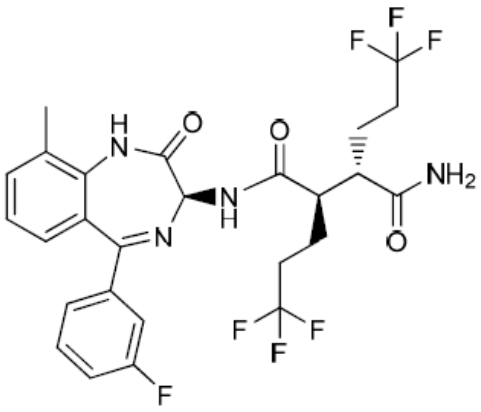
is showing promising results in current clinical trials for the treatment of various cancers (see US Patent 8,629,136, incorporated herein by reference). Crystalline forms of pharmaceutically active agents, such as those disclosed in US 8,629,136, that possess desirable physiochemical properties, such as high bioavailability, solubility, melting point, and crystallinity, were identified.

[003] US Patent 9,273,014, incorporated herein by reference, describes the preparation of Compound 1 and some of its uses. However, crystalline structures of Compound 1 were not disclosed. Crystalline forms of Compound 1 having desirable physiochemical properties are therefore needed to provide forms of Compound 1 with high bioavailability, solubility, melting point, and crystallinity.

SUMMARY

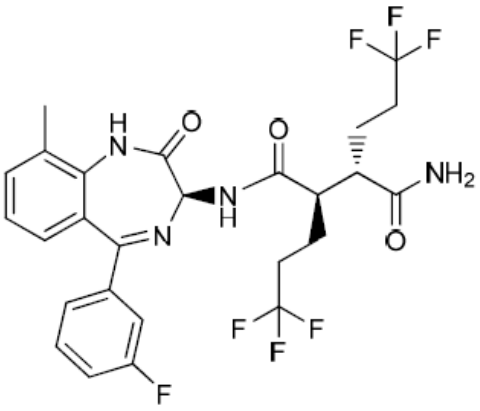
[004] In one aspect, the present disclosure provides a crystalline form of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide, represented by the structure of Compound 1:



(1),

wherein the crystalline form comprises N-2 crystalline form, IPA2-1 crystalline form, M3-1 crystalline form, P4 crystalline form, P5 crystalline form, P6 crystalline form, or any combination thereof.

[005] In another aspect, the present disclosure provides a crystalline form of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide, represented below:

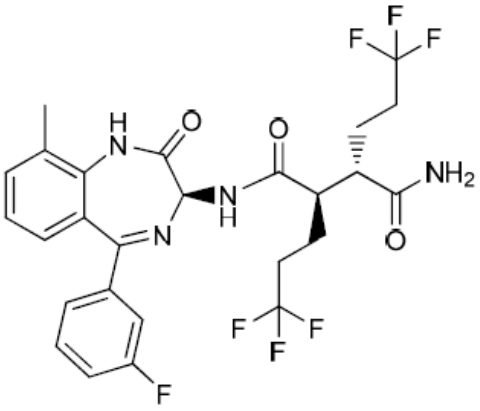


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(1),

wherein the crystalline form comprises a P1 crystalline form; and the P1 crystalline form is crystallized via desolvation of crystalline form IPA2-1 or M3-1, wherein IPA2-1 and M3-1 are additional crystalline forms of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide.

[006] In another aspect, the present disclosure provides a crystalline form of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide, represented below:

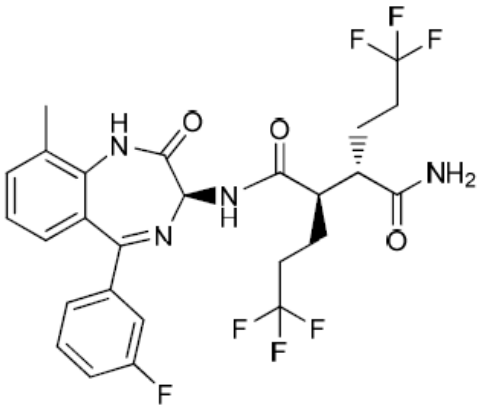


,

(1),

wherein the crystalline form comprises a P2 crystalline form; and the P2 crystalline form is crystallized from crystalline form P1 as described above and which was slurried in ethyl acetate.

[007] In another aspect, the present disclosure provides a crystalline form of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide, represented below:



,

(1),

wherein the crystalline form comprises a P3 crystalline form; and the P3 crystalline form is crystallized from crystalline form P1 as described above and which was slurried in acetonitrile.

[008] In another aspect, the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of the crystalline form as described above and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts PXRD patterns of the N-2 form at room temperature (bottom), 165℃ (middle) and 270℃ (top).

Figure 2 depicts the PXRD pattern of the IPA2-1 form.

Figure 3 depicts the PXRD pattern of the M3-1 form.

Figure 4 depicts the PXRD pattern of the P4 form.

Figure 5 depicts the PXRD pattern of the P5 form.

Figure 6 depicts the PXRD pattern of the P6 form.

Figure 7 depicts the PXRD pattern of the E2-1 form.

Figure 8 depicts the PXRD pattern of the P1 form.

Figure 9 depicts the PXRD pattern of the P2 form.

Figure 10 depicts the PXRD pattern of the P3 form.

Example 5: Alternative synthesis of the N-2 form:

[0067] Form N-2 was also prepared as follows:

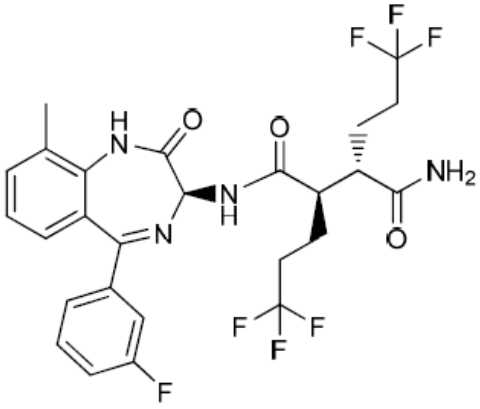
- Compound 1 was added to a reactor under nitrogen;
- 4.0 mL/g equivalent of acetic acid was added to the reactor;
- the contents of the reactor were adjusted to 20 ± 5°C;
- the contents of the reactor were agitated at 20 ± 5°C until all solids dissolved;
- the contents of the reactor were transferred across a polish filter;
- 1.0 mL/g equivalent of acetic acid was added to the reactor;
- the contents of the reactor were transferred across a polish filter;
- the combined polish filtrates were transferred back to the reactor;
- 5.5 g/g equivalents of water were added to the reactor at a rate that maintains the internal temperature at ≤ 25°C;
- the product in the reactor was isolated by vacuum filtration;
- 8.74 g/g equivalents of water were added to the reactor;
- the contents of the reactor were transferred to a filter;
- 8.74 g/g equivalents of water were added to the reactor;
- the contents of the reactor were transferred to a filter;
- the product from the filter was transferred to a drying tray;
- the product was dried at 50 ± 5°C until a constant weight was obtained;
- the product was sampled and tested by HPLC for residual acetic acid and water content; and
- the dried product was put in an appropriate container and labeled.

[0068] The crude compound 1 dissolved in acetic acid was polish filtered using a disc filter, PTFE 0.45µM disposable filter and a 3-piece Hydradyne 1 µM membrane. The obtained dried product from several different batches was characterized by XRPD and had a diffractogram corresponding to the N-2 form (**Figures 17-18**). NMR, MS, FTIR and HPLC showed that the obtained compound batches characterized in **Figure 18** is Compound 1. HPLC showed that assay purity was between 98.3-101.7% (corrected for water, total volatiles and acetic acid content). Particle size distribution showed X_{10}=3.3 µm, X_{50}=11.3 µm and X_{90}=45.7 µm for one batch and X_{10}=3.2 µm, X_{50}=12.2 µm and X_{90}=33.4 µm for the second batch. The data demonstrated high batch to batch reproducibility.

CLAIMS

What is claimed is:

1. A crystalline form of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide, represented by the structure of Compound 1:



(1),

wherein the crystalline form comprises N-2 crystalline form, IPA2-1 crystalline form, M3-1 crystalline form, P4 crystalline form, P5 crystalline form, P6 crystalline form, or any combination thereof.

2. The crystalline form of claim 1, wherein the crystalline form comprises the N-2 crystalline form, optionally wherein said N-2 crystalline form is crystallized from ethanol/water and optionally wherein said N-2 crystalline form is prepared via dissolution of Compound 1 in acetic acid followed by addition of water which results in crystallization of Compound 1.

3. The crystalline form of claim 2, wherein said crystalline form N-2 is characterized by an XRPD pattern having peaks at 14.92±0.3, 15.49±0.3, 19.3±0.3, 19.64±0.3 and 21.57±0.3 degrees two theta (2θ); or characterized by unit cell parameters of a=4.84±0.3Å, b=18.47±0.3Å, c=15.67±0.3Å, α=90°, β=91.62±0.5°, γ=90°, unit cell volume is 1399.51±0.5Å^3, number of compound per asymmetric unit is 1 and space group is $P2_1$, optionally wherein said crystalline form is characterized by said XRPD pattern which has additional peaks at 11.12±0.3 and 12.23±0.3 degrees two theta (2θ).

4. The crystalline form of claim 1, wherein the crystalline form comprises the IPA2-1 crystalline form, optionally wherein said IPA2-1 crystalline form is crystallized from isopropyl alcohol (IPA).

5. The crystalline form of claim 4, wherein said IPA2-1 crystalline form is characterized by an XRPD pattern having peaks at 7.71±0.3, 12.96±0.3, 13.12±0.3, 14.84±0.3 and 19.35±0.3 degrees two theta (2θ); or characterized by unit cell parameters of a=11.93±0.3Å, b=8.57±0.3Å, c=17.42±0.3Å, α=90°, β=105.16±0.5°, γ=90°, unit cell volume is 1718.67±0.5Å^3, number of compound per asymmetric unit is 1 and space group is $P2_1$ optionally wherein said XRPD pattern has additional peaks at 21.62±0.3 and 21.83±0.3 degrees two theta (2θ).

6. The crystalline form of claim 1, wherein the crystalline form comprises the M3-1 crystalline form, optionally wherein said M3-1 crystalline form is crystallized from methanol.

7. The crystalline form of claim 6, wherein said crystalline form M3-1 is characterized by an XRPD pattern having peaks at 7.96±0.3, 13.26±0.3, 19.19±0.3 and 21.56±0.3 degrees two theta (2θ); or characterized by unit cell parameters of a=11.72±0.3Å, b=8.36±0.3Å, c=17.41±0.3Å, α=90°, β=108.62±0.5°, γ=90°, unit cell volume is 1616.59±0.5Å^3, number of compound per asymmetric unit is 1 and space group is $P2_1$.

8. The crystalline form of claim 1, wherein the crystalline form comprises the P4 crystalline form, optionally wherein said P4 crystalline form is crystallized from v/v 1:1 MeCN/MTBE, 1:2 DCM/Heptane, 1:1 DCM/MTBE or 1:1 MEK/Cyclohexane.

9. The crystalline form of claim 8, wherein said crystalline form P4 is characterized by an XRPD pattern having peaks at 7.16±0.3, 16.02±0.3, 18.62±0.3, 20.32±0.3 and 21.14±0.3 degrees two theta (2θ), optionally wherein said XRPD pattern has additional peaks at 12.04±0.3 and 23.56±0.3 degrees two theta (2θ).

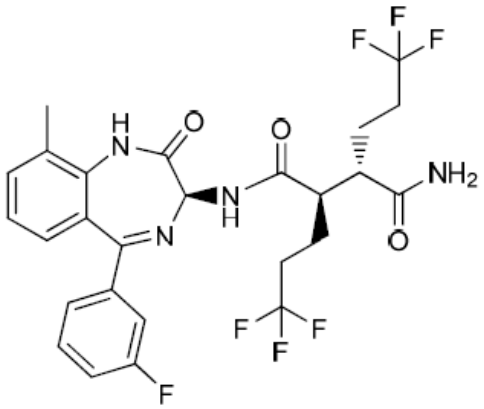
10. The crystalline form of claim 1, wherein the crystalline form comprises the P5 crystalline form, optionally wherein said P5 crystalline form is crystallized from acetone:water 1:1 v/v.

11. The crystalline form of claim 10, wherein said crystalline form P5 is characterized by an XRPD pattern having peaks at 6.5±0.3, 10.99±0.3, 17.36±0.3, 19.49±0.3 and 21.84±0.3 degrees two theta (2θ), optionally wherein said XRPD pattern has additional peaks at 14.78±0.3 and 20.26±0.3 degrees two theta (2θ).

12. The crystalline form of claim 1, wherein the crystalline form comprises the P6 crystalline form, optionally wherein said P6 crystalline form is crystallized from ethanol:water 1:1 v/v.

13. The crystalline form of claim 12, wherein said crystalline form P6 is characterized by an XRPD pattern having peaks at 3.52±0.3, 10.00±0.3, 12.36±0.3, 19.32±0.3 and 20.40±0.3 degrees two theta (2θ), optionally wherein said XRPD pattern has additional peaks at 14.2±0.3 and 16.04±0.3 degrees two theta (2θ).

14. A crystalline form of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide, represented below:

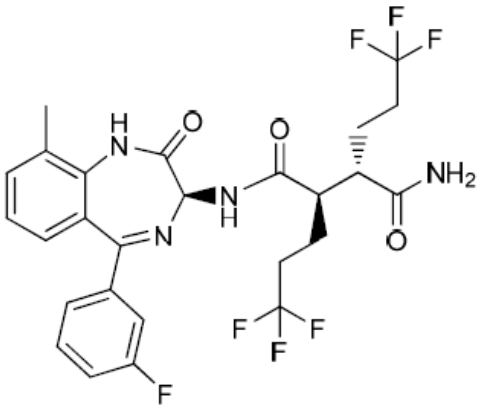


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wherein the crystalline form comprises a P1 crystalline form; and the P1 crystalline form is crystallized via desolvation of crystalline form IPA2-1 or M3-1, wherein IPA2-1 and M3-1 are additional crystalline forms of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide.

15. The crystalline form of claim 14, wherein said crystalline form P1 is characterized by an XRPD pattern having peaks at 8.04±0.3, 14.64±0.3, 16.1±0.3, 19.52±0.3 and 21.94±0.3 degrees two theta (2θ), optionally wherein said XRPD pattern has additional peaks at 20.46±0.3 and 25.1±0.3 degrees two theta (2θ).

16. A crystalline form of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide, represented below:

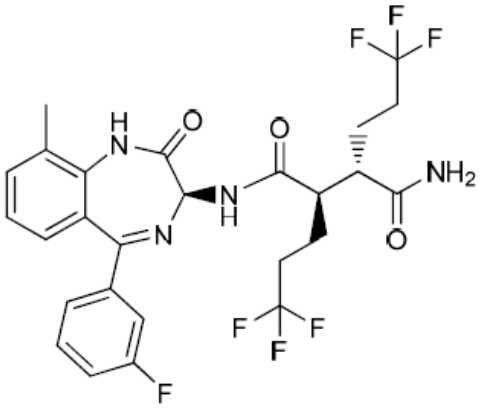


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wherein the crystalline form comprises a P2 crystalline form; and the P2 crystalline form is crystallized from crystalline form P1 according to claim 14 which was slurried in ethyl acetate.

17. The crystalline form of claim 16, wherein said crystalline form P2 is characterized by an XRPD pattern having peaks at 7.35±0.3, 14.61±0.3, 19.2±0.3, 23.15±0.3 and 26.4±0.3 degrees two theta (2θ), optionally wherein said XRPD pattern has additional peaks at 11.04±0.3 and 23.71±0.3 degrees two theta (2θ).

18. A crystalline form of (2R,3S)-N-((3S)-5-(3-fluorophenyl)-9-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2,3-bis(3,3,3-trifluoropropyl)succinimide, represented below:



,

wherein the crystalline form comprises a P3 crystalline form; and the P3 crystalline form is crystallized from crystalline form P1 according to claim 14 which was slurried in acetonitrile.

19. The crystalline form of claim 18, wherein said crystalline form P3 is characterized by an XRPD pattern having peaks at 7.45±0.3, 14.76±0.3, 19.02±0.3, 19.44±0.3 and 21.41±0.3 degrees two theta (2θ), optionally wherein said XRPD pattern has additional peaks at 11.11±0.3 and 22.15±0.3 degrees two theta (2θ).

20. A pharmaceutical composition comprising a therapeutically effective amount of the crystalline form according to any one of claims 1, 14, 16 and 18 and a pharmaceutically acceptable carrier.

21. The composition of claim 20, wherein the composition is in a solid state, suspension or emulsion form, optionally wherein said solid state form is a tablet, optionally wherein said suspension comprises the crystalline form and propylene glycol.