

INHIBITORS OF LYSINE SPECIFIC DEMETHYLASE-1

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application 62/020,886, filed July 3, 2014, which is incorporated herein by reference in its entirety.

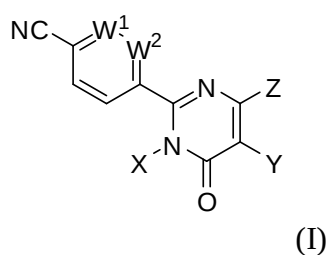
BACKGROUND

[0002] A need exists in the art for an effective treatment of cancer and neoplastic disease.

BRIEF SUMMARY OF THE INVENTION

[0003] Provided herein are substituted heterocyclic derivative compounds and pharmaceutical compositions comprising said compounds. The subject compounds and compositions are useful for inhibition lysine specific demethylase-1 (LSD-1). Furthermore, the subject compounds and compositions are useful for the treatment of cancer, such as prostate cancer, breast cancer, bladder cancer, lung cancer and/or melanoma and the like. The substituted heterocyclic derivative compounds described herein are based upon a central heterocyclic ring system, such as a thiazole or pyrimidinone, or the like. Said central heterocyclic ring system is further substituted with additional substituents, such as for example, a 4-cyanophenyl group and a heterocyclyl group.

[0004] One ~~example embodiment~~ provides a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof,



wherein,

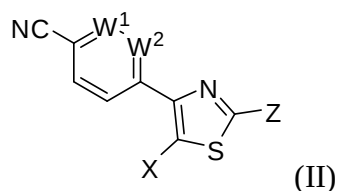
W^1 and W^2 are independently chosen from N, C-H, or C-F;

X is chosen from hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclylalkyl, optionally substituted aralkyl, optionally substituted heteroarylalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is chosen from hydrogen, halogen, optionally substituted alkyl, or optionally substituted cycloalkylalkyl; and

Z is chosen from an optionally substituted group chosen from *N*-heterocyclyl, -*O*-heterocyclalkyl, -N(H)-heterocyclalkyl, -N(H)-alkyl, -N(Me)-alkyl, or -N(Me)-heterocyclalkyl.

[0005] One exampleembodiment provides a compound having the structure of Formula (II), or a pharmaceutically acceptable salt thereof,



wherein,

W^1 and W^2 are independently chosen from N, C-H, or C-F;

X is chosen from hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkylamino, optionally substituted alkynyl, optionally substituted cycloalkylalkynyl, optionally substituted (cycloalkylalkyl)alkynyl, optionally substituted heterocyclalkynyl, optionally substituted (heterocyclalkyl)alkynyl, optionally substituted aryl, or optionally substituted heteroaryl; and

Z is chosen from an optionally substituted group chosen from *N*-heterocyclyl, -C(O)-*N*-heterocyclyl, -*O*-heterocyclalkyl, -N(H)-heterocyclalkyl, -N(H)-alkyl, -N(Me)-alkyl, or -N(Me)-heterocyclalkyl.

[0006] One exampleembodiment provides a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0007] One exampleembodiment provides a method of regulating gene transcription in a cell comprising inhibiting lysine-specific demethylase 1 activity by exposing the lysine-specific demethylase 1 enzyme to a compound of Formula (I).

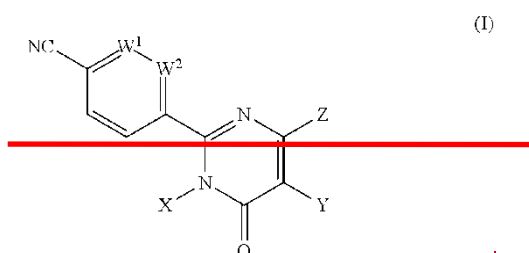
[0008] One exampleembodiment provides a method of treating cancer in a patient in need thereof, comprising administering to the patient a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0009] One exampleembodiment provides a pharmaceutical composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0010] One ~~example embodiment~~ provides a method of regulating gene transcription in a cell comprising inhibiting lysine-specific demethylase 1 activity by exposing the lysine-specific demethylase 1 enzyme to a compound of Formula (II).

[0011] One ~~example embodiment~~ provides a method of treating cancer in a patient in need thereof, comprising administering to the patient a compound of Formula (II), or a pharmaceutically acceptable salt thereof.

~~**[0011a]** One embodiment provides a compound having the structure of Formula (I);~~



~~wherein the compound of Formula (I) includes a pharmaceutically acceptable salt thereof, and wherein:~~

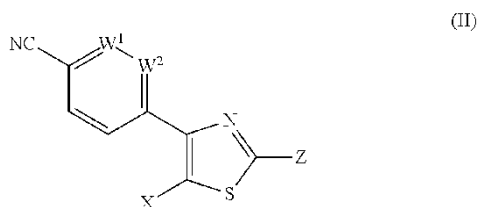
~~W¹ and W² are independently chosen from N, C—H, or C—F;~~

~~X is chosen from hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclalkyl, optionally substituted aralkyl, optionally substituted heteroarylalkyl, optionally substituted aryl, or optionally substituted heteroaryl;~~

~~Y is chosen from hydrogen, halogen, or methyl; and~~

~~Z is chosen from alkamino, alkoxy, heterocyclyl, heterocyclamino, heterocyclalkamino, or heterocyclalkoxy, each of which is optionally substituted.~~

[0011ab] In one aspect, the present disclosure refers to~~One embodiment provides~~ a compound having the structure of Formula (II)



wherein the compound of Formula (II) includes a pharmaceutically acceptable salt thereof, and wherein:

W¹ and W² are independently chosen from N, C—H, or C—F;

X is chosen from optionally substituted alkyl, optionally substituted alkyloxy, optionally substituted alkylamino, optionally substituted alkynyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclalkynyl, optionally substituted

(heterocyclalkyl)alkynyl, optionally substituted aryl, optionally substituted aryloxy, or optionally substituted heteroaryl; and

Z is an optionally substituted group chosen from *N*-heterocycl, C(O)-*N*-heterocycl, -O-heterocyclalkyl, -N(H)-heterocyclalkyl, -N(H)-alkyl, -N(Me)-alkyl, or -N(Me)-heterocyclalkylalkamino, alkoxy, heterocycl, heterocyclamino, heterocyclalkamino, heterocyclcarbonyl, or heterocyclalkoxy.

[0011be] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as described herein and a pharmaceutically acceptable excipient

[0011c] In another aspect, the present disclosure refers to a method of modulating gene transcription in a cell comprising inhibiting lysine-specific demethylase 1 activity by contacting the lysine-specific demethylase 1 enzyme with the compound as described herein.

[0011d] In another aspect, the present disclosure refers to~~One embodiment provides~~ a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating acute myeloid leukemia, breast or prostate cancer in a patient in need thereof.

[0011ed] In another aspect, the present disclosure refers to~~One embodiment provides~~ a pharmaceutical composition as described herein for use in therapy.

INCORPORATION BY REFERENCE

[0012] 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.

DETAILED DESCRIPTION OF THE INVENTION

[0013] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a

numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

Definitions

[0014] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

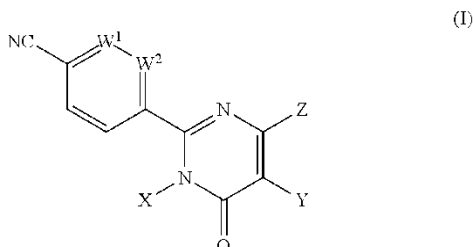
[0015] "Amino" refers to the -NH_2 radical.

[0016] "Cyano" refers to the -CN radical.

CLAIMS

We Claim:

1. ~~A compound having the structure of Formula (I),~~



~~wherein the compound of Formula (I) includes a pharmaceutically acceptable salt thereof, and
wherein:~~

~~W¹ and W² are independently chosen from N, C—H, or C—F;~~

~~X is chosen from hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl,
optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted
heterocyclalkyl, optionally substituted aralkyl, optionally substituted heteroarylalkyl,
optionally substituted aryl, or optionally substituted heteroaryl;~~

~~Y is chosen from hydrogen, halogen, or methyl; and~~

~~Z is chosen from alkamino, alkoxy, heterocyclyl, heterocyclylamino, heterocyclalkamino, or
heterocyclalkoxy, each of which is optionally substituted.~~

2. The compound of claim 1, wherein W² is C—H.

3. The compound of claim 1, wherein W¹ is C—F.

4. The compound of claim 1, wherein X is optionally substituted aryl in which the aryl is phenyl.

5. The compound of claim 1, wherein X is optionally substituted heteroaryl selected from
indazolyl or pyridinyl.

6. The compound of claim 1, wherein Z is optionally substituted heterocyclyl selected from
piperidinyl, aminopiperidinyl, pyrrolopyridinyl, or diazaspitrodecanyl.

~~7. The compound of claim 1, wherein Z is optionally substituted heterocyclamino, heterocyclalkamino, or heterocyclalkoxy, wherein the heterocycl moiety is pyrrolidinyl.~~

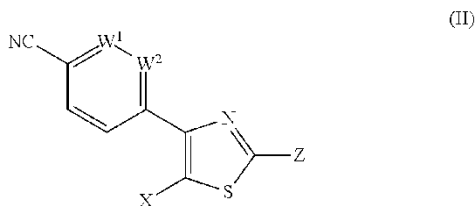
~~8. The compound of claim 1, wherein Z is optionally substituted alkamino is aminopropyl(methyl)amino.~~

~~9. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient.~~

~~10. A method of modulating gene transcription in a cell comprising inhibiting lysine-specific demethylase 1 activity by contacting the lysine-specific demethylase 1 enzyme with the compound of claim 1.~~

~~11. Use of the pharmaceutical composition of claim 9 in the manufacture of a medicament for treating acute myeloid leukemia, breast or prostate cancer in a patient in need thereof.~~

12. A compound having the structure of Formula (II)



wherein the compound of Formula (II) includes a pharmaceutically acceptable salt thereof, and wherein:

W¹ and W² are independently chosen from N, C—H, or C—F;

X is chosen from optionally substituted alkyl, optionally substituted alkyloxy, optionally substituted alkylamino, optionally substituted alkynyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclalkynyl, optionally substituted (heterocyclalkyl)alkynyl,

optionally substituted aryl, optionally substituted aryloxy, or optionally substituted heteroaryl;
and

Z is chosen from an optionally substituted group chosen from *N*-heterocyclyl, C(O)-*N*-heterocyclyl, -O-heterocyclalkyl, -N(H)-heterocyclalkyl, -N(H)-alkyl, -N(Me)-alkyl, or -N(Me)-heterocyclalkyl ~~Z is an optionally substituted group chosen from alkamino, alkoxy, heterocyclyl, heterocycllamino, heterocyclalkamino, heterocyclcarbonyl, or heterocyclalkoxy.~~

213. The compound of claim 142, wherein W¹ is C—H or C—F, and W² is C—H.

314. The compound of claim 142, wherein X is optionally substituted aryl, and wherein the optionally substituted aryl is optionally substituted phenyl.

415. The compound of claim 142, wherein X is optionally substituted heteroaryl selected from optionally substituted indazolyl, azaindolyl, azaindazolyl, benzimidazolyl, imidazopyridinyl or pyrazolyl.

516. The compound of claim 142, wherein X is optionally substituted alkynyl, and wherein the substituent is hydroxy(dimethyl), tetrahydrofuranyl, tetrahydrofuranylhdroxy, oxetanehydroxy, (cyclopropyl)hydroxy, or (cyclopentyl)hydroxy.

617. The compound of claim 142, wherein Z is optionally substituted *N*-heterocyclyl~~heterocyclyl~~ selected from optionally substituted aminopiperidinyl, decahydropyrroloazapinyl, octahydropyrropiperadinyl or diaspirodecanyl.

718. The compound of claim 12, wherein Z is optionally substituted C(O)-*N*-heterocyclyl~~heterocyclcarbonyl~~, wherein the optionally substituted C(O)-*N*-heterocyclyl~~heterocyclcarbonyl~~ is piperidinylcarbonyl.

8. The compound of claim 1, wherein the compound is selected from

4-[2-(4-aminopiperidin-1-yl)-5-(1-methyl-1H-indazol-5-yl)-1,3-thiazol-4-yl]benzonitrile;

cis-4-(2-{decahydropyrrolo[3,4-d]azepin-6-yl}-5-(1-methyl-1H-indazol-5-yl)-1,3-thiazol-4-yl)benzonitrile;

4-[2-(4-aminopiperidin-1-yl)-5-{1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl}-1,3-thiazol-4-yl]benzonitrile;

4-[2-(4-aminopiperidin-1-yl)-5-{1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl}-1,3-thiazol-4-yl]benzonitrile;

4-(2-{2,8-diazaspiro[4.5]decan-8-yl}-5-(1-methyl-1H-indazol-5-yl)-1,3-thiazol-4-yl)benzonitrile;

4-[5-(1-methyl-1H-indazol-5-yl)-2-{octahydro-1H-pyrrolo[3,2-c]pyridin-5-yl}-1,3-thiazol-4-yl]benzonitrile;

4-[5-(1-methyl-1H-indazol-5-yl)-2-{octahydro-1H-pyrrolo[3,4-c]pyridin-5-yl}-1,3-thiazol-4-yl]benzonitrile;

4-[2-(4-aminopiperidin-1-yl)-5-(1-methyl-1H-1,3-benzodiazol-5-yl)-1,3-thiazol-4-yl]benzonitrile;

4-[2-(4-aminopiperidin-1-yl)-5-{3-methyl-3H-imidazo[4,5-b]pyridin-6-yl}-1,3-thiazol-4-yl]benzonitrile;

cis-4-(2-{decahydropyrrolo[3,4-d]azepin-6-yl}-5-(1-methyl-1H-1,3-benzodiazol-5-yl)-1,3-thiazol-4-yl)benzonitrile;

-cis-4-(2-{decahydropyrrolo[3,4-d]azepin-6-yl}-5-{1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl}-1,3-thiazol-4-yl)benzonitrile;

4-[2-(4-aminopiperidin-1-yl)-5-[1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl]-1,3-thiazol-4-yl]benzonitrile;

4-(2-{decahydropyrrolo[3,4-d]azepin-6-yl}-5-[1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl]-1,3-thiazol-4-yl)benzonitrile;

4-{5-[1-(cyclopropylmethyl)-1H-pyrazol-4-yl]-2-{decahydropyrrolo[3,4-d]azepin-6-yl}-1,3-thiazol-4-yl}benzonitrile;

4-{5-[1-(cyclopropylmethyl)-1H-pyrazol-4-yl]-2-{decahydropyrrolo[3,4-d]azepin-6-yl}-1,3-thiazol-4-yl}benzonitrile;

4-{2-[(3R)-3-aminopiperidine-1-carbonyl]-5-(1-methyl-1H-1,3-benzodiazol-5-yl)-1,3-thiazol-4-yl}benzonitrile;

4-{2-[(3S)-3-aminopiperidine-1-carbonyl]-5-(1-methyl-1H-1,3-benzodiazol-5-yl)-1,3-thiazol-4-yl}benzonitrile;

4-[2-(4-aminopiperidine-1-carbonyl)-5-(1-methyl-1H-1,3-benzodiazol-5-yl)-1,3-thiazol-4-yl]benzonitrile;

4-{2-[(3R)-3-aminopiperidine-1-carbonyl]-5-(4-methylphenyl)-1,3-thiazol-4-yl}benzonitrile;

4-{2-[(3R)-3-aminopiperidine-1-carbonyl]-5-{3-methyl-3H-imidazo[4,5-b]pyridin-6-yl}-1,3-thiazol-4-yl}benzonitrile;

4-{2-[(3R)-3-aminopiperidine-1-carbonyl]-5-[1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl]-1,3-thiazol-4-yl}benzonitrile;

4-{2-[(3R)-3-aminopiperidine-1-carbonyl]-5-[1-(cyclopropylmethyl)-1H-pyrazol-4-yl]-1,3-thiazol-4-yl}benzonitrile;

4-[2-(4-aminopiperidin-1-yl)-5-(3-hydroxy-3-methylbut-1-yn-1-yl)-1,3-thiazol-4-yl]benzonitrile;

4-[2-(4-aminopiperidin-1-yl)-5-(3-hydroxy-3-methylbut-1-yn-1-yl)-1,3-thiazol-4-yl]benzonitrile;

4-[2-(4-aminopiperidin-1-yl)-5-{3-methyl-3H-imidazo[4,5-b]pyridin-6-yl}-1,3-thiazol-4-yl]-2-fluorobenzonitrile;

4-[4-(4-aminopiperidin-1-yl)-1-(4-cyclopropylphenyl)-6-oxypyrimidin-2-yl]-2-fluorobenzonitrile;

4-[4-(1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,2-c]pyridin-5-yl)-1-(4-cyclopropylphenyl)-6-oxypyrimidin-2-yl]-2-fluorobenzonitrile;

4-[4-(1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c]pyridin-5-yl)-1-(4-cyclopropylphenyl)-6-oxypyrimidin-2-yl]-2-fluorobenzonitrile;

4-[1-(4-cyclopropylphenyl)-4-(2,8-diazaspiro[4.5]decan-8-yl)-6-oxypyrimidin-2-yl]-2-fluorobenzonitrile;

4-[4-(4-aminopiperidin-1-yl)-1-(3-fluoro-4-methoxyphenyl)-6-oxypyrimidin-2-yl]-2-fluorobenzonitrile;

4-[4-(4-aminopiperidin-1-yl)-1-(2-methylindazol-5-yl)-6-oxypyrimidin-2-yl]-2-fluorobenzonitrile;

4-[4-(4-aminopiperidin-1-yl)-1-(4-methoxyphenyl)-6-oxypyrimidin-2-yl]-2-fluorobenzonitrile;

4-[4-(4-aminopiperidin-1-yl)-1-(4-cyclopropyl-3-fluorophenyl)-6-oxopyrimidin-2-yl]-2-fluorobenzonitrile; and
4-[2-(4-aminopiperidin-1-yl)-5-{2-methyl-2H-indazol-5-yl}pyrazin-2-yl]-1,3-thiazol-4-yl]benzonitrile.

919. A pharmaceutical composition comprising the compound of claim 142 and a pharmaceutically acceptable excipient.

1020. A method of modulating gene transcription in a cell comprising inhibiting lysine-specific demethylase 1 activity by contacting the lysine-specific demethylase 1 enzyme with the compound of claim 142.

1124. Use of the pharmaceutical composition of claim 919 in the manufacture of a medicament for treating acute myeloid leukemia, breast or prostate cancer in a patient in need thereof.

~~22. The pharmaceutical composition of claim 9 for use in therapy.~~

2312. The pharmaceutical composition of claim 919 for use in therapy.