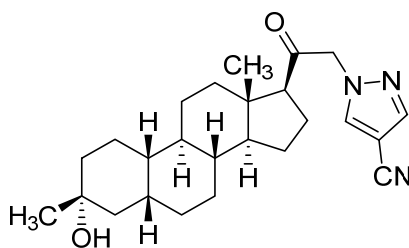


CNS-related diseases. Crystalline forms of such a steroid described herein are directed toward this end.

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] Thus, in one aspect, described herein is a crystalline compound of Formula (I):



Formula (I)

also referred to herein as “Compound 1.”

[0006a] In another aspect of the present disclosure, there is provided a method for transforming a crystalline compound having an XRPD pattern substantially as depicted in FIG. 1A, to the crystalline compound having an XRPD pattern substantially as depicted in FIG. 3A, the method comprising crystallization from a solubilized form of Compound 1 or slurry conversion.

[0006b] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a crystalline compound disclosed herein, and a pharmaceutically acceptable excipient.

[0006c] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or pharmaceutically acceptable composition disclosed herein, in the manufacture of a medicament for treating a CNS-related disorder in a subject in need thereof.

[0006d] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or pharmaceutically acceptable composition disclosed herein, in the manufacture of a medicament for treating a neurological disorder, a psychiatric disorder, a seizure disorder, a neuroinflammatory disorder, a glaucoma or metabolic disorder, a sensory deficit disorder, in a subject in need thereof.

[0006e] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or pharmaceutically acceptable composition disclosed herein, in the manufacture of a medicament for use as a neuroprotectant.

[0006f] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or pharmaceutically acceptable composition disclosed herein, in the manufacture of a medicament for use as an analgesic or other agent for pain control.

[0006g] In another aspect of the present disclosure, there is provided a compound disclosed herein, or pharmaceutically acceptable composition disclosed herein, for use in treating a CNS-related disorder, a neurological disorder, a psychiatric disorder, a seizure disorder, a neuroinflammatory disorder, a glaucoma or metabolic disorder, a sensory deficit disorder, or for use as a neuroprotectant, an analgesic or other agent for pain control.

[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;

[0044] In some embodiments, crystalline Compound 1 has an XRPD pattern substantially as depicted in FIG. 13A.

[0045] In some embodiments, crystalline Compound 1 has an XRPD pattern substantially as depicted in FIG. 14A.

[0046] In some embodiments, crystalline Compound 1 has an XRPD pattern substantially as any of those depicted in FIG. 16.

[0047] In one embodiment, the present disclosure describes a method for transforming the crystalline compound of claim 5 to the crystalline compound of claim 10, the method comprising crystallization from a solubilized form of Compound 1 or slurry conversion.

[0048] In some embodiments, the transformation is performed using ethyl acetate as a solvent at a temperature from about 50 °C to about 70 °C, e.g., from 60 °C to 65 °C.

[0049] In some embodiments, the transformation is performed in the presence of seed crystals of the crystalline compound of claim 10 at a loading from about 0.1% to about 5.0%, e.g. from 0.2% to 1.0%, of the total amount of Compound 1 present.

[0050] In one embodiment, the present disclosure describes a pharmaceutical composition comprising a crystalline form of Compound 1, and a pharmaceutically acceptable excipient.

[0051] In one embodiment, the present disclosure describes a method for treating a CNS-related disorder in a subject in need thereof, comprising administering to the subject an effective amount of Compound 1, *e.g.*, a crystalline solid form of Compound 1 described herein, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0052] In some embodiments, 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.

[0053] In some embodiments, crystalline Compound 1 is administered orally, parenterally, intradermally, intrathecally, intramuscularly, subcutaneously, vaginally, as a buccal, sublingually, rectally, as a topical, inhalation, intranasal, or transdermally.

[0054] In some embodiments, crystalline Compound 1 is administered chronically.

[0055] In another embodiment, provided herein is a method of treating a neurological disorder, a psychiatric disorder, a seizure disorder, a neuroinflammatory disorder, a glaucoma or metabolic disorder, a sensory deficit disorder, in a subject in need thereof, comprising administering to the subject an effective amount of Compound 1 or a pharmaceutically acceptable composition thereof.

[0056] In another embodiment, provided herein, is a method of using Compound 1 or a pharmaceutically acceptable composition thereof, as a neuroprotectant, comprising

administering to a subject in need thereof an effective amount of Compound 1 or a pharmaceutically acceptable composition thereof.

[0057] In another embodiment, provided herein, is a method of using Compound 1 or a pharmaceutically acceptable composition thereof, as an analgesic or other agent for pain control, comprising administering to a subject in need thereof an effective amount of Compound 1 or a pharmaceutically acceptable composition thereof. In some embodiments, the compound or pharmaceutically acceptable composition is used as an analgesic or other agent for pain control to treat inflammatory pain, neuropathic pain, fibromyalgia, or peripheral neuropathy.

[0058] As used herein, “XRPD” refers to X-ray powder diffraction. As used herein, “VT-XRPD” refers to variable temperature-X-ray powder diffraction. As used herein, “TGA” refers to thermogravimetric analysis. As used herein, DSC refers to differential scanning calorimetry. As used herein, “NMR” refers to nuclear magnetic resonance. As used herein, “DVS” refers to dynamic vapor sorption. As used herein, “DCM” refers to dichloromethane. As used herein, “EtOAc” refers to ethyl acetate. As used herein, “MeOH” refers to methanol. As used herein, “MBTE” refers to methyl tert-butyl ether. As used herein, “RH” refers to relative humidity. As used herein, “RT” refers to room temperature.

[0059] As used herein, "crystalline" refers to a solid having a highly regular chemical structure, i.e., having long range structural order in the crystal lattice. The molecules are arranged in a regular, periodic manner in the 3-dimensional space of the lattice. In particular, a crystalline form may be produced as one or more single crystalline forms. For the purposes of this application, the terms "crystalline form", "single crystalline form," "crystalline solid form," "solid form," and "polymorph" are synonymous and used interchangeably; the terms distinguish between crystals that have different properties (*e.g.*, different XRPD patterns and/or different DSC scan results).

[0060] The term "substantially crystalline" refers to forms that may be at least a particular weight percent crystalline. Particular weight percentages are 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or any percentage between 70% and 100%. In certain embodiments, the particular weight percent of crystallinity is at least 90%. In certain other embodiments, the particular weight percent of crystallinity is at least 95%. In some embodiments, Compound 1 can be a substantially crystalline sample of any of the crystalline solid forms described herein (*e.g.*, Forms, A, B, C, D, E, F, H, I, J, K, L, M, N, O, and P).

[0061] The term "substantially pure" relates to the composition of a specific crystalline solid form of Compound 1 that may be at least a particular weight percent free of impurities and/or other solid forms of Compound 1. Particular weight percentages are 70%, 75%, 80%, 85%,

32. The crystalline compound of claim 1, having an XRPD pattern substantially as depicted in FIG. **13A**.
33. The crystalline compound of claim 1, having an XRPD pattern substantially as depicted in FIG. **14A**.
34. The crystalline compound of claim 1, having any of the XRPD patterns substantially as depicted in FIG. **16**.
35. A method for transforming the crystalline compound of claim 11 to the crystalline compound of claim 19, the method comprising crystallization from a solubilized form of Compound 1 or slurry conversion.
36. The method of claim 35, wherein the transformation is performed using ethyl acetate as a solvent at a temperature from about 50 °C to about 70 °C.
37. The method of claim 35, wherein the transformation is performed in the presence of seed crystals of the crystalline compound of claim 13 at a loading from about 0.1% to about 5.0%, of the total amount of Compound 1 present.
38. A pharmaceutical composition comprising a crystalline compound of any one of the preceding claims, and a pharmaceutically acceptable excipient.
39. Use of a compound of any one of claims 1 to 22, or pharmaceutically acceptable composition of claim 38, in the manufacture of a medicament for treating a CNS-related disorder in a subject in need thereof.
40. The use of claim 39, 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.
41. The use of claim 39, wherein the medicament is to be administered orally, parenterally, intradermally, intrathecally, intramuscularly, subcutaneously, vaginally, as a buccal, sublingually, rectally, as a topical, inhalation, intranasal, or transdermally to the subject.

42. The use of claim 39, wherein the medicament is to be administered chronically to the subject.
43. Use of a compound of any one of claims 1 to 22, or pharmaceutically acceptable composition of claim 38, in the manufacture of a medicament for treating a neurological disorder, a psychiatric disorder, a seizure disorder, a neuroinflammatory disorder, a glaucoma or metabolic disorder, a sensory deficit disorder, in a subject in need thereof.
44. Use of a compound of any one of claims 1 to 16, or pharmaceutically acceptable composition of claim 38, in the manufacture of a medicament for use as a neuroprotectant.
45. Use of a compound of any one of claims 1 to 22, or pharmaceutically acceptable composition of claim 38, in the manufacture of a medicament for use as an analgesic or other agent for pain control.
46. The use of claim 45, wherein the medicament is an analgesic or other agent for pain control to treat inflammatory pain, neuropathic pain, fibromyalgia, or peripheral neuropathy.
47. A compound of any one of claims 1 to 22, or pharmaceutically acceptable composition of claim 38, for use in treating a CNS-related disorder, a neurological disorder, a psychiatric disorder, a seizure disorder, a neuroinflammatory disorder, a glaucoma or metabolic disorder, a sensory deficit disorder, or for use as a neuroprotectant, an analgesic or other agent for pain control.