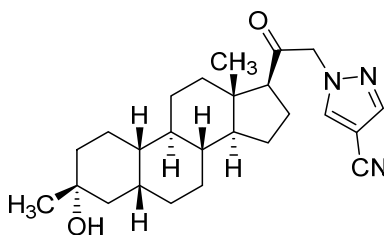


CNS-related diseases. Crystalline forms of such a steroid described herein are directed toward this end.

SUMMARY

[0005] The present disclosure relates, in part, to novel forms (for example, certain crystalline forms described herein) of a 19-nor (i.e., C19 desmethyl) compound. Generally, a solid compound's efficacy as a drug can be affected by the properties of the solid it comprises.

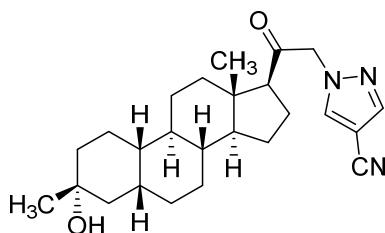
[0006] The present disclosure provides a crystalline compound of Formula (I):



Formula (I)

also referred to herein as “Compound 1.”

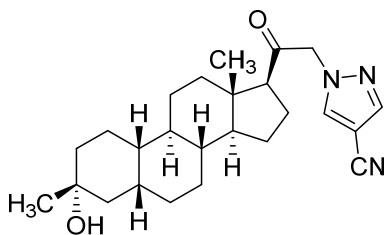
[0006a] In one aspect of the present disclosure, there is provided a crystalline solid form of Compound 1:



Compound 1,

having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ , between and including 11.6 to 12.0 degrees in 2θ , between and including 13.2 to 13.6 degrees in 2θ , between and including 14.2 to 14.6 degrees in 2θ , between and including 14.6 to 15.0 degrees in 2θ , between and including 16.8 to 17.2 degrees in 2θ , between and including 20.5 to 20.9 degrees in 2θ , between and including 21.3 to 21.7 degrees in 2θ , between and including 21.4 to 21.8 degrees in 2θ , and between and including 22.4 to 22.8 degrees in 2θ .

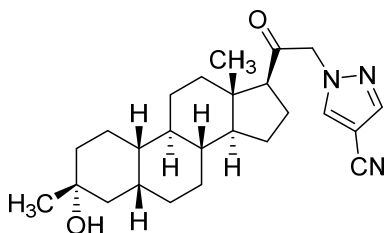
[0006b] In another aspect of the present disclosure, there is provided a crystalline solid form of Compound 1:



Compound 1,

having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ , between and including 14.6 to 15.0 degrees in 2θ , between and including 16.8 to 17.2 degrees in 2θ , between and including 20.5 to 20.9 degrees in 2θ , between and including 21.3 to 21.7 degrees in 2θ .

[0006c] In a further aspect of the present disclosure, there is provided a crystalline solid form of Compound 1:



Compound 1,

having an XRPD pattern comprising peaks at 9.9 degrees in 2θ , 14.8 degrees in 2θ , 17.0 degrees in 2θ , 20.7 degrees in 2θ , and 21.5 degrees in 2θ .

[0006d] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a crystalline solid form of Compound 1 disclosed herein, and a pharmaceutically acceptable excipient.

[0006e] In another aspect of the present disclosure, there is provided a use of a crystalline solid form of Compound 1 disclosed herein, or a pharmaceutical composition disclosed herein, for the manufacture of a medicament for the treatment of a comorbid disorder, neurological disorder, a psychiatric disorder, a seizure disorder, a neuroinflammatory disorder, a glaucoma or metabolic disorder, or a sensory deficit disorder, in a subject in need thereof.

[0006f] In a further aspect of the present disclosure, there is provided a use of a crystalline solid form of Compound 1 disclosed herein, or a pharmaceutical composition disclosed herein, for the manufacture of a medicament for the treatment of a CNS-related disorder in a subject in need thereof.

[0006g] In another aspect of the present disclosure, there is provided a use of a crystalline solid form of Compound 1 disclosed herein, or a pharmaceutical composition disclosed herein, for the manufacture of a medicament of a neuroprotectant.

[0006h] In a further aspect of the present disclosure, there is provided a use of a crystalline solid form of Compound 1 disclosed herein, or a pharmaceutical composition disclosed herein, for the manufacture of a medicament for use as an analgesic or other agent for pain control.

[0006i] In another aspect of the present disclosure, there is provided a method for preparing a crystalline solid form of Compound 1 disclosed herein, the method comprising:

providing Form A of Compound 1 in isopropyl alcohol, isopropyl acetate, ethyl acetate, or a combination thereof, and

performing a crystallization step to obtain a crystalline solid form of Compound 1 disclosed herein,

wherein Form A of Compound 1 has an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ , between and including 10.6 to 11.0 degrees in 2θ , between and including 13.0 to 13.4 degrees in 2θ , between and including 18.7 to 19.1 degrees in 2θ , and between and including 21.4 to 21.8 degrees in 2θ .

[0007] In some embodiments, a solubilized form of the crystalline form of Compound 1 is converted to a different crystalline form of Compound 1 by slow evaporation, anti-solvent addition, slow-cooling, solution vapor diffusion, solid vapor diffusion, fast evaporation, reverse anti-solvent addition, and water activity experiments.

[0008] In some embodiments, a crystalline form of Compound 1 is converted to a different crystalline form of Compound 1 by slurry conversion.

In some embodiments, physical or chemical parameters of a solid form of Compound 1 are evaluated from one or more of the following analytical techniques: X-ray powder diffraction (XRPD) analysis, e.g., variable-temperature XRPD (VT-XRPD) analysis, single-crystal X-ray crystallography, thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR) spectroscopy or solid-state NMR spectroscopy, Raman spectroscopy, or dynamic vapor sorption (DVS).

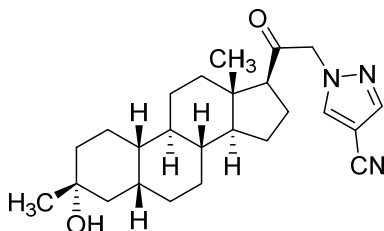
[0009] In embodiments, each solid form is characterized and identified with parameters obtained from one or more of the aforementioned analytical methods:

X-ray diffraction patterns presented with degrees 2-theta (2θ) as the abscissa and peak intensity as the ordinate as determined by analysis with XRPD. These patterns are also referred to herein as XRPD patterns;

CLAIMS

What is claimed is:

1. A crystalline solid form of Compound 1:

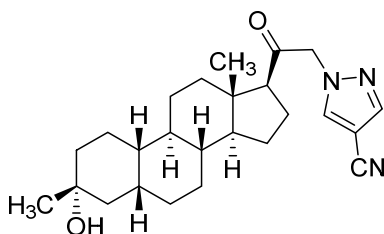


Compound 1,

having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ , between and including 11.6 to 12.0 degrees in 2θ , between and including 13.2 to 13.6 degrees in 2θ , between and including 14.2 to 14.6 degrees in 2θ , between and including 14.6 to 15.0 degrees in 2θ , between and including 16.8 to 17.2 degrees in 2θ , between and including 20.5 to 20.9 degrees in 2θ , between and including 21.3 to 21.7 degrees in 2θ , between and including 21.4 to 21.8 degrees in 2θ , and between and including 22.4 to 22.8 degrees in 2θ .

2. The crystalline solid form of claim 1, wherein the peak between and including 9.7 to 10.1 is 9.9 degrees in 2θ , the peak between and including 11.6 to 12.0 is 11.8 degrees in 2θ , the peak between and including 13.2 to 13.6 is 13.4 degrees in 2θ , the peak between and including 14.2 to 14.6 is 14.4 degrees in 2θ , the peak between and including 14.6 to 15.0 degrees is 14.8 in 2θ , the peak between and including 16.8 to 17.2 is 17.0 degrees in 2θ , the peak between and including 20.5 to 20.9 is 20.7 degrees in 2θ , the peak between and including 21.3 to 21.7 is 21.5 degrees in 2θ , the peak between and including 21.4 to 21.8 is 21.6 degrees in 2θ , and the peak between and including 22.4 to 22.8 is 22.6 degrees in 2θ .

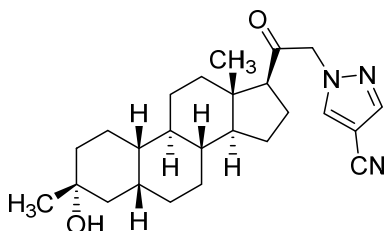
3. A crystalline solid form of Compound 1:



Compound 1,

having an XRPD pattern comprising peaks between and including 9.7 to 10.1 degrees in 2θ , between and including 14.6 to 15.0 degrees in 2θ , between and including 16.8 to 17.2 degrees in 2θ , between and including 20.5 to 20.9 degrees in 2θ , between and including 21.3 to 21.7 degrees in 2θ .

4. A crystalline solid form of Compound 1:



Compound 1,

having an XRPD pattern comprising peaks at 9.9 degrees in 2θ , 14.8 degrees in 2θ , 17.0 degrees in 2θ , 20.7 degrees in 2θ , and 21.5 degrees in 2θ .

5. A pharmaceutical composition comprising a crystalline solid form of Compound 1 of any one of claims 1-4, and a pharmaceutically acceptable excipient.
6. Use of a crystalline solid form of Compound 1 of any one of claims 1-4, or a pharmaceutical composition of claim 5, for the manufacture of a medicament for the treatment of a comorbid disorder, neurological disorder, a psychiatric disorder, a seizure disorder, a neuroinflammatory disorder, a glaucoma or metabolic disorder, or a sensory deficit disorder, in a subject in need thereof.
7. The use of claim 6, wherein the disorder is a neurological disorder.
8. The use of claim 7, wherein the neurological disorder is a neurodegenerative disorder.
9. The use of claim 8, wherein the neurodegenerative disorder is tinnitus.
10. The use of claim 7, wherein the neurological disorder is a movement disorder.
11. The use of claim 10, wherein the movement disorder is tremor.
12. The use of claim 11, wherein the tremor is essential tremor.
13. The use of claim 6, wherein the disorder is a psychiatric disorder.
14. The use of claim 13, wherein the psychiatric disorder is a mood disorder.

15. The use of claim 14, wherein the mood disorder is a major depressive disorder (MDD).
16. The use of claim 14, wherein the mood disorder is postpartum depression (PPD).
17. The use of claim 13, wherein the psychiatric disorder is an anxiety disorder.
18. The use of claim 17, wherein the anxiety disorder is generalized anxiety disorder.
19. The use of claim 13, wherein the psychiatric disorder is a psychotic disorder.
20. The use of claim 19, wherein the psychotic disorder is bipolar disorder.
21. Use of a crystalline solid form of Compound 1 of any one of claims 1-4, or a pharmaceutical composition of claim 5, for the manufacture of a medicament for the treatment of a CNS-related disorder in a subject in need thereof.
22. The use of claim 21, wherein the CNS-related disorder is a sleep disorder, a mood disorder, a schizophrenia spectrum disorder, a convulsive disorder, a disorder of memory and/or cognition, a movement disorder, a personality disorder, autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, or tinnitus.
23. Use of a crystalline solid form of Compound 1 of any one of claims 1-4, or a pharmaceutical composition of claim 5, for the manufacture of a medicament of a neuroprotectant.
24. Use of a crystalline solid form of Compound 1 of any one of claims 1-4, or a pharmaceutical composition of claim 5, for the manufacture of a medicament for use as an analgesic or other agent for pain control.
25. The use of claim 24, wherein the compound is used as an analgesic or other agent for pain control to treat inflammatory pain, neuropathic pain, fibromyalgia, or peripheral neuropathy.
26. The use of any one of claims 6-25, wherein the crystalline solid form of Compound 1 is to be administered orally, parenterally, intradermally, intrathecally, intramuscularly, subcutaneously, vaginally, as a buccal, sublingually, rectally, as a topical, inhalation, intranasal, or transdermally.
27. The use of claim 26, wherein the crystalline solid form of Compound 1 is to be administered orally.

28. The use of claim 26, wherein the crystalline solid form of Compound 1 is to be administered chronically.
29. A method for preparing a crystalline solid form of Compound 1 of any one of claims 1-4, the method comprising:
- providing Form A of Compound 1 in isopropyl alcohol, isopropyl acetate, ethyl acetate, or a combination thereof, and
- performing a crystallization step to obtain a crystalline solid form of Compound 1 of any one of claims 1-4,
- wherein Form A of Compound 1 has an XRPD pattern comprising peaks between and including 9.3 to 9.7 degrees in 2θ , between and including 10.6 to 11.0 degrees in 2θ , between and including 13.0 to 13.4 degrees in 2θ , between and including 18.7 to 19.1 degrees in 2θ , and between and including 21.4 to 21.8 degrees in 2θ .
30. The method of claim 29, wherein the crystallization step is performed via slurry conversion.
31. The method of claim 30, wherein Form A of Compound 1 is in a mixture of isopropyl alcohol and isopropyl acetate.
32. The method of claim 31, wherein the mixture is heated at a temperature of about 50 °C.
33. The method of claim 29, wherein Form A of Compound 1 is in ethyl acetate.
34. The method of claim 33, wherein Form A of Compound 1 is solubilized when in ethyl acetate.
35. The method of claim 34, wherein the solubilized Form A of Compound 1 is heated at a temperature of about 65 °C.
36. The method of any one of claims 32-35, further comprising adding seed crystals of a crystalline solid form of Compound 1 of any one of claims 1-4 at a loading from about 0.1% to about 5.0% of the total amount of Compound 1 present.