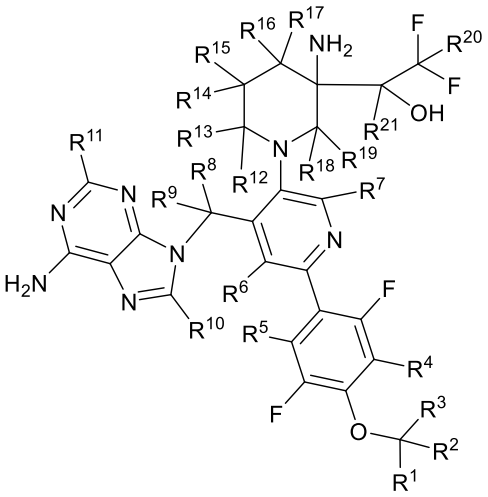
SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a compound represented by Formula I:



(I)

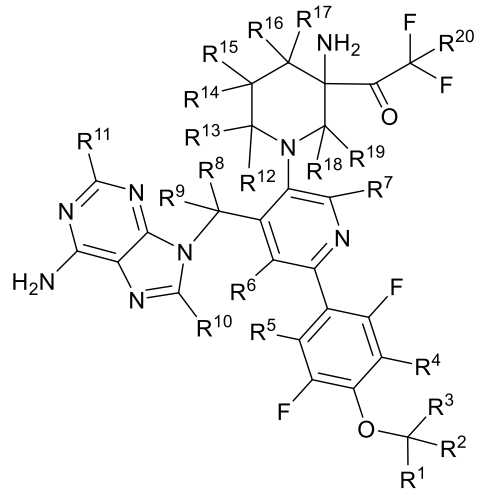
or a pharmaceutically acceptable salt thereof; wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%;

provided that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} is Z.

[0005b] In another aspect of the present disclosure, there is provided a compound represented by Formula II:



(II)

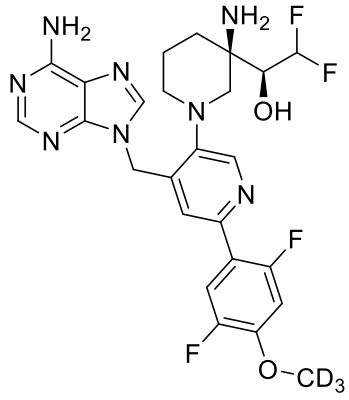
or a pharmaceutically acceptable salt thereof; wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%.

[0005c] In a further aspect of the present disclosure, there is provided a compound in Table 1 or 2 herein, or a pharmaceutically acceptable salt thereof.

[0005d] In another aspect of the present disclosure, there is provided a compound selected from



and a pharmaceutically acceptable salt thereof.

[0005e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

[0005f] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

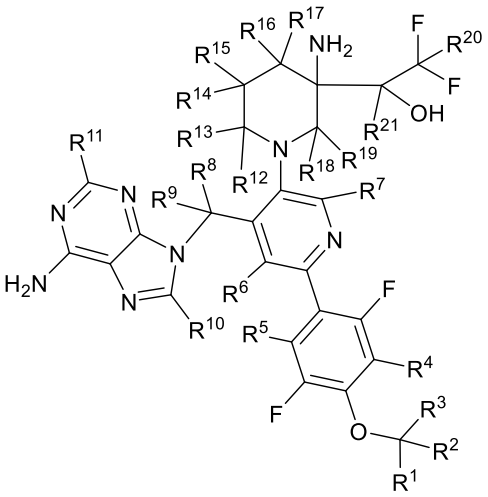
[0005g] In a further aspect of the present dislcosure, there is provided a use of a compound disclosed herein, in the manufature of a medicament for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2).

[0005h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for inhibiting the activity of nuclear SET domain-containing protein 2 (NSD2).

[0005i] In a further aspect of the present disclosure, there is provided a compound disclosed herein, for use in therapy.

[0006] The disclosure provides deuterium-enriched piperidinyl-methyl-purine amines and related compounds, pharmaceutical compositions, their use for inhibiting NSD2, and their use in the treatment of a disease or condition, such as cancer. In particular, one example

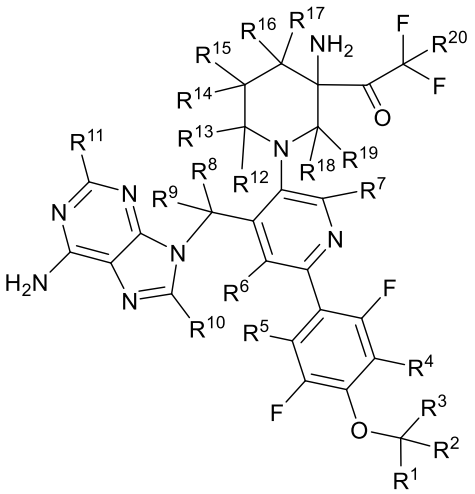
of the disclosure provides a collection of deuterium-enriched piperidinyl-methyl-purine amines and related compounds, such as a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. Further description of additional collections of deuterium-enriched piperidinyl-methyl-purine amines and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0007] Another example of the disclosure provides a collection of difluoromethylketone-substituted piperidinyl-methyl-purine amines and related compounds, including deuterium-enriched compounds, such as a compound represented by Formula II:



(II)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. Further description of additional collections of difluoromethylketone-substituted piperidinyl-methyl-purine amines and related compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0008] Another example of the disclosure provides a method of treating a disease or condition mediated by NSD2 in a subject. The method comprises administering a therapeutically effective amount of a compound described herein, such as a compound of Formula I or II, to a subject in need thereof to treat the disease or condition, as further described in the detailed description.

[0009] Another example of the disclosure provides a method of inhibiting the activity of nuclear SET domain-containing protein 2 (NSD2). The method comprises contacting a NSD2 with an effective amount of a compound described herein, such as a compound of Formula I or II, to inhibit the activity of said NSD2, as further described in the detailed description.

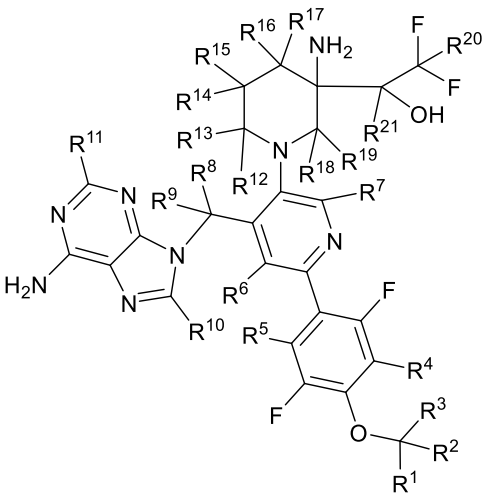
DETAILED DESCRIPTION

[0010] The invention provides deuterium-enriched piperidinyl-methyl-purine amines and related compounds, pharmaceutical compositions, their use for inhibiting NSD2, and their use in the treatment of a disease or condition, such as cancer. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology. Such techniques are explained in the literature, such as in "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992); "Handbook of experimental immunology" (D.M. Weir & C.C. Blackwell, eds.); "Current protocols in molecular biology" (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and "Current protocols in immunology" (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety.

[0011] Deuterium-enriched refers to the feature that the compound has a quantity of deuterium that is greater than in naturally occurring compounds or synthetic compounds prepared from substrates having the naturally occurring distribution of isotopes. The threshold amount of deuterium enrichment is specified in certain instances in this disclosure, and all percentages given for the amount of deuterium present are mole percentages.

Claims:

1. A compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

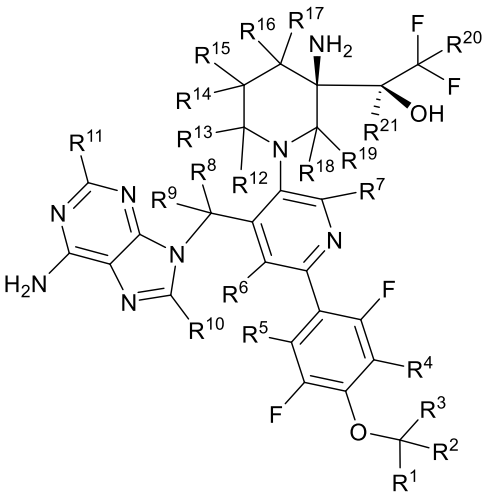
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%;

provided that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} is Z.

2. The compound of claim 1, wherein the compound is a compound of Formula I.

3. The compound of claim 1, wherein the compound is represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%;

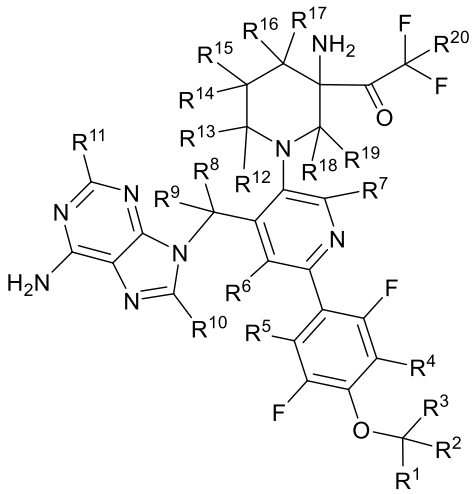
provided that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} is Z.

4. The compound of claim 3, wherein the compound is a compound of Formula I-A.

5. The compound of any one of claims 1-4, wherein R^{21} is Z.

6. The compound of any one of claims 1-4, wherein R^{21} is H.

7. A compound represented by Formula II:



(II)

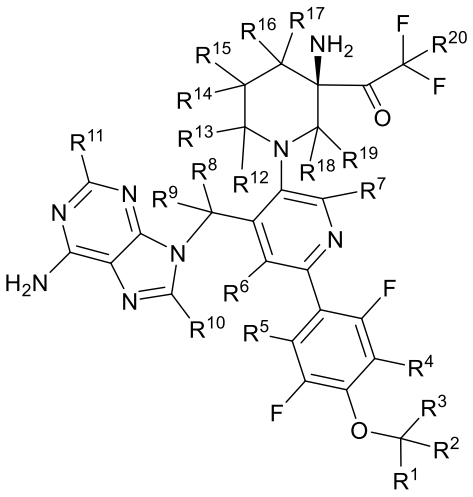
or a pharmaceutically acceptable salt thereof; wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%.

8. The compound of claim 7, wherein the compound is a compound of Formula II.

9. The compound of claim 7, wherein the compound is represented by Formula II-A:



(II-A)

or a pharmaceutically acceptable salt thereof; wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or Z; and

Z is H or D, provided that the abundance of deuterium in Z is at least 75%.

10. The compound of claim 9, wherein the compound is a compound of Formula II-A.

11. The compound of any one of claims 7-10, wherein at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} is Z.

12. The compound of any one of claims 1-11, wherein R^1, R^2, and R^3 are Z.

13. The compound of any one of claims 1-11, wherein R^1, R^2, and R^3 are H.

14. The compound of any one of claims 1-13, wherein R^4, R^5, R^6, and R^7 are H.

15. The compound of any one of claims 1-14, wherein R^8 and R^9 are Z.

16. The compound of any one of claims 1-14, wherein R^8 and R^9 are H.

17. The compound of any one of claims 1-16, wherein R^{10} and R^{11} are H.

18. The compound of any one of claims 1-17, wherein R^{12} and R^{13} are Z.

19. The compound of any one of claims 1-17, wherein R^{12} and R^{13} are H.

20. The compound of any one of claims 1-19, wherein R^{14}, R^{15}, R^{16}, and R^{17} are H.

21. The compound of any one of claims 1-20, wherein R^{18} and R^{19} are Z.

22. The compound of any one of claims 1-20, wherein R^{18} and R^{19} are H.

23. The compound of any one of claims 1-22, wherein R^{20} is Z.

24. The compound of any one of claims 1-22, wherein R^{20} is H.

25. The compound of any one of claims 1-24, wherein the abundance of deuterium in Z is at least 90%.

26. The compound of any one of claims 1-24, wherein the abundance of deuterium in Z is at least 95%.

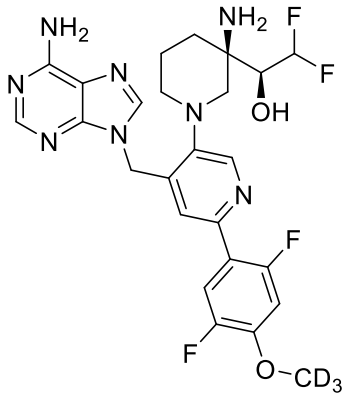
27. The compound of any one of claims 1-26, wherein the compound has an enantiomeric excess of at least 85%.

28. The compound of any one of claims 1-26, wherein the compound has an enantiomeric excess of at least 90%.

29. The compound of any one of claims 1-26, wherein the compound has an enantiomeric excess of at least 95%.

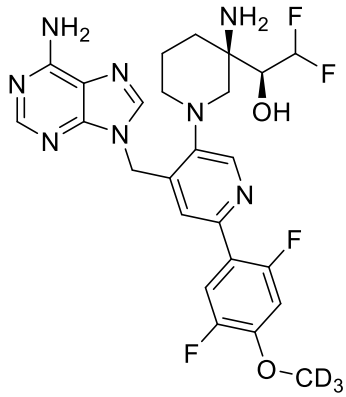
30. A compound in Table 1 or 2 herein, or a pharmaceutically acceptable salt thereof.

31. A compound selected from



and a pharmaceutically acceptable salt thereof.

32. The compound of claim 31, wherein the compound is



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33. A pharmaceutical composition comprising a compound of any one of claims 1-30 and a pharmaceutically acceptable carrier.

34. A pharmaceutical composition comprising a compound of claim 31 and a pharmaceutically acceptable carrier.

35. Use of a compound of any one of claims 1-32, in the manufature of a medicament for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2).

36. The use of claim 35, wherein said disease or condition mediated by NSD2 is cancer.

37. The use of claim 35, wherein said disease or condition mediated by NSD2 is selected from a solid tumor, leukemia, myeloma, lymphoma, and hypertension.

38. The use of claim 35, wherein said disease or condition mediated by NSD2 is breast cancer, cervical cancer, skin cancer, ovarian cancer, gastric cancer, prostate cancer, pancreatic cancer, lung cancer, hepatocellular carcinoma, head and neck cancer, peripheral nerve sheath tumor, osteosarcoma, multiple myeloma, neuroblastoma, leukemia, non-Hodgkin's lymphoma, or pulmonary arterial hypertension.

39. The use of claim 35, wherein said disease or condition mediated by NSD2 is acute lymphoblastic leukemia, skin squamous cell carcinoma, or mantle cell lymphoma.

40. The use of claim 35, wherein said disease or condition mediated by NSD2 is prostate cancer.

41. The use of claim 35, wherein said disease or condition mediated by NSD2 is lung cancer.

42. The use of claim 35, wherein said disease or condition mediated by NSD2 is non-small cell lung cancer.

43. The use of any one of claims 35-42, wherein the subject is a human.

44. Use of a compound of any one of claims 1-32, in the manufacture of a medicament for inhibiting the activity of nuclear SET domain-containing protein 2 (NSD2).

45. A compound of any one of claims 1-32, for use in therapy.