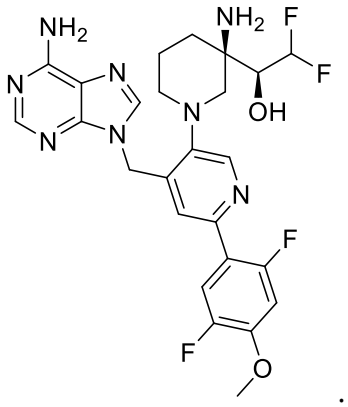
inhibit NSD2 would be beneficial to patients suffering from an NSD2-related disease or condition.

[0005] The present invention addresses the foregoing needs and provides other related advantages.

SUMMARY

[0006] The disclosure provides piperidinyl-methyl-purine amine D-tartaric acid salts, crystalline forms, pharmaceutical compositions, their use in inhibiting NSD2, and their use in the treatment of a disease or condition, such as cancer. In particular, one aspect of the disclosure provides a compound that is a D-tartaric acid salt of the following compound:



.

In certain examples, the compound is in crystalline form. One benefit of the D-tartaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is that it has low hygroscopicity. In contrast to the fumaric acid salt, sulfuric acid salt, hydrochloric acid salt, and various other salts of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol that were observed to form hydrates, the D-tartaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol could be obtained in anhydrous form and had low hygroscopicity in long-duration stability studies. Another benefit of the D-tartaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is that it displays greater solubility in water than, for example, (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-

difluoroethan-1-ol free base or (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol fumaric acid salt. Yet another benefit of the D-tartaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol is that it displayed very good stability to long term storage, showing a high degree of purity after storage in a one year stability study and no detectable loss of crystallinity as measured by XRPD analysis. Further description of additional features of the compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0006a] Another aspect of the disclosure provides a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier

[0006b] Another aspect of the disclosure provides a use of a compound disclosed herein, in the manufacture of a medicament for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2) in a subject.

[0007] Another example of the disclosure provides a method for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2). The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a D-tartaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, to treat the disease or condition.

[0007a] Another aspect of the disclosure provides a *in vitro* method of inhibiting the activity of nuclear SET domain-containing protein 2 (NSD2), comprising contacting a NSD2 with an effective amount of a compound disclosed herein to inhibit the activity of said NSD2.

[0008] 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 D-tartaric acid salt of (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol, to inhibit the activity of said NSD2.

[0008a] Another aspect of the present disclosure provides a compound disclosed herein, for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

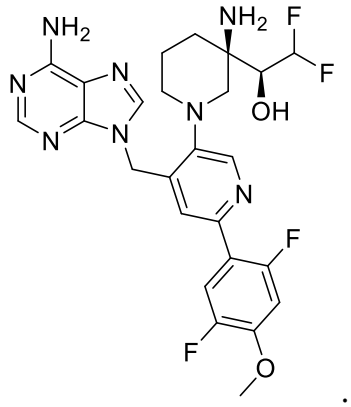
[0009] **FIG. 1** depicts an X-ray powder diffractogram of one batch of crystalline (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol D-tartaric acid salt, as further described in Example 4.

[0010] **FIG. 2** depicts an X-ray powder diffractogram of a second batch of crystalline (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-(2,5-difluoro-4-methoxyphenyl)pyridin-3-yl)piperidin-3-yl)-2,2-difluoroethan-1-ol D-tartaric acid salt, as further described in Example 4.

[0011] **FIG. 3** depicts a thermogravimetric analysis curve and differential scanning calorimetry curve of crystalline (*S*)-1-((*R*)-3-amino-1-(4-((6-amino-9*H*-purin-9-yl)methyl)-6-

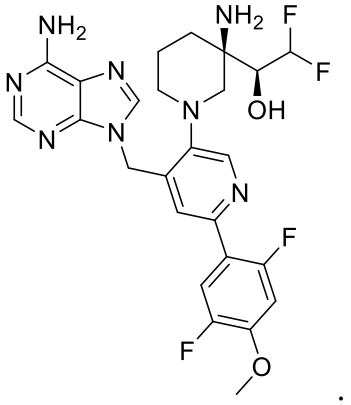
Claims:

1. A compound that is a D-tartaric acid salt of the following compound:



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2. The compound of claim 1, wherein the mole ratio of D-tartaric acid to the following compound is about 1:1:



.

3. The compound of claim 1 or 2, wherein the compound is in crystalline form.

4. The compound of claim 3, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 6.0 ± 0.2, 8.8 ± 0.2, 10.6 ± 0.2, 10.9 ± 0.2, 15.9 ± 0.2, 20.9 ± 0.2, and 23.9 ± 0.2.

5. The compound of claim 4, wherein the X-ray powder diffraction pattern further comprises a peak at the following diffraction angle (2θ): 15.1 ± 0.2.

6. The compound of claim 4 or 5, wherein the X-ray powder diffraction pattern further comprises a peak at the following diffraction angle (2θ): 17.7 ± 0.2.

7. The compound of any one of claims 4-6, wherein the X-ray powder diffraction pattern further comprises a peak at the following diffraction angle (2θ): 19.0 ± 0.2.

8. The compound of any one of claims 4-7, wherein the X-ray powder diffraction pattern further comprises a peak at the following diffraction angle (2θ): 21.4 ± 0.2.

9. The compound of any one of claims 4-8, wherein the X-ray powder diffraction pattern further comprises a peak at the following diffraction angle (2θ): 22.7 ± 0.2.

10. The compound of any one of claims 4-9, wherein the X-ray powder diffraction pattern further comprises a peak at the following diffraction angle (2θ): 24.3 ± 0.2.

11. The compound of any one of claims 4-10, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 25%.

12. The compound of any one of claims 4-10, wherein the relative intensity of the peak at said diffraction angles (2θ) is at least 15%.

13. The compound of claim 3 characterized by the following X-ray powder diffraction pattern expressed in terms of diffraction angle 2θ, inter-planar distances d, and relative intensity (expressed as a percentage with respect to the most intense peak):

Angle [2θ]	**d-spacing [Å]**	**Relative Intensity [%]**
6.0	14.7	40
8.8	10.0	36
10.6	8.4	53
10.9	8.1	44
13.5	6.5	15
15.1	5.9	31
15.4	5.8	18
15.9	5.6	100
16.6	5.3	6
17.7	5.0	35
17.9	5.0	16
18.8	4.7	16
19.0	4.7	26
20.0	4.4	22
20.9	4.3	57
21.4	4.1	30
21.9	4.1	18
22.0	4.0	21
22.7	3.9	29
22.9	3.9	12
23.0	3.9	22

Angle [2θ]	d-spacing [Å]	Relative Intensity [%]
23.4	3.8	5
23.9	3.7	41
24.3	3.7	25
24.8	3.6	8
25.3	3.5	9
25.8	3.4	9
26.2	3.4	5
27.8	3.2	7
28.0	3.2	6
28.4	3.1	14
28.6	3.1	7
29.5	3.0	7
30.3	2.9	9
31.4	2.8	6
31.7	2.8	5
32.0	2.8	10
32.6	2.7	5
32.9	2.7	16
34.9	2.6	5
35.8	2.5	7
38.8	2.3	5

.

14. The compound of claim 3, wherein the X-ray powder diffraction pattern is substantially as shown in FIG. 1.

15. The compound of claim 3, wherein the X-ray powder diffraction pattern is substantially as shown in FIG. 2.

16. The compound of any one of claims 3-15, wherein the compound has a melting point onset as determined by differential scanning calorimetry in the range of from about 225 degrees Celsius to about 240 degrees Celsius.

17. The compound of any one of claims 3-15, wherein the compound has a melting point onset as determined by differential scanning calorimetry at about 233 degrees Celsius.

18. The compound of any one of claims 3-15, wherein the compound has a differential scanning calorimetry curve substantially the same as shown in FIG. 4.

19. A pharmaceutical composition comprising a compound of any one of claims 1-18 and a pharmaceutically acceptable carrier.

20. Use of a compound of any one of claims 1-18, in the manufacture of a medicament for treating a disease or condition mediated by nuclear SET domain-containing protein 2 (NSD2) in a subject.

21. The use of claim 20, wherein said disease or condition mediated by NSD2 is cancer.

22. The use of claim 20, wherein said disease or condition mediated by NSD2 is selected from a solid tumor, leukemia, myeloma, lymphoma, and hypertension.

23. The use of claim 20, 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.

24. The use of claim 20, wherein said disease or condition mediated by NSD2 is acute lymphoblastic leukemia, skin squamous cell carcinoma, or mantle cell lymphoma.

25. The use of claim 20, wherein said disease or condition mediated by NSD2 is multiple myeloma.

26. The use of claim 20, wherein said disease or condition mediated by NSD2 is prostate cancer.

27. The use of claim 20, wherein said disease or condition mediated by NSD2 is lung cancer.

28. The use of claim 20, wherein said disease or condition mediated by NSD2 is non-small cell lung cancer.

29. The use of any one of claims 20-28, wherein the subject is a human.

30. A *in vitro* method of inhibiting the activity of nuclear SET domain-containing protein 2 (NSD2), comprising contacting a NSD2 with an effective amount of a compound of any one of claims 1-18 to inhibit the activity of said NSD2.

31. A compound of any one of claims 1-18, for use in therapy.