

Sodium hydroxide (4.4 mg)	No solid formed (6.4 mg)	Amorphous solid* (4.9 mg)	Amorphous solid (5.2 mg)	Crystalline solid* (4.6 mg)
Tris (13.3 mg)	No solid formed (16.6 mg)	No solid formed* (14.5 mg)	Gum (14.6 mg)	Some white solid crystalline (14.7 mg)

*Added 2 mL of heptanes after the first week.

Determining whether a solid would form was just one factor in this evaluation. Although crystalline solids formed when making salts using calcium, potassium, and sodium, the crystalline solids were too hygroscopic to continue the evaluation. Hygroscopicity data was not obtained for many of these salts because it was observed mainly through visualization. For example, as the calcium and potassium salt forms were being collected on filter paper, the solid material turned to a gum. Compound 1 as the choline salt was isolated; hygroscopicity was found to be more than 20% weight change at 30% relative humidity. Moreover, although a solid was obtained for the salts of diethanolamine, diethylamine, and piperazine, these salts were not pursued. See, e.g., C. Saal, A. Becker, Euro. J. of Pharm Sci 49 (2013) 614-623; G. Steffen Paulekuhn, et al, J. Med. Chem. 2007, 6665-6672.

Furthermore, although a solid was obtained, additional evaluation, like ^1H NMR was used to determine whether a salt actually formed. In some instances, the solid obtained was Compound 1 (as the free acid) and not associated with the counterion.

At ambient temperature with RH above 20%, Form 2 is the more stable form between Form 1 and Form 2. Solvent conditions affect whether Form 1 or Form 2 is obtained. It was determined that a critical water activity of 0.2 in IPA/water provides crystalline Form 2. The following solvents, when used in the presence of water, provide Form 2: 5% to 15% water/acetone, 4% water/96% acetonitrile, 1% water/99% butyl acetate, 1% water/99% isopropyl acetate, 1% water/99% ethyl acetate, 2% water/ 98% dichloroethylene, 2% water/98% methyl ethyl ketone, 3 to 6.0% water/97 to 94% 2-methyltetrahydrofuran, and 4%water/96% n-propanol.

Compound 1 also faced challenges regarding solubility. Table 2 provides the solubility of Compound 1 (as the free acid) and various salts. Compound 1 (as the free acid) proved to be an unacceptable form for making a dosage form for routine oral administration. Although Compound 1 (as the free acid) was crystalline, thermodynamic solubility was not consistent. The calcium salt had an extremely low solubility at low pH.

CLAIMS

What is claimed is:

1. A crystalline 2-amino-2-(hydroxymethyl)propane-1,3-diol salt of 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid.
- 5 2. The crystalline salt of claim 1, wherein the ratio of 4-(4-(1-isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid and the salt is 1:1.
3. The crystalline salt of claim 1 or claim 2, wherein the crystalline salt is an anhydrous crystalline salt.
- 10 4. The anhydrous crystalline salt of claim 3, wherein said anhydrous crystalline salt has a PXRD pattern comprising peaks at diffraction angles of 9.6, 10.7, and 11.3 2θ , $\pm 0.2^\circ 2\theta$.
5. The anhydrous crystalline salt of either claim 3 or claim 4, wherein said anhydrous crystalline salt has a Raman spectrum comprising peak shifts at 1511, 1561, and 1615 cm^{-1} , $\pm 2 \text{ cm}^{-1}$.
- 15 6. The anhydrous crystalline salt of any of claims 3 to 5, wherein said anhydrous crystalline salt has a ^{13}C ssNMR spectrum comprising chemical shifts at 22.9, 146.2, and 161.9 ppm, ± 0.2 ppm.
7. The anhydrous crystalline salt of claim 3, wherein said anhydrous crystalline salt has an analytical parameter selected from the group consisting of a Raman spectrum comprising peak
20 shifts at 1511 and 1615 cm^{-1} , $\pm 2 \text{ cm}^{-1}$, and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 22.9, 146.2, or 161.9 ppm, ± 0.2 ppm.
8. The crystalline salt of claim 1 or claim 2, wherein the crystalline salt is a trihydrate crystalline salt.
9. The trihydrate crystalline salt of claim 8, wherein said trihydrate crystalline salt has a
25 PXRD pattern comprising peaks at diffraction angles of 8.4, 9.0, and 10.5 2θ , $\pm 0.2^\circ 2\theta$.
10. The trihydrate crystalline salt of either claim 8 or claim 9, wherein said trihydrate crystalline salt has a Raman spectrum comprising peak shifts at 1507, 1557, and 1610 cm^{-1} , $\pm 2 \text{ cm}^{-1}$.
11. The trihydrate crystalline salt of any of claims 8 to 10, wherein said trihydrate crystalline
30 salt has a ^{13}C ssNMR spectrum comprising chemical shifts at 19.2, 149.5, and 163.8 ppm, ± 0.2 ppm.

12. The trihydrate crystalline salt of claim 8, wherein said trihydrate crystalline salt has an analytical parameter selected from the group consisting of
- a PXRD pattern comprising peaks at diffraction angles of 8.4 and 9.0 2Θ , $\pm 0.2^\circ$ 2Θ ,
 - 5 a Raman spectrum comprising peak shifts at 1557 and 1610 cm^{-1} , $\pm 2 \text{ cm}^{-1}$, and
 - a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.
13. The trihydrate crystalline salt of claim 8, wherein said trihydrate crystalline salt has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at
- 10 diffraction angles of 8.4 and 9.0 2Θ , $\pm 0.2^\circ$ 2Θ , and a Raman spectrum comprising at least one peak shift at 1507, 1557, or 1610 cm^{-1} , $\pm 2 \text{ cm}^{-1}$.
14. The trihydrate crystalline salt of claim 8, wherein said trihydrate crystalline salt has an analytical parameter selected from the group consisting of a PXRD pattern comprising peaks at
- 15 diffraction angles of 8.4 and 9.0 2Θ , $\pm 0.2^\circ$ 2Θ , and a ^{13}C ssNMR spectrum comprising at least one chemical shift at 19.2, 149.5, or 163.8 ppm, ± 0.2 ppm.
15. A pharmaceutical composition comprising the crystalline salt of any of the claims 1 to 14 in a therapeutically effective amount with a pharmaceutically acceptable carrier.
16. The crystalline salt of any of claims 1 to 14 for use in the treatment of a disease selected from NAFLD, NASH, and T2D.
- 20 17. Use of the crystalline salt of any of claims 1 to 14 in the manufacture of a medicament for the treatment of a disease selected from NAFLD, NASH, and T2D.