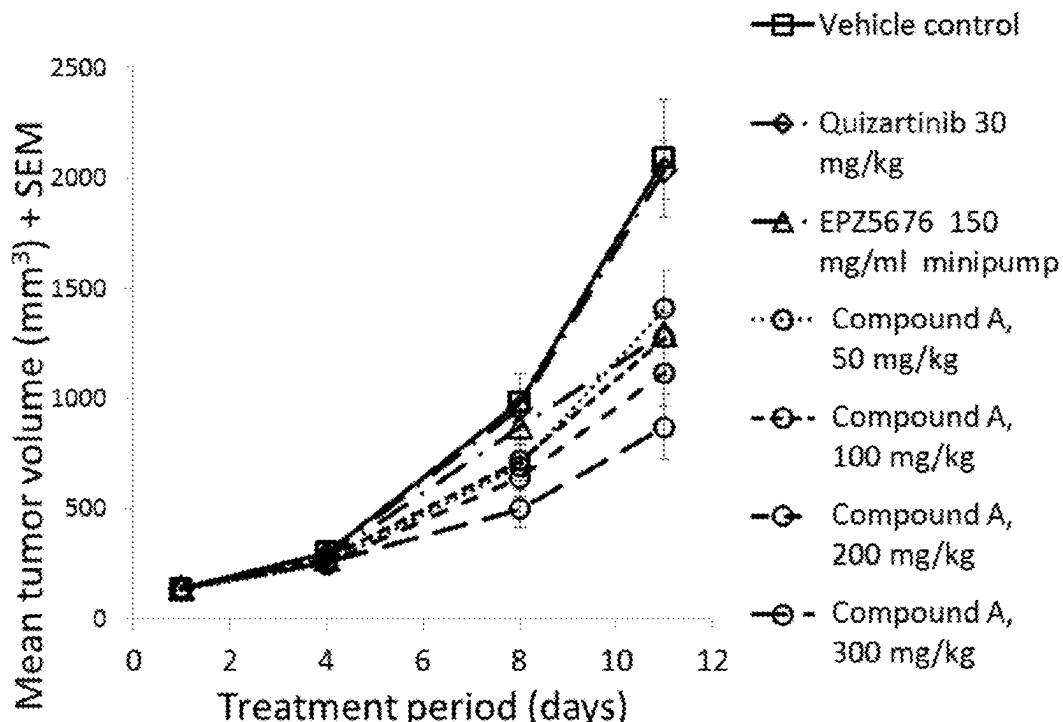


FIG. 1

Amino acid sequence of human menin, isoform 1 (SEQ ID NO: 1):

MGLKAAQKTLFPLRSIDDVVRLFAAELGREEPDLVLLSLVLGFVEHFLAVNRVIPTNVPE
LTFQPSPAPDPPGGLTYFPVADLSIIAALYARFTAQIRGAVDLSLYPREGGVSSRELVKK
VSDVIWNSLSRSYFKDRAHIQSLFSFITGWSPVGTKLDSSGVAFAVVGACQALGLRDVHL
ALSEDHAWVVFGPNGEQTAEVTHWGKGNEDRRGQTVNAGVAERSWLYLKGSYMRCDRKME
VAFMVCAINPSIDLHTDSLELLQLQQKLLWLLYDLGHLERYPMALGNLADLEELEPTPGR
PDPLTLYHKGIASAKTYYRDEHIYPYMLAGYHCRNRNAEALQAWADTATVIQDNYCR
EDEEIYKEFFEVANDVIPNLLKEAASLLEAGEERPGEQSQGTQSQGSALQDPPECFAHLLR
FYDGICKWEEGSPTPVLHVWATFLVQSLGRFEGQVRQKVRIVSREAEAAEAEWGEEA
REGRRRGPRRESKPEEPPPKPALDKGLGTQGAVGSGPPRKPPGTVAGTARGPEGGSTA
QVPAPTASPPPEGPVLTQSEKMKGMKELLVATKINSSAIKLQLTAQSQVQMKKQKVSTP
SDYTLSFLKRQRKGL

FIG. 2

Amino acid sequence of human menin, isoform 2 (SEQ ID NO: 2):

MGLKAAQKTLFPLRSIDDVVRLFAAEELGREEPDLVLLSLVLGFVEHFLAVNRVIPTNVPE
LTFQPSPAPDPPGGLTYFPVADLSIIAALYARFTAQIRGAVDLSLYPREGGVSSRELVKK
VSDVIWNSLSRSYFKDRAHIQSLFSFITGTKLDSSGVAFAVVGACQALGLRDVHLALSED
HAWVVFGPNGEQTAEVTHGKGNEDRRGQTVNAGVAERSWLYLKGSYMRCDRKMEVAFMV
CAINPSIDLHTSLELLQLQQKLLWLLYDLGHLERİPMALGNLADLEELEPTPGRPDPLT
LYHKGIASAKTYYRDEHIYPYMLAGYHCRNRNVREALQAWADATATVIQDYNYCREDEEI
YKEFFEVANDVIPNLLKEAASLLEAGEERPGEQSQGTQSQGSALQDPECFAHLLRFYDGI
CKWEEGSPTPVLHVGWATFLVQSLGRFEGQVRQKVRIVSREAAEAEEPWGEEAREGRR
RGPRRESKPEEPPPDKGLGTGQGAVSGPPRKPPGTVAGTARGPEGGSTAQVPAP
TASPPPEGPVLTQSEKMKGMKELLVATKINSSAIKLQLTAQSQVQMKKQKVSTPSDYTL
SFLKRQRKGL

FIG. 3

Amino acid sequence of human menin, isoform 3 (SEQ ID NO: 3):

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MGLKAAQKTLFPLRSIDDVVRLFAAELGREEPDLVLLSLVLGFVEHFLAVNRVIPTNVPE  
LTFQPSPAPDPPGGLTYFPVADLSIAALYARFTAQIRGAVDLSLYPREGGVSSRELVKK  
VSDVIWNSLSRSYFKDRAHIQSLFSFITGTKLDSSGVAFAVVGACQALGLRDVHLALSED  
HAWSWLYLKGSYMRCDRKMEVAFMVCAINPSIDLHTDSLELLQLQQKLLWLLYDLGHLER  
YPMALGNLADLELEPTPGRPDPLTLYHKGIASAKTYYRDEHIYPYMLAGYHCRNRNVR  
EALQAWADTAATVIQDYNYCREDEEIYKEFFEVANDVIPNLLKEAASLLEAGEERPGEQSQ  
GTQSQGSALQDPPECFAHLLRFYDGICKWEEGSPTPVLVHGWTFLVQSLGRFEGQVRQKV  
RIVSREAEAAEAEWPGEAREGRRRGPRRESKPEEPPPCKPALDKGLGTGQGAVSGPP  
RKPPGTVAGTAGPPEGGSTAQVPAPTASPPPEGPVLTQSEKMKGMKELLVATKINSSAI  
KLQLTAQSQVQMKKQKVSTPSDYLTSFLKRQRKGL
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FIG. 4

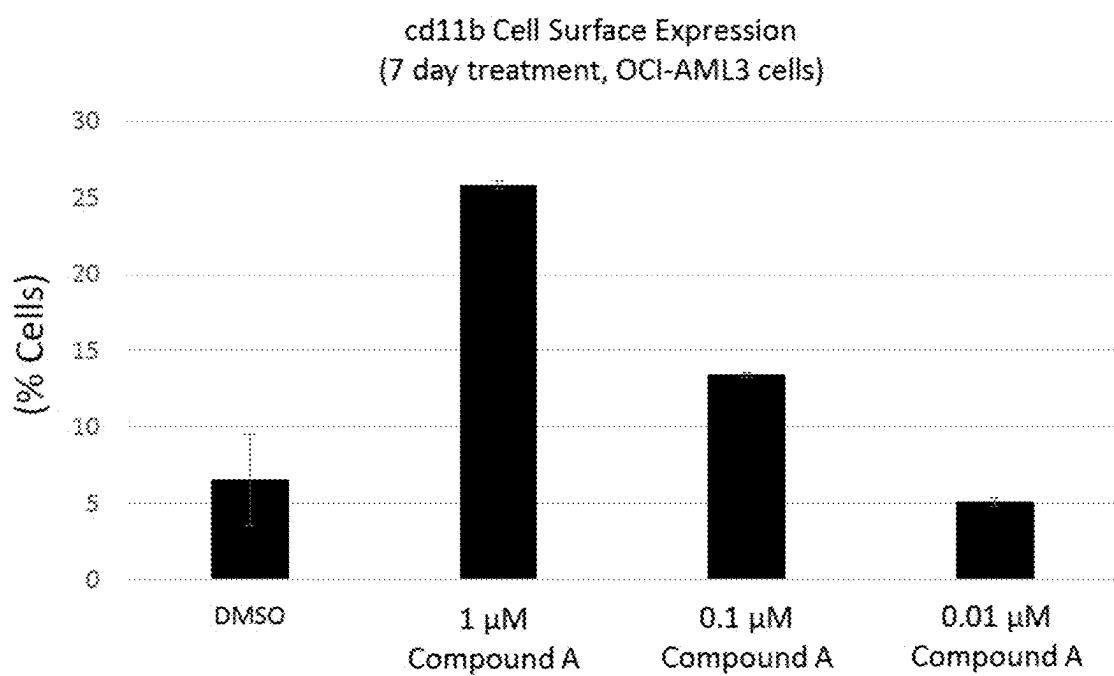


FIG. 5

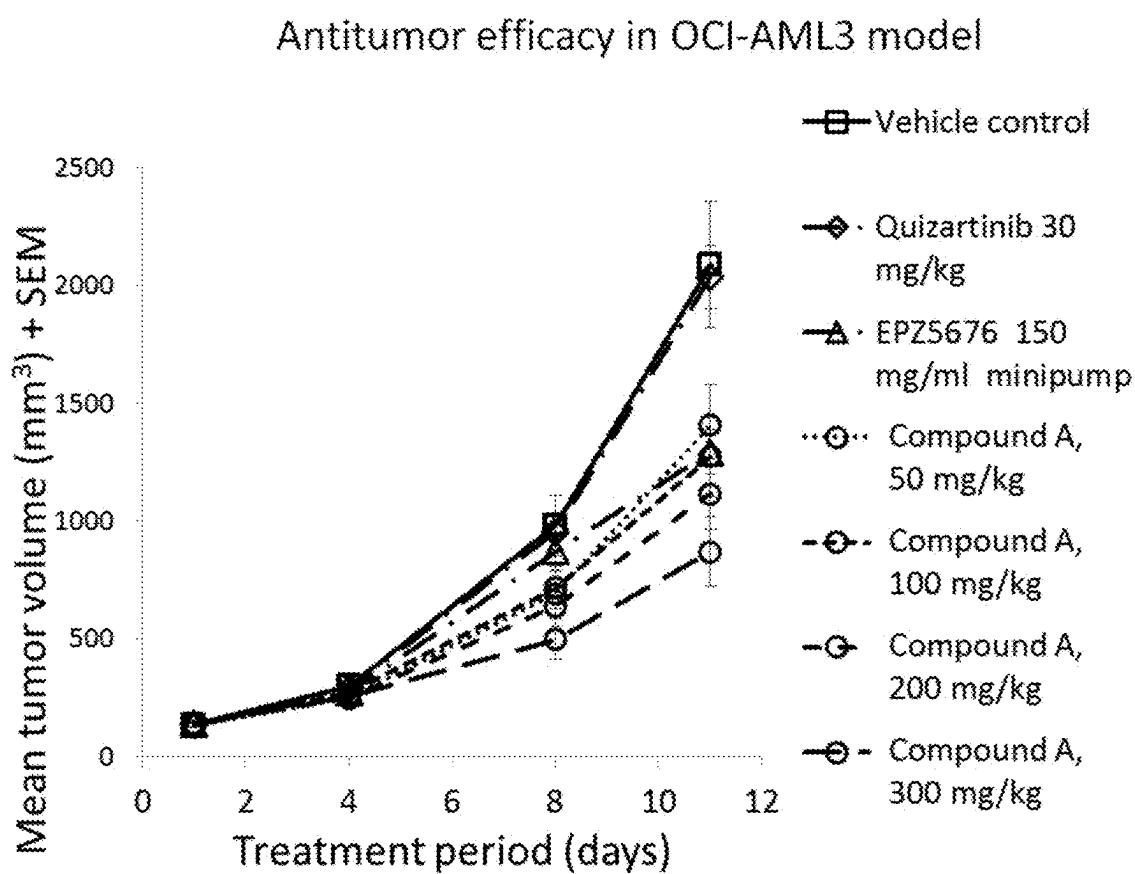


FIG. 6A

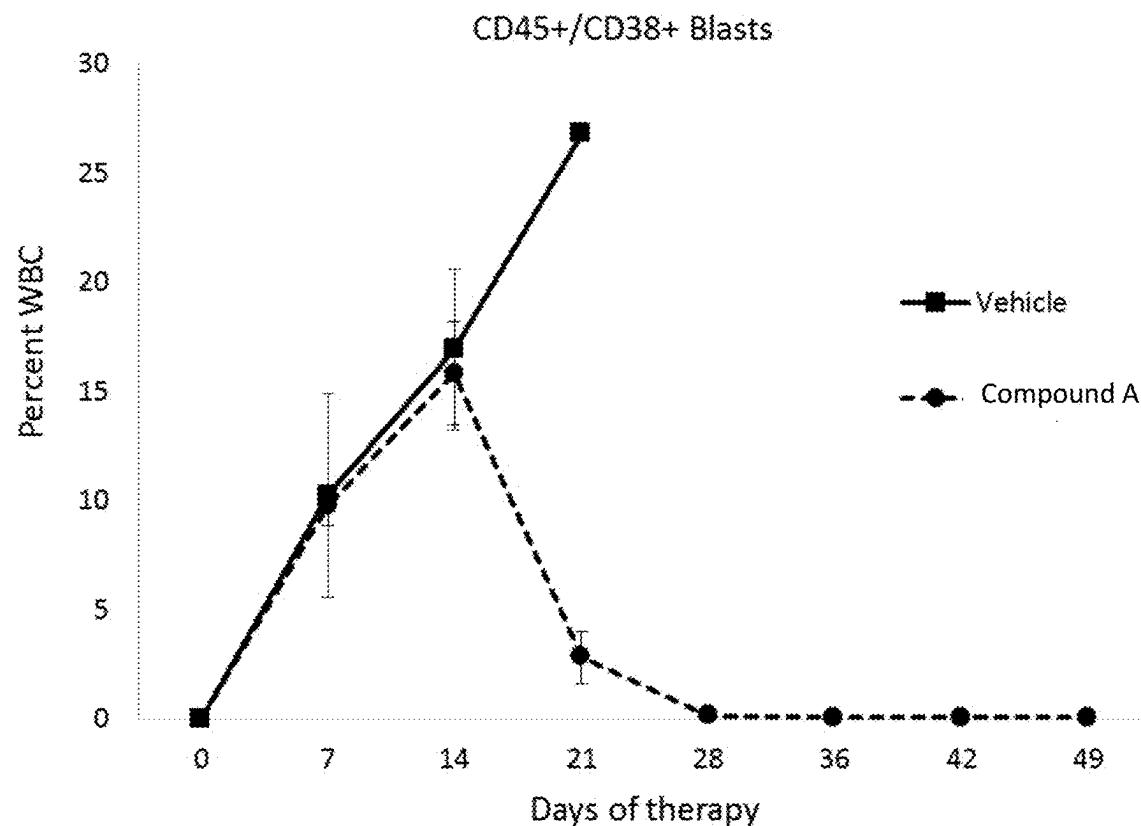


FIG. 6B

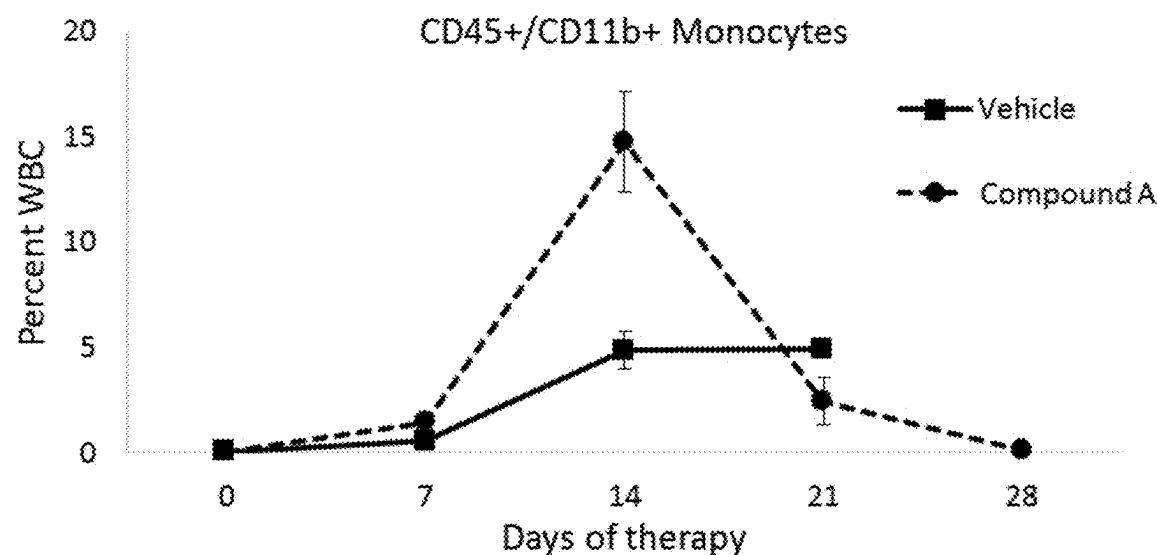


FIG. 6C

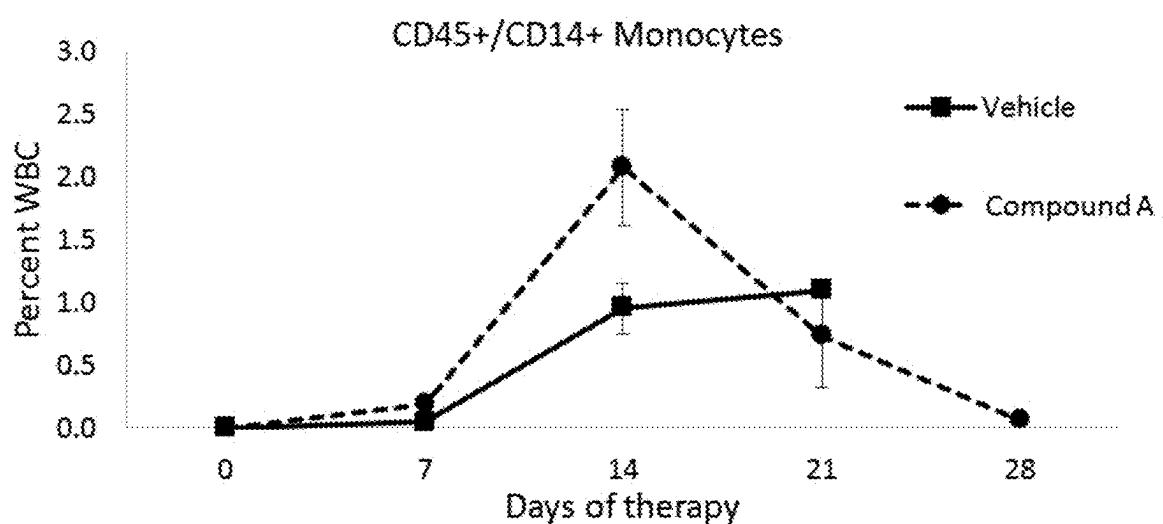


FIG. 7A

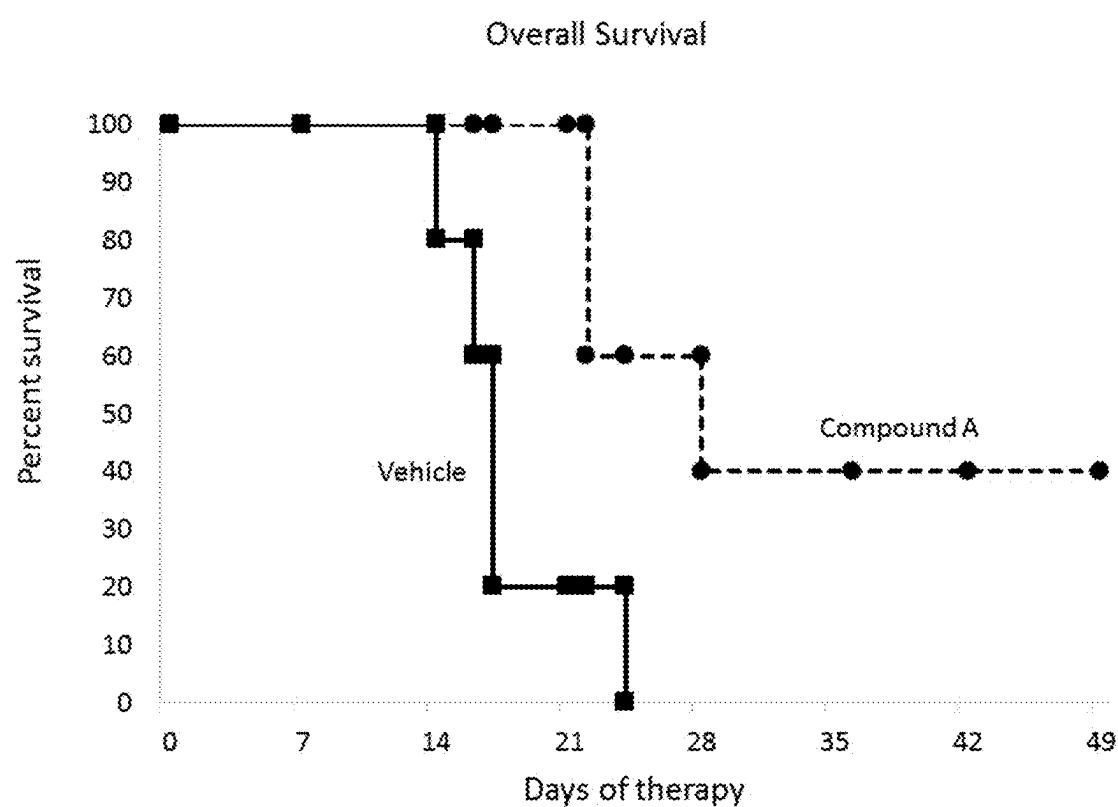


FIG. 7B

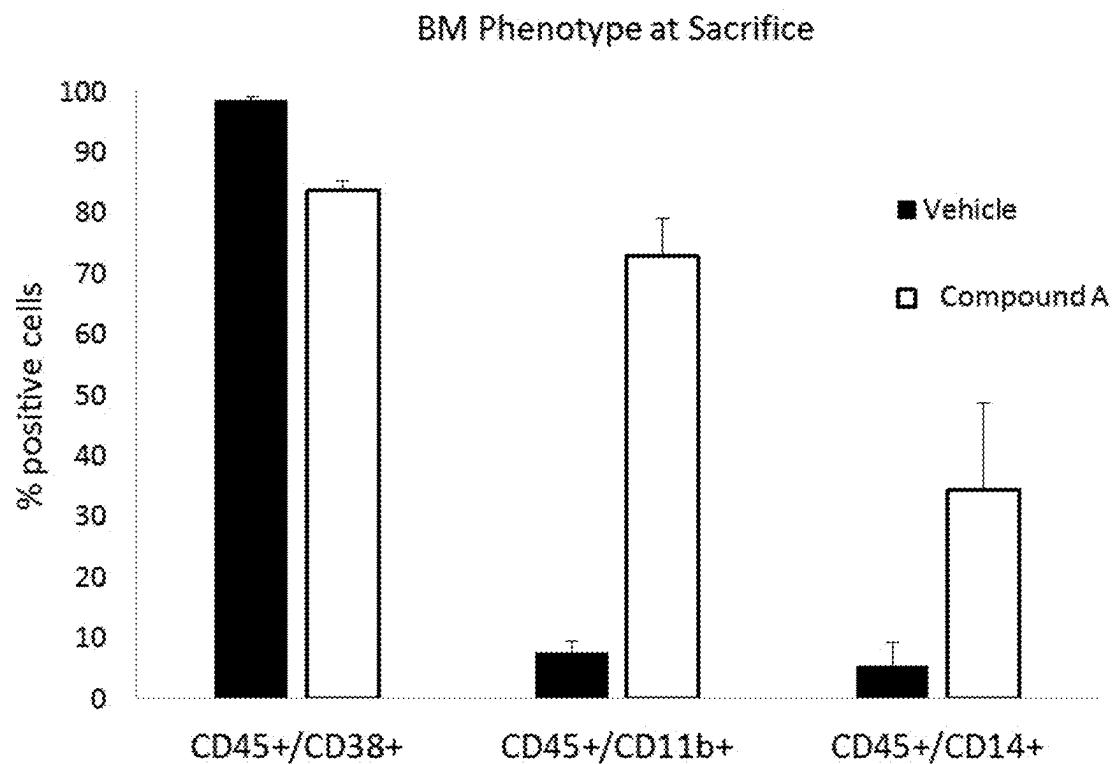


FIG. 7C

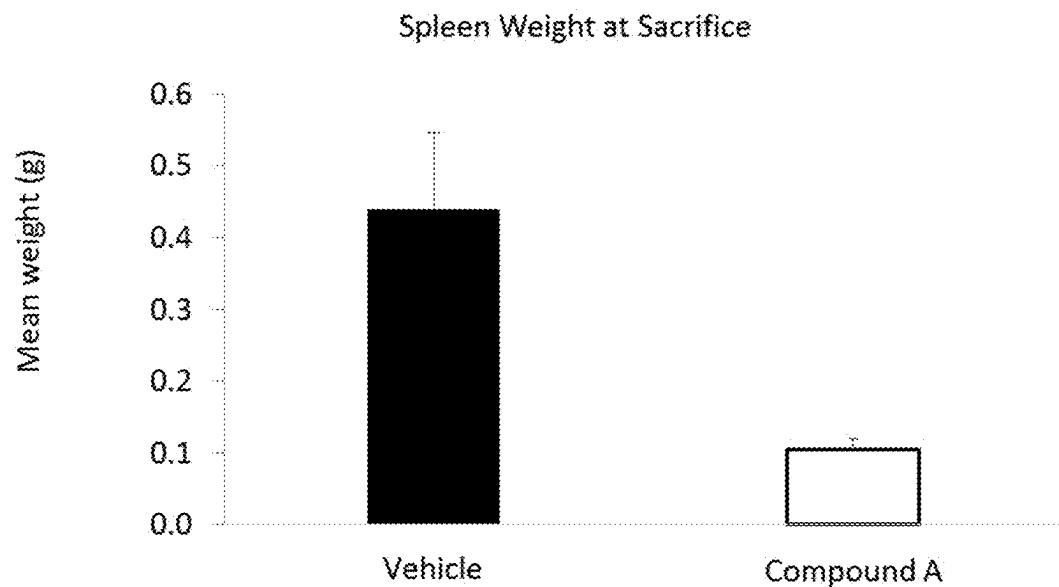


FIG. 8A

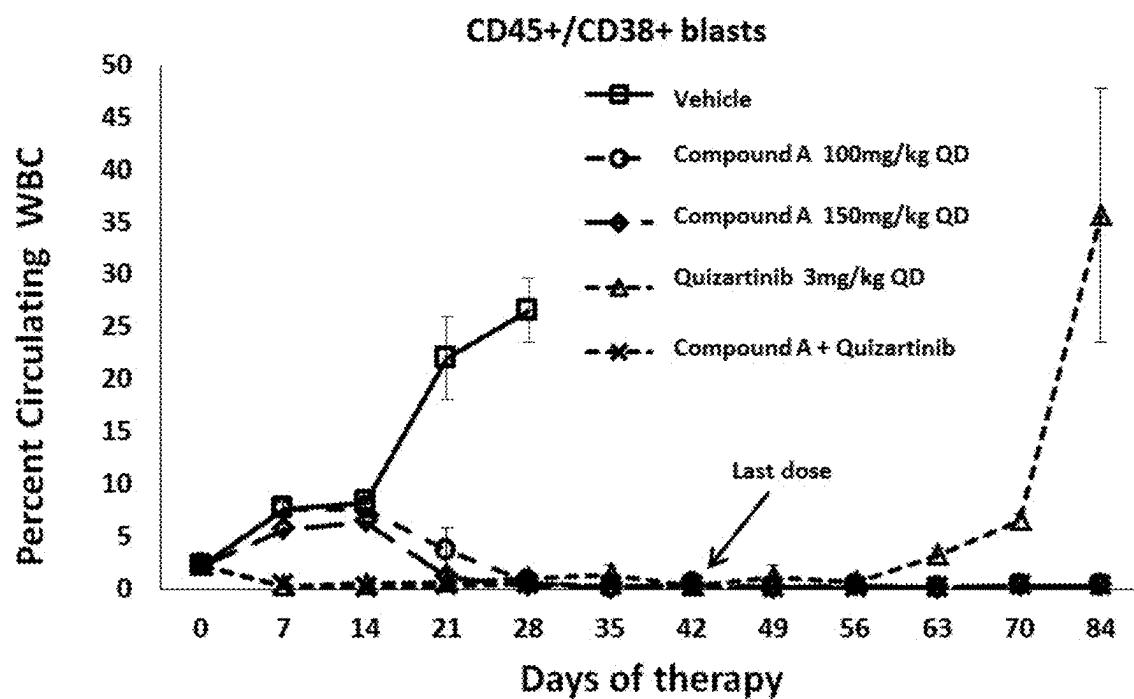


FIG. 8B

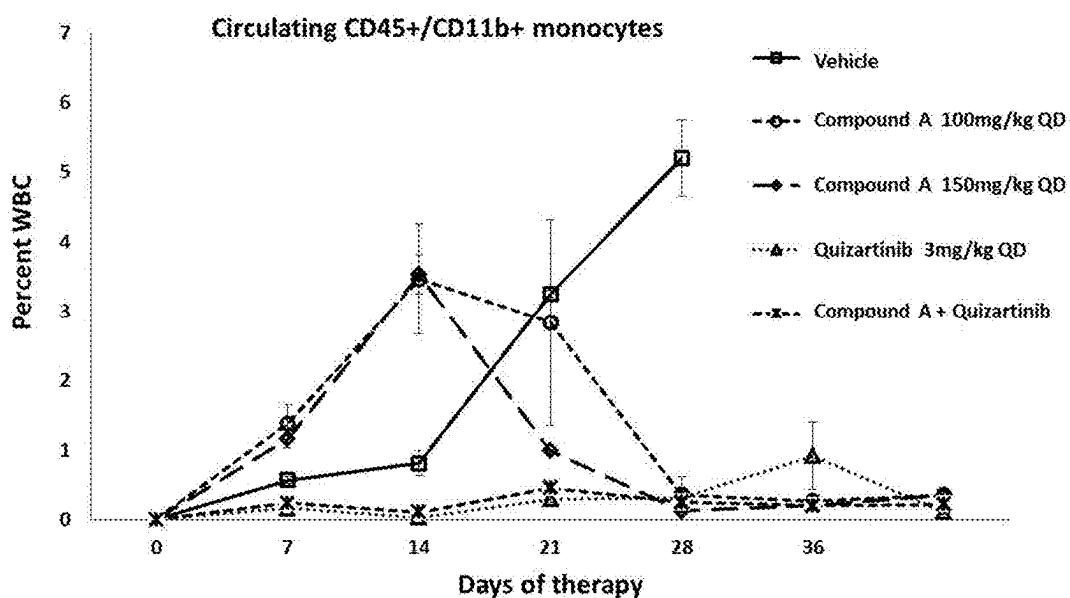


FIG. 9A

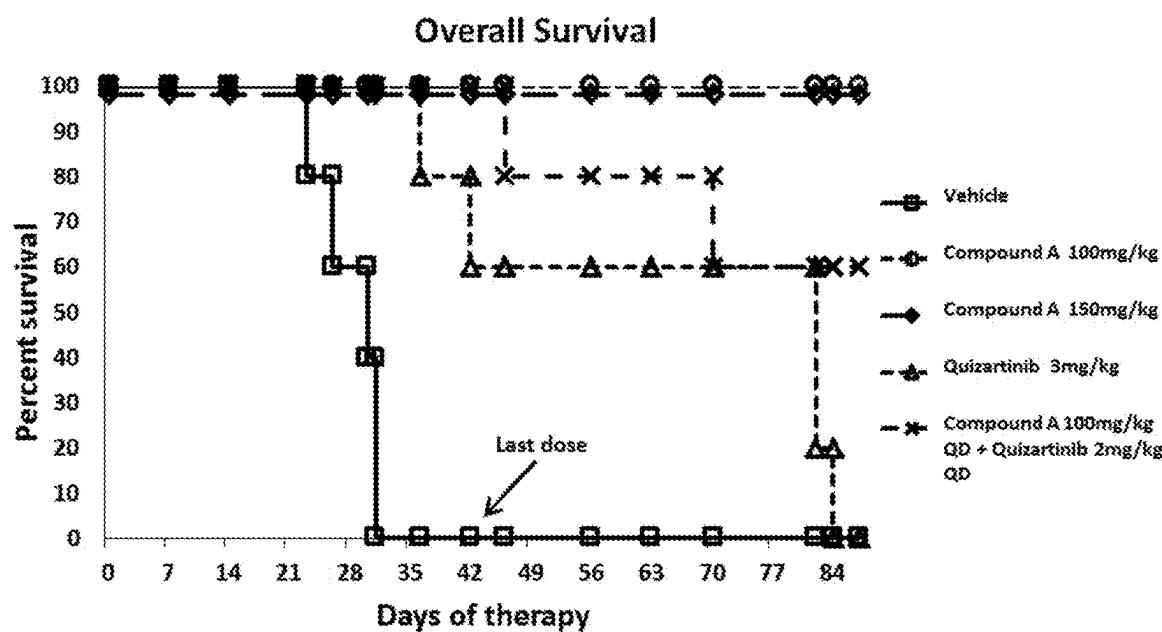


FIG. 9B

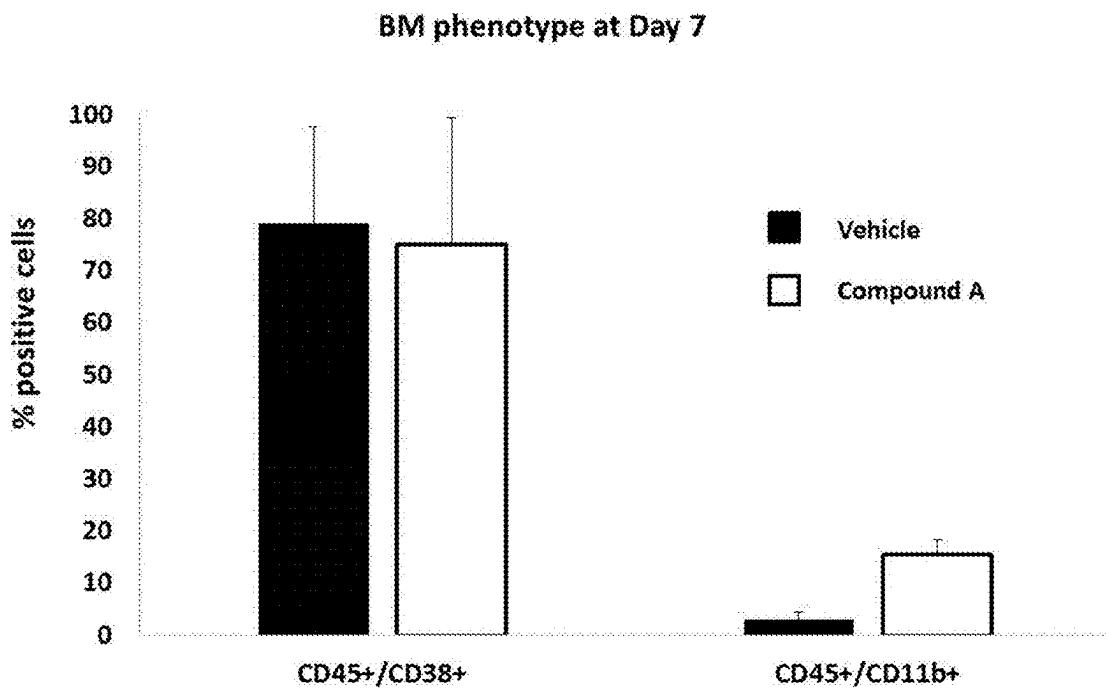


FIG. 9C

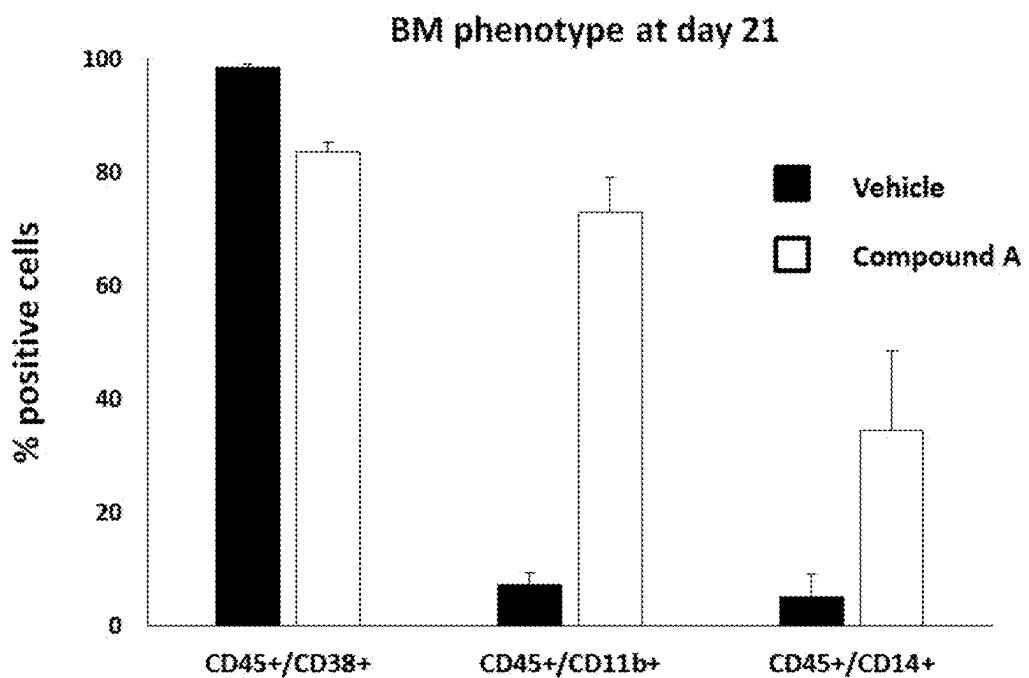


FIG. 9D

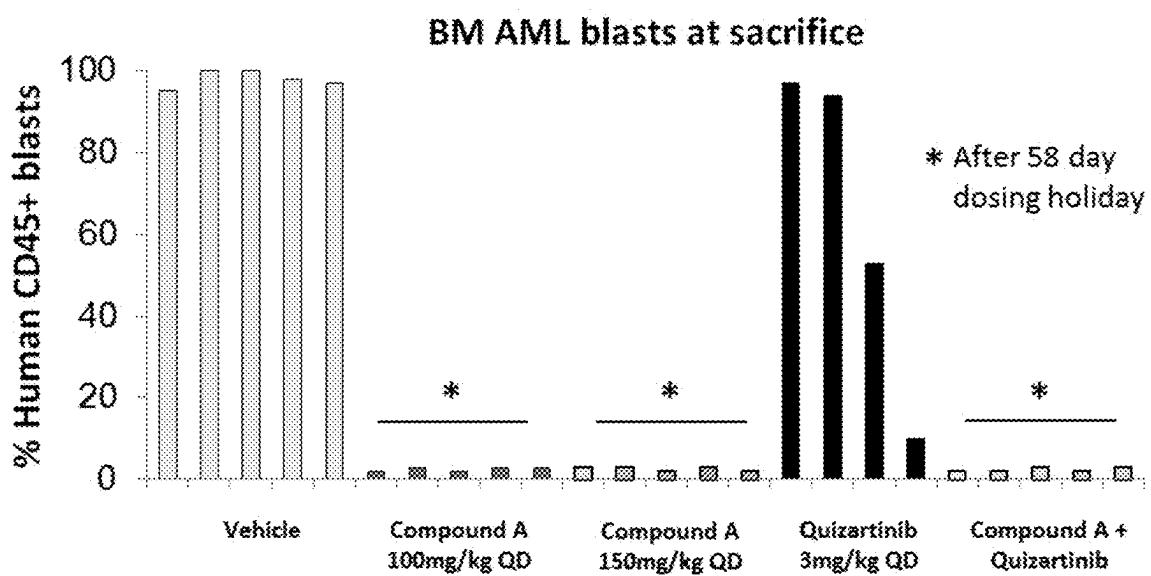


FIG. 9E

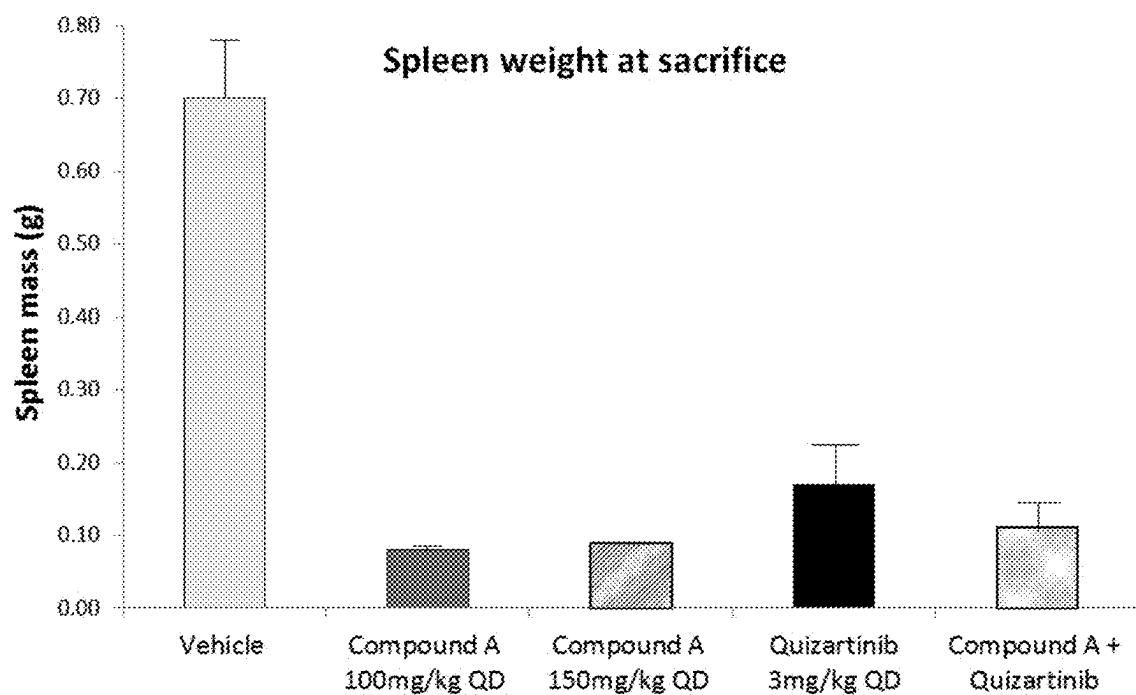


FIG. 10

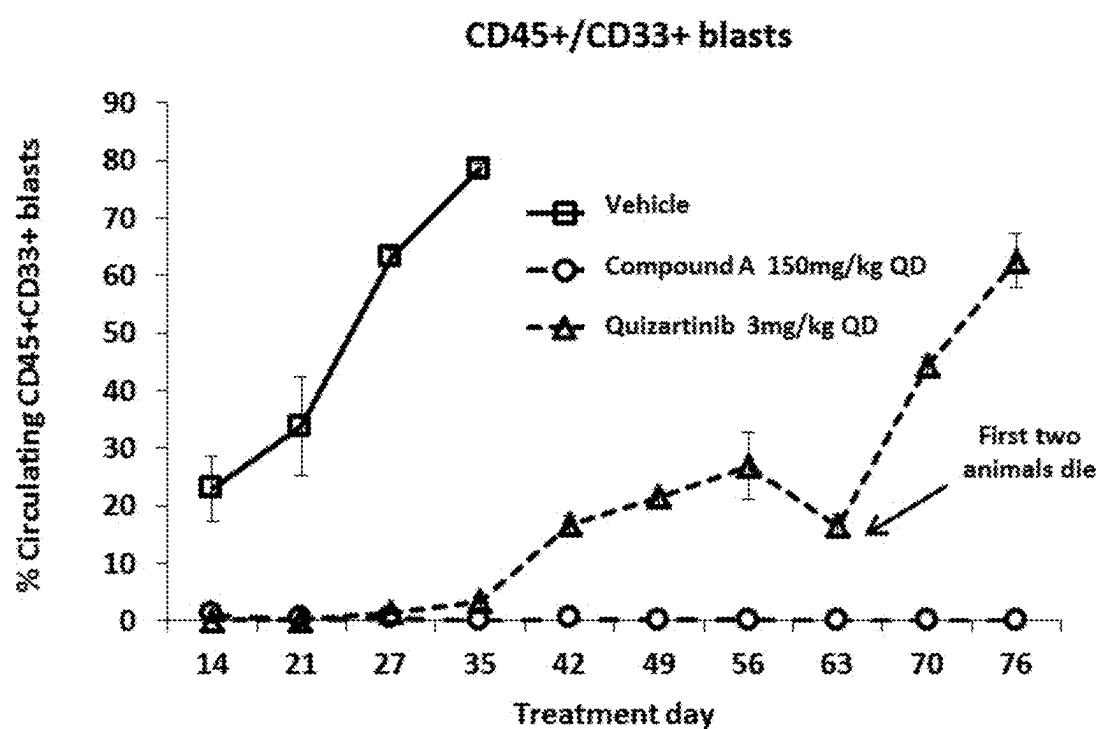


FIG. 11

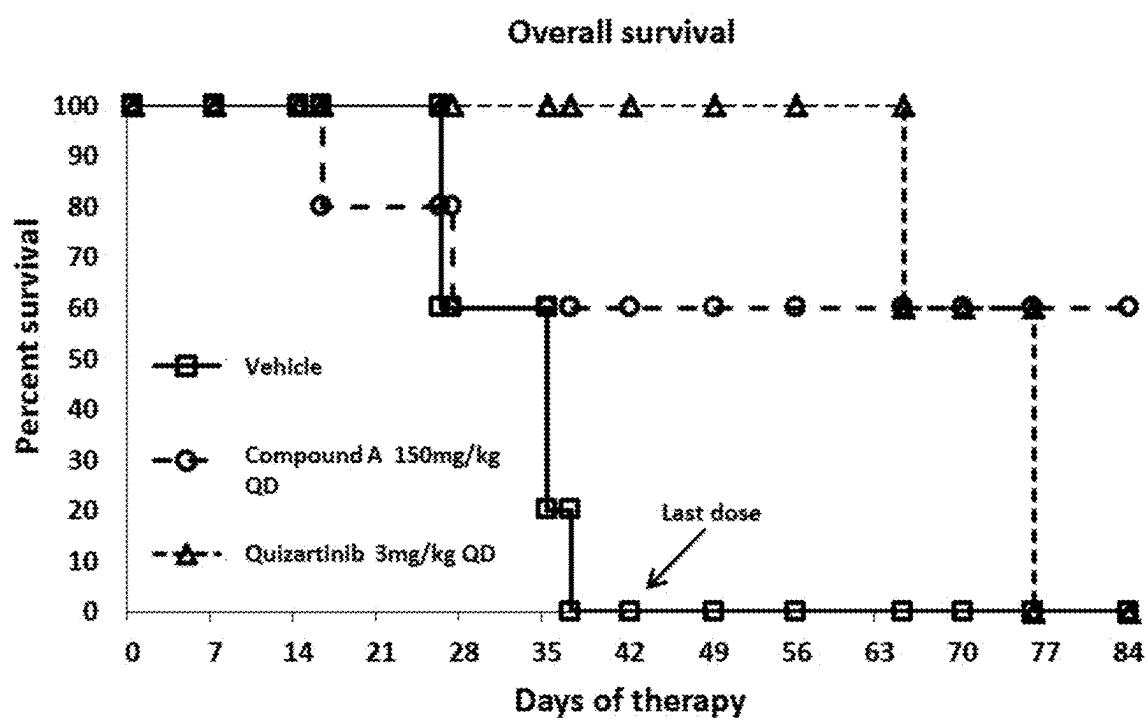


FIG. 12

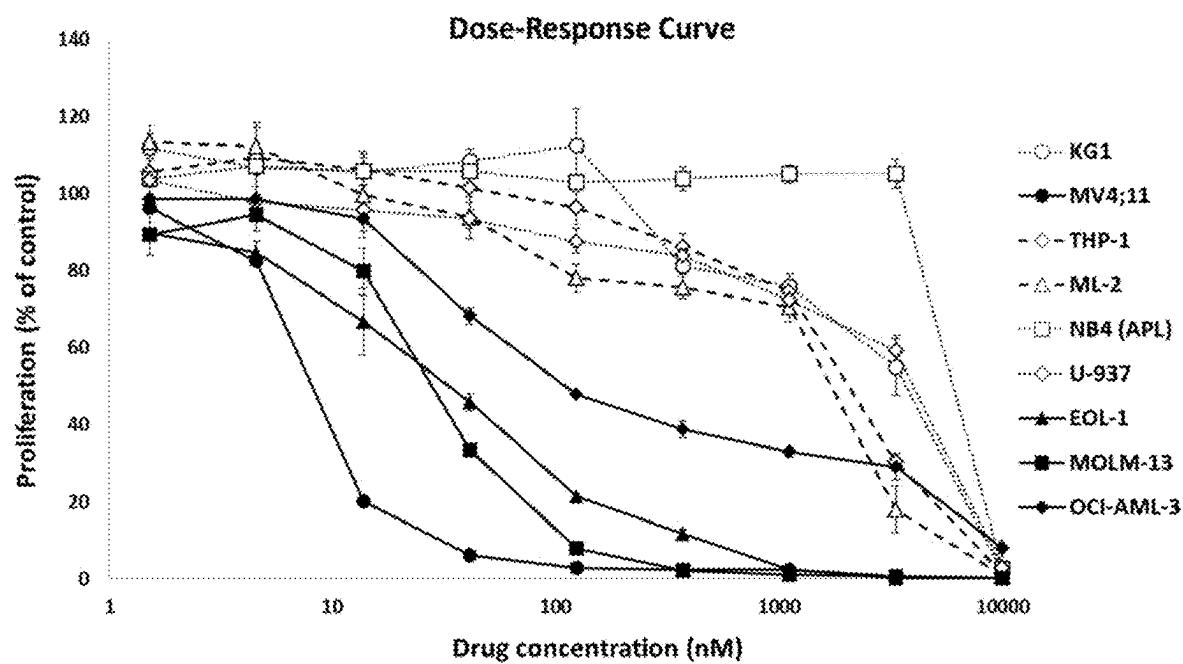
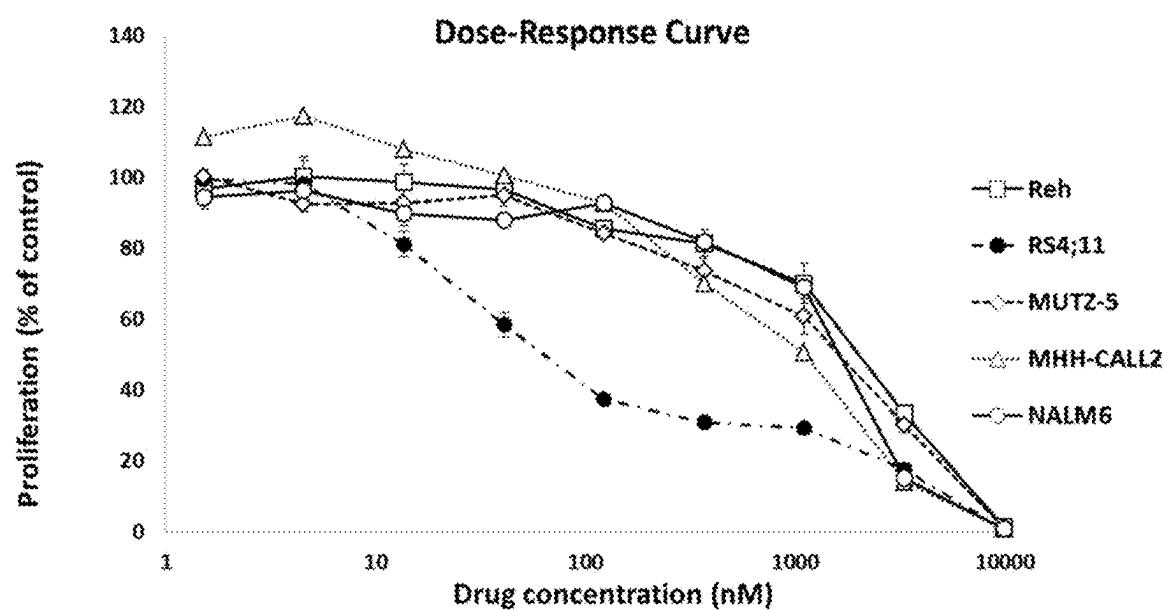


FIG. 13



METHODS FOR TREATING HEMATOLOGICAL MALIGNANCIES AND EWING'S SARCOMA

CROSS-REFERENCE

[0001] This patent application is a continuation of U.S. patent application Ser. No. 18/418,061, filed Jan. 19, 2024, which is a continuation of U.S. patent application Ser. No. 16/494,556, filed Sep. 16, 2019, now U.S. Pat. No. 11,944,627, which is a National Stage of International Application No. PCT/US2018/023804, filed Mar. 22, 2018, issued on Apr. 2, 2024, which claims the benefit of U.S. Provisional Application No. 62/476,710, filed Mar. 24, 2017; U.S. Provisional Application No. 62/561,119, filed Sep. 20, 2017; U.S. Provisional Application No. 62/577,640, filed Oct. 26, 2017; and U.S. Provisional Application No. 62/635,256, filed Feb. 26, 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 XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on Jan. 16, 2025, is named 47535727302_SL.txt and is 5,216 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. The protein-protein interaction between MLL and menin has been shown to play an important role in the development of many diseases. 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). Menin binds to the N-terminus of MLL proteins, including MLL1, MLL2, and MLL-fusion proteins.

[0004] Aberrant expression of HOX genes has been implicated in many diseases, including hematological malignancies such as acute myeloid leukemia (AML), and Ewing's sarcoma.

[0005] Certain hematological malignancies are characterized by the presence of a specific genetic abnormality or mutation, including a nucleoporin 98 (NUP98) gene fusion (Xu et al.; *Cancer Cell*. 2016 Dec. 12; 30(6):863-878), mutation in the nucleophosmin (NPM1) gene (Kuhn et al.; *Cancer Discov*. 2016 October; 6(10):1166-1181), mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene (Spencer et al.; *Leukemia*. 2015 June; 29(6):1279-89), or mixed lineage leukemia (MLL) gene amplification (Tang et al.; *Hum Pathol*. 2015 January; 46(1):65-73). Ewing's sarcoma shows aberrant overexpression of posterior HOXD genes, in particular the HOXD13 gene. Ewing's sarcoma tumors and cell lines express high levels of menin and MLL1, which are required for tumor maintenance and

progression, and HOXD13 is a downstream target of MLL1 (Svoboda et al.; *Oncotarget*. 2017 Jan. 3; 8(1):458-471).

SUMMARY OF THE INVENTION

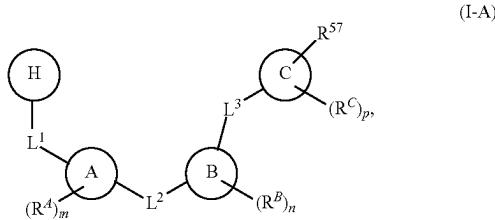
[0006] A novel therapeutic strategy is urgently needed to treat these diseases. Small molecule inhibitors that block the menin-MLL interaction are thus valuable targets for treating hematological malignancies and Ewing's sarcoma.

[0007] The present disclosure addresses a need in the art by providing compositions and methods for treating hematological malignancies, such as acute myeloid leukemia, or Ewing's sarcoma using a menin inhibitor. The menin inhibitor can inhibit the protein-protein interaction of menin with an MLL protein (e.g., MLL1, MLL2, or MLL fusion protein). The compositions and methods herein may be useful for treating diseases dependent on the activity of menin, MLL1, and/or MLL2, such as a hematological malignancy or Ewing's sarcoma.

[0008] In one aspect, the present disclosure provides a method of treating acute myeloid leukemia in a subject exhibiting a nucleoporin 98 (NUP98) gene fusion, mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, or mixed lineage leukemia (MLL) gene amplification, the method comprising administering to a subject in need thereof a menin inhibitor. In some embodiments, the subject exhibits a nucleoporin 98 (NUP98) gene fusion. In some embodiments, the nucleoporin 98 (NUP98) gene fusion is a gene fusion of NUP98 and a homeodomain partner gene. In some embodiments, the nucleoporin 98 (NUP98) gene fusion is a gene fusion of NUP98 and a non-homeodomain partner gene. In some embodiments, 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. In some embodiments, the subject exhibits a mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene. In some embodiments, the mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene is a mutation of R882. In some embodiments, the mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene is not a mutation of R882. In some embodiments, the mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene is a frameshift deletion, missense mutation, nonsense mutation, splice-site substitution, splice-site deletion, or whole-gene deletion. In some embodiments, the subject exhibits a mixed lineage leukemia (MLL) gene amplification.

[0009] In one 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 MHLL, or elevated MEIS1 expression levels; and (b) administering a menin inhibitor 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.

[0010] In some embodiments, the menin inhibitor is a compound of Formula (I-A):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0011] H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0012] A is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0013] B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0014] C is 3- to 12-membered heterocycle;

[0015] L^1 , L^2 and L^3 are each independently selected from bond, —O—, —S—, —N(R^{51})—, —N(R^{51})CH₂—, —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, alkynylene, alkynylene, heteroalkynylene, 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;

[0016] R^A , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^A groups, 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;

[0017] m, n and p are each independently an integer from 0 to 6;

[0018] R^{50} is independently selected at each occurrence from:

[0019] halogen, —NO₂, —CN, —OR 52 , —SR 52 , —N(R^{52})₂, —NR 53 R 54 , —S(=O)R 52 , —S(=O)R 52 , —S(=O)N(R^{52})₂, —S(=O)NR 53 R 54 , —NR 52 S(=O)R 52 , —NR 52 S(=O)N(R^{52})₂, —NR 52 S(=O)NR 53 R 54 , —C(O)R 52 , —C(O)OR 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)NR 53 R 54 , —C(O)N(R^{52})₂, —C(O)NR 53 R 54 , —P(O)(OR 52)₂, —P(O)(OR 52)R 52 , —P(O)(NR 52)₂, —P(O)(NR 52)(OR 52), —P(O)(NR 52)R 52 , —P(O)(NR 52)(OR 52), —P(O)(NR 52)₂, —O, —S, —N(R^{52});

[0020] 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, —NO₂, —CN, —OR 52 , —SR 52 , —N(R^{52})₂, —NR 53 R 54 , —S(=O)R 52 , —S(=O)O 52 , —S(=O)N(R^{52})₂, —S(=O)NR 53 R 54 , —NR 52 S(=O)R 52 , —NR 52 S(=O)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)NR 53 R 54 , —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)(OR 52)R 52 , —P(O)(NR 52)₂, —P(O)(NR 52)(OR 52), —P(O)(NR 52)R 52 , —P(O)(NR 52)(OR 52), —C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

[0021] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0022] 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, —NO₂, —CN, —OR 52 , —SR 52 , —N(R^{52})₂, —NR 53 R 54 , —S(=O)R 52 , —S(=O)O 52 , —S(=O)N(R^{52})₂, —S(=O)NR 53 R 54 , —NR 52 S(=O)R 52 , —NR 52 S(=O)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)NR 53 R 54 , —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)(OR 52)R 52 , —P(O)(NR 52)₂, —P(O)(NR 52)(OR 52), —P(O)(NR 52)R 52 , —P(O)(NR 52)(OR 52), —C₁₋₆ alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0023] R^{51} is independently selected at each occurrence from:

[0024] hydrogen, —C(O)R 52 , —C(O)OR 52 , —C(O)N(R^{52})₂, —C(O)NR 53 R 54 ;

[0025] 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, —NO₂, —CN, —OR 52 , —SR 52 , —N(R^{52})₂, —NR 53 R 54 , —S(=O)R 52 , —S(=O)O 52 , —S(=O)N(R^{52})₂, —S(=O)NR 53 R 54 , —NR 52 S(=O)R 52 , —NR 52 S(=O)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)NR 53 R 54 , —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)(OR 52)R 52 , —P(O)(NR 52)₂, —P(O)(NR 52)(OR 52), —P(O)(NR 52)R 52 , —P(O)(NR 52)(OR 52), —C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

[0026] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0027] 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, —NO₂, —CN, —OR 52 , —SR 52 , —N(R^{52})₂, —NR 53 R 54 , —S(=O)R 52 ,

$\text{—S(=O)}_2\text{R}^{52}$, $\text{—S(=O)}_2\text{N(R}^{52}\text{)}_2$, —S(=O)
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 —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)NR}^{52}\text{C(O)OR}^{52}$,
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 $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)N(R}^{52}\text{)}_2$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$,
 $\text{—C(O)N(R}^{52}\text{)}_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$,
 $\text{—P(O)(OR}^{52}\text{)}_2$, $\text{—P(O)(R}^{52}\text{)}_2$, $\text{—P(O)(OR}^{52}\text{)}(\text{R}^{52})$,
 $\text{—P(O)(NR}^{52}\text{)}(\text{R}^{52})$, $\text{—NR}^{52}\text{P(O)(R}^{52})$, $\text{—P(O)(NR}^{52}\text{)}_2$,
 $\text{—P(O)(NR}^{52}\text{)}_2$, $=\text{O}$, $=\text{S}$, $=\text{N(R}^{52}\text{)}$,
 C_{1-6} alkyl, C_{1-20} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0028] 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, $=\text{CN}$, $=\text{NO}_2$, $=\text{NH}_2$, $=\text{NHCH}_3$, $=\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $=\text{OH}$, $=\text{OCH}_3$, $=\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

[0029] 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} ;

[0030] R^{57} is selected from:

[0031] halogen, $=\text{NO}_2$, $=\text{CN}$, $=\text{SR}^{52}$, $=\text{NR}^{53}\text{R}^{54}$,
 $=\text{S(=O)}\text{R}^{52}$, $=\text{S(=O)}_2\text{R}^{53}$, $=\text{S(=O)}_2\text{N(R}^{52}\text{)}_2$,
 $=\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $=\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $=\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52}\text{)}_2$,
 $=\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $=\text{C(O)OR}^{52}$,
 $=\text{OC(O)R}^{52}$, $=\text{OC(O)OR}^{52}$, $=\text{OC(O)N(R}^{52}\text{)}_2$,
 $=\text{OC(O)NR}^{53}\text{R}^{54}$, $=\text{NR}^{52}\text{C(O)OR}^{52}$,
 $=\text{NR}^{52}\text{C(O)N(R}^{52}\text{)}_2$, $=\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$,
 $=\text{C(O)NH(C}_{1-6}\text{ alkyl)}$, $=\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{P(O)(OR}^{52}\text{)}_2$,
 $=\text{P(O)(R}^{52}\text{)}_2$, $=\text{P(O)(OR}^{52}\text{)}(\text{R}^{52})$, $=\text{P(O)(NR}^{52}\text{)}(\text{R}^{52})$,
 $=\text{NR}^{52}\text{P(O)(R}^{52})$, $=\text{P(O)(NR}^{52}\text{)}_2$, $=\text{P(O)(NR}^{52}\text{)}(\text{R}^{52})$,
 $=\text{P(O)(NR}^{52}\text{)}_2$, $=\text{S}$, $=\text{N(R}^{52}\text{)}$; and

[0032] 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 $=\text{NO}_2$, $=\text{CN}$, $=\text{SR}^{52}$, $=\text{N(R}^{52}\text{)}_2$,
 $=\text{NR}^{53}\text{R}^{54}$, $=\text{S(=O)}\text{R}^{52}$, $=\text{S(=O)}_2\text{R}^{52}$, $=\text{S(=O)}_2\text{N(R}^{52}\text{)}_2$,
 $=\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $=\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$,
 $=\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$,
 $=\text{C(O)R}^{52}$, $=\text{C(O)OR}^{52}$, $=\text{OC(O)R}^{52}$,
 $=\text{OC(O)NR}^{53}\text{R}^{54}$, $=\text{NR}^{52}\text{C(O)OR}^{52}$,
 $=\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{P(O)(OR}^{52}\text{)}_2$,
 $=\text{P(O)(R}^{52}\text{)}_2$, $=\text{P(O)(OR}^{52}\text{)}(\text{R}^{52})$, $=\text{P(O)(NR}^{52}\text{)}(\text{R}^{52})$,
 $=\text{NR}^{52}\text{P(O)(R}^{52})$, $=\text{P(O)(NR}^{52}\text{)}_2$, $=\text{P(O)(NR}^{52}\text{)}(\text{R}^{52})$,
 $=\text{P(O)(NR}^{52}\text{)}_2$, $=\text{S}$, and $=\text{N(R}^{52}\text{)}$; and

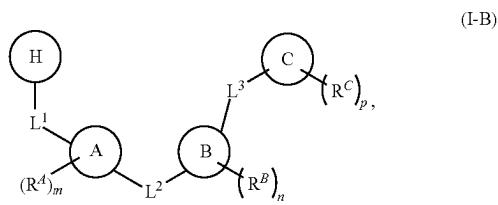
[0033] R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $=\text{CN}$, $=\text{NO}_2$, $=\text{NH}_2$, $=\text{NHCH}_3$, $=\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $=\text{OH}$, $=\text{OCH}_3$, $=\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle,

[0034] wherein for a compound or salt of Formula (I-A), when C is azetidinylene, piperidinylene or piperazinylene and R^{57} is $=\text{S(=O)}_2\text{R}^{58}$, $=\text{S(=O)}_2\text{N(R}^{52}\text{)}_2$, or $=\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$.

[0035] p is an integer from 1 to 6; and/or

[0036] L^3 is substituted with one or more R^{50} , wherein L^3 is not $=\text{CH}_2\text{CH(OH)}$.

[0037] In some embodiments, the menin inhibitor is a compound of Formula (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

[0038] H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0039] A, B and C are each independently selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0040] L^1 and L^2 are each independently selected from bond, $=\text{O}$, $=\text{S}$, $=\text{N(R}^{51}\text{)}$, $=\text{N(R}^{51}\text{)CH}_2$, $=\text{C(O)}$, $=\text{C(O)O}$, $=\text{OC(O)}$, $=\text{OC(O)O}$, $=\text{C(O)N(R}^{51}\text{)}$, $=\text{C(O)N(R}^{51}\text{)C(O)}$, $=\text{C(O)N(R}^{51}\text{)C(O)N(R}^{51}\text{)}$, $=\text{N(R}^{51}\text{)C(O)}$, $=\text{N(R}^{51}\text{)C(O)O}$, $=\text{OC(O)N(R}^{51}\text{)}$, $=\text{C(NR}^{51}\text{)}$, $=\text{N(R}^{51}\text{)C(NR}^{51}\text{)}$, $=\text{C(NR}^{51}\text{)N(R}^{51}\text{)}$, $=\text{N(R}^{51}\text{)C(NR}^{51}\text{)N(R}^{51}\text{)}$, $=\text{S(O)}_2$, $=\text{OS(O)}$, $=\text{S(O)O}$, $=\text{S(O)}$, $=\text{OS(O)}_2$, $=\text{S(O)O}_2$, $=\text{N(R}^{51}\text{)S(O)}_2$, $=\text{S(O)}_2\text{N(R}^{51}\text{)}$, $=\text{N(R}^{51}\text{)S(O)}$, $=\text{S(O)N(R}^{51}\text{)}$, $=\text{N(R}^{51}\text{)S(O)}_2\text{N(R}^{51}\text{)}$, $=\text{N(R}^{51}\text{)S(O)}_2$; alkylene, alkenylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50} ;

[0041] L^3 is selected from alkylene, alkenylene, and alkynylene, each of which is substituted with one or more R^{56} and optionally further substituted with one or more R^{50} ;

[0042] R^A , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^A groups, 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;

[0043] m, n and p are each independently an integer from 0 to 6;

[0044] R^{50} is independently selected at each occurrence from:

[0045] halogen, $=\text{NO}_2$, $=\text{CN}$, $=\text{OR}^{52}$, $=\text{SR}^{52}$, $=\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{53}\text{R}^{54}$, $=\text{S(=O)}\text{R}^{52}$, $=\text{S(=O)}_2\text{R}^{52}$, $=\text{S(=O)}_2\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $=\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $=\text{C(O)R}^{52}$, $=\text{C(O)OR}^{52}$, $=\text{OC(O)R}^{52}$, $=\text{OC(O)NR}^{53}\text{R}^{54}$, $=\text{NR}^{52}\text{C(O)R}^{52}$, $=\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{C(O)N(R}^{52}\text{)}_2$, $=\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{P(O)(OR}^{52}\text{)}_2$, $=\text{P(O)(R}^{52}\text{)}_2$, $=\text{P(O)(OR}^{52}\text{)}(\text{R}^{52})$, $=\text{P(O)(NR}^{52}\text{)}(\text{R}^{52})$, $=\text{NR}^{52}\text{P(O)(R}^{52})$, $=\text{P(O)(NR}^{52}\text{)}_2$, $=\text{P(O)(NR}^{52}\text{)}(\text{R}^{52})$, $=\text{P(O)(NR}^{52}\text{)}_2$, $=\text{S}$, and $=\text{N(R}^{52}\text{)}$; and

[0046] 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, $=\text{NO}_2$, $=\text{CN}$, $=\text{OR}^{52}$, $=\text{SR}^{52}$, $=\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{53}\text{R}^{54}$, $=\text{S(=O)}\text{R}^{52}$,

$-S(=O)R^{52}$, $-S(=O)N(R^{52})_2$, $-S(=O)$
 $NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)N$
 $(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$,
 $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC$
 $(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$,
 $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C$
 $(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$,
 $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)OR^{52}(R^{52})^2$,
 $-P(O)(NR^{52})R^{52}$, $-NR^{52}P(O)(R^{52})$, $-P(O)$
 $(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=NR^{52}$,
 C_{3-12} carbocycle, and 3- to 12-membered hetero-
cycle; and

[0047] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0048] 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, $—NO_2$, $—CN$, $—OR^{52}$, $—SR^{52}$, $—N(R^{52})_2$, $—NR^{53}R^{54}$, $—S(=O)R^{52}$, $—S(=O)R^{52}_2$, $—S(=O)_2N(R^{52})_2$, $—S(=O)_2NR^{53}R^{54}$, $—NR^{52}S(=O)R^{52}$, $—NR^{52}S(=O)N(R^{52})_2$, $—NR^{52}S(=O)NR^{53}R^{54}$, $—C(O)R^{52}$, $—C(O)R^{52}_2$, $—OC(O)R^{52}$, $—OC(O)OR^{52}$, $—OC(O)N(R^{52})_2$, $—OC(O)NR^{53}R^{54}$, $—NR^{52}C(O)R^{52}$, $—NR^{52}C(O)OR^{52}$, $—NR^{52}C(O)N(R^{52})_2$, $—NR^{52}C(O)NR^{53}R^{54}$, $—C(O)N(R^{52})_2$, $—C(O)NR^{53}R^{54}$, $—P(O)(OR^{52})_2$, $—P(O)(R^{52})_2$, $—P(O)(OR^{52})(R^{52})_2$, $—P(O)(NR^{52})(R^{52})_2$, $—NR^{52}P(O)(R^{52})_2$, $—P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0049] R^{51} is independently selected at each occurrence from:

[0050] hydrogen, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$;

[0051] C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)R⁵², —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, —O—S—N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

[0052] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0053] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵²,

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

[0054] R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, —O=O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle;

[0055] R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R⁵⁰;

[0056] R⁵⁶ is independently selected at each occurrence from:

[0057] $-\text{NO}_2$, $-\text{OR}^{59}$, $-\text{SR}^{52}$, $-\text{NR}^{53}\text{R}^{54}$,
 $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$,
 $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}$
 $(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})$
 R^{52} , $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$,
 $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})$
 R^{52} , $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$,
 $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})$
 $\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})$
 $(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P}(\text{O})$
 (R^{52}) , $-\text{P}(\text{O})(\text{NR}^{52})(\text{OR}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$,
 $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
 C_{3-12} carbocycle and 3- to 12-membered heterocycle.

[0058] wherein each C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl in R⁵⁶ is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵⁹, —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)=O₂R⁵², —S(=O)N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)R⁵², —P(O)(NR⁵²)R⁵², —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle;

[0059] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁶ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)R⁵², —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²),

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

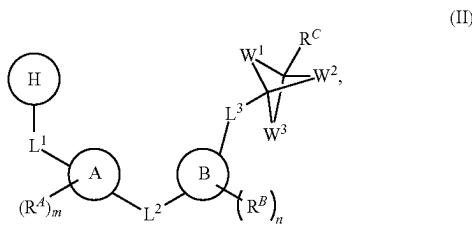
[0060] further wherein R^{56} optionally forms a bond to ring C; and

[0061] R^{59} is independently selected at each occurrence from 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, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle,

[0062] wherein for a compound or salt of Formula (I-B), when R^{56} is $-\text{CH}_3$, L^3 is not further substituted with $-\text{OH}$, $-\text{NH}_2$, or $-\text{CN}$.

[0063] In some embodiments, R^C is selected from $-\text{C}(\text{O})\text{R}^{52}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $=\text{O}$, 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.

[0064] In some embodiments, the menin inhibitor is a compound of Formula (II):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0065] H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0066] A is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0067] B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0068] L^1 , L^2 and L^3 are each independently selected from bond, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{NR}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})-$, $-\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{S}(\text{O})_2-$, $-\text{OS}(\text{O})-$, $-\text{S}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})\text{N}(\text{R}^{51})-$; alkylene, alkynylene, alkynylene, heteroalkynylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50} ;

[0069] R^4 , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^4 groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0070] m and n are each independently an integer from 0 to 6;

[0071] W^1 is C_{1-4} alkylene, optionally substituted with one or more R^{50} ;

[0072] W^2 is selected from a bond; and C_{1-4} alkylene, optionally substituted with one or more R^{50} ;

[0073] W^3 is selected from absent; and C_{1-4} alkylene, optionally substituted with one or more R^{50} ;

[0074] R^{50} is independently selected at each occurrence from:

[0075] halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$;

[0076] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0077] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0078] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0079] R^{51} is independently selected at each occurrence from:

[0080] hydrogen, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$;

[0081] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$,

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

[0082] C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0083] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0084] R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

[0085] 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}

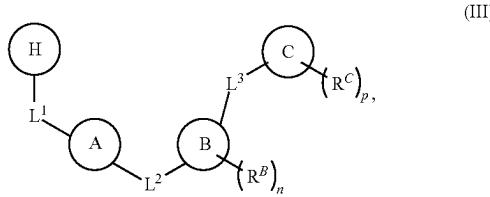
[0086] wherein for a compound or salt of Formula (II), when W^3 is absent:

[0087] W^1 is C_1 alkylene, W^2 is a bond, and L^3 is not a bond;

[0088] W^1 is C_{2-4} alkylene and W^2 is a bond; or

[0089] W^1 and W^2 are each C_1 alkylene and L^3 is not a bond, wherein each C_1 alkylene is independently optionally substituted with one or more R^{50} .

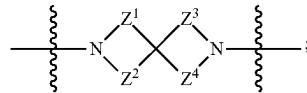
[0090] In some embodiments, the menin inhibitor is a compound of Formula (III):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0091] H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0092] A is



[0093] each of Z^1 , Z^2 , Z^3 , and Z^4 is independently selected from $-\text{C}(\text{R}^{41})(\text{R}^{42})$, $-\text{C}(\text{R}^{41})(\text{R}^{42})$, $-\text{C}(\text{R}^{41})(\text{R}^{42})$, $-\text{C}(\text{O})$, and $-\text{C}(\text{R}^{41})(\text{R}^{42})-\text{C}(\text{O})$, wherein no more than one of Z^1 , Z^2 , Z^3 , and Z^4 is $-\text{C}(\text{O})$ or $-\text{C}(\text{R}^{41})(\text{R}^{42})-\text{C}(\text{O})$;

[0094] B is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0095] C is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0096] L^1 , L^2 and L^3 are each independently selected from bond, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{NR}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})-$, $-\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{S}(\text{O})_2-$, $-\text{OS}(\text{O})-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})\text{N}(\text{R}^{51})-$; alkylene, 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;

[0097] 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 bridge or ring;

[0098] R^C is independently selected at each occurrence from hydrogen and R^{50} , or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0099] R^{41} and R^{42} are each independently selected at each occurrence from hydrogen and R^{50} ;

[0100] n is an integer from 0 to 6;

[0101] p is an integer from 1 to 6;

[0102] R^{50} is independently selected at each occurrence from:

[0103] halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})\text{R}^{52}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{R}^{52})_2\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})_2\text{R}^{52}$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$;

[0104] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$,

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

[0105] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0106] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N(R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S(=O)}\text{R}^{52}$, $-\text{S(=O)}_2\text{R}^{52}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{S(=O)}$
 $\text{—NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $-\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$,
 $-\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} ,
 —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)N(R}^{52})_2$,
 $\text{—OC(O)NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C(O)R}^{52}$,
 $-\text{NR}^{52}\text{C(O)OR}^{52}$, $-\text{NR}^{52}\text{C(O)N(R}^{52})_2$, $-\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$,
 $-\text{C(O)N(R}^{52})_2$, $-\text{C(O)NR}^{53}\text{R}^{54}$,
 $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(R}^{52})_2$, $-\text{P(O)(OR}^{52})(\text{R}^{52})$,
 $-\text{P(O)(NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P(O)(R}^{52})$, $-\text{P(O)}$
 $(\text{NR}^{52})(\text{OR}^{52})$, $-\text{P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N(R}^{52})$,
 C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0107] R^{51} is independently selected at each occurrence from:

[0108] hydrogen, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{C(O)}$
 $\text{N(R}^{52})_2$, $-\text{C(O)NR}^{53}\text{R}^{54}$;

[0109] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N(R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S(=O)}\text{R}^{52}$, $-\text{S(=O)}_2\text{R}^{52}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{S(=O)}$
 $\text{—NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $-\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$,
 $-\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} ,
 —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)N(R}^{52})_2$,
 $\text{—OC(O)NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C(O)R}^{52}$,
 $-\text{NR}^{52}\text{C(O)OR}^{52}$, $-\text{NR}^{52}\text{C(O)N(R}^{52})_2$, $-\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$,
 $-\text{C(O)N(R}^{52})_2$, $-\text{C(O)NR}^{53}\text{R}^{54}$,
 $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(R}^{52})_2$, $-\text{P(O)(OR}^{52})(\text{R}^{52})$,
 $-\text{P(O)(NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P(O)(R}^{52})$, $-\text{P(O)}$
 $(\text{NR}^{52})(\text{OR}^{52})$, $-\text{P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N(R}^{52})$,
 C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

[0110] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

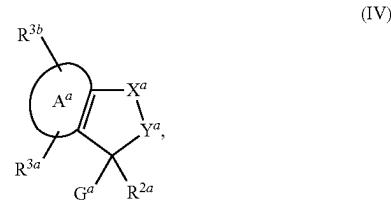
[0111] wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N(R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S(=O)}\text{R}^{52}$, $-\text{S(=O)}_2\text{R}^{52}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{S(=O)}$
 $\text{—NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $-\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$,
 $-\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} ,
 —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)N(R}^{52})_2$,
 $\text{—OC(O)NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C(O)R}^{52}$,

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

[0112] 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, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

[0113] 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} .

[0114] In some embodiments, the menin inhibitor is a compound of Formula (IV):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:



is a fused thienyl or fused phenyl group;

[0115] G^a is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-\text{E}^1\text{-R}^{4a}$ and optionally further substituted with one or more R^{50} ;

[0116] R^{2a} is selected from hydrogen, alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl;

[0117] R^{3a} and R^{3b} are each independently selected from hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0118] X^a and Y^a is selected from $-\text{N(R}^{52})\text{—C(=O)}$, $-\text{C(=O)}\text{—O—}$, $-\text{C(=O)}\text{—N(R}^{52})\text{—}$, $-\text{CH}_2\text{N(R}^{52})\text{—CH}_2$, $-\text{C(=O)}\text{N(R}^{52})\text{—CH}_2$, $-\text{CH}_2\text{CH}_2\text{N(R}^{52})\text{—}$, $-\text{CH}_2\text{N(R}^{52})\text{—C(=O)}$, and $-\text{CH}_2\text{O—CH}_2$; or

[0119] X^a and Y^a do not form a chemical bond, wherein:

[0120] X^a is selected from hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy; and

[0121] Y^a is selected from cyano, hydroxy, and $-\text{CH}_2\text{R}^{50}$;

[0122] E^1 is selected from absent, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{N}(\text{R}^{52})-$, $-\text{[C(R}^{14a}\text{)}_2]_{1-5}\text{O}-$, $-\text{[C(R}^{14a}\text{)}_2]_{1-5}\text{NR}^{52}-$, $-\text{[C(R}^{14a}\text{)}_2]_{1-5}-$, $-\text{CH}_2(=\text{O})-$, and $-\text{S}(=\text{O})_2-$;

[0123] R^{4a} is selected from hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl;

[0124] R^{14a} is selected from hydrogen and alkyl;

[0125] R^{50} is independently selected at each occurrence from:

[0126] halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2$
 $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{OC(O)OR}^{52}$, $-\text{OC(O)NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(OR}^{52})(\text{R}^{52})$, $-\text{P(O)(NR}^{52})_2$, $-\text{NR}^{52}\text{P(O)(R}^{52})$, $-\text{P(O)(NR}^{52})(\text{OR}^{52})$, $-\text{P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$;

[0127] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{OC(O)OR}^{52}$, $-\text{OC(O)NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $-\text{C(O)N}(\text{R}^{52})_2$, $-\text{C(O)NR}^{53}\text{R}^{54}$, $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(OR}^{52})(\text{R}^{52})$, $-\text{P(O)(NR}^{52})_2$, $-\text{NR}^{52}\text{P(O)(R}^{52})$, $-\text{P(O)(NR}^{52})(\text{OR}^{52})$, $-\text{P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0128] C_{3-12} carbocycle and 3- to 12-membered heterocycle.

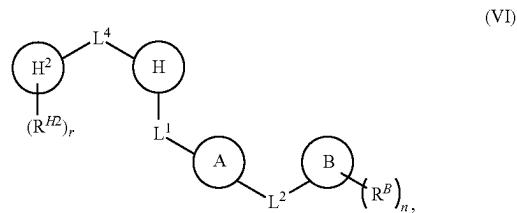
[0129] wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{OC(O)OR}^{52}$, $-\text{OC(O)NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $-\text{C(O)N}(\text{R}^{52})_2$, $-\text{C(O)NR}^{53}\text{R}^{54}$, $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(R}^{52})(\text{R}^{52})$, $-\text{P(O)(OR}^{52})(\text{R}^{52})$, $-\text{P(O)(NR}^{52})_2$, $-\text{NR}^{52}\text{P(O)(R}^{52})$, $-\text{P(O)(NR}^{52})(\text{OR}^{52})$, $-\text{P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0130] 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} carbo-

cycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $=\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

[0131] 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} .

[0132] In some embodiments, the menin inhibitor is a compound of Formula (VI):

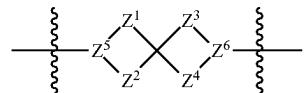


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0133] H^2 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0134] H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0135] A is



[0136] each of Z^1 , Z^2 , Z^3 , and Z^4 is independently selected from $-\text{C}(\text{R}^{41})(\text{R}^{42})$, $-\text{C}(\text{R}^{41})\text{R}^{42}$, $-\text{O}-$, $-\text{C}(\text{R}^{41})\text{R}^{42}-\text{O}-$, $-\text{C}(\text{R}^{41})\text{R}^{42}-\text{N}(\text{R}^{51})-$, $-\text{C(O)-}$, $-\text{C}(\text{R}^{41})(\text{R}^{42})-\text{C(O)-}$, and $-\text{N=C(NH}_2-$, wherein no more than one of Z^1 , Z^2 , Z^3 , and Z^4 is $-\text{O}-$, $-\text{C}(\text{R}^{41})(\text{R}^{42})-\text{O}-$, $-\text{C}(\text{R}^{41})\text{R}^{42}-\text{N}(\text{R}^{51})-$, $-\text{C(O)-}$, $-\text{C}(\text{R}^{41})(\text{R}^{42})-\text{C(O)-}$, or $-\text{N=C(NH}_2-$;

[0137] Z^5 and Z^6 are independently selected from $-\text{C}(\text{R}^{43})-$ and $-\text{N}-$;

[0138] B is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0139] L^1 , L^2 and L^4 are each independently selected from bond, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{C(O)-}$, $-\text{C(O)O}-$, $-\text{OC(O)-}$, $-\text{OC(O)O}-$, $-\text{C(O)N}(\text{R}^{51})-$, $-\text{C(O)N}(\text{R}^{51})\text{C(O)-}$, $-\text{C(O)N}(\text{R}^{51})\text{C(O)N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C(O)-}$, $-\text{N}(\text{R}^{51})\text{C(O)O}-$, $-\text{OC(O)N}(\text{R}^{51})-$, $-\text{C}(\text{NR}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})-$, $-\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{S(O)2-}$, $-\text{S(O)O}-$, $-\text{S(O)-}$, $-\text{OS(O)2-}$, $-\text{S(O)2O}-$, $-\text{N}(\text{R}^{51})\text{S(O)2-}$, $-\text{S(O)2N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S(O)-}$, $-\text{S(O)N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S(O)2N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S(O)N}(\text{R}^{51})-$; alkylene, alkynylene, 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 L¹, L² or L⁴ can together optionally form a bridge or ring;

[0140] R^B is independently selected at each occurrence from hydrogen and R⁵⁰, or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0141] R^{H2} is independently selected at each occurrence from R⁵⁰, or two R^{H2} groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0142] R^{A1}, R^{A2} and R^{A3} are each independently selected at each occurrence from hydrogen and R⁵⁰;

[0143] n is an integer from 0 to 6;

[0144] r is an integer from 1 to 6;

[0145] R⁵⁰ is independently selected at each occurrence from:

[0146] halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²);

[0147] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

[0148] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0149] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)

(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0150] R⁵¹ is independently selected at each occurrence from:

[0151] hydrogen, —C(O)R⁵², —C(O)OR⁵², —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴;

[0152] C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

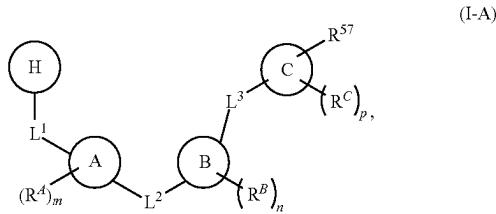
[0153] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0154] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0155] R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, =O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle; and

[0156] R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R⁵⁰.

[0157] In one aspect, the present disclosure provides a method of treating acute myeloid leukemia in a subject exhibiting a mutation in the nucleophosmin (NPM1) gene, the method comprising administering to a subject in need thereof a compound of Formula (I-A):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0158] H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0159] A is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0160] B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0161] C is 3- to 12-membered heterocycle;

[0162] 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, alkynylene, alkynylene, heteroalkynylene, 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;

[0163] R^A , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^A groups, 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;

[0164] m, n and p are each independently an integer from 0 to 6;

[0165] R^{50} is independently selected at each occurrence from:

[0166] halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)R^{52}_2$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)$, OR^{52} , $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})_2$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$;

[0167] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$,

$-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)R^{52}_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})_2$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0168] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0169] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)R^{52}_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)NR^{53}R^{54}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})_2$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0170] R^{51} is independently selected at each occurrence from:

[0171] hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

[0172] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)R^{52}_2$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})_2$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

[0173] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0174] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)R^{52}_2$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$,

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

[0175] 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 , $\text{—NHCH}_2\text{CH}_3$, =O , —OH , —OCH_3 , $\text{—OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

[0176] 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} ;

[0177] R^{57} is selected from:

[0178] halogen, —NO_2 , —CN , —SR^{52} , $\text{—NR}^{53}\text{R}^{54}$, —S(=O)R^{52} , —S(=O)_2R^{58} , $\text{—S(=O)_2N(R}^{52})_2$, $\text{—S(=O)_2NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{S(=O)_2R}^{52}$, $\text{—NR}^{52}\text{S(=O)_2NR}^{53}\text{R}^{54}$, —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)N(R}^{52})_2$, $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—C(O)NH(C}_{1-6}\text{ alkyl)}$, $\text{—C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})(\text{R}^{52})$, $\text{—NR}^{52}\text{P(O)(R}^{52})$, $\text{—P(O)(NR}^{52})_2$, $\text{—P(O)(NR}^{52})_2$, $\text{—S, =N(R}^{52})$; and

[0179] 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} , $\text{—N(R}^{52})_2$, $\text{—NR}^{53}\text{R}^{54}$, —S(=O)R^{52} , —S(=O)_2R^{52} , $\text{—S(=O)}_2\text{N(R}^{52})_2$, $\text{—S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{S(=O)_2N(R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)_2NR}^{53}\text{R}^{54}$, —C(O)R^{52} , $\text{—CO(OR}^{52})$, —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)N(R}^{52})_2$, $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)R}^{52}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)N(R}^{52})_2$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(R}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})(\text{R}^{52})$, $\text{—NR}^{52}\text{P(O)(R}^{52})$, $\text{—P(O)(NR}^{52})(\text{OR}^{52})$, $\text{—P(O)(NR}^{52})_2$, $\text{—S, and =N(R}^{52})$; and

[0180] 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 , $\text{—NHCH}_2\text{CH}_3$, =O , —OH , —OCH_3 , $\text{—OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle,

[0181] wherein for a compound or salt of Formula (I-A), when C is azetidinylene, piperidinylene or piperazinylene and R^{57} is —S(=O)_2R^{58} , $\text{—S(=O)_2N(R}^{52})_2$, or $\text{—NR}^{52}\text{S(=O)_2R}^{52}$.

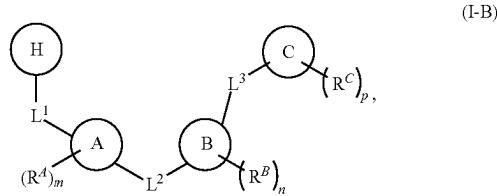
[0182] p is an integer from 1 to 6; and/or

[0183] L^3 is substituted with one or more R^{50} , wherein L^3 is not $\text{—CH}_2\text{CH(OH)}$.

[0184] In one aspect, the present disclosure provides a method of treating a hematological malignancy 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 a combination thereof, the method comprising administering to a subject in need thereof a compound of Formula (I-A).

[0185] In one aspect, the present disclosure provides a method of treating acute myeloid leukemia in a subject exhibiting a mutation in the nucleophosmin (NPM1) gene, the method comprising administering to a subject in need thereof a compound of Formula (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

[0186] H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0187] A, B and C are each independently selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0188] L^1 and L^2 are each independently selected from bond, —O— , —S— , $\text{—N(R}^{51})_2$, $\text{—N(R}^{51})\text{CH}_2$, —C(O)— , —C(O)O— , —OC(O)— , —OC(O)O— , $\text{—C(O)N(R}^{51})_2$, $\text{—C(O)N(R}^{51})\text{C(O)—}$, $\text{—C(O)N(R}^{51})\text{C(O)N(R}^{51})_2$, $\text{—N(R}^{51})\text{C(O)—}$, $\text{—N(R}^{51})\text{C(O)N(R}^{51})_2$, $\text{—N(R}^{51})\text{C(O)O—}$, $\text{—OC(O)N(R}^{51})_2$, $\text{—C(NR}^{51})_2$, $\text{—N(R}^{51})\text{C(NR}^{51})_2$, $\text{—C(NR}^{51})\text{N(R}^{51})_2$, —S(O)_2 , —OS(O)— , —S(O)O— , —S(O)— , —OS(O)_2 , $\text{—S(O)}_2\text{O—}$, $\text{—N(R}^{51})\text{S(O)}_2$, $\text{—S(O)}_2\text{N(R}^{51})_2$, $\text{—N(R}^{51})\text{S(O)}_2$, $\text{—S(O)N(R}^{51})_2$, $\text{—N(R}^{51})\text{S(O)(R}^{51})_2$; alkylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50} ;

[0189] L^3 is selected from alkylene, alkenylene, and alkynylene, each of which is substituted with one or more R^{56} and optionally further substituted with one or more R^{50} ;

[0190] R^4 , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^4 groups, 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;

[0191] m, n and p are each independently an integer from 0 to 6;

[0192] R^{50} is independently selected at each occurrence from:

[0193] halogen, —NO_2 , —CN , —OR^{52} , —SR^{52} , $\text{—N(R}^{52})_2$, $\text{—NR}^{53}\text{R}^{54}$, —S(=O)R^{52} , —S(=O)_2R^{52} , $\text{—S(=O)_2N(R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)_2R}^{52}$, $\text{—NR}^{52}\text{S(=O)_2NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{S(=O)_2NR}^{53}\text{R}^{54}$, —C(O)R^{52} , —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)N(R}^{52})_2$, $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)R}^{52}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $\text{—C(O)N(R}^{52})_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(R}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})_2$, $\text{—S, and =N(R}^{52})$.

(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²);

[0194] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵²R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵²R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)N(R⁵²)R⁵⁴, —C(O)R⁵², —NR⁵²S(=O)NR⁵²R⁵⁴, —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵²R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵²R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵²R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

[0195] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0196] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵²R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵²R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)N(R⁵²)R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵²R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵²R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵²R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0197] R⁵¹ is independently selected at each occurrence from:

[0198] hydrogen, —C(O)R⁵², —C(O)OR⁵², —C(O)N(R⁵²)₂, —C(O)NR⁵²R⁵⁴,

[0199] C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵²R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵²R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)N(R⁵²)R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵²R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵²R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵²R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

[0200] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0201] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently optionally substituted with one or more substituents

selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵²R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵²R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)N(R⁵²)R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵²R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵²R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵²R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0202] R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, =O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle;

[0203] R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R⁵⁰;

[0204] R⁵⁶ is independently selected at each occurrence from:

[0205] —NO₂, —OR⁵⁹, —SR⁵², —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)N(R⁵²)R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0206] wherein each C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl in R⁵⁶ is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵⁹, —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)N(R⁵²)R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle;

[0207] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁶ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)N(R⁵²)R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle;

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

[0208] further wherein R^{56} optionally forms a bond to ring C; and

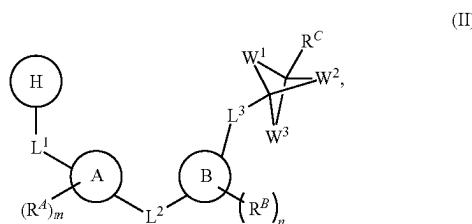
[0209] R^{59} is independently selected at each occurrence from C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle,

[0210] wherein for a compound or salt of Formula (I-B), when R^{56} is $-\text{CH}_3$, L^3 is not further substituted with $-\text{OH}$, $-\text{NH}_2$, or $-\text{CN}$.

[0211] In one aspect, the present disclosure provides a method of treating a hematologic malignancy 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 a combination thereof, the method comprising administering to a subject in need thereof a compound of Formula (I-B).

[0212] In some embodiments, R^C is selected from $-\text{C}(\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $=\text{O}$, 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.

[0213] In one aspect, the present disclosure provides a method of treating acute myeloid leukemia in a subject exhibiting a mutation in the nucleophosmin (NPM1) gene, the method comprising administering to a subject in need thereof a compound of Formula (II):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0214] H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0215] A is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0216] B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0217] L^1 , L^2 and L^3 are each independently selected from bond, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{NR}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})-$, $-\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{S}(\text{O})_2-$, $-\text{OS}(\text{O})-$, $-\text{S}(\text{O})\text{O}-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})\text{N}(\text{R}^{51})-$; alkylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50} ;

[0218] R^A , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^A groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0219] m and n are each independently an integer from 0 to 6;

[0220] W^1 is C_{1-4} alkylene, optionally substituted with one or more R^{50} ;

[0221] W^2 is selected from a bond; and C_{1-4} alkylene, optionally substituted with one or more R^{50} ;

[0222] W^3 is selected from absent; and C_{1-4} alkylene, optionally substituted with one or more R^{50} ;

[0223] R^{50} is independently selected at each occurrence from:

[0224] halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$;

[0225] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0226] C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0227] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

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

[0228] R^{51} is independently selected at each occurrence from:

[0229] hydrogen, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$,

[0230] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

[0231] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0232] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0233] R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

[0234] 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}

[0235] wherein for a compound or salt of Formula (II), when W^3 is absent:

[0236] W^1 is C_1 alkylene, W^2 is a bond, and L^3 is not a bond;

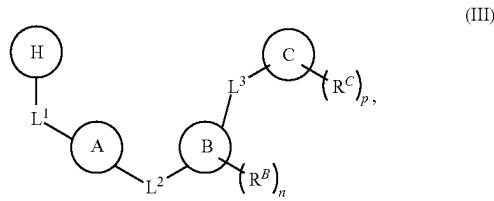
[0237] W^1 is C_{2-4} alkylene and W^2 is a bond; or

[0238] W^1 and W^2 are each C_1 alkylene and L^3 is not a bond, wherein each C_1 alkylene is independently optionally substituted with one or more R^{50} .

[0239] In one aspect, the present disclosure provides a method of treating a hematological malignancy 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 a combination thereof, the method comprising administering to a subject in need thereof a compound of Formula (II).

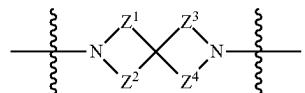
[0240] In one aspect, the present disclosure provides a method of treating a hematological malignancy in a subject exhibiting a mutation in the nucleophosmin (NPM1) gene, DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, FMS-like tyrosine kinase-3 (FLT3) gene, isocitrate dehydrogenase 1 (IDH1) gene, isocitrate dehydrogenase 2 (IDH2) gene, or combination thereof, the method comprising administering to a subject in need thereof a compound of Formula (III):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0241] H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0242] A is



[0243] each of Z^1 , Z^2 , Z^3 , and Z^4 is independently selected from $-\text{C}(\text{R}^{41})(\text{R}^{42})$, $-\text{C}(\text{R}^{41})(\text{R}^{42})$, $-\text{C}(\text{O})$, and $-\text{C}(\text{R}^{41})(\text{R}^{42})-\text{C}(\text{O})$, wherein no more than one of Z^1 , Z^2 , Z^3 , and Z^4 is $-\text{C}(\text{O})$ or $-\text{C}(\text{R}^{41})(\text{R}^{42})-\text{C}(\text{O})$;

[0244] B is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0245] C is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0246] L^1 , L^2 and L^3 are each independently selected from bond, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{NR}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})-$, $-\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{S}(\text{O})_2-$, $-\text{OS}(\text{O})-$, $-\text{S}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})\text{N}(\text{R}^{51})-$; alkylene, alkynylene, 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 L¹, L² or L³ can together optionally form a bridge or ring;

[0247] R^B is independently selected at each occurrence from R⁵⁰, or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0248] R^C is independently selected at each occurrence from hydrogen and R⁵⁰, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0249] R^{A1} and R^{A2} are each independently selected at each occurrence from hydrogen and R⁵⁰;

[0250] n is an integer from 0 to 6;

[0251] p is an integer from 1 to 6;

[0252] R⁵⁰ is independently selected at each occurrence from:

[0253] halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, —O, —S, —N(R⁵²);

[0254] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, —O, —S, —N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

[0255] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0256] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, —O, —S, —N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle;

(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, —O, —S, —N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0257] R⁵¹ is independently selected at each occurrence from:

[0258] hydrogen, —C(O)R⁵², —C(O)OR⁵², —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴;

[0259] C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(R⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, —O, —S, —N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

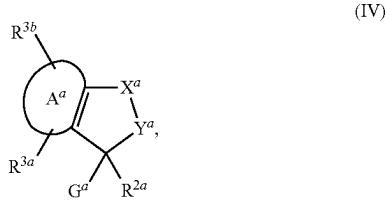
[0260] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0261] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(R⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, —O, —S, —N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0262] R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, —O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle; and

[0263] R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R⁵⁰.

[0264] In one aspect, the present disclosure provides a method of treating a hematological malignancy 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, the method comprising administering to a subject in need thereof a compound of Formula (IV):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:



is a fused thienyl or fused phenyl group;

[0265] G^a is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle, each of which is substituted with -E¹-R^{4a} and optionally further substituted with one or more R⁵⁰;

[0266] R^{2a} is selected from hydrogen, alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl;

[0267] R^{3a} and R^{3b} are each independently selected from hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0268] X^a-Y^a is selected from -N(R⁵²)-C(=O)-, -C(=O)-O-, -C(=O)-N(R⁵²)-, -CH₂N(R⁵²)-CH₂-, -C(=O)N(R⁵²)-CH₂-, -CH₂CH₂-N(R⁵²)-, -CH₂N(R⁵²)-C(=O)-, and -CH₂O-CH₂; or

[0269] X^a and Y^a do not form a chemical bond, wherein:

[0270] X^a is selected from hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy; and

[0271] Y^a is selected from cyano, hydroxy, and -CH₂R⁵⁰;

[0272] E¹ is selected from absent, -C(=O)-, -C(=O)N(R⁵²)-, -[C(R^{14a})₂]₁₋₅O-, -[C(R^{14a})₂]₁₋₅NR⁵²-, -[C(R^{14a})₂]₁₋₅-, -CH₂(=O)-, and -S(=O)₂;

[0273] R^{4a} is selected from hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl;

[0274] R^{14a} is selected from hydrogen and alkyl;

[0275] R⁵⁰ is independently selected at each occurrence from:

[0276] halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)R⁵², -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)R⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -P(O)(NR⁵²)₂, -O, =S, =N(R⁵²);

OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²);

[0277] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)R⁵², -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

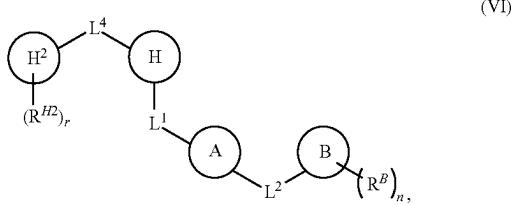
[0278] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0279] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)R⁵², -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0280] R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, -NO₂, -NH₂, -NHCH₃, -NHCH₂CH₃, =O, -OH, -OCH₃, -OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle; and

[0281] R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R⁵⁰.

[0282] In one aspect, the present disclosure provides a method of treating a hematological malignancy 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, the method comprising administering to a subject in need thereof a compound of Formula (VI):

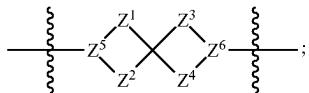


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0283] H^2 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0284] H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0285] A is



[0286] each of Z^1 , Z^2 , Z^3 , and Z^4 is independently selected from $-C(R^{41})(R^{42})-$, $-C(R^{41})(R^{42})-$, $-C(R^{41})(R^{42})-$, $-O-$, $-C(R^{41})(R^{42})-O-$, $-C(R^{41})(R^{42})-N(R^{51})-$, $-C(O)-$, $-C(R^{41})(R^{42})-C(O)-$, and $-N=C(NH_2)-$, wherein no more than one of Z^1 , Z^2 , Z^3 , and Z^4 is $-O-$, $-C(R^{41})(R^{42})-O-$, $-C(R^{41})(R^{42})-N(R^{51})-$, $-C(O)-$, $-C(R^{41})(R^{42})-C(O)-$, or $-N=C(NH_2)-$;

[0287] Z^5 and Z^6 are independently selected from $-C(R^{43})-$ and $-N-$;

[0288] B is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0289] L^1 , L^2 and L^4 are each independently selected from bond, $-O-$, $-S-$, $-N(R^{51})-$, $-N(R^{51})CH_2-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, $-OS(O)-$, $-S(O)O-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$; alkylene, alkynylene, alkynylene, heteroalkynylene, 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^4 can together optionally form a bridge or ring;

[0290] R^B is independently selected at each occurrence from hydrogen and R^{50} , or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0291] 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;

[0292] R^{41} , R^{42} and R^{43} are each independently selected at each occurrence from hydrogen and R^{50} ;

[0293] n is an integer from 0 to 6;

[0294] r is an integer from 1 to 6;

[0295] R^{50} is independently selected at each occurrence from:

[0296] halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)_2R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)NR^{53}R^{54}$, $-P(O)OR^{52}$, $-P(O)(OR^{52})_2$, $-P(O)(NR^{52})_2$, $-NR^{52}P(O)R^{52}$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})OR^{52}$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$;

[0297] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)_2R^{54}$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)NR^{53}R^{54}$, $-P(O)OR^{52}$, $-P(O)(OR^{52})_2$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})R^{52}$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})OR^{52}$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0298] C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0299] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)_2R^{54}$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)NR^{53}R^{54}$, $-P(O)OR^{52}$, $-P(O)(OR^{52})_2$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})R^{52}$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})OR^{52}$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0300] R^{51} is independently selected at each occurrence from:

[0301] hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

[0302] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)_2R^{54}$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)NR^{53}R^{54}$, $-P(O)OR^{52}$, $-P(O)(OR^{52})_2$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})R^{52}$, $-P(O)(NR^{52})_2$, $-P(O)(NR^{52})OR^{52}$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$;

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

[0303] C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0304] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{OR}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0305] 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, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

[0306] 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} .

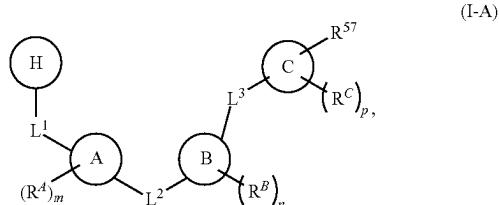
[0307] In some embodiments, the hematological malignancy is selected from a malignant lymphoma, a leukemia, a mature B cell neoplasm, a mature T cell and natural killer (NK) cell neoplasm, a precursor lymphoid neoplasm, Hodgkin lymphoma (HL), a plasma cell tumor, a mast cell tumor, a neoplasm of histiocytes and accessory lymphoid cells, an immunoproliferative disease, a myeloid leukemia, and a myelodysplastic syndrome (MDS). In some embodiments, the hematological malignancy 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 hematological malignancy is acute myeloid leukemia. In some embodiments, a relapse of the hematological malignancy is prevented.

[0308] In some embodiments, the mutation in the nucleophosmin (NPM1) gene is a mutation in exon 12 of the NPM1 gene. In some embodiments, the mutation in the nucleophosmin (NPM1) gene is a frameshift mutation. In some embodiments, the mutation in the nucleophosmin (NPM1) gene comprises an insertion of two to nine bases, such as the insertion is of four bases. In some embodiments, the insertion of four bases is selected from TCTG, CATG, CCTG,

CGTG, CAGA, CTTG, and TATG. In some embodiments, the insertion is of nine bases. In some embodiments, the insertion of nine bases is selected from CTCTTGCCCC and CCCTGGAGA. In some embodiments, the mutation in the nucleophosmin (NPM1) gene comprises a deletion of nucleotides 965 through 969 (GGAGG). In some embodiments, the subject further exhibits a mutation in the FLT3 gene. In some embodiments, the mutation in the FLT3 gene is an internal tandem duplication. In some embodiments, the subject further exhibits a mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene.

[0309] In some embodiments, the mutation in the FLT3 gene is in the tyrosine kinase domain. In some embodiments, the mutation is in the nucleophosmin (NPM1) gene and FMS-like tyrosine kinase-3 (FLT3) gene. In some embodiments, the mutation is in the nucleophosmin (NPM1) gene, DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene, isocitrate dehydrogenase 2 (IDH2) gene, and FMS-like tyrosine kinase-3 (FLT3) gene. In some embodiments, the subject exhibits a mutation in the DNA (cytosine-5)-methyltransferase 3A (DNMT3A) gene.

[0310] In one aspect, the present disclosure provides a method of treating Ewing's sarcoma, the method comprising administering to a subject in need thereof a compound of Formula (I-A):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0311] H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0312] A is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0313] B is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0314] C is 3- to 12-membered heterocycle;

[0315] L^1 , L^2 and L^3 are each independently selected from bond, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{NR}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})-$, $-\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{S}(\text{O})_2-$, $-\text{OS}(\text{O})-$, $-\text{S}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})\text{N}(\text{R}^{51})-$; alkylene, alkynylene, heteroalkynylene, heteroalkenylene, and heteroalkylenylene, 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;

[0316] R^A , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^A groups, 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;

[0317] m, n and p are each independently an integer from 0 to 6;

[0318] R⁵⁰ is independently selected at each occurrence from:

[0319] halogen, --NO_2 , --CN , --OR^{52} , --SR^{52} ,
 $\text{--N(R}^{52})_2$, $\text{--NR}^{53}\text{R}^{54}$, --S(=O)R^{52} , --S(=O)
 --R^{52} , $\text{--S(=O)}_2\text{N(R}^{52})_2$, $\text{--S(=O)}_2\text{NR}^{53}\text{R}^{54}$,
 $\text{--NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $\text{--NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$,
 $\text{--NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, --C(O)R^{52} , --C(O)OR^{52} ,
 --OC(O)R^{52} , --OC(O)OR^{52} , $\text{--OC(O)N(R}^{52})_2$,
 $\text{--OC(O)NR}^{53}\text{R}^{54}$, $\text{--NR}^{52}\text{C(O)R}^{52}$, $\text{--NR}^{52}\text{C(O)}$
 OR^{52} , $\text{--NR}^{52}\text{C(O)N(R}^{52})_2$, $\text{--NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$,
 $\text{--C(O)N(R}^{52})_2$, $\text{--C(O)NR}^{53}\text{R}^{54}$, $\text{--P(O)(OR}^{52})_2$,
 $\text{--P(O)(R}^{52})_2$, $\text{--P(O)(OR}^{52})(\text{R}^{52})$, $\text{--P(O)(NR}^{52})$
 (R^{52}) , $\text{--NR}^{52}\text{P(O)(R}^{52})$, $\text{--P(O)(NR}^{52})(\text{OR}^{52})$,
 $\text{--P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N(R}^{52})$;

[0320] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})\text{O}_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{NR}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})(\text{N}(\text{R}^{52}))_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{OR}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0321] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle.

[0322] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)N(R^{52})_2$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)R^{52}$, $-P(O)R^{52}$, $-P(O)OR^{52}$, $-P(O)NR^{52}$, $-NR^{52}P(O)R^{52}$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0323] R⁵¹ is independently selected at each occurrence from:

[0324] hydrogen, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$; 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, $-\text{NO}_2$,

—CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)R⁵³O⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, —S(=O)R⁵², —S(=O)N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

[0325] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0326] 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, $—NO_2$, $—CN$, $—OR^{52}$, $—SR^{52}$, $—N(R^{52})_2$, $—NR^{53}R^{54}$, $—S(=O)R^{52}$, $—S(=O)_2R^{52}$, $—S(=O)N(R^{52})_2$, $—S(=O)NR^{53}R^{54}$, $—NR^{52}S(=O)_2R^{52}$, $—NR^{52}S(=O)N(R^{52})_2$, $—NR^{52}S(=O)NR^{53}R^{54}$, $—C(O)R^{52}$, $—C(O)OR^{52}$, $—OC(O)R^{52}$, $—OC(O)OR^{52}$, $—OC(O)N(R^{52})_2$, $—OC(O)NR^{53}R^{54}$, $—NR^{52}C(O)R^{52}$, $—NR^{52}C(O)OR^{52}$, $—NR^{52}C(O)N(R^{52})_2$, $—NR^{52}C(O)NR^{53}R^{54}$, $—C(O)N(R^{52})_2$, $—C(O)NR^{53}R^{54}$, $—P(O)OR^{52})_2$, $—P(O)(R^{52})_2$, $—P(O)(OR^{52})(R^{52})$, $—P(O)(NR^{52})(R^{52})$, $—NR^{52}P(O)(R^{52})$, $—P(O)(OR^{52})$, $—P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})_2$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0327] 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;

[0328] 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} ;

[0329] R⁵⁷ is selected from:

[0330] halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{SR}^{52}$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{58}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{S}=\text{N}(\text{R}^{52})$; and

[0331] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from —NO₂, —CN, —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)

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

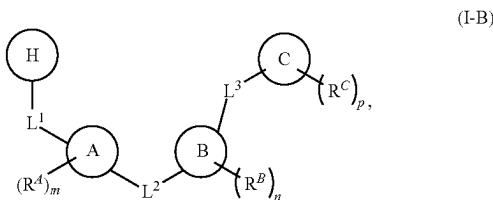
[0332] R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle,

[0333] wherein for a compound or salt of Formula (I-A), when C is azetidinylene, piperidinylene or piperauzinylene and R^{57} is $-\text{S}(=\text{O})_2\text{R}^{58}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, or $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$.

[0334] p is an integer from 1 to 6; and/or

[0335] L^3 is substituted with one or more R^{50} , wherein L^3 is not $-\text{CH}_2\text{CH}(\text{OH})-$.

[0336] In one aspect, the present disclosure provides a method of treating Ewing's sarcoma, the method comprising administering to a subject in need thereof a compound of Formula (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

[0337] H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0338] A, B and C are each independently selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0339] L^1 and L^2 are each independently selected from bond, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{NR}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})-$, $-\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{S}(\text{O})_2-$, $-\text{OS}(\text{O})-$, $-\text{S}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})\text{N}(\text{R}^{51})-$; alkylene, alkynylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50} ;

[0340] L^3 is selected from alkylene, alkynylene, and alkynylene, each of which is substituted with one or more R^{56} and optionally further substituted with one or more R^{50} ;

[0341] R^4 , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^4 groups, 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;

[0342] m, n and p are each independently an integer from 0 to 6;

[0343] R^{50} is independently selected at each occurrence from:

[0344] halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$;

[0345] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0346] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0347] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0348] R^{51} is independently selected at each occurrence from:

[0349] hydrogen, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$;

[0350] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$,

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

[0351] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0352] 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} , $\text{—N}(\text{R}^{52})_2$, $\text{—NR}^{53}\text{R}^{54}$, $\text{—S(=O)\text{R}^{52}}$, $\text{—S(=O)}_2\text{R}^{52}$, $\text{—S(=O)}_2\text{N}(\text{R}^{52})_2$, $\text{—S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $\text{—NR}^{52}\text{S(=O)}_2\text{N}(\text{R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} , —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)N}(\text{R}^{52})_2$, $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)R}^{52}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)N}(\text{R}^{52})_2$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $\text{—C(O)N(R}^{52})_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(R}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})(\text{R}^{52})$, $\text{—NR}^{52}\text{P(O)(R}^{52})$, —P(O)
 $(\text{NR}^{52})(\text{OR}^{52})$, $\text{—P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0353] 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 , $\text{—NHCH}_2\text{CH}_3$, $=\text{O}$, $=\text{OH}$, $—\text{OCH}_3$, $—\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

[0354] 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} ;

[0355] R^{56} is independently selected at each occurrence from:

[0356] —NO_2 , —OR^{59} , —SR^{52} , $\text{—NR}^{53}\text{R}^{54}$, $\text{—S(=O)\text{R}^{52}}$, $\text{—S(=O)}_2\text{R}^{52}$, $\text{—S(=O)}_2\text{N}(\text{R}^{52})_2$, $\text{—S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $\text{—NR}^{52}\text{S(=O)}_2\text{N}(\text{R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} , —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)N}(\text{R}^{52})_2$, $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)R}^{52}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)N}(\text{R}^{52})_2$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $\text{—C(O)N(R}^{52})_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(R}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})(\text{R}^{52})$, $\text{—NR}^{52}\text{P(O)(R}^{52})$, $\text{—P(O)(NR}^{52})(\text{OR}^{52})$, $\text{—P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0357] wherein each C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl in R^{56} is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO_2 , —CN , —OR^{59} , —SR^{52} , $\text{—N}(\text{R}^{52})_2$, $\text{—NR}^{53}\text{R}^{54}$, $\text{—S(=O)\text{R}^{52}}$, $\text{—S(=O)}_2\text{R}^{52}$, $\text{—S(=O)}_2\text{N}(\text{R}^{52})_2$, —S(=O)

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

[0358] wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, —NO_2 , —CN , —OR^{52} , —SR^{52} , $\text{—N}(\text{R}^{52})_2$, $\text{—NR}^{53}\text{R}^{54}$, $\text{—S(=O)\text{R}^{52}}$, $\text{—S(=O)}_2\text{N}(\text{R}^{52})_2$, $\text{—S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $\text{—NR}^{52}\text{S(=O)}_2\text{N}(\text{R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} , —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)N}(\text{R}^{52})_2$, $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)R}^{52}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)N}(\text{R}^{52})_2$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $\text{—C(O)N(R}^{52})_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(R}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})(\text{R}^{52})$, $\text{—NR}^{52}\text{P(O)(R}^{52})$, $\text{—P(O)(NR}^{52})(\text{OR}^{52})$, $\text{—P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

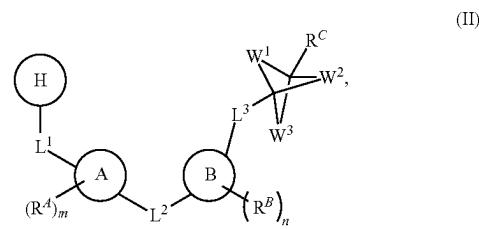
[0359] further wherein R^{56} optionally forms a bond to ring C; and

[0360] R^{59} is independently selected at each occurrence from 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 , $\text{—NHCH}_2\text{CH}_3$, $=\text{O}$, $=\text{OH}$, $—\text{OCH}_3$, $—\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle,

[0361] wherein for a compound or salt of Formula (I-B), when R^{56} is $—\text{CH}_3$, L^3 is not further substituted with $=\text{OH}$, $=\text{NH}_2$, or $=\text{CN}$.

[0362] In some embodiments, R^C is selected from $—\text{C(O)R}^{52}$, $—\text{S(=O)\text{R}^{52}}$, $—\text{S(=O)}_2\text{R}^{52}$, $—\text{S(=O)}_2\text{N}(\text{R}^{52})_2$, $—\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $—\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $=\text{O}$, 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.

[0363] In one aspect, the present disclosure provides a method of treating Ewing's sarcoma, the method comprising administering to a subject in need thereof a compound of Formula (II):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0364] H is selected from C₅₋₁₂ carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R⁵⁰;

[0365] A is selected from bond, C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0366] B is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0367] L¹, L² and L³ are each independently selected from bond, —O—, —S—, —N(R⁵¹)—, —N(R⁵¹)CH₂—, —C(O)—, —C(O)O—, —OC(O)—, —OC(O)O—, —C(O)N(R⁵¹)—, —C(O)N(R⁵¹)C(O)—, —C(O)N(R⁵¹)C(O)N(R⁵¹)—, —N(R⁵¹)C(O)—, —N(R⁵¹)C(O)NR⁵¹—, —N(R⁵¹)C(O)O—, —OC(O)NR⁵¹—, —C(NR⁵¹)—, —N(R⁵¹)C(NR⁵¹)—, —C(NR⁵¹)N(R⁵¹)—, —N(R⁵¹)C(NR⁵¹)N(R⁵¹)—, —S(O)₂—, —OS(O)—, —S(O)O—, —OS(O)₂—, —S(O)₂O—, —N(R⁵¹)S(O)₂—, —S(O)₂N(R⁵¹)—, —N(R⁵¹)S(O)N(R⁵¹)—, —N(R⁵¹)S(O)N(R⁵¹)—; alkylene, alkynylene, alkynylene, heteroalkynylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R⁵⁰;

[0368] R⁴, R^B and R^C are each independently selected at each occurrence from R⁵⁰, or two R⁴ groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0369] m and n are each independently an integer from 0 to 6;

[0370] W¹ is C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰;

[0371] W² is selected from a bond; and C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰;

[0372] W³ is selected from absent; and C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰;

[0373] R⁵⁰ is independently selected at each occurrence from:

[0374] halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)N(R⁵³R⁵⁴), —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²);

[0375] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)N(R⁵³R⁵⁴), —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

[0376] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0377] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)N(R⁵³R⁵⁴), —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0378] R⁵¹ is independently selected at each occurrence from:

[0379] hydrogen, —C(O)R⁵², —C(O)OR⁵², —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴;

[0380] C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)N(R⁵³R⁵⁴), —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

[0381] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0382] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)N(R⁵³R⁵⁴), —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0383] R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 2- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHC₃H₃, —NHCH₂CH₃, —O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle; and

[0384] R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R⁵⁰

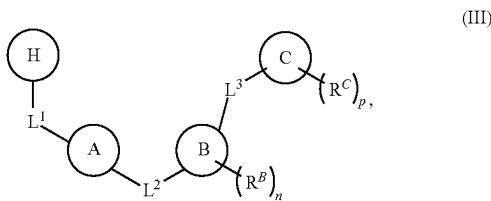
[0385] wherein for a compound or salt of Formula (II), when W^3 is absent:

[0386] W^1 is C_1 alkylene, W^2 is a bond, and L^3 is not a bond;

[0387] W^1 is C_{2-4} alkylene and W^2 is a bond; or

[0388] W^1 and W^2 are each C_1 alkylene and L^3 is not a bond, wherein each C_1 alkylene is independently optionally substituted with one or more R^{50} .

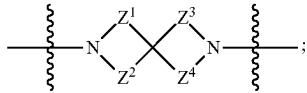
[0389] In one aspect, the present disclosure provides a method of treating Ewing's sarcoma, the method comprising administering to a subject in need thereof a compound of Formula (III):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0390] H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0391] A is



[0392] each of Z^1 , Z^2 , Z^3 , and Z^4 is independently selected from $-C(R^{41})(R^{42})-$, $-C(R^{41})(R^{42})-$, $-C(R^{41})(R^{42})-$, $-C(O)-$, and $-C(R^{41})(R^{42})-C(O)-$, wherein no more than one of Z^1 , Z^2 , Z^3 , and Z^4 is $-C(O)-$ or $-C(R^{41})(R^{42})-C(O)-$;

[0393] B is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0394] C is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0395] 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, alkynylene, 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;

[0396] 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 bridge or ring;

[0397] R^C is independently selected at each occurrence from hydrogen and R^{50} , or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0398] R^{41} and R^{42} are each independently selected at each occurrence from hydrogen and R^{50} ;

[0399] n is an integer from 0 to 6;

[0400] p is an integer from 1 to 6;

[0401] R^{50} is independently selected at each occurrence from:

[0402] halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)NR^{53}R^{54}$, $-S(=O)(O)R^{52}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(OR^{52})R^{52}$, $-P(O)(NR^{52})_2$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$;

[0403] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)OR^{52}$, $-S(=O)NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(OR^{52})R^{52}$, $-P(O)(NR^{52})_2$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0404] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0405] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)OR^{52}$, $-S(=O)NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(OR^{52})R^{52}$, $-P(O)(NR^{52})_2$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0406] R^{51} is independently selected at each occurrence from:

[0407] hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

[0408] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)N(R^{52})_2$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)N(R^{52})_2$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

[0409] C_{3-12} carbocycle and 3- to 12-membered heterocycle;

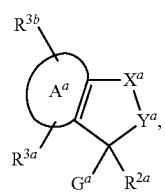
[0410] wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)N(R^{52})_2$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)N(R^{52})_2$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0411] 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; and

[0412] 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} .

[0413] In one aspect, the present disclosure provides a method of treating Ewing's sarcoma, the method comprising administering to a subject in need thereof a compound of Formula (IV):

(IV)



or a pharmaceutically acceptable salt or prodrug thereof, wherein:



is a fused thienyl or fused phenyl group;

[0414] G^a is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-E^1-R^{4a}$ and optionally further substituted with one or more R^{50} ;

[0415] R^{2a} is selected from hydrogen, alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl;

[0416] R^{3a} and R^{3b} are each independently selected from hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0417] X^a-Y^a is selected from $-N(R^{52})-C(=O)-$, $-C(=O)-O-$, $-C(=O)-N(R^{52})-$, $-CH_2N(R^{52})-CH_2-$, $-C(=O)N(R^{52})-CH_2-$, $-CH_2N(R^{52})-C(=O)-$, and $-CH_2O-CH_2-$; or

[0418] X^a and Y^a do not form a chemical bond, wherein:

[0419] X^a is selected from hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy; and

[0420] Y^a is selected from cyano, hydroxy, and $-CH_2R^{50}$;

[0421] E^1 is selected from absent, $-C(=O)-$, $-C(=O)N(R^{52})-$, $-[C(R^{14a})_2]_{1-5}O-$, $-[C(R^{14a})_2]_{1-5}NR^{52}-$, $-[C(R^{14a})_2]_{1-5}-$, $-CH_2(=O)-$, and $-S(=O)_2-$;

[0422] R^{4a} is selected from hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl;

[0423] R^{14a} is selected from hydrogen and alkyl;

[0424] R^{50} is independently selected at each occurrence from:

[0425] halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)N(R^{52})_2$, $-S(=O)NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)N(R^{52})_2$, $-NR^{52}S(=O)NR^{53}R^{54}$, $-C(O)R^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$;

[0426] 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, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)N(R^{52})_2$, $-S(=O)NR^{53}R^{54}$,

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

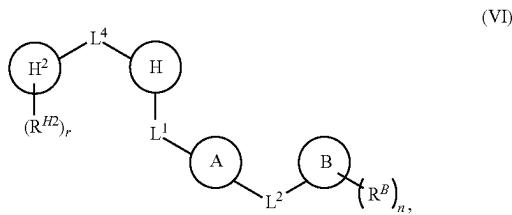
[0427] C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0428] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{OR}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0429] 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, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

[0430] 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} .

[0431] In one aspect, the present disclosure provides a method of treating Ewing's sarcoma, the method comprising administering to a subject in need thereof a compound of Formula (VI):

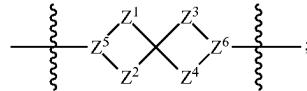


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0432] H^2 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0433] H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0434] A is



[0435] each of Z^1 , Z^2 , Z^3 , and Z^4 is independently selected from $-\text{C}(\text{R}^{41})(\text{R}^{42})$, $-\text{C}(\text{R}^{41})(\text{R}^{42})$, $-\text{O}$, $-\text{C}(\text{R}^{41})(\text{R}^{42})\text{O}$, $-\text{C}(\text{R}^{41})(\text{R}^{42})\text{N}(\text{R}^{51})$, $-\text{C}(\text{O})$, $-\text{C}(\text{R}^{41})(\text{R}^{42})\text{C}(\text{O})$, and $-\text{N}=\text{C}(\text{NH}_2)$, wherein no more than one of Z^1 , Z^2 , Z^3 , and Z^4 is $-\text{O}$, $-\text{C}(\text{R}^{41})(\text{R}^{42})$, $-\text{C}(\text{O})$, $-\text{C}(\text{R}^{41})(\text{R}^{42})\text{C}(\text{O})$, or $-\text{N}=\text{C}(\text{NH}_2)$;

[0436] Z^5 and Z^6 are independently selected from $-\text{C}(\text{R}^{43})$ and $-\text{N}$;

[0437] B is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0438] L^1 , L^2 and L^4 are each independently selected from bond, $-\text{O}$, $-\text{S}$, $-\text{N}(\text{R}^{51})$, $-\text{N}(\text{R}^{51})\text{CH}_2$, $-\text{C}(\text{O})$, $-\text{C}(\text{O})\text{O}$, $-\text{OC}(\text{O})$, $-\text{OC}(\text{O})\text{O}$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{O}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{51})$, $-\text{C}(\text{NR}^{51})$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})$, $-\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})$, $-\text{S}(\text{O})_2$, $-\text{OS}(\text{O})$, $-\text{S}(\text{O})$, $-\text{OS}(\text{O})_2$, $-\text{S}(\text{O})_2\text{O}$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{51})$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})$, $-\text{S}(\text{O})\text{N}(\text{R}^{51})$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})\text{N}(\text{R}^{51})$; alkylene, 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^4 can together optionally form a bridge or ring;

[0439] R^B is independently selected at each occurrence from hydrogen and R^{50} , or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0440] 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;

[0441] R^{41} , R^{42} and R^{43} are each independently selected at each occurrence from hydrogen and R^{50} ;

[0442] n is an integer from 0 to 6;

[0443] r is an integer from 1 to 6;

[0444] R^{50} is independently selected at each occurrence from:

[0445] halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$;

[0446] C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally substi-

tuted at each occurrence with one or more substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0447] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0448] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0449] R^{51} is independently selected at each occurrence from:

[0450] hydrogen, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$;

[0451] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{NR}^{52}\text{P}(\text{O})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

[0452] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0453] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$

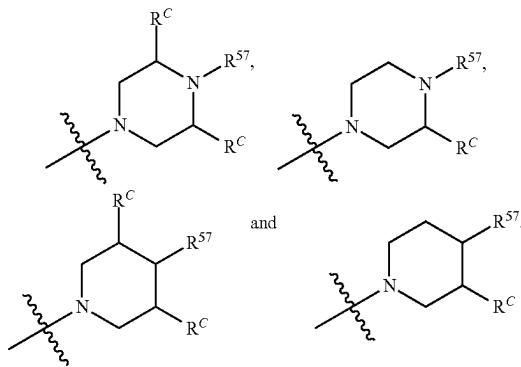
$(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$,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

[0454] 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, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

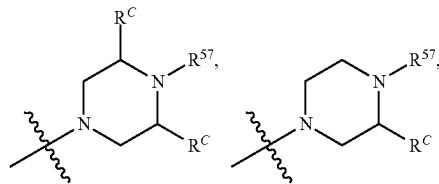
[0455] R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50} .

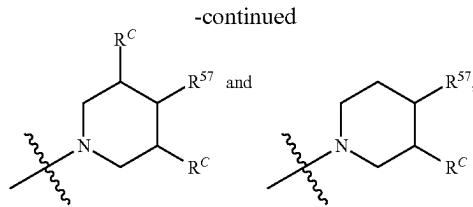
[0456] In some embodiments, the subject exhibits an EWSR1-FLI1 gene fusion, EWSR1-ERG gene fusion, or EWSR1-FEV gene fusion. In some embodiments, the subject exhibits a FUS-NCATc2 gene fusion, CIC-FOXO4 gene fusion, or ETV6-NTRK3 gene fusion. In some embodiments, the subject exhibits a mutation in a STAG2 gene, mutation in a TP53 gene, or CDKN2A deletion.

[0457] In some embodiments, for a compound of Formula (I-A) or Formula (I-B), C is 5- to 12-membered heterocycle, wherein the heterocycle comprises at least one nitrogen atom. In some embodiments, the heterocycle is saturated. In some embodiments, the heterocycle is selected from piperidinyl and piperazinyl. In some embodiments, C is selected from:



In some embodiments, R^{57} is selected from $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{58}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, and $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$. In some embodiments, C is selected from:



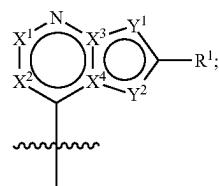


wherein R⁵⁷ is selected from —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵²; and C₁₋₁₀ alkyl substituted with one or more substituents selected from —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, and —NR⁵²S(=O)₂R⁵². In some embodiments, for a compound of Formula (I-A) or Formula (I-B), R⁵⁷ is selected from —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, and —NR⁵²S(=O)₂R⁵². In some embodiments, for a compound of Formula (I-A) or Formula (I-B), R⁵⁷ is selected from —S(=O)CH₃, —S(=O)₂CH₃, —S(=O)₂NH₂, —NHS(=O)₂CH₃, and —S(=O)₂NHCH₃. In some embodiments, for a compound of Formula (I-A) or Formula (I-B), R^C is selected from C₁₋₃ alkyl and C₁₋₃ haloalkyl.

[0458] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), or Formula (III), H is 5- to 12-membered heterocycle, optionally substituted with one or more R⁵⁰; A is 3- to 12-membered heterocycle; and B is 3- to 12-membered heterocycle.

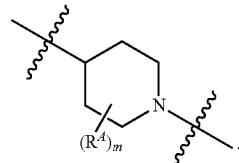
[0459] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II) or Formula (III), H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R⁵⁰. In some embodiments, H is thieno-pyrimidinyl, optionally substituted with one or more R⁵⁰.

[0460] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), or Formula (III), H is

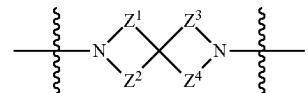


X¹ and X² are each independently selected from CR² and N; X³ and X⁴ are each independently selected from C and N; Y¹ and Y² are each independently selected from CR³, N, NR⁴, O, and S; R¹, R² and R³ are each independently selected at each occurrence from hydrogen and R⁵⁰; and R⁴ is selected from R⁵¹. In some embodiments, X³ and X⁴ are each C. In some embodiments, X¹ is CR², and R² is selected from hydrogen, halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, —CH₂OH, —CH₂OR⁵², —CH₂NH₂, —CH₂N(R⁵²)₂, C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alk-enyl, and C₂₋₃ alkynyl. In some embodiments, X¹ is CR², and R² is selected from hydrogen, halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alk-enyl, and C₂₋₃ alkynyl. In some embodiments, X² is N. In some embodiments, Y² is CR³, and R³ is selected from hydrogen, halogen, —OH, —N(R⁵²)₂, —CN, —C(O)OR⁵², C₁₋₃ alkyl, and C₁₋₃ haloalkyl. In some embodiments, R¹ is C₁₋₃ haloalkyl.

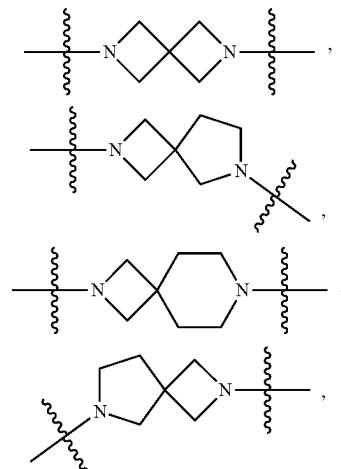
[0461] In some embodiments, for a compound of Formula (I-A), Formula (I-B), or Formula (II), A is 5- to 8-membered heterocycle. In some embodiments, A is 6-membered monocyclic heterocycle. In some embodiments, the heterocycle comprises at least one nitrogen atom. In some embodiments, A is selected from piperidinylene and piperazinylene. In some embodiments, A is



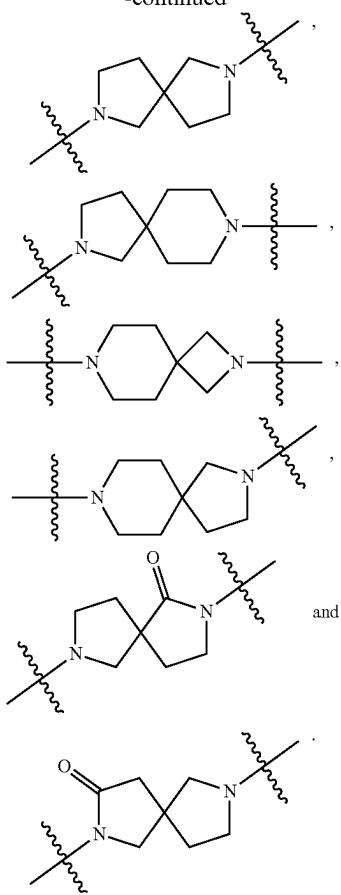
[0462] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), Formula (III), or Formula (VI), A is 7- to 12-membered spirocyclic heterocycle or C₇₋₁₂ spirocyclic carbocycle. In some embodiments, A is 7- to 12-membered spirocyclic heterocycle, such as 7- to 10-membered spirocyclic heterocycle. In some embodiments, A is



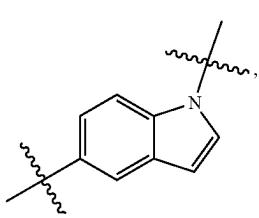
wherein each of Z¹, Z², Z³, and Z⁴ is independently selected from —C(R⁴¹)(R⁴²)—, —C(R⁴¹)(R⁴²)—C(R⁴¹)(R⁴²)—, —C(O)—, and —C(R⁴¹)(R⁴²)—C(O)—, wherein no more than one of Z¹, Z², Z³, and Z⁴ is —C(O)— or —C(R⁴¹)(R⁴²)—C(O)—; and R⁴¹ and R⁴² are each independently selected at each occurrence from hydrogen and R⁵⁰. In some embodiments, R⁴¹ and R⁴² are each independently selected at each occurrence from hydrogen, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, —CN, —NO₂, and —OH. In some embodiments, A is selected from:



-continued



[0463] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), Formula (III), or Formula (VI), B is 6- to 12-membered bicyclic heterocycle. In some embodiments, the heterocycle comprises at least one nitrogen atom. In some embodiments, B is indolylene. In some embodiments, B is



optionally substituted with one or more R^B.

[0464] In some embodiments, for a compound of Formula (I-A), Formula (I-B), or Formula (II), H is thienopyrimidinyl substituted with one or more R⁵⁰; A is selected from piperidinylene and piperazinylene; and B is indolylene.

[0465] In some embodiments, for a compound of Formula (I-A), Formula (I-B), or Formula (II), H is substituted with —CH₂CF₃.

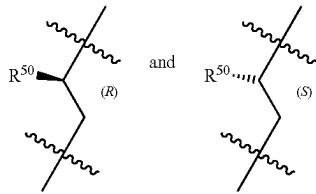
[0466] In some embodiments, for a compound of Formula (I-A), Formula (I-B), or Formula (II), m is 0. In some

embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), Formula (III), or Formula (VI), n is an integer from 1 to 3.

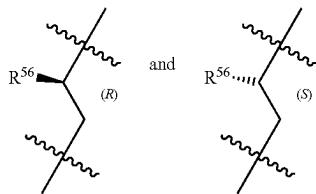
[0467] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), Formula (III), or Formula (VI), L¹ comprises less than 10 atoms. In some embodiments, L¹ is —N(R⁵¹)—.

[0468] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), Formula (III), or Formula (VI), L² comprises less than 10 atoms. In some embodiments, L² is C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰. In some embodiments, L² is selected from —CH₂—, —N(R⁵¹)—, —N(R⁵¹)CH₂—, —N(R⁵¹)C(O)—, and —N(R⁵¹)S(O)₂—.

[0469] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), or Formula (III), L³ comprises less than 20 atoms. In some embodiments, L³ is C₁₋₆ alkylene, optionally substituted with one or more R⁵⁰. In some embodiments, L³ is C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰. In some embodiments, L³ is —CH₂—. In some embodiments, L³ is C₂ alkylene substituted with at least one C₁₋₃ alkyl or C₁₋₃ haloalkyl, and optionally further substituted with one or more R⁵⁰. In some embodiments, L³ is substituted with =O, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₃ alkyl(cyclopropyl), C₁₋₃ alkyl(NR⁵²C(O)R⁵²) or —O(C₁₋₆ alkyl). In some embodiments, L³ is substituted with —CH₃. In some embodiments, L³ is selected from



In some embodiments, R⁵⁰ is methyl. In some embodiments, L³ is selected from



In some embodiments, R⁵⁶ is methyl.

[0470] In some embodiments, for a compound of Formula (I-A), Formula (I-B), or Formula (II), H is thienopyrimidinyl, optionally substituted with one or more R⁵⁰; A is 3- to 12-membered heterocycle; B is 6- to 12-membered bicyclic heterocycle; m is an integer from 0 to 3; and n is an integer from 1 to 3.

[0471] In some embodiments, for a compound of Formula (I-A),

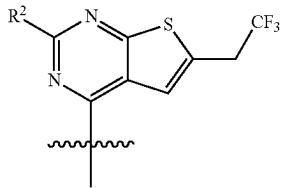
[0472] H is thienopyrimidinyl, optionally substituted with one or more R⁵⁰;

[0473] A is selected from piperidinylene and piperazinylene;

- [0474] B is indolylene;
- [0475] L¹ and L² are each independently selected from —O—, —S—, —NH—, and —CH₂—;
- [0476] L³ is selected from bond, —O—, —S—, —N(R⁵¹)—, —N(R⁵¹)CH₂—, —C(O)—, —C(O)O—, —OC(O)—, —OC(O)O—, —C(O)N(R⁵¹)—, —C(O)N(R⁵¹)C(O)—, —C(O)N(R⁵¹)C(O)N(R⁵¹)—, —N(R⁵¹)C(O)—, —N(R⁵¹)C(O)N(R⁵¹)—, —N(R⁵¹)C(O)O—, —OC(O)N(R⁵¹)—, —C(NR⁵¹)—, —N(R⁵¹)C(NR⁵¹)—, —C(NR⁵¹)N(R⁵¹)—, —N(R⁵¹)C(NR⁵¹)N(R⁵¹)—, —S(O)₂—, —OS(O)—, —S(O)O—, —S(O)—, —OS(O)₂—, —S(O)₂O—, —N(R⁵¹)S(O)₂—, —S(O)N(R⁵¹)—, —S(O)₂N(R⁵¹)—, —N(R⁵¹)S(O)—, —S(O)N(R⁵¹)—, —N(R⁵¹)S(O)₂N(R⁵¹)—, —N(R⁵¹)S(O)N(R⁵¹)—; alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R⁵⁰, wherein two R⁵⁰ groups attached to the same atom or different atoms of L³ can together optionally form a ring;
- [0477] R⁴, R^B and R^C are each independently selected at each occurrence from R⁵⁰, or two R⁴ groups, two R^B groups or two R^C groups attached to the same atom or different atoms can together optionally form a ring;
- [0478] m is an integer from 0 to 3;
- [0479] n is an integer from 1 to 3;
- [0480] p is an integer from 0 to 6;
- [0481] R⁵⁷ is selected from:
- [0482] —S(=O)R⁵², —S(=O)₂R⁵⁸, —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)NH(C₁₋₆ alkyl), —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂; and
- [0483] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from —S(=O)R⁵², —S(=O)₂R⁵⁸, —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)NH(C₁₋₆ alkyl), —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, and —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂; and
- [0484] R⁵⁸ is selected from hydrogen; and C₁₋₂₀ alkyl, C₃₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, =O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle.
- [0485] In some embodiments, for a compound of Formula (I-B),
- [0486] H is thienopyrimidinyl, optionally substituted with one or more R⁵⁰,
- [0487] A is selected from piperidinylene and piperazinylene;
- [0488] B is indolylene;
- [0489] L¹ and L² are each independently selected from —O—, —S—, —NH—, and —CH₂—;
- [0490] L³ is selected from C₁₋₆ alkylene, C₂₋₆ alkylene, and C₂₋₆ alkynylene, each of which is substituted with one or more R⁵⁶ and optionally further substituted with one or more R⁵⁰;
- [0491] R^A, R^B and R^C are each independently selected at each occurrence from R⁵⁰, or two R^A groups, 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;
- [0492] m is an integer from 0 to 3;
- [0493] n is an integer from 1 to 3;
- [0494] p is an integer from 0 to 6;
- [0495] R⁵⁶ is independently selected at each occurrence from:
- [0496] —OR⁵⁹, =O, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl,
- [0497] wherein each C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl in R⁵⁶ is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵⁹, —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —OC(O)NR⁵², —NR⁵²C(O)R⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle;
- [0498] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁶ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —OC(O)NR⁵², —NR⁵²C(O)R⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl; and
- [0499] further wherein R⁵⁶ optionally forms a bond to ring C; and
- [0500] R⁵⁹ is independently selected at each occurrence from C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, =O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle.
- [0501] In some embodiments, for a compound of Formula (I-A), R⁵⁷ is selected from —S(=O)R⁵⁸, —S(=O)₂N(R⁵²)₂, and —S(=O)₂NR⁵³R⁵⁴. In some embodiments, R⁵⁷ is selected from —S(=O)₂CH₃ and —S(=O)₂NHCH₃.

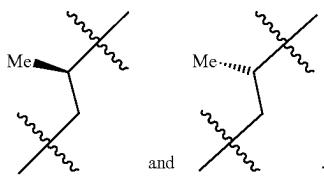
[0502] In some embodiments, for a compound of Formula (I-A), C is substituted with $-\text{S}(=\text{O})_2\text{R}^{58}$, $-\text{S}(=\text{O})_2(\text{R}^{52})_2$, or $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$.

[0503] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), or Formula (III), H is



and R^2 is selected from hydrogen, halogen, $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, C_{1-3} alkyl, C_{1-3} alkyl- OR^{52} , C_{1-3} alkyl- $\text{N}(\text{R}^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, R^2 is selected from $-\text{NH}_2$, $-\text{CH}_3$, and $-\text{NHCH}_3$.

[0504] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), or Formula (III), L^3 is selected from



[0505] In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI), the compound is provided as a substantially pure stereoisomer. In some embodiments, the stereoisomer is provided in at least 90% enantiomeric excess. In some embodiments, for a compound of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI), the compound is isotopically enriched. In some embodiments, for a compound of Formula (I-A) or Formula (I-B), the compound is selected from Table 1. In some embodiments, for a compound of Formula (II), the compound is selected from Table 2. In some embodiments, for a compound of Formula (III), the compound is selected from Table 3, Table 5 or Table 7. In some embodiments, for a compound of Formula (IV), the compound is selected from Table 4. In some embodiments, for a compound of Formula (VI), the compound is selected from Table 6.

[0506] In some embodiments, for a compound of Formula (II), 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, W^1 , W^2 and W^3 are each C_1 alkylene. In some embodiments, W^1 and W^2 are each C_1 alkylene and W^3 is absent.

[0507] In some embodiments, for a compound of Formula (II), R^C is selected from $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^2\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})(\text{N}(\text{R}^{52}))_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, and $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$.

[0508] In some embodiments, a method described herein further comprises reducing an expression of a target gene. In

some embodiments, the target gene is selected from Hoxa5, Hoxa7, Hoxa9, Hoxa10, Hoxb2, Hoxb3, Hoxb4, Hoxb5, Hoxb8, Hoxd10, Hoxd11, Hoxd13, DLX2, PBX3, Meis1, Mir196b, Flt3, and Bahcc1. In some embodiments, the target gene is Hoxa9, DLX2, PBX3, or Meis1. In some embodiments, a method described herein further comprises administering a second therapeutic agent. In some embodiments, the second therapeutic agent is a DOT1L inhibitor. In some embodiments, the second therapeutic agent is a FLT3 inhibitor. In some embodiments, the FLT3 inhibitor is quizartinib. In some embodiments, the FLT3 inhibitor is midostaurin. In some embodiments, the subject is human. In some embodiments, a method described herein further comprises obtaining a nucleic acid sample from the subject. In some embodiments, the nucleic acid sample comprises a nucleic acid selected from genomic DNA, cDNA, circulating tumor DNA, cell-free DNA, RNA, and mRNA. In some embodiments, a method described herein further comprises obtaining a biological sample from the subject. In some embodiments, the biological sample is a tissue sample. In some embodiments, the tissue sample is fixed, paraffin-embedded, fresh, or frozen. In some embodiments, the tissue sample is derived from fine needle, core, or other types of biopsy. In some embodiments, the biological sample is whole blood or plasma. In some embodiments, a method described herein further comprises conducting a nucleic acid analysis on the nucleic acid sample. In some embodiments, the nucleic acid analysis comprises PCR, sequencing, hybridization, microarray, SNP, cell-free nucleic acid analysis, or whole genome sequencing. In some embodiments, 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, or mixed lineage leukemia (MLL) gene amplification. In some embodiments, a method described herein further comprises testing the subject 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, or mixed lineage leukemia (MLL) gene amplification.

[0509] In some embodiments, 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 embodiments, a method described herein further comprises testing the subject 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 embodiments, the subject has been tested for the presence of an MLL rearrangement, a partial tandem duplication of MHLL, or elevated MEIS1 expression levels. In some embodiments, a method described herein further comprises testing the subject for the presence of an MLL rearrangement, a partial tandem duplication of MHLL, or elevated MEIS1 expression levels.

INCORPORATION BY REFERENCE

[0510] 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

[0511] The novel features of the invention are set forth with particularity in the appended claims.

[0512] 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:

[0513] FIG. 1 is an amino acid sequence of human menin, isoform 1 (SEQ ID NO: 1).

[0514] FIG. 2 is an amino acid sequence of human menin, isoform 2 (SEQ ID NO: 2).

[0515] FIG. 3 is an amino acid sequence of human menin, isoform 3 (SEQ ID NO: 3).

[0516] FIG. 4 depicts cd11b cell surface expression in compound treated OCI-AML3 cells.

[0517] FIG. 5 depicts the change in volume of OCI-AML3 tumors in vehicle and compound treated mice.

[0518] FIGS. 6A, 6B and 6C depict percentages of CD45+/CD38+ blasts, CD45+/CD11b+ monocytes, and CD45+/CD14+ monocytes in vehicle and compound treated AM7577 models.

[0519] FIGS. 7A, 7B and 7C depict overall survival, bone marrow phenotype at sacrifice, and spleen weight at sacrifice in vehicle and compound treated AM7577 models.

[0520] FIGS. 8A and 8B depict percentages of CD45+/CD38+ blasts and CD45+/CD11b+ monocytes in vehicle, compound and quizartinib treated AM7577 models.

[0521] FIGS. 9A, 9B, 9C, 9D and 9E depict overall survival, bone marrow phenotype after seven and 21 days, bone marrow AML blasts at sacrifice, and spleen weight at sacrifice in vehicle, compound and quizartinib treated AM7577 models.

[0522] FIG. 10 depicts percentages of CD45+/CD33+ blasts in vehicle, compound and quizartinib treated LXFE 2734 models.

[0523] FIG. 11 depicts overall survival in vehicle, compound and quizartinib treated LXFE 2734 models.

[0524] FIG. 12 depicts dose-response curves for acute myeloid leukemia cells treated with Compound A.

[0525] FIG. 13 depicts dose-response curves for B-cell acute lymphoblastic leukemia cells treated with Compound A.

DETAILED DESCRIPTION OF THE INVENTION

[0526] The present invention provides compositions and methods useful for treating hematological malignancies and Ewing's sarcoma. In one aspect, the present invention 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. 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.

isocitrate dehydrogenase 2 (IDH2) gene, or mixed lineage leukemia (MLL) gene amplification. In one aspect, the present invention 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. In some embodiments, the subject exhibits a partial tandem duplication of MLL (MLL-PTD). A subject method typically involves administering to a subject in need thereof a menin inhibitor. In some embodiments, the menin inhibitor administered for treating the hematological malignancy is a compound of Formula (I-A) or a compound of Formula (I-B). In some embodiments, the menin inhibitor administered for treating the hematological malignancy is a compound of Formula (II). In some embodiments, the menin inhibitor administered for treating the hematological malignancy is a compound of Formula (III). In some embodiments, the menin inhibitor administered for treating the hematological malignancy is a compound of Formula (IV). In some embodiments, the menin inhibitor administered for treating the hematological malignancy is a compound of Formula (VI).

[0527] In a separate aspect, the present invention provides a method of treating Ewing's sarcoma, by administering to a subject in need thereof a menin inhibitor. In some embodiments, the menin inhibitor administered for treating Ewing's sarcoma is a compound of Formula (I-A) or a compound of Formula (I-B). In some embodiments, the menin inhibitor administered for treating Ewing's sarcoma is a compound of Formula (II). In some embodiments, the menin inhibitor administered for treating Ewing's sarcoma is a compound of Formula (III). In some embodiments, the menin inhibitor administered for treating Ewing's sarcoma is a compound of Formula (IV). In some embodiments, the menin inhibitor administered for treating Ewing's sarcoma is a compound of Formula (VI).

[0528] 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.

[0529] 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.

[0530] 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.

[0531] 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, CAT G, CCTG, CGTG, CAGA, CTTG, and TATG). In some cases, the insertion is of nine bases (e.g., CTCTTGCCCC and CCCTGGAGA). In some cases, the mutation in the nucleophosmin (NPM1) gene comprises a deletion of nucleotides 965 through 969 (GGAGG).

[0532] 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.

[0533] 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.

[0534] 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.

[0535] 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.

[0536] 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 DNMT3A mutation. In some cases, the subject exhibits an NPM1 mutation and a FLT3 mutation.

[0537] 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 rearrangement. The subject may exhibit MLL partial tandem duplications.

[0538] 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.

[0539] The subject may exhibit elevated myeloid ectopic 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 collectively 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.

[0540] The present disclosure provides compounds for modulating the interaction of menin with proteins such as MLL1 and 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 M-LL1, MLL2, MLL fusion proteins, and menin, such as hematological malignancies and Ewing's sarcoma. In some cases, the hematological malignancy 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, and/or mixed lineage leukemia (MLL) gene amplification. 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.

[0541] In some aspects, the present disclosure provides a compound or salt thereof 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.

[0542] 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.

[0543] "Nucleoporin 98 (NUP98) gene fusion" refers to a gene which encodes a protein with an N-terminal fragment of NUP98 fused with a partner protein. "Nucleoporin 98 (NUP98) fusion protein" refers to a protein with an N-terminal fragment of NUP98 fused with a partner protein. Non-limiting examples of a partner protein include 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. NUP98 fusion proteins may be created through the joining of a gene that codes for NUP98 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.

[0544] "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, TOP3 A, 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.

[0545] 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.

[0546] "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.

[0547] "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 heteraryl. 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.

[0548] "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 ($4n+2$) 7r-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, benzoxazolyl, 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-1H-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, quinoliny, 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. thiényl). 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.

[0549] 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.

[0550] 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 ^1H (protium), ^2H (deuterium), and ^3H (tritium). Protium is the most abundant isotope of hydrogen in nature.

[0551] 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.

[0552] "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 "(\pm)" 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.

[0553] 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.

[0554] 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.

[0555] 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 alkoxy carbonyl, a formyl, or an acyl), a thio-carbonyl (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 sulphydryl, 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 ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-OC(O)-N(R^a)R^t$ (where t is 1 or 2), $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-S(O)R^a$ (where t is 1 or 2), $-R^b-S(O)OR^a$ (where t is 1 or 2), and $-R^b-S(O)N(R^a)_2$ (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 ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)R^a$ (where t is 1 or 2), $-R^b-S(O)R^a$ (where t is 1 or 2), $-R^b-S(O)OR^a$ (where t is 1 or 2) and $-R^b-S(O)N(R^a)_2$ (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 ($=N-NH_2$), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)R^a$, $-R^b-N(R^a)S(O)OR^a$ (where t is 1 or 2), $-R^b-S(O)R^a$ (where t is 1 or 2), $-R^b-S(O)OR^a$ (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.

[0556] 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 substi-

tuted variants. For example, reference to a "heteroaryl" group or moiety implicitly includes both substituted and unsubstituted variants.

[0557] 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 $-OCH_2-$.

[0558] 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, 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.

[0559] 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.

[0560] 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. [0561] 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.

[0562] 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.

[0563] 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, MHLL2, 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.

[0564] 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.

[0565] “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.

[0566] 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 subject by various methods, including intravenous, oral, intramuscular, intrap-

eritoneal, intravesical, subcutaneous, transdermal, buccal, or inhalation or in the form of a suppository.

[0567] “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.

[0568] “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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI)). 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.

[0569] The term “*in vivo*” refers to an event that takes place in a subject’s body.

[0570] 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.

[0571] “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.

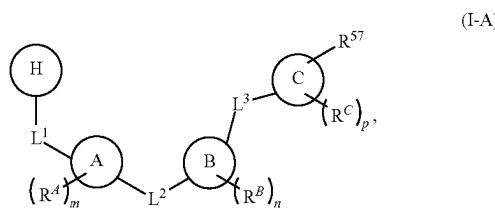
[0572] “Pharmaceutically acceptable carrier, diluent or excipient” includes without limitation any adjuvant, carrier,

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.

[0573] 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, such as hematological malignancies or Ewing's sarcoma. 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.

[0574] 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.

[0575] In certain aspects, the present disclosure provides a compound of Formula (I-A):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0576] H is selected from C₅₋₁₂ carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R⁵⁰;

[0577] A is selected from bond, C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0578] B is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0579] C is 3- to 12-membered heterocycle;

[0580] L¹, L² and L³ are each independently selected from bond, —O—, —S—, —N(R⁵¹)—, —N(R⁵¹)CH₂—, —C(O)—, —C(O)O—, —OC(O)—, —OC(O)O—, —C(O)N(R⁵¹)—, —C(O)N(R⁵¹)C(O)—, —C(O)N(R⁵¹)C(O)N(R⁵¹)—, —N(R⁵¹)C(O)—, —N(R⁵¹)C(O)N(R⁵¹)—, —N(R⁵¹)C(O)O—, —OC(O)N(R⁵¹)—, —C(NR⁵¹)—, —N(R⁵¹)C(NR⁵¹)—, —C(NR⁵¹)N(R⁵¹)—, —N(R⁵¹)C(NR⁵¹)N(R⁵¹)—, —S(O)₂—,

—OS(O)—, —S(O)O—, —S(O)—, —OS(O)₂—, —S(O)₂O—, —N(R⁵¹)S(O)₂—, —S(O)₂N(R⁵¹)—, —N(R⁵¹)S(O)—, —S(O)N(R⁵¹)—, —N(R⁵¹)S(O)₂N(R⁵¹)—, —N(R⁵¹)S(O)N(R⁵¹)—; alkylene, alkynylene, alkynylene, heteroalkynylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R⁵⁰, wherein two R⁵⁰ groups attached to the same atom or different atoms of any one of L¹, L² or L³ can together optionally form a bridge or ring;

[0581] R^A, R^B and R^C are each independently selected at each occurrence from R⁵⁰, or two R^A groups, 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;

[0582] m, n and p are each independently an integer from 0 to 6;

[0583] R⁵⁰ is independently selected at each occurrence from:

[0584] halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²);

[0585] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)R⁵², —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

[0586] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0587] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)R⁵², —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²)

(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0588] R⁵¹ is independently selected at each occurrence from:

[0589] hydrogen, —C(O)R⁵², —C(O)OR⁵², —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴;

[0590] C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)NR⁵³R⁵⁴, —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

[0591] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0592] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0593] R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, =O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle;

[0594] R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R⁵⁰;

[0595] R⁵⁷ is selected from:

[0596] halogen, —NO₂, —CN, —SR⁵², —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵⁸, —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)NH(C₁₋₆ alkyl), —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)

(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =S, =N(R⁵²); and

[0597] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from —NO₂, —CN, —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)NR⁵², —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²), —P(O)(NR⁵²)₂, =S, and =N(R⁵²); and

[0598] R⁵⁸ is selected from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, =O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle,

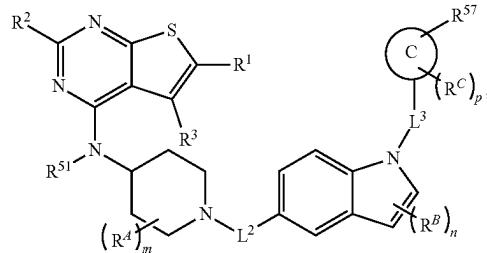
[0599] wherein for a compound or salt of Formula (I-A), when C is azetidinylene, piperidinylene or piperaazinylene and R⁵⁷ is —S(=O)₂R⁵⁸, —S(=O)₂N(R⁵²)₂, or —NR⁵²S(=O)R⁵².

[0600] p is an integer from 1 to 6; and/or

[0601] L³ is substituted with one or more R⁵⁰, wherein L³ is not —CH₂CH(OH)—.

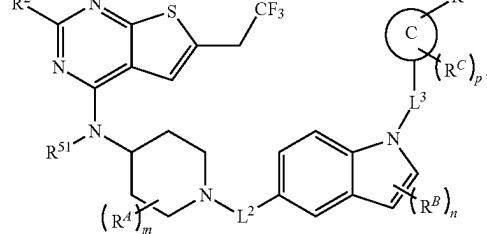
[0602] In certain aspects, a compound of Formula (I-A) may be represented by:

(I-A-1)



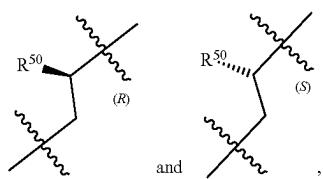
such as

(I-A-2)

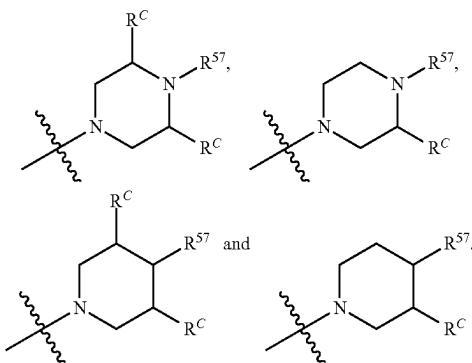


wherein R¹, R² and R³ are each independently selected at each occurrence from hydrogen and R⁵⁰. In some embodiments, R¹ is selected from R⁵⁰. In some embodiments, R¹ is

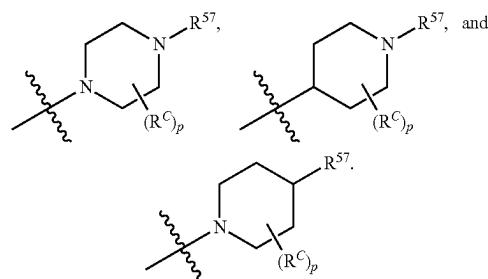
C_{1-3} haloalkyl, such as $—CH_2CF_3$. In some embodiments, R^2 is selected from R^{50} . In some embodiments, R^2 is selected from hydrogen, halogen, $—OH$, $—OR^{52}$, $—NH_2$, $—N(R^{52})_2$, $—CN$, C_{1-3} alkyl, C_{1-3} alkyl- OR^{52} , C_{1-3} alkyl- $N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, 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^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, R^{51} is selected from selected from hydrogen and alkyl, such as R^{51} is hydrogen. In some embodiments, R^4 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, m is 0. 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, n is an integer from 1 to 4, such as an integer from 2 to 3. In some embodiments, n is 2. In some embodiments, L^3 is selected from C_{1-6} alkylene, C_{2-6} alkylene, 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



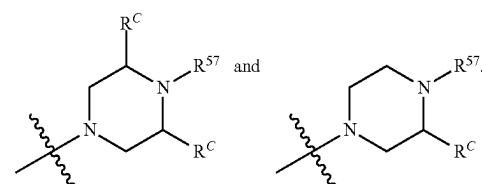
where R^{50} is optionally methyl. In some embodiments, C is 3- to 12-membered heterocycle, such as 5- to 12-membered heterocycle. In some embodiments, the heterocycle is saturated. In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, 8- to 10-membered fused bicyclic heterocycle, 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



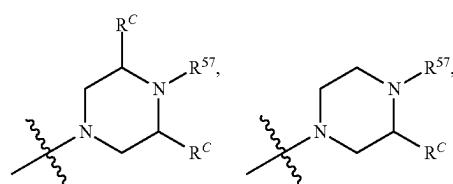
In some embodiments, C is selected from



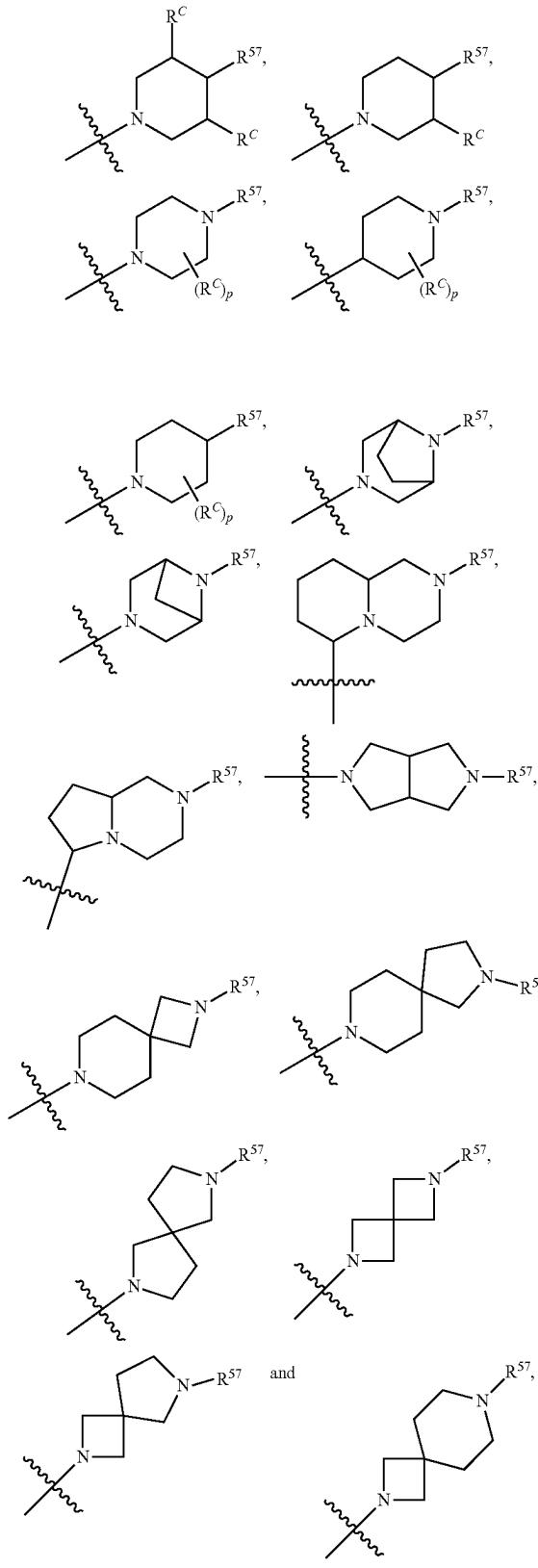
In some embodiments, C is selected from



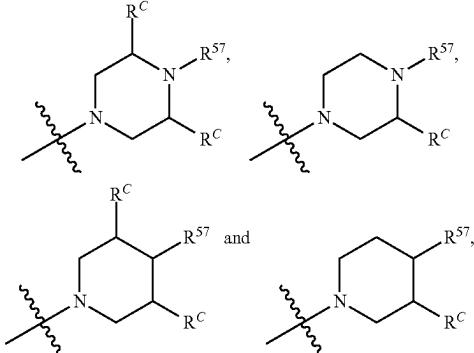
In some embodiments, C is selected from



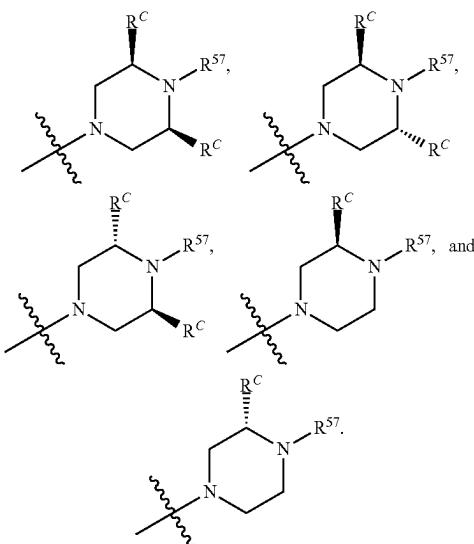
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optionally substituted with one or more R^C . In some embodiments, C is selected from

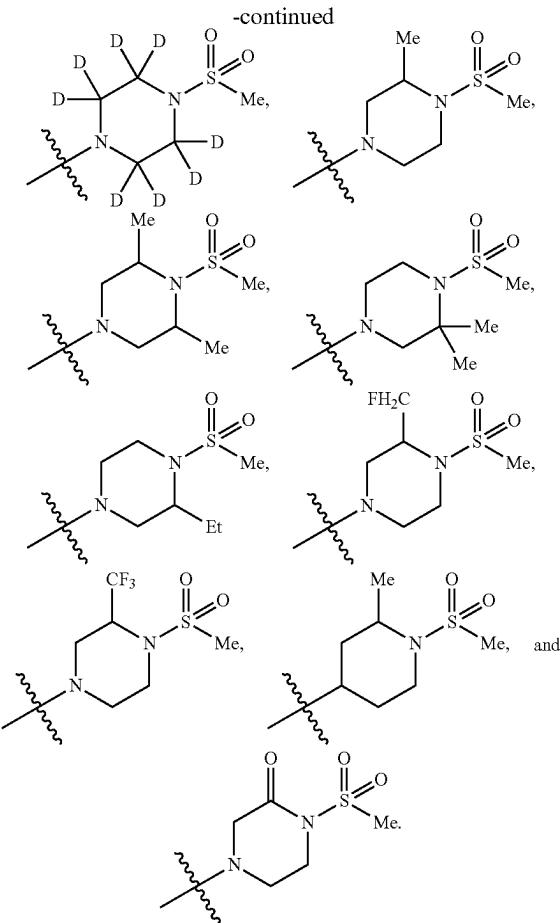
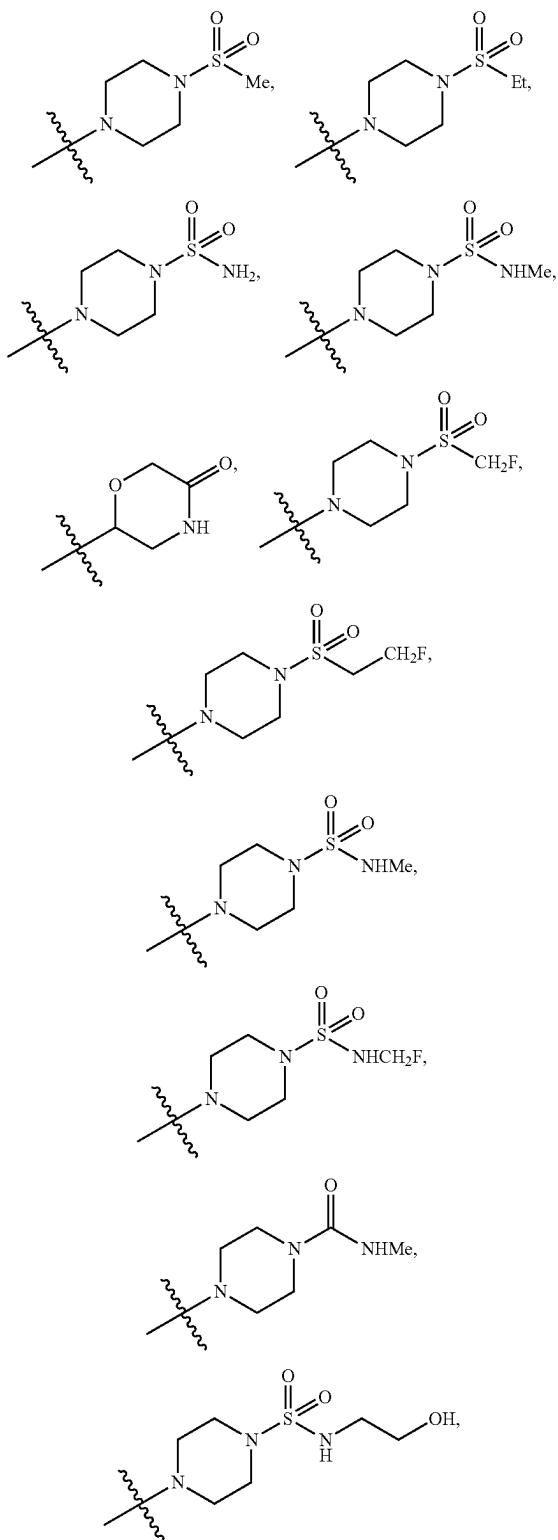


wherein R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$; and C_{1-10} alkyl substituted with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, and $-NR^{52}S(=O)_2R^{52}$.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



In some embodiments, R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, C_{1-6} alkyl, and C_{1-6} alkyl substituted with $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)$

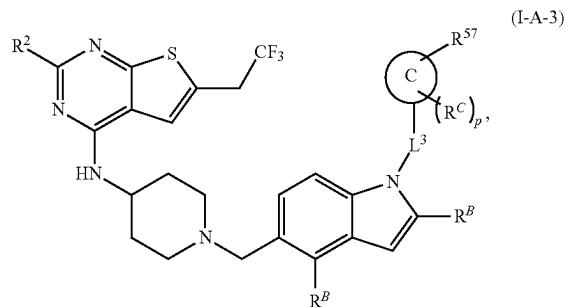
OR^{52} , $-\text{NR}^{52}\text{C(O)N(R}^{52})_2$, $-\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $-\text{C(O)N(R}^{52})_2$ or $-\text{C(O)NR}^{53}\text{R}^{54}$. In some embodiments, C is selected from



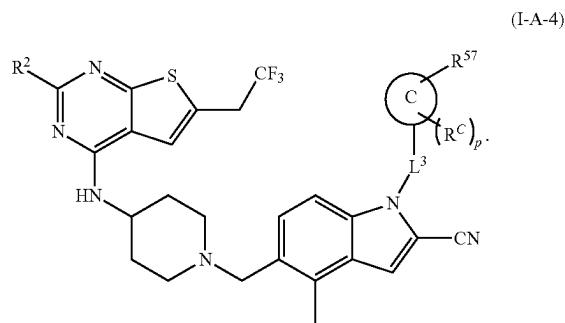
In some embodiments, R^C is selected from $-\text{C(O)R}^{52}$, $-\text{S(=O)R}^{52}$, $-\text{S(=O)}_2\text{R}^{52}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $=\text{O}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, or 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 $-\text{CH}_3$. 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 $-\text{S(=O)}_2\text{R}^{58}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $-\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $-\text{C(O)NH(C}_{1-6}\text{ alkyl)}$, $-\text{C(O)NR}^{53}\text{R}^{54}$; 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 $-\text{S(=O)}_2\text{R}^{58}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $-\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $-\text{C(O)NH(C}_{1-6}\text{ alkyl)}$, $-\text{C(O)NR}^{53}\text{R}^{54}$. In some embodiments, R^{57} is selected from $-\text{S(=O)}_2\text{R}^{58}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $-\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, and C_{1-6} alkyl substituted with one or more substituents selected from $-\text{S(=O)}_2\text{R}^{58}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $-\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$, and $-\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$. In some embodiments, R^{57} is selected from $-\text{S(=O)}\text{R}^{52}$, $-\text{S(=O)}_2\text{R}^{58}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, and $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$. In some embodiments, R^{57} is selected

from $-\text{S}(=\text{O})\text{CH}_3$, $-\text{S}(=\text{O})_2\text{CH}_3$, $-\text{S}(=\text{O})_2\text{NH}_2$, $-\text{NHS}(=\text{O})_2\text{CH}_3$, and $-\text{S}(=\text{O})_2\text{NHCH}_3$.

[0603] In certain aspects, a compound of Formula (I-A) may be represented by:

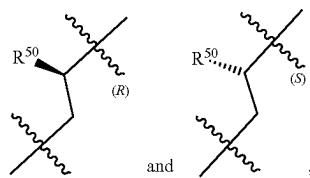


such as

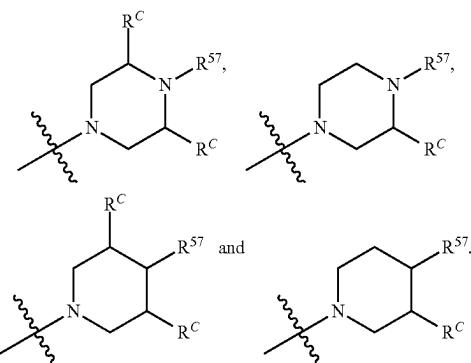


In some embodiments, R^2 is selected from R^{50} . In some embodiments, R^2 is selected from hydrogen, halogen, $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, C_{1-3} alkyl, C_{1-3} alkyl- OR^{52} , C_{1-3} alkyl- $\text{N}(\text{R}^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, R^2 is selected from halogen, $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, C_{1-3} alkyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OR}^{52}$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(\text{R}^{52})_2$, C_{1-3} alkyl- $\text{N}(\text{R}^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, and C_{1-2} alkyl. Optionally, R^2 is selected from $-\text{NH}_2$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{NHCH}_3$. In some embodiments, R^B is selected from halogen, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $=\text{O}$, 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, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, C_{1-3} alkyl, and optionally substituted C_{1-3} alkyl, such as R^B is selected from halogen, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, 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

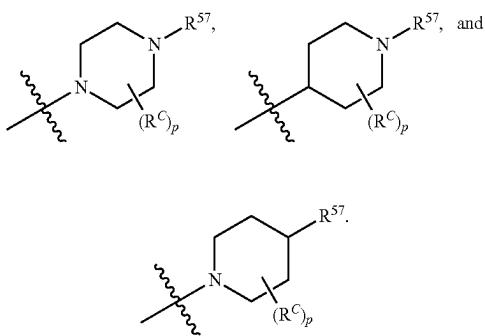
least one C_{1-3} alkyl or C_{1-3} haloalkyl, and optionally further substituted with one or more R^{50} . In some embodiments, L^3 is substituted with $=\text{O}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-3} alkyl(cyclopropyl), C_{1-3} alkyl($\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$) or $-\text{O}(\text{C}_{1-6}$ alkyl). In some embodiments, L^3 is substituted with $-\text{CH}_3$. In some embodiments, L^3 is selected from



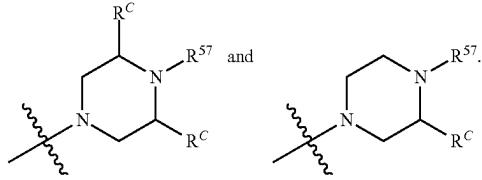
where R^{50} is optionally methyl. In some embodiments, C is 3- to 12-membered heterocycle, such as 5- to 12-membered heterocycle. In some embodiments, the heterocycle is saturated. In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, 8- to 10-membered fused bicyclic heterocycle, 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



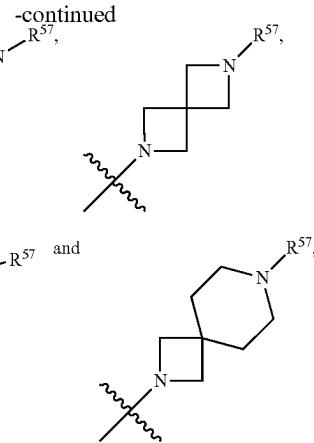
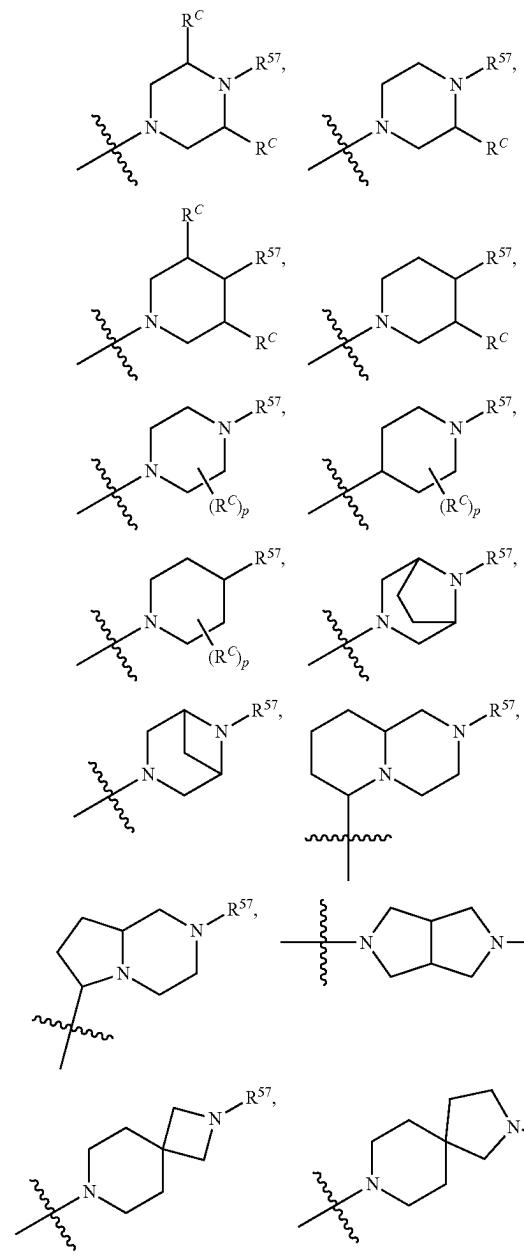
In some embodiments, C is selected from



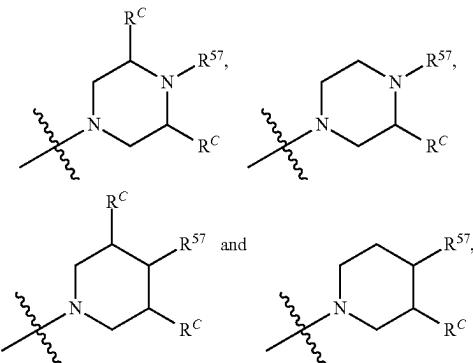
In some embodiments, C is selected from



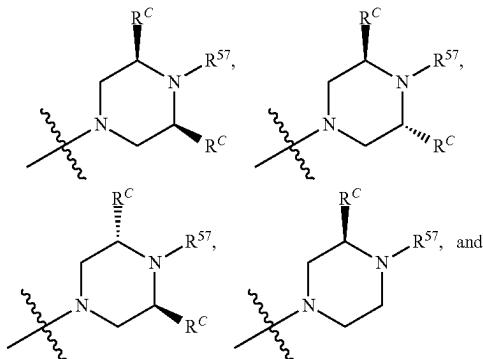
In some embodiments, C is selected from



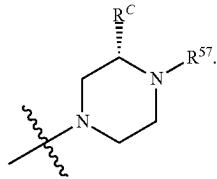
optionally substituted with one or more R^C. In some embodiments, C is selected from



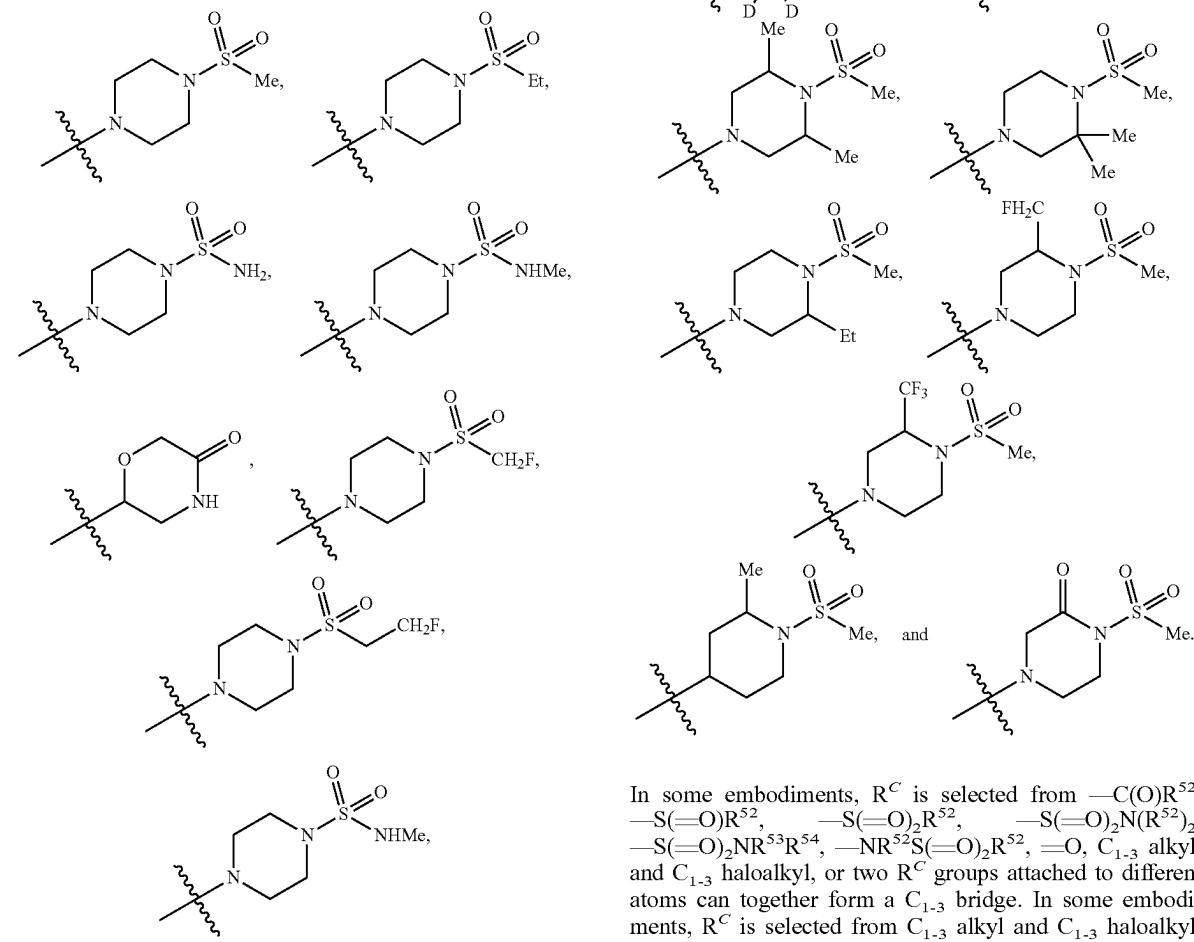
wherein R⁵⁷ is selected from —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R²; and C₁₋₁₀ alkyl substituted with one or more substituents selected from —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, and —NR⁵²S(=O)R⁵². In some embodiments, R⁵⁷ is selected from —S(=O)R⁵², —S(=O)₂R³⁸, —S(=O)N(R⁵²)₂, and —NR⁵²S(=O)R⁵², such as R⁵⁷ is selected from —S(=O)CH₃, —S(=O)₂CH₃, —S(=O)₂NH₂, —NHS(=O)₂CH₃, and —S(=O)₂NHCH₃. In some embodiments, C is selected from



-continued



In some embodiments, R^C is selected from —N(R²)₂, —NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —C(O)R⁵², —C(O)OR², —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, and —C(O)NR⁵³R⁵⁴. In some embodiments, R^C is selected from —N(R⁵²)₂, —NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —C(O)R⁵², —C(O)OR⁵², —NR⁵²C(O)R⁵², R⁵²C(O)R⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR³³R³⁴, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted with —N(R⁵²)₂, —NR³R⁴, —NR⁵²S(=O)₂R⁵², —C(O)R⁵², —C(O)OR⁵², —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, or —C(O)NR⁵³R⁵⁴. In some embodiments, C is selected from

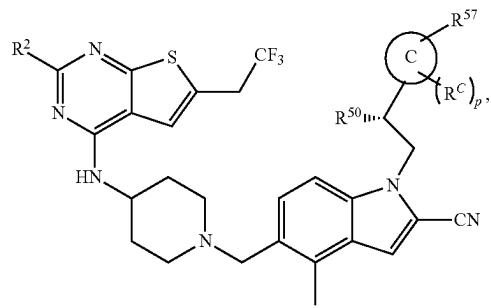


In some embodiments, R^C is selected from —C(O)R⁵², —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², ==O, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, or two R^C groups attached to different atoms can together form a C₁₋₃ bridge. In some embodiments, R^C is selected from C₁₋₃ alkyl and C₁₋₃ haloalkyl, such as —CH₃. 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, R⁵⁷ is selected from —S(=O)₂R⁵⁸, —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)OR⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)NH(C₁₋₆ alkyl), —C(O)NR⁵³R⁵⁴; and C₁₋₆ alkyl and C₂₋₆ alkenyl, each of which is independently substituted at each occurrence with one or more substituents selected from —S(=O)OR⁵⁸, —S(=O)OR⁵²₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)OR⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)NH(C₁₋₆ alkyl), —C(O)NR⁵³R⁵⁴. In some embodiments, R⁵⁷ is selected from —S(=O)OR⁵⁸, —S(=O)N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)OR⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, and C₁₋₆ alkyl substituted with one or more substituents selected from —S(=O)OR⁵⁸, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)OR⁵², —NR⁵²S(=O)N(R⁵²)₂, and —NR⁵²S(=O)NR⁵³R⁵⁴. In some embodiments, R⁵⁷ is selected from —S(=O)OR⁵², —S(=O)OR⁵⁸, —S(=O)N(R⁵²)₂, and —NR⁵²S(=O)OR⁵². In some embodiments, R⁵⁷ is selected from —S(=O)CH₃, —S(=O)CH₃, —S(=O)NH₂, —NHS(=O)CH₃, and —S(=O)NHCH₃.

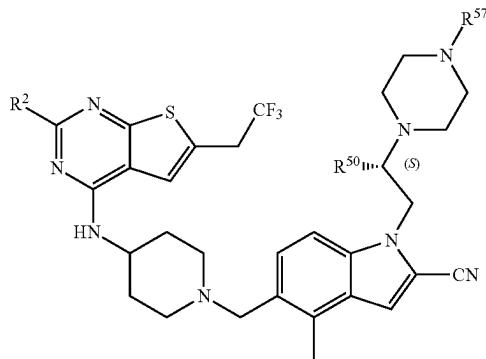
[0604] In certain aspects, a compound of Formula (I-A) may be represented by:

(I-A-5)



such as

(I-A-6)

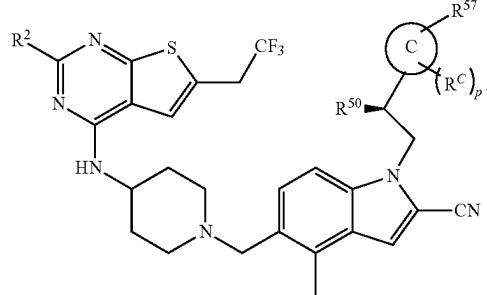


In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, such as piperidinyl and piperazinyl. In some embodiments, R⁵⁰ is selected from deuterium, C₁₋₄ alkyl, C₁₋₄ haloalkyl, and —OR⁵², such as R⁵⁰ is methyl. In some embodiments, R⁵⁷ is selected from —S(=O)R⁵²,

—S(=O)₂R⁵⁸, —S(=O)₂N(R⁵²)₂, and —NR⁵²S(=O)R⁵², such as R⁵⁷ is selected from —S(=O)CH₃, —S(=O)CH₂CH₃, —S(=O)NH₂, —NHS(=O)CH₃, and —S(=O)NHCH₃. In some embodiments, R⁵⁷ is —S(=O)CH₃. In some embodiments, R⁵⁰ is methyl and R⁵⁷ is —S(=O)CH₂CH₃. In some embodiments, R² is selected from hydrogen, halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, —CH₂OH, —CH₂OR⁵², —CH₂NH₂, —CH₂N(R⁵²)₂, C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl, such as R² is selected from —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, and C₁₋₂ alkyl. In some embodiments, R² is methyl or —NHCH₃. In some embodiments, R² is H.

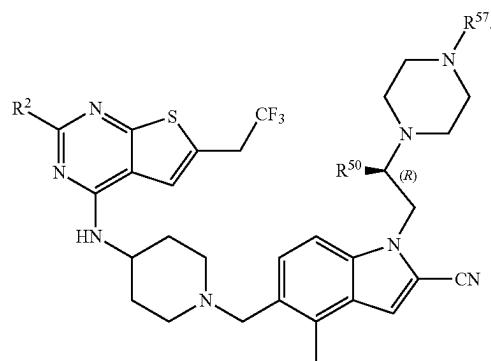
[0605] In certain aspects, a compound of Formula (I-A) may be represented by:

(I-A-7)



such as

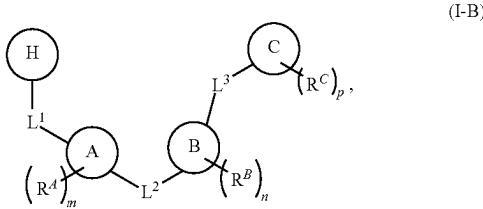
(I-A-8)



In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, such as piperidinyl and piperazinyl. In some embodiments, R⁵⁰ is selected from deuterium, C₁₋₄ alkyl, C₁₋₄ haloalkyl, and —OR⁵², such as R⁵⁰ is methyl. In some embodiments, R⁵⁷ is selected from —S(=O)R⁵², —S(=O)OR⁵⁸, —S(=O)N(R⁵²)₂, and —NR⁵²S(=O)R⁵², such as R⁵⁷ is selected from —S(=O)CH₃, —S(=O)CH₂CH₃, —S(=O)NH₂, —NHS(=O)CH₃, and —S(=O)NHCH₃. In some embodiments, R⁵⁷ is —S(=O)CH₃. In some embodiments, R⁵⁰ is methyl and R⁵⁷ is —S(=O)CH₂CH₃. In some embodiments, R² is selected from hydrogen, halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, —CH₂OH, —CH₂OR⁵², —CH₂NH₂, —CH₂N(R⁵²)₂, C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl, such as R² is selected from —OH, —OR⁵², —NH₂,

$-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, and C_{1-2} alkyl. In some embodiments, R^2 is methyl or $-\text{NHCH}_3$. In some embodiments, R^2 is H.

[0606] In certain aspects, the present disclosure provides a compound of Formula (I-B):



or a pharmaceutically acceptable salt thereof, wherein:

[0607] H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0608] A, B and C are each independently selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0609] L^1 and L^2 are each independently selected from bond, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{C}(\text{NR}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})-$, $-\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C}(\text{NR}^{51})\text{N}(\text{R}^{51})-$, $-\text{S}(\text{O})_2-$, $-\text{OS}(\text{O})-$, $-\text{S}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})-$, $-\text{S}(\text{O})\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})_2\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{S}(\text{O})\text{N}(\text{R}^{51})-$; alkylene, alkynylene, alkynylene, heteroalkynylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R^{50} ;

[0610] L^3 is selected from alkylene, alkenylene, and alkynylene, each of which is substituted with one or more R^{56} and optionally further substituted with one or more R^{50} .

[0611] R^4 , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^4 groups, 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;

[0612] m, n and p are each independently an integer from 0 to 6;

[0613] R^{50} is independently selected at each occurrence from:

[0614] halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$;

[0615] 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 substitu-

ents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0616] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0617] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{2-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0618] R^{51} is independently selected at each occurrence from:

[0619] hydrogen, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$;

[0620] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

[0621] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0622] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})\text{R}^{52}$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{NR}^{52})\text{R}^{52}$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

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

[0623] R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, =O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle;

[0624] 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} ;

[0625] R⁵⁶ is independently selected at each occurrence from:

[0626] —NO₂, —OR⁵⁹, —SR⁵², —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0627] wherein each C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl in R^{56} is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $—NO_2$, $—CN$, $—OR^{59}$, $—SR^{52}$, $—N(R^{52})_2$, $—NR^{53}R^{54}$, $—S(=O)R^{52}$, $—S(=O)R^{52}_2$, $—S(=O)_2R^{52}$, $—S(=O)_2N(R^{52})_2$, $—S(=O)_2N(R^{52})R^{54}$, $—NR^{53}R^{54}$, $—NR^{52}S(=O)R^{52}$, $—NR^{52}S(=O)_2N(R^{52})_2$, $—NR^{52}S(=O)_2N(R^{52})R^{54}$, $—C(O)R^{52}$, $—C(O)R^{52}_2$, $—OC(O)R^{52}$, $—OC(O)R^{52}_2$, $—OC(O)NR^{53}R^{54}$, $—NR^{52}C(O)R^{52}$, $—NR^{52}C(O)R^{52}_2$, $—NR^{52}C(O)NR^{53}R^{54}$, $—C(O)N(R^{52})_2$, $—C(O)NR^{53}R^{54}$, $—P(O)(OR^{52})_2$, $—P(O)(R^{52})_2$, $—P(O)(OR^{52})(R^{52})_2$, $—P(O)(NR^{52})(R^{52})_2$, $—NR^{52}P(O)(R^{52})_2$, $—P(O)(NR^{52})_2$, $—P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})_2$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

[0628] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁶ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C

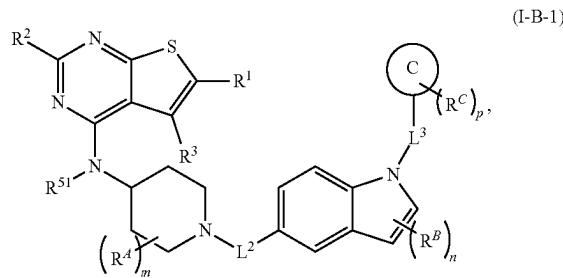
(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl; and

[0629] further wherein R⁵⁶ optionally forms a bond to ring C; and

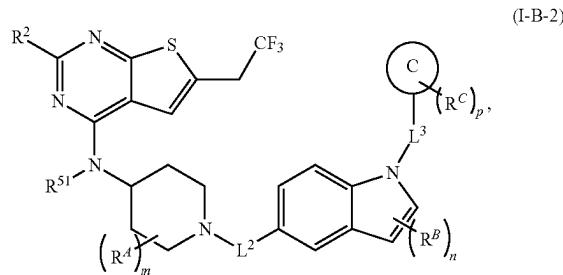
[0630] R⁵⁹ is independently selected at each occurrence from C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, =O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle,

[0631] wherein for a compound or salt of Formula (I-B), when R^{56} is $-CH_3$, L^3 is not further substituted with $-OH$, $-NH_2$, or $-CN$.

[0632] In certain aspects, a compound of Formula (I-B) may be represented by:

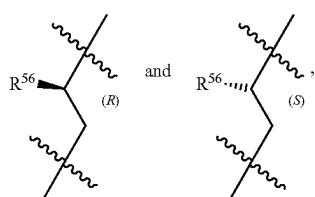


such as

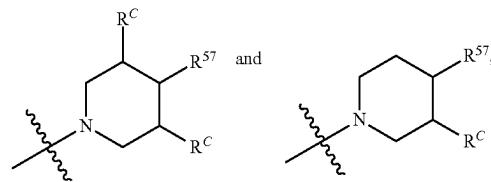
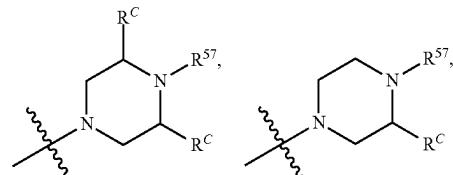


wherein R¹, R² and R³ are each independently selected at each occurrence from hydrogen and R⁵⁰. In some embodiments, R¹ is selected from R⁵⁰. In some embodiments, R¹ is C₁₋₃ haloalkyl, such as —CH₂CF₃. In some embodiments, R² is selected from R⁵⁰. In some embodiments, R² is selected from hydrogen, halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, C₁₋₃ alkyl-OR⁵², C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl. In some embodiments, R² is selected from halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, —CH₂OH, —CH₂OR⁵², —CH₂NH₂, —CH₂N(R⁵²)₂, C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl, such as R² is selected from —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, and C₁₋₂ alkyl. Optionally, R² is selected from —NH₂,

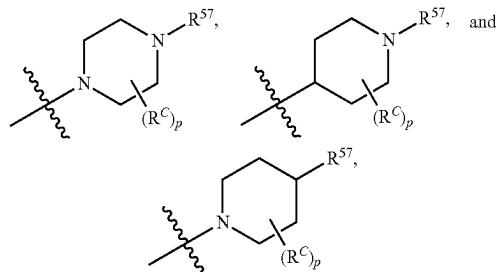
$-\text{CH}_3$, $-\text{OCH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{NHCH}_3$. In some embodiments, R^3 is selected from hydrogen, halogen, $-\text{OH}$, $-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, $-\text{C(O)OR}^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{51} is selected from selected from hydrogen and alkyl, such as R^{51} is hydrogen. In some embodiments, R^4 is selected from halogen, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{C(O)N}(\text{R}^{52})_2$, $-\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{O}$, 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, m is 0. In some embodiments, L^2 is selected from $-\text{O}-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{C(O)N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{C(O)}-$, $-\text{N}(\text{R}^{51})\text{S(O)}_2-$, $-\text{S(O)}_2\text{N}(\text{R}^{51})-$, 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 $-\text{CH}_2-$, $-\text{N}(\text{R}^{51})-$, $-\text{N}(\text{R}^{51})\text{CH}_2-$, $-\text{N}(\text{R}^{51})\text{C(O)}-$, and $-\text{N}(\text{R}^{51})\text{S(O)}_2-$. In some embodiments, L^2 is $-\text{CH}_2-$. 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, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{C(O)N}(\text{R}^{52})_2$, $-\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{O}$, 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, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, C_{1-3} alkyl, and optionally substituted C_{1-3} alkyl, such as R^B is selected from halogen, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, and C_{1-2} alkyl. In some embodiments, n is an integer from 1 to 4, such as an integer from 2 to 3. In some embodiments, n is 2. In some embodiments, L^3 is selected from alkylene, alkenylene, and alkynylene, each of which is substituted with one or more R^{56} and optionally further substituted with one or more R^{50} . 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^{56} and optionally further substituted with one or more R^{50} . In some embodiments, L^3 is selected from C_{1-6} alkylene, which is substituted with one or more R^{56} and optionally further 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 $=\text{O}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-3} alkyl(cyclopropyl), C_{1-3} alkyl($\text{NR}^{52}\text{C(O)R}^{52}$) or $-\text{O}(\text{C}_{1-6}$ alkyl). In some embodiments, L^3 is substituted with $-\text{CH}_3$. In some embodiments, L^3 is selected from



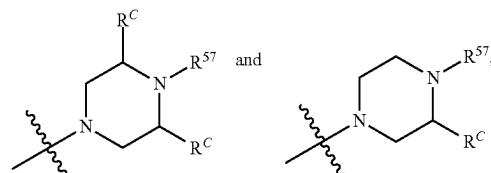
where R^{56} is optionally methyl. In some embodiments, C is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, such as 5- to 12-membered heterocycle. In some embodiments, the heterocycle is saturated. In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, 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



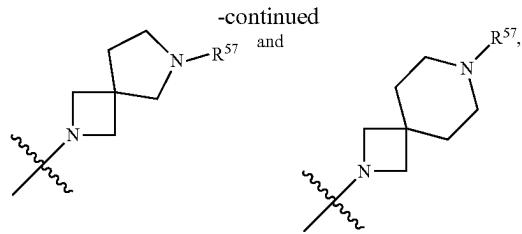
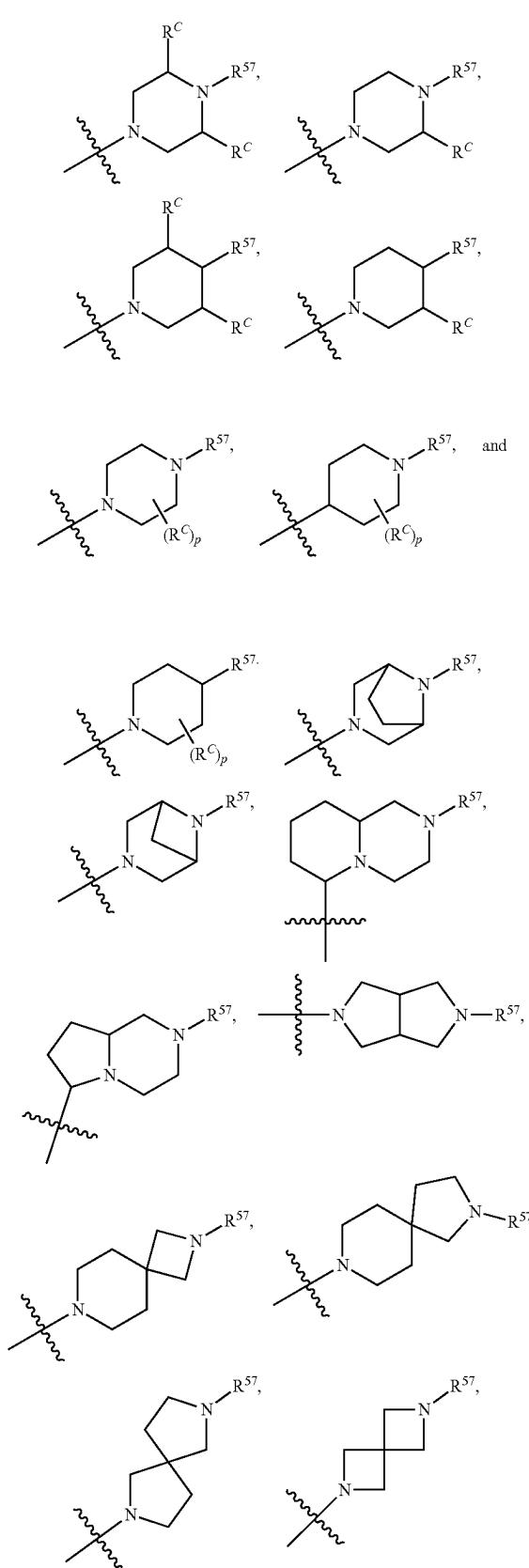
wherein R is selected from hydrogen and R^{50} . In some embodiments, C is selected from



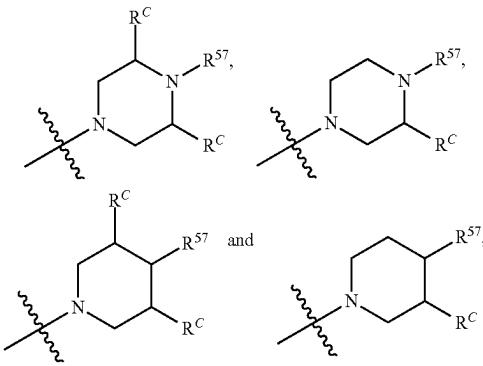
wherein R^{57} is selected from hydrogen and R^{50} . In some embodiments, C is selected from



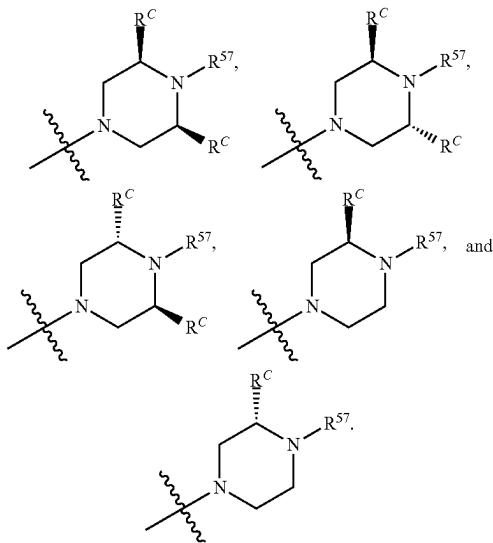
wherein R^{57} is selected from hydrogen and R^{50} . In some embodiments, C is selected from



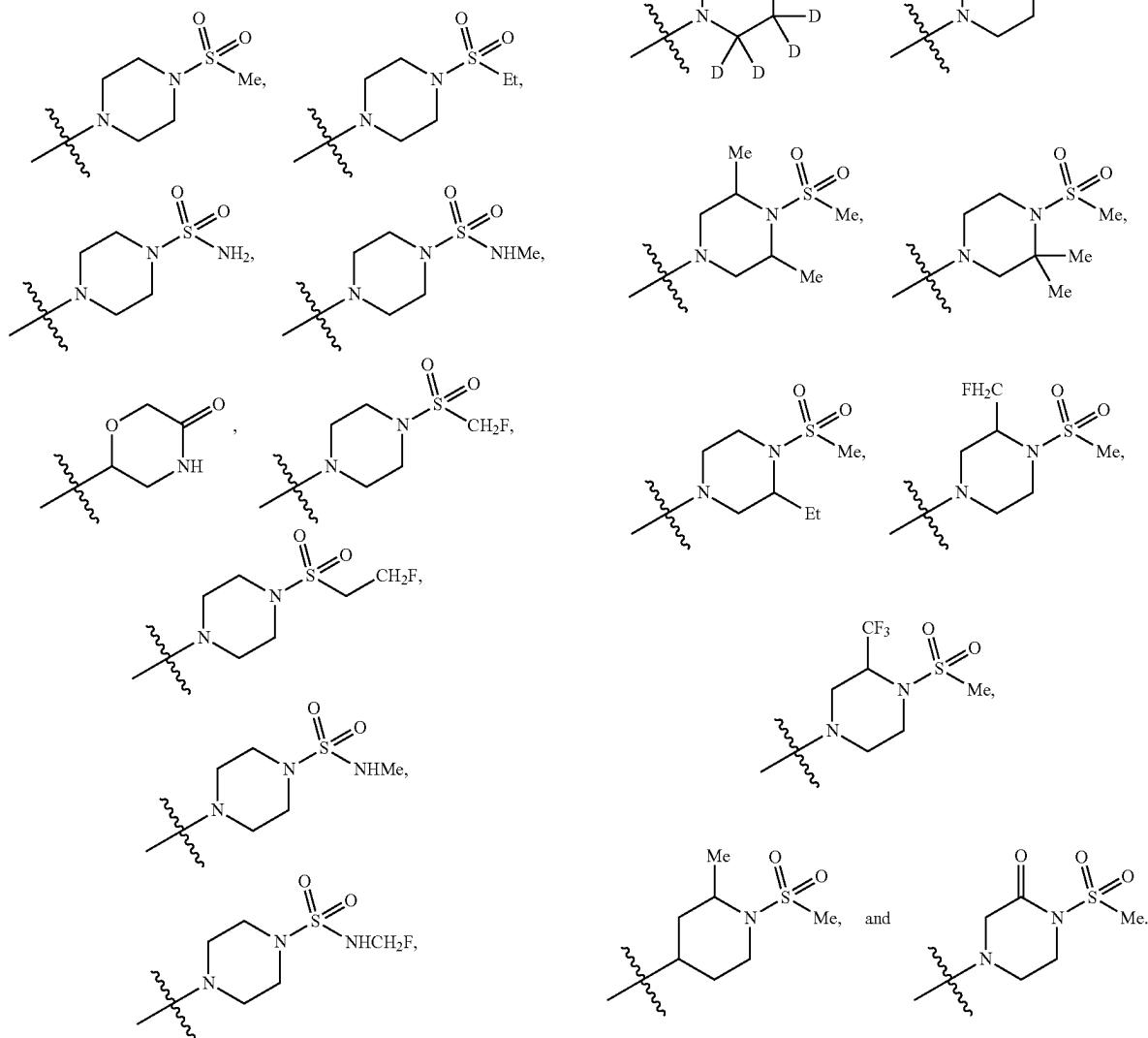
optionally substituted with one or more R^C, wherein R⁵⁷ is selected from hydrogen and R⁵⁰. In some embodiments, C is selected from



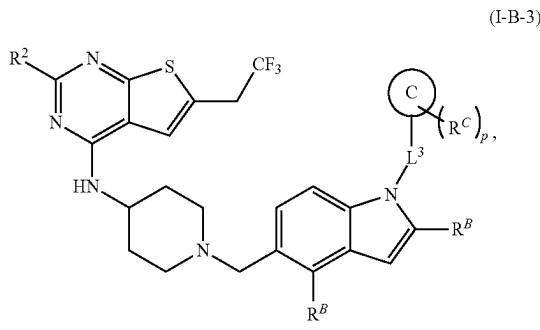
wherein R⁵⁷ is selected from —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵²; and C₁₋₁₀ alkyl substituted with one or more substituents selected from —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, and —NR⁵²S(=O)R⁵². In some embodiments, R⁵⁷ is selected from —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, and —NR⁵²S(=O)R⁵², such as R⁵⁷ is selected from —S(=O)CH₃, —S(=O)₂CH₃, —S(=O)₂NH₂, —NHS(=O)₂CH₃, and —S(=O)₂NHCH₃. In some embodiments, C is selected from



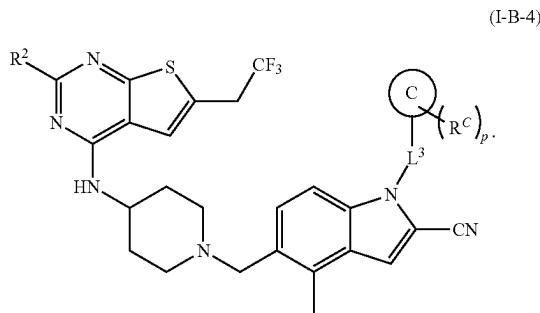
In some embodiments, R^C is selected from $-\text{C}(\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $=\text{O}$, 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 $-\text{CH}_3$. 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^C is selected from $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, and $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$. In some embodiments, R^C is selected from $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, C_{1-6} alkyl, and C_{1-6} alkyl substituted with $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, or $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$. In some embodiments, C is selected from



[0633] In certain aspects, a compound of Formula (I-B) may be represented by:

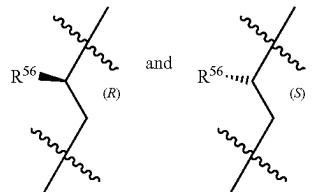


such as

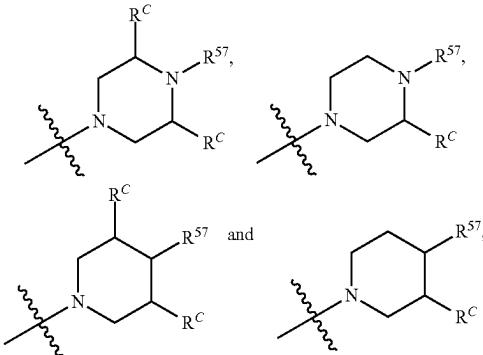


In some embodiments, R^2 is selected from R^{50} . In some embodiments, R^2 is selected from hydrogen, halogen, $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(R^{52})_2$, $-\text{CN}$, C_{1-3} alkyl, C_{1-3} alkyl- OR^{52} , C_{1-3} alkyl- $\text{N}(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, R^2 is selected from halogen, $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(R^{52})_2$, $-\text{CN}$, C_{1-3} alkyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OR}^{52}$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(R^{52})_2$, C_{1-3} alkyl- $\text{N}(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(R^{52})_2$, $-\text{CN}$, and C_{1-2} alkyl. Optionally, R^2 is selected from $-\text{NH}_2$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{NHCH}_3$. In some embodiments, R^B is selected from halogen, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(R^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{C(O)N}(R^{52})_2$, $-\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{O}$, 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, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(R^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, C_{1-3} alkyl, and optionally substituted C_{1-3} alkyl, such as R^B is selected from halogen, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{N}(R^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, and C_{1-2} alkyl. In some embodiments, L^3 is selected from alkylene, alkylene, and alkynylene, each of which is substituted with one or more R^{56} and optionally further substituted with one or more R^{50} . 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^{56} and optionally further substituted with one or more R^{50} . In some embodiments, L^3 is selected from C_{1-6} alkylene, which is substituted with one or more R^{56} and optionally further substituted with

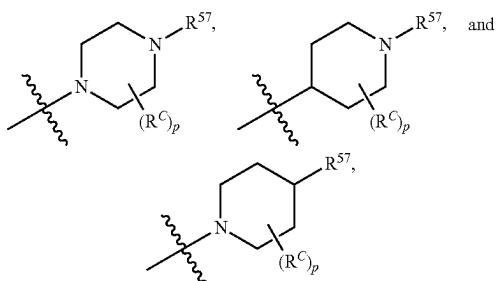
one or more R^{50} . In some embodiments, L^3 is C_2 alkylene substituted with at least one C_{1-3} alkyl or C_{1-3} haloalkyl, and optionally further substituted with one or more R^{50} . In some embodiments, L^3 is substituted with $=\text{O}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-3} alkyl(cyclopropyl), C_{1-3} alkyl($\text{NR}^{52}\text{C(O)R}^{52}$) or $-\text{O}(C_{1-6}$ alkyl). In some embodiments, L^3 is substituted with $-\text{CH}_3$. In some embodiments, L^3 is selected from



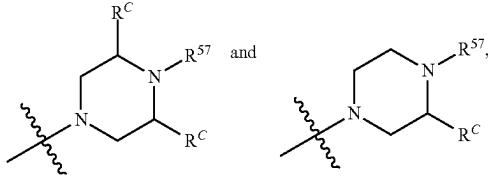
where R^{56} is optionally methyl. In some embodiments, C is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, such as 5- to 12-membered heterocycle. In some embodiments, the heterocycle is saturated. In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, 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



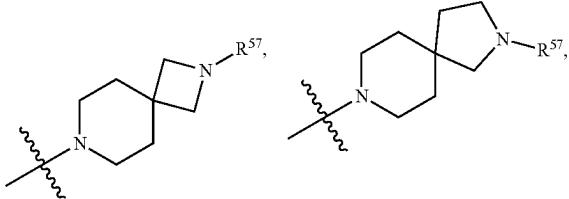
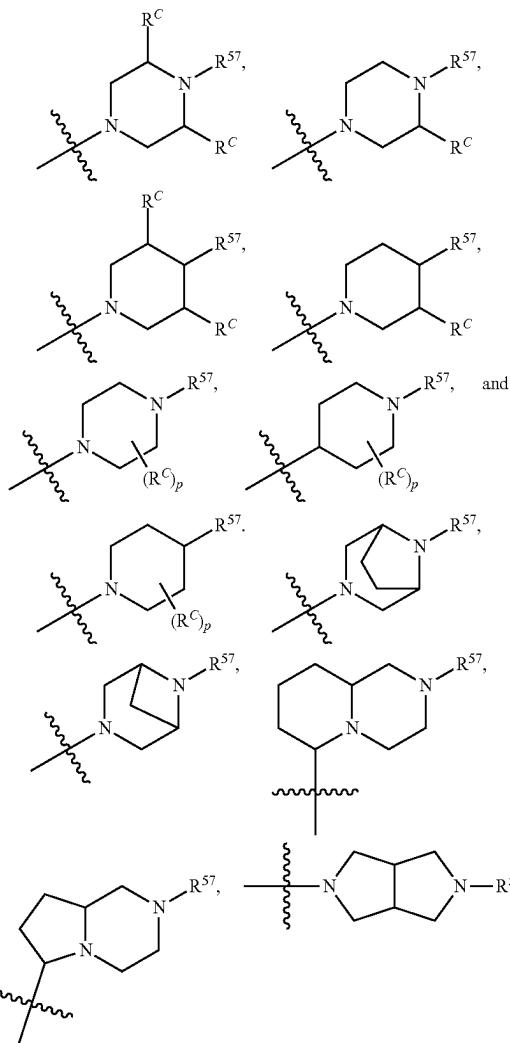
wherein R^{57} is selected from hydrogen and R^{50} . In some embodiments, C is selected from



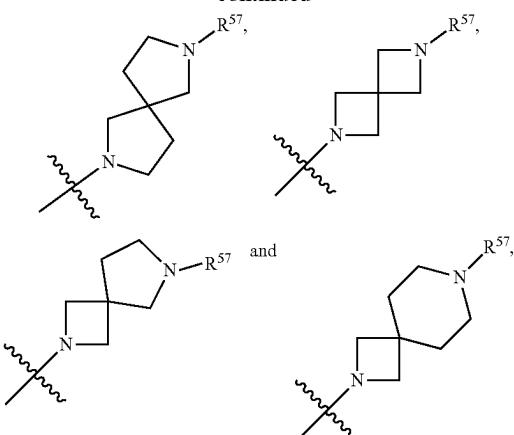
wherein R^{57} is selected from hydrogen and R^{50} . In some embodiments, C is selected from



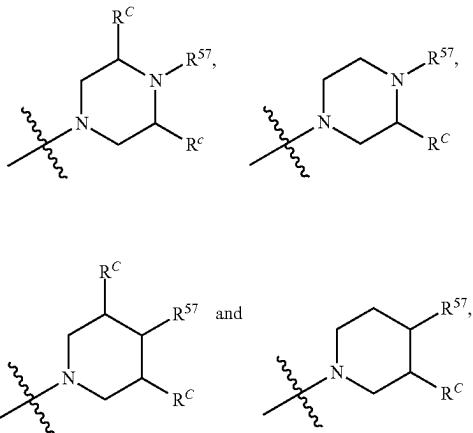
wherein R^{57} is selected from hydrogen and R^{50} . In some embodiments, C is selected from



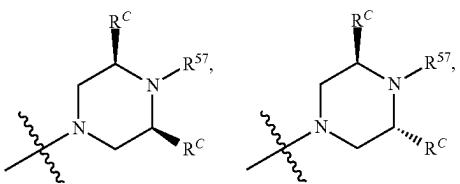
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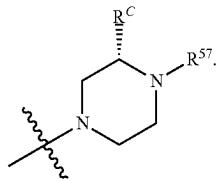
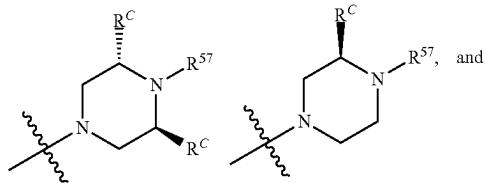
optionally substituted with one or more R^C , wherein R^{57} is selected from hydrogen and R^{50} . In some embodiments, C is selected from



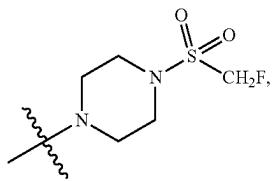
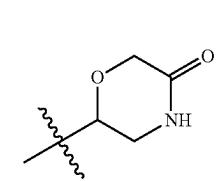
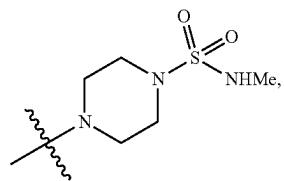
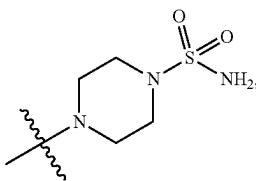
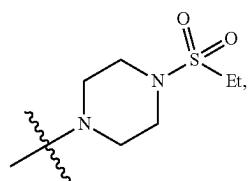
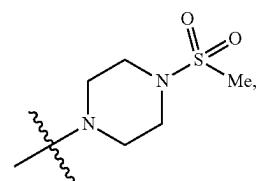
wherein R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$; and C_{1-10} alkyl substituted with one or more substituents selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, and $-NR^{52}S(=O)_2R^{52}$. In some embodiments, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, 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



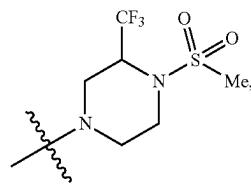
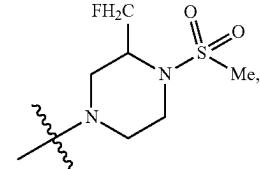
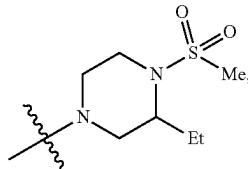
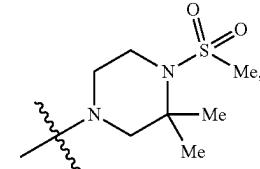
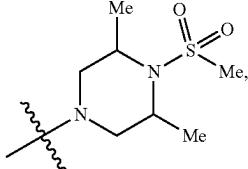
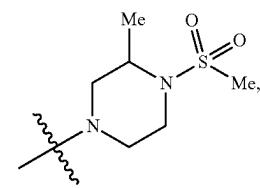
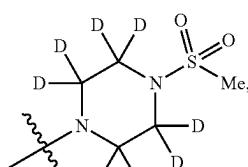
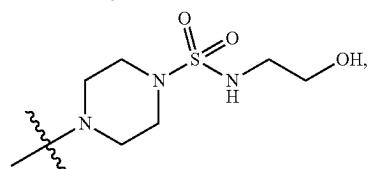
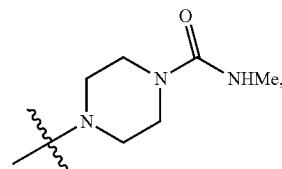
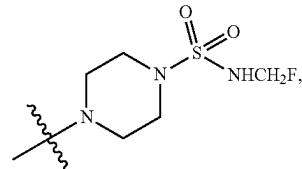
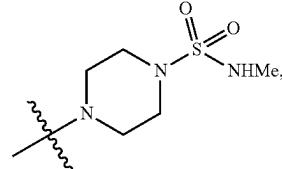
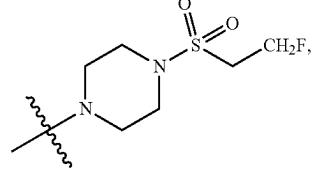
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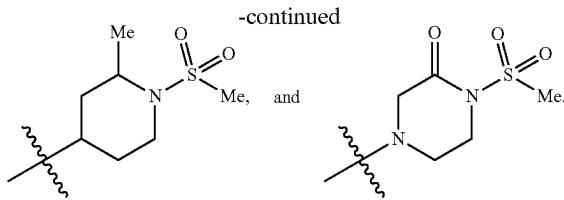


In some embodiments, R^C is selected from —C(O)R⁵², —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —O, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, or two R^C groups attached to different atoms can together form a C₁₋₃ bridge. In some embodiments, R^C is selected from C₁₋₃ alkyl and C₁₋₃ haloalkyl, such as —CH₃. 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^C is selected from —N(R⁵²)₂, —NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —C(O)R⁵², —C(O)OR⁵², —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, and —C(O)NR⁵³R⁵⁴. In some embodiments, R^C is selected from —N(R⁵²)₂, —NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —C(O)R⁵², —C(O)OR⁵², —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, C₁₋₆ alkyl, and C₁₋₆ alkyl substituted with —N(R⁵²)₂, —NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —C(O)R⁵², —C(O)OR⁵², —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, or —C(O)NR⁵³R⁵⁴. In some embodiments, C is selected from

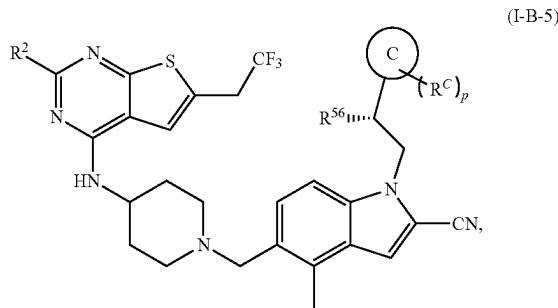


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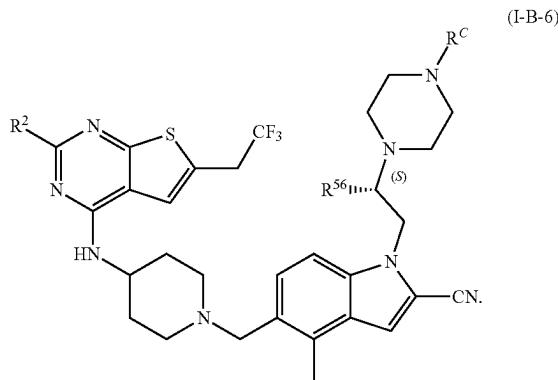




[0634] In certain aspects, a compound of Formula (I-B) may be represented by:



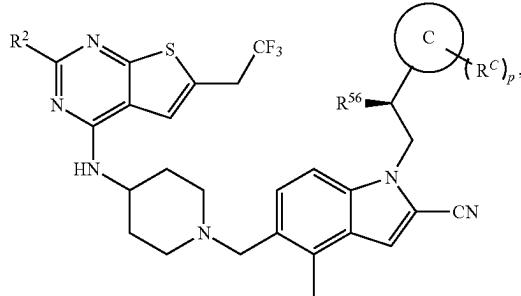
such as



In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, such as piperidinyl and piperazinyl. In some embodiments, R⁵⁶ is selected from deuterium, C₁₋₄ alkyl, C₁₋₄ haloalkyl, and —OR⁵⁹, such as R⁵⁶ is methyl. In some embodiments, R^C is selected from —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, and —NR⁵²S(=O)R⁵², such as R^C is selected from —S(=O)CH₃, —S(=O)CH₂CH₃, —S(=O)NH₂, —NHS(=O)CH₃, and —S(=O)NHCH₃. In some embodiments, p is an integer from 1 to 3, such as p is 1. In some embodiments, R^C is —S(=O)₂CH₃. In some embodiments, R⁵⁶ is methyl and R^C is —S(=O)CH₃. In some embodiments, R² is selected from hydrogen, halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, —CH₂OH, —CH₂OR⁵², —CH₂NH₂, —CH₂N(R⁵²)₂, C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl, such as R² is selected from —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, and C₁₋₂ alkyl. In some embodiments, R² is methyl or —NHCH₃. In some embodiments, R² is H.

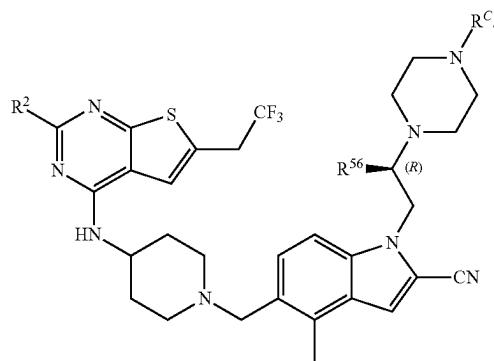
[0635] In certain aspects, a compound of Formula (I-B) may be represented by:

(I-B-7)



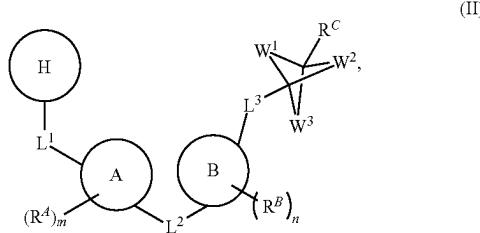
such as

(I-B-8)



In some embodiments, C is selected from 5- to 7-membered monocyclic heterocycle, such as piperidinyl and piperazinyl. In some embodiments, R⁵⁶ is selected from deuterium, C₁₋₄ alkyl, C₁₋₄ haloalkyl, and —OR⁵⁹, such as R⁵⁶ is methyl. In some embodiments, R^C is selected from —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, and —NR⁵²S(=O)R⁵², such as R^C is selected from —S(=O)CH₃, —S(=O)CH₂CH₃, —S(=O)NH₂, —NHS(=O)CH₃, and —S(=O)NHCH₃. In some embodiments, p is an integer from 1 to 3, such as p is 1. In some embodiments, R^C is —S(=O)₂CH₃. In some embodiments, R⁵⁶ is methyl and R^C is —S(=O)CH₃. In some embodiments, R² is selected from hydrogen, halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, —CH₂OH, —CH₂OR⁵², —CH₂NH₂, —CH₂N(R⁵²)₂, C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl, such as R² is selected from —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, and C₁₋₂ alkyl. In some embodiments, R² is methyl or —NHCH₃. In some embodiments, R² is H.

[0636] In certain aspects, the present disclosure provides a compound of Formula (II):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0637] H is selected from C₅₋₁₂ carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R⁵⁰;

[0638] A is selected from bond, C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0639] B is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0640] L¹, L² and L³ are each independently selected from bond, —O—, —S—, —N(R⁵¹)—, —N(R⁵¹)CH₂—, —C(O)—, —C(O)O—, —OC(O)—, —OC(O)O—, —C(O)N(R⁵¹)—, —C(O)N(R⁵¹)C(O)—, —C(O)N(R⁵¹)C(O)N(R⁵¹)—, —N(R⁵¹)C(O)—, —N(R⁵¹)C(O)N(R⁵¹)—, —N(R⁵¹)C(O)O—, —OC(O)N(R⁵¹)—, —C(NR⁵¹)—, —N(R⁵¹)C(NR⁵¹)—, —C(NR⁵¹)N(R⁵¹)—, —N(R⁵¹)C(NR⁵¹)N(R⁵¹)—, —S(O)₂—, —OS(O)—, —S(O)O—, —S(O)—, —OS(O)₂—, —S(O)₂O—, —N(R⁵¹)S(O)₂—, —S(O)₂N(R⁵¹)—, —N(R⁵¹)S(O)—, —S(O)N(R⁵¹)—, —N(R⁵¹)S(O)₂N(R⁵¹)—, —N(R⁵¹)S(O)N(R⁵¹)—; alkylene, alkynylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R⁵⁰,

[0641] R^A, R^B and R^C are each independently selected at each occurrence from R⁵⁰, or two R^A groups or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0642] m and n are each independently an integer from 0 to 6;

[0643] W¹ is C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰;

[0644] W² is selected from a bond; and C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰;

[0645] W³ is selected from absent; and C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰;

[0646] R⁵⁰ is independently selected at each occurrence from:

[0647] halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²);

[0648] C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substi-

tuted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

[0649] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0650] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

[0651] R⁵¹ is independently selected at each occurrence from:

[0652] hydrogen, —C(O)R⁵², —C(O)OR⁵², —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴;

[0653] C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

[0654] C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

[0655] wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —O, —S, —N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

$\text{—P(O)(OR}^{52}\text{)}_2$, $\text{—P(O)(R}^{52}\text{)}_2$, $=\text{O}$, $=\text{S}$, $=\text{N(R}^{52}\text{)}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0656] R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 2- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $=\text{CN}$, $=\text{NO}_2$, $=\text{NH}_2$, $=\text{NHCH}_3$, $=\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $=\text{OH}$, $—\text{OCH}_3$, $—\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

[0657] 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}

[0658] wherein for a compound or salt of Formula (II), when W^3 is absent:

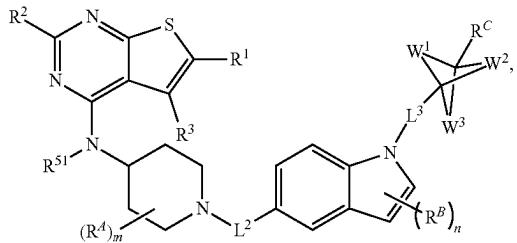
[0659] W^1 is C_1 alkylene, W^2 is a bond, and L^3 is not a bond;

[0660] W^1 is C_{2-4} alkylene and W^2 is a bond; or

[0661] W^1 and W^2 are each C_1 alkylene and L^3 is not a bond, wherein each C_1 alkylene is independently optionally substituted with one or more R^{50} .

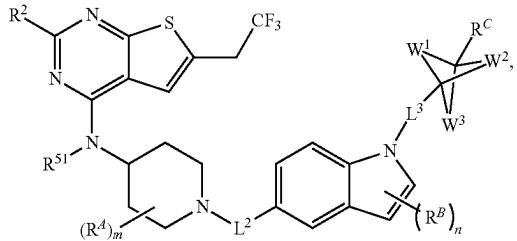
[0662] In certain aspects, a compound of Formula (II) may be represented by:

(II-A)



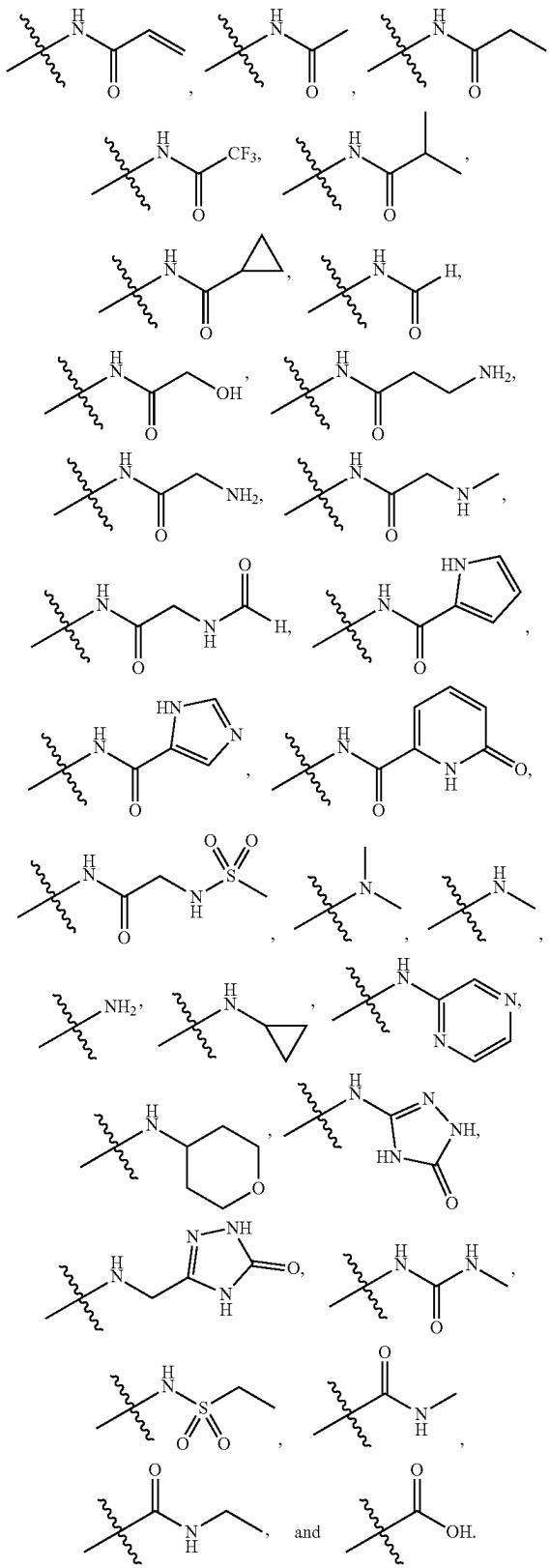
such as

(II-B)

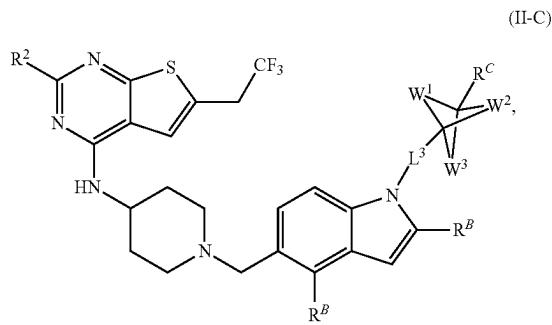


wherein R^1 , R^2 and R^3 are each independently selected at each occurrence from hydrogen and R^{50} . In some embodiments, R^1 is selected from R^{50} . In some embodiments, R^1 is C_{1-3} haloalkyl, such as $—\text{CH}_2\text{CF}_3$. In some embodiments, R^2 is selected from R^{50} . In some embodiments, R^2 is selected from hydrogen, halogen, $=\text{OH}$, $=\text{OR}^{52}$, $=\text{NH}_2$, $=\text{N(R}^{52}\text{)}_2$, $=\text{CN}$, C_{1-3} alkyl, C_{1-3} alkyl- OR^{52} , C_{1-3} alkyl- $\text{N(R}^{52}\text{)}_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, R^2 is selected from halogen, $=\text{OH}$, $=\text{OR}^{52}$, $=\text{NH}_2$, $=\text{N(R}^{52}\text{)}_2$, $=\text{CN}$, C_{1-3} alkyl, $—\text{CH}_2\text{NH}_2$, $—\text{CH}_2\text{N(R}^{52}\text{)}_2$, C_{1-3} alkyl- $\text{N(R}^{52}\text{)}$

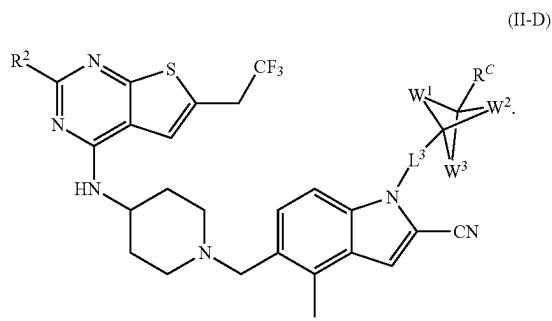
$_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from $=\text{OH}$, $=\text{OR}^{52}$, $=\text{NH}_2$, $=\text{N(R}^{52}\text{)}_2$, $=\text{CN}$, and C_{1-2} alkyl. Optionally, R^2 is selected from $=\text{NH}_2$, $=\text{CH}_3$, $=\text{OCH}_3$, $=\text{CH}_2\text{OH}$, and $=\text{NHCH}_3$. In some embodiments, R^3 is selected from hydrogen, halogen, $=\text{OH}$, $=\text{N(R}^{52}\text{)}_2$, $=\text{CN}$, $=\text{C(O)OR}^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{51} is selected from selected from hydrogen and alkyl, such as R^{51} is hydrogen. In some embodiments, R^4 is selected from halogen, $=\text{CN}$, $=\text{OR}^{52}$, $=\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{53}\text{R}^{54}$, $=\text{C(O)R}^{52}$, $=\text{C(O)OR}^{52}$, $=\text{OC(O)R}^{52}$, $=\text{NR}^{52}\text{C(O)R}^{52}$, $=\text{C(O)N(R}^{52}\text{)}_2$, $=\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{O}$, 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, m is an integer from 0 to 3. In some embodiments, m is 0. In some embodiments, L^2 is selected from $=\text{O}$, $=\text{N(R}^{51}\text{)}$, $=\text{N(R}^{51}\text{)CH}_2$, $=\text{C(O)N(R}^{51}\text{)}$, $=\text{N(R}^{51}\text{)C(O)}$, $=\text{N(R}^{51}\text{)S(O)}_2$, $=\text{S(O)}_2\text{N(R}^{51}\text{)}$, 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 $=\text{CH}_2$, $=\text{N(R}^{51}\text{)}$, $=\text{N(R}^{51}\text{)CH}_2$, $=\text{N(R}^{51}\text{)C(O)}$, and $=\text{N(R}^{51}\text{)S(O)}_2$. In some embodiments, L^2 is $=\text{CH}_2$. 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, $=\text{CN}$, $=\text{OR}^{52}$, $=\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{53}\text{R}^{54}$, $=\text{C(O)R}^{52}$, $=\text{C(O)OR}^{52}$, $=\text{OC(O)R}^{52}$, $=\text{NR}^{52}\text{C(O)R}^{52}$, $=\text{C(O)N(R}^{52}\text{)}_2$, $=\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{O}$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, optionally substituted C_{1-10} alkyl, and optionally substituted C_{2-10} alkynyl. In some embodiments, R^B is selected from halogen, $=\text{CN}$, $=\text{OR}^{52}$, $=\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{53}\text{R}^{54}$, C_{1-3} alkyl, and optionally substituted C_{1-3} alkyl, such as R^B is selected from halogen, $=\text{CN}$, $=\text{OR}^{52}$, $=\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{53}\text{R}^{54}$, and C_{1-2} alkyl. In some embodiments, n is an integer from 1 to 4, such as an integer from 2 to 3. In some embodiments, n is 2. In some embodiments, L^3 is C_{1-4} alkylene, optionally substituted with one or more R^{50} . In some embodiments, L^3 is C_{1-2} alkylene, optionally substituted with one or more R^{50} . In some embodiments, L^3 is $=\text{CH}_2$. In some embodiments, W^1 is C_{1-4} alkylene, optionally substituted with one or more R^{50} . In some embodiments, W^1 is C_{1-2} alkylene, optionally substituted with one or more R^{50} . In some embodiments, W^1 is C_{1-2} alkylene, such as C_1 alkylene or $=\text{CH}_2$. In some embodiments, W^2 is C_{1-4} alkylene, optionally substituted with one or more R^{50} . In some embodiments, W^2 is C_{1-2} alkylene, optionally substituted with one or more R^{50} . In some embodiments, W^2 is C_{1-2} alkylene, such as C_1 alkylene or $=\text{CH}_2$. In some embodiments, W^3 is absent. In some embodiments, W^3 is C_{1-4} alkylene, optionally substituted with one or more R^{50} . In some embodiments, W^3 is C_{1-2} alkylene, optionally substituted with one or more R^{50} . In some embodiments, W^3 is C_{1-2} alkylene, such as C_1 alkylene or $=\text{CH}_2$. In some embodiments, R^C is selected from $=\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{53}\text{R}^{54}$, $=\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $=\text{C(O)R}^{52}$, $=\text{C(O)OR}^{52}$, $=\text{NR}^{52}\text{C(O)R}^{52}$, $=\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{C(O)NR}^{53}\text{R}^{54}$, and $=\text{C(O)NR}^{53}\text{R}^{54}$. In some embodiments, R^C is selected from $=\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{53}\text{R}^{54}$, $=\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $=\text{C(O)R}^{52}$, $=\text{C(O)OR}^{52}$, $=\text{NR}^{52}\text{C(O)R}^{52}$, $=\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{C(O)NR}^{53}\text{R}^{54}$, and $=\text{C(O)NR}^{53}\text{R}^{54}$. In some embodiments, R^C is selected from $=\text{N(R}^{52}\text{)}_2$, $=\text{NR}^{53}\text{R}^{54}$, $=\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $=\text{C(O)R}^{52}$, $=\text{C(O)OR}^{52}$, $=\text{NR}^{52}\text{C(O)R}^{52}$, $=\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $=\text{C(O)NR}^{53}\text{R}^{54}$, and $=\text{C(O)NR}^{53}\text{R}^{54}$.



[0663] In certain aspects, a compound of Formula (II) may be represented by:

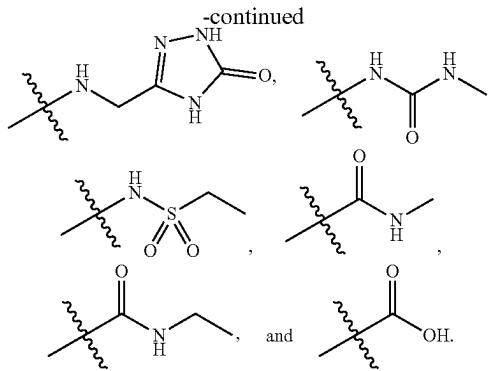
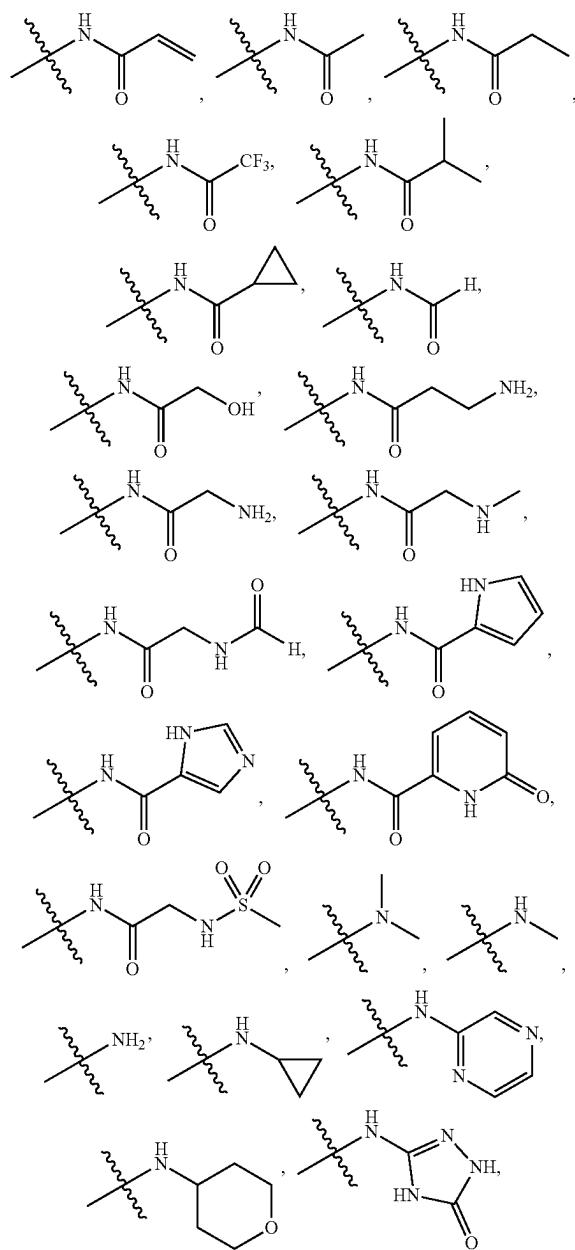


such as

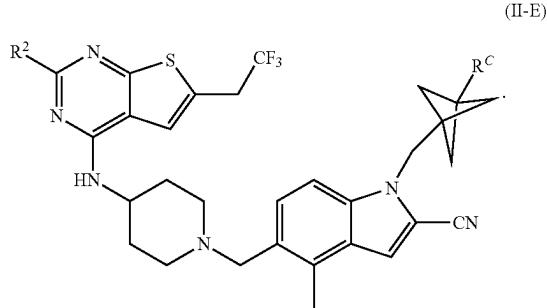


In some embodiments, R² is selected from R⁵⁰. In some embodiments, R² is selected from hydrogen, halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, C₁₋₃ alkyl-OR⁵², C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl. In some embodiments, R² is selected from halogen, —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, C₁₋₃ alkyl, —CH₂OH, —CH₂OR⁵², —CH₂NH₂, —CH₂N(R⁵²)₂, C₁₋₃ alkyl-N(R⁵²)₂, C₁₋₃ haloalkyl, C₂₋₃ alkenyl, and C₂₋₃ alkynyl, such as R² is selected from —OH, —OR⁵², —NH₂, —N(R⁵²)₂, —CN, and C₁₋₂ alkyl. Optionally, R² is selected from —NH₂, —CH₃, —OCH₃, —CH₂OH, and —NHCH₃. In some embodiments, R^B is selected from halogen, —CN, —OR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —NR⁵²C(O)R⁵², —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —O, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, optionally substituted C₁₋₁₀ alkyl, optionally substituted C₂₋₁₀ alkenyl, and optionally substituted C₂₋₁₀ alkynyl. In some embodiments, R^B is selected from halogen, —CN, —OR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, C₁₋₃ alkyl, and optionally substituted C₁₋₃ alkyl, such as R^B is selected from halogen, —CN, —OR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, and C₁₋₂ alkyl. In some embodiments, L³ is C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰. In some embodiments, L³ is C₁₋₂ alkylene, optionally substituted with one or more R⁵⁰. In some embodiments, L³ is —CH₂—. In some embodiments, W¹ is C₁₋₄ alkylene, optionally substituted with one or more R⁵⁰. In some embodiments, W¹ is C₁₋₂ alkylene, such as C₁ alkylene or —CH₂—. In some embodiments, W² is C₁₋₄ alkylene, optionally substituted

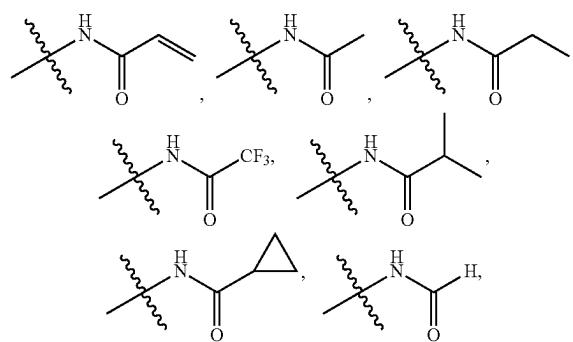
with one or more R^{50} . In some embodiments, W^2 is C_{1-2} alkylene, optionally substituted with one or more R^{50} . In some embodiments, W^2 is C_{1-2} alkylene, such as C_1 alkylene or $—CH_2—$. In some embodiments, W^3 is absent. In some embodiments, W^3 is C_{1-4} alkylene, optionally substituted with one or more R^{50} . In some embodiments, W^3 is C_{1-2} alkylene, optionally substituted with one or more R^{50} . In some embodiments, W^3 is C_{1-2} alkylene, such as C_1 alkylene or $—CH_2—$. 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

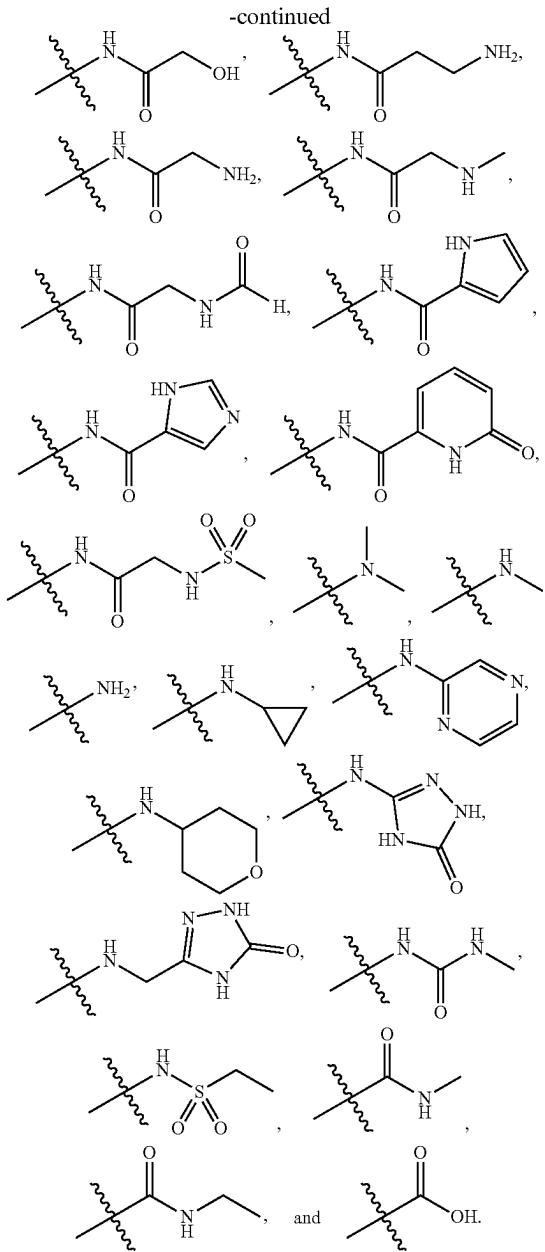


[0664] In certain aspects, a compound of Formula (II) may be represented by:

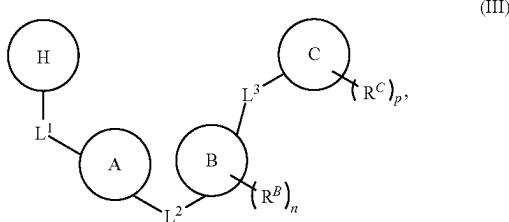


In some embodiments, R^2 is selected from R^{50} . In some embodiments, R^2 is selected from hydrogen, halogen, $—OH$, $—OR^{52}$, $—NH_2$, $—N(R^{52})_2$, $—CN$, C_{1-3} alkyl, C_{1-3} alkyl- OR^{52} , C_{1-3} alkyl- $N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, 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^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





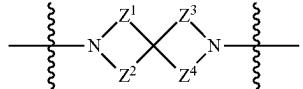
[0665] In certain aspects, the present disclosure provides a compound of Formula (III):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0666] H is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R⁵⁰;

[0667] A is



[0668] each of Z¹, Z², Z³, and Z⁴ is independently selected from —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 Z¹, Z², Z³, and Z⁴ is —C(O)— or —C(R^{A1})(R^{A2})—C(O)—;

[0669] B is selected from bond, C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0670] C is selected from bond, C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

[0671] L¹, L² and L³ are each independently selected from bond, —O—, —S—, —N(R⁵¹)—, —N(R⁵¹)CH₂—, —C(O)—, —C(O)O—, —OC(O)—, —OC(O)O—, —C(O)N(R⁵¹)—, —C(O)N(R⁵¹)C(O)—, —C(O)N(R⁵¹)C(O)N(R⁵¹)—, —N(R⁵¹)C(O)—, —N(R⁵¹)C(O)O—, —OC(O)N(R⁵¹)—, —C(NR⁵¹)—, —N(R⁵¹)C(NR⁵¹)—, —C(NR⁵¹)N(R⁵¹)—, —N(R⁵¹)C(NR⁵¹)N(R⁵¹)—, —S(O)₂—, —OS(O)—, —S(O)O—, —S(O)—, —OS(O)₂—, —S(O)₂O—, —N(R⁵¹)S(O)₂—, —S(O)₂N(R⁵¹)—, —N(R⁵¹)S(O)—, —S(O)N(R⁵¹)—, —N(R⁵¹)S(O)N(R⁵¹)—, —N(R⁵¹)S(O)(N(R⁵¹))—; alkylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, each of which is optionally substituted with one or more R⁵⁰, wherein two R⁵⁰ groups attached to the same atom or different atoms of any one of L¹, L² or L³ can together optionally form a bridge or ring;

[0672] R^B is independently selected at each occurrence from R⁵⁰, or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0673] R^C is independently selected at each occurrence from hydrogen and R⁵⁰, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0674] R^{A1} and R^{A2} are each independently selected at each occurrence from hydrogen and R⁵⁰;

[0675] n is an integer from 0 to 6;

[0676] p is an integer from 1 to 6;

[0677] R⁵⁰ is independently selected at each occurrence from:

[0678] halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)N(R⁵²)₂, —S(=O)NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)OR⁵², —P(O)R⁵², —P(O)OR⁵², —P(O)OR⁵², —P(O)NR⁵², —NR⁵²P(O)R⁵², —P(O)NR⁵²(OR⁵²), —P(O)NR⁵²;

[0679] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0680] C_{3-12} carbocycle and 3- to 12-membered heterocycle.

[0681] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0682] R^{51} is independently selected at each occurrence from:

[0683] hydrogen, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$;

[0684] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

[0685] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

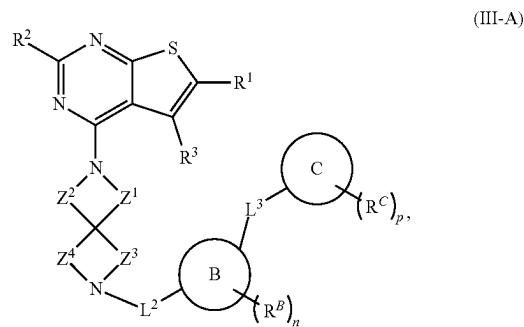
[0686] wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$,

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

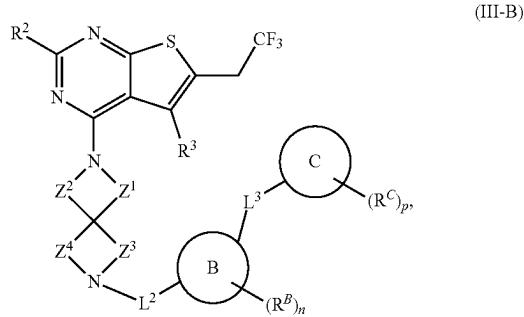
[0687] R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

[0688] 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} .

[0689] In certain aspects, a compound of Formula (III) may be represented by:



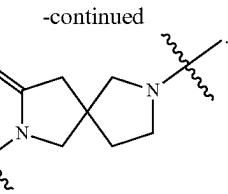
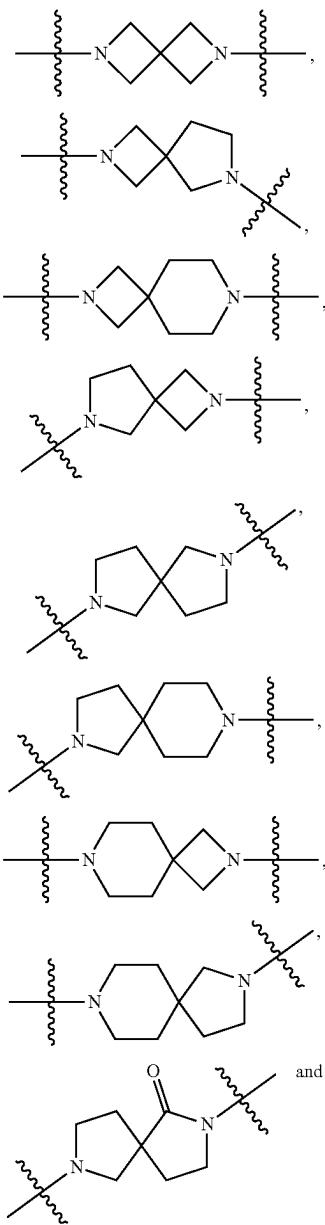
such as



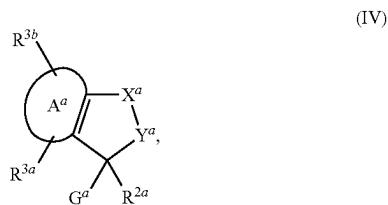
wherein R^1 , R^2 and R^3 are each independently selected at each occurrence from hydrogen and R^{50} . In some embodiments, R^1 is selected from R^{50} . In some embodiments, R^1 is C_{1-3} haloalkyl, such as $-\text{CH}_2\text{CF}_3$. In some embodiments, R^2 is selected from hydrogen and R^{50} . In some embodiments, R^2 is selected from hydrogen, halogen, $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, C_{1-3} alkyl, C_{1-3} alkyl-

OR^{52} , C_{1-3} alkyl- $\text{N}(\text{R}^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some embodiments, R^2 is selected from halogen, $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, C_{1-3} alkyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OR}^{52}$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(\text{R}^{52})_2$, C_{1-3} alkyl- $\text{N}(\text{R}^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl, such as R^2 is selected from $-\text{OH}$, $-\text{OR}^{52}$, $-\text{NH}_2$, $-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, and C_{1-2} alkyl. Optionally, R^2 is selected from $-\text{NH}_2$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{CH}_2\text{OH}$, and $-\text{NHCH}_3$. In some embodiments, R^3 is selected from hydrogen, halogen, $-\text{OH}$, $-\text{N}(\text{R}^{52})_2$, $-\text{CN}$, $-\text{C}(\text{O})\text{OR}^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{52} is selected from selected from hydrogen and alkyl, such as R^{52} is hydrogen.

[0690] In some embodiments, for a compound of Formula (III), A is selected from



[0691] In certain aspects, the present disclosure provides a compound of Formula (IV):



or a pharmaceutically acceptable salt or prodrug thereof, wherein:



is a fused thienyl or fused phenyl group;

[0692] G^a is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is substituted with $-\text{E}^1\text{-R}^{4a}$ and optionally further substituted with one or more R^{50} ,

[0693] R^{2a} is selected from hydrogen, alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl;

[0694] R^{3a} and R^{3b} are each independently selected from hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

[0695] $\text{X}^a\text{-Y}^a$ is selected from $-\text{N}(\text{R}^{52})\text{-C}(=\text{O})-$, $-\text{C}(=\text{O})\text{-O}-$, $-\text{C}(=\text{O})\text{-N}(\text{R}^{52})-$, $-\text{CH}_2\text{N}(\text{R}^{52})\text{-CH}_2-$, $-\text{CH}_2\text{CH}_2\text{-N}(\text{R}^{52})-$, $-\text{CH}_2\text{N}(\text{R}^{52})\text{-C}(=\text{O})-$, and $-\text{CH}_2\text{O}\text{-CH}_2-$; or

[0696] X^a and Y^a do not form a chemical bond, wherein:

[0697] X^a is selected from hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy; and

[0698] Y^a is selected from cyano, hydroxy, and $-\text{CH}_2\text{R}^{50}$;

[0699] E^1 is selected from absent, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{N}(\text{R}^{52})-$, $-[\text{C}(\text{R}^{14a})_2]_{1-5}\text{O}-$, $-[\text{C}(\text{R}^{14a})_2]_{1-5}\text{NR}^{52}-$, $-[\text{C}(\text{R}^{14a})_2]_{1-5}-$, $-\text{CH}_2(=\text{O})-$, and $-\text{S}(=\text{O})_2-$;

[0700] R^{4a} is selected from hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted

aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, aralkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl;

[0701] R^{14a} is selected from hydrogen and alkyl;

[0702] R^{50} is independently selected at each occurrence from:

[0703] halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$;

[0704] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

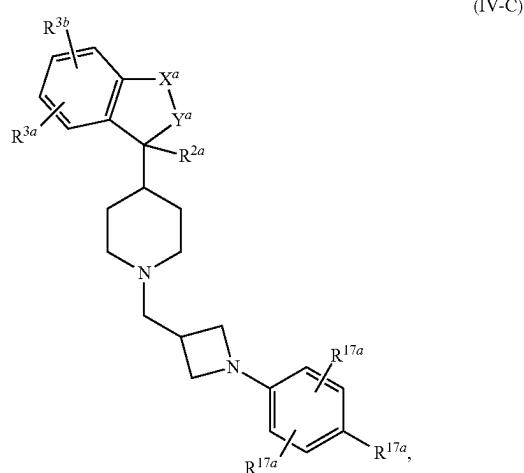
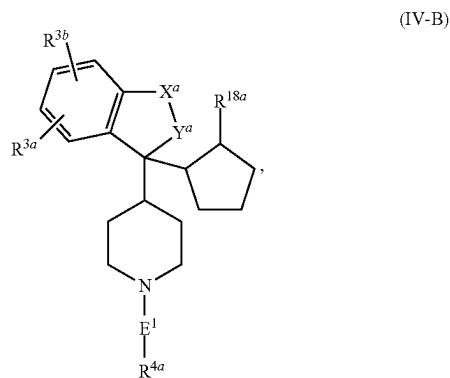
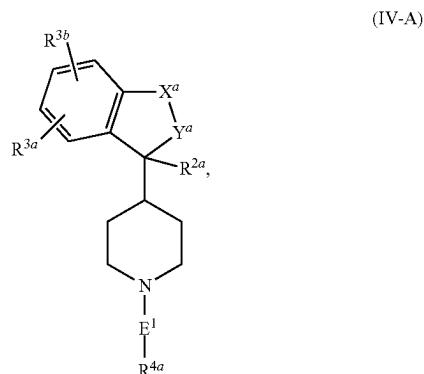
[0705] C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0706] 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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{OR}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})(\text{R}^{52})$, $-\text{P}(\text{O})(\text{NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0707] 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, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

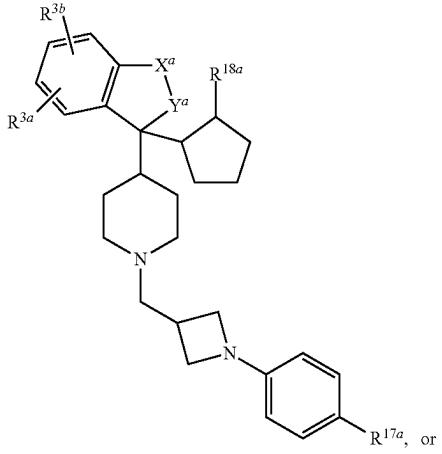
[0708] R^{53} and R^{54} are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R^{50} .

[0709] In some embodiments, for a compound of Formula (IV), G^a is piperidinyl. In some embodiments, a compound of Formula (IV) is represented by:

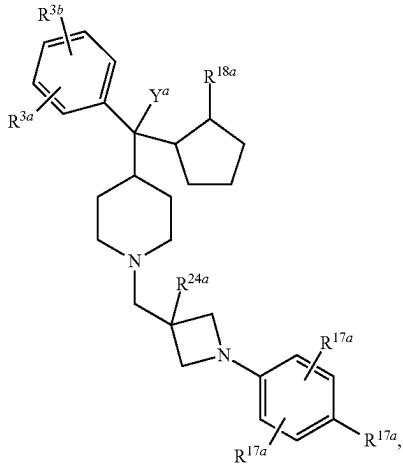


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(IV-D)



(IV-E)



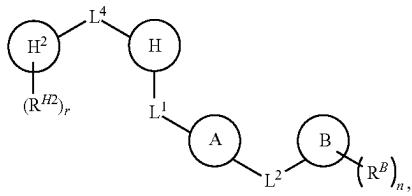
[0710] wherein R^{17a} and R^{18a} is independently selected from hydrogen and R^{50} , and

[0711] R^{24a} is selected from hydrogen and fluoro.

[0712] In some embodiments, for a compound of Formula (IV), R^{3a} and R^{3b} are independently selected from hydrogen and halo. In some embodiments, X^a and Y^a do not form a chemical bond, and X^a is hydrogen. In some embodiments, R^{4a} is selected from hydrogen; and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclo, heteroaryl, aralkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl, each of which is optionally substituted with one or more substituents selected from R^{50} . In some embodiments, R^{4a} is R^{50} -substituted heterocyclo.

[0713] In certain aspects, the present disclosure provides a compound of Formula (VI):

(VI)

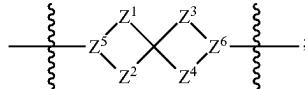


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

[0714] H^2 is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0715] H is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

[0716] A is



[0717] each of Z^1 , Z^2 , Z^3 , and Z^4 is independently selected from $—C(R^{41})(R^{42})$, $—C(R^{41})(R^{42})$, $—O$, $—C(R^{41})(R^{42})—O$, $—C(R^{41})(R^{42})—N(R^{51})$, $—C(O)$, $—C(R^{41})(R^{42})—C(O)$, and $—N=C(NH_2)$, wherein no more than one of Z^1 , Z^2 , Z^3 , and Z^4 is $—O$, $—C(R^{41})(R^{42})—O$, $—C(R^{41})(R^{42})—N(R^{51})$, $—C(O)$, $—C(R^{41})(R^{42})—C(O)$, or $—N=C(NH_2)$;

[0718] Z^5 and Z^6 are independently selected from $—C(R^{43})$ and $—N$;

[0719] B is selected from bond, C_{3-12} carbocycle and 3- to 12-membered heterocycle;

[0720] L^1 , L^2 and L^4 are each independently selected from bond, $—O$, $—S$, $—N(R^{51})$, $—N(R^{51})CH_2$, $—C(O)$, $—C(O)O$, $—OC(O)$, $—OC(O)O$, $—C(O)N(R^{51})$, $—C(O)N(R^{51})C(O)$, $—C(O)NR^{51}C(O)NR^{51}$, $—N(R^{51})C(O)O$, $—N(R^{51})C(O)O$, $—OC(O)N(R^{51})$, $—C(NR^{51})$, $—N(R^{51})C(NR^{51})$, $—C(NR^{51})N(R^{51})$, $—N(R^{51})C(NR^{51})N(R^{51})$, $—S(O)_2$, $—OS(O)_2$, $—S(O)O$, $—S(O)_2$, $—N(R^{51})S(O)_2$, $—S(O)N(R^{51})$, $—N(R^{51})S(O)_2N(R^{51})$, $—N(R^{51})S(O)N(R^{51})$; alkylene, 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^4 can together optionally form a bridge or ring;

[0721] R^B is independently selected at each occurrence from hydrogen and R^{50} , or two R^B groups attached to the same atom or different atoms can together optionally form a bridge or ring;

[0722] 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;

[0723] R^{41} , R^{42} and R^{43} are each independently selected at each occurrence from hydrogen and R^{50} ;

[0724] n is an integer from 0 to 6;

[0725] r is an integer from 1 to 6;

[0726] R^{50} is independently selected at each occurrence from:

[0727] halogen, $—NO_2$, $—CN$, $—OR^{52}$, $—SR^{52}$, $—N(R^{52})_2$, $—NR^{53}R^{54}$, $—S(=O)R^{52}$, $—S(=O)_2R^{52}$, $—S(=O)_2N(R^{52})_2$, $—S(=O)_2NR^{53}R^{54}$, $—NR^{52}S(=O)_2R^{52}$, $—NR^{52}S(=O)_2N(R^{52})$, $—NR^{52}S(=O)_2NR^{53}R^{54}$, $—C(O)R^{52}$, $—C(O)OR^{52}$,

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

[0728] 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} , $\text{—N(R}^{52})_2$, $\text{—NR}^{53}\text{R}^{54}$, —S(=O)R^{52} , $\text{—S(=O)}_2\text{R}^{52}$, $\text{—S(=O)}_2\text{N(R}^{52})_2$, —S(=O)
 $\text{—NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $\text{—NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)}_2\text{N(R}^{52})$, $\text{—NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} , —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)R}^{52}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)N(R}^{52})_2$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $\text{—C(O)N(R}^{52})_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(R}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle; and

[0729] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0730] 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} , $\text{—N(R}^{52})_2$, $\text{—NR}^{53}\text{R}^{54}$, —S(=O)R^{52} , $\text{—S(=O)}_2\text{R}^{52}$, $\text{—S(=O)}_2\text{N(R}^{52})_2$, —S(=O)
 $\text{—NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $\text{—NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)}_2\text{N(R}^{52})$, $\text{—NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} , —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)R}^{52}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)N(R}^{52})_2$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $\text{—C(O)N(R}^{52})_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(R}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})(\text{R}^{52})$, $\text{—NR}^{52}\text{P(O)(R}^{52})$, $\text{—P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

[0731] R^{51} is independently selected at each occurrence from:

[0732] hydrogen, —C(O)R^{52} , —C(O)OR^{52} , $\text{—C(O)N(R}^{52})_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$;

[0733] 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} , $\text{—N(R}^{52})_2$, $\text{—NR}^{53}\text{R}^{54}$, —S(=O)R^{52} , $\text{—S(=O)}_2\text{R}^{52}$, $\text{—S(=O)}_2\text{N(R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $\text{—NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)}_2\text{N(R}^{52})$, $\text{—NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} , —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)R}^{52}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)N(R}^{52})_2$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $\text{—C(O)N(R}^{52})_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(R}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})(\text{R}^{52})$, $\text{—NR}^{52}\text{P(O)(R}^{52})$, $\text{—P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle and 3- to 12-membered heterocycle; and

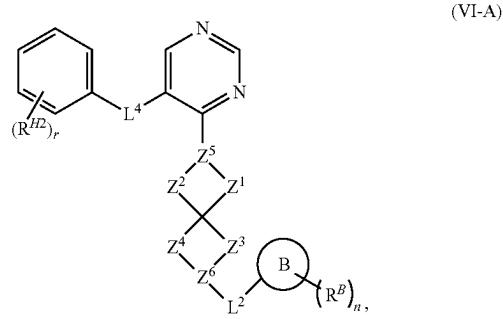
[0734] C_{3-12} carbocycle and 3- to 12-membered heterocycle,

[0735] 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} , $\text{—N(R}^{52})_2$, $\text{—NR}^{53}\text{R}^{54}$, —S(=O)R^{52} , $\text{—S(=O)}_2\text{R}^{52}$, $\text{—S(=O)}_2\text{N(R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $\text{—NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$, $\text{—NR}^{52}\text{S(=O)}_2\text{N(R}^{52})$, $\text{—NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, —C(O)R^{52} , —C(O)OR^{52} , —OC(O)R^{52} , —OC(O)OR^{52} , $\text{—OC(O)NR}^{53}\text{R}^{54}$, $\text{—NR}^{52}\text{C(O)R}^{52}$, $\text{—NR}^{52}\text{C(O)OR}^{52}$, $\text{—NR}^{52}\text{C(O)N(R}^{52})_2$, $\text{—NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $\text{—C(O)N(R}^{52})_2$, $\text{—C(O)NR}^{53}\text{R}^{54}$, $\text{—P(O)(OR}^{52})_2$, $\text{—P(O)(R}^{52})_2$, $\text{—P(O)(OR}^{52})(\text{R}^{52})$, $\text{—P(O)(NR}^{52})(\text{R}^{52})$, $\text{—NR}^{52}\text{P(O)(R}^{52})$, $\text{—P(O)(NR}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

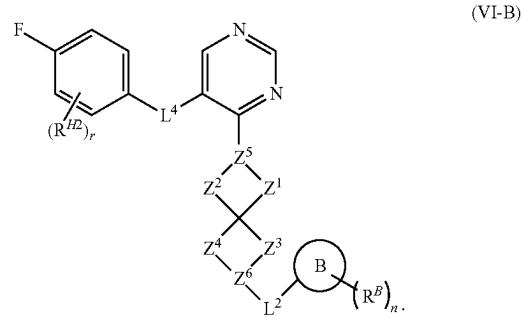
[0736] R^{52} is independently selected at each occurrence from hydrogen; and C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN , —NO_2 , —NH_2 , —NHCH_3 , $\text{—NHCH}_2\text{CH}_3$, $=\text{O}$, —OH , —OCH_3 , $\text{—OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

[0737] 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} .

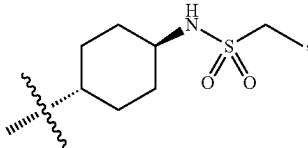
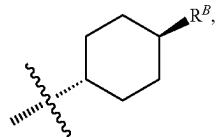
[0738] In certain aspects, a compound of Formula (VI) may be represented by:



such as

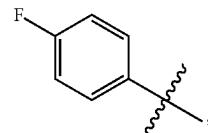
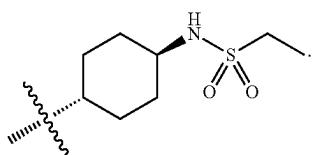


In some embodiments, L^4 is selected from $—O—$ and $—NH—$. In some embodiments, Z^5 and Z^6 are each N. In some embodiments, B is C_{3-12} carbocycle, such as cyclohexane. In some embodiments, B is such as



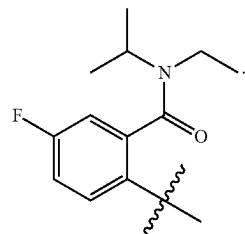
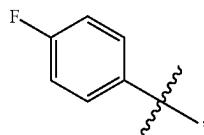
and H^2 is optionally R^{H2} -substituted

such as



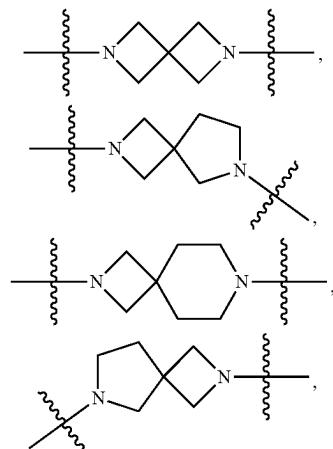
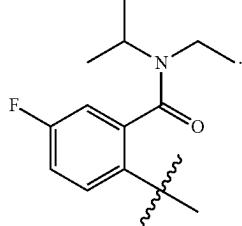
such as

In some embodiments, H^2 is

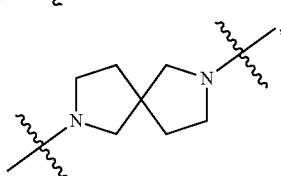
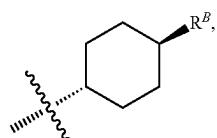


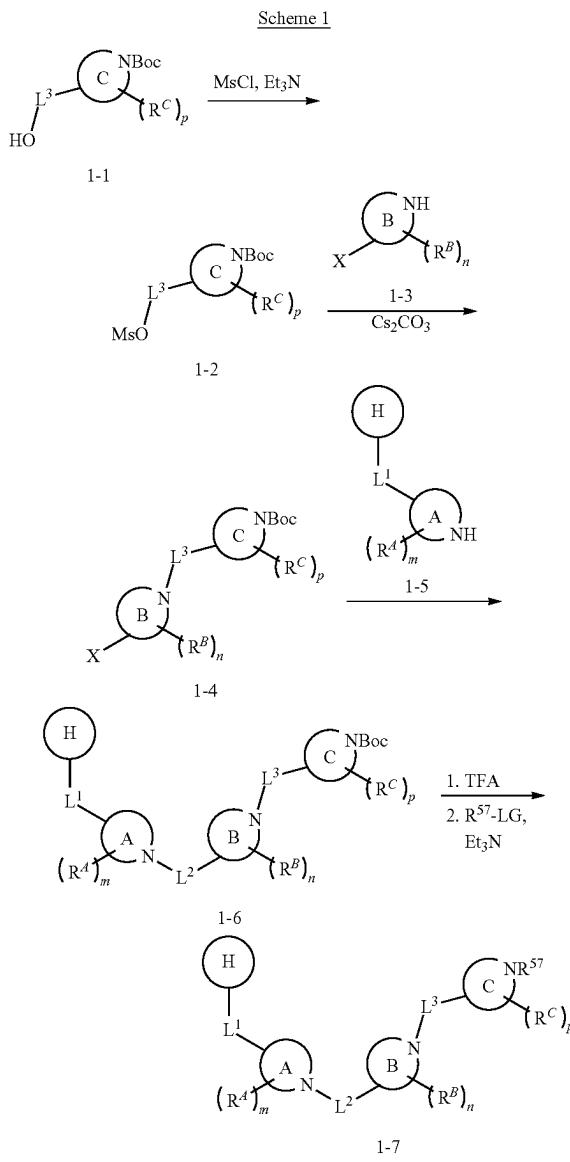
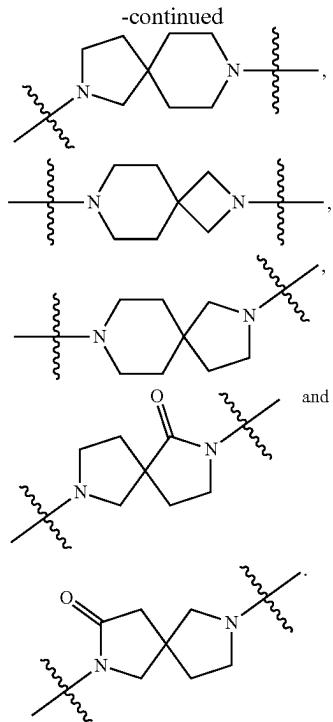
optionally further substituted with one or more R^{H2} . In some embodiments, H^2 is

[0739] In some embodiments, for a compound of Formula (VI), A is selected from



In some embodiments, L^4 is selected from $—O—$ and $—NH—$, Z^5 and Z^6 are each N, B is B is





[0740] 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.

[0741] The chemical entities described herein for use in the subject methods 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.

[0742] 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.

[0743] In general, compounds of the disclosure for use in the subject methods, including compounds of Formula (I-A), (I-B), (II), (III) and (VI), may be prepared by the following reaction scheme:

[0744] In some embodiments, a compound of Formula 1-7 may be prepared according to Scheme 1. For example, methanesulfonyl chloride can be added to a solution of alcohol 1-1 and triethylamine to afford mesylate 1-2. Addition of mesylate 1-2 to a solution of Cs₂CO₃ and amine 1-3 can provide a compound of Formula 1-4. Coupling of 1-4 to amine 1-5 can proceed according to methods known in the art to give a compound of Formula 1-6. Addition of TFA can reveal the free amine, which can optionally be reacted with R⁵⁷-LG, wherein LG is a suitable leaving group, to afford a compound of Formula 1-7.

[0745] In some embodiments, a compound of the present disclosure for use in the subject methods, for example, a compound of a formula given in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6 or Table 7, 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 for use in the subject

methods may include, but are not limited to, a compound or salt thereof selected from Table 1, Table 2, Table 3, Table 4, Table 5, Table 6 or Table 7.

TABLE 1

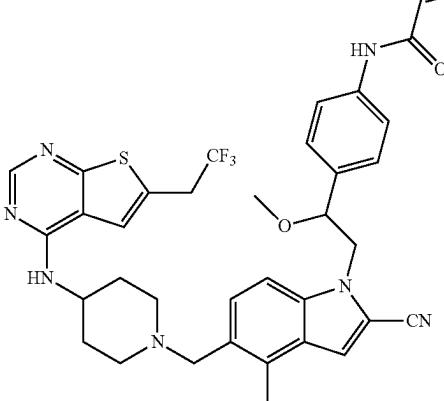
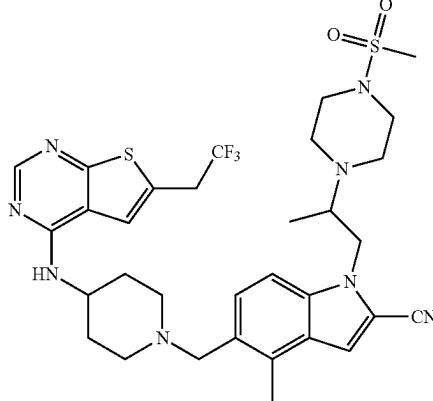
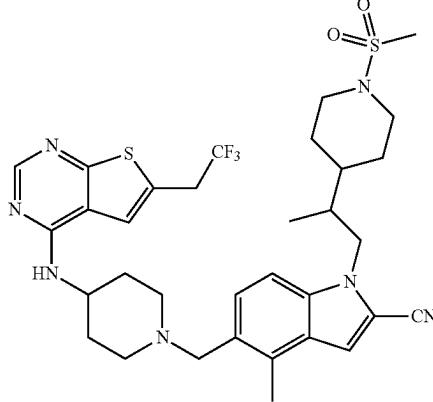
No.	Structure
I-1	 <p>MW (calc'd) 687.78 m/z (found) 688.45 [M + H]⁺</p>
I-2	 <p>MW (calc'd) 688.83 m/z (found) 689.40 [M + H]⁺</p>
I-3	 <p>MW (calc'd) 687.84 m/z (found) 688.45 [M + H]⁺</p>

TABLE 1-continued

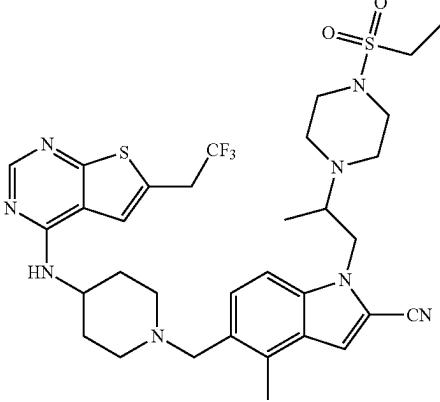
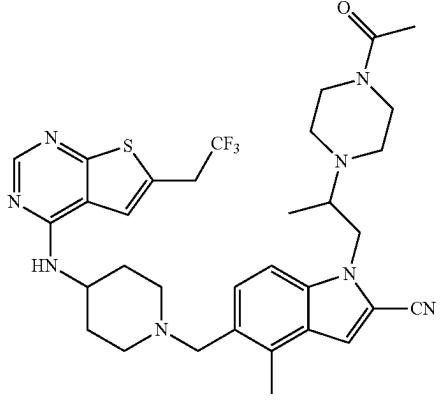
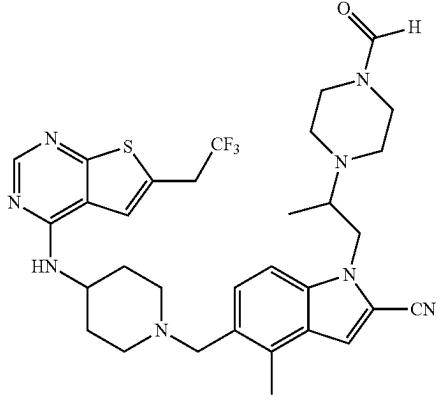
No.	Structure
I-4	 <p>MW (calc'd) 702.86 m/z (found) 703.55 [M + H]⁺</p>
I-5	 <p>MW (calc'd) 652.78 m/z (found) 653.55 [M + H]⁺</p>
I-6	 <p>MW (calc'd) 638.75 m/z (found) 639.50 [M + H]⁺</p>

TABLE 1-continued

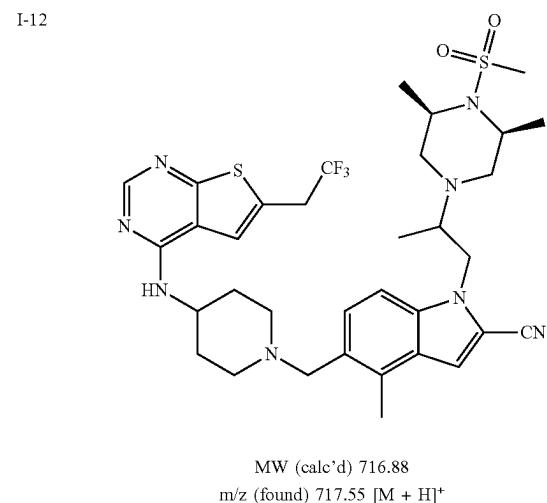
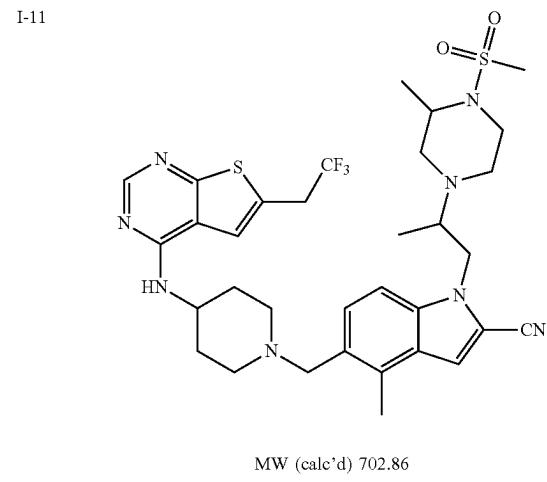
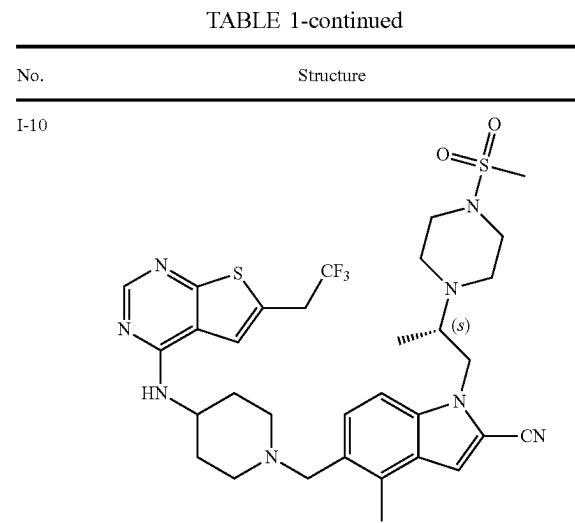
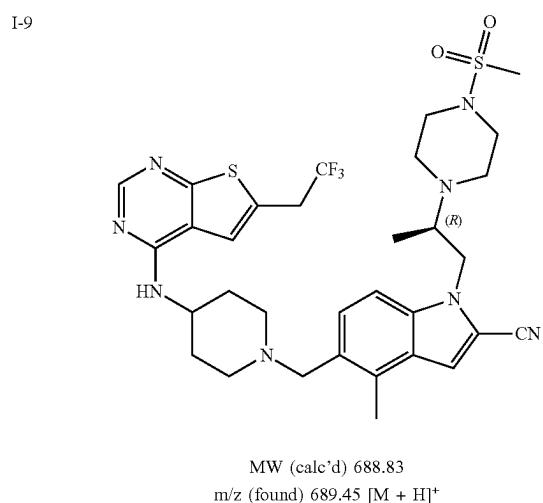
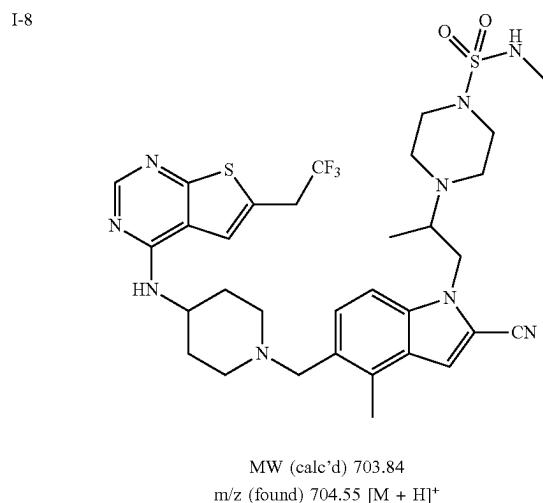
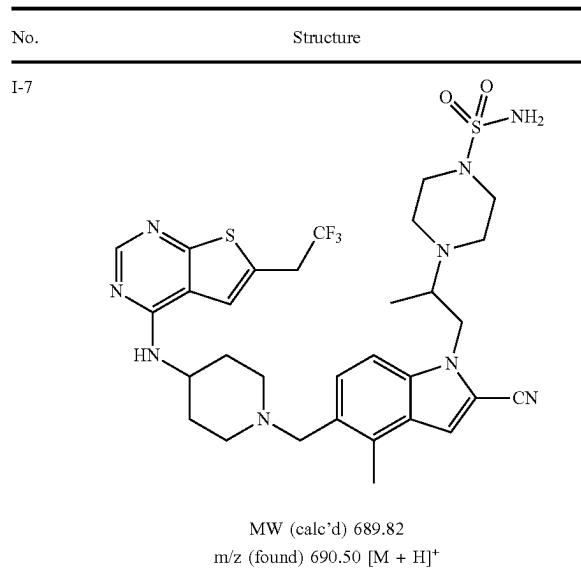


TABLE 1-continued

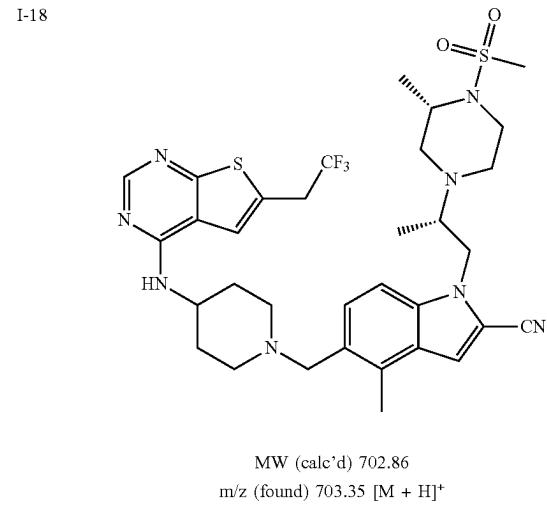
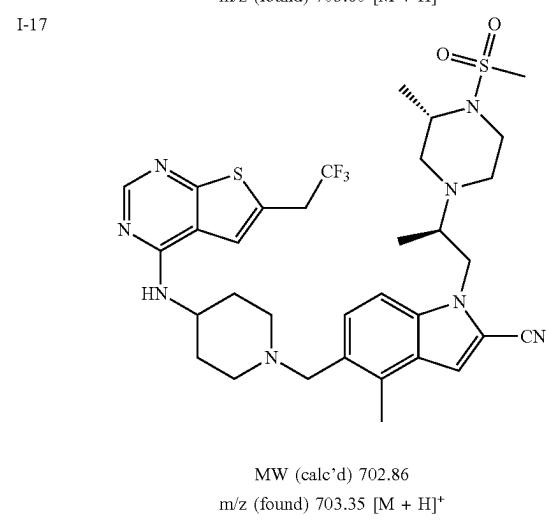
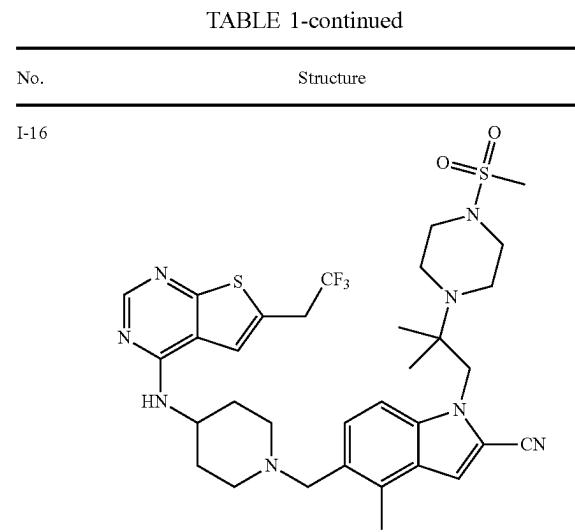
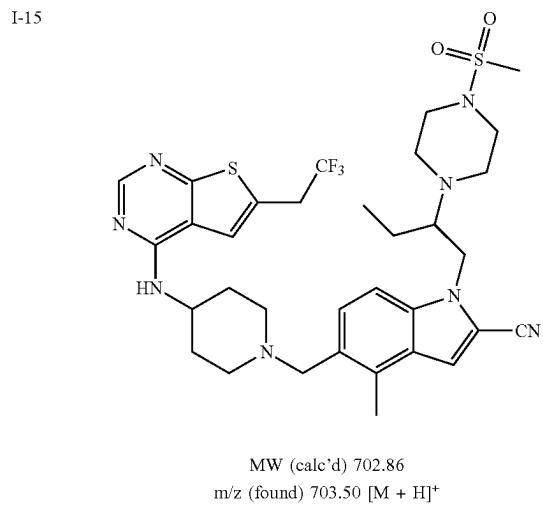
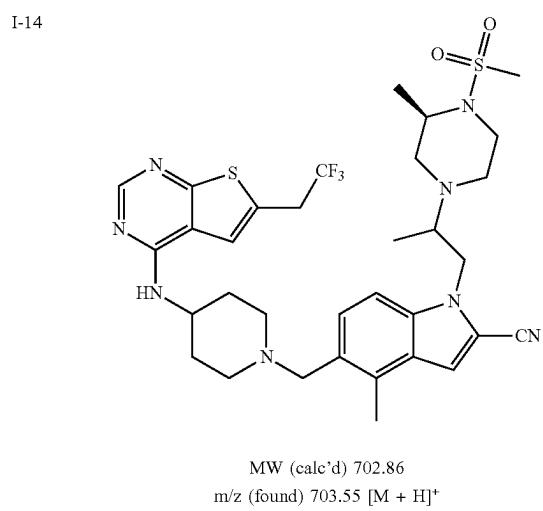
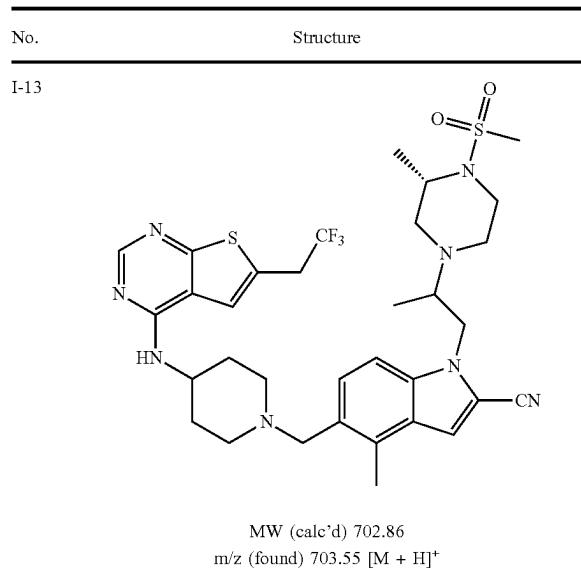
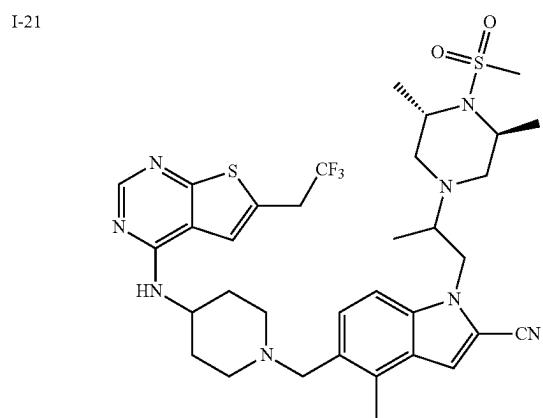
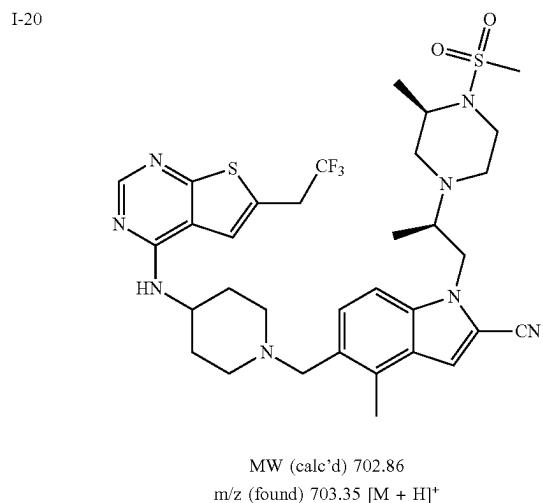
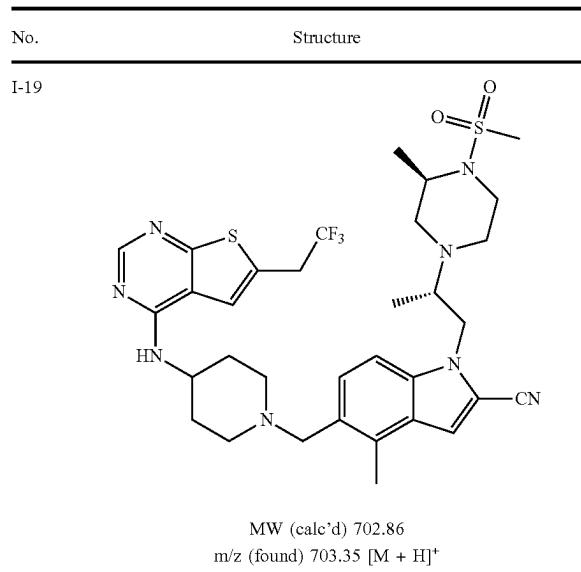
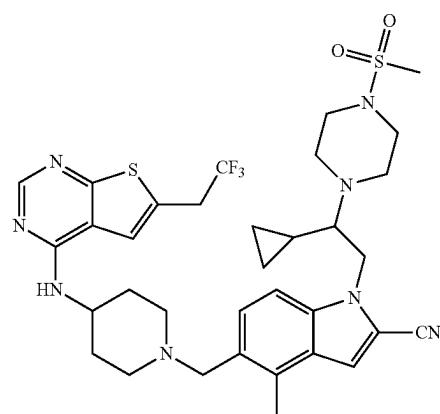
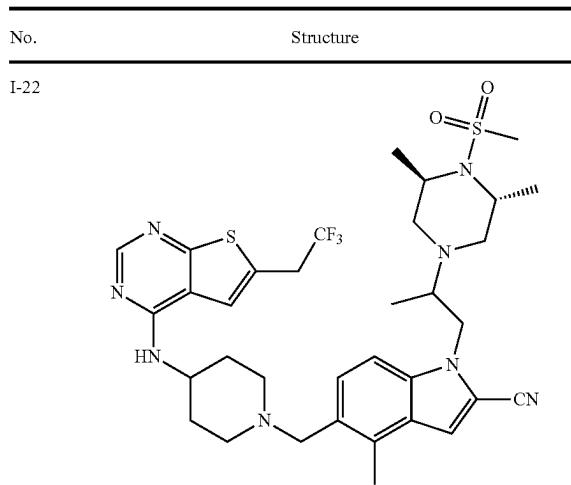


TABLE 1-continued

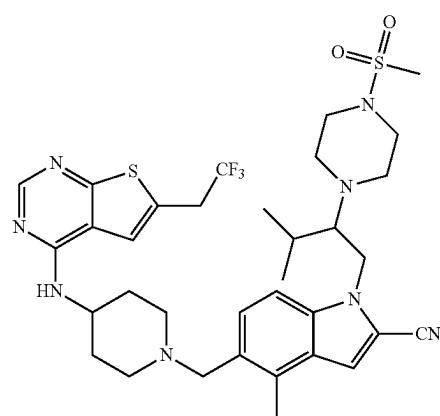


MW (calc'd) 716.88
m/z (found) 717.35 [M + H]⁺

TABLE 1-continued



MW (calc'd) 714.87
m/z (found) 715.25 [M + H]⁺



MW (calc'd) 716.88
m/z (found) 717.45 [M + H]⁺

TABLE 1-continued

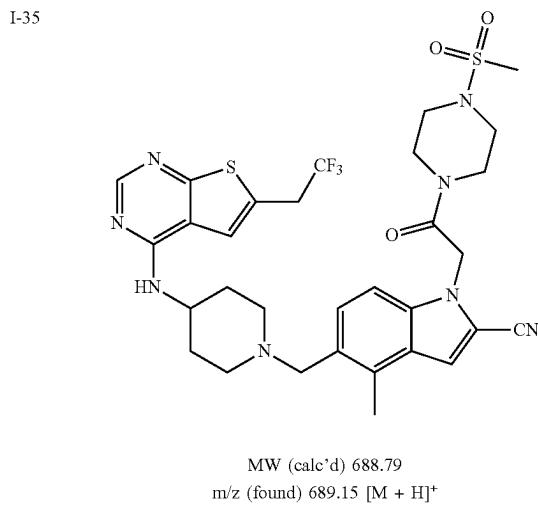
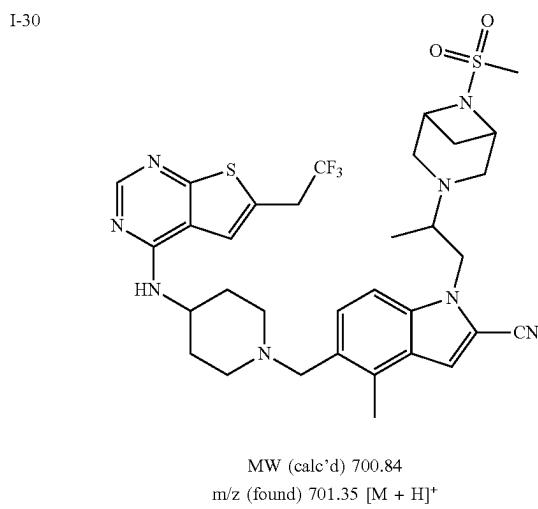
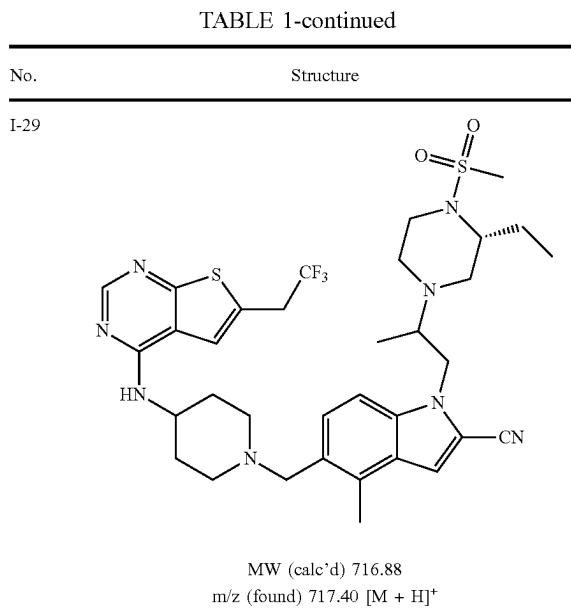
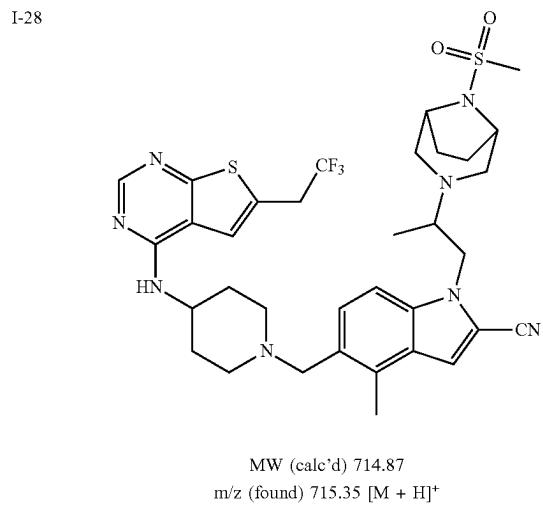
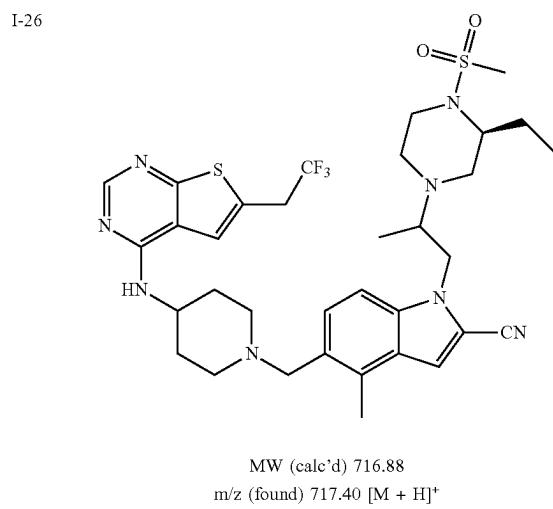
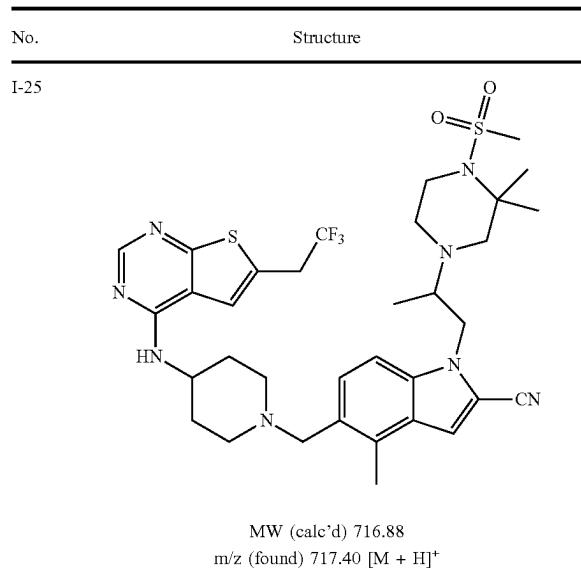


TABLE 1-continued

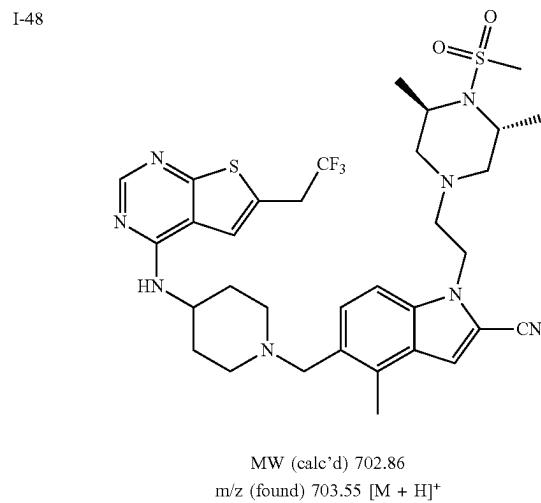
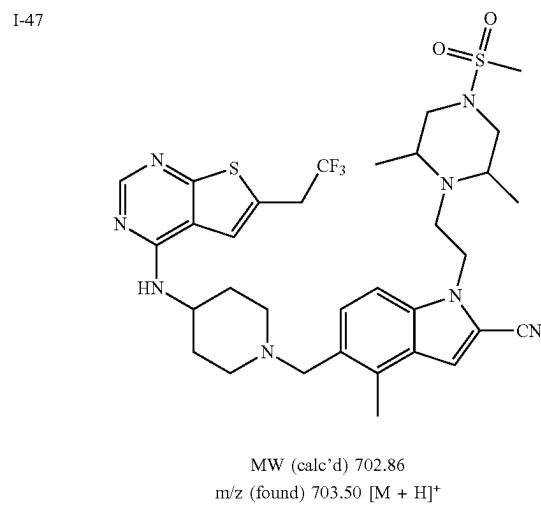
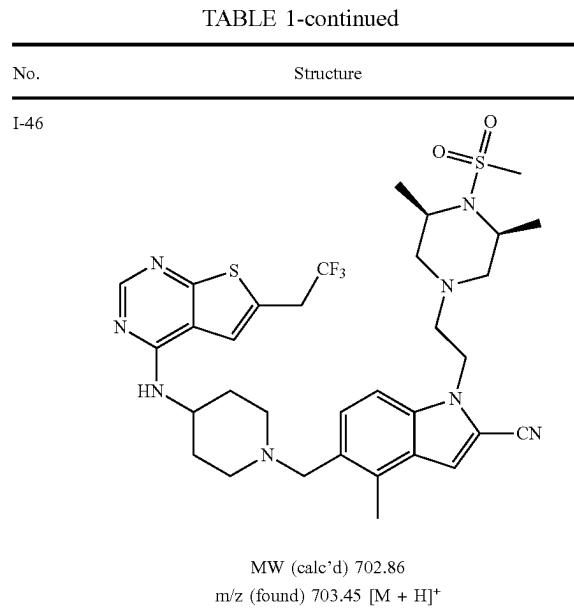
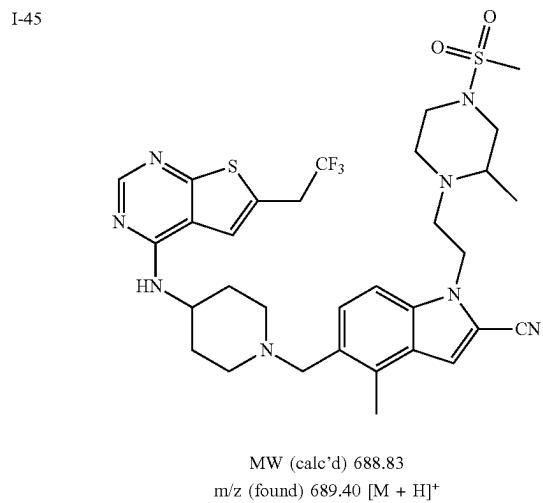
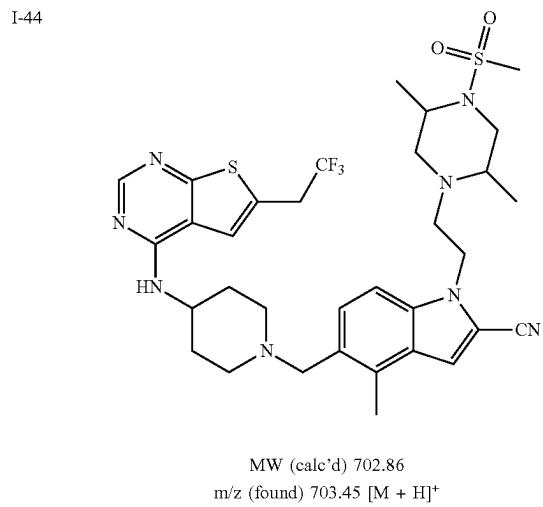
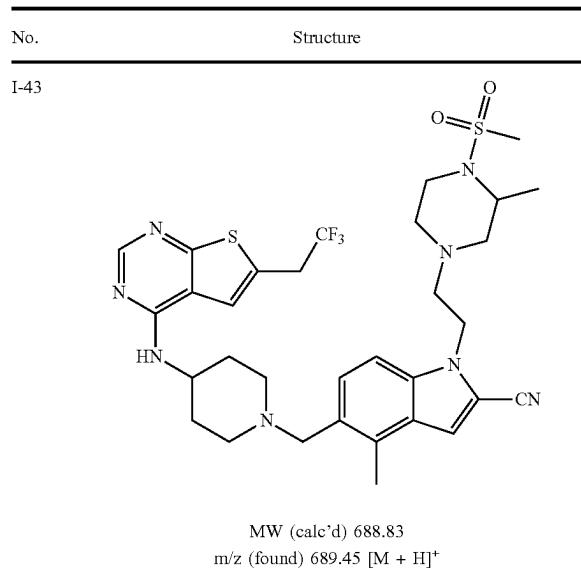


TABLE 1-continued

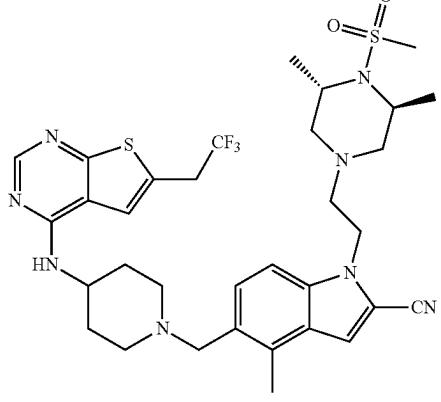
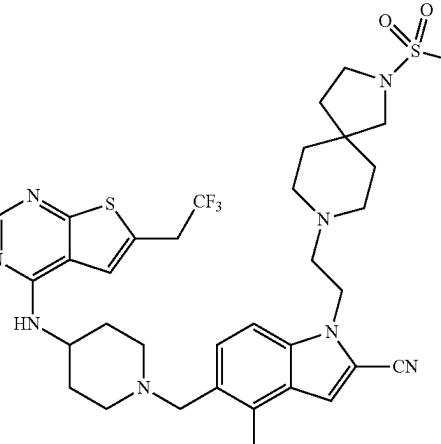
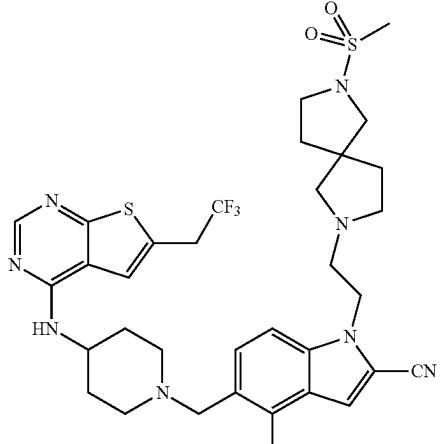
No.	Structure
I-49	
	MW (calc'd) 702.86 m/z (found) 703.55 [M + H] ⁺
I-52	
	MW (calc'd) 728.89 m/z (found) 729.55 [M + H] ⁺
I-53	
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TABLE 1-continued

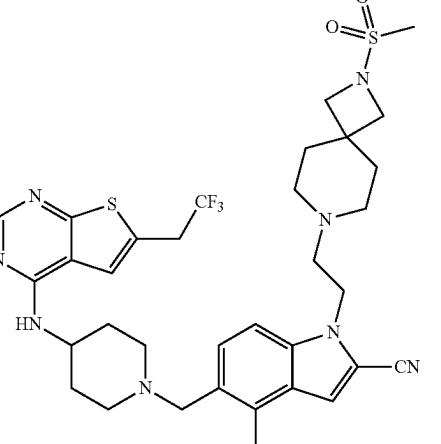
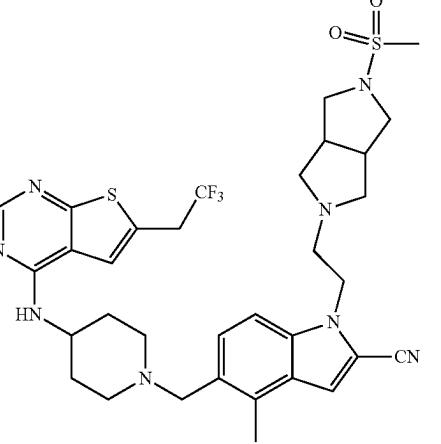
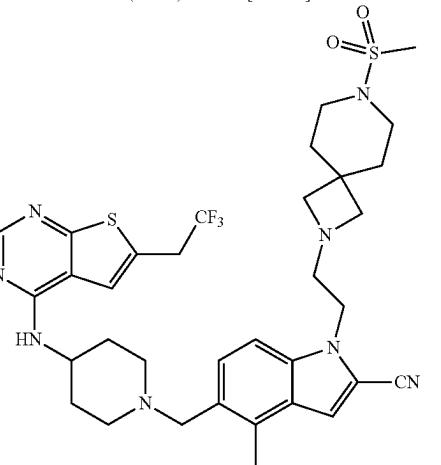
No.	Structure
I-54	
	MW (calc'd) 714.87 m/z (found) 715.30 [M + H] ⁺
I-55	
	MW (calc'd) 700.84 m/z (found) 701.30 [M + H] ⁺
I-56	
	MW (calc'd) 714.87 m/z (found) 715.35 [M + H] ⁺

TABLE 1-continued

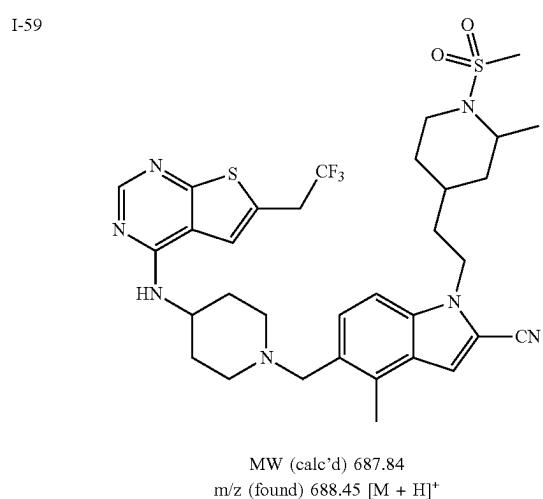
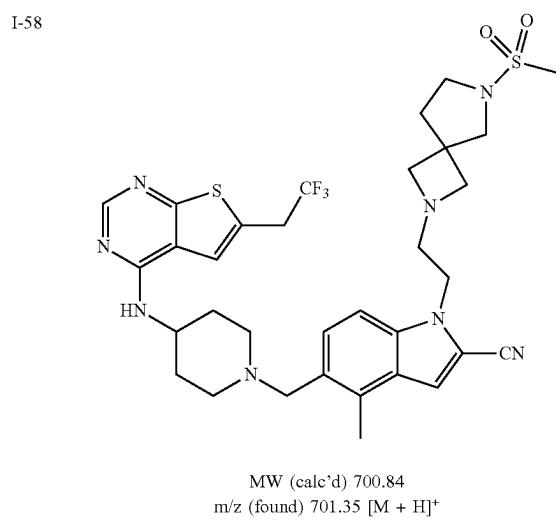
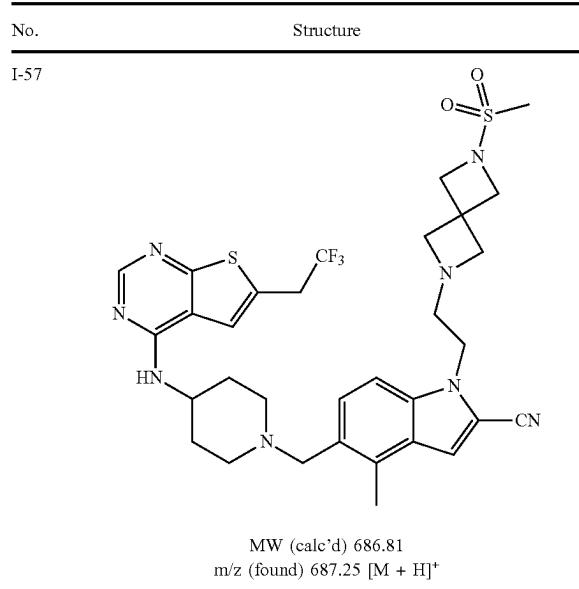


TABLE 1-continued

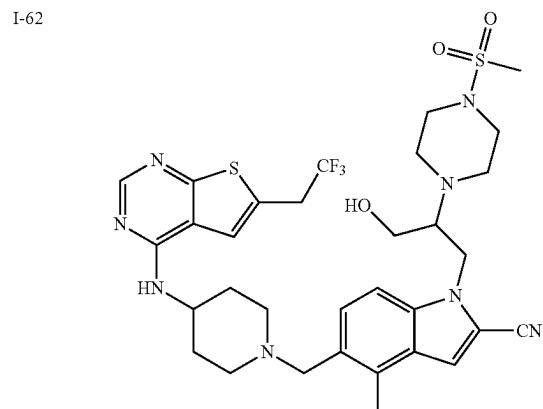
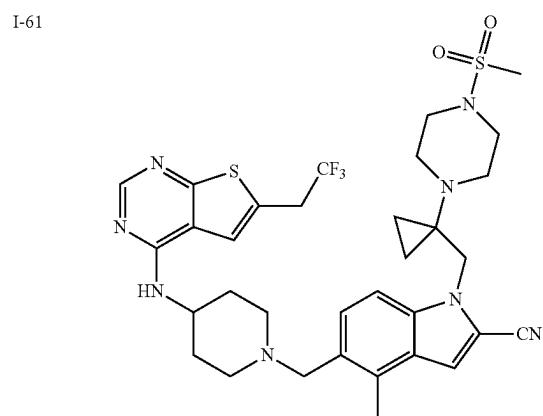
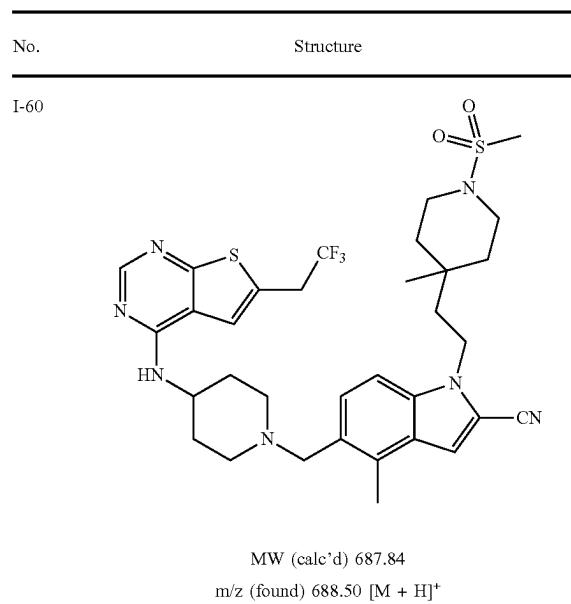


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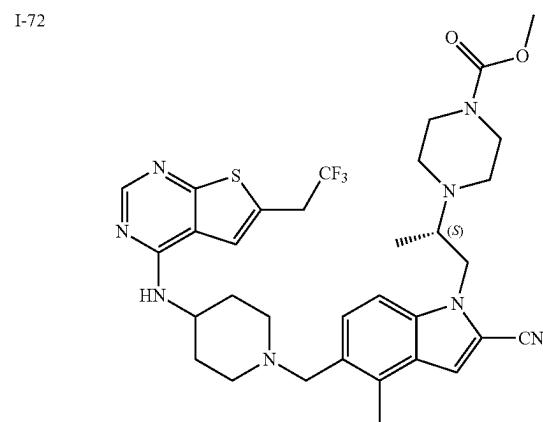
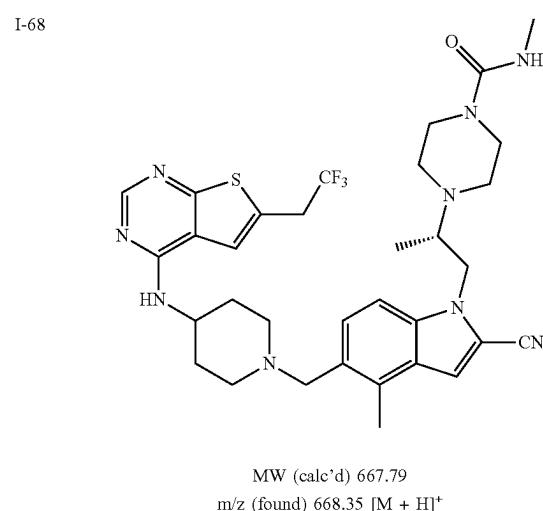
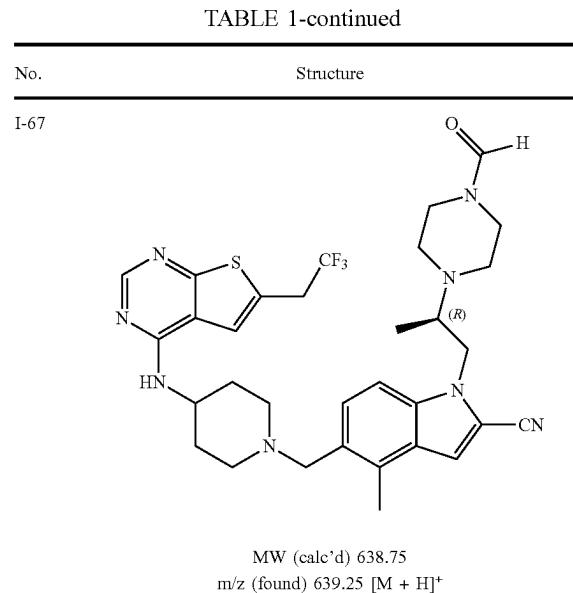
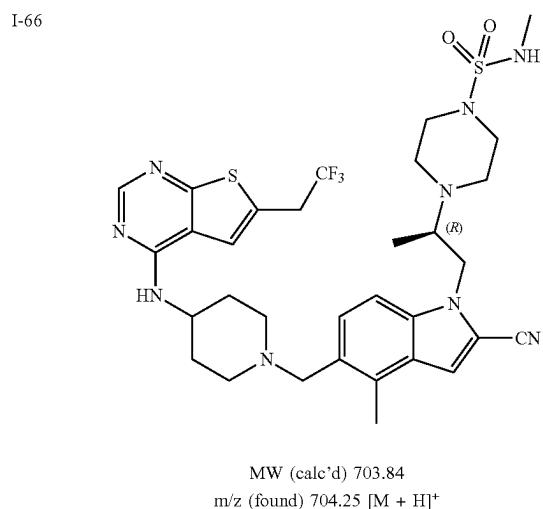
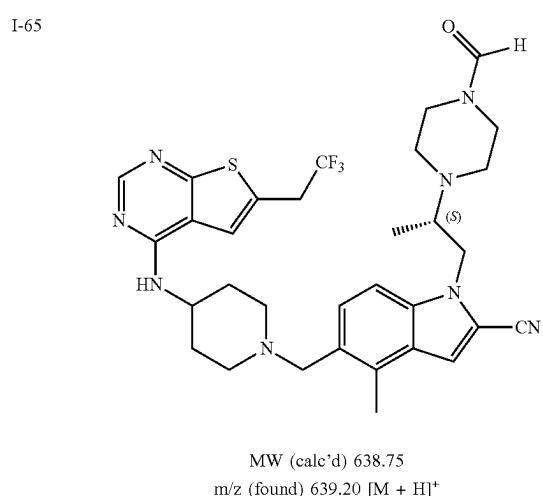
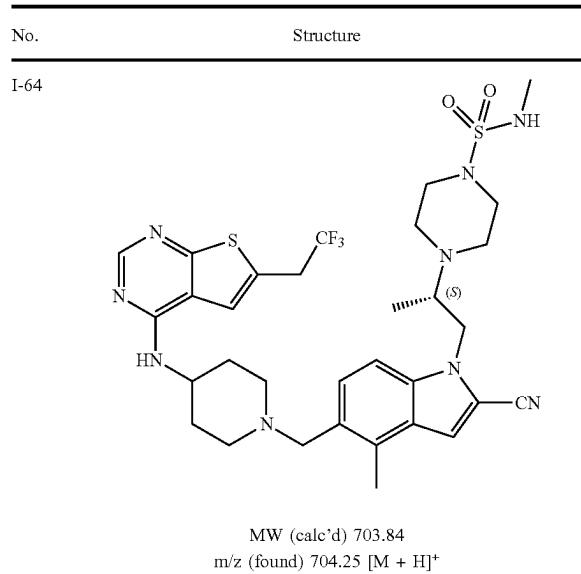
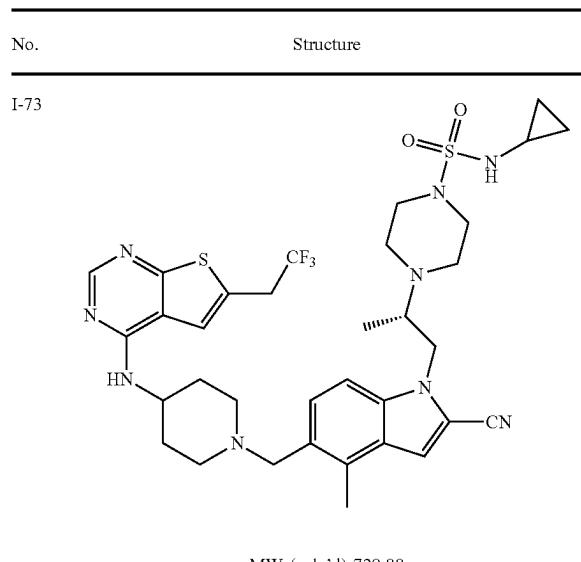


TABLE 1-continued



MW (calc'd) 729.88
m/z (found) 730.30 [M + H]⁺

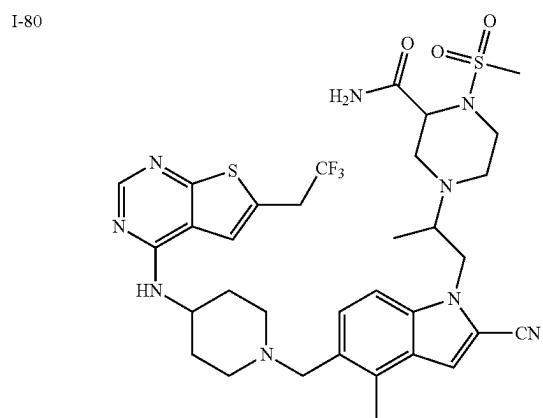
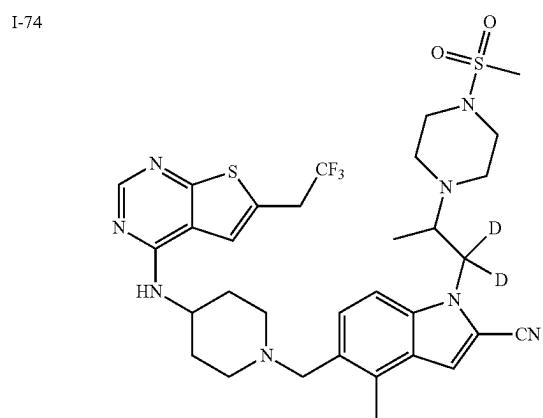
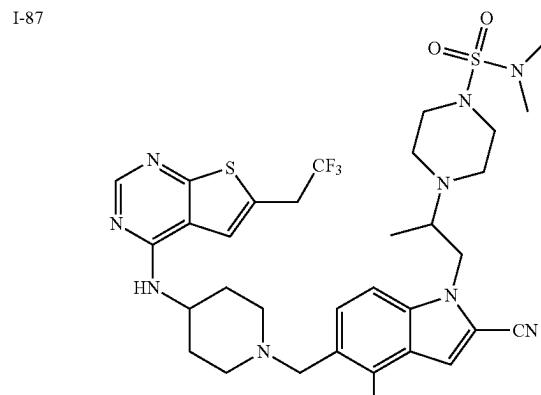
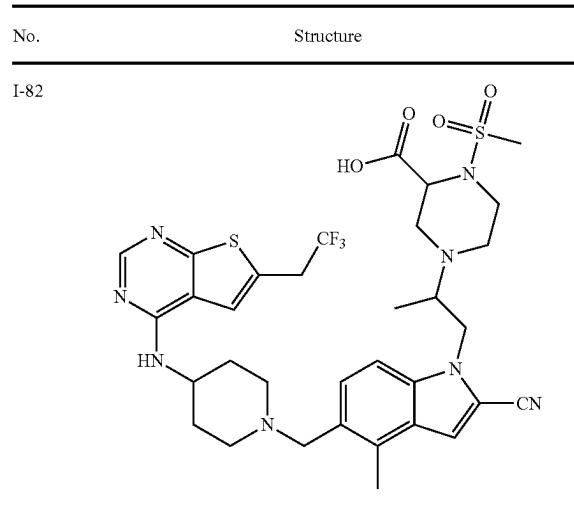
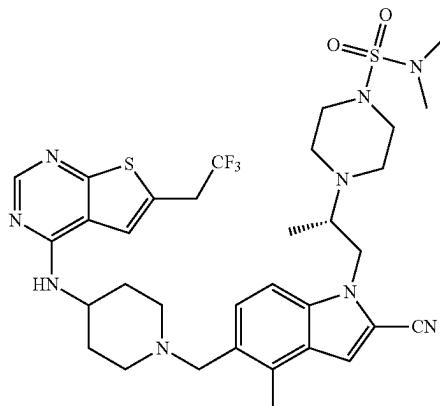


TABLE 1-continued



MW (calc'd) 717.29
m/z (found) 718.35 [M + H]⁺



MW (calc'd) 717.29
m/z (found) 718.25 [M + H]⁺

TABLE 1-continued

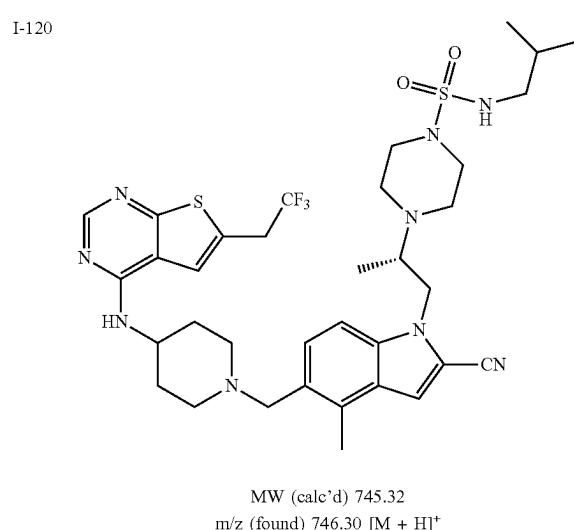
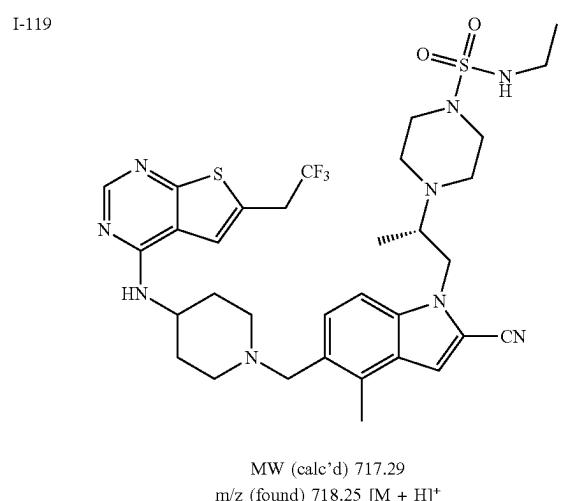
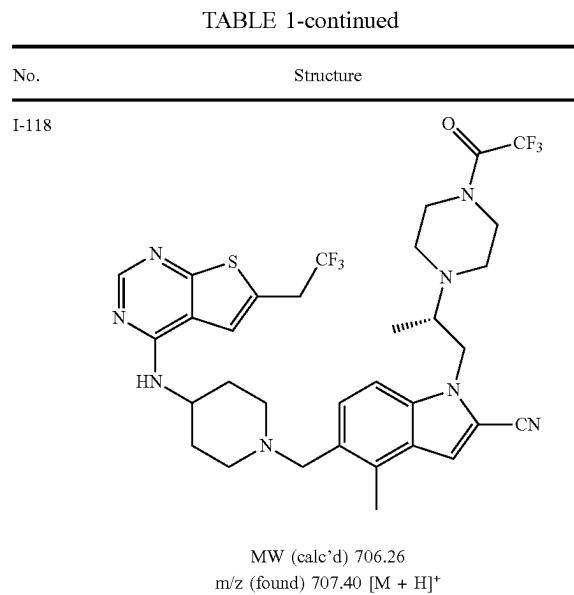
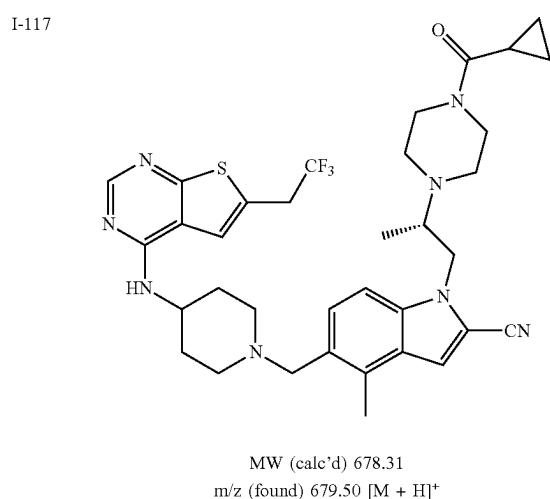
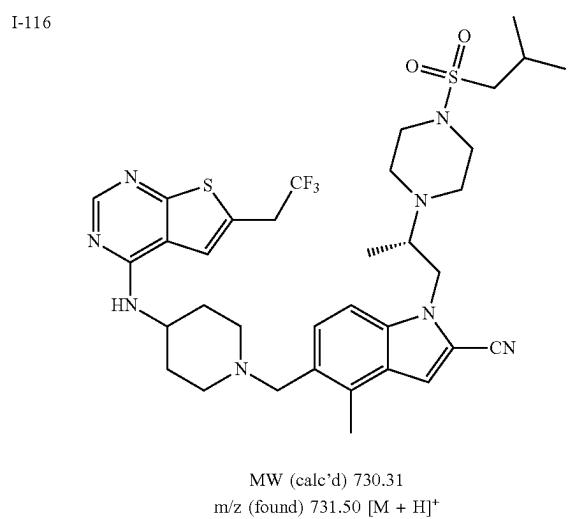
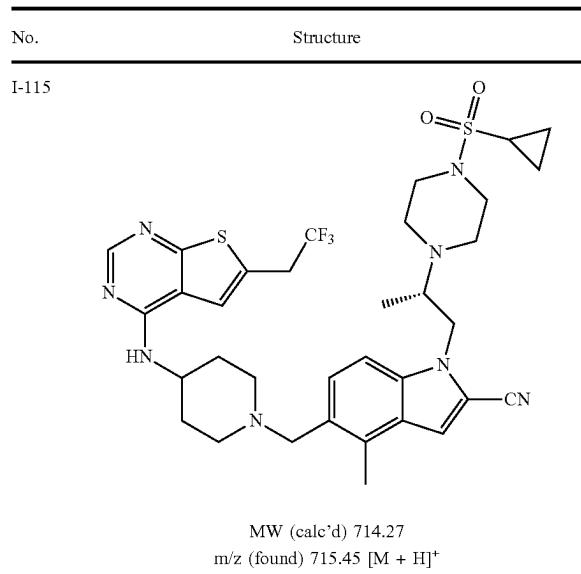


TABLE 1-continued

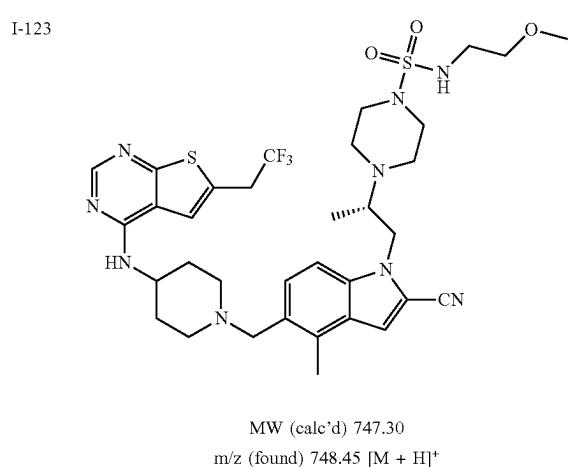
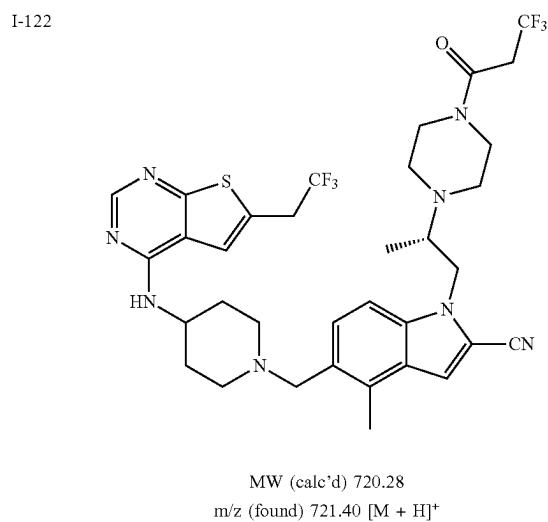
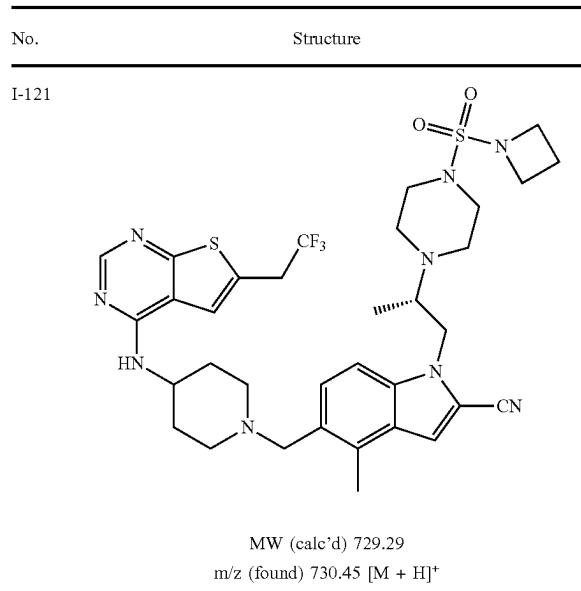


TABLE 1-continued

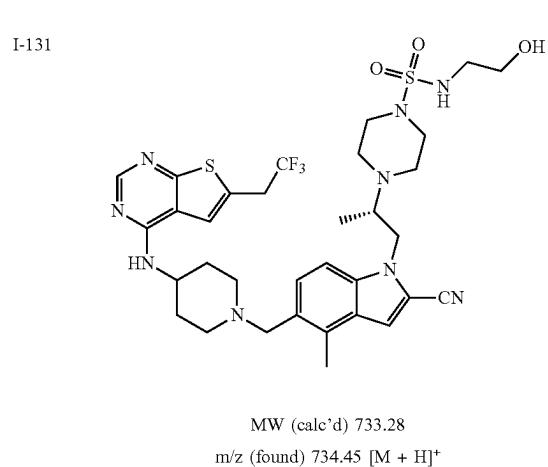
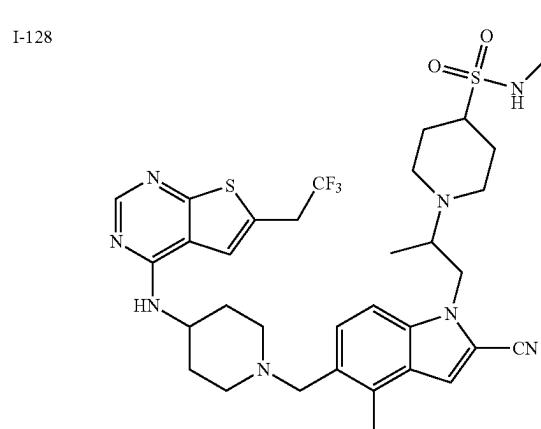
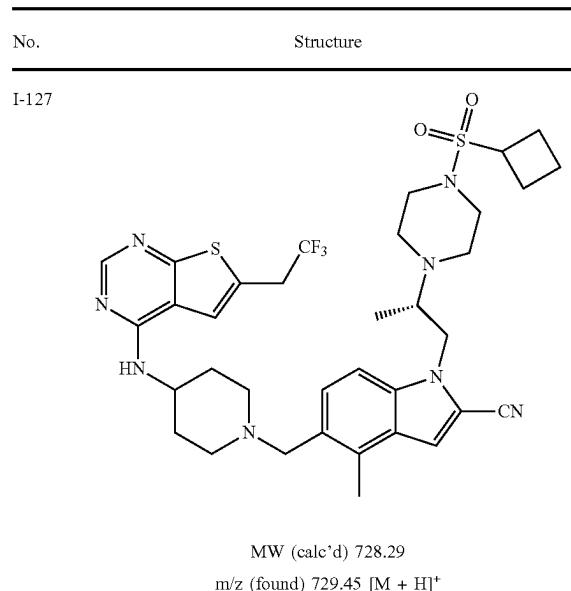


TABLE 1-continued

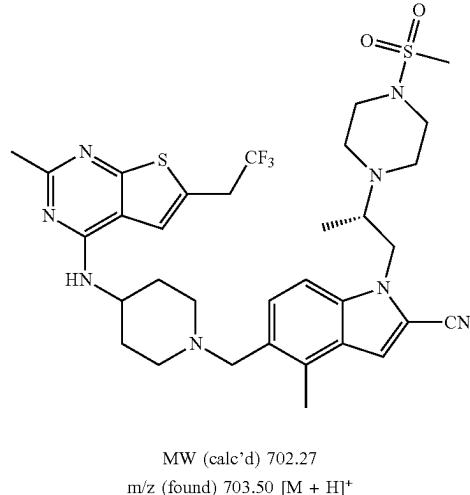
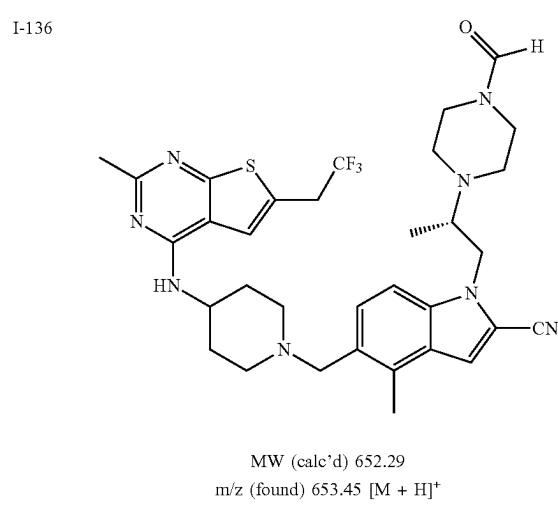
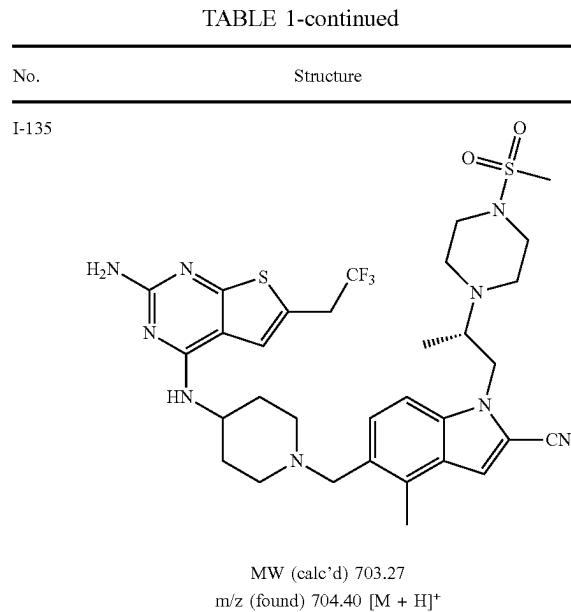
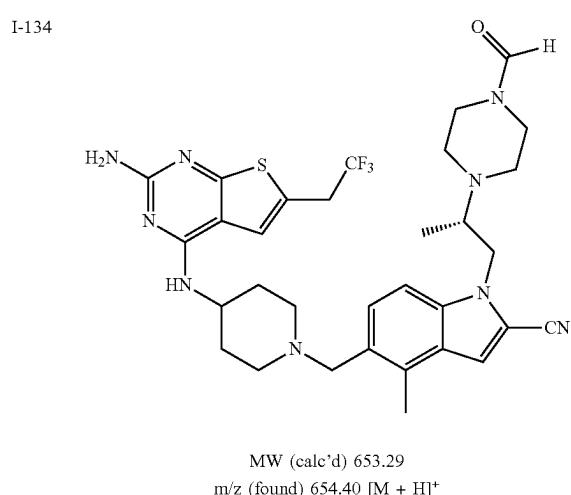
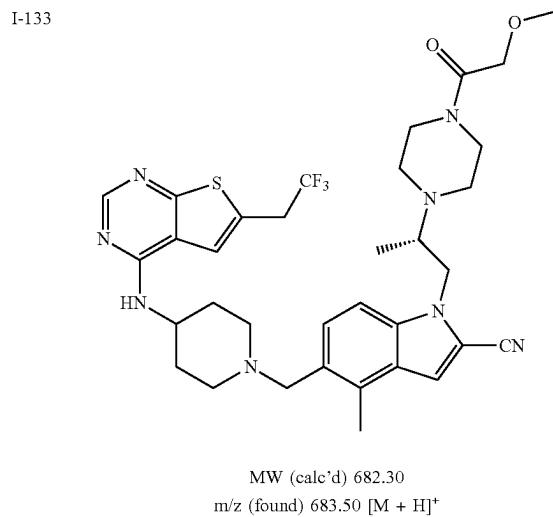
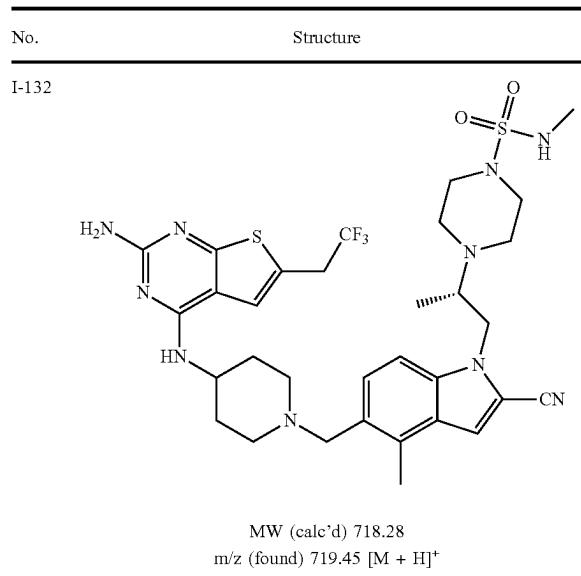


TABLE 1-continued

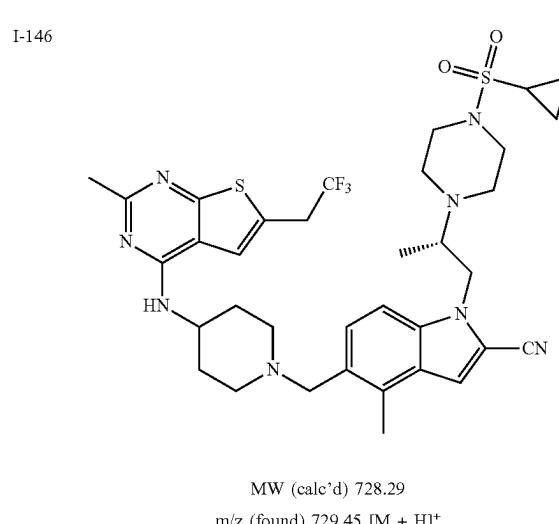
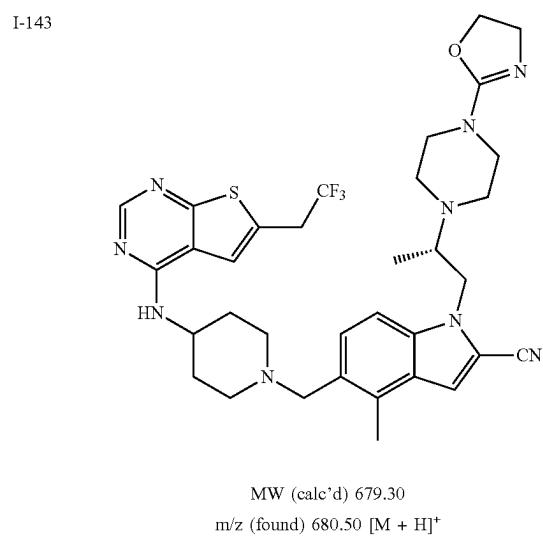
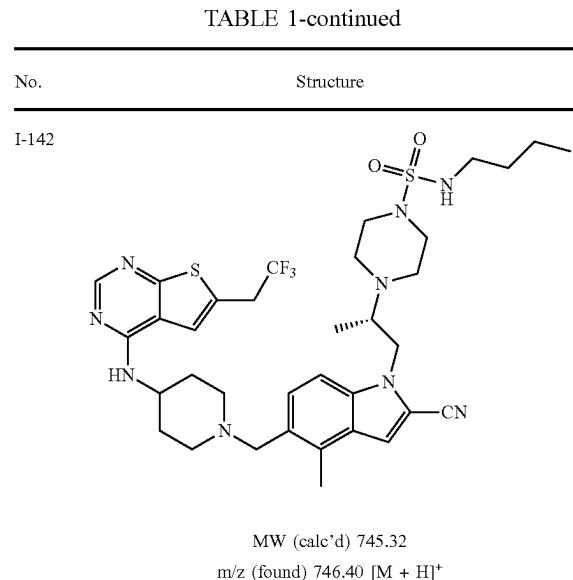
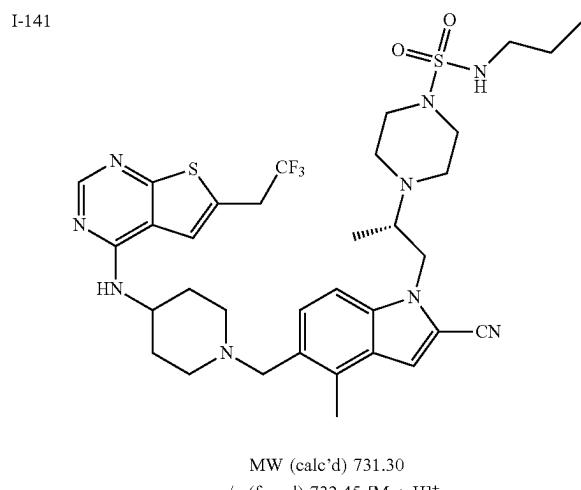
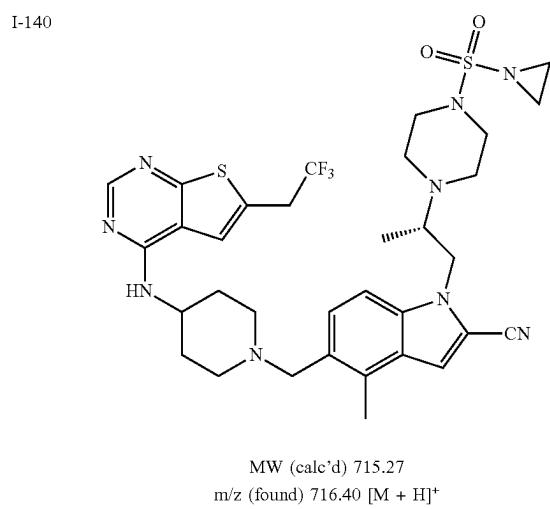
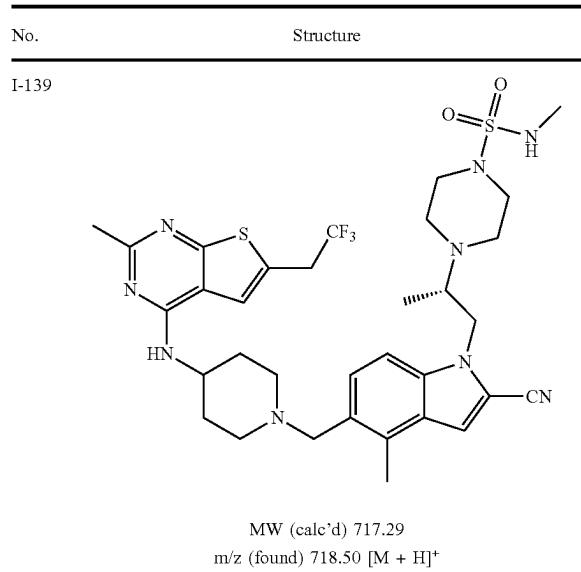
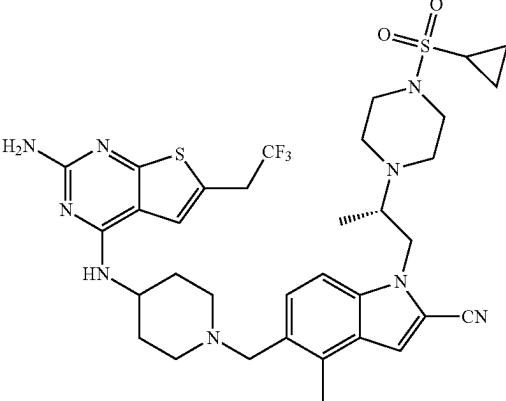
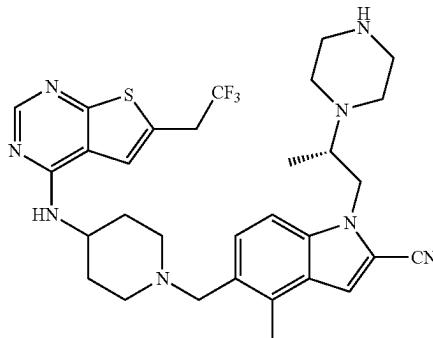


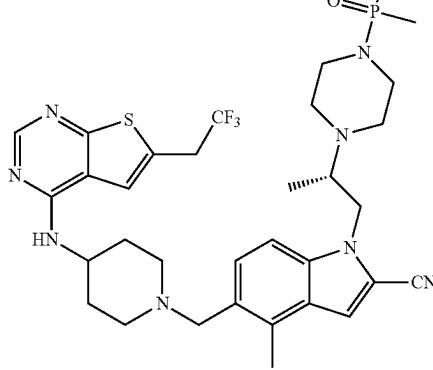
TABLE 1-continued

No.	Structure
I-147	

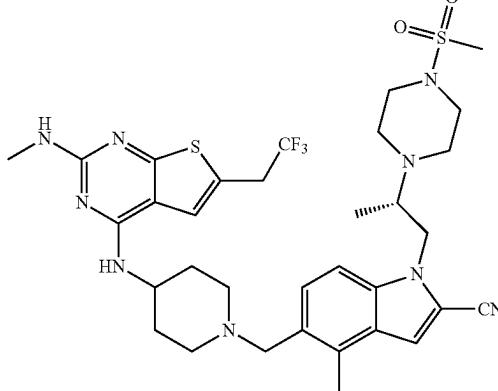
MW (calc'd) 729.29
m/z (found) 730.40 [M + H]⁺

No.	Structure
I-148	

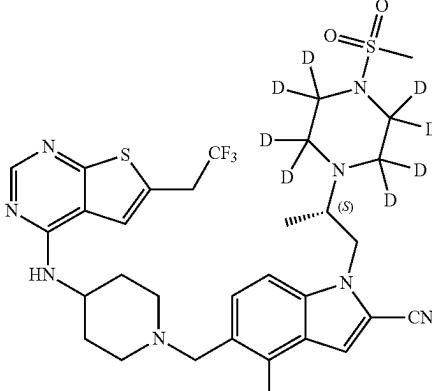
MW (calc'd) 610.28
m/z (found) 611.3 [M + H]⁺

No.	Structure
I-150	

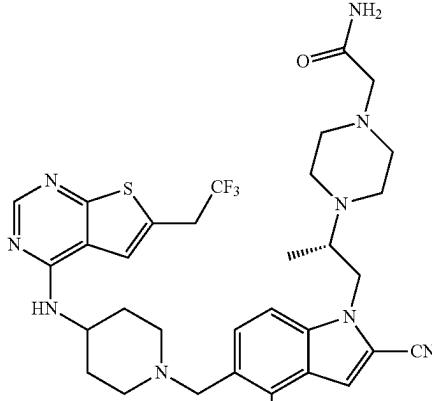
MW (calc'd) 686.29
m/z (found) 687.3 [M + H]⁺

No.	Structure
I-151	

MW (calc'd) 717.29
m/z (found) 718.55 [M + H]⁺

No.	Structure
I-153	

MW (calc'd) 696.31

No.	Structure
I-154	

MW (calc'd) 667.30
m/z (found) 668.35 [M + H]⁺

TABLE 1-continued

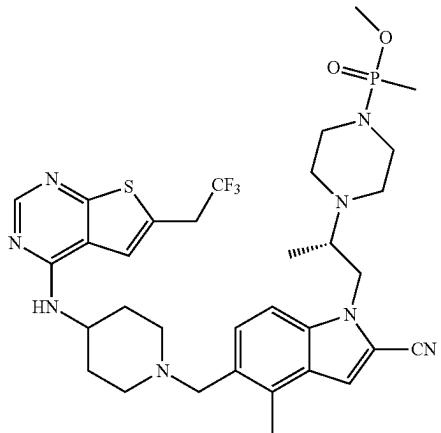
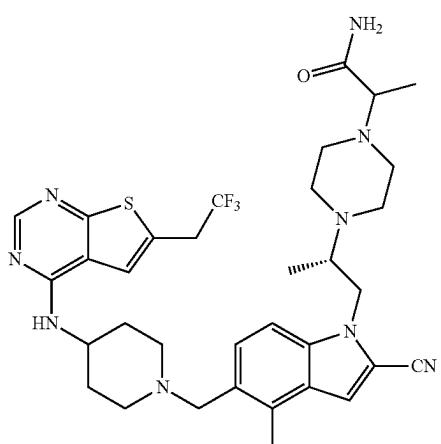
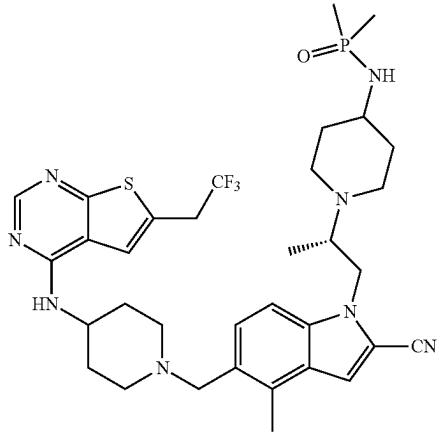
No.	Structure
I-155	
	MW (calc'd) 702.28 m/z (found) 703.35 [M + H] ⁺
I-156	
	MW (calc'd) 681.32 m/z (found) 682.45 [M + H] ⁺
I-157	
	MW (calc'd) 700.30 m/z (found) 701.40 [M + H] ⁺

TABLE 1-continued

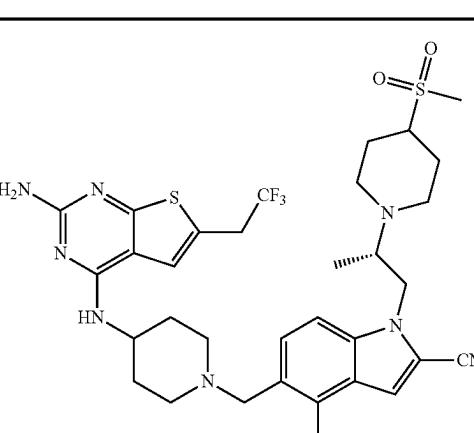
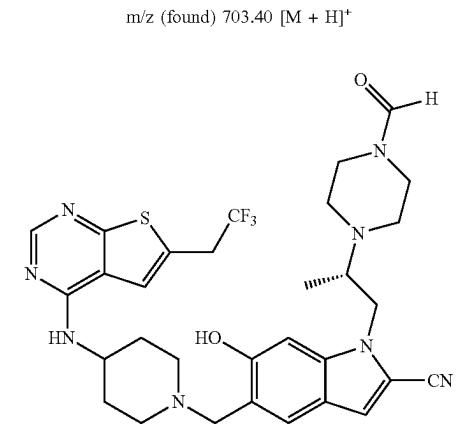
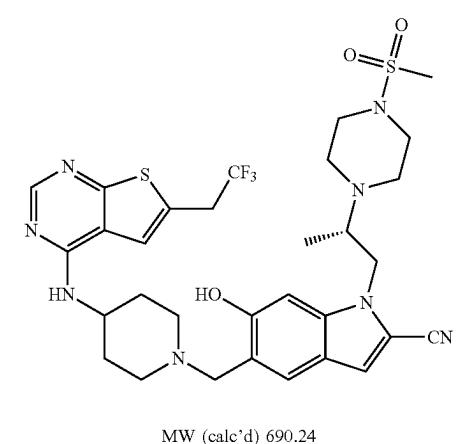
No.	Structure
I-158	
	MW (calc'd) 702.27 m/z (found) 703.40 [M + H] ⁺
I-159	
	MW (calc'd) 640.26 m/z (found) 641.40 [M + H] ⁺
I-160	
	MW (calc'd) 690.24 m/z (found) 691.35 [M + H] ⁺

TABLE 1-continued

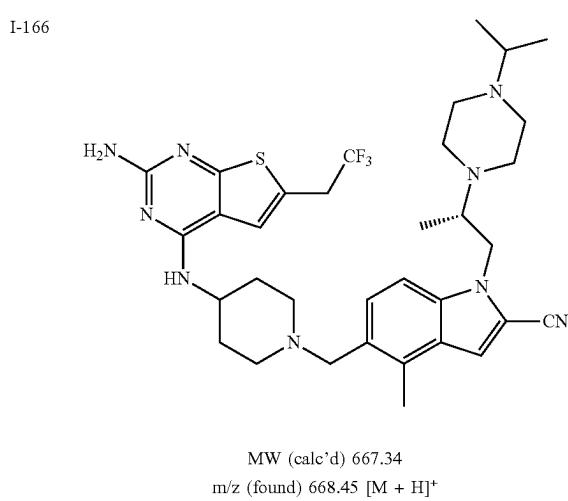
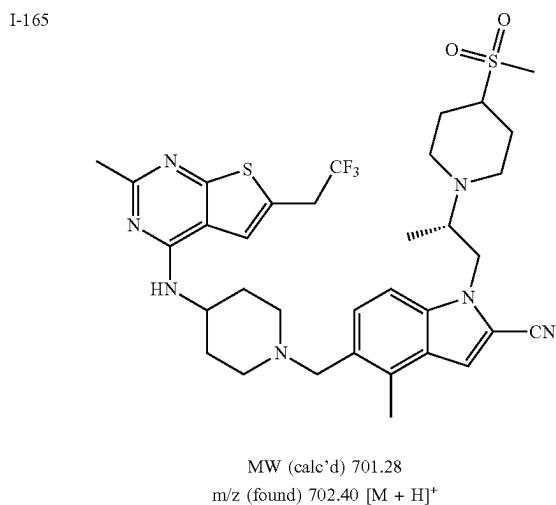
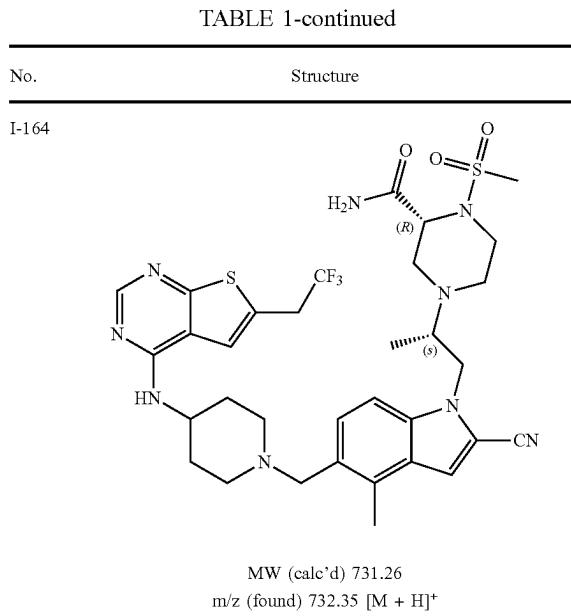
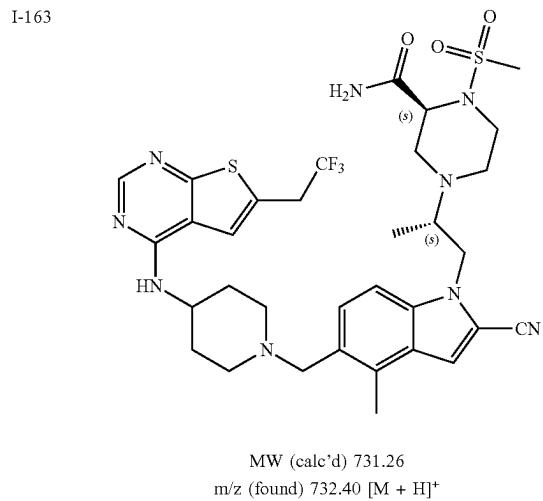
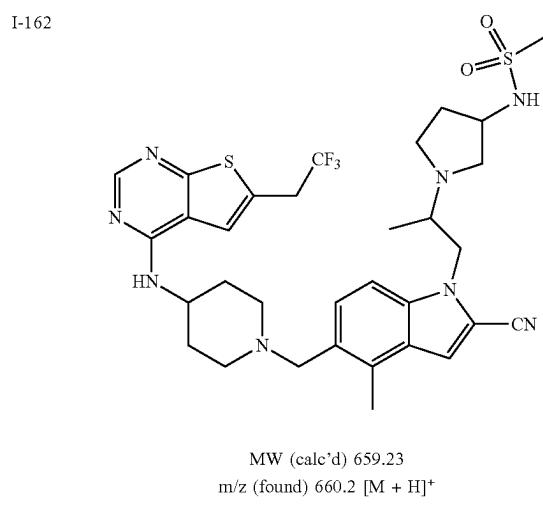
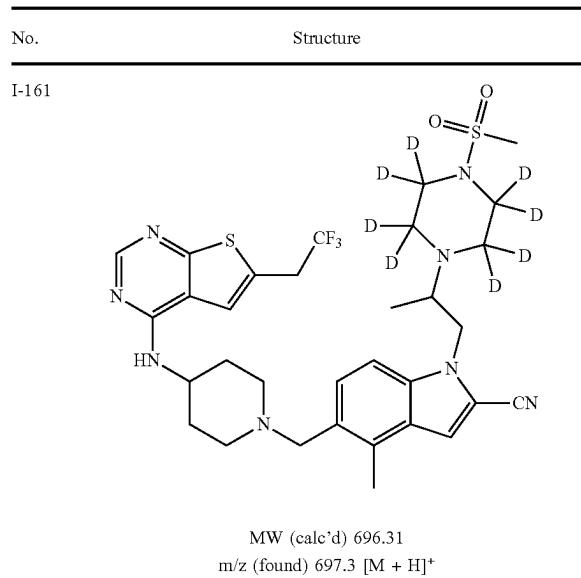
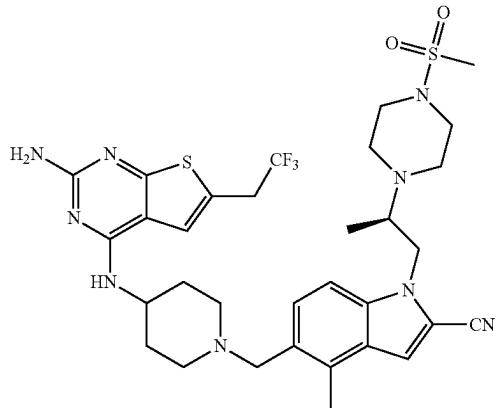


TABLE 1-continued

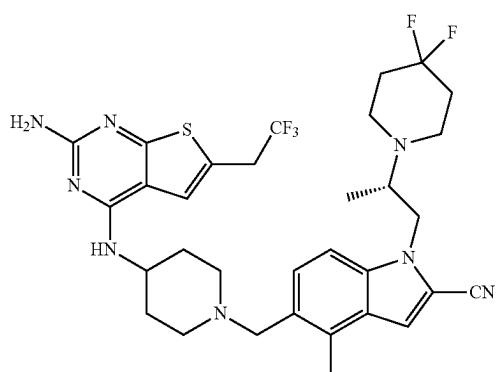
No.	Structure
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I-167



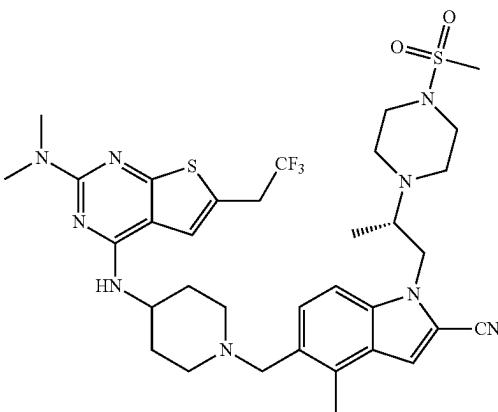
MW (calc'd) 703.27
m/z (found) 704.40 [M + H]⁺

I-168



MW (calc'd) 660.28
m/z (found) 661.40 [M + H]⁺

I-170

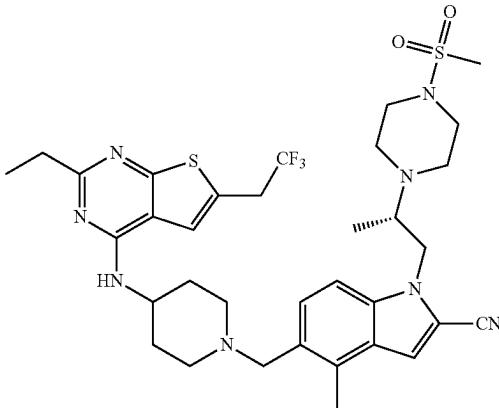


MW (calc'd) 731.30
m/z (found) 732.40 [M + H]⁺

TABLE 1-continued

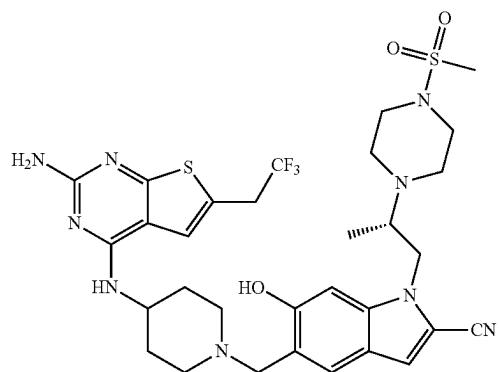
No.	Structure
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I-171



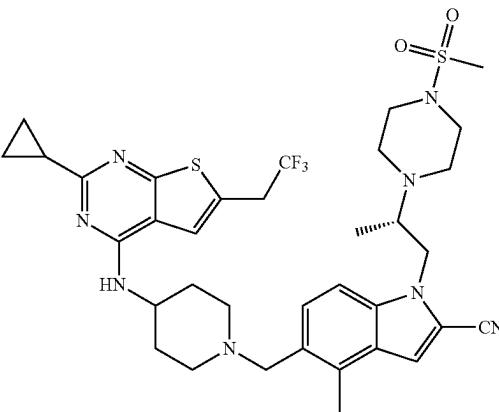
MW (calc'd) 716.29
m/z (found) 717.45 [M + H]⁺

I-172



MW (calc'd) 705.25
m/z (found) 706.45 [M + H]⁺

I-173



MW (calc'd) 728.29
m/z (found) 729.45 [M + H]⁺

TABLE 1-continued

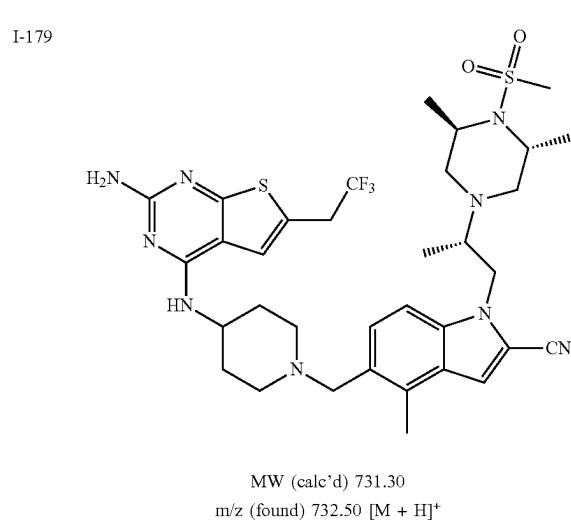
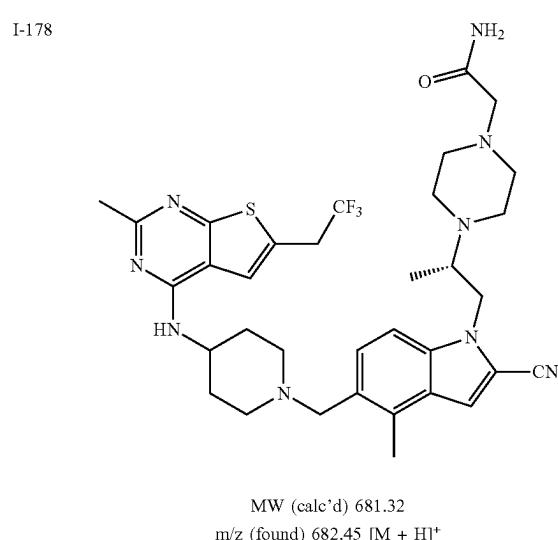
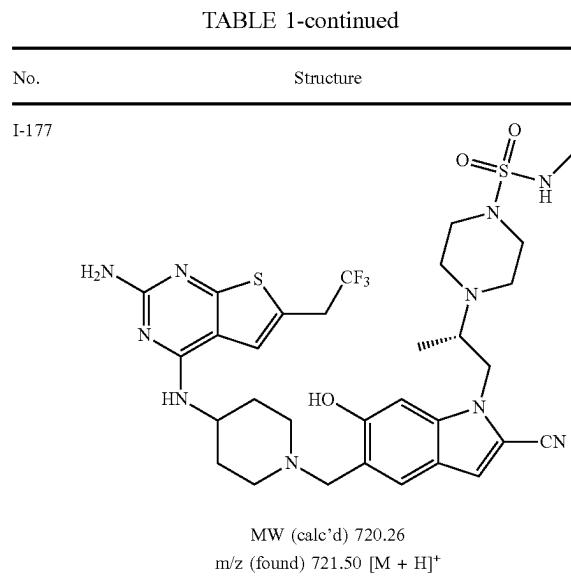
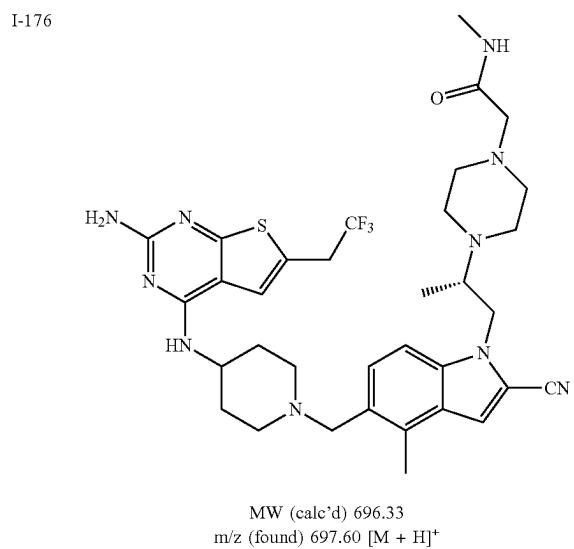
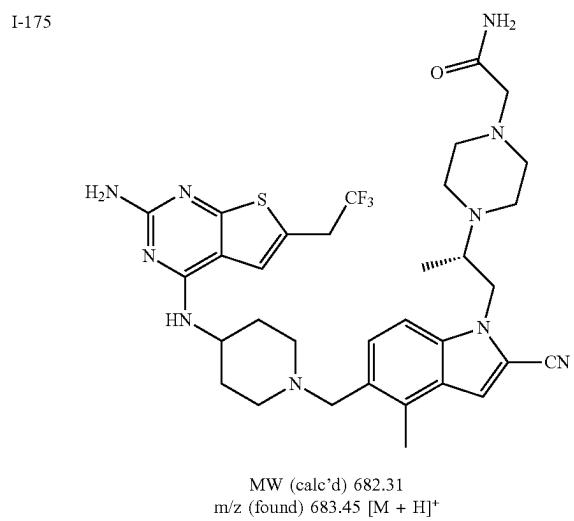
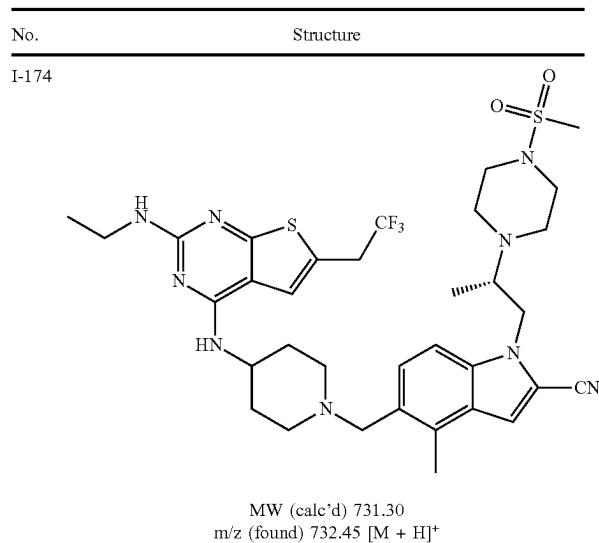


TABLE 1-continued

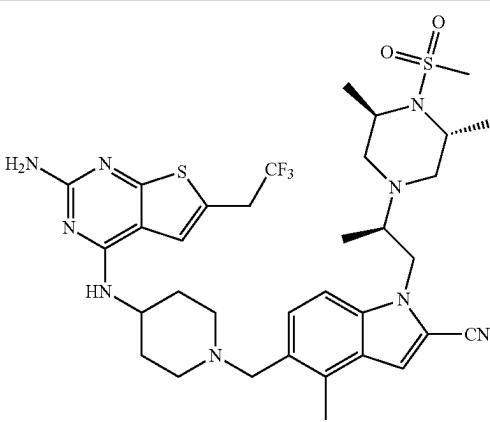
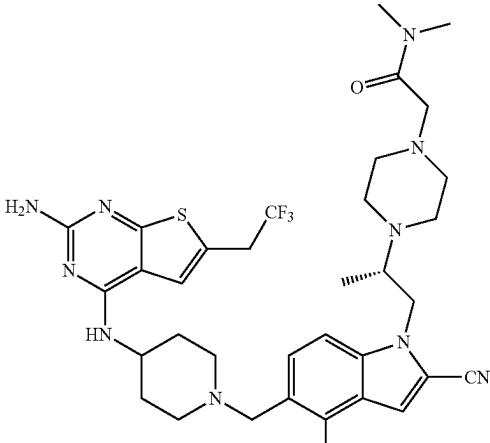
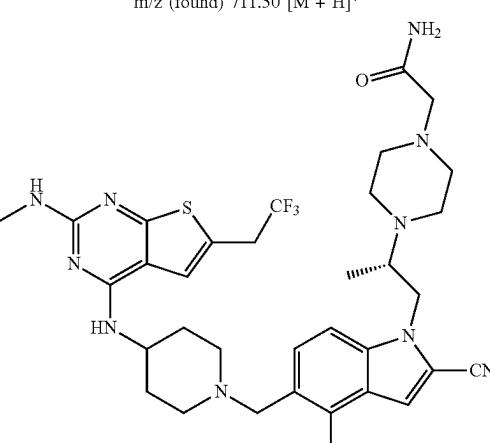
No.	Structure
I-180	
	MW (calc'd) 731.30 m/z (found) 732.50 [M + H] ⁺
I-181	
	MW (calc'd) 710.35 m/z (found) 711.50 [M + H] ⁺
I-182	
	MW (calc'd) 696.33 m/z (found) 697.60 [M + H] ⁺

TABLE 1-continued

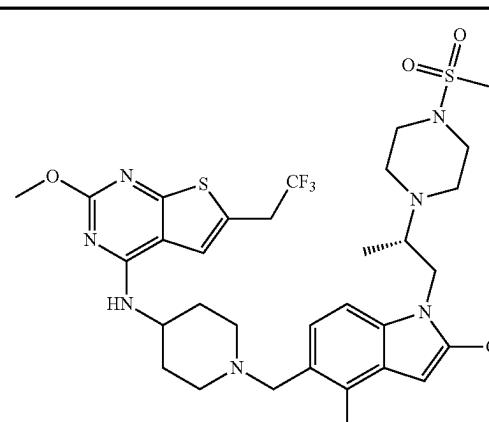
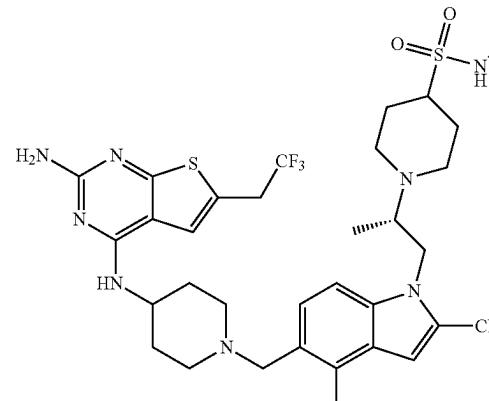
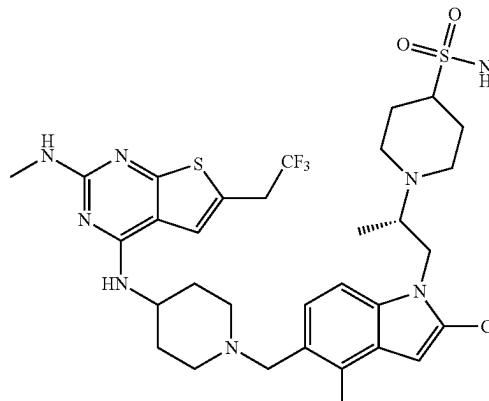
No.	Structure
I-183	
	MW (calc'd) 718.27 m/z (found) 719.45 [M + H] ⁺
I-184	
	MW (calc'd) 717.29 m/z (found) 718.45 [M + H] ⁺
I-185	
	MW (calc'd) 731.30 m/z (found) 732.45 [M + H] ⁺

TABLE 1-continued

No.	Structure
I-186	

MW (calc'd) 716.29
m/z (found) 717.45 [M + H]⁺

I-187

MW (calc'd) 733.28
m/z (found) 734.45 [M + H]⁺

I-188

MW (calc'd) 626.28
m/z (found) 627.40 [M + H]⁺

TABLE 1-continued

MW (calc'd) 710.35
m/z (found) 711.45 [M + H]⁺

I-190

MW (calc'd) 665.32
m/z (found) 666.45 [M + H]⁺

I-191

Chemical structure I-191 is a complex organic molecule. It features a central 2-(trifluoromethyl)-4-thiopyrimidine core. Attached to the 5-position is an *N*-methylamino group (*H*₃*N*-CH₂-). Attached to the 4-position is a long-chain substituent: a 2-(cyclohexylmethyl)-4-phenylpyrimidine-6-carbonitrile moiety. This side chain consists of a cyclohexylmethyl group linked to a pyrimidine ring, which is then connected to a phenyl ring carrying a cyano group (*CN*). The entire structure is labeled with the identifier I-191.

MW (calc'd) 724.36
m/z (found) 725.45 [M + H]⁺

TABLE 1-continued

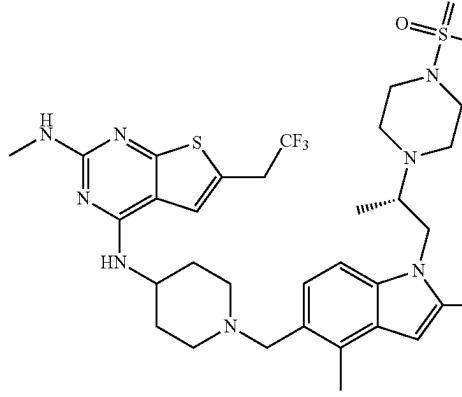
No.	Structure
I-192	 <p>MW (calc'd) 732.30 m/z (found) 733.45 [M + H]⁺</p>

TABLE 1-continued

I-193

MW (calc'd) 716.29
m/z (found) 717.45 [M + H]⁺

I-196

MW (calc'd) 788.32
 m/z (found) 789.45 [M + H]⁺

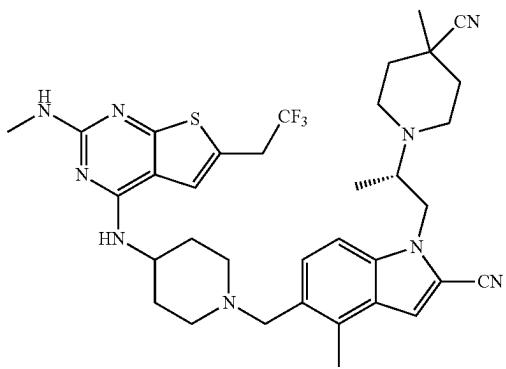
I-194

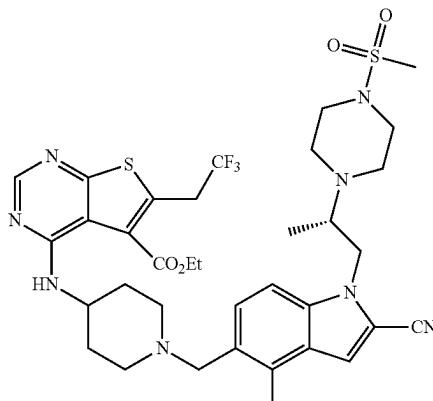
MW (calc'd) 719.26
m/z (found) 720.55 [M + H]⁺

I-197

MW (calc'd) 774.31
m/z (found) 775.5 [M + H]⁺

TABLE 1-continued

No.	Structure
I-199	 <p>MW (calc'd) 677.32 m/z (found) 678.55 [M + H]⁺</p>

No.	Structure
I-200	 <p>MW (calc'd) 760.28 m/z (found) 761.40 [M + H]⁺</p>

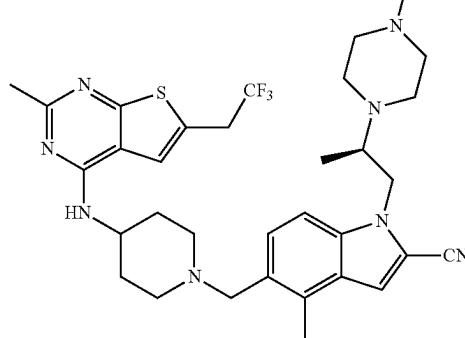
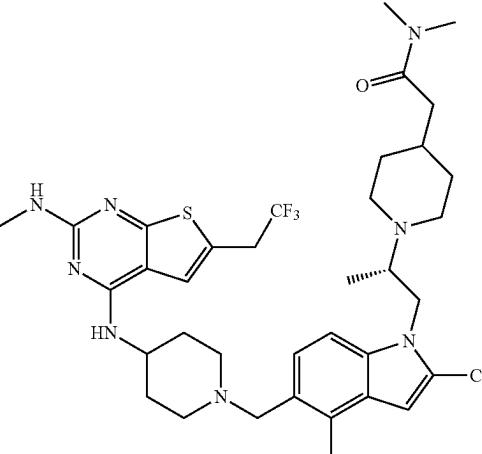
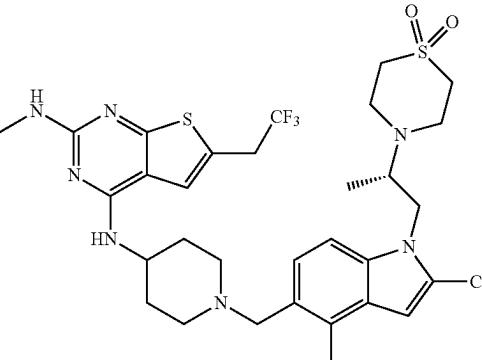
No.	Structure
I-201	 <p>MW (calc'd) 702.27 m/z (found) 703.45 [M + H]⁺</p>

TABLE 1-continued

No.	Structure
I-202	 <p>MW (calc'd) 723.37 m/z (found) 724.55 [M + H]⁺</p>

No.	Structure
I-203	 <p>MW (calc'd) 688.26 m/z (found) 689.40 [M + H]⁺</p>

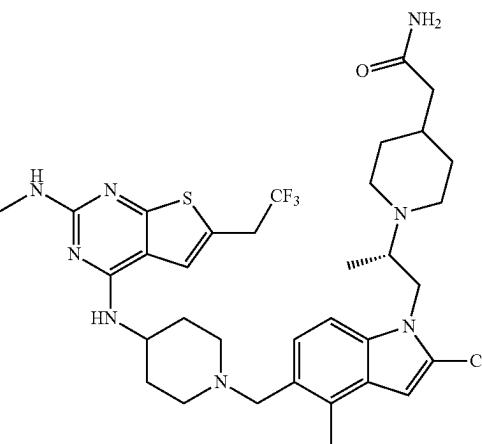
No.	Structure
I-204	 <p>MW (calc'd) 695.33 m/z (found) 696.60 [M + H]⁺</p>

TABLE 1-continued

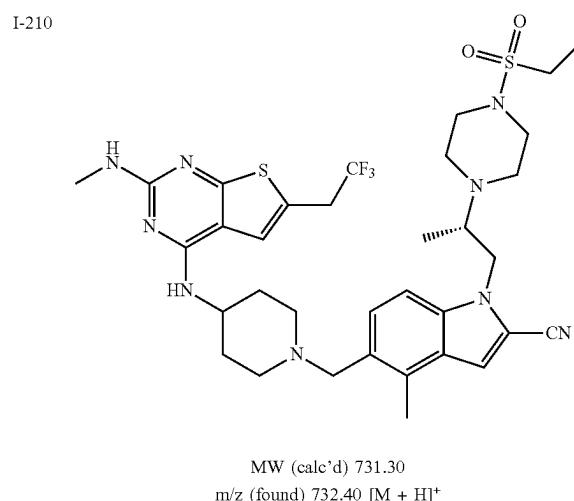
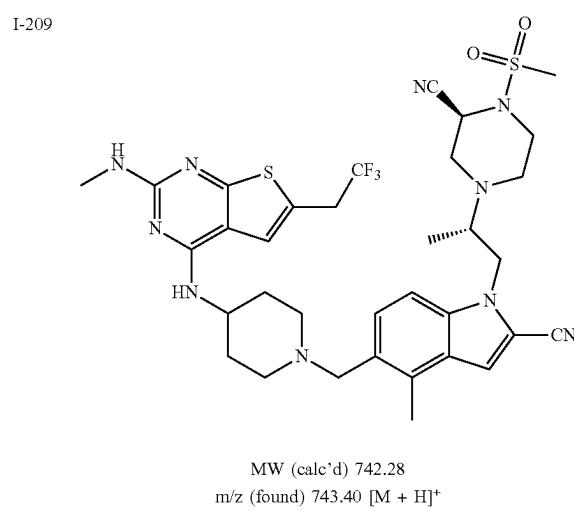
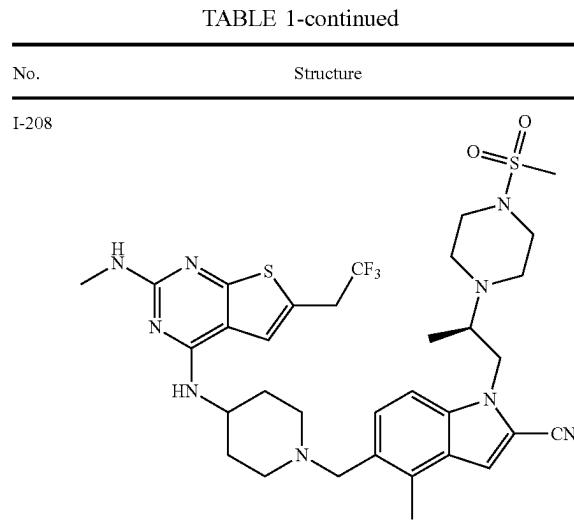
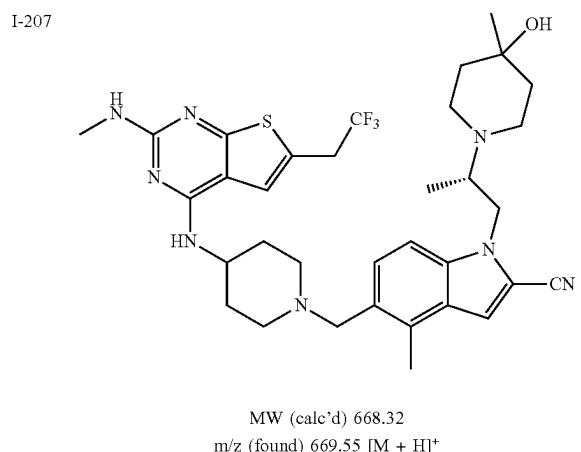
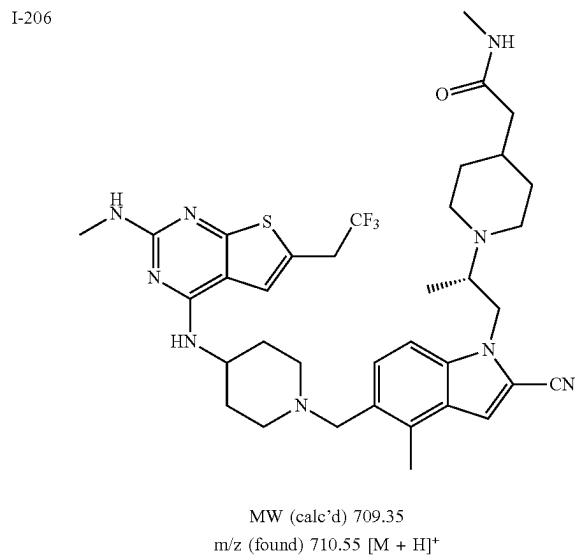
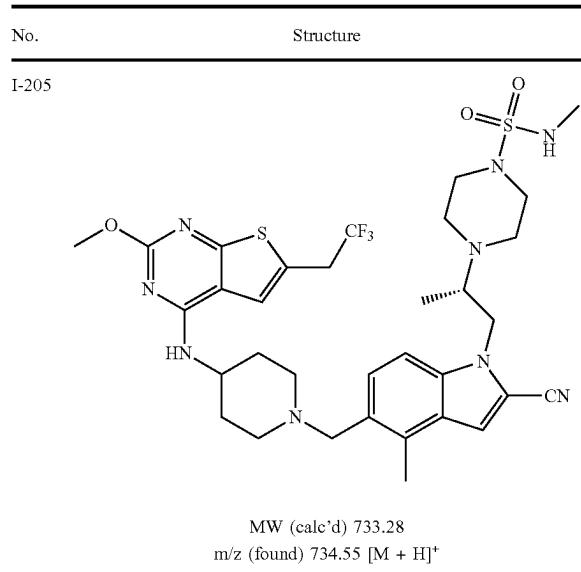


TABLE 1-continued

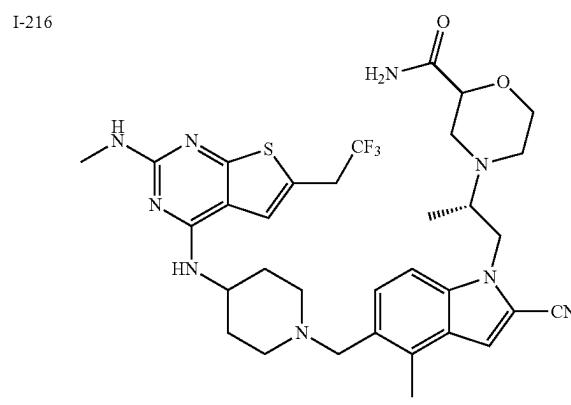
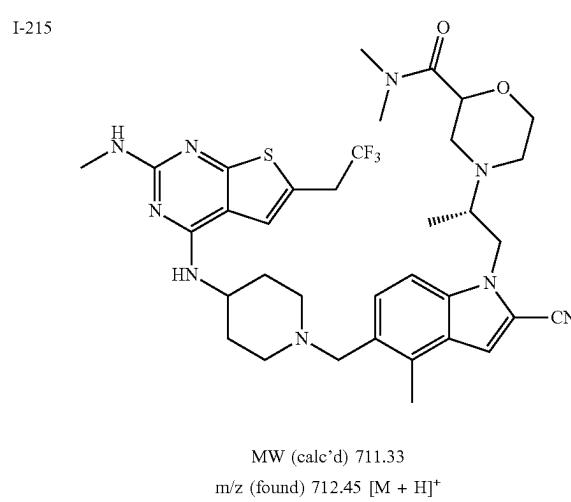
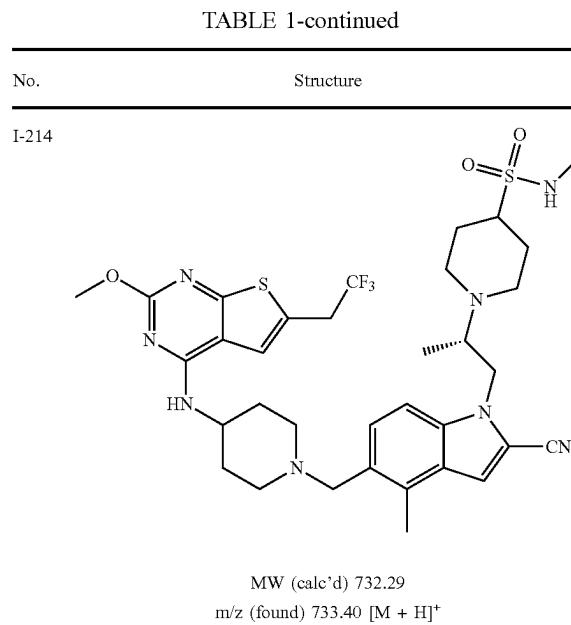
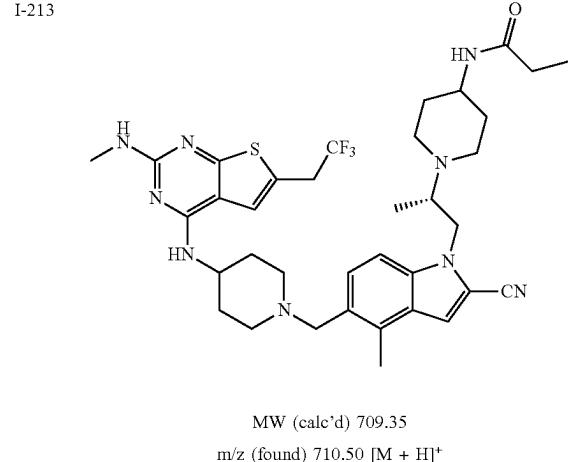
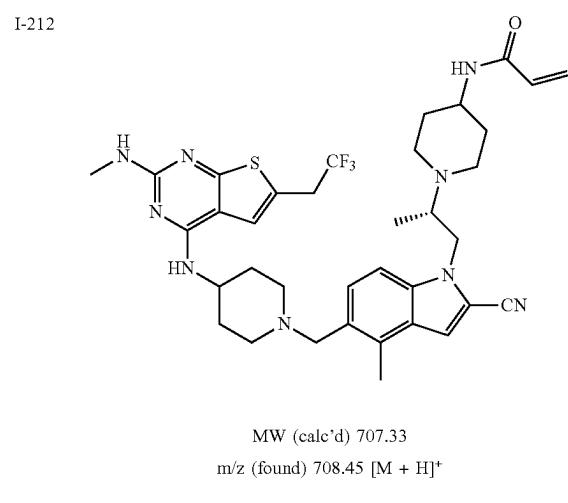
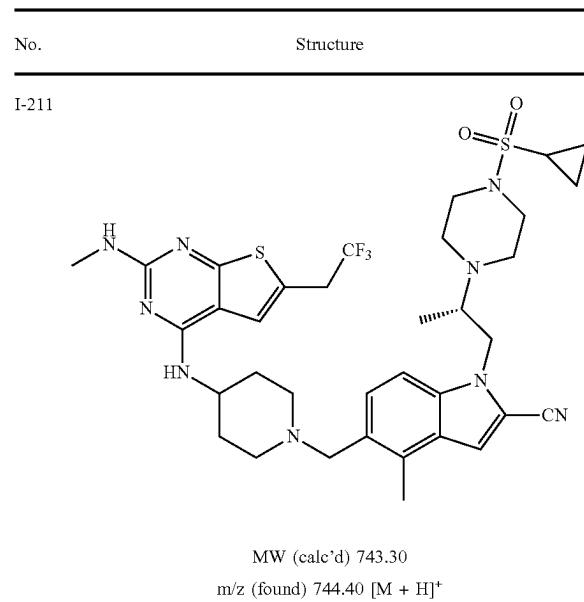


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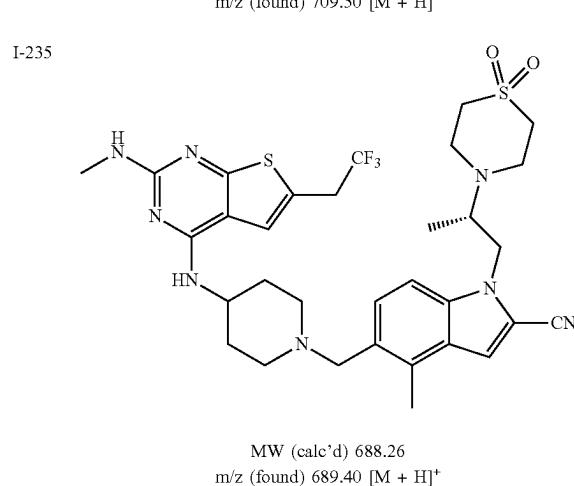
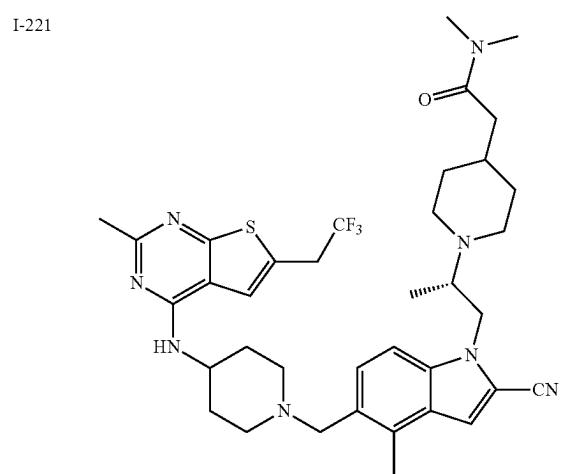
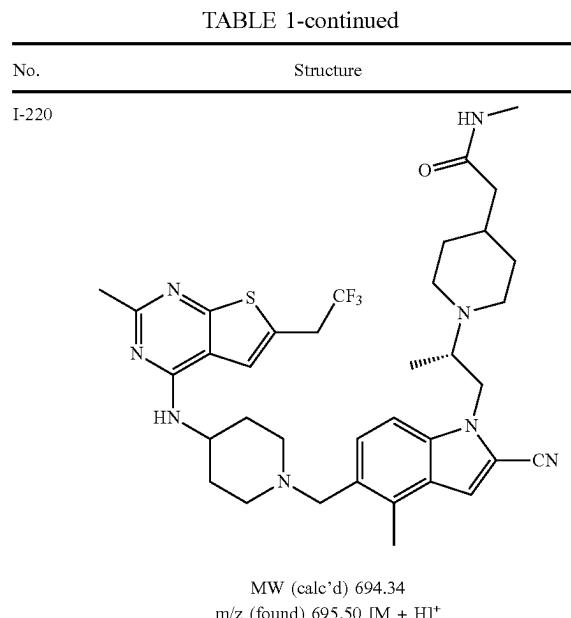
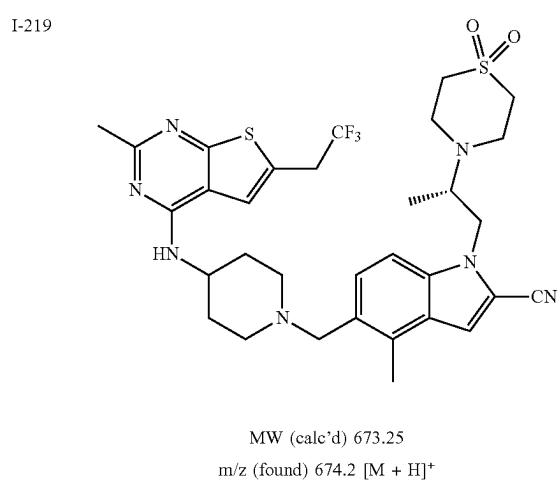
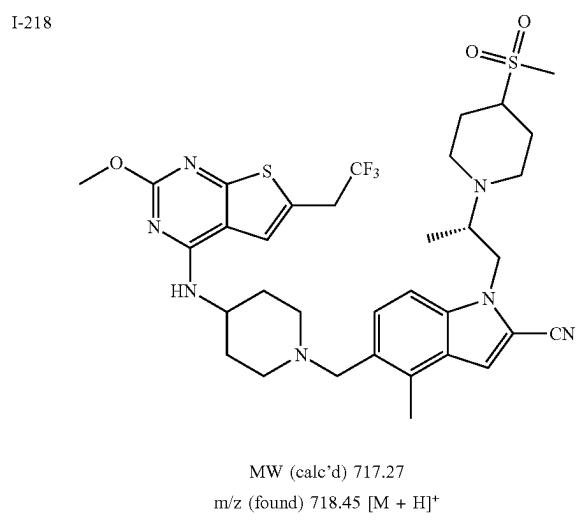
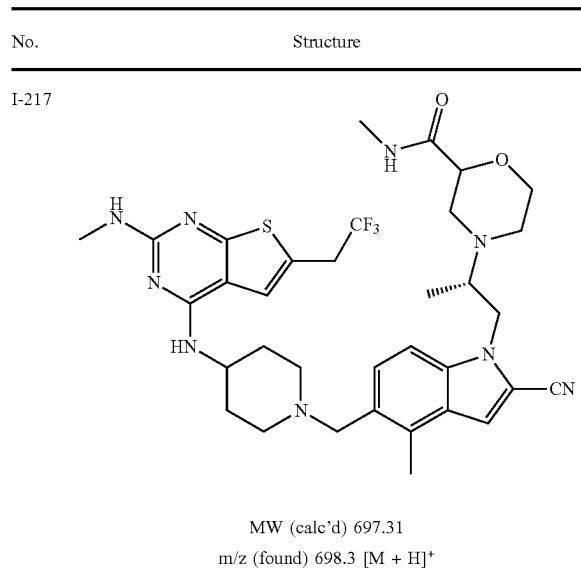
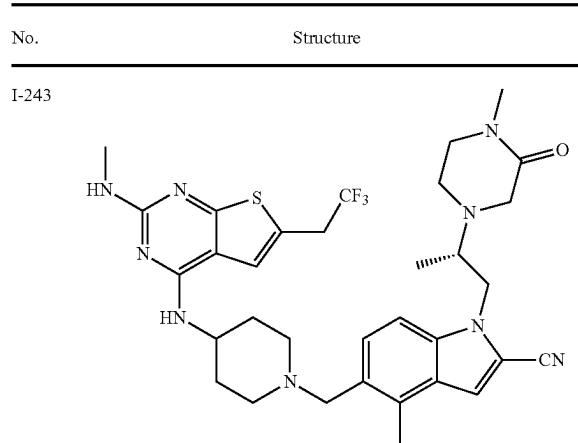
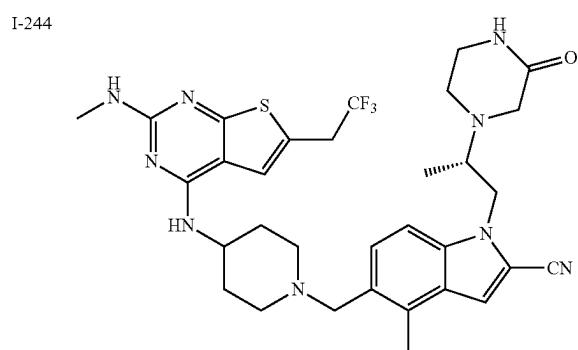


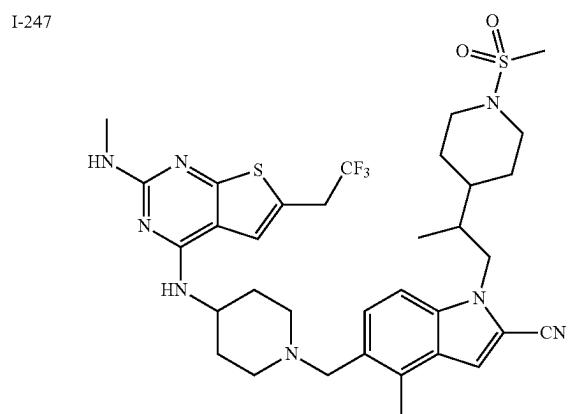
TABLE 1-continued



MW (calc'd) 667.30
m/z (found) 668.45 [M + H]⁺

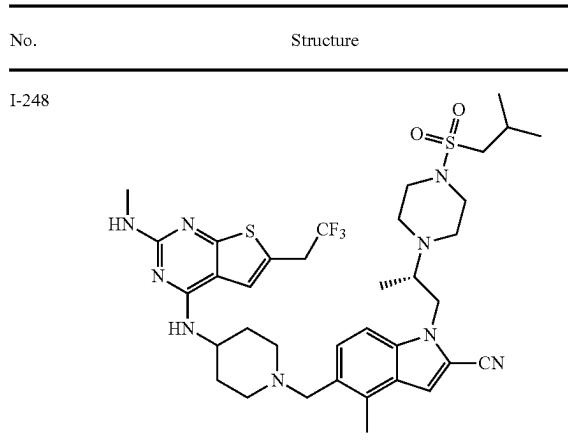


MW (calc'd) 653.29
m/z (found) 654.45 [M + H]⁺

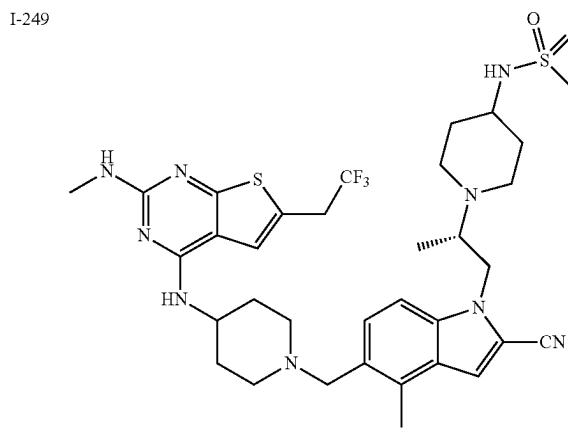


MW (calc'd) 716.29
m/z (found) 717.56 [M + H]⁺

TABLE 1-continued



MW (calc'd) 759.33
m/z (found) 760.50 [M + H]⁺



MW (calc'd) 731.30
m/z (found) 732.45 [M + H]⁺

TABLE 1-continued

No.	Structure
I-250	
	MW (calc'd) 621.26 m/z (found) 622.2 [M + H] ⁺

TABLE 1-continued

No.	Structure
I-252	
	MW (calc'd) 731.30 m/z (found) 732.3 [M + H] ⁺

TABLE 2

No.	Structure
II-1	

MW (calc'd) 633.73
m/z (found) 634.45 [M + H]⁺

TABLE 2-continued

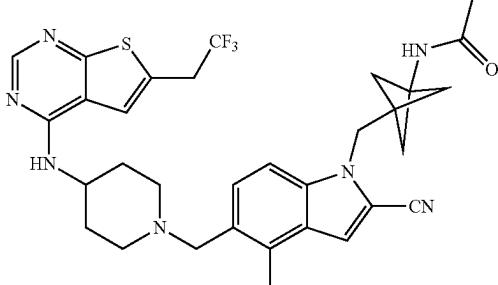
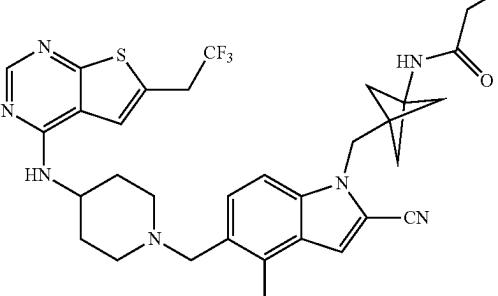
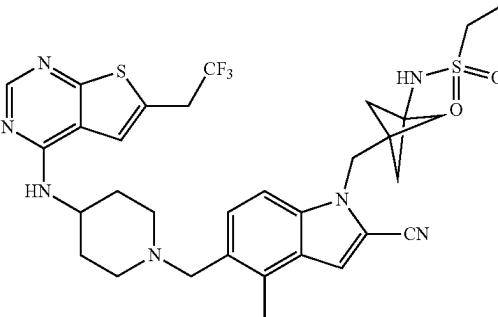
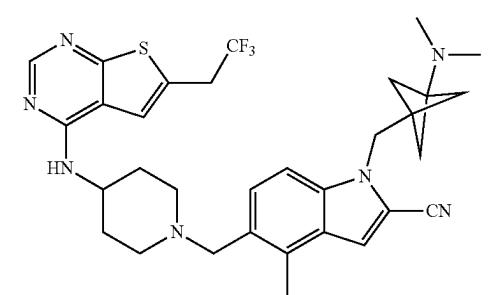
No.	Structure
II-2	 <p>MW (calc'd) 621.72 m/z (found) 622.40 [M + H]⁺</p>
II-3	 <p>MW (calc'd) 635.75 m/z (found) 636.45 [M + H]⁺</p>
II-4	 <p>MW (calc'd) 671.8 m/z (found) 672.45 [M + H]⁺</p>
II-5	 <p>MW (calc'd) 607.74 m/z (found) 608.55 [M + H]⁺</p>

TABLE 2-continued

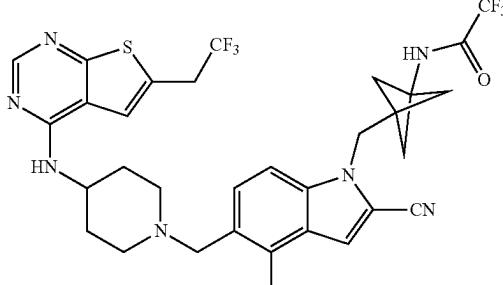
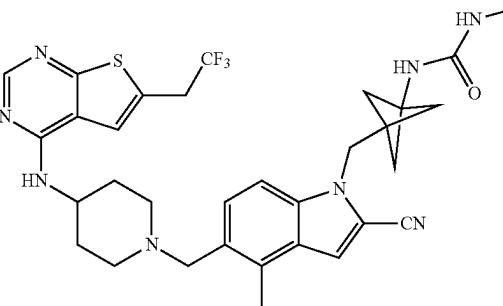
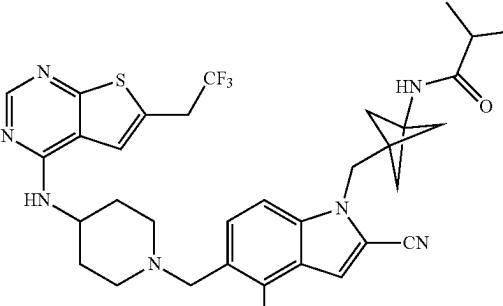
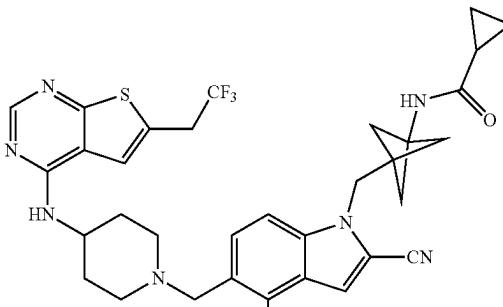
No.	Structure
II-6	 <p>MW (calc'd) 675.69 m/z (found) 676.40 [M + H]⁺</p>
II-7	 <p>MW (calc'd) 636.73 m/z (found) 637.30 [M + H]⁺</p>
II-8	 <p>MW (calc'd) 649.77 m/z (found) 650.30 [M + H]⁺</p>
II-9	 <p>MW (calc'd) 647.76 m/z (found) 648.30 [M + H]⁺</p>

TABLE 2-continued

TABLE 2-continued

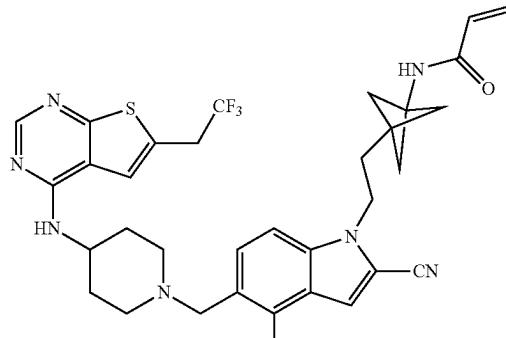
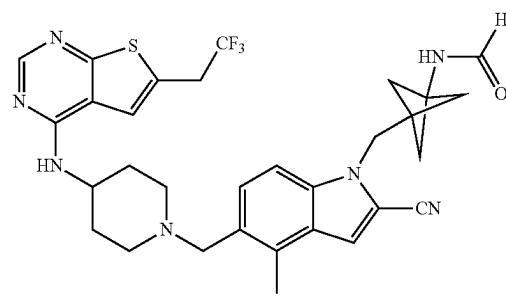
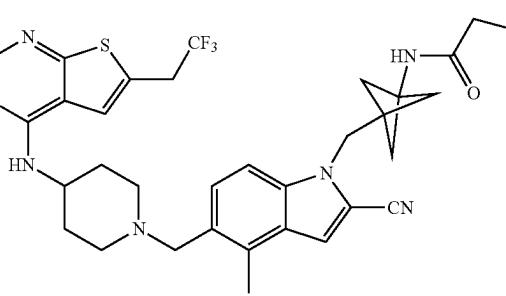
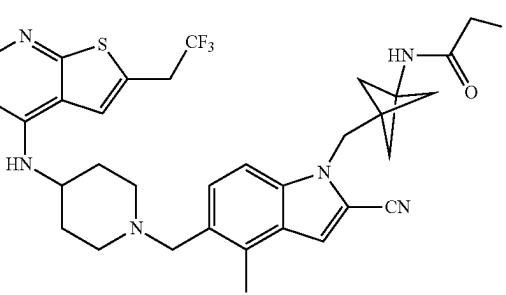
No.	Structure
II-14	
	MW (calc'd) 647.76 m/z (found) 648.35 [M + H] ⁺
II-15	
	MW (calc'd) 607.69 m/z (found) 608.30 [M + H] ⁺
II-16	
	MW (calc'd) 637.72 m/z (found) 638.30 [M + H] ⁺
II-17	
	MW (calc'd) 636.73 m/z (found) 637.30 [M + H] ⁺

TABLE 2-continued

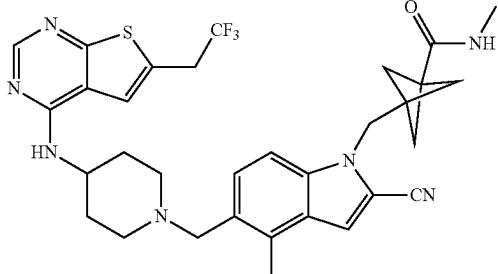
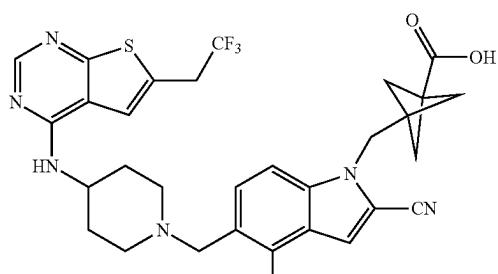
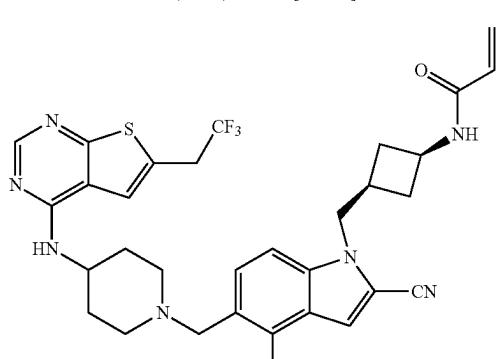
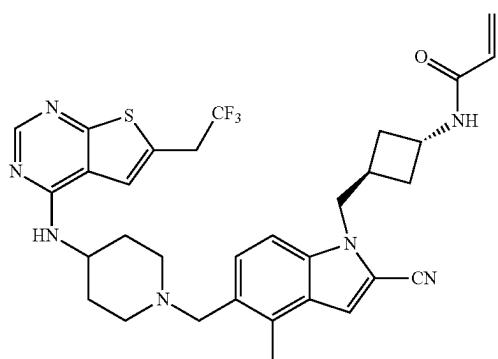
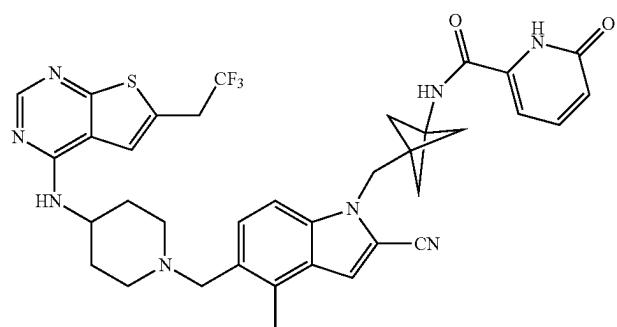
No.	Structure
II-18	
	MW (calc'd) 621.72 m/z (found) 622.35 [M + H] ⁺
II-20	
	MW (calc'd) 608.68 m/z (found) 609.20 [M + H] ⁺
II-29	
	MW (calc'd) 621.72 m/z (found) 622.40 [M + H] ⁺
II-30	
	MW (calc'd) 621.72 m/z (found) 622.40 [M + H] ⁺

TABLE 2-continued

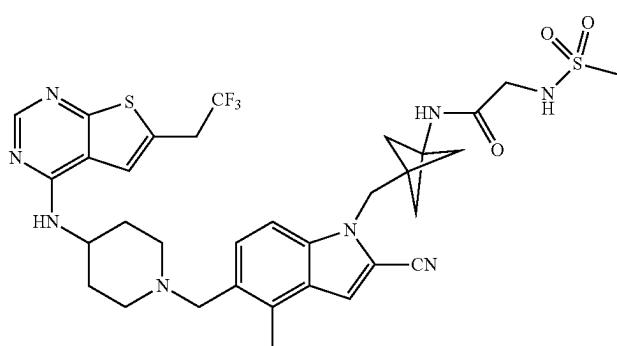
No.	Structure
II-31	<p>MW (calc'd) 609.71 m/z (found) 610.40 [M + H]⁺</p>
II-32	<p>MW (calc'd) 609.71 m/z (found) 610.40 [M + H]⁺</p>
II-33	<p>MW (calc'd) 664.74 m/z (found) 665.55 [M + H]⁺</p>
II-34	<p>MW (calc'd) 672.77 m/z (found) 673.45 [M + H]⁺</p>

TABLE 2-continued

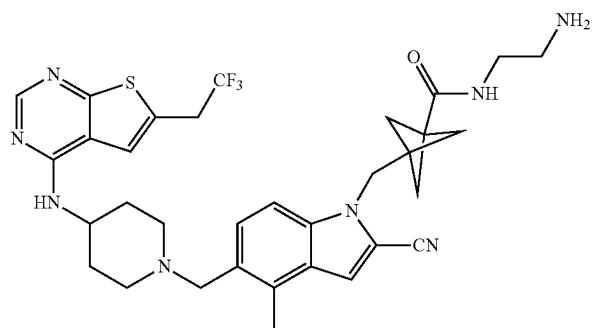
No.	Structure
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II-
35

MW (calc'd) 700.78
 m/z (found) 699.45 [M - H]⁻

II-
36

MW (calc'd) 714.82
 m/z (found) 715.40 [M + H]⁺

II-
37

MW (calc'd) 650.76
 m/z (found) 651.45 [M + H]⁺

TABLE 2-continued

No.	Structure
II-38	<p>MW (calc'd) 673.75 m/z (found) 674.35 [M + H]⁺</p>
II-39	<p>MW (calc'd) 650.76 m/z (found) 651.25 [M + H]⁺</p>

TABLE 3

No.	Structure
III-1	

TABLE 3-continued

No.	Structure
III-2	

TABLE 3-continued

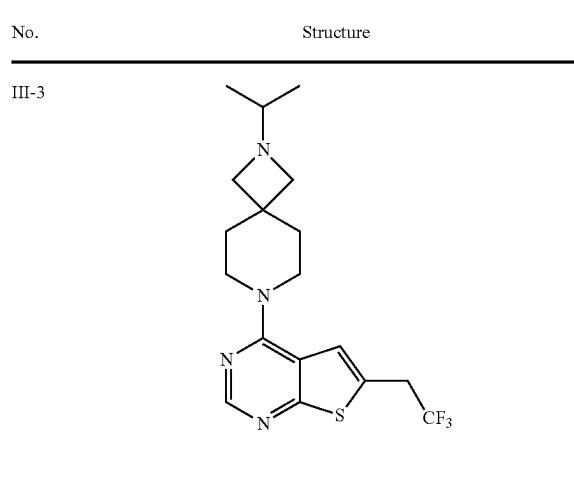


TABLE 3-continued

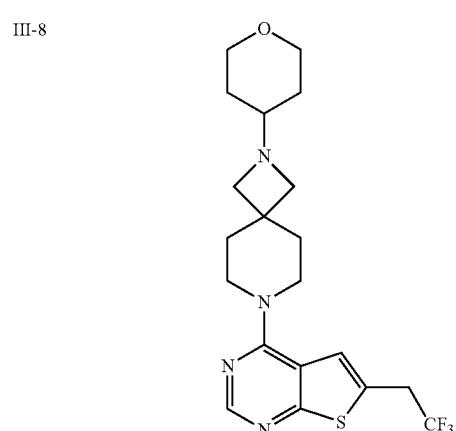
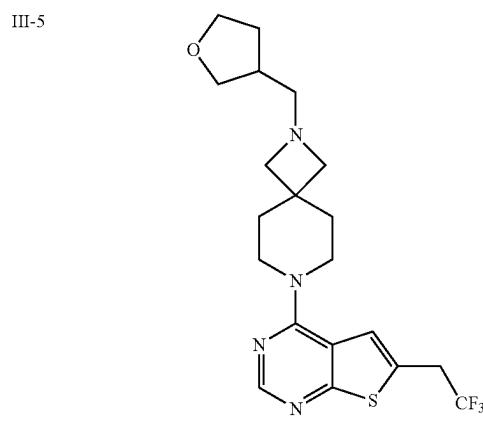
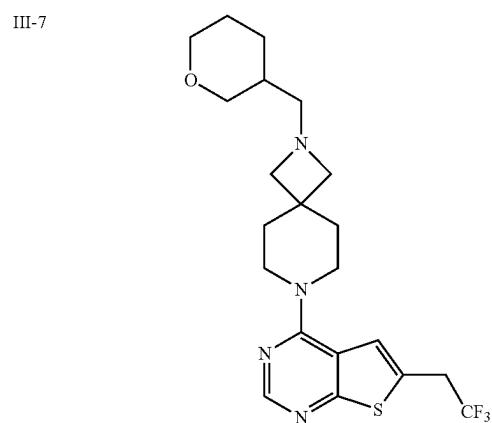
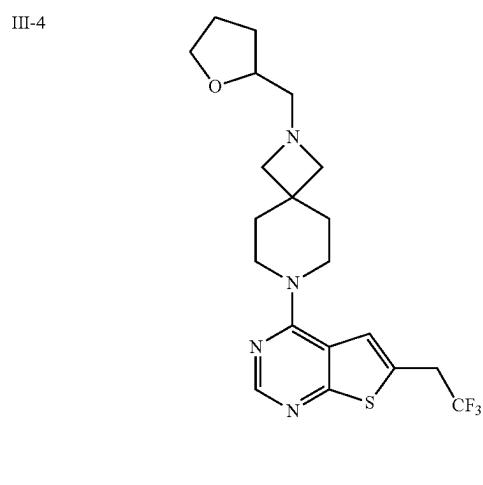
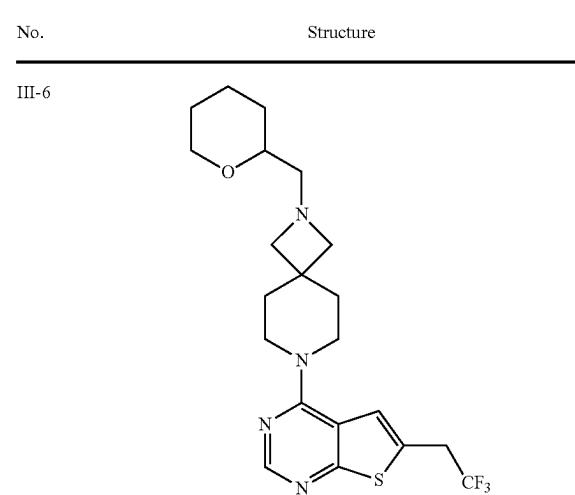


TABLE 3-continued

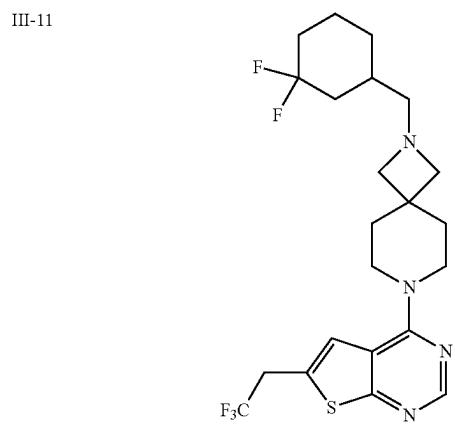
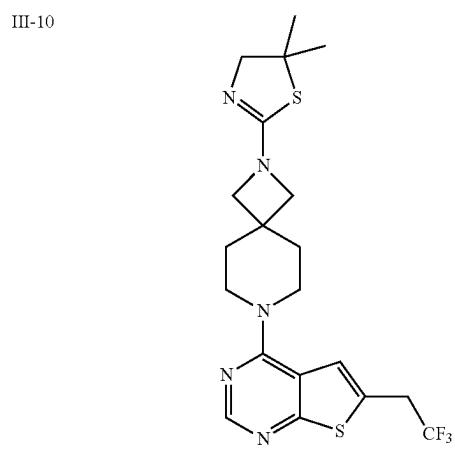
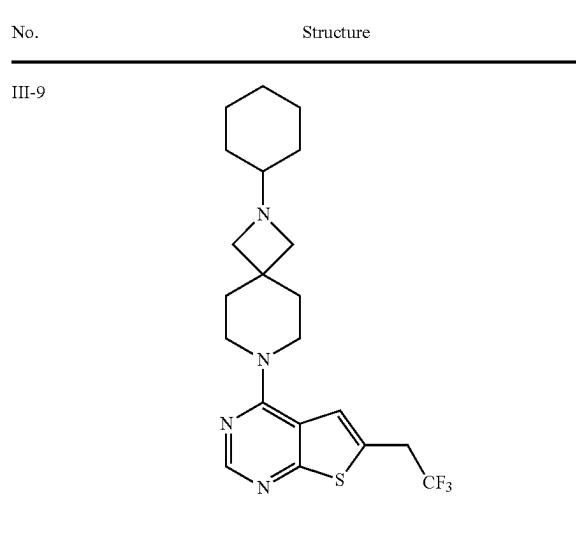


TABLE 3-continued

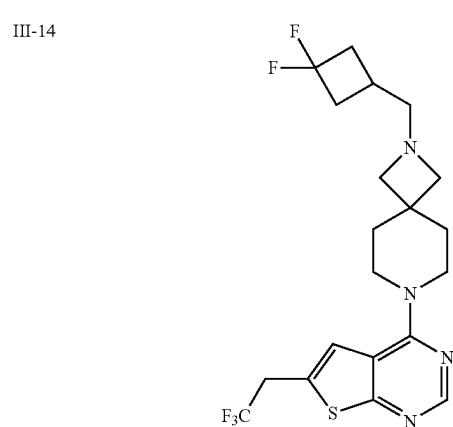
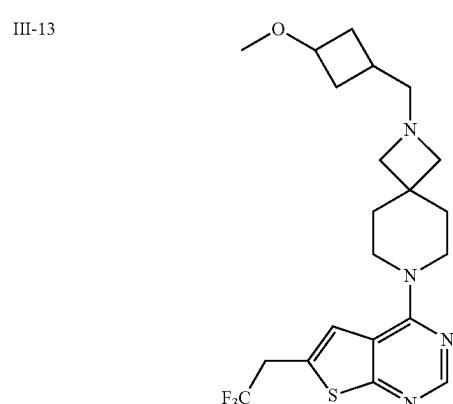
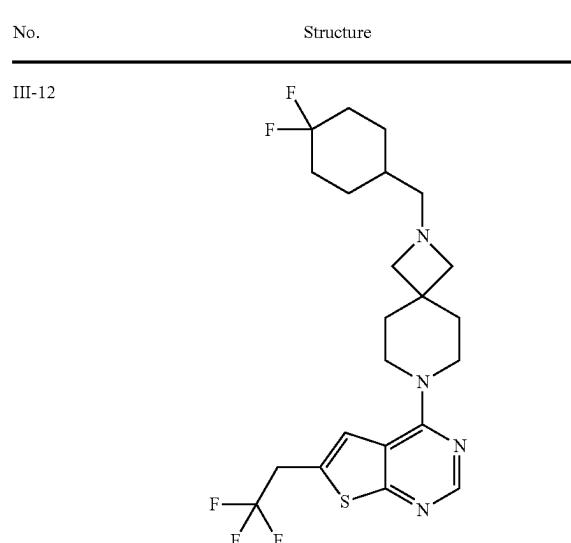
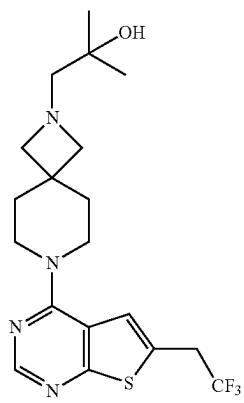


TABLE 3-continued

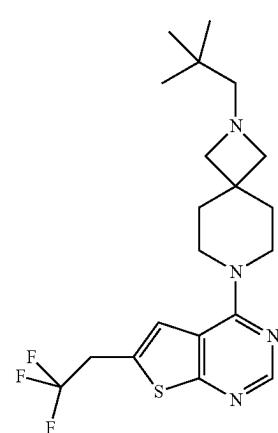
No.	Structure
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III-15

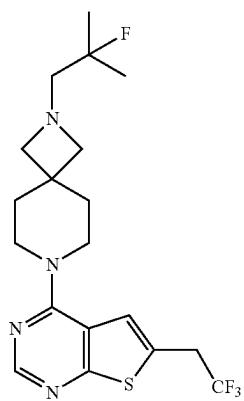


No.	Structure
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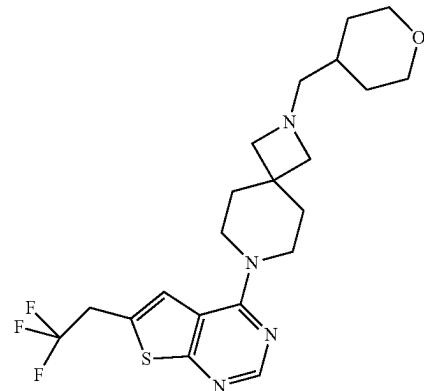
III-18



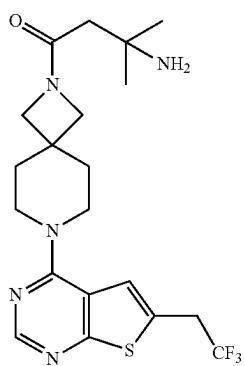
III-16



III-19



III-17



III-20

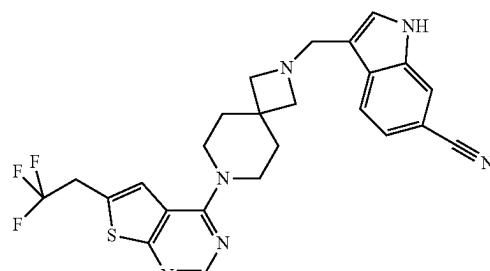


TABLE 3-continued

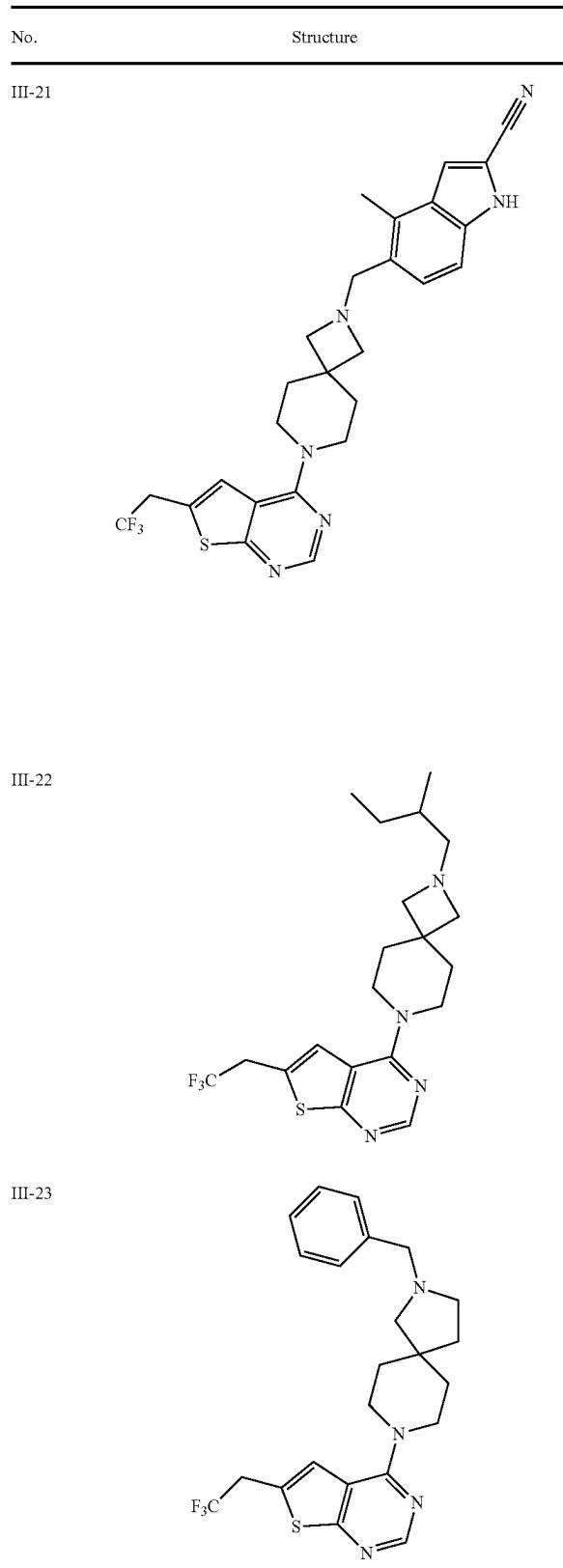


TABLE 3-continued

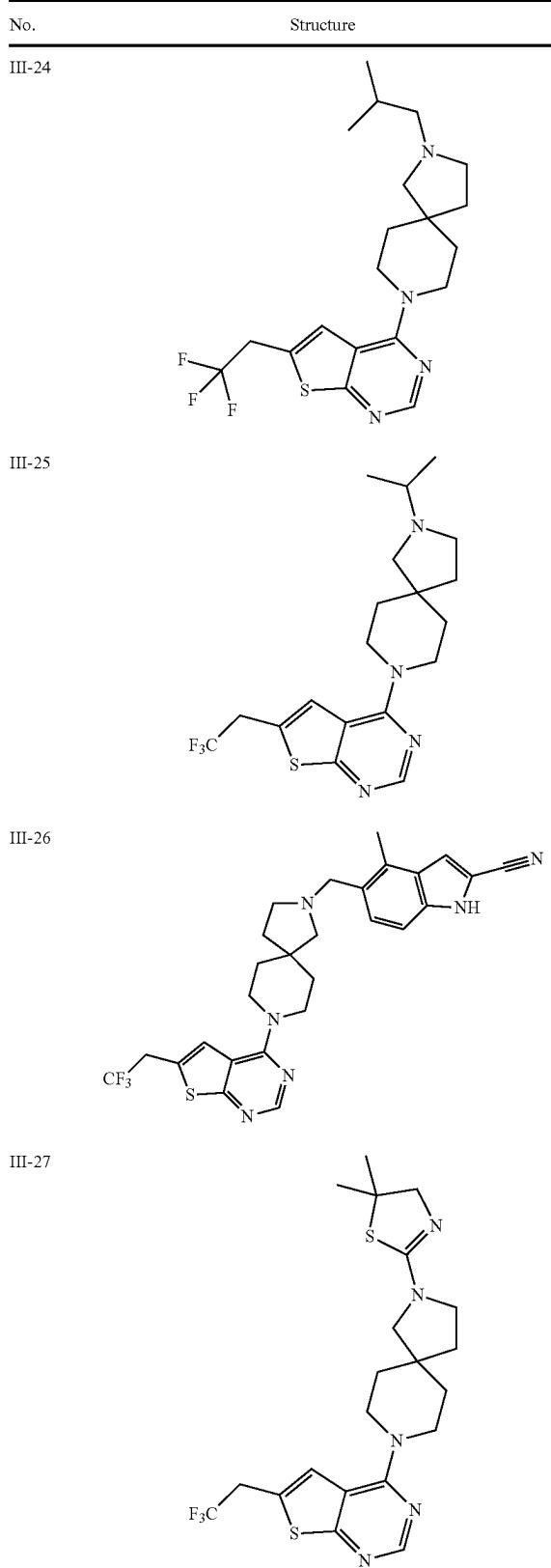


TABLE 3-continued

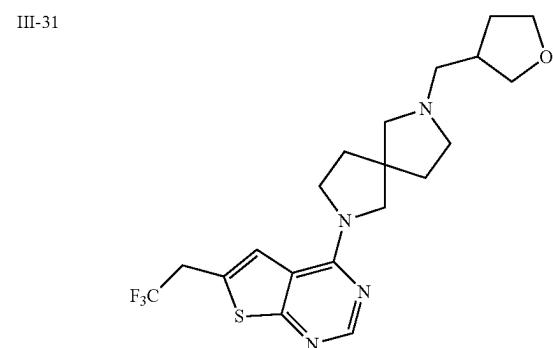
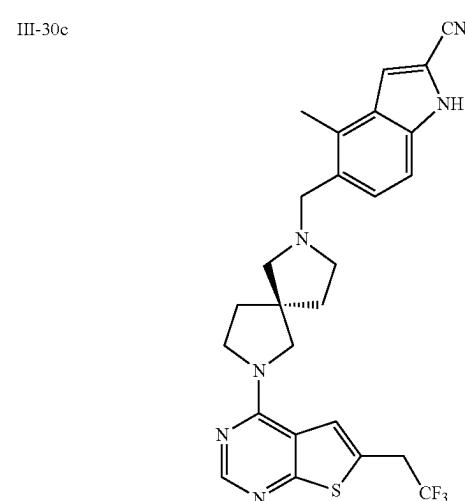
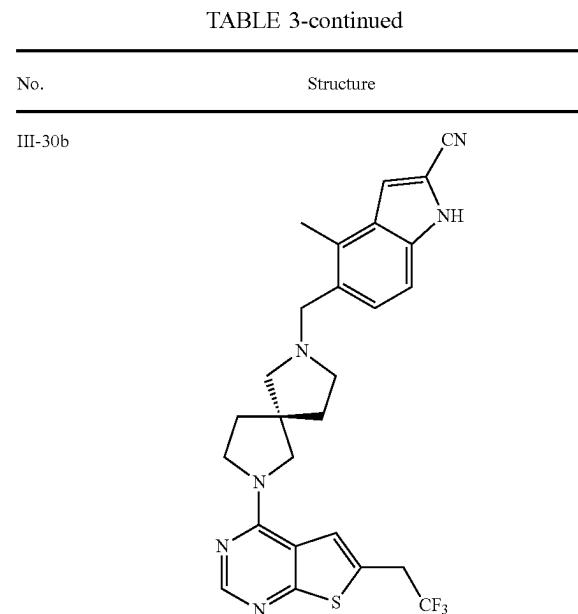
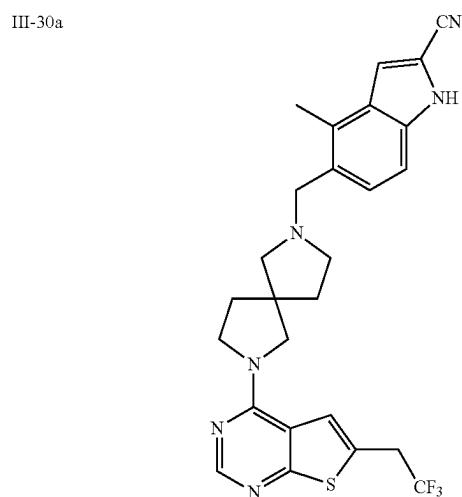
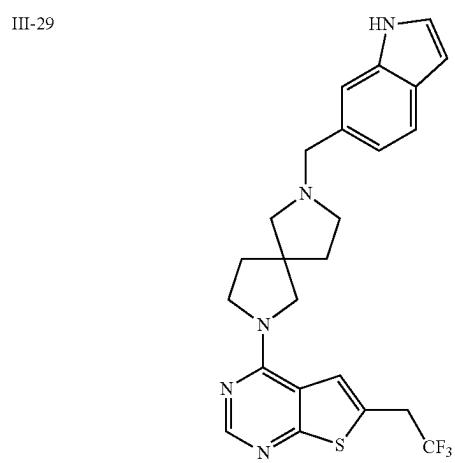
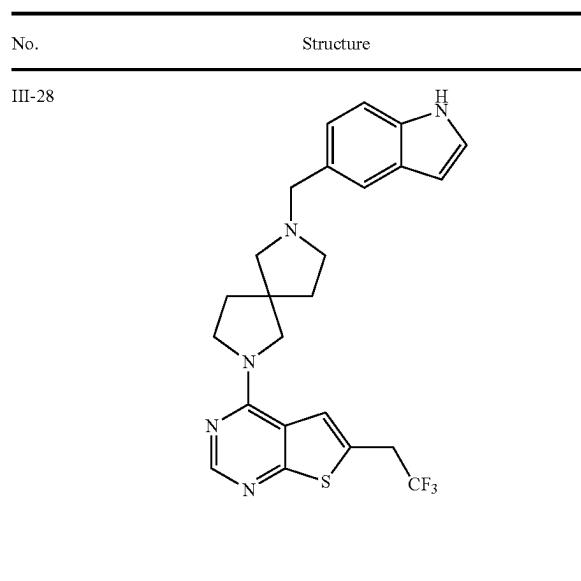


TABLE 3-continued

No.	Structure
III-32	
III-33	
III-34	
III-38	

TABLE 3-continued

No.	Structure
III-35	
III-36	
III-37	
III-39	

TABLE 3-continued

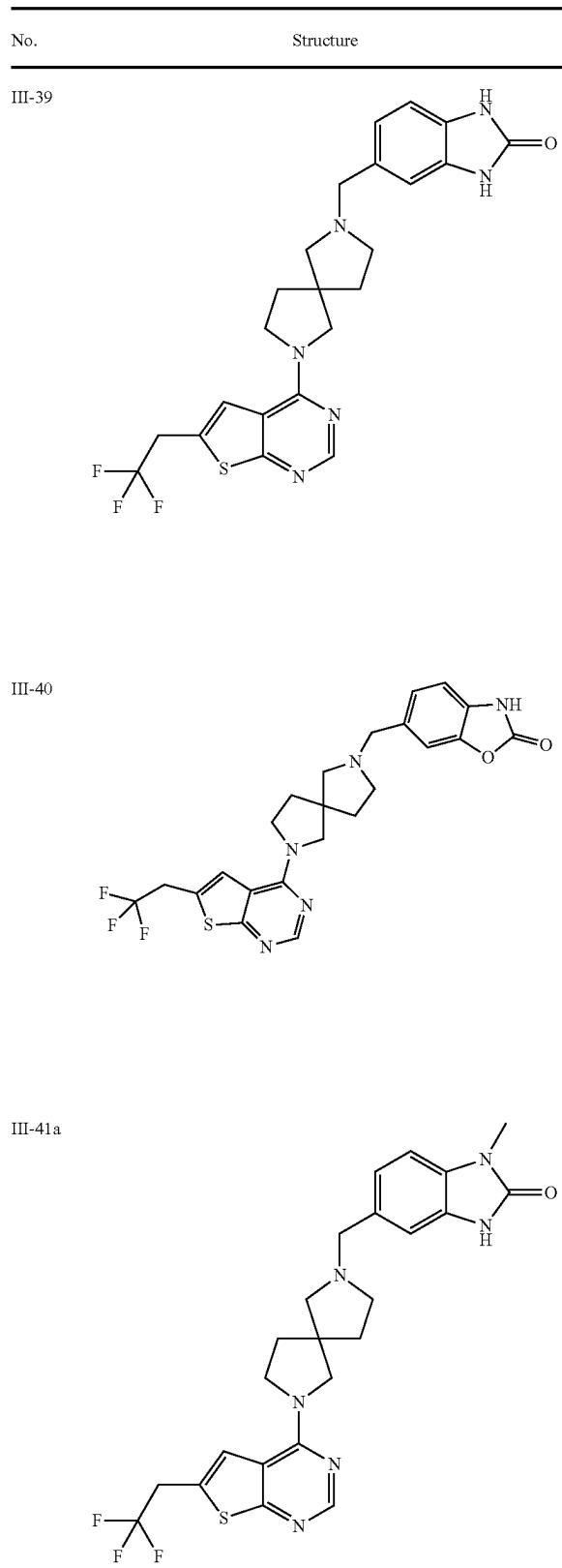


TABLE 3-continued

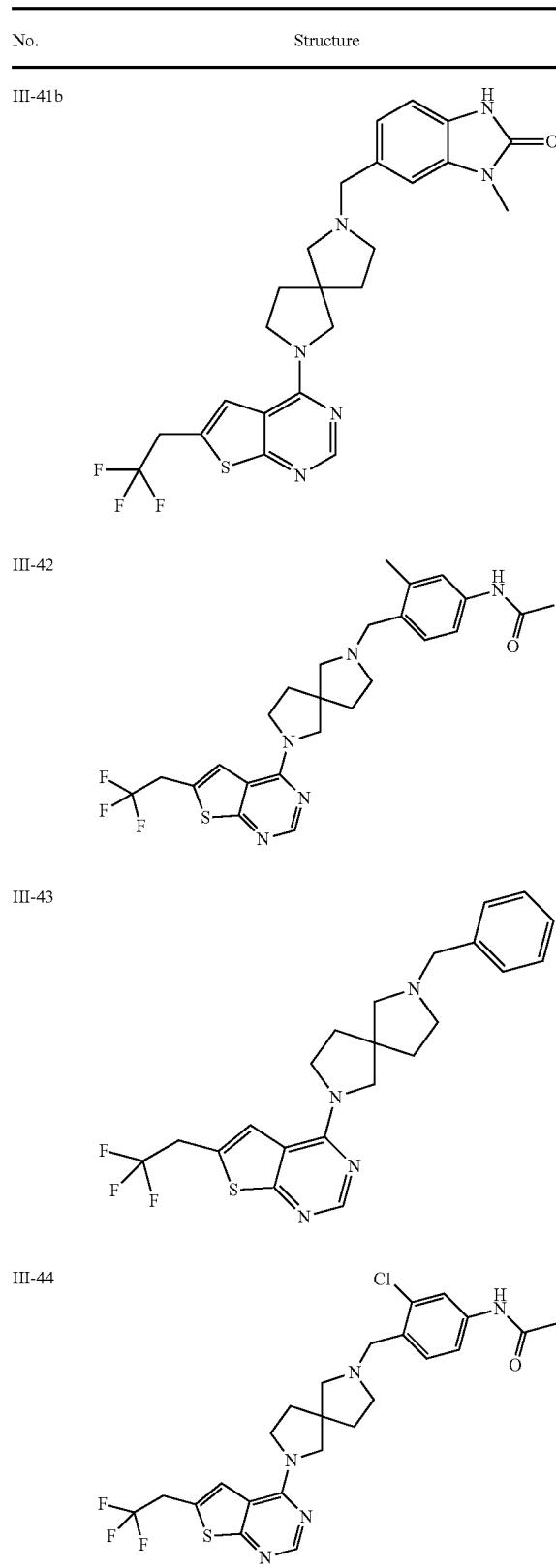


TABLE 3-continued

No.	Structure
III-45	
III-46	
III-47	
III-48	

TABLE 3-continued

No.	Structure
III-49	
III-50	
III-51	
III-52	
III-53	

TABLE 3-continued

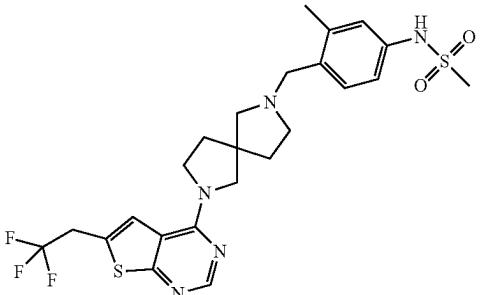
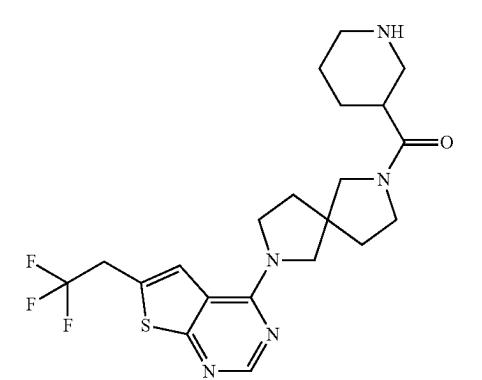
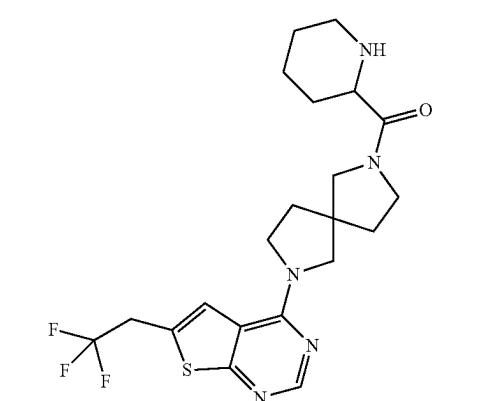
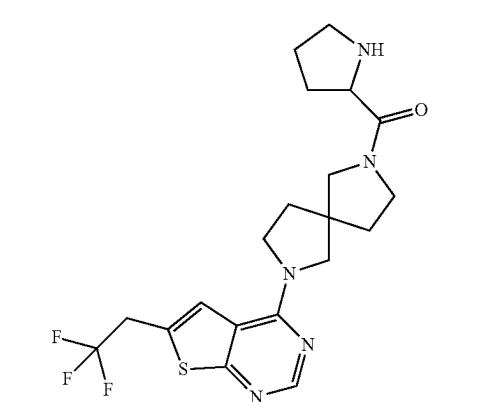
No.	Structure
III-54	
III-55	
III-56	
III-57	

TABLE 3-continued

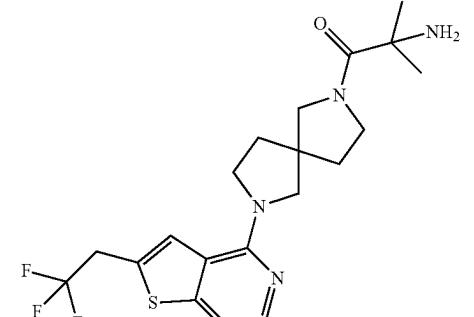
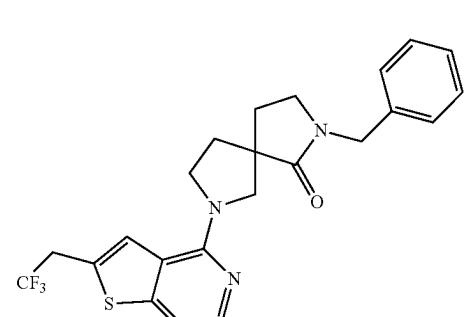
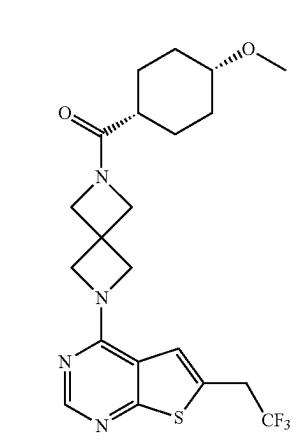
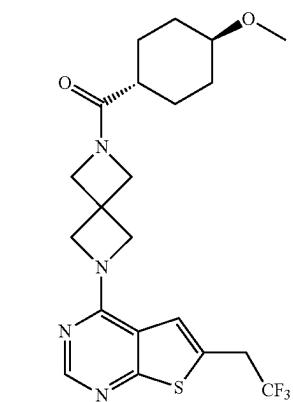
No.	Structure
III-58	
III-59	
III-60a	
III-60b	

TABLE 3-continued

No.	Structure
III-61	
III-62	
III-63	
III-64	

TABLE 3-continued

No.	Structure
III-65	
III-66	
III-67	

TABLE 3-continued

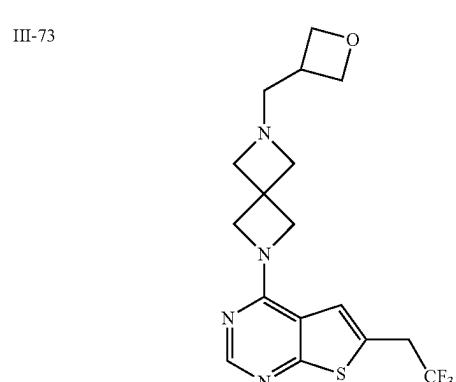
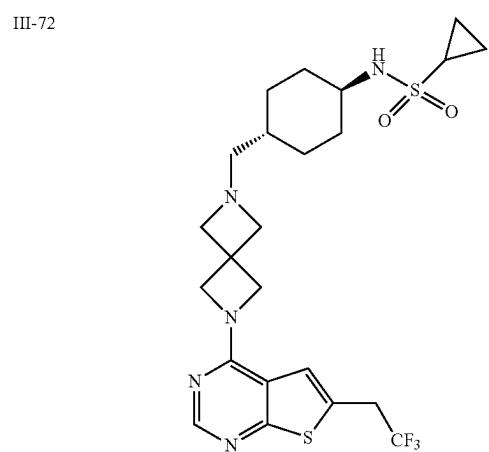
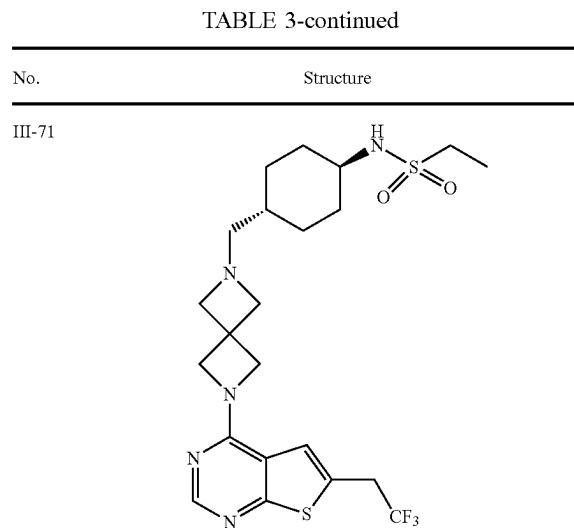
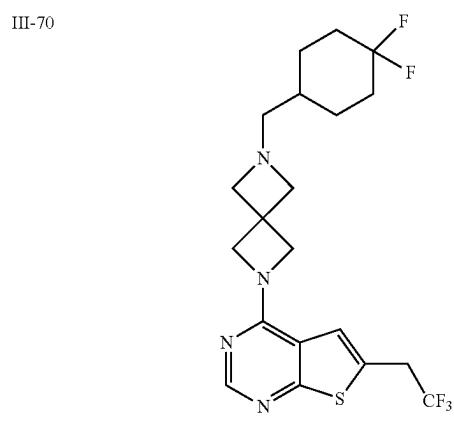
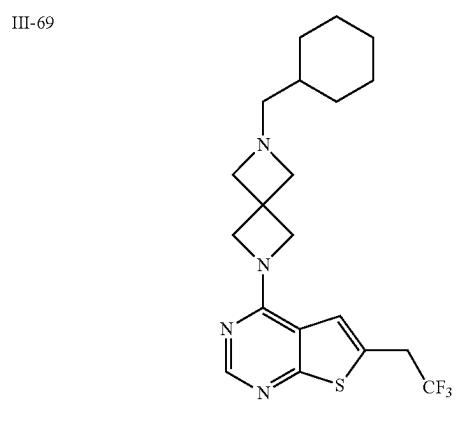
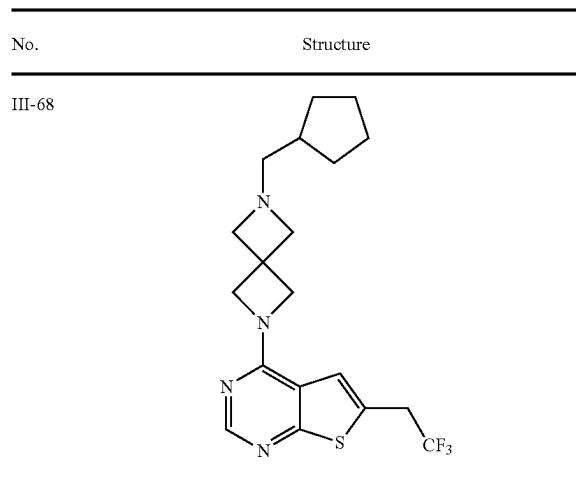


TABLE 3-continued

No.	Structure
III-74	
III-75	
III-76	
III-77	

TABLE 3-continued

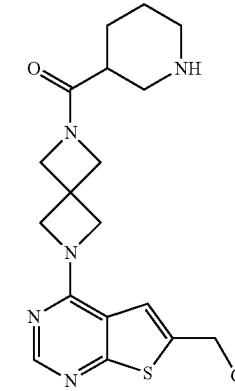
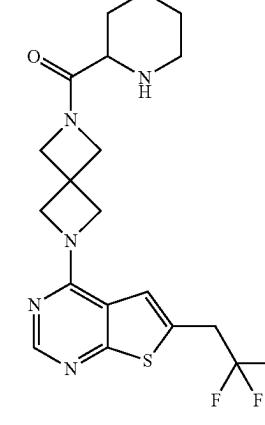
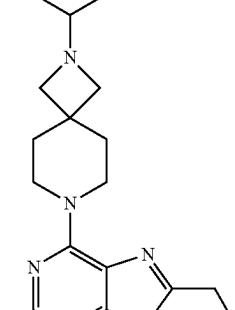
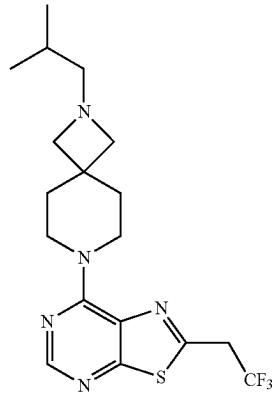
No.	Structure
III-78	
III-79	
III-80	

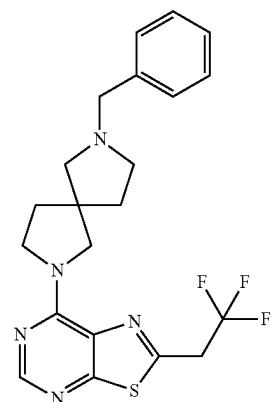
TABLE 3-continued

No.	Structure
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III-81



III-82



III-83

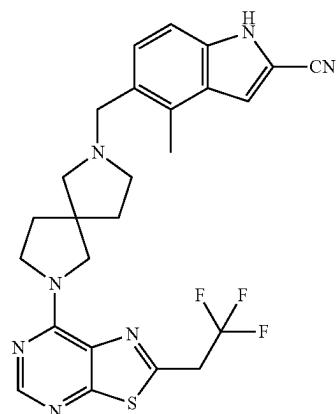
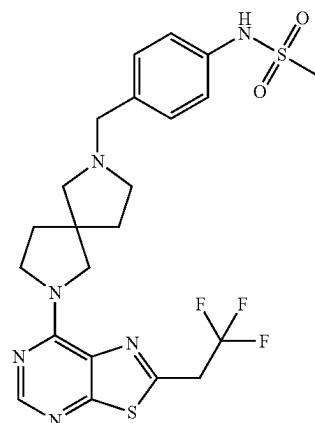


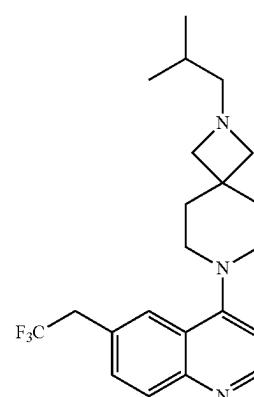
TABLE 3-continued

No.	Structure
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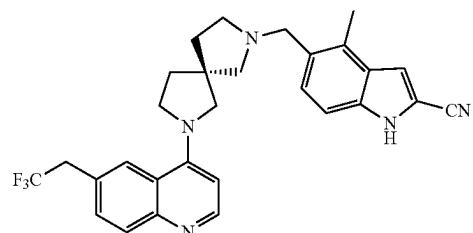
III-84



III-85



III-86a



III-86b

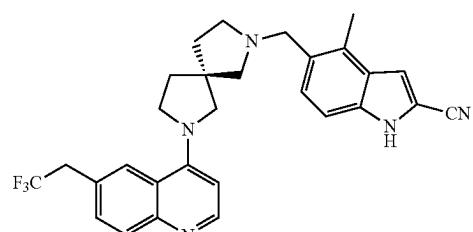
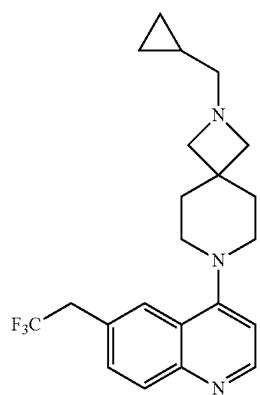


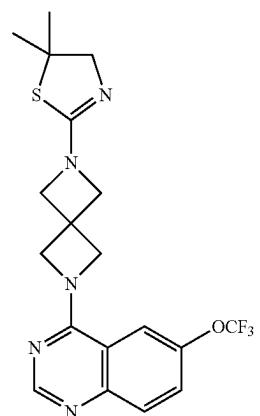
TABLE 3-continued

No.	Structure
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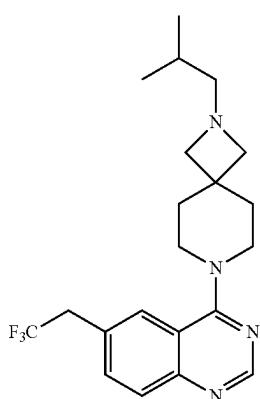
III-87



III-88



III-89



III-90

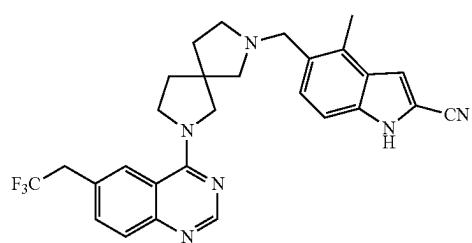
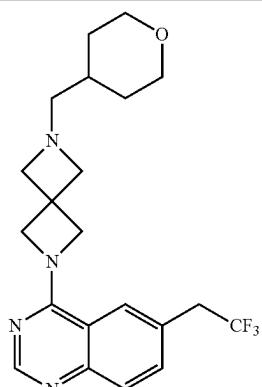


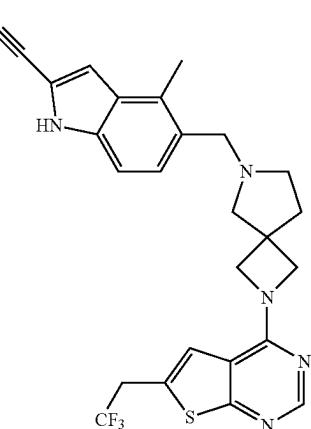
TABLE 3-continued

No.	Structure
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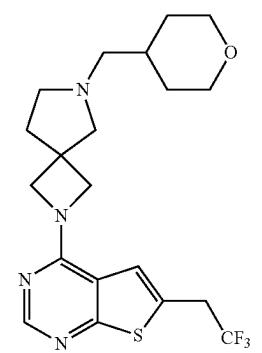
III-91



III-92



III-93



III-94

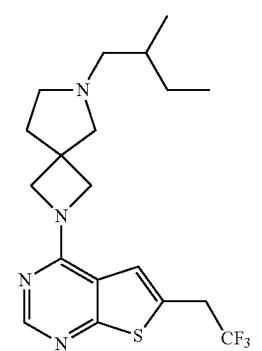


TABLE 3-continued

No.	Structure
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III-95

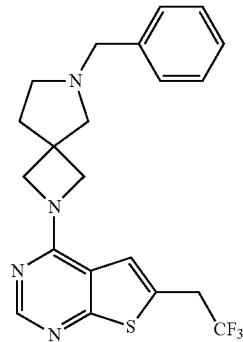
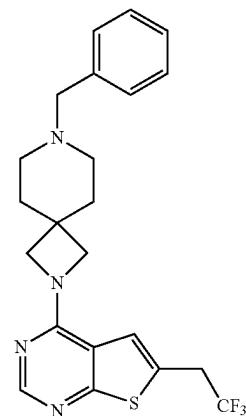


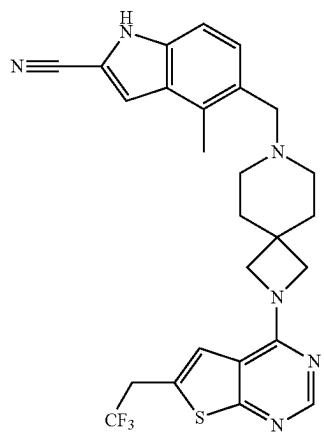
TABLE 3-continued

No.	Structure
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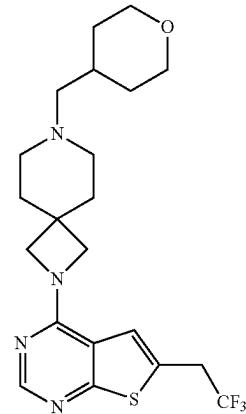
III-98



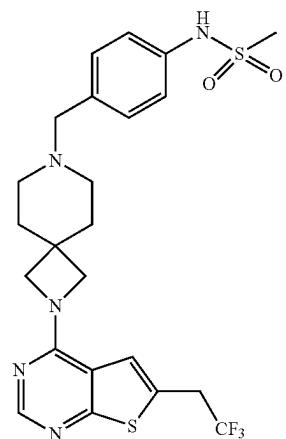
III-96



III-99



III-97



III-100

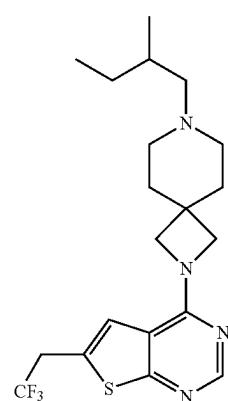


TABLE 3-continued

No.	Structure
III-101	

TABLE 3-continued

No.	Structure
III-104	

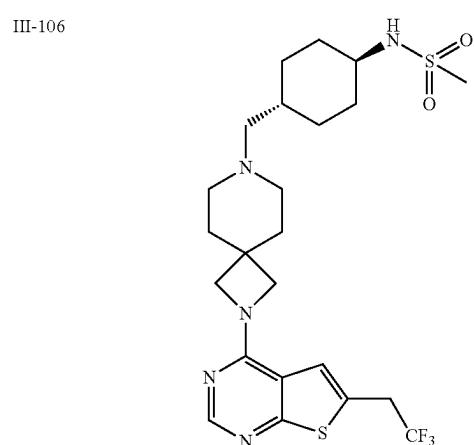
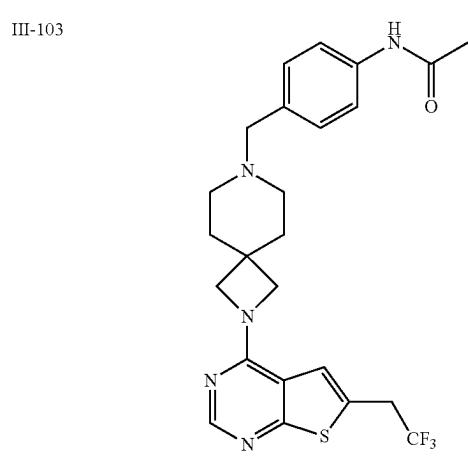
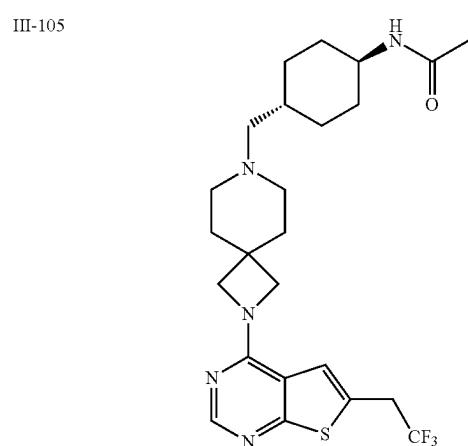
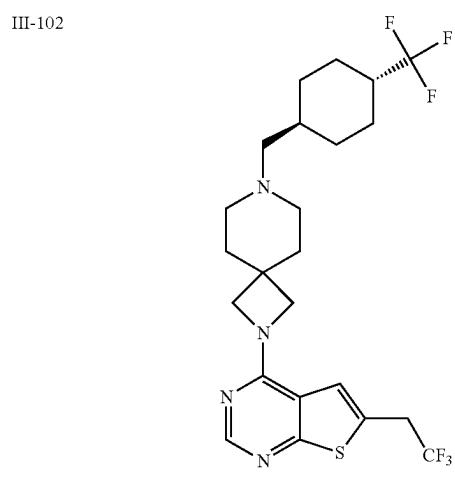


TABLE 3-continued

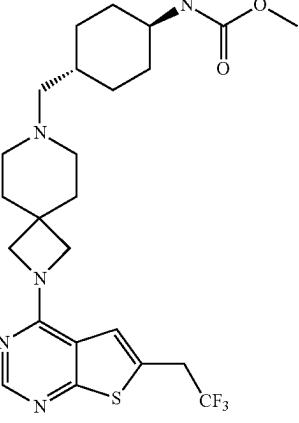
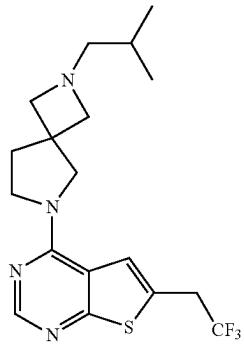
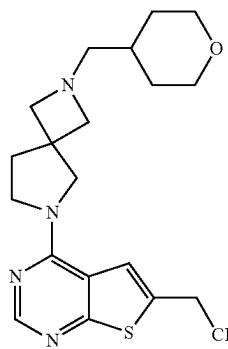
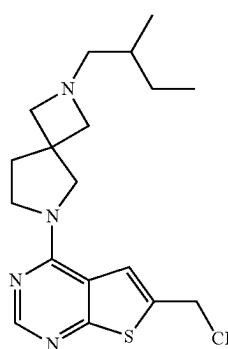
No.	Structure
III-107	
III-108	
III-109	
III-110	

TABLE 3-continued

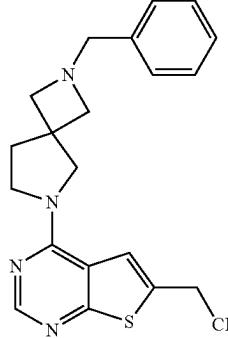
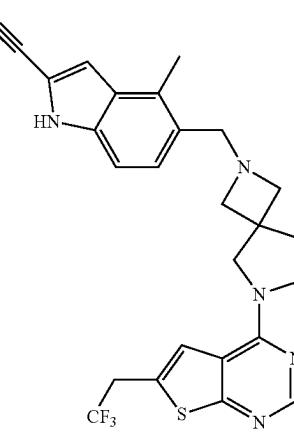
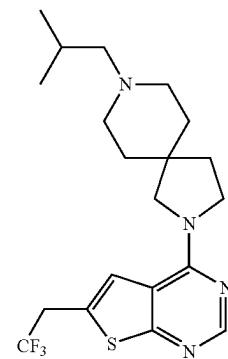
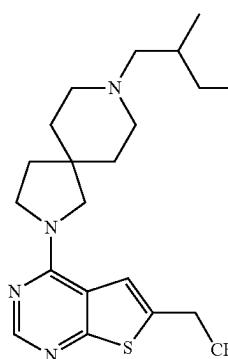
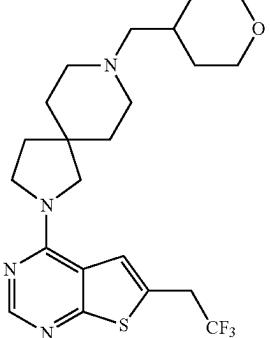
No.	Structure
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III-112	
III-113	
III-114	

TABLE 3-continued

No.	Structure
III-115	

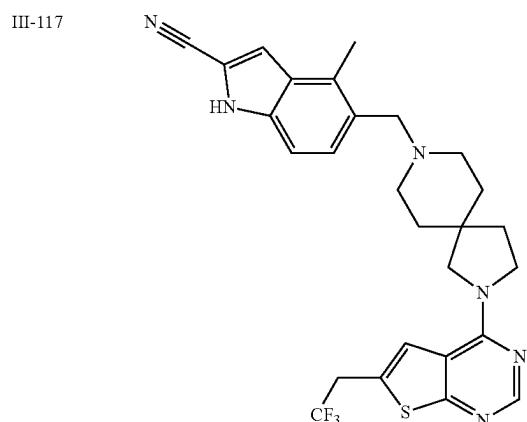
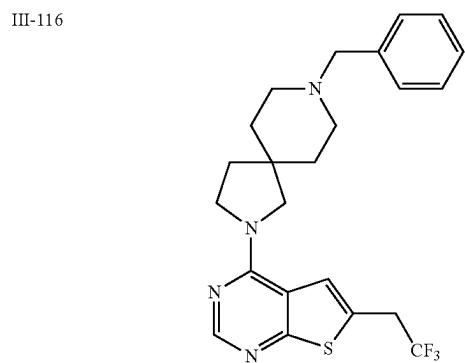
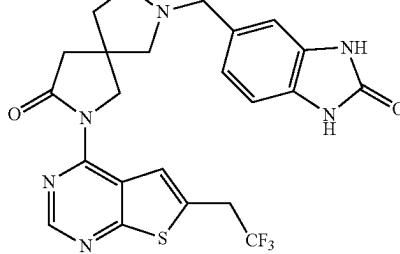
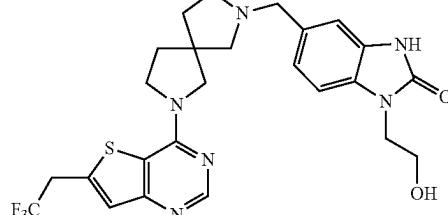


TABLE 3-continued

No.	Structure
III-118	
III-119	

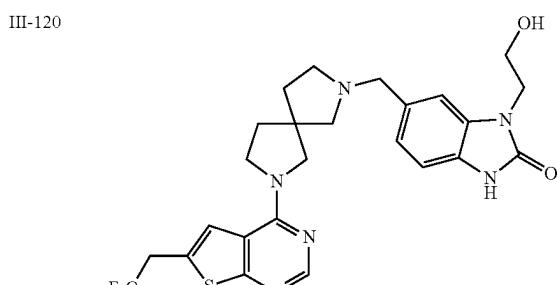


TABLE 4

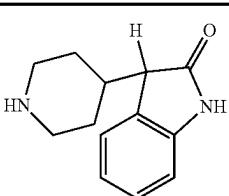
No.	Structure
IV-1	

TABLE 4-continued

No.	Structure
IV-2	
IV-3	
IV-4	
IV-5	
IV-6	
IV-7	

TABLE 4-continued

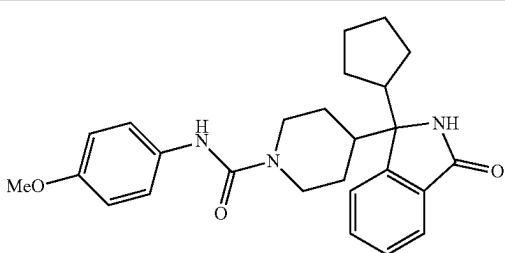
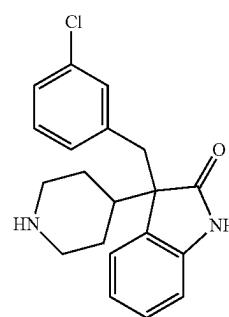
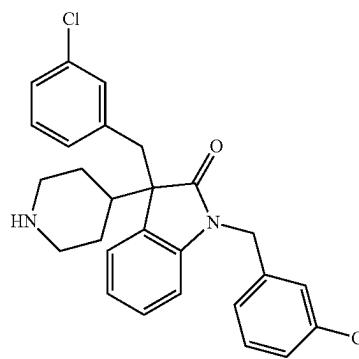
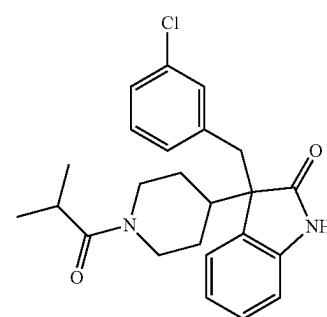
No.	Structure
IV-8	
IV-9	
IV-10	
IV-11	

TABLE 4-continued

No.	Structure
IV-12	
IV-13	
IV-14	
IV-15	
IV-16	

TABLE 4-continued

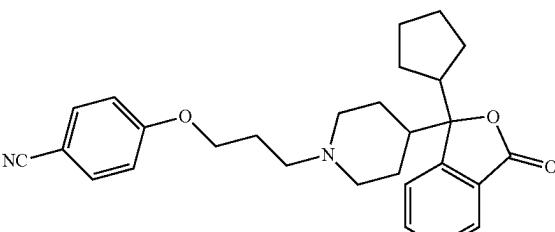
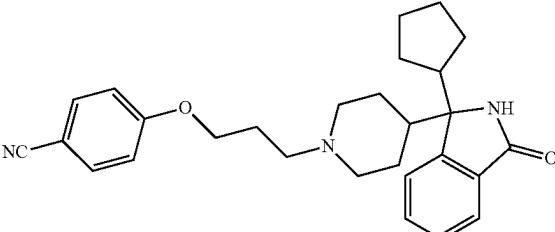
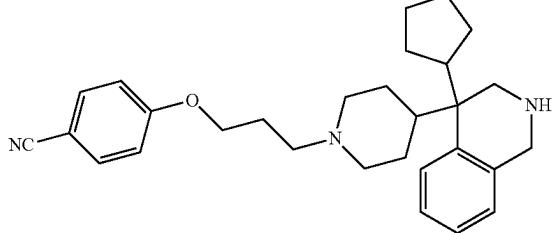
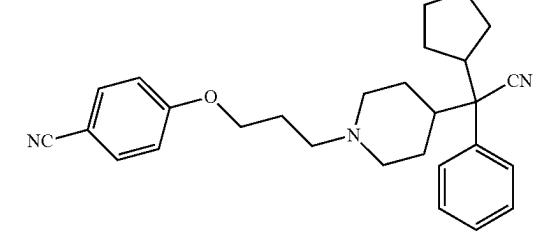
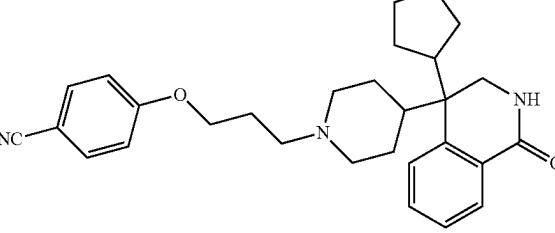
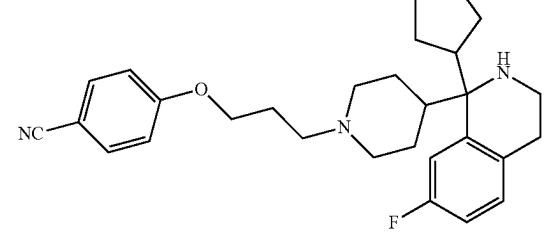
No.	Structure
IV-17	
IV-18	
IV-19	
IV-20	
IV-21	
IV-22	

TABLE 4-continued

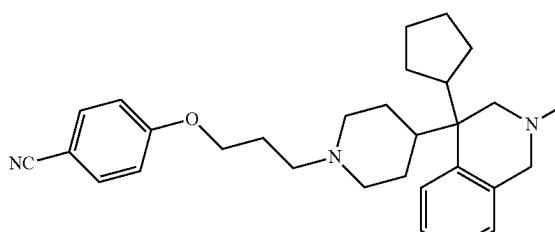
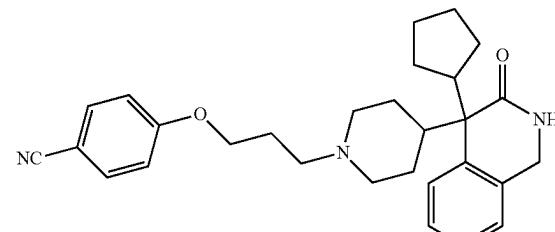
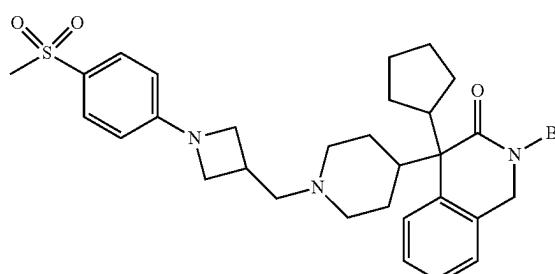
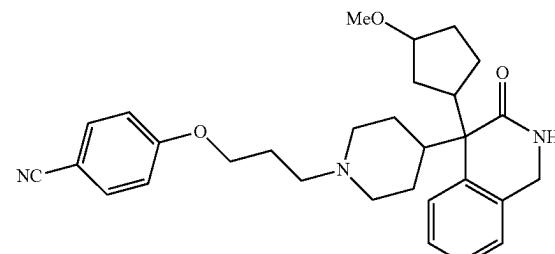
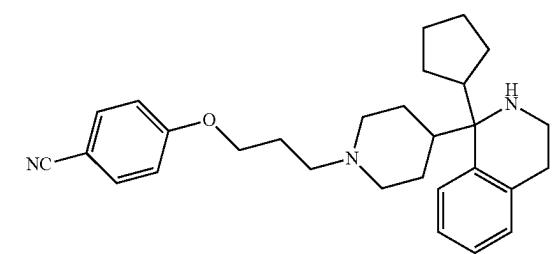
No.	Structure
IV-23	
IV-24	
IV-25	
IV-26	
IV-27	

TABLE 4-continued

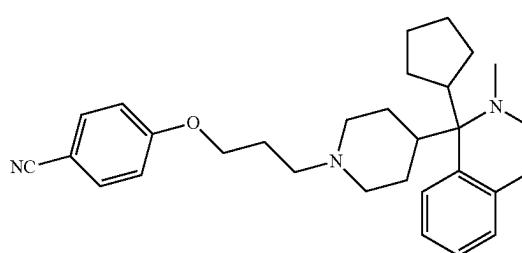
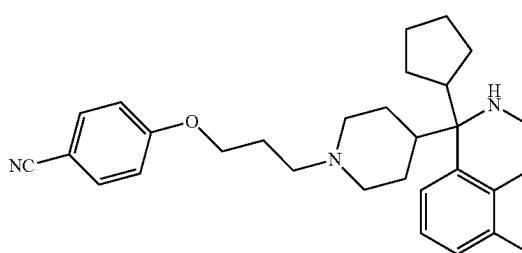
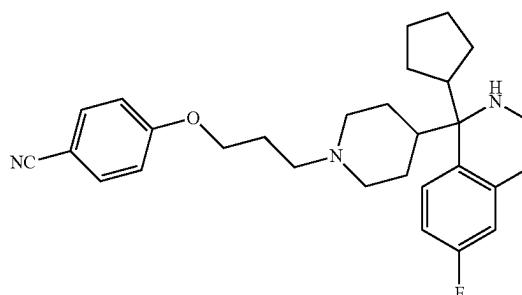
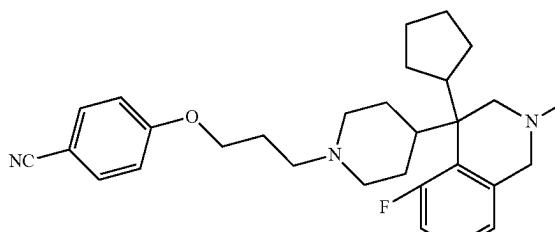
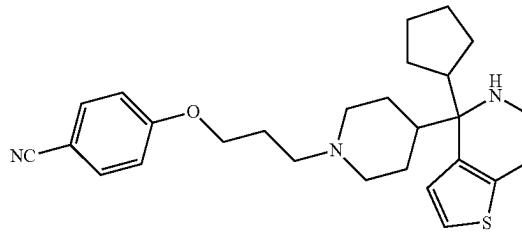
No.	Structure
IV-28	
IV-29	
IV-30	
IV-31	
IV-32	

TABLE 4-continued

No.	Structure
IV-33	
IV-34	
IV-35	
IV-36	
IV-37	
IV-38	

TABLE 4-continued

No.	Structure
IV-39	
IV-40	
IV-41	
IV-42	
IV-43	

TABLE 4-continued

No.	Structure
IV-44	
IV-45	
IV-46	
IV-47	
IV-48	

TABLE 4-continued

No.	Structure
IV-49	
IV-50	
IV-51	
IV-52	
IV-53	

TABLE 4-continued

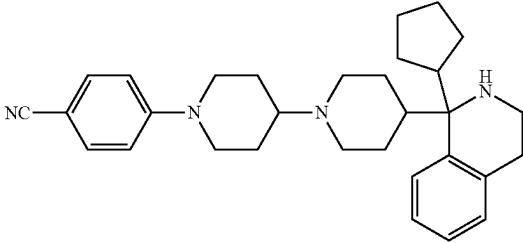
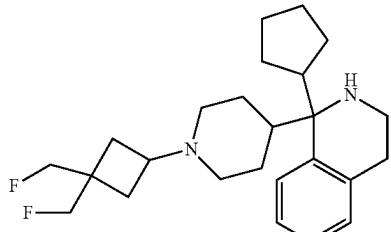
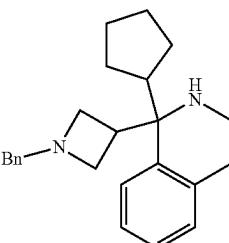
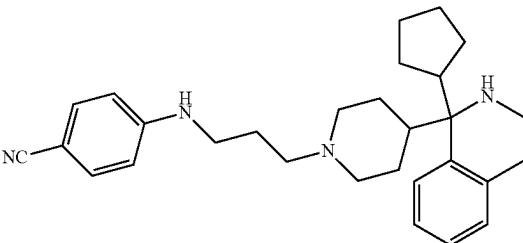
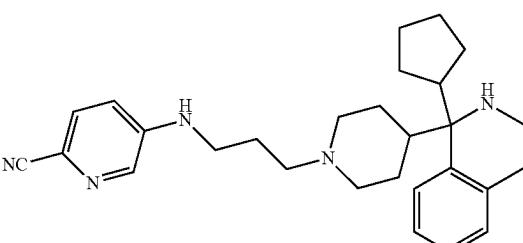
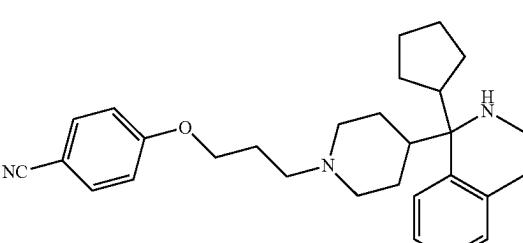
No.	Structure
IV-54	
IV-55	
IV-56	
IV-57	
IV-58	
IV-59	

TABLE 4-continued

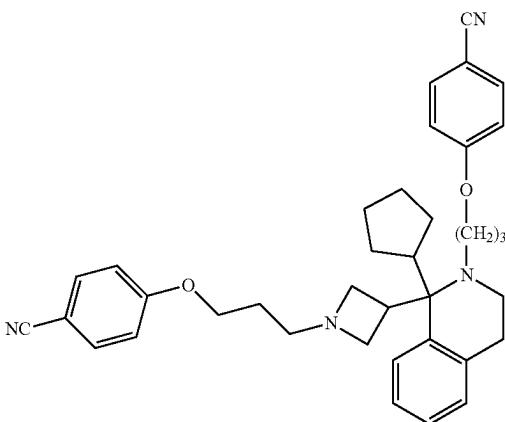
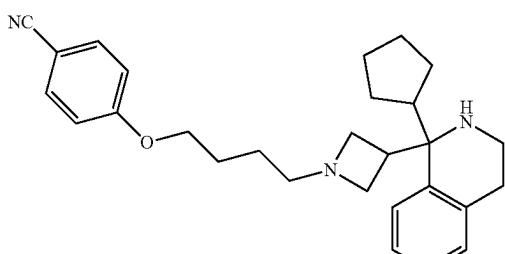
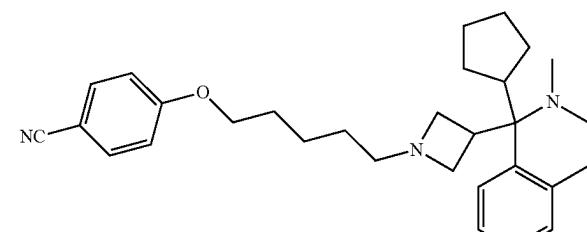
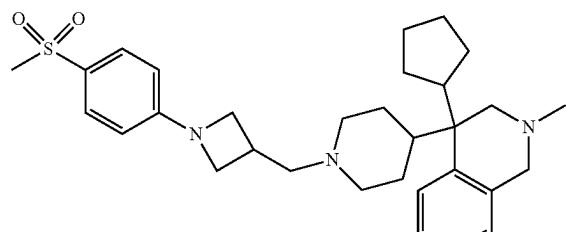
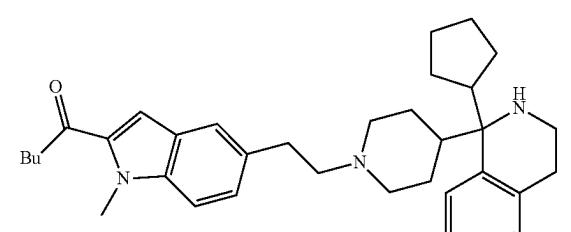
No.	Structure
IV-60	
IV-61	
IV-62	
IV-63	
IV-64	

TABLE 4-continued

No.	Structure
IV-65	
IV-66	
IV-67	
IV-68	
IV-69	
IV-70	

TABLE 4-continued

No.	Structure
IV-71	
IV-72	
IV-73	
IV-74	
IV-75	

TABLE 4-continued

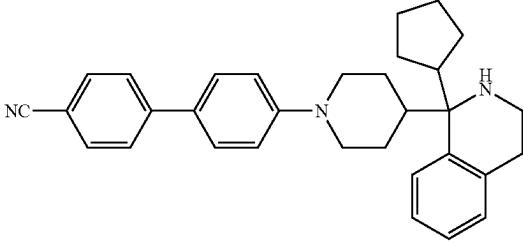
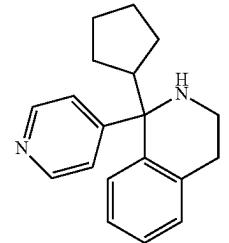
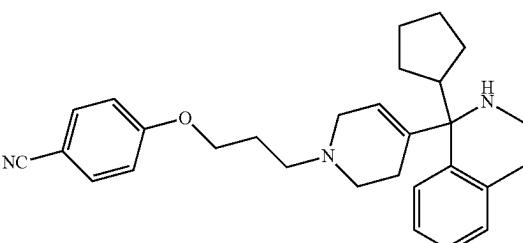
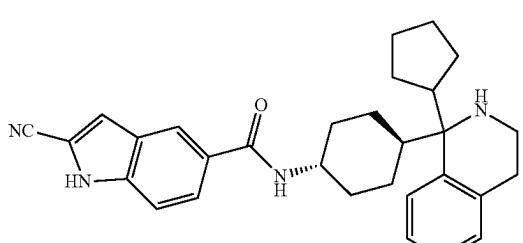
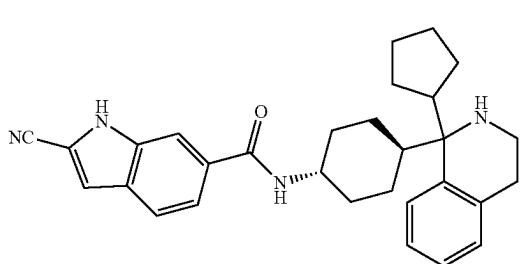
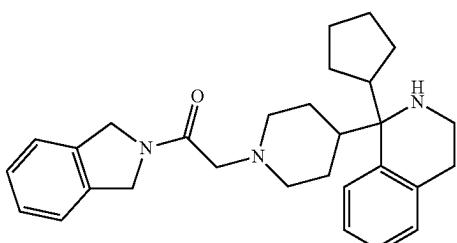
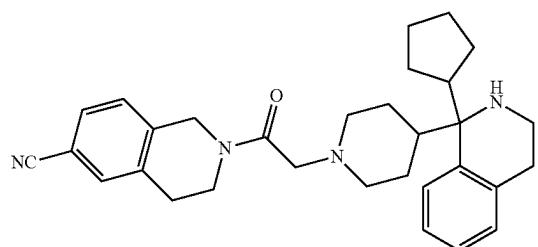
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IV-77	
IV-78	
IV-79	
IV-80	
IV-81	

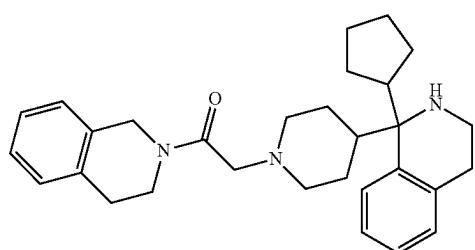
TABLE 4-continued

No.	Structure
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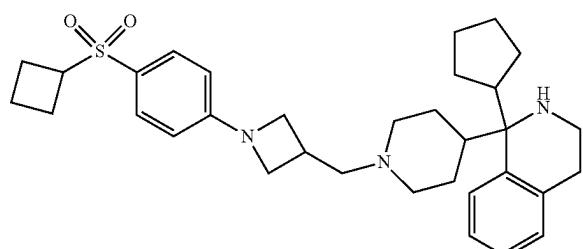
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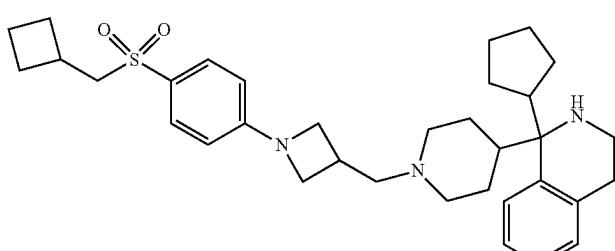
IV-83



IV-84



IV-85



IV-86

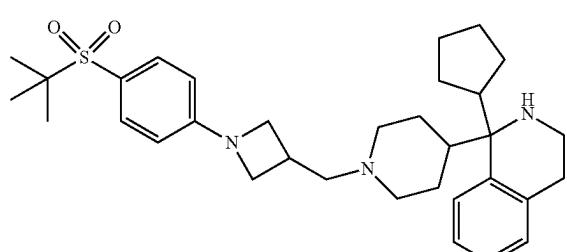


TABLE 4-continued

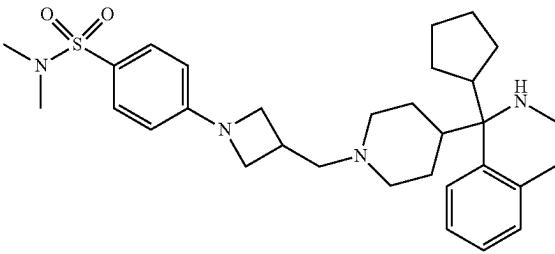
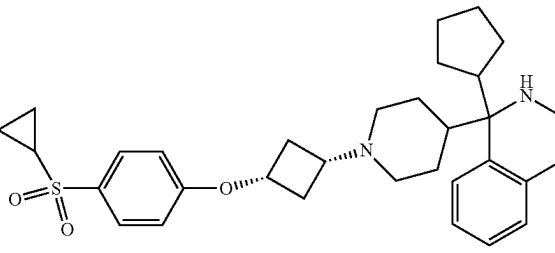
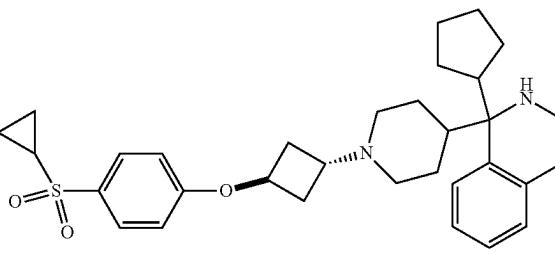
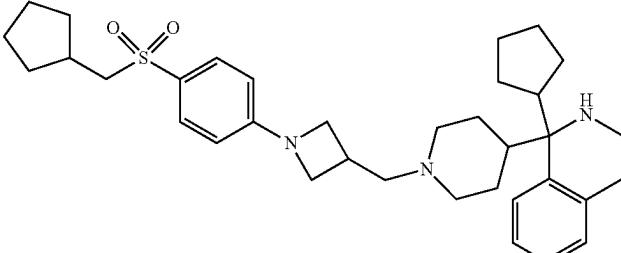
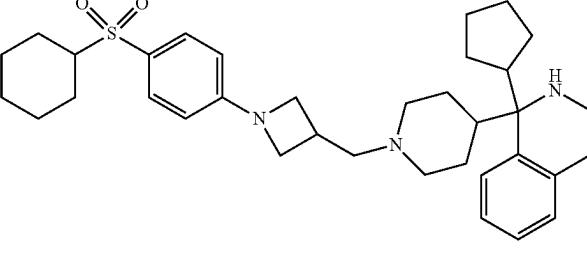
No.	Structure
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IV-88	
IV-89	
IV-90	
IV-91	

TABLE 4-continued

No.	Structure
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IV-93	
IV-94	
IV-95	
IV-96	

TABLE 4-continued

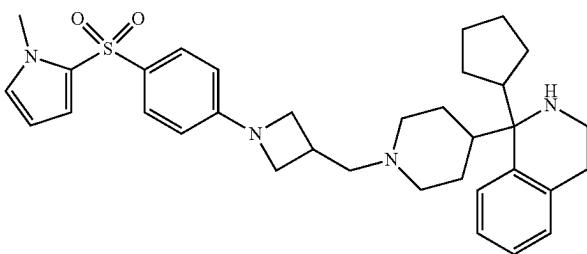
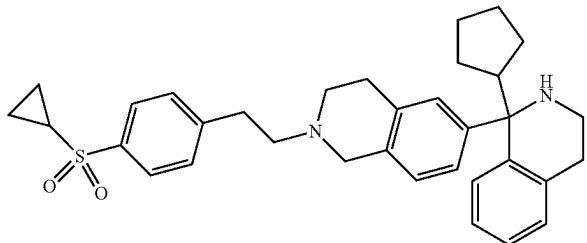
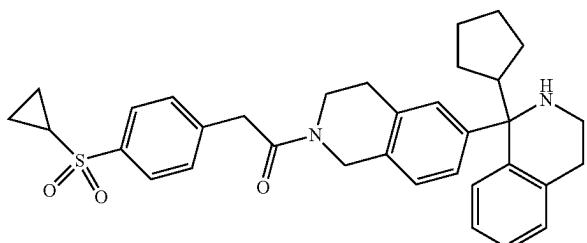
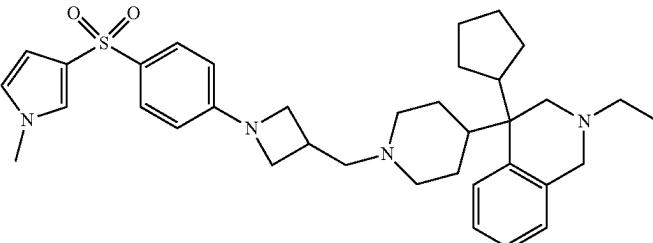
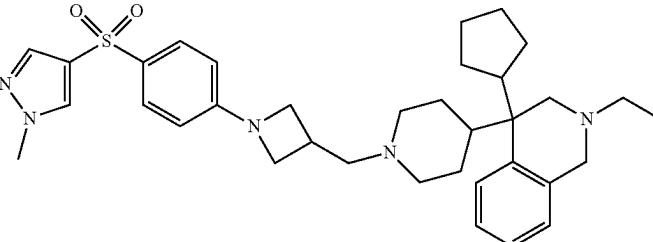
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IV-100	
IV-101	

TABLE 4-continued

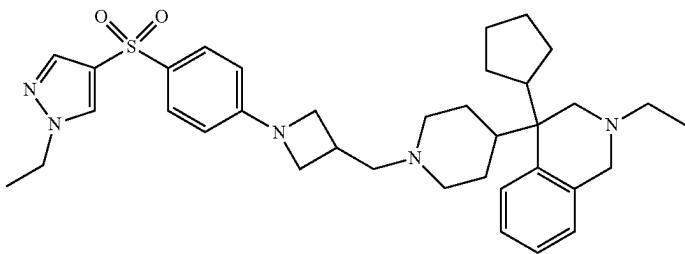
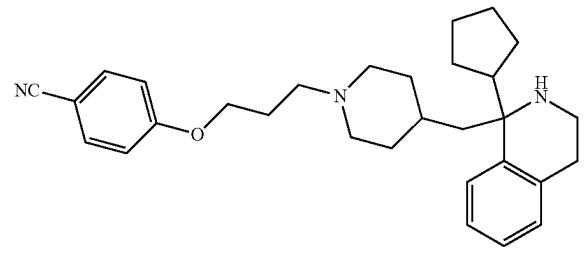
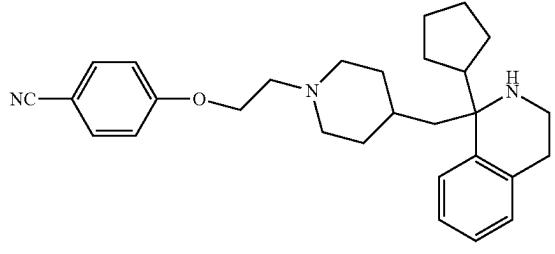
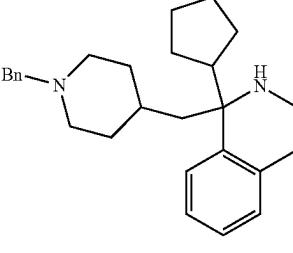
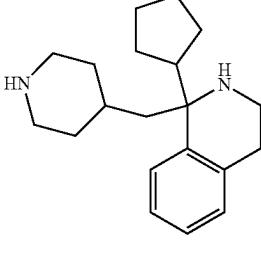
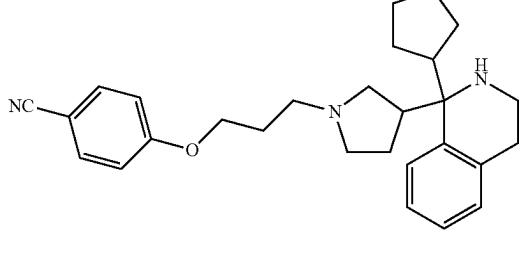
No.	Structure
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IV-105	
IV-106	
IV-107	

TABLE 4-continued

No.	Structure
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IV-109	
IV-110	
IV-111	
IV-112	

TABLE 4-continued

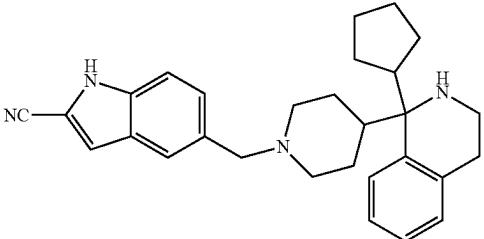
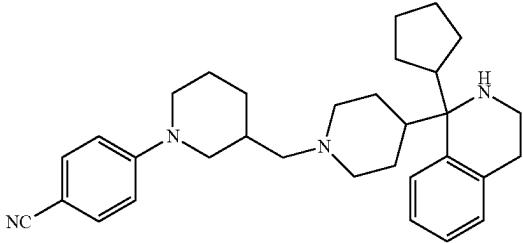
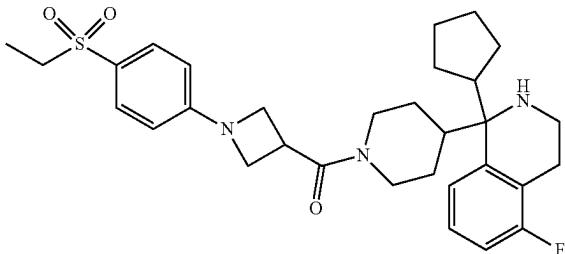
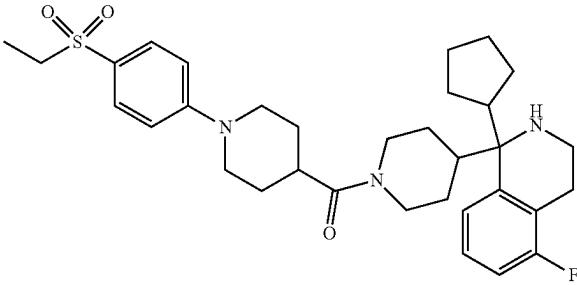
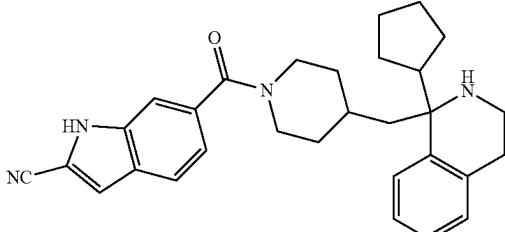
No.	Structure
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IV-114	
IV-115	
IV-116	
IV-117	

TABLE 4-continued

No.	Structure
IV-118	
IV-119	
IV-120	
IV-121	
IV-122	

TABLE 4-continued

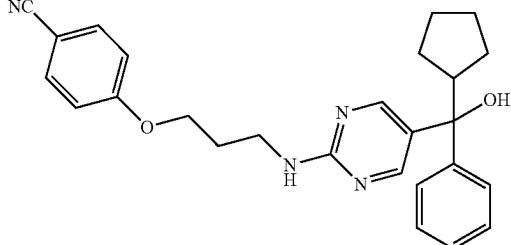
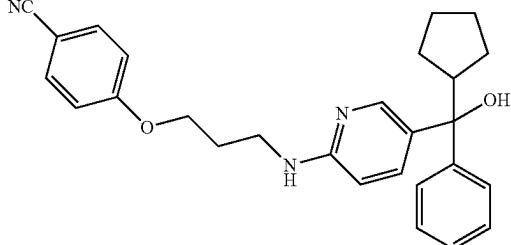
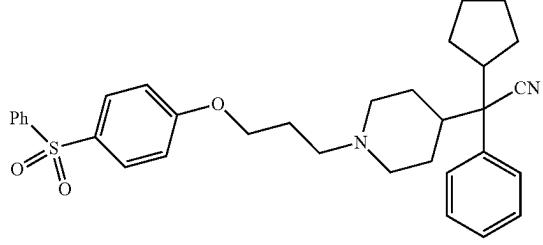
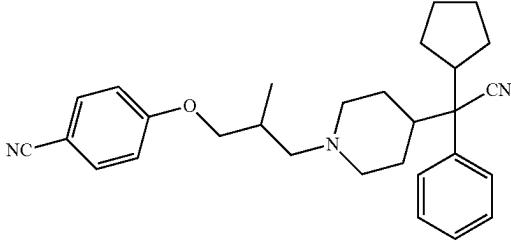
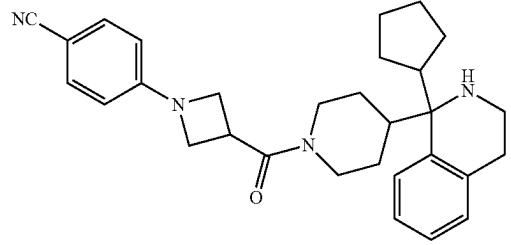
No.	Structure
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IV-124	
IV-125	
IV-126	
IV-127	

TABLE 4-continued

No.	Structure
IV-128	
IV-129	
IV-130	
IV-131	
IV-132	

TABLE 4-continued

No.	Structure
IV-133	
IV-134	
IV-135	
IV-136	
IV-137	

TABLE 4-continued

No.	Structure
IV-138	
IV-139	
IV-140	
IV-141	
IV-142	

TABLE 4-continued

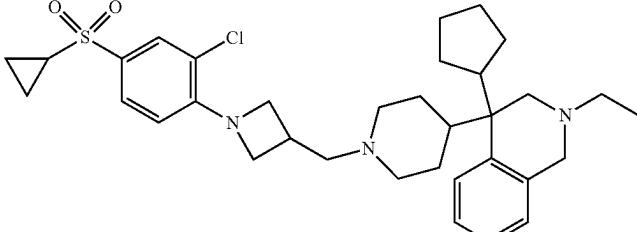
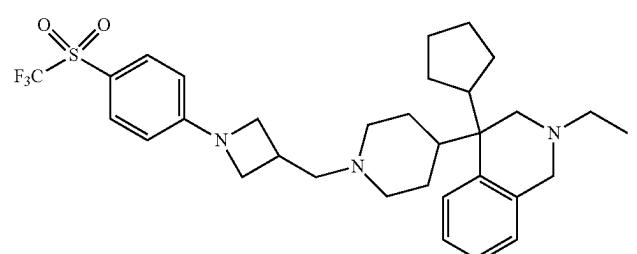
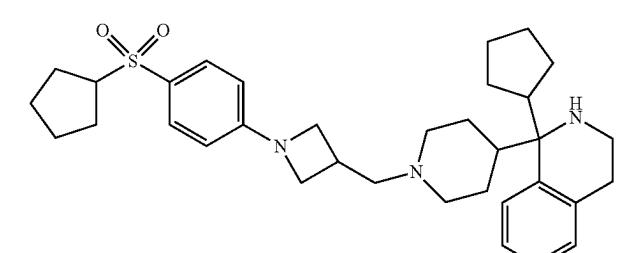
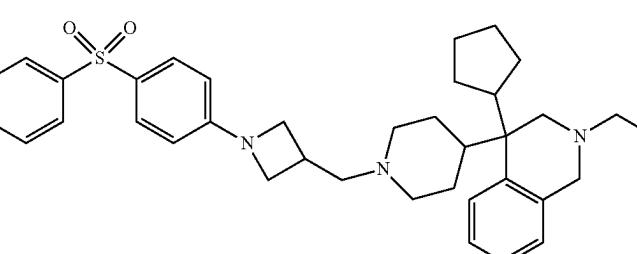
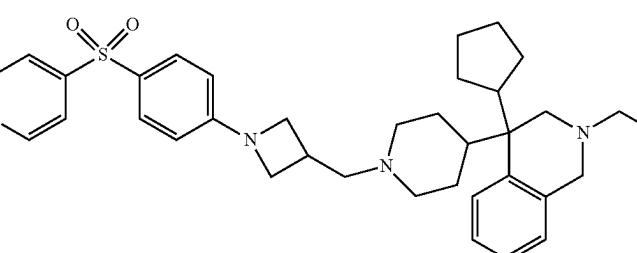
No.	Structure
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IV-144	
IV-145	
IV-146	
IV-147	

TABLE 4-continued

No.	Structure
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IV-149	
IV-150	
IV-151	
IV-152	

TABLE 4-continued

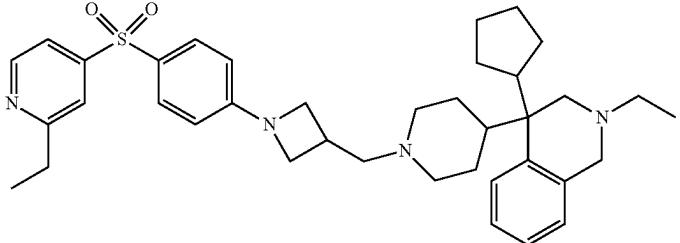
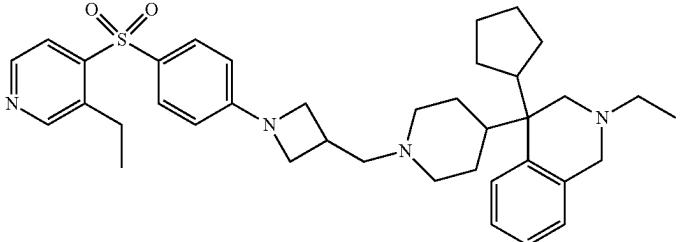
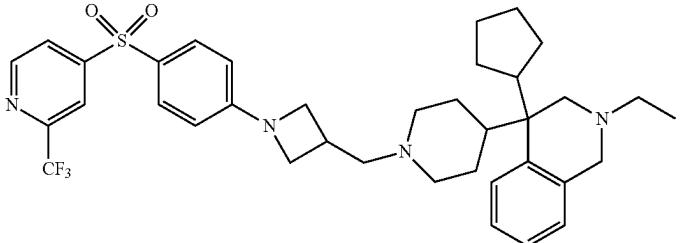
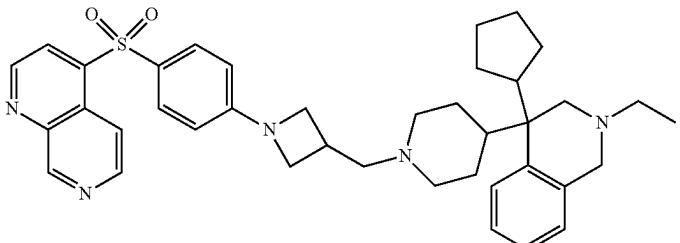
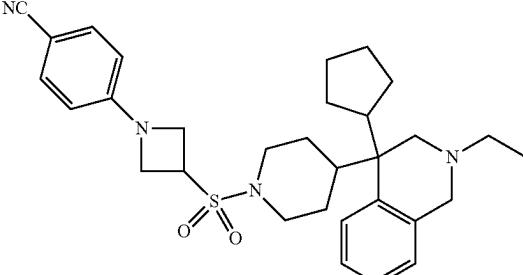
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IV-154	
IV-155	
IV-156	
IV-157	

TABLE 4-continued

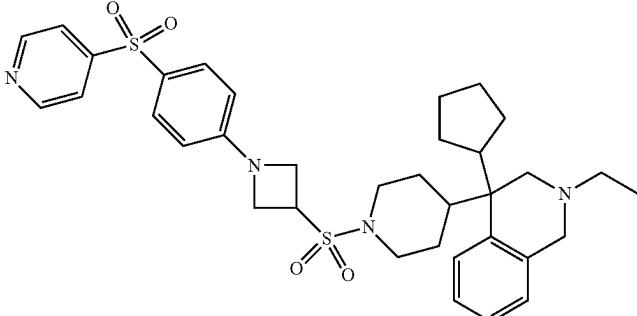
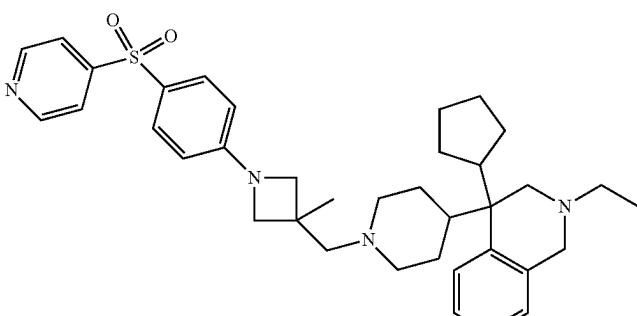
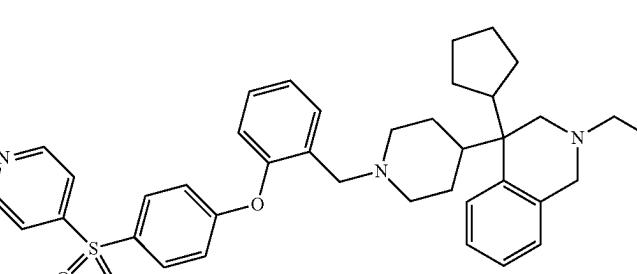
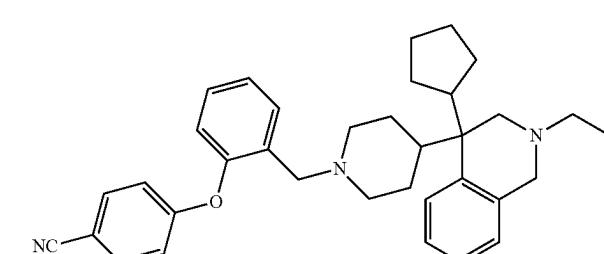
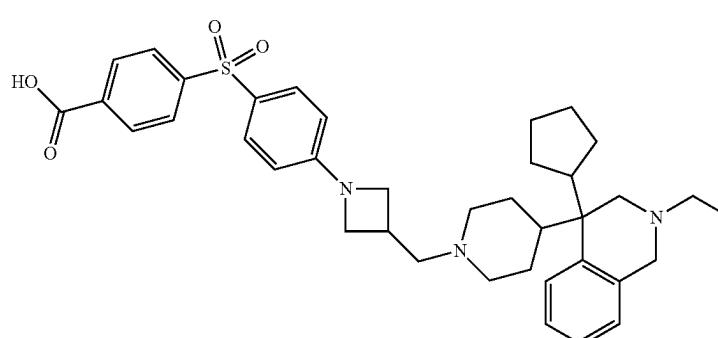
No.	Structure
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IV-159	
IV-160	
IV-161	
IV-162	

TABLE 4-continued

No.	Structure
IV-163	
IV-164	
IV-165	
IV-166	
IV-167	

TABLE 4-continued

No.	Structure
IV-168	
IV-169	
IV-170	
IV-171	
IV-172	

TABLE 4-continued

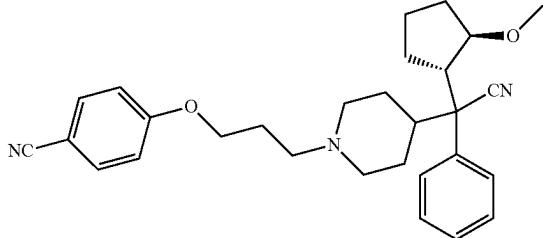
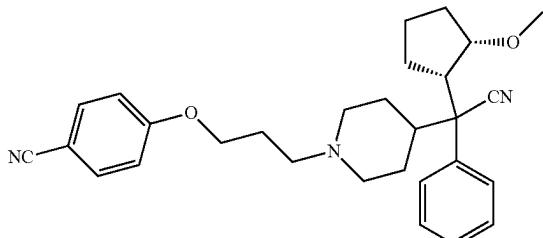
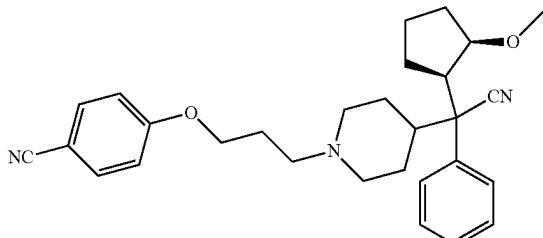
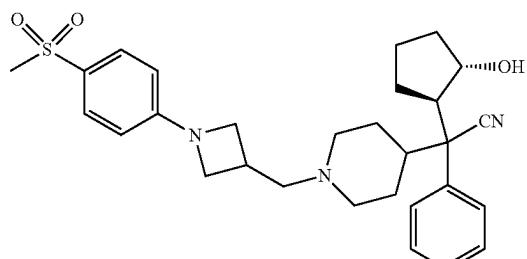
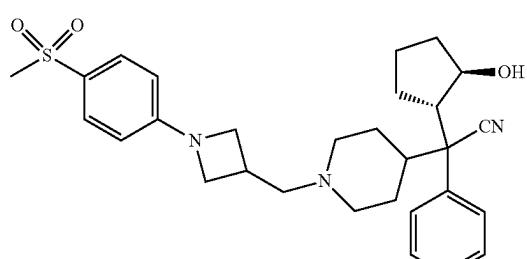
No.	Structure
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IV-174	
IV-175	
IV-176	
IV-177	

TABLE 4-continued

No.	Structure
IV-178	
IV-179	
IV-180	
IV-181	
IV-182	

TABLE 4-continued

No.	Structure
IV-183	
IV-184	
IV-185	
IV-186	
IV-187	

TABLE 4-continued

No.	Structure
IV-188	
IV-189	
IV-190	
IV-191	
IV-192	

TABLE 4-continued

No.	Structure
IV-193	
IV-194	
IV-195	
IV-196	
IV-197	

TABLE 4-continued

No.	Structure
IV-198	
IV-199	
IV-200	
IV-201	
IV-202	

TABLE 4-continued

No.	Structure
IV-203	
IV-204	
IV-205	
IV-206	
IV-207	

TABLE 4-continued

No.	Structure
IV-208	
IV-209	
IV-210	
IV-211	
IV-212	

TABLE 4-continued

No.	Structure
IV-213	
IV-214	
IV-215	
IV-216	
IV-217	

TABLE 4-continued

No.	Structure
IV-218	
IV-219	
IV-220	
IV-221	
IV-222	

TABLE 4-continued

No.	Structure
IV-223	
IV-224	
IV-225	
IV-226	
IV-227	

TABLE 4-continued

No.	Structure
IV-228	
IV-229	
IV-230	
IV-231	
IV-232	

TABLE 4-continued

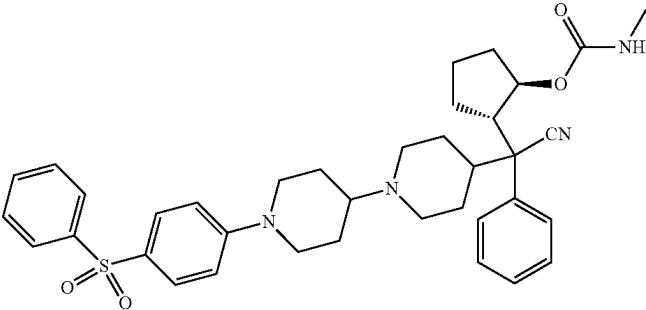
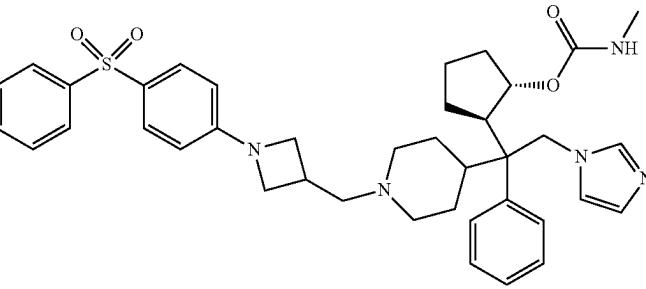
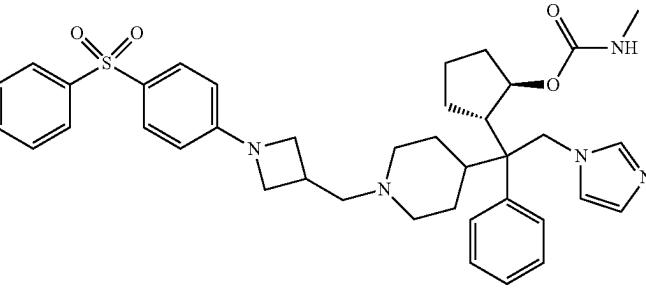
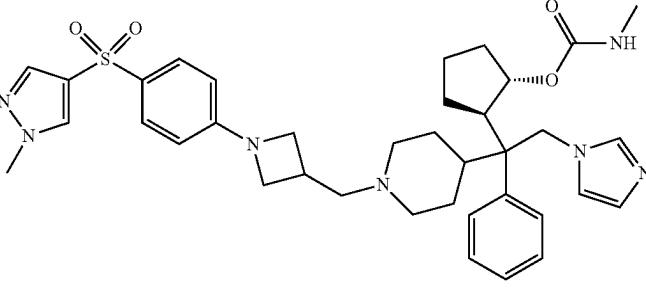
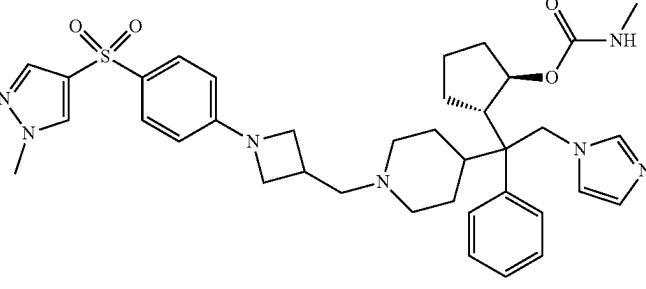
No.	Structure
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IV-235	
IV-236	
IV-237	

TABLE 4-continued

No.	Structure
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IV-240	
IV-241	
IV-242	

TABLE 4-continued

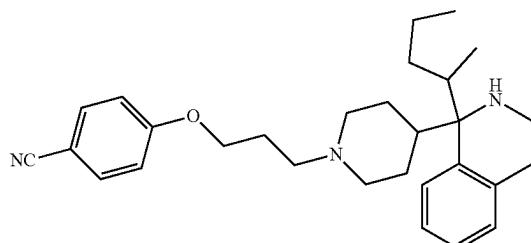
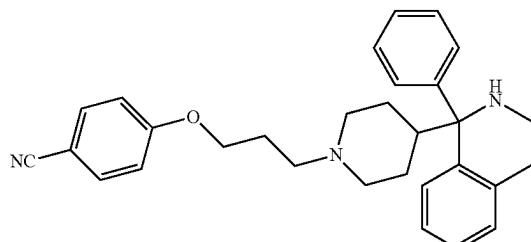
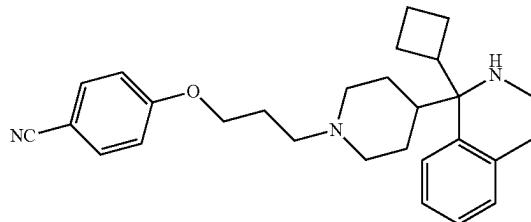
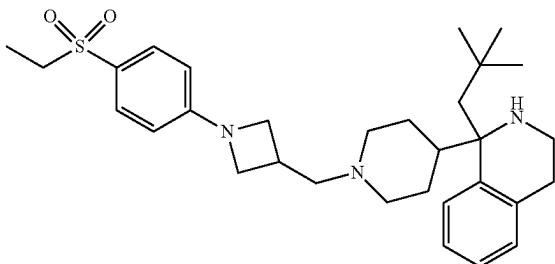
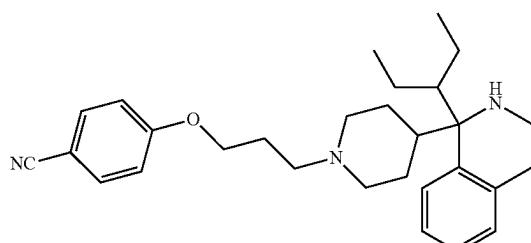
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IV-247	

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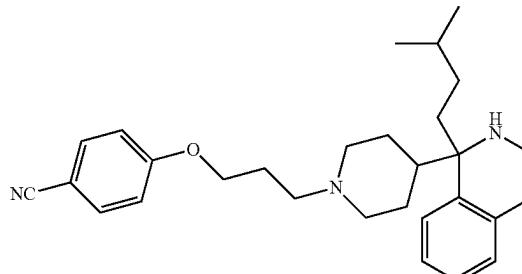
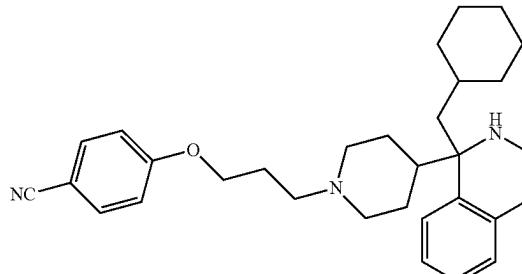
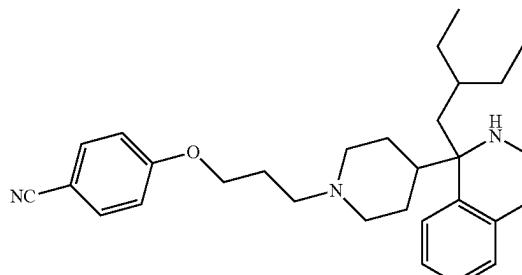
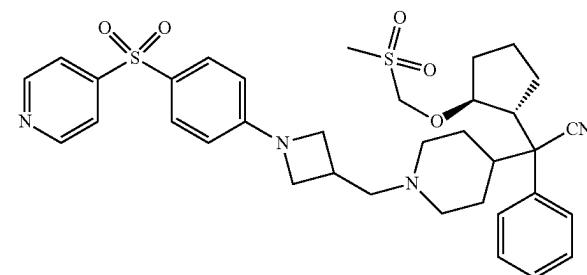
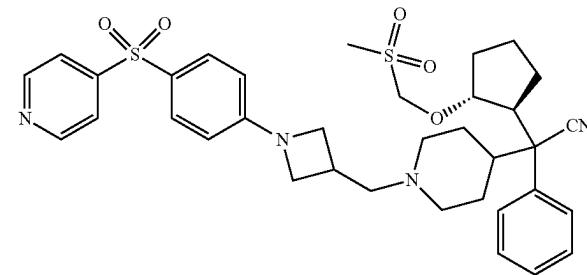
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IV-250	
IV-251	
IV-252	

TABLE 4-continued

No.	Structure
IV-253	
IV-254	
IV-255	
IV-256	
IV-257	

TABLE 4-continued

No.	Structure
IV-258	
IV-259	
IV-260	
IV-261	
IV-262	

TABLE 4-continued

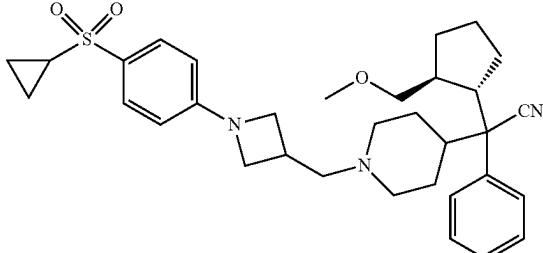
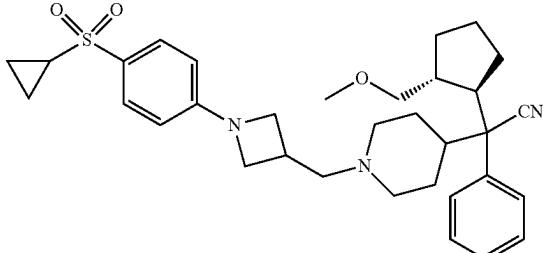
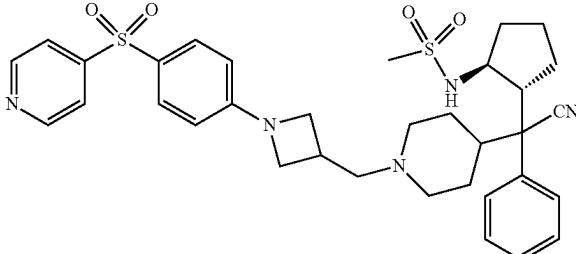
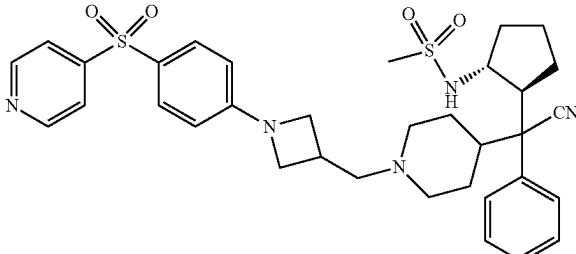
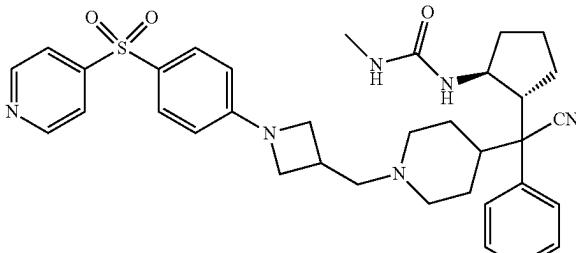
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IV-265	
IV-266	
IV-267	

TABLE 4-continued

No.	Structure
IV-268	
IV-269	
IV-270	
IV-271	
IV-272	

TABLE 4-continued

No.	Structure
IV-273	
IV-274	
IV-275	
IV-276	
IV-277	

TABLE 4-continued

No.	Structure
IV-278	
IV-279	
IV-280	
IV-281	
IV-282	

TABLE 4-continued

No.	Structure
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IV-284	
IV-285	
IV-286	
IV-287	

TABLE 4-continued

No.	Structure
IV-288	
IV-289	
IV-290	
IV-291	
IV-292	

TABLE 4-continued

No.	Structure
IV-293	
IV-294	
IV-295	
IV-296	
IV-297	

TABLE 4-continued

No.	Structure
IV-298	
IV-299	
IV-300	
IV-301	
IV-302	

TABLE 4-continued

No.	Structure
IV-303	
IV-304	
IV-305	
IV-306	
IV-307	

TABLE 4-continued

No.	Structure
IV-308	
IV-309	
IV-310	
IV-311	
IV-312	

TABLE 4-continued

No.	Structure
IV-313	
IV-314	
IV-315	
IV-316	
IV-317	

TABLE 4-continued

No.	Structure
IV-318	
IV-319	
IV-320	
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IV-322	

TABLE 4-continued

No.	Structure
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IV-327	

TABLE 4-continued

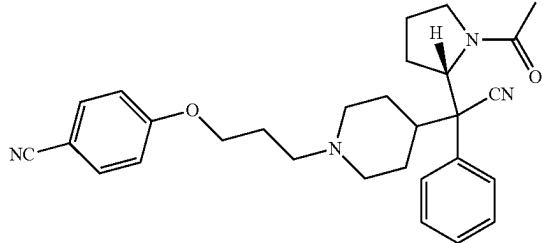
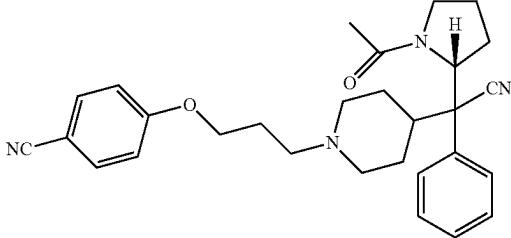
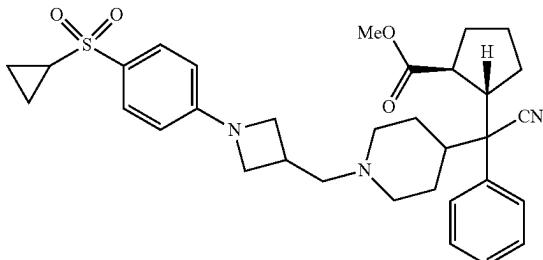
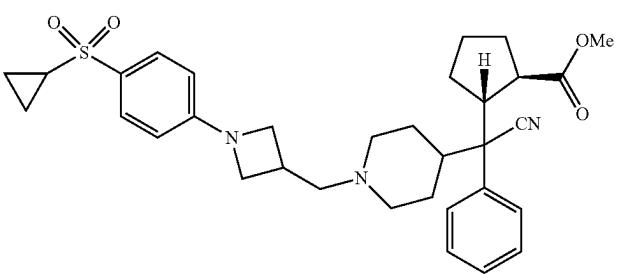
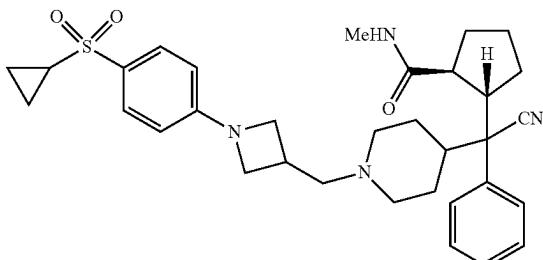
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IV-330	
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IV-332	

TABLE 4-continued

No.	Structure
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IV-336	
IV-337	

TABLE 4-continued

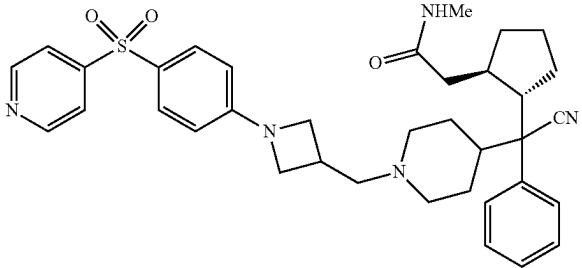
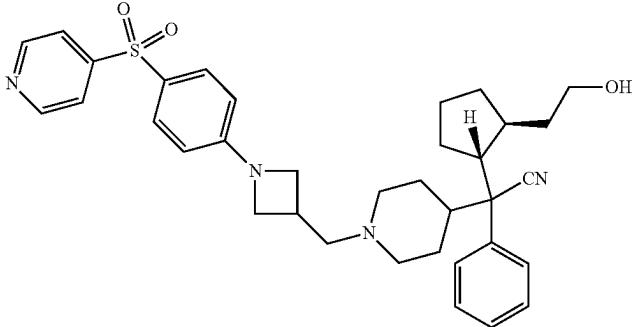
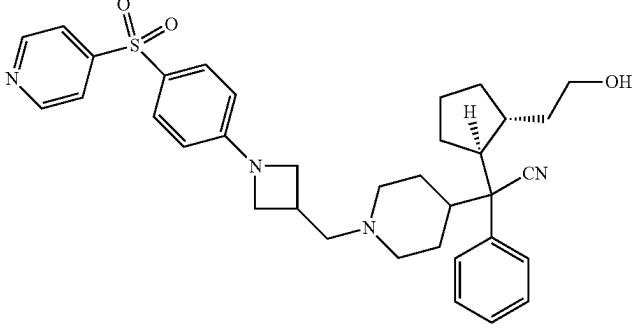
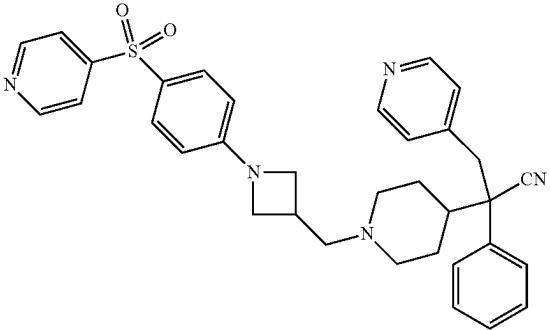
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IV-341	

TABLE 4-continued

No.	Structure
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IV-345	

TABLE 4-continued

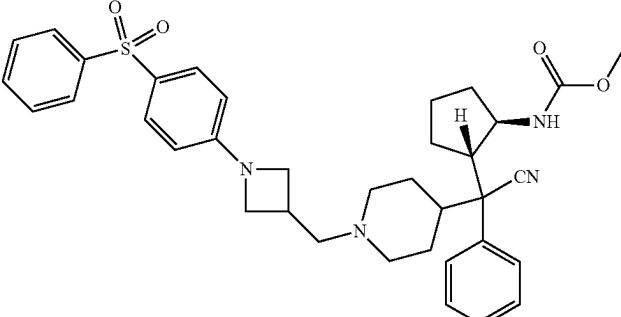
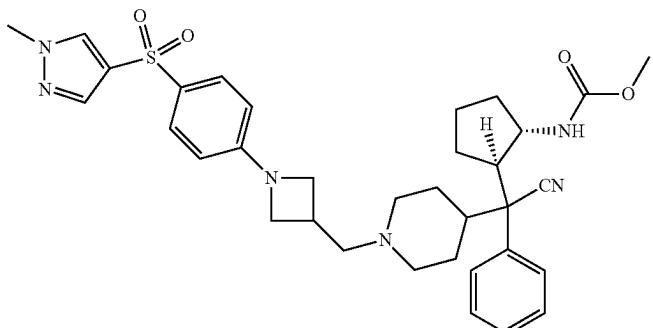
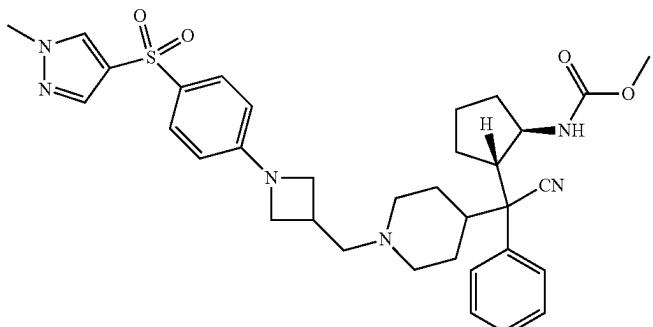
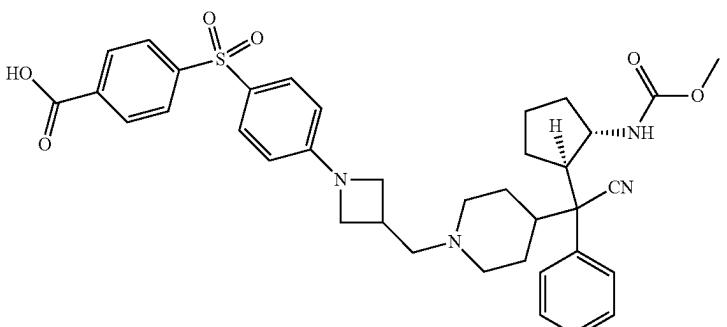
No.	Structure
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TABLE 4-continued

No.	Structure
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TABLE 4-continued

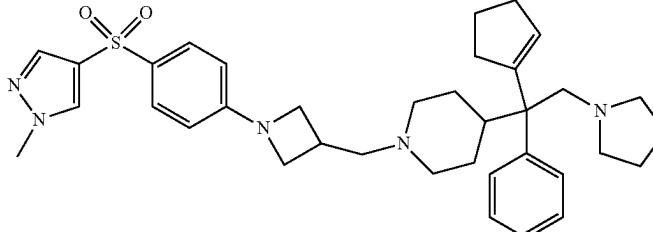
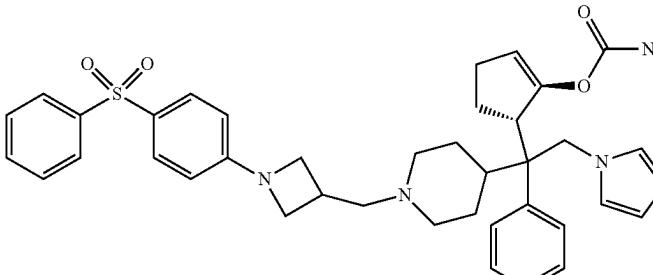
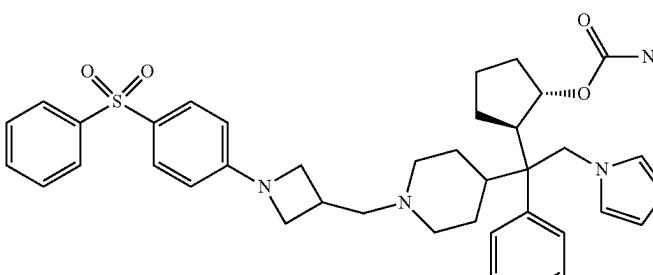
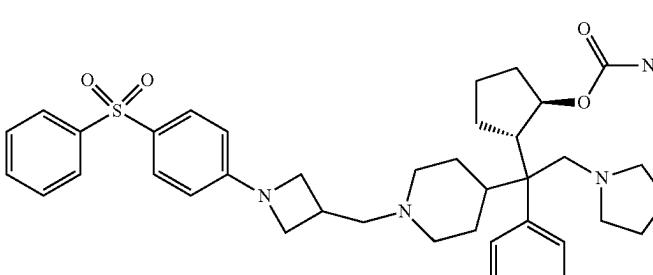
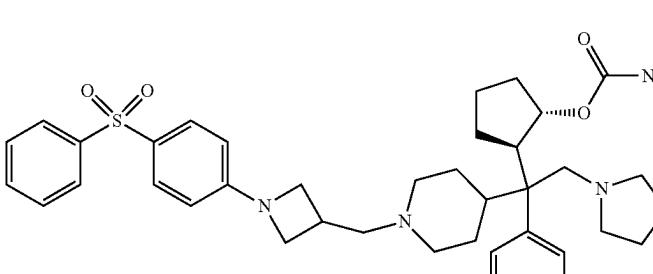
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IV-357	
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IV-359	

TABLE 4-continued

No.	Structure
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IV-364	

TABLE 4-continued

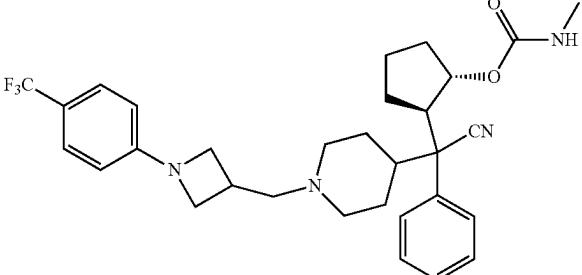
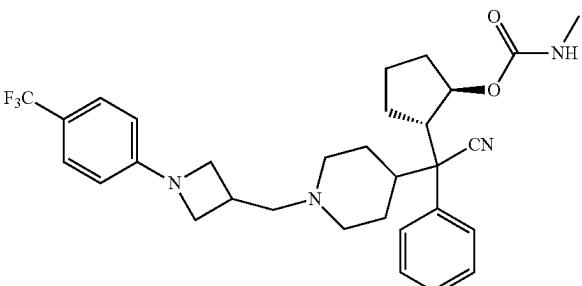
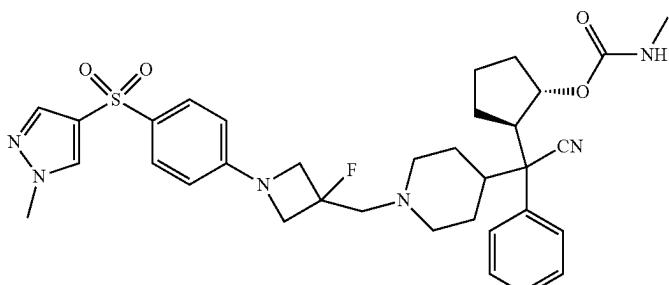
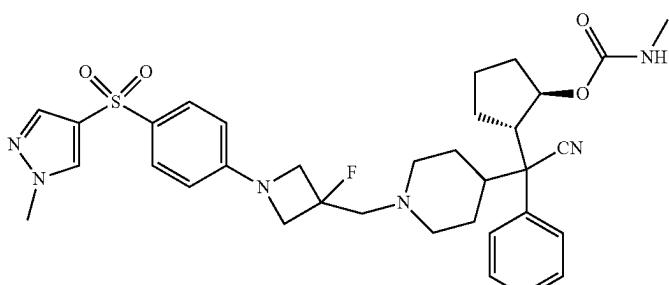
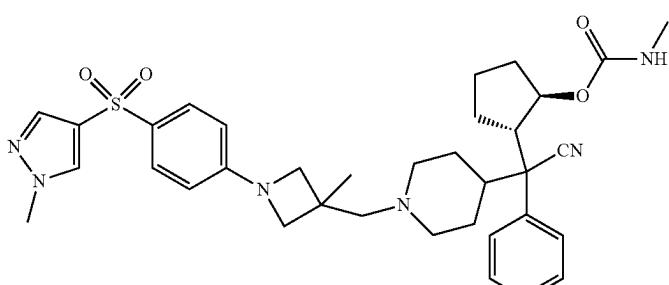
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IV-368	
IV-369	

TABLE 4-continued

No.	Structure
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IV-372	
IV-373	
IV-374	

TABLE 4-continued

No.	Structure
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IV-378	
IV-379	

TABLE 4-continued

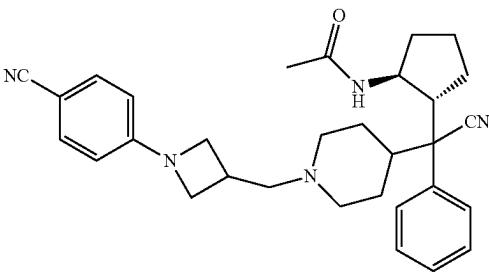
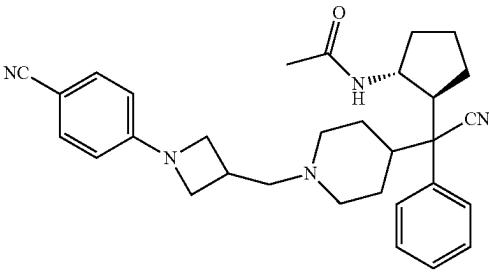
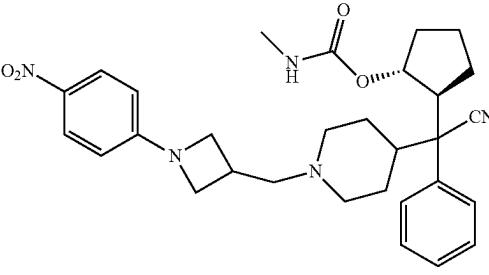
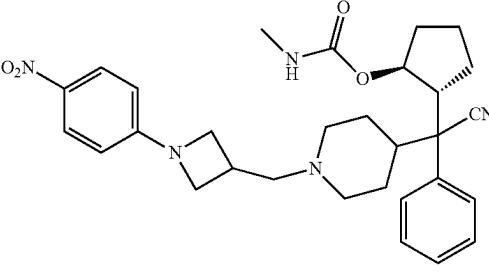
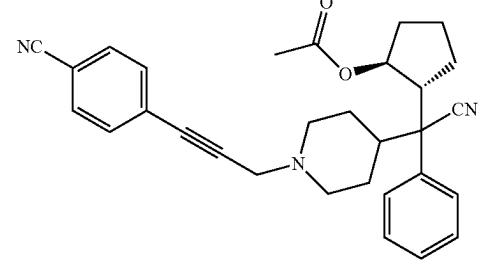
No.	Structure
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IV-382	
IV-383	
IV-384	

TABLE 4-continued

No.	Structure
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IV-389	

TABLE 4-continued

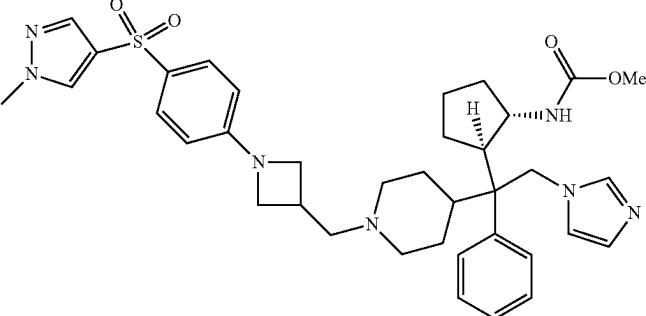
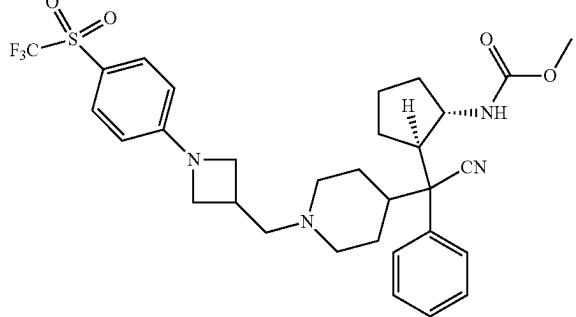
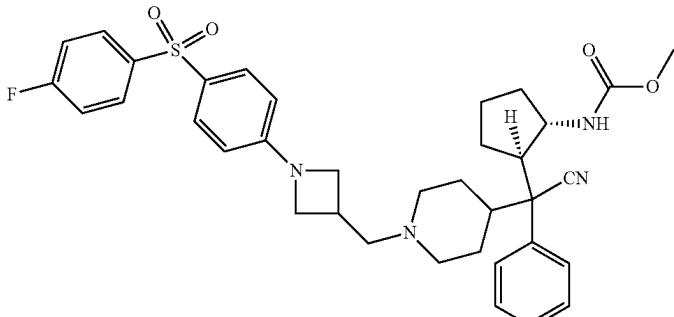
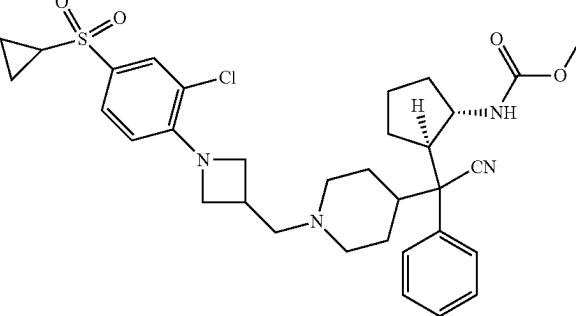
No.	Structure
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IV-393	

TABLE 4-continued

No.	Structure
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IV-397	

TABLE 4-continued

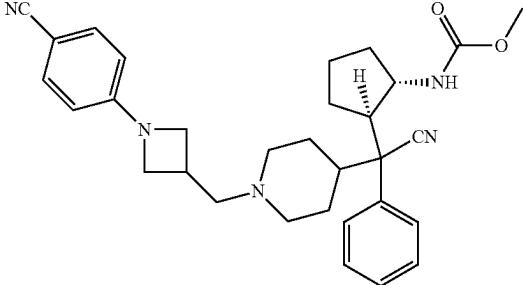
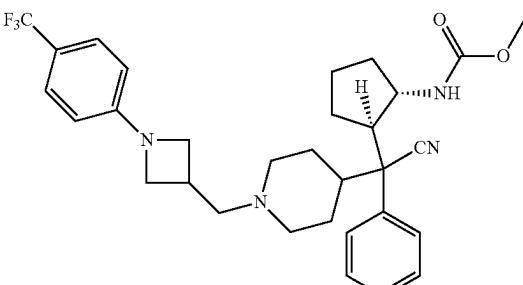
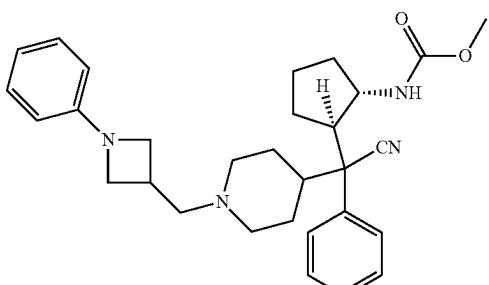
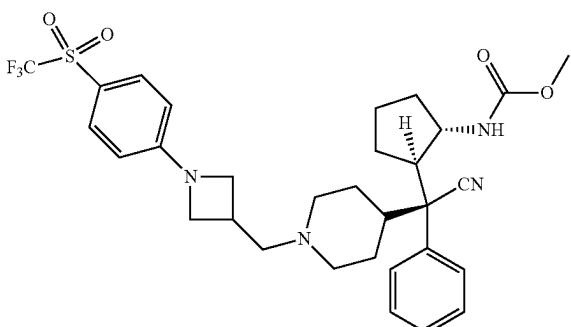
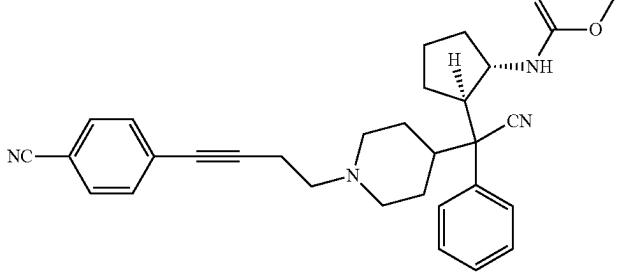
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IV-402	

TABLE 4-continued

No.	Structure
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IV-407	

TABLE 4-continued

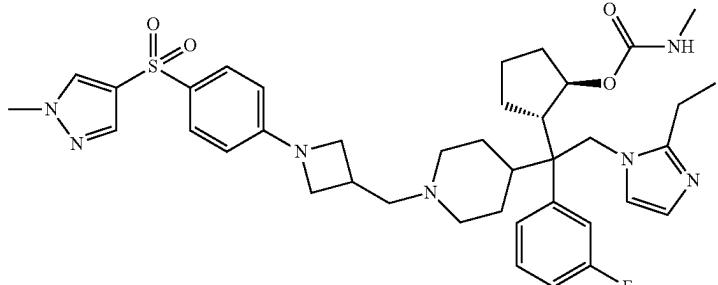
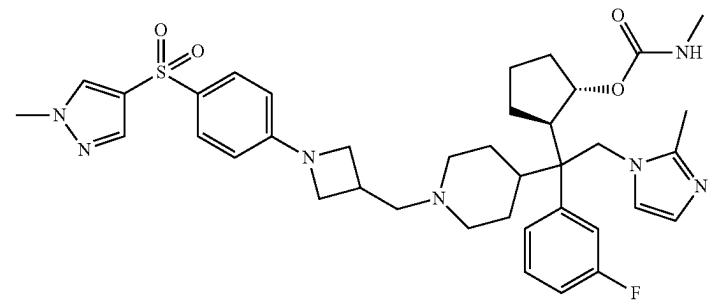
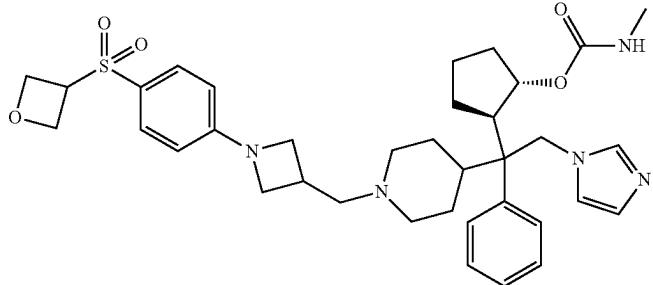
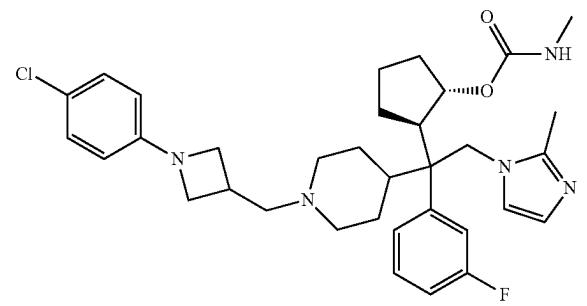
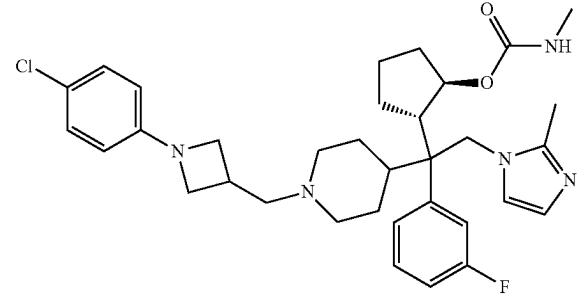
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IV-410	
IV-411	
IV-412	

TABLE 4-continued

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IV-414	
IV-415	
IV-416	
IV-417	

TABLE 4-continued

No.	Structure
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IV-420	
IV-421	

TABLE 4-continued

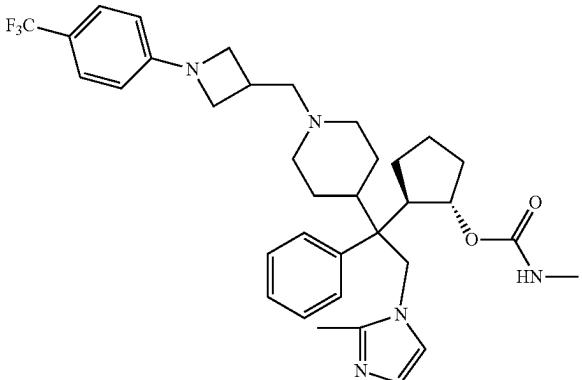
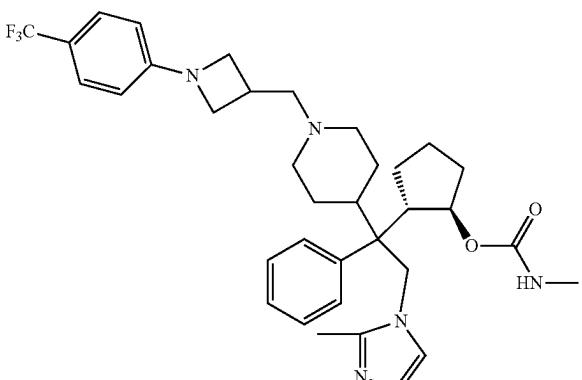
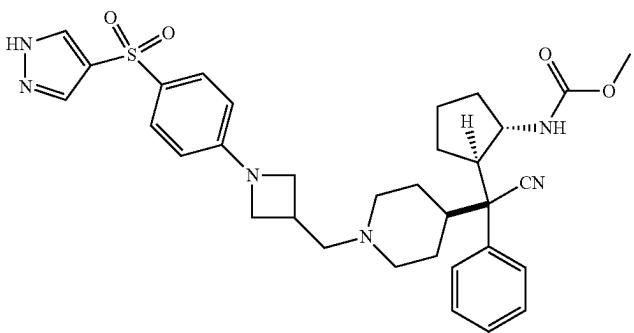
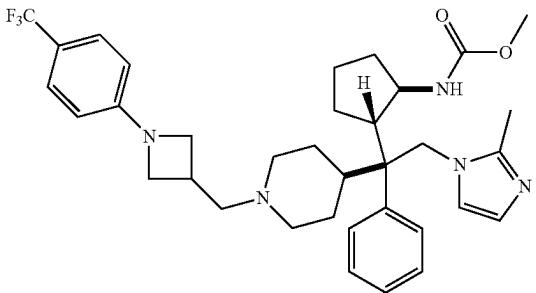
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TABLE 4-continued

No.	Structure
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IV-429	

TABLE 4-continued

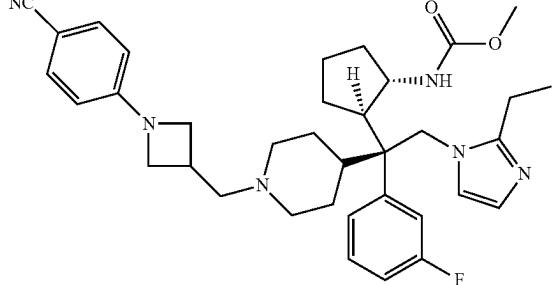
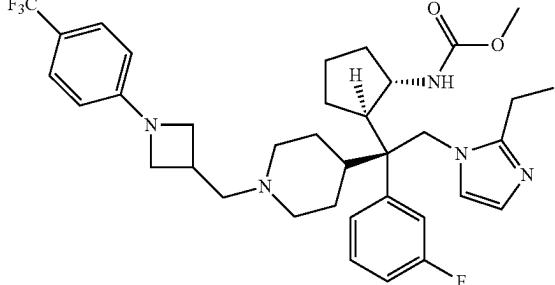
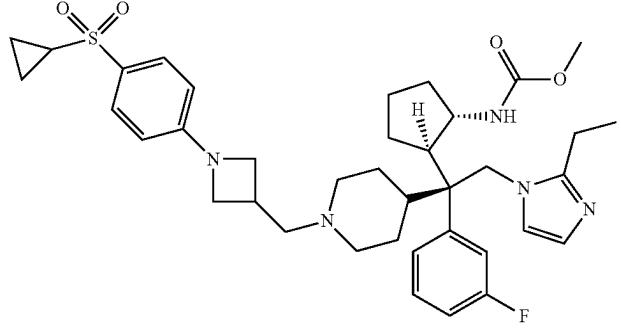
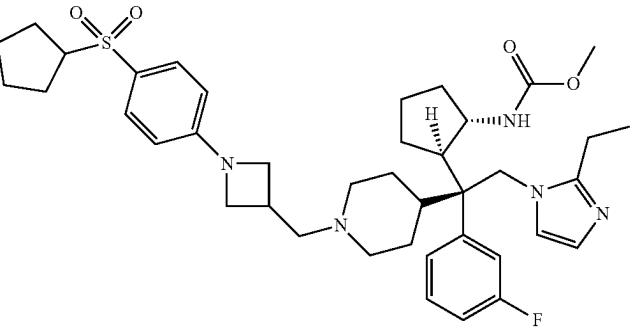
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IV-433	

TABLE 4-continued

No.	Structure
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IV-436	
IV-437	
IV-438	

TABLE 4-continued

No.	Structure
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IV-441	
IV-442	
IV-443	

TABLE 4-continued

No.	Structure
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IV-445	
IV-446	
IV-447	
IV-448	

TABLE 4-continued

No.	Structure
IV-449	
IV-450	
IV-451	
IV-452	
IV-453	

TABLE 4-continued

No.	Structure
IV-454	
IV-455	
IV-456	
IV-457	
IV-458	

TABLE 4-continued

No.	Structure
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IV-463	

TABLE 4-continued

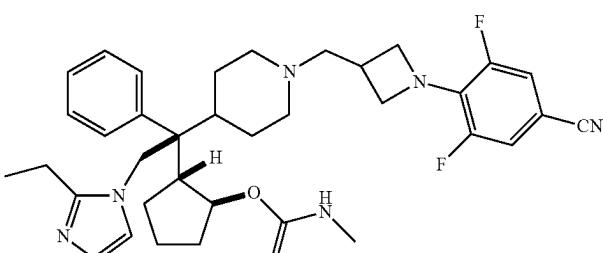
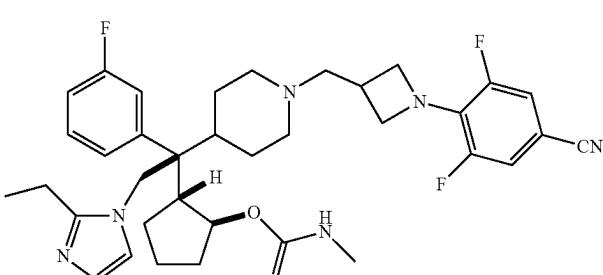
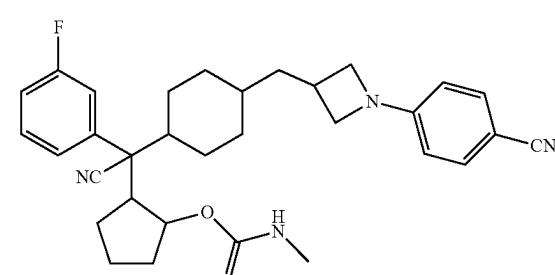
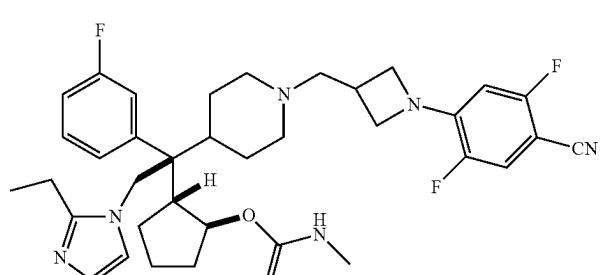
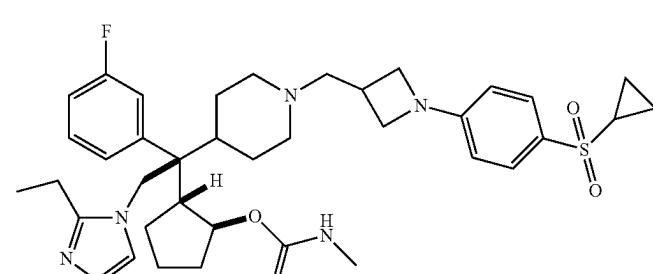
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IV-468	

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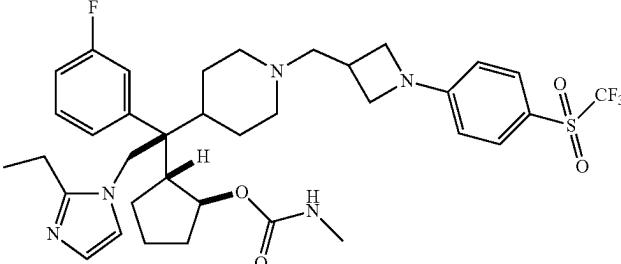
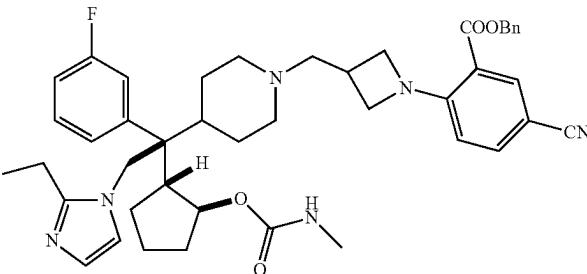
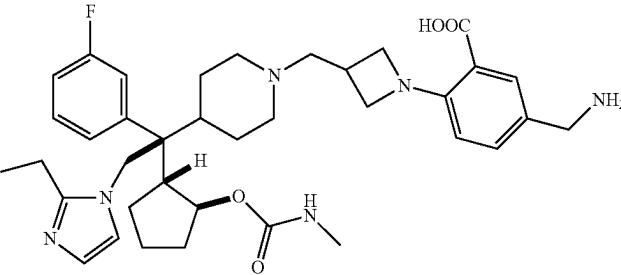
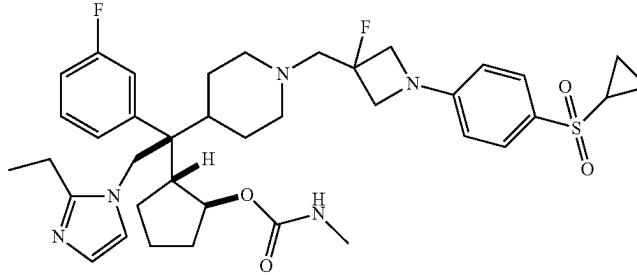
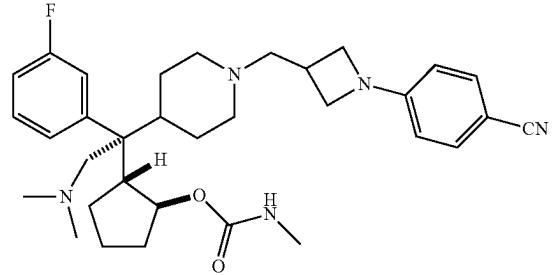
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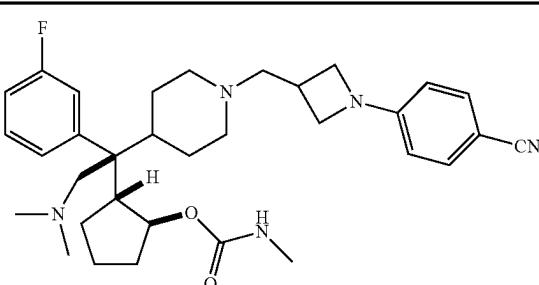
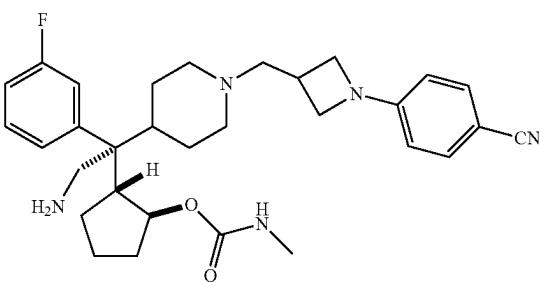
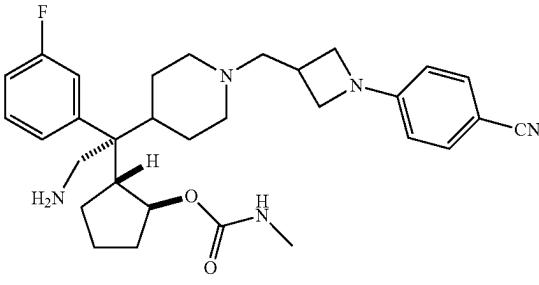
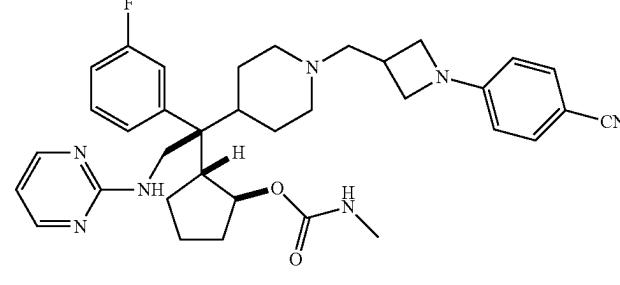
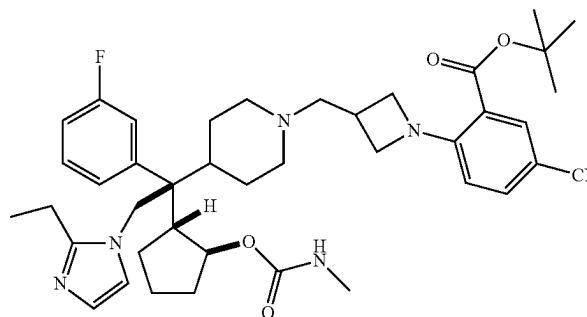
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IV-476	
IV-477	
IV-478	

TABLE 4-continued

No.	Structure
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IV-481	
IV-482	
IV-483	

TABLE 4-continued

No.	Structure
IV-484	
IV-485	
IV-486	
IV-487	
IV-488	

TABLE 4-continued

No.	Structure
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IV-492	
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IV-494	

TABLE 4-continued

No.	Structure
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IV-499	

TABLE 4-continued

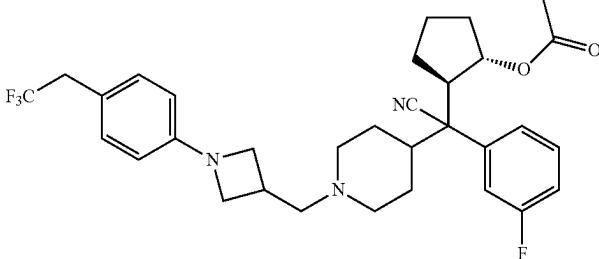
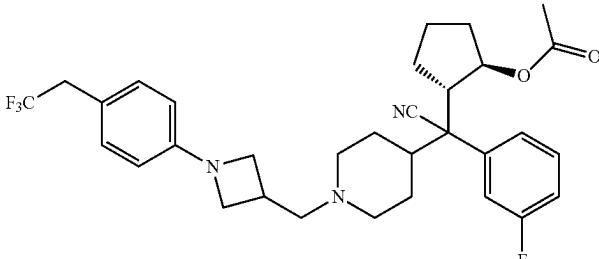
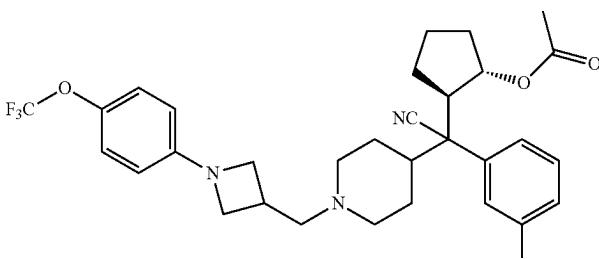
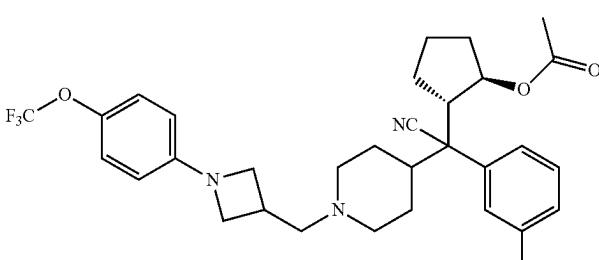
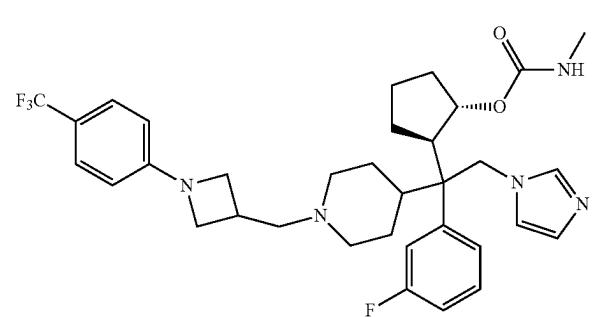
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IV-504	

TABLE 4-continued

No.	Structure
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IV-507	
IV-508	
IV-509	

TABLE 4-continued

No.	Structure
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IV-511	
IV-512	
IV-513	
IV-514	

TABLE 4-continued

No.	Structure
IV-515	
IV-516	
IV-517	
IV-518	

TABLE 4-continued

No.	Structure
IV-519	
IV-520	

TABLE 5

No.	Structure
V-1	

TABLE 5-continued

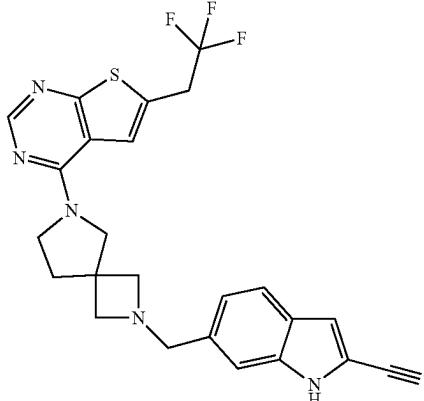
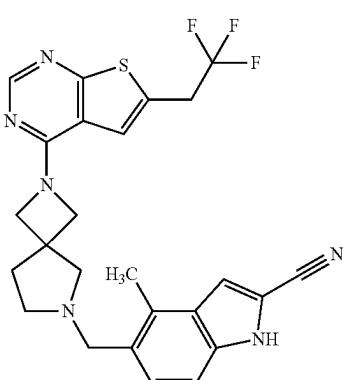
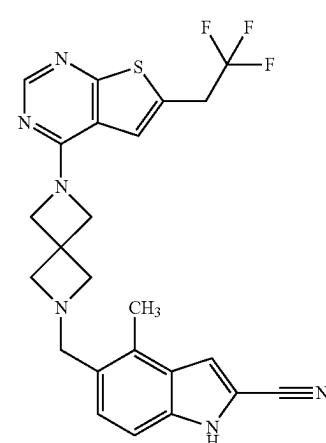
No.	Structure
V-2	
V-3	
V-4	

TABLE 5-continued

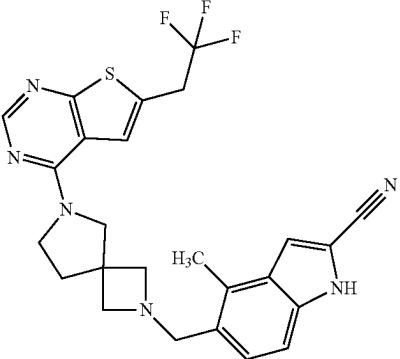
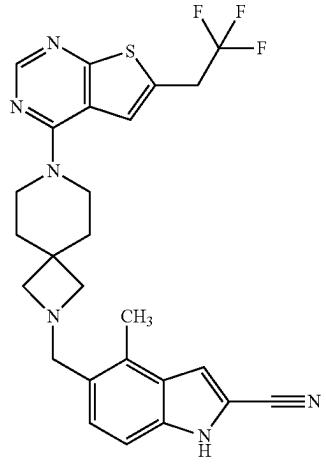
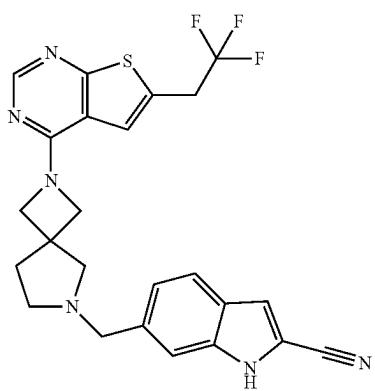
No.	Structure
V-5	
V-6	
V-7	

TABLE 5-continued

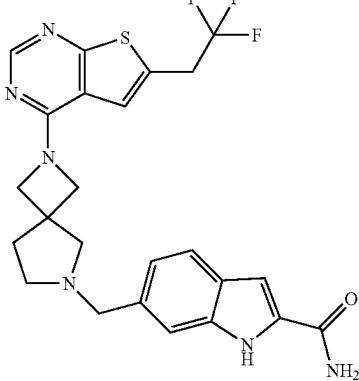
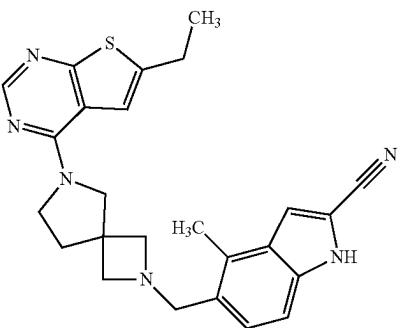
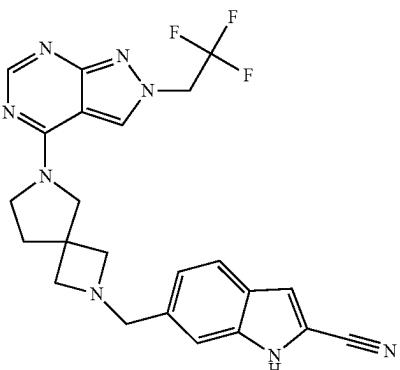
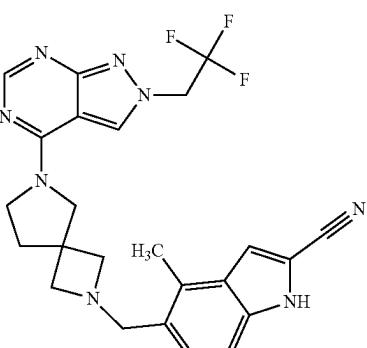
No.	Structure
V-8	
V-9	
V-10	
V-11	

TABLE 5-continued

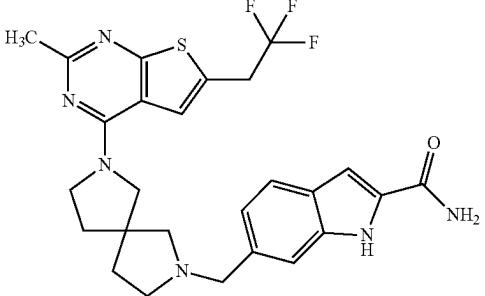
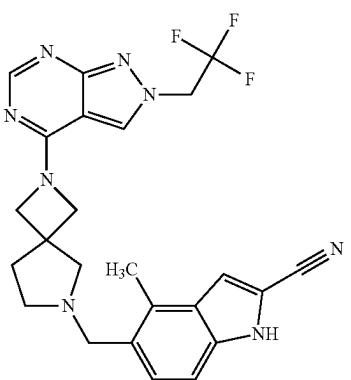
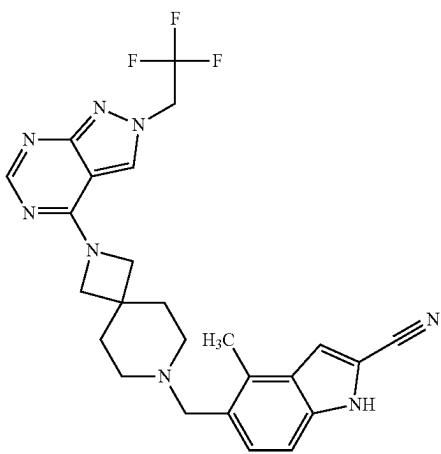
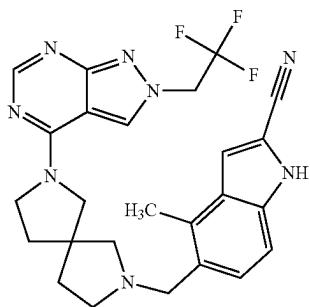
No.	Structure
V-12	
V-13	
V-14	
V-15	

TABLE 5-continued

No.	Structure
V-16	
V-17	
V-18	

TABLE 5-continued

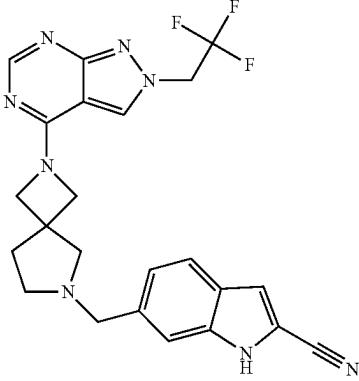
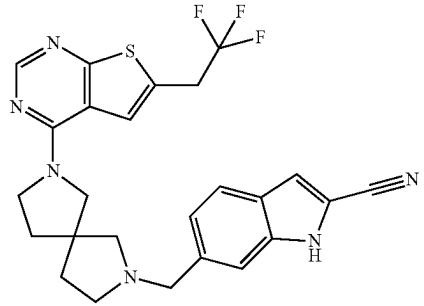
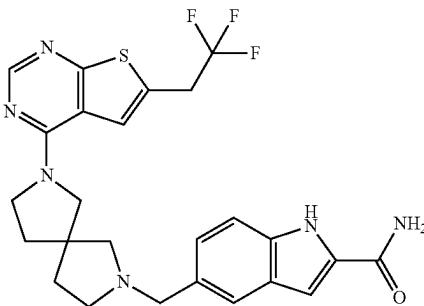
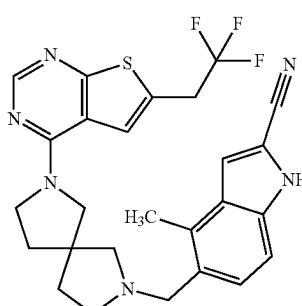
No.	Structure
V-19	
V-20	
V-21	
V-22	

TABLE 5-continued

No.	Structure
V-23	
V-24	
V-25	

TABLE 5-continued

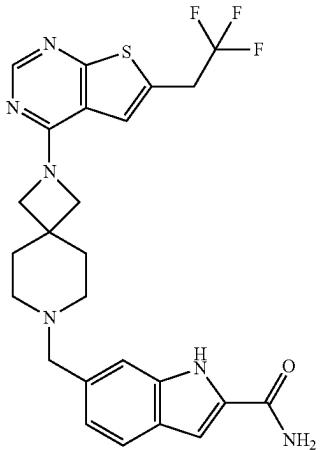
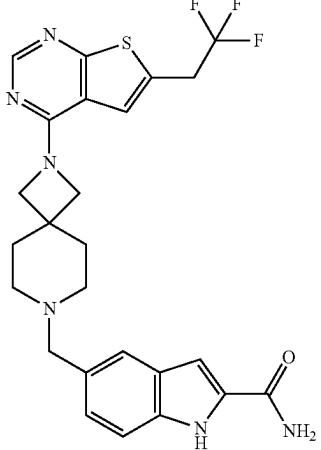
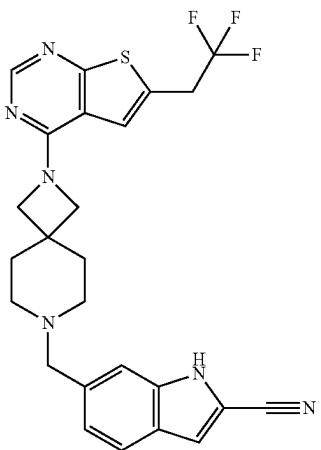
No.	Structure
V-26	
V-27	
V-28	

TABLE 5-continued

No.	Structure
V-29	<p>Chemical structure V-29: A complex molecule featuring a 2-(4-fluorophenyl)-6-thiopyrimidine core. It is substituted at the 4-position with a 2-(cyclopropylmethyl)piperazine ring, which is further substituted at the 2-position with a 2-(2-methylindolin-3-yl)ethyl group.</p>
V-30	<p>Chemical structure V-30: A complex molecule featuring a 2-(4-fluorophenyl)-6-thiopyrimidine core. It is substituted at the 4-position with a 2-(cyclopropylmethyl)piperazine ring, which is further substituted at the 2-position with a 2-(2-methylindolin-3-yl)ethyl group.</p>
V-31	<p>Chemical structure V-31: A complex molecule featuring a 2-(4-fluorophenyl)-6-thiopyrimidine core. It is substituted at the 4-position with a 2-(cyclopropylmethyl)piperazine ring, which is further substituted at the 2-position with a 2-(2-(aminoacetyl)indolin-3-yl)ethyl group.</p>

TABLE 5-continued

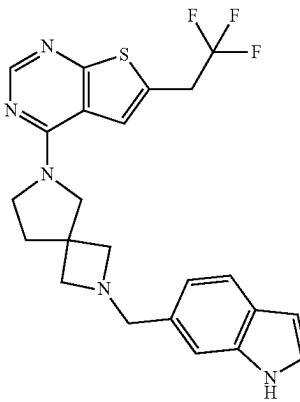
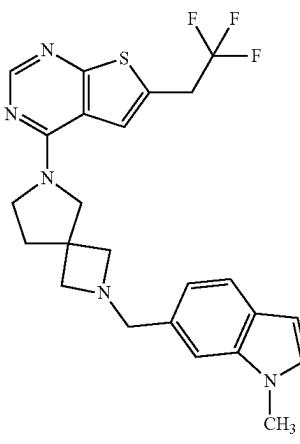
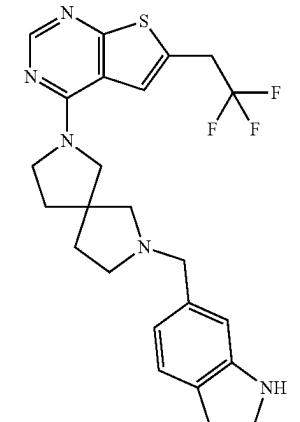
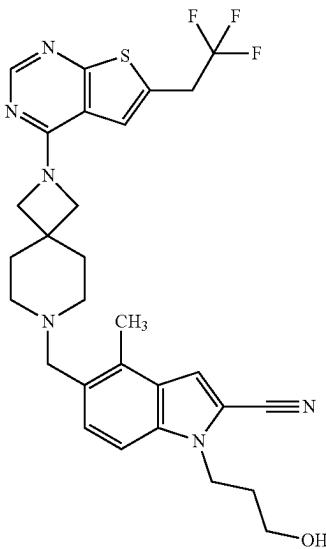
No.	Structure
V-32	
V-33	
V-34	

TABLE 5-continued

No.	Structure
V-35	
V-36	
V-37	

TABLE 5-continued

No.	Structure
V-38	

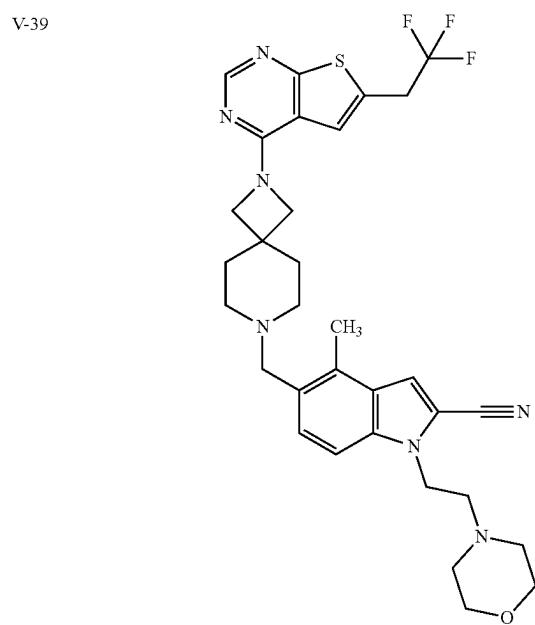


TABLE 5-continued

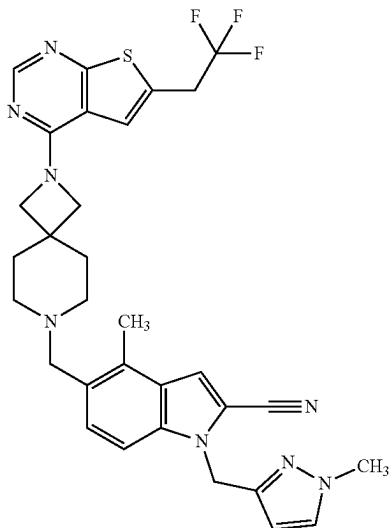
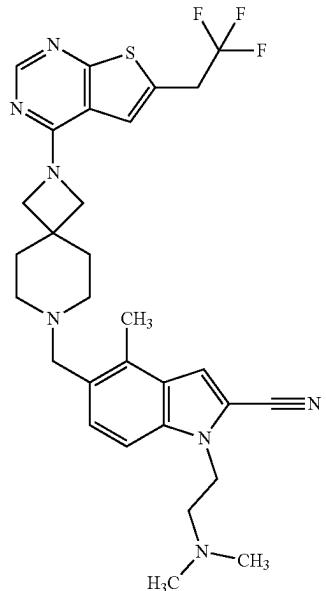
No.	Structure
V-40	
V-41	

TABLE 5-continued

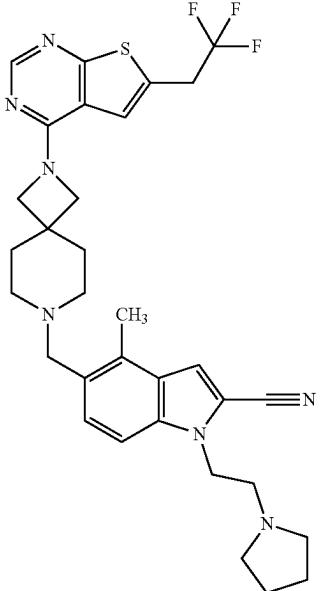
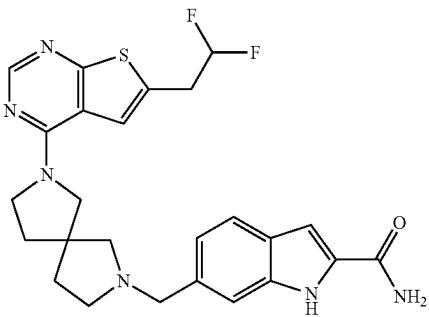
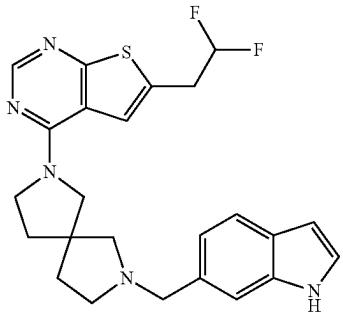
No.	Structure
V-42	
V-43	
V-44	

TABLE 5-continued

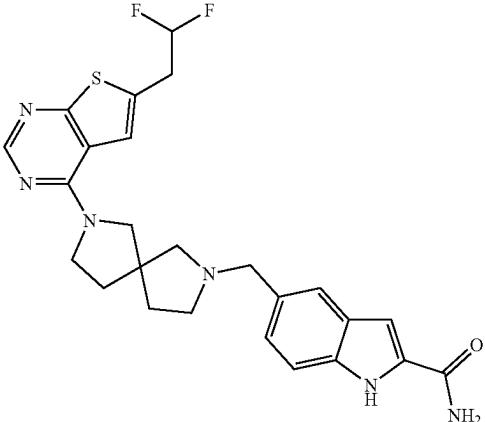
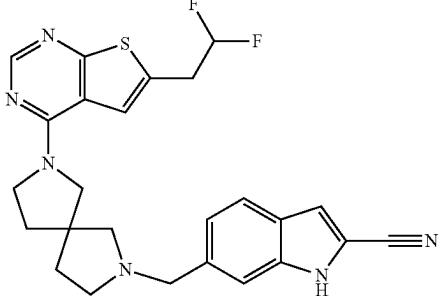
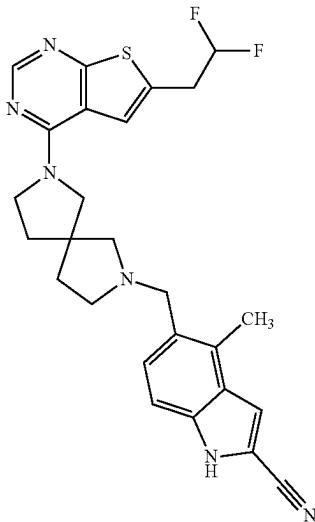
No.	Structure
V-45	
V-46	
V-47	

TABLE 5-continued

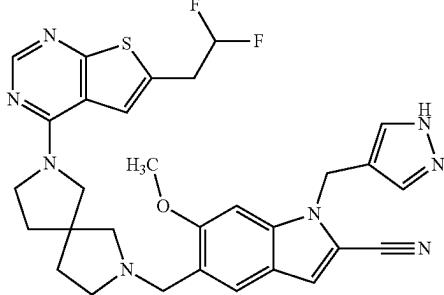
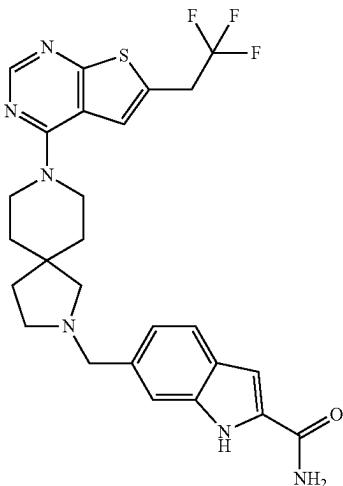
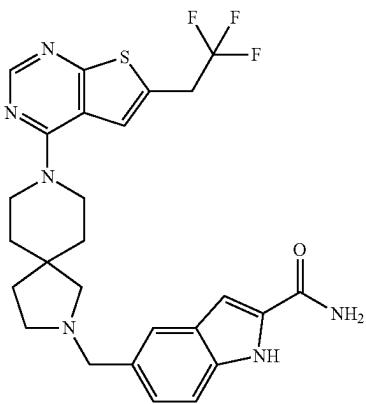
No.	Structure
V-48	
V-49	
V-50	

TABLE 5-continued

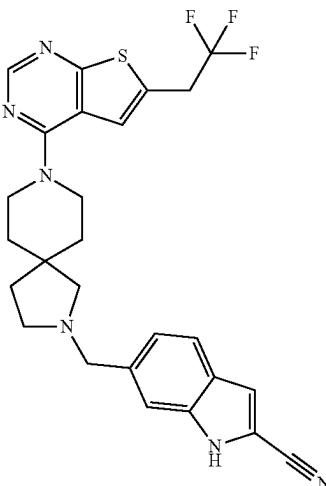
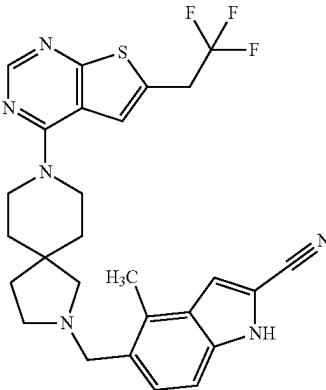
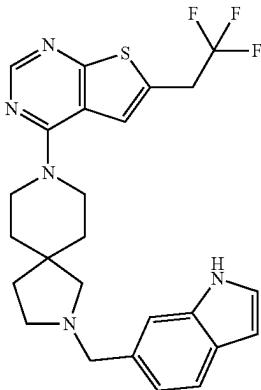
No.	Structure
V-51	
V-52	
V-53	

TABLE 5-continued

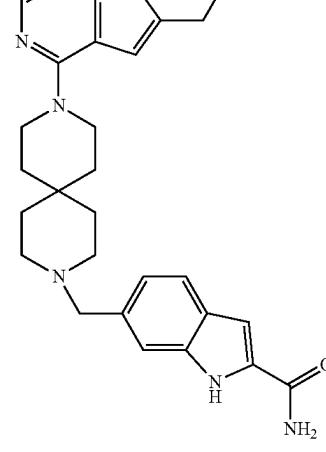
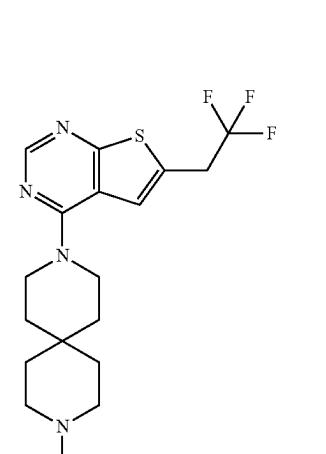
No.	Structure
V-54	
V-55	

TABLE 5-continued

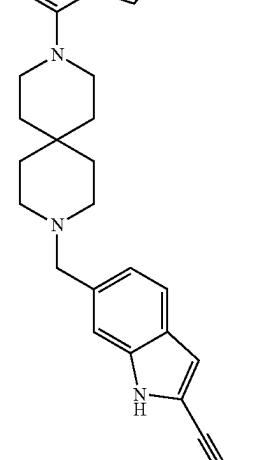
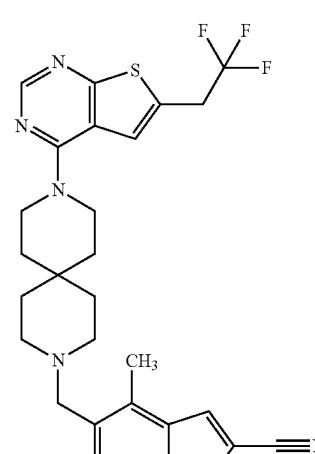
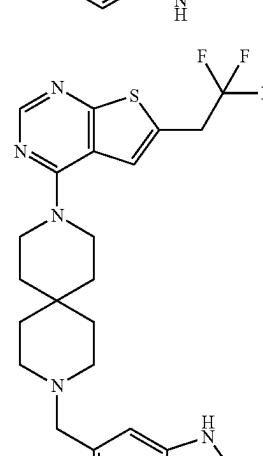
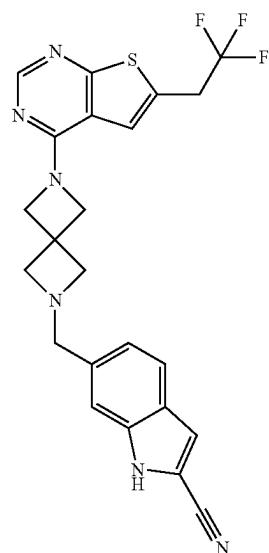
No.	Structure
V-56	
V-57	
V-58	

TABLE 5-continued

No.	Structure
-----	-----------

V-59



V-60

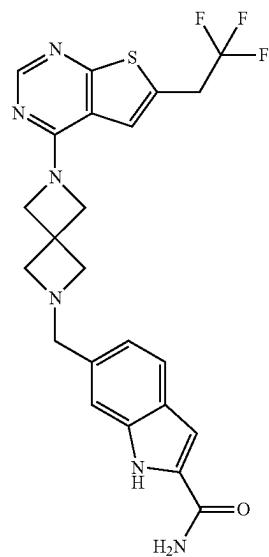


TABLE 5-continued

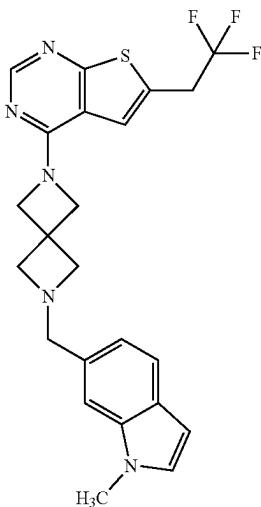
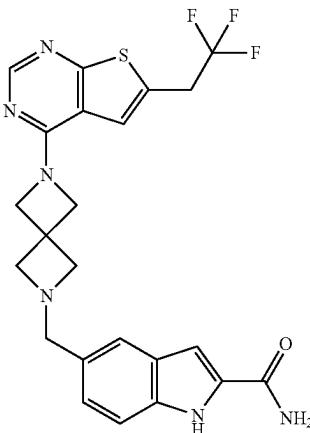
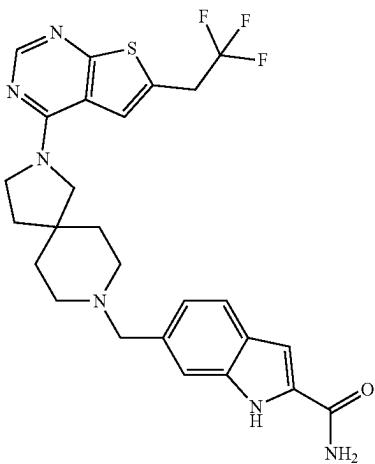
No.	Structure
V-61	
V-62	
V-63	

TABLE 5-continued

No.	Structure
V-64	
V-65	
V-66	
V-67	

TABLE 5-continued

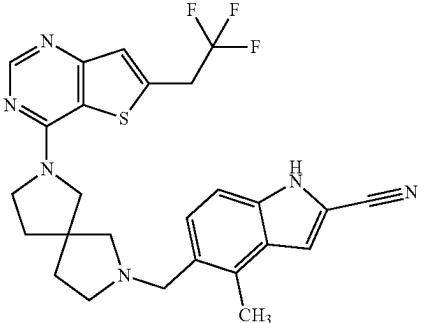
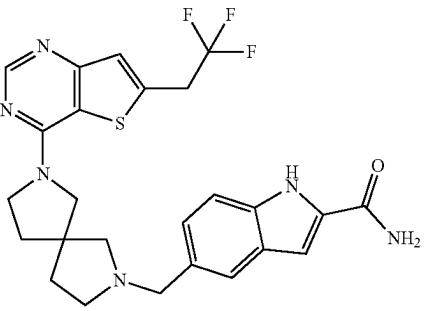
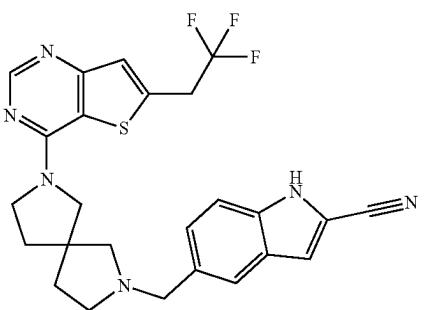
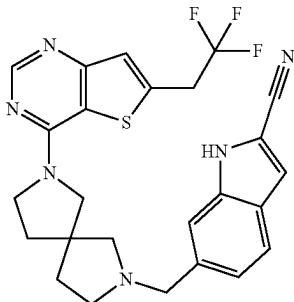
No.	Structure
V-68	
V-69	
V-70	
V-71	

TABLE 5-continued

No.	Structure
V-72	
V-73	
V-74	
V-75	

TABLE 5-continued

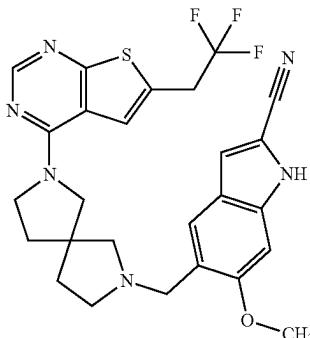
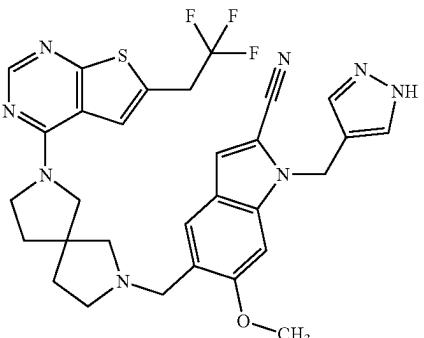
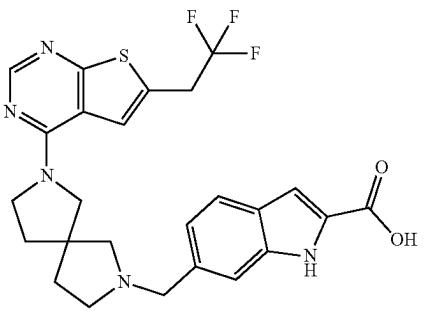
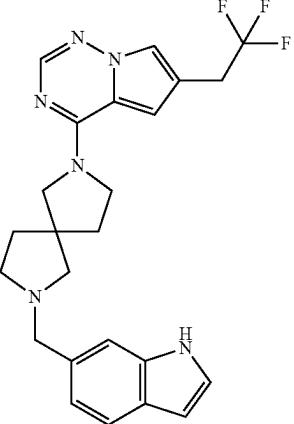
No.	Structure
V-76	
V-77	
V-78	
V-79	

TABLE 5-continued

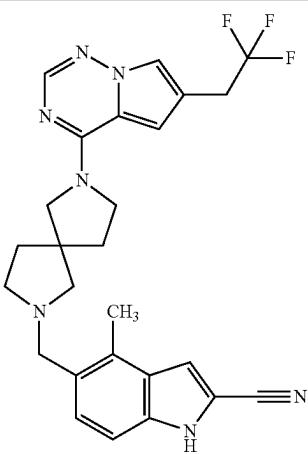
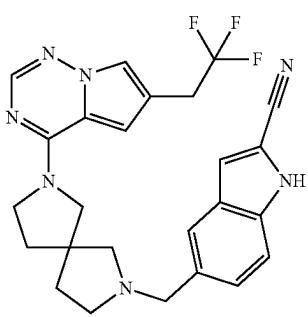
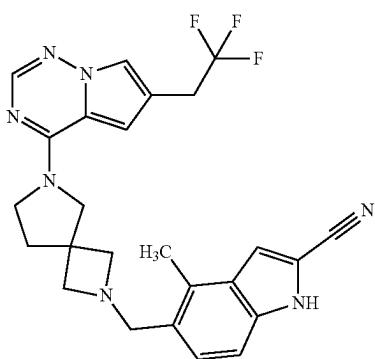
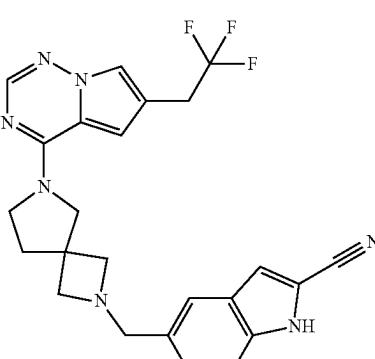
No.	Structure
V-80	
V-81	
V-82	
V-83	

TABLE 5-continued

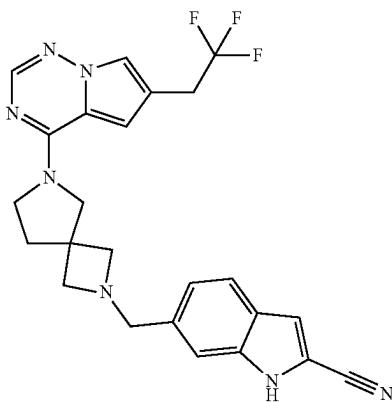
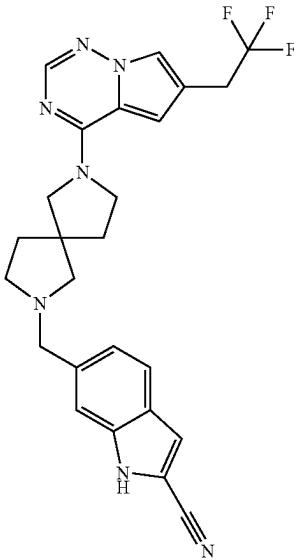
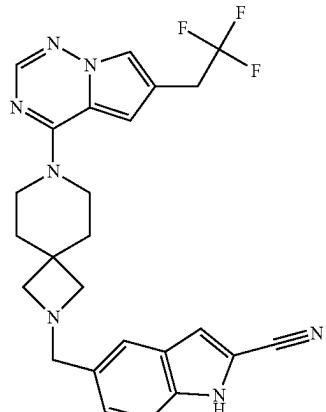
No.	Structure
V-84	
V-85	
V-86	

TABLE 5-continued

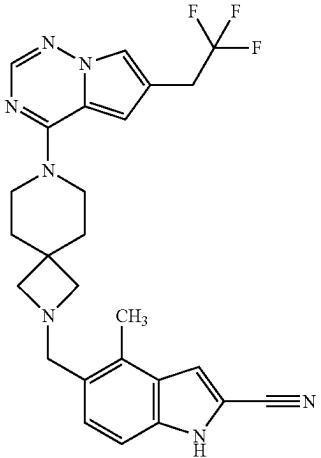
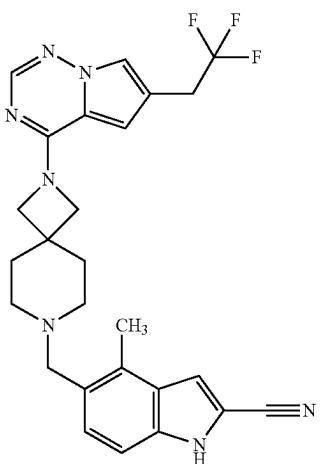
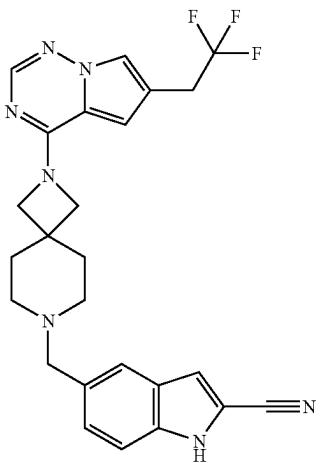
No.	Structure
V-87	
V-88	
V-89	

TABLE 5-continued

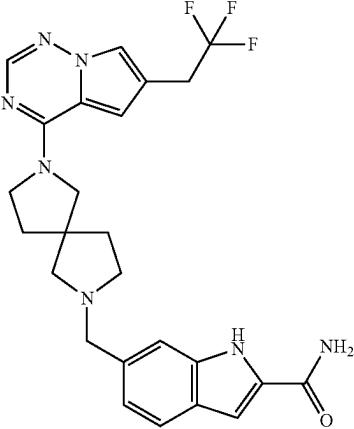
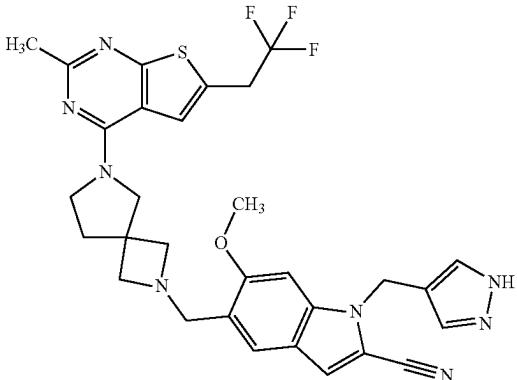
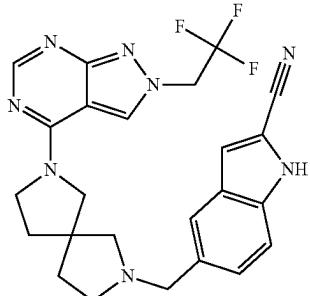
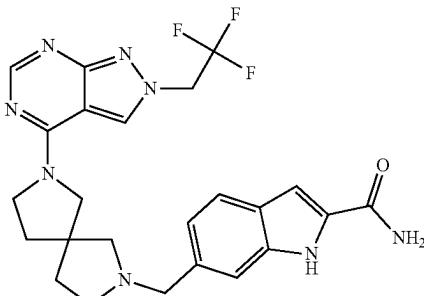
No.	Structure
V-90	
V-91	
V-92	
V-93	

TABLE 5-continued

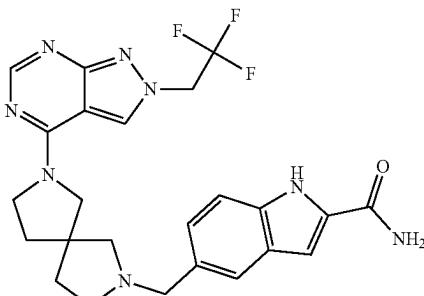
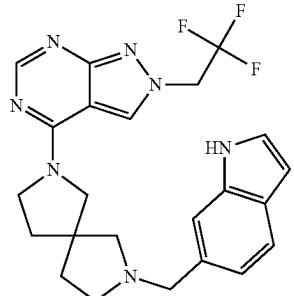
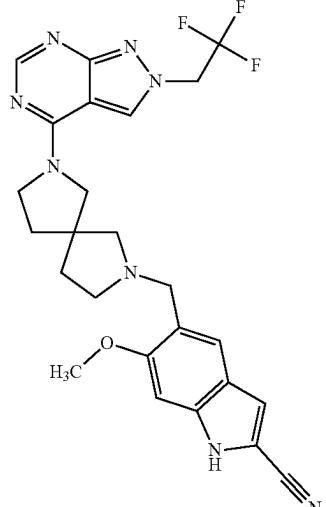
No.	Structure
V-94	
V-95	
V-96	

TABLE 5-continued

No.	Structure
V-97	
V-98	
V-99	

TABLE 5-continued

No.	Structure
V-100	
V-101	
V-102	
V-103	

TABLE 5-continued

No.	Structure
V-104	
V-105	
V-106	

TABLE 5-continued

No.	Structure
V-107	<p>Chemical structure V-107: A complex molecule consisting of a 2-(4-fluorophenyl)-6-(4-(2-(2,2,2-trifluoroethyl)pyrrolidin-1-yl)cyclohexyl)imidazo[1,2-b]pyrimidine core attached to a 2-(4-(2-(2-(2-aminoacetyl)indolin-3-yl)phenyl)pyrrolidin-1-yl)cyclohexyl group.</p>
V-108	<p>Chemical structure V-108: A complex molecule consisting of a 2-(4-fluorophenyl)-6-(4-(2-(2-(2-(2-aminoacetyl)indolin-3-yl)phenyl)pyrrolidin-1-yl)cyclohexyl)imidazo[1,2-b]pyrimidine core attached to a 2-(4-(2-(2-(2-aminoacetyl)indolin-3-yl)phenyl)pyrrolidin-1-yl)cyclohexyl group.</p>
V-109	<p>Chemical structure V-109: A complex molecule consisting of a 2-(4-fluorophenyl)-6-(4-(2-(2-(2-(2-aminoacetyl)indolin-3-yl)phenyl)pyrrolidin-1-yl)cyclohexyl)imidazo[1,2-b]pyrimidine core attached to a 2-(4-(2-(2-(2-aminoacetyl)indolin-3-yl)phenyl)pyrrolidin-1-yl)cyclohexyl group.</p>

TABLE 5-continued

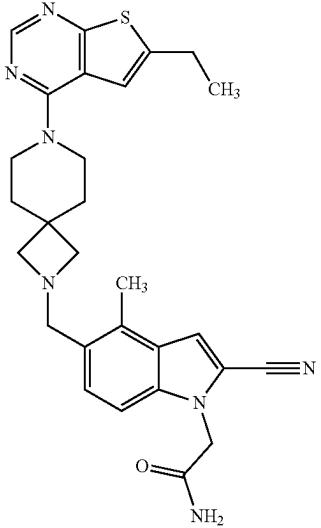
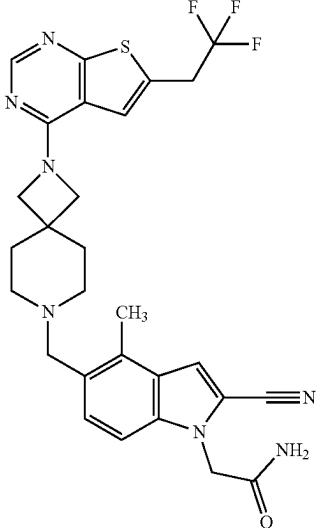
No.	Structure
V-110	
V-111	

TABLE 5-continued

No.	Structure
V-112	
V-113	
V-114	

TABLE 5-continued

No.	Structure
V-115	
V-116	
V-117	
V-118	

TABLE 5-continued

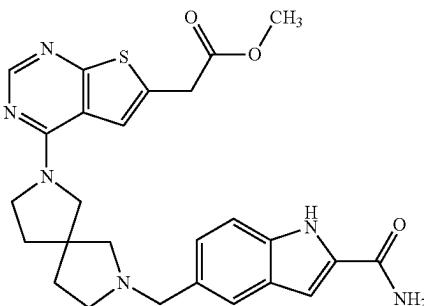
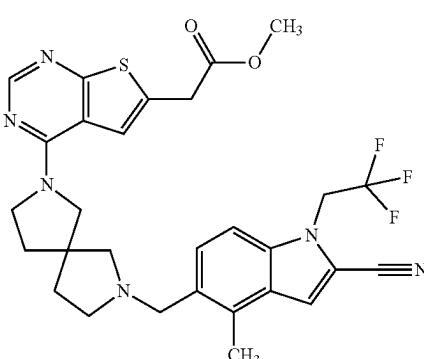
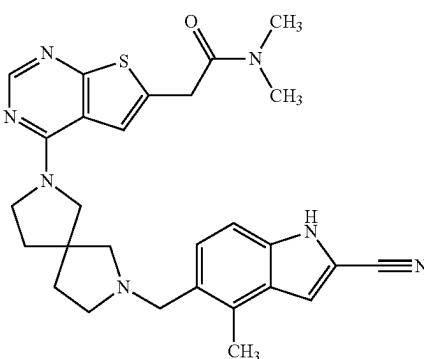
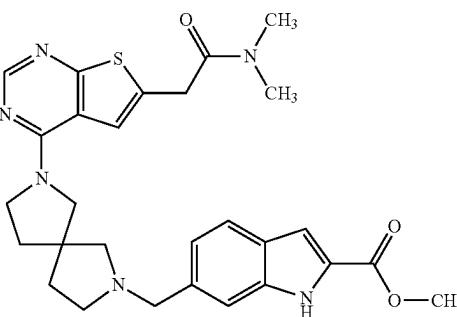
No.	Structure
V-119	
V-120	
V-121	
V-122	

TABLE 5-continued

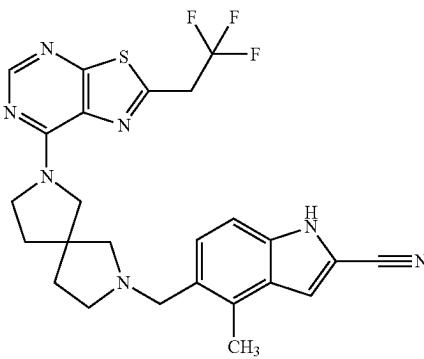
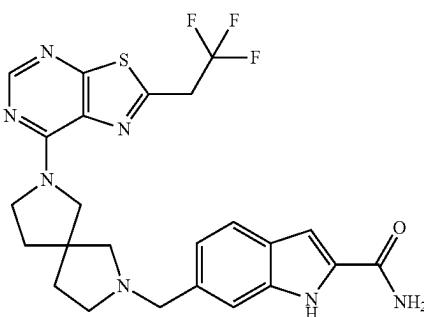
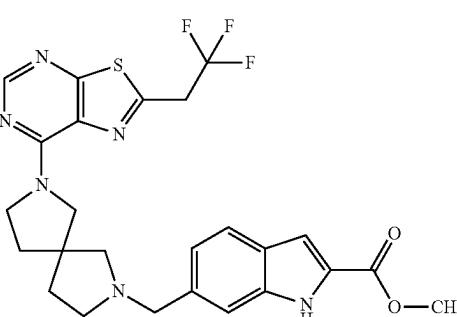
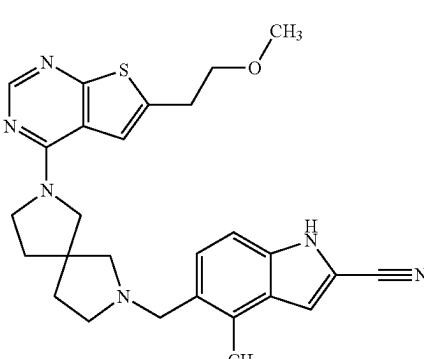
No.	Structure
V-123	
V-124	
V-125	
V-126	

TABLE 5-continued

No.	Structure
V-127	<p>Chemical structure V-127: A complex molecule consisting of a 2-thienylpyrimidine core substituted with a 2-methylpropoxy group. This core is connected via a methylene bridge to a piperazine ring, which is further substituted with a 4-(2-methylpropoxy)phenyl group. The phenyl ring has an amide side chain at the para position.</p>
V-128	<p>Chemical structure V-128: Similar to V-127, but the amide group on the phenyl ring is replaced by an acetoxy group (O-CH₃).</p>
V-129	<p>Chemical structure V-129: Similar to V-127, but the amide group on the phenyl ring is replaced by a cyano group (-C≡N) and a methyl group (-CH₃) is added to the phenyl ring.</p>
V-130	<p>Chemical structure V-130: Similar to V-127, but the amide group on the phenyl ring is replaced by a cyano group (-C≡N) and a methyl group (-CH₃) is added to the phenyl ring. Additionally, a trifluoromethyl group (-CF₃) is attached to the nitrogen atom of the piperazine ring.</p>

TABLE 5-continued

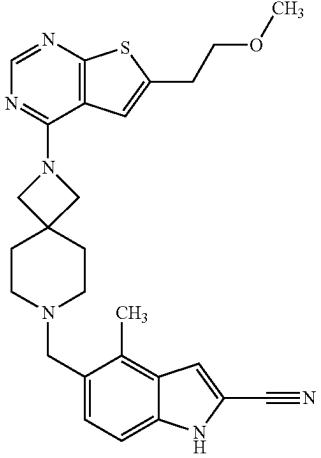
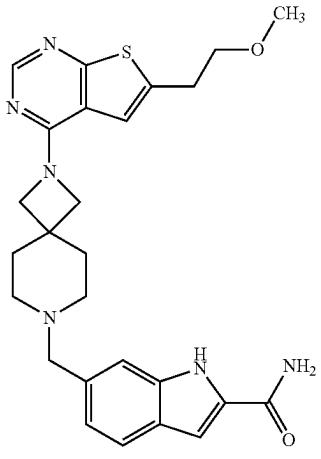
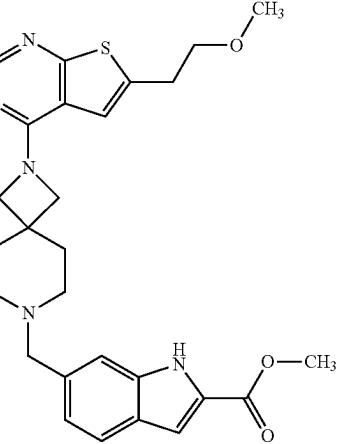
No.	Structure
V-131	
V-132	
V-133	

TABLE 5-continued

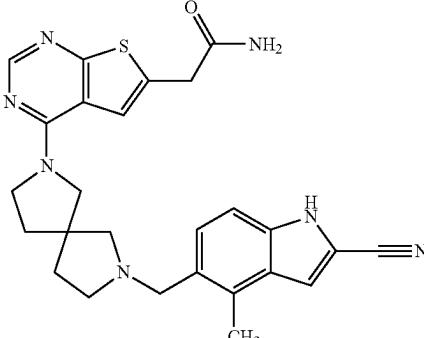
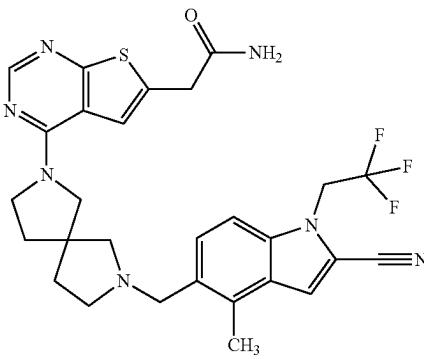
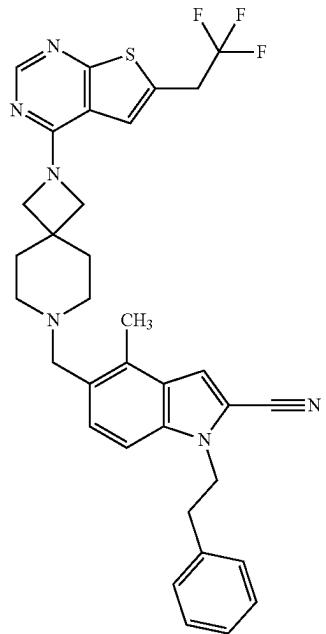
No.	Structure
V-134	 <p>Chemical structure of compound V-134: A 2-thienyl group is attached to a 4-(4-methyl-1H-inden-3-yl)-1,2-dihydro-1,2-dihydroimidazole-2-carboxamide core. The core has a 4-amino group and a 2-acetyl group.</p>
V-135	 <p>Chemical structure of compound V-135: A 2-thienyl group is attached to a 4-(4-methyl-1H-inden-3-yl)-1,2-dihydro-1,2-dihydroimidazole-2-carboxamide core, which is substituted with a trifluoromethyl group at the 7-position.</p>
V-136	 <p>Chemical structure of compound V-136: A 2-thienyl group is attached to a 4-(4-methyl-1H-inden-3-yl)-1,2-dihydro-1,2-dihydroimidazole-2-carboxamide core, which is substituted with a phenyl group at the 7-position.</p>

TABLE 5-continued

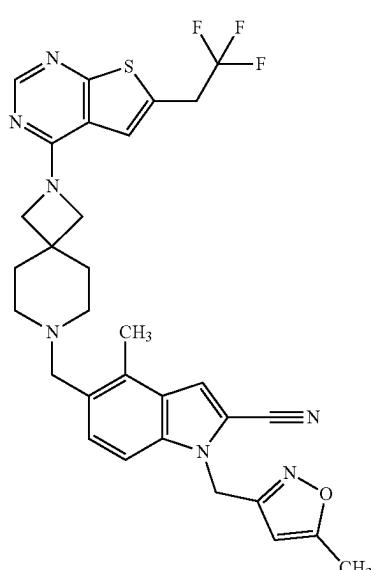
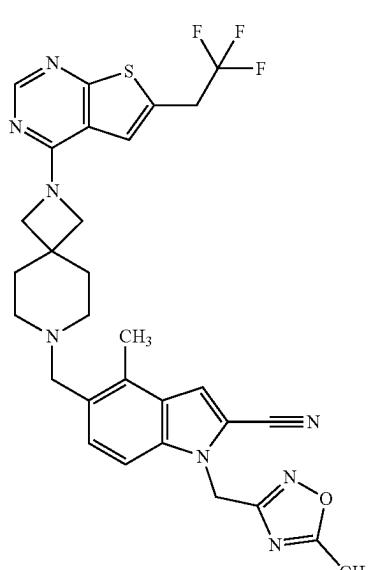
No.	Structure
V-137	
V-138	

TABLE 5-continued

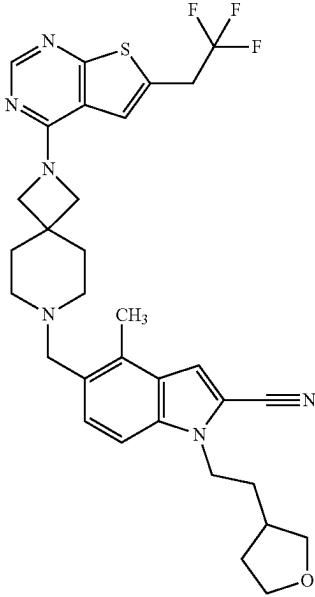
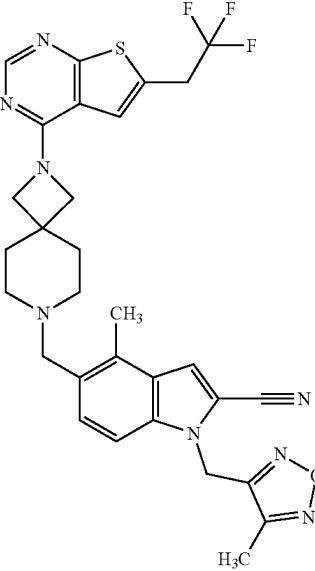
No.	Structure
V-139	
V-140	

TABLE 5-continued

No.	Structure
V-141	

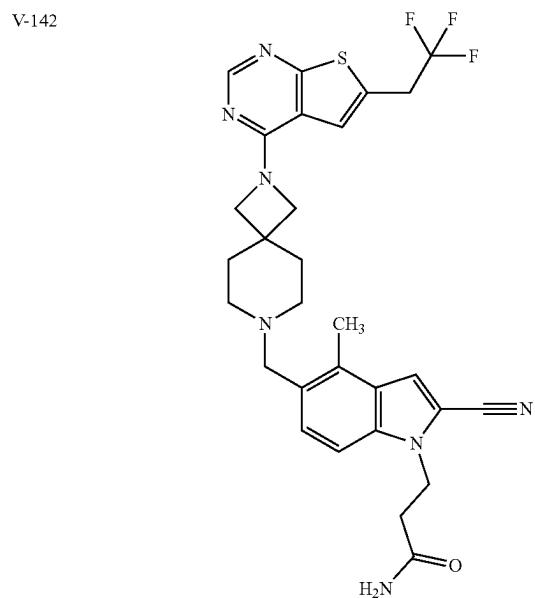
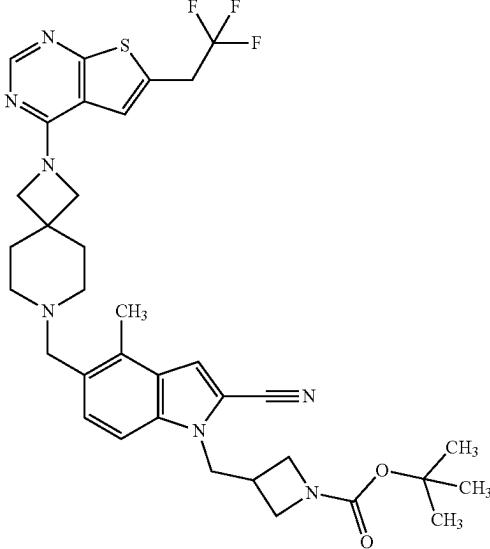


TABLE 5-continued

No.	Structure
V-143	

V-144

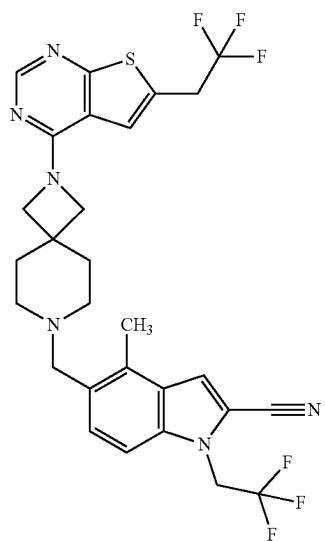


TABLE 5-continued

No.	Structure
V-145	
V-146	
V-147	

TABLE 5-continued

No.	Structure
V-148	<p>Chemical structure V-148: A complex molecule consisting of a tryptamine-like core with an amide group at position 5, linked via a piperazine ring to a 2-(4-fluorobutyl)thieno[2,3-d]pyrimidine derivative.</p>
V-149	<p>Chemical structure V-149: A complex molecule consisting of a tryptamine-like core with an amide group at position 5, linked via a piperazine ring to a 2-(4-methyl-1-phenylbutyl)thieno[2,3-d]pyrimidine derivative.</p>
V-150	<p>Chemical structure V-150: A complex molecule consisting of a tryptamine-like core with an amide group at position 5, linked via a piperazine ring to a 2-(4-methyl-1-phenylbutyl)thieno[2,3-d]pyrimidine derivative, identical to V-149.</p>

TABLE 5-continued

No.	Structure
V-151	
V-152	
V-153	

TABLE 6

No.	Structure
VI-1	
VI-2	
VI-3	

TABLE 6-continued

No.	Structure
VI-4	
VI-5	
VI-6	

TABLE 6-continued

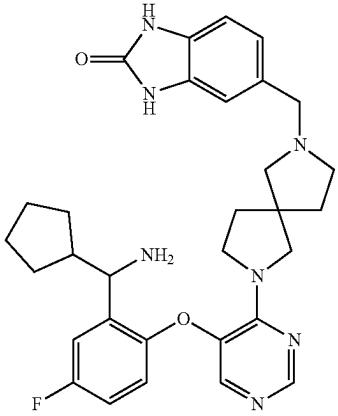
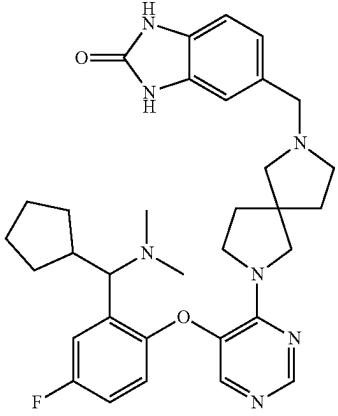
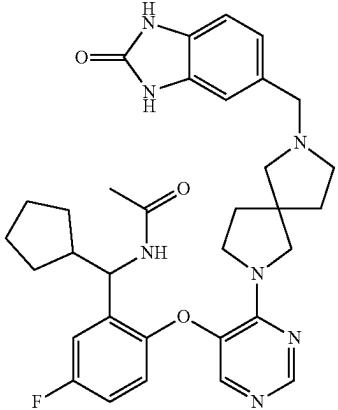
No.	Structure
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VI-8	
VI-9	

TABLE 6-continued

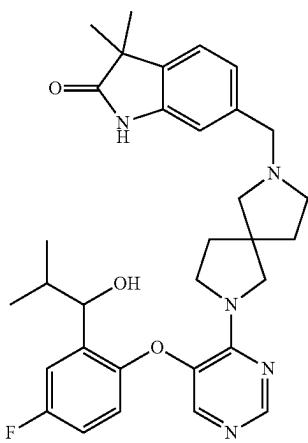
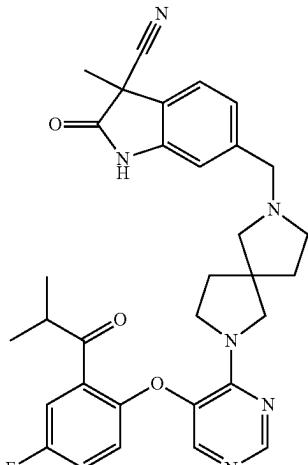
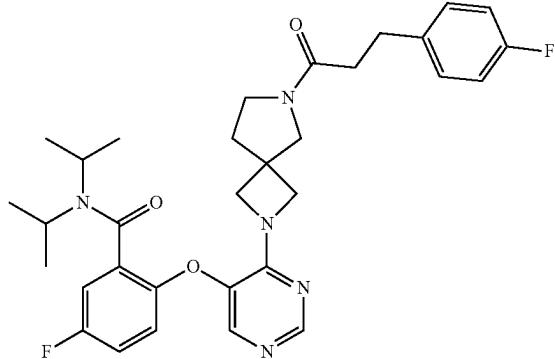
No.	Structure
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VI-11	
VI-12	

TABLE 6-continued

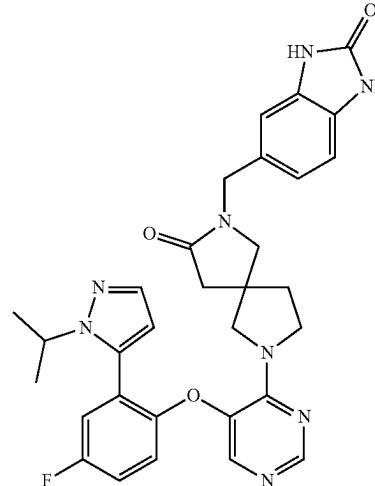
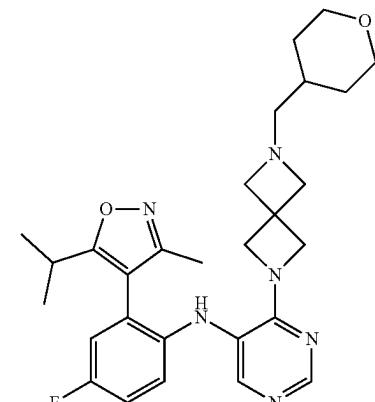
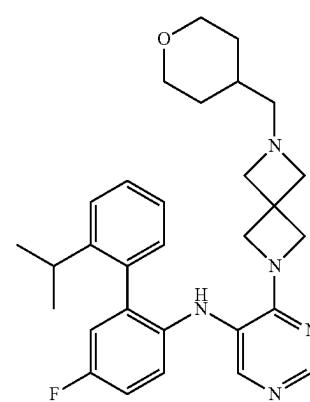
No.	Structure
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VI-14	
VI-15	

TABLE 6-continued

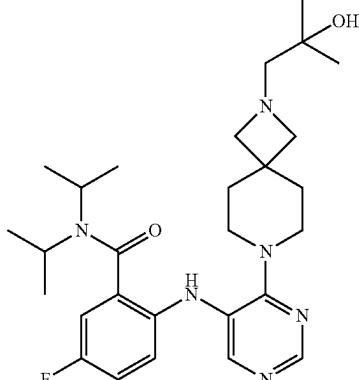
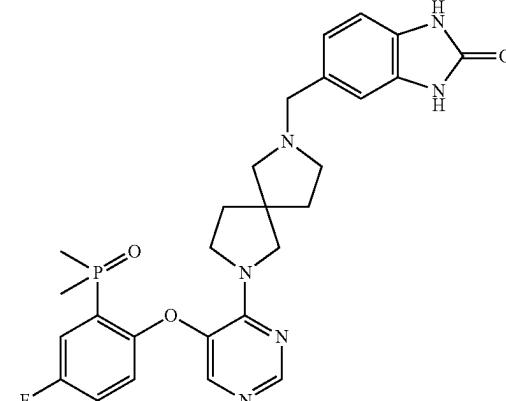
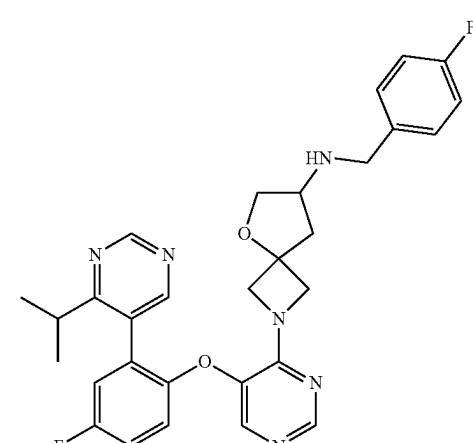
No.	Structure
VI-16	
VI-17	
VI-18	

TABLE 6-continued

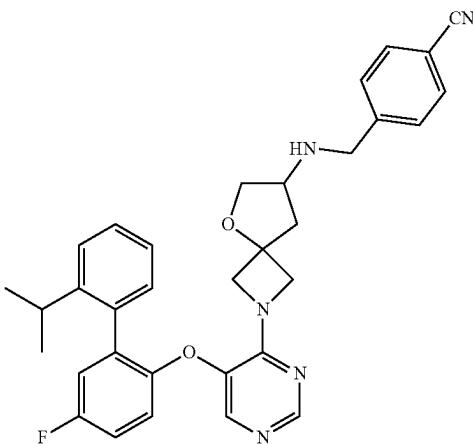
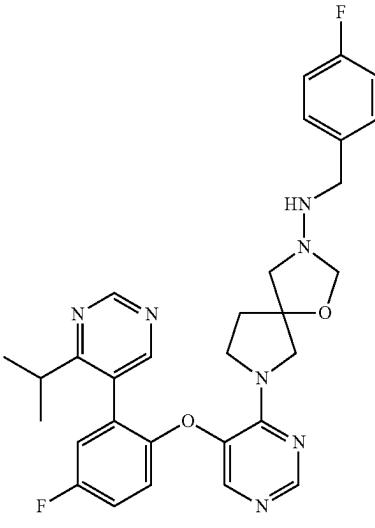
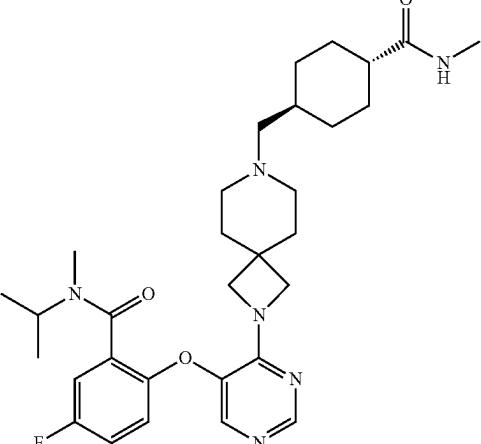
No.	Structure
VI-19	
VI-20	
VI-21	

TABLE 6-continued

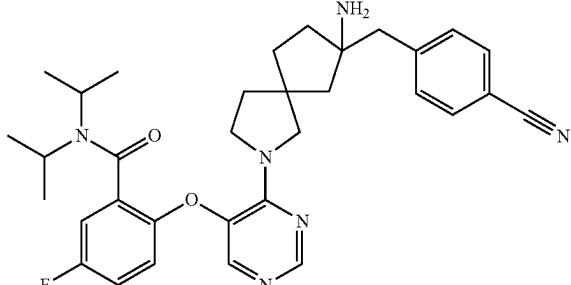
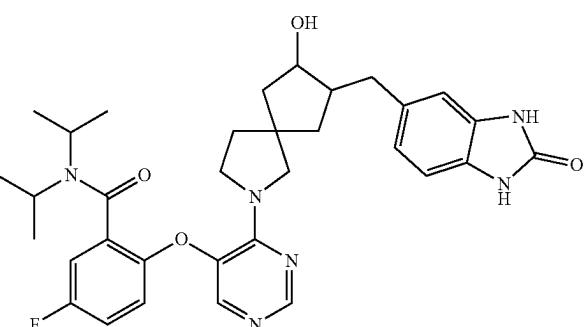
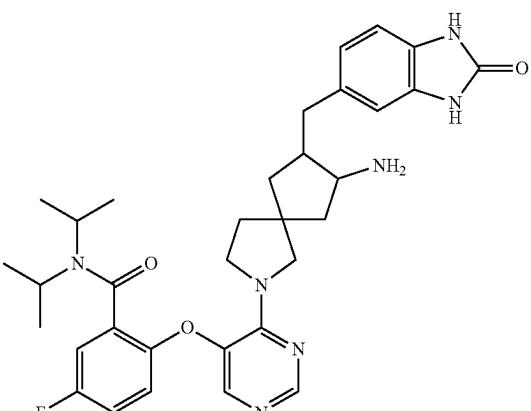
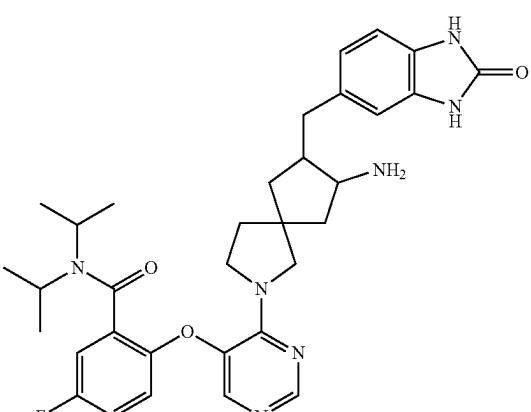
No.	Structure
VI-22	
VI-23	
VI-24	
VI-25	

TABLE 6-continued

No.	Structure
VI-26	
VI-27	
VI-28	
VI-29	

TABLE 6-continued

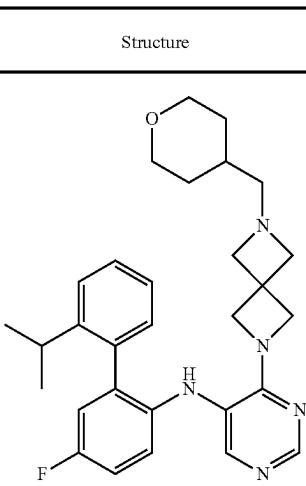
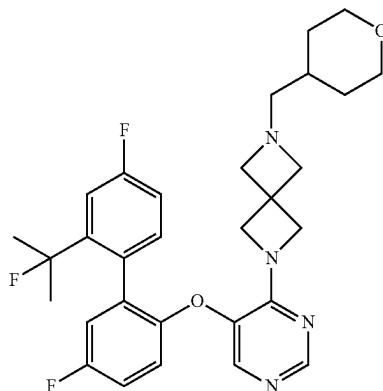
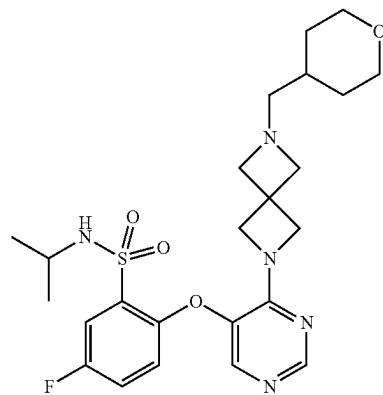
No.	Structure
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VI-31	
VI-32	

TABLE 6-continued

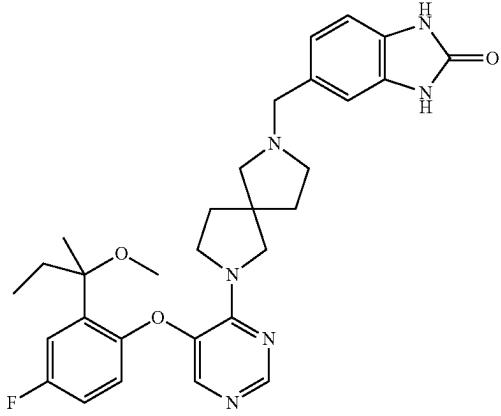
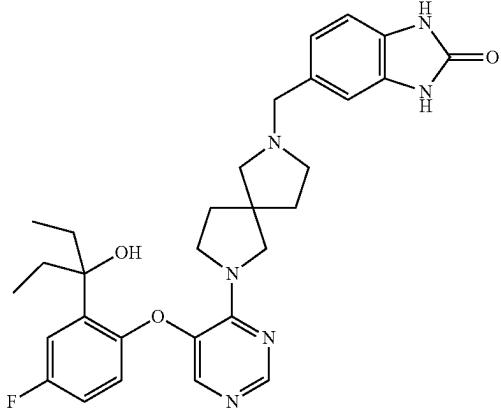
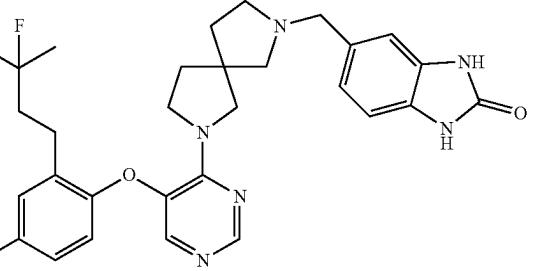
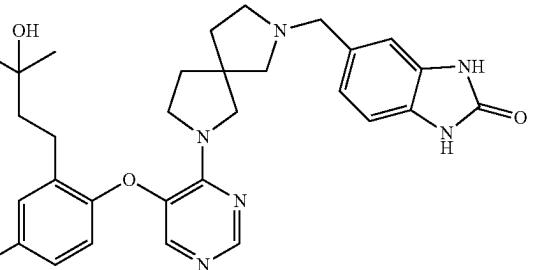
No.	Structure
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VI-34	
VI-35	
VI-36	

TABLE 6-continued

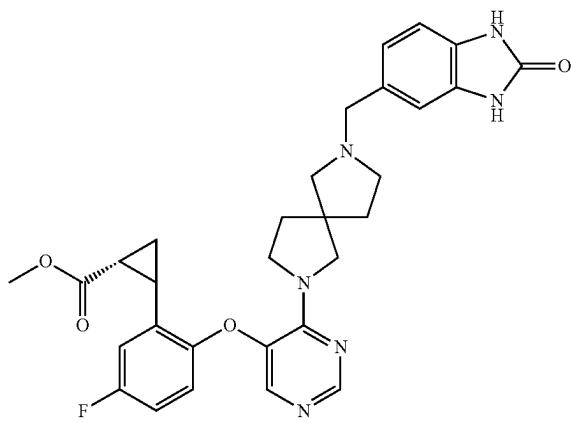
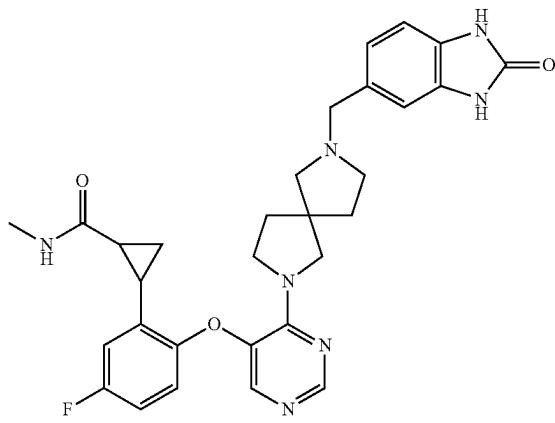
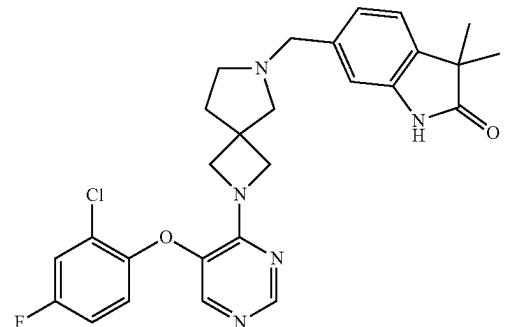
No.	Structure
VI-37	
VI-38	
VI-39	

TABLE 6-continued

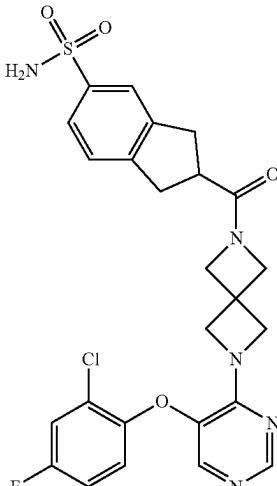
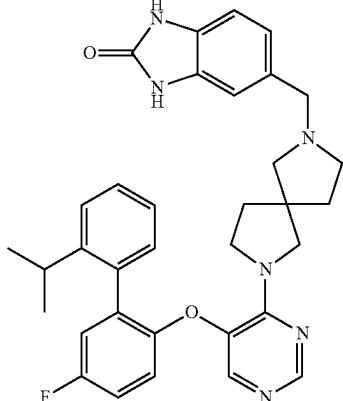
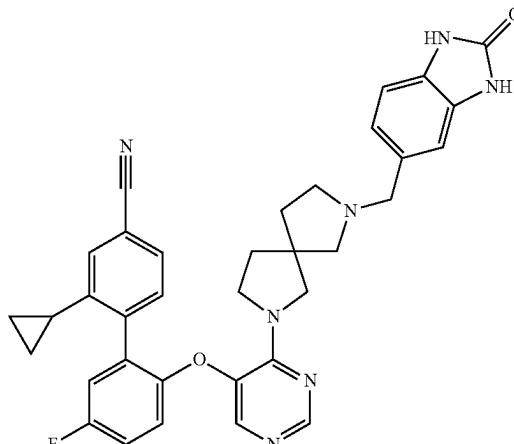
No.	Structure
VI-40	
VI-41	
VI-42	

TABLE 6-continued

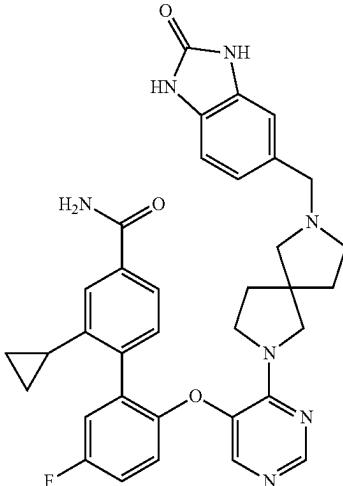
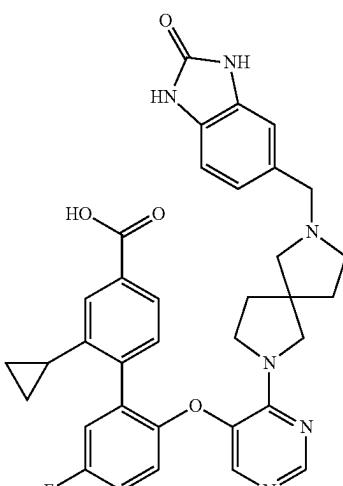
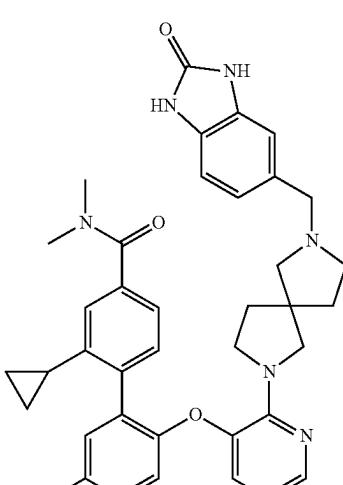
No.	Structure
VI-43	
VI-44	
VI-45	

TABLE 6-continued

No.	Structure
VI-46	
VI-47	
VI-48	
VI-49	

TABLE 6-continued

No.	Structure
VI-50	
VI-51	
VI-52	
VI-53	

TABLE 6-continued

No.	Structure
VI-54	
VI-55	
VI-56	

TABLE 6-continued

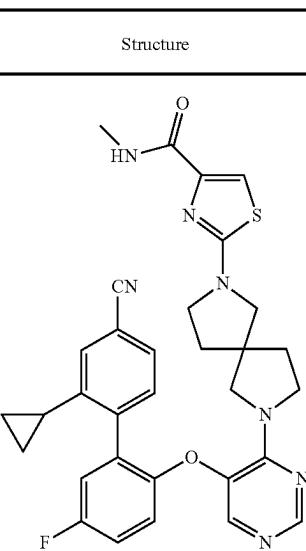
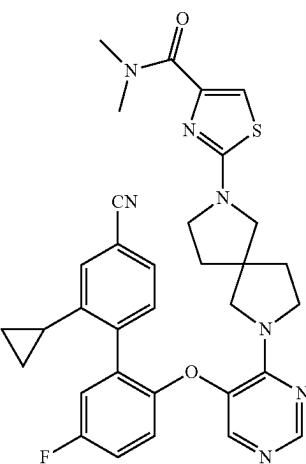
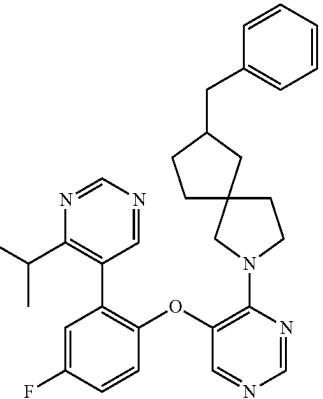
No.	Structure
VI-57	
VI-58	
VI-59	

TABLE 6-continued

No.	Structure
VI-60	
VI-61	
VI-62	
VI-63	

TABLE 6-continued

No.	Structure
VI-64	
VI-65	
VI-66	

TABLE 6-continued

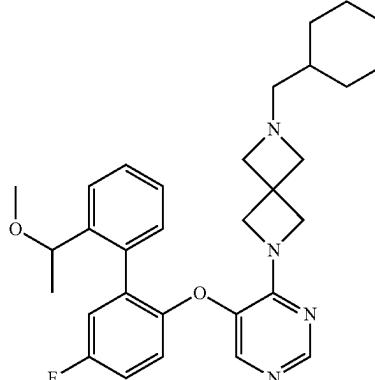
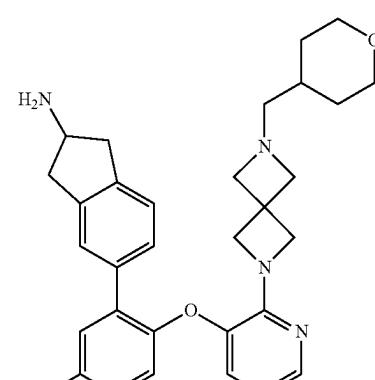
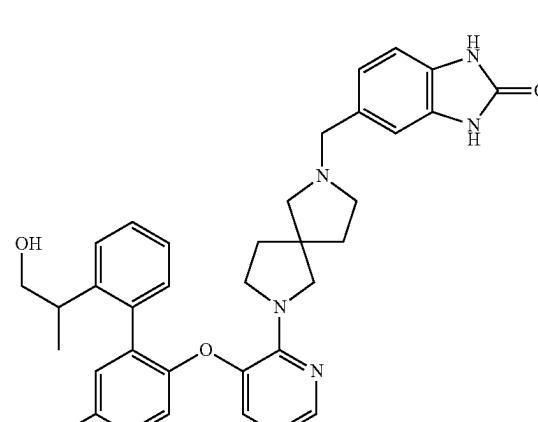
No.	Structure
VI-67	
VI-68	
VI-69	

TABLE 6-continued

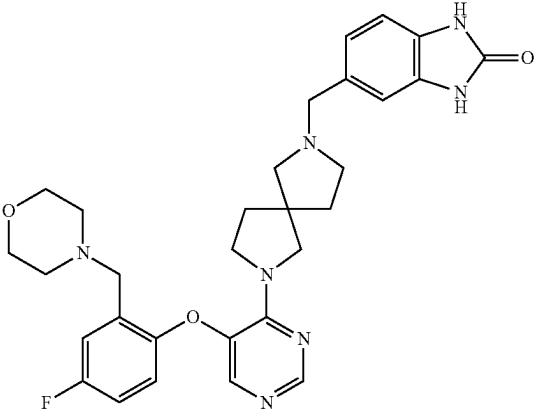
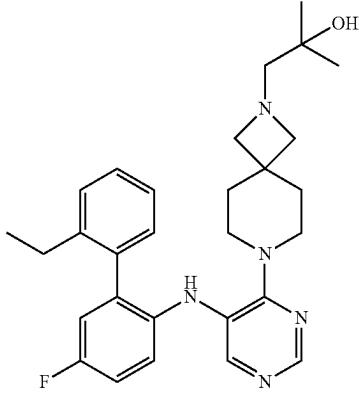
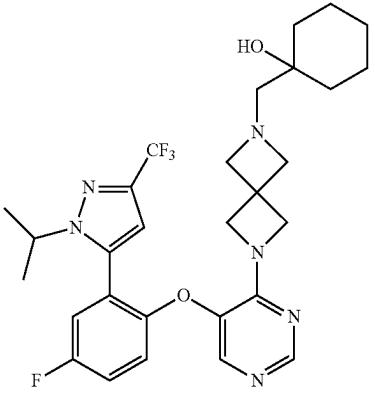
No.	Structure
VI-70	
VI-71	
VI-72	

TABLE 6-continued

No.	Structure
VI-73	
VI-74	
VI-75	

TABLE 6-continued

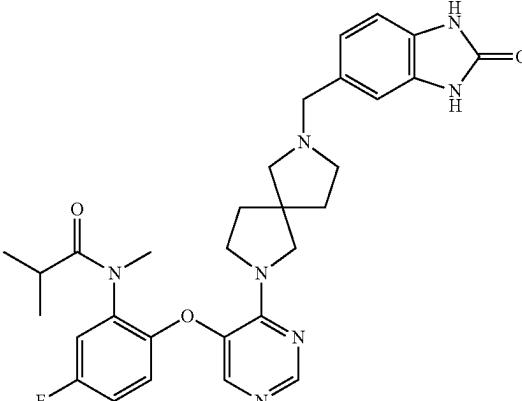
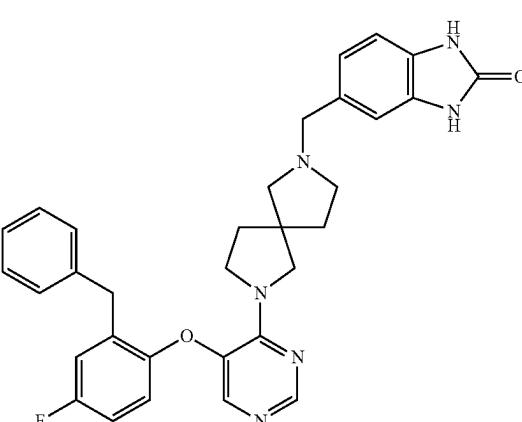
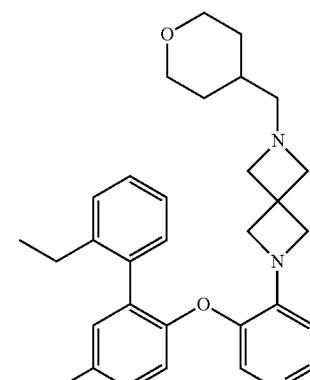
No.	Structure
VI-76	
VI-77	
VI-78	

TABLE 6-continued

No.	Structure
VI-79	
VI-80	
VI-81	

TABLE 6-continued

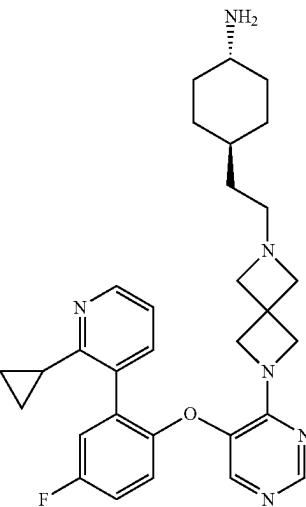
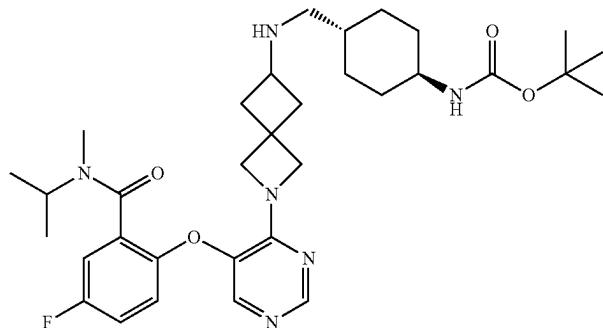
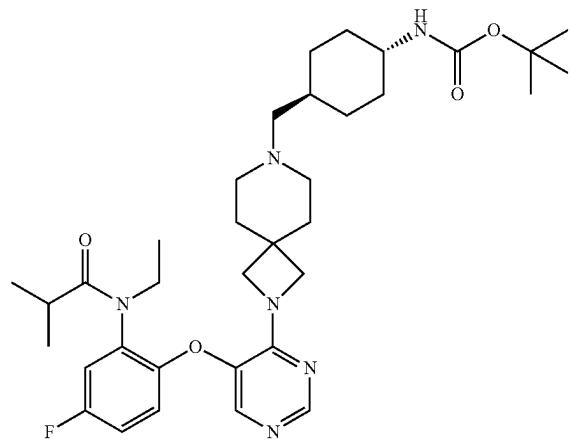
No.	Structure
VI-82	
VI-83	
VI-84	

TABLE 6-continued

No.	Structure
VI-85	
VI-86	
VI-87	

TABLE 6-continued

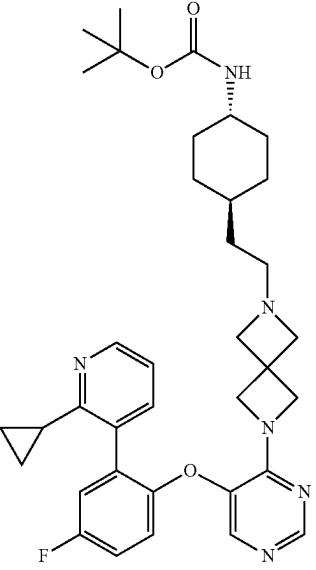
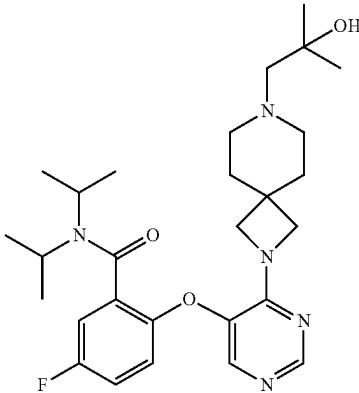
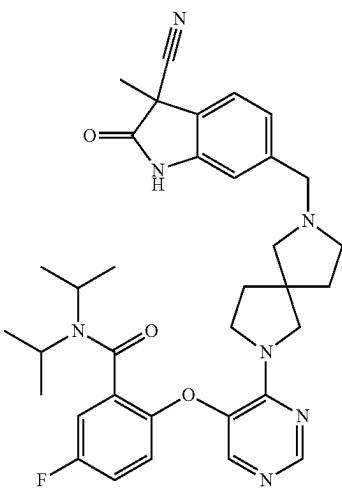
No.	Structure
VI-88	
VI-89	
VI-90	

TABLE 6-continued

No.	Structure
VI-91	
VI-92	
VI-93	

TABLE 6-continued

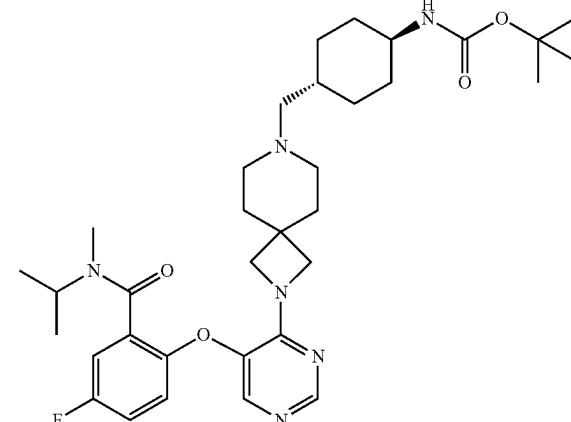
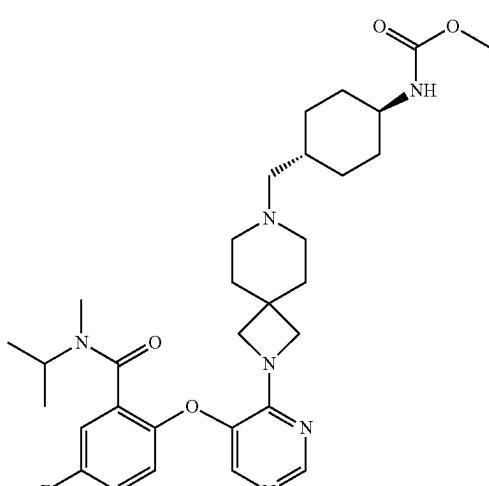
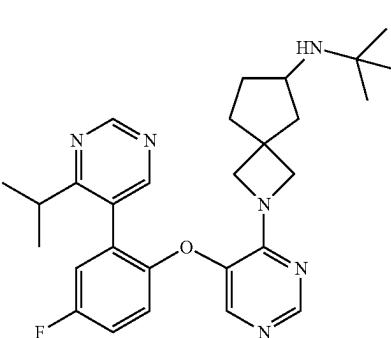
No.	Structure
VI-94	
VI-95	
VI-96	

TABLE 6-continued

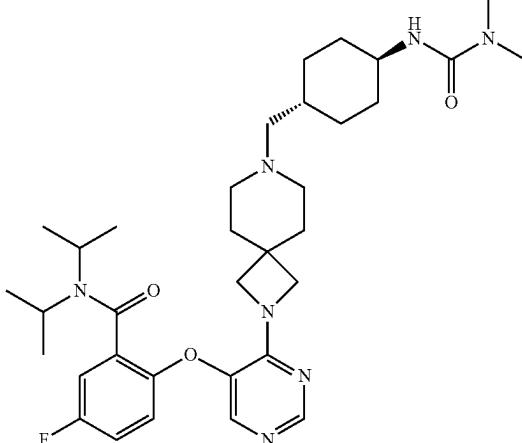
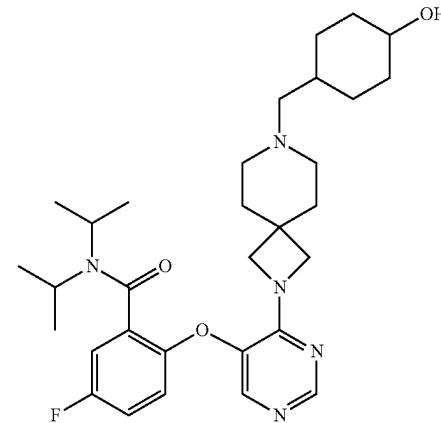
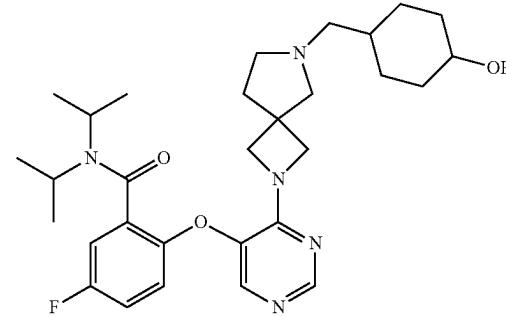
No.	Structure
VI-97	
VI-98	
VI-99	

TABLE 6-continued

No.	Structure
VI-100	
VI-101	
VI-102	
VI-103	

TABLE 6-continued

No.	Structure
VI-104	
VI-105	
VI-106	

TABLE 6-continued

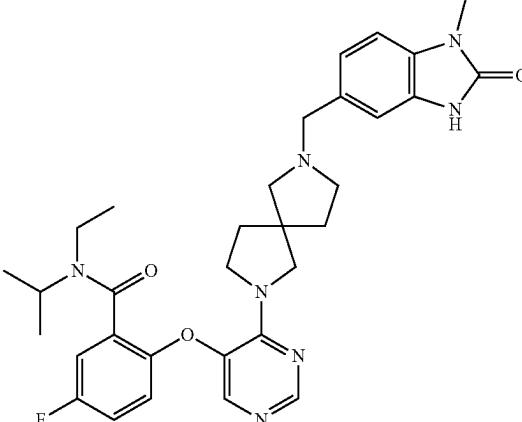
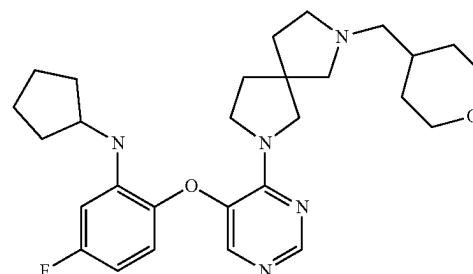
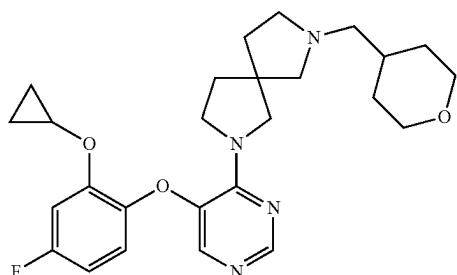
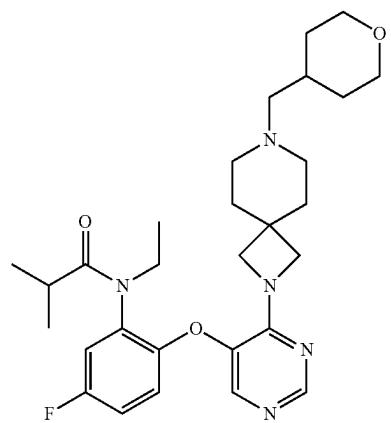
No.	Structure
VI-107	
VI-108	
VI-109	
VI-110	

TABLE 6-continued

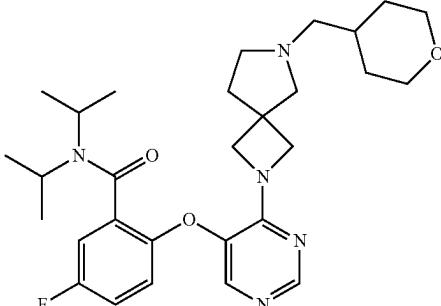
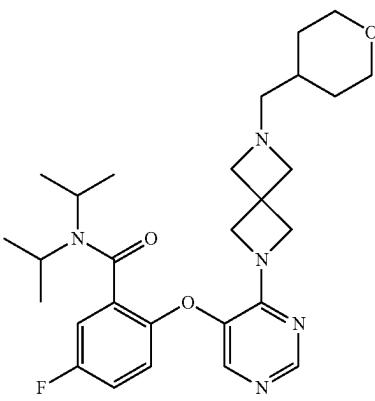
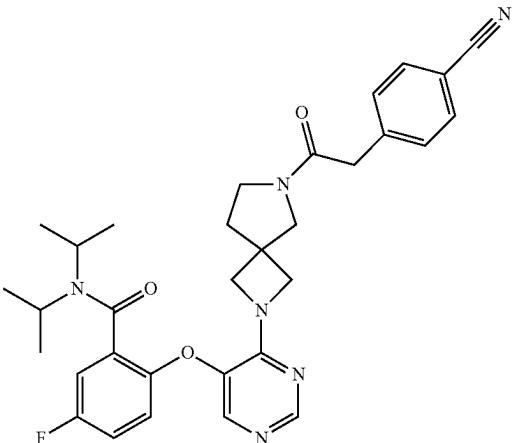
No.	Structure
VI-111	
VI-112	
VI-113	

TABLE 6-continued

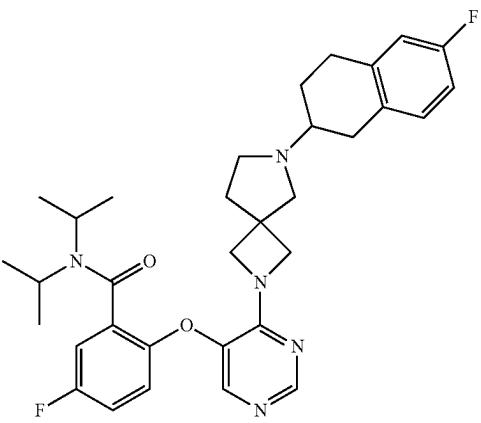
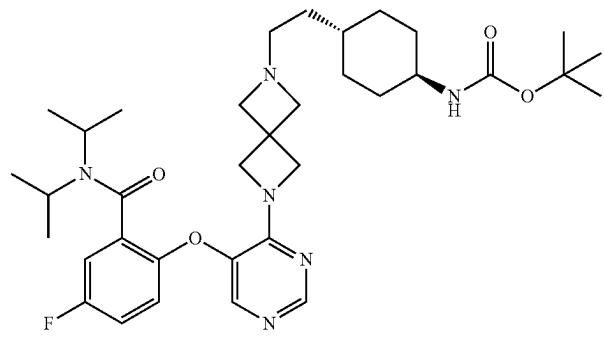
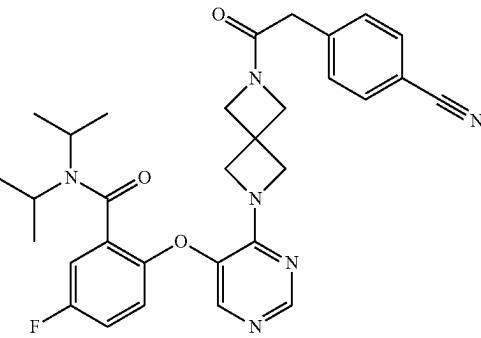
No.	Structure
VI-114	
VI-115	
VI-116	

TABLE 6-continued

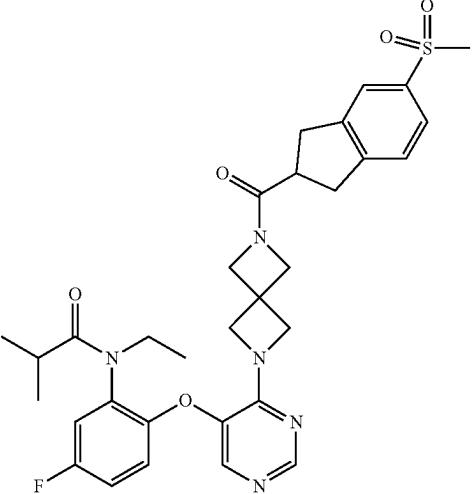
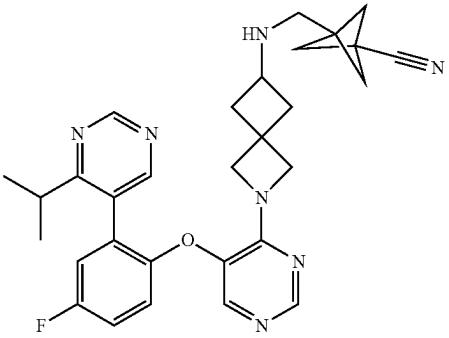
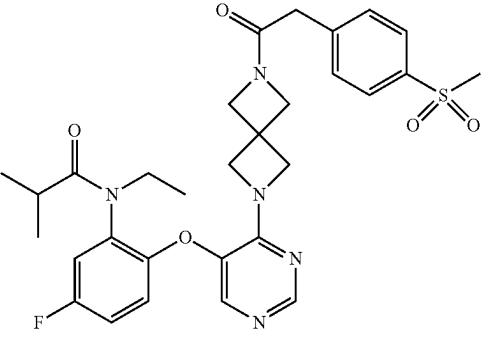
No.	Structure
VI-117	
VI-118	
VI-119	

TABLE 6-continued

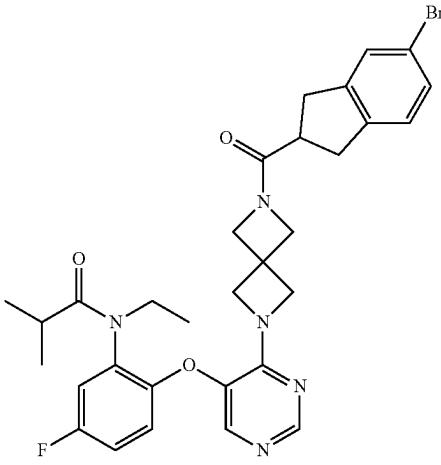
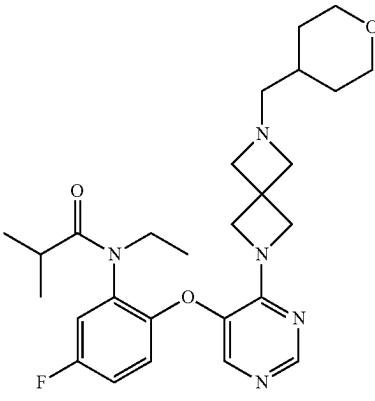
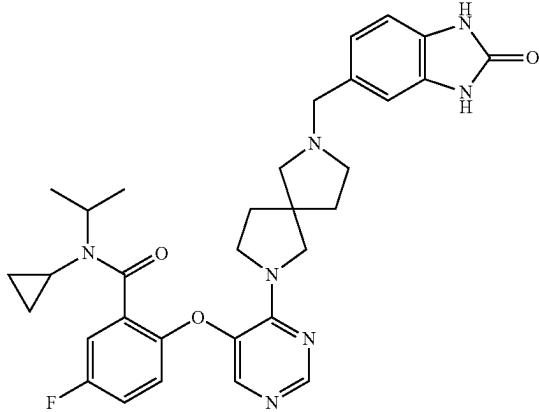
No.	Structure
VI-120	
VI-121	
VI-122	

TABLE 6-continued

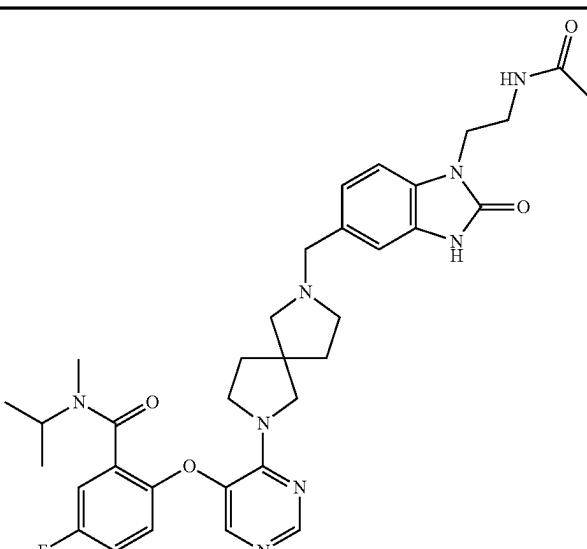
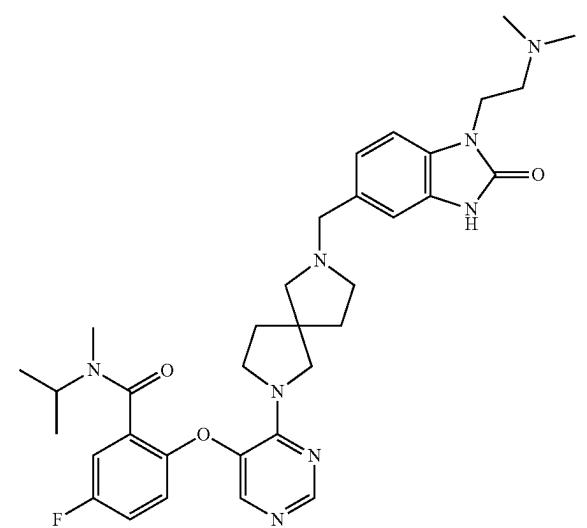
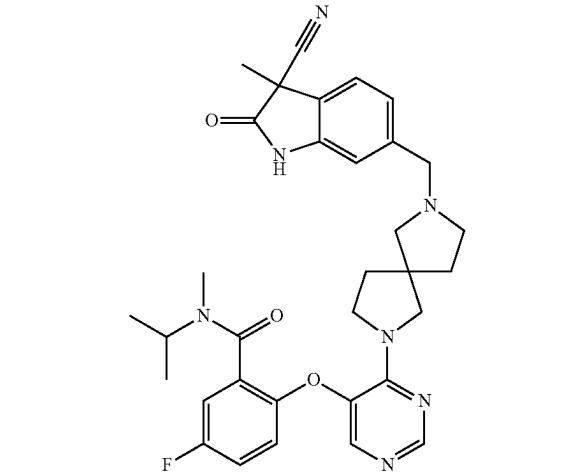
No.	Structure
VI-123	
VI-124	
VI-125	

TABLE 6-continued

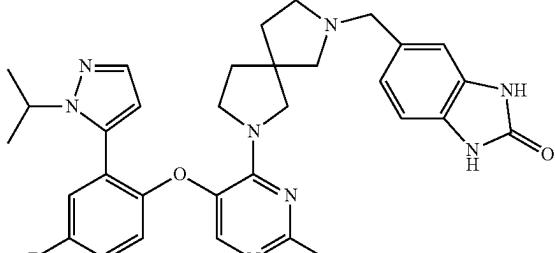
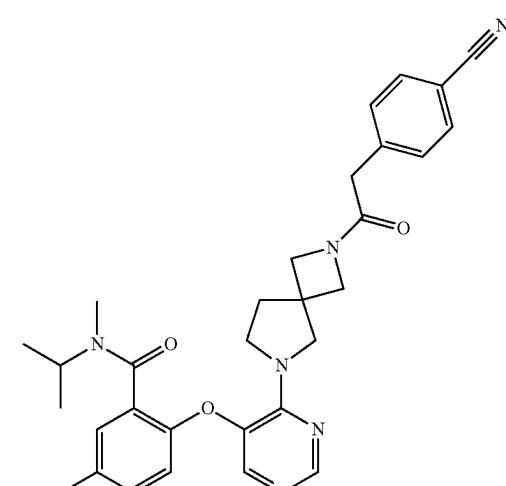
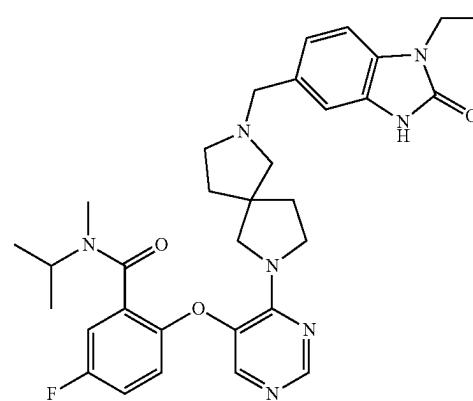
No.	Structure
VI-126	
VI-127	
VI-128	

TABLE 6-continued

No.	Structure
VI-129	
VI-130	
VI-131	

TABLE 6-continued

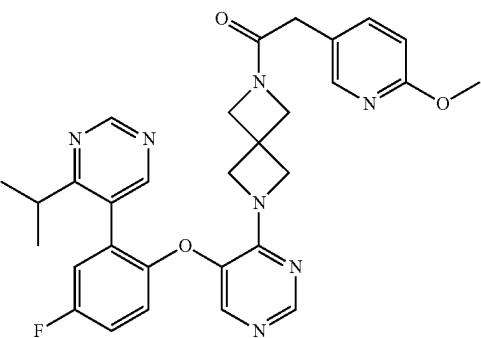
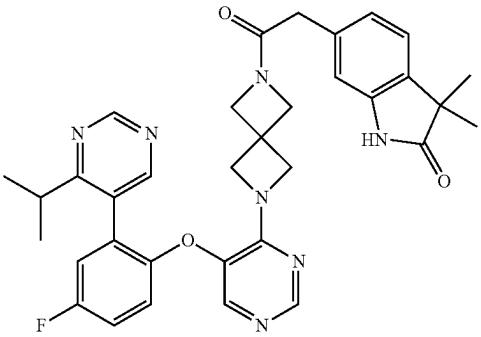
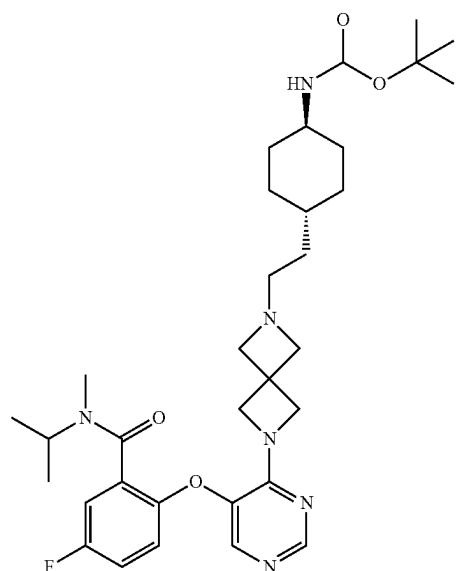
No.	Structure
VI-132	
VI-133	
VI-134	

TABLE 6-continued

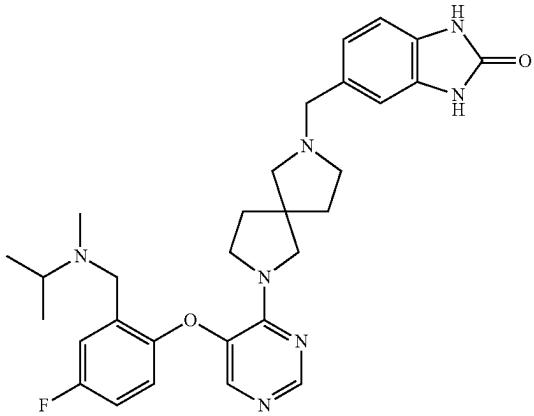
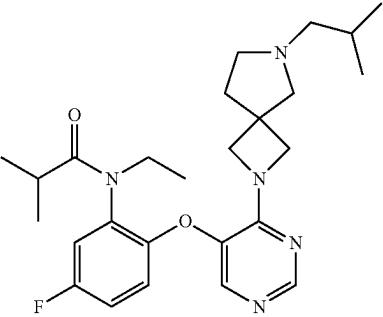
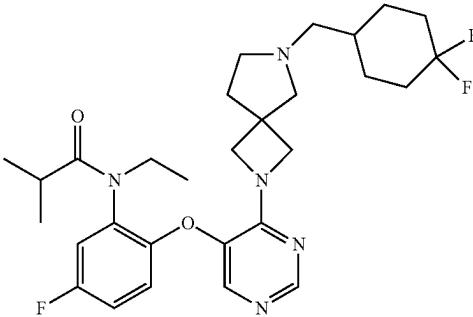
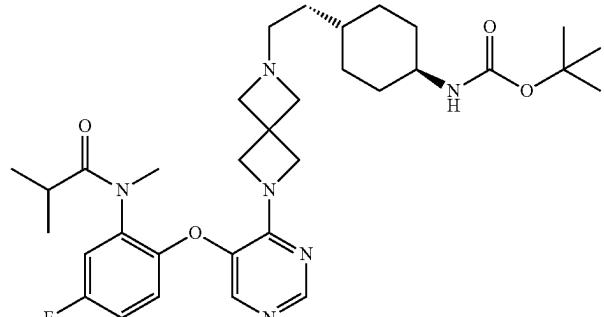
No.	Structure
VI-135	
VI-136	
VI-137	
VI-138	

TABLE 6-continued

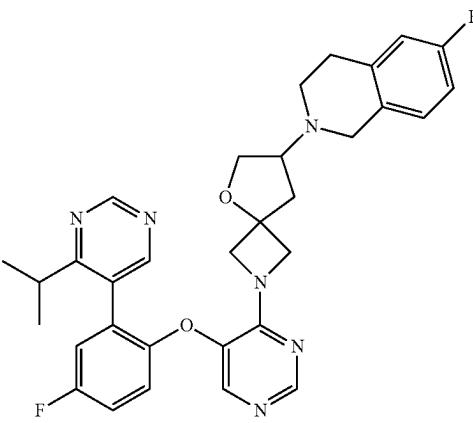
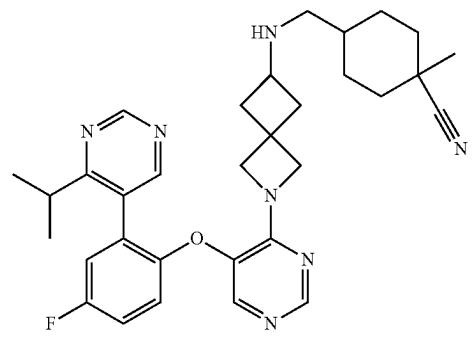
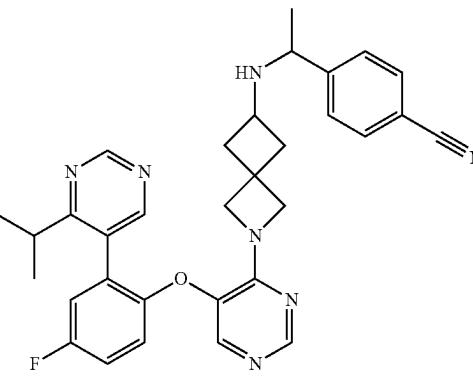
No.	Structure
VI-139	
VI-140	
VI-141	

TABLE 6-continued

No.	Structure
VI-142	
VI-143	
VI-144	

TABLE 6-continued

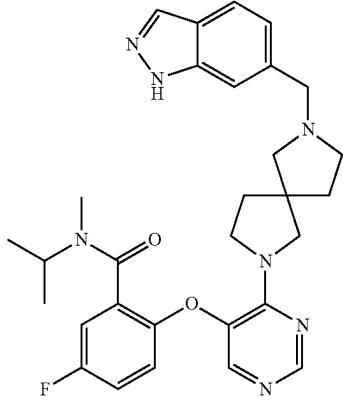
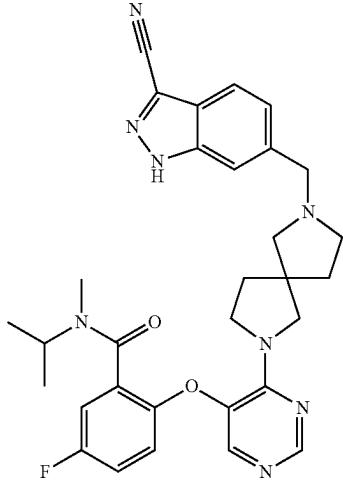
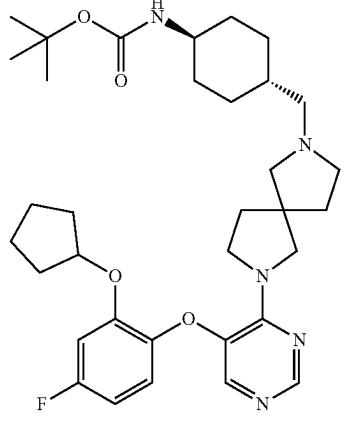
No.	Structure
VI-145	
VI-146	
VI-147	

TABLE 6-continued

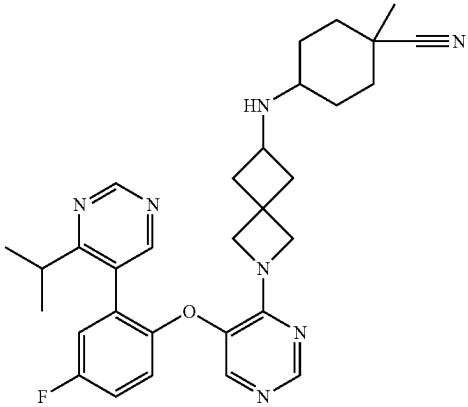
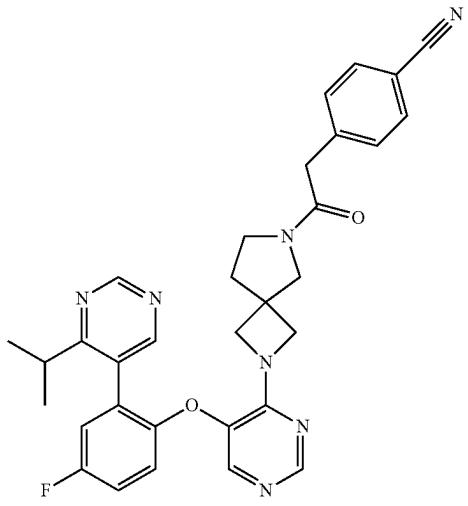
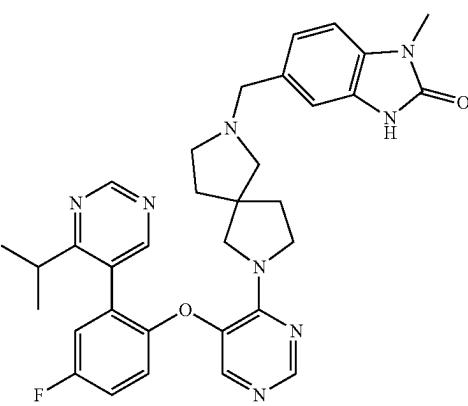
No.	Structure
VI-148	
VI-149	
VI-150	

TABLE 6-continued

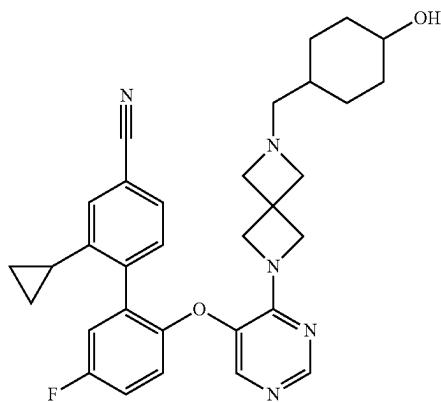
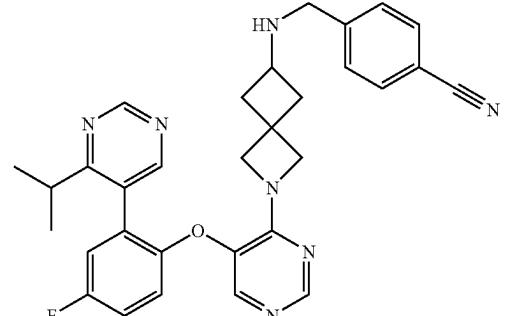
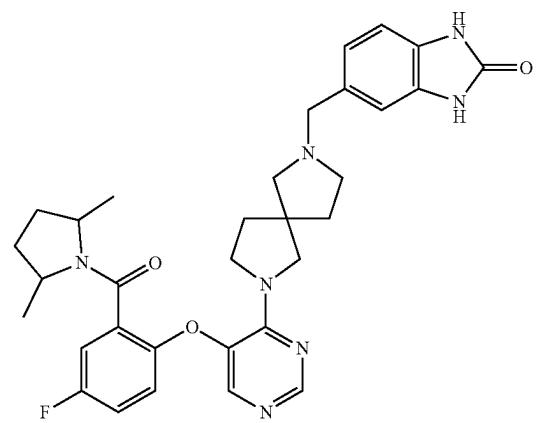
No.	Structure
VI-151	
VI-152	
VI-153	

TABLE 6-continued

No.	Structure
VI-154	
VI-155	
VI-156	
VI-157	

TABLE 6-continued

No.	Structure
VI-158	
VI-159	
VI-160	
VI-161	

TABLE 6-continued

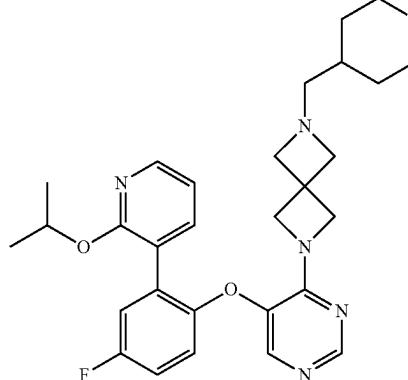
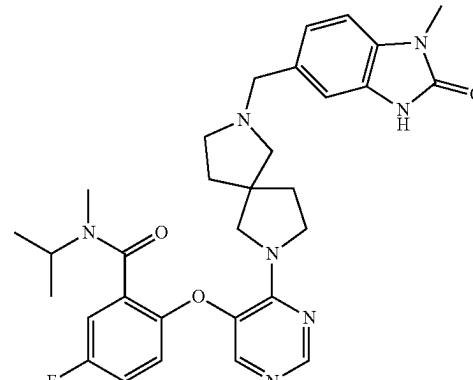
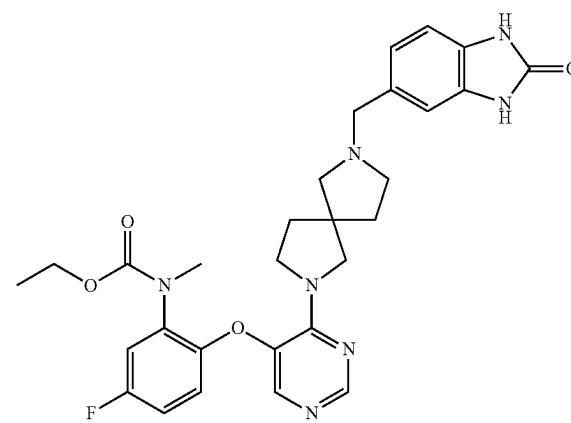
No.	Structure
VI-162	
VI-163	
VI-164	

TABLE 6-continued

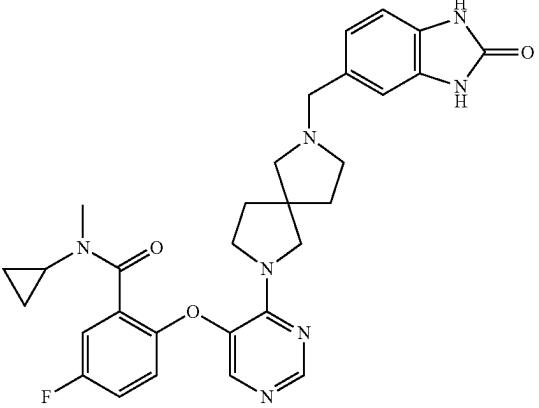
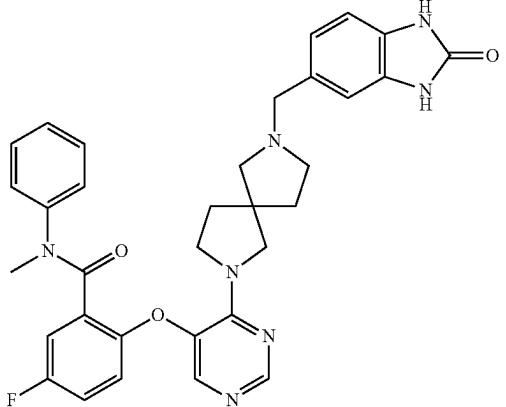
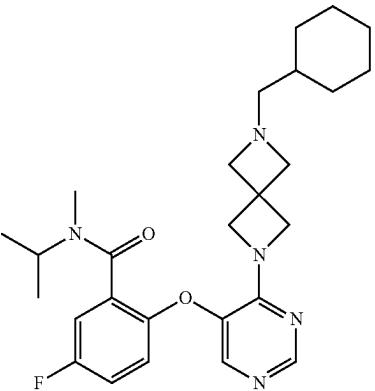
No.	Structure
VI-165	
VI-166	
VI-167	

TABLE 6-continued

No.	Structure
VI-168	
VI-169	
VI-170	

TABLE 6-continued

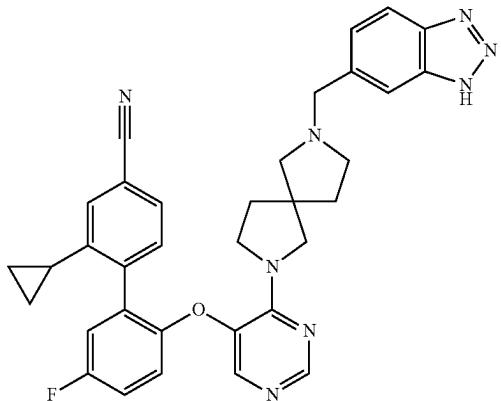
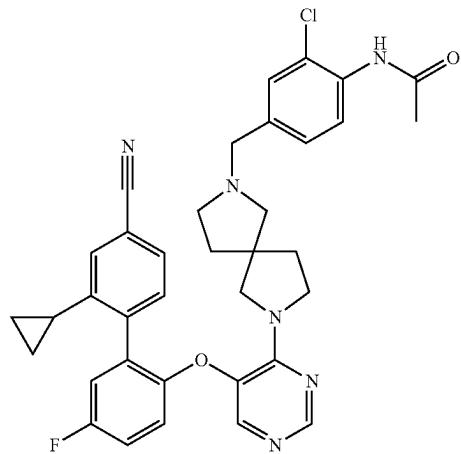
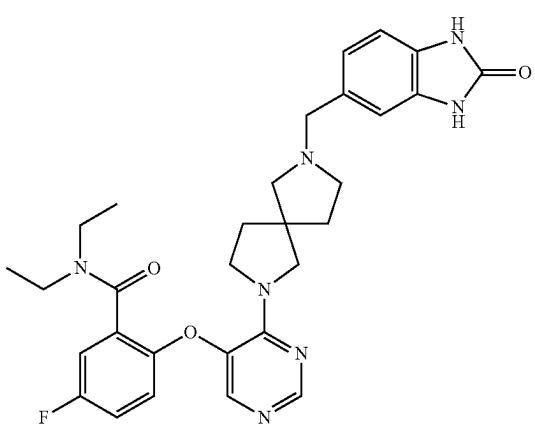
No.	Structure
VI-171	
VI-172	
VI-173	

TABLE 6-continued

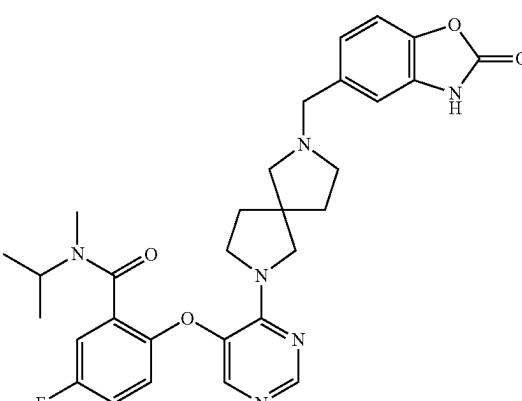
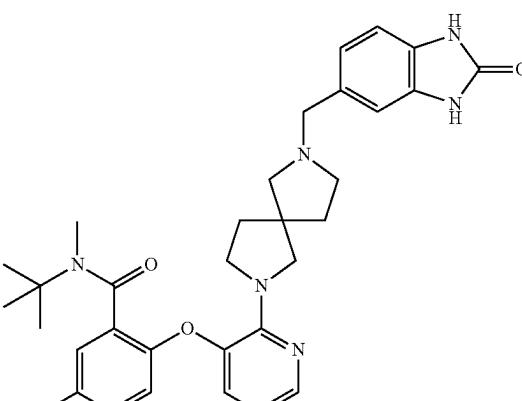
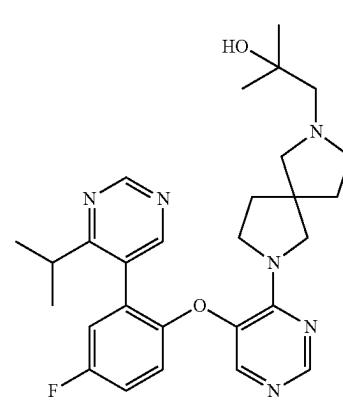
No.	Structure
VI-174	
VI-175	
VI-176	

TABLE 6-continued

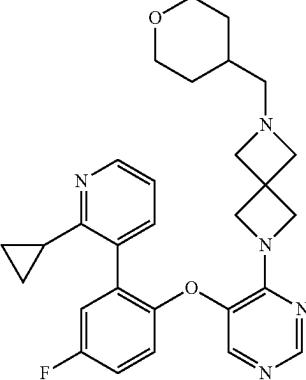
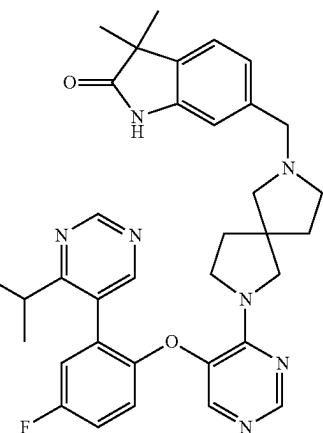
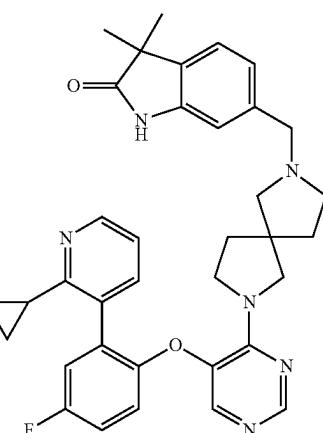
No.	Structure
VI-177	
VI-178	
VI-179	

TABLE 6-continued

No.	Structure
VI-180	
VI-181	
VI-182	

TABLE 6-continued

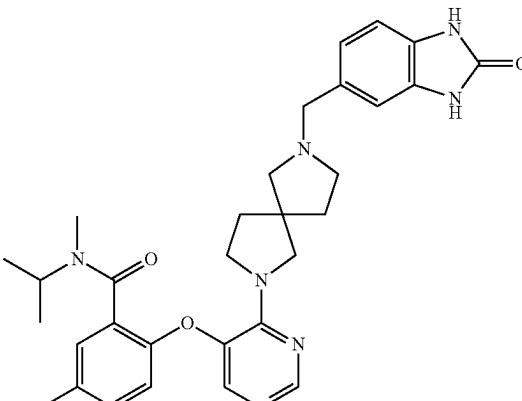
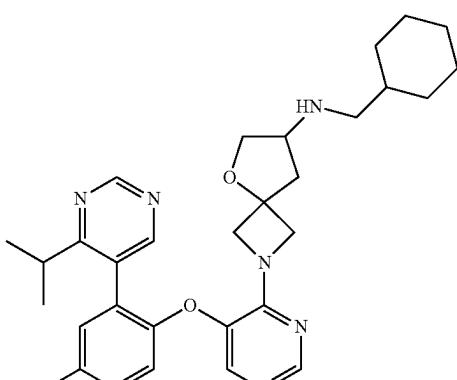
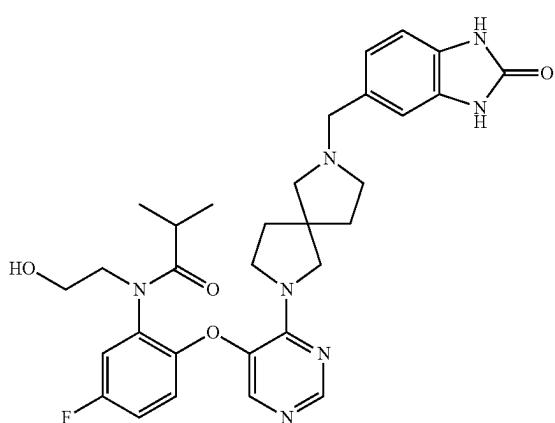
No.	Structure
VI-183	
VI-184	
VI-185	

TABLE 6-continued

No.	Structure
VI-186	
VI-187	
VI-188	

TABLE 6-continued

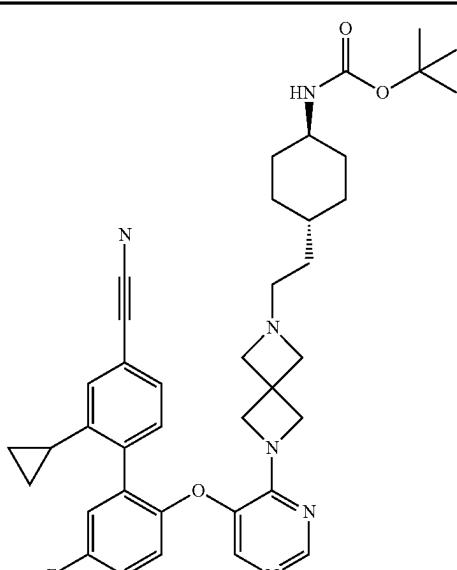
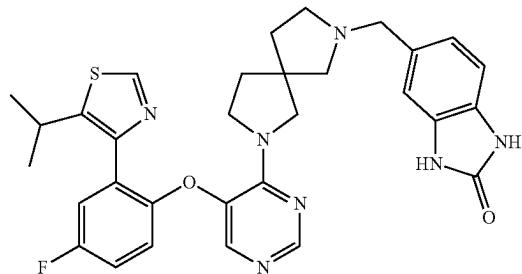
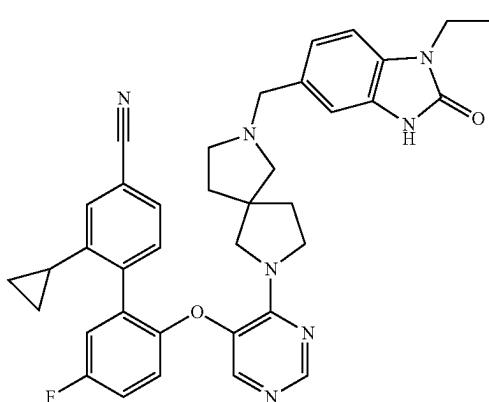
No.	Structure
VI-189	
VI-190	
VI-191	

TABLE 6-continued

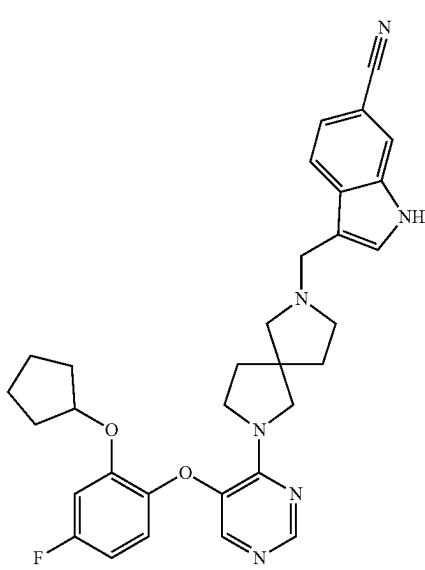
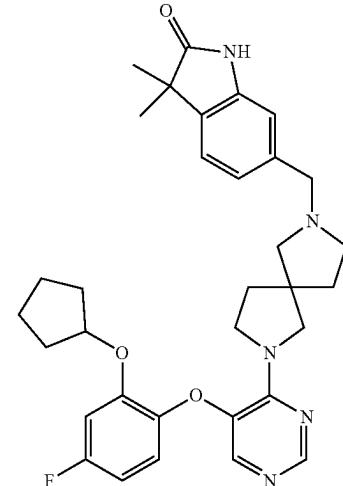
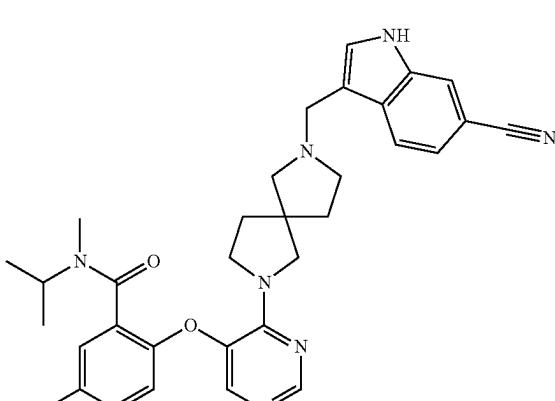
No.	Structure
VI-192	
VI-193	
VI-194	

TABLE 6-continued

No.	Structure
VI-195	
VI-196	
VI-197	

TABLE 6-continued

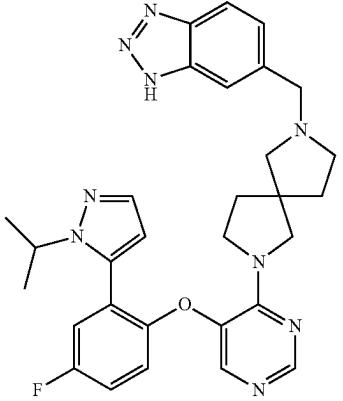
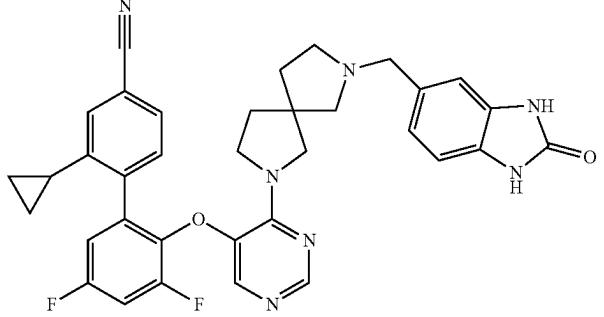
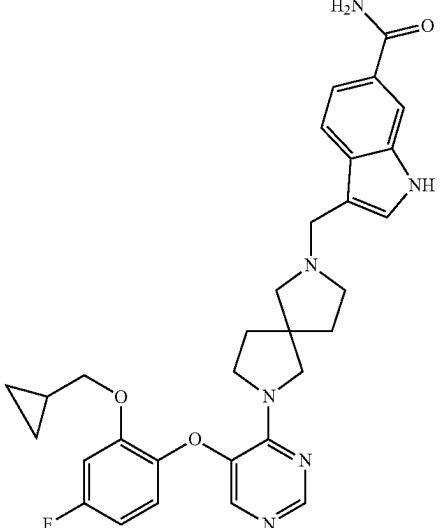
No.	Structure
VI-198	
VI-199	
VI-200	

TABLE 6-continued

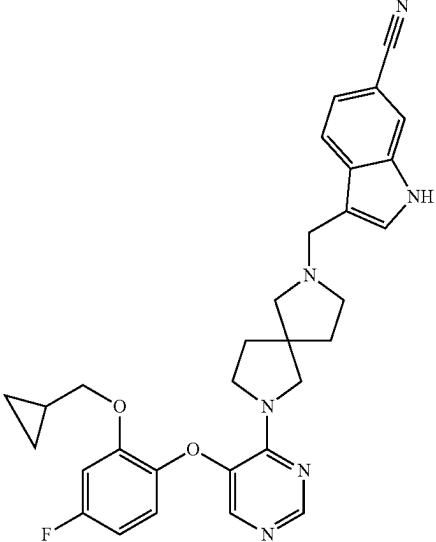
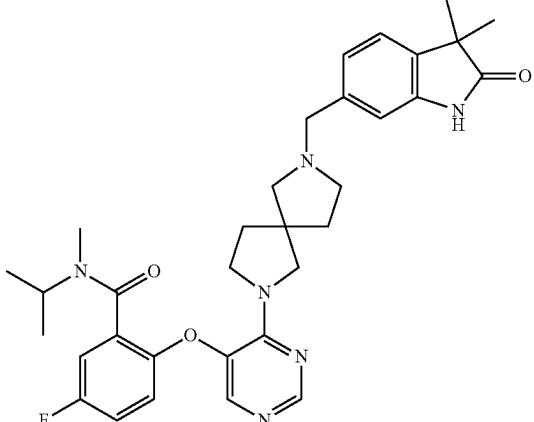
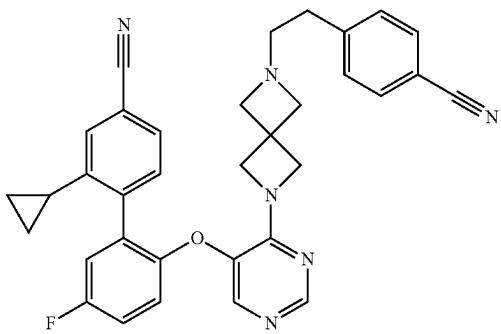
No.	Structure
VI-201	
VI-202	
VI-203	

TABLE 6-continued

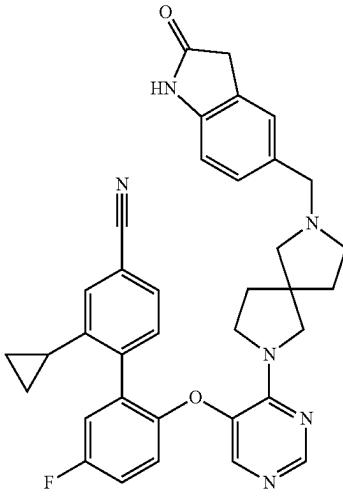
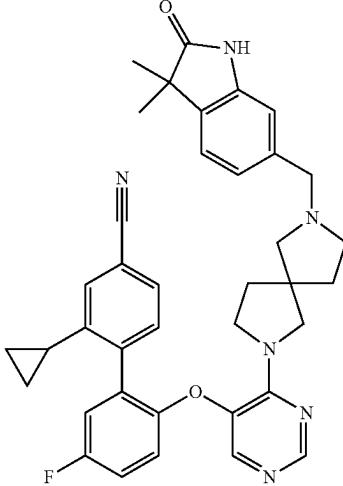
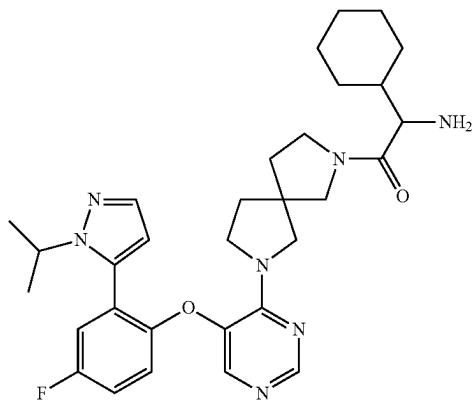
No.	Structure
VI-204	
VI-205	
VI-206	

TABLE 6-continued

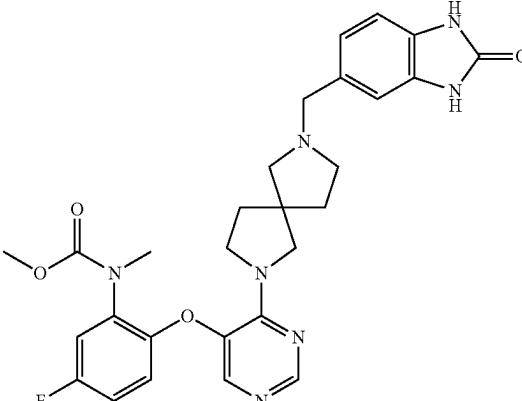
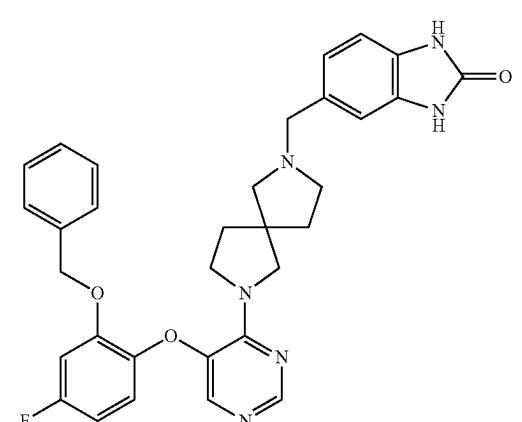
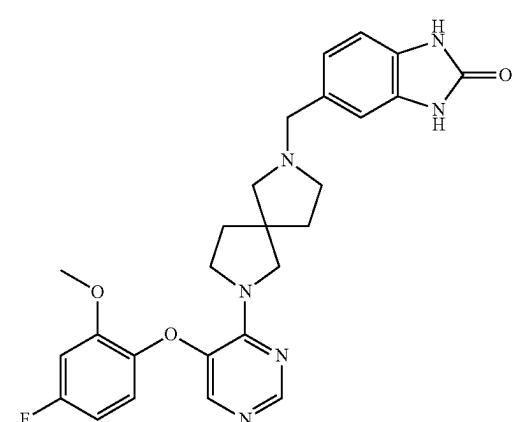
No.	Structure
VI-207	
VI-208	
VI-209	

TABLE 6-continued

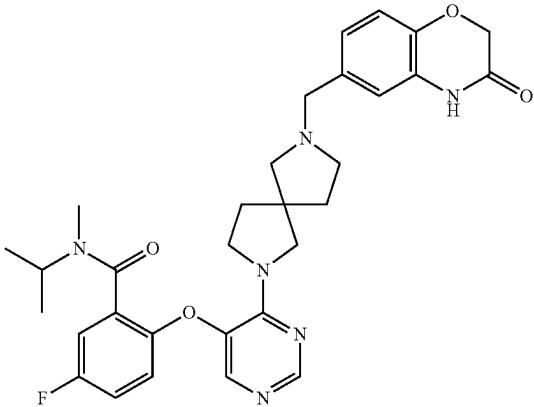
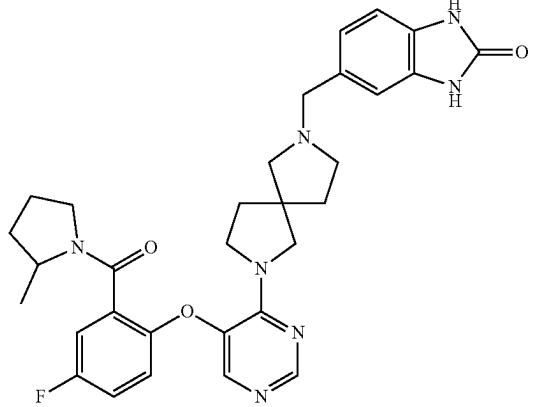
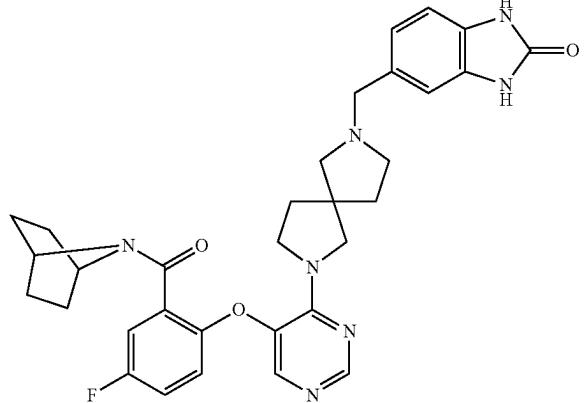
No.	Structure
VI-210	
VI-211	
VI-212	

TABLE 6-continued

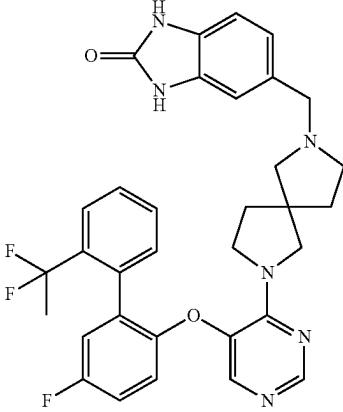
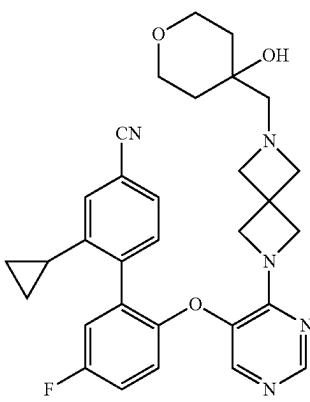
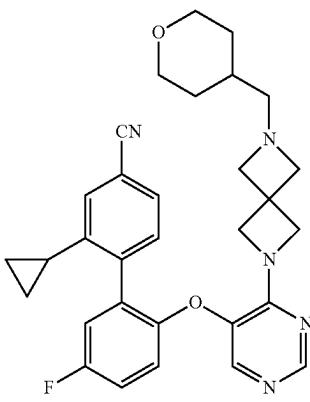
No.	Structure
VI-213	
VI-214	
VI-215	

TABLE 6-continued

No.	Structure
VI-216	
VI-217	
VI-218	

TABLE 6-continued

No.	Structure
VI-219	
VI-220	
VI-221	

TABLE 6-continued

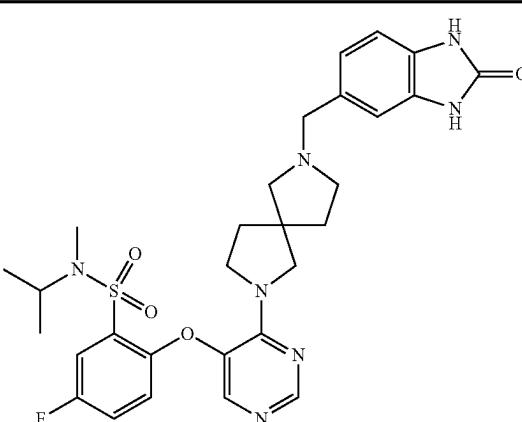
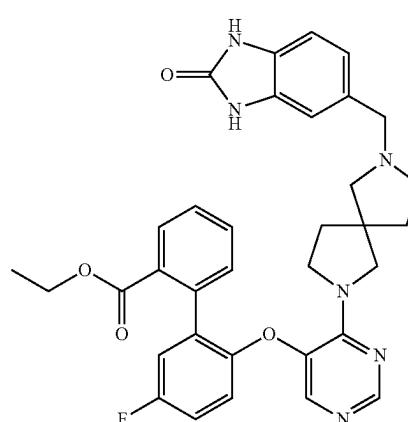
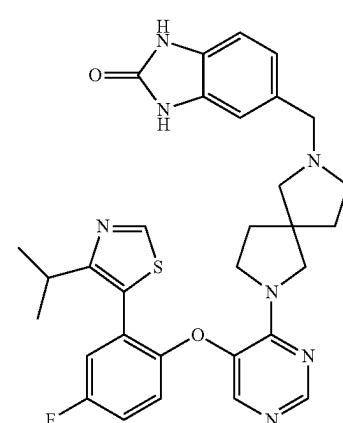
No.	Structure
VI-222	
VI-223	
VI-224	

TABLE 6-continued

No.	Structure
VI-225	
VI-226	
VI-227	
VI-228	

TABLE 6-continued

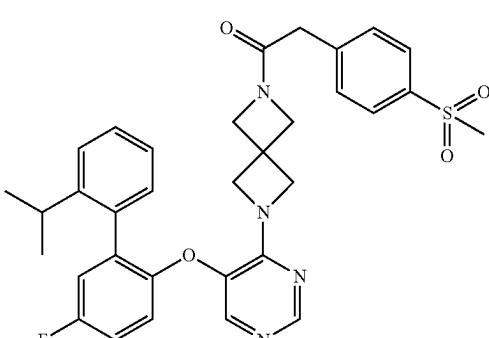
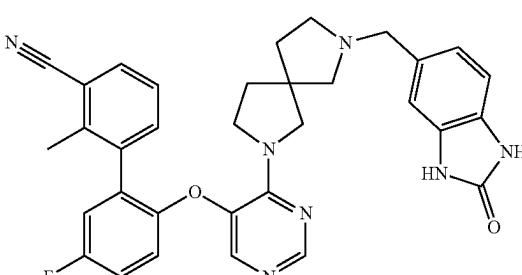
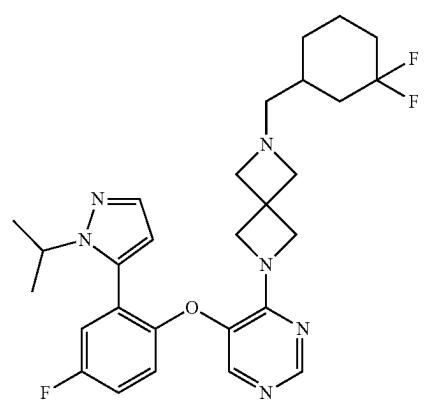
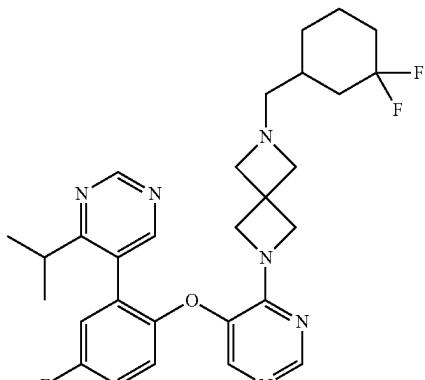
No.	Structure
VI-229	
VI-230	
VI-231	
VI-232	

TABLE 6-continued

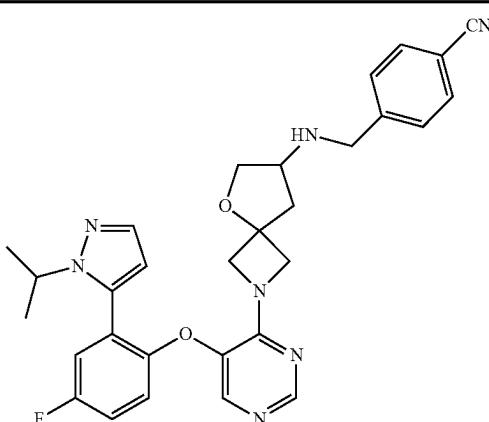
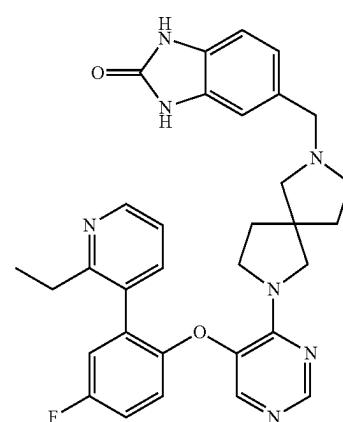
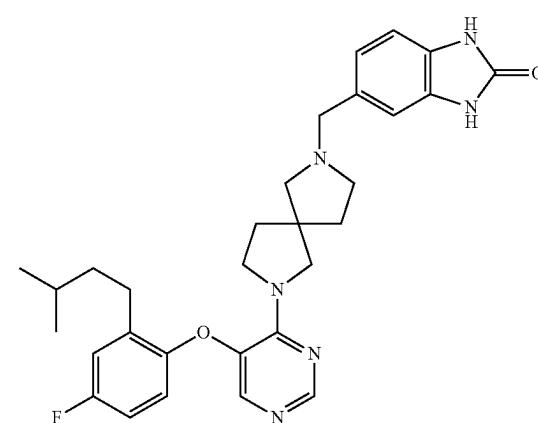
No.	Structure
VI-233	
VI-234	
VI-235	

TABLE 6-continued

No.	Structure
VI-236	
VI-237	
VI-238	

TABLE 6-continued

No.	Structure
VI-239	
VI-240	
VI-241	
VI-242	

TABLE 6-continued

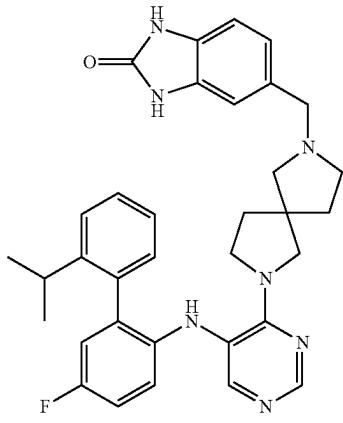
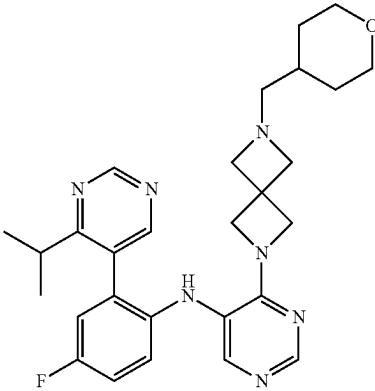
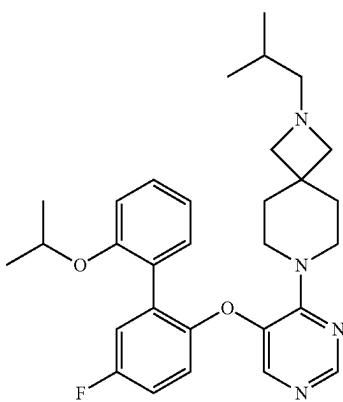
No.	Structure
VI-243	
VI-244	
VI-245	

TABLE 6-continued

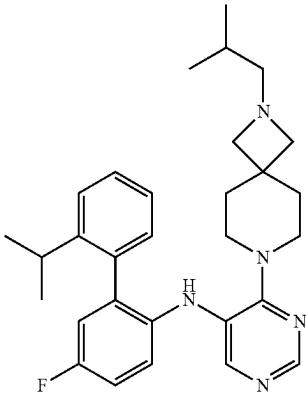
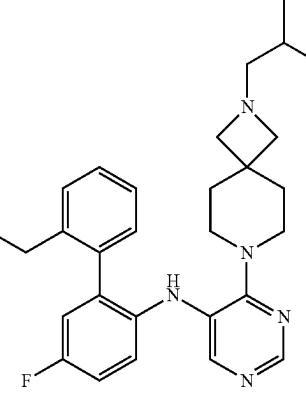
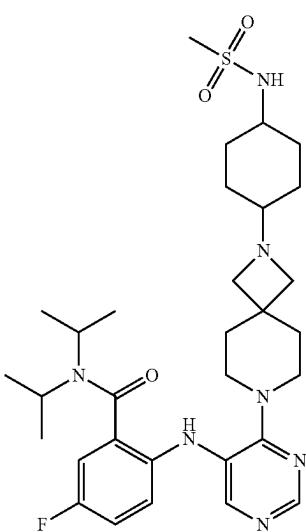
No.	Structure
VI-246	
VI-247	
VI-248	

TABLE 6-continued

TABLE 6-continued

No.	Structure
VI-253	

TABLE 7

No.	Structure
VII-1	
VII-2	

TABLE 7-continued

No.	Structure
VII-3	
VII-4	

TABLE 7-continued

No.	Structure
VII-5	
VII-6	
VII-7	

TABLE 7-continued

No.	Structure
VII-8	
VII-9	
VII-10	

TABLE 7-continued

No.	Structure
VII-11	
VII-12	
VII-13	
VII-14	

TABLE 7-continued

No.	Structure
VII-15	
VII-16	
VII-17	
VII-18	
VII-19	

TABLE 7-continued

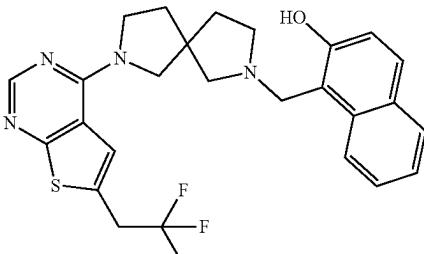
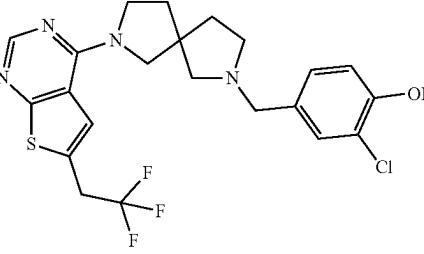
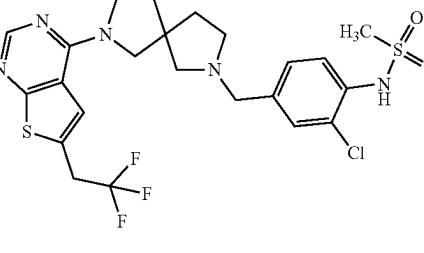
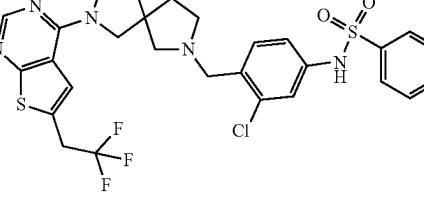
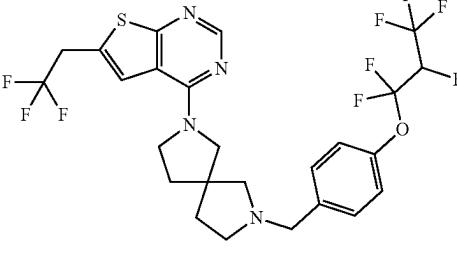
No.	Structure
VII-20	
VII-21	
VII-22	
VII-23	
VII-24	

TABLE 7-continued

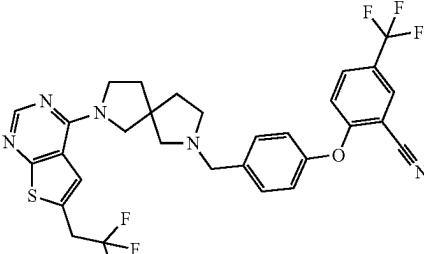
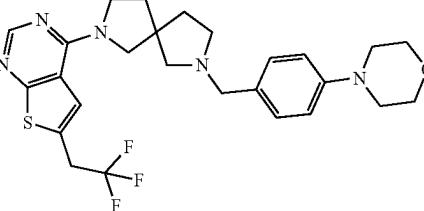
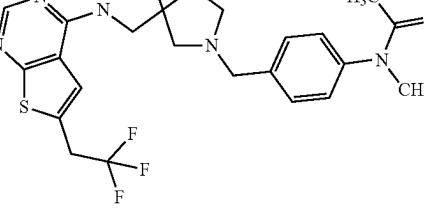
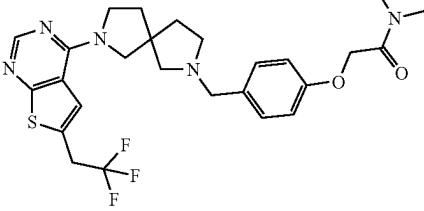
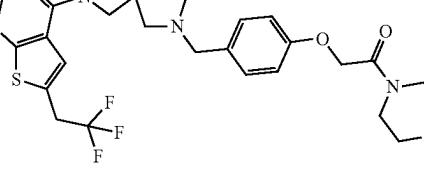
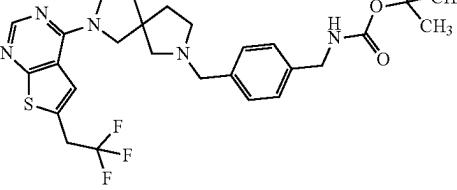
No.	Structure
VII-25	
VII-26	
VII-27	
VII-28	
VII-29	
VII-30	

TABLE 7-continued

No.	Structure
VII-31	
VII-32	
VII-33	
VII-34	
VII-35	

TABLE 7-continued

No.	Structure
VII-36	
VII-37	
VII-38	
VII-39	
VII-40	

TABLE 7-continued

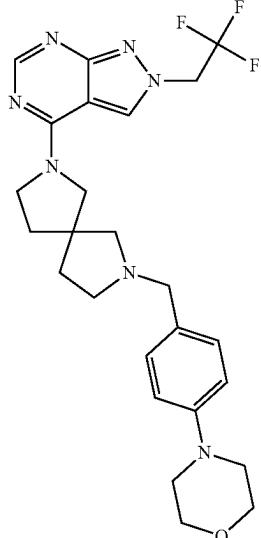
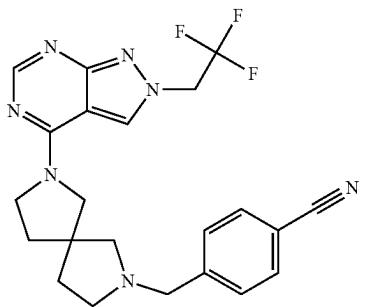
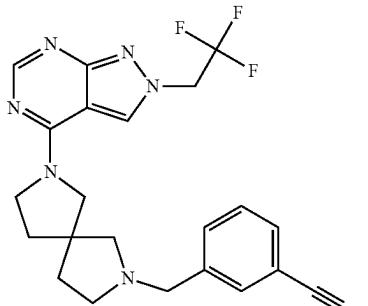
No.	Structure
VII-41	
VII-42	
VII-43	

TABLE 7-continued

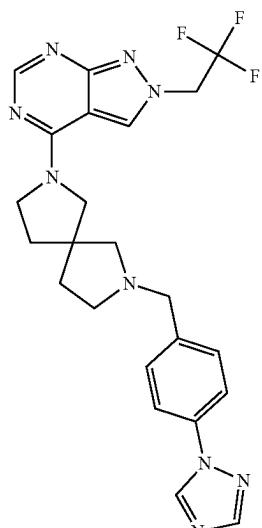
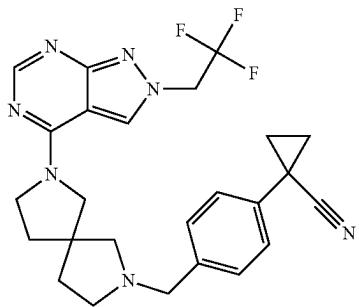
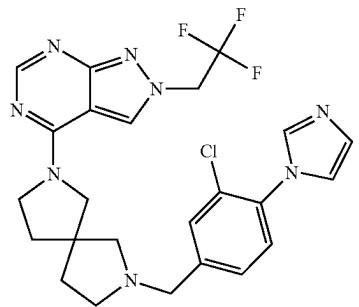
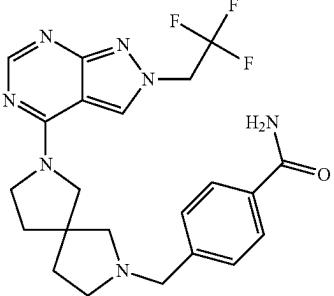
No.	Structure
VII-44	
VII-45	
VII-46	
VII-47	

TABLE 7-continued

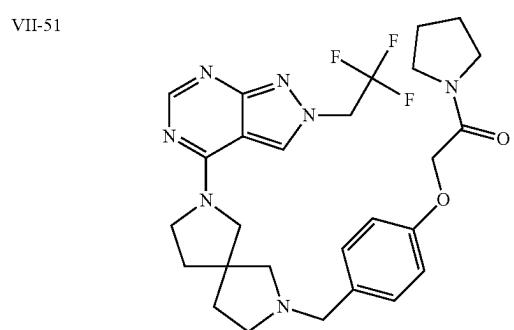
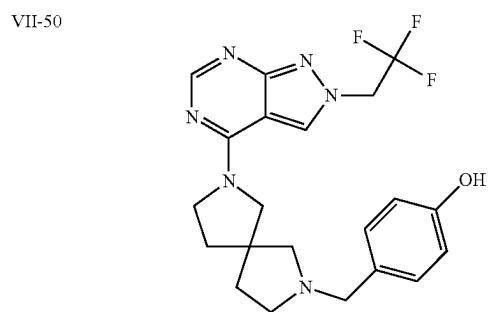
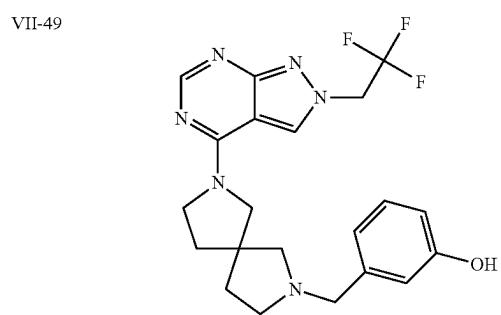
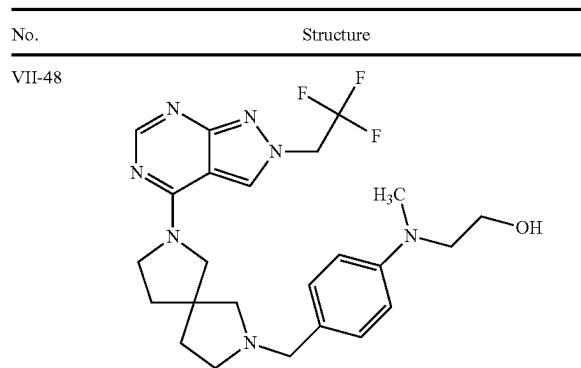


TABLE 7-continued

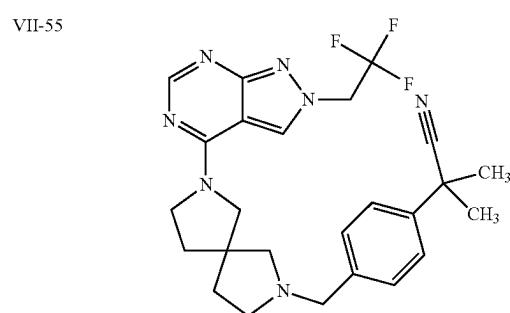
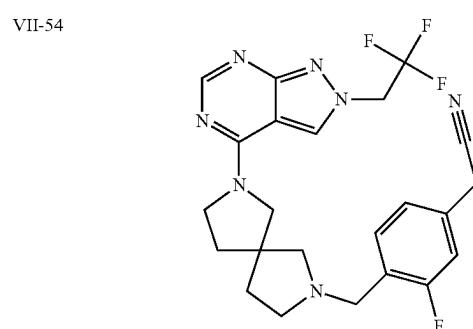
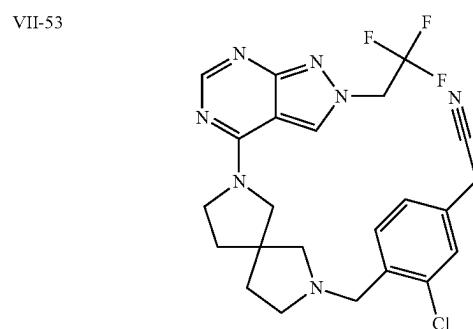
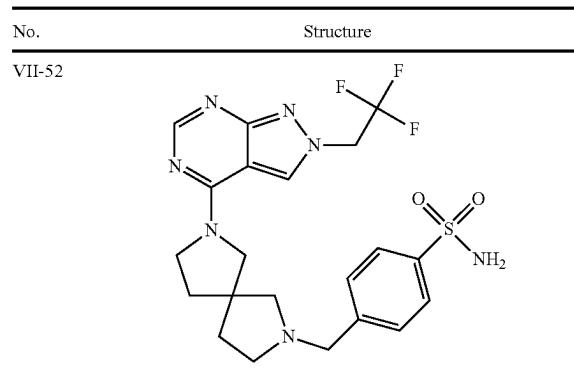


TABLE 7-continued

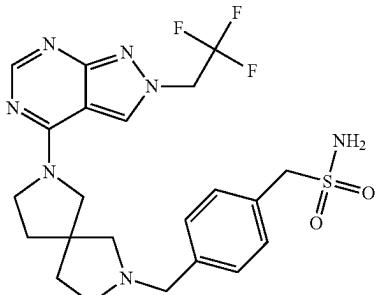
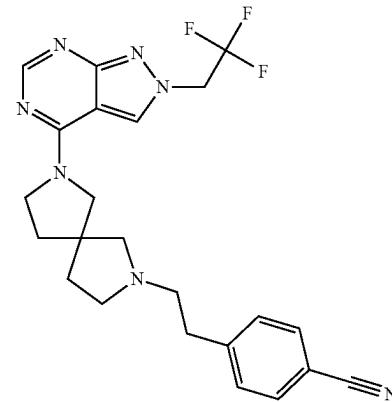
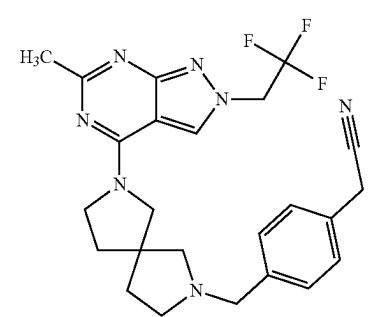
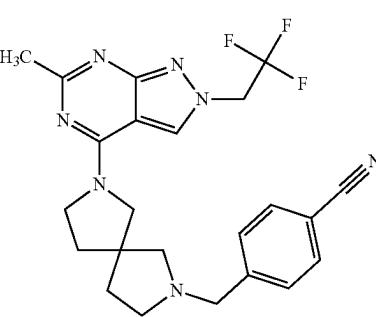
No.	Structure
VII-56	
VII-57	
VII-58	
VII-59	

TABLE 7-continued

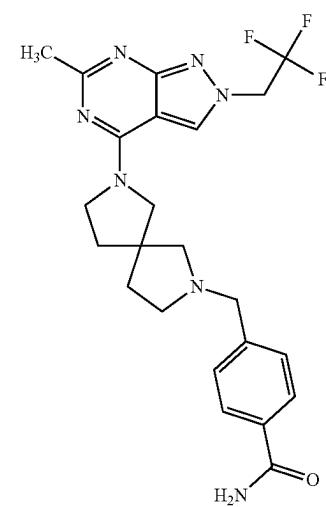
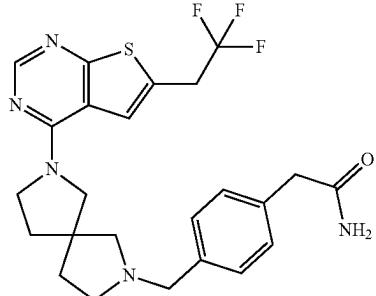
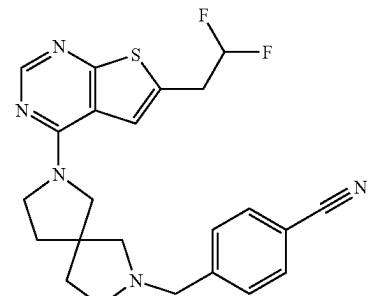
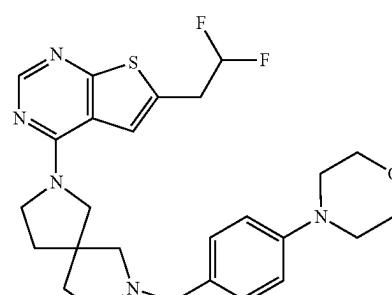
No.	Structure
VII-60	
VII-61	
VII-62	
VII-63	

TABLE 7-continued

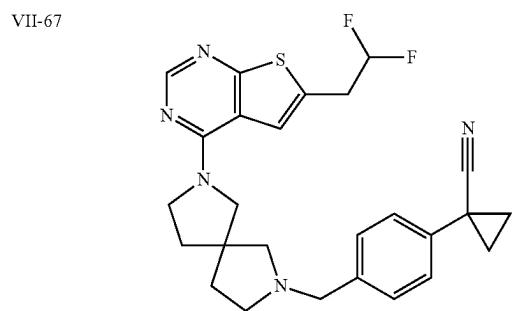
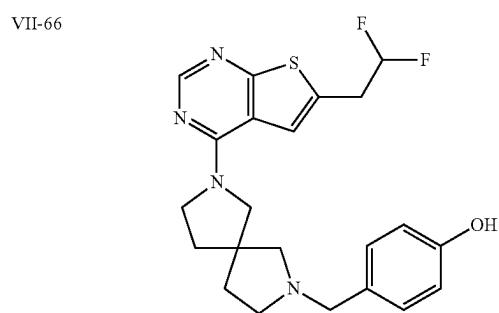
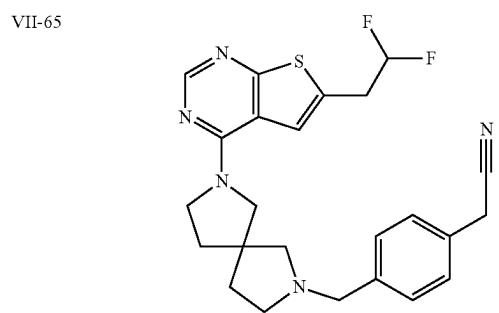
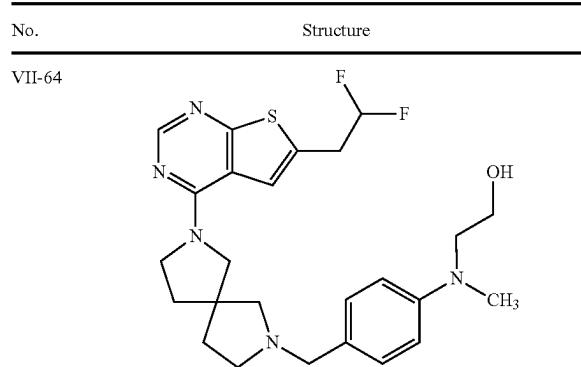


TABLE 7-continued

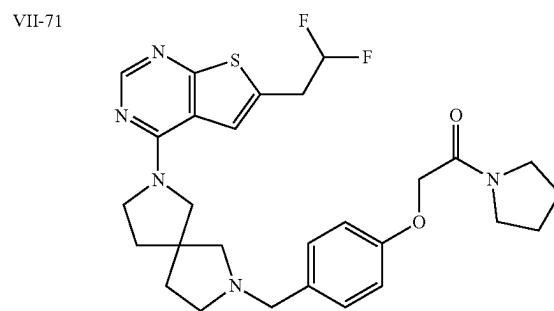
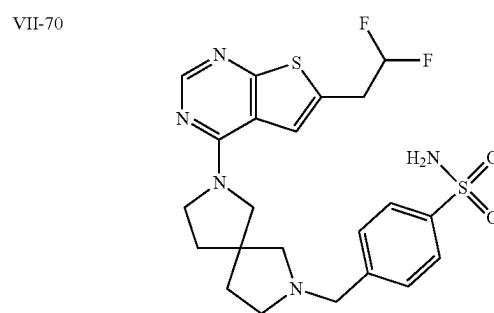
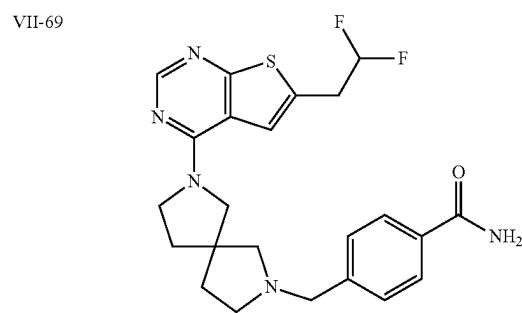
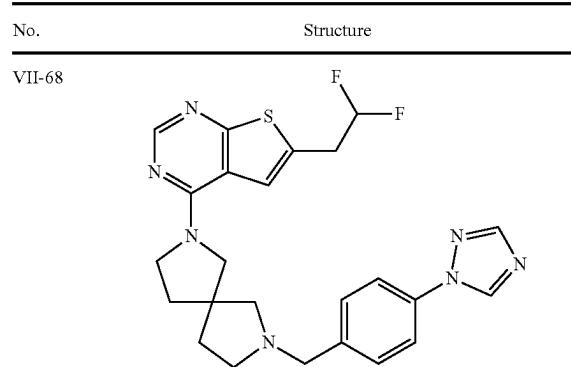


TABLE 7-continued

No.	Structure
VII-72	
VII-73	
VII-74	
VII-75	

TABLE 7-continued

No.	Structure
VII-76	
VII-77	
VII-78	
VII-79	

TABLE 7-continued

No.	Structure
VII-80	
VII-81	
VII-82	
VII-83	

TABLE 7-continued

No.	Structure
VII-84	
VII-85	
VII-86	

TABLE 7-continued

No.	Structure
VII-87	
VII-88	
VII-89	

TABLE 7-continued

No.	Structure
VII-90	
VII-91	
VII-92	

TABLE 7-continued

No.	Structure
VII-93	
VII-94	
VII-95	
VII-96	

TABLE 7-continued

No.	Structure
VII-97	
VII-98	
VII-99	
VII-100	

TABLE 7-continued

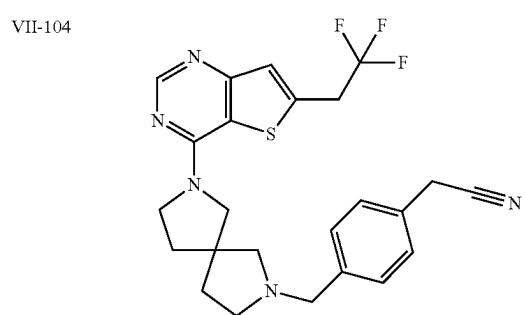
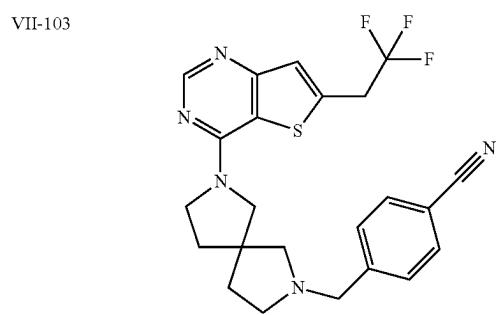
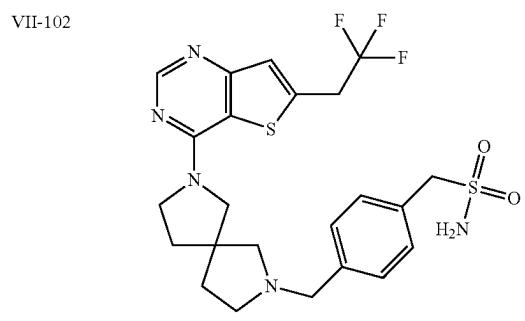
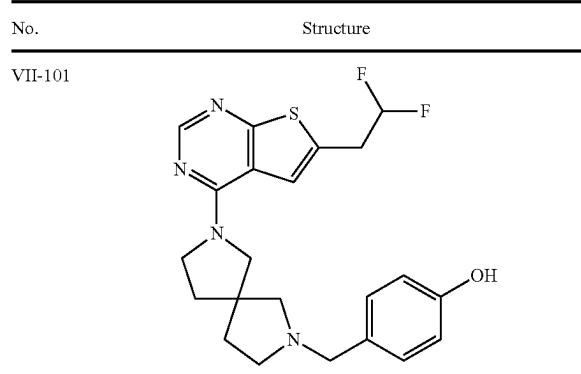


TABLE 7-continued

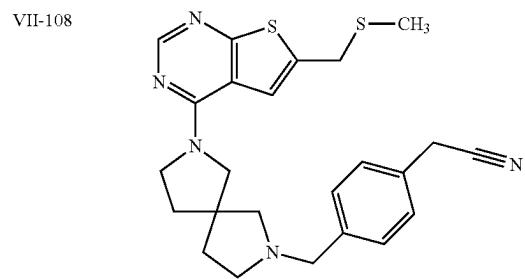
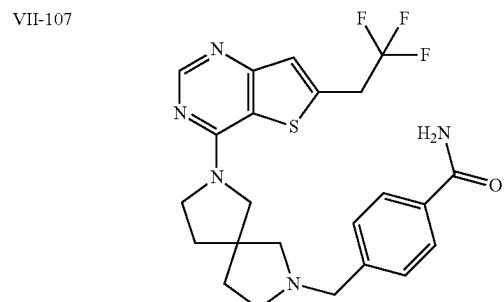
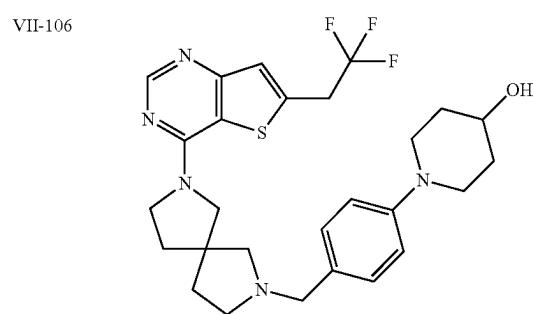
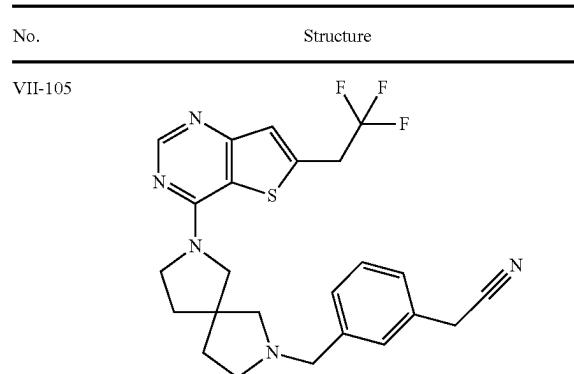


TABLE 7-continued

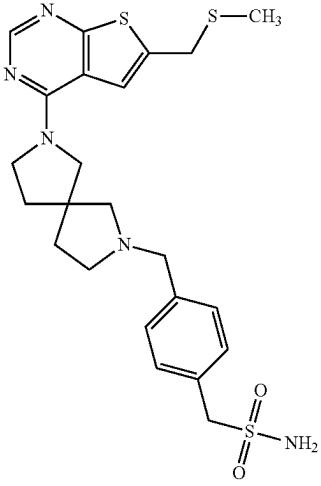
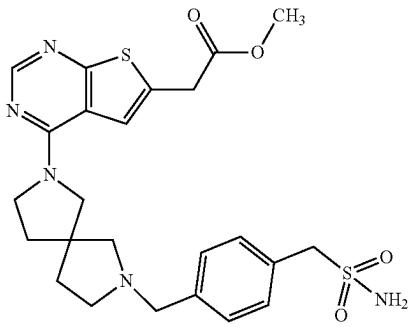
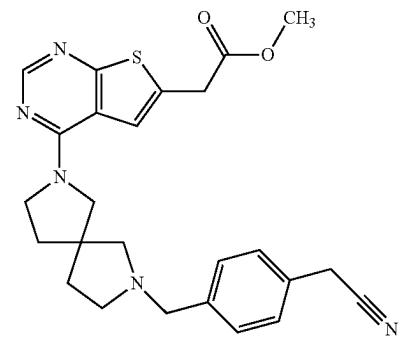
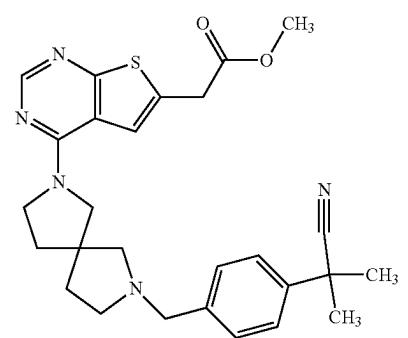
No.	Structure
VII-109	
VII-110	
VII-111	
VII-112	

TABLE 7-continued

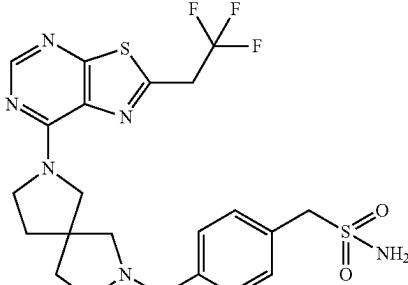
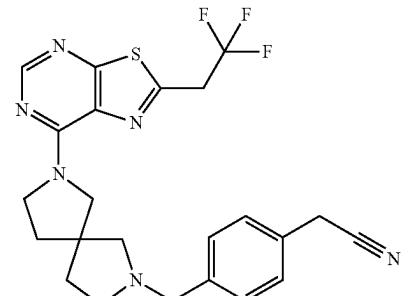
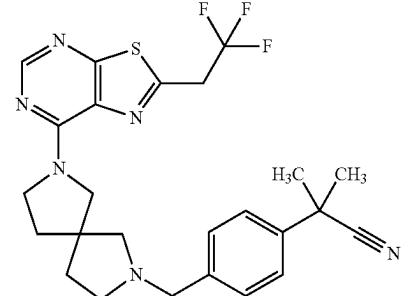
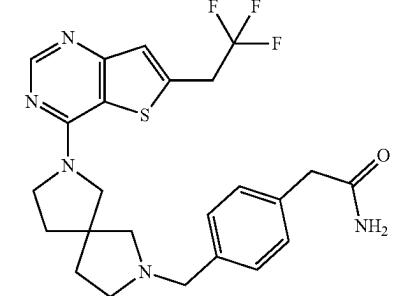
No.	Structure
VII-113	
VII-114	
VII-115	
VII-116	

TABLE 7-continued

No.	Structure
VII-117	<p>The structure consists of a purine ring system. At the 6-position, there is a phenyl ring attached to a pyrrolidine-1-yl group. The pyrrolidine ring is substituted at its 2-position with a 2-(4-(2,2,2-trifluoroethyl)phenyl) group. The piperazine-2-yl group is attached to the pyrrolidine ring at its 1-position. The 4-position of the piperazine ring is substituted with an aminoethylphenyl group.</p>

TABLE 7-continued

No.	Structure
VII-120	<p style="text-align: center;"> <chem>CN1CC[C@H]2[C@@H]1CC[C@H]3[C@H]2CN4CC[C@H]5[C@H]4CC[C@H]6C(F)(F)C(F)C6C5C(F)(F)C(F)F</chem> </p>

VII-118

CN(C)S(=O)(=O)Cc1ccc(cc1)C[C@H](c2ccccc2)C3CC[C@H]3C[C@H]3C[C@H]3N3Cc4cc5nc6nc7cc(C(F)(F)F)cc(C(F)(F)F)cc7nc6n5

VII-121

The chemical structure of VII-121 consists of a purine ring system attached to a piperazine ring. The piperazine ring is substituted at one position with a benzyl sulfonamide group ($\text{C}_6\text{H}_5\text{CH}_2\text{S}(=\text{O})_2\text{NH}_2$). The purine ring is also linked to the piperazine ring at its 2-position.

VII-119

CN(C)CCCOc1ccc(cc1)N(C)C2CCCCN2Cc3ccccc3Cc4nc5nc6cc(C(F)(F)F)cc(C(F)(F)F)c6cc5n4

VII-122

Chemical structure of compound VII-122:

CN1CCN(Cc2ccc(cc2)Cc3c(cnc4cc(F)(F)C(F)F)nc3)CC1

TABLE 7-continued

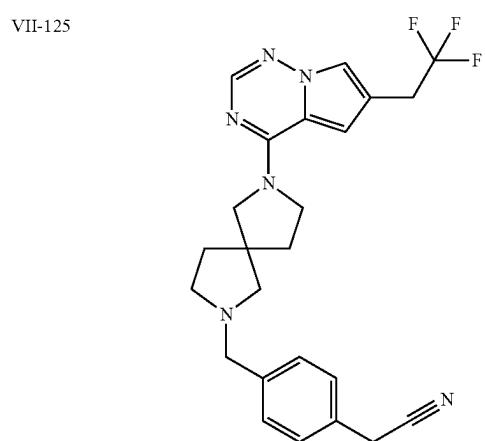
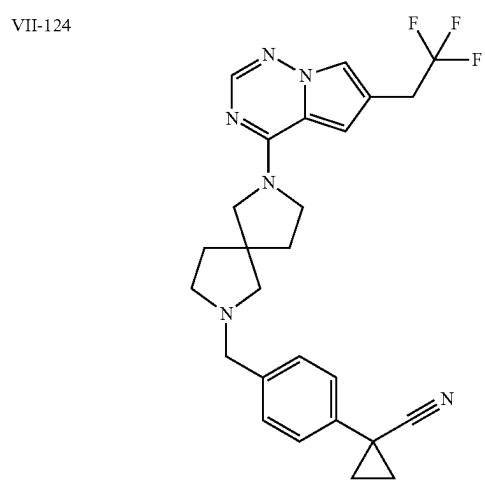
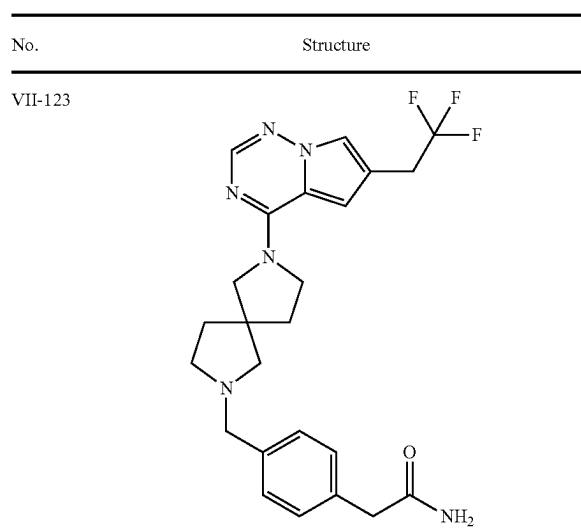


TABLE 7-continued

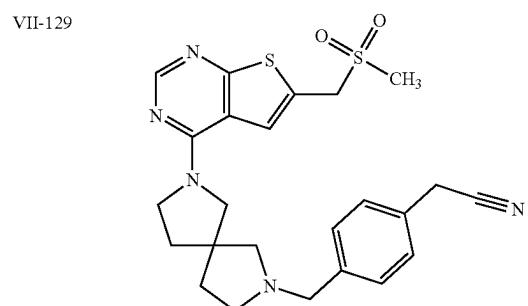
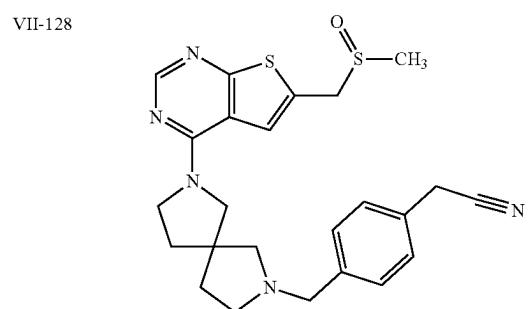
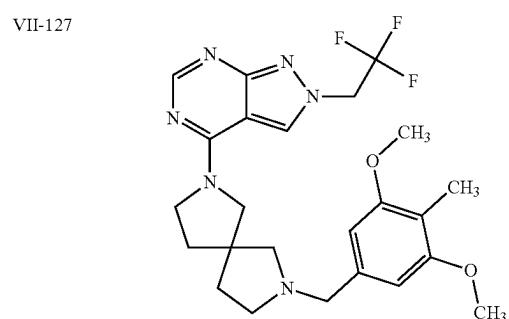
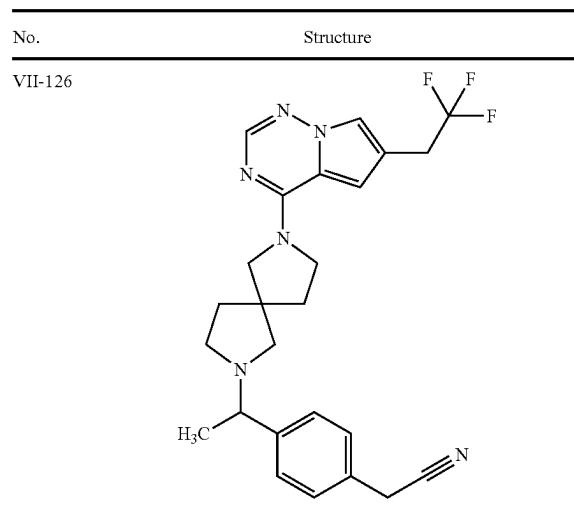


TABLE 7-continued

No.	Structure
VII-130	
VII-131	
VII-132	

Pharmaceutical Compositions

[0746] 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) and a pharmaceutically acceptable carrier.

[0747] 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.

[0748] 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.

[0749] In certain embodiments, a composition of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0750] The compound of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI), 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.

[0751] In some embodiments, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) is used for treatment of an acute condition.

[0752] In some embodiments, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0753] Administration of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) is administered chronically on an ongoing basis, e.g., for the treatment of chronic effects.

[0754] In some embodiments, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) may be found by routine experimentation in light of the instant disclosure.

[0755] In some embodiments, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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 & Wilkins 1999).

[0756] Provided herein are pharmaceutical compositions comprising a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI), or a pharmaceutically acceptable salt thereof.

[0757] A pharmaceutical composition, as used herein, refers to a mixture of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) may be used singly or in combination with one or more therapeutic agents as components of mixtures.

[0758] In one embodiment, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0759] In another embodiment, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) is formulated for oral administration. A compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0760] 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI), 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.

[0761] 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.

[0762] In certain embodiments, a therapeutically effective amount of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0763] In other embodiments, a therapeutically effective amount of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula

(VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) is formulated for parenteral 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0764] In still other embodiments, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) is administered topically. A compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0765] In yet other embodiments, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI). 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI), 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.

[0766] In other embodiments, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) and a suitable powder base such as lactose or starch.

[0767] In still other embodiments, a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0768] 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0769] Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI), 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0770] Methods for the preparation of compositions comprising a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI). 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0771] In some embodiments, a pharmaceutical composition comprising a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0772] 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.

[0773] 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.

[0774] 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.

[0775] 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.

[0776] 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.

[0777] 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.

[0778] 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.

[0779] 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.

[0780] 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0781] 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.

[0782] In some embodiments, the concentration of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0783] In some embodiments, the concentration of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0784] In some embodiments, the concentration of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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%, approxi-

mately 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.

[0785] In some embodiments, the concentration of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0786] In some embodiments, the amount of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0787] In some embodiments, the amount of a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

[0788] 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.

[0789] 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.

[0790] 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI), 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.

[0791] 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.

Methods

[0792] The present disclosure provides a method of treating a hematological malignancy, such as acute myeloid leukemia, or Ewing's sarcoma. A subject method typically involves administering to a subject in need thereof a menin inhibitor. The menin inhibitor can inhibit the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein). Inhibition of the interaction of menin and one or more proteins (e.g., MLL1, MLL2, an MLL fusion protein) 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., M-LL1, MLL2,

an MLL fusion protein, 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 M-LL1, MLL2, and/or an MLL fusion protein (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.

[0793] 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., acute myeloid leukemia and Ewing's sarcoma).

[0794] 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) to a subject in need thereof.

[0795] 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 lymphocytic 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 Burkittlymphoma/leukemia); mature T cell and natural killer (NK) cell neoplasms (such as T-cell polylymphocytic 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 lymphoma, 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 cellularity HL, nodular sclerosis cellular phase HL, lymphocyte-rich HL, nodular sclerosis grade 1 HL, nodular sclerosis grade 2 HL lymphocyte depleted HL, lymphocytic-histiocytic predominance HL, mixed 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).

[0796] In practicing any of the subject methods, the hematological malignancy may be 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 hematological malignancy is acute myeloid leukemia.

[0797] 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.

[0798] 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.

[0799] 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.

[0800] 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.

[0801] 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.

[0802] Methods for 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 use a variety of samples. Similarly, methods for determining whether a tumor or cancer comprises an MLL rearrangement, elevated MEIS1 expression levels, or partial tandem duplication of MLL (MLL-PTD) 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 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.

[0803] 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 a hematological malignancy or Ewing's sarcoma.

[0804] 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-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI). 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.

[0805] 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. 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 an IDH2 inhibitor such as enasidenib.

[0806] 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.

[0807] 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 cyclophosphamide (CYTOXANTM); alkyl sulfonates such as busulfan, improsulfan and pipsulfan; aziridines such as benzodopa, carbiquone, meturedopa, and uredopa; ethylenimines and methylamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylololomelamine; nitrogen mustards such as chlorambucil, chloraphazine, chlophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxidehydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabacin, carminomycin, carzinophilin, Casodex™, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-S-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodothricin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pterothenate, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxypyrimidine, doxifluridine, enocitabine, flouxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as folinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestramycin; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitrocrine; pentostatin; phenacetin; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK™; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichloroethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman;

gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g., paclitaxel (TAXOL™, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERE™, 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, (Nolvadex™), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprorelin, 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-demethoxy-geldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastics, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Bircodar, 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.

[0808] This disclosure further relates to a method for using a compound or salt of Formula (I-A), Formula (I-B), Formula (II), Formula (III), Formula (IV), or Formula (VI) 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.

[0809] 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.

[0810] 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.

[0811] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 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 CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published Oct. 24, 1996), WO 96/27583 (published Mar. 7, 1996), European Patent Application No. 97304971.1 (filed Jul. 8, 1997), European Patent Application No. 99308617.2 (filed Oct. 29, 1999), WO 98/07697 (published Feb. 26, 1998), WO 98/03516 (published Jan. 29, 1998), WO 98/34918 (published Aug. 13, 1998), WO 98/33768 (published Aug. 6, 1998), WO 98/30566 (published Jul. 16, 1998), European Patent Publication 606,046 (published Jul. 13, 1994), European Patent Publication 931,788 (published Jul. 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published Oct. 21, 1999), WO 99/52889 (published Oct. 21, 1999), WO 99/29667 (published Jun. 17, 1999), PCT International Application No. PCT/IB98/01113 (filed Jul. 21, 1998), European Patent Application No. 99302232.1 (filed Mar. 25, 1999), Great Britain Patent Application No. 9912961.1 (filed Jun. 3, 1999), U.S. Provisional Application No. 60/148,464 (filed Aug. 12, 1999), U.S. Pat. No. 5,863,949 (issued Jan. 26, 1999), U.S. Pat. No. 5,861,510 (issued Jan. 19, 1999), and European Patent Publication 780,386 (published Jun. 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-11, MMP-12,

and MMP-13). Some specific examples of MMP inhibitors useful in the disclosure are AG-3340, RO 32-3555, and RS 13-0830.

[0812] Autophagy inhibitors include, but are not limited to, chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), baflomycin 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.

[0813] 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.

[0814] 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, dihydro-morphine, 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, pirebuterol, 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.

[0815] 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, adrenocorticotrophic 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.

[0816] 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, P-adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

[0817] 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, 0-adrenergic receptor antagonists, agents for the treatment of hypercholesterolemia, and agents for the treatment of dyslipidemia.

[0818] 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, R-lactam antibiotics, an agent comprising an aminoglycoside, protein synthesis inhibitors, drugs used in the chemotherapy of tuberculosis, *Mycobacterium avium* complex disease, and leprosy, anti-fungal agents, antiviral agents including nonretroviral agents and antiretroviral agents.

[0819] 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 (ce-tuximab, panitumumab, trastuzumab), anti CD20 antibodies (rituximab, tositumomab), and other antibodies such as alemtuzumab, bevacizumab, and gemtuzumab.

[0820] 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.

[0821] 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 doxorubicin, taxotere (taxol), and/or cisplatin (carboplatin). For treating ovarian cancer, one may combine a compound of the present disclosure with cisplatin (carboplatin), taxotere, doxorubicin, 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.

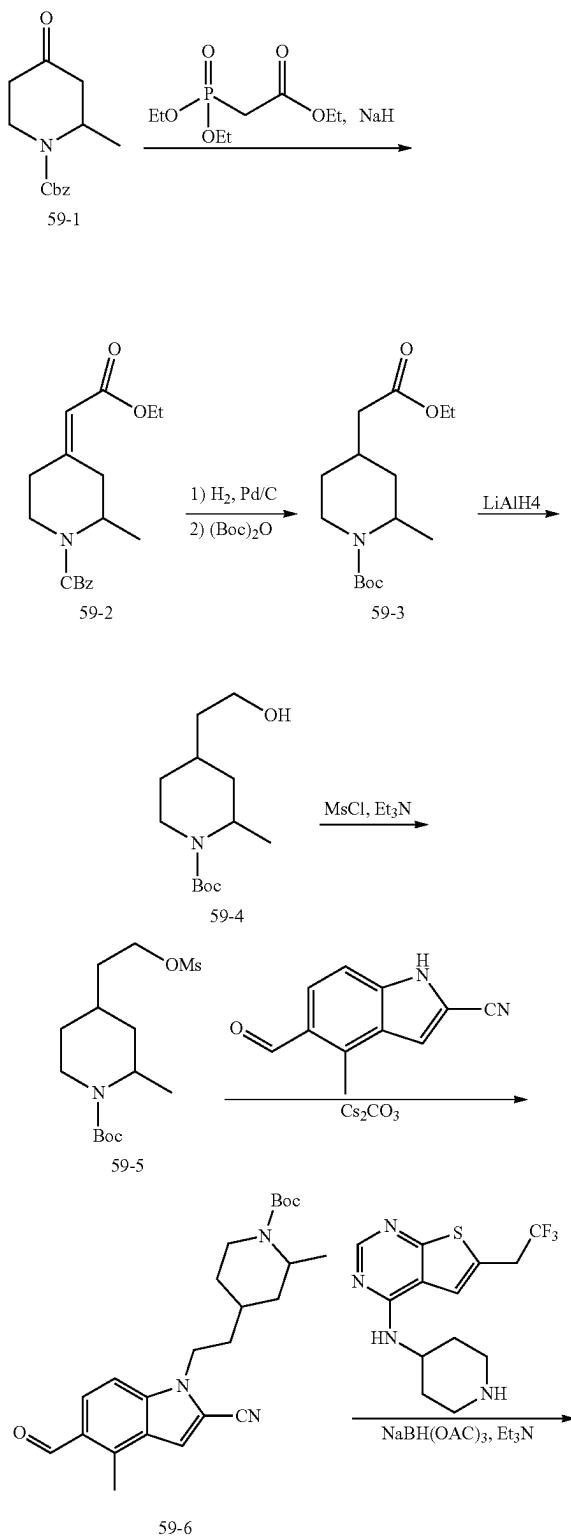
[0822] Further therapeutic agents that can be combined with a compound of the disclosure are found in Goodman and Gilman's "The Pharmacological Basis of Therapeutics" Tenth Edition edited by Hardman, Limbird and Gilman or the Physician's Desk Reference, both of which are incorporated herein by reference in their entirety.

[0823] 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.

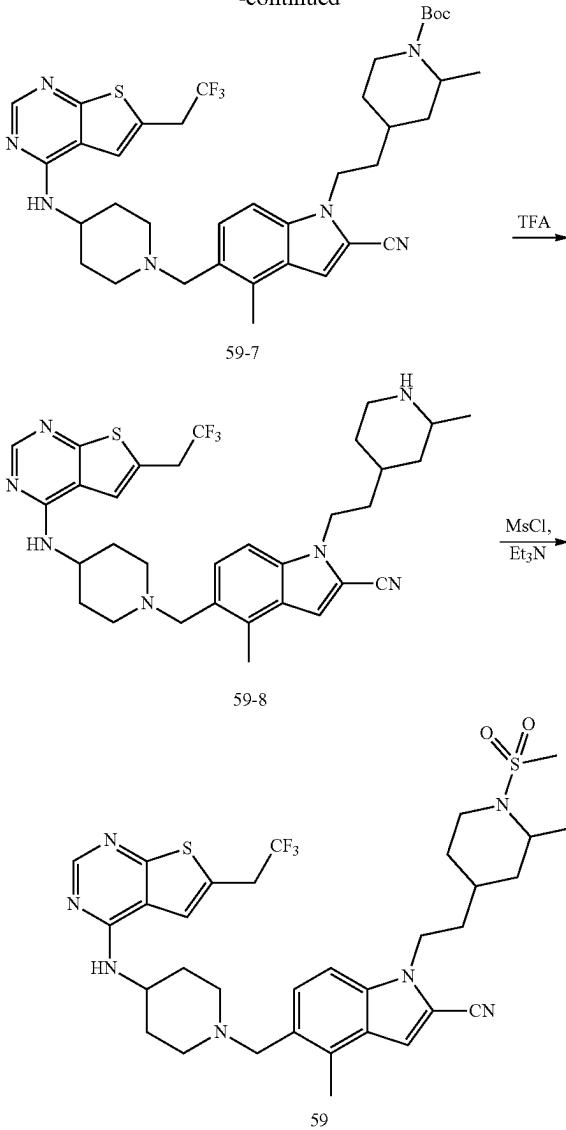
[0824] The following examples are given for the purpose of illustrating various embodiments of the disclosure and are not meant to limit the present disclosure in any fashion. The present examples, along with the methods and compositions described herein, are presently representative of preferred embodiments, 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

Example 1: Synthesis of Compound I-59 in Table 1



-continued



[0825] Step A: Preparation of Compound I-59-2: To a solution of ethyl-2-(diethoxyphosphor-acetate (1.91 g, 8.5 mmol) in THE (30 mL) was added NaH (421 mg, 10.5 mmol) at 0°C. The reaction was stirred at 0°C for 0.5 hour before I-59-1 (2 g, 8 mmol) was added. The reaction mixture was stirred at room temperature for 5 h. Ice-water (50 mL) was added, and the product extracted with ethyl acetate (50 mL×2). The combined organic layer was washed with brine (50 mL), dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (eluted 20% EtOAc in pet. ether) to afford 2.15 g of I-59-2 as a white solid (yield: 85%).

[0826] Step B: Preparation of Compound I-59-3: To a solution of I-59-2 (905 mg, 2.85 mmol) in MeOH (20 mL) was added (Boc)₂O (1.24 g, 5.71 mmol) and Pd/C catalyst. The reaction mixture was stirred at room temperature for 8 hours under H₂. TLC showed the reaction was complete. The reaction was filtered and concentrated. The residue was

purified by silica gel column chromatography (eluted 20% EtOAc in pet. ether) to give I-59-3 as a solid (740 mg, yield: 91%).

[0827] Step C: Preparation of Compound I-59-4: To a solution of I-59-3 (670 mg, 2.35 mmol) in THF (20 mL) was added LiAlH₄ (179 mg, 4.7 mmol) at 0° C. The reaction was stirred at 0° C. for 2 h, then 0.2 mL H₂O, 0.2 mL 15% NaOH, and 0.5 mL H₂O added. The mixture was stirred at room temperature for 1 h. The mixture was filtered and the organic solution was concentrated. The residue was purified by silica gel column chromatography (eluted 40% EtOAc in pet. ether) to give I-59-4 as a solid (525 mg, yield: 92%).

[0828] Step D: Preparation of Compound I-59-5: To a solution of I-59-4 (486 mg, 2 mmol) and Et₃N (404 mg, 4 mmol) in CH₂Cl₂ (20 mL) was added MsCl (344 mg, 3 mmol) at 0° C. The reaction was stirred at room temperature for 1 h. TLC showed the reaction was complete. The combined organic layer was washed with H₂O and brine, dried over sodium sulfate and concentrated in vacuo to afford 500 mg of I-59-5 as a white solid (yield: 78%).

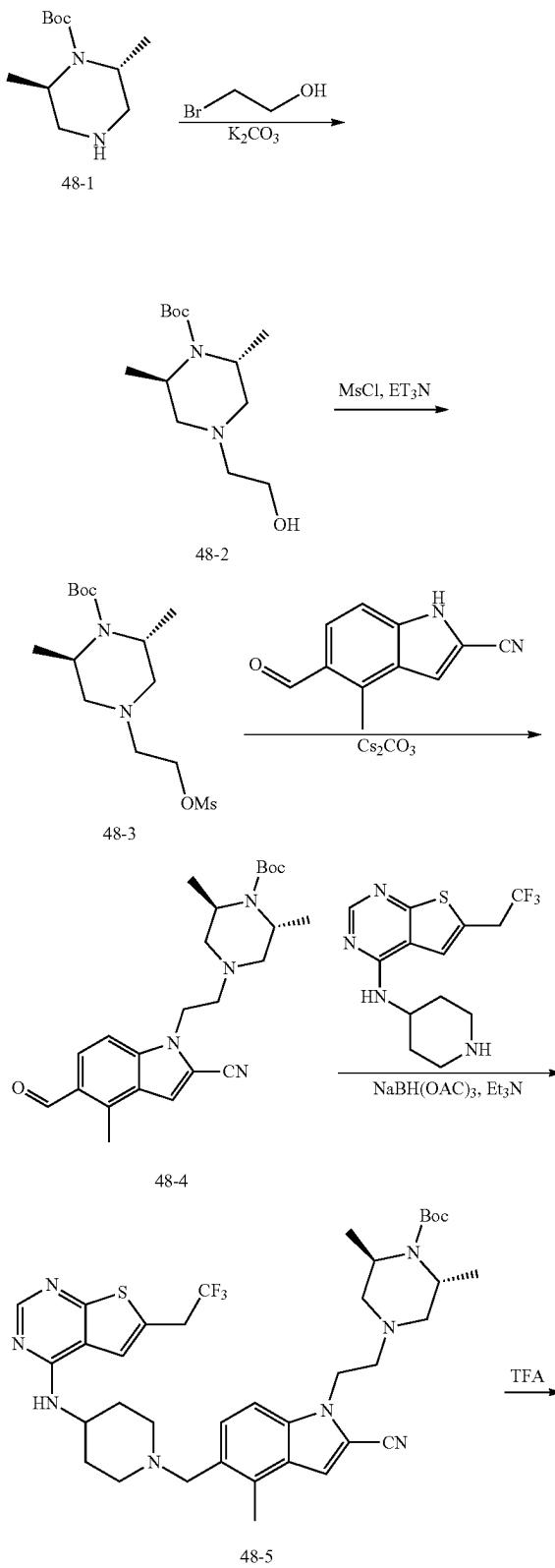
[0829] Step E: Preparation of Compound I-59-6: A mixture of I-59-5 (500 mg, 1.56 mmol), Cs₂CO₃ (846 mg, 2.33 mmol), and 5-formyl-4-methyl-1H-indole-2-carbonitrile (143 mg, 0.78 mmol) was mixed in DMF (20 mL). The reaction mixture was heated at 85° C. for 3 h. EtOAc (200 mL) was added into the resulting mixture. The combined organic layer was washed with H₂O and brine, dried over sodium sulfate and concentrated. The residue was purified by flash column (eluted 30% EtOAc in pet. ether) to afford 278 mg of I-59-6 as a white solid (yield: 43%).

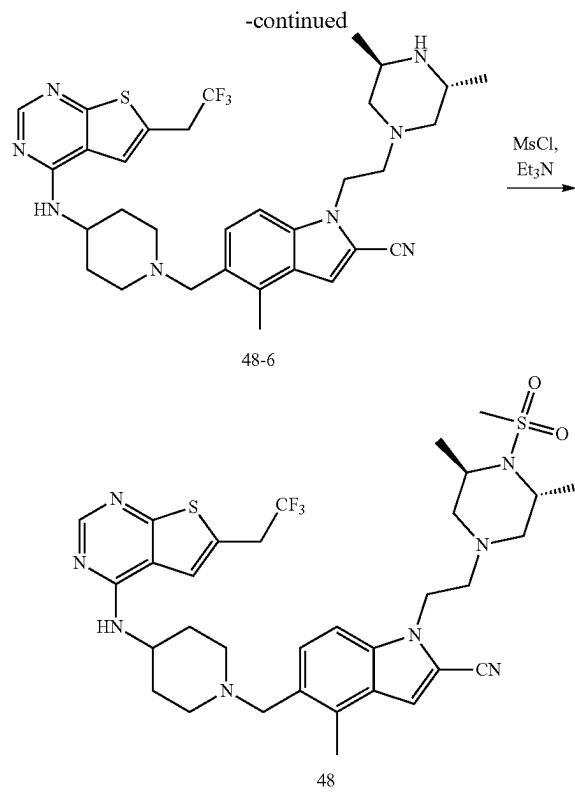
[0830] Step F: Preparation of Compound I-59-7: A mixture of I-59-6 (278 mg, 0.68 mmol), N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine (280 mg, 0.88 mmol) and Et₃N (412 mg, 4.08 mmol) in CH₂Cl₂ (20 mL) was stirred at room temperature for 1 hour. NaBH(OAc)₃ (865 mg, 4.08 mmol) was added to the reaction under ice bath and the reaction mixture stirred at room temperature overnight. The solvent was removed by vacuum and the residue was purified by silica gel column chromatography (eluted 2.5% MeOH in dichloromethane) to give I-59-7 as a white solid (400 mg, yield: 82%).

[0831] Step G: Preparation of Compound I-59-8: A solution of I-59-7 (200 mg, 0.28 mmol) in TFA (15 mL) was stirred at room temperature for 2 hours. Solvent was removed and a solution of NH₃ (7N) in MeOH (10 mL) was added. The resulting mixture was concentrated and the residue was purified by silica gel column chromatography (eluted 10% MeOH in dichloromethane) to give I-59-8 as an oil (164 mg, yield: 96%).

[0832] Step H: Preparation of Compound I-59: To a solution of I-59-8 (127 mg, 0.21 mmol) and Et₃N (43 mg, 0.42 mmol) in CH₂Cl₂ (20 mL) was added MsCl (29 mg, 0.25 mmol) at 0° C. The reaction was stirred at room temperature for 1 h. TLC showed the reaction was complete. The combined organic layer was washed with H₂O and brine, dried over sodium sulfate, and concentrated in vacuo to afford 45 mg of I-59 as a white solid (yield: 31%). ¹H NMR (400 MHz, DMSO) δ: 8.33 (s, 1H), 7.87 (s, 1H), 7.67 (s, 1H) 7.45-7.56 (m, 3H), 4.35-4.32 (m, 2H), 4.08-4.02 (m, 4H), 3.57-3.54 (m, 3H), 3.17 (m, 1H), 2.88-2.83 (m, 6H), 2.54 (s, 3H), 2.20-1.47 (m, 12H), 1.25 (d, 3H). ESI-MS m/z: 688.84 (M+H).

Example 2: Synthesis of Compound I-48 in Table 1





[0833] Step A: Preparation of Compound I-48-2: A mixture of I-48-1 (300 mg, 1.40 mmol), 2-bromoethanol (347 mg, 2.80 mmol) and K_2CO_3 (772 mg, 5.60 mmol) in CH_3CN (30 mL) was stirred at 90° C. under N_2 overnight. TLC showed the reaction was complete. Solid was removed by filtration and solvent was removed under vacuum. The residue was purified by silica gel column chromatography (eluted 2.5% MeOH in dichloromethane) to give I-48-2 as a yellow oil (296 mg, yield: 82%).

[0834] Step B: Preparation of Compound I-48-3: To a mixture of I-48-2 (296 mg, 1.15 mmol) and Et_3N (232 mg, 2.30 mmol) in dichloromethane (20 mL) was added $MsCl$ (197 mg, 1.73 mmol) at 0° C. The reaction mixture was stirred at room temperature for 1 h. TLC showed the reaction was complete. Saturated aqueous $NaHCO_3$ was added to the reaction mixture. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by silica gel column chromatography (eluted petroleum) to give I-48-3 as an oil (270 mg, yield: 70%).

[0835] Step C: Preparation of Compound I-48-4: A mixture of I-48-3 (270 mg, 0.8 mmol), 5-formyl-4-methyl-1H-indole-2-carbonitrile (123 mg, 0.67 mmol) and Cs_2CO_3 (524 mg, 1.6 mmol) in DMF (10 mL) was stirred at 80° C. under N_2 overnight. Solid was removed by filtration before the reaction mixture was diluted with water and ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 , concentrated and purified by silica gel column chromatography (eluted 20% ethyl acetate in petroleum) to give I-48-4 as an oil (169 mg, yield: 50%). ESI-MS m/z: 424.54 (M+H).

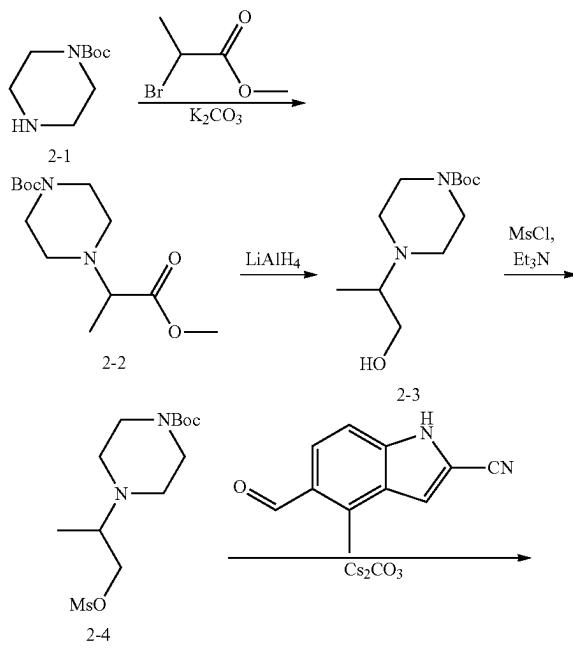
[0836] Step D: Preparation of Compound I-48-5: A mixture of I-48-4 (169 mg, 0.4 mmol), N-(piperidin-4-yl)-6-(

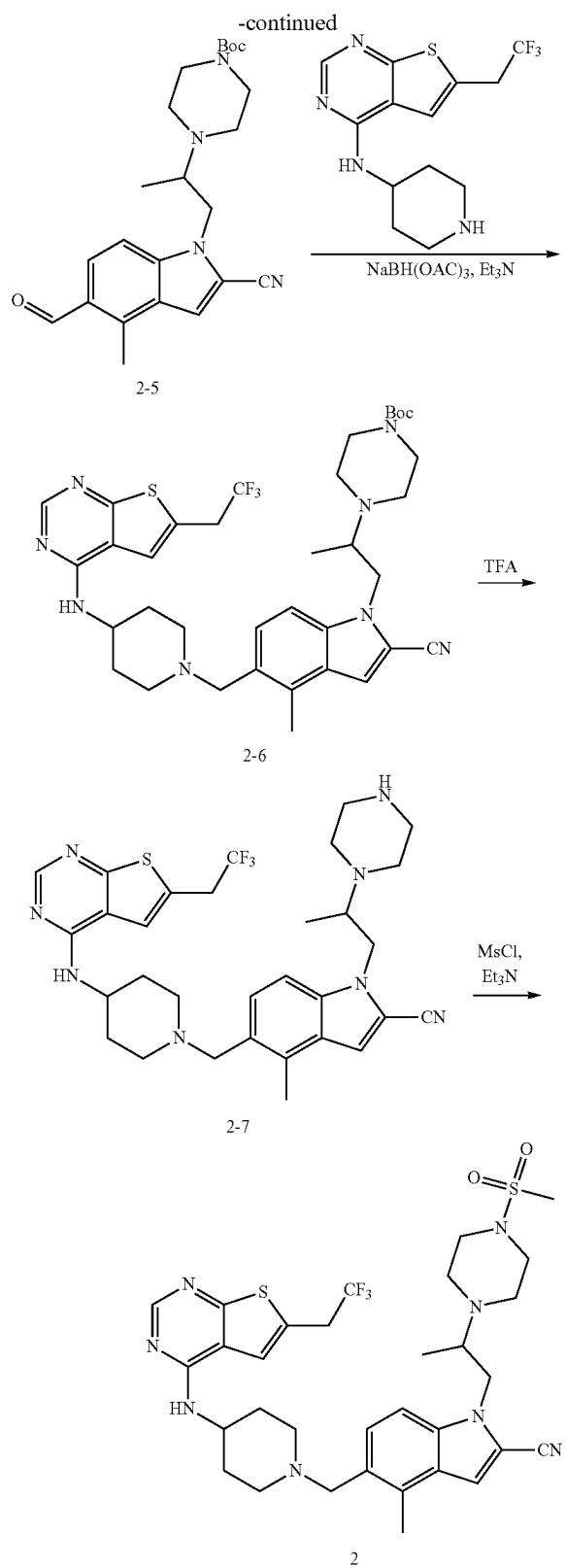
2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine (190 mg, 0.6 mmol) and Et_3N (242 mg, 2.4 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 1 hour. $NaBH(OAc)_3$ (508 mg, 2.4 mmol) was added to the reaction under ice bath cooling and the mixture reaction was stirred at room temperature overnight. Solvent was removed by vacuum and the residue was purified by silica gel column chromatography (eluted 2.5% MeOH in dichloromethane) to give I-48-5 as an oil (174 mg, yield: 60%). ESI-MS m z: 724.88 (M+H).

[0837] Step E: Preparation of Compound I-48-6: To a solution of I-48-5 (174 mg, 0.24 mmol) in CH_2Cl_2 (15 mL) was added TFA (5 mL). The reaction was stirred at room temperature for 2 hours before solvent was removed. A solution of $NH_3/MeOH$ (7N, 10 mL) was added and the resulting mixture was concentrated. The residue and purified by silica gel column chromatography (eluted 10% MeOH in dichloromethane) to give I-48-6 as an oil (120 mg, yield: 80%). ESI-MS m z: 624.30 (M+H).

[0838] Step F: Preparation of Compound I-48: To a mixture of I-48-6 (120 mg, 0.192 mmol) and Et_3N (39 mg, 0.384 mmol) in CH_2Cl_2 (10 mL) was added slowly methanesulfonyl chloride (33 mg, 0.288 mmol) in CH_2Cl_2 (5 mL) at -20° C. under N_2 . The reaction mixture was stirred at room temperature for 2 hours. TLC showed the reaction was complete. Saturated aqueous $NaHCO_3$ was added to the reaction mixture. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 , concentrated and purified by silica gel column chromatography (eluted 10% MeOH in dichloromethane) to give final product I-48 as a solid (54 mg, yield: 40%). 1H NMR (400 MHz, $CDCl_3$) δ: 8.48 (s, 1H), 7.38 (d, 1H), 7.21 (s, 1H), 7.15 (d, 1H), 7.08 (s, 1H), 5.10 (d, 1H), 4.34 (m, 2H), 4.24 (m, 1H), 3.87 (m, 2H), 3.65 (m, 4H), 2.93 (m, 5H), 2.71 (m, 2H), 2.63 (m, 2H), 2.57 (s, 3H), 2.29 (m, 2H), 2.21 (m, 2H), 2.10 (d, 2H), 1.61 (m, 2H), 1.31 (d, 6H); ESI-MS m z: 702.27 (M+H).

Example 3: Synthesis of Compound I-2 in Table 1





[0839] Step A: Preparation of Compound I-2-2: To a suspension of K_2CO_3 (3.6 g, 26.5 mmol) and tert-butyl

piperazine-1-carboxylate (1.0 g, 5.3 mmol) in CH_3CN (15 mL) was added methyl 2-bromopropanoate (2.2 g, 13.4 mmol). The reaction was stirred at 80° C. for 10 hours. TLC showed that the reaction was complete. The reaction mixture was allowed to cool to room temperature, then the solid filtered off and solvent removed under vacuum. The residue was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}=50:1$) to give tert-butyl 4-(1-methoxy-1-oxopropan-2-yl)piperazine-1-carboxylate (I-2-2) as a brown oil (1.4 g, yield: 99%).

[0840] Step B: Preparation of Compound I-2-3: To a solution of tert-butyl 4-(1-methoxy-1-oxopropan-2-yl)piperazine-1-carboxylate (540 mg, 2 mmol) in THF (10 mL) was added LiAlH_4 (1.0 mL, 2.5 mol in THF) at 0° C. dropwise. The reaction mixture was stirred at the same temperature for 2 hours. TLC showed that the reaction was complete. The reaction was quenched with EtOAc . The reaction was partitioned between EtOAc and H_2O , and the organic layer was washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum and the residue was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}=20:1$) to give tert-butyl 4-(1-hydroxypropan-2-yl)piperazine-1-carboxylate (I-2-3) as a brown oil (300 mg, yield: 65%).

[0841] Step C: Preparation of Compound 1-2-5: To a solution of tert-butyl 4-(1-hydroxypropan-2-yl)piperazine-1-carboxylate (200 mg, 0.82 mmol) and Et_3N (171 mg, 1.64 mmol) in CH_2Cl_2 (10 mL) was added MsCl (112 mg, 0.98 mmol) at 0° C. The reaction was stirred at room temperature for 30 min. The reaction was quenched with NaHCO_3 , washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum to give tert-butyl 4-(1-((methylsulfonyloxy)propan-2-yl)piperazine-1-carboxylate (I-2-4), used in the next step without further purification.

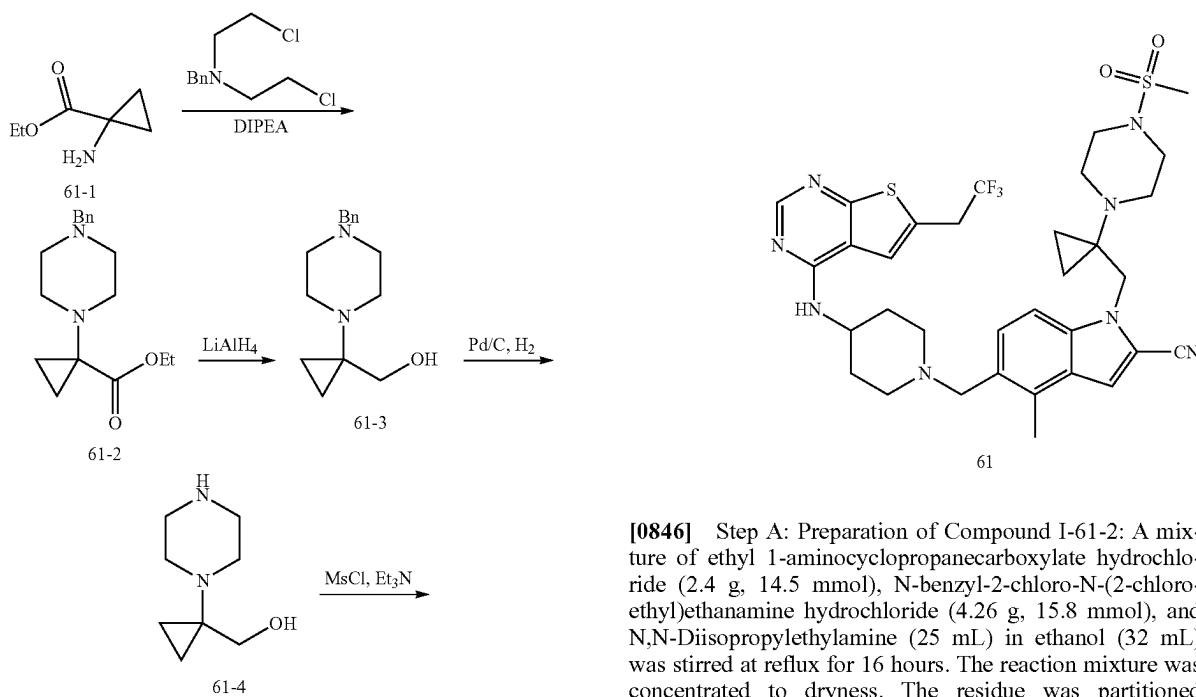
[0842] To a mixture of Cs_2CO_3 (682 mg, 2.1 mmol) and 5-formyl-4-methyl-1H-indole-2-carbonitrile (77 mg, 0.42 mmol) in DMF was added tert-butyl 4-(1-((methylsulfonyloxy)propan-2-yl)piperazine-1-carboxylate in DMF. The reaction was stirred at 100° C. for 10 hours. The reaction mixture was partitioned between EtOAc and H_2O , and the organic layer was washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether/ $\text{EtOAc}=5:1:3:1$) to give tert-butyl 4-(1-(2-cyano-S-formyl-4-methyl-1H-indol-1-yl)propan-2-yl)piperazine-1-carboxylate (I-2-5) as a yellow solid (90 mg, yield: 53%).

[0843] Step D: Preparation of Compound I-2-6: A mixture of tert-butyl 4-(1-(2-cyano-S-formyl-4-methyl-1H-indol-1-yl)propan-2-yl)piperazine-1-carboxylate (90 mg, 0.22 mmol), 6-(2,2,2-trifluoroethyl)-N-(piperidin-4-yl)thieno-[2,3-d]pyrimidin-4-amine (100 mg, 0.26 mmol) and Et_3N (130 mg, 1.32 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 1 hour before $\text{NaBH}(\text{OAc})_3$ (280 mg, 1.32 mmol) was added. The reaction mixture was stirred at room temperature overnight, then partitioned between CH_2Cl_2 and NaHCO_3 . The organic layer was washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum and the residue was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2:\text{MeOH}=50:1:20:1$) to give tert-butyl 4-(1-(2-cyano-4-methyl-S-((4-((6-(2,2,2-trifluoroethyl)amino)piperidin-1-yl)methyl)-1H-indol-1-yl)propan-2-yl)piperazine-1-carboxylate (I-2-6) as a yellow solid (130 mg, yield: 81%).

[0844] Step E: Preparation of Compound I-2-7: To a solution of tert-butyl 4-(2-(2-cyano-4-methyl-S-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indol-1-yl)-1-hydroxyethyl)piperidine-1-carboxylate (130 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) was added TFA (2 mL). The reaction was stirred for 4 hours before solvent was removed under vacuum. The residue was diluted with CH_2Cl_2 and washed with NaHCO_3 . The organic layer was washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum and the residue (I-2-7) was used without further purification as a yellow foam (100 mg, yield: 98%).

[0845] Step F: Preparation of Compound I-2: To a solution of 4-methyl-1-(2-(piperazin-1-yl)propyl)-S-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (60 mg, 0.1 mmol) and Et_3N (36 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) was added MsCl (21 mg, 0.2 mmol) at 0° C. The reaction was stirred at room temperature for 30 min. The reaction was quenched by NaHCO_3 , washed with brine and dried over Na_2SO_4 . Solvent was removed and the residue was purified by Prep-TLC ($\text{CH}_2\text{Cl}_2:\text{MeOH}=15:1$) to give 4-methyl-1-(2-(4-(methylsulfonyl)piperazin-1-yl)propyl)-S-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (compound I-2) as a white solid (10 mg, yield: 20%). ^1H NMR (400 MHz, CDCl_3) 8.48 (s, 1H), 7.36 (d, 1H), 7.20 (s, 1H), 7.00-7.15 (m, 2H), 5.16 (d, 1H), 4.20-4.40 (m, 2H), 4.00-4.10 (m, 1H), 3.60-3.70 (m, 4H), 3.10-3.30 (m, 5H), 2.80-2.90 (m, 4H), 2.77 (s, 3H), 2.57 (s, 3H), 1.56-2.53 (m, 8H), 1.08 (d, 3H). ESI-MS m/z: 689.25 ($\text{M}+\text{H}$).

Example 4: Synthesis of Compound I-61 in Table 1



[0846] Step A: Preparation of Compound I-61-2: A mixture of ethyl 1-aminocyclopropanecarboxylate hydrochloride (2.4 g, 14.5 mmol), N-benzyl-2-chloro-N-(2-chloroethyl)ethanamine hydrochloride (4.26 g, 15.8 mmol), and N,N-Diisopropylethylamine (25 mL) in ethanol (32 mL) was stirred at reflux for 16 hours. The reaction mixture was concentrated to dryness. The residue was partitioned between dichloromethane and water. Two layers were sepa-

rated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated. The residue was purified by silica gel column (pet. ether/EtOAc=1:0~10:1) to give ethyl 1-(4-benzylpiperazin-1-yl)cyclopropanecarboxylate (I-61-2, 1.8 g, yield: 43%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ : 7.37-7.27 (m, 5H), 4.19-4.13 (m, 2H), 3.54 (s, 2H), 3.00 (brs, 2H), 2.39 (brs, 2H), 1.31-1.26 (m, 5H), 7.52 (m 1H), 0.93-0.91 (m, 2H).

[0847] Step B: Preparation of Compound I-61-3: To a mixture of ethyl 1-(4-benzylpiperazin-1-yl)cyclopropanecarboxylate (880 mg, 3 mmol) in THF (12 mL) was added LiAlH_4 (290 mg, 6 mmol) slowly at 0° C. The resulting mixture was stirred at 0° C. for 1 h. Water (0.5 mL) was added, followed by ethyl acetate (20 mL). Solid was filtered off and solvent was removed. The residue was purified by silica gel column (pet. ether/EtOAc=3:1) to give (1-(4-benzylpiperazin-1-yl)cyclopropyl)methanol (I-61-3, 660 mg, yield: 88%) as a white solid.

[0848] Step C: Preparation of Compound I-61-4: A mixture of (1-(4-benzylpiperazin-1-yl)cyclopropyl)methanol (600 mg, 2.4 mmol) and Pd/C (10%, 50 mg) in ethanol (10 mL) was stirred at 50° C. overnight under H_2 . The reaction mixture was filtered and the filtrate concentrated to give (1-(piperazin-1-yl)cyclopropyl)methanol (I-61-4) as an oil (400 mg, yield: 96%). The crude product was used in the next step without further purification.

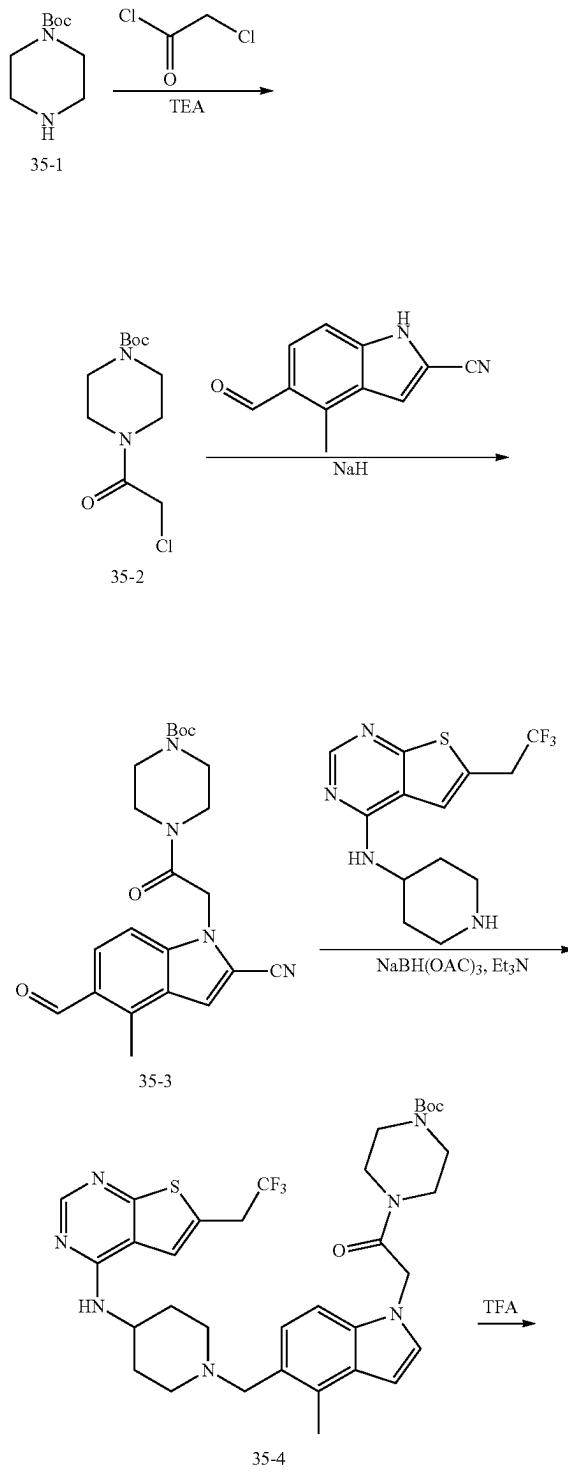
[0849] Step D: Preparation of Compound I-61-5: To a mixture of (1-(piperazin-1-yl)cyclopropyl)methanol (400 mg, 2.5 mmol) in dichloromethane (10 mL) was added Et_3N (1.1 mL, 7.5 mmol), followed by a mixture of methanesulfonyl chloride (925 mg, 7.5 mmol) in dichloromethane (5 mL). The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with water and CH_2Cl_2 . The organic layer was dried over Na_2SO_4 , and concentrated to give a crude product (1-(4-(methylsulfonyl)piperazin-1-yl)cyclopropyl)methyl methanesulfonate (I-61-5) as a brown oil (500 mg).

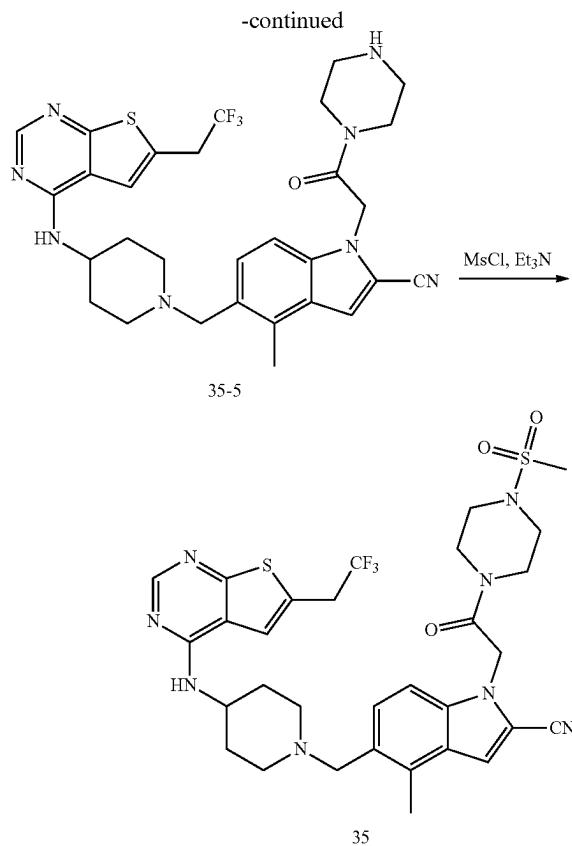
[0850] Step E: Preparation of Compound I-61-6: A mixture of crude (1-(4-(methylsulfonyl)piperazin-1-yl)cyclopropyl)methyl methanesulfonate (500 mg), 5-formyl-4-methyl-1H-indole-2-carbonitrile (200 mg, 1.1 mmol), and K_2CO_3 (800 mg, 5.8 mmol) in acetonitrile was stirred at 80° C. overnight. The mixture was filtered and the filtrate was concentrated to dryness. The residue was purified by silica gel column (pet. ether/EtOAc=3:1) to give 5-formyl-4-methyl-1-((1-(4-(methylsulfonyl)piperazin-1-yl)cyclopropyl)methyl)-1H-indole-2-carbonitrile (I-61-6, 330 mg) as a brown solid. ESI-MS m z: 401 ($\text{M}+\text{H}$).

[0851] Step F: Preparation of Compound I-61: A mixture of 5-formyl-4-methyl-1-((1-(4-(methylsulfonyl)piperazin-1-yl)cyclopropyl)methyl)-1H-indole-2-carbonitrile (330 mg, crude), N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine hydrochloride (391 mg, 1.1 mmol), and Et_3N (0.5 mL) in dichloromethane (12 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water and CH_2Cl_2 . The organic layer was separated, dried over Na_2SO_4 , and concentrated. The residue was purified by silica gel column (dichloromethane/methanol=50:1-30:1) to give a crude product. The crude product was purified by Prep-TLC with dichloromethane/methanol (7% NH_3/MeOH)=50:1 to give the product (compound I-61) as a colorless solid (12 mg). ESI-MS m z: 701 ($\text{M}+\text{H}$). ^1H NMR (400 MHz, CDCl_3) δ : 8.46 (s, 1H), 7.20-7.28 (m, 3H),

4.30-4.36 (m, 3H), 3.84 (brs, 2H), 3.61-3.68 (m, 2H), 3.09-3.13 (m, 6H), 2.76 (s, 3H), 2.64-2.66 (m, 4H), 2.59 (s, 3H), 2.40-2.48 (m, 2H), 2.14-2.18 (m, 2H), 1.87-1.90 (m, 2H), 0.79-0.82 (t, 2H), 0.61-0.64 (t, 2H).

Example 5: Synthesis of Compound 1-35 in Table 1





[0852] Step A: Preparation of Compound I-35-2: A mixture of tert-butyl piperazine-1-carboxylate (1.9 g, 10 mmol) and Et₃N (3 g, 30 mmol) in CH₂Cl₂ (40 mL) was stirred at 0° C. before 2-chloroacetyl chloride (2.2 g, 20 mmol) was added slowly. The reaction mixture was stirred at 0° C. under N₂ for 4 hr. TLC showed that the reaction was complete. The reaction mixture was partitioned between CH₂Cl₂ and H₂O, and the organic layer was washed with brine and dried over Na₂SO₄. Solvent was removed under vacuum and the residue (I-35-2) was used without further purifications as light yellow oil (2.5 g, yield: 95%).

[0853] Step B: Preparation of Compound I-35-3: To a mixture of N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine (1 g, 4 mmol), and 5-formyl-4-methyl-1H-indole-2-carbonitrile (540 mg, 3 mmol) in THF (10 mL) was added NaH (180 mg, 4.5 mmol) at 0° C. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was then partitioned between EtOAc and H₂O, and the organic layer was washed with brine and dried over Na₂SO₄. Solvent was removed under vacuum and the residue purified by silica gel column chromatography (pet. ether:EtOAc=10:1:1:1) to give tert-butyl 4-(2-(2-cyano-S-formyl-4-methyl-1H-indol-1-yl)acetyl)piperazine-1-carboxylate (I-35-3) as a light yellow solid (60 mg, yield: 4%).

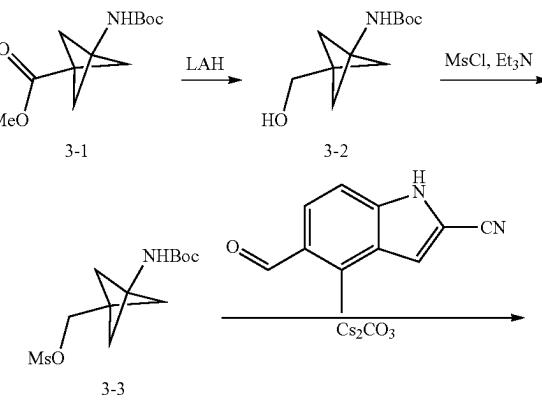
[0854] Step C: Preparation of Compound I-35-4: A mixture of methyl tert-butyl 4-(2-(2-cyano-5-formyl-4-methyl-1H-indol-1-yl)acetyl)piperazine-1-carboxylate (40 mg, 0.1 mmol), N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine hydrochloride (60 mg, 0.2 mmol) and Et₃N (60 mg, 0.6 mmol) in CH₂Cl₂ (5 mL) was stirred

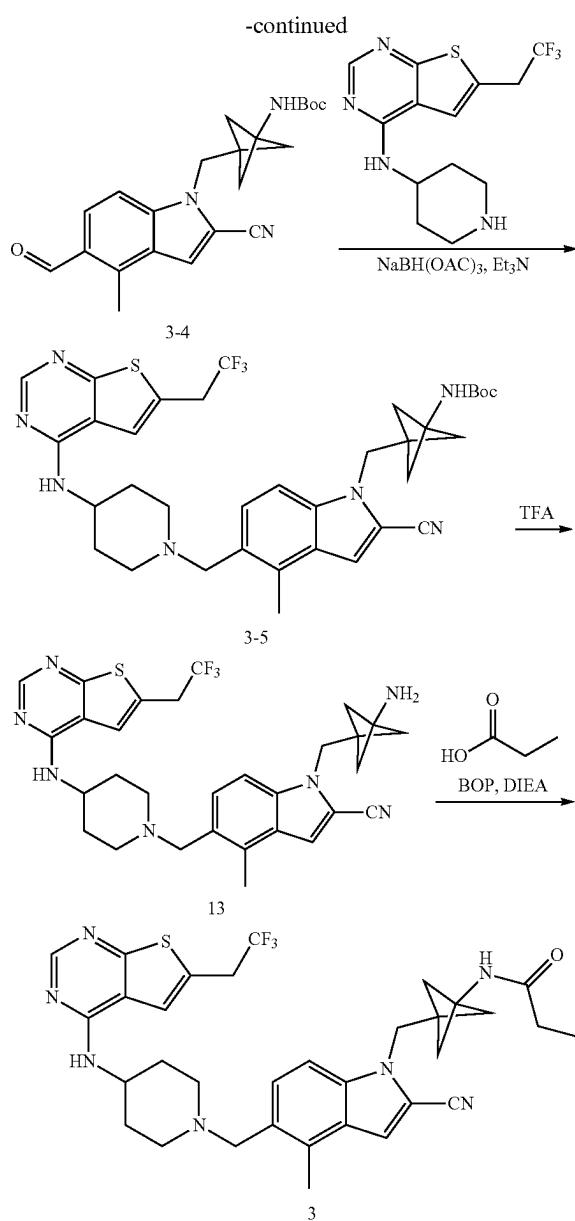
at room temperature for 2 hours. NaBH(OAc)₃ (120 mg, 0.6 mmol) was then added to the reaction with ice bath cooling. The reaction mixture was stirred at room temperature overnight. The reaction was partitioned between CH₂Cl₂ and NaHCO₃, and the organic layer was washed with brine and dried over Na₂SO₄. Solvent was removed under vacuum and the residue was purified by silica gel column chromatography (CH₂Cl₂:MeOH=100:1-20:1) to give tert-butyl 4-(2-(2-cyano-4-methyl-S-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indol-1-yl)acetyl)piperazine-1-carboxylate (I-35-4) as a yellow solid (40 mg, yield: 55%).

[0855] Step D: Preparation of Compound I-35-5: A solution of tert-butyl 4-(2-(2-cyano-4-methyl-S-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indol-1-yl)acetyl)piperazine-1-carboxylate (40 mg, 0.06 mmol) in HCl-MeOH (10 mL) was stirred at room temperature for 16 h. TLC showed that the reaction was complete. Solvent was removed under vacuum and the residue (I-35-5) was used without further purification in next step as a yellow solid (35 mg, yield: 85%).

[0856] Step E: Preparation of Compound I-35: To a mixture of 4-methyl-1-(2-oxo-2-(piperazin-1-yl)ethyl)-S-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (35 mg, 0.05 mmol) and Et₃N (15 mg, 0.15 mmol) in CH₂Cl₂ (10 mL) was slowly added MsCl (12 mg, 0.1 mmol) at 0° C. The reaction mixture was stirred at room temperature for 4 hours and then partitioned between CH₂Cl₂ and NaHCO₃. The organic layer was washed with brine and dried over Na₂SO₄. Solvent was removed under vacuum and the residue was purified by Prep-TLC (CH₂Cl₂:MeOH=20:1) to give 4-methyl-1-(2-(4-(methylsulfonyl)piperazin-1-yl)-2-oxoethyl)-S-((4-((6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1H-indole-2-carbonitrile (compound I-35) as a white solid (16 mg, yield: 56%). ¹H NMR (400 MHz, CDCl₃) 8.42 (s, 1H), 7.84–7.76 (m, 1H), 7.33–7.22 (m, 3H), 5.15 (s, 2H), 4.37–4.08 (m, 2H), 3.78 (s, 3H), 3.69–3.61 (m, 2H), 3.44–3.30 (m, 5H), 2.86 (s, 3H), 2.70–2.54 (m, 4H), 2.15–2.06 (m, 3H), 1.35–1.23 (m, 4H), 0.91–0.85 (m, 2H).

Example 6: Synthesis of Compounds II-13 and II-3
in Table 2





[0857] Step A: Preparation of Compound II-3-2: To a solution of II-3-1 (6 g, 25 mmol) in THF (100 mL) was added LiAlH₄ (1.5 g, 37 mol) in small portions at 0° C. The reaction was stirred until the TLC showed that the reaction was complete (about 2 h). The reaction mixture was quenched by addition of EtOAc and partitioned between EtOAc and H₂O. The organic layer was washed with brine and dried over Na₂SO₄. Solvent was removed under vacuum to give II-3-2 as a yellow solid (5.2 g, yield: 97%).

[0858] Step B: Preparation of Compound II-3-4: To a solution of II-3-2 (800 mg, 3.7 mmol) and Et₃N (740 mg, 7.4 mmol) in CH₂Cl₂ (10 mL) was added MsCl (428 mg, 4.4 mmol) at 0° C. The reaction was stirred at room temperature for 30 min, then quenched by addition of NaHCO₃, washed with brine and dried over Na₂SO₄. Solvent was removed under vacuum to give II-3-3, which was used in the next step without further purification.

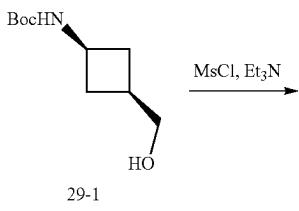
[0859] To a mixture of Cs₂CO₃ (3.0 g, 9.3 mmol) and 5-formyl-4-methyl-1H-indole-2-carbonitrile (800 mg, 4.4 mmol) in DMF (10 mL) was added II-3-3 in DMF. The reaction mixture was stirred at 100° C. for 10 h. The reaction mixture was then partitioned between EtOAc and H₂O. The organic layer was washed with brine and dried over Na₂SO₄. Solvent was removed under vacuum and the residue purified by silica gel column chromatography (pet. ether/EtOAc=5: 1~3:1) to give II-3-4 as a yellow solid (600 mg, yield: 42% according to alcohol).

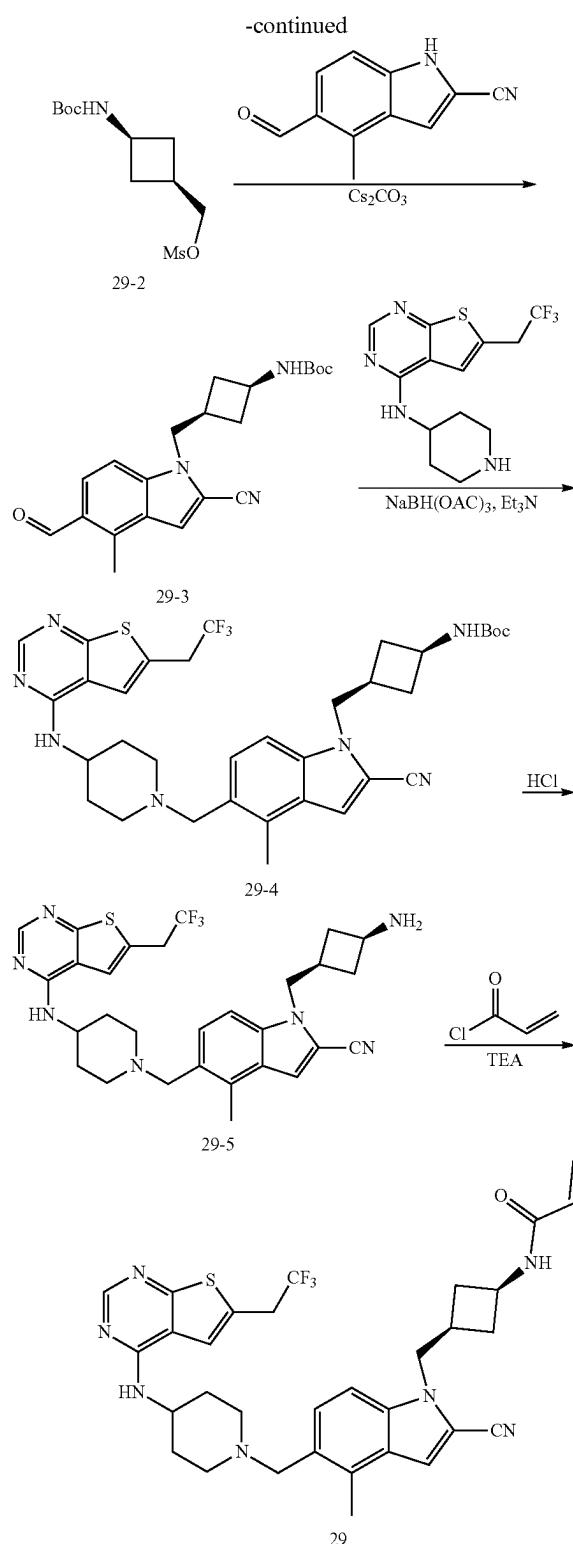
[0860] Step C: Preparation of Compound II-3-5: A mixture of II-3-4 (2.2 g, 5.8 mmol), 6-(2,2,2-trifluoroethyl)-N-(piperidin-4-yl)thieno-[2,3-d]pyrimidin-4-amine (2.3 g, 6.9 mmol) and Et₃N (3.5 g, 34 mmol) in CH₂Cl₂ (50 mL) was stirred at room temperature for 1 hour before NaBH(OAc)₃ (7.3 g, 34 mmol) was added to the reaction. The reaction mixture was stirred at room temperature overnight. The reaction mixture was then partitioned between CH₂Cl₂ and NaHCO₃. The organic layer was washed with brine and dried over Na₂SO₄. Solvent was removed under vacuum and the residue was purified by silica gel column chromatography (CH₂Cl₂:MeOH=50:1-20:1) to give II-3-5 as a yellow solid (3.9 g, yield: 98%).

[0861] Step D: Preparation of Compound II-13: To a solution of II-3-5 (3.9 g, 5.7 mmol) in CH₂Cl₂ (30 mL) was added TFA (20 mL). The reaction mixture was stirred for 4 h at room temperature. Solvent was removed under vacuum to afford a residue, which was diluted with CH₂Cl₂ and washed with NaHCO₃. The organic layer was washed with brine and dried over Na₂SO₄. Solvent was removed under vacuum and the residue was purified by silica gel column chromatography (CH₂Cl₂:MeOH=10:1) to give compound II-13 as a white foam (2.6 g, yield: 79%).

[0862] Step E: Preparation of Compound II-3: To a solution of propionic acid (450 mg, 6.0 mmol), BOP (3.0 g, 6.9 mmol) and iPr₂NEt (3.0 g, 23 mmol) in CH₂Cl₂ (30 mL) was added compound II-13 (2.7 g, 4.6 mmol). The reaction mixture was stirred at room temperature for 30 min before it was quenched by NaHCO₃, washed with brine and dried over Na₂SO₄. Solvent was removed and the residue purified by silica gel column chromatography (CH₂Cl₂:MeOH=10:1) to afford compound II-3 (1.8 g, yield: 61%). ¹H NMR (400 MHz, CDCl₃): 8.49 (s, 1H), 7.34 (d, 1H), 7.21 (s, 1H), 7.11 (d, 1H), 7.08 (s, 1H), 5.78 (s, 1H), 5.07 (d, 1H), 4.45 (s, 2H), 4.25 (m, 1H), 3.61-3.70 (m, 4H), 2.93 (m, 2H), 2.57 (s, 3H), 2.33-2.20 (m, 2H), 2.00-2.13 (m, 2H), 2.02 (s, 6H), 1.90 (s, 3H), 1.50-1.70 (m, 2H).

Example 7: Synthesis of Compound II-29 in Table 2





[0863] Step A: Preparation of Compound II-29-2: To a solution of II-29-1 (200 mg, 1.0 mmol) and Et₃N (202 mg, 2.0 mmol) in CH₂Cl₂ (10 mL) was added MsCl (172 mg, 1.5 mmol) at 0° C. The reaction mixture was stirred at room temperature overnight before water was added to the reac-

tion. The solution mixture was extracted with CH_2Cl_2 3 times. The organic layer was washed with brine and dried over Na_2SO_4 . The solution was filtered and concentrated to give II-29-2 as a white solid (250 mg, yield: 90%).

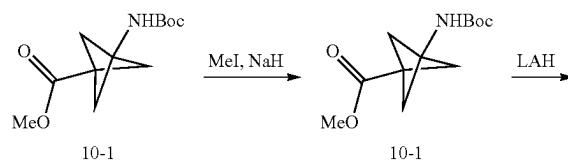
[0864] Step B: Preparation of Compound II-29-3: A mixture of II-29-2 (250 mg, 0.9 mmol), 5-formyl-4-methyl-1H-indole-2-carbonitrile (82 mg, 0.45 mmol) and Cs_2CO_3 (438 mg, 1.35 mmol) in DMF (6 mL) was stirred at 60° C. for 6 hours before water (15 mL) was added. The reaction mixture was extracted with ethyl acetate (20 mL×3). The combined organic solution was washed with brine and dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by silica gel column chromatography (33% EtOAc in pet. ether to 50% EtOAc in pet. ether) to give II-29-3 as a yellow solid (110 mg, yield: 33%).

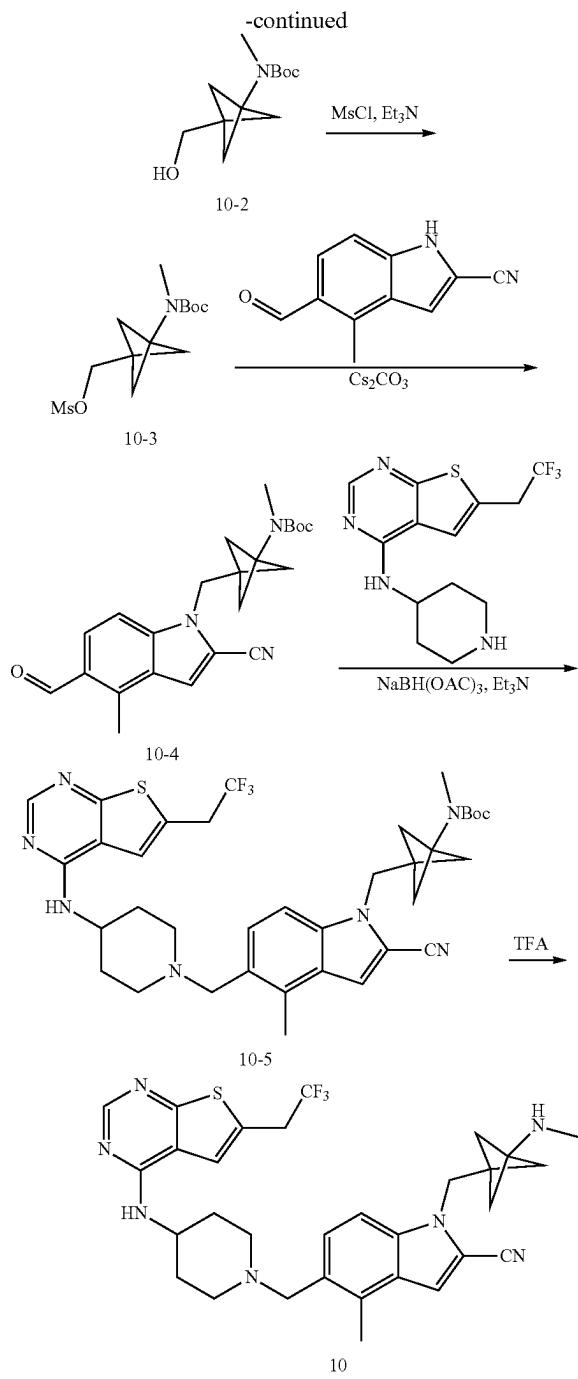
[0865] Step C: Preparation of Compound II-29-4: A mixture of II-29-3 (110 mg, 0.3 mmol), 6-(2,2,2-trifluoroethyl)-N-(piperidin-4-yl)thieno[2,3-d]pyrimidin-4-amine hydrochloride (116 mg, 0.3 mmol) and Et₃N (185 mg, 1.8 mmol) in CH₂Cl₂ (20 mL) was stirred at room temperature for 1 hour before NaBH(OAc)₃ (381 mg, 1.8 mmol) was added to the reaction under ice bath. The reaction mixture was stirred at room temperature overnight. Solvent was removed by vacuum and the residue was purified by silica gel column chromatography (2.5% MeOH in CH₂Cl₂) to give II-29-4 as a solid (180 mg, yield: 90%).

[0866] Step D: Preparation of Compound II-29-5: A solution of tert-butyl carbamate II-29-4 (180 mg, 0.27 mmol) in HCl/MeOH (10 mL) was stirred at room temperature for 2 hours. Solvent was removed and a solution of NH₃ (7N) in MeOH (10 mL) was added. The reaction mixture was stirred for 10 minutes before solvent was removed and the residue purified by silica gel column chromatography (10% MeOH in CH₂Cl₂) to give II-29-5 as an oil (100 mg, yield: 65%).

[0867] Step E: Preparation of Compound II-29: To a mixture of II-29-5 (100 mg, 0.17 mmol) and Et₃N (27 mg, 0.26 mmol) in CH₂Cl₂/THF (10 mL, 1:1) was add slowly acryloyl chloride (19 mg, 0.21 mmol) at -78°C under N₂. The mixture was stirred at room temperature for 15 min, then NH₃·MeOH was added. Solvent was removed and the residue was purified by silica gel column chromatography (10% MeOH in CH₂Cl₂) to give final product II-29 as a solid (78 mg, yield: 71%). ¹H NMR (400 MHz, DMSO): δ: 8.32 (s, 1H), 7.81~7.80 (d, 1H), 7.64 (s, 1H), 7.55 (s, 1H), 7.39 (s, 1H), 7.34~7.32 (m, 2H), 6.16~6.01 (m, 2H), 5.57~6.54 (m, 1H), 4.33~4.31 (d, 2H), 4.09~4.00 (m, 4H), 3.68 (s, 3H), 2.86~2.85 (m, 2H), 2.45~2.41 (m, 1H), 2.26~2.24 (m, 2H), 2.10 (brs, 2H), 1.99 (s, 1H), 1.89 (brs, 2H), 1.75~1.67 (m, 2H), 1.57 (brs, 2H); ESI-MS m/z: 622.40 (M+H).

Example 8: Synthesis of Compound II-10 in Table 2





[0868] Step A: Preparation of Compound II-10-1: To a solution of II-3-1 (300 mg, 1.24 mmol) in DMF (15 mL) was added NaH (210 mg, 2.5 mmol) at 0° C. The reaction mixture was stirred at the same temperature for 20 min before iodomethane (50 mg, 2.5 mmol) was added. The resulting mixture was stirred at room temperature for 3 h before water was added. The reaction mixture was extracted with ethyl acetate. The combined organic layer was concentrated to dryness. The residue was purified by silica gel column (pet. ether/EtOAc=5:1) to give II-10-1 (310 mg, yield: 97%) as a colorless oil.

[0869] Step B: Preparation of Compound II-10-2: To a mixture of methyl ester II-10-1 (310 mg, 1.21 mmol) in THF (10 mL) was slowly added LiAlH₄ at 0° C. The reaction mixture was stirred at room temperature for 1 h before water (0.2 mL) was added, followed by EtOAc. The reaction mixture was filtered and concentrated to dryness. The residue was purified by silica gel column (pet. ether/EtOAc=3:1) to give II-10-2 (237 mg, yield: 86%).

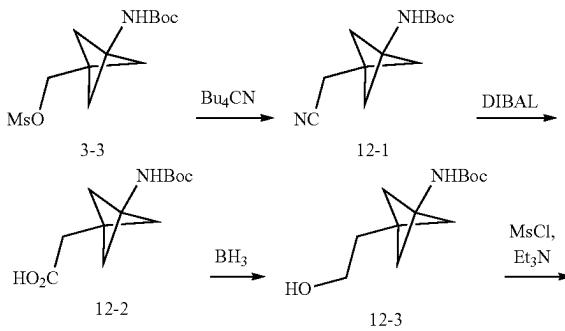
[0870] Step C: Preparation of Compound II-10-3: To a solution of II-10-2 (230 mg, 1.01 mmol) in CH₂Cl₂ was added Et₃N (0.42 mL, 3.03 mmol) at 0° C., followed by methanesulfonyl chloride (231 mg, 2.02 mmol). The resulting mixture was stirred at room temperature for 1 h. CH₂Cl₂ was added, the mixture was washed with NaHCO₃, and the organic layer was washed with brine and dried over Na₂SO₄. Solvent was removed to give II-10-3 (330 mg) as a brown oil.

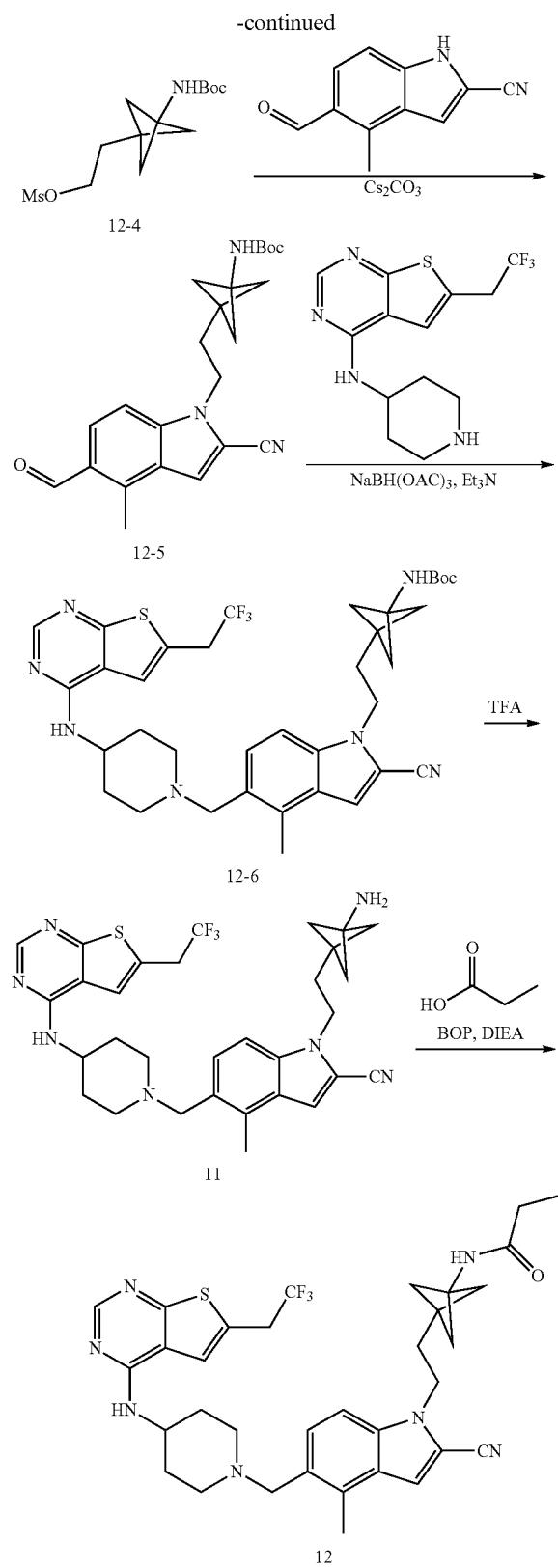
[0871] Step D: Preparation of Compound II-10-4: A mixture of crude II-10-3 (330 mg), 5-formyl-4-methyl-1H-indole-2-carbonitrile (200 mg, 1.08 mmol), and Cs₂CO₃ (1 g, 3.24 mmol) in DMF (10 mL) was stirred at 100° C. overnight. Water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by silica gel column (pet. ether/EtOAc=4:1) to give II-10-4 (177 mg, yield: 41%). ESI-MS m/z: 394 (M+H).

[0872] Step E: Preparation of Compound II-10-5: A mixture of II-10-4 (177 mg, 0.45 mmol), N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine hydrochloride (238 mg, 0.68 mmol), Et₃N (0.2 mL, 1.3 mmol), and NaBH(OAc)₃ in CH₂Cl₂ was stirred at room temperature overnight. The reaction mixture was diluted with CH₂Cl₂, washed with brine, and concentrated. The residue was purified by silica gel column (CH₂Cl₂/MeOH=30:1) to give II-10-5 (210 mg, yield: 67%). ESI-MS m/z: 694 (M+H).

[0873] Step F: Preparation of Compound II-10: A solution of II-10-5 (100 mg, 0.14 mmol), TFA (1 mL) in CH₂Cl₂ (5 mL) was stirred at room temperature for 3 h. The mixture was concentrated and the residue dissolved in CH₂Cl₂, washed with NaHCO₃, dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column (CH₂Cl₂/MeOH=30:1) to give II-10 (50 mg, yield: 58%). ESI-MS m/z: 594 (M+H). ¹H NMR (400 MHz, CDCl₃) δ: 8.48 (s, 1H), 7.38 (d, 1H), 7.22 (s, 1H), 71.5 (s, 1H), 7.13 (s, 1H), 5.23 (brs, 1H), 4.46 (s, 2H), 4.26-4.28 (m, 1H), 3.62-3.69 (m, 4H), 2.97 (d, 2H), 2.63 (s, 3H), 2.31-2.37 (m, 5H), 2.08-2.14 (m, 2H), 1.65-1.73 (m, 8H).

Example 9: Synthesis of Compounds II-11 and II-12 in Table 2





[0874] Step A: Preparation of Compound II-12-1: A mixture of II-3-3 and Bu_4CN (3.5 g, 13 mmol) in CH_3CN (30

mL) was stirred under reflux for 10 h until TLC showed that the reaction was complete. Solvent was removed and the residue was purified by silica gel column chromatography (pet. ether/EtOAc=3:1) to give II-12-1 as a white solid (1.0 g, yield: 86% according to alcohol).

[0875] Step B: Preparation of Compound II-12-2: To a solution of II-12-1 (460 mg, 2 mmol) in CH_2Cl_2 was added DIBAL-H (6 mmol) dropwise at -78°C . and the reaction mixture stirred at the same temperature for 2 h. The reaction was quenched with NH_4Cl and dried over Na_2SO_4 . Solvent was removed under vacuum and the residue was purified by silica gel column chromatography (pet. ether/EtOAc=5:1-3:1) to give II-12-2 as a white solid (200 mg, yield: 44%).

[0876] Step C: Preparation of Compound II-12-3: To a solution of II-12-2 (200 mg, 1 mmol) in THF was added BH_3/THF (4 mmol) dropwise at -78°C . The reaction was stirred for 10 h before it was quenched by MeOH. Solvent was removed under vacuum to give II-12-3 as a white solid (200 mg, yield: 99%), used in the next step without further purifications.

[0877] Step D: Preparation of Compound II-12-5: To a solution of II-12-3 (120 mg, 0.54 mmol) and Et_3N (109 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added MsCl (73 mg, 0.63 mmol) at 0°C . The reaction was stirred at room temperature for 30 min. The reaction was quenched by NaHCO_3 , washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum to give crude II-12-4, used in the next step without further purification.

[0878] To a mixture of Cs_2CO_3 (400 mg, 1.2 mmol) and 5-formyl-4-methyl-1H-indole-2-carbonitrile (70 mg, 0.3 mmol) in DMF (10 mL) was added II-12-4 in DMF. The reaction was stirred at 100°C . for 10 h. The reaction mixture was partitioned between EtOAc and H_2O . The organic layer was washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum to get a residue, which was purified by silica gel column chromatography (pet. ether/EtOAc=5:1-3:1) to give II-12-5 as a white solid (100 mg, yield: 52% 2 steps).

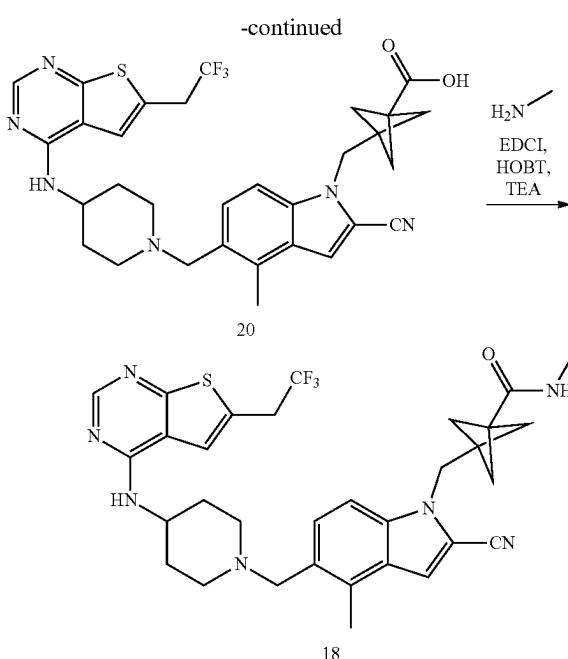
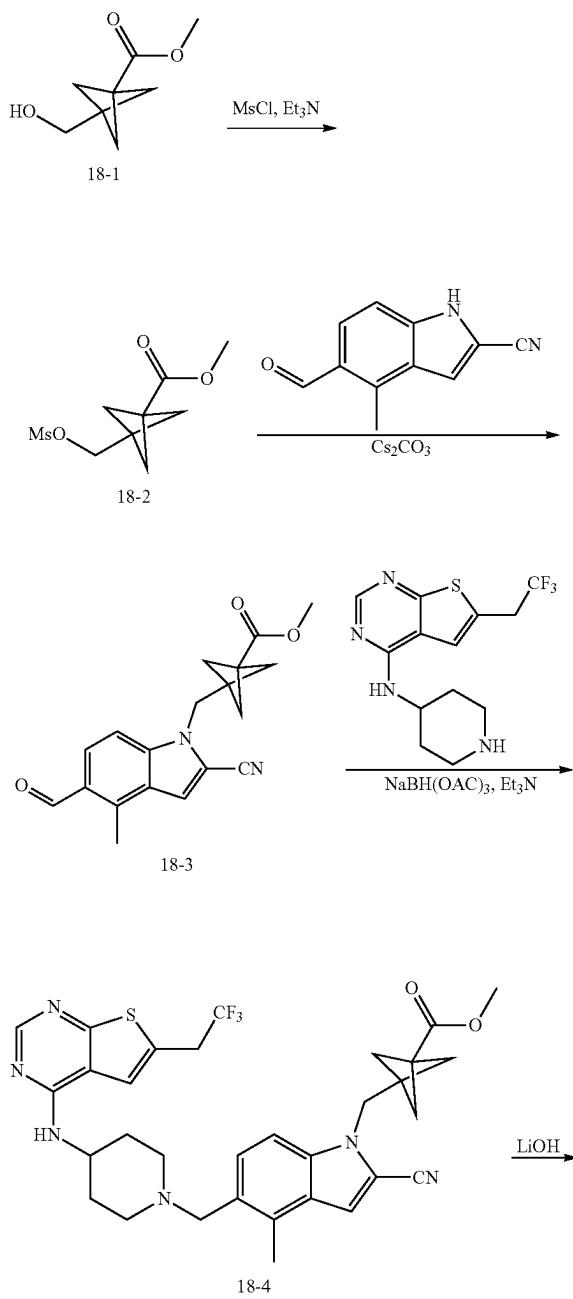
[0879] Step E: Preparation of Compound II-12-6: A mixture of II-12-5 (30 mg, 0.1 mmol), 6-(2,2,2-trifluoroethyl)-N-(piperidin-4-yl)thieno-[2,3-d]pyrimidin-4-amine (50 mg, 0.12 mmol) and Et_3N (60 mg, 0.6 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 1 hour before $\text{NaBH}(\text{OAc})_3$ (130 mg, 0.6 mmol) was added. The mixture reaction was stirred at room temperature overnight. The reaction was partitioned between CH_2Cl_2 and NaHCO_3 , and the organic layer was washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum to give a residue, which was purified by silica gel column chromatography (CH_2Cl_2 : MeOH=50:1-20:1) to give II-12-6 as a yellow solid (40 mg, yield: 60%).

[0880] Step F: Preparation of Compound II-11: To a solution of II-12-6 (130 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) was added TFA (2 mL). The reaction was stirred for 4 h at room temperature. Solvent was removed under vacuum to give a residue, which was diluted with CH_2Cl_2 and washed with NaHCO_3 . The organic layer was washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum to give compound II-11 as a yellow foam (100 mg, crude).

[0881] Step G: Preparation of Compound II-12: To a solution of propionic acid (6 mg, 0.07 mmol), BOP (40 g, 0.09 mmol), and iPr_2NEt (40 mg, 0.3 mmol) in CH_2Cl_2 (10 mL) was added compound II-11 (35 mg, 0.06 mmol), then the reaction was stirred at room temperature for 30 min. The

reaction was quenched by addition of NaHCO_3 , washed with brine and dried over Na_2SO_4 . Solvent was removed give a residue, which was purified by Prep-TLC (CH_2Cl_2 : $\text{MeOH}=10:1$) to give II-12 (10 mg, yield: 30%). ^1H NMR (400 MHz, CDCl_3) 8.46 (s, 1H), 7.51 (d, 1H), 7.17~7.22 (m, 3H), 5.85 (s, 1H), 5.79 (br, 1H), 4.23~4.32 (m, 3H), 3.86 (s, 2H), 3.66 (q, 2H), 3.12 (m, 2H), 2.58 (s, 3H), 2.53~2.40 (m, 2H), 2.20~2.14 (m, 6H), 1.99 (s, 6H), 1.86~1.90 (m, 2H), 1.12 (t, 3H). ESI-MS m/z: 650.25 ($\text{M}+\text{H}$).

Example 10: Synthesis of Compounds II-20 and II-18 in Table 2



[0882] Step A: Preparation of Compound II-18-2: A mixture of II-18-1 and Et_3N (600 mg, 6 mmol) in CH_2Cl_2 was stirred at 0°C . before MsCl (460 mg, 4 mmol) was added slowly. The reaction mixture was stirred at 0°C . under N_2 for 2 hr. TLC showed that the reaction was complete. The reaction mixture was partitioned between CH_2Cl_2 and H_2O , and the organic layer was washed with brine and dried over Na_2SO_4 . Solvent was removed under vacuum and the resulting compound (II-18-2) was used without further purification as a light yellow oil (460 mg, yield: 99%).

[0883] Step B: Preparation of Compound II-18-3: A mixture of crude II-18-2 (460 mg, 2 mmol), 5-formyl-4-methyl-1H-indole-2-carbonitrile (440 mg, 2.4 mmol) and Cs_2CO_3 (1.3 g, 4 mmol) in DMF (10 mL) was stirred at 60°C . for 4 hours. The reaction was cooled and the solid was removed by filtration. The reaction mixture was partitioned between EtOAc and H_2O , and the organic layer was washed by brine and dried over Na_2SO_4 . Solvent was removed under vacuum to give a residue, which was purified by silica gel column chromatography (pet. ether: $\text{EtOAc}=10:1$ -4:1) to give II-18-3 as a light yellow solid (280 mg, yield: 43%). ESI-MS m/z: 323 ($\text{M}+\text{H}$).

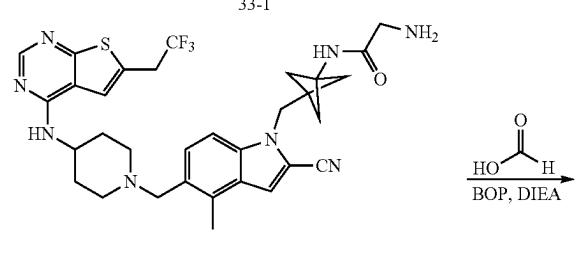
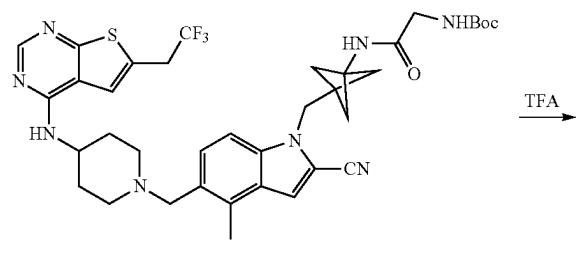
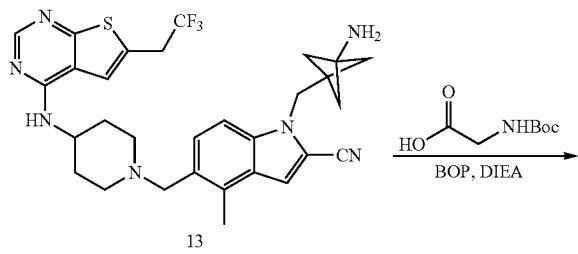
[0884] Step C: Preparation of Compound II-18-4: A mixture of II-18-3 (280 mg, 0.87 mmol), N-(piperidin-4-yl)-6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-amine hydrochloride (435 mg, 1.35 mmol) and Et_3N (400 mg, 4 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 2 hours before $\text{NaBH}(\text{OAc})_3$ (570 mg, 2.7 mmol) was added with ice bath cooling. The reaction mixture was stirred at room temperature overnight. The reaction was partitioned between CH_2Cl_2 and NaHCO_3 , and the organic layer was washed by brine and dried over Na_2SO_4 . Solvent was removed under vacuum to give a residue, which was purified by silica gel column chromatography (pet. ether: $\text{EtOAc}=10:1$ ~1:1) to give II-18-4 as a yellow solid (300 mg, yield: 56%). ESI-MS m/z: 623 ($\text{M}+\text{H}$).

[0885] Step D: Preparation of Compound II-20: To a solution of II-18-4 (180 mg, 0.3 mmol) in water (4 mL) and

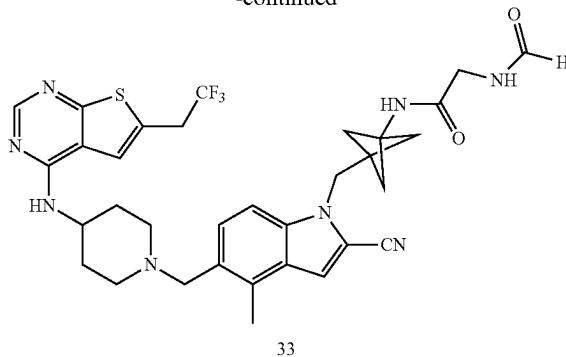
THF (10 mL) was added LiOH (24 mg, 0.6 mmol). The reaction was stirred at room temperature for 16 h. TLC showed that the reaction was complete. The pH of the mixture was adjusted to pH 4 with HCl (a.q., 1N). The reaction mixture was diluted with EtOAc and the organic layer was dried over Na_2SO_4 . Solvent was removed under vacuum to give compound II-20, which was used without further purification as a yellow solid (130 mg, yield: 75%).

[0886] Step E: Preparation of Compound II-18: A mixture of crude compound II-20 (40 mg, 0.07 mmol), methylamine hydrochloride (30 mg, 0.44 mmol), EDCI (40 mg, 0.28 mmol), HOBT (15 mg, 0.11 mmol) and Et_3N (50 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 40 hours. The reaction mixture was partitioned between CH_2Cl_2 and NaHCO_3 , and the organic layer was washed by brine and dried over Na_2SO_4 . The solvent was removed under vacuum to give a residue, which was purified by prep-TLC ($\text{CH}_2\text{Cl}_2\text{-MeOH}=10:1$) to provide compound II-18 as a white solid (15 mg, yield: 35%). ^1H NMR (400 MHz, MeOD) 8.31 (s, 1H), 7.54 (s, 1H), 7.41~7.32 (m, 3H), 4.45 (s, 2H), 4.24~4.17 (m, 1H), 3.89~3.81 (m, 2H), 3.74 (s, 2H), 3.08~3.05 (m, 2H), 2.66 (s, 3H), 2.60 (s, 3H), 2.40~2.34 (m, 2H), 2.07~2.03 (m, 2H), 1.88 (s, 6H), 1.76~1.70 (m, 2H). ESI-MS m/z: 622 (M+H).

Example 11: Synthesis of Compounds II-17 and II-33 in Table 2



-continued



[0887] Step A: Preparation of Compound II-33-1: A mixture of compound II-13 (190 mg, 0.33 mmol), 2-(tert-butoxycarbonyl)acetic acid (79 mg, 0.43 mmol), benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (229 mg, 0.5 mmol), and iPr₂NEt (0.3 mL, 1.65 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min. Water was added and the resulting mixture was extracted with CH_2Cl_2 . The organic layer was concentrated and the residue was purified by silica gel column ($\text{CH}_2\text{Cl}_2\text{-MeOH}=20:1$) to give 33-1 (210 mg, yield: 87%) as a solid. ESI-MS m/z: 737 (M+H).

[0888] Step B: Preparation of Compound II-17: A mixture of II-33-1 (230 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) and trifluoroacetic acid (5 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated to dryness and the residue was dissolved in $\text{NH}_3\text{/MeOH}$ (7N). The mixture was concentrated to dryness. The residue was purified by silica gel column to give compound II-17 as a yellow solid (210 mg, yield: 83%). ESI-MS m/z: 637 (M+H).

[0889] Step C: Preparation of Compound II-33: A mixture of compound II-17 (50 mg, 0.08 mmol), formic acid (8 mg, 0.16 mmol), benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (52 mg, 0.12 mmol), and iPr₂NEt (0.07 mL, 0.4 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min. Water was added and the resulting reaction mixture was extracted with CH_2Cl_2 . The organic layer was concentrated and the residue was purified by silica gel column ($\text{CH}_2\text{Cl}_2\text{-MeOH}=15:1$) to give compound II-33 as a solid (40 mg, yield: 77%). ^1H NMR (400 MHz, CD₃OD) δ: 8.30 (s, 1H), 8.09 (s, 1H), 7.52 (s, 1H), 7.30~7.34 (m, 3H), 4.51 (s, 2H), 4.20 (m, 1H), 3.67~3.85 (m, 6H), 3.07~3.10 (m, 2H), 2.59 (s, 3H), 2.34~2.44 (m, 2H), 2.05~2.08 (m, 2H), 1.96 (s, 6H), 1.62~1.76 (m, 2H). ESI-MS m/z: 664 (M+H).

Example 12: Fluorescence Polarization Assay

[0890] 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 rota-

tional 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 IC₅₀ determination.

[0891] Table 8 shows biological activities of selected compounds in a fluorescence polarization assay. Compound numbers correspond to the numbers and structures provided in Tables 1-7 and Examples 1-11.

TABLE 8

	Less than 50 nM (+++)	50 nM to less than 250 nM (++)	250 nM to 1000 nM (++)	Greater than 1000 nM (+)
Menin	I-6, I-8, I-10, I-12,	I-2, I-4, I-5, I-7,	I-1, I-3, I-24, I-26,	I-9, I-15, I-16, I-23,
MLL 4-43	I-13, I-14, I-18, I-20,	I-11, I-17, I-19, I-21,	I-44, I-45, I-52, I-53,	I-35, I-47, I-60, I-62,
IC ₅₀ (nM)	I-22, I-28, I-64, I-65, I-73, I-80, I-89, I-115, I-119, I-123, I-131, I-132, I-134, I-135, I-136, I-138, I-139, I-141, I-147, I-148, I-151, I-154, I-158, I-163, I-165, I-166, I-172, I-175, I-176, I-177, I-178, I-181, I-182, I-183, I-184, I-186, I-187, I-189, I-191, I-192, I-193, I-194, I-196, I-197, I-202, I-203, I-204, I-205, I-206, I-207, I-209, I-210, I-212, I-213, I-214, I-215, I-216, I-217, I-218, I-219, I-220, I-221, I-243, I-244, I-247, I-248, I-249, II-7, II-15, II-17, II-35, II-37, II-39	I-25, I-29, I-30, I-43, I-46, I-48, I-49, I-54, I-61, I-68, I-72, I-74, I-87, I-116, I-117, I-120, I-121, I-122, I-127, I-128, I-133, I-140, I-142, I-143, I-146, I-150, I-153, I-155, I-156, I-159, I-160, I-161, I-162, I-164, I-167, I-168, I-171, I-174, I-179, I-180, I-185, I-188, I-190, I-195, I-199, I-208, I-211, II-1, II-2, II-3, II-8, II-9, II-10, II-13, II-16, II-18, II-29, II-30, II-32, II-34, II-36, II-38, III-30a, III-38	I-55, I-56, I-57, I-58, I-59, I-66, I-67, I-82, I-118, I-157, I-173, I-201, II-4, II-5, II-6, II-11, II-14, II-31, II-33, III-48	I-170, I-200, II-12, II-20

Example 13: Homogenous Time-Resolve Fluorescence (HTRF) Assay

[0892] 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 (Eu³⁺-cryptate) donor to the allophycocyanin (XL665) acceptor, combined with time-resolved detection. An Eu³⁺-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.

Example 14: Menin Engagement Assay

[0893] Sample Preparation: 2.5 μL of 100 μM compound is added to 47.5 μL of 526 nM menin in PBS (5 μM compound 500 nM menin in 5% DMSO final concentration). The reaction is incubated at room temperature for

variable lengths of time and quenched with 2.5 μL of 4% formic acid (FA, 0.2% final concentration). Method: A Thermo Finnigan Surveyor Autosampler, PDA Plus UV detector and MS Pump along with an LTQ linear ion trap mass spectrometer were used to collect sample data under XCalibur software control. A 5 μL sample in “no waste” mode was injected onto a Phenomenex Jupiter 5 u 300A C₅ (guard column) 2×4.00 mm at 45° C. Mobile phase composition: Buffer A (95:5 water:acetonitrile, 0.1% FA) and Buffer B (acetonitrile, 0.1% FA). Gradient elution was used with an initial mobile phase of 85:15 (Buffer A:B) and a flow rate of 250 μL/min. Upon injection, 85:15 A:B was held for

1.3 min, Buffer B was increased to 90% over 3.2 min, held for 1 min, and then returned to initial conditions in 0.1 min and held for 2.4 min. The total run time is 8 min. A post-column divert valve employed to direct void volume salts to waste was used for the first 2 min of the sample method. Blank injection of Buffer A is used in between each of the sample injections. A needle wash of 1:1 acetonitrile: water with 0.1% FA was used. The electrospray ionization (ESI) source used a 300° C. capillary temperature, 40 units sheath gas flow, 20 units aux gas flow, 3 units sweep gas flow, 3.5 kV spray voltage, 120 V tube lens. Data Collection: Data collection was performed in the positive ion full scan mode 550-1500 Da, 10 microscans, 200 ms max ion time. Data analysis: Protein mass spectra were acquired as XCalibur datafiles. The best scans were added together using XCalibur Qual Browser. The spectra were displayed using “View/Spectrum List with a Display option to display all peaks. The Edit/Copy cell menu was used to copy the mass spectrum into the PC clipboard. The spectrum in the PC clipboard was pasted into Excel. The first two columns (m/z and Intensity) were kept and the third column (Relative) was deleted. The remaining two columns were then saved as a tab delimited file (m/z and intensity) as filename.txt from Excel. The Masslynx Databridge program was then used to convert the filename.txt tab delimited file to Masslynx format. In some cases, an external calibration using a (similarly converted) myoglobin spectrum was applied in

Masslynx to correct the m/z values of the menin protein m/z data. MaxEnt1 software from the MassLynx software suite was used for deconvolution of the mass spectrum to yield the average MW of the protein(s). The percentage of covalent adduct formation was determined from the deconvoluted spectrum and used to calculate the reaction rate (k) of the covalent reaction.

Example 15: Cell Culture

[0894] Cells expressing a genetic fusion abnormality and/or genetic mutation can be cultured and maintained according to a variety of existing methods. Cell lines are typically maintained under standard conditions, for example using recommended protocols from ATCC, DSMZ, or Children's Oncology Group cell bank (cogcell.org).

[0895] For example, NP23 cell lines (e.g., 106A, 748T, 1057d, and 961C) are established from single-cell suspensions prepared from BM (1×10^6 cells) and maintained in Iscove's Modified Dulbecco's Medium (IMDM) supplemented with 20% FBS, 100 mmol/L L-glutamine, and 100 g/mL penicillin/streptomycin (Invitrogen).

[0896] The AML cell lines OCI-AML3, SET2, MOLM13, and HL60 can be cultured under standard conditions using RPMI supplemented with 10% fetal bovine serum (FBS) and 1% Penicillin/Streptomycin (PS). OCI-AML2 cells can be cultured under standard conditions using alpha-MEM supplemented with 10% fetal bovine serum (FBS) and 1% Penicillin/Streptomycin (PS).

[0897] The MLL-amplified myeloid cell line UoC-M1 can be cultured under standard conditions using 90% McCoy's 5a medium supplemented with +10% heat-inactivated FBS. The cells are seeded at approximately 0.5×10^6 cells/mL and split at a ratio 1:2 every 2-3 days to maintain cell densities of approximately $0.5\text{--}1.5 \times 10^6$ cells/ml. Adherent cells can be detached by tapping or using trypsin/EDTA.

[0898] Ewing's sarcoma cell line TC-71 can be grown in a base medium of Iscove's Modified Dulbecco's Medium supplemented with 20% Fetal Bovine Serum, 4 mM L-Glutamine, and 1×ITS (5 pg/mL insulin, 5 µg/mL transferrin, 5 ng/mL selenous acid) at 37.0° C. and in 5% CO₂ and 20% O₂.

[0899] Ewing's sarcoma cell line A-673 can be grown in Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum.

[0900] Cell line authentication testing (ATCC) can be used to verify the identity and purity of human cell lines.

[0901] Murine leukemia cells are cultured in DMEM supplemented with 15% FBS, 1% PS, and cytokines (SCF 100 ng/µl, IL-3 20 ng/µl, and IL-6 20 ng/µl).

Example 16: Cell Proliferation Assay

[0902] The ability of a compound of the present disclosure to inhibit the growth of selected cells was 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) or MTT cell proliferation assay (ATCC® 30-1010K) or cell counting. Compounds of the present disclosure can be tested in both acute myeloid leukemia cell lines or Ewing's sarcoma cell lines and control cell lines without the genetic

abnormality or mutation being investigated (e.g., K562, REH, U937, KG-1, and/or HL-60). Selected cells can include, but are not limited to, cells such as human leukemia cell, acute myeloid leukemia cell, Ewing's sarcoma cell (e.g., SK-NEP-1, EW5, EW8, TC-71, TC-106, CHLA258, CHLA-9, CHLA-10, SK-ES-1, Hs 822.T, A-673, A-4573, Hs 863.T, RD-ES, CHLA-25, CHLA-32, CHLA-99, COG-E-352, TC-32, SK-N-MC), VCaP, LNCaP, 22RV1, DU145, LNCaP-AR, MV4; 11, KOPN-8, ML-2, MOLM-13, RS4; 11, SEM, bone marrow cells (BMCs), myeloblast cell, lymphoblast cell, NUP98 gene fusion cell (e.g., NUP98-PHF23 cell), NUP98-PHF23 (NP23) myeloblast cell (e.g., 961C), NUP98-PHF23 (NP23) lymphoblast cell (e.g., 748T, 106A), cell with an NPM1 mutation (e.g., OCI-AML3), cell without an NPM1 mutation, cell with a DNMT3A mutation (e.g., OCI-AML3, OCI-AML2, SET2), cell without a DNMT3A mutation, cell with a FLT3 mutation, cell without a FLT3 mutation, cell with an IDH1 mutation, cell without an IDH1 mutation, cell with an IDH2 mutation, cell without an IDH2 mutation, cell with a mixed lineage leukemia (MLL) gene amplification (e.g., UoC-M1, 2L1), cell without a mixed lineage leukemia (MLL) gene amplification, MLL-AF9, MLL-AF4, MLL-ENL, HM-2, E2A-HLF, REH, U937, HL-60, NB4, K562, KG-1, and OCI-AML2 cells. Cells were plated at relevant concentrations, for example about 1×10^5 – 2×10^5 cells per well in a 96-well plate. A compound of the present disclosure was added at a concentration up to about 2 µM with seven or eight, 2-fold serial dilutions for each compound. Cells were incubated at 37° C. for a period of time, for example, 72 hours, then cells in the control wells were counted. Media was changed to restore viable cell numbers to the original concentration, and compounds were re-supplied. Proliferation was measured about 72 hours later or about 96 hours later using Promega CellTiter-Glo® reagents or MTT reagents, as per kit instructions. One or more compounds disclosed herein, e.g., a compound provided in Table 1, 2, 3, 4, 5, 6 or 7 having an IC₅₀ value of less than 1 µM, preferably less than 100 nM or less than 50 nM (a measurement reflecting the ability of the compound to disrupt the menin-MLL interaction, measured in accordance with Example 12), are expected to inhibit the proliferation of acute myeloid leukemia cell lines or Ewing's sarcoma cell lines while having a much weaker inhibitory effect on the proliferation of the control cell lines (e.g., K562 and REH cells) at the same concentration. Certain compounds disclosed herein exhibited GI₅₀ values in the range of 5 nM to 25 nM when tested in MV4; 11 cells (MLL-AF4 AML), MOLM13 cells (MLL-AF9 AML), murine bone marrow cells (rRMLL-AF9 AML), KOPN8 (MLL-ENL AML) cells, RS4; 11 cells (MLL-AF4 ALL, MLL-rearranged, MEIS1^{high}), or SEM (MLL-AF4 ALL) cells. As used in the Examples, the GI₅₀ value of a compound is the concentration of the compound for 50% of maximal inhibition of cell proliferation. It is expected that one or more menin inhibitors disclosed herein are able to inhibit growth of acute myeloid leukemia cells or Ewing's sarcoma cells by 50% at a concentration no more than 100 nM, preferably at a concentration no more than 50 nM, in some situations exhibiting GI₅₀ values in the range of 1 nM to 50 nM.

[0903] Table 9 shows biological activities of selected compounds in a cell proliferation assay. Compound numbers correspond to the numbers and structures provided in Tables 1-7 and Examples 1-11.

TABLE 9

	Less than 10 nM (++++)	10 nM to less than 50 nM (+++)	50 nM to less than 250 nM (++)	250 nM to 1000 nM (+)
MLL-AF9	I-132, I-135, I-151,	I-10, I-80, I-138,		I-9
BMC GI ₅₀ (nM)	I-163, I-165, I-172, I-177, I-183, I-199, I-203, I-205, I-207, I-214	I-139, I-171, I-174, I-175, I-176, I-181, I-217		

Example 17: Colony-Forming Unit Assays

[0904] Colony-forming unit assays are performed by pre-treating test cells with a menin inhibitor disclosed herein or vehicle control for several days (e.g., about 6 days) and then plating equal numbers of viable cells in soft agar for approximately 2-4 weeks in the absence of compound. The cells being tested can include, but are not limited to, human leukemia cell, acute myeloid leukemia cell, Ewing's sarcoma cell (e.g., SK-NEP-1, EW5, EW8, TC-71, TC-106, CHLA258, CHLA-9, CHLA-10, SK-ES-1, Hs 822.T, A-673, A-4573, Hs 863.T, RD-ES, CHLA-25, CHLA-32, CHLA-99, COG-E-352, TC-32, SK-N-MC), VCaP, LNCaP, 22RV1, DU145, LNCaP-AR, MV4; 11, KOPN-8, ML-2, MOLM-13, RS4; 11, SEM, bone marrow cells (BMCs), myeloblast cell, lymphoblast cell, NUP98 gene fusion cell (e.g., NUP98-PHF23 cell), NUP98-PHF23 (NP23) myeloblast cell (e.g., 961C), NUP98-PHF23 (NP23) lymphoblast cell (e.g., 748T, 106A), cell with an NPM1 mutation (e.g., OCI-AML3), cell without an NPM1 mutation, cell with a DNMT3A mutation (e.g., OCI-AML3, OCI-AML2, SET2), cell without a DNMT3A mutation, cell with a FLT3 mutation, cell without a FLT3 mutation, cell with an IDH1 mutation, cell without an IDH1 mutation, cell with an IDH2 mutation, cell without an IDH2 mutation, cell with a mixed lineage leukemia (MLL) gene amplification (e.g., UoC-M1, 2L1), cell without a mixed lineage leukemia (MLL) gene amplification, MLL-AF9, MLL-AF4, MLL-ENL, HM-2, E2A-HLF, REH, U937, HL-60, NB4, K562, KG-1, and OCI-AML2 cells. It is expected that pre-treatment with the menin inhibitor leads to a significant reduction in colony formation in soft agar.

[0905] NP23 BM colony-forming unit (CFU) assays are performed using MethoCult GF M3434 (STEMCELL Technologies; www.stemcell.com), according to the manufacturer's instructions. One or more of the menin inhibitors disclosed herein are solubilized in dimethyl sulfoxide (DMSO; Sigma). Cells are seeded at 2×10⁵/mL for drug treatment assays.

Example 18: RT-PCR Analysis of Protein Downstream Targets

[0906] The effect of a compound of the present disclosure on expression of one or more downstream targets of menin, an MLL protein, NUP98 fusion protein, FMS-like tyrosine kinase-3 (FLT3), isocitrate dehydrogenase 1 (IDH1), isocitrate dehydrogenase 2 (IDH2), nucleophosmin (NPM1), or DNA (cytosine-5)-methyltransferase 3A (DNMT3A) is assessed by RT-PCR. Test 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. The cells being tested

can include, but are not limited to, human leukemia cell, acute myeloid leukemia cell, Ewing's sarcoma cell (e.g., SK-NEP-1, EW5, EW8, TC-71, TC-106, CHLA258, CHLA-9, CHLA-10, SK-ES-1, Hs 822.T, A-673, A-4573, Hs 863.T, RD-ES, CHLA-25, CHLA-32, CHLA-99, COG-E-352, TC-32, SK-N-MC), VCaP, LNCaP, 22RV1, DU145, LNCaP-AR, MV4; 11, KOPN-8, ML-2, MOLM-13, RS4; 11, SEM, bone marrow cells (BMCs), myeloblast cell, lymphoblast cell, NUP98 gene fusion cell (e.g., NUP98-PHF23 cell), NUP98-PHF23 (NP23) myeloblast cell (e.g., 961C), NUP98-PHF23 (NP23) lymphoblast cell (e.g., 748T, 106A), cell with an NPM1 mutation (e.g., OCI-AML3), cell without an NPM1 mutation, cell with a FLT3 mutation, cell without a FLT3 mutation, cell with an IDH1 mutation, cell without an IDH1 mutation, cell with an IDH2 mutation, cell without an IDH2 mutation, cell with a mixed lineage leukemia (MLL) gene amplification (e.g., UoC-M1, 2L1), cell without a mixed lineage leukemia (MLL) gene amplification, MLL-AF9, MLL-AF4, MLL-ENL, HM-2, E2A-HLF, REH, U937, HL-60, NB4, K562, KG-1, and OCI-AML2 cells. 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, 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, for example one or more of Hoxa9, DLX2, PBX3, and Meis1.

[0907] In NUP98 gene fusion cells, effective inhibition of the menin-MLL interaction is expected to result in the downregulation of one or more downstream targets, for example one or more of Hoxa5, Hoxa7, Hoxa9, Hoxa10, Hoxb5, Meis1, Mir196b, and/or Bahcc1.

[0908] In cells with an NPM1 mutation, effective inhibition of the menin-MLL interaction is expected to result in the downregulation of one or more downstream targets, for example one or more of Hoxa9, Hoxa10, Hoxb2, Hoxb3, Hoxb4, Meis1, and/or FOt3.

[0909] In cells with a DNMT3A mutation, effective inhibition of the menin-MLL interaction is expected to result in the downregulation of one or more downstream targets, for example one or more of Hoxa9, Hoxb3, Hoxb8, and/or Meis1.

[0910] In Ewing's sarcoma cells, effective inhibition of the menin-MLL interaction is expected to result in the downregulation of one or more downstream targets, for example one or more of Hoxd10, Hoxd11, and/or Hoxd13.

[0911] Example 19: Cellular ThermalShift Assay (CETSA). For the cell lysate CETSA experiments, cultured cells from cell lines expressing menin 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×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 (50 µL) 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×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.

[0912] 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 (30 µL) and lysed using 2 cycles of freeze-thawing with liquid nitrogen. The soluble fractions are isolated and analyzed by western blot.

[0913] 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 50 µL aliquots and heated at different temperatures. Soluble fractions are isolated and analyzed by western blot.

[0914] It is expected that the aliquots treated with one or more of the menin inhibitors disclosed herein exhibit increased thermal stabilization of menin compared to the control aliquots.

Example 20: CETSA-like dot-blot experiments onpurifiedproteins

[0915] 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×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.

[0916] 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).

Example 21: FACS Analysis of Cell Surface cd11b Expression

[0917] The ability of a compound of the present disclosure to induce the expression of the differentiation marker cd11b on selected cells was tested using a flow cytometry based assay. Cells were plated at relevant concentrations, for example about 2×10^5 - 4×10^5 cells per mL in a tissue culture flask. A compound of the present disclosure was added at a concentration up to about 2 µM with 3 or 4, 10-fold serial dilutions for each compound. Cells were incubated at 37° C. for a period of time, for example, approximately 3 days, and cells in the control wells were counted. Media was changed to restore viable cell numbers to the original concentration, and compounds were re-supplied. Cell surface expression of cd11b was measured about 72-96 hours later using standard cell staining methods. Cells were washed with saline with 1% fetal bovine serum, incubated with fluorescently labeled antibody specific for cd11b, washed extensively to remove excess antibody, and assessed for staining by flow cytometry. One or more compounds disclosed herein, e.g., a compound provided in Table 1, 2, 3, 4, 5, 6 or 7 having an IC₅₀ value of less than 1 µM, preferably less than 100 nM (a measurement reflecting the ability of the compound to disrupt the menin-MLL interaction, measured in accordance with Example 12), are expected to induce expression of cd11b on the surface of acute myeloid leukemia cell lines or Ewing's sarcoma cells. As shown in FIG. 4, expression of differentiation marker cd11b was elevated in Compound A-treated OCI-AML3 cells relative to DMSO-treated cells.

Example 22: Cell Apoptosis Assay Using Flow Cytometry

[0918] Cells expressing a genetic abnormality and/or mutation disclosed herein are subjected to an apoptosis assay in the presence or absence of a menin inhibitor disclosed herein. A compound of the present disclosure is added at a concentration up to about 10 µM (e.g., at a concentration of about 50 nM, 100 nM, 200 nM, 500 nM, 1 µM, 2 µM, 5 µM, or 10 µM). Cells are analyzed at one or more time points after treatment (e.g., at approximately 6 hours, 12 hours, 24 hours, 2 days, 3 days, 5 days, or 7 days after treatment).

[0919] Changes in cell apoptosis in the presence of a menin inhibitor disclosed herein can be detected by flow cytometry by Annexin V staining. Annexin V is a protein that has a high affinity for the membrane phosphatidylserine (PS), which is translocated from the inner face of the plasma membrane to the cell surface after cells initiate apoptosis. Once on the cell surface, PS can be detected by staining with a fluorescent conjugate of Annexin V (e.g., Annexin V-FITC). Detection can be analyzed by flow cytometry or fluorescence microscopy. Apoptosis can be differentiated from necrosis when Annexin V staining is performed in combination with staining with a cell viability dye (e.g., propidium iodide (PI), SYTOX Blue (Invitrogen), or DAPI). Viable cells are counted by flow cytometry using a viability stain. Cells are split and replated with fresh media and drug every 3-4 days. Apoptosis assays can be conducted using Annexin V-FITC Apoptosis Detection Kit I following the

manufacturer's recommended protocol. It is expected that treatment with one or more of the menin inhibitors disclosed herein can lead to increased apoptosis of acute myeloid leukemia or Ewing's sarcoma cells compared with vehicle-treated cells.

Example 23: Pharmacokinetic Studies in Mice

[0920] 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, e.g., 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×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).

Example 24: Efficacy Study in Mouse Xenograft Tumor Model

[0921] One or more compounds disclosed herein, e.g., a compound provided in Table 1, 2, 3, 4, 5, 6 or 7 having an IC₅₀ value of less than 1 µM, preferably less than 50 nM (a measurement reflecting the ability of the compound to disrupt the menin-MLL interaction, measured in accordance with Example 12), are expected to provide suppression of acute myeloid leukemia or Ewing's sarcoma tumor growth in mouse xenograft models. Immunocompromised 8-10 week-old female nude (nu/nu) mice were used for in vivo efficacy studies in accordance with IACUC guidelines. The nude mice were implanted subcutaneously with approximately 5×10⁶ selected cells/mouse. The selected cells can include, but are not limited to, human acute myeloid leukemia cells (e.g., NUP98 gene fusion cell (e.g., NUP98-PHF23 cell), NUP98-PHF23 (NP23) myeloblast cell (e.g., 961C), NUP98—PHF23 (NP23) lymphoblast cell (e.g., 748T, 106A), cell with an NPM1 mutation (e.g., OCI-AML3), cell with a FLT3 mutation, cell with an IDH1 mutation, cell with an IDH2 mutation, cell with a DNMT3A mutation (e.g., OCI-AML3, OCI-AML2, SET2), cell with a mixed lineage leukemia (MLL) gene amplification (e.g., UoC-M1, 2L1)) or Ewing's sarcoma cells (e.g., SK-NEP-1, EW5, EW8, TC-71, TC-106, CHLA258, CHLA-9, CHLA-10, SK-ES-1, Hs 822.T, A-673, A-4573, Hs 863.T, RD-ES, CHLA-25, CHLA-32, CHLA-99, COG-E-352, TC-32, SK-N-MC) such as those available from ATCC. When the tumor reached a size of approximately 150 to 250 mm³, the tumor-bearing mice were randomly assigned to a vehicle control or a compound treatment group (8 mice per group). Mice in each treatment group were administered a compound of the present disclosure by oral gavage or intraperitoneal injection in an appropriate amount and frequency at the dosage indicated (e.g., 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 were measured twice weekly. Tumor volumes were calculated by measuring two perpendicular diameters with calipers ($V=(length \times width^2)/2$). Percentage tumor growth inhibition (% TGI=1-[change of tumor volume in treatment group/change of tumor volume in control group]*100) was used to evaluate anti-tumor efficacy. Statistical significance was evaluated using a one-tailed, two sample ttest. P<0.05 is considered statistically significant. It is expected that the animal group being treated with one or more of the menin inhibitors disclosed herein exhibits reduction in tumor volume compared to the vehicle control group. A compound provided in Table 1, 2, 3, 4, 5, 6 or 7 having an IC₅₀ value of less than 50 nM (a measurement reflecting the ability of the compound to disrupt the menin-MLL interaction, measured in accordance with Example 12) is expected to inhibit tumor growth and induced tumor regression relative to the vehicle control group in a dose-dependent manner.

[0922] As shown in FIG. 5, a compound provided in Table 8 having an IC₅₀ value of less than 50 nM (a measurement reflecting the ability of the compound to disrupt the menin-HLL interaction, measured in accordance with Example 12), labeled Compound A throughout the figures, inhibited OCI-AML3 tumor growth relative to the vehicle control group and relative to quizartinib (FLT3 inhibitor) treated and EPZ5676 (DOT1L inhibitor) treated mice in a dose-dependent manner.

Example 25: Efficacy Study in Xenotransplantation Mouse Model

[0923] One or more compounds disclosed herein, e.g., a compound provided in Table 1, 2, 3, 4, 5, 6 or 7 having an IC₅₀ value of less than 1 µM, preferably less than 50 nM (a measurement reflecting the ability of the compound to disrupt the menin-MLL interaction, measured in accordance with Example 12), are expected to provide suppression of acute myeloid leukemia or Ewing's sarcoma tumor growth in a xenotransplantation mouse model. Immunocompromised 8-10 week-old female NSG mice are used for in vivo efficacy studies in accordance with IACUC guidelines. Luciferase expressing test cells are engrafted intravenously via tail vein injection (1×10⁷ cells/animal). Test cells can include, but are not limited to, human acute myeloid leukemia cells (e.g., NUP98 gene fusion cell (e.g., NUP98-PHF23 cell), NUP98-PHF23 (NP23) myeloblast cell (e.g., 961C), NUP98-PHF23 (NP23)lymphoblast cell (e.g., 748T, 106A), cell with an NPM1 mutation (e.g., OCI-AML3), cell with a FLT3 mutation, cell with an IDH1 mutation, cell with an IDH2 mutation, cell with a DNMT3A mutation (e.g., OCI-AML3, OCI-AML2, SET2), cell with a mixed lineage leukemia (MLL) gene amplification (e.g., UoC-M1, 2L1)) and Ewing's sarcoma cells (e.g., SK-NEP-1, EW5, EW8, TC-71, TC-106, CHLA258, CHLA-9, CHLA-10, SK-ES-1, Hs 822.T, A-673, A-4573, Hs 863.T, RD-ES, CHLA-25, CHLA-32, CHLA-99, COG-E-352, TC-32, SK-N-MC). When the mean luminescence of the cells reaches approximately 1.5×10⁶, 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 was measured

several days (e.g., 6 days) after initiating the treatment with compound or vehicle. It is expected that treatment with one or more of the menin inhibitors disclosed herein inhibit tumor growth and induce tumor regression relative to the vehicle control group.

[0924] Animals are sacrificed several days after treatment (e.g., on Day 7) and bone marrow samples are collected and prepared for gene expression analysis. Expression levels of target genes including, but not limited to, HOXA9, DLX2, PBX3, and/or MEIS1 are measured by qRT-PCR and can be presented as fold changes normalized to GAPDH expression. Expression of differentiation marker CD11b is expected to be elevated in bone marrow samples from menin inhibitor treated animals, suggesting that these cells undergo differentiation. The expression levels of tested downstream target genes including MEIS1 and HOXA9 are expected to be substantially reduced upon treatment with one or more of the menin inhibitors disclosed herein, consistent with inhibition of leukemia progression induced by this compound.

Example 26: Survival Study in Xenotransplantation Mouse Model

[0925] For survival studies in the xenotransplantation xenograft model, 6 to 8-week old female NSG mice are intravenously injected with 1×10^7 luciferase-expressing cells (e.g., Ewing's sarcoma cells or cells harboring a NUP98 gene fusion, NPM1 mutation, FLT3 mutation, IDH1 mutation, IDH2 mutation, DNMT3A mutation, or mixed lineage leukemia (MLL) gene amplification). Several days after the transplantation (e.g., at day 12 after transplantation), treatment is initiated with one or more of the menin inhibitors disclosed herein, 120 mg/kg, bid., p.o. or vehicle (20% 2-hydroxypropyl-b-cyclodextrin with 5% cremophore) and is continued for approximately 22 consecutive days. It is expected that treatment with one or more of the menin inhibitors disclosed herein extends median survival time relative to the vehicle control group.

[0926] Alternatively, 6 to 8-week old female NSG mice are intravenously injected with 0.5×10^6 cells (e.g., Ewing's sarcoma cells or acute myeloid leukemia cells such as cells harboring a NUP98 gene fusion, NPM1 mutation (including the patient-derived xenograft (PDX) models AM7577 and LEXFAM 2734), FLT3 mutation (including the patient-derived xenograft (PDX) models AM7577 and LEXFAM 2734), IDH1 mutation, IDH2 mutation (including the patient-derived xenograft (PDX) model AM7577), DNMT3A mutation (including the patient-derived xenograft (PDX) model AM7577), or mixed lineage leukemia (MLL) gene amplification).

[0927] Several days after transplantation (e.g., approximately 2, 3, 4, 5, 6, or 7 days or longer after transplantation), treatment is initiated with one or more of the menin inhibitors disclosed herein, ~75 mg/kg, b.i.d., p.o. or vehicle (20% 2-hydroxypropyl-b-cyclodextrin with 5% cremophore) and is continued for 16 consecutive days in the compound treated mice or until terminal leukemia or Ewing's sarcoma develops in the vehicle-treated mice. It is expected that treatment with one or more of the menin inhibitors disclosed herein extends median survival time relative to the vehicle control group.

[0928] Similarly, a ~120 mg/kg b.i.d. treatment regimen of one or more of the menin inhibitors disclosed herein is initiated several days (e.g., on day 6) after cell transplantation and continued for approximately 16 consecutive days in

the compound treated mice or until terminal leukemia or Ewing's sarcoma develops in the vehicle-treated mice. It is expected that treatment with one or more of the menin inhibitors disclosed herein extends median survival time relative to the vehicle control group.

Example 27: Serial Bleed FACS Analysis and Survival Study in AM7577 Mouse Model

[0929] For survival studies in the xenotransplantation xenograft model, 3 to 4-week old female NOD/SCID mice were intravenously injected with approximately $1-2 \times 10^6$ AM7577 cells (NPM1/DNMT3A^{mut} disseminated AML PDX model with an additional mutation in IDH2). Several days after transplantation (e.g., approximately 2, 3, 4, 5, 6, or 7 days or longer after transplantation), treatment was initiated with Compound A, ~200 mg/kg, p.o., qd, in 5 mice or vehicle (20% 2-hydroxypropyl-b-cyclodextrin with 5% cremophore), p.o., qd, in 5 mice and was continued for 3-5 weeks in the compound treated mice or until terminal leukemia developed in the vehicle-treated mice.

[0930] Human leukemia cells were detected by FACS weekly starting from week 4 post-cell inoculation. Eye bleed (~50 µL) was collected and anti-human CD45 antibody, anti-human CD11b antibody, anti-human CD14 antibody, and anti-human CD38 antibody were added. Samples were incubated on ice for 30 min in the dark. Red blood cell lysing buffer (1 mL) was added to each tube, samples were mixed thoroughly, and samples were incubated on ice for another 30 min in the dark. Cells were washed twice with ice cold PBS (2 mL), and the supernatant was discarded. Cells were re-suspended in FACS wash buffer (150 µL), and the samples were analyzed using FACS. FIG. 6A-6C depict percentages of CD45+/CD38+ blasts, CD45+/CD11b+ monocytes, and CD45+/CD14+ monocytes in vehicle and compound treated AM7577 models. Treatment with Compound A reversed leukemic progression and induced myeloid differentiation.

[0931] Spleen weight was measured for sacrificed animals. Blood and bone marrow cells of sacrificed animals were tested with anti-human CD45 antibody, anti-human CD11b antibody, anti-human CD14 antibody, and anti-human CD38 antibody. FIG. 7A depicts overall survival in vehicle and compound treated AM7577 models. Two out of five animals treated with Compound A demonstrated lasting complete remissions. Treatment with Compound A prolonged survival compared to treatment with vehicle. FIG. 7B depicts bone marrow phenotype at sacrifice in vehicle and compound treated AM7577 models. Compound A treated animals that succumbed to disease had differentiated human cells in the bone marrow. All vehicle treated animals had ~100% undifferentiated human blasts in bone marrow. Peripheral disease was completely cleared in all treated animals. FIG. 7C depicts spleen weight at sacrifice in vehicle and compound treated AM7577 models. Spleen weight was normal in compound treated animals at sacrifice but increased by an average of over four-fold over normal in vehicle-treated animals at sacrifice.

Example 28: Generation of Transgenic NP23 Mice

[0932] PCR primers are used to introduce Sfi I and Not I restriction sites and a C-terminal V5 epitope tag into the NP23 transgene construct, as described in Gough et al.; Cancer Discov. 2014 May; 4(5):564-77. This PCR product

is subcloned into the Sfi I and Not I sites of the HS21/45-vav vector (Ogilvy et al., Blood. 1999 Sep. 15; 94(6):1855-63), placing the expression of the fusion gene under the control of hematopoietic-specific Vav regulatory elements. Founders are generated by injection of the purified Pme I-released fragment from p898/NP23-2 containing Vav 1-NP23-V5-vav 2 into C57BL/6 zygotes. Positive NP23 founder mice are bred with WT C57BL/6, and pups are genotyped for the NP23 transgene by PCR with the forward and reverse primers NUPPHF(C)F and PHF23R1. WT controls are age-matched littermate controls.

Example 29: Chromatin immunoprecipitation (ChIP) and ChIP-Seq Assay

[0933] Chromatin immunoprecipitation (ChIP) is performed using the Zymo-Spin ChIP kit (Zymo Research Corp, Irvine, CA), according to the manufacturer's instructions, or using a ChIP-IT kit from Active Motif, following the manufacturer's recommended protocol with minor modifications (Gough et al.: Cancer Discov. 2014 May; 4(5):564-77). Antibodies used can include anti-menin (Bethyl A300-105A), 4 pg; anti-HLL (Millipore 05-765), 10 pg; anti-H3K4me3 (Invitrogen 49-1005), 2 pg; anti-histone H3 (Cell Signaling Technology 2650), 15 pg anti-H3K4me3 (17-614; Millipore), anti-H3K27me3 (07-449; Millipore), anti-V5 (R960-25; Life Technologies), anti-FLAG (M2; Sigma-Aldrich), and anti-RNA polymerase II (CTD4H8; Santa Cruz Biotechnology). Non-immune rabbit or mouse IgG can be used as negative controls.

[0934] It is expected that treatment with one or more of the menin inhibitors disclosed herein leads to a reduction in H3K4me3 enrichment at genes found to be downregulated in Example 18, suggesting epigenetic repression and decreased transcriptional activity. It can also be expected that treatment with one or more of the menin inhibitors disclosed herein leads to an increase in total H3 levels at the promoters for genes found to be downregulated in Example 18, suggesting chromatin compaction.

Example 30: Serial bleed FACS analysis and survival study in AM7577 mouse model

[0935] For survival studies in the xenotransplantation xenograft model, 6 to 8-week old female NOD/SCID mice were intravenously injected with approximately $1\text{-}2\times10^6$ AM7577 cells ($\text{NPM1}^{\text{mut}}/\text{DNMT3A}^{\text{mut}}/\text{FLT3-ITD}$ disseminated AML PDX model with an additional mutation in IDH2). Several weeks after transplantation (e.g., approximately 3 weeks after transplantation, when average tumor burden reaches 2-4% of hCD45+ cells), treatment was initiated with Compound A, ~100 mg/kg, p.o., qd in 5 mice, Compound A ~150 mg/kg, p.o., qd, in 5 mice, quizartinib ~3 mg/kg, p.o., qd in 5 mice, a combination of Compound A (~100 mg/kg, p.o., qd) and quizartinib (~2 mg/kg, p.o., qd) in 5 mice, or vehicle (20% 2-hydroxypropyl-b-cyclodextrin with 5% cremophore), p.o., qd, in 5 mice and was continued for 3-5 weeks in the compound treated mice or until terminal leukemia developed in the vehicle-treated mice.

[0936] Human leukemia cells were detected by FACS weekly starting from week 3 post-cell inoculation. Eye bleed (~50 μL) was collected and anti-human CD45 antibody, anti-human CD11b antibody, anti-human CD14 antibody, and anti-human CD38 antibody were added. Samples were incubated on ice for 30 min in the dark. Red blood cell lysing

buffer (1 mL) was added to each tube, samples were mixed thoroughly, and samples were incubated on ice for another 30 min in the dark. Cells were washed twice with ice cold PBS (2 mL), and the supernatant was discarded. Cells were re-suspended in FACS wash buffer (150 μL), and the samples were analyzed using FACS. FIGS. 8A and 8B depict percentages of CD45+/CD38+ blasts and circulating CD45+/CD11b+ monocytes. Treatment with Compound A and a combination of Compound A and quizartinib reversed leukemic progression and induced myeloid differentiation. Treatment with only quizartinib showed evidence of leukemia breakout after 63 days.

[0937] Spleen weight was measured for sacrificed animals. Blood and bone marrow cells of sacrificed animals were tested with anti-human CD45 antibody, anti-human CD11b antibody, anti-human CD14 antibody, and anti-human CD38 antibody. FIG. 9A depicts overall survival in vehicle, Compound A, quizartinib and Compound A+quizartinib treated AM7577 models. All animals treated with Compound A demonstrated lasting complete remissions, including those treated with a combination of Compound A and quizartinib. Treatment with quizartinib showed evidence of leukemia breakout and dose-dependency in rate of clearance of leukemia. Treatment with Compound A and quizartinib prolonged survival compared to treatment with vehicle, but quizartinib only treatment resulted in no surviving animals after 84 days. FIGS. 9B and 9C depict bone marrow phenotype after treatment for seven and 21 days, respectively, in vehicle and Compound A treated AM7577 models. FIG. 9D depicts bone marrow AML blasts at sacrifice in vehicle, Compound A, quizartinib, and Compound A+quizartinib treated animals. The data gathered for Compound A and Compound A+quizartinib treated animals were obtained after a 58 day dosing holiday. FIG. 9E depicts spleen weight at sacrifice in vehicle, Compound A, quizartinib, and Compound A+quizartinib treated animals. Compound A treated animals that succumbed to disease had differentiated human cells in the bone marrow. Vehicle treated animals had ~80% undifferentiated human blasts in bone marrow.

Example 31: Serial Bleed FACS Analysis and Survival Study in LXFE 2734 Mouse Model

[0938] For survival studies in the xenotransplantation xenograft model, 4 to 6-week old female NOG mice were intravenously injected with approximately 3×10^6 LXFE 2734 cells ($\text{NPM1}^{\text{mut}}/\text{DNMT3A-WT}/\text{FLT3}^{\text{mut}}$ disseminated AML PDX model). Several weeks after transplantation (e.g., approximately 2 or 3 weeks after transplantation), treatment was initiated with Compound A, ~150 mg/kg, p.o., qd in 5 mice, quizartinib ~3 mg/kg p.o., qd in 5 mice, or vehicle (20% 2-hydroxypropyl-b-cyclodextrin with 5% cremophore), p.o., qd, in 5 mice and was continued for 3-5 weeks in the compound treated mice or until terminal leukemia developed in the vehicle-treated mice.

[0939] Human leukemia cells were detected by FACS biweekly starting from week 2 post-cell inoculation. Li-heparin whole blood was collected and anti-human CD45 antibody, anti-human CD11b antibody, anti-human CD14 antibody, and anti-human CD33 antibody were added. FIG. 10 depicts percentages of CD45+/CD33+ blasts. Treatment with Compound A reversed leukemic progression and showed no evidence of peripheral leukemia. Treatment with quizartinib showed evidence of leukemia relapse.

[0940] Spleen weight was measured for sacrificed animals. Blood and bone marrow cells of sacrificed animals were tested with anti-human CD45 antibody, anti-human CD11b antibody, anti-human CD14 antibody, and anti-human CD33 antibody. FIG. 11 depicts overall survival in vehicle and Compound A and quizartinib treated LXFE 2734 models. Treatment with Compound A and quizartinib prolonged survival compared to treatment with vehicle, with no quizartinib treated animals surviving after 77 days.

Example 32: Cell Proliferation Assay

[0941] The ability of a compound of the present disclosure to inhibit the growth of selected cells was 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), MTT cell proliferation assay (ATCC® 30-1010K) or cell counting. The efficacy of one or more compounds of the present disclosure was tested in KG1, MV4; 11, THP-1, ML-2, NB4 (APL), U-937, EOL-1, MOLM-13 and OCI-AML3 acute myeloid leukemia cells and Reh, RS4; 11, MUTZ-5, MHH-CALL2 and NALM6 B-cell acute lymphoblastic leukemia cells. Cells were plated at relevant concentrations, for example about 1×10^5 - 2×10^5 cells per well in a 96-well plate. A compound of the present disclosure was added at a concentration up to about 10 μ M with seven or eight, 2-fold serial dilutions. Cells were incubated at 37° C. for a period of time, for example, 72 hours, then cells in the control wells were counted. Media was changed to restore viable cell numbers to the original concentration, and compounds were re-supplied. Proliferation was measured about 72 hours later or about 96 hours later using Promega CellTiter-Glo® reagents or MTT reagents, as per kit instructions. One or more compounds disclosed herein, e.g., a compound provided in Table 1, 2, 3, 4, 5, 6 or 7 having an IC₅₀ value of less than 1 μ M, preferably less than 100 nM or less than 50 nM (a measurement reflecting the ability of the compound to

disrupt the menin-MLL interaction, measured in accordance with Example 12), are expected to inhibit the proliferation of acute myeloid leukemia cell lines or B-cell acute lymphoblastic leukemia cell lines. Certain cell lines were responsive to treatment with one or more compounds disclosed herein, such as MV4; 11 cells (MLL-AF4 AML, MLL-rearranged, MEIS1^{high}), MOLM13 cells (MLL-AF9 AML, MLL-rearranged, MEIS1^{high}) OCI-AML3 cells (AML, NPM1^{mut}, DNMT3A^{mut}), EOL-1 cells (AML, MLL-PTD), and RS4; 11 cells (MLL-AF4 ALL, MLL-rearranged, MEIS1^{high}). Certain cell lines were less responsive to treatment with one or more compounds disclosed herein, such as THP-1 (AML, MLL-rearranged, MEIS1^{low}, RAS^{mut}), ML-2 (AML, MLL-rearranged, MEIS1^{low}, RAS^{mut}), Reh (B-ALL, MLL-WT), MUTZ-5 (B-ALL, MLL-WT), MHH-CALL2 (B-ALL, MLL-WT), and NALM6 (B-ALL, MLL-WT).

[0942] It is expected that one or more menin inhibitors disclosed herein are able to inhibit growth of acute myeloid leukemia cells or acute lymphoblastic leukemia cells by 50% at a concentration no more than 1000 nM, preferably at a concentration no more than 100 nM, more preferably at a concentration no more than 50 nM, in some situations exhibiting GI₅₀ values in the range of 1 nM to 50 nM. FIG. 12 depicts dose-response curves for acute myeloid leukemia cells treated with Compound A. Dose-response curves for B-cell acute lymphoblastic leukemia cells treated with Compound A are presented in FIG. 13.

[0943] While preferred embodiments of the present invention 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 invention. It should be understood that various alternatives to the embodiments of the invention 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.

SEQUENCE LISTING

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VSDVIWNSLS RSYFKDRAHI QSLFSFITGW SPVGTKLDS GVAFAVGAC QALGLRDVHL 180
ALSDEHAWVV FGPNGEQTAE VTWHGKGNEED RRGQTVNAGV AERSWLYLKG SYMRCDRKME 240
VAFMVCAINP SIDLHTDSLE LLQLQQQLLW LLYDLGHLER YPMALGNLAD LEELEPTPGR 300
PDPLTLYHKG IASAKTYYRD EHYPYMYLA GHCRNRRNVR EALQAWADTA TVIQDYNYCR 360
EDEEYLKEFF EVANDVPINL LKEAASLLEA GEERPGEQSQ GTQSQGSALQ DPECFAHLLR 420
FYDGICKWEE GSPTPVLHVG WATFLVQSLG RFEQGVRQKV RIVSREAEAA EAEEPWGEEA 480
REGRRRGPRR ESKPEEPPPP KKPALDKGLG TGQGAVSGPP RKPPGTVAGT ARGPEGGSTA 540
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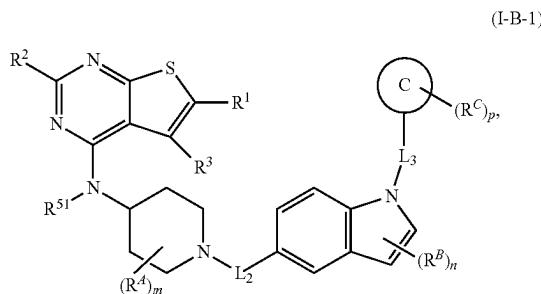
- continued

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HAWVVFGPN	EQTAEVTWHG	KGNEDRRGQT	VNAGVAERSW	LYLKGSYMRC	DRKMEVAFMV	240
CAINPSIDLH	TDSLELLQLQ	QKLWLWLYDL	GHLYRYPMAL	GNLADLEELE	PTPGRPDPLT	300
LYHKGIASAK	TYYRDEHIYP	YMLLAGYHCR	NRNVREALQA	WADTATVIQD	YNYCREDEEI	360
YEKEFFEVAND	VIPNLKKEAA	SLLEAGEERP	GEQSQGTQSQ	GSALQDPCECF	AHLLRFYDGI	420
CKWEEGSPTP	VLHVGWATFL	VQSLGRFEGQ	VRQKVRIIVSR	EAAEAAEAEPP	WGEEAREGRR	480
RGPRESKPE	EPPPPDKPAL	DKGLGTGQGA	VSGPGRKPVG	TVAGTARGPE	GGSTAQVPA	540
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source		1..575				
		mol_type = protein				
		organism = Homo sapiens				
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HAWSWLYLKG	SYMCRDRKME	VAFMVCAINP	SIDLHTDSL	LLQLQKQLW	LLYDLGHLER	240
YPMALGNLAD	LEELEPTPGF	PDPPLTLYHKG	IASAKTYR	EHIYPYMYLA	GYHCRNRNVR	300
EALQAWADTA	TVIQDYNYCR	EDEEUYKEFF	EVANDVIPNL	LKEAASLLEA	GEERPGEQSQ	360
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RIVSREAAA	EAEEPWGEEA	REGRRRGPRR	ESKPPEPPPP	KKPALDKGLG	TGQGAVSGPP	480
RKPPGTWAGT	ARGPEGGSTA	QVPAFTASPP	PEGPVLTFQ	EKMKGKELL	VATKINSSAI	540
KLQLTAQSQV	QMKKQKVSTP	SDYTLSFLKR	QRKGL			575

1.-149. (canceled)

150. A method of treating a hematological malignancy in a subject exhibiting a nucleoporin (NUP98) gene fusion comprising administering to the subject a menin inhibitor.

151. The method of claim 150, wherein the menin inhibitor is a compound of Formula (I-B-1):



or a pharmaceutically acceptable salt thereof, wherein: C is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

L₂ is selected from bond, —C(O)—, —C(O)O—, —C(O)N(R⁵¹)—, —C(O)N(R⁵¹)C(O)—, —C(O)N(R⁵¹)C(O)N(R⁵¹)—, —C(NR⁵¹)—, —C(NR⁵¹)N(R⁵¹)—, —S(O)₂—, —S(O)O—, —S(O)—, —S(O)₂O—, —S(O)₂N(R⁵¹)—, —S(O)N(R⁵¹)—, alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, wherein each alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene is optionally substituted with one or more R⁵⁰;

L₃ is selected from alkylene, alkenylene, and alkynylene, each of which is substituted with one or more R⁵⁶ and optionally further substituted with one or more R⁵⁰; R¹ and R³ are each independently selected from hydrogen and R⁵⁰;

R² is R⁵⁰;

R⁴, R^B, and R^C are each independently selected at each occurrence from R⁵⁰, or two R⁴ groups, 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 and p are each independently an integer from 0 to 6; n is an integer from 0 to 5;

R⁵⁰ is independently selected at each occurrence from:

halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)N(R⁵²)₂, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, and —P(O)(R⁵²)₂, or two R⁵⁰ groups attached to the same carbon are taken together to form =O, =S, or =N(R⁵²);

C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is optionally substituted at each occurrence with one or more substituents independently selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)R⁵², —S(=O)N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)R⁵², —NR⁵²S(=O)N(R⁵²)₂, —NR⁵²S(=O)NR⁵³R⁵⁴, —C(O)R⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)N(R⁵²)₂, —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)N(R⁵²)₂, —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle, wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is optionally substituted with one or more substituents independently selected from

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

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted at each occurrence with one or more substituents independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{OC(O)OR}^{52}$, $-\text{OC(O)N}(\text{R}^{52})_2$, $-\text{OC(O)NR}^{52}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)OR}^{52}$, $-\text{NR}^{52}\text{C(O)N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})_2$, 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 optionally substituted with one or more substituents independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{OC(O)OR}^{52}$, $-\text{OC(O)N}(\text{R}^{52})_2$, $-\text{OC(O)NR}^{52}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)OR}^{52}$, $-\text{NR}^{52}\text{C(O)N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})_2$, 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, C_{1-6} heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, 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;

R^{56} is independently selected at each occurrence from:

$-\text{NO}_2$, $-\text{OR}^{59}$, $-\text{SR}^{52}$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(\text{=O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{OC(O)OR}^{52}$, $-\text{OC(O)N}(\text{R}^{52})_2$, $-\text{OC(O)NR}^{52}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)OR}^{52}$, $-\text{NR}^{52}\text{C(O)N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(R}^{52})_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle and 3- to 12-membered heterocycle, or two R^{56} groups

attached to the same carbon are taken together to form $=\text{O}$, $=\text{S}$, or $=\text{N}(\text{R}^{52})_2$,

wherein each C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl in R^{56} is optionally substituted at each occurrence with one or more substituents independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{59}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{OC(O)OR}^{52}$, $-\text{OC(O)N}(\text{R}^{52})_2$, $-\text{OC(O)NR}^{52}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)OR}^{52}$, $-\text{NR}^{52}\text{C(O)N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})_2$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

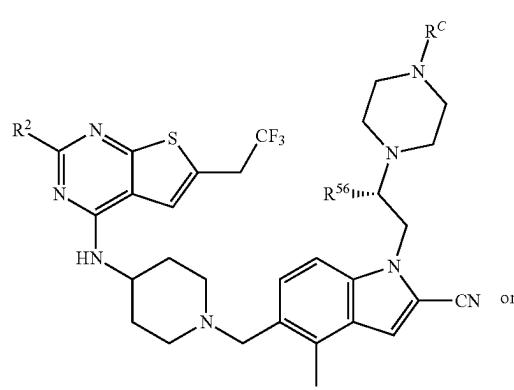
wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is optionally substituted with one or more substituents independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(\text{=O})\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(\text{=O})_2\text{N}(\text{R}^{52})_2$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{OC(O)OR}^{52}$, $-\text{OC(O)N}(\text{R}^{52})_2$, $-\text{OC(O)NR}^{52}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)OR}^{52}$, $-\text{NR}^{52}\text{C(O)N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{C(O)NR}^{52}$, $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})_2$, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

further wherein R^{56} optionally forms a bond to ring C; and

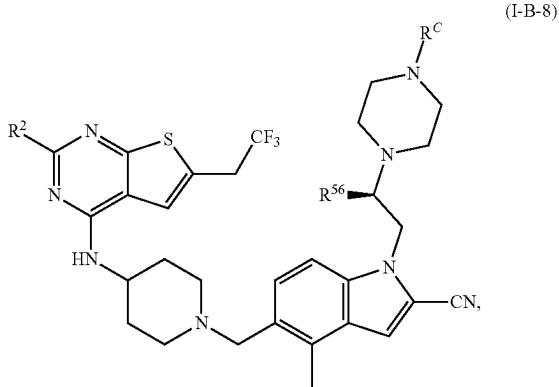
R^{59} is independently selected at each occurrence from C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-6} heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; wherein when R^{56} is $-\text{CH}_3$, L^3 is not further substituted with $-\text{OH}$, $-\text{NH}_2$, or $-\text{CN}$.

152. The method of claim 151, wherein the compound of Formula (I-B-1) is a compound of Formula (I-B-6) or Formula (I-B-8):

(I-B-6)

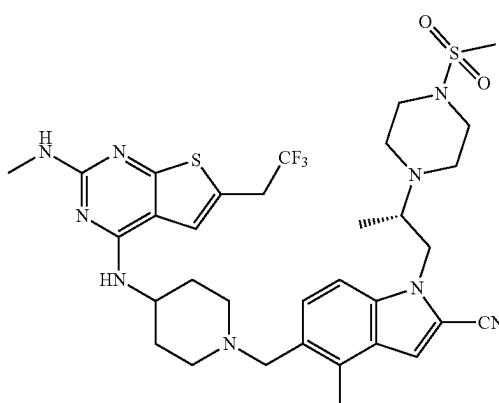


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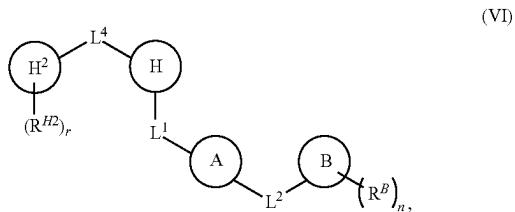
or a pharmaceutically acceptable salt thereof.

153. The method of claim **151**, wherein the compound of Formula (I-B-1) is



or a pharmaceutically acceptable salt thereof.

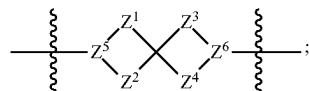
154. The method of claim 150, wherein the menin inhibitor is a compound of Formula (VI):



or a pharmaceutically acceptable salt thereof, wherein: H² is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

H is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R⁵⁰;

A is



each of Z^1 , Z^2 , Z^3 , and Z^4 is independently selected from $-\text{C}(\text{R}^{A1})(\text{R}^{A2})-$, $-\text{C}(\text{R}^{A1})(\text{R}^{A2})-\text{C}(\text{R}^{A1})$
 $(\text{R}^{A2})-$, $-\text{O}-$, $-\text{C}(\text{R}^{A1})(\text{R}^{A2})-\text{O}-$, $-\text{C}(\text{R}^{A1})$
 $(\text{R}^{A2})-\text{N}(\text{R}^{S1})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{R}^{A1})(\text{R}^{A2})-\text{C}$
 $(\text{O})-$, and $-\text{N}=\text{C}(\text{NH}_2)-$, wherein no more than
one of Z^1 , Z^2 , Z^3 , and Z^4 is $-\text{O}-$, $-\text{C}(\text{R}^{A1})(\text{R}^{A2})-$
 $\text{O}-$, $-\text{C}(\text{R}^{A1})(\text{R}^{A2})-\text{N}(\text{R}^{S1})-$, $-\text{C}(\text{O})-$,
 $-\text{C}(\text{R}^{A1})(\text{R}^{A2})-\text{C}(\text{O})-$, or $-\text{N}=\text{C}(\text{NH}_2)-$;
 Z^5 and Z^6 are independently selected from $-\text{C}(\text{R}^{A3})-$
and $-\text{N}-$;

B is selected from bond, C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

L^1 , L^2 and L^4 are each independently selected from bond, $-O-$, $-S-$, $-N(R^{51})-$, $-N(R^{51})CH_2-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, $-OS(O)-$, $-S(O)O-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, $-N(R^{51})S(O)N(R^{51})-$; alkylene, alkynylene, alkyne, heteroalkylene, heteroalkynylene, 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^4 can together optionally form a bridge or ring;

R^B is independently selected at each occurrence from hydrogen and 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^{A1} , R^{A2} and R^{A3} are each independently selected at each occurrence from hydrogen and R^{50} ;

n is an integer from 0 to 6;

r is an integer from 1 to 6;

R^{50} is independently selected at each occurrence from:
 halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$,
 $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$,
 $-S(=O)N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)R^{52}$,
 $(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)R^{53}R^{54}$,
 $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$,
 $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)R^{53}R^{54}$,
 $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$,
 $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$,
 $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$,
 $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})_2$.

(R⁵²), —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²); C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)NR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)₂, —NR⁵²P(O)(R⁵²), —P(O)(NR⁵²)(OR⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle, wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl; R⁵¹ is independently selected at each occurrence from: hydrogen, —C(O)R⁵², —C(O)OR⁵², —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴; C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —NR⁵²S(=O)₂R⁵², —NR⁵²S(=O)₂N(R⁵²)₂, —NR⁵²S(=O)₂NR⁵³R⁵⁴, —C(O)R⁵², —C(O)OR⁵², —OC(O)R⁵², —OC(O)OR⁵², —OC(O)NR⁵³R⁵⁴, —NR⁵²C(O)R⁵², —NR⁵²C(O)OR⁵², —NR⁵²C(O)NR⁵², —NR⁵²C(O)NR⁵³R⁵⁴, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

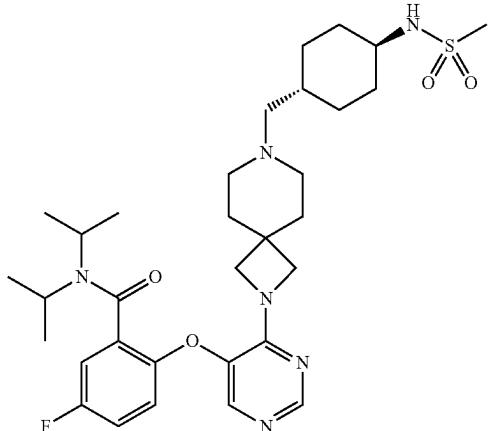
C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle, wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently optionally substituted with one or more substituents selected from halogen, —NO₂, —CN, —OR⁵², —SR⁵², —N(R⁵²)₂, —NR⁵³R⁵⁴, —S(=O)R⁵², —S(=O)₂R⁵², —S(=O)₂N(R⁵²)₂, —S(=O)₂NR⁵³R⁵⁴, —C(O)N(R⁵²)₂, —C(O)NR⁵³R⁵⁴, —P(O)(OR⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)₂, —P(O)(R⁵²)₂, —P(O)(OR⁵²)(R⁵²), —P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, —CN, —NO₂, —NH₂, —NHCH₃, —NHCH₂CH₃, =O, —OH, —OCH₃, —OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle; and

R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle.

155. The method of claim 154, wherein the compound is selected from compounds in Table 6 and pharmaceutically acceptable salts thereof.

156. The method of claim 154, wherein the compound is



or a pharmaceutically acceptable salt thereof.

157. The method of claim 150, wherein the NUP98 gene fusion is a gene fusion of NUP98 and a homeodomain partner gene.

158. The method of claim 150, wherein the NUP98 gene fusion is a gene fusion of NUP98 and a non-homeodomain partner gene.

159. The method of claim 150, wherein the 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.

160. The method of claim 150, wherein the 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, SETBP1, LEDGF, CCDC28,

HMGB3, IQCG, RAP1GDS1, ADD3, DDX10, TOP1, TOP2B, LNP1, RARG, ANKRD28, and POU1F1.

161. The method of claim **150**, wherein the NUP98 gene fusion is a gene fusion of NUP98 and a partner gene selected from HOXA9, HOXA11, HOXA13, HHEX, NSD1, CCDC28, HMGB3, DDX10, TOP1, and LNP1.

162. The method of claim **150**, wherein the subject further exhibits a mutation in the FLT3 gene.

163. The method of claim **162**, wherein the mutation in the FLT3 gene is an internal tandem duplication.

164. The method of claim **162**, wherein the mutation in the FLT3 gene is in the tyrosine kinase domain.

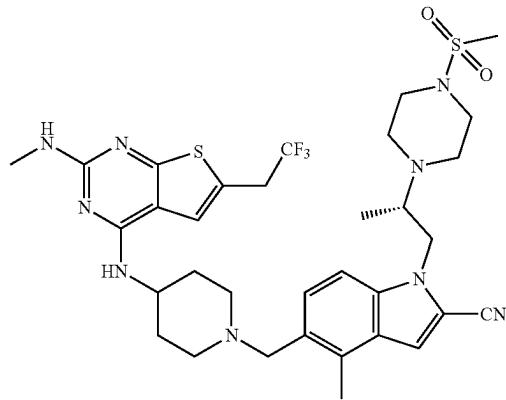
165. The method of claim **150**, wherein the subject further exhibits a mutation in the isocitrate dehydrogenase 1 (IDH1) gene or isocitrate dehydrogenase 2 (IDH2) gene.

166. The method of claim **150**, wherein the hematological malignancy is acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, multiple myeloma, mixed lineage leukemia or myelodysplastic syndrome.

167. The method of claim **150**, wherein the hematological malignancy is acute myeloid leukemia.

168. The method of claim **150**, wherein the hematological malignancy is acute lymphocytic leukemia.

169. A method of treating a hematological malignancy in a subject exhibiting a nucleoporin (NUP98) gene fusion comprising administering to the subject a menin inhibitor is



or a pharmaceutically acceptable salt thereof.

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