

INHIBITORS OF LYSINE SPECIFIC DEMETHYLASE-1

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application 62/018,365, filed June 27, 2014, which is incorporated herein by reference in its entirety.

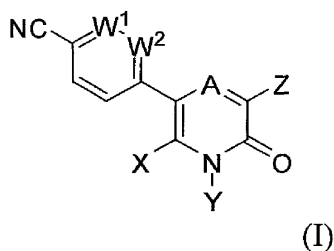
BACKGROUND

[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 pyridinone or pyrazinone, 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 embodiment provides a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof,



wherein,

A is N or C-R, wherein R is hydrogen or optionally substituted alkyl;

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

X is hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclalkyl, optionally substituted aralkyl, optionally substituted heteroarylalkyl, optionally substituted alkynyl, optionally

substituted carbocyclalkynyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is optionally substituted alkyl, optionally substituted cycloalkylalkyl, heterocyclalkyl or aralkyl; and

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

[0005] One embodiment provides a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0006] One 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 (I).

[0007] One embodiment 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.

[0007a] One embodiment provides the use of a compound of Formula (I), wherein Y is optionally substituted alkyl, optionally substituted aralkyl, cycloalkylalkyl, or heterocyclalkyl; X is H, optionally substituted aryl, or optionally substituted heteroaryl; W1 is CH, CF or N; W2 is CH or CF; Z is optionally substituted *N*-heterocycl, -*N*(H)-heterocyclalkyl, or -*O*-heterocyclalkyl; and A is N or CH, in the manufacture of a medicament for regulating gene transcription in a cell by inhibiting lysine-specific demethylase 1.

[0007b] One embodiment provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating acute myeloid leukemia or breast cancer in a patient in need thereof.

INCORPORATION BY REFERENCE

[0008] 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

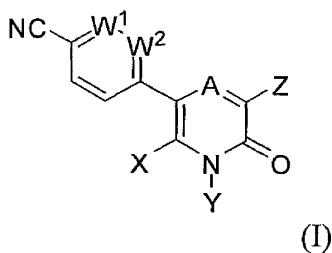
[0009] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the

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),

CLAIMS

We Claim:

1. A compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein,

A is N or C-R, wherein R is hydrogen or optionally substituted alkyl;

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

X is hydrogen, halogen, optionally substituted alkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclalkyl, optionally substituted aralkyl, optionally substituted heteroarylalkyl, optionally substituted alkynyl, optionally substituted carbocyclalkynyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is optionally substituted alkyl, optionally substituted cycloalkylalkyl, heterocyclalkyl or aralkyl; and

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

2. The compound or pharmaceutically acceptable salt of claim 1, wherein W² is C-H.
3. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein W¹ is C-F.
4. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein W¹ is C-H.
5. The compound or pharmaceutically acceptable salt of claim 1 or 2, wherein W¹ is N.
6. The compound or pharmaceutically acceptable salt of claims 1-5, wherein X is hydrogen.
7. The compound or pharmaceutically acceptable salt of claims 1-5, wherein X is optionally substituted alkyl.
8. The compound or pharmaceutically acceptable salt of claims 1-5, wherein X is optionally substituted alkyne.
9. The compound or pharmaceutically acceptable salt of claim 1-5, wherein X is optionally substituted carbocyclalkynyl.
10. The compound or pharmaceutically acceptable salt of claims 1-5, wherein X is optionally substituted aryl, or optionally substituted heteroaryl.

26. The compound or pharmaceutically acceptable salt of claims 1-25, wherein Y is optionally substituted cycloalkylalkyl.
27. The compound or pharmaceutically acceptable salt of claims 1-25, wherein Y is optionally substituted alkyl.
28. The compound or pharmaceutically acceptable salt of claims 1-25, wherein Y is optionally substituted heterocyclalkyl.
29. The compound or pharmaceutically acceptable salt of claims 1-25, wherein Y is optionally substituted aralkyl.
30. The compound or pharmaceutically acceptable salt of claim 27, wherein the optionally substituted alkyl is an optionally substituted C₁-C₃ alkyl.
31. The compound or pharmaceutically acceptable salt of claim 27, wherein the optionally substituted alkyl is an optionally substituted C₁ alkyl.
32. The compound or pharmaceutically acceptable salt of claim 27, wherein the optionally substituted alkyl is a methyl group.
33. The compound or pharmaceutically acceptable salt of any of the preceding claims, wherein A is N.
34. The compound or pharmaceutically acceptable salt of any one of claims 1-32, wherein A is C-R.
35. The compound or pharmaceutically acceptable salt of any one of claims 1-32, wherein A is C-R, and R is hydrogen
36. The compound or pharmaceutically acceptable salt of any one of claims 1-32, wherein A is C-R and R is optionally substituted alkyl.
37. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
38. Use of a compound of Formula (I), wherein Y is optionally substituted alkyl, optionally substituted aralkyl, cycloalkylalkyl, or heterocyclalkyl; X is H, optionally substituted aryl, or optionally substituted heteroaryl; W₁ is CH, CF or N; W₂ is CH or CF; Z is optionally substituted N-heterocycl, -N(H)-heterocyclalkyl, or -O-heterocyclalkyl; and A is N or CH, in the manufacture of a medicament for regulating gene transcription in a cell by inhibiting lysine-specific demethylase 1.
39. Use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating acute myeloid leukemia or breast cancer in a patient in need thereof.