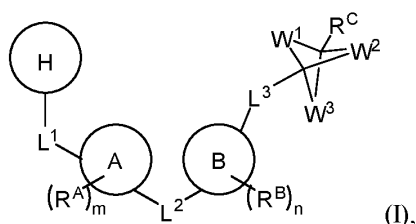


CLAIMS

What is claimed is:

1. 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;

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;

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;

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

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

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

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

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)₂N(R⁵²)₂, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂N(R⁵²)₂, -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);

C₁₋₁₀ 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)₂N(R⁵²)₂, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂N(R⁵²)₂, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -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, -P(O)(R⁵²)₂, =O, =S, =N(R⁵²);

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

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

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

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

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

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{51} is independently optionally substituted with one or more substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N(R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S(=O)R}^{52}$, $-\text{S(=O)}_2\text{R}^{52}$, $-\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S(=O)}_2\text{R}^{52}$, $-\text{NR}^{52}\text{S(=O)}_2\text{N(R}^{52})_2$, $-\text{NR}^{52}\text{S(=O)}_2\text{NR}^{53}\text{R}^{54}$, $-\text{C(O)R}^{52}$, $-\text{C(O)OR}^{52}$, $-\text{OC(O)R}^{52}$, $-\text{OC(O)OR}^{52}$, $-\text{OC(O)N(R}^{52})_2$, $-\text{OC(O)NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C(O)R}^{52}$, $-\text{NR}^{52}\text{C(O)OR}^{52}$, $-\text{NR}^{52}\text{C(O)N(R}^{52})_2$, $-\text{NR}^{52}\text{C(O)NR}^{53}\text{R}^{54}$, $-\text{C(O)N(R}^{52})_2$, $-\text{C(O)NR}^{53}\text{R}^{54}$, $-\text{P(O)(OR}^{52})_2$, $-\text{P(O)(R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N(R}^{52})$, 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, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle; and

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} ,

wherein for a compound or salt of Formula (I), when W^3 is absent:

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

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

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} .

2. The compound of claim 1, wherein W^1 , W^2 and W^3 are each independently selected from C_{1-4} alkylene, wherein each C_{1-4} alkylene is optionally substituted with one or more R^{50} .

3. The compound of claim 2, wherein W^1 , W^2 and W^3 are each C_1 alkylene.

4. The compound of claim 1, wherein W^1 and W^2 are each C_1 alkylene and W^3 is absent.

5. The compound of any one of the preceding claims, wherein R^C is selected from $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$, $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, and $-C(O)NR^{53}R^{54}$.

6. The compound of any one of the preceding claims, wherein:

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

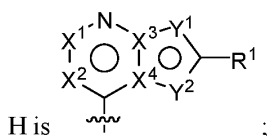
A is 3- to 12-membered heterocycle; and

B is 3- to 12-membered heterocycle.

7. The compound of any one of the preceding claims, wherein H is 6- to 12-membered bicyclic heterocycle, optionally substituted with one or more R^{50} .

8. The compound of claim 7, wherein H is thienopyrimidinyl, optionally substituted with one or more R^{50} .

9. The compound of claim 7, wherein:



X^1 and X^2 are each independently selected from CR^2 and N;

X^3 and X^4 are each independently selected from C and N;

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} .

10. The compound of claim 9, wherein X^3 and X^4 are each C.

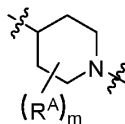
11. The compound of claim 9 or 10, wherein X^1 is CR^2 , and R^2 is selected from hydrogen, halogen, $-OH$, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, $-CN$, C_{1-3} alkyl, C_{1-3} alkyl- $N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

12. The compound of claim 9 or 10, wherein X^1 is CR^2 , and R^2 is selected from hydrogen, halogen, $-OH$, $-OR^{52}$, $-NH_2$, $-N(R^{52})_2$, $-CN$, C_{1-3} alkyl, $-CH_2OH$, $-CH_2OR^{52}$, $-CH_2NH_2$, $-CH_2N(R^{52})_2$, C_{1-3} alkyl- $N(R^{52})_2$, C_{1-3} haloalkyl, C_{2-3} alkenyl, and C_{2-3} alkynyl.

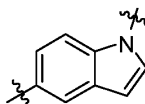
13. The compound of any one of claims 9 to 12, wherein X^2 is N.

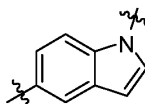
14. The compound of any one of claims 9 to 13, wherein Y^2 is CR^3 , and R^3 is selected from hydrogen, halogen, $-OH$, $-N(R^{52})_2$, $-CN$, $-C(O)OR^{52}$, C_{1-3} alkyl, and C_{1-3} haloalkyl.

15. The compound of any one of claims 9 to 14, wherein R^1 is C_{1-3} haloalkyl.
16. The compound of any one of the preceding claims, wherein A is 5- to 8-membered heterocycle.
17. The compound of claim 16, wherein A is 6-membered monocyclic heterocycle.
18. The compound of claim 16 or 17, wherein the heterocycle comprises at least one nitrogen atom.
19. The compound of claim 18, wherein A is selected from piperidinylene and piperazinylene.



20. The compound of claim 19, wherein A is $(R^A)_m$.
21. The compound of any one of the preceding claims, wherein B is 6- to 12-membered bicyclic heterocycle.
22. The compound of claim 21, wherein the heterocycle comprises at least one nitrogen atom.
23. The compound of claim 22, wherein B is indolylene.



24. The compound of claim 23, wherein B is , optionally substituted with one or more R^B .
25. The compound of claim 6, wherein:
H is thienopyrimidinyl substituted with one or more R^{50} ;
A is selected from piperidinylene and piperazinylene; and
B is indolylene.

26. The compound of any one of the preceding claims, wherein H is substituted with - CH_2CF_3 .
27. The compound of any one of the preceding claims, wherein m is 0.
28. The compound of any one of the preceding claims, wherein n is an integer from 1 to 3.
29. The compound of any one of the preceding claims, wherein L^1 comprises less than 10 atoms.
30. The compound of any one of the preceding claims, wherein L^1 is $-N(R^{51})-$.
31. The compound of any one of the preceding claims, wherein L^2 comprises less than 10 atoms.
32. The compound of any one of the preceding claims, wherein L^2 is C_{1-4} alkylene, optionally substituted with one or more R^{50} .
33. The compound of any one of claims 1 to 31, wherein L^2 is selected from $-CH_2-$, $-N(R^{51})-$, $-N(R^{51})CH_2-$, $-N(R^{51})C(O)-$, and $-N(R^{51})S(O)_2-$.
34. The compound of any one of the preceding claims, wherein L^3 comprises less than 20 atoms.

35. The compound of any one of the preceding claims, wherein L^3 is C_{1-4} alkylene, optionally substituted with one or more R^{50} .
36. The compound of any one of the preceding claims, wherein L^3 is $-CH_2-$.
37. The compound of any one of the preceding claims, wherein the compound is isotopically enriched.
38. A compound selected from Table 1.
39. A pharmaceutical composition comprising a compound of any one of the preceding claims and a pharmaceutically acceptable carrier.
40. The pharmaceutical composition of claim 39, wherein the pharmaceutical composition is formulated for oral administration.
41. The pharmaceutical composition of claim 39, wherein the pharmaceutical composition is formulated for injection.
42. 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 38.
43. A method of inhibiting a menin-MLL interaction, comprising contacting menin with an effective amount of a compound of any one of claims 1 to 38, wherein inhibition of the interaction is evidenced by a reduction in expression of an MLL fusion protein target gene.
44. The method of claim 43, wherein the MLL fusion protein target gene is *HOXA9*, *DLX2*, or *MEIS1*.
45. A method of stabilizing menin, comprising contacting menin with a compound of any one of claims 1 to 38.
46. The method of any one of claims 42-45, wherein the contacting comprises contacting a cell that expresses menin.
47. The method of any one of claims 42-45, comprising administering a second therapeutic agent.
48. The method of any one of claims 42-45, wherein the contacting takes place *in vivo*.
49. The method of any one of claims 42-45, wherein the contacting takes place *in vitro*.
50. A method of treating a disease or condition associated with MLL fusion proteins, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1 to 38.
51. 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 of any one of claims 1 to 38.
52. The method of claim 50 or 51, wherein the disease or condition comprises a leukemia, hematologic malignancy, solid tumor cancer, prostate cancer, breast cancer, liver cancer, brain tumor, or diabetes.
53. The method of claim 52, wherein the leukemia comprises AML, ALL, Mixed Lineage

Leukemia or a leukemia with Partial Tandem Duplications of MLL.

54. A method of treating a disorder mediated by chromosomal rearrangement on chromosome 11q23 in a subject in need thereof, the method comprising: administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 38.

55. A method of treating a disorder mediated by an interaction between menin and another protein, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 38.

56. The method of any one of claims 50-55, wherein the subject is a human.

57. A kit comprising a pharmaceutical composition of claim 39 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.