

effective amount of a pharmaceutical composition of a compound or salt of Formula (I). In some embodiments, the disease or condition comprises a leukemia, hematologic malignancy, solid tumor cancer, prostate cancer, breast cancer, liver cancer, brain tumor, or diabetes. In some embodiments, the leukemia comprises AML, ALL, Mixed Lineage Leukemia or a leukemia with Partial Tandem Duplications of MLL.

[0019] In certain aspects, the present disclosure provides a method of treating a disorder mediated by chromosomal rearrangement on chromosome 11q23 in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound or salt of Formula (I). In certain aspects, the present disclosure provides a method of treating a disorder mediated by an interaction between menin and another protein, comprising administering to a subject in need thereof a therapeutically effective amount of a compound or salt of Formula (I). In some embodiments, the subject is a human.

[0020] In certain aspects, the present disclosure provides a kit comprising a pharmaceutical composition described herein and instructions for using the composition to treat a subject suffering from a disease or condition mediated by an interaction between menin and another protein.

[0020a] In certain aspects, the present disclosure provides a use of a compound or salt as described herein 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.

INCORPORATION BY REFERENCE

[0021] 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

[0022] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0023] **FIG. 1** is an amino acid sequence of human menin, isoform 1 (SEQ ID NO: 1).

[0024] **FIG. 2** is an amino acid sequence of human menin, isoform 2 (SEQ ID NO: 2).

[0025] **FIG. 3** is an amino acid sequence of human menin, isoform 3 (SEQ ID NO: 3).

[0026] **FIG. 4** depicts the change in volume of MV4;11 tumors in vehicle and compound A treated mice.

[0027] **FIG. 5** depicts the change in volume of MV4;11 tumors in vehicle and compound B treated mice.

DETAILED DESCRIPTION OF THE INVENTION

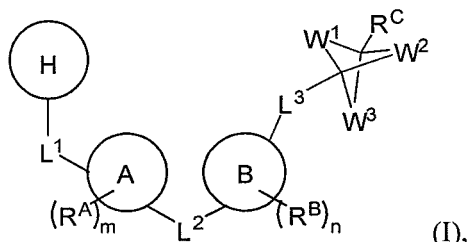
[0028] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0029] “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,

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)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);

C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently

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,

wherein for a compound or salt of Formula (I), when W³ is absent:

W¹ is C₁ alkylene, W² is a bond, and L³ is not a bond;

W¹ is C₂₋₄ alkylene and W² is a bond; or

W¹ and W² are each C₁ alkylene and L³ is not a bond, wherein each C₁ alkylene is independently optionally substituted with one or more R⁵⁰.

2. The compound of claim 1, wherein W¹, W² and W³ are each independently selected from C₁₋₄ alkylene, wherein each C₁₋₄ alkylene is optionally substituted with one or more R⁵⁰.

3. The compound of claim 2, wherein W¹, W² and W³ are each C₁ alkylene.

4. The compound of any one of the preceding claims, wherein 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.

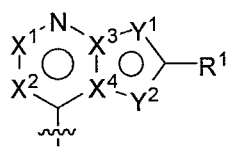
5. The compound of any one of the preceding claims, wherein:

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.

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



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.

7. The compound of claim 6, wherein 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 alkenyl, and C₂₋₃ alkynyl.

8. The compound of claim 6 or 7, wherein:

X^2 is N;

R^1 is C_{1-3} haloalkyl;

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.

9. The compound of claim 5, wherein:

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

A is selected from piperidinylene and piperazinylene; and

B is indolylene.

10. The compound of any one of the preceding claims, wherein m is 0.

11. The compound of any one of the preceding claims, wherein n is an integer from 1 to 3.

12. The compound of any one of the preceding claims, wherein L^1 is $-N(R^{51})-$.

13. 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} .

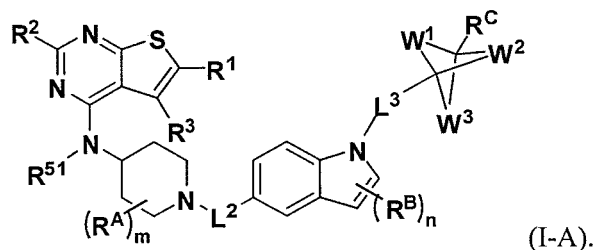
14. The compound of any one of the preceding claims, wherein L^3 is C_{1-4} alkylene, optionally substituted with one or more R^{50} .

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

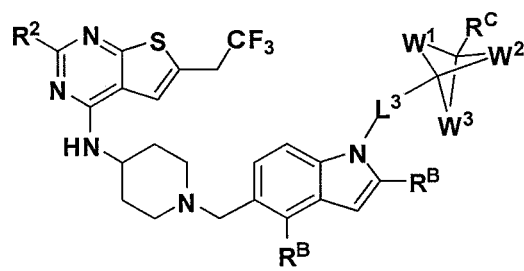
16. A method of inhibiting an interaction of menin with one or more of MLL1, MLL2, an MLL fusion protein, and an MLL Partial Tandem Duplication, comprising contacting menin with an effective amount of a compound of any one of claims 1 to 14.

17. Use of a compound or salt of any one of claims 1 to 14 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.

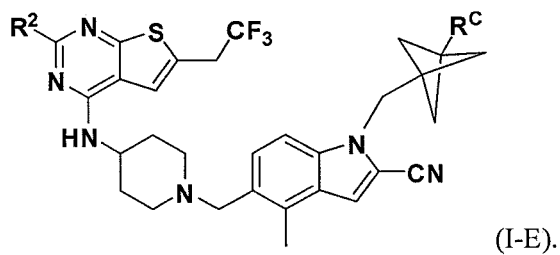
18. The compound of claim 1, wherein the compound has the structure of Formula (I-A):



19. The compound of claim 18, wherein the compound has the structure of Formula (I-C):



20. The compound of claim 19, wherein the compound has the structure of Formula (I-E):



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

