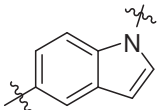


some embodiments, A is selected from piperidinylene and piperazinylene, such as

[0012] For a compound of Formula (I), B may be 6- to 12-membered bicyclic heterocycle. In some embodiments, the heterocycle comprises at least one nitrogen atom. In some embodiments, B is

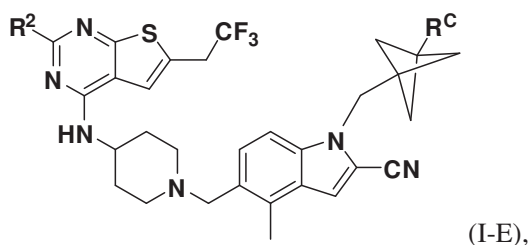


indolylene, such as, optionally substituted with one or more R^B .

[0013] In some embodiments, for a compound of Formula (I), H is thienopyrimidinyl substituted with one or more R^{50} ; A is selected from piperidinylene and piperazinylene; and B is indolylene.

[0014] In some embodiments, for a compound of Formula (I), H is substituted with $-CH_2CF_3$. In some embodiments, m is 0. In some embodiments, n is an integer from 1 to 3. In some embodiments, L^1 comprises less than 10 atoms. In some embodiments, L^1 is $-N(R^{51})-$. In some embodiments, L^2 comprises less than 10 atoms. In some embodiments, L^2 is C_{1-4} 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^3 comprises less than 20 atoms. In some embodiments, L^3 is C_{1-4} alkylene, optionally substituted with one or more R^{50} . In some embodiments, L^3 is $-CH_2-$. In some embodiments, a compound of Formula (I) is selected from Table 1.

[0014a] In certain aspects, the present disclosure provides a compound of Formula (I-E):



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

R^2 is hydrogen or R^{50} ;

R^C is R^{50} ;

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

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

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

OC(O)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;

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, -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, optionally substituted with one or more R⁵⁰.

[0015] In certain aspects, the present disclosure provides a pharmaceutical composition comprising a compound or salt of Formula (I) and a pharmaceutically acceptable carrier. In certain aspects, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (I-E) and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In some embodiments, the pharmaceutical composition is formulated for injection.

[0016] In certain aspects, the present disclosure provides a method of inhibiting an interaction of menin with one or more of MLL1, MLL2, an MLL fusion protein, and an MLL Partial Tandem Duplication, comprising contacting menin with an effective amount of a compound or salt of Formula (I). In certain aspects, the present disclosure provides a method of inhibiting 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 of Formula (I-E). In certain aspects, the present disclosure provides a method of inhibiting a menin-MLL interaction, comprising contacting menin with an effective amount of a compound or salt of Formula (I), wherein inhibition of the interaction is evidenced by a reduction in expression of an MLL fusion protein target gene. In certain aspects, the present disclosure provides a method of stabilizing menin, comprising contacting menin with a compound or salt of Formula (I).

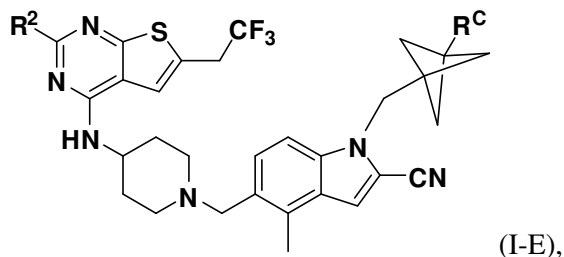
[0017] In practicing any of the subject methods, the MLL fusion protein target gene may be *HoxA9*, *DLX2*, or *MEIS1*. The contacting may comprise contacting a cell that expresses menin. In some embodiments, the method comprises administering a second therapeutic agent. In some embodiments, the contacting takes place *in vivo*. In some embodiments, the contacting takes place *in vitro*.

[0018] In certain aspects, the present disclosure provides a method of treating a disease or condition associated with MLL fusion proteins, comprising administering to a subject in need thereof an effective amount of a compound or salt of Formula (I). In certain aspects, the present disclosure provides a method of treating a disease or condition in a subject, comprising administering to the subject a therapeutically

CLAIMS

What is claimed is:

1. A compound of Formula (I-E):



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

R^2 is hydrogen or R^{50} ;

R^C is R^{50} ;

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

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

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

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

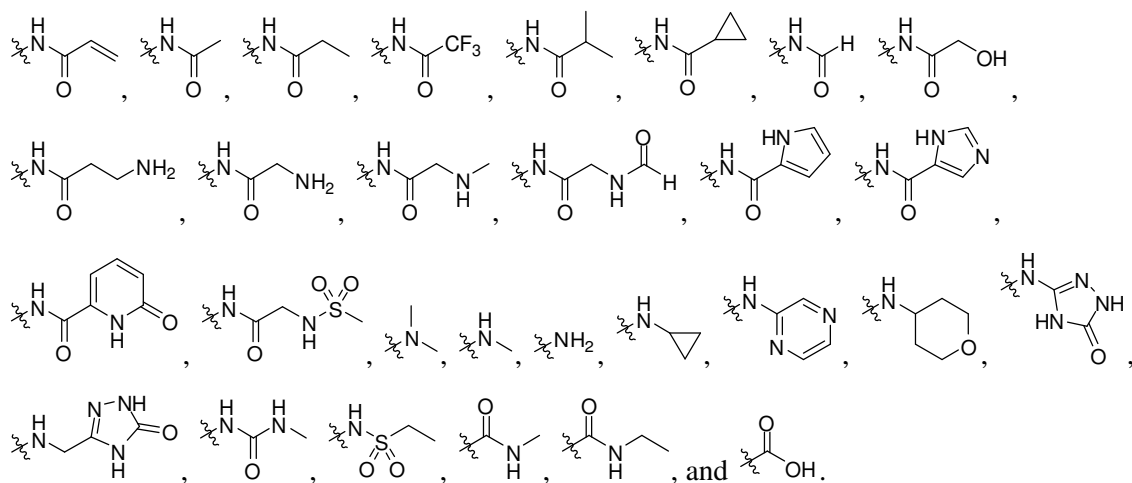
wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{50} is independently optionally substituted with one or more substituents selected from halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$,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

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

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} .

2. The compound of claim 1, wherein R^C is selected from -N(R^{52})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.

3. The compound of claim 1, wherein R^C is selected from



4. The compound of claim 1, wherein R^2 is selected from hydrogen, halogen, -OH, -OR⁵², -NH₂, -N(R⁵²)₂, -CN, C_{1-3} alkyl, C_{1-3} alkyl-N(R⁵²)₂, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

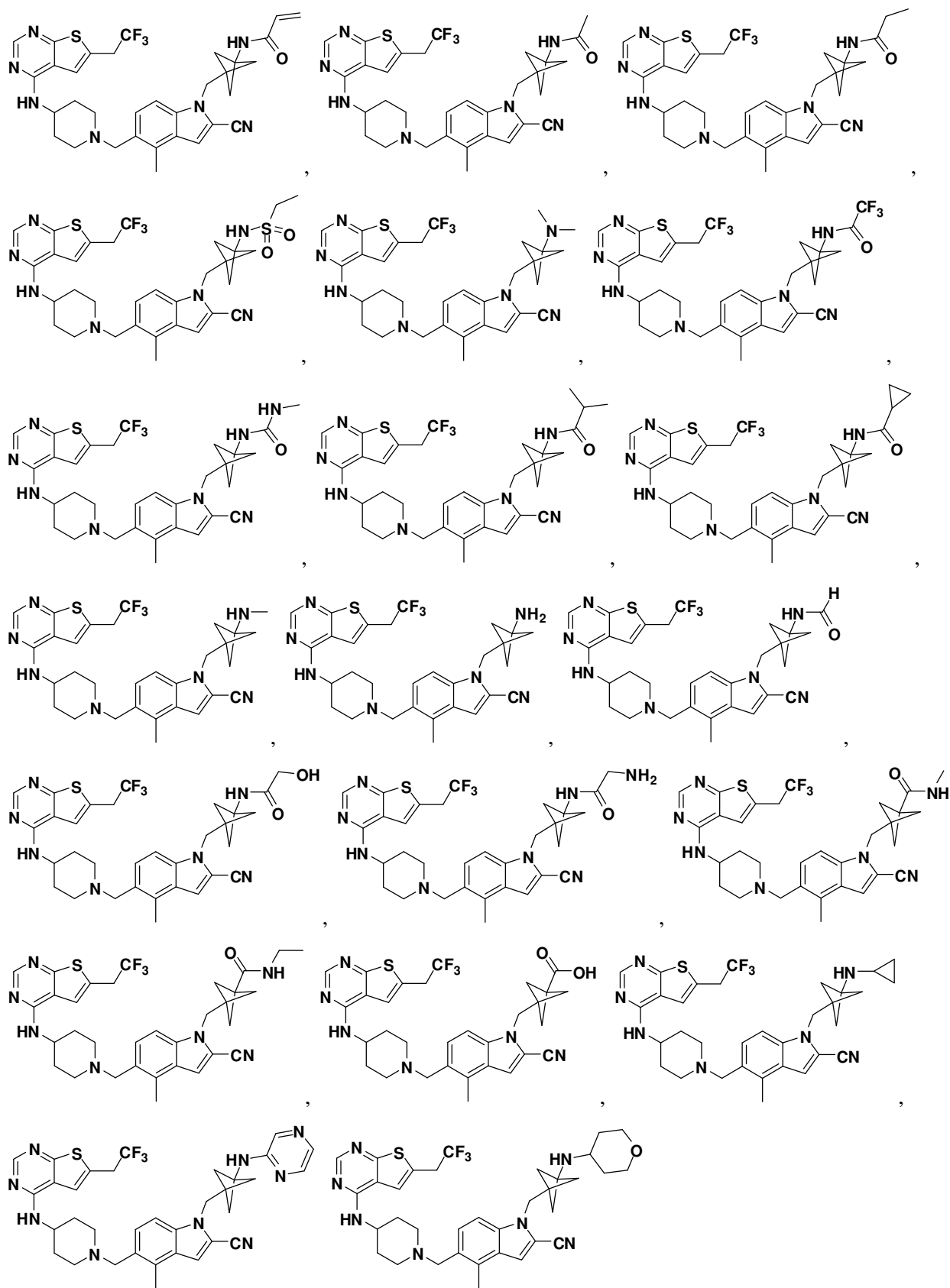
5. The compound of claim 1, wherein R^2 is selected from hydrogen, halogen, -OH, -OR⁵², -NH₂, -N(R⁵²)₂, -CN, C_{1-3} alkyl, -CH₂OH, -CH₂OR⁵², -CH₂NH₂, -CH₂N(R⁵²)₂, C_{1-3} alkyl-N(R⁵²)₂, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

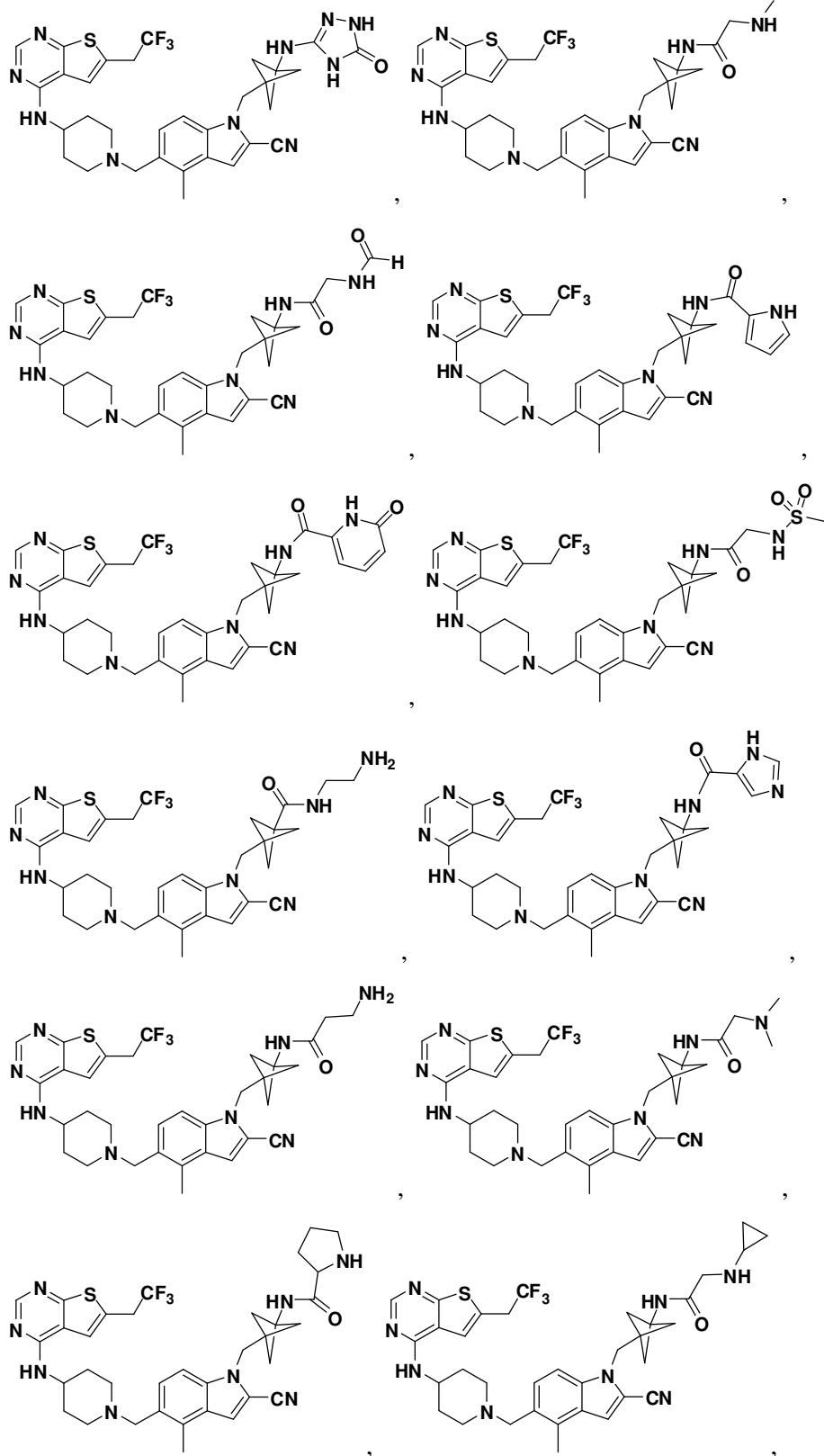
6. The compound of claim 1, wherein R^2 is selected from -NH₂, -CH₃, -OCH₃, -CH₂OH, and -NHCH₃.

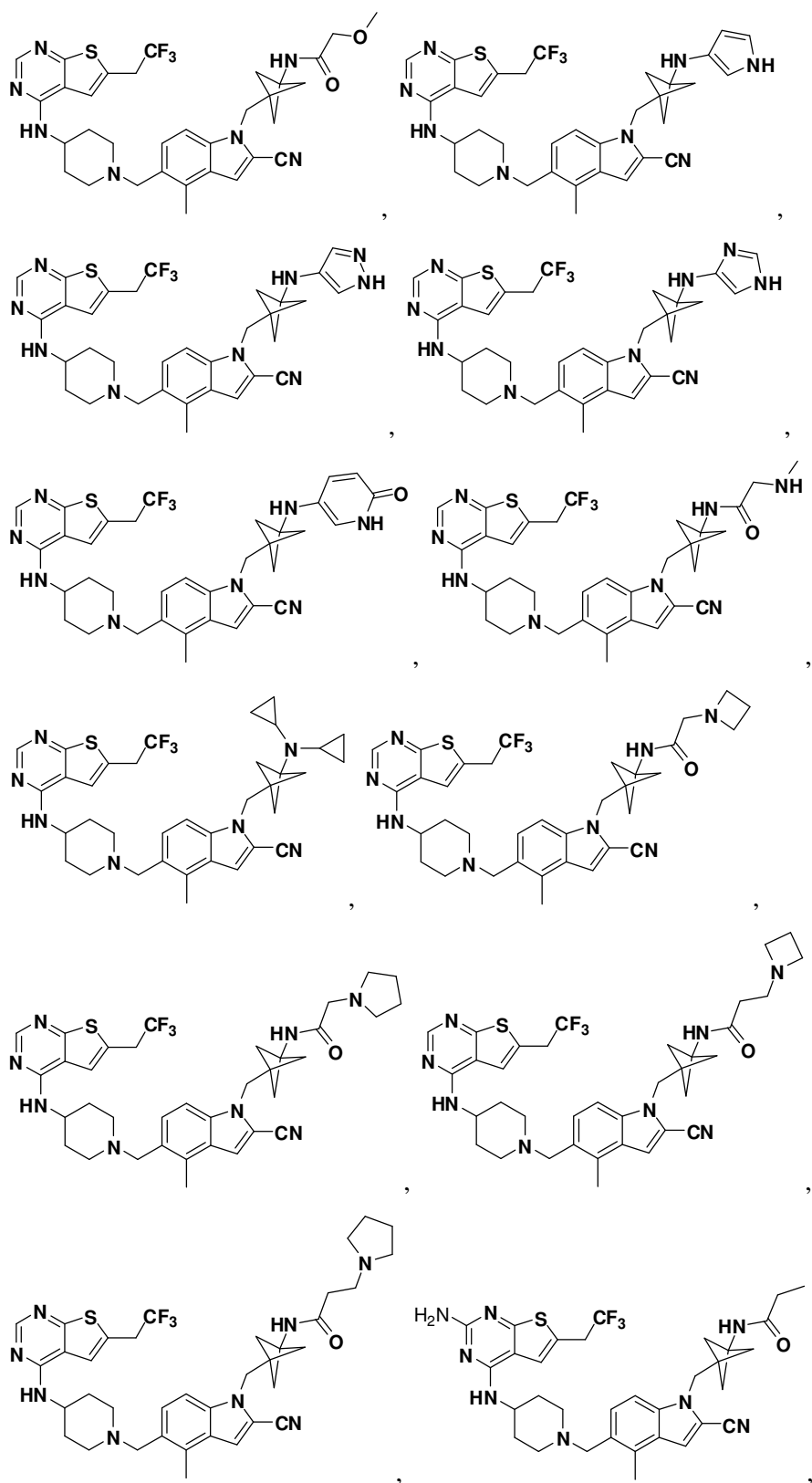
7. The compound of claim 1, wherein R^2 is methyl or -NHCH₃.

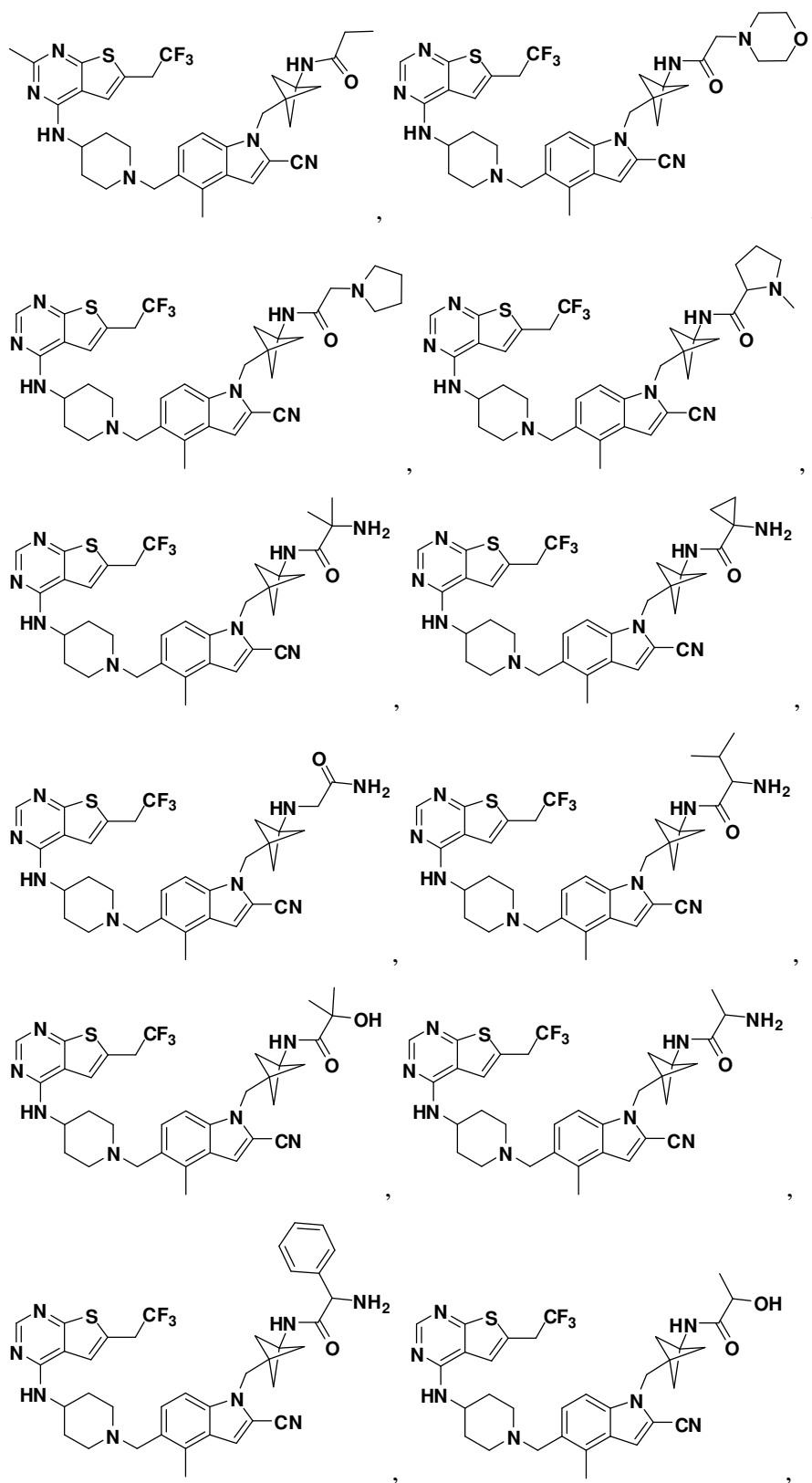
8. The compound of claim 1, wherein R^2 is H.

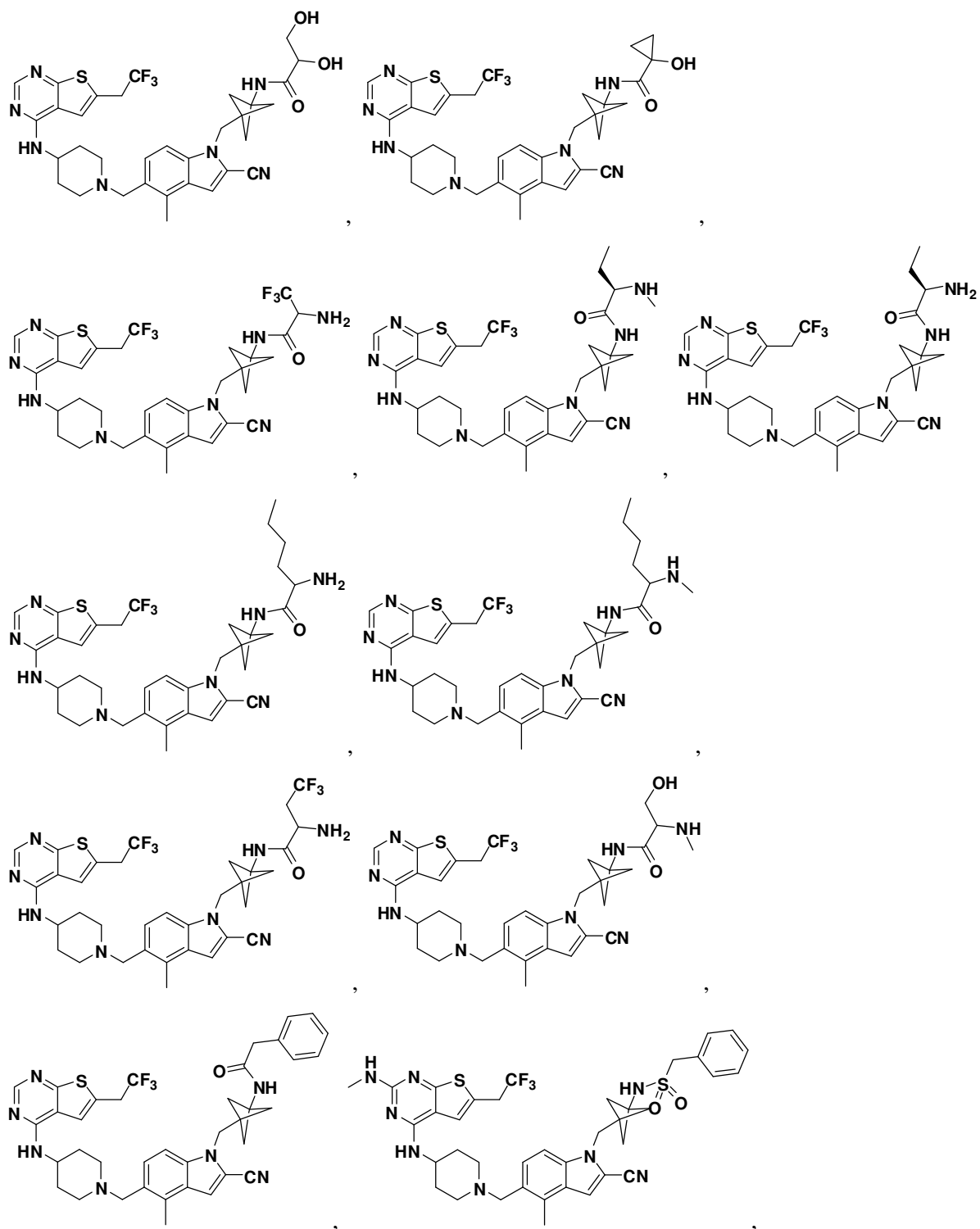
9. The compound of claim 1, wherein the compound is selected from the group consisting of:

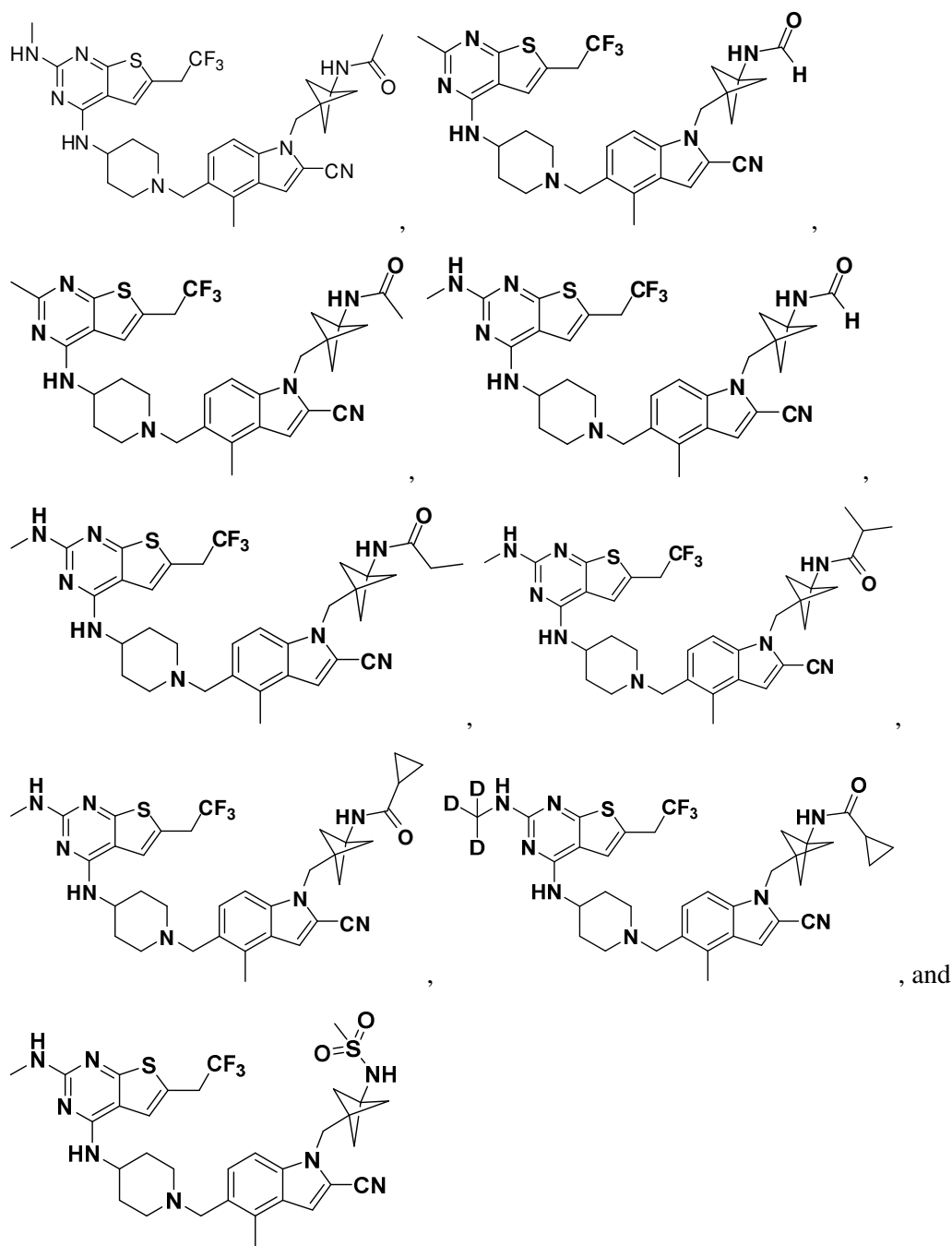












10. A pharmaceutical composition comprising a compound of any one of the preceding claims and a pharmaceutically acceptable carrier.

11. 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 of any one of claims 1 to 9.

12. Use of a compound or salt of any one of claims 1 to 9 in the manufacture of a medicament for the treatment of a leukemia, a hematologic malignancy, a solid tumor cancer, prostate

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