

SUBSTITUTED INHIBITORS OF MENIN-MLL AND METHODS OF USE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/309,372, filed March 16, 2016; U.S. Provisional Application No. 62/334,369, filed May 10, 2016; U.S. Provisional Application No. 62/431,389, filed December 7, 2016; and U.S. Provisional Application No. 62/446,640, filed January 16, 2017, which applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] The mixed-lineage leukemia (MLL) protein is a histone methyltransferase critical for the epigenetic regulation of gene transcription. Many acute leukemias, including acute myeloblastic leukemia (AML), acute lymphoblastic leukemia (ALL) and mixed-lineage leukemia (MLL), are characterized by the presence of chimeric MLL fusion proteins that result from chromosomal translocations of the *MLL* gene located at chromosome 11, band q23 (11q23). Chimeric MLL fusion proteins retain approximately 1,400 amino acids of the N-terminus of MLL, but are fused with one of approximately 80 partner proteins (e.g., AF4, AF9, ENL, AF10, ELL, AF6, AF1p, GAS7). MLL fusion proteins lack the original histone methyltransferase activity of the C-terminus of MLL and gain the ability to regulate transcription of numerous oncogenes, including *HOX* and *MEIS1*, resulting in increased cell proliferation and decreased cell differentiation, ultimately leading to leukemogenesis.

[0003] The menin protein, which is encoded by the Multiple Endocrine Neoplasia (MEN) gene, is a ubiquitously expressed nuclear protein that engages in interactions with DNA processing and repair proteins, chromatin modifying proteins and numerous transcription factors (Agarwal, et al.; *Horm Metab Res*, 2005, 37(6): 369-374). The association of menin with the N-terminus of MLL fusion proteins is necessary for the observed oncogenic activity of MLL fusion proteins. This association has been shown to constitutively up-regulate the expression of *HOX* and *MEIS1* oncogenes and impairs proliferation and differentiation of hematopoietic cells leading to leukemia development. Since menin has been shown to function as a general oncogenic cofactor in MLL-related leukemias, the interaction between menin and MLL fusion proteins and MLL represents a potential chemotherapeutic target.

[0004] Patients, especially infants, with leukemias harboring chromosomal translocations of the *MLL* gene have a dismal prognosis, with less than a 40% five year survival rate (Slany; *Haematologica*, 2009, 94(7): 984-993). A novel therapeutic strategy is urgently needed to treat these leukemias. Small molecule inhibitors that block the menin-MLL interaction are thus valuable targets for treating diseases involving the MLL fusion proteins.

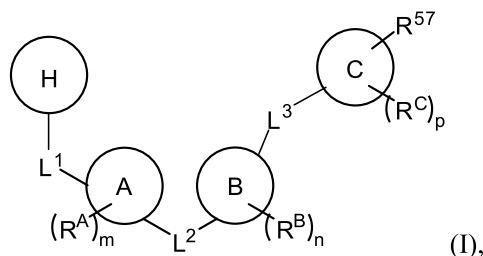
SUMMARY

[0005] The present disclosure addresses a need in the art by providing compositions and methods for inhibiting the protein-protein interaction of menin with MLL1, MLL2 and MLL-fusion oncoproteins. The compositions and methods herein may be useful for treating diseases dependent on the activity of MLL1, MLL2, MLL fusion proteins, and/or menin such as leukemia, solid cancers, and diabetes. In some

examples, a compound of the disclosure interacts non-covalently with menin and inhibits the interaction of menin with MLL. In some examples, a compound of the disclosure covalently binds menin and inhibits the interaction of menin with MLL.

[0006] In some examples of a compound provided herein, the compound non-covalently or covalently binds to any one or more isoforms of menin, for example, isoform 1 (SEQ ID NO: 1), isoform 2 (SEQ ID NO: 2) or isoform 3 (SEQ ID NO: 3) of menin. In certain examples, the menin protein shares 60% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or 99% or more sequence identity with isoform 1 (SEQ ID NO: 1), isoform 2 (SEQ ID NO: 2) or isoform 3 (SEQ ID NO: 3).

[0007] In one example, the present disclosure provides a compound of Formula (I):



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

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

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

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

C is 3- to 12-membered heterocycle;

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, 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 any one of L¹, L² or L³ can together optionally form a bridge or ring;

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;

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

R⁵⁰ is independently selected at each occurrence 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)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -

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, -NO₂, -NH₂, -NHCH₃, -NHCH₂CH₃, =O, -OH, -OCH₃, -OCH₂CH₃, C_{3-12} carbocycle, or 3- to 6-membered heterocycle;

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

R^{57} is selected from:

halogen, -NO₂, -CN, -SR⁵², -NR⁵³R⁵⁴, -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, -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)NR⁵³R⁵⁴, -C(O)NH(C₁₋₆ alkyl), -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, =S, =N(R⁵²); and

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently substituted at each occurrence with one or more substituents selected from -NO₂, -CN, -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)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, =S, and =N(R⁵²); and

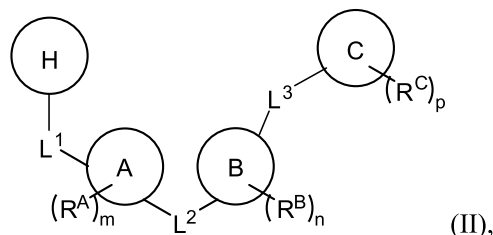
R^{58} is selected from hydrogen; and C_{1-20} alkyl, C_{3-20} alkenyl, C_{2-20} alkynyl, 1- to 6-membered heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, -NO₂, -NH₂, -NHCH₃, -NHCH₂CH₃, =O, -OH, -OCH₃, -OCH₂CH₃, C_{3-12} carbocycle, or 3- to 6-membered heterocycle,

wherein for a compound or salt of Formula (I), when C is azetidinylen, piperidinylen or piperazinylen and R^{57} is -S(=O)₂R⁵⁸, -S(=O)₂N(R⁵²)₂, or -NR⁵²S(=O)₂R⁵²:

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

L^3 is substituted with one or more R^{50} , wherein L^3 is not -CH₂CH(OH)-.

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



or a pharmaceutically acceptable salt thereof, wherein:

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} ;

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

carbocycle, and 3- to 12-membered heterocycle;

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)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)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; and

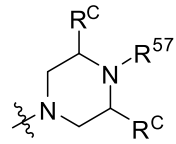
further wherein R⁵⁶ optionally forms a bond to ring C; and

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,

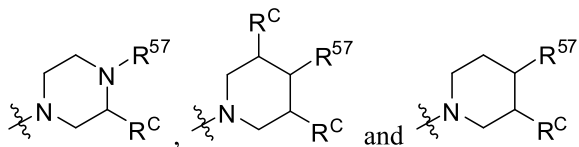
wherein for a compound or salt of Formula (II), when R⁵⁶ is -CH₃, L³ is not further substituted with -OH, -NH₂, or -CN.

[0009] In some examples, for a compound of Formula (II), 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.

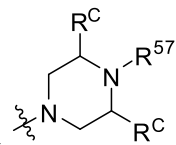
[0010] For a compound of Formula (I) or (II), C may be 5- to 12-membered heterocycle, wherein the heterocycle comprises at least one nitrogen atom. In some examples, the heterocycle is saturated. In some examples, the heterocycle is selected from piperidinyl and piperazinyl.



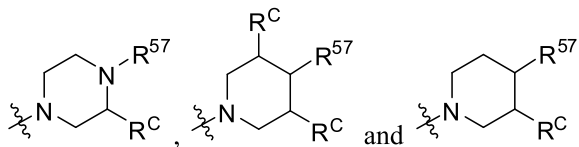
[0011] In some examples, for a compound of Formula (I), C is selected from



. In some examples, R⁵⁷ is selected from -S(=O)R⁵², -S(=O)₂R⁵⁸, -S(=O)₂N(R⁵²)₂, and -NR⁵²S(=O)₂R⁵².



[0012] In some examples, for a compound of Formula (II), C is selected from



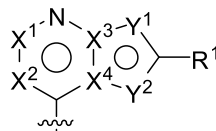
, wherein R⁵⁷ is selected from -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵²; and C₁₋₁₀ alkyl substituted with one or more substituents selected from -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, and -NR⁵²S(=O)₂R⁵².

In some examples, R^{57} is selected from $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, and $-NR^{52}S(=O)_2R^{52}$. In some examples, R^{57} is selected from $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-S(=O)_2NH_2$, $-NHS(=O)_2CH_3$, and $-S(=O)_2NHCH_3$.

[0013] For a compound of Formula (I) or (II), R^C may be selected from C_{1-3} alkyl and C_{1-3} haloalkyl.

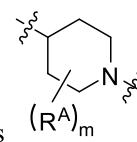
[0014] In some examples, for a compound of Formula (I) or (II), H is 5- to 12-membered heterocycle, optionally substituted with one or more R^{50} ; A is 3- to 12-membered heterocycle; and B is 3- to 12-membered heterocycle.

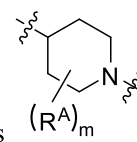
[0015] For a compound of Formula (I) or (II), H may be 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50} . In some examples, H is thienopyrimidinyl, optionally



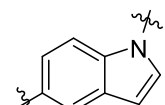
substituted with one or more R^{50} . In some examples, H is ; X^1 and X^2 are each independently selected from CR^2 and N; X^3 and X^4 are each independently selected from C and N; Y^1 and Y^2 are each independently selected from CR^3 , N, NR^4 , O, and S; R^1 , R^2 and R^3 are each independently selected at each occurrence from hydrogen and R^{50} ; and R^4 is selected from R^{51} . In some examples, X^3 and X^4 are each C. In some examples, X^1 is CR^2 , and R^2 is selected from hydrogen, halogen, $-OH$, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, $-CN$, C_{1-3} alkyl, C_{1-3} alkyl- $N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some examples, X^1 is CR^2 , and R^2 is selected from hydrogen, halogen, $-OH$, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, $-CN$, C_{1-3} alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, C_{1-3} alkyl- $N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl. In some examples, X^2 is N. In some examples, Y^2 is CR^3 , and R^3 is selected from hydrogen, halogen, $-OH$, $-N(R^{52})_2$, $-CN$, $-C(O)OR^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some examples, R^1 is C_{1-3} haloalkyl.

[0016] For a compound of Formula (I) or (II), A may be 5- to 8-membered heterocycle, such as 6-membered monocyclic heterocycle. In some examples, the heterocycle comprises at least one nitrogen



atom. In some examples, A is selected from piperidinylene and piperazinylene, such as .

[0017] For a compound of Formula (I) or (II), B may be 6- to 12-membered bicyclic heterocycle. In some examples, the heterocycle comprises at least one nitrogen atom. In some examples, B is indolylene,

such as , optionally substituted with one or more R^B .

[0018] In some examples, for a compound of Formula (I) or (II), H is thienopyrimidinyl substituted with one or more R^{50} ; A is selected from piperidinylene and piperazinylene; and B is indolylene.

[0019] For a compound of Formula (I) or (II), H may be substituted with $-CH_2CF_3$. In some

examples, m is 0. In some examples, n is an integer from 1 to 3. In some examples, L^1 comprises less than 10 atoms. In some examples, L^1 is $-N(R^{51})-$. In some examples, L^2 comprises less than 10 atoms. In some examples, L^2 is C_{1-4} alkylene, optionally substituted with one or more R^{50} .

In some examples, 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 examples, L^3 comprises less than 20 atoms. In some examples, L^3 is C_{1-6} alkylene, optionally substituted with one or more R^{50} . In some examples, 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 examples, 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 examples, L^3 is substituted with $-CH_3$. In some examples, a compound of Formula (I) or (II) is selected from Table 1.

[0020] For a compound of Formula (I), L^3 may be selected from  and . Optionally, R^{50} is methyl.

In some examples, for a compound of Formula (II), L^3 is selected from  and . Optionally, R^{56} is methyl. In certain examples, the present disclosure provides a substantially pure stereoisomer of a compound of Formula (I) or (II). Optionally, the stereoisomer is provided in at least 90% enantiomeric excess.

[0021] In some examples, for a compound of Formula (I) or (II), H is thienopyrimidinyl, optionally substituted with one or more R^{50} ; 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.

[0022] In some examples, for a compound of Formula (I):

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

A is selected from piperidinylene and piperazinylene;

B is indolylene;

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

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

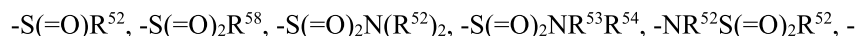
R^A , R^B and R^C are each independently selected at each occurrence from R^{50} , or two R^A groups, two R^B groups or two R^C groups attached to the same atom or different atoms can together optionally form a ring;

m is an integer from 0 to 3;

n is an integer from 1 to 3;

p is an integer from 0 to 6;

R^{57} is selected from:



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

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

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

[0023] In some examples, for a compound of Formula (II):

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

A is selected from piperidinylene and piperazinylene;

B is indolylene;

L^1 and L^2 are each independently selected from $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, and $-\text{CH}_2-$;

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} ;

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;

m is an integer from 0 to 3;

n is an integer from 1 to 3;

p is an integer from 0 to 6;

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

$-\text{OR}^{59}$, $=\text{O}$, C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl,

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, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{59}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

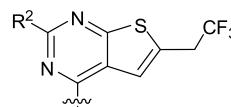
wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

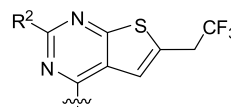
C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl; and

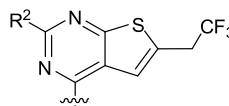
further wherein R⁵⁶ optionally forms a bond to ring C; and

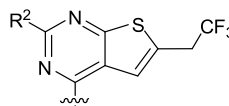
R⁵⁹ is independently selected at each occurrence from C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, -NO₂, -NH₂, -NHCH₃, -NHCH₂CH₃, =O, -OH, -OCH₃, -OCH₂CH₃, C₃₋₁₂ carbocycle,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

[0024] For a compound of Formula (I), R⁵⁷ may be selected from -S(=O)₂R⁵⁸, -S(=O)₂N(R⁵²)₂, and -S(=O)₂NR⁵³R⁵⁴, such as -S(=O)₂CH₃ and -S(=O)₂NHCH₃. For a compound of Formula (II), C may be substituted with -S(=O)₂R⁵⁸, -S(=O)₂N(R⁵²)₂, or -S(=O)₂NR⁵³R⁵⁴.



[0025] In some examples, for a compound of Formula (I) or (II), H is  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 alkenyl, and C₂₋₃ alkynyl. Optionally, R² is selected from -NH₂, -CH₃, and -NHCH₃. In



some examples, for a compound of Formula (I) or (II), H is  and 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. Optionally, R² is selected from -NH₂, -CH₃, -OCH₃, -CH₂OH,

and -NHCH₃. For a compound of Formula (I) or (II), L³ may be selected from  and .

[0026] In certain examples, the present disclosure provides a pharmaceutical composition comprising a compound or salt of Formula (I) or (II) and a pharmaceutically acceptable carrier. In some examples, the pharmaceutical composition is formulated for oral administration. In some examples, the pharmaceutical composition is formulated for injection.

[0027] In certain examples, the present disclosure provides a method of inhibiting an interaction of menin with one or more of MLL1, MLL2, an MLL fusion protein, and an MLL Partial Tandem Duplication, comprising contacting menin with an effective amount of a compound or salt of Formula (I) or (II). In certain examples, the present disclosure provides a method of inhibiting a menin-MLL interaction, comprising contacting menin with an effective amount of a compound or salt of Formula (I) or (II), wherein inhibition of the interaction is evidenced by a reduction in expression of an MLL fusion protein target gene. In certain examples, the present disclosure provides a method of stabilizing menin, comprising contacting menin with a compound or salt of Formula (I) or (II).

[0028] In practicing any of the subject methods, the MLL fusion protein target gene may be *HOXA9*,

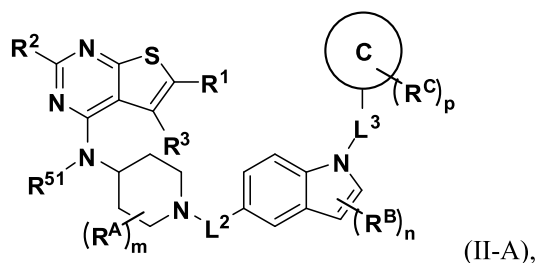
DLX2, or *MEIS1*. The contacting may comprise contacting a cell that expresses menin. In some examples, the method comprises administering a second therapeutic agent. In some examples, the contacting takes place *in vivo*. In some examples, the contacting takes place *in vitro*.

[0029] In certain examples, the present disclosure provides a method of treating a disease or condition associated with MLL fusion proteins, comprising administering to a subject in need thereof an effective amount of a compound or salt of Formula (I) or (II). In certain examples, the present disclosure provides a method of treating a disease or condition in a subject, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition of a compound or salt of Formula (I) or (II). In some examples, the disease or condition comprises a leukemia, hematologic malignancy, solid tumor cancer, prostate cancer, breast cancer, liver cancer, brain tumor, or diabetes. In some examples, the leukemia comprises AML, ALL, Mixed Lineage Leukemia or a leukemia with Partial Tandem Duplications of MLL.

[0030] In certain examples, the present disclosure provides a method of treating a disorder mediated by chromosomal rearrangement on chromosome 11q23 in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound or salt of Formula (I) or (II). In certain examples, the present disclosure provides a method of treating a disorder mediated by an interaction between menin and another protein, comprising administering to a subject in need thereof a therapeutically effective amount of a compound or salt of Formula (I) or (II). In some examples, the subject is a human.

[0031] In certain examples, the present disclosure provides a kit comprising a pharmaceutical composition described herein and instructions for using the composition to treat a subject suffering from a disease or condition mediated by an interaction between menin and another protein.

[0031a] In certain aspects, the present disclosure provides, a compound of Formula (II-A):



or a pharmaceutically acceptable salt thereof, wherein:

C is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

L² is C₁₋₄ alkylene;

L³ is C₁₋₄ alkylene substituted with one or more R⁵⁶, R⁵⁶ is -CH₃;

R¹ is C₁₋₃ haloalkyl;

R² is selected from halogen, -OR⁵², -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;

R³ is selected from hydrogen, halogen, -OH, -N(R⁵²)₂, -CN, -C(O)OR⁵², C₁₋₃alkyl, and C₁₋₃haloalkyl;

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;

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

R⁵⁰ is independently selected at each occurrence 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)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 are taken together to form =O, =S, or =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)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 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)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), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

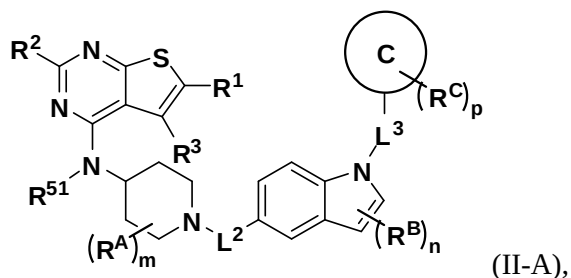
R⁵¹ is independently selected at each occurrence from:

hydrogen and C₁₋₆ alkyl;

CLAIMS

What is claimed is:

1. A compound of Formula (II-A):



or a pharmaceutically acceptable salt thereof, wherein:

C is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;

L² is C₁₋₄ alkylene;

L³ is C₁₋₄ alkylene substituted with one or more R⁵⁶, and R⁵⁶ is -CH₃;

R¹ is C₁₋₃ haloalkyl;

R² is selected from halogen, -OR⁵², -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;

R³ is selected from hydrogen, halogen, -OH, -N(R⁵²)₂, -CN, -C(O)OR⁵², C₁₋₃alkyl, and C₁₋₃haloalkyl;

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;

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

R⁵⁰ is independently selected at each occurrence 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)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 are taken together to form =O, =S, or =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)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 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)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;

R⁵¹ is independently selected at each occurrence from:

hydrogen and C₁₋₆ alkyl;

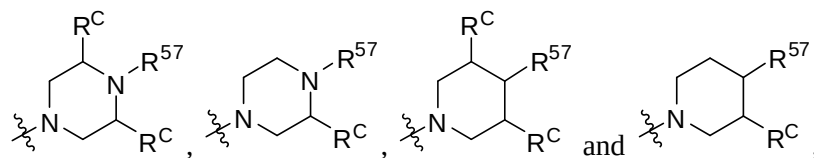
R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, -CN, -NO₂, -NH₂, -NHCH₃, -NHCH₂CH₃, =O, -OH, -OCH₃, -OCH₂CH₃, 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.

2. The compound of claim 1, wherein each R^C is independently selected from -C(O)R⁵², -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², C₁₋₃ alkyl, and C₁₋₃ haloalkyl, or two R^C groups attached to different atoms can together form a C₁₋₃ bridge, or two R^C groups are taken together to form =O.

3. The compound of claim 1 or 2, wherein C is 5- to 12-membered saturated heterocycle, wherein the heterocycle comprises at least one nitrogen atom.

4. The compound of claim 1, wherein C is selected from:



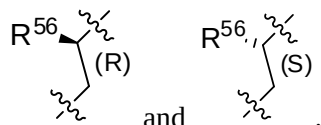
wherein R⁵⁷ is selected from -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², and C₁₋₁₀ alkyl, wherein the C₁₋₁₀ alkyl is substituted with one or more substituents selected from -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, and -NR⁵²S(=O)₂R⁵².

5. The compound of any one of the preceding claims, wherein m is 0 and n is an integer from 1 to 3.

6. The compound of any one of the preceding claims, wherein R^2 is selected from $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, $-CN$, and C_{1-2} alkyl.

7. The compound of any one of claims 1 to 5, wherein R^2 is selected from $-NH_2$, $-CH_3$, $-OCH_3$, $-CH_2OH$, and $-NHCH_3$.

8. The compound of any one of the preceding claims, wherein L^3 is selected from

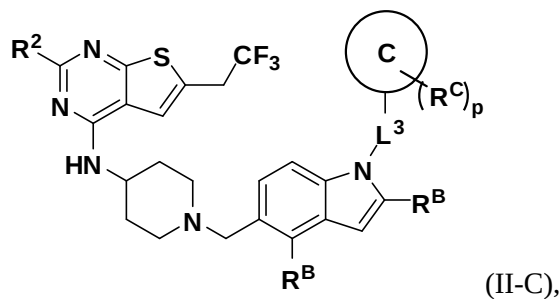


9. The compound of claim 1, wherein L^3 is .

10. The compound of claim 1, wherein L^3 is .

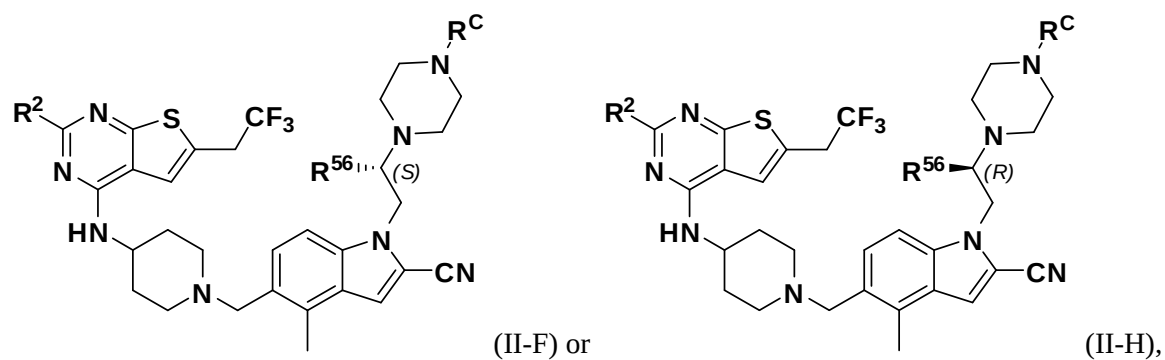
11. The compound of claim 1, wherein the compound is a stereoisomer provided in at least 90% enantiomeric excess.

12. The compound of claim 1, wherein the compound has the structure of Formula (II-C):



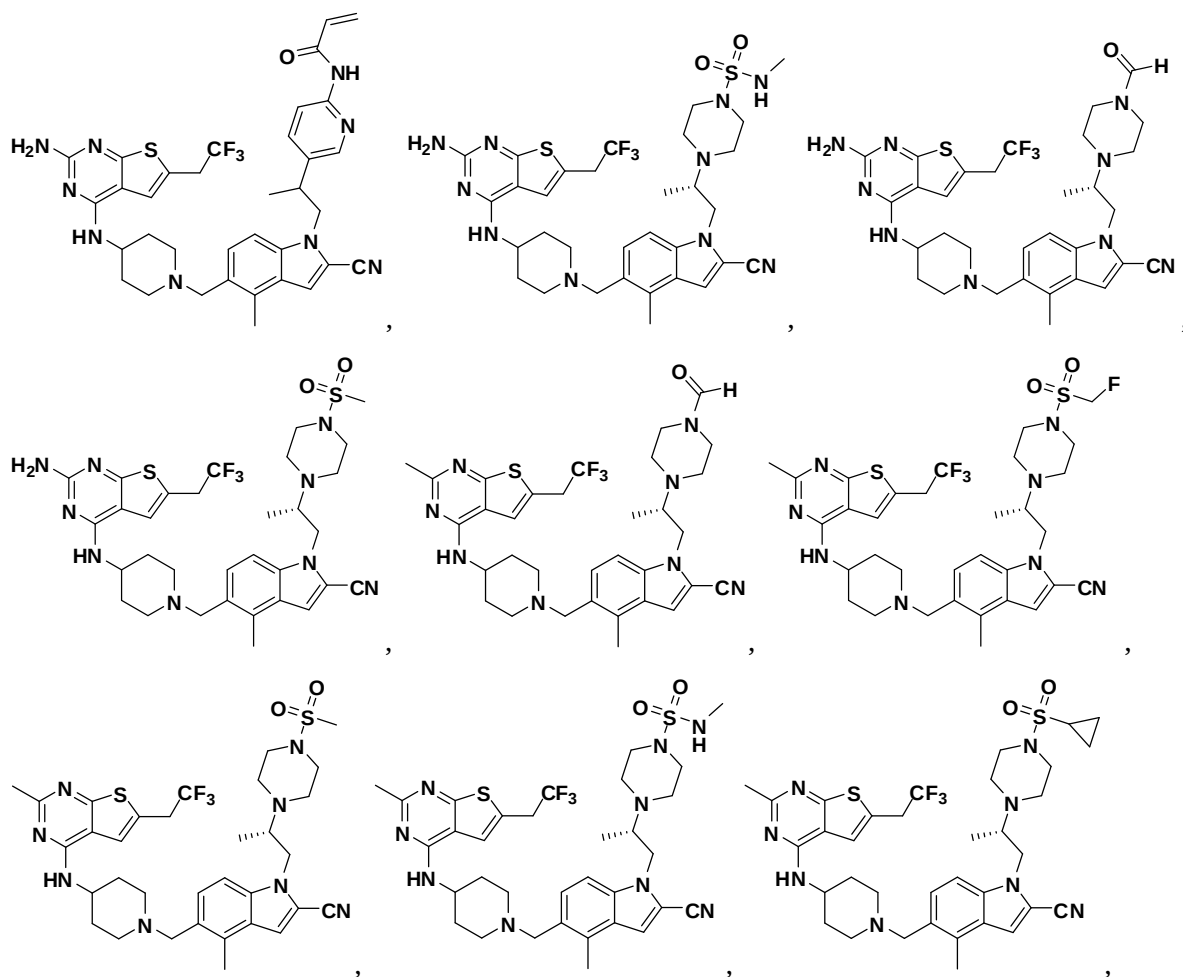
or a pharmaceutically acceptable salt thereof.

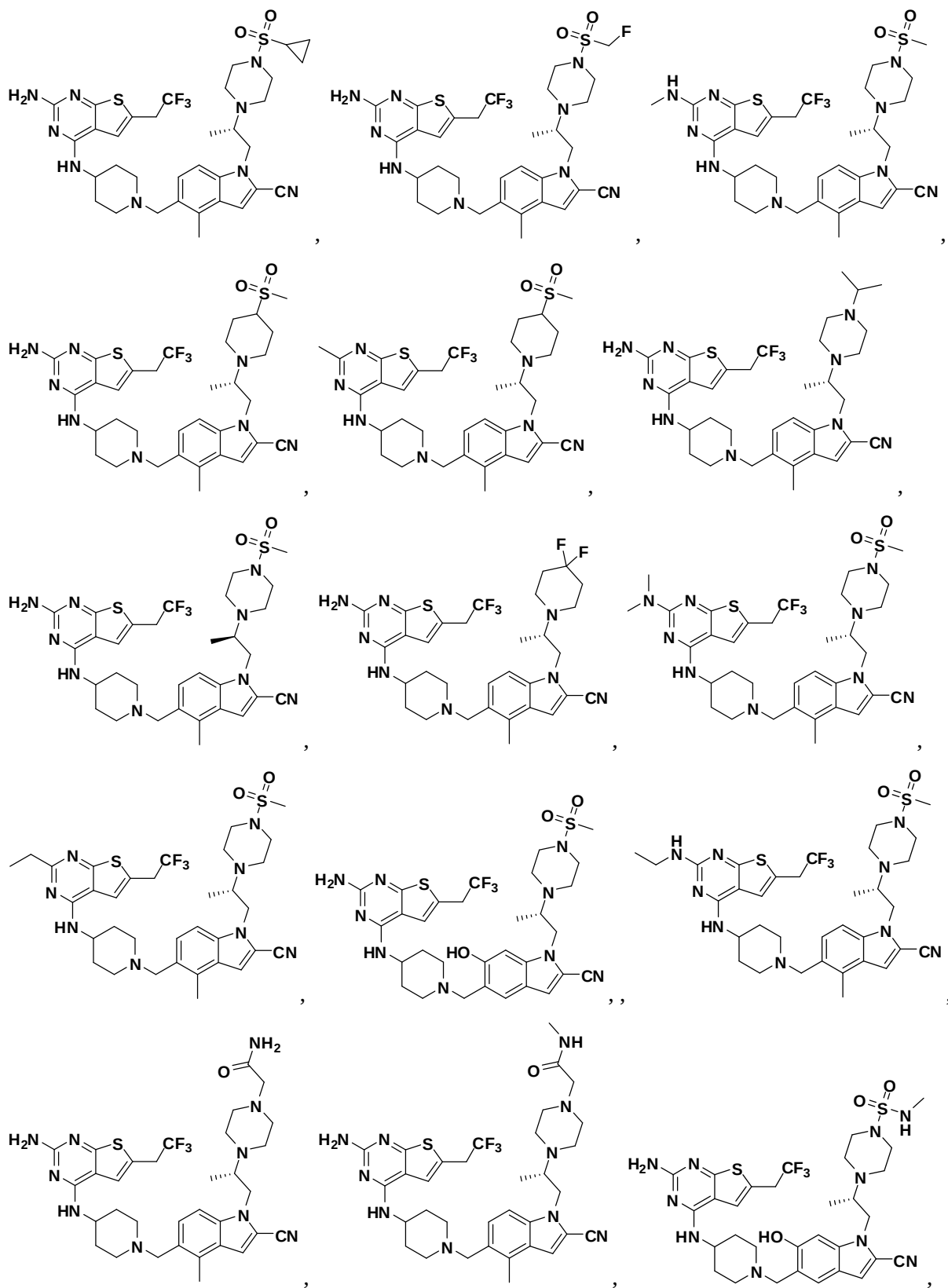
13. The compound of claim 1, wherein the compound has the structure of Formula (II-F) or Formula (II-H):

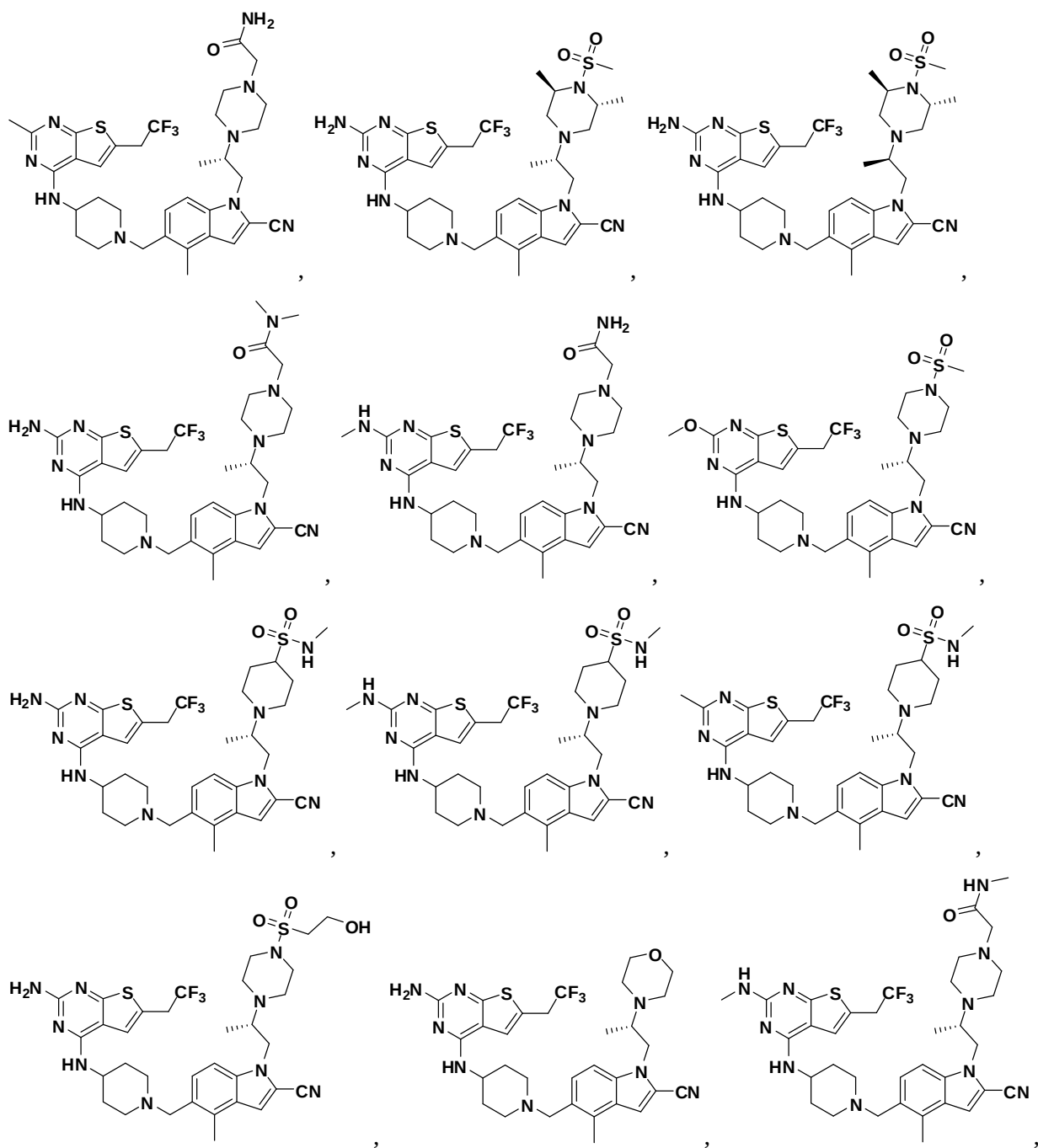


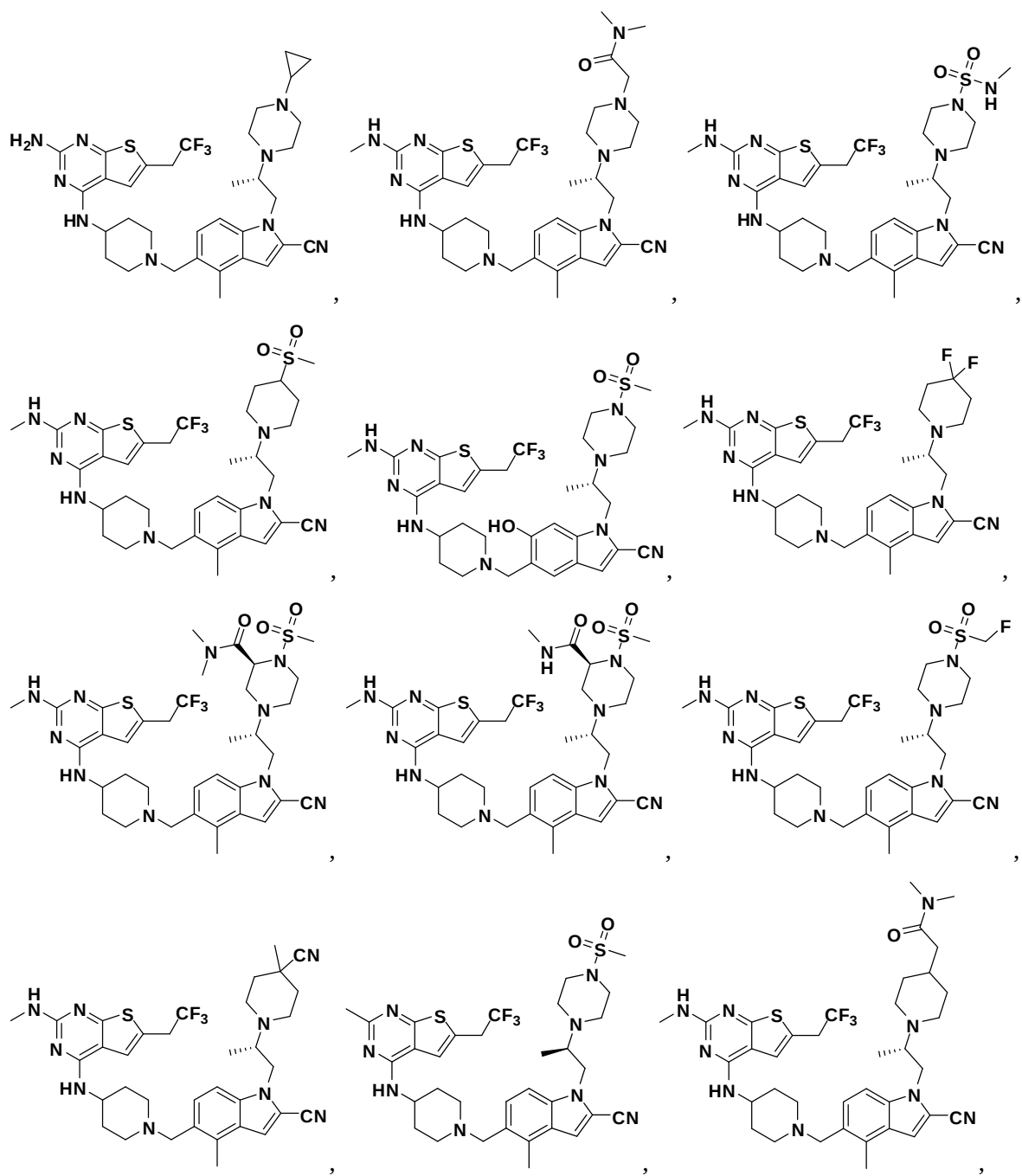
or a pharmaceutically acceptable salt thereof.

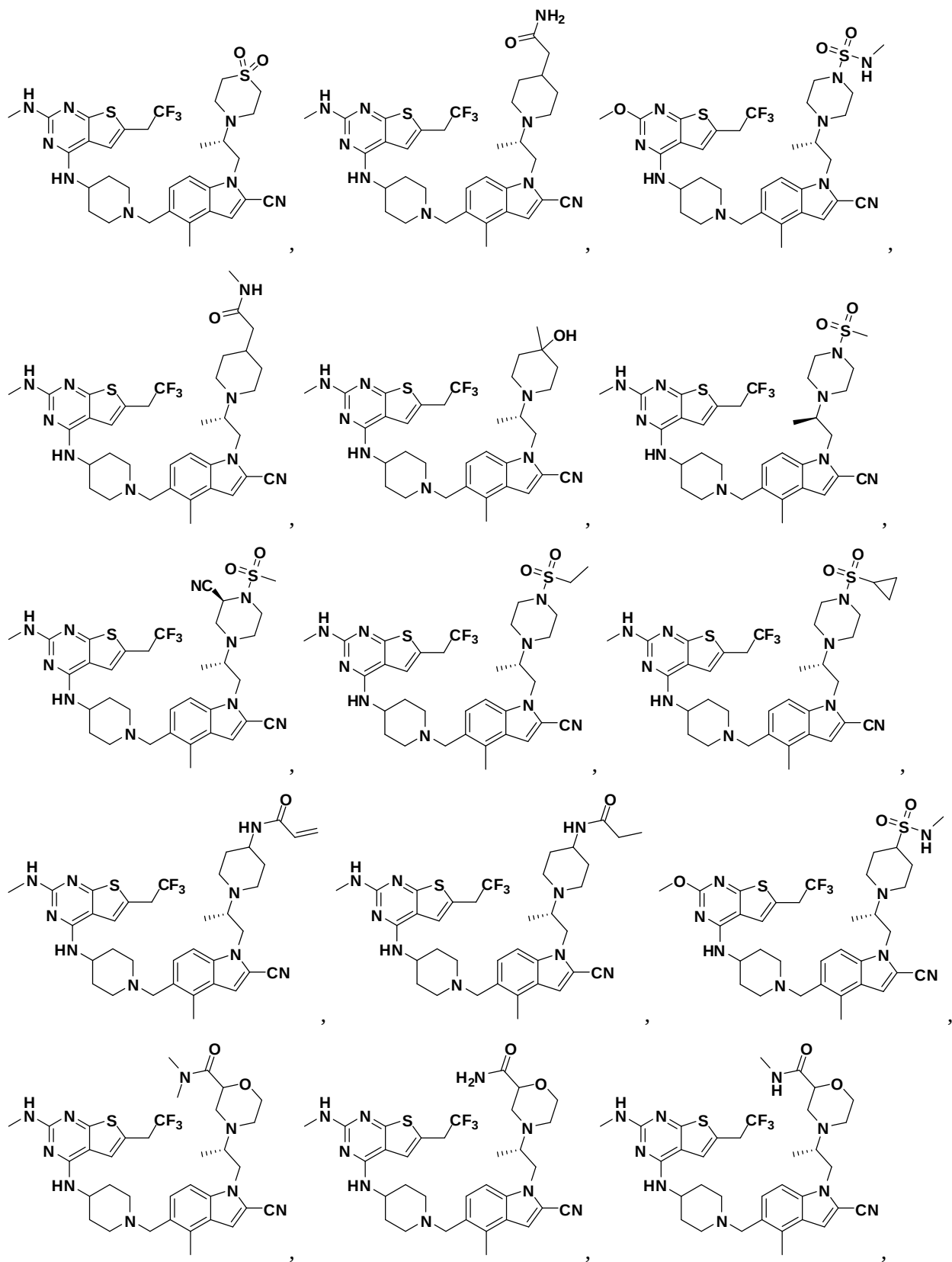
14. The compound of claim 1, wherein the compound is:

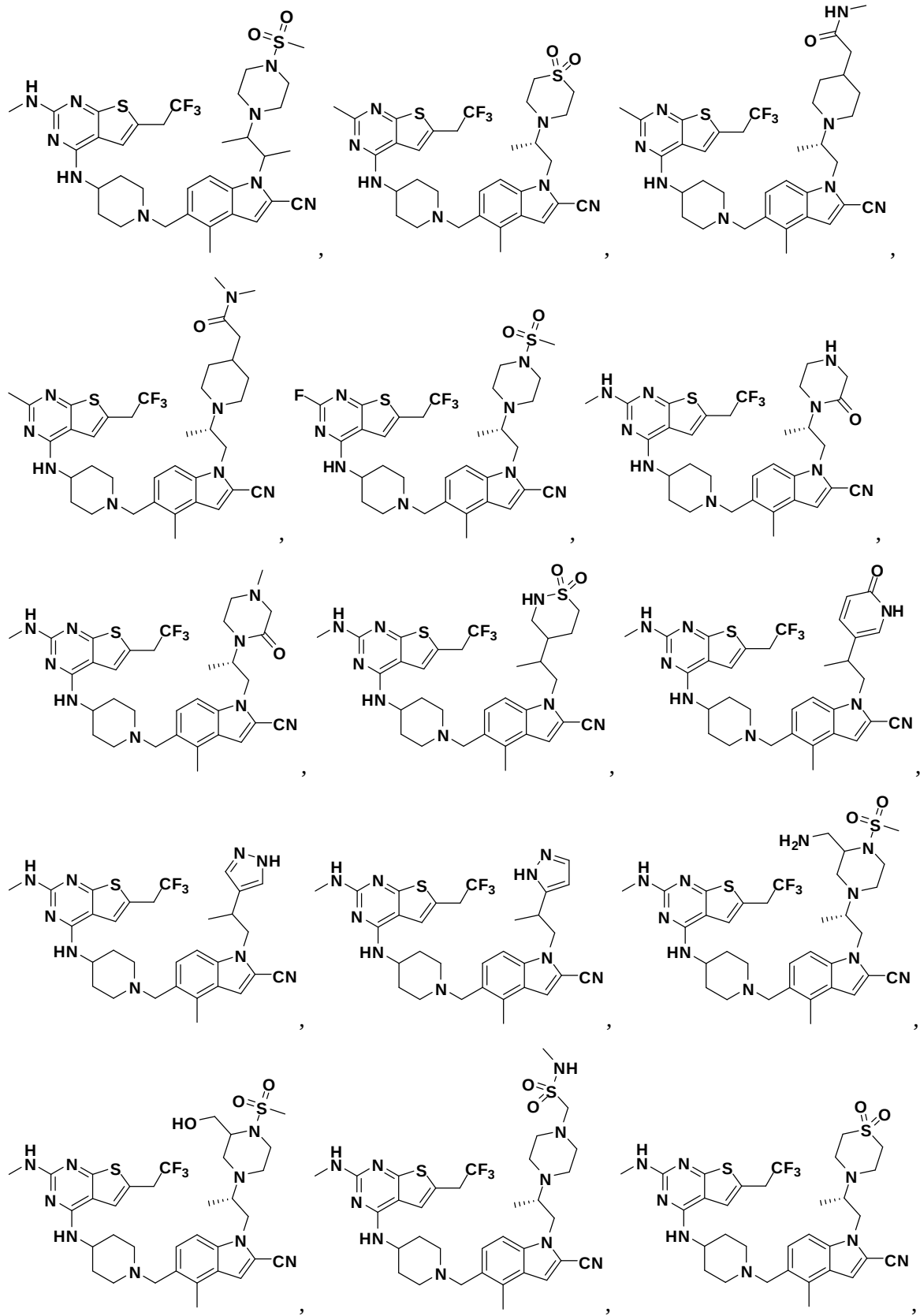




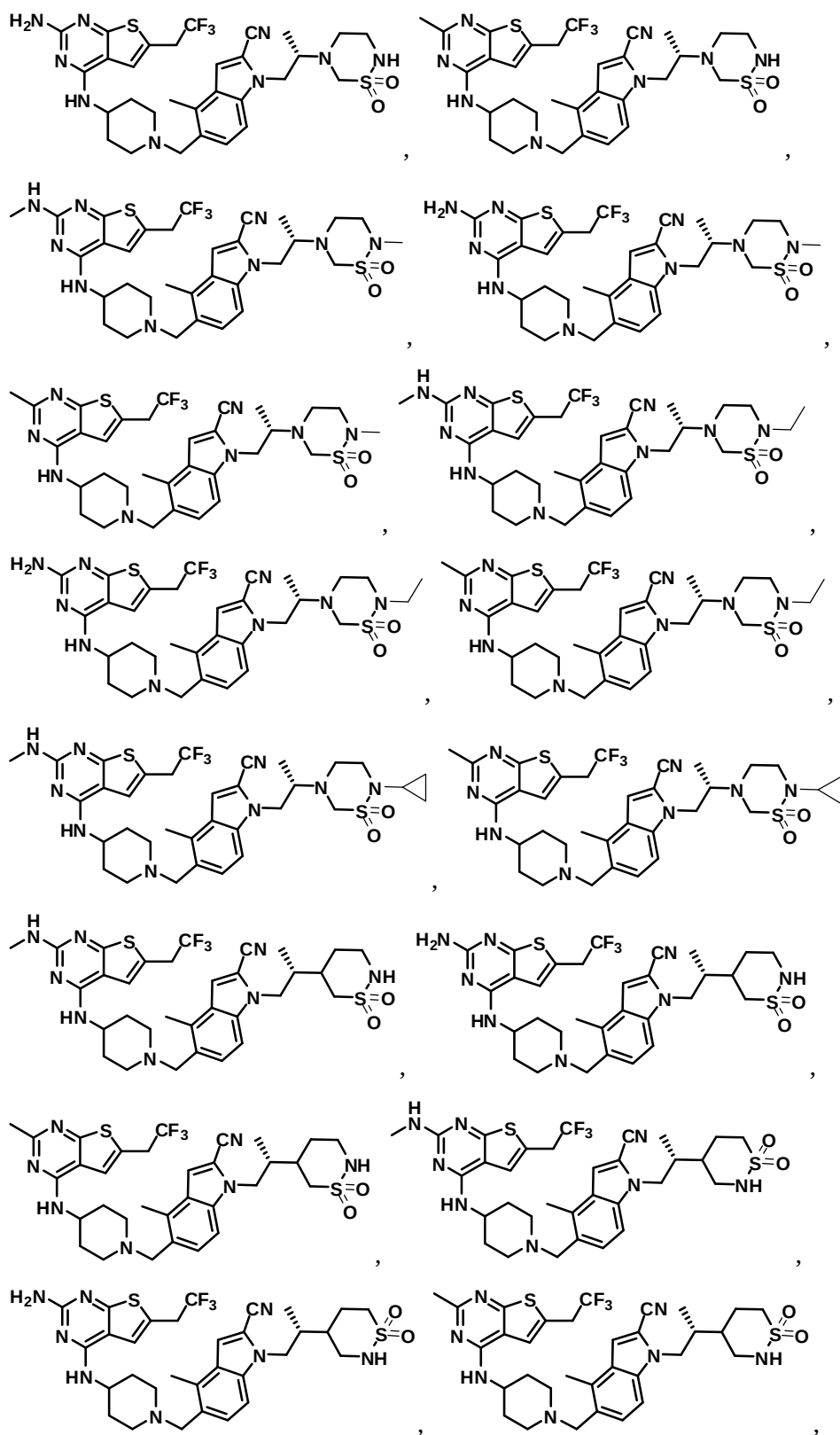


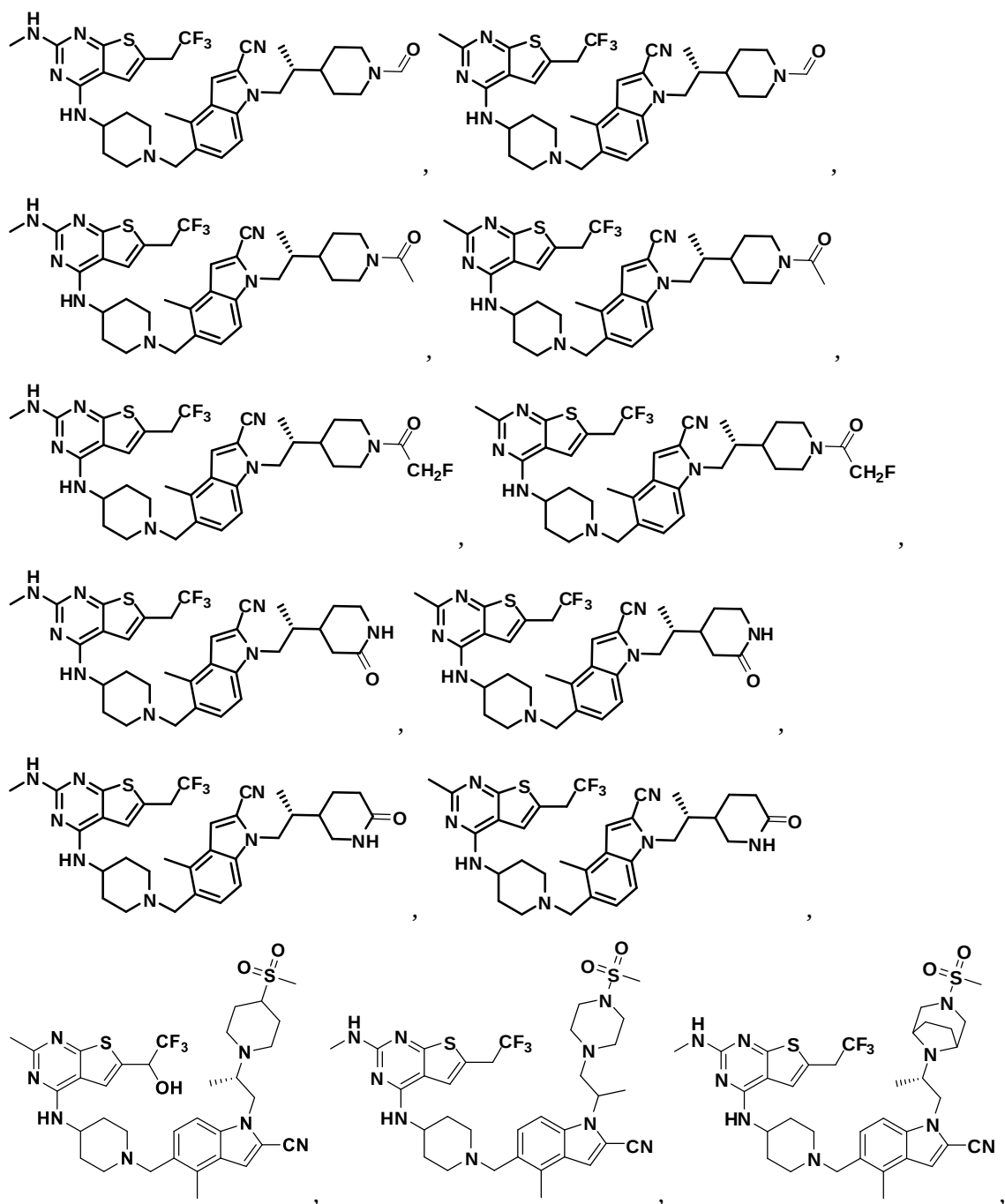


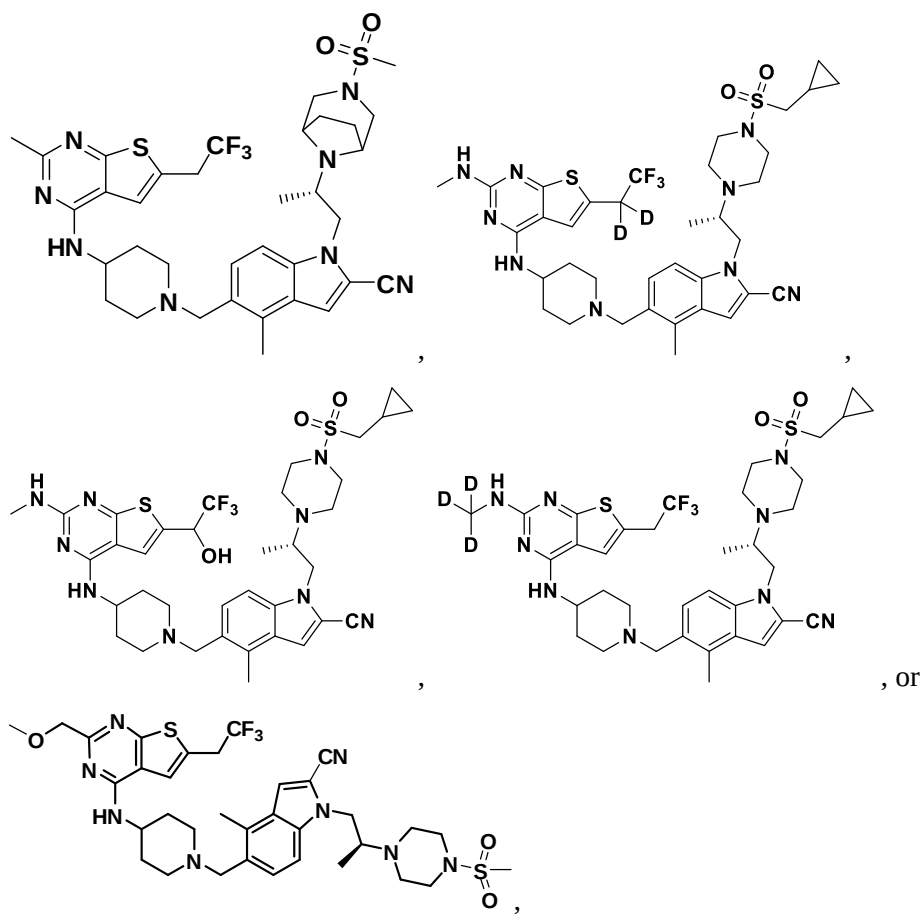






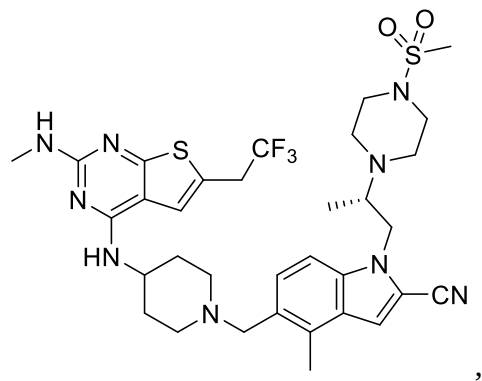






or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound of any one of the preceding claims and a pharmaceutically acceptable carrier.

17. Use of a compound or salt of any one of claims 1 to 15 in the manufacture of a medicament for the treatment of leukemia, a hematologic malignancy, a solid tumor cancer, prostate

cancer, breast cancer, liver cancer, a brain tumor, or diabetes.