CRYSTALLINE FORMS OF A MAGL INHIBITOR

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/423,126, filed on November 16, 2016, which is herein incorporated by reference in its entirety.

BACKGROUND

[0002] Monoacylglycerol lipase (MAGL) is an enzyme responsible for hydrolyzing endocannabinoids such as 2-AG (2-arachidonoylglycerol), an arachidonate based lipid, in the nervous system. The serine hydrolase α-β-hydrolase domain 6 (ABHD6) is another lipid mediator.

SUMMARY OF THE INVENTION

[0003] Described herein is the MAGL inhibitor 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, including pharmaceutically acceptable solvates (including hydrates), polymorphs, and amorphous phases, and methods of uses thereof. Also described are pharmaceutically acceptable salts of the MAGL inhibitor 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, including pharmaceutically acceptable solvates (including hydrates), polymorphs, and amorphous phases, and methods of uses thereof. 1,1,1,3,3,3-Hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, as well as the pharmaceutically acceptable salts thereof, are used in the manufacture of medicaments for the treatment of diseases or conditions that are associated with MAGL activity.

[0004] Also described herein are methods for preparing crystalline forms of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate. Further described are pharmaceutical compositions that include the crystalline forms and methods of using the MAGL inhibitor in the treatment of diseases or conditions (including diseases or conditions wherein irreversible inhibition of MAGL provides therapeutic benefit to a mammal having the disease or condition).

[0005] In one embodiment is a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt, including solvate thereof.

[0005a] In one aspect, described herein is a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt, or solvate thereof.

[0006] In another embodiment, the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a free base.

(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-HCl salt Form 1. In some embodiments, the pharmaceutical composition comprises crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-HCl salt Form 2. In some embodiments, the pharmaceutical composition comprises crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate bis-HCl salt. In some embodiments, the pharmaceutical composition comprises crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate fumarate salt. In some embodiments, the pharmaceutical composition comprises crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mesylate salt. In some embodiments, the pharmaceutical composition comprises crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate besylate salt Form 1. In some embodiments, the pharmaceutical composition comprises crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate besylate salt Form 2. In some embodiments, the pharmaceutical composition is in a form suitable for oral administration to a mammal. In some embodiments, the pharmaceutical composition is an oral solid dosage form. In some embodiments, the pharmaceutical composition comprises about 0.5 mg to about 1000 mg of crystalline 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate.

[0032a] In another aspect, provided herein is a pharmaceutical composition comprising the crystalline form as described herein, or a pharmaceutically acceptable salt, or solvate thereof, and at least one inactive ingredient selected from pharmaceutically acceptable carriers, diluents, and excipients.

[0033] In another aspect, provided herein is 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt, or solvate thereof, for use in medicine.

[0033a] In another aspect, provided herein is a pharmaceutical composition as described herein for use in therapy.

[0034] In another aspect, provided herein is a method of treating pain in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein. In some embodiments is a method of treating pain in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical composition of 1,1,1,3,3,3-

hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein. In some embodiments the pain is neuropathic pain. In some embodiments, the pain is inflammatory pain.

[0034a] In another aspect, provided herein is a use of a crystalline form as described herein or a pharmaceutical composition as described herein in the manufacture of a medicament for treating pain in a patient in need thereof.

[0035] In another aspect, provided herein is a method of treating epilepsy/seizure disorder, multiple sclerosis, neuromyelitis optica (NMO), Tourette syndrome, Alzheimer disease, or abdominal pain associated with irritable bowel syndrome in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein. In some embodiments is a method of treating epilepsy/seizure disorder, multiple sclerosis, neuromyelitis optica (NMO), Tourette syndrome, Alzheimer disease, or abdominal pain associated with irritable bowel syndrome in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical composition of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein.

[0035a] In another aspect, provided herein is a use of a crystalline form as described herein or a pharmaceutical composition as described herein in the manufacture of a medicament for treating epilepsy/seizure disorder, multiple sclerosis, neuromyelitis optica (NMO), Tourette syndrome, Alzheimer disease, or abdominal pain associated with irritable bowel syndrome in a patient in need thereof.

[0036] In another aspect, provided herein is a method of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclussive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein. In some embodiments is a method of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclussive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical

composition of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein.

[0036a] In another aspect, provided herein is a use of a crystalline form as described herein or a pharmaceutical composition as described herein in the manufacture of a medicament for treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclussive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof.

[0037] In another aspect, provided herein is a method of treating dystonia in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein. In some embodiments is a method of treating dystonia in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical composition of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate as described herein.

[0037a] In another aspect, provided herein is a use of a crystalline form as described herein or a pharmaceutical composition as described herein in the manufacture of a medicament for treating dystonia in a patient in need thereof.

[0038] In another aspect, provided herein is a pharmaceutically acceptable salt of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), wherein the pharmaceutically acceptable salt is a mono-hydrochloride salt, bis-hydrochloride salt, fumarate salt, besylate salt, or mesylate salt. In some embodiments, the

CLAIMS

We Claim:

1. A crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt, or solvate thereof.
2. The crystalline form of claim 1, wherein the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a free base.
3. The crystalline form of claim 2, wherein the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate free base has at least one of the following properties:
   (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 1**;
   (b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 7.8° 2-Theta, 12.0° 2-Theta, 18.5° 2-Theta, 19.0° 2-Theta, 19.6° 2-Theta and 21.2° 2-Theta;
   (c) a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 2**;
   (d) a DSC thermogram substantially similar to the one set forth in **Figure 3**;
   (e) a DSC thermogram with an endotherm having an onset at about 80°C;
   (f) infrared (IR) spectrum substantially similar to the one set forth in **Figure 6**;
   (g) infrared (IR) spectrum with peaks at about 1735 cm^{-1}, 1427 cm^{-1}, 1102 cm^{-1}, 982 cm^{-1}, and 888 cm^{-1};
   (h) non-hygroscopicity; or
   (i) combinations thereof.
4. The crystalline form of claim 3, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 1**.
5. The crystalline form of claim 3, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 7.8° 2-Theta, 12.0° 2-Theta, 18.5° 2-Theta, 19.0° 2-Theta, 19.6° 2-Theta and 21.2° 2-Theta.
6. The crystalline form of claim 3, wherein the crystalline form has a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 2**.
7. The crystalline form of claim 3, wherein the crystalline form has a DSC thermogram substantially similar to the one set forth in **Figure 3**.
8. The crystalline form of claim 3, wherein the crystalline form has a DSC thermogram with an endotherm having an onset at about 80°C.
9. The crystalline form of claim 3, wherein the crystalline form has an infrared (IR) spectrum substantially similar to the one set forth in **Figure 6**.

10. The crystalline form of claim 3, wherein the crystalline form has an infrared (IR) spectrum with peaks at about 1735 cm^{-1}, 1427 cm^{-1}, 1102 cm^{-1}, 982 cm^{-1}, and 888 cm^{-1}.
11. The crystalline form of claim 3, wherein the crystalline form is non-hygroscopic.
12. The crystalline form of claim 3, wherein the crystalline form is characterized as having properties (a), (b), (c), (d), (e), (f), (g), and (h).
13. The crystalline form of any one of claims 3-12, wherein the crystalline form is obtained from acetone, acetone/water, acetonitrile, anisole, dichloromethane, diisopropyl ether, dimethylacetamide, dimethylformamide, dimethylsulfoxide, 1,4-dioxane, ethanol, ethyl acetate, isopropyl acetate, methanol, methanol/water, methyethyl ketone, methyl isobutyl ketone, N-methyl-2-pyrrolidone, 2-propanol, 2-propanol/water, *tert*-butyl methyl ketone, tetrahydrofuran, toluene, water, 1-butanol, 2-ethoxyethanol, 2-methyl tetrahydrofuran, benzonitrile, chlorobenzene, heptane, hexane, or *tert*-amyl alcohol.
14. The crystalline form of claim 1, wherein the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a mono-hydrochloride salt, bis-hydrochloride salt, fumarate salt, besylate salt, or mesylate salt; or solvate thereof.
15. The crystalline form of claim 14, wherein the pharmaceutically acceptable salt of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a mono-hydrochloride salt, or solvate thereof.
16. The crystalline form of claim 15, wherein the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt is Form 1 having at least one of the following properties:
    (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 9**;
    (b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 6.4° 2-Theta, 14.9° 2-Theta, 16.9° 2-Theta, 18.4° 2-Theta, and 20.9° 2-Theta;
    (c) a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 10**;
    (d) a DSC thermogram substantially similar to the one set forth in **Figure 11**;
    (e) a DSC thermogram with an endotherm having an onset at about 182°C;
    (f) non-hygroscopicity; or
    (g) combinations thereof.
17. The crystalline form of claim 16, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 9**.

18. The crystalline form of claim 16, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 6.4° 2-Theta, 14.9° 2-Theta, 16.9° 2-Theta, 18.4° 2-Theta, and 20.9° 2-Theta.
19. The crystalline form of claim 16, wherein the crystalline form has a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 10**.
20. The crystalline form of claim 16, wherein the crystalline form has a DSC thermogram substantially similar to the one set forth in **Figure 11**.
21. The crystalline form of claim 16, wherein the crystalline form has a DSC thermogram with an endotherm having an onset at about 182°C.
22. The crystalline form of claim 16, wherein the crystalline form is non-hygroscopic.
23. The crystalline form of claim 16, wherein the crystalline form is characterized as having properties (a), (b), (c), (d), (e), and (f).
24. The crystalline form of any one of claims 16-23, wherein the crystalline form is obtained from acetonitrile, 1,4-dioxane, ethyl acetate, methanol, *tert*-butylmethyl ether, or 2-propanol.
25. The crystalline form of claim 15, wherein the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mono-hydrochloride salt is Form 2 having at least one of the following properties:
    (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 28**;
    (b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.6° 2-Theta, 14.3° 2-Theta, 15.6° 2-Theta, 19.0° 2-Theta, 19.8° 2-Theta, and 20.7° 2-Theta;
    (c) a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 26**;
    (d) a DSC thermogram substantially similar to the one set forth in **Figure 27**;
    (e) a DSC thermogram with an endotherm having an onset at about 201°C;
    (f) an infrared spectrum substantially similar to the one set forth in **Figure 29**;
    (g) infrared (IR) spectrum with peaks at about 1729 cm^{-1}, 1426 cm^{-1}, 1102 cm^{-1}, 984 cm^{-1}, and 907 cm^{-1};
    (h) non-hygroscopicity; or
    (i) combinations thereof.
26. The crystalline form of claim 25, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 28**.

27. The crystalline form of claim 25, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.6° 2-Theta, 14.3° 2-Theta, 15.6° 2-Theta, 19.0° 2-Theta, 19.8° 2-Theta, and 20.7° 2-Theta.
28. The crystalline form of claim 25, wherein the crystalline form has a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 26**.
29. The crystalline form of claim 25, wherein the crystalline form has a DSC thermogram substantially similar to the one set forth in **Figure 27**.
30. The crystalline form of claim 25, wherein the crystalline form has a DSC thermogram with an endotherm having an onset at about 201°C.
31. The crystalline form of claim 25, wherein the crystalline form has an infrared (IR) spectrum substantially similar to the one set forth in **Figure 29**.
32. The crystalline form of claim 25, wherein the crystalline form has an infrared (IR) spectrum with peaks at about 1729 cm^{-1}, 1426 cm^{-1}, 1102 cm^{-1}, 984 cm^{-1}, and 907 cm^{-1}.
33. The crystalline form of claim 25, wherein the crystalline form is non-hygroscopic.
34. The crystalline form of claim 25, wherein the crystalline form is characterized as having properties (a), (b), (c), (d), (e), (f), (g), and (h).
35. The crystalline form of any one of claims 25-34, wherein the crystalline form is obtained from acetone, acetonitrile, anisole, dichloromethane, diisopropyl ether, ethanol, ethyl acetate, isopropyl acetate, methanol, methylethyl ketone, methyl isobutyl ketone, *tert*-butylmethyl ether, 2-propanol, tetrahydrofuran, toluene, 2-ethoxyethanol, 2-methyl tetrahydrofuran, or *tert*-amyl alcohol.
36. The crystalline form of claim 14, wherein the pharmaceutically acceptable salt of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a bis-hydrochloride salt, or solvate thereof.
37. The crystalline form of claim 36, wherein the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate bis-hydrochloride salt has at least one of the following properties:
    (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 17**;
    (b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 6.4° 2-Theta, 12.0° 2-Theta, 12.5° 2-Theta, 14.3° 2-Theta, 18.5° 2-Theta, and 22.8° 2-Theta;
    (c) a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 18**;
    (d) a DSC thermogram substantially similar to the one set forth in **Figure 19**;

(e) a DSC thermogram with an endotherm having an onset at about 154°C; or

(f) combinations thereof.

38. The crystalline form of claim 37, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 17**.

39. The crystalline form of claim 37, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 6.4° 2-Theta, 12.0° 2-Theta, 12.5° 2-Theta, 14.3° 2-Theta, 18.5° 2-Theta, and 22.8° 2-Theta.

40. The crystalline form of claim 37, wherein the crystalline form has a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 18**.

41. The crystalline form of claim 37, wherein the crystalline form has a DSC thermogram substantially similar to the one set forth in **Figure 19**.

42. The crystalline form of claim 37, wherein the crystalline form has a DSC thermogram with an endotherm having an onset at about 154°C.

43. The crystalline form of claim 37, wherein the crystalline form is characterized as having properties (a), (b), (c), (d), and (e).

44. The crystalline form of any one of claims 37-43, wherein the crystalline form is obtained from *tert*-butylmethyl ether and 5 equivalents of HCl.

45. The crystalline form of claim 14, wherein the pharmaceutically acceptable salt of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a fumarate salt, or solvate thereof.

46. The crystalline form of claim 45, wherein the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate fumarate salt has at least one of the following properties:

(a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 42**;

(b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks 13.6° 2-Theta, 14.1° 2-Theta, 14.3° 2-Theta, 20.0° 2-Theta, and 21.9° 2-Theta;

(c) a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 44**;

(d) a DSC thermogram substantially similar to the one set forth in **Figure 45**;

(e) a DSC thermogram with an endotherm having an onset at about 126°C;

(f) non-hygroscopicity; or

(g) combinations thereof.

47. The crystalline form of claim 46, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 42**.
48. The crystalline form of claim 46, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 13.6° 2-Theta, 14.1° 2-Theta, 14.3° 2-Theta, 20.0° 2-Theta, and 21.9° 2-Theta.
49. The crystalline form of claim 46, wherein the crystalline form has a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 44**.
50. The crystalline form of claim 46, wherein the crystalline form has a DSC thermogram substantially similar to the one set forth in **Figure 45**.
51. The crystalline form of claim 46, wherein the crystalline form has a DSC thermogram with an endotherm having an onset at about 126°C.
52. The crystalline form of claim 46, wherein the crystalline form is non-hygroscopic.
53. The crystalline form of claim 46, wherein the crystalline form is characterized as having properties (a), (b), (c), (d), (e), and (f).
54. The crystalline form of any one of claims 46-53, wherein the crystalline form is obtained from 1-butanol, 1-propanol, 2-propanol, acetone/water mixtures, acetonitrile/water mixtures, ethanol, methyl acetate/water, methyl ethyl ketone/water, methanol/acetonitrile and 2-methoxyethanol/acetonitrile.
55. The crystalline form of claim 14, wherein the pharmaceutically acceptable salt of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a mesylate salt, or solvate thereof.
56. The crystalline form of claim 55, wherein the crystalline form of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate mesylate salt has at least one of the following properties:
    (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 38**;
    (b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.6° 2-Theta, 12.4° 2-Theta, 14.6° 2-Theta, 16.5° 2-Theta, 17.7° 2-Theta, and 19.7° 2-Theta;
    (c) a thermo-gravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Figure 40**;
    (d) a DSC thermogram substantially similar to the one set forth in **Figure 41**;
    (e) a DSC thermogram with an endotherm having an onset at about 179°C; or
    (f) combinations thereof.

57. The crystalline form of claim 56, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Figure 38**.
58. The crystalline form of claim 56, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.6° 2-Theta, 12.4° 2-Theta, 14.6° 2-Theta, 16.5° 2-Theta, 17.7° 2-Theta, and 19.7° 2-Theta.
59. The crystalline form of claim 56, wherein the crystalline form has a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Figure 40**.
60. The crystalline form of claim 56, wherein the crystalline form has a DSC thermogram substantially similar to the one set forth in **Figure 41**.
61. The crystalline form of claim 56, wherein the crystalline form has a DSC thermogram with an endotherm having an onset at about 179°C.
62. The crystalline form of claim 56, wherein the crystalline form is characterized as having properties (a), (b), (c), (d), and (e).
63. The crystalline form of any one of claims 56-62, wherein the crystalline form is obtained from *tert*-butylmethyl ether, ethyl acetate, tetrahydrofuran, water/acetone, water/acetonitrile, or water/2-propanol.
64. The crystalline form of any one of claims 3-63, wherein the crystalline form is unsolvated.
65. The crystalline form of any one of claims 3-64, wherein the crystalline form is anhydrous.
66. A pharmaceutical composition comprising the crystalline form of any one of claims 1-65, or a pharmaceutically acceptable salt, or solvate thereof, and at least one inactive ingredient selected from pharmaceutically acceptable carriers, diluents, and excipients.
67. The crystalline form of any one of any one of claims 1-65 for use in medicine.
68. The pharmaceutical composition of claim 66 for use in therapy.
69. Use of a crystalline form of any one of claims 1-65 or a pharmaceutical composition of claim 66 in the manufacture of a medicament for treating pain in a patient in need thereof.
70. The use of claim 69, wherein the pain is neuropathic pain.
71. The use of claim 69, wherein the pain is inflammatory pain.
72. Use of a crystalline form of any one of claims 1-65 or a pharmaceutical composition of claim 66 in the manufacture of a medicament for treating epilepsy/seizure disorder, multiple sclerosis, neuromyelitis optica (NMO), Tourette syndrome, Alzheimer disease, or abdominal pain associated with irritable bowel syndrome in a patient in need thereof.
73. Use of a crystalline form of any one of claims 1-65 or a pharmaceutical composition of claim 66 in the manufacture of a medicament for treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine,

vasoocclussive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof.

74. Use of a crystalline form of any one of claims 1-65 or a pharmaceutical composition of claim 66 in the manufacture of a medicament for treating dystonia in a patient in need thereof.

75. 1,1,1,3,3,3-Hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt, or solvate thereof, for use in medicine.

76. A pharmaceutically acceptable salt of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), wherein the pharmaceutically acceptable salt is a mono-hydrochloride salt, bis-hydrochloride salt, fumarate salt, besylate salt, or mesylate salt.

77. The pharmaceutically acceptable salt of claim 76, wherein the pharmaceutically acceptable is a mono-hydrochloride salt.

78. The pharmaceutically acceptable salt of claim 76, wherein the pharmaceutically acceptable is a bis-hydrochloride salt.

79. The pharmaceutically acceptable salt of claim 76, wherein the pharmaceutically acceptable is a fumarate salt.

80. The pharmaceutically acceptable salt of claim 76, wherein the pharmaceutically acceptable is a besylate salt.

81. The pharmaceutically acceptable salt of claim 76, wherein the pharmaceutically acceptable is a mesylate salt.

82. The pharmaceutically acceptable salt of any one of claims 76-81, wherein the pharmaceutically acceptable salt is crystalline.

83. The pharmaceutically acceptable salt of any one of claims 76-81, wherein the pharmaceutically acceptable salt is amorphous.