INHIBITORS OF LYSINE SPECIFIC DEMETHYLASE-1

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/046,842, filed September 5, 2014, the entire contents of which are hereby incorporated by reference.

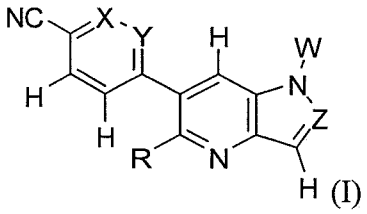
BACKGROUND

[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 pyrazine, 4-azaindole, 4-azaindazole, pyrimidine or pyrazole, or the like. Said central heterocyclic ring system is further substituted with 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,



(I)

wherein,

X and Y are each independently chosen from C-H, C-F, C-CH_3, or N;

Z is chosen from C-H or N;

R is chosen from hydrogen, halogen, aryl, heteroaryl, heterocyclyl, carbocyclyl, alkoxy, cycloalkylalkyloxy, or aralkyloxy

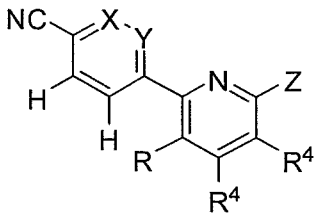
W is –L-G, heterocyclyl, or heteroaryl;

L is alkylene;

G is $-N(R^1)_2$, heterocyclyl, or heteroaryl; and

R^1 is hydrogen or alkyl.

[0004a] One embodiment provides a compound having the structure selected from Formula (IVb), (IVc), (IVd), (IVe), (IVf) or (IVg) or a pharmaceutically acceptable salt thereof: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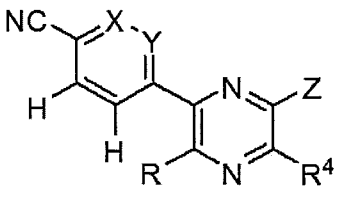
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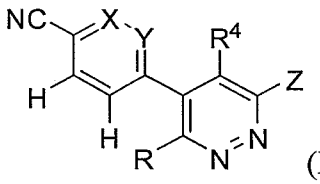
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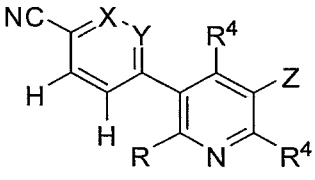
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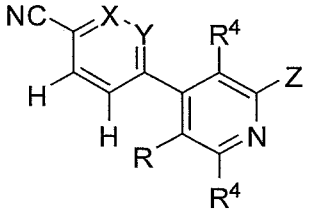
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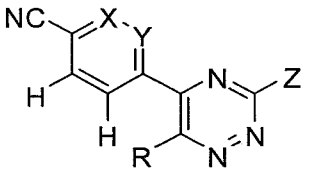

(IVg),

wherein,

X and Y are each independently chosen from C-H, C-F, C-CH_3, or N;

Z is chosen –G, –N(R^1)-G, –N(R^1)-CH_2-G, or -O-CH_2-G;

G is optionally substituted 5-, 8-, 9-, or 10-membered heterocyclyl or 6-membered heterocyclyl substituted with NH2, NH(CH3) or N$(CH3)_2$;

R^4 is hydrogen, halogen, C_1-C_3 alkyl or C_1-C_3 alkoxy; and

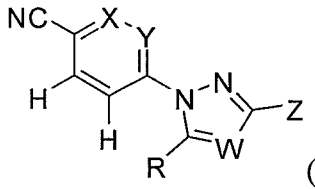
R is aryl substituted with methoxy and halogen, optionally substituted heteroaryl, optionally substituted alkynyl, or optionally substituted cycloalkylalkynyl.

[0004b] One embodiment provides a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0004c] One embodiment provides a use of a compound as described herein, in the manufacture of a medicament for regulating gene transcription in a cell by inhibiting lysine-specific demethylase 1 activity.

[0004d] One embodiment provides a use of a pharmaceutical composition comprising a compound as described herein, in the manufacture of a medicament for treating cancer in a patient in need thereof.

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



(II)

wherein,

X and Y are each independently chosen from C-H, C-F, C-CH3, or N;

W is chosen from C-H, C-F, C-Cl, C-CH_3, C-CF_3, C-OCH_3, C-OCH_2CH_3, or N;

Z is chosen –G, -CH_2-G, –CH_2-CH_2-G, –N(R^1)-G, –N(R^1)-CH_2-G, –O-G, -O-CH_2-G, or –C(O)N(R^2)(R^3);

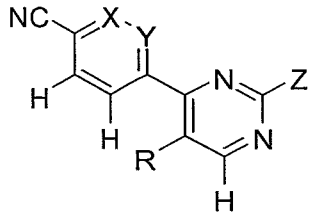
G is carbocyclyl, aryl, heterocyclyl or heteroaryl;

R^1 is hydrogen or alkyl;

R^2 and R^3 are independently selected from hydrogen, alkyl, heterocyclyl, heterocyclylalkyl, or optionally, R^2 and R^3 join to form an N-linked heterocyclyl ring system;

R is chosen from aryl, halogen, heteroaryl, heterocyclyl, carbocyclyl, alkoxy, cycloalkylalkyloxy, or aralkyloxy.

[0006] One embodiment provides a compound having the structure of Formula (III), or a pharmaceutically acceptable salt thereof,



(III)

wherein,

X and Y are each independently chosen from C-H, C-F, C-CH3, or N;

Z is chosen –G, -CH_2-G, –CH_2-CH_2-G, –N(R^1)-G, –N(R^1)-CH_2-G, –O-G, -O-CH_2-G, or –C(O)N(R^2)(R^3);

G is carbocyclyl, aryl, heterocyclyl or heteroaryl;

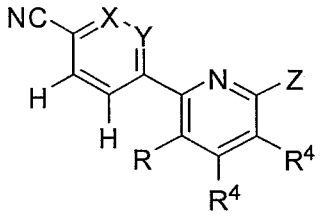
R^1 is hydrogen or alkyl;

R^2 and R^3 are independently selected from hydrogen, alkyl, heterocyclyl, heterocyclylalkyl, or optionally, R^2 and R^3 join to form an N-linked heterocyclyl ring system;

CLAIMS

We Claim:

1. A compound having the structure selected from Formula (IVb), (IVc), (IVd), (IVe), (IVf) or (IVg) or a pharmaceutically acceptable salt thereof: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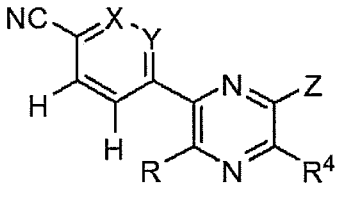
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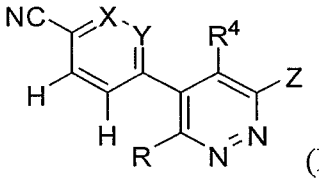
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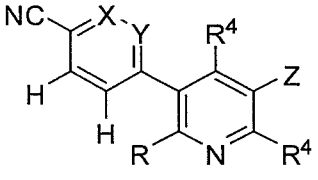
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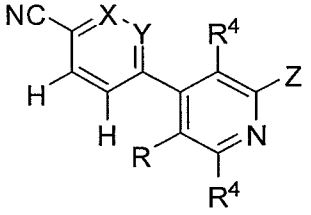
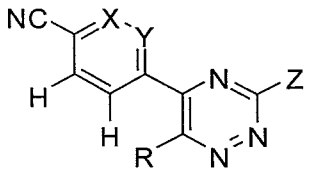

(IVf),



(IVg),

wherein,

X and Y are each independently chosen from C-H, C-F, C-CH_3, or N;

Z is chosen –G, –N(R^1)-G, –N(R^1)-CH_2-G, or -O-CH_2-G;

G is optionally substituted 5-, 8-, 9-, or 10-membered heterocyclyl or 6-membered heterocyclyl substituted with NH2, NH(CH3) or $N(CH3)_2$;

R^4 is hydrogen, halogen, C_1-C_3 alkyl or C_1-C_3 alkoxy; and

R is aryl substituted with methoxy and halogen, optionally substituted heteroaryl, optionally substituted alkynyl, or optionally substituted cycloalkylalkynyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R is aryl or heteroaryl.

3. The compound of any one of claims 1-2, or pharmaceutically acceptable salt thereof, wherein X is C-H.

4. The compound of any one of claims 1-2, or pharmaceutically acceptable salt thereof, wherein X is C-F.

5. The compound of any one of claims 1-2, or pharmaceutically acceptable salt thereof, wherein Y is C-H.

6. The compound or pharmaceutically acceptable salt of any one of claims 1-2, wherein X is C-H and Y is C-H.

7. The compound of any one of claims 1-6, or pharmaceutically acceptable salt thereof, wherein Z is -O-CH_2-G.

8. The compound of any one of claims 1-6 or pharmaceutically acceptable salt thereof, wherein Z is –N(R^1)-CH_2-G.

9. The compound of any one of claims 1-6, or pharmaceutically acceptable salt thereof, wherein Z is –N(R^1)-G.

10. The compound of any one of claims 1-6, or pharmaceutically acceptable salt thereof, wherein Z is –G.

11. The compound of claim 8 or 9, or pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

12. The compound of any one of claims 1-11, or pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

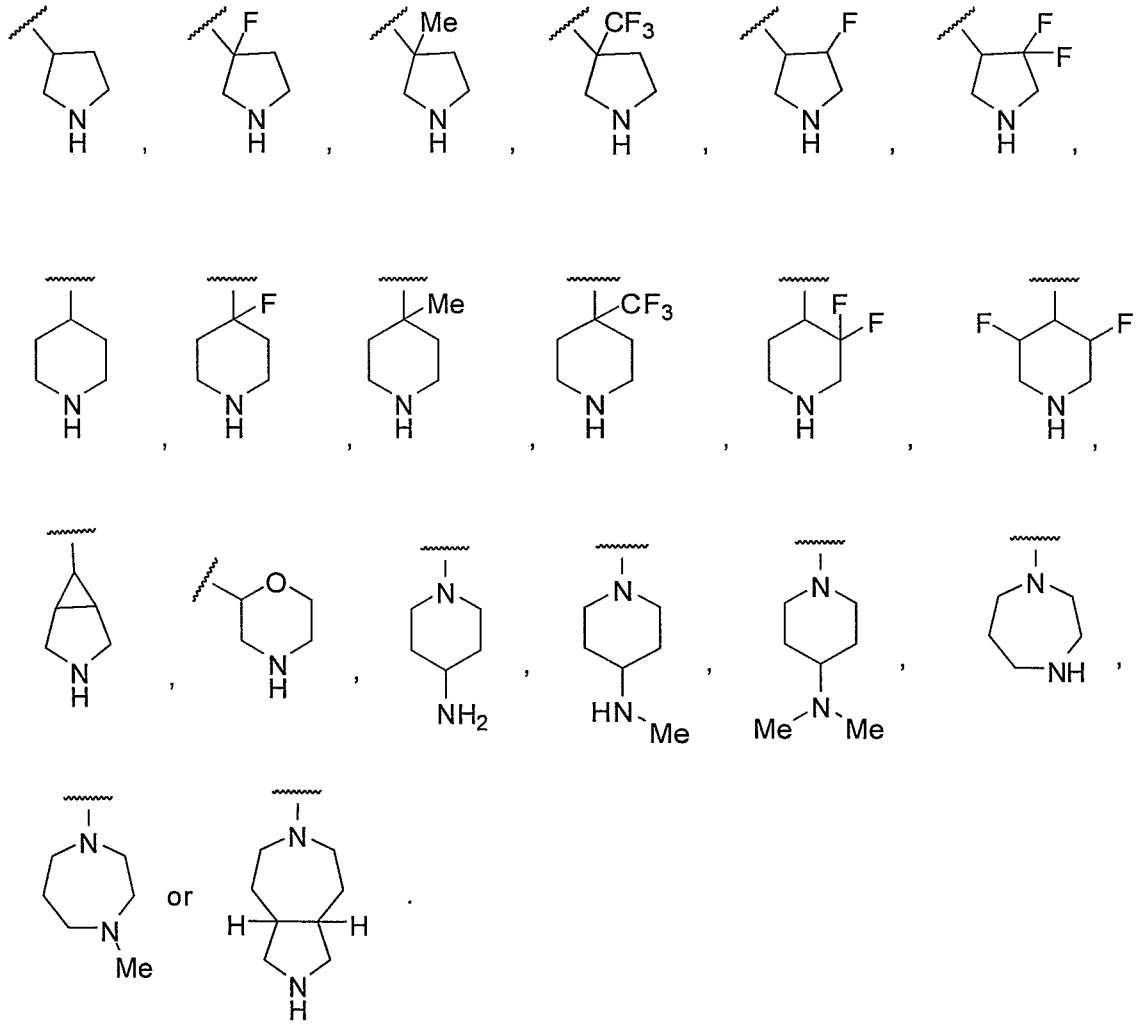
13. The compound of any one of claims 1-11, or pharmaceutically acceptable salt thereof, wherein R^4 is C_1-C_3 alkoxy.

14. The compound of any one of claims 1-13, or pharmaceutically acceptable salt thereof, wherein G is a heterocyclyl.

15. The compound of any one of claims 1-14, or pharmaceutically acceptable salt thereof, wherein G is a nitrogen-containing heterocyclyl.

16. The compound of claim 15, or pharmaceutically acceptable salt thereof, wherein the nitrogen-containing heterocyclyl is a 5- or 6-membered heterocyclyl.

17. The compound of claim 15, or pharmaceutically acceptable salt thereof, wherein the heterocyclyl is chosen from:

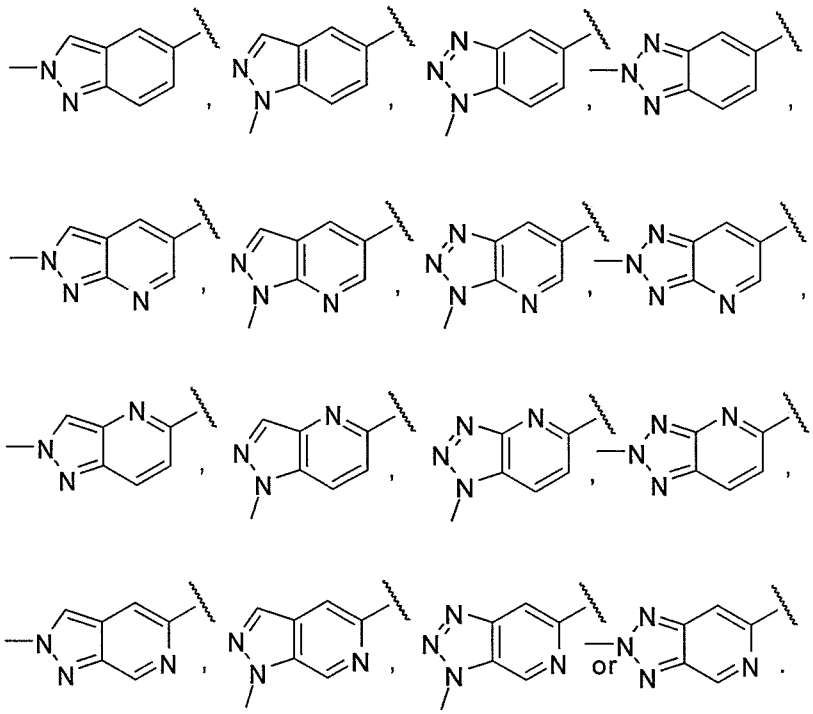


18. The compound of any one of claims 1-17, or pharmaceutically acceptable salt thereof, wherein R is heteroaryl.

19. The compound of claim 18, or pharmaceutically acceptable salt thereof, wherein R is a monocyclic nitrogen-containing heteroaryl.

20. The compound of claim 18, or pharmaceutically acceptable salt thereof, wherein R is a bicyclic nitrogen-containing heteroaryl.

21. The compound of claim 20, or pharmaceutically acceptable salt thereof, wherein R is chosen from:



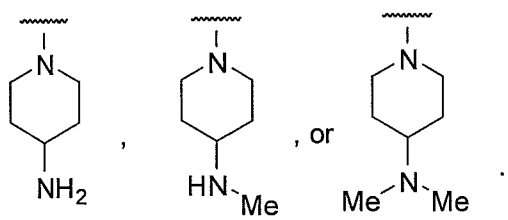
22. The compound of any one of claims 1-17, or pharmaceutically acceptable salt thereof, wherein R is aryl.

23. The compound of claim 22, or pharmaceutically acceptable salt thereof, wherein the aryl is an optionally substituted phenyl group.

24. The compound of claim 22, or pharmaceutically acceptable salt thereof, wherein the optionally substituted phenyl group is chosen from 4-methylphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-cyanophenyl, 4-(methylsulfonyl)phenyl, or 4-trifluoromethylphenyl.

25. The compound of claim 22, or pharmaceutically acceptable salt thereof, wherein the optionally substituted phenyl group is chosen from 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, or 3-chloro-4-methoxyphenyl.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein G is



27. A pharmaceutical composition comprising a compound as described in any one of claims 1-26, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

28. Use of a compound as described in any one of claims 1-26, in the manufacture of a medicament for regulating gene transcription in a cell by inhibiting lysine-specific demethylase 1 activity.

29. Use of a pharmaceutical composition comprising a compound as described in any one of claims 1-26, in the manufacture of a medicament for treating cancer in a patient in need thereof.