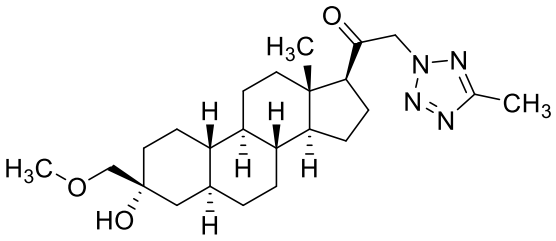
susceptible to excitatory inputs (i.e., reduced neuron excitability). In other words, the higher the chloride ion concentration in the neuron, the lower the brain excitability (the level of arousal).

[0005] New and improved crystalline forms of neuroactive steroids are needed that act as modulating agents for brain excitability, as well as agents for the prevention and treatment of CNS-related diseases. Crystalline forms of such a neuroactive steroid described herein are directed toward this end.

SUMMARY

[0005a] In a first aspect of the present disclosure, there is provided a crystalline form of Compound (**1**), wherein Compound (**1**) is represented by the following structural formula:



Compound (**1**), and

wherein the crystalline form is crystalline anhydrous Compound (**1**).

[0005b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a crystalline form as disclosed herein, and a pharmaceutically acceptable excipient.

[0005c] In yet another aspect of the present disclosure, there is provided a use of a crystalline form as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for modulating a $GABA_A$ receptor in a subject in need thereof.

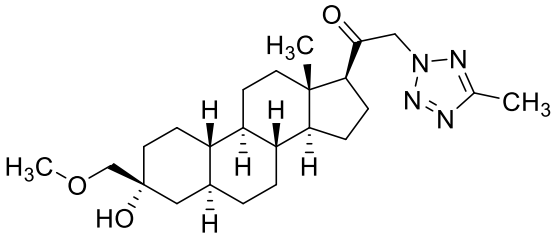
[0005d] In a further aspect of the present disclosure, there is provided a use of a crystalline form as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a $GABA_A$ receptor mediated CNS-related disorder in a subject in need thereof.

[0005e] In another aspect of the present disclosure, there is provided a use of a crystalline form as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a CNS-related disorder in a subject in need thereof.

[0005f] In yet another aspect of the present disclosure, there is provided a use of a crystalline form as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inducing sedation and/or anesthesia in a subject in need thereof.

[0005g] In a further aspect of the present disclosure, there is provided a crystalline form as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in therapy.

[0006] The present disclosure provides a crystalline form of Compound (**1**), wherein Compound (**1**) is represented by the following structural formula:



Compound (**1**), and wherein the crystalline form is crystalline anhydrous Compound (**1**).

[0007] In some examples, the crystalline form is characterized by one or more peaks corresponding to 2-theta values measured in degrees of 15.4 ± 0.3, 15.6 ± 0.3, 18.1 ± 0.3, 18.8 ± 0.3, and 22.6 ± 0.3 in an X-ray powder diffraction pattern. In other examples, the crystalline form is further characterized by one or more peaks corresponding to 2-theta values measured in degrees of 9.4 ± 0.3, 11.9 ± 0.3, 22.2 ± 0.3, and 23.4 ± 0.3 in an X-ray powder diffraction pattern.

[0008] In some examples, the crystalline form is characterized by one or more peaks corresponding to 2-theta values measured in degrees of 15.4 ± 0.2, 15.6 ± 0.2, 18.1 ± 0.2, 18.8 ± 0.2, and 22.6 ± 0.2 in an X-ray powder diffraction pattern. In other examples, the crystalline form is further characterized by one or more peaks corresponding to 2-theta values measured in degrees of 9.4 ± 0.2, 11.9 ± 0.2, 22.2 ± 0.2, and 23.4 ± 0.2 in an X-ray powder diffraction pattern.

[0009] In some examples, the crystalline form has an endotherm at a T_{onset} from about 146 °C to about 157 °C when heated at a rate of 10 °C/min starting at a temperature of about 30 °C.

[0010] In some examples, the crystalline form is characterized by one or more peaks corresponding to 200.0 ± 0.3 ppm, 164.3 ± 0.3 ppm, 81.3 ± 0.3 ppm, 70.5 ± 0.3 ppm, and 62.2 ± 0.3 ppm in a ^{13}C SSNMR spectrum. In some examples, the crystalline form is

further characterized by one or more peaks corresponding to 60.9 ± 0.3 ppm, 60.0 ± 0.3 ppm, 56.7 ± 0.3 ppm, 47.8 ± 0.3 ppm, and 45.9 ± 0.3 ppm in a ^{13}C SSNMR spectrum. In other examples, the crystalline form is further characterized by one or more peaks corresponding to 42.6 ± 0.3 ppm, 39.3 ± 0.3 ppm, 38.3 ± 0.3 ppm, 35.5 ± 0.3 ppm, 25.8 ± 0.3 ppm, and 22.9 ± 0.3 ppm in a ^{13}C SSNMR spectrum.

[0011] In some examples, the crystalline form is characterized by one or more peaks corresponding to 2-theta values measured in degrees of 8.9 ± 0.3, 14.6 ± 0.3, 16.4 ± 0.3, 18.0 ± 0.3, and 20.0 ± 0.3 in an X-ray powder diffraction pattern. In some examples, the crystalline form is further characterized by one or more peaks corresponding to 2-theta values measured in degrees of 11.6 ± 0.3, 15.0 ± 0.3, 17.4 ± 0.3, 21.2 ± 0.3, and 29.0 ± 0.3 in an X-ray powder diffraction pattern. In other examples, the crystalline form is further characterized by one or more peaks corresponding to 2-theta values measured in degrees of 9.6 ± 0.3, 12.9 ± 0.3, and 29.6 ± 0.3 in an X-ray powder diffraction pattern.

[0012] In some examples, the crystalline form is characterized by one or more peaks corresponding to 2-theta values measured in degrees of 8.9 ± 0.2, 14.6 ± 0.2, 16.4 ± 0.2, 18.0 ± 0.2, and 20.0 ± 0.2 in an X-ray powder diffraction pattern. In some examples, the crystalline form is further characterized by one or more peaks corresponding to 2-theta values measured in degrees of 11.6 ± 0.2, 15.0 ± 0.2, 17.4 ± 0.2, 21.2 ± 0.2, and 29.0 ± 0.2 in an X-ray powder diffraction pattern. In other examples, the crystalline form is further characterized by one or more peaks corresponding to 2-theta values measured in degrees of 9.6 ± 0.2, 12.9 ± 0.2, and 29.6 ± 0.2 in an X-ray powder diffraction pattern.

[0013] In some examples, the crystalline form has an endotherm at a T_{onset} from about 160 °C to about 166 °C when heated at a rate of 10 °C/min starting at a temperature of about 30 °C. In other examples, the crystalline form (or Compound (**1**)) degrades at a temperature of about 200 °C or greater.

[0014] In some examples, the crystalline form is further characterized by one or more peaks corresponding to 200.2 ± 0.3 ppm, 199.1 ± 0.3 ppm, 162.8 ± 0.3 ppm, 82.9 ± 0.3 ppm, 82.1 ± 0.3 ppm, and 12.6 ± 0.3 ppm in a ^{13}C SSNMR spectrum. In some examples, the crystalline form is further characterized by one or more peaks corresponding to 70.4 ± 0.3 ppm, 63.6 ± 0.3 ppm, 49.7 ± 0.3 ppm, 35.5 ± 0.3 ppm, and 15.5 ± 0.3 ppm in a ^{13}C SSNMR spectrum. In other examples, the crystalline form is further characterized by one or more peaks corresponding to 62.9 ± 0.3 ppm, 61.4 ± 0.3 ppm, 60.6 ± 0.3 ppm, 45.4 ± 0.3 ppm, and 37.9 ± 0.3 ppm in a ^{13}C SSNMR spectrum.

[0015] In some examples, the crystalline form of Compound (**1**) is substantially pure. For instance, the crystalline form is substantially free of impurities (e.g., comprises fewer than about 30 wt% of impurities, fewer than about 25 wt% of impurities, fewer than about 10 wt% of impurities, fewer than about 5 wt% of impurities, fewer than about 1 wt% of impurities, fewer than about 0.5 wt% of impurities, fewer than about 0.1 wt% of impurities, or fewer than about 0.05 wt% of impurities).

[0016] Another example of the present disclosure provides a pharmaceutical composition comprising a crystalline form described herein, and a pharmaceutically acceptable excipient.

[0017] Another example of the present disclosure provides a method of modulating a $GABA_A$ receptor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form described herein or a pharmaceutical composition described herein.

[0018] Another example of the present disclosure provides a method of modulating a $GABA_A$ receptor mediated CNS-related disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form described herein or a pharmaceutical composition described herein.

[0019] Another example of the present disclosure provides a method of treating a CNS-related disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form described herein or a pharmaceutical composition described herein.

[0020] In some implementations, 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, an autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus. For example, the CNS-related disorder is a mood disorder. In other examples, the mood disorder is depression. For instance, the depression is postpartum depression. In other instances, the depression is a major depressive disorder. For example, the major depressive disorder is a moderate major depressive disorder. And, in other examples, the major depressive disorder is a severe major depressive disorder.

[0021] In some implementations, the CNS-related disorder is tremor (e.g., essential tremor).

[0022] In some implementations, the CNS-related disorder is seizure.

[0023] In some implementations, the CNS-related disorder is epilepsy.

[0024] In some implementations, the CNS-related disorder is status epilepticus. For example, the status epilepticus is convulsive status epilepticus or non-convulsive status

epilepticus. In some instances, the status epilepticus is convulsive status epilepticus selected from early status epilepticus, established status epilepticus, refractor status epilepticus, and super-refractory status epilepticus. In other instances, the status epilepticus is non-convulsive status epilepticus selected from generalized status epilepticus and partial complex status epilepticus.

[0025] Another example of the present disclosure provides a method for inducing sedation and/or anesthesia in a subject in need thereof, comprising administering to the subject an effective amount of a crystalline form described herein or a pharmaceutical composition described herein.

DESCRIPTION OF THE DRAWINGS

[0026] The following figures are presented by way of example and are not intended to limit the scope of the claimed invention.

[0027] Figure 1 depicts an exemplary XRPD pattern of Form S1 of Compound (**1**).

[0028] Figure 2 depicts an exemplary thermogram of a TGA/DSC thermal analysis of Form S1 of Compound (**1**) including a TG curve and DSC curve.

[0029] Figure 3 depicts an exemplary ^{13}C solid state NMR spectrum of Form S1 of Compound (**1**).

[0030] Figure 4 depicts an exemplary DVS isotherm plot of Form S1 of Compound (**1**) at 25 °C.

[0031] Figure 5 depicts an exemplary XRPD pattern of Form S4 of Compound (**1**).

[0032] Figure 6 depicts exemplary XRPD patterns for Form S1 (top) and Form S4 (bottom) of Compound (**1**).

[0033] Figure 7 depicts an exemplary thermogram of a TGA/DSC thermal analysis of Form S4 of Compound (**1**) including a TG curve and DSC curve.

[0034] Figure 8 is an enantiotropy diagram illustrating the relationship between Form S1 and Form S4 of Compound (**1**).

[0035] Figure 9 depicts an exemplary ^{13}C solid state NMR spectrum of Form S4 of Compound (**1**).

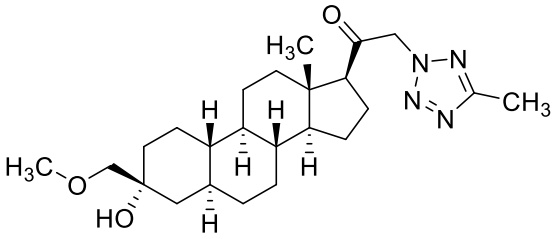
[0036] Figure 10 depicts an overlay of exemplary ^{13}C solid state NMR spectra for Form S1 (solid lines) and Form S4 (dashed lines) of Compound (**1**).

[0037] Figure 11 depicts an exemplary DVS isotherm plot of Form S4 of Compound (**1**) at 25 °C.

[0038] Figure 12 is a diagram illustrating interconversion conditions for Form S1 and Form S4 of Compound (**1**).

WHAT IS CLAIMED IS:

1. A crystalline form of Compound (**1**), wherein Compound (**1**) is represented by the following structural formula:



Compound (**1**), and

wherein the crystalline form is crystalline anhydrous Compound (**1**).

2. The crystalline form of claim 1, wherein the crystalline form is characterized by one or more peaks corresponding to 2-theta values measured in degrees of 15.4 ± 0.3, 15.6 ± 0.3, 18.1 ± 0.3, 18.8 ± 0.3, and 22.6 ± 0.3 in an X-ray powder diffraction pattern.

3. The crystalline form of claim 2, wherein the crystalline form is further characterized by one or more peaks corresponding to 2-theta values measured in degrees of 9.4 ± 0.3, 11.9 ± 0.3, 22.2 ± 0.3, and 23.4 ± 0.3 in an X-ray powder diffraction pattern.

4. The crystalline form of any one of claims 1-3, wherein the crystalline form has an endotherm at a T_{onset} from about 146 °C to about 157 °C when heated at a rate of 10 °C/min starting at a temperature of about 30 °C.

5. The crystalline form of any one of claims 1-4, wherein the crystalline form is characterized by one or more peaks corresponding to 200.0 ± 0.3 ppm, 164.3 ± 0.3 ppm, 81.3 ± 0.3 ppm, 70.5 ± 0.3 ppm, and 62.2 ± 0.3 ppm in a ^{13}C SSNMR spectrum.

6. The crystalline form of claim 5, wherein the crystalline form is further characterized by one or more peaks corresponding to 60.9 ± 0.3 ppm, 60.0 ± 0.3 ppm, 56.7 ± 0.3 ppm, 47.8 ± 0.3 ppm, and 45.9 ± 0.3 ppm in a ^{13}C SSNMR spectrum.

7. The crystalline form of claim 6, wherein the crystalline form is further characterized by one or more peaks corresponding to 42.6 ± 0.3 ppm, 39.3 ± 0.3 ppm, 38.3 ± 0.3 ppm, 35.5 ± 0.3 ppm, 25.8 ± 0.3 ppm, and 22.9 ± 0.3 ppm in a ^{13}C SSNMR spectrum.

8. The crystalline form of claim 1, wherein the crystalline form is characterized by one or more peaks corresponding to 2-theta values measured in degrees of 8.9 ± 0.3, 14.6 ± 0.3, 16.4 ± 0.3, 18.0 ± 0.3, and 20.0 ± 0.3 in an X-ray powder diffraction pattern.

9. The crystalline form of claim 8, wherein the crystalline form is further characterized by one or more peaks corresponding to 2-theta values measured in degrees of 11.6 ± 0.3, 15.0 ± 0.3, 17.4 ± 0.3, 21.2 ± 0.3, and 29.0 ± 0.3 in an X-ray powder diffraction pattern.

10. The crystalline form of claim 9, wherein the crystalline form is further characterized by one or more peaks corresponding to 2-theta values measured in degrees of 9.6 ± 0.3, 12.9 ± 0.3, and 29.6 ± 0.3 in an X-ray powder diffraction pattern.

11. The crystalline form of any one of claims 1 or 8-10, wherein the crystalline form has an endotherm at a T_{onset} from about 160 °C to about 166 °C when heated at a rate of 10 °C/min starting at a temperature of about 30 °C.

12. The crystalline form of any one of claims 1 or 8-11, wherein the crystalline form degrades at a temperature of about 200 °C or greater.

13. The crystalline form of any one of claims 1 or 8-12, wherein the crystalline form is further characterized by one or more peaks corresponding to 200.2 ± 0.3 ppm, 199.1 ± 0.3 ppm, 162.8 ± 0.3 ppm, 82.9 ± 0.3 ppm, 82.1 ± 0.3 ppm, and 12.6 ± 0.3 ppm in a ^{13}C SSNMR spectrum.

14. The crystalline form of claim 13, wherein the crystalline form is further characterized by one or more peaks corresponding to 70.4 ± 0.3 ppm, 63.6 ± 0.3 ppm, 49.7 ± 0.3 ppm, 35.5 ± 0.3 ppm, and 15.5 ± 0.3 ppm in a ^{13}C SSNMR spectrum.

15. The crystalline form of claim 14, wherein the crystalline form is further characterized by one or more peaks corresponding to 62.9 ± 0.3 ppm, 61.4 ± 0.3 ppm, 60.6 ± 0.3 ppm, 45.4 ± 0.3 ppm, and 37.9 ± 0.3 ppm in a ^{13}C SSNMR spectrum.

16. A pharmaceutical composition comprising a crystalline form of any one of claims 1-15, and a pharmaceutically acceptable excipient.

17. Use of a crystalline form of any one of claims 1-15, or a pharmaceutical composition of claim 16, in the manufacture of a medicament for modulating a $GABA_A$ receptor in a subject in need thereof.

18. Use of a crystalline form of any one of claims 1-15, or a pharmaceutical composition of claim 16, in the manufacture of a medicament for treating a $GABA_A$ receptor mediated CNS-related disorder in a subject in need thereof.

19. Use of a crystalline form of any one of claims 1-15, or a pharmaceutical composition of claim 16, in the manufacture of a medicament for treating a CNS-related disorder in a subject in need thereof.

20. The use of claim 18 or claim 19, 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, an autism spectrum disorder, pain, traumatic brain injury, a vascular disease, a substance abuse disorder and/or withdrawal syndrome, tinnitus, or status epilepticus.

21. The use of any one of claims 18-20, wherein the CNS-related disorder is a mood disorder.

22. The use of claim 21, wherein the mood disorder is depression.

23. The use of claim 22, wherein the depression is postpartum depression.

24. The use of claim 22, wherein the depression is a major depressive disorder.

25. The use of claim 24, wherein the major depressive disorder is a moderate major depressive disorder.

26. The use of claim 24, wherein the major depressive disorder is a severe major depressive disorder.

27. The use of claim 18 or claim 19, wherein the CNS-related disorder is tremor.

28. The use of claim 27, wherein the tremor is essential tremor.

29. The use of claim 18 or claim 19, wherein the CNS-related disorder is seizure.

30. The use of claim 18 or claim 19, wherein the CNS-related disorder is epilepsy.

31. The use of claim 18 or claim 19, wherein the CNS-related disorder is status epilepticus.

32. The use of claim 31, wherein the status epilepticus is convulsive status epilepticus or non-convulsive status epilepticus.

33. The use of claim 32, wherein the status epilepticus is convulsive status epilepticus selected from early status epilepticus, established status epilepticus, refractor status epilepticus, and super-refractory status epilepticus.

34. The use of claim 32, wherein the status epilepticus is non-convulsive status epilepticus selected from generalized status epilepticus and partial complex status epilepticus.

35. Use of a crystalline form of any one of claims 1-15, or a pharmaceutical composition of claim 16, in the manufacture of a medicament for inducing sedation and/or anesthesia in a subject in need thereof.

36. A crystalline form of any one of claims 1-15, or a pharmaceutical composition of claim 16, for use in therapy.