



(51) International Patent Classification:

C07D 487/04 (2006.01) A61P 37/00 (2006.01)
A61P 35/00 (2006.01) A61K 31/4985 (2006.01)

(21) International Application Number:

PCT/US2020/019071

(22) International Filing Date:

20 February 2020 (20.02.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/809,337 22 February 2019 (22.02.2019) US

(71) Applicant: GILEAD SCIENCES, INC. [US/US]; 333 Lakeside Drive, Foster City, California 94404 (US).

(72) Inventors: ANDRES, Patricia; c/o AMRI, Inc., 26 Corporate Circle, Albany, Indiana 12203 (US). FUNG, Peter C.; c/o Gilead Sciences Inc., 333 Lakeside Drive, Foster City, California 94404 (US). GIGUERE, Pierre; c/o Gilead Sciences Inc., 333 Lakeside Drive, Foster City, California 94404 (US). LAI, Chiajen; c/o Gilead Sciences Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

STEWART, Craig; 10 D Street, Natick, Massachusetts 01760 (US). TENG, Jing; c/o AMRI, Inc., 26 Corporate Circle, Albany, Indiana 12203 (US). TRAN, Duong D.; c/o Gilead Sciences Inc., 333 Lakeside Drive, Foster City, California 94404 (US). TRANTCHEVA, Iva; 488 Bernice Lane, Sonoma, California 95476 (US). YARMUCH, Brian; c/o Gilead Sciences Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

(74) Agent: POLSTER, Philip B. et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(54) Title: SOLID FORMS OF CONDENSED PYRAZINES AS SYK INHIBITORS

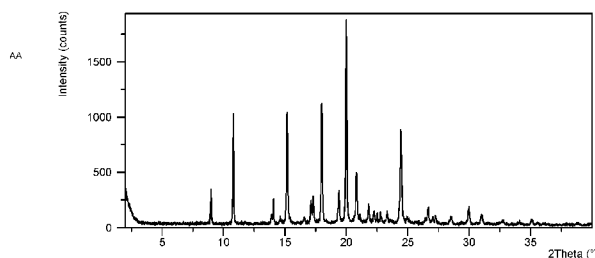
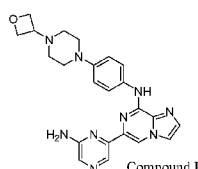


FIGURE 1



Formula 1

(57) Abstract: Solid forms of the compound, 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine, and solid forms of salts or co-crystals of Compound I, were prepared and characterized: (Formula I) Also provided are processes of making the solid forms and methods of use thereof.



(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

SOLID FORMS OF CONDENSED PYRAZINES AS SYK INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

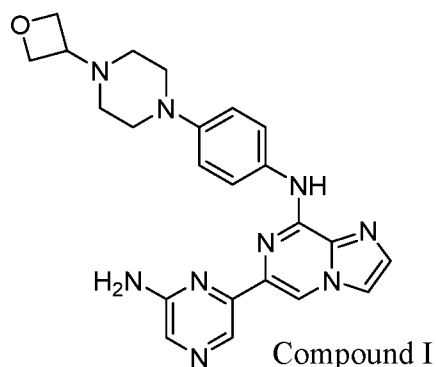
[0001] This application claims the benefit of priority to U.S. Provisional Patent Application No. 62/809,337, filed 22 February 2019, the contents of which are incorporated herein by reference in their entirety.

FIELD

[0002] The present disclosure relates to polymorphs and polymorph pharmaceutical compositions of compounds that inhibit Spleen Tyrosine Kinase (Syk) activity. The disclosure also relates to methods of preparing such polymorphs and polymorph pharmaceutical compositions, and the use of such polymorphs and pharmaceutical compositions in treating subjects with various diseases, including cancer and inflammatory conditions.

BACKGROUND

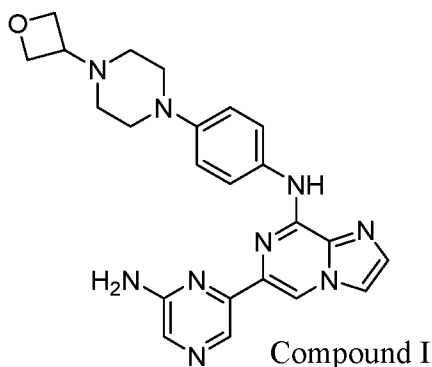
[0003] The inhibition of Spleen Tyrosine Kinase (Syk) activity may be useful for treating certain types of cancer and autoimmune diseases. One such compound that has been found to inhibit Syk activity is represented by Compound I:



or a pharmaceutically acceptable salt thereof. Compound I is useful in the treatment of diseases and conditions mediated by Syk as demonstrated in U.S. Patent 9,290,505, which is incorporated herein by reference in its entirety. U.S. Patent 9,290,505 discloses crystalline forms of mono mesylate salts and succinate salts of Compound I, namely, Compound I Mono-MSA Forms I and II and Compound I Succinate Forms I and II. There is a need for polymorph forms of compounds that are efficacious and have improved bioavailability and/or physical properties.

SUMMARY

[0004] The present disclosure provides a crystalline form of Compound I:



wherein the crystalline form is Compound I Form I, Compound I Form II, Compound I Form III, Compound I Form V, Compound I Form VII, Compound I Form VIII, Compound I Form IX, Compound I Form XIII or Compound I Form XIV.

[0005] The present disclosure also provides pharmaceutical compositions comprising the crystalline forms of Compound I or crystalline forms of salts or co-crystals of Compound I. The disclosure also provides processes for making crystalline forms of Compound I or crystalline forms of salts or co-crystals of Compound I. The disclosure also provides methods for using crystalline forms of Compound I or crystalline forms of salts or co-crystals of Compound I in Syk mediated diseases or conditions.

[0006] One embodiment is directed to crystalline 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Form I). Compound I Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 15.2, 18.0 and 20.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0007] One embodiment is directed to crystalline 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Form II). Compound I Form II can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 19.5, 20.8 and 22.2 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0008] One embodiment is directed to crystalline 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Form III). Compound I Form III can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 7.6, 14.2 and 20.8 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0009] One embodiment is directed to crystalline 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Form V). Compound I Form V can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 17.7, 19.7 and 22.7 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0010] One embodiment is directed to crystalline 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Form VII). Compound I Form VII can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 8.4, 18.6 and 20.6 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

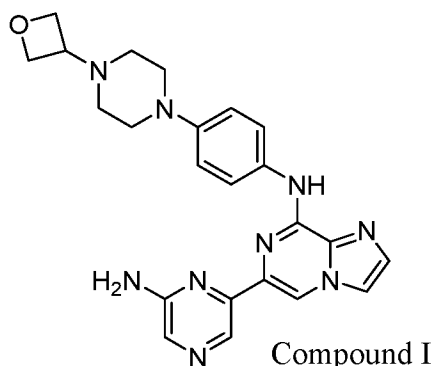
[0011] One embodiment is directed to crystalline 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Form VIII). Compound I Form VIII can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 18.3, 20.8 and 21.9 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0012] One embodiment is directed to crystalline 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Form IX). Compound I Form IX can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 14.0, 16.7 and 18.2 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0013] One embodiment is directed to crystalline 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Form XIII). Compound I Form XIII can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 9.6, 19.3 and 20.8 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0014] One embodiment is directed to crystalline 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Form XIV). Compound I Form XIV can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 19.4, 22.5 and 23.3 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0015] In one embodiment, the present disclosure provides a crystalline form of a sesqui-succinate salt, a hemi-succinate salt, a mono-HCl salt, a sesqui-adipate salt, a mono-adipate salt, a bis-citrate salt, a sesqui-fumarate salt, a bis-gentisate salt, a mono-besylate (mono-BSA) salt, a sesqui-oxalate salt or a co-crystal of Compound I:



wherein the crystalline form or the co-crystal is Compound I Sesqui-Succinate Form III, Compound I Sesqui-Succinate Form IV, Compound I Sesqui-Succinate Form V, Compound I Hemi-Succinate Form I, Compound I Mono-HCl salt Form I, Compound I Mono-HCl salt Form II, Compound I Mono-HCl salt Form III, Compound I Sesqui-Adipate Form I, Compound I Mono-Adipate Form I, Compound I Bis-Citrate Form I, Compound I Sesqui-Fumarate Form I, Compound I Bis-Gentisate Form I, Compound I Mono-BSA salt Form I and Compound I Sesqui-Oxalate Form I.

[0016] One embodiment is directed to a crystalline sesqui-succinate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Sesqui-Succinate Form III). Compound I Sesqui-Succinate Form III can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 7.8, 16.5 and 21.4 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0017] One embodiment is directed to a crystalline sesqui-succinate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Sesqui-Succinate Form IV). Compound I Sesqui-Succinate Form IV can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 16.6, 22.4 and 25.2 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0018] One embodiment is directed to a crystalline sesqui-succinate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Sesqui-Succinate Form V). Compound I Sesqui-Succinate Form V can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 5.9, 23.3 and 24.7 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0019] One embodiment is directed to a crystalline hemi-succinate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-

amine (Compound I Hemi-Succinate Form I). Compound I Hemi-Succinate Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 20.8, 23.1 and 25.5 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0020] One embodiment is directed to a crystalline mono-HCl salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Mono-HCl salt Form I). Compound I Mono-HCl salt Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 8.7, 19.3 and 21.4 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0021] One embodiment is directed to a crystalline mono-HCl salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Mono-HCl salt Form II). Compound I Mono-HCl salt Form II can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 6.3, 11.3 and 17.7 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0022] One embodiment is directed to a crystalline mono-HCl salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Mono-HCl salt Form III). Compound I Mono-HCl salt Form III can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 8.6, 17.8 and 24.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0023] One embodiment is directed to a crystalline sesqui-adipate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Sesqui-Adipate Form I). Compound I Sesqui-Adipate Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 11.3, 16.6 and 24.8 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0024] One embodiment is directed to a crystalline mono-adipate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Mono-Adipate Form I). Compound I Mono-Adipate Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 4.9, 19.9 and 21.1 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0025] One embodiment is directed to a crystalline bis-citrate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-

amine (Compound I Bis-Citrate Form I). Compound I Bis-Citrate Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 6.4, 18.1 and 18.9 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0026] One embodiment is directed to a crystalline sesqui-fumarate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Sesqui-Fumarate Form I). Compound I Sesqui-Fumarate Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 15.3, 22.8 and 25.8 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0027] One embodiment is directed to a crystalline bis-gentisate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Bis-Gentisate Form I). Compound I Bis-Gentisate Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 6.7, 16.7 and 25.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0028] One embodiment is directed to a crystalline mono-BSA salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Mono-BSA Form I). Compound I Mono-BSA Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 8.8, 11.8 and 20.2 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0029] One embodiment is directed to a crystalline sesqui-oxalate salt or a co-crystal of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I Sesqui-Oxalate Form I). Compound I Sesqui-Oxalate Form I can be characterized by an X-ray powder diffractogram comprising the following peaks ($\pm 0.2^\circ 2\theta$) at 16.1, 23.0 and 26.1 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0030] One embodiment is directed to a pharmaceutical composition comprising a compound selected from Compound I Form I, Compound I Form II, Compound I Form III, Compound I Form IV, Compound I Form V, Compound I Form VI, Compound I Form VII, Compound I Form VIII, Compound I Form IX, Compound I Form X, Compound I Form XI, Compound I Form XII, Compound I Form XIII, Compound I Form XIV, Compound I Sesqui-Succinate Form III, Compound I Sesqui-Succinate Form IV, Compound I Sesqui-Succinate Form V, Compound I Hemi-Succinate Form I, Compound I Mono-HCl salt Form I, Compound I Mono-HCl salt Form II, Compound I Mono-HCl salt Form III, Compound I HCl material A, Compound I HCl

material B, Compound I Sesqui-Adipate Form I, Compound I Mono-Adipate Form I, Compound I Bis-Citrate Form I, Compound I Sesqui-Fumarate Form I, Compound I Bis-Gentisate Form I, Compound I Mono-BSA Form I, and Compound I Sesqui-Oxalate and a pharmaceutically acceptable excipient.

[0031] Another embodiment is directed to a method for treating a disease or condition selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease, and a cancer in a subject in need thereof, comprising administering to the subject a therapeutic effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, or a combination thereof, as described herein.

[0032] In one embodiment, the disease or condition is selected from the group consisting of asthma, rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease, and systemic lupus erythematosus. In another embodiment, the disease or condition is rheumatoid arthritis.

[0033] In another embodiment, the disease or condition is a cancer selected from the group consisting of a hematologic malignancy and a solid tumor. In another embodiment, the hematologic malignancy is lymphoma, multiple myeloma or leukemia.

[0034] Still an additional embodiment includes, optionally in combination with any other embodiment described herein, is the use of one or more of crystalline forms of Compound I or one or more crystalline forms of a salt or co-crystal of Compound I in the manufacture of a medicament for treating subjects suffering from or at risk of a disease or condition selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease, and a cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] Figure 1 is an X-ray powder diffractogram of Compound I Form I.

[0036] Figure 2 is a differential scanning calorimetry (DSC) curve of Compound I Form I.

[0037] Figure 3 is a thermogravimetric analysis (TGA) curve of Compound I Form I.

[0038] Figure 4 is a dynamic vapor sorption (DVS) curve of Compound I Form I.

[0039] Figure 5 is an X-ray powder diffractogram of Compound I Form II.

- [0040] Figure 6 is a DSC curve of Compound I Form II.
- [0041] Figure 7 is a TGA curve of Compound I Form II.
- [0042] Figure 8 is a DVS curve of Compound I Form II.
- [0043] Figure 9 is an X-ray powder diffractogram of Compound I Form III.
- [0044] Figure 10 is a DSC curve of Compound I Form III.
- [0045] Figure 11 is a TGA curve of Compound I Form III.
- [0046] Figure 12 is an X-ray powder diffractogram of Compound I Form V.
- [0047] Figure 13 is a DSC curve of Compound I Form V.
- [0048] Figure 14 is a TGA curve of Compound I Form V.
- [0049] Figure 15 is a DVS curve of Compound I Form V.
- [0050] Figure 16 is an X-ray powder diffractogram of Compound I Form VII.
- [0051] Figure 17 is a DSC curve of Compound I Form VII.
- [0052] Figure 18 is a TGA curve of Compound I Form VII.
- [0053] Figure 19 is an X-ray powder diffractogram of Compound I Form VIII.
- [0054] Figure 20 is a DSC curve of Compound I Form VIII.
- [0055] Figure 21 is a TGA curve of Compound I Form VIII.
- [0056] Figure 22 is an X-ray powder diffractogram of Compound I Form IX.
- [0057] Figure 23 is a DSC curve of Compound I Form IX.
- [0058] Figure 24 is a TGA curve of Compound I Form IX.
- [0059] Figure 25 is an X-ray powder diffractogram of Compound I Form XIII.
- [0060] Figure 26 is an X-ray powder diffractogram of Compound I Form XIV.
- [0061] Figure 27 is a DSC curve of Compound I Form XIV.

- [0062] Figure 28 is a TGA curve of Compound I Form XIV.
- [0063] Figure 29 is a DVS curve of Compound I Form XIV.
- [0064] Figure 30 is an X-ray powder diffractogram of Compound I Sesqui-Succinate Form III.
- [0065] Figure 31 is a DSC curve of Compound I Sesqui-Succinate Form III.
- [0066] Figure 32 is a TGA curve of Compound I Sesqui-Succinate Form III.
- [0067] Figure 33 is an X-ray powder diffractogram of Compound I Sesqui-Succinate Form IV.
- [0068] Figure 34 is a DSC curve of Compound I Sesqui-Succinate Form IV.
- [0069] Figure 35 is a TGA curve of Compound I Sesqui-Succinate Form IV.
- [0070] Figure 36 is an X-ray powder diffractogram of Compound I Sesqui-Succinate Form V.
- [0071] Figure 37 is a DSC curve of Compound I Sesqui-Succinate Form V.
- [0072] Figure 38 is a TGA curve of Compound I Sesqui-Succinate Form V.
- [0073] Figure 39 is an X-ray powder diffractogram of Compound I Hemi-Succinate Form I.
- [0074] Figure 40 is a DSC curve of Compound I Hemi-Succinate Form I.
- [0075] Figure 41 is a TGA curve of Compound I Hemi-Succinate Form I.
- [0076] Figure 42 is a DVS curve of Compound I Hemi-Succinate Form I.
- [0077] Figure 43 is an X-ray powder diffractogram of Compound I Mono-HCl Salt Form I.
- [0078] Figure 44 is a TGA curve of Compound I Mono-HCl Salt Form I.
- [0079] Figure 45 is an X-ray powder diffractogram of Compound I Mono-HCl Salt Form II.
- [0080] Figure 46 is a TGA curve of Compound I Mono-HCl Salt Form II.
- [0081] Figure 47 is a DVS curve of Compound I Mono-HCl Salt Form II.
- [0082] Figure 48 is an X-ray powder diffractogram of Compound I Mono-HCl Salt Form III.

- [0083] Figure 49 is a DSC curve of Compound I Mono-HCl Salt Form III.
- [0084] Figure 50 is a TGA curve of Compound I Mono-HCl Salt Form III.
- [0085] Figure 51 is an X-ray powder diffractogram of Compound I Sesqui Adipate Form I.
- [0086] Figure 52 is a DSC curve of Compound I Sesqui Adipate Form I.
- [0087] Figure 53 is a TGA curve of Compound I Sesqui Adipate Form I.
- [0088] Figure 54 is a DVS curve of Compound I Sesqui Adipate Form I.
- [0089] Figure 55 is an X-ray powder diffractogram of Compound I Mono Adipate Form I.
- [0090] Figure 56 is a DSC curve of Compound I Mono Adipate Form I.
- [0091] Figure 57 is a TGA curve of Compound I Mono Adipate Form I.
- [0092] Figure 58 is an X-ray powder diffractogram of Compound I Bis-Citrate Form I.
- [0093] Figure 59 is a DSC curve of Compound I Bis-Citrate Form I.
- [0094] Figure 60 is a TGA curve of Compound I Bis-Citrate Form I.
- [0095] Figure 61 is an X-ray powder diffractogram of Compound I Sesqui-Fumarate Form I.
- [0096] Figure 62 is a TGA curve of Compound I Sesqui-Fumarate Form I.
- [0097] Figure 63 is an X-ray powder diffractogram of Compound I Bis-Gentisate Form I.
- [0098] Figure 64 is a DSC curve of Compound I Bis-Gentisate Form I.
- [0099] Figure 65 is a TGA curve of Compound I Bis-Gentisate Form I.
- [0100] Figure 66 is an X-ray powder diffractogram of Compound I Mono-BSA Salt Form I.
- [0101] Figure 67 is a DSC curve of Compound I Mono-BSA Salt Form I.
- [0102] Figure 68 is a TGA curve of Compound I Mono-BSA Salt Form I.
- [0103] Figure 69 is a DVS curve of Compound I Mono-BSA Salt Form I.
- [0104] Figure 70 is an X-ray powder diffractogram of Compound I Sesqui-Oxalate Form I.

[0105] Figure 71 is a DSC curve of Compound I Sesqui-Oxalate Form I.

[0106] Figure 72 is a TGA curve of Compound I Sesqui-Oxalate Form I.

[0107] Figure 73 is a calculated X-ray powder diffractogram of Compound I Form IV.

[0108] Figure 74 is a calculated X-ray powder diffractogram of Compound I Form VI.

[0109] Figure 75 is an X-ray powder diffractogram of Compound I Form X.

[0110] Figure 76 is an X-ray powder diffractogram of Compound I Form XI.

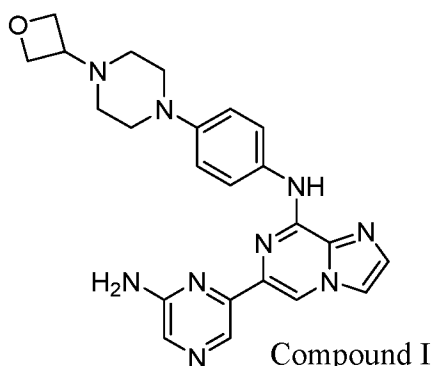
[0111] Figure 77 is a calculated X-ray powder diffractogram of Compound I Form XII.

[0112] Figure 78 is an X-ray powder diffractogram of Compound I HCl Material A.

[0113] Figure 79 is an X-ray powder diffractogram of Compound I HCl Material B.

DETAILED DESCRIPTION

[0114] The compound named 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine is useful in treatments for subjects suffering from or at risk of spleen tyrosine kinase (Syk) mediated disease or condition and has the following structure:



[0115] The present disclosure relates to crystalline forms of Compound I and crystalline forms of salts or co-crystals of Compound I and processes for making the crystalline forms and use thereof.

Definitions

[0116] The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

[0117] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0118] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term “about” includes the indicated amount $\pm 10\%$. In other embodiments, the term “about” includes the indicated amount $\pm 5\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 1\%$. For example, when used in the context of quantitative measurements, the term “about” would refer to the indicated amount $\pm 10\%$, $\pm 5\%$ or $\pm 1\%$. Also, the term “about X” includes description of “X”. Also, the singular forms “a” and “the” include plural references unless the context clearly dictates otherwise. Thus, *e.g.*, reference to “the compound” includes a plurality of such compounds and reference to “the assay” includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0119] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0120] The term “therapeutically effective amount” refers to an amount of the compound as described herein that is sufficient to effect treatment as defined above, when administered to a patient (particularly a human) in need of such treatment in one or more doses. The therapeutically effective amount will vary, depending upon the patient, the disease being treated, the weight and/or age of the patient, the severity of the disease, or the manner of administration as determined by a qualified prescriber or care giver.

[0121] The term “salt” refers to a salt of Compound I. In some cases, the “salt” of Compound I is a pharmaceutically acceptable salt. Compound I is capable of forming, for example, acid addition salts by virtue of the presence of amino groups. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include, but are not limited to, acetic acid, adipic acid, citric acid, gentisic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like.

[0122] The term “co-crystal” refers to a molecular complex of an ionized or non-ionized Compound I and one or more non-ionized co-crystal formers (such as a pharmaceutically acceptable salt) connected through non-covalent interactions.

[0123] The term “solvate” refers to a crystal form with either a stoichiometric or non-stoichiometric amount of solvent incorporated into the crystal structure. Similarly, the term “hydrate” refers specifically to a crystal form with either a stoichiometric or non-stoichiometric amount of water incorporated into the crystal structure.

[0124] In addition, abbreviations as used herein have respective meanings as follows:

Aq.	Aqueous
d	Doublet
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DSC	Differential scanning calorimetry
DVS	Dynamic vapor sorption
EtOAc	Ethyl acetate
EtOH	Ethanol
IPAc	Isopropyl acetate
LCMS	Liquid chromatography - mass spectrometry
m	Multiplet
MEK	Methyl ethyl ketone
MeOH	Methanol
2-MeTHF	2-Methyl tetrahydrofuran
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
RH	Relative humidity
RT	Room temperature

s	Singlet
TGA	Thermogravimetric analysis
XRPD	X-ray powder diffraction
THF	Tetrahydrofuran

Crystalline Forms of Compound I

[0125] As described generally above, the present disclosure provides crystalline forms of Compound I and crystalline forms of salts or co-crystals of Compound I.

Compound I Form I

[0126] Compound I Form I is an unsolvated form. Compound I Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 15.2, 18.0 and 20.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 10.8, 20.8 and 24.4 $^\circ 2\theta$. Compound I Form I can be characterized by an X-ray powder (XRPD) diffractogram as substantially shown in Figure 1. In one embodiment, Compound I Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 20.0, 18.0, 15.2, 10.8, 24.4, 20.8, 9.0, 19.4, 17.3 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0127] In some embodiments, Compound I Form I can be characterized by a differential scanning calorimetry (DSC) curve comprising an endotherm having an onset temperature of about 253 $^\circ\text{C}$. The endotherm can comprise a peak at about 256 $^\circ\text{C}$. In another embodiment, Compound I Form I can be characterized by a DSC curve substantially as shown in Figure 2. In some embodiments, Compound I Form I can be characterized by thermogravimetric analysis (TGA) curve substantially as shown in Figure 3. In some embodiments, Compound I Form I can be characterized by a dynamic vapor sorption (DVS) curve substantially as shown in Figure 4. As can be determined from Figure 4, Compound I Form I can be slightly hygroscopic, absorbing up to about 0.8 wt. % water at 25 $^\circ\text{C}$ and 95% RH. Compound I Form I is a monoclinic crystalline form having unit cell parameters: a equal to 8.62 \AA , b equal to 19.71 \AA , c equal to 13.46 \AA , α equal to 90 $^\circ$, β equal to 108.34 $^\circ$ and γ equal to 90 $^\circ$.

Compound I Form II

[0128] Compound I Form II can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 19.5, 20.8 and 22.2 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 18.1, 24.5 and 28.9 $^\circ 2\theta$. Compound I Form II can be characterized by an X-ray powder diffractogram as substantially shown in Figure 5. In one embodiment, Compound I Form II can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 20.8, 19.5, 22.2, 18.1, 28.9, 24.5, 31.7, 11.8 and 15.3 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0129] In some embodiments, Compound I Form II can be characterized by a DSC curve comprising endotherms having onset temperatures of about 155 $^\circ\text{C}$ and 253 $^\circ\text{C}$. The endotherms can comprise peaks at about 162 $^\circ\text{C}$ and 257 $^\circ\text{C}$. In another embodiment, Compound I Form II can be characterized by a DSC curve substantially as shown in Figure 6. In some embodiments, Compound I Form II can be characterized by a TGA curve substantially as shown in Figure 7. In some embodiments, Compound I Form II can be characterized by a DVS curve substantially as shown in Figure 8. DVS analysis shows that it is slightly hygroscopic, absorbing up to about 2 wt. % water at 25 $^\circ\text{C}$ and 95% RH.

Compound I Form III

[0130] Compound I Form III is a hydrated form. Compound I Form III can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 7.6, 14.2 and 20.8 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 6.2, 9.3 and 16.9 $^\circ 2\theta$. Compound I Form III can be characterized by an X-ray powder diffractogram as substantially shown in Figure 9. In one embodiment, Compound I Form III can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 7.6, 14.2, 20.8, 16.9, 9.3, 6.2, 16.7, 11.5 and 6.9 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0131] In some embodiments, Compound I Form III can be characterized by a DSC curve comprising an endotherm having an onset temperature and a peak at about 95 $^\circ\text{C}$. In another embodiment, Compound I Form III can be characterized by a DSC curve substantially as shown in Figure 10. In some embodiments, Compound I Form III can be characterized by a TGA curve substantially as shown in Figure 11.

Compound I Form IV

[0132] Compound I Form IV is a mono-methanol solvate. Compound I Form IV can be characterized by a calculated X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 19.2, 20.9 and 21.4 $^\circ 2\theta$. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 8.7, 17.4 and 19.6 $^\circ 2\theta$. Compound I Form IV can be characterized by an X-ray powder diffractogram as substantially shown in Figure 73. In one embodiment, Compound I Form IV can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 21.4, 20.9, 19.2, 19.6, 8.7, 17.4, 11.4, 15.3 and 12.1 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0133] Compound I Form IV is a monoclinic crystalline form having unit cell parameters: a equal to 14.29 Å, b equal to 14.57 Å, c equal to 11.57 Å, α equal to 90 $^\circ$, β equal to 92.41 $^\circ$ and γ equal to 90 $^\circ$.

Compound I Form V

[0134] Compound I Form V is a monohydrate. Compound I Form V can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 17.7, 19.7 and 22.7 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 8.6, 14.0 and 20.0 $^\circ 2\theta$. Compound I Form V can be characterized by an X-ray powder diffractogram as substantially shown in Figure 12. In one embodiment, Compound I Form V can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 19.7, 22.7, 17.7, 14.0, 20.0, 8.6, 14.9, 21.3 and 17.2 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0135] In some embodiments, Compound I Form V can be characterized by a DSC curve comprising an endotherm having an onset temperature of about 117 $^\circ\text{C}$ and 258 $^\circ\text{C}$. The endotherms comprise peaks at about 119 $^\circ\text{C}$ and 256 $^\circ\text{C}$. In another embodiment, Compound I Form V can be characterized by a DSC curve substantially as shown in Figure 13. In some embodiments, Compound I Form V can be characterized by a TGA curve substantially as shown in Figure 14. In another embodiment, Compound I Form V can be characterized by a DVS curve substantially as shown in Figure 15. As can be determined from Figure 15, Compound I Form V can be slightly hygroscopic, absorbing up to about 0.5 wt. % water at 25 $^\circ\text{C}$ and 95% RH. Compound I Form V is a monoclinic crystalline form having unit cell parameters: a equal to

10.55 Å, b equal to 17.75 Å, c equal to 13.33 Å, α equal to 90 °, β equal to 108.3 ° and γ equal to 90 °. When heated to about 150 °C, Compound I Form V dehydrates to Compound I Form I.

Compound I Form VI

[0136] Compound I Form VI is a mono-ethanol solvate. Compound I Form VI can be characterized by a calculated X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 18.9, 20.4 and 21.0 $^\circ 2\theta$. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 8.5, 19.3 and 25.1 $^\circ 2\theta$. Compound I Form VI can be characterized by an X-ray powder diffractogram as substantially shown in Figure 74. In one embodiment, Compound I Form VI can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 21.0, 20.4, 18.9, 19.3, 8.5, 25.1, 11.3, 15.3 and 17.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0137] Compound I Form VI is a monoclinic crystalline form having unit cell parameters: a equal to 14.52 Å, b equal to 14.91 Å, c equal to 11.58 Å, α equal to 90 °, β equal to 91.82 ° and γ equal to 90 °. When heated to elevated temperatures, Compound I Form VI desolvates to Compound I Form I

Compound I Form VII

[0138] Compound I Form VII is an isopropanol solvate. Compound I Form VII can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.4, 18.6 and 20.6 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 19.0, 20.2 and 24.6 $^\circ 2\theta$. Compound I Form VII can be characterized by an X-ray powder diffractogram as substantially shown in Figure 16. In one embodiment, Compound I Form VII can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 20.6, 18.6, 20.2, 19.0, 8.4, 24.6, 16.8, 22.1 and 24.1 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0139] In some embodiments, Compound I Form VII can be characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having onset temperatures of about 117 °C and 153 °C. The endotherms comprise a peak at about 123 °C and 160 °C. In another embodiment, Compound I Form VII can be characterized by a DSC curve substantially as shown in Figure 17. In some embodiments, Compound I Form VII can be characterized by a

TGA curve substantially as shown in Figure 18. When heated to about 100 °C, Compound I Form VII desolvates to Compound I Form II.

Compound I Form VIII

[0140] Compound I Form VIII is a DMF solvate. Compound I Form VIII can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 18.3, 20.8 and 21.9 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 14.8, 25.0 and 27.4 $^\circ 2\theta$. Compound I Form VIII can be characterized by an X-ray powder diffractogram as substantially shown in Figure 19. In one embodiment, Compound I Form VIII can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 20.8, 18.3, 21.9, 14.8, 27.4, 25.0, 22.8, 25.2 and 22.5 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0141] In some embodiments, Compound I Form VIII can be characterized by a DSC curve comprising endotherms having onset temperatures of about 133 °C, 236 °C and 256 °C. The endotherms comprise peaks at about 134 °C, 240 °C and 258 °C. In another embodiment, Compound I Form VIII can be characterized by a DSC curve substantially as shown in Figure 20. In some embodiments, Compound I Form VIII can be characterized by a TGA curve substantially as shown in Figure 21. When heated to about 180 °C, Compound I Form VIII desolvates to Compound I Form I.

Compound I Form IX

[0142] Compound I Form IX is a tri-hydrate mono-methanolate. Compound I Form IX can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 14.0, 16.7 and 18.2 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 7.6, 12.1 and 18.7 $^\circ 2\theta$. Compound I Form IX can be characterized by an X-ray powder diffractogram as substantially shown in Figure 22. In one embodiment, Compound I Form IX can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 14.0, 16.7, 18.2, 12.1, 7.6, 18.7, 6.1, 26.1 and 25.6 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0143] In some embodiments, Compound I Form IX can be characterized by a differential scanning calorimetry (DSC) curve comprising a broad endotherm between temperatures of about 40 °C and 110 °C. In another embodiment, the DSC curve can comprise a further endotherm having an onset temperature of about 259 °C. In another embodiment, Compound I Form IX can be characterized by a DSC curve substantially as shown in Figure 23. In some embodiments, Compound I Form IX can be characterized by a TGA curve substantially as shown in Figure 24. Compound I Form IX is a monoclinic crystalline form having unit cell parameters: a equal to 6.92 Å, b equal to 28.97 Å, c equal to 12.73 Å, α equal to 90 °, β equal to 92.53 ° and γ equal to 90 °. When dried in a vacuum overnight at about 50 °C with a nitrogen purge, Compound I Form IX desolvates to amorphous Compound I.

Compound I Form X

[0144] Compound I Form X can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.1, 12.2 and 20.3 °2 θ , as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 4.1, 19.1 and 21.4 °2 θ . Compound I Form X can be characterized by an X-ray powder diffractogram as substantially shown in Figure 75. In one embodiment, Compound I Form X can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 720.3, 8.1, 12.2, 4.1, 21.4, 19.1, 23.7, 15.3 and 22.6 °2 θ , as determined on a diffractometer using Cu-K α radiation.

Compound I Form XI

[0145] Compound I Form XI can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 19.2, 21.2 and 24.6 °2 θ , as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 19.5, 20.1 and 25.3 °2 θ . Compound I Form XI can be characterized by an X-ray powder diffractogram as substantially shown in Figure 76. In one embodiment, Compound I Form XI can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 24.6, 19.2, 21.2, 19.5, 20.1, 25.3, 21.6, 29.3 and 7.2 °2 θ , as determined on a diffractometer using Cu-K α radiation.

Compound I Form XII

[0146] Compound I Form XII is a mono-acetonitrile solvate. Compound I Form XII can be characterized by a calculated X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.6, 19.3 and $20.7^\circ 2\theta$. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 17.2, 18.8 and $24.5^\circ 2\theta$. Compound I Form XII can be characterized by an X-ray powder diffractogram as substantially shown in Figure 77. In one embodiment, Compound I Form XII can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 20.7, 19.3, 8.6, 18.8, 24.5, 17.2, 15.0, 28.4 and $19.5^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0147] Compound I Form XII is a monoclinic crystalline form having unit cell parameters: a equal to 14.55 Å, b equal to 14.53 Å, c equal to 11.77 Å, α equal to 90° , β equal to 90.46° and γ equal to 90° .

Compound I Form XIII

[0148] Compound I Form XIII is a propylene glycol solvate. Compound I Form XIII can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 9.6, 19.3 and $20.8^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 21.8, 22.2 and $25.4^\circ 2\theta$. Compound I Form XIII can be characterized by an X-ray powder diffractogram as substantially shown in Figure 25. In one embodiment, Compound I Form XIII can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 9.6, 19.3, 22.2, 20.8, 21.8, 25.4, 21.0, 19.1 and $6.4^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

Compound I Form XIV

[0149] Compound I Form XIV can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 19.4, 22.5 and $23.3^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 13.9, 16.7 and $24.3^\circ 2\theta$. Compound I Form XIV can be characterized by an X-ray powder diffractogram as substantially shown in Figure 26. In one embodiment, Compound I Form XIV can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least

five peaks ($\pm 0.2^\circ 2\theta$) selected from 19.4, 23.3, 22.5, 16.7, 24.3, 13.9, 18.8, 18.3 and $21.1^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0150] In some embodiments, Compound I Form XIV can be characterized by a differential scanning calorimetry (DSC) curve comprising a broad endotherm between temperatures of about 25 °C and 100 °C. In another embodiment, the DSC curve further comprises an endotherm having onset temperature of about 258 °C. In another embodiment, Compound I Form XIV can be characterized by a DSC curve substantially as shown in Figure 27. In some embodiments, Compound I Form XIV can be characterized by a TGA curve substantially as shown in Figure 28. In some embodiments, Compound I Form XIV can be characterized by a DVS curve substantially as shown in Figure 29.

Crystalline Forms of Salts or Co-crystals of Compound I

[0151] The crystalline forms of salts or co-crystals of Compound I are discussed below.

Compound I Sesqui-Succinate Form III

[0152] Compound I Sesqui-Succinate Form III is an ethyl acetate solvate (contains about 0.4 mol. eq. of ethyl acetate). Compound I Sesqui-Succinate Form III can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 7.8, 16.5 and $21.4^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 12.2, 16.0 and $24.5^\circ 2\theta$. Compound I Sesqui-Succinate Form III can be characterized by an X-ray powder diffractogram as substantially shown in Figure 30. In one embodiment, Compound I Sesqui-Succinate Form III can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 16.5, 24.5, 7.8, 16.0, $21.4^\circ 2\theta$, 15.9, 12.2, 8.2 and $6.0^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0153] In some embodiments, Compound I Sesqui-Succinate Form III can be characterized by a DSC curve comprising endotherms having onset temperatures of about 118 °C, 136 °C and 186 °C. The endotherms can comprise peaks at about 123 °C, 141 °C and 190 °C. In another embodiment, Compound I Sesqui-Succinate Form III can be characterized by a DSC curve substantially as shown in Figure 31. In some embodiments, Compound I Sesqui-Succinate Form III can be characterized by a TGA curve substantially as shown in Figure 32. When heated to

about 150 °C, Compound I Sesqui-Succinate Form III converts to Compound I Succinate Form I which is disclosed in the U.S. Patent 9,290,505.

Compound I Sesqui-Succinate Form IV

[0154] Compound I Sesqui-Succinate Form IV is a MEK solvate. Compound I Sesqui-Succinate Form IV can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 16.6, 22.4 and 25.2 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 7.9, 11.7 and 21.7 $^\circ 2\theta \pm 0.2^\circ$. Compound I Sesqui-Succinate Form IV can be characterized by an X-ray powder diffractogram as substantially shown in Figure 33. In one embodiment, Compound I Sesqui-Succinate Form IV can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 16.6, 25.2, 22.4, 7.9, 11.7, 7.6, 21.7, 11.4 and 20.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0155] In some embodiments, Compound I Sesqui-Succinate Form IV can be characterized by a DSC curve comprising endotherms having onset temperatures of about 142 °C and 183 °C. The endotherms comprise peaks at about 148 °C and 188 °C. In another embodiment, Compound I Sesqui-Succinate Form IV can be characterized by a DSC curve is substantially as shown in Figure 34. In some embodiments, Compound I Sesqui-Succinate Form IV can be characterized by a TGA curve substantially as shown in Figure 35.

Compound I Sesqui-Succinate Form V

[0156] Compound I Sesqui-Succinate Form V is a THF solvate. Compound I Sesqui-Succinate Form V can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 5.9, 23.3 and 24.7 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 16.3, 26.4 and 28.6 $^\circ 2\theta$. Compound I Sesqui-Succinate Form V can be characterized by an X-ray powder diffractogram as substantially shown in Figure 36. In one embodiment, Compound I Sesqui-Succinate Form V can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 24.7, 5.9, 23.3, 16.3, 28.6, 26.4, 14.9, 21.9 and 21.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0157] In some embodiments, Compound I Sesqui-Succinate Form V can be characterized by a DSC curve comprising endotherms having onset temperatures of about 115 °C, 128 °C, 148 °C

and 178 °C. The endotherms comprise peaks at about 123 °C, 135 °C, 153 °C and 183 °C. In another embodiment, Compound I Sesqui-Succinate Form V can be characterized by a DSC curve substantially as shown in Figure 37. In some embodiments, Compound I Sesqui-Succinate Form V can be characterized by a TGA curve substantially as shown in Figure 38. When heated to about 150 °C, Compound I Sesqui-Succinate Form V converts to Compound I Succinate Form I which is disclosed in the U.S. Patent 9,290,505.

Compound I Hemi-Succinate Form I

[0158] Compound I Hemi-Succinate Form I is a monohydrate. Compound I Hemi-Succinate Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 20.8, 23.1 and 25.5 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 20.1, 21.2 and 28.1 $^\circ 2\theta$. Compound I Hemi-Succinate Form I can be characterized by an X-ray powder diffractogram as substantially shown in Figure 39. In one embodiment, Compound I Hemi-Succinate Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 20.8, 23.1, 25.5, 20.1, 21.2, 28.1, 10.6, 13.2 and 16.5 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0159] In some embodiments, Compound I Hemi-Succinate Form I can be characterized by a DSC curve comprising an endotherm having an onset temperature of about 128 °C. The endotherm comprises a peak at about 140 °C. In another embodiment, Compound I Hemi-Succinate Form I can be characterized by a DSC curve substantially as shown in Figure 40. In some embodiments, Compound I Hemi-Succinate Form I can be characterized by a TGA curve substantially as shown in Figure 41. In some embodiments, Compound I Hemi-Succinate Form I can be characterized by a DVS curve substantially as shown in Figure 42. DVS analysis shows that it is slightly hygroscopic with an uptake of about 0.4 wt. % of water at 90% RH at 25 °C. Compound I Hemi-Succinate Form I is a monoclinic crystalline form having unit cell parameters: a equal to 15.68 Å, b equal to 9.63 Å, c equal to 17.66 Å, α equal to 90 °, β equal to 108.12 ° and γ equal to 90 °.

Compound I Mono-HCl salt Form I

[0160] Compound I Mono-HCl salt Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.7, 19.3 and 21.4 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks

($\pm 0.2^\circ 2\theta$) at 17.4, 19.6 and 20.9 $^\circ 2\theta$. Compound I Mono-HCl salt Form I can be characterized by an X-ray powder diffractogram as substantially shown in Figure 43. In one embodiment, Compound I Mono-HCl salt Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 21.4, 8.7, 19.3, 20.9, 19.6, 17.4, 12.1, 6.2 and 6.9 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0161] In some embodiments, Compound I Mono-HCl salt Form I can be characterized by a TGA curve substantially as shown in Figure 44.

Compound I Mono-HCl salt Form II

[0162] Compound I Mono-HCl salt Form II can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 6.3, 11.3 and 17.7 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 7.0, 8.9 and 15.7 $^\circ 2\theta$. Compound I Mono-HCl salt Form II can be characterized by an X-ray powder diffractogram as substantially shown in Figure 45. In one embodiment, Compound I Mono-HCl salt Form II can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 17.7, 6.3, 11.3, 7.0, 15.7, 8.9, 19.8, 23.9 and 13.3 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0163] In some embodiments, Compound I Mono-HCl salt Form II can be characterized by a TGA curve substantially as shown in Figure 46. In some embodiments, Compound I Mono-HCl salt Form II can be characterized by a DVS curve substantially as shown in Figure 47. DVS analysis shows that it absorbs up to about 16 wt. % of water at 90% RH at 25 $^\circ\text{C}$ (very hygroscopic).

Compound I Mono-HCl salt Form III

[0164] Compound I Mono-HCl salt Form III is a di-propylene glycol solvate. Compound I Mono-HCl salt Form III can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.6, 17.8 and 24.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 12.8, 26.9 and 28.9 $^\circ 2\theta$. Compound I Mono-HCl salt Form III can be characterized by an X-ray powder diffractogram as substantially shown in Figure 48. In one embodiment, Compound I Mono-HCl

salt Form III can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 24.0, 17.8, 8.6, 28.9, 12.8, 26.9, 18.4, 24.6 and $33.3^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0165] In some embodiments, Compound I Mono-HCl salt Form III can be characterized by a DSC curve comprising endotherms having an onset temperature of about 125°C . The endotherm comprises a peak at about 126°C . In another embodiment, Compound I Mono-HCl salt Form III can be characterized by a DSC curve substantially as shown in Figure 49. In some embodiments, Compound I Mono-HCl salt Form III can be characterized by a TGA curve substantially as shown in Figure 50. Compound I Mono-HCl salt Form III is a triclinic crystalline form having unit cell parameters: a equal to 11.03 \AA , b equal to 12.13 \AA , c equal to 12.89 \AA , α equal to 66.9° , β equal to 79.52° and γ equal to 83.88° .

Compound I Sesqui-Adipate Form I

[0166] Compound I Sesqui-Adipate Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 11.3, 16.6 and $24.8^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 7.7, 11.9 and $15.7^\circ 2\theta$. Compound I Sesqui-Adipate Form I can be characterized by an X-ray powder diffractogram as substantially shown in Figure 51. In one embodiment, Compound I Sesqui-Adipate Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 16.6, 24.8, 11.3, 15.7, 11.9, 7.7, 5.7, 28.3 and $25.0^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0167] In some embodiments, Compound I Sesqui-Adipate Form I can be characterized by a DSC curve comprising endotherms having an onset temperature of about 168°C . The endotherm comprises a peak at about 171°C . In another embodiment, Compound I Sesqui-Adipate Form I can be characterized by a DSC curve is substantially as shown in Figure 52. In some embodiments, Compound I Sesqui-Adipate Form I can be characterized by a TGA curve substantially as shown in Figure 53. In some embodiments, Compound I Sesqui-Adipate Form I can be characterized by a DVS curve substantially as shown in Figure 54. DVS analysis shows that it is moderately hygroscopic, showing an uptake of about 2.1 wt. % of water at 90% RH at 25°C . Compound I Sesqui-Adipate Form I is triclinic crystalline form having unit cell parameters: a equal to 8.10 \AA , b equal to 13.38 \AA , c equal to 16.46 \AA , α equal to 71.91° , β equal to 79.15° and γ equal to 76.92° .

Compound I Mono-Adipate Form I

[0168] Compound I Mono-Adipate Form I is a THF solvate. Compound I Mono-Adipate Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 4.9, 19.9 and 21.1 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 18.4, 19.5 and 21.7 $^\circ 2\theta$. Compound I Mono-Adipate Form I can be characterized by an X-ray powder diffractogram as substantially shown in Figure 55. In one embodiment, Compound I Mono-Adipate Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 21.1, 4.9, 19.9, 18.4, 19.5, 21.7, 20.4, 8.9 and 18.8 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0169] In some embodiments, Compound I Mono-Adipate Form I can be characterized by a DSC curve comprising endotherms having onset temperatures of about 91 $^\circ\text{C}$ and 194 $^\circ\text{C}$. The endotherms comprise peak at about 103 $^\circ\text{C}$ and 197 $^\circ\text{C}$. In another embodiment, Compound I Mono-Adipate Form I can be characterized by a DSC curve substantially as shown in Figure 56. In some embodiments, Compound I Mono-Adipate Form I can be characterized by a TGA curve substantially as shown in Figure 57. Compound I Mono-Adipate Form I is monoclinic crystalline form having unit cell parameters: a equal to 11.04 \AA , b equal to 31.08 \AA , c equal to 22.23 \AA , α equal to 90.00 $^\circ$, β equal to 100.23 $^\circ$ and γ equal to 90.00 $^\circ$.

Compound I Bis-Citrate Form I

[0170] Compound I Bis-Citrate Form I is a THF solvate. Compound I Bis-Citrate Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 6.4, 18.1 and 18.9 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 8.6, 17.8 and 19.9 $^\circ 2\theta$. Compound I Bis-Citrate Form I can be characterized by an X-ray powder diffractogram as substantially shown in Figure 58. In one embodiment, Compound I Bis-Citrate Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 6.4, 18.9, 18.1, 8.6, 19.9, 19.5, 17.8, 17.5 and 14.3 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0171] In some embodiments, Compound I Bis-Citrate Form I can be characterized by a DSC curve comprising a broad endotherm between temperatures of about 22 $^\circ\text{C}$ and 87 $^\circ\text{C}$. The DSC curve can further comprise endotherms having onset temperature of about 121 $^\circ\text{C}$ and 168 $^\circ\text{C}$.

In another embodiment, Compound I Bis-Citrate Form I can be characterized by a DSC curve is substantially as shown in Figure 59. In some embodiments, Compound I Bis-Citrate Form I can be characterized by a TGA curve substantially as shown in Figure 60.

Compound I Sesqui-Fumarate Form I

[0172] Compound I Sesqui-Fumarate Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 15.3, 22.8 and 25.8 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 7.8, 11.6 and 26.3 $^\circ 2\theta$. Compound I Sesqui-Fumarate Form I can be characterized by an X-ray powder diffractogram as substantially shown in Figure 61. In one embodiment, Compound I Sesqui-Fumarate Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 15.3, 22.8, 25.8, 7.8, 26.3, 11.6, 23.2, 19.4 and 9.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0173] In some embodiments, Compound I Sesqui-Fumarate Form I can be characterized by a TGA curve substantially as shown in Figure 62.

Compound I Bis-Gentisate Form I

[0174] Compound I Bis-Gentisate Form I is a THF solvate. Compound I Bis-Gentisate Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 6.7, 16.7 and 25.0 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 7.7, 17.9 and 23.3 $^\circ 2\theta$. Compound I Bis-Gentisate Form I can be characterized by an X-ray powder diffractogram as substantially shown in Figure 63. In one embodiment, Compound I Bis-Gentisate Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 25.0, 6.7, 16.7, 7.7, 17.9, 23.3, 18.2, 7.1 and 17.6 $^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0175] In some embodiments, Compound I Bis-Gentisate Form I can be characterized by a DSC curve comprising endotherms having peaks at about 54 $^\circ\text{C}$ and 151 $^\circ\text{C}$. In another embodiment, Compound I Bis-Gentisate Form I can be characterized by a DSC curve substantially as shown in Figure 64. In some embodiments, Compound I Bis-Gentisate Form I can be characterized by a TGA curve substantially as shown in Figure 65. Compound I

Bis-Gentisate Form I is a triclinic crystalline form having unit cell parameters: a equal to 12.06 Å, b equal to 13.73 Å, c equal to 14.88 Å, α equal to 64.57 °, β equal to 73.71 ° and γ equal to 77.01 °.

Compound I Mono-BSA Form I

[0176] Compound I Mono-BSA Form I is a hydrated form. Compound I Mono-BSA Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.8, 11.8 and $20.2^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 10.9, 15.8 and $25.7^\circ 2\theta$. Compound I Mono-BSA Form I can be characterized by an X-ray powder diffractogram as substantially shown in Figure 66. In one embodiment, Compound I Mono-BSA Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 11.8, 8.8, 20.2, 25.7, 10.9, 15.8, 23.4, 20.9 and $21.2^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation.

[0177] In some embodiments, Compound I Mono-BSA Form I can be characterized by a DSC curve comprising an endotherm having an onset temperature of about 80 °C. The endotherm can comprise a peak at about 97 °C. In another embodiment, Compound I Mono-BSA Form I can be characterized by a DSC curve substantially as shown in Figure 67. In some embodiments, Compound I Mono-BSA Form I can be characterized by a TGA curve substantially as shown in Figure 68. In some embodiments, Compound I Mono-BSA Form I can be characterized by a DVS curve substantially as shown in Figure 69. DVS analysis shows that it is slightly hygroscopic, picks up about 1.5 wt. % of water at 85% RH at 25 °C. However, it is very hygroscopic above 85% RH as there is a > 15 wt. % change at 95% RH and 25 °C which lead to deliquescence.

Compound I Sesqui-Oxalate Form I

[0178] Compound I Sesqui-Oxalate Form I can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 16.1, 23.0 and $26.1^\circ 2\theta$, as determined on a diffractometer using Cu-K α radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 11.9, 19.2 and $20.8^\circ 2\theta$. Compound I Sesqui-Oxalate Form I can be characterized by an X-ray powder diffractogram as substantially shown in Figure 70. In one embodiment, Compound I Sesqui-Oxalate Form I can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 16.1, 23.0,

26.1, 11.9, 20.8, 19.2, 20.0, 25.1 and 17.7 °2θ, as determined on a diffractometer using Cu-Kα radiation.

[0179] In some embodiments, Compound I Sesqui-Oxalate Form I can be characterized by a DSC curve comprising an endotherm having an onset temperature of about 193 °C. The endotherm can comprise a peak at about 197 °C. In another embodiment, Compound I Sesqui-Oxalate Form I can be characterized by a DSC curve substantially as shown in Figure 71. In some embodiments, Compound I Sesqui-Oxalate Form I can be characterized by a TGA curve substantially as shown in Figure 72.

Compound I HCl Material A

[0180] Compound I HCl Material A can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.1, 15.3 and 19.3 °2θ, as determined on a diffractometer using Cu-Kα radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 7.6, 17.4 and 20.6 °2θ. Compound I HCl Material A can be characterized by an X-ray powder diffractogram as substantially shown in Figure 78. In one embodiment, Compound I HCl Material A can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 8.1, 15.3, 19.3, 7.6, 20.6, 17.4, 9.4, 12.7 and 16.7 °2θ, as determined on a diffractometer using Cu-Kα radiation.

Compound I HCl Material B

[0181] Compound I HCl Material B can be characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 17.7, 19.6 and 22.6 °2θ, as determined on a diffractometer using Cu-Kα radiation. The diffractogram can comprise additional peaks ($\pm 0.2^\circ 2\theta$) at 20.0, 21.9 and 25.7 °2θ. Compound I HCl Material B can be characterized by an X-ray powder diffractogram as substantially shown in Figure 79. In one embodiment, Compound I HCl Material B can be characterized by an X-ray powder diffractogram comprising at least three, at least four or at least five peaks ($\pm 0.2^\circ 2\theta$) selected from 19.6, 22.6, 17.7, 20.0, 25.7, 21.9, 10.0, 26.0 and 27.6 °2θ, as determined on a diffractometer using Cu-Kα radiation.

Synthesis of Compound I

[0182] Compound I can be synthesized according to methods known to persons skilled in the art, such as the synthetic procedure described in Example 1.

Formulations and Administration

[0183] Crystalline forms of Compound I or crystalline forms of a salt or a co-crystal of Compound I are usually administered in the form of pharmaceutical compositions. This disclosure therefore provides pharmaceutical compositions that contain, as the active ingredient, one or more of the crystalline forms described and one or more pharmaceutically acceptable vehicle, such as excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. The pharmaceutical compositions may be administered alone or in combination with other therapeutic agents. Such compositions are prepared in a manner well known in the pharmaceutical art (see, *e.g.*, Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, PA 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.)

[0184] In some embodiments, a pharmaceutical composition comprises crystalline forms of Compound I or crystalline forms of a salt or a co-crystal of Compound I, or combinations thereof. In some embodiments, a pharmaceutical composition comprises Compound I Form I, Compound I Form II, Compound I Form III, Compound I Form IV, Compound I Form V, Compound I Form VII, Compound I Form VIII, Compound I Form IX, Compound I Form X, Compound I Form XI, Compound I Form XII, Compound I Form XIII, Compound I Form XIV, Compound I Sesqui-Succinate Form III, Compound I Sesqui-Succinate Form IV, Compound I Sesqui-Succinate Form V, Compound I Hemi-Succinate Form I, Compound I Mono-HCl salt Form I, Compound I Mono-HCl salt Form II, Compound I Mono-HCl salt Form III, Compound I Sesqui-Adipate Form I, Compound I Mono-Adipate Form I, Compound I Bis-Citrate Form I, Compound I Sesqui-Fumarate Form I, Compound I Bis-Gentisate Form I, Compound I Mono-BSA salt Form I or Compound I Sesqui-Oxalate Form I.

[0185] In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form II, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical

composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form III, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form IV, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form V, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form V, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form VI, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form VII, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form VIII, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form IX, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form X, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form XI, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form XII, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form XIII, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Form XIV, and no more than 5%, 4%, 3%, 2% or 1% of other forms.

[0186] In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Sesqui-Succinate Form III, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Sesqui-Succinate Form IV, and no more than 5%, 4%, 3%, 2% or 1% of other

forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Sesqui-Succinate Form V, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Hemi-Succinate Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Mono-HCl salt Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Mono-HCl salt Form II, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Mono-HCl salt Form III, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Sesqui-Adipate Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Mono-Adipate Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Bis-Citrate Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Sesqui-Fumarate Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Bis-Gentisate Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Mono-BSA salt Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms. In some embodiments, a pharmaceutical composition comprises a compound of Formula I, wherein at least 95% of Formula I is Compound I Sesqui-Oxalate Form I, and no more than 5%, 4%, 3%, 2% or 1% of other forms.

[0187] The pharmaceutical compositions may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, for example as described in those patents and patent applications incorporated by reference, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically,

as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

[0188] One mode for administration is parenteral, particularly by injection. The forms in which the crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. Aqueous solutions in saline may also conventionally be used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[0189] Sterile injectable solutions can be prepared by incorporating a compound according to the present disclosure in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which can yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. In some embodiments, for parenteral administration, sterile injectable solutions are prepared containing a therapeutically effective amount, *e.g.*, 0.1 to 1000 mg, of a crystalline form as described herein. It will be understood, however, that the amount of the compound actually administered usually will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual subject, the severity of the subject's symptoms, and the like.

[0190] Oral administration is another route for administration of the of a crystalline form as described herein. Administration may be via capsule or enteric coated tablets, or the like. In making the pharmaceutical compositions that include crystalline forms of Compound I or the crystalline forms of a salt or co-crystal of Compound I, the active ingredient can be diluted by an

excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0191] Some examples of suitable excipients in an oral formulation include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0192] The pharmaceutical compositions as described herein can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the methods of the present disclosure employs transdermal delivery devices (patches). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present disclosure in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, *e.g.*, U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0193] In some embodiments, the compositions described herein are formulated in a unit dosage form. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient (*e.g.*, a tablet, capsule, ampoule). The compounds are generally administered in a pharmaceutically effective amount. In some embodiments, for oral

administration, each dosage unit contains from about 1 mg to about 5000 mg, about 1 mg to about 4000 mg, about 1 mg to about 3000 mg, about 1 mg to about 2000 mg, about 2 mg to about 2000 mg, about 5 mg to about 2000 mg, about 10 mg to about 2000 mg, about 1 mg to about 1000 mg, about 2 mg to about 1000 mg, about 5 mg to about 1000 mg, about 10 mg to about 1000 mg, about 25 mg to about 1000 mg, about 50 mg to about 1000 mg, about 75 mg to about 1000 mg, about 100 mg to about 1000 mg, about 125 mg to about 1000 mg, about 150 mg to about 1000 mg, about 175 mg to about 1000 mg, about 200 mg to about 1000 mg, about 225 mg to about 1000 mg, about 250 mg to about 1000 mg, about 300 mg to about 1000 mg, about 350 mg to about 1000 mg, about 400 mg to about 1000 mg, about 450 mg to about 1000 mg, about 500 mg to about 1000 mg, about 550 mg to about 1000 mg, about 600 mg to about 1000 mg, about 650 mg to about 1000 mg, about 700 mg to about 1000 mg, about 750 mg to about 1000 mg, about 800 mg to about 1000 mg, about 850 mg to about 1000 mg, about 900 mg to about 1000 mg, about 950 mg to about 1000 mg, about 1 mg to about 750 mg, about 2 mg to about 750 mg, about 5 mg to about 750 mg, about 10 mg to about 750 mg, about 25 mg to about 750 mg, about 50 mg to about 750 mg, about 75 mg to about 750 mg, about 100 mg to about 750 mg, about 125 mg to about 750 mg, about 150 mg to about 750 mg, about 175 mg to about 750 mg, about 200 mg to about 750 mg, about 225 mg to about 750 mg, about 250 mg to about 750 mg, about 300 mg to about 750 mg, about 350 mg to about 750 mg, about 400 mg to about 750 mg, about 450 mg to about 750 mg, about 500 mg to about 750 mg, about 550 mg to about 750 mg, about 600 mg to about 750 mg, about 650 mg to about 750 mg, about 700 mg to about 750 mg, about 1 mg to about 500 mg, about 2 mg to about 500 mg, about 5 mg to about 500 mg, about 10 mg to about 500 mg, about 25 mg to about 500 mg, about 50 mg to about 500 mg, about 75 mg to about 500 mg, about 100 mg to about 500 mg, about 125 mg to about 500 mg, about 150 mg to about 500 mg, about 175 mg to about 500 mg, about 200 mg to about 500 mg, about 225 mg to about 500 mg, about 250 mg to about 500 mg, about 300 mg to about 500 mg, about 350 mg to about 500 mg, about 400 mg to about 500 mg, about 450 mg to about 500 mg, about 1 mg to about 400 mg, about 2 mg to about 400 mg, about 5 mg to about 400 mg, about 10 mg to about 400 mg, about 25 mg to about 400 mg, about 50 mg to about 400 mg, about 75 mg to about 400 mg, about 100 mg to about 400 mg, about 125 mg to about 400 mg, about 150 mg to about 400 mg, about 175 mg to about 400 mg, about 200 mg to about 400 mg, about 225 mg to about 400 mg, about 250 mg to about 400 mg, about 300 mg to about 400 mg, about 350 mg to about 400 mg, about 1 mg to about 300 mg, about 2 mg to about 300 mg, about 5 mg to about 300 mg, about 10 mg to about 300 mg, about 25 mg to about 300 mg, about 50 mg to about 300 mg, about 75 mg to about 300 mg, about 100 mg to about 300 mg, about 125 mg to about 300

mg, about 150 mg to about 300 mg, about 175 mg to about 300 mg, about 200 mg to about 300 mg, about 225 mg to about 300 mg, about 250 mg to about 300 mg, about 1 mg to about 250 mg, about 2 mg to about 250 mg, about 5 mg to about 250 mg, about 10 mg to about 250 mg, about 25 mg to about 250 mg, about 50 mg to about 250 mg, about 75 mg to about 250 mg, about 100 mg to about 250 mg, about 125 mg to about 250 mg, about 150 mg to about 250 mg, about 175 mg to about 250 mg, about 200 mg to about 250 mg, about 225 mg to about 250 mg, about 1 mg to about 225 mg, about 2 mg to about 225 mg, about 5 mg to about 225 mg, about 10 mg to about 225 mg, about 25 mg to about 225 mg, about 50 mg to about 225 mg, about 75 mg to about 225 mg, about 100 mg to about 225 mg, about 125 mg to about 225 mg, about 150 mg to about 225 mg, about 175 mg to about 225 mg, about 200 mg to about 225 mg, about 1 mg to about 200 mg, about 2 mg to about 200 mg, about 5 mg to about 200 mg, about 10 mg to about 200 mg, about 25 mg to about 200 mg, about 50 mg to about 200 mg, about 75 mg to about 200 mg, about 100 mg to about 200 mg, about 125 mg to about 200 mg, about 150 mg to about 200 mg, about 175 mg to about 200 mg, about 1 mg to about 175 mg, about 2 mg to about 175 mg, about 5 mg to about 175 mg, about 10 mg to about 175 mg, about 25 mg to about 175 mg, about 50 mg to about 175 mg, about 75 mg to about 175 mg, about 100 mg to about 175 mg, about 125 mg to about 175 mg, about 150 mg to about 175 mg, about 1 mg to about 150 mg, about 2 mg to about 150 mg, about 5 mg to about 150 mg, about 10 mg to about 150 mg, about 25 mg to about 150 mg, about 50 mg to about 150 mg, about 75 mg to about 150 mg, about 100 mg to about 150 mg, about 125 mg to about 150 mg, about 1 mg to about 125 mg, about 2 mg to about 125 mg, about 5 mg to about 125 mg, about 10 mg to about 125 mg, about 25 mg to about 125 mg, about 50 mg to about 125 mg, about 75 mg to about 125 mg, about 100 mg to about 125 mg, about 1 mg to about 100 mg, about 2 mg to about 100 mg, about 5 mg to about 100 mg, about 10 mg to about 100 mg, about 25 mg to about 100 mg, about 50 mg to about 100 mg, or about 75 mg to about 100 mg of a crystalline forms of Compound I or a crystalline forms of a salt or co-crystal of Compound I.

[0194] In some embodiments, for oral administration, each dosage unit contains about 1 mg, about 2 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I.

[0195] The dosages for oral administration described above may be administered once daily (QD) or twice daily (BID). In some embodiments, the crystalline form of Compound I or the crystalline form of a salt or a co-crystal of Compound I, or a pharmaceutical composition thereof, is administered orally at a unit dosage of about 1 mg QD, about 2 mg QD, about 5 mg QD, about 10 mg QD, about 15 mg QD, about 20 mg QD, about 25 mg QD, about 30 mg QD, about 35 mg QD, about 40 mg QD, about 45 mg QD, about 50 mg QD, about 75 mg QD, about 100 mg QD, about 125 mg QD, about 150 mg QD, about 175 mg QD, about 200 mg QD, about 225 mg QD, about 250 mg QD, about 300 mg QD, about 350 mg QD, about 400 mg QD, about 450 mg QD, about 500 mg QD, about 550 mg QD, about 600 mg QD, about 650 mg QD, about 700 mg QD, about 750 mg QD, about 800 mg QD, about 850 mg QD, about 900 mg QD, about 950 mg QD, or about 1000 mg QD. In some embodiments, it is administered orally at a unit dosage of about 1 mg BID, about 2 mg BID, about 5 mg BID, about 10 mg BID, about 15 mg BID, about 20 mg BID, about 25 mg BID, about 30 mg BID, about 35 mg BID, about 40 mg BID, about 45 mg BID, about 50 mg BID, about 75 mg BID, about 100 mg BID, about 125 mg BID, about 150 mg BID, about 175 mg BID, about 200 mg BID, about 225 mg BID, about 250 mg BID, about 300 mg BID, about 350 mg BID, about 400 mg BID, about 450 mg BID, about 500 mg BID, about 550 mg BID, about 600 mg BID, about 650 mg BID, about 700 mg BID, about 750 mg BID, about 800 mg BID, about 850 mg BID, about 900 mg BID, about 950 mg BID, or about 1000 mg BID.

[0196] In some embodiments, for parenteral administration, each dosage unit contains from 0.1 mg to 1 g, 0.1 mg to 700 mg, or 0.1 mg to 100 mg of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I.

[0197] For any of the dosage units as described herein, it will be understood, however, that the amount of the compound actually administered usually will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual subject, the severity of the subject's symptoms, and the like.

[0198] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of the crystalline form of Compound I or the crystalline form of a salt or a co-crystal of Compound I. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the

composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0199] The tablets or pills as described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0200] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions comprising the crystalline forms of Compound I or crystalline forms of salts of Compound I, may contain suitable pharmaceutically acceptable excipients as described supra. Preferably, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

Dosing Regimen

[0201] In the methods provided herein, the crystalline form of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, or a pharmaceutical composition thereof, is administered in a therapeutically effective amount to achieve its intended purpose. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. In some embodiments (methods of treating cancer), a therapeutically effective amount of the crystalline form, may (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent, and preferably stop cancer cell infiltration into peripheral organs; (iv) inhibit (*e.g.*, slow to some extent and preferably stop) tumor metastasis; (v) inhibit tumor growth; (vi) delay

occurrence and/or recurrence of a tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer. In various embodiments, the amount is sufficient to ameliorate, palliate, lessen, and/or delay one or more of symptoms of cancer.

[0202] The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one of ordinary skill in the art.

[0203] The dosing regimen of the crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, in the methods provided herein may vary depending upon the indication, route of administration, and severity of the condition, for example. Depending on the route of administration, a suitable dose can be calculated according to body weight, body surface area, or organ size. The final dosing regimen is determined by the attending physician in view of good medical practice, considering various factors that modify the action of drugs, *e.g.*, the specific activity of the compound, the identity and severity of the disease state, the responsiveness of the subject, the age, condition, body weight, sex, and diet of the subject, and the severity of any infection. Additional factors that can be taken into account include time and frequency of administration, drug combinations, reaction sensitivities, and tolerance/response to therapy. Further refinement of the doses appropriate for treatment involving any of the formulations mentioned herein is done routinely by the skilled practitioner without undue experimentation, especially in light of the dosing information and assays disclosed, as well as the pharmacokinetic data observed in human clinical trials. Appropriate doses can be ascertained through use of established assays for determining concentration of the agent in a body fluid or other sample together with dose response data.

[0204] The formulation and route of administration chosen may be tailored to the individual subject, the nature of the condition to be treated in the subject, and generally, the judgment of the attending practitioner. For example, the compounds can be linked to an antibody that recognizes a marker that is selective or specific for cancer cells, so that the compounds are brought into the vicinity of the cells to exert their effects locally, as previously described. *See e.g.*, Pietersz et al., *Immunol. Rev.*, 129:57 (1992); Trail et al., *Science*, 261:212 (1993); and Rowlinson-Busza et al., *Curr. Opin. Oncol.*, 4:1142 (1992).

[0205] The therapeutically effective amount of the crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, may be provided in a single dose or

multiple doses to achieve the desired treatment endpoint. As used herein, “dose” refers to the total amount of an active ingredient (*e.g.*, the crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I) to be taken each time by a subject (*e.g.*, a human). The dose administered, for example for oral administration described above, may be administered once daily (QD), twice daily (BID), three times daily, four times daily, or more than four times daily. In some embodiments, the dose is administered once daily. In some embodiments, the dose is administered twice daily.

[0206] In some embodiments, exemplary doses of the crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, for a human subject may be from about 10 mg to about 1000 mg, about 20 mg to about 1000 mg, about 30 mg to about 1000 mg, about 40 mg to about 1000 mg, about 50 mg to about 1000 mg, about 60 mg to about 1000 mg, about 10 mg to about 750 mg, about 20 mg to about 750 mg, about 30 mg to about 750 mg, about 40 mg to about 750 mg, about 50 mg to about 750 mg, about 60 mg to about 500 mg, about 90 mg to about 500 mg, about 120 mg to about 500 mg, about 10 mg to about 400 mg, about 20 mg to about 400 mg, about 30 mg to about 400 mg, about 40 mg to about 400 mg, about 50 mg to about 400 mg, about 60 mg to about 400 mg, about 90 mg to about 400 mg, about 120 mg to about 400 mg, about 10 mg to about 120 mg, about 20 mg to about 120 mg, about 30 mg to about 120 mg, about 60 mg to about 120 mg or about 90 mg to about 120 mg.

[0207] In some embodiments, exemplary doses of the crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, for a human subject may be about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 75 mg, about 100 mg, about 120 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg or about 300 mg.

[0208] In other embodiments, the methods provided comprise continuing to treat the subject (*e.g.*, a human) by administering the doses herein, at which clinical efficacy is achieved or reducing the doses by increments to a level at which efficacy can be maintained. In some embodiments, the methods provided comprise administering to the subject (*e.g.*, a human) an initial daily dose of 100 mg to 1000 mg of the crystalline compound and administering subsequent daily doses of the crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, over at least 6 days, wherein each subsequent daily dose is increased by 50 mg to 400 mg. Thus, it should also be understood that the dose may be increased by increments until clinical efficacy is achieved. Increments of about 25 mg, about 50

mg, about 100 mg, or about 125mg, or about 150 mg, or about 200 mg, or about 250 mg, or about 300 mg can be used to increase the dose. The dose can be increased daily, every other day, two, three, four, five or six times per week, or once per week.

[0209] The frequency of dosing will depend on the pharmacokinetic parameters of the compound administered, the route of administration, and the particular disease treated. The dose and frequency of dosing may also depend on pharmacokinetic and pharmacodynamic, as well as toxicity and therapeutic efficiency data.

[0210] The crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, may be administered under fed conditions. The term fed conditions or variations thereof refers to the consumption or uptake of food, in either solid or liquid forms, or calories, in any suitable form, before or at the same time when the compounds or pharmaceutical compositions thereof are administered. For example, the crystalline form may be administered to the subject (*e.g.*, a human) within minutes or hours of consuming calories (*e.g.*, a meal). In some embodiments, it may be administered to the subject (*e.g.*, a human) within 5-10 minutes, about 30 minutes, or about 60 minutes consuming calories.

[0211] In some embodiments a crystalline form of Compound I or a crystalline forms of a salt or a co-crystal of Compound I, may be administered as a 30 mg tablet orally once daily.

Articles of Manufacture and Kits

[0212] Compositions (including, for example, formulations and unit dosages) comprising the crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, as described herein, can be prepared and placed in an appropriate container, and labeled for treatment of an indicated condition. Accordingly, provided is also an article of manufacture, such as a container comprising a unit dosage form of the crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, and a label containing instructions for use of the compounds. In some embodiments, the article of manufacture is a container comprising a unit dosage form of the crystalline compound. The article of manufacture may be a bottle, vial, ampoule, single-use disposable applicator, or the like, containing the pharmaceutical composition provided in the present disclosure. The container may be formed from a variety of materials, such as glass or plastic and in one aspect also contains a label on, or associated with, the container which indicates directions for use in the treatment of cancer or inflammatory conditions. It should be understood that the active ingredient may be packaged in any material capable of improving chemical and physical stability, such as an aluminum foil

bag. In some embodiments, diseases or conditions indicated on the label can include, for example, treatment of cancer.

[0213] Any pharmaceutical composition provided in the present disclosure may be used in the articles of manufacture, the same as if each and every composition were specifically and individually listed for use in an article of manufacture.

[0214] Kits comprising a pharmaceutical composition comprising a crystalline form of Compound I, or a crystalline form of a salt or a co-crystal of Compound I, are also provided. For example, a kit can comprise unit dosage forms of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, as described herein, and a package insert containing instructions for use of the composition in treatment of a medical condition. In some embodiments, the kit comprises a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, and at least one pharmaceutically acceptable vehicle. The instructions for use in the kit may be for treating a cancer, including, for example, a hematologic malignancy. In some embodiments, the instructions are directed to use of the pharmaceutical composition for the treatment of cancer, such as leukemia or lymphoma, including relapsed and refractory leukemia or lymphoma. In some embodiments, the instructions for use in the kit may be for treating a hematologic cancer selected from the group consisting of small lymphocytic lymphoma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, refractory iNHL, mantle cell lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphoma, immunoblastic large cell lymphoma, lymphoblastic lymphoma, Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes), Nodal marginal zone lymphoma (+/- monocytoid B-cells), extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type, cutaneous T-cell lymphoma, extranodal T-cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, mycosis fungoides, B-cell lymphoma, diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, small non-cleaved cell lymphoma, Burkitt's lymphoma, multiple myeloma, plasmacytoma, acute lymphocytic leukemia, T-cell acute lymphoblastic leukemia, B-cell acute lymphoblastic leukemia, B-cell prolymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, juvenile myelomonocytic leukemia, minimal residual disease, hairy cell leukemia, primary myelofibrosis, secondary myelofibrosis, chronic myeloid leukemia, myelodysplastic syndrome, myeloproliferative disease, and Waldenstrom's macroglobulinemia. In one embodiment, the instructions for use in the kit may be for treating chronic lymphocytic leukemia or non-Hodgkin's lymphoma. In one embodiment,

the NHL is diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, lymphoplasmacytic lymphoma, and marginal zone lymphoma. In one embodiment, the hematologic malignancy is indolent non-Hodgkin's lymphoma. In some embodiments, diseases or conditions indicated on the label can include, for example, treatment of cancer.

[0215] In some instances, the instructions are directed to use of the pharmaceutical composition for the treatment of a solid tumor, wherein the solid tumor is from a cancer selected from the group consisting of pancreatic cancer, urological cancer, bladder cancer, colorectal cancer, colon cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, thyroid cancer, gall bladder cancer, lung cancer (*e.g.* non-small cell lung cancer, small-cell lung cancer), ovarian cancer, cervical cancer, gastric cancer, endometrial cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain tumors (*e.g.*, glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma), bone cancer, soft tissue sarcoma, retinoblastomas, neuroblastomas, peritoneal effusions, malignant pleural effusions, mesotheliomas, Wilms tumors, trophoblastic neoplasms, hemangiopericytomas, Kaposi's sarcomas, myxoid carcinoma, round cell carcinoma, squamous cell carcinomas, esophageal squamous cell carcinomas, oral carcinomas, cancers of the adrenal cortex, ACTH-producing tumors.

[0216] In some instances, the instructions are directed to use of the pharmaceutical composition for the treatment of an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction. In some embodiments, the instructions are directed to use of the pharmaceutical composition for the treatment of an autoimmune disease. In some embodiments, the instructions are directed to use of the pharmaceutical composition for the treatment of an autoimmune disease selected from the group consisting of cutaneous lupus erythematosus, myasthenia gravis, rheumatoid arthritis, acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiple sclerosis, Sjogren's syndrome, psoriasis, autoimmune hemolytic anemia, asthma, ulcerative colitis, Crohn's disease, irritable bowel disease, and chronic obstructive pulmonary disease. In some embodiments, the autoimmune disease is selected from the group consisting of asthma, rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease and systemic lupus erythematosus.

[0217] Any pharmaceutical composition provided in the present disclosure may be used in the kits, the same as if each and every composition were specifically and individually listed for use a kit.

[0218] The methods and crystalline forms described herein will typically be used in therapy for human subjects. However, they may also be used to treat similar or identical indications in other animal subjects. One or more crystalline forms of Compound I and/or one or more crystalline forms of salts or co-crystals of Compound I as described herein can be administered by different routes, including injection (*i.e.* parenteral, including intravenous, intraperitoneal, subcutaneous, and intramuscular), oral, transdermal, transmucosal, rectal, or inhalant.

Methods

[0219] In some embodiments, the disclosure provides a method for treating a disease or condition mediated by a Syk kinase in a subject in need thereof, by administering to the subject a therapeutically effective amount one or more crystalline forms of Compound I and/or one or more crystalline forms of salts or co-crystals of Compound I as described herein.

[0220] In some embodiments, the disclosure provides a method for treating a disease or condition selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease, and a cancer in a subject in need thereof, comprising administering to the subject a therapeutic effective amount of one or more crystalline forms of Compound I and/or one or more crystalline forms of salts or co-crystals of Compound I as described herein.

[0221] In some embodiments, the disease or condition is a cancer selected from the group consisting of a hematologic malignancy and a solid tumor. In some embodiments, the disease or condition is a hematologic malignancy selected from the group consisting of lymphoma, multiple myeloma, or leukemia.

[0222] In some embodiments, the disease or condition is selected from the group consisting of small lymphocytic lymphoma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, refractory iNHL, mantle cell lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphoma, immunoblastic large cell lymphoma, lymphoblastic lymphoma, Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes), Nodal marginal zone lymphoma (+/- monocytoid B-cells), Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type, cutaneous T-cell lymphoma, extranodal T-cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, mycosis fungoides, B-cell lymphoma, diffuse large B-cell lymphoma, Mediastinal large B-cell lymphoma, Intravascular large B-cell lymphoma, Primary effusion lymphoma, small non-cleaved cell lymphoma, Burkitt's lymphoma, multiple myeloma, plasmacytoma, acute lymphocytic leukemia, T-cell acute lymphoblastic leukemia, B-cell acute lymphoblastic

leukemia, B-cell prolymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, juvenile myelomonocytic leukemia, minimal residual disease, hairy cell leukemia, primary myelofibrosis, secondary myelofibrosis, chronic myeloid leukemia, myelodysplastic syndrome, myeloproliferative disease, and Waldenstrom's macroglobulinemia.

[0223] In some embodiments, the disease or condition is a solid tumor, wherein the solid tumor is from a cancer selected from the group consisting of pancreatic cancer, urological cancer, bladder cancer, colorectal cancer, colon cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, thyroid cancer, gall bladder cancer, lung cancer (*e.g.* non-small cell lung cancer, small-cell lung cancer), ovarian cancer, cervical cancer, gastric cancer, endometrial cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain tumors (*e.g.*, glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma), bone cancer, soft tissue sarcoma, retinoblastomas, neuroblastomas, peritoneal effusions, malignant pleural effusions, mesotheliomas, Wilms tumors, trophoblastic neoplasms, hemangiopericytomas, Kaposi's sarcomas, myxoid carcinoma, round cell carcinoma, squamous cell carcinomas, esophageal squamous cell carcinomas, oral carcinomas, cancers of the adrenal cortex, and ACTH-producing tumors.

[0224] In some embodiments, the disease or condition is selected from the group consisting of lupus, such as systemic lupus erythematosus and cutaneous lupus erythematosus, myasthenia gravis, Goodpasture's syndrome, glomerulonephritis, hemorrhage, pulmonary hemorrhage, atherosclerosis, rheumatoid arthritis, psoriatic arthritis, monoarticular arthritis, osteoarthritis, gouty arthritis, spondylitis, Behçet disease, autoimmune thyroiditis, Reynaud's syndrome, acute disseminated encephalomyelitis, chronic idiopathic thrombocytopenic purpura, multiple sclerosis, Sjögren's syndrome, autoimmune hemolytic anemia, tissue graft rejection, hyperacute rejection of transplanted organs, allograft rejection, graft-versus-host disease, diseases involving leukocyte diapedesis, disease states due to leukocyte dyscrasia and metastasis, granulocyte transfusion-associated syndromes, cytokine-induced toxicity, scleroderma, vasculitis, asthma, psoriasis, chronic inflammatory bowel disease, ulcerative colitis, Crohn's disease, necrotizing enterocolitis, irritable bowel syndrome, dermatomyositis, Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, type I diabetes mellitus, sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, and toxic shock syndrome, multiple organ injury syndrome secondary to septicemia, trauma, hypovolemic shock, allergic conjunctivitis, vernal conjunctivitis, and thyroid-associated ophthalmopathy, eosinophilic granuloma, eczema,

chronic bronchitis, acute respiratory distress syndrome, allergic rhinitis, coryza, hay fever, bronchial asthma, silicosis, pulmonary sarcoidosis, pleurisy, alveolitis, emphysema, pneumonia, bacterial pneumonia, bronchiectasis, and pulmonary oxygen toxicity, reperfusion injury of the myocardium, brain, or extremities, thermal injury, cystic fibrosis, keloid formation or scar tissue formation, fever and myalgias due to infection, and brain or spinal cord injury due to minor trauma, diseases involving leukocyte diapedesis, acute hypersensitivity, delayed hypersensitivity, urticaria, food allergies, skin sunburn, inflammatory pelvic disease, urethritis, uveitis, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, alcoholic hepatitis, gastritis, enteritis, contact dermatitis, atopic dermatitis, gingivitis, appendicitis, pancreatitis, cholecystitis, polycythemia vera, essential thrombocythemia, and polycystic kidney disease.

[0225] In some embodiments, the disease or condition is selected from the group consisting of systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiple sclerosis, Sjogren's syndrome, psoriasis, autoimmune hemolytic anemia, asthma, ulcerative colitis, Crohn's disease, irritable bowel disease, and chronic obstructive pulmonary disease, cutaneous lupus erythematosus, systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiple sclerosis, Sjogren's syndrome, psoriasis, autoimmune hemolytic anemia, asthma, ulcerative colitis, Crohn's disease, irritable bowel disease, and chronic obstructive pulmonary disease.

[0226] In some embodiments, the disease or condition is selected from the group consisting of asthma, rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease, and systemic lupus erythematosus. In some embodiments, wherein the disease or condition is rheumatoid arthritis. In some embodiments, the subject is human.

[0227] In some embodiments, this disclosure provides the methods as described herein, wherein the crystalline form is administered intravenously, intramuscularly, parenterally, nasally or orally. In some embodiments, the crystalline form is administered QD orally. In some embodiments, the crystalline form is administered BID orally.

[0228] In some embodiments, this disclosure provides crystalline forms of Compound I or crystalline forms of salts of Compound I, as described herein, for use in therapy. In some embodiments, this disclosure provides a use of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, as described herein, in the manufacture of a

medicament for the treatment of a disease or condition selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease, and a cancer.

[0229] In some embodiments, this disclosure provides a use of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, as described herein, in the manufacture of a medicament for the treatment of rheumatoid arthritis.

[0230] In some embodiments, this disclosure provides a use of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, as described herein, in the manufacture of a medicament for the treatment of a hematologic malignancy. In some embodiments, the hematologic malignancy is lymphoma, multiple myeloma or leukemia.

Monotherapy and Combination Therapies

[0231] Also provided are methods of treatment in which a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I is the only active agent given to a subject and also includes methods of treatment in which a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, is given to a subject in combination with one or more additional active agents. Both monotherapy and combination therapies are intended and described for use in the methods detailed herein, such as in a method of treating any of the diseases or conditions detailed herein and for use with any subject detailed herein.

Monotherapy

[0232] In some embodiments, a method of treating cancer, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction comprises administering to a subject in need thereof an effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, wherein the subject is not undergoing therapy for the same disease or condition with another agent or procedure.

[0233] In some embodiments where the crystalline form is administered as a monotherapy to the subject who has been diagnosed with or is suspected of having a cancer, the subject may be a human who is (i) refractory to at least one anti-cancer therapy, or (ii) in relapse after treatment with at least one anti-cancer therapy, or both (i) and (ii). In some of embodiments, the subject is refractory to at least two, at least three, or at least four anti-cancer therapies (including, for example, standard or experimental chemotherapies). For example, in some embodiments, the subject may be a human who is (i) refractory to a therapy using an anti-CD20 antibody, an

alkylating agent (*e.g.*, bendamustine), a purine analog (*e.g.*, fludarabine), an anthracycline, or any combination thereof; (ii) in relapse after treatment with an anti-CD20 antibody, an alkylating agent (*e.g.*, bendamustine), a purine analog (*e.g.*, fludarabine), an anthracycline, or any combination thereof, or both (i) and (ii).

[0234] A human subject who is refractory to at least one anti-cancer therapy and/or is in relapse after treatment with at least one anti-cancer therapy, as described above, may have undergone one or more prior therapies. In some embodiments, such subjects have undergone one, two, three, or four, or at least one, at least two, at least three, at least four, or at least five, or between one and ten, between one and nine, between one and eight, between one and seven, between one and six, between one and five, or between one and four, anti-cancer therapies prior to treatment using the methods described herein (*e.g.*, prior to the administration of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, as a monotherapy).

[0235] It should be understood that when a subject (*e.g.* a human) is treated with of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, as a monotherapy, the subject may also undergo one or more other therapies that are not anti-cancer therapies.

[0236] In some embodiments, a method of treating a comorbidity of a cancer, including but not limited to CLL, in a subject (*e.g.*, a human) who has been diagnosed with cancer, *e.g.* CLL, wherein the method comprises administering a therapy to treat the comorbidity in combination with a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, or a pharmaceutical composition thereof, to the subject. In some embodiments, the comorbidity is selected from the group consisting of one or more other cancers (*e.g.* breast, head and neck, lung, melanoma, non-Hodgkin's T-cell lymphoma, prostate, colon, small intestine, gynecologic and urinary tract), hypertension, hyperlipidemia, coronary artery disease, peripheral vascular diseases, cardiomyopathy, valvular heart disease, atrial fibrillation, cerebrovascular disease (*e.g.* transient ischemic attack, stroke), chronic obstructive pulmonary disease, joint disease, peptic ulcer, inflammatory bowel disease, psychiatric illness, thyroid disease, benign prostate hyperplasia, diabetes mellitus, and osteoarthritis.

Combination Therapies

[0237] In some embodiments, a method of treating cancer, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction comprises

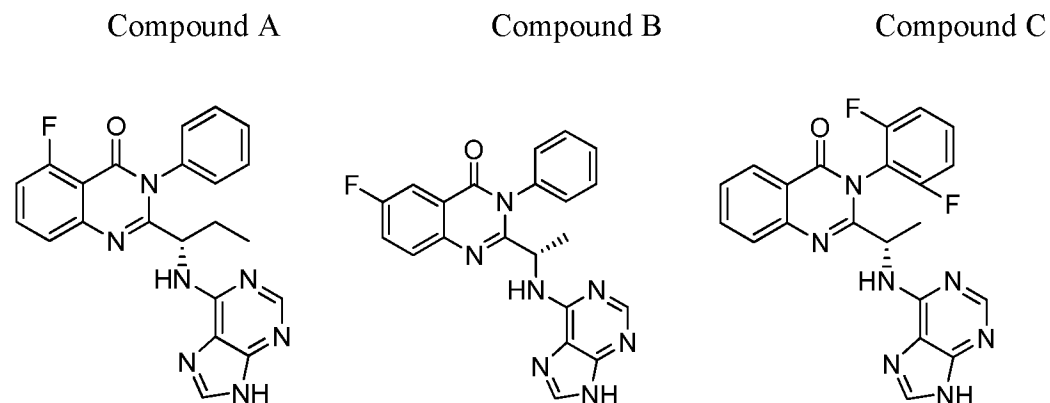
administering to a subject in need thereof an effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, together with a second active agent, which can be useful for treating a cancer, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction. For example the second agent may be an anti-inflammatory agent. Treatment with the second active agent may be prior to, concomitant with, or following treatment with a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I. In some embodiments, a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, is combined with another active agent in a single dosage form. In one embodiment, the invention provides a product comprising a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, and an additional therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy, *e.g.* a method of treating a cancer, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction.

[0238] Provided herein are also methods of treatment in which the a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, administered to a subject (*e.g.*, a human) who has been diagnosed with or is suspected of having a cancer is given to the subject in combination with one or more additional therapies, including one or more of the anti-cancer therapies described above. Thus, in some embodiments, the method for treating cancer in a subject (*e.g.*, a human) in need thereof, comprises administering to the subject a therapeutically effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, together with one or more additional therapies, which can be useful for treating the cancer. The one or more additional therapies may involve the administration of one or more therapeutic agents. Suitable anti-cancer therapeutics that may be used in combination with a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I include, but are not limited to, one or more agents selected from the group consisting of chemotherapeutic agents (*e.g.* mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, doxorubicin), radiotherapeutic antitumor agents, topoisomerase I inhibitors (*e.g.* camptothecin or topotecan), topoisomerase II inhibitors (*e.g.* daunomycin and etoposide), alkylating agents (*e.g.* cyclophosphamide, melphalan and BCNU), tubulin directed agents (*e.g.* taxol and vinblastine), PI3K inhibitors (*e.g.* compounds A, B, and C below), inhibitors of lysyl oxidase-like 2, and biological agents (*e.g.* antibodies such as anti CD20 antibody, IDEC 8, immunotoxins, and cytokines).

[0239] In some embodiments, the method for treating cancer in a subject (*e.g.*, a human) in need thereof, comprises administering to the subject a therapeutically effective amount of a compound of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, or a pharmaceutical composition thereof with one or more additional therapies selected from the group consisting of fludarabine, rituximab, obinutuzumab, alemtuzumab, cyclophosphamide, chlorambucil, doxorubicin, doxorubicin hydrochloride, vincristine, vincristine sulfate, melphalan, busulfan, carmustine, prednisone, prednisolone, dexamethasone, methotrexate, cytarabine, mitoxantrone, mitoxantrone hydrochloride, bortezomib, temsirolimus, carboplatin, etoposide, thalidomide, cisplatin, lumiliximab, anti-TRAIL, bevacizumab, galiximab, epratuzumab, SGN-40, anti-CD74, ofatumumab, ha20, PRO131921, CHIR-12.12, apolizumab, milatuzumab, bevacizumab, yttrium-90-labeled ibritumomab tiuxetan, tositumomab, iodine-131 tositumomab, ifosfamide, GTO-99 vaccine, oblimersen, flavopiridol, PD0332991, R-roscovitine, styryl sulfones, Obatoclox, TRAIL, Anti-TRAIL DR4 and DR5 antibodies, Everolimus, BMS-345541, Curcumin, Vorinostat, lenalidomide, Geldanamycin, perifosine, sildenafil citrate, CC-5103, simvastatin, enzastaurin, campath-1H, DT PACE, antineoplaston A10, antineoplaston AS2-1, beta alethine, filgrastim, recombinant interferon alfa, dolastatin 10, indium In 111 monoclonal antibody MN-14, anti-thymocyte globulin, cyclosporine, mycophenolate mofetil, therapeutic allogeneic lymphocytes, tacrolimus, thiotepa, paclitaxel, aldesleukin, docetaxel, ifosfamide, mesna, recombinant interleukin-12, recombinant interleukin-11, ABT-263, denileukin difitox, tanespimycin, everolimus, pegfilgrastim, vorinostat, alvocidib, recombinant flt3 ligand, recombinant human thrombopoietin, lymphokine-activated killer cells, amifostine trihydrate, aminocamptothecin, irinotecan hydrochloride, caspofungin acetate, clofarabine, epoetin alfa, nelarabine, pentostatin, sargramostim, vinorelbine ditartrate, WT-1 analog peptide vaccine, WT1 126-134 peptide vaccine, fenretinide, ixabepilone, oxaliplatin, monoclonal antibody CD19, monoclonal antibody CD20, omega-3 fatty acids, octreotide acetate, motexafin gadolinium, arsenic trioxide, tipifarnib, autologous human tumor-derived HSPPC-96, veltuzumab, bryostatin 1, PEGylated liposomal hydrochloride, peripheral blood stem cell transplantation, autologous hematopoietic stem cell transplantation, autologous bone marrow transplantation, infusion of stem cells, bone marrow ablation with stem cell support, *in vitro*-treated peripheral blood stem cell transplantation, umbilical cord blood transplantation, low-LET cobalt-60 gamma ray therapy, bleomycin, conventional surgery, radiation therapy, and nonmyeloablative allogeneic hematopoietic stem cell transplantation.

[0240] In some embodiments, the one or more additional therapies involve the use of a phosphatidylinositol 3-kinase (PI3K) inhibitor, including for example, Compounds A, B or C, or

a pharmaceutically acceptable salt of such compounds. The structures of Compounds A, B and C are provided below.



[0241] In other embodiments of the methods described above involving the use of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with one or more additional therapies, the one or more additional therapies is other than a therapy using Compound A, Compound B, or Compound C, or a pharmaceutically acceptable salt or a co-crystal of such compounds. In one embodiment of the methods described above involving the use of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with one or more additional therapies, the one or more additional therapies is other than a therapy using Compound A, or a pharmaceutically acceptable salt. In another embodiment of the methods described above involving the use of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with one or more additional therapies, the one or more additional therapies is other than a therapy using Compound B, or a pharmaceutically acceptable salt or co-crystal thereof. In yet another embodiment of the methods described above involving the use of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with one or more additional therapies, the one or more additional therapies is other than a therapy using Compound C, or a pharmaceutically acceptable salt or co-crystal thereof.

[0242] In other embodiments, the one or more additional therapeutic agent may be an inhibitors of lysyl oxidase-like 2 (LOXL2) and a substance that bind to LOXL2, including for example, a humanized monoclonal antibody (mAb) with an immunoglobulin IgG4 isotype directed against human LOXL2.

[0243] The crystalline forms of Compound I or the crystalline forms of a salt or a co-crystal of Compound I, as described herein, can be useful as chemosensitizing agents, and, thus, can be

useful in combination with other chemotherapeutic drugs, in particular, drugs that induce apoptosis.

[0244] A method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a subject (*e.g.*, human) undergoing chemotherapy a chemotherapeutic agent together with a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, or a pharmaceutical composition thereof, in an amount sufficient to increase the sensitivity of cancer cells to the chemotherapeutic agent is also provided herein. Examples of other chemotherapeutic drugs that can be used in combination with chemical entities described herein include topoisomerase I inhibitors (camptothecin or topotecan), topoisomerase II inhibitors (*e.g.* daunomycin and etoposide), alkylating agents (*e.g.* cyclophosphamide, melphalan and BCNU), tubulin directed agents (*e.g.* taxol and vinblastine), and biological agents (*e.g.* antibodies such as anti CD20 antibody, IDEC 8, immunotoxins, and cytokines). In one embodiment of the method for increasing sensitivity of cancer cells to chemotherapy, the chemotherapeutic agent is other than Compound A, or a pharmaceutically acceptable salt or co-crystal thereof. In another embodiment of the method for increasing sensitivity of cancer cells to chemotherapy, the chemotherapeutic agent is other than Compound B, or a pharmaceutically acceptable salt or co-crystal thereof. In yet another embodiment of the method for increasing sensitivity of cancer cells to chemotherapy, the chemotherapeutic agent is other than Compound C, or a pharmaceutically acceptable salt or co-crystal thereof.

[0245] In some embodiments, a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, is used in combination with Rituxan® (Rituximab) or other agents that work by selectively depleting CD20+ B-cells.

[0246] Included herein are methods of treating cancer, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction comprising administering to a subject in need thereof an effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, or a pharmaceutical composition thereof, in combination with an anti-inflammatory agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX- 2 specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor receptor (TNF) receptors antagonists, immunosuppressants and methotrexate. Examples of NSAIDs include, but are not limited to ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone,

sulfasalazine, tolmetin sodium, and hydroxychloroquine. Examples of NSAIDs also include COX-2 specific inhibitors (*i.e.*, a compound that inhibits COX-2 with an IC₅₀ that is at least 50-fold lower than the IC₅₀ for COX-1) such as celecoxib, valdecoxib, lumiracoxib, etoricoxib and/or rofecoxib.

[0247] In a further embodiment, the anti-inflammatory agent is a salicylate. Salicylates include but are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates. The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be chosen from cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone. In some embodiments, the anti-inflammatory therapeutic agent is a gold compound such as gold sodium thiomalate or auranofin. In some embodiments, the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

[0248] In some embodiments, combinations in which at least one anti-inflammatory compound is an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as entanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody are used.

[0249] In some embodiments, combinations in which at least one therapeutic agent is an immunosuppressant compound such as methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, or mycophenolate mofetil are used.

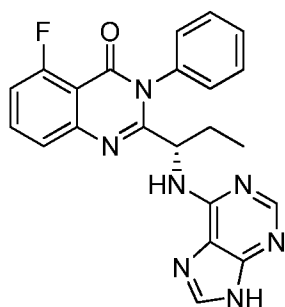
[0250] In some embodiments, combinations with filgotinib are used. In some embodiments, combinations with methotrexate are used.

[0251] Provided herein are also methods of treatment in which a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, administered to a subject (*e.g.*, a human) who has been diagnosed with or is suspected of having an autoimmune disease is given to the subject in combination with one or more anti-inflammatory or immunosuppressant agents selected from the group consisting of ibuprofen, flurbiprofen, naproxen, naproxen sodium, diclofenac, diclofenac sodium, misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, hydroxychloroquine, celecoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, acetylsalicylic acid, sodium salicylate, choline salicylate, magnesium salicylate, cortisone, dexamethasone, methylprednisolone, prednisolone,

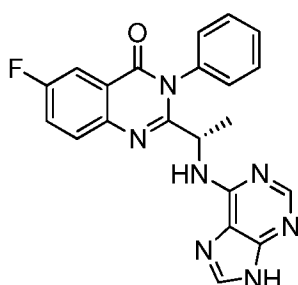
prednisolone sodium phosphate, prednisone, gold sodium thiomalate, auranofin, methotrexate, dihydroorotate leflunomide, leflunomide, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, eculizumab, pexelizumab, entanercept, and infliximab.

[0252] Provided herein are methods of treatment in which a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, administered to a subject (*e.g.*, a human) is the only anti-cancer therapy regimen administered to the subject. Provided herein are methods of treatment in which a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, administered to a subject (*e.g.*, a human), wherein the subject is not undergoing any other anti-cancer treatments. In one variation, the subject is not undergoing any other anti-cancer treatments using one or more PI3K inhibitors. Such PI3K inhibitors may include, in certain embodiments, Compounds A, B and C, whose structures are provided below.

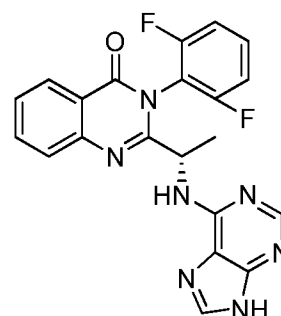
Compound A



Compound B



Compound C



[0253] In one variation, the subject is not undergoing any other anti-cancer treatments using Compound A, or a pharmaceutically acceptable salt thereof. In another variation, the subject is not undergoing any other anti-cancer treatments using Compound B, or a pharmaceutically acceptable salt thereof. In yet another variation, the subject is not undergoing any other anti-cancer treatments using Compound C, or a pharmaceutically acceptable salt thereof.

[0254] In some embodiments where a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy treatment regimen to the subject, the subject may be a human who is (i) refractory to at least one anti-cancer therapy, or (ii) in relapse after treatment with at least one anti-cancer therapy, or both (i) and (ii). In some of

embodiments, the subject is refractory to at least two, at least three, or at least four anti-cancer therapy (including, for example, standard or experimental chemotherapies).

[0255] It should be understood that when a subject (*e.g.* a human) is treated with a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, as a monotherapy treatment regimen as described by this disclosure, the subject may also undergo one or more other therapies that are not anti-cancer therapies.

[0256] In some embodiments, there is provided a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, and a therapeutically effective amount of a vinca-alkaloid, or a pharmaceutically acceptable salt, wherein: the vinca-alkaloid is selected from the group consisting of vincristine, vindesine, vinorelbine and vinblastine, and the subject is a human who is (i) refractory to at least one anti-cancer treatment, or (ii) in relapse after treatment with at least one anti-cancer therapy, or a combination thereof. In certain other embodiments, there is provided a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt, and a therapeutically effective amount of a vinca-alkaloid, or a pharmaceutically acceptable salt, wherein the vinca-alkaloid is selected from the group consisting of vincristine, vindesine, vinorelbine and vinblastine, and wherein further the subject is a human who is not undergoing any other anti-cancer treatments; and the subject is (i) refractory to at least one anti-cancer treatment, or (ii) in relapse after treatment with at least one anti-cancer therapy, or a combination thereof.

[0257] In some embodiments, there is provided a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, and a therapeutically effective amount of a vinca-alkaloid, or a pharmaceutically acceptable salt, wherein: the vinca-alkaloid is selected from the group consisting of vincristine and vinblastine, and the subject is a human who is (i) refractory to at least one anti-cancer treatment, or (ii) in relapse after treatment with at least one anti-cancer therapy, or a combination thereof. In certain other embodiments, there is provided a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt, and a therapeutically effective amount of a

vinca-alkaloid, or a pharmaceutically acceptable salt, wherein the vinca-alkaloid is selected from the group consisting of vincristine and vinblastine, and wherein further the subject is a human who is not undergoing any other anti-cancer treatments; and the subject is (i) refractory to at least one anti-cancer treatment, or (ii) in relapse after treatment with at least one anti-cancer therapy, or a combination thereof.

[0258] In one embodiment, there is provided a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, and a therapeutically effective amount of a vinca-alkaloid, or a pharmaceutically acceptable salt, wherein the vinca-alkaloid is vincristine, and the subject is a human who is (i) refractory to at least one anti-cancer treatment, or (ii) in relapse after treatment with at least one anti-cancer therapy, or a combination thereof. In one other embodiment, there is provided a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt, and a therapeutically effective amount of a vinca-alkaloid, or a pharmaceutically acceptable salt, wherein the vinca-alkaloid is vincristine, and wherein further the subject is a human who is not undergoing any other anti-cancer treatments; and the subject is (i) refractory to at least one anti-cancer treatment, or (ii) in relapse after treatment with at least one anti-cancer therapy, or a combination thereof.

[0259] In one embodiment, there is provided a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, and a therapeutically effective amount of a vinca-alkaloid, or a pharmaceutically acceptable salt, wherein: wherein the vinca-alkaloid is vinblastine, and the subject is a human who is (i) refractory to at least one anti-cancer treatment, or (ii) in relapse after treatment with at least one anti-cancer therapy, or a combination thereof. In one other embodiment, there is provided a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt, and a therapeutically effective amount of a vinca-alkaloid, or a pharmaceutically acceptable salt, and wherein further the subject is a human who is not undergoing any other anti-cancer treatments; and the subject is (i) refractory to at least one anti-cancer treatment, or (ii) in relapse after treatment with at least one anti-cancer therapy, or a combination thereof.

[0260] In yet other embodiments where a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy treatment regimen to the subject, the subject may have a 17p deletion, a TP53 mutation, NOTCH1, a SF3B1 mutation, a 11q deletion, or any combination thereof. In some embodiments where a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy treatment regimen to the subject, the subject has a 17p deletion, a TP53 mutation, or a combination thereof. In another embodiments a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, is administered as a monotherapy treatment regimen to the subject, the subject has NOTCH1, a SF3B1 mutation, a 11q deletion, or any combination thereof.

[0261] Provided herein are also methods of treatment in which a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, in combination with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, administered to a subject (*e.g.*, a human) is given to a subject (*e.g.*, a human) in additional combination with one or more additional therapies, including one or more of the anti-cancer therapies described above. Thus, in some embodiments, the method for treating cancer in a subject (*e.g.*, a human) in need thereof, comprises administering to the subject a therapeutically effective amount of a crystalline form of Compound I or a crystalline form of a salt or a co-crystal of Compound I, or a pharmaceutical composition thereof, in combination with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, together with one or more additional therapies, which can be useful for treating the cancer. The one or more additional therapies may involve the administration of one or more therapeutic agents as described herein.

[0262] For example, in other embodiments, the one or more additional therapeutic agent may be an inhibitors of lysyl oxidase-like 2 (LOXL2) and a substance that bind to LOXL2, including for example, a humanized monoclonal antibody (mAb) with an immunoglobulin IgG4 isotype directed against human LOXL2.

[0263] In other embodiments, the one or more additional therapeutic agent may be an anti-inflammatory agent. Treatment with the one or more additional therapeutic agent may be prior to, concomitant with, or following treatment with the pharmaceutical composition described herein. In some embodiments, the pharmaceutical composition described herein, is combined

with another therapeutic agent in a single dosage form, which is then administered prior to, concomitant with or subsequent to administration with a vinca-alkaloid, or a pharmaceutically acceptable salt thereof, of this disclosure. Suitable antitumor therapeutics that may be used in combination with at least one chemical entity described herein include, but are not limited to, chemotherapeutic agents, for example mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, doxorubicin, or a combination comprising at least one of the foregoing chemotherapeutic agents. Radiotherapeutic antitumor agents may also be used, alone or in combination with chemotherapeutic agents.

[0264] It should be understood that any combinations of the additional therapeutic agents described above may be used, as if each and every combination was individually listed. For example, in some embodiments, the additional therapeutic agents include a PI3K inhibitor and a LOXL2 inhibitor.

[0265] It should be understood that any combinations of the additional therapeutic agents described above may be used, as if each and every combination was individually listed. For example, in some embodiments, the additional therapeutic agents include a PI3K inhibitor and a LOXL2 inhibitor.

EXAMPLES

Instrumental Techniques

X-Ray Powder Diffraction (XRPD)

[0266] X-ray powder diffraction (XRPD) analysis was conducted on a diffractometer (PANalytical XPERT-PRO, PANalytical B. V., Almelo, Netherlands) using copper radiation ($\text{Cu K}\alpha$, $\lambda = 1.541874 \text{ \AA}$). Samples were spread evenly on a zero background sample plate. The generator was operated at a voltage of 45 kV and amperage of 40 mA. Slits were Soller 0.02 rad, antiscatter 1.0° , and divergence. Scans were performed from 2 to $40^\circ 2\theta$ with a 0.0167 step size. Data analysis was performed using X'Pert Data Viewer V1.2d (PANalytical B.V., Almelo, Netherlands). X-ray powder diffraction analysis was also conducted on a diffractometer (Rigaku MiniFlex, Rigaku Corporation, Beijing, China) using copper radiation ($\text{Cu K}\alpha$, $\lambda = 1.541874 \text{ \AA}$). Samples were spread evenly on a zero background sample plate. The generator was operated at a voltage of 40 kV and amperage of 15 mA. Scans were performed from 2 to $40^\circ 2\theta$ with a 0.050 degree step size and a speed of 2 degrees/minute. Data analysis was also

performed using X'Pert Data Viewer V1.2d (PANalytical B.V., Almelo, Netherlands). The XRPD peaks are in the range of $\pm 0.2^\circ 2\theta$.

Differential Scanning Calorimetry (DSC)

[0267] Differential Scanning Calorimetry (DSC) was run by loading 1-5 mg of material into a crimped Tzero standard aluminum pan and heating the sample at $10^\circ\text{C}/\text{min}$ from 20°C to 300°C or above. The sample and reference pans were under a $50\text{ mL}/\text{min}$ nitrogen purge. Data analysis was completed using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE). The DSC endotherm peaks and onset temperatures are in the range of $\pm 3^\circ\text{C}$.

Thermogravimetric Analysis (TGA)

[0268] Thermogravimetric analysis (TGA) was used to evaluate sample weight loss as a function of temperature by loading 1-10 mg of material onto a an aluminum weigh pan (TA Instruments, New Castle, DE) and heated the sample to 350°C or above at a rate of $10^\circ\text{C}/\text{min}$. The sample and reference pans were under a $60\text{ mL}/\text{min}$ and $40\text{ mL}/\text{min}$ nitrogen purge, respectively. Data analysis was completed using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE).

[0269] Thermogravimetric analysis with Mass Spectrometry (TA Discovery Series TGA and MS) was used to determine what was associated with the sample weight loss as a function of temperature (TA Instruments, New Castle). A sample ($\sim 2 - 5\text{ mg}$) was placed in a platinum pan and heated up to 300°C or above at a heating rate of $10 - 20^\circ\text{C}/\text{min}$. The sample and reference pans were under a $25\text{ mL}/\text{min}$ and $10\text{ mL}/\text{min}$ nitrogen purge, respectively. Data analysis was completed using TA Instruments Trios Software v. 4.0 (TA Instruments, New Castle, DE).

Dynamic Vapor Sorption/Desorption (DVS)

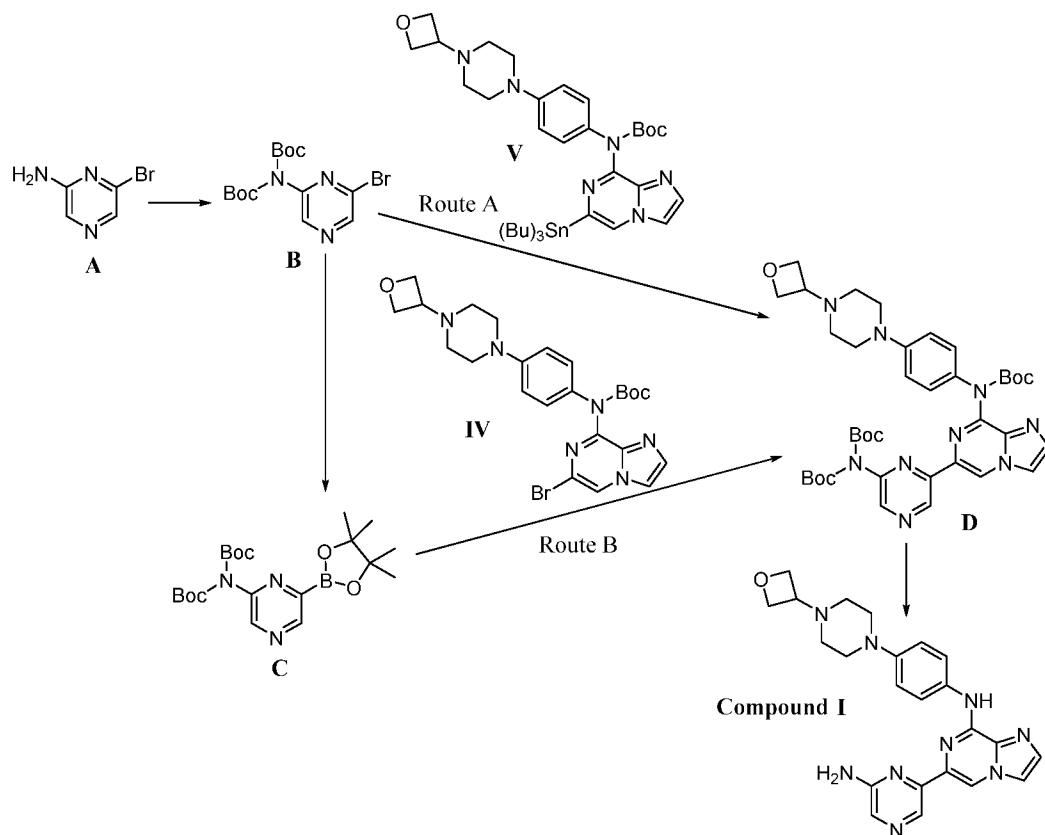
[0270] Hygroscopicity was studied using dynamic vapor sorption (DVS, TA Q5000 SA, TA Instruments, New Castle, DE or DVS, DVS Intrinsic, Surface Measurement Systems, London, UK). A sample (2-20 mg) was placed in an aluminum DVS pan and loaded on the sample side of the twin pan balance. The water sorption and desorption were studied as a function of relative humidity (RH) at 25°C . In 10% RH increments, the relative humidity was increased from 5% RH to 95% RH and then decreased back to 5%. Each relative humidity increment had an equilibration time of 180 minutes, unless weight change % was less than 0.002% in 30

minutes. Data analysis was performed using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE) for TA DVS runs and Microsoft Excel for SMS DVS runs.

Example 1: Preparation of Compound I

[0271] Compound I was synthesized as shown in Scheme I below:

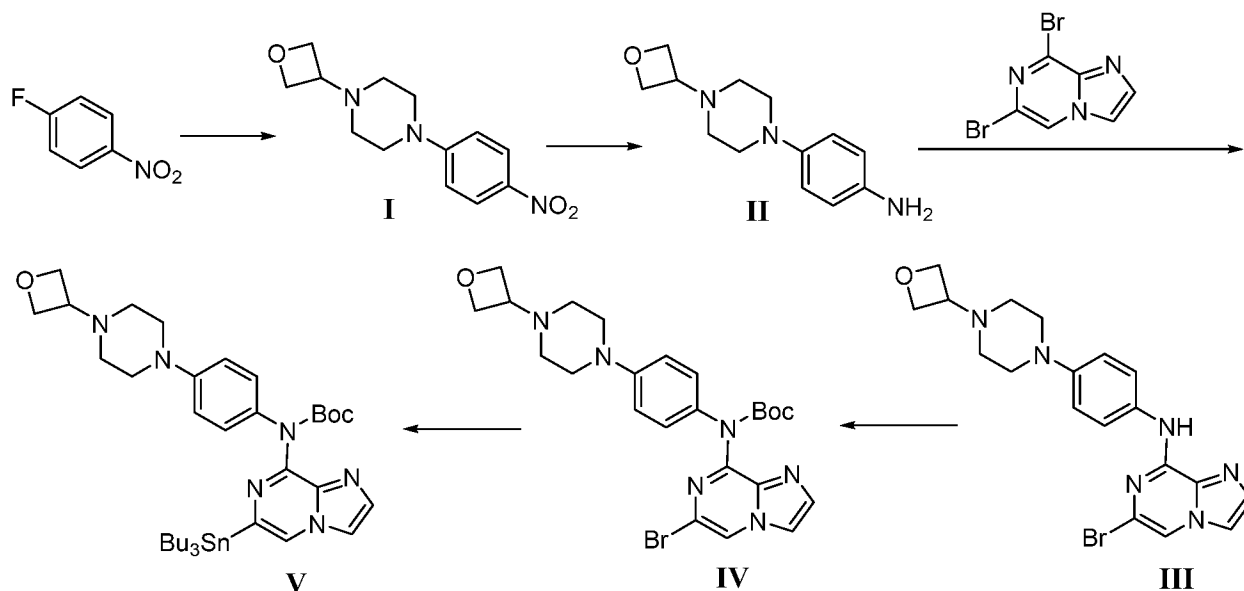
Scheme I



[0272] The compounds IV and V in Scheme I were prepared as shown in scheme II below.

Preparation of tert-Butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate IV and tert-butyl 4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate V

Scheme II



[0273] 1-(4-Nitrophenyl)-4-(oxetan-3-yl)piperazine I: In a 500 mL round bottom flask, 1-(oxetan-3-yl)piperazine (3.02 g, 21.26 mmoles), potassium carbonate (5.87 g, 42.52 mmoles), 1-fluoro-4-nitrobenzene (3.00 g, 21.26 mmoles) was combined in acetonitrile (33 mL) and stirred under nitrogen overnight at 100 °C. The mixture was diluted with water (100 mL) and extracted with DCM (100 mL x 3), dried over anhydrous sodium carbonate, filtered and the filtrate was concentrated. The residue was dissolved in minimal DCM using a sonicator and crashed out with hexane. The precipitate was filtered, washed with hexane and dried to provide the title Compound I.

[0274] 4-(4-(Oxetan-3-yl)piperazin-1-yl)aniline II: In a hydrogenation vessel, 1-(4-nitrophenyl)-4-(oxetan-3-yl)piperazine I (4.70 g, 17.85 mmoles) was dissolved as much as possible in MeOH (26 mL) and DCM (5 mL). Pd/C (10%) (2.85 g, 2.68 mmoles) was added and the reaction was stored under nitrogen. The reaction was shaken on the Parr hydrogenator at 45 PSI. After 15 minutes, the reaction was fully recharged to 45 PSI and shaken for an additional hour. The material was filtered over celite, washed with 25% MeOH/DCM and concentrated to provide the title Compound II.

[0275] 6-Bromo-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine III: To 4-(4-(oxetan-3-yl)piperazin-1-yl)aniline II (2.00 g, 8.57 mmoles), Hunig's base

(3.29 mL) and 6,8-dibromoimidazo[1,2-a]pyrazine (2.37 g, 8.57 mmol) was added in DMF (43 mL). The reaction was stirred at 85 °C in a pressure tube for overnight. The material was quenched with saturated sodium bicarbonate, extracted with DCM (120 mL x 3) and the organic layers were combined and washed with water (120 mL x 3), dried over anhydrous sodium carbonate and concentrated. The crude material was purified using a 120 g Isco column and eluted off using a stepwise gradient of 0-60% (10% MeOH/DCM). The desired fractions were combined and concentrated to provide the title Compound III.

[0276] tert-Butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate IV: 6-bromo-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine III (1000 mg, 2.33 mmol), di-tert-butyl dicarbonate (1016.72 mg, 4.66 mmol) and N,N-dimethylpyridin-4-amine (21.34 mg, 0.17 mmol) were stirred in DCM (1.01 mL) and refluxed at 65 °C for 3h. The reaction was diluted with 100 mL of DCM, washed with H₂O (x3), dried, filtered and concentrated. The crude material was dissolved in minimal DCM, loaded onto a preloaded silica loader and eluted off a 40 g column using 0-30% MeOH/DCM over 20 column volumes. The desired fractions were combined and concentrated to provide the title compound. This compound is used in Example 2.

[0277] tert-Butyl 4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate V: In a 350 mL p-tube, tert-butyl 6-bromoimidazo[1,2-a]pyrazin-8-yl(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate IV (8150 mg, 15.39 mmol), 1,1,1,2,2,2-hexabutylstannane (11.67 mL, 23.09 mmol), tetrakis(triphenylphosphine)palladium (889.43 mg, 0.77 mmol), and tetrabutylammonium iodide (5686.03 mg, 15.39 mmol) were combined in dioxane (62 mL) and heated to 110 °C overnight. According to LCMS, no starting material remained. The reaction was absorbed onto celite and eluted off a 160 g alumina column using a 0-10-20-30-100% (50% EtOAc/Hex-Hex) gradient holding at 50% for 10-15 column volumes over 50-60 column volumes to provide the title compound V.

[0278] 2-Bis(tert-butoxycarbonyl)amino-6-bromopyrazine B: To a mixture of 6-bromopyrazin-2-amine (5 g, 28.7 mmol) and di-tert-butyl dicarbonate (25.09 g, 114.94 mmol) was added DCM (10 mL) followed by DMAP (0.351 g, 29 mmol). The reaction was heated to 55 °C for 1h, cooled to RT, the reaction was partitioned between water and DCM, purified on silica gel and concentrated to provide of 2-bis(tert-butoxycarbonyl)amino-6-bromopyrazine B. LCMS-ESI⁺ (*m/z*): [M+H]⁺: 374.14. ¹H NMR (DMSO) δ: 8.84(d, 2H), 1.39 (s, 18H).

[0279] tert-Butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate D – route A: tert-Butyl 4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate **V** (215 mg, 0.291 mmol), was combined with 2-bis(tert-butoxycarbonyl)amino-6-bromopyrazine **XIV** (217.58 mg, 0.581 mmol), bis(triphenylphosphine)palladium(II) dichloride (30.61 mg, 0.044 mmol) and 1,4-dioxane (5ml). The reaction mixture was stirred in a microwave reactor at 120 °C for 30 min. The reaction mixture was quenched with saturated KF, extracted with EtOAc, purified on silica gel, eluted with EtOAc. The desired fractions were combined and concentrated to provide 100 mg (46% yield) of tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate **D**. LCMS-ESI⁺ (*m/z*): [M+H]⁺: 744.4. ¹H NMR (300 MHz d₆-DMSO) δ: 9.37 (s, 1H), 9.18 (s, 1H), 8.77 (s, 1H), 8.33 (d, 1H), 7.87 (d, 1H), 7.28-7.25 (d, 2H), 6.92-6.89 (d, 2H), 4.55-4.41 (m, 4H), 3.4 (m, 1H), 3.14-3.11 (m, 4H), 2.37-2.34 (m, 4H), 1.37 (s, 18H), 1.3 (s, 9H).

[0280] tert-Butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate D – route B: Step 1: To a dry 250 mL round-bottomed flask was added 2-bis(tert-butoxycarbonyl)amino-6-bromopyrazine **B** (1.0 g, 1.0 equiv, 2.67 mmol), KOAc (790 mg, 8.02 mmol, 3.0 equiv), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (750 mg, 2.94 mmol, 1.1 equiv), Pd₂(dba)₃ (171 mg, 0.187 mmol, 0.07 equiv) and X-phos (128 mg, 0.267 mmol, 0.1 equiv) followed by 1,4-dioxane (25 mL) and the solution was sonicated for 5 min and then purged with N₂ gas for 5 min. The flask with contents was then placed under N₂ atmosphere and heated at 110 °C for 90 min. Once full conversion to the pinacolboronate was achieved by LCMS, the reaction was removed from heat and allowed to cool to RT. Once cool, the reaction contents were filtered through Celite and the filter cake was washed 3 x 20 mL EtOAc. The resultant solution was then concentrated down to a deep red-orange syrup providing N, N-BisBoc 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-amine **C**, which was used directly in the next step.

[0281] Step 2: The freshly formed N, N-Bis-Boc-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-amine **C** (2.67 mmol based on 100% conversion, 2.0 equiv based on bromide) was dissolved in 20 mL of 1,2-dimethoxyethane and to that solution was added tert-butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate **IV** (707 mg, 1.34 mmol, 1.0 equiv), Na₂CO₃ (283 mg, 2.67 mmol, 2.0 equiv), Pd(PPh₃)₄ (155 mg,

0.134 mmol, 0.1 equiv) and water (10 mL) and the solution was degassed for 5 min using N₂ gas. The reaction was then placed under N₂ atmosphere and heated at 110 °C for 90 min. LCMS showed complete consumption of the bromide starting material and the reaction was removed from heat and allowed to cool to RT. The reaction was diluted with 100 mL water and 100 mL 20% MeOH/DCM and the organic layer was recovered, extracted 1 x sat. NaHCO₃, 1 x sat brine and then dried over Na₂SO₄. The solution was then filtered and concentrated down to an orange-red solid. The sample was then slurried in warm MeOH, sonicated then filtered, washing 2 x 20 mL with cold MeOH and then the cream-colored solid was dried on hi-vacuum overnight to yield 905 mg of tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate **D**.

[0282] 6-(6-Aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Compound I): To a solution of tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate **D** (200 mg, 0.269 mmol) in DCM (2 mL) was added TFA (0.5 mL, 6.578 mmol). The reaction was stirred at rt for 16h, saturated sodium bicarbonate was added, extracted with EtOAc and purified on silica gel, eluted with 5%MeOH / EtOAc, 20%MeOH / EtOAc. The desired fractions were combined and concentrated to provide **Compound I**. LCMS-ESI⁺ (*m/z*): [M+H]⁺: 444.2. ¹H NMR (300 MHz d₆-DMSO) δ: 9.5 (s, 1H), 8.588 (s, 1H), 8.47 (s, 1H), 8.12 (d, 1H), 7.95-7.92 (d, 2H), 7.88 (s, 1H), 7.62 (s, 1H), 6.99-6.96 (d, 2H), 6.46 (s, 2H), 4.57-4.53 (m, 2H), 4.48-4.44 (m, 2H), 3.43 (m, 1H), 3.15-3.12 (m, 4H), 2.41-2.38 (m, 4H).

Example 2: Preparation of Compound I Form I

[0283] Compound I Form I was prepared by slurrying about 50 mg of Compound I Form IV in EtOAc, IPAc, MEK, or 2-MeTHF at room temperature. It can also be formed by desolvating Compound I Form V and VIII at elevated temperatures. Alternatively, it can be formed by slurrying amorphous Compound I in THF, followed by filtration and drying under vacuum at 50 °C.

[0284] An X-ray powder diffractogram for Compound I Form I was obtained as described above and is shown in Figure 1. A DSC analysis was performed as described above and the DSC curve is shown in Figure 2. A TGA curve was obtained as described above and is shown in Figure 3. A DVS curve was obtained as described above and is shown in Figure 4. A single crystal structure was obtained for Compound I Form I indicating that it is a monoclinic

crystalline form having unit cell parameters: a equal to 8.62 Å, b equal to 19.71 Å, c equal to 13.46 Å, α equal to 90 °, β equal to 108.34 ° and γ equal to 90 °.

Example 3: Preparation of Compound I Form II

[0285] Compound I Form II was prepared as an unsolvated form by slurring about 50 mg of Compound I in acetonitrile at room temperature. It can also be prepared by desolvating Compound I Form IV, VI, VII, and XII at elevated temperatures.

[0286] An X-ray powder diffractogram for Compound I Form II was obtained as described above and is shown in Figure 5. A DSC analysis was performed as described above and the DSC curve is shown in Figure 6. A TGA curve was obtained as described above and is shown in Figure 7. A DVS curve was obtained as described above and is shown in Figure 8.

Example 4: Preparation of Compound I Form III

[0287] Compound I Form III was prepared by slurring a mixture of Compound I Form II and Compound I Form IV in water at room temperature.

[0288] An X-ray powder diffractogram for Compound I Form III was obtained as described above and is shown in Figure 9. A DSC analysis was performed as described above and the DSC curve is shown in Figure 10. A TGA curve was obtained as described above and is shown in Figure 11.

Example 5: Preparation of Compound I Form IV

[0289] Compound I Form IV was prepared by heating 5 mg of Compound I Succinate Form I in 1 mL of MeOH with a heat gun until the solids dissolve completely, then letting the sample cool to room temperature over a couple of days. A single crystal structure was obtained for Compound I Form IV indicating that it is a monoclinic crystalline form having unit cell parameters: a equal to 14.29 Å, b equal to 14.57 Å, c equal to 11.57 Å, α equal to 90 °, β equal to 92.41 ° and γ equal to 90 °. A calculated X-ray powder diffractogram for Compound I Form IV was obtained and is shown in Figure 73.

Example 6: Preparation of Compound I Form V

[0290] Compound I Form V was prepared by slurring Compound I Form XIV in a mixture of isopropanol and water (9:1 vol.) at room temperature.

[0291] An X-ray powder diffractogram for Compound I Form V was obtained as described above and is shown in Figure 12. A DSC analysis was performed as described above and the DSC curve is shown in Figure 13. A TGA curve was obtained as described above and is shown in Figure 14. A DVS curve was obtained as described above and is shown in Figure 15.

Example 7: Preparation of Compound I Form VI

[0292] Compound I Form VI was prepared by heating 7 mg of amorphous Compound I in 1 mL of EtOH with a heat gun until the solids dissolve completely, then letting the sample cool to room temperature. A single crystal structure was obtained for Compound I Form VI indicating that it is a monoclinic crystalline form having unit cell parameters: a equal to 14.52 Å, b equal to 14.91 Å, c equal to 11.58 Å, α equal to 90°, β equal to 91.82° and γ equal to 90°. A calculated X-ray powder diffractogram for Compound I Form VI was obtained and is shown in Figure 74.

Example 8: Preparation of Compound I Form VII

[0293] Compound I Form VII was prepared by slurring Compound I Form III in isopropanol at room temperature.

[0294] An X-ray powder diffractogram for Compound I Form VII was obtained as described above and is shown in Figure 16. A DSC analysis was performed as described above and the DSC curve is shown in Figure 17. A TGA curve was obtained as described above and is shown in Figure 18.

Example 9: Preparation of Compound I Form VIII

[0295] Compound I Form VIII was prepared by distilling off DMF from a solution of Compound I in DMF and charging heptane.

[0296] An X-ray powder diffractogram for Compound I Form VIII was obtained as described above and is shown in Figure 19. A DSC analysis was performed as described above and the DSC curve is shown in Figure 20. A TGA curve was obtained as described above and is shown in Figure 21.

Example 10: Preparation of Compound I Form IX

[0297] Compound I Form IX was prepared by slurring Compound I Form VIII in MeOH/water (1:1 vol.) at room temperature.

[0298] An X-ray powder diffractogram for Compound I Form IX was obtained as described above and is shown in Figure 22. A DSC analysis was performed as described above and the DSC curve is shown in Figure 23. A TGA curve was obtained as described above and is shown in Figure 24. A single crystal structure was obtained for Compound I Form VI indicating that it is a monoclinic crystalline form having unit cell parameters: a equal to 6.92 Å, b equal to 28.97 Å, c equal to 12.73 Å, α equal to 90 °, β equal to 92.53 ° and γ equal to 90 °.

Example 11: Preparation of Compound I Form X

[0299] Compound I Form X was prepared by slurring Compound I in dichloromethane at room temperature.

[0300] An X-ray powder diffractogram for Compound I Form X was obtained as described above and is shown in Figure 75.

Example 12: Preparation of Compound I Form XI

[0301] Compound I Form XI was prepared by slurring Compound I in THF at room temperature.

[0302] An X-ray powder diffractogram for Compound I Form XI was obtained as described above and is shown in Figure 76.

Example 13: Preparation of Compound I Form XII

[0303] Compound I Form XII was prepared by heating 5 mg of amorphous Compound I in 1 mL of acetonitrile with a heat gun until the solids dissolve completely, then letting the sample cool to room temperature.

[0304] An X-ray powder diffractogram for Compound I Form XII was obtained as described above and is shown in Figure 77. A single crystal structure was obtained for Compound I Form XII indicating that it is a monoclinic crystalline form having unit cell parameters: a equal to 14.55 Å, b equal to 14.53 Å, c equal to 11.77 Å, α equal to 90 °, β equal to 90.46 ° and γ equal to 90 °.

Example 14: Preparation of Compound I Form XIII

[0305] Compound I Form XIII was prepared by slurring Compound I Form XIV in propylene glycol at room temperature.

[0306] An X-ray powder diffractogram for Compound I Form XIII was obtained as described above and is shown in Figure 25. A single crystal structure was obtained for Compound I Form XII indicating that it is a monoclinic crystalline form having unit cell parameters: a equal to 14.55 Å, b equal to 14.53 Å, c equal to 11.77 Å, α equal to 90°, β equal to 90.46° and γ equal to 90°.

Example 15: Preparation of Compound I Form XIV

[0307] Compound I Form XIV was prepared by drying Compound I Form V in a vacuum oven at about 50 °C with a nitrogen purge overnight.

[0308] An X-ray powder diffractogram for Compound I Form XIV was obtained as described above and is shown in Figure 26. A DSC analysis was performed as described above and the DSC curve is shown in Figure 27. A TGA curve was obtained as described above and is shown in Figure 28. A DVS curve was obtained as described above and is shown in Figure 29.

Example 16: Preparation of Compound I Succinate Form I

[0309] Compound I Succinate Form I was prepared by slurring Compound I with 1.5 mol. eq. of succinic acid in THF at room temperature. Compound I Succinate Form I is disclosed in the U.S. Patent 9,290,505.

Example 17: Preparation of Compound I Sesqui-Succinate Form III

[0310] Compound I Sesqui-Succinate Form III was prepared by cooling 100 mL of EtOAc to 10 °C and then charging 5 g Compound I Form VIII and 1.6 mol. eq. succinic acid.

[0311] An X-ray powder diffractogram for Compound I Sesqui-Succinate Form III was obtained as described above and is shown in Figure 30. A DSC analysis was performed as described above and the DSC curve is shown in Figure 31. A TGA curve was obtained as described above and is shown in Figure 32.

Example 18: Preparation of Compound I Sesqui-Succinate Form IV

[0312] Compound I Sesqui-Succinate Form IV was prepared by charging 50 mg Compound I Form IV and 1.6 mol. eq. succinic acid into 1 mL of MEK at room temperature.

[0313] An X-ray powder diffractogram for Compound I Sesqui-Succinate Form IV was obtained as described above and is shown in Figure 33. A DSC analysis was performed as

described above and the DSC curve is shown in Figure 34. A TGA curve was obtained as described above and is shown in Figure 35.

Example 19: Preparation of Compound I Sesqui-Succinate Form V

[0314] Compound I Sesqui-Succinate Form V was prepared by dissolving Compound I Succinate Form I in 16 volumes of THF/Water (19:1 vol.) at 55 °C, then cooling to 30 °C to vacuum distill off water. More THF was charged into the reactor and distilled further until the KF is about 2%. The reactor contents were then cooled to about 22 °C and Compound I Sesqui-Succinate Form V was isolated.

[0315] An X-ray powder diffractogram for Compound I Sesqui-Succinate Form V was obtained as described above and is shown in Figure 36. A DSC analysis was performed as described above and the DSC curve is shown in Figure 37. A TGA curve was obtained as described above and is shown in Figure 38.

Example 20: Preparation of Compound I Hemi-Succinate Form I

[0316] Compound I Hemi-Succinate Form I was prepared by charging 16 g of amorphous Compound I and 1.5 mol. eq. succinic acid in 7 volumes of THF/water (2:1 vol.) at 60 °C, then cooling to room temperature.

[0317] An X-ray powder diffractogram for Compound I Hemi-Succinate Form I was obtained as described above and is shown in Figure 39. A DSC analysis was performed as described above and the DSC curve is shown in Figure 40. A TGA curve was obtained as described above and is shown in Figure 41. A DVS curve was obtained as described above and is shown in Figure 42. A single crystal structure was obtained for Compound I Hemi-Succinate Form I indicating that it is a monoclinic crystalline form having unit cell parameters: a equal to 15.68 Å, b equal to 9.63 Å, c equal to 17.66 Å, α equal to 90 °, β equal to 108.12 ° and γ equal to 90 °.

Example 21: Preparation of Compound I Mono-HCl salt Form I

[0318] Compound I Mono-HCl salt Form I was prepared by slurring Compound I Form IV with 10 vol. of MeOH and 1 mol. eq. of conc. HCl (aq.) at room temperature. The solids were filtered off and placed in a vacuum oven at about 25 °C.

[0319] An X-ray powder diffractogram for Compound I Mono-HCl salt Form I was obtained as described above and is shown in Figure 43. A TGA curve was obtained as described above and is shown in Figure 44.

Example 22: Preparation of Compound I Mono-HCl salt Form II

[0320] Compound I Mono-HCl salt Form II was prepared by slurrying Compound I Mono-HCl Salt Form I in water at room temperature.

[0321] An X-ray powder diffractogram for Compound I Mono-HCl salt Form II was obtained as described above and is shown in Figure 45. A TGA curve was obtained as described above and is shown in Figure 46. A DVS curve was obtained as described above and is shown in Figure 47.

Example 23: Preparation of Compound I Mono-HCl salt Form III

[0322] Compound I Mono-HCl salt Form III was prepared by charging 1 mol. eq. of conc. HCl to 10 mL of water containing 1 g of Compound I to make a solution at room temperature, then removing the water and slurrying the remaining solids in propylene glycol. The solids were initially amorphous but crystallized after about 2 years in storage at room temperature.

[0323] An X-ray powder diffractogram for Compound I Mono-HCl salt Form III was obtained as described above and is shown in Figure 48. A DSC curve was obtained as described above and is shown in Figure 49. A TGA curve was obtained as described above and is shown in Figure 50. A DVS curve was obtained as described above and is shown in Figure 51. A single crystal structure was obtained for Compound I Mono-HCl salt Form III indicating that it is a triclinic crystalline form having unit cell parameters: a equal to 11.03 Å, b equal to 12.13 Å, c equal to 12.89 Å, α equal to 66.9°, β equal to 79.52° and γ equal to 83.88°.

Example 24: Preparation of Compound I Sesqui-Adipate Form I

[0324] Compound I Sesqui-Adipate Form I was prepared by slurrying Compound I with about 2.1 mol. eq. of 0.1 N adipic acid in THF at room temperature.

[0325] An X-ray powder diffractogram for Compound I Sesqui-Adipate Form I was obtained as described above and is shown in Figure 51. A DSC curve was obtained as described above and is shown in Figure 52. A TGA curve was obtained as described above and is shown in Figure 53. A DVS curve was obtained as described above and is shown in Figure 54. A single

crystal structure was obtained for Compound I Sesqui-Adipate Form I indicating that it is a triclinic crystalline form having unit cell parameters: a equal to 8.10 Å, b equal to 13.38 Å, c equal to 16.46 Å, α equal to 71.91 °, β equal to 79.15 ° and γ equal to 76.92 °.

Example 25: Preparation of Compound I Mono-Adipate Form I

[0326] Compound I Mono-Adipate Form I was prepared by slurring Compound I with about 2.1 mol. eq. of 0.1 N adipic acid in THF at room temperature.

[0327] An X-ray powder diffractogram for Compound I Mono-Adipate Form I was obtained as described above and is shown in Figure 55. A DSC curve was obtained as described above and is shown in Figure 56. A TGA curve was obtained as described above and is shown in Figure 57. A single crystal structure was obtained for Compound I Mono-Adipate Form I indicating that it is a monoclinic crystalline form having unit cell parameters: a equal to 11.04 Å, b equal to 31.08 Å, c equal to 22.23 Å, α equal to 90.00 °, β equal to 100.23 ° and γ equal to 90.00 °.

Example 26: Preparation of Compound I Bis-Citrate Form I

[0328] Compound I Bis-Citrate Form I was prepared by slurring Compound I with about 2.1 mol. eq. of 0.1 N citric acid in THF at room temperature.

[0329] An X-ray powder diffractogram for Compound I Bis-Citrate Form I was obtained as described above and is shown in Figure 58. A DSC curve was obtained as described above and is shown in Figure 59. A TGA curve was obtained as described above and is shown in Figure 60.

Example 27: Preparation of Compound I Sesqui-Fumarate Form I

[0330] Compound I Sesqui-Fumarate Form I was prepared by slurring Compound I with about 2.1 mol. eq. of fumaric acid in THF at room temperature.

[0331] An X-ray powder diffractogram for Compound I Sesqui-Fumarate Form I was obtained as described above and is shown in Figure 61. A TGA curve was obtained as described above and is shown in Figure 62.

Example 28: Preparation of Compound I Bis-Gentisate Form I

[0332] Compound I Bis-gentisate Form I was prepared by slurring Compound I with about 2.1 mol. eq. of gentisic acid in THF at room temperature.

[0333] An X-ray powder diffractogram for Compound I Bis-gentisate Form I was obtained as described above and is shown in Figure 63. A DSC curve was obtained as described above and is shown in Figure 64. A TGA curve was obtained as described above and is shown in Figure 65. A single crystal structure was obtained for Compound I Bis-gentisate Form I indicating that it is a triclinic crystalline form having unit cell parameters: a equal to 12.06 Å, b equal to 13.73 Å, c equal to 14.88 Å, α equal to 64.57°, β equal to 73.71° and γ equal to 77.01°.

Example 29: Preparation of Compound I Mono-BSA Form I

[0334] Compound I Mono-BSA salt Form I was prepared by charging 1 mol. eq. of BSA to 10 mL of water containing 1 g of Compound I to make a solution at room temperature, then removing the water and slurring the remaining solids in MeOH.

[0335] An X-ray powder diffractogram for Compound I HCl Material A was obtained as described above and is shown in Figure 66. A DSC curve was obtained as described above and is shown in Figure 67. A TGA curve was obtained as described above and is shown in Figure 68. A DVS curve was obtained as described above and is shown in Figure 69.

Example 30: Preparation of Compound I Sesqui-Oxalate Form I

[0336] Compound I Sesqui-Oxalate Form I was prepared by charging Compound I to 1.8 eq. of oxalic acid in 16 vol. of THF at 40 °C.

[0337] An X-ray powder diffractogram for Compound I HCl Material B was obtained as described above and is shown in Figure 70. A DSC curve was obtained as described above and is shown in Figure 71. A TGA curve was obtained as described above and is shown in Figure 72.

Example 31: Preparation of Compound I HCl Material A

[0338] Compound I HCl Material A was prepared by slurring Compound I Mono-HCl Salt Form I in isopropanol at room temperature.

[0339] An X-ray powder diffractogram for Compound I Sesqui-Oxalate Form I was obtained as described above and is shown in Figure 78.

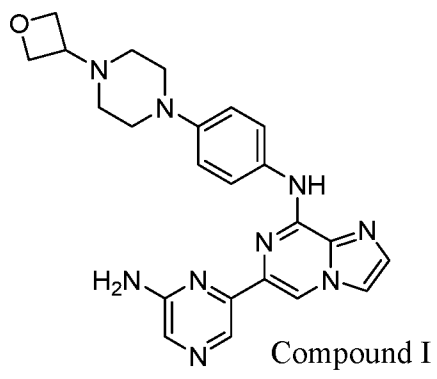
Example 32: Preparation of Compound I HCl Material B

[0340] Compound I HCl Material B was prepared by slurring Compound I Mono-HCl Salt Form I in toluene at room temperature.

[0341] An X-ray powder diffractogram for Compound I Sesqui-Oxalate Form I was obtained as described above and is shown in Figure 79.

WHAT IS CLAIMED IS:

1. A crystalline form of Compound I:



wherein the crystalline form is Compound I Form I, Compound I Form II, Compound I Form III, Compound I Form V, Compound I Form VII, Compound I Form VIII, Compound I Form IX, Compound I Form XIII or Compound I Form XIV.

2. The crystalline form of Compound I according to claim 1, wherein the crystalline form is Compound I Form I.
3. Compound I Form I according to claim 2 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 15.2, 18.0 and 20.0 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
4. Compound I Form I according claim 3, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 10.8, 20.8 and 24.4 $^\circ 2\theta$.
5. Compound I Form I according to any of claims 2-4 characterized by an X-ray powder diffractogram substantially as shown in Figure 1.
6. Compound I Form I according to any of claims 2-5 characterized by a differential scanning calorimetry (DSC) curve comprising an endotherm having an onset temperature of about 253 $^\circ\text{C}$.
7. Compound I Form I according to any of claims 2-6 characterized by a DSC curve substantially as shown in Figure 2.
8. Compound I Form I according to any of claims 2-7 characterized by:
 - i) a thermogravimetric analysis (TGA) curve substantially as shown in Figure 3; or

- ii) a dynamic vapor sorption (DVS) curve substantially as shown in Figure 4.
9. Compound I Form I according to any of claims 2-8, wherein the Compound I Form I is a monoclinic crystalline form having unit cell parameters: a equal to 8.62 Å, b equal to 19.71 Å, c equal to 13.46 Å, α equal to 90 °, β equal to 108.34 ° and γ equal to 90 °.
10. The crystalline form of Compound I according to claim 1, wherein the crystalline form is Compound I Form II.
11. Compound I Form II according to claim 10 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 19.5, 20.8 and 22.2 °2 θ as determined on a diffractometer using Cu-K α radiation.
12. Compound I Form II according to claim 11, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 18.1, 24.5 and 28.9 °2 θ .
13. Compound I Form II according to any of claims 10-12 characterized by an X-ray powder diffractogram substantially as shown in Figure 5.
14. Compound I Form II according to any of claims 10-13 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having peaks at about 162 °C and 257 °C.
15. Compound I Form II according to any of claims 10-14 characterized by a DSC curve substantially as shown in Figure 6.
16. Compound I Form II according to any of claims 10-15 characterized by:
- i) thermogravimetric analysis (TGA) curve substantially as shown in Figure 7; or
- ii) a dynamic vapor sorption (DVS) curve substantially as shown in Figure 8.
17. The crystalline form of Compound I according to claim 1, wherein the crystalline form is Compound I Form III.
18. Compound I Form III according to claim 17 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 7.6, 14.2 and 20.8 °2 θ as determined on a diffractometer using Cu-K α radiation.

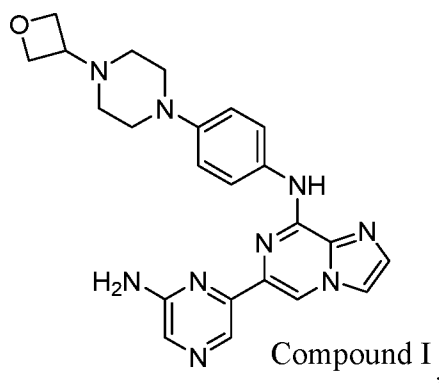
19. Compound I Form III according to claim 18, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 6.2, 9.3 and 16.9 $^\circ 2\theta$.
20. Compound I Form III according to any of claims 17-19 characterized by an X-ray powder diffractogram substantially as shown in Figure 9.
21. Compound I Form III according to any of claims 17-20 characterized by a differential scanning calorimetry (DSC) curve comprising an endotherm having an onset temperature of about 95 $^\circ\text{C}$.
22. Compound I Form III according to any of claims 17-21 characterized by a DSC curve substantially as shown in Figure 10.
23. Compound I Form III according to any of claims 17-22 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 11.
24. Compound I Form III according to any of claims 17-23, wherein Compound I Form III is a hydrated form.
25. The crystalline form of Compound I according to claim 1, wherein the crystalline form is Compound I Form V.
26. Compound I Form V according to claim 25 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 17.7, 19.7 and 22.7 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
27. Compound I Form V according to claim 26, the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 8.6, 14.0 and 20.0 $^\circ 2\theta$.
28. Compound I Form V according to any of claims 25-27 characterized by an X-ray powder diffractogram substantially as shown in Figure 12.
29. Compound I Form V according to any of claims 25-28 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having onset temperatures of about 107 $^\circ\text{C}$ and 258 $^\circ\text{C}$.
30. Compound I Form V according to any of claims 25-29 characterized by a DSC curve substantially as shown in Figure 13.

31. Compound I Form V according to any of claims 25-30 characterized by:
 - i) a thermogravimetric analysis (TGA) curve substantially as shown in Figure 14; or
 - ii) a dynamic vapor sorption (DVS) curve substantially as shown in Figure 15.
32. Compound I Form V according to any of claims 25-31, wherein Compound I Form V is a monohydrate.
33. Compound I Form V according to any of claims 25-32, wherein the Compound I Form V is a monoclinic crystalline form having unit cell parameters: a equal to 10.55 Å, b equal to 17.75 Å, c equal to 13.33 Å, α equal to 90 °, β equal to 108.3 ° and γ equal to 90 °.
34. The crystalline form of Compound I according to claim 1, wherein the crystalline form is Compound I Form VII.
35. Compound I Form VII according to claim 34 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.4, 18.6 and 20.6 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
36. Compound I Form VII according to claim 35 wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 19.0, 20.2 and 24.6 $^\circ 2\theta$.
37. Compound I Form VII according to any of claims 34-36 characterized by an X-ray powder diffractogram substantially as shown in Figure 16.
38. Compound I Form VII according to any of claims 34-37 characterized by a differential scanning calorimetry (DSC) curve comprising an endotherms having onset temperatures of about 117 °C and 153 °C.
39. Compound I Form VII according to any of claims 34-38 characterized by a DSC curve substantially as shown in Figure 17.
40. Compound I Form VII according to any of claims 34-39 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 18.
41. Compound I Form VII according to any of claims 34-40, wherein Compound I Form VII is an isopropanol solvate.

42. The crystalline form of Compound I according to claim 1, wherein the crystalline form is Compound I Form VIII.
43. Compound I Form VIII according to claim 42 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 18.3, 20.8 and 21.9 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
44. Compound I Form VIII according to claim 43, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 14.8, 25.0 and 27.4 $^\circ 2\theta$.
45. Compound I Form VIII according to any of claims 42-44 characterized by an X-ray powder diffractogram substantially as shown in Figure 19.
46. Compound I Form VIII according to any of claims 42-45 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having onset temperatures of about 133 $^\circ\text{C}$, 236 $^\circ\text{C}$ and 256 $^\circ\text{C}$.
47. Compound I Form VIII according to any of claims 42-46 characterized by a DSC curve substantially as shown in Figure 20.
48. Compound I Form VIII according to any of claims 42-47 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 21.
49. Compound I Form VIII according to any of claims 42-48, wherein Compound I Form VIII is a dimethylformamide solvate.
50. The crystalline form of Compound I according to claim 1, which is Compound I Form IX.
51. Compound I Form IX according to claim 50 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 14.0, 16.7 and 18.2 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
52. Compound I Form IX according to claim 51, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 7.6, 12.1 and 18.7 $^\circ 2\theta$.
53. Compound I Form IX according to any of claims 50-52 characterized by an X-ray powder diffractogram substantially as shown in Figure 22.

54. Compound I Form IX according to any of claims 50-53 characterized by a differential scanning calorimetry (DSC) curve comprising a broad endotherm between temperatures of about 40 °C and 110 °C.
55. Compound I Form IX according to claim 54, wherein the DSC curve further comprises an endotherm having onset temperature of about 259 °C.
56. Compound I Form IX according to any of claims 50-55 characterized by a DSC curve substantially as shown in Figure 23.
57. Compound I Form IX according to any of claims 50-56 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 24.
58. Compound I Form IX according to any of claims 50-57, wherein Compound I Form IX is a tri-hydrate mono-methanolate.
59. Compound I Form IX according to any of claims 50-58, wherein the Compound I Form IX is a monoclinic crystalline form having unit cell parameters: a equal to 6.92 Å, b equal to 28.97 Å, c equal to 12.73 Å, α equal to 90 °, β equal to 92.53 ° and γ equal to 90 °.
60. The crystalline form of Compound I according to claim 1, which is Compound I Form XIII.
61. Compound I Form XIII according to claim 60 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) ($\pm 0.2^\circ 2\theta$) at 9.6, 19.3 and 20.8 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
62. Compound I Form XIII according to claim 61, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 21.8, 22.2 and 25.4 $^\circ 2\theta$.
63. Compound I Form XIII according to any of claims 60-62 characterized by an X-ray powder diffractogram substantially as shown in Figure 25.
64. Compound I Form XIII according to any of claims 60-63, wherein Compound I Form XIII is a mono-acetonitrile solvate.
65. The crystalline form of Compound I according to claim 1, which is Compound I Form XIV.

66. Compound I Form XIV according to claim 65 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 19.4, 22.5 and 23.3 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
67. Compound I Form XIV according to claim 66, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 13.9, 16.7 and 24.3 $^\circ 2\theta$.
68. Compound I Form XIV according to any of claims 65-67 characterized by an X-ray powder diffractogram substantially as shown in Figure 26.
69. Compound I Form XIV according to any of claims 65-68 characterized by a differential scanning calorimetry (DSC) curve comprising a broad endotherm between temperatures of about 25 $^\circ\text{C}$ and 100 $^\circ\text{C}$.
70. Compound I Form XIV according to claim 69, wherein the DSC curve further comprises an endotherm having onset temperature of about 258 $^\circ\text{C}$.
71. Compound I Form XIV according to any of claims 65-70 characterized by a DSC curve substantially as shown in Figure 27.
72. Compound I Form XIV according to any of claims 65-71 characterized by:
- i) a thermogravimetric analysis (TGA) curve substantially as shown in Figure 28; or
 - ii) a dynamic vapor sorption (DVS) curve substantially as shown in Figure 29.
73. A crystalline form of a sesqui-succinate salt, a hemi-succinate salt, a mono-HCl salt, a sesqui-adipate salt, a mono-adipate salt, a bis-citrate salt, a sesqui-fumarate salt, a bis-gentisate, a mono-BSA salt, a sesqui-oxalate or a co-crystal of Compound I :



wherein the crystalline form or the co-crystal is Compound I Sesqui-Succinate Form III, Compound I Sesqui-Succinate Form IV, Compound I Sesqui-Succinate Form V, Compound I Hemi-Succinate Form I, Compound I Mono-HCl salt Form I, Compound I Mono-HCl salt Form II, Compound I Mono-HCl salt Form III, Compound I Sesqui-Adipate Form I, Compound I Mono-Adipate Form I, Compound I Bis-Citrate Form I, Compound I Sesqui-Fumarate Form I, Compound I Bis-Gentisate Form I, Compound I Mono-BSA salt Form I and Compound I Sesqui-Oxalate Form I.

74. The crystalline form of a sesqui-succinate salt or a co-crystal of Compound I according to claim 73, which is Compound I Sesqui-Succinate Form III.

75. Compound I Sesqui-Succinate Form III according to claim 74 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 7.8, 16.5 and $21.4^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.

76. Compound I Sesqui-Succinate Form III according to claim 75, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 12.2, 16.0 and $24.5^\circ 2\theta$.

77. Compound I Sesqui-Succinate Form III according to any of claims 74-76 characterized by an X-ray powder diffractogram substantially as shown in Figure 30.

78. Compound I Sesqui-Succinate Form III according to any of claims 74-77 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having onset temperatures of about 118 °C, 136 °C and 186 °C.

79. Compound I Sesqui-Succinate Form III according to any of claims 74-78 characterized by a DSC curve substantially as shown in Figure 31.

80. Compound I Sesqui-Succinate Form III according to any of claims 74-79 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 32.

81. The crystalline form of a sesqui-succinate salt or a co-crystal of Compound I according to claim 73, which is Compound I Sesqui-Succinate Form IV.

82. Compound I Sesqui-Succinate Form IV according to claim 78 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 16.6, 22.4 and $25.2^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.

83. Compound I Sesqui-Succinate Form IV according to claim 79, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 7.9, 11.7 and 21.7 $^\circ 2\theta$.
84. Compound I Sesqui-Succinate Form IV according to any of claims 78-80 characterized by an X-ray powder diffractogram substantially as shown in Figure 33.
85. Compound I Sesqui-Succinate Form IV according to any of claims 78-81 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having onset temperatures of about 142 $^\circ\text{C}$ and 183 $^\circ\text{C}$.
86. Compound I Sesqui-Succinate Form IV according to any of claims 78-82 characterized by a DSC curve substantially as shown in Figure 34.
87. Compound I Sesqui-Succinate Form IV according to any of claims 78-83 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 35.
88. The crystalline form of a sesqui-succinate salt or a co-crystal of Compound I according to claim 73, which is Compound I Sesqui-Succinate Form V.
89. Compound I Sesqui-Succinate Form V according to claim 88 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 5.9, 23.3 and 24.7 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
90. Compound I Sesqui-Succinate Form V according to claim 89, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 16.3, 26.4 and 28.6 $^\circ 2\theta$.
91. Compound I Sesqui-Succinate Form V according to any of claims 88-90 characterized by an X-ray powder diffractogram substantially as shown in Figure 36.
92. Compound I Sesqui-Succinate Form V according to any of claims 88-91 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having onset temperatures of about 115 $^\circ\text{C}$, 128 $^\circ\text{C}$, 148 $^\circ\text{C}$ and 178 $^\circ\text{C}$.
93. Compound I Sesqui-Succinate Form V according to any of claims 88-92 characterized by a DSC curve substantially as shown in Figure 37.
94. Compound I Sesqui-Succinate Form V according to any of claims 88-93 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 38.

95. The crystalline form of a hemi-succinate salt or a co-crystal of Compound I according to claim 73, which is Compound I Hemi-Succinate Form I.
96. Compound I Hemi-Succinate Form I according to claim 95 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 20.8, 23.1 and 25.5 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
97. Compound I Hemi-Succinate Form I according to claim 96, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 20.1, 21.2 and 28.1 $^\circ 2\theta$.
98. Compound I Hemi-Succinate Form I according to any of claims 95-97 characterized by an X-ray powder diffractogram substantially as shown in Figure 39.
99. Compound I Hemi-Succinate Form I according to any of claims 95-98 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having an onset temperature of about 128 $^\circ\text{C}$.
100. Compound I Hemi-Succinate Form I according to any of claims 95-99 characterized by a DSC curve substantially as shown in Figure 40.
101. Compound I Hemi-Succinate Form I according to any of claims 95-100 characterized by:
- i) a thermogravimetric analysis (TGA) curve substantially as shown in Figure 41; or
 - ii) a dynamic vapor sorption (DVS) curve substantially as shown in Figure 42.
102. The crystalline form of a mono-HCl salt or a co-crystal of Compound I according to claim 73, which is Compound I Mono-HCl salt Form I.
103. Compound I Mono-HCl salt Form I according to claim 102 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.7, 19.3 and 21.4 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
104. Compound I Mono-HCl salt Form I according to claim 103, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 17.4, 19.6 and 20.9 $^\circ 2\theta$.
105. Compound I Mono-HCl salt Form I according to any of claims 102-104 characterized by an X-ray powder diffractogram substantially as shown in Figure 43.

106. Compound I Mono-HCl salt Form I according to any of claims 102-105 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 44.
107. The crystalline form of a mono-HCl salt or a co-crystal of Compound I according to claim 73, which is Compound I Mono-HCl salt Form II.
108. Compound I Mono-HCl salt Form II according to claim 107 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 6.3, 11.3 and 17.7 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
109. Compound I Mono-HCl salt Form II according to claim 108, wherein the X-ray powder diffractogram further comprises peaks ($\pm 0.2^\circ 2\theta$) at 7.0, 8.9 and 15.7 $^\circ 2\theta$.
110. Compound I Mono-HCl salt Form II according to any of claims 107-109 characterized by an X-ray powder diffractogram substantially as shown in Figure 45.
111. Compound I Mono-HCl salt Form II according to any of claims 107-110 characterized by:
- i) a thermogravimetric analysis (TGA) curve substantially as shown in Figure 46; or
 - ii) a dynamic vapor sorption (DVS) curve substantially as shown in Figure 47.
112. The crystalline form of a mono-HCl salt or a co-crystal of Compound I according to claim 73, which is Compound I Mono-HCl salt Form III.
113. Compound I Mono-HCl salt Form III according to claim 112 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.6, 17.8 and 24.0 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
114. Compound I Mono-HCl salt Form III according to claim 113, further characterized by peaks ($\pm 0.2^\circ 2\theta$) at 12.8, 26.9 and 28.9 $^\circ 2\theta$.
115. Compound I Mono-HCl salt Form III according to any of claims 112-114 characterized by an X-ray powder diffractogram substantially as shown in Figure 48.
116. Compound I Mono-HCl salt Form III according to any of claims 112-115 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having an onset temperature of about 125 $^\circ\text{C}$.

117. Compound I Mono-HCl salt Form III according to any of claims 112-114 characterized by a DSC curve substantially as shown in Figure 49.
118. Compound I Mono-HCl salt Form III according to any of claims 112-115 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 50.
119. The crystalline form of a sesqui-adipate salt or a co-crystal of Compound I according to claim 73, which is Compound I Sesqui-Adipate Form I.
120. Compound I Sesqui-Adipate Form I according to claim 119 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 11.3, 16.6 and 24.8 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
121. Compound I Sesqui-Adipate Form I according to claim 120, further characterized by peaks ($\pm 0.2^\circ 2\theta$) at 7.7, 11.9 and 15.7 $^\circ 2\theta$.
122. Compound I Sesqui-Adipate Form I according to any of claims 119-121 characterized by an X-ray powder diffractogram substantially as shown in Figure 51.
123. Compound I Sesqui-Adipate Form I according to any of claims 119-122 characterized by a differential scanning calorimetry (DSC) curve comprising endotherm having an onset temperature of about 168 $^\circ\text{C}$.
124. Compound I Sesqui-Adipate Form I according to any of claims 119-123 characterized by a DSC curve substantially as shown in Figure 52.
125. Compound I Sesqui-Adipate Form I according to any of claims 119-124 characterized by:
- i) a thermogravimetric analysis (TGA) curve substantially as shown in Figure 53; or
 - ii) a dynamic vapor sorption (DVS) curve substantially as shown in Figure 54.
126. Compound I Sesqui-Adipate Form I according to any of claims 119-125, wherein the Compound I Sesqui-Adipate Form I is a triclinic crystalline form having unit cell parameters: a equal to 8.10 \AA , b equal to 13.38 \AA , c equal to 16.46 \AA , α equal to 71.91 $^\circ$, β equal to 79.15 $^\circ$ and γ equal to 76.92 $^\circ$.

127. The crystalline form of a mono-adipate salt or a co-crystal of Compound I according to claim 73, which is Compound I Mono-Adipate Form I.

128. Compound I Mono-Adipate Form I according to claim 127 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 4.9, 19.9 and 21.1 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.

129. Compound I Mono-Adipate Form I according to claim 128, further characterized by peaks ($\pm 0.2^\circ 2\theta$) at 18.4, 19.5 and 21.7 $^\circ 2\theta$.

130. Compound I Mono-Adipate Form I according to any of claims 127-129 characterized by an X-ray powder diffractogram substantially as shown in Figure 55.

131. Compound I Mono-Adipate Form I according to any of claims 127-130 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having onset temperatures of about 91 $^\circ\text{C}$ and 194 $^\circ\text{C}$.

132. Compound I Mono-Adipate Form I according to any of claims 127-131 characterized by a DSC curve substantially as shown in Figure 56.

133. Compound I Mono-Adipate Form I according to any of claims 127-130 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 57.

134. Compound I Mono-Adipate Form I according to any of claims 127-133, wherein the Compound I Mono-Adipate Form I is a monoclinic crystalline form having unit cell parameters: a equal to 11.04 \AA , b equal to 31.08 \AA , c equal to 22.23 \AA , α equal to 90.00 $^\circ$, β equal to 100.23 $^\circ$ and γ equal to 90.00 $^\circ$.

135. The crystalline form of a bis-citrate salt or a co-crystal of Compound I according to claim 73, which is Compound I Bis-Citrate Form I.

136. Compound I Bis-Citrate Form I according to claim 135 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 6.4, 18.1 and 18.9 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.

137. Compound I Bis-Citrate Form I according to claim 136, further characterized by peaks ($\pm 0.2^\circ 2\theta$) at 8.6, 17.8 and 19.9 $^\circ 2\theta$.

138. Compound I Bis-Citrate Form I according to any of claims 135-137 characterized by an X-ray powder diffractogram substantially as shown in Figure 58.
139. Compound I Bis-Citrate Form I according to any of claims 135-138 characterized by a differential scanning calorimetry (DSC) curve comprising a broad endotherm between temperatures of about 22 °C and 87 °C.
140. Compound I Bis-Citrate Form I according to claim 139, wherein the DSC curve further comprises an endotherm having onset temperature of about 121 °C.
141. Compound I Bis-Citrate Form I according to any of claims 135-140 characterized by a DSC curve substantially as shown in Figure 59.
142. Compound I Bis-Citrate Form I according to any of claims 135-141 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 60.
143. The crystalline form of a sesqui-fumarate salt or a co-crystal of Compound I according to claim 73, which is Compound I Sesqui-Fumarate Form I.
144. Compound I Sesqui-Fumarate Form I according to claim 143 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 15.3, 22.8 and 25.8 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
145. Compound I Sesqui-Fumarate Form I according to claim 144, further characterized by peaks ($\pm 0.2^\circ 2\theta$) at 7.8, 11.6 and 26.3 $^\circ 2\theta$.
146. Compound I Sesqui-Fumarate Form I according to any of claims 143-145 characterized by an X-ray powder diffractogram substantially as shown in Figure 61.
147. Compound I Sesqui-Fumarate Form I according to any of claims 143-146 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 62.
148. The crystalline form of a bis-gentisate salt or a co-crystal of Compound I according to claim 73, which is Compound I Bis-Gentisate Form I.
149. Compound I Bis-Gentisate Form I according to claim 148 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 6.7, 16.7 and 25.0 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.

150. Compound I Bis-Gentisate Form I according to claim 149, further characterized by peaks ($\pm 0.2^\circ 2\theta$) at 7.7, 17.9 and 23.3 $^\circ 2\theta$.
151. Compound I Bis-Gentisate Form I according to any of claims 148-150 characterized by an X-ray powder diffractogram substantially as shown in Figure 63.
152. Compound I Bis-Gentisate Form I according to any of claims 148-151 characterized by a differential scanning calorimetry (DSC) curve comprising endotherms having peaks at about 54 $^\circ\text{C}$ and 151 $^\circ\text{C}$.
153. Compound I Bis-Gentisate Form I according to claim 148-152 characterized by a DSC curve substantially as shown in Figure 64.
154. Compound I Bis-Gentisate Form I according to any of claims 148-153 characterized by a thermogravimetric analysis (TGA) curve substantially as shown in Figure 65.
155. Compound I Bis-Gentisate Form I according to any of claims 148-154, wherein the Compound I Bis-Gentisate Form I is a triclinic crystalline form having unit cell parameters: a equal to 12.06 \AA , b equal to 13.73 \AA , c equal to 14.88 \AA , α equal to 64.57 $^\circ$, β equal to 73.71 $^\circ$ and γ equal to 77.01 $^\circ$.
156. The crystalline form of a mono-BSA salt or a co-crystal of Compound I according to claim 73, which is Compound I Mono-BSA Form I.
157. Compound I Mono-BSA Form I according to claim 156 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 8.8, 11.8 and 20.2 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
158. Compound I Mono-BSA Form I according to claim 157, further characterized by peaks ($\pm 0.2^\circ 2\theta$) at 10.9, 15.8 and 25.7 $^\circ 2\theta$.
159. Compound I Mono-BSA Form I according to any of claims 156-158 characterized by an X-ray powder diffractogram substantially as shown in Figure 66.
160. Compound I Mono-BSA Form I according to any of claims 156-159 characterized by a differential scanning calorimetry (DSC) curve comprising an endotherm having an onset temperature of about 80 $^\circ\text{C}$.

161. Compound I Mono-BSA Form I according to claims 156-160 characterized by a DSC curve substantially as shown in Figure 67.
162. Compound I Mono-BSA Form I according to any of claims 156-161 characterized by:
- i) thermogravimetric analysis (TGA) curve substantially as shown in Figure 68; or
 - ii) a dynamic vapor sorption (DVS) curve substantially as shown in Figure 69.
163. The crystalline form of a sesqui-oxalate salt or a co-crystal of Compound I according to claim 73, which is Compound I Sesqui-Oxalate Form I.
164. Compound I Sesqui-Oxalate Form I according to claim 163 characterized by an X-ray powder diffractogram comprising peaks ($\pm 0.2^\circ 2\theta$) at 16.1, 23.0 and 26.1 $^\circ 2\theta$ as determined on a diffractometer using Cu-K α radiation.
165. Compound I Sesqui-Oxalate Form I according to claim 164, further characterized by peaks ($\pm 0.2^\circ 2\theta$) at 11.9, 19.2 and 20.8 $^\circ 2\theta$.
166. Compound I Sesqui-Oxalate Form I according to any of claims 163-165 characterized by an X-ray powder diffractogram substantially as shown in Figure 70.
167. Compound I Sesqui-Oxalate Form I according to any of claims 163-166 characterized by a differential scanning calorimetry (DSC) curve comprising an endotherm having an onset temperature of about 193 $^\circ\text{C}$.
168. Compound I Sesqui-Oxalate Form I according to any of claims 163-167 characterized by a DSC curve substantially as shown in Figure 71.
169. Compound I Sesqui-Oxalate Form I according to any of claims 163-168 characterized by thermogravimetric analysis (TGA) curve substantially as shown in Figure 72.
170. A pharmaceutical composition comprising a crystalline form of Compound 1 according to claim 1 or a crystalline form of a sesqui-succinate salt, a hemi-succinate salt, a mono-HCl salt, a sesqui-adipate salt, a mono-adipate salt, a bis-citrate salt, a sesqui-fumarate salt, a bis-gentisate, a mono-BSA salt, a sesqui-oxalate or a co-crystal of Compound I according to claim 73 and a pharmaceutically acceptable excipient.

171. A method for treating a disease or condition selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease, and a cancer in a subject in need thereof, comprising administering to the subject a therapeutic effective amount of a crystalline form as in claims 1 or 73 or a pharmaceutical composition of claim 170.

172. The method of claim 171, wherein the disease or condition is a cancer selected from the group consisting of a hematologic malignancy and a solid tumor.

173. The method of claim 172, wherein the disease or condition is a hematologic malignancy selected from the group consisting of lymphoma, multiple myeloma or leukemia.

174. The method of Claim 173, wherein the disease or condition is selected from the group consisting of small lymphocytic lymphoma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma, refractory iNHL, mantle cell lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphoma, immunoblastic large cell lymphoma, lymphoblastic lymphoma, Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes), Nodal marginal zone lymphoma (+/- monocytoid B-cells), Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type, cutaneous T-cell lymphoma, extranodal T-cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, mycosis fungoides, B-cell lymphoma, diffuse large B-cell lymphoma, Mediastinal large B-cell lymphoma, Intravascular large B-cell lymphoma, Primary effusion lymphoma, small non-cleaved cell lymphoma, Burkitt's lymphoma, multiple myeloma, plasmacytoma, acute lymphocytic leukemia, T-cell acute lymphoblastic leukemia, B-cell acute lymphoblastic leukemia, B-cell prolymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, juvenile myelomonocytic leukemia, minimal residual disease, hairy cell leukemia, primary myelofibrosis, secondary myelofibrosis, chronic myeloid leukemia, myelodysplastic syndrome, myeloproliferative disease, and Waldenstrom's macroglobulinemia.

175. The method of claim 172, wherein the disease or condition is a solid tumor, wherein the solid tumor is from a cancer selected from the group consisting of pancreatic cancer, urological cancer, bladder cancer, colorectal cancer, colon cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, thyroid cancer, gall bladder cancer, lung cancer (*e.g.* non-small cell lung cancer, small-cell lung cancer), ovarian cancer, cervical cancer, gastric cancer, endometrial cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain tumors (*e.g.*, glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma), bone cancer, soft tissue sarcoma,

retinoblastomas, neuroblastomas, peritoneal effusions, malignant pleural effusions, mesotheliomas, Wilms tumors, trophoblastic neoplasms, hemangiopericytomas, Kaposi's sarcomas, myxoid carcinoma, round cell carcinoma, squamous cell carcinomas, esophageal squamous cell carcinomas, oral carcinomas, cancers of the adrenal cortex, and ACTH-producing tumors.

176. The method of claim 171, wherein the disease or condition is selected from the group consisting of systemic lupus erythematosus, myasthenia gravis, Goodpasture's syndrome, glomerulonephritis, hemorrhage, pulmonary hemorrhage, atherosclerosis, rheumatoid arthritis, psoriatic arthritis, monoarticular arthritis, osteoarthritis, gouty arthritis, spondylitis, Behçet disease, autoimmune thyroiditis, Reynaud's syndrome, acute disseminated encephalomyelitis, chronic idiopathic thrombocytopenic purpura, multiple sclerosis, Sjögren's syndrome, autoimmune hemolytic anemia, tissue graft rejection, hyperacute rejection of transplanted organs, allograft rejection, graft-versus-host disease, diseases involving leukocyte diapedesis, disease states due to leukocyte dyscrasia and metastasis, granulocyte transfusion-associated syndromes, cytokine-induced toxicity, scleroderma, vasculitis, asthma, psoriasis, chronic inflammatory bowel disease, ulcerative colitis, Crohn's disease, necrotizing enterocolitis, irritable bowel syndrome, dermatomyositis, Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, type I diabetes mellitus, sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, and toxic shock syndrome, multiple organ injury syndrome secondary to septicemia, trauma, hypovolemic shock, allergic conjunctivitis, vernal conjunctivitis, and thyroid-associated ophthalmopathy, eosinophilic granuloma, eczema, chronic bronchitis, acute respiratory distress syndrome, allergic rhinitis, coryza, hay fever, bronchial asthma, silicosis, pulmonary sarcoidosis, pleurisy, alveolitis, emphysema, pneumonia, bacterial pneumonia, bronchiectasis, and pulmonary oxygen toxicity, reperfusion injury of the myocardium, brain, or extremities, thermal injury, cystic fibrosis, keloid formation or scar tissue formation, fever and myalgias due to infection, and brain or spinal cord injury due to minor trauma, diseases involving leukocyte diapedesis, acute hypersensitivity, delayed hypersensitivity, urticaria, food allergies, skin sunburn, inflammatory pelvic disease, urethritis, uveitis, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, alcoholic hepatitis, gastritis, enteritis, contact dermatitis, atopic dermatitis, gingivitis, appendicitis, pancreatitis, cholecystitis, polycythemia vera, essential thrombocythemia, and polycystic kidney disease.

177. The method of claim 171, wherein the disease or condition is selected from the group consisting of cutaneous lupus erythematosus, systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiple sclerosis, Sjogren's syndrome, psoriasis, autoimmune hemolytic anemia, asthma, ulcerative colitis, Crohn's disease, irritable bowel disease, and chronic obstructive pulmonary disease.

178. The method of claim 171, wherein the disease or condition is selected from the group consisting of asthma, rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease, and systemic lupus erythematosus.

179. The method of claim 171, wherein the disease or condition is rheumatoid arthritis.

180. The method of any one of claims 171-179, wherein the subject is human.

181. The method of any one of claims 171-180, wherein the crystalline form is administered intravenously, intramuscularly, parenterally, nasally or orally.

182. The method of Claim 171, wherein the crystalline form is administered QD orally.

183. The method of claim 171, wherein the crystalline form of is administered BID orally.

184. The crystalline form of Compound I as in claims 1 or 73 or a pharmaceutical composition of claim 170 for use in therapy.

185. Use of a crystalline form of Compound I as in claims 1 or 73, in the manufacture of a medicament for the treatment of a disease or condition selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease, and a cancer.

186. Use of a crystalline form of Compound I as in claims 1 or 73, in the manufacture of a medicament for the treatment of rheumatoid arthritis.

187. Use of a crystalline form of Compound I as in claims 1 or 73, in the manufacture of a medicament for the treatment of a hematologic malignancy.

188. The use of claim 187, wherein the hematologic malignancy is lymphoma, multiple myeloma or leukemia.

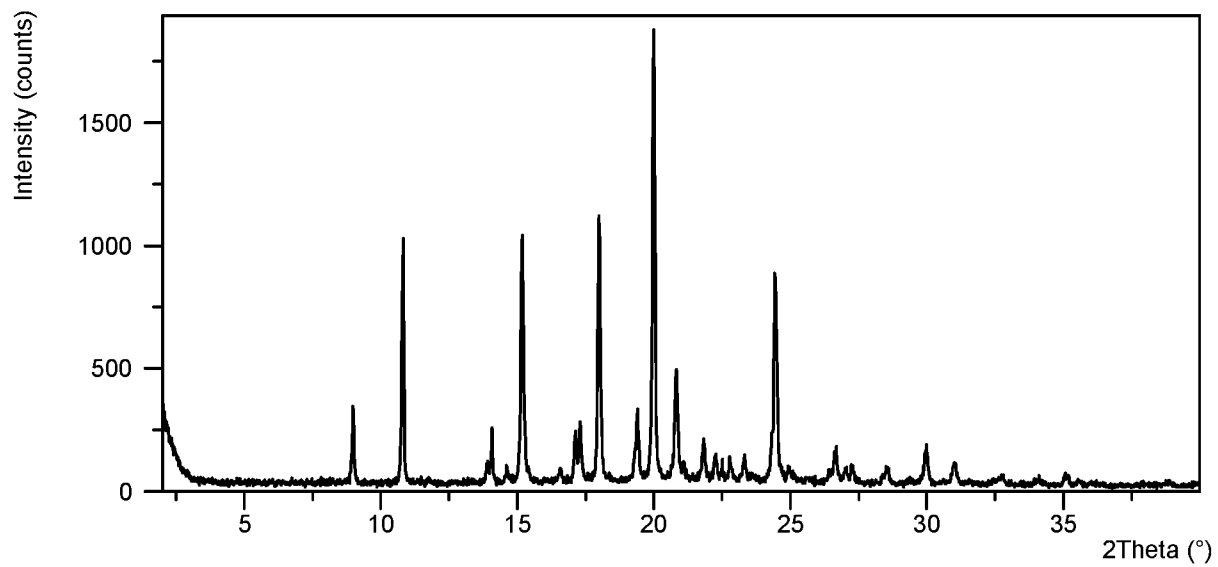


FIGURE 1

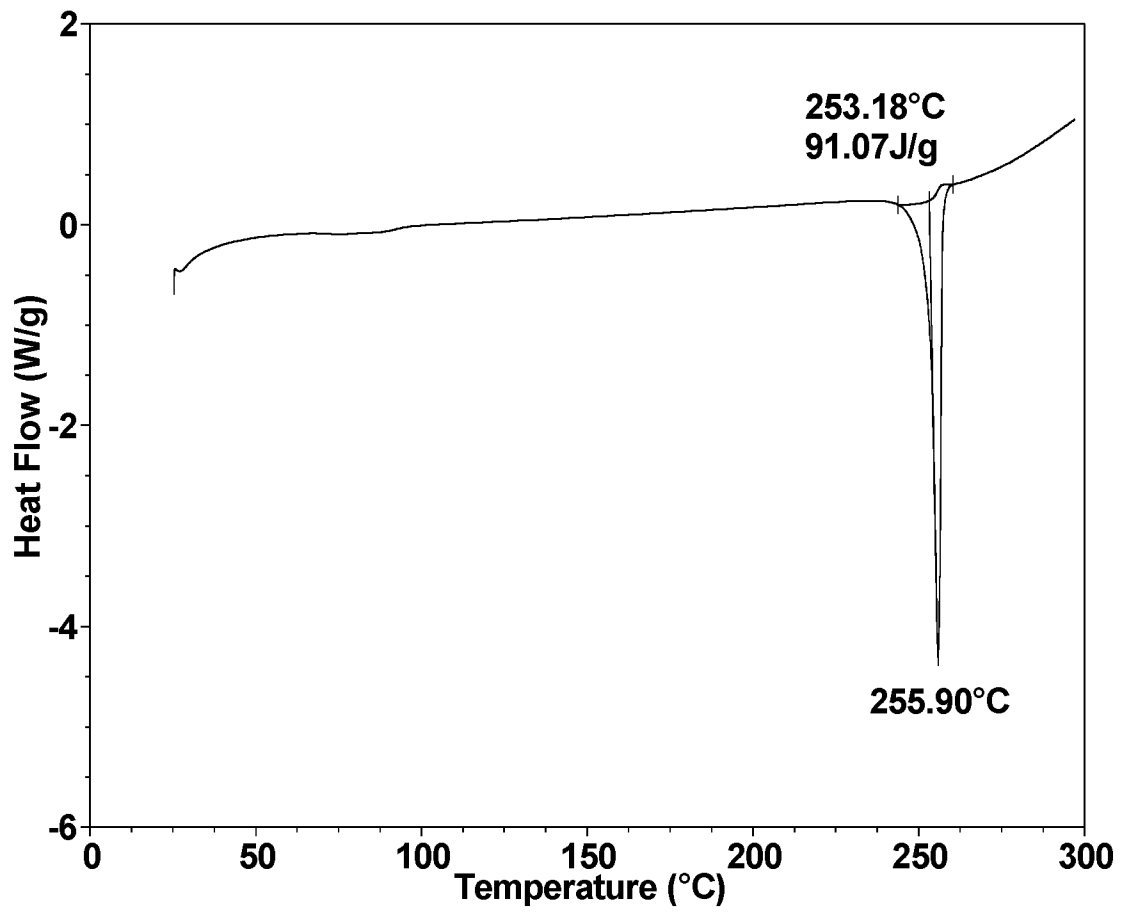


FIGURE 2

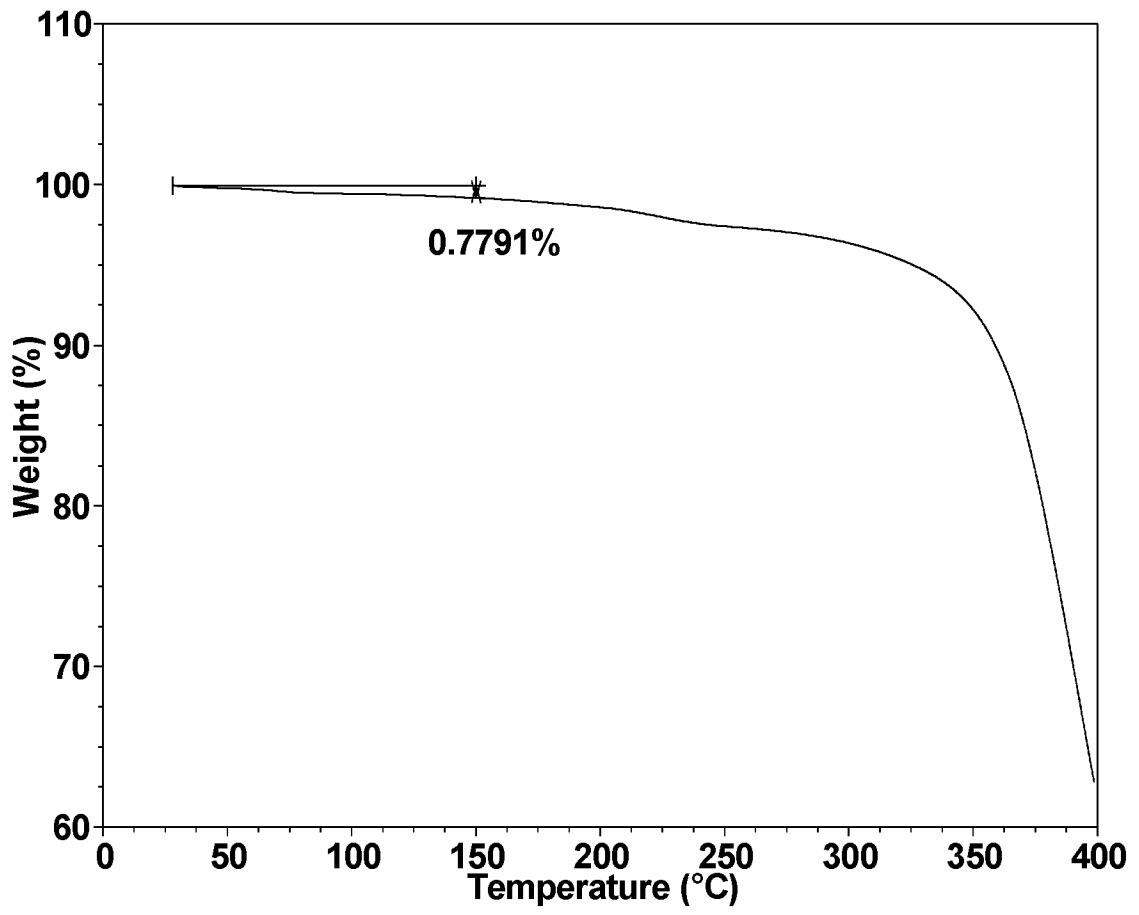


FIGURE 3

z

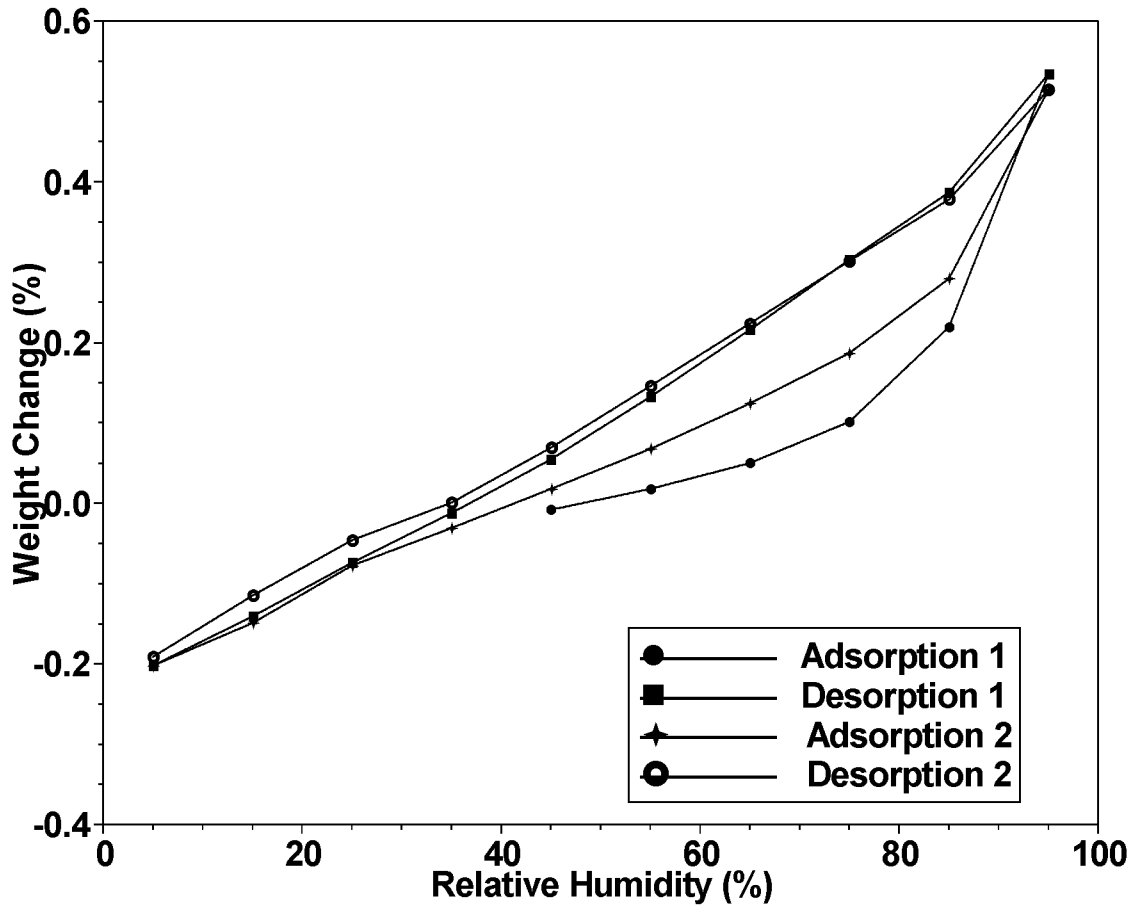


FIGURE 4

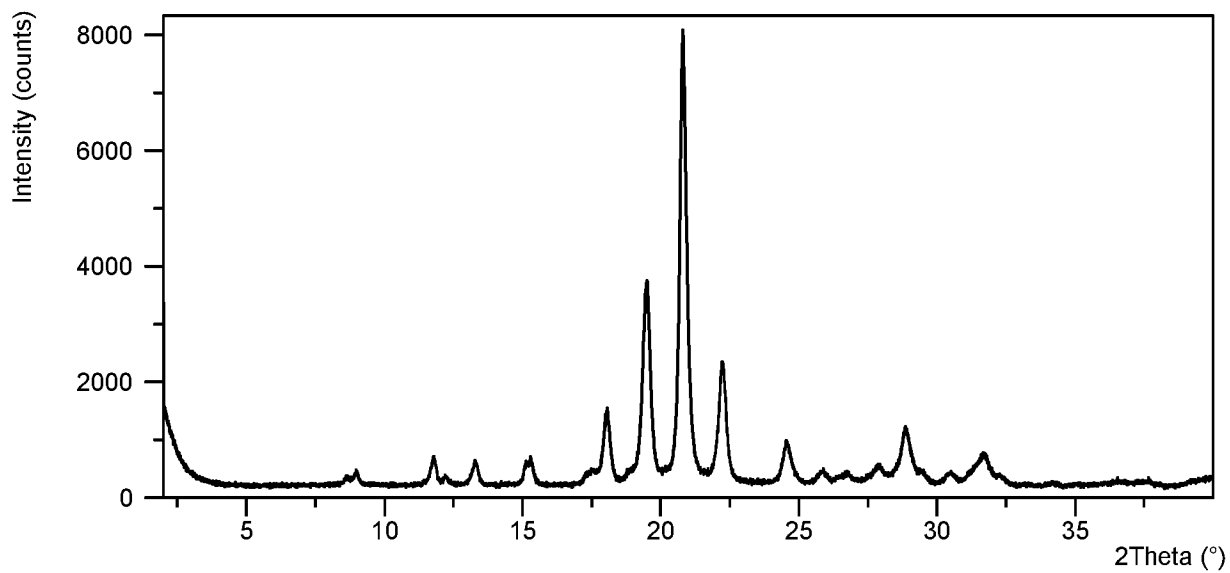


FIGURE 5

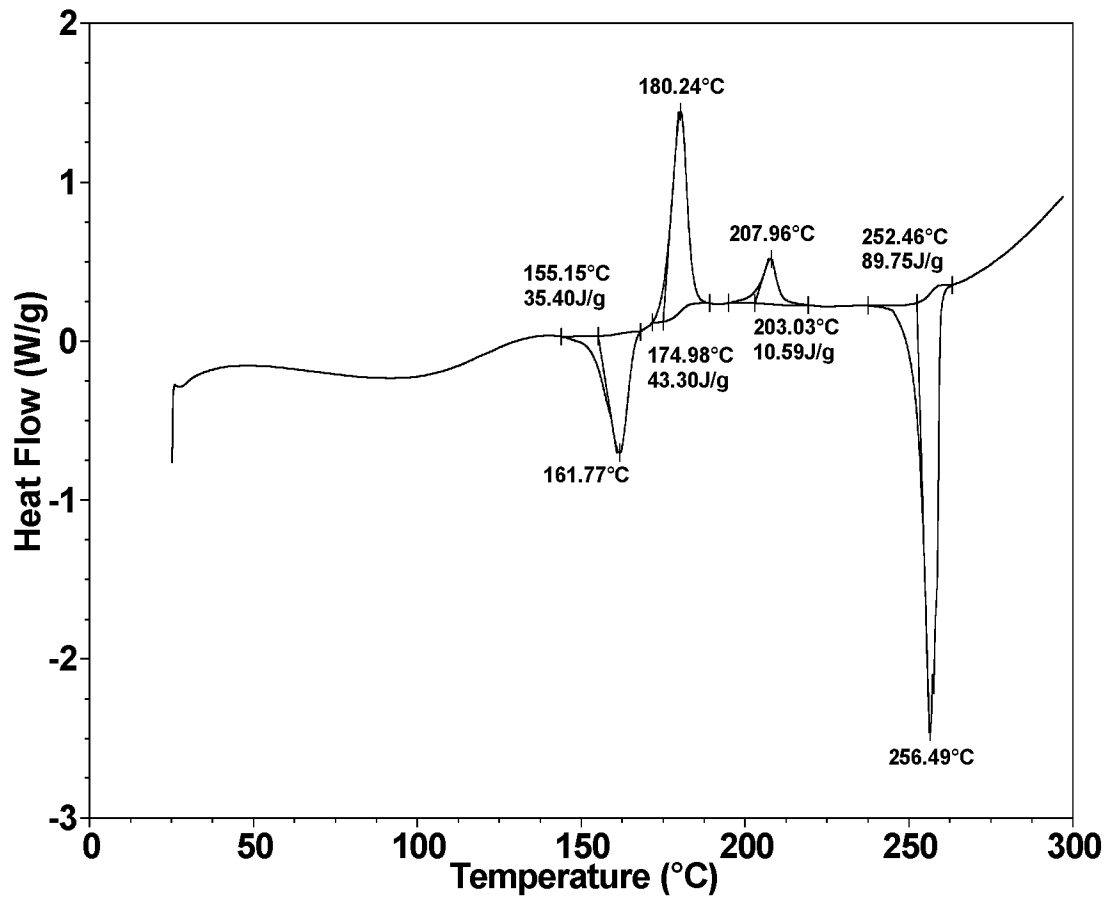


FIGURE 6

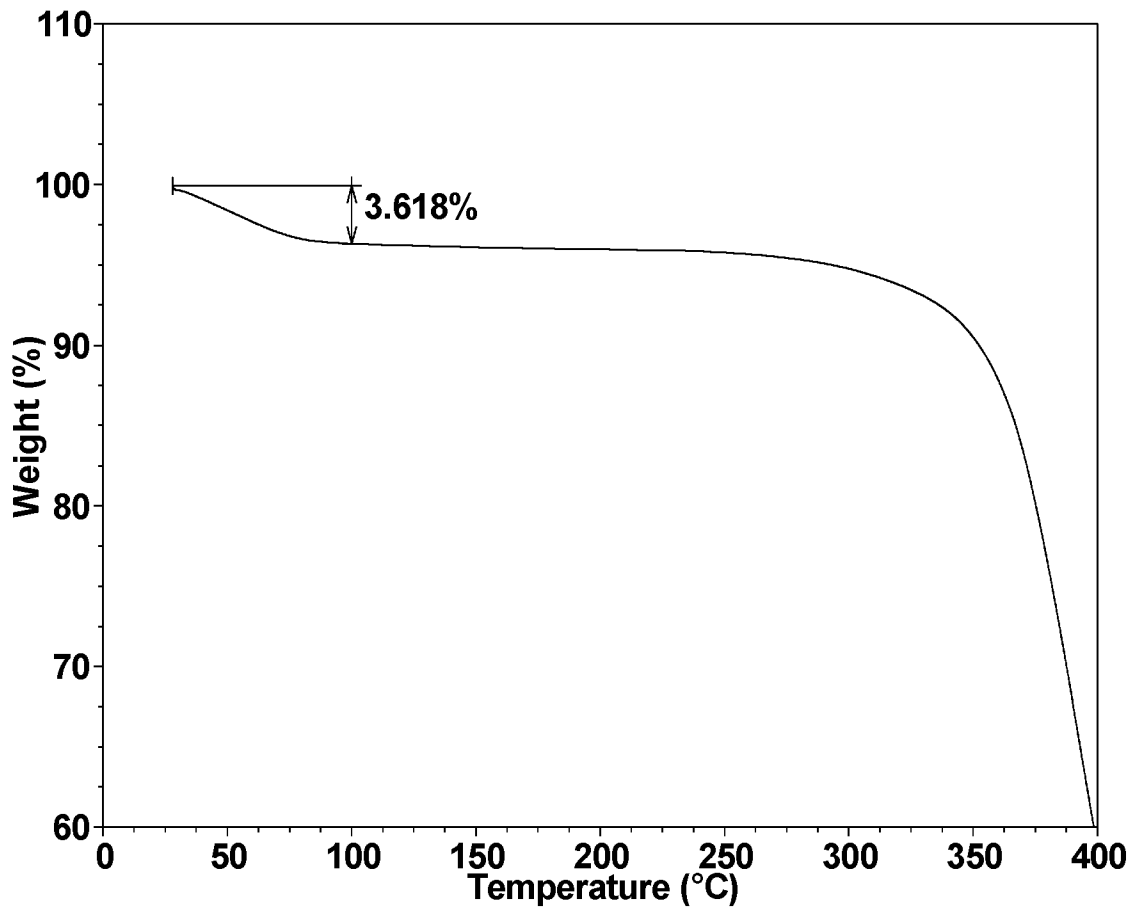


FIGURE 7

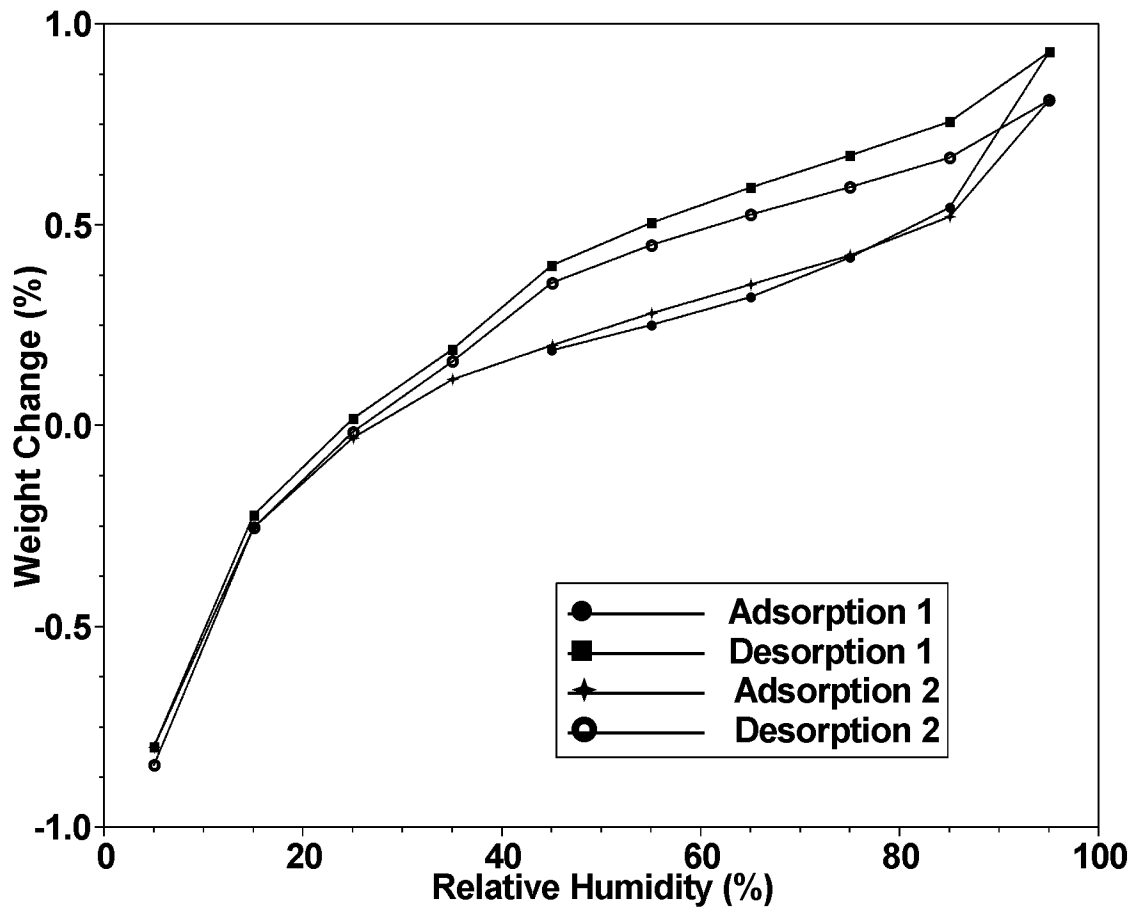


FIGURE 8

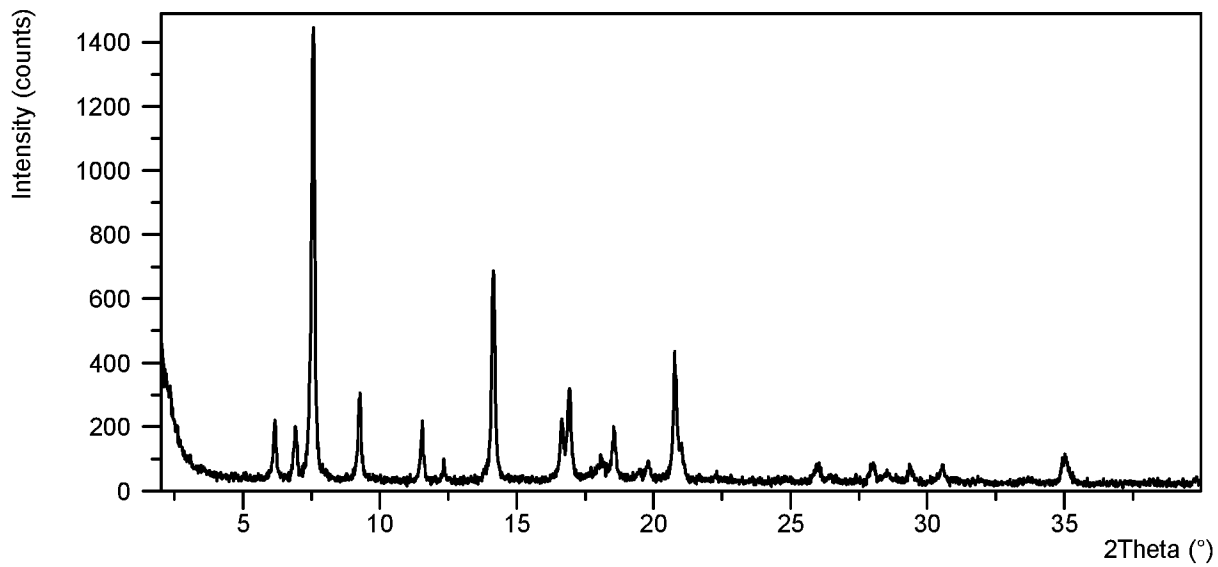


FIGURE 9

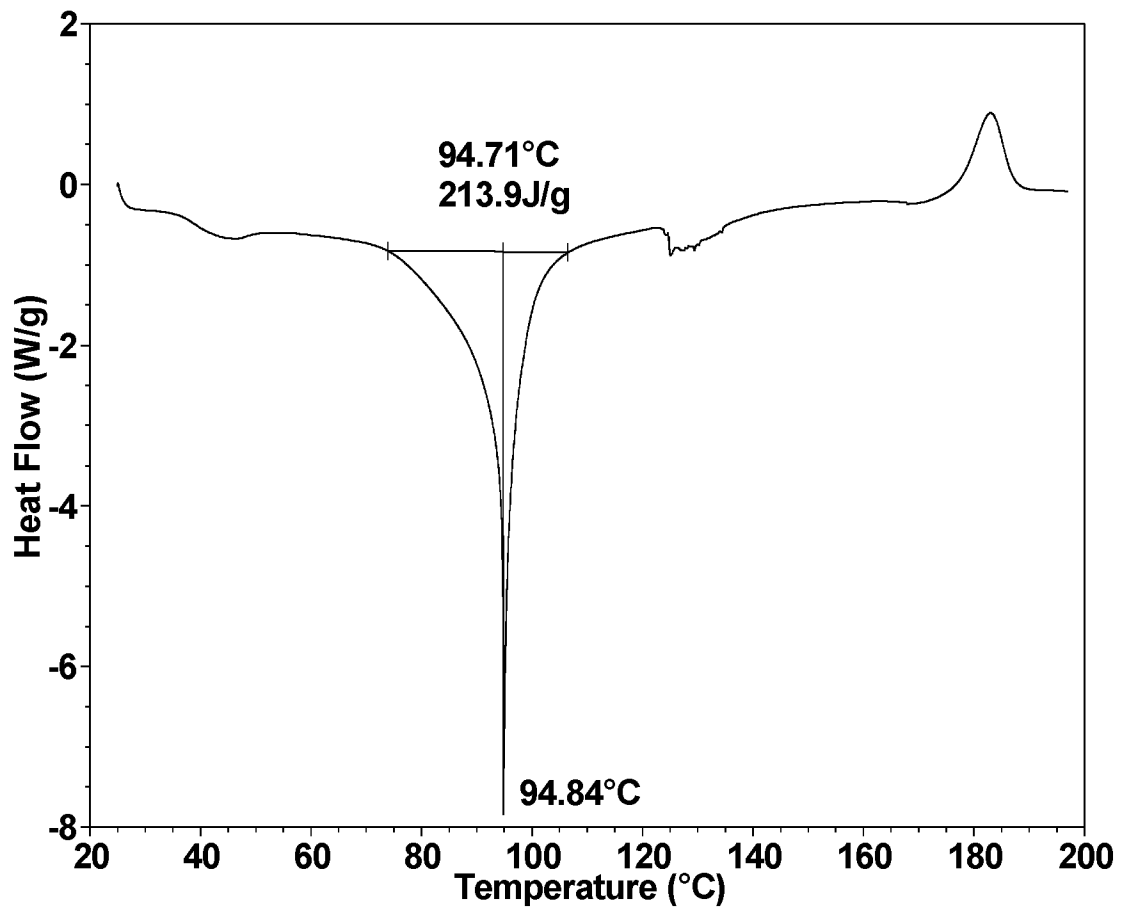


FIGURE 10

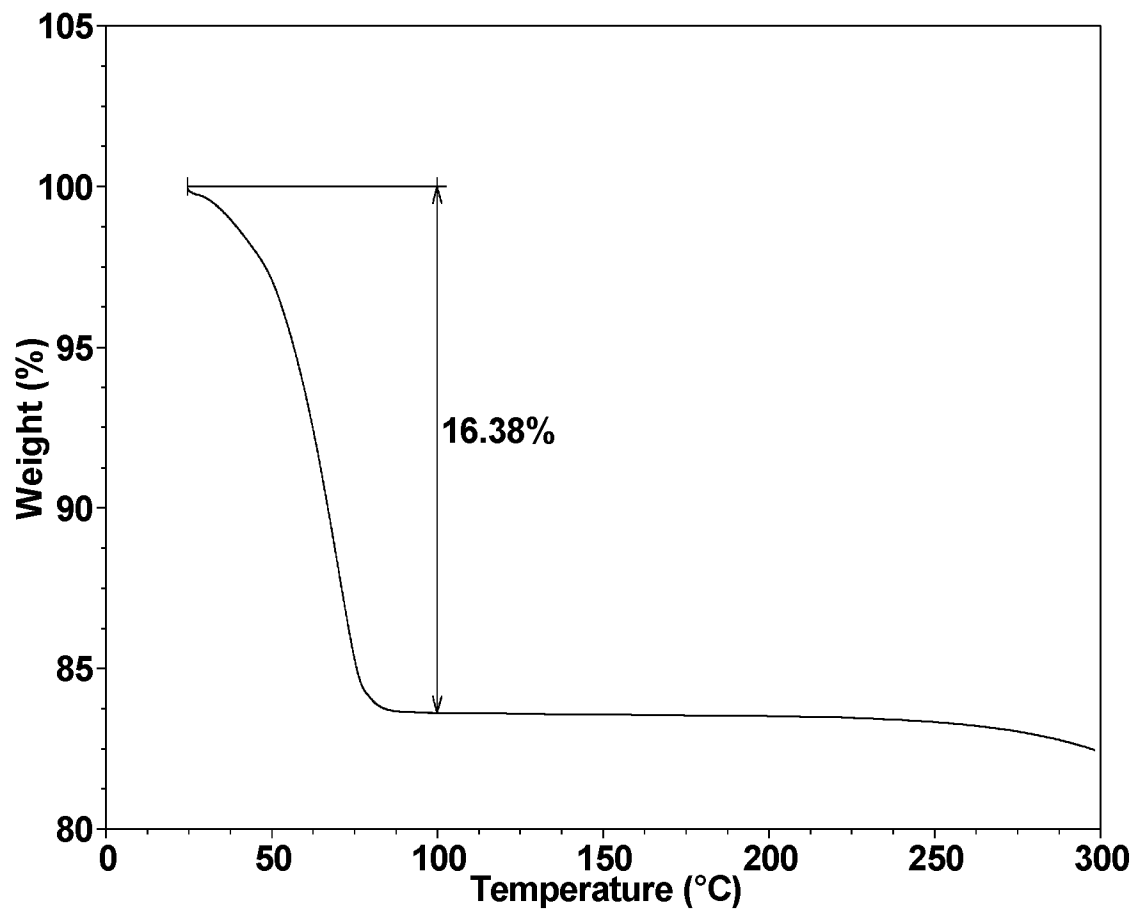


FIGURE 11

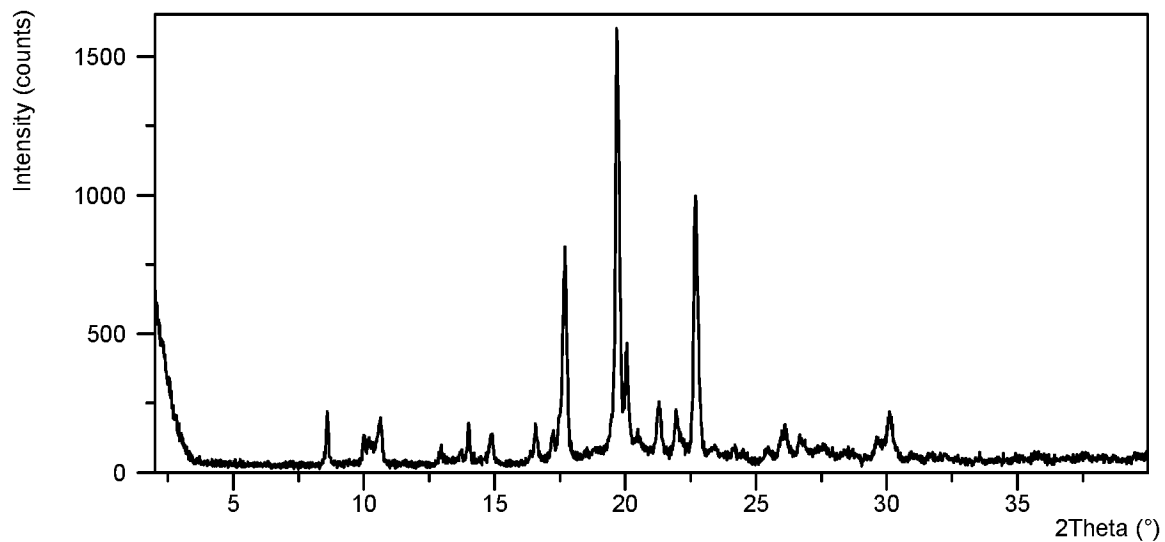


FIGURE 12

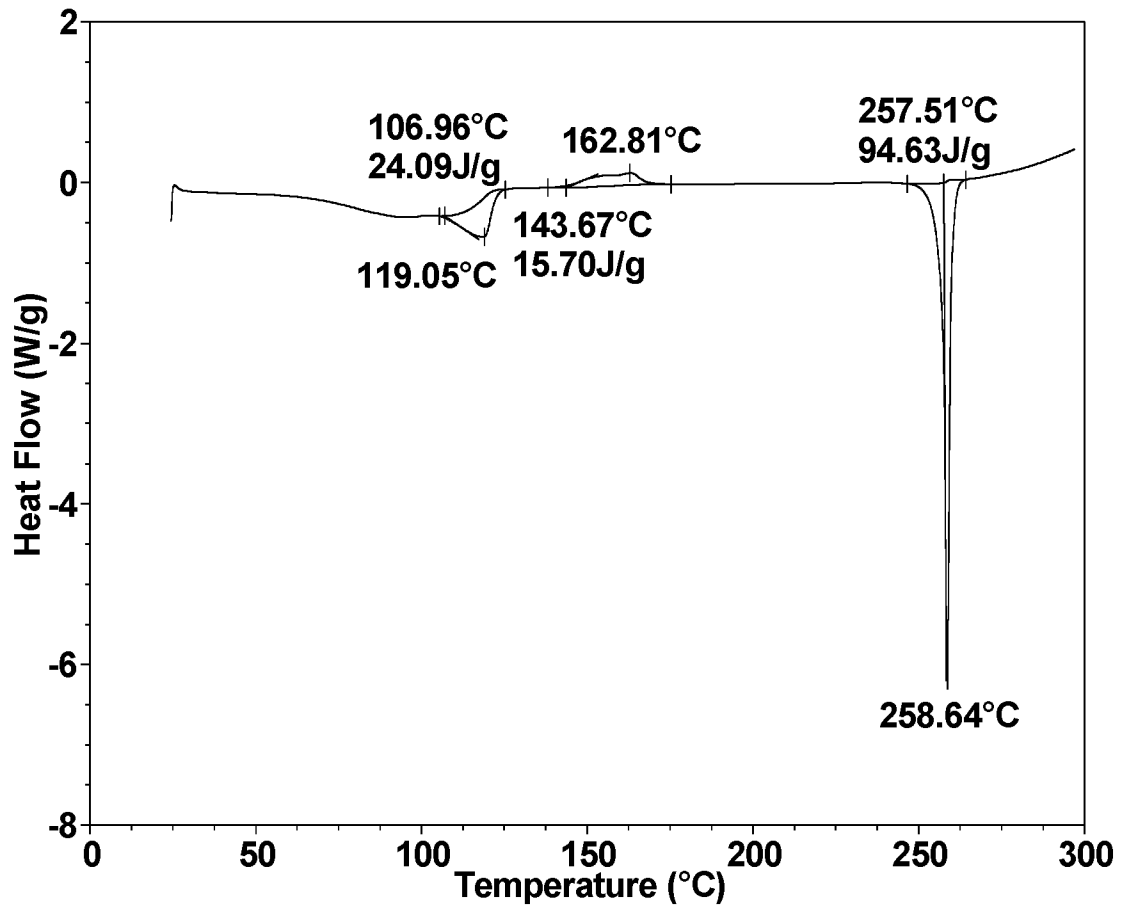


FIGURE 13

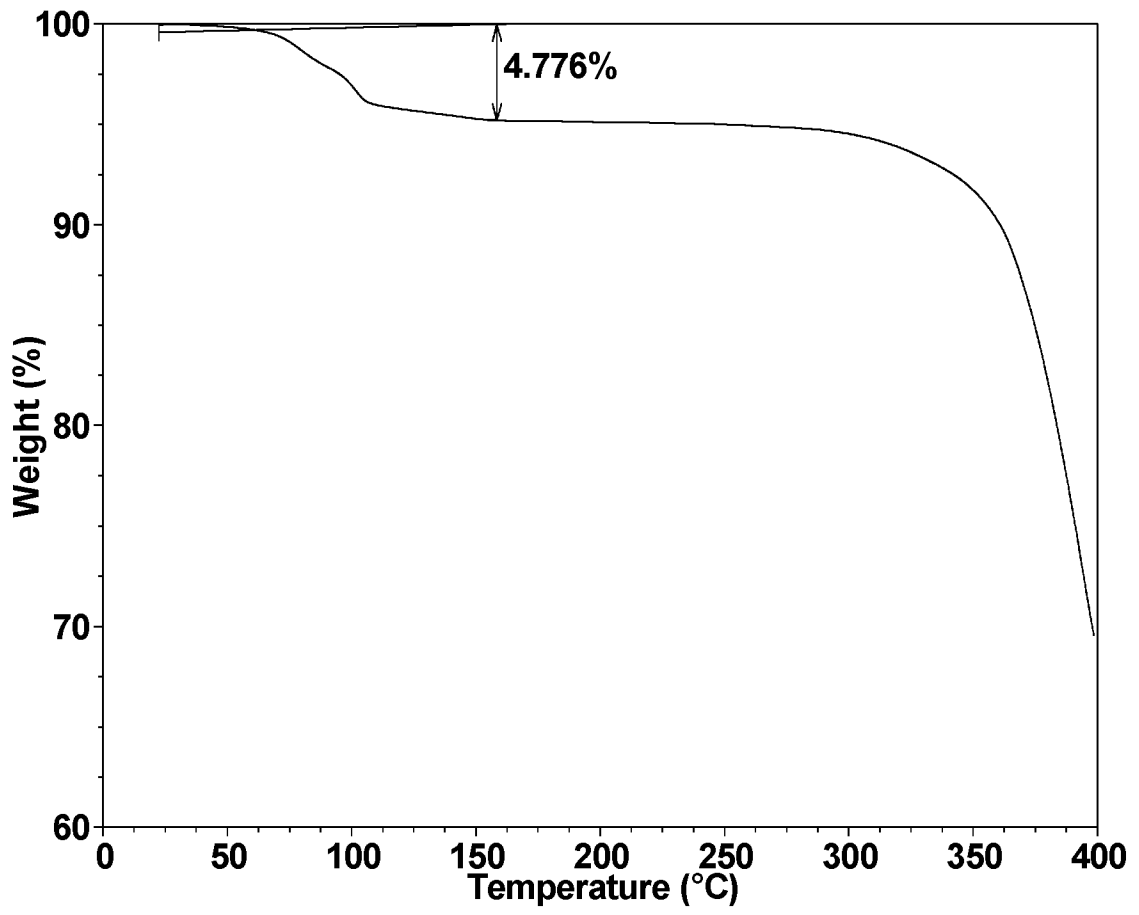


FIGURE 14

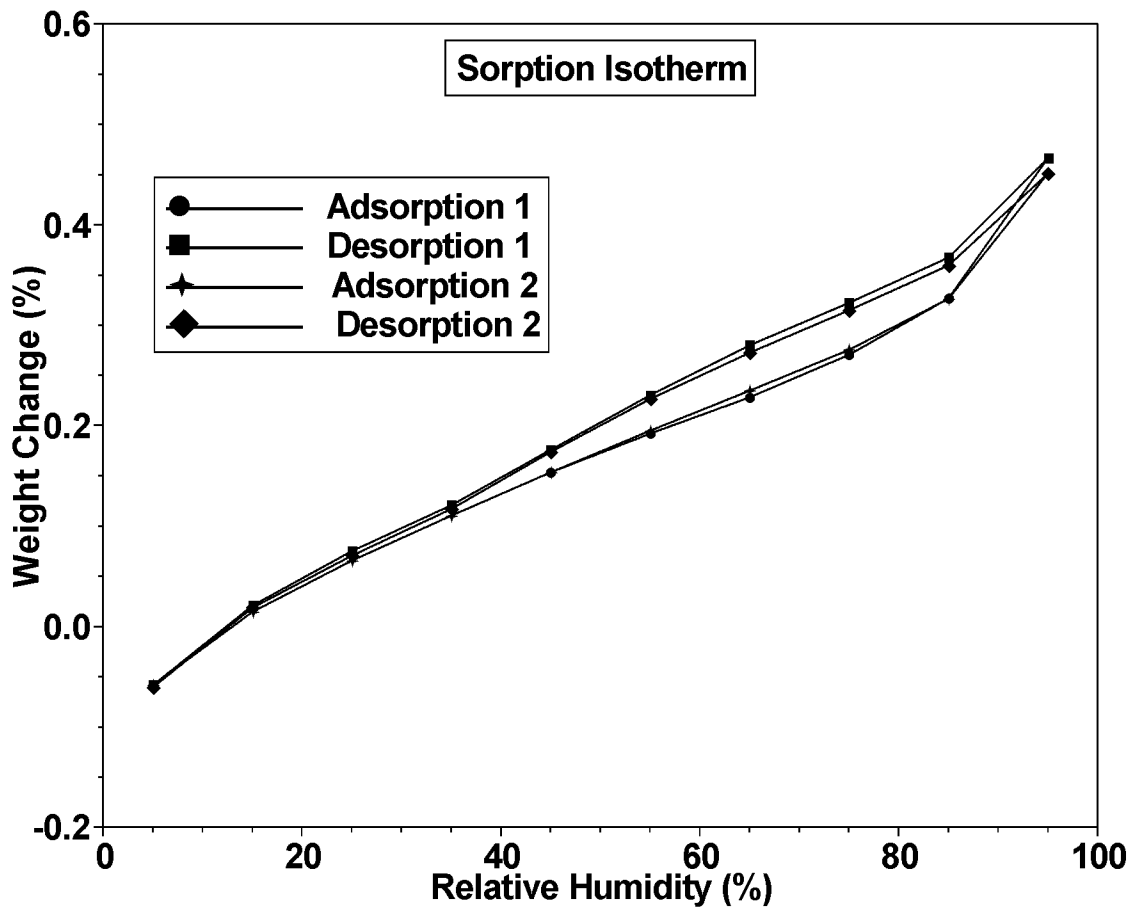


FIGURE 15

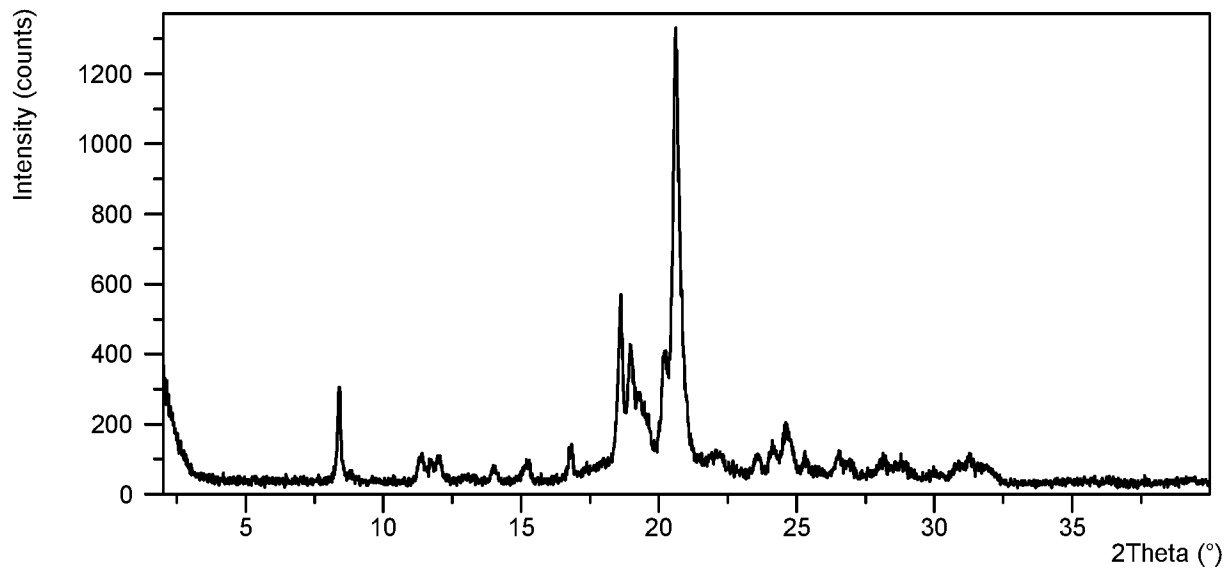


FIGURE 16

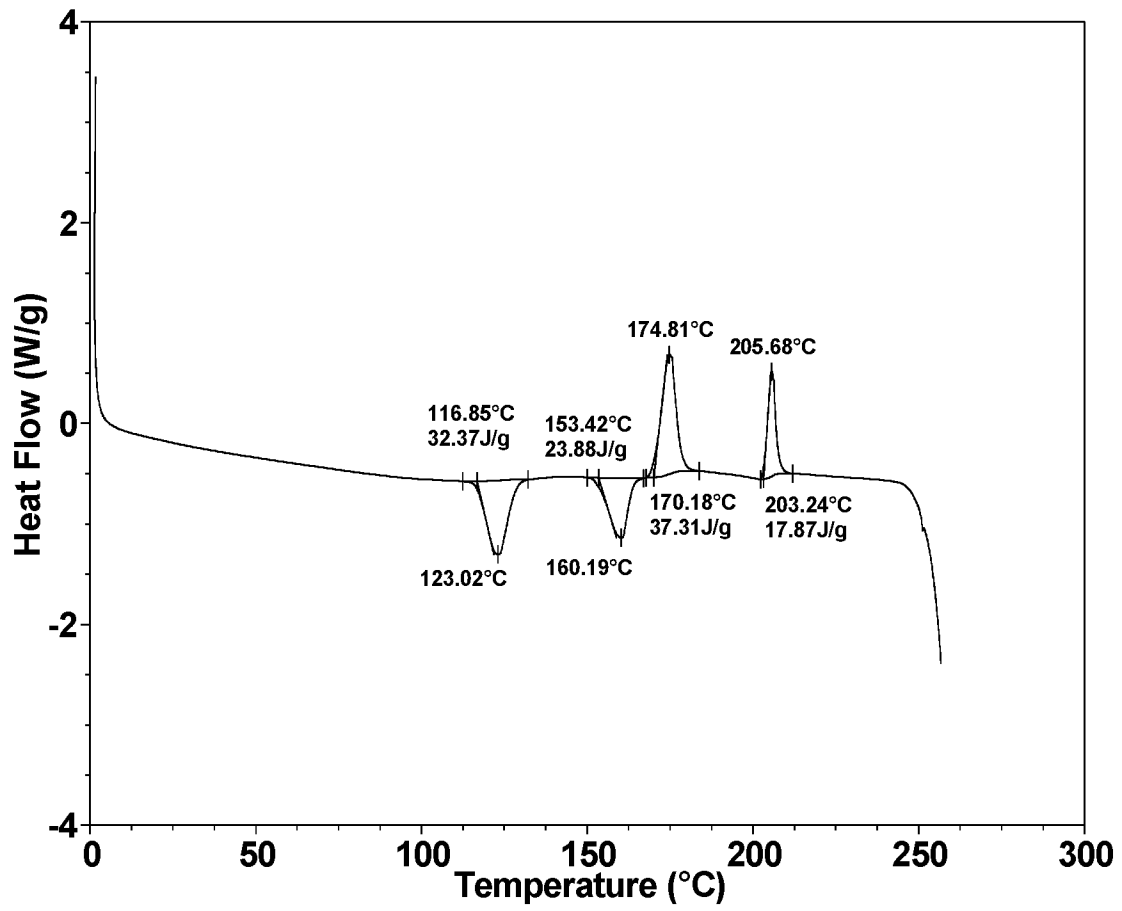


FIGURE 17

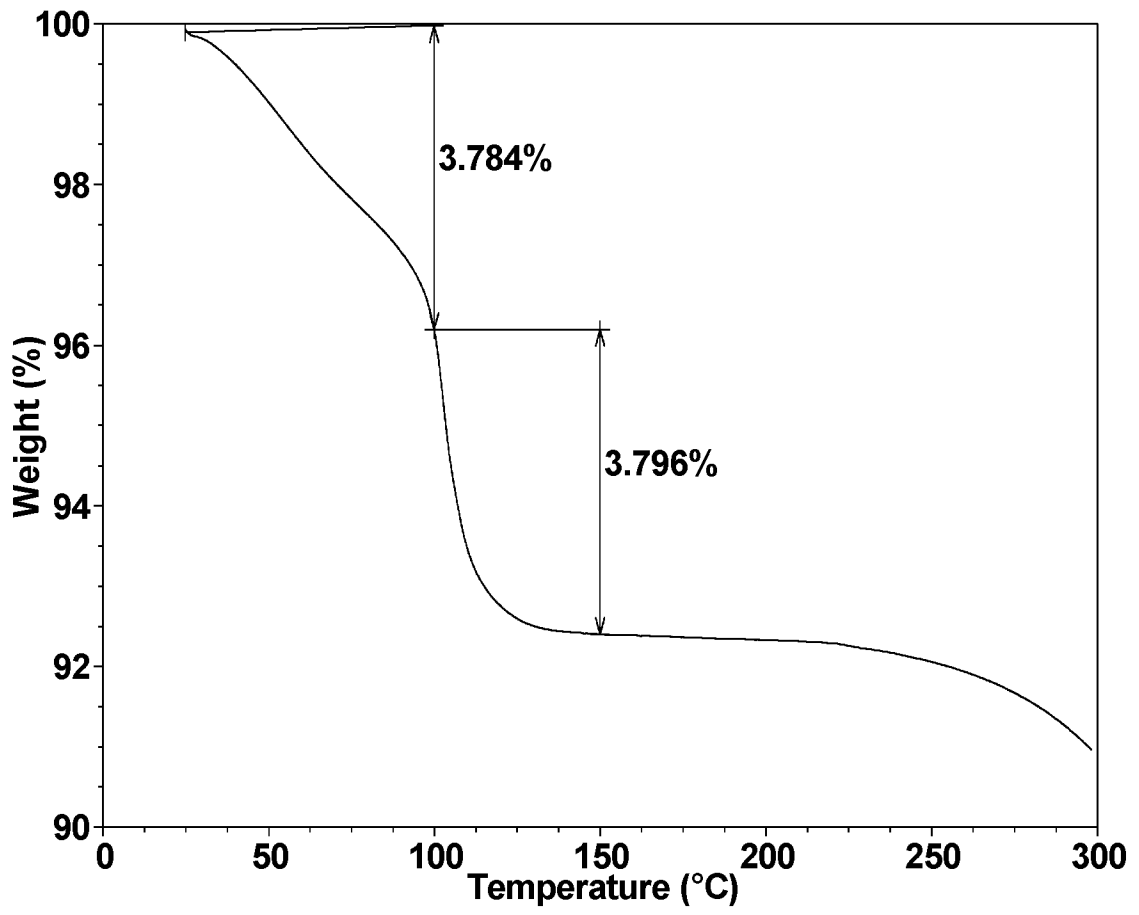


FIGURE 18

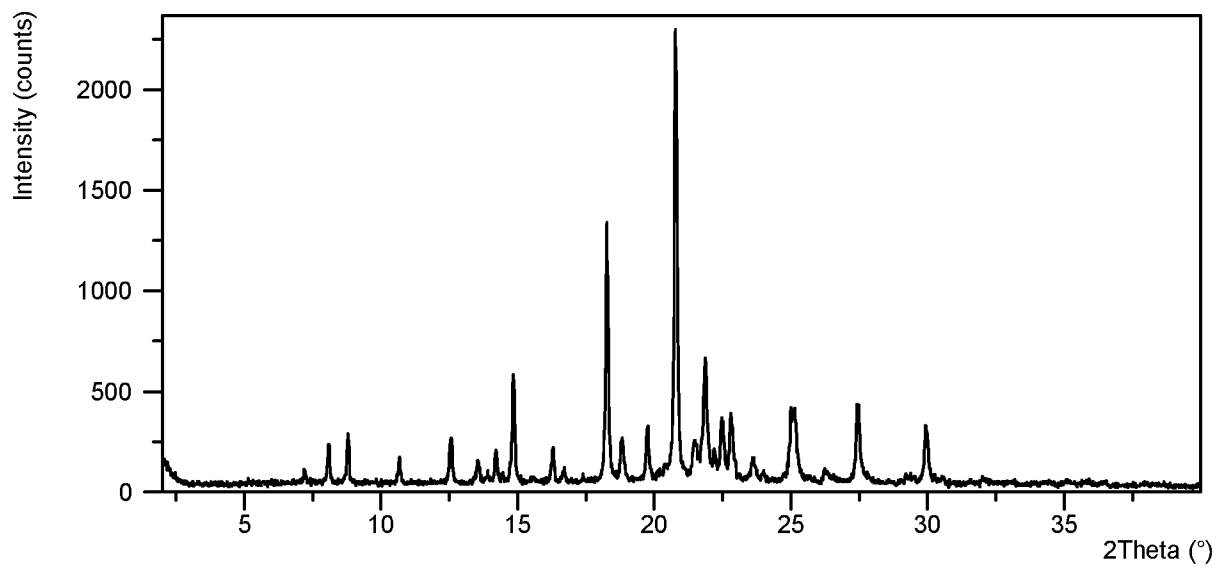


FIGURE 19

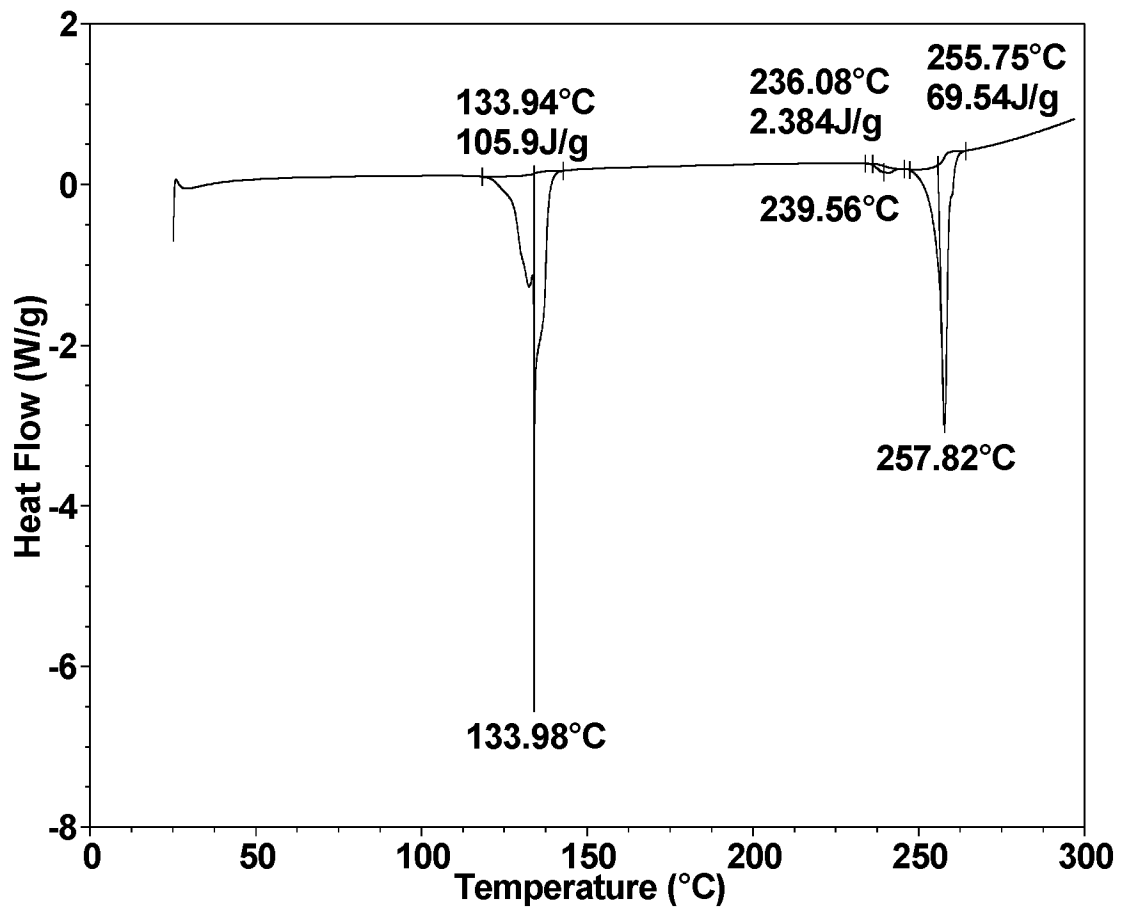


FIGURE 20

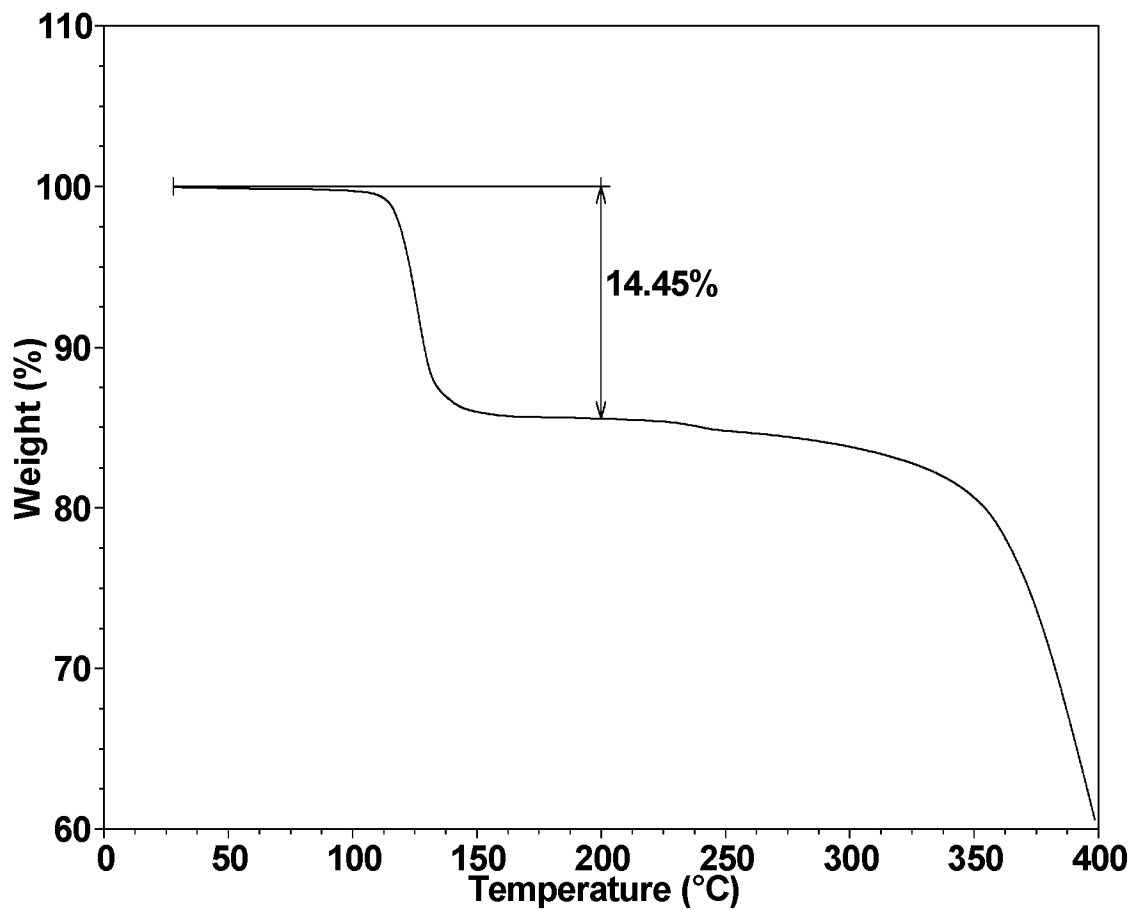


FIGURE 21

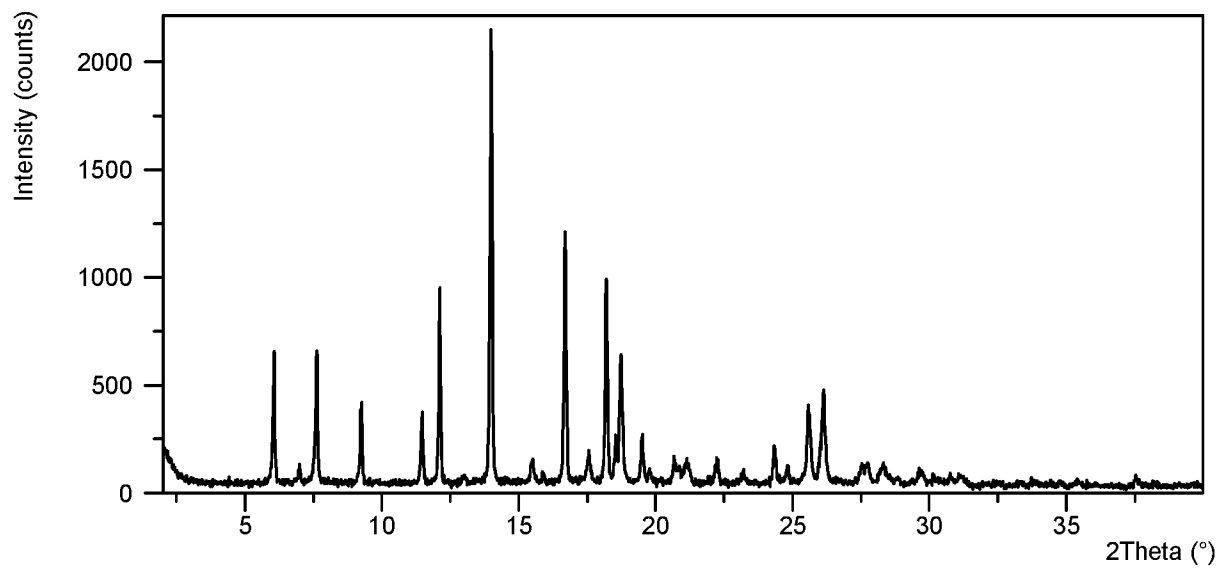


FIGURE 22

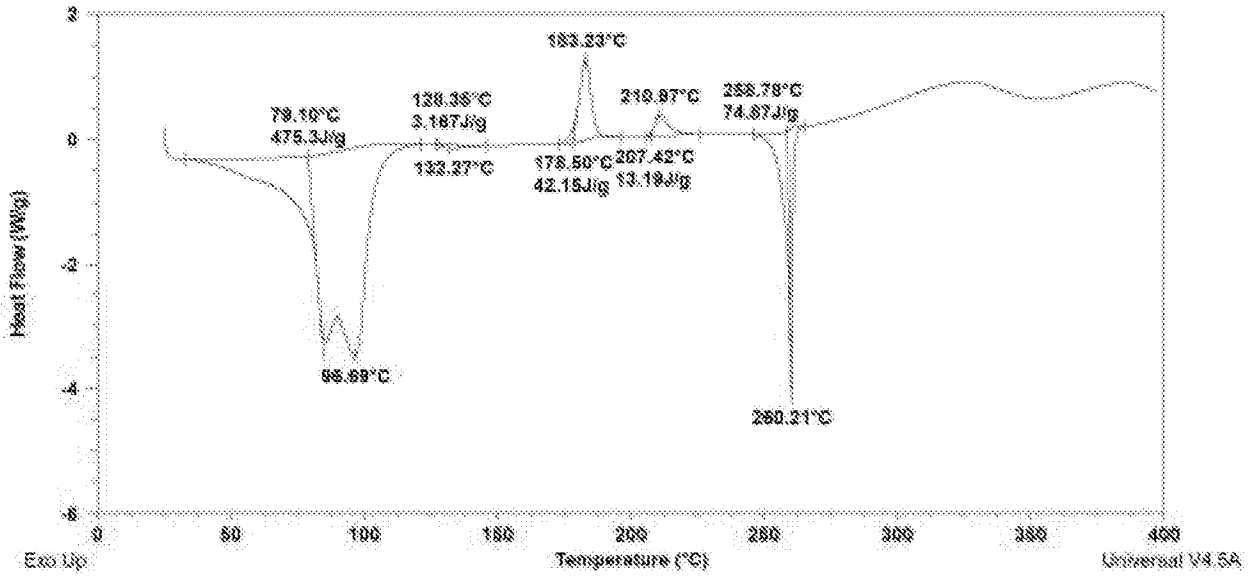


FIGURE 23

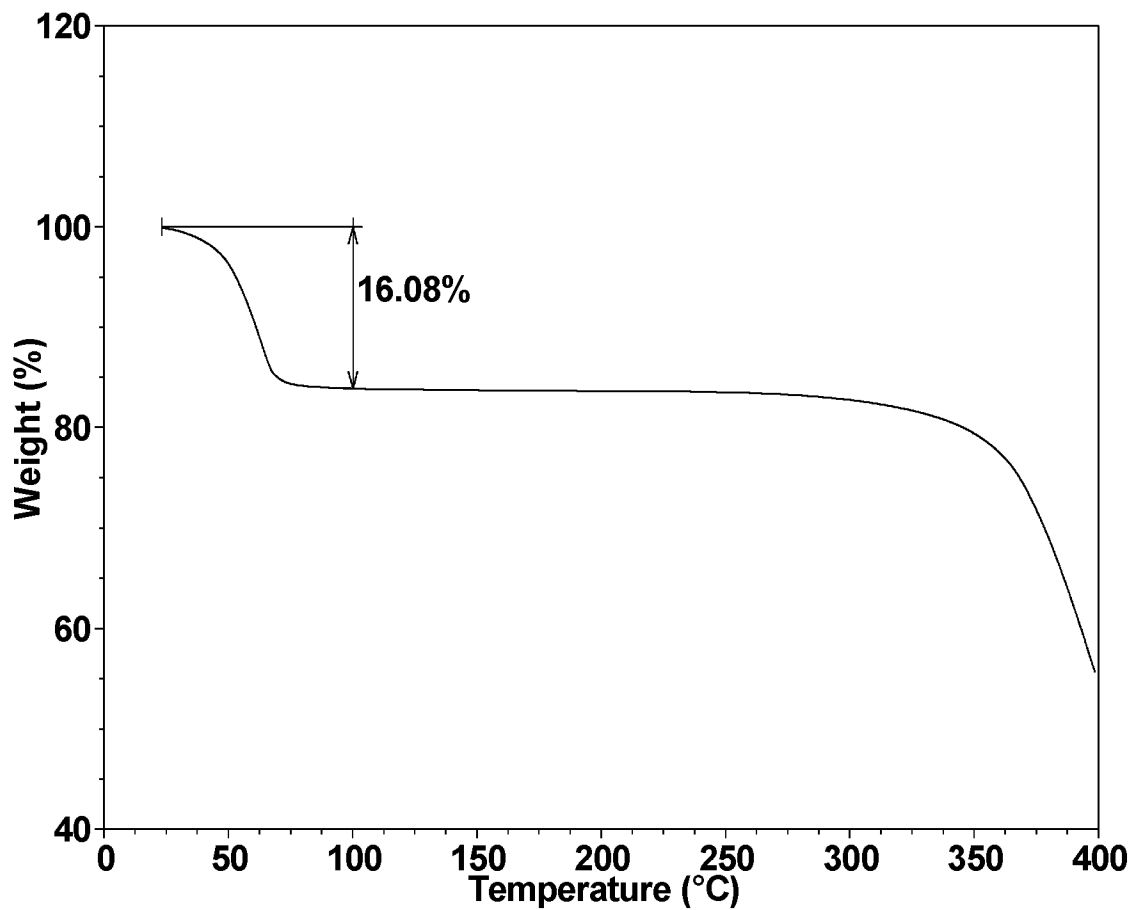


FIGURE 24

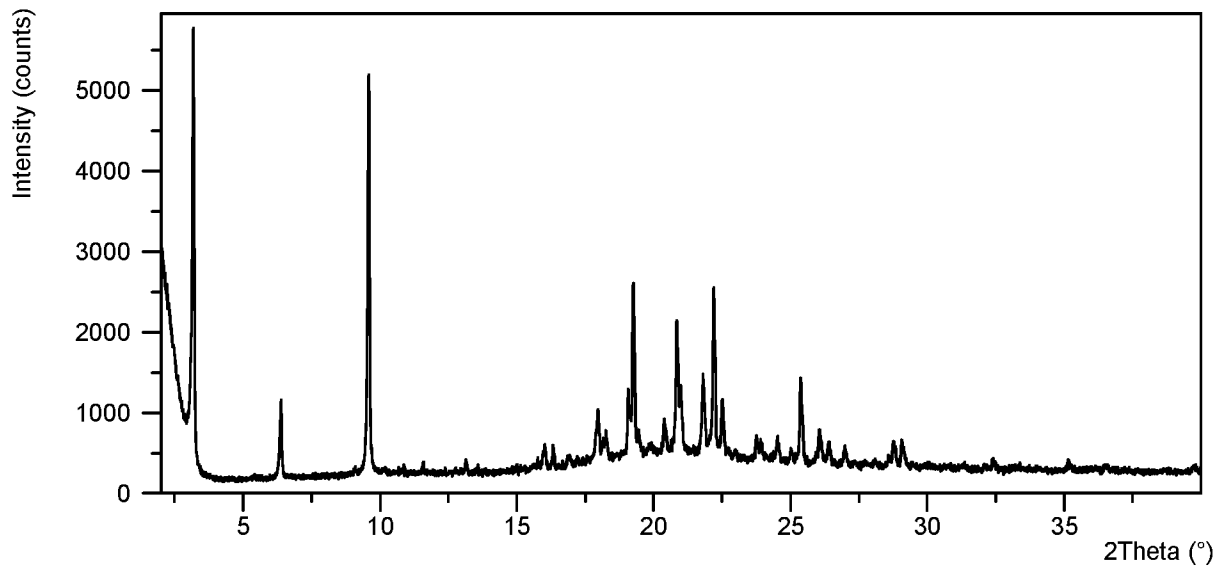


FIGURE 25

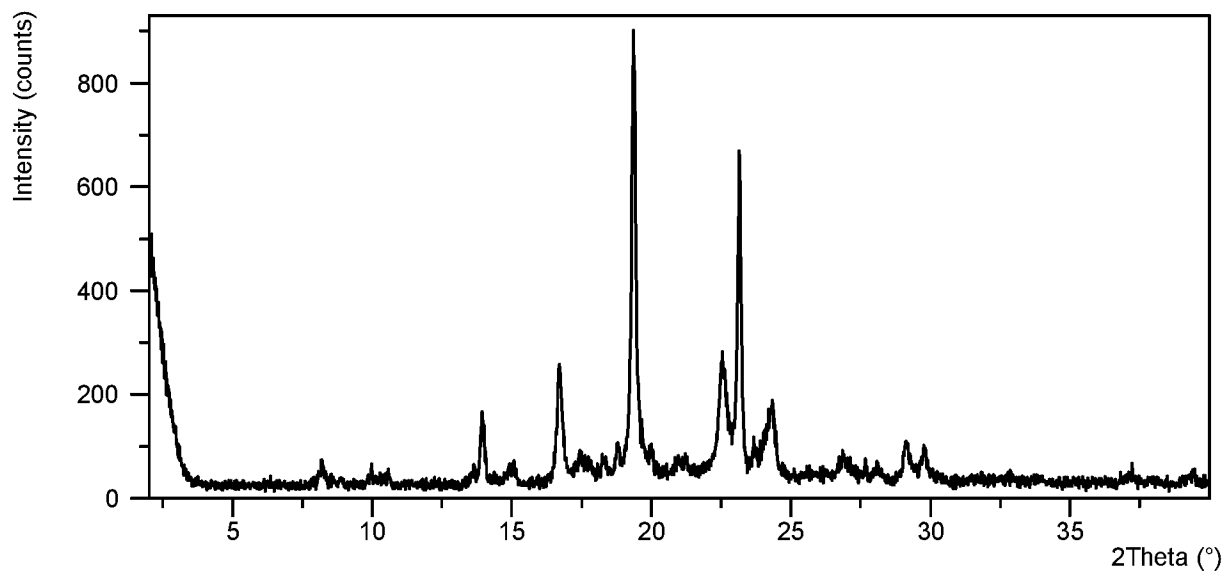


FIGURE 26

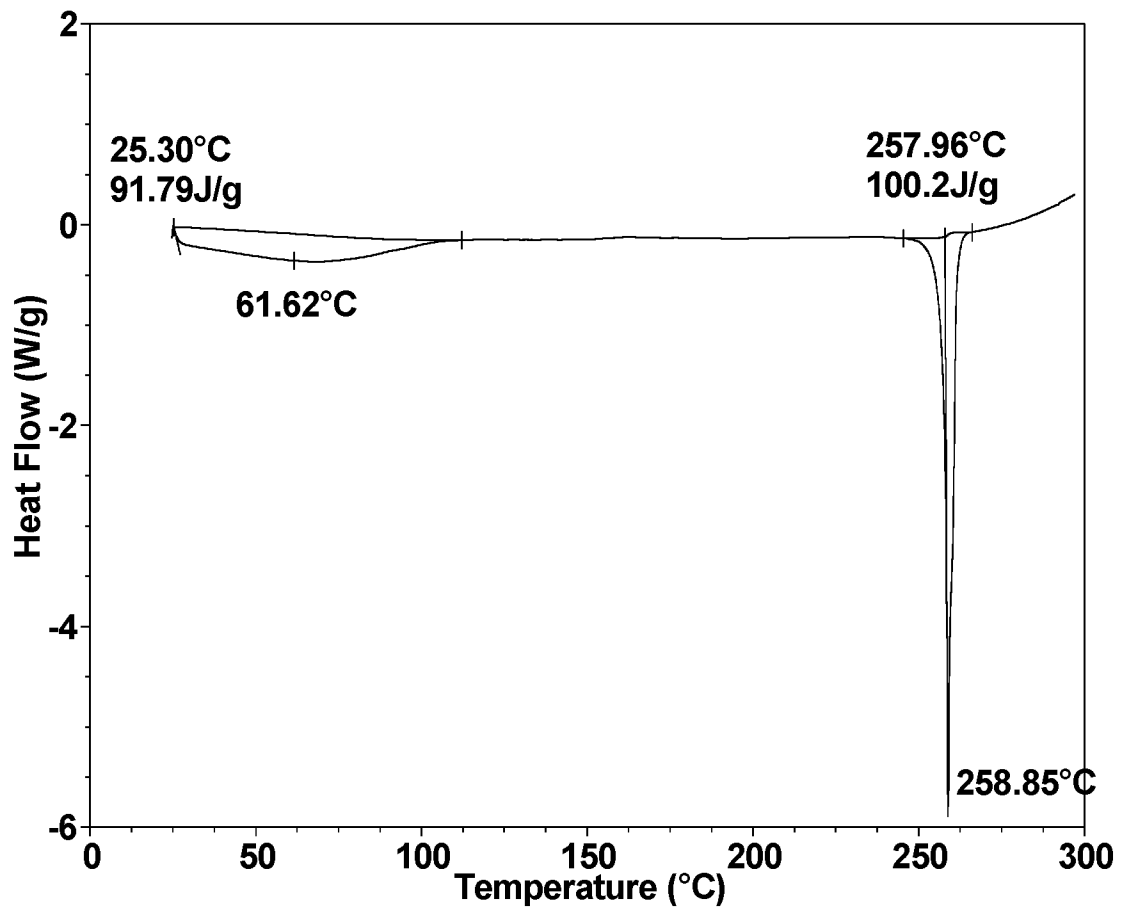


FIGURE 27

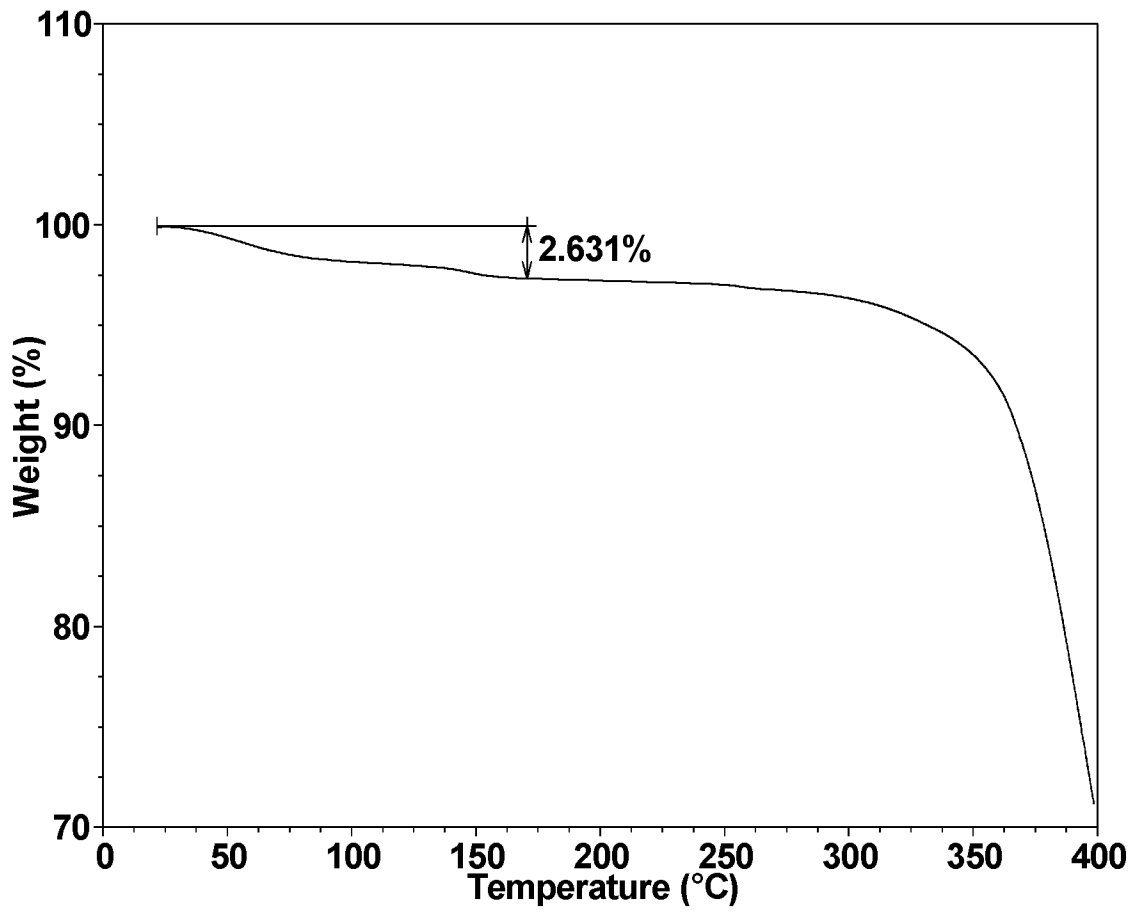


FIGURE 28

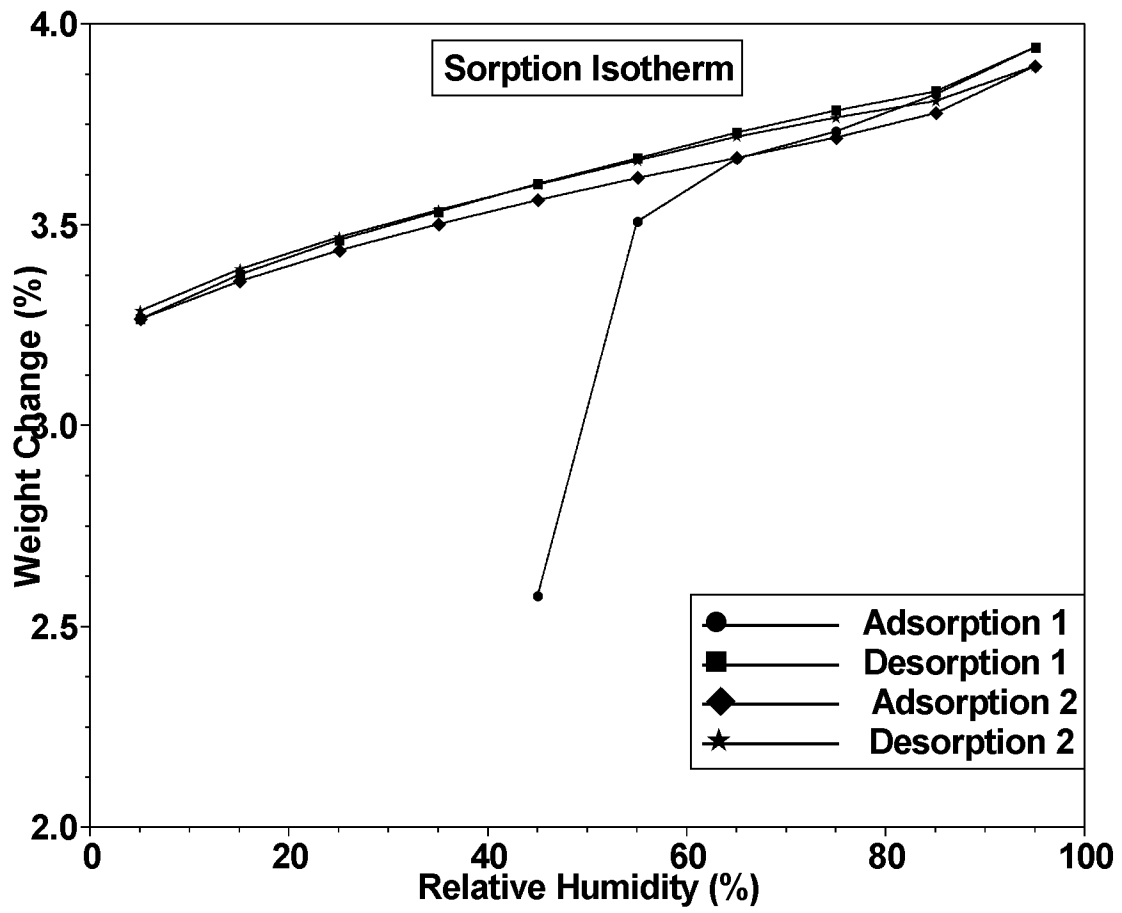


FIGURE 29

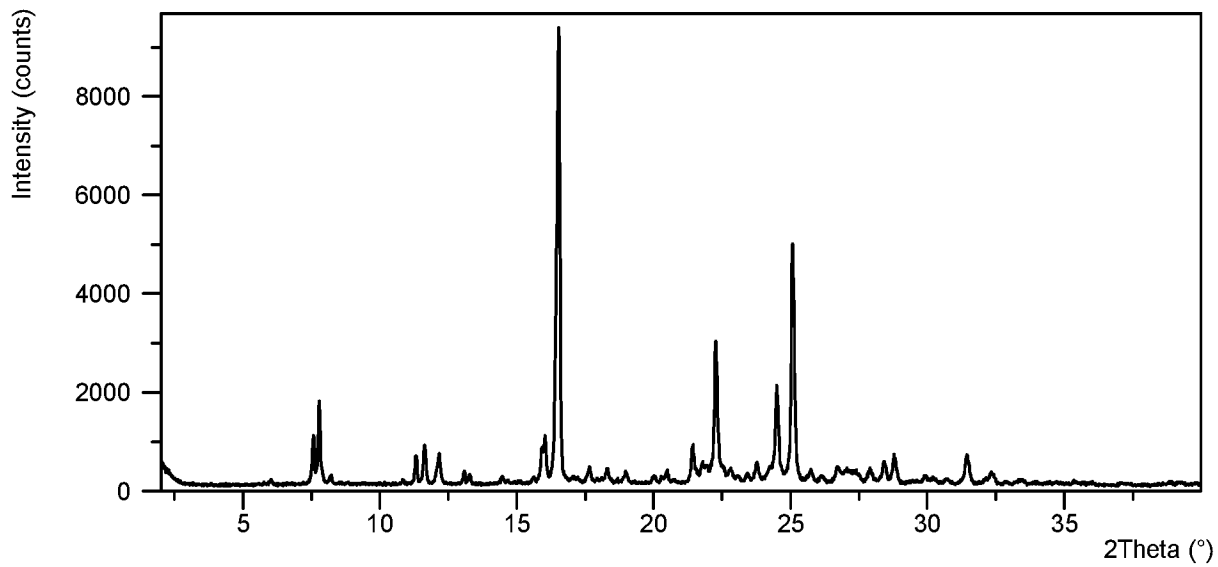


FIGURE 30

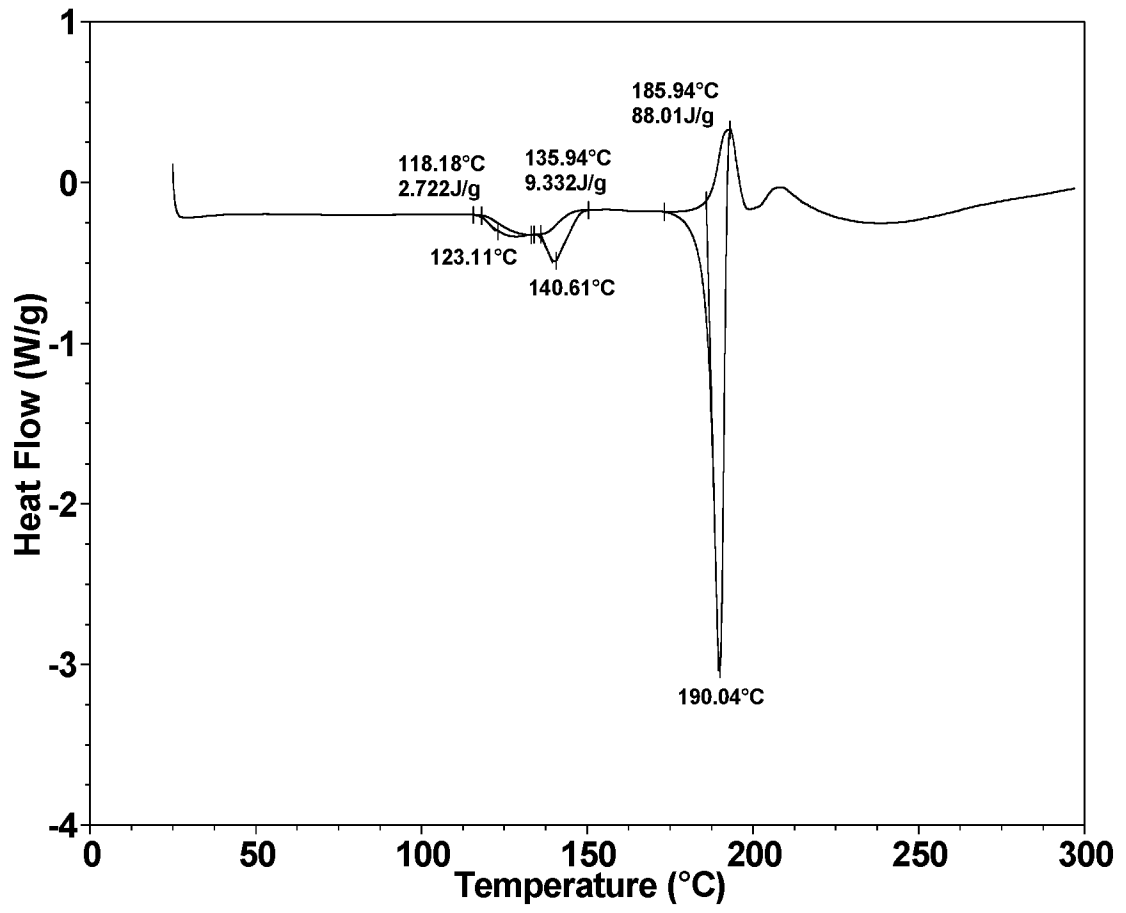


FIGURE 31

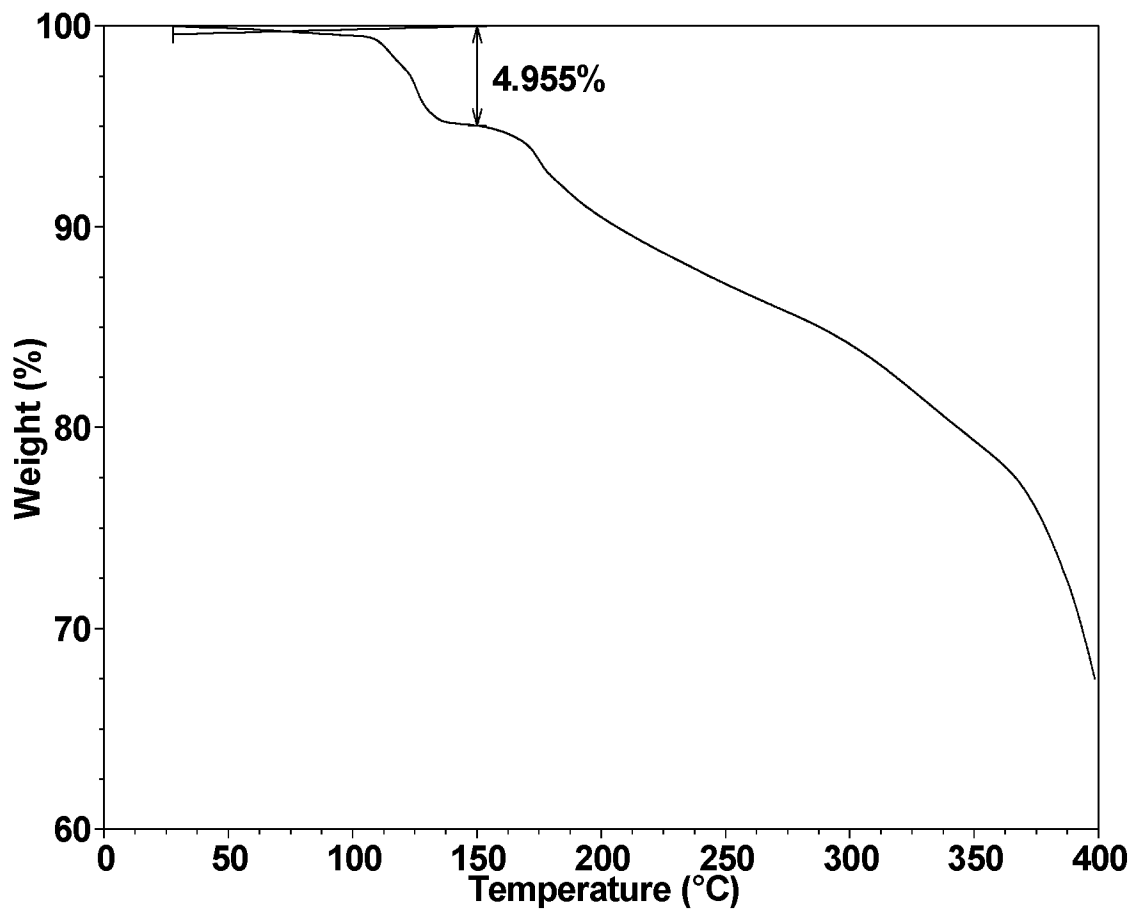


FIGURE 32

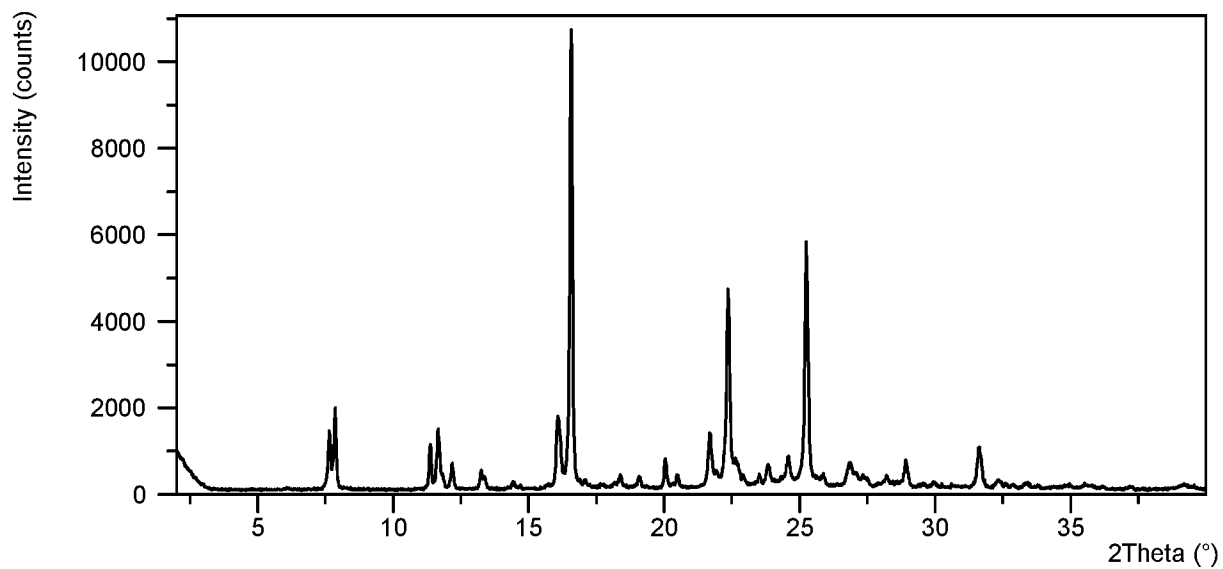


FIGURE 33

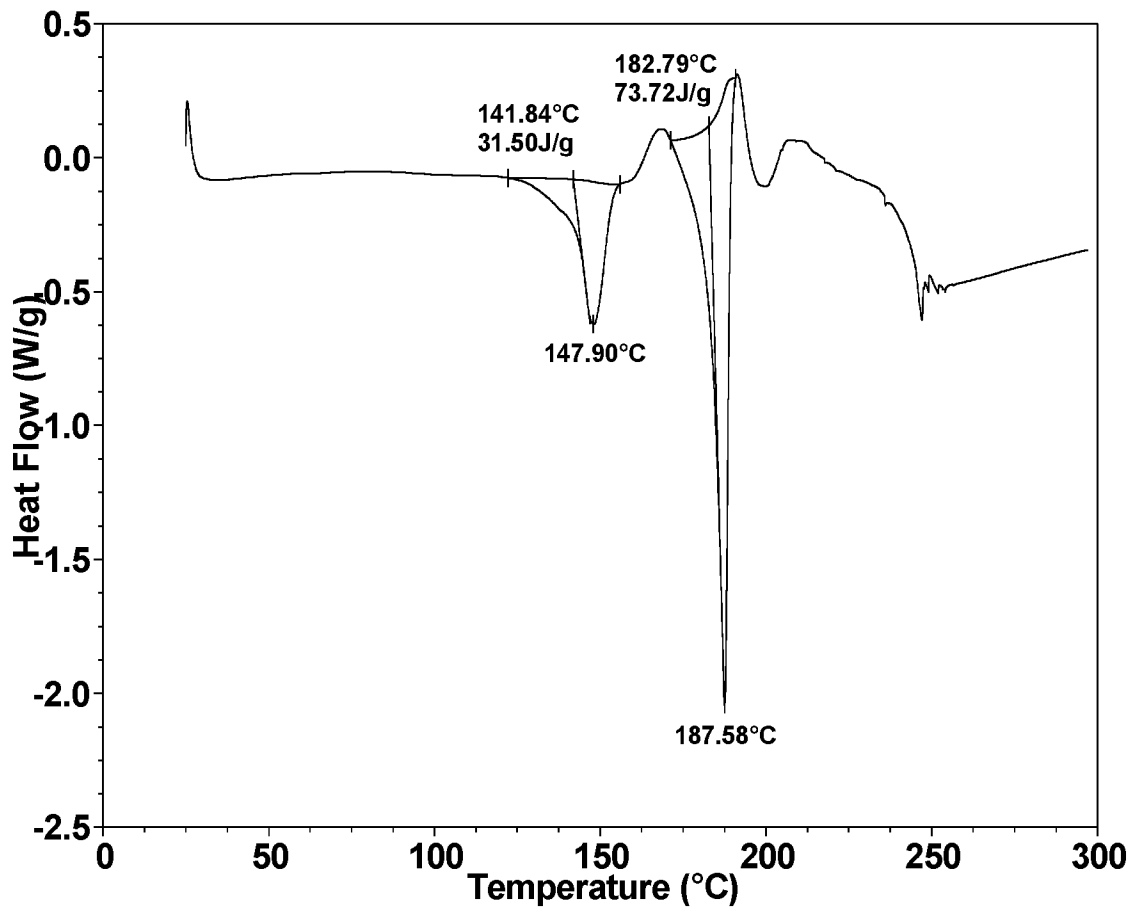


FIGURE 34

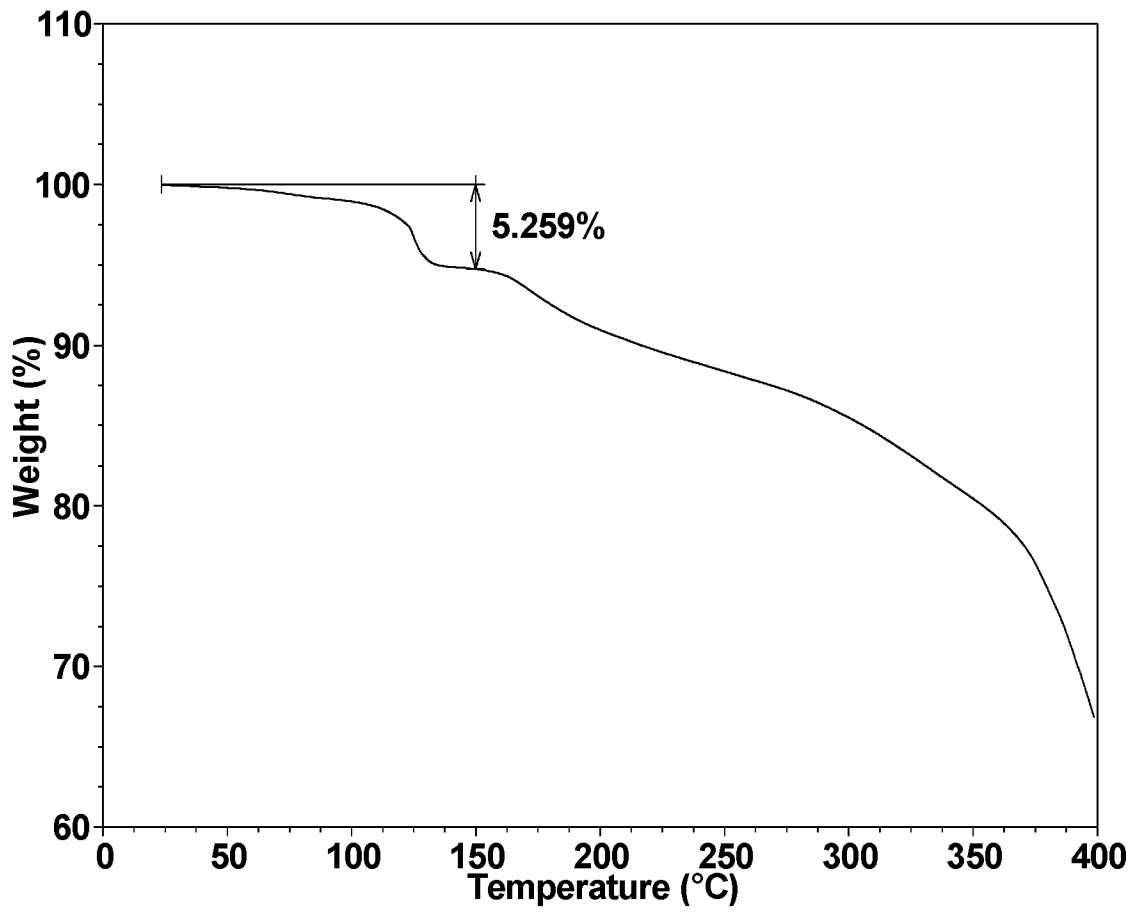


FIGURE 35

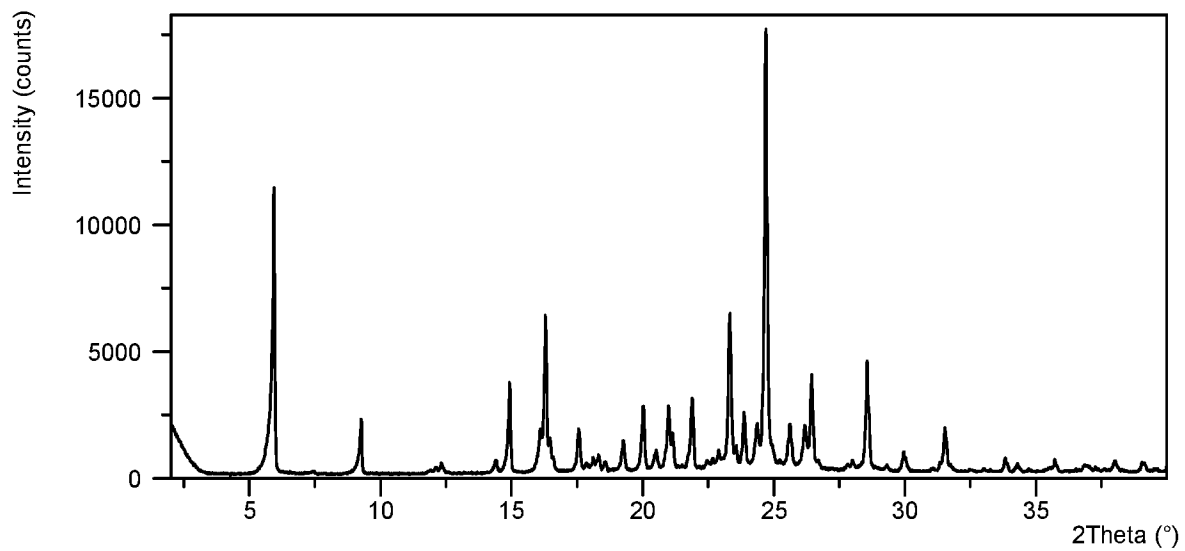


FIGURE 36

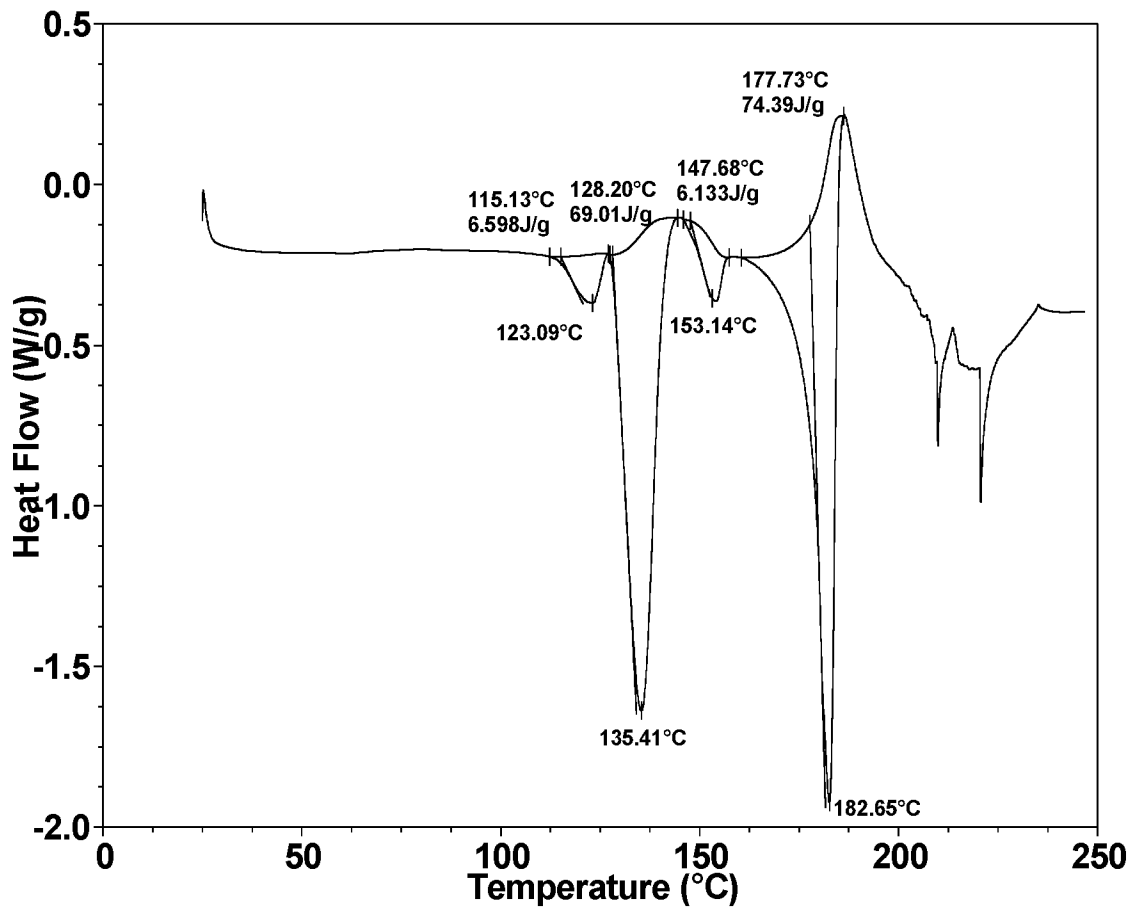


FIGURE 37

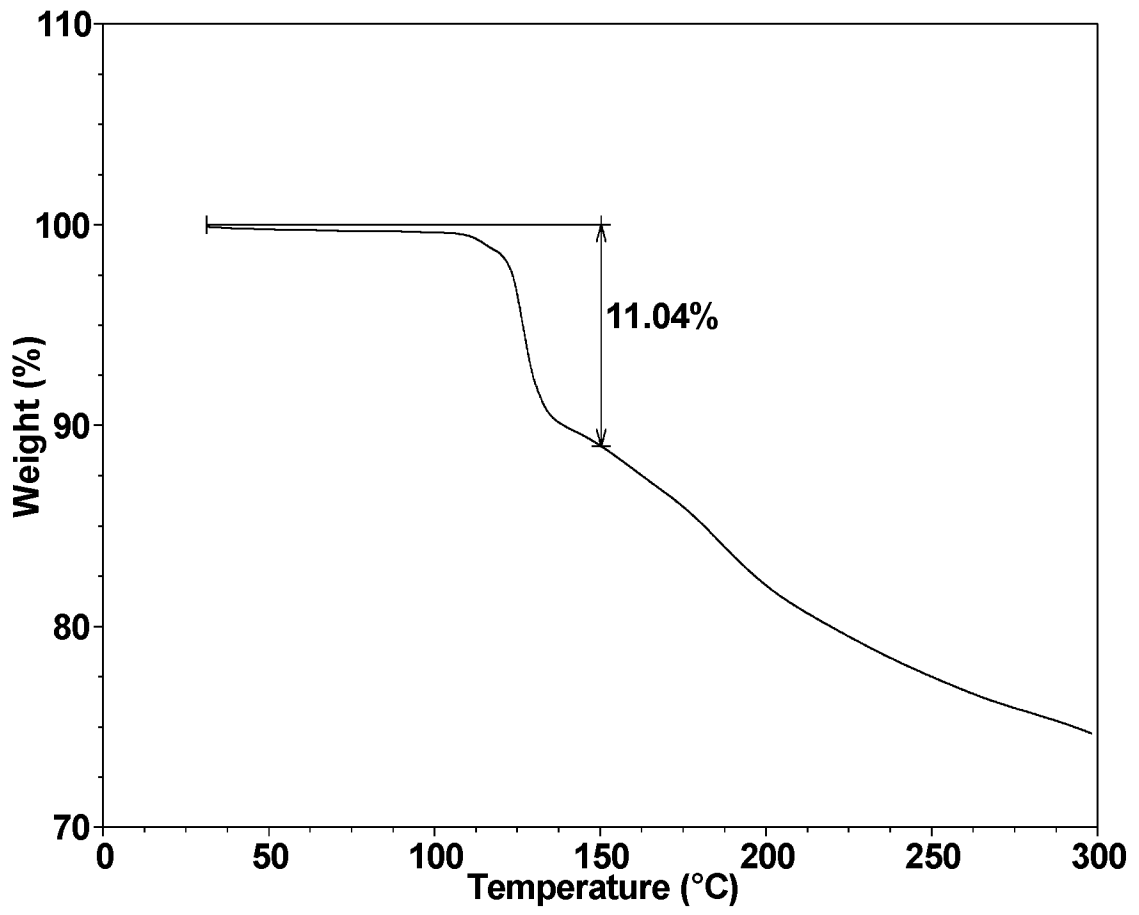


FIGURE 38

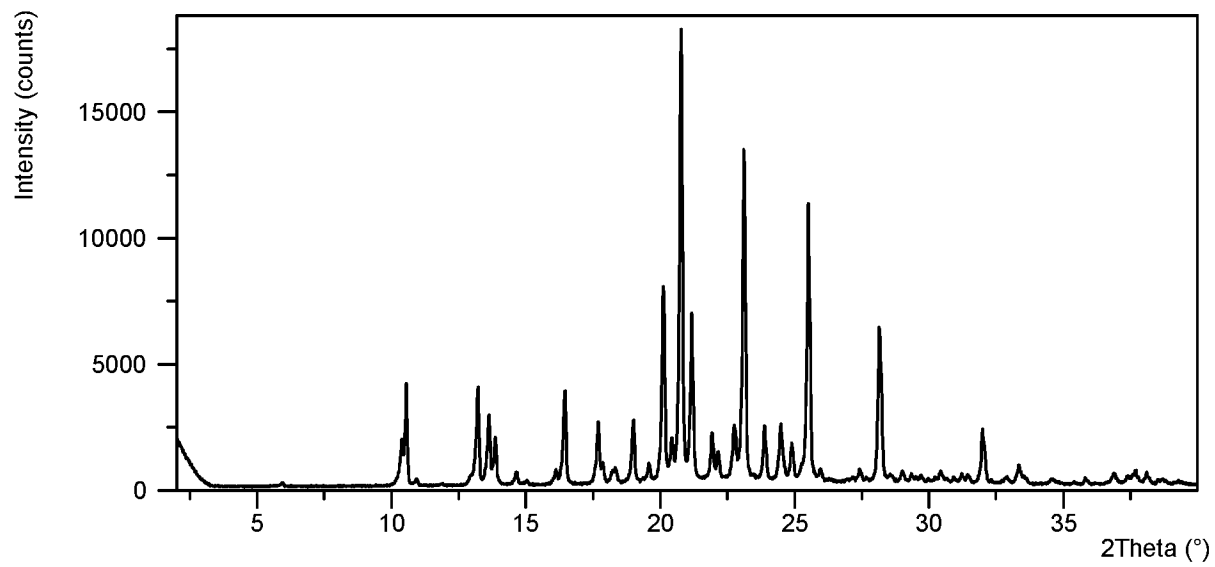


FIGURE 39

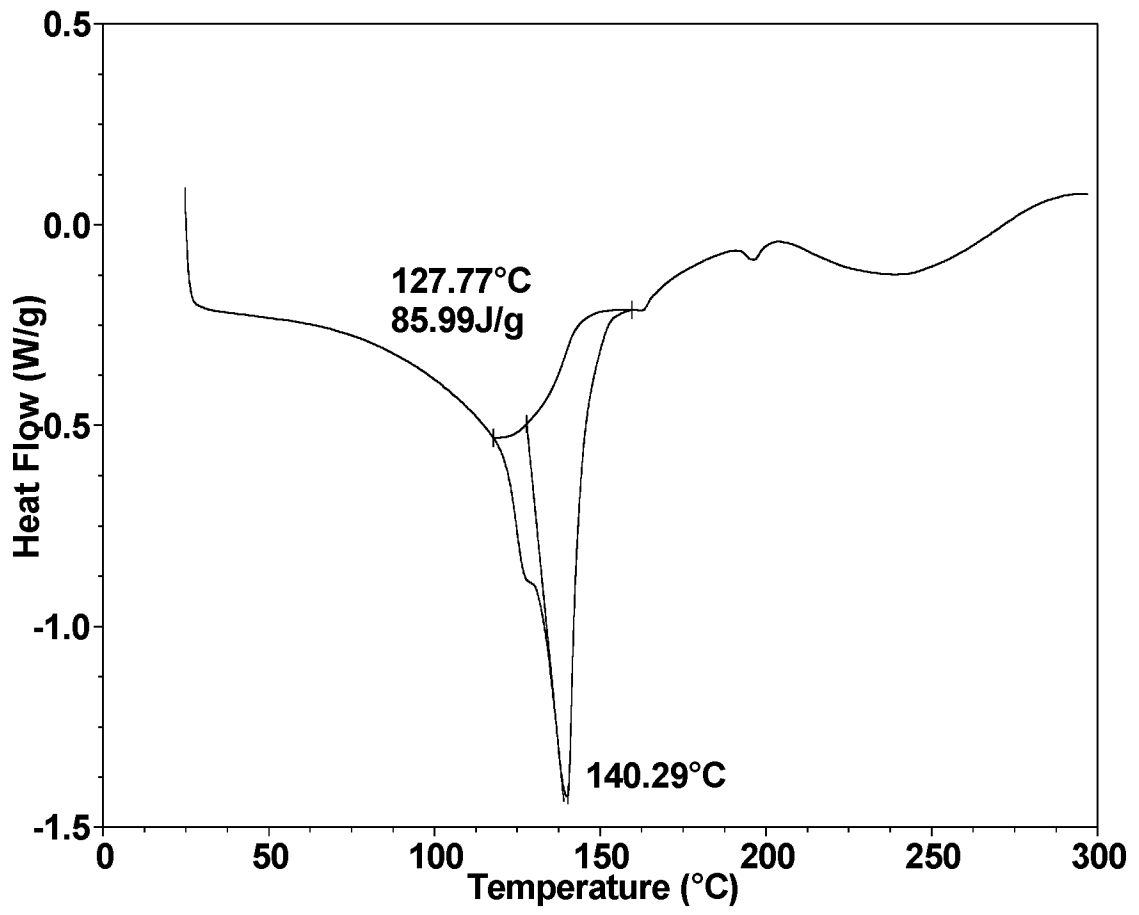


FIGURE 40

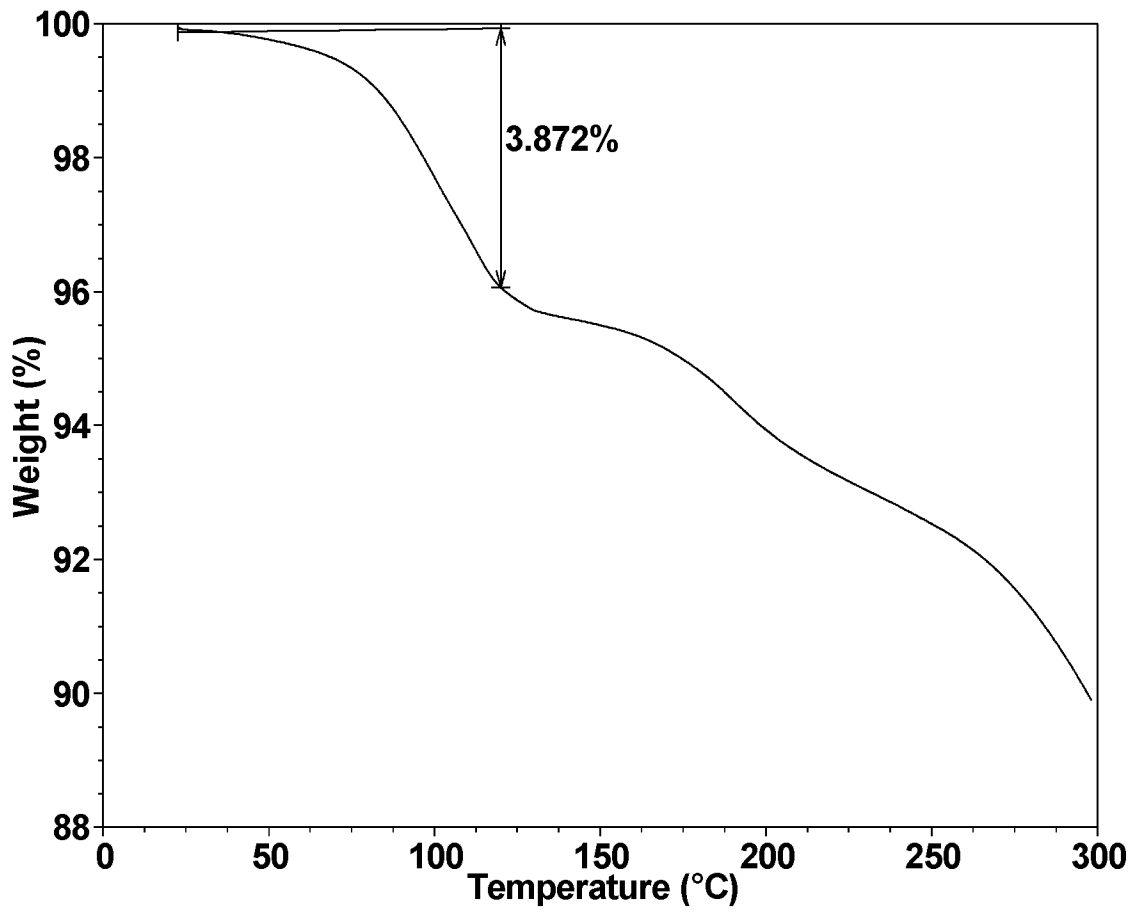


FIGURE 41

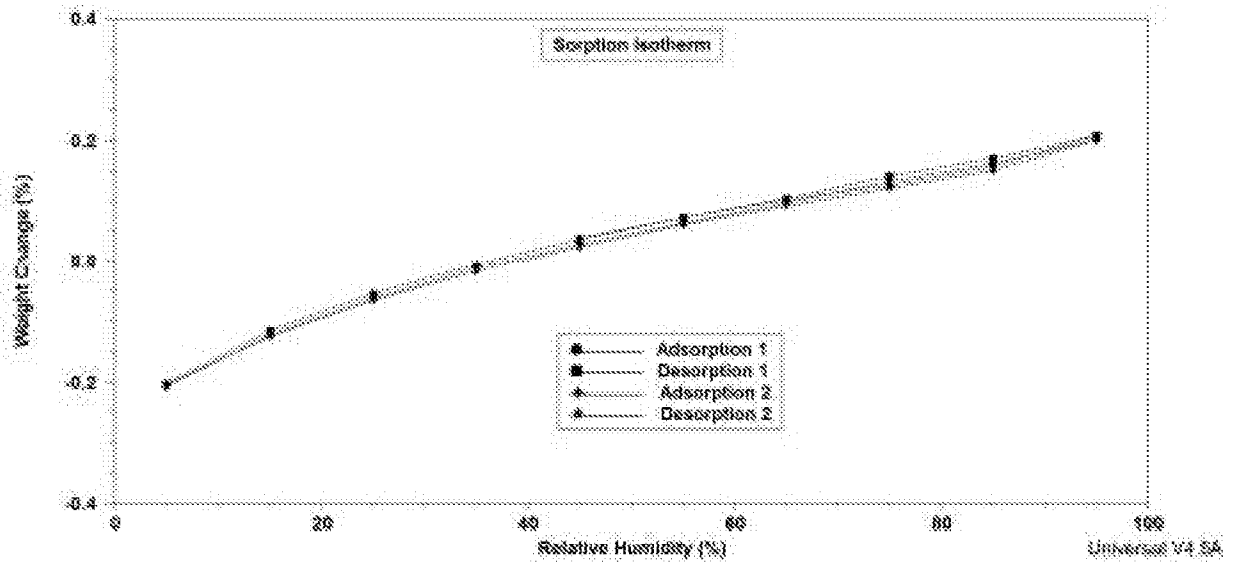


FIGURE 42

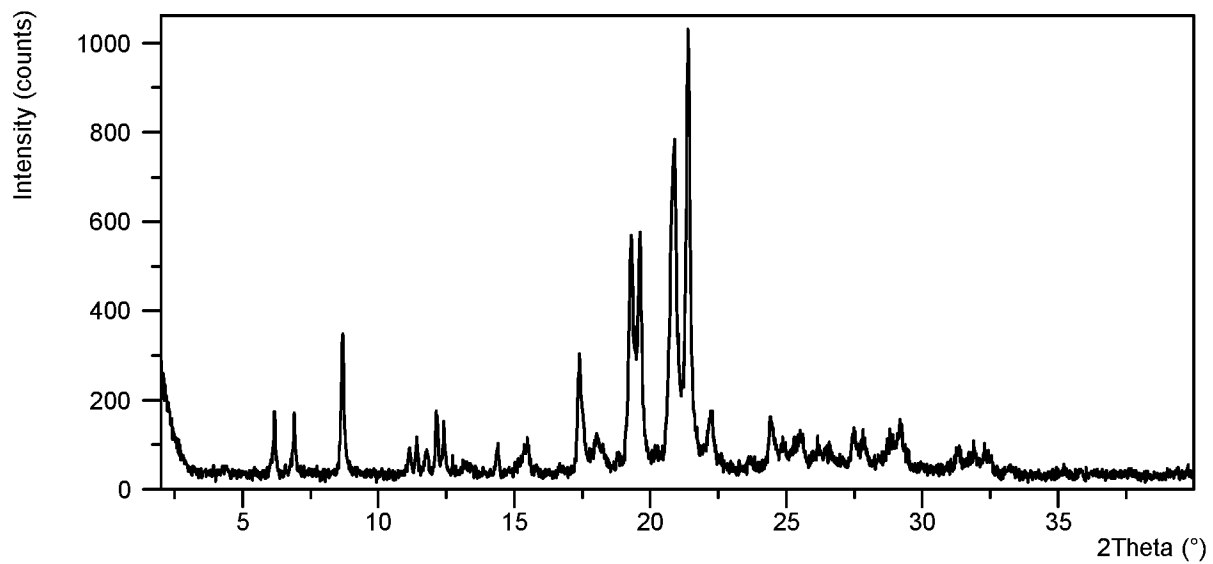


FIGURE 43

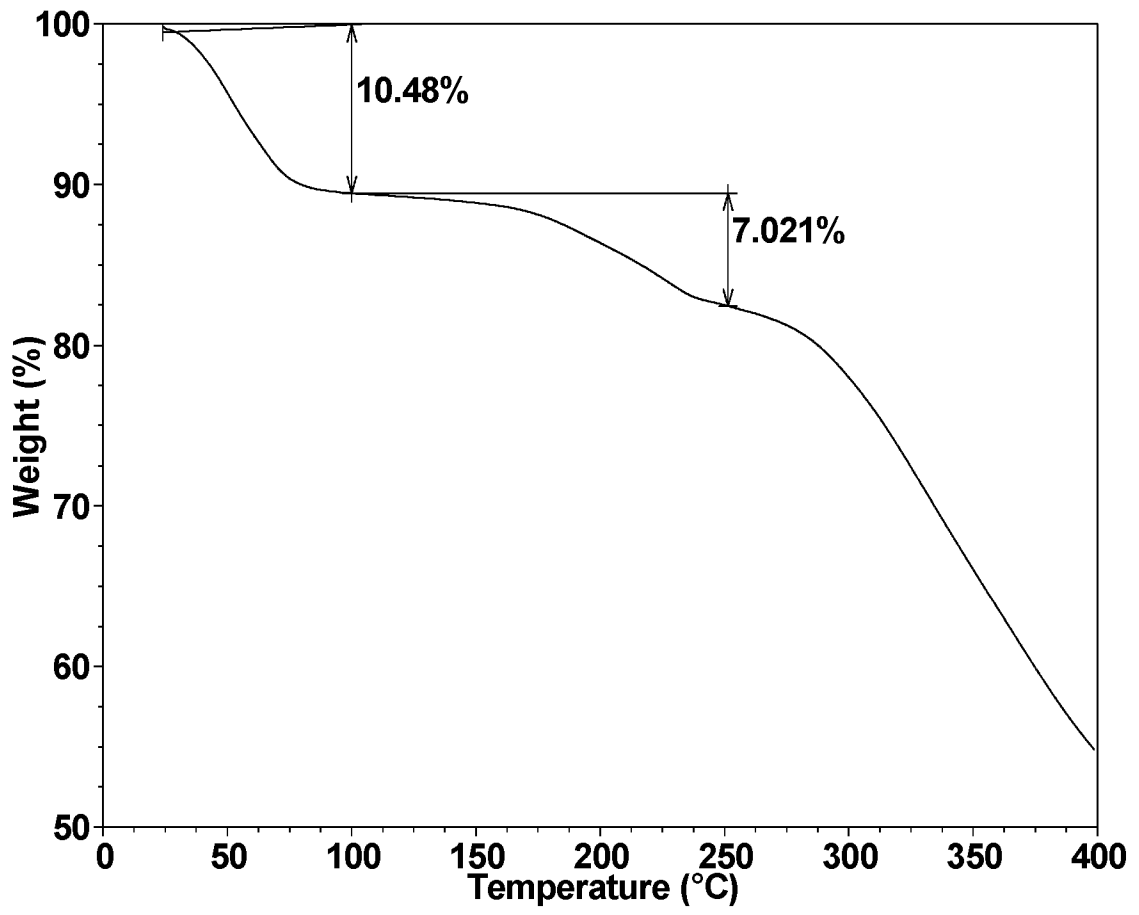


FIGURE 44

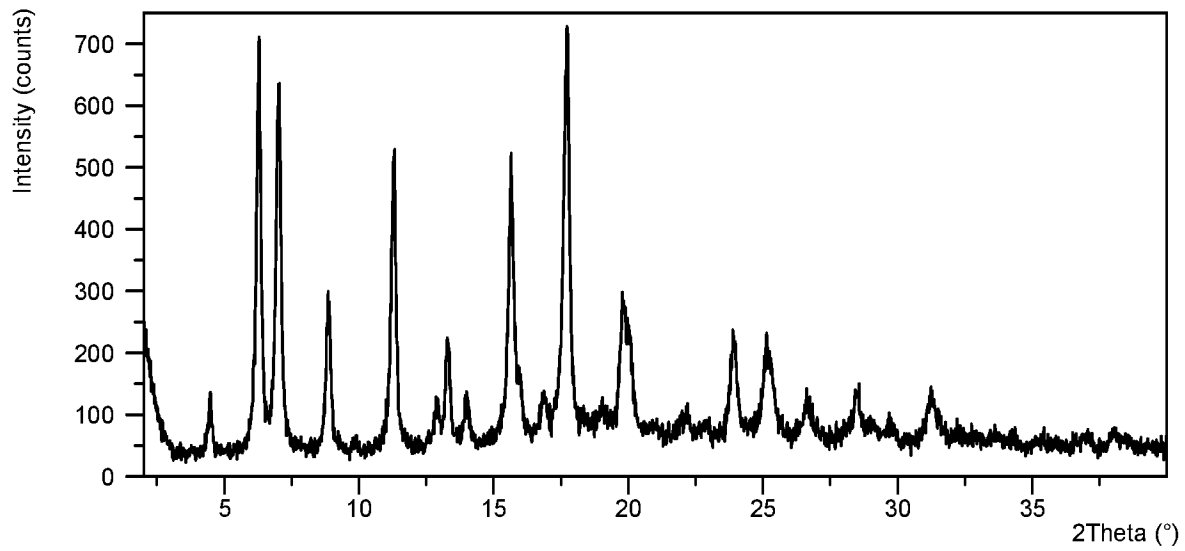


FIGURE 45

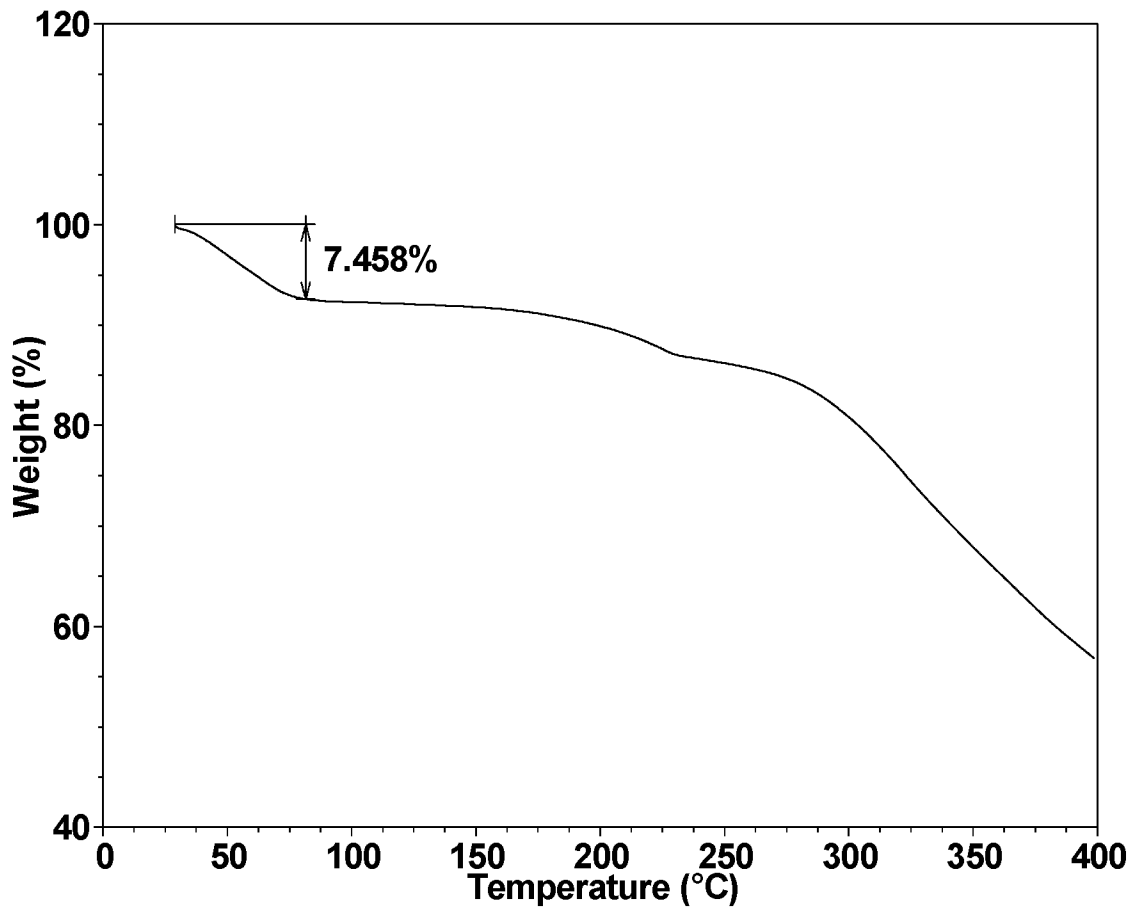


FIGURE 46

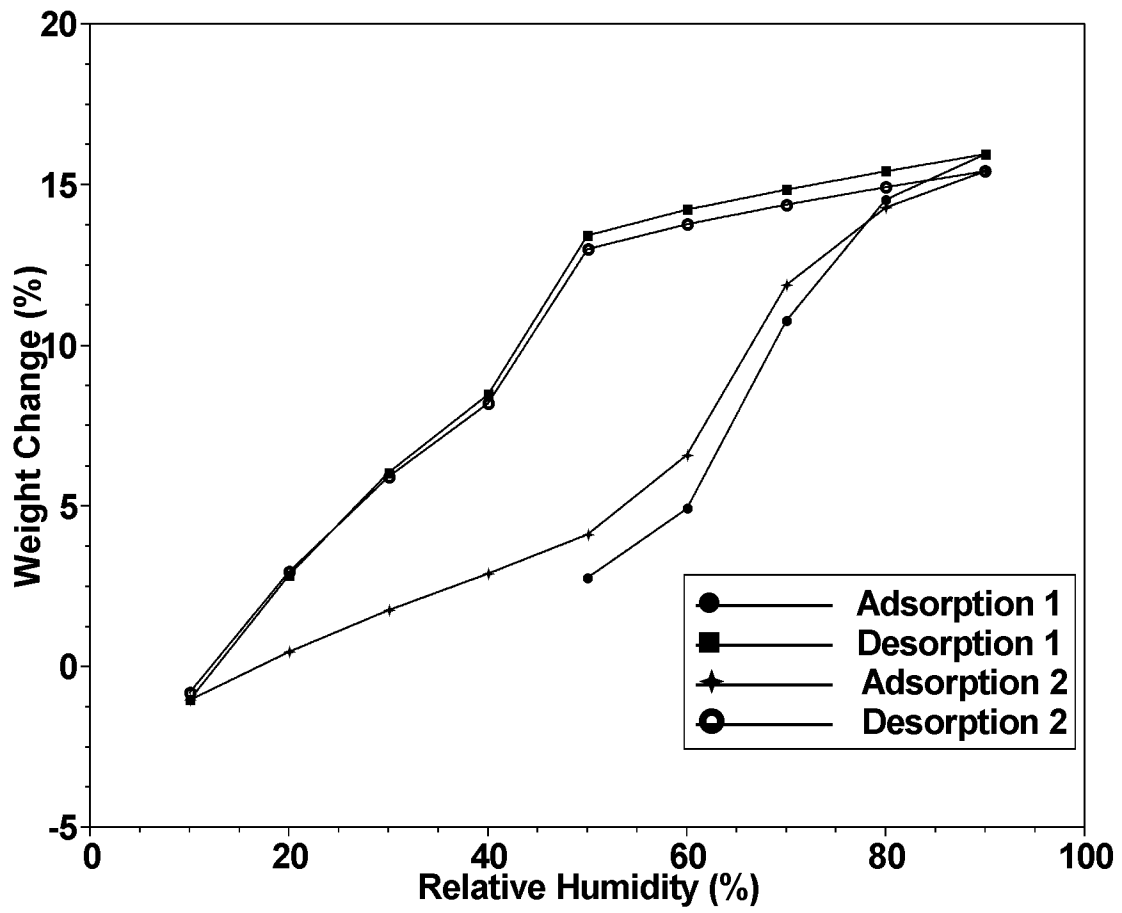


FIGURE 47

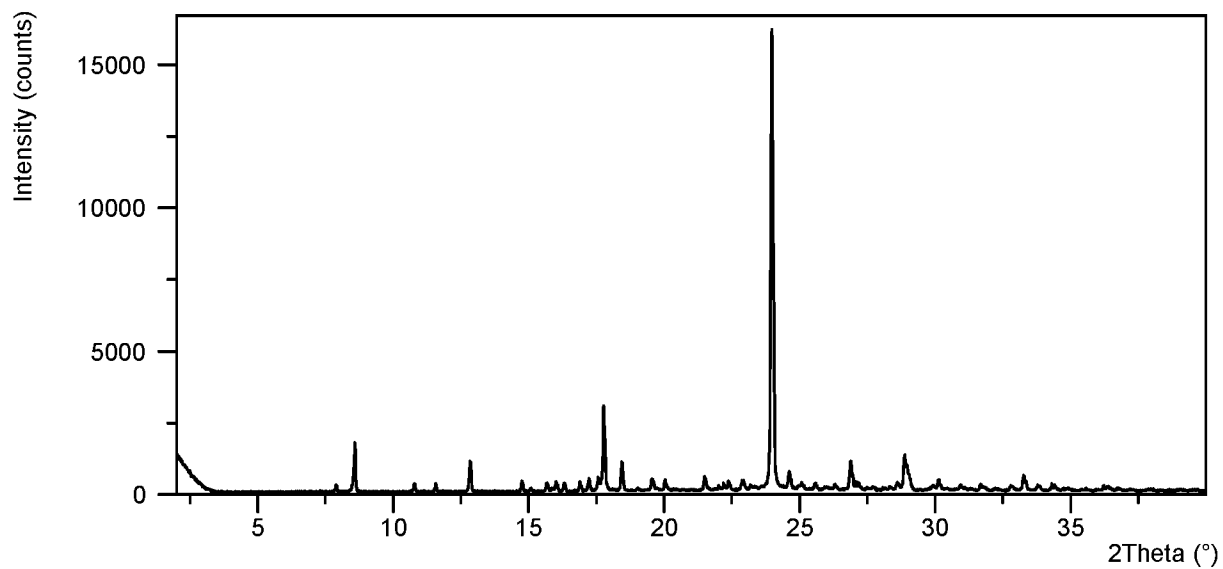


FIGURE 48

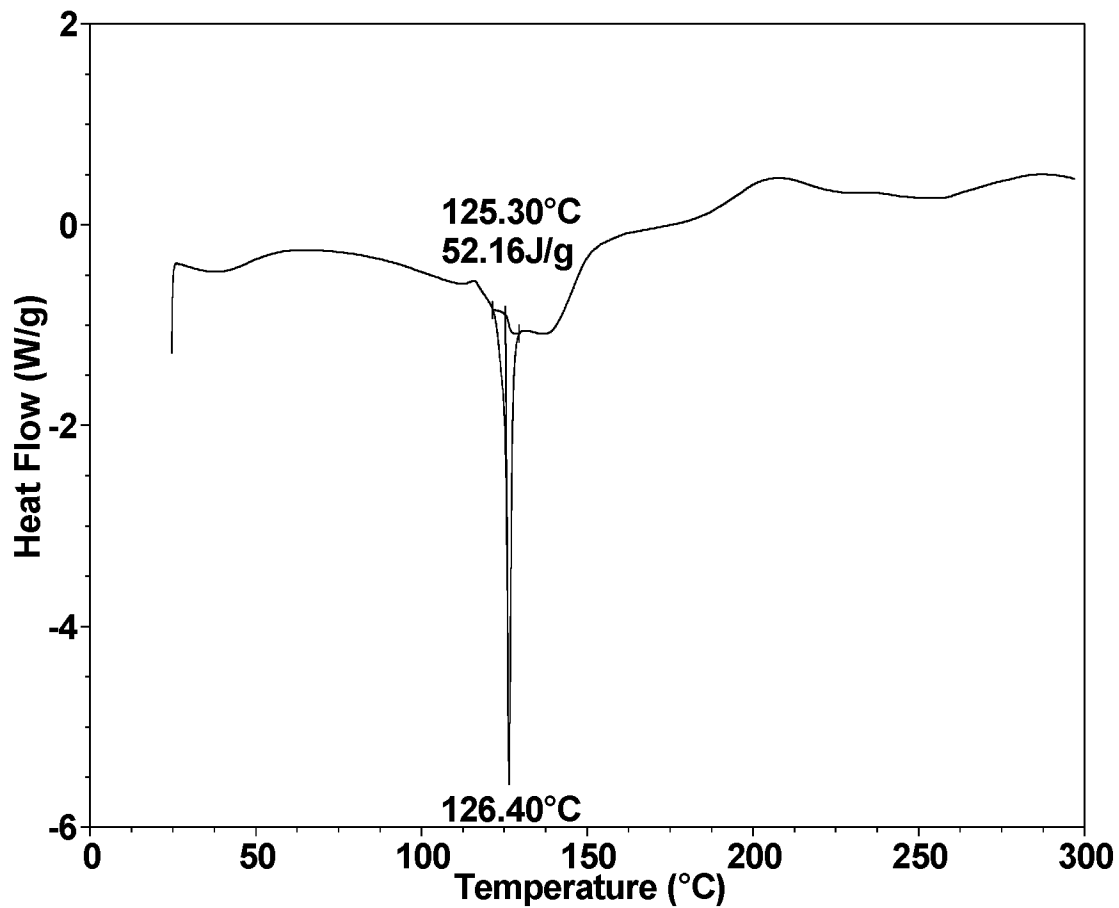


FIGURE 49

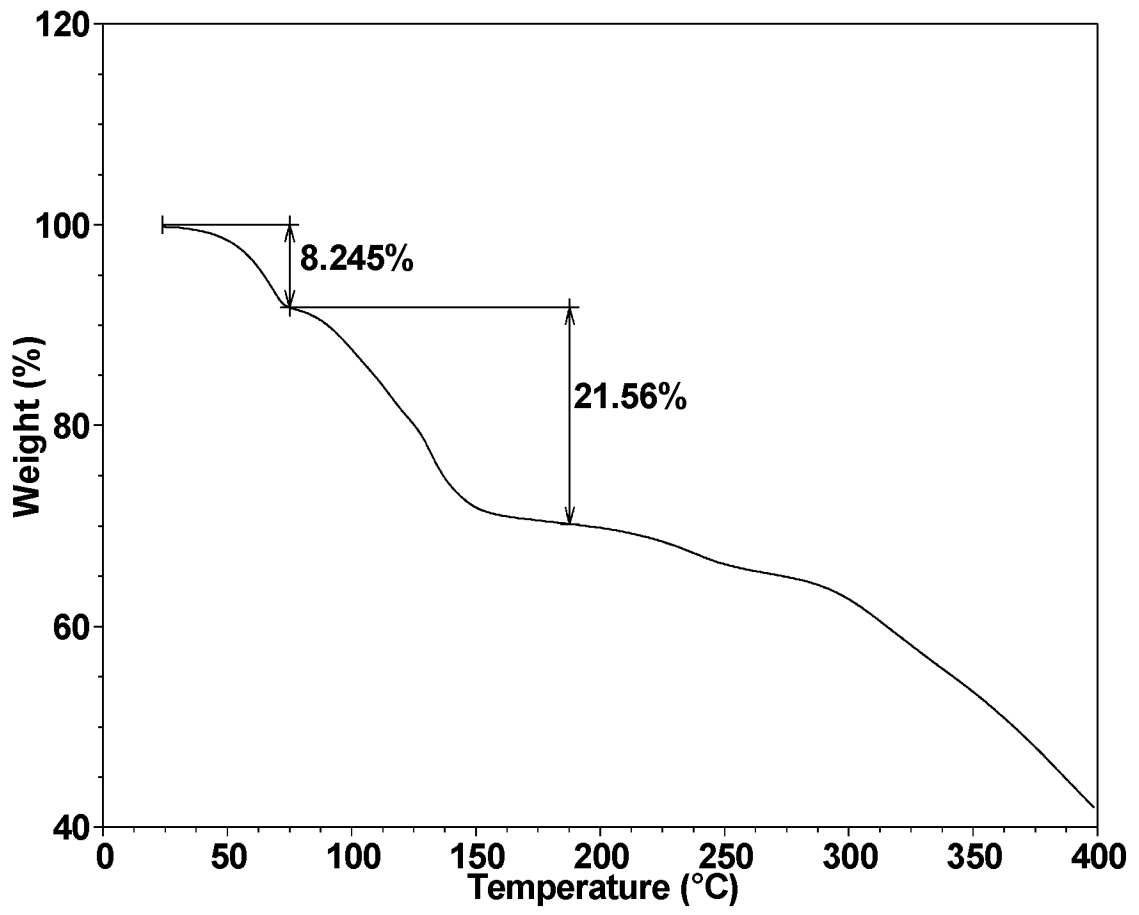


FIGURE 50

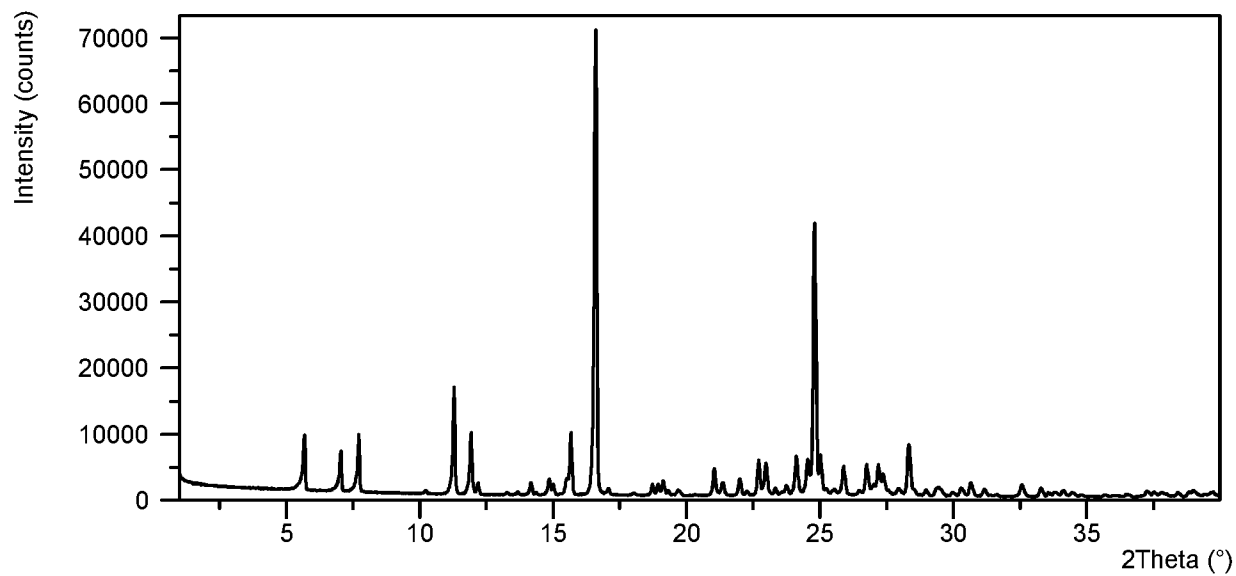


FIGURE 51

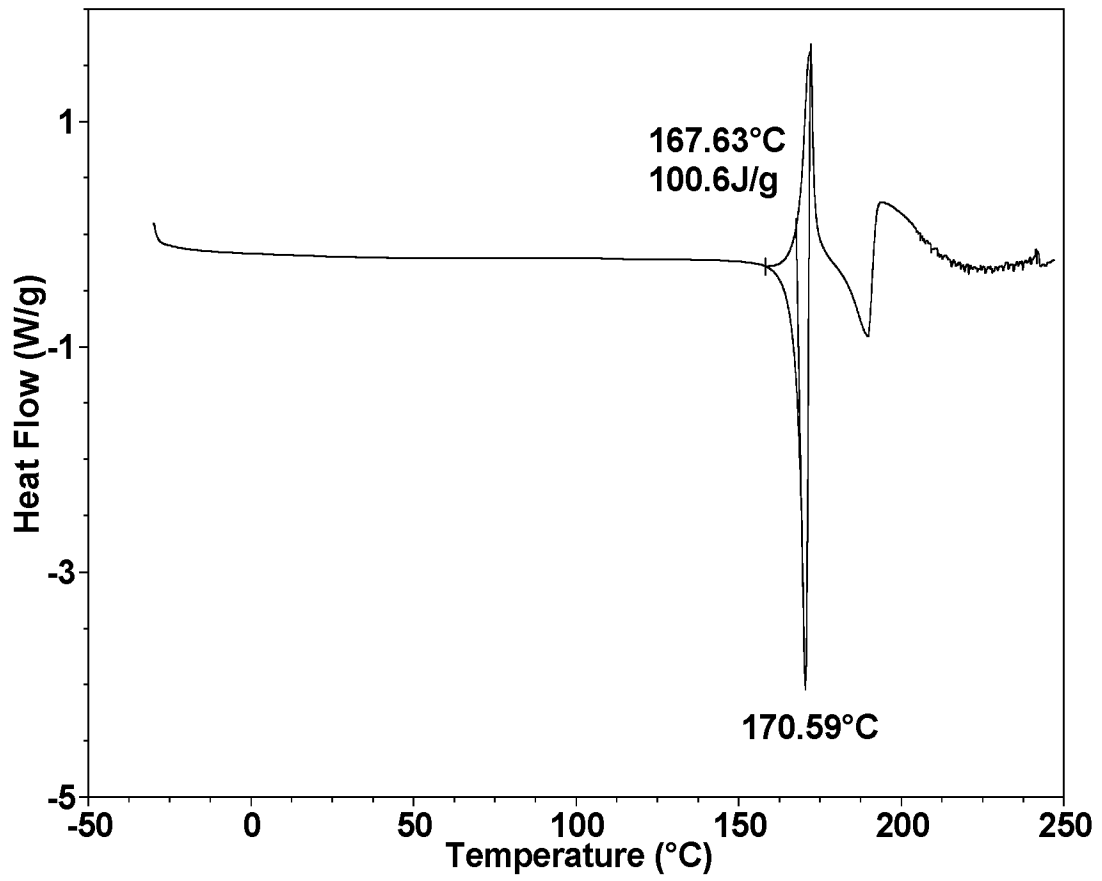


FIGURE 52

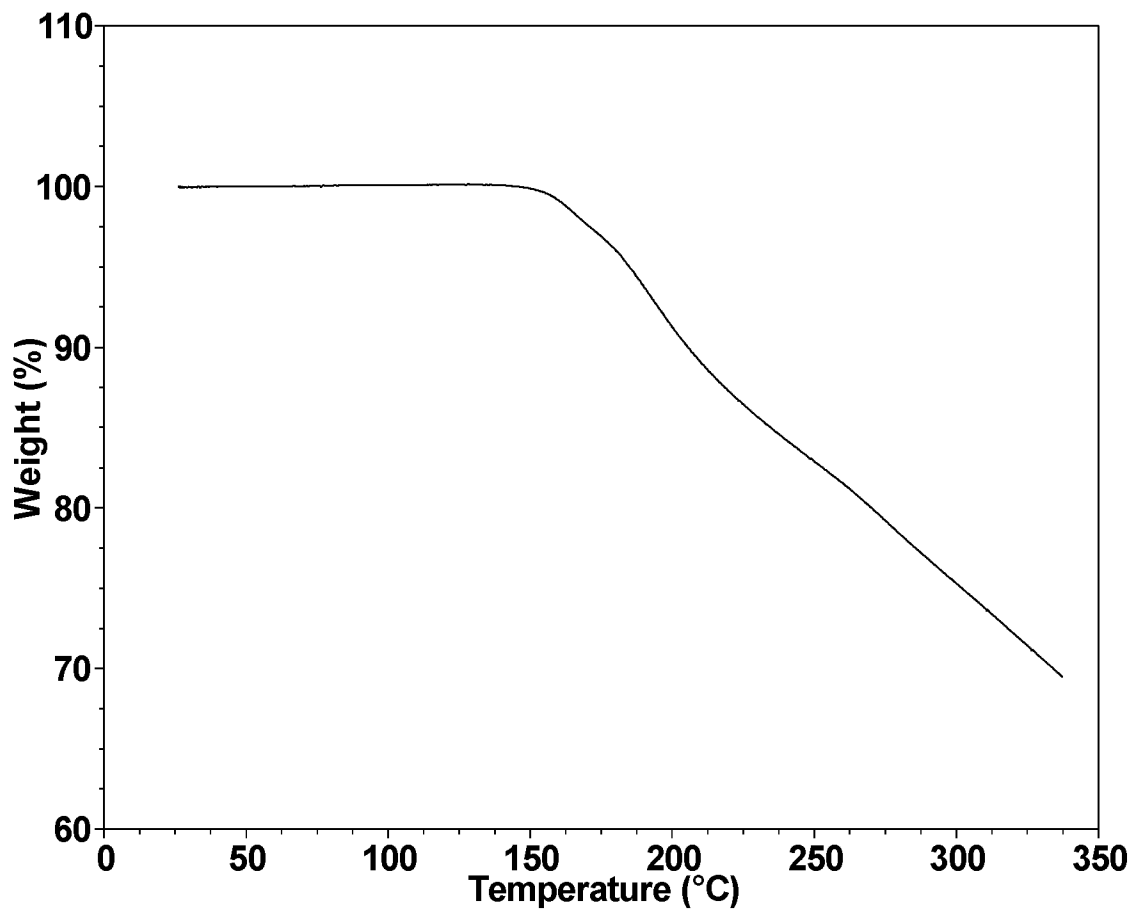


FIGURE 53

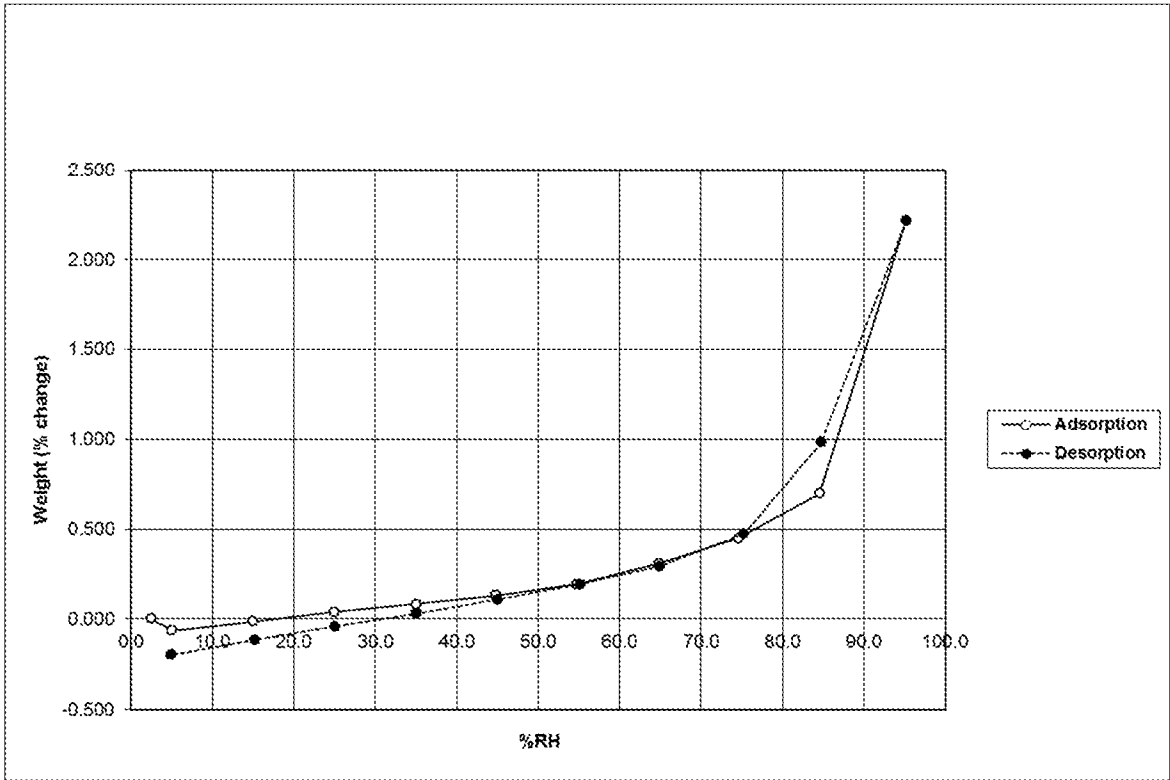


FIGURE 54

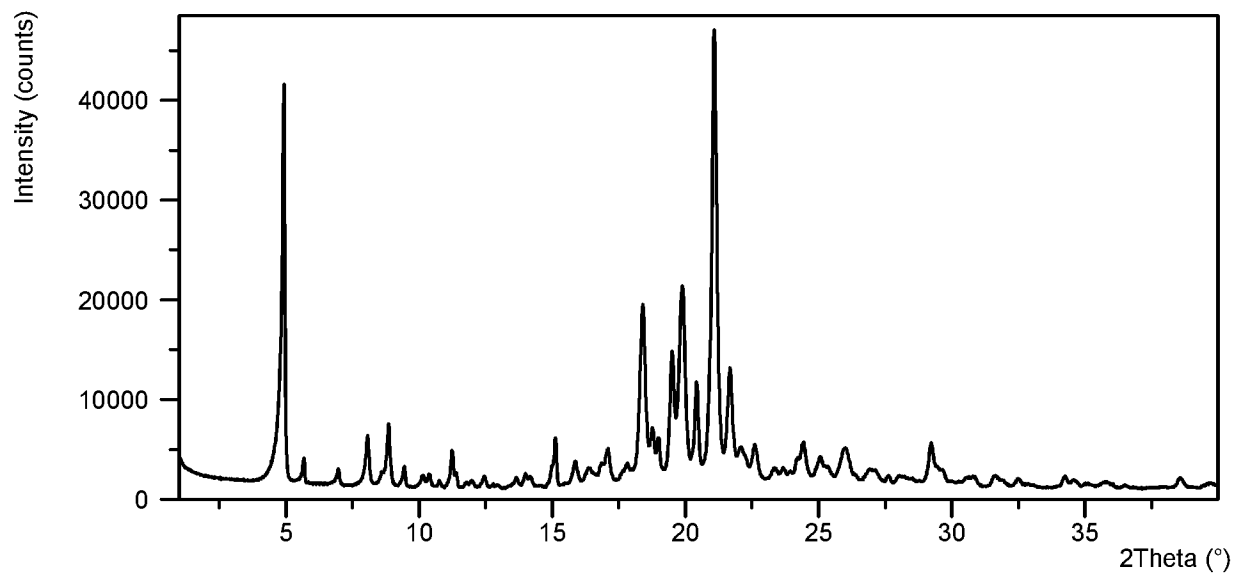


FIGURE 55

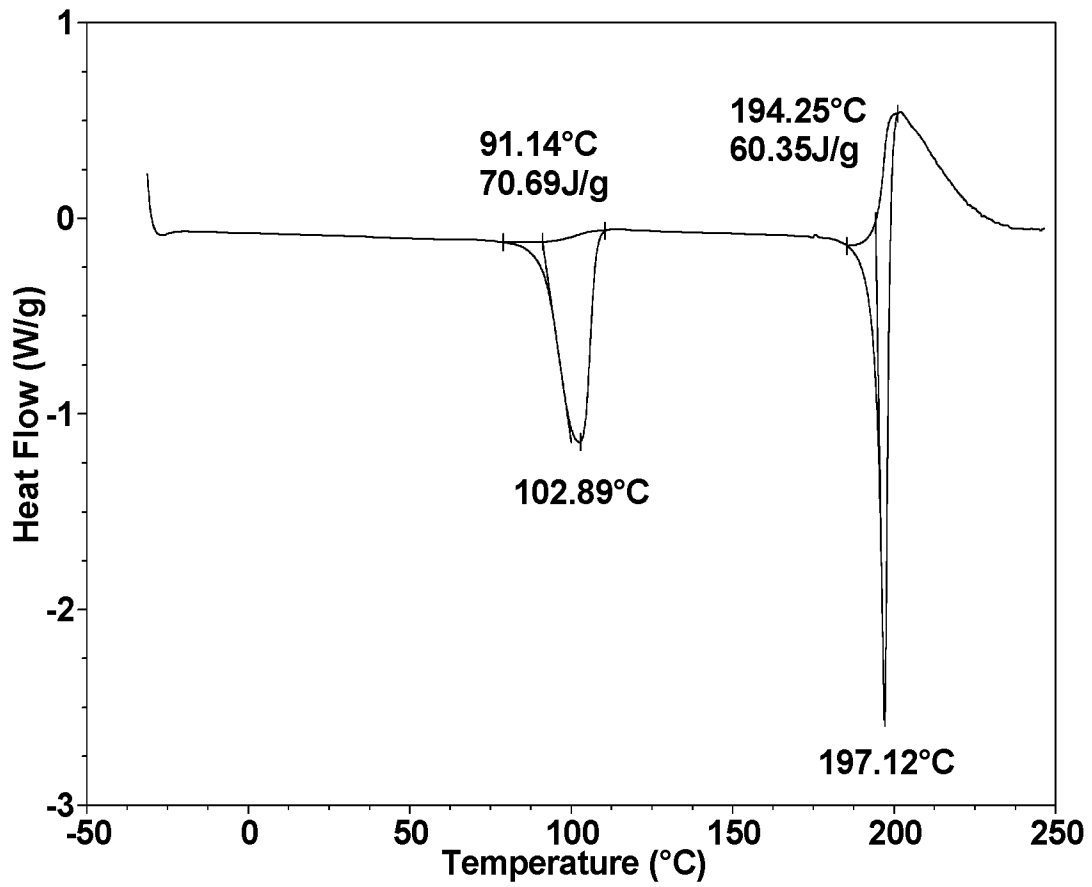


FIGURE 56

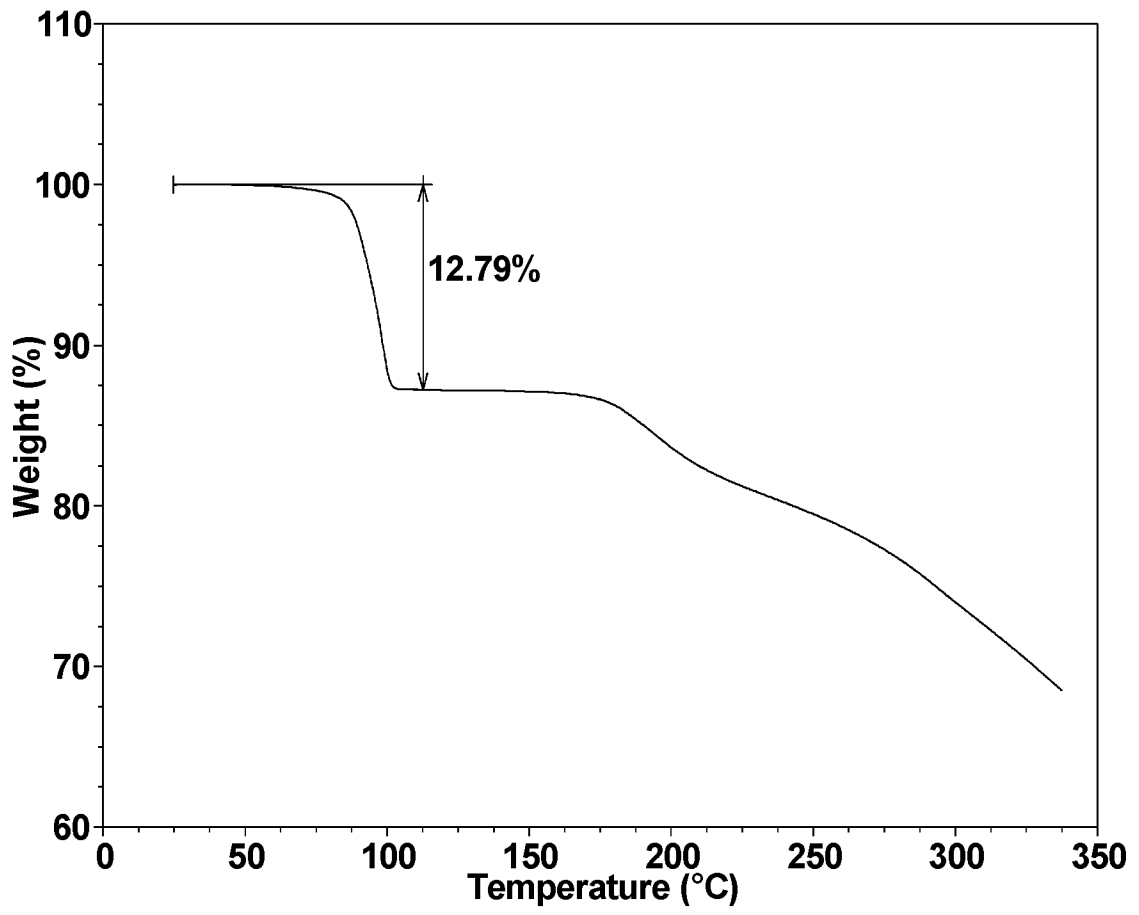


FIGURE 57

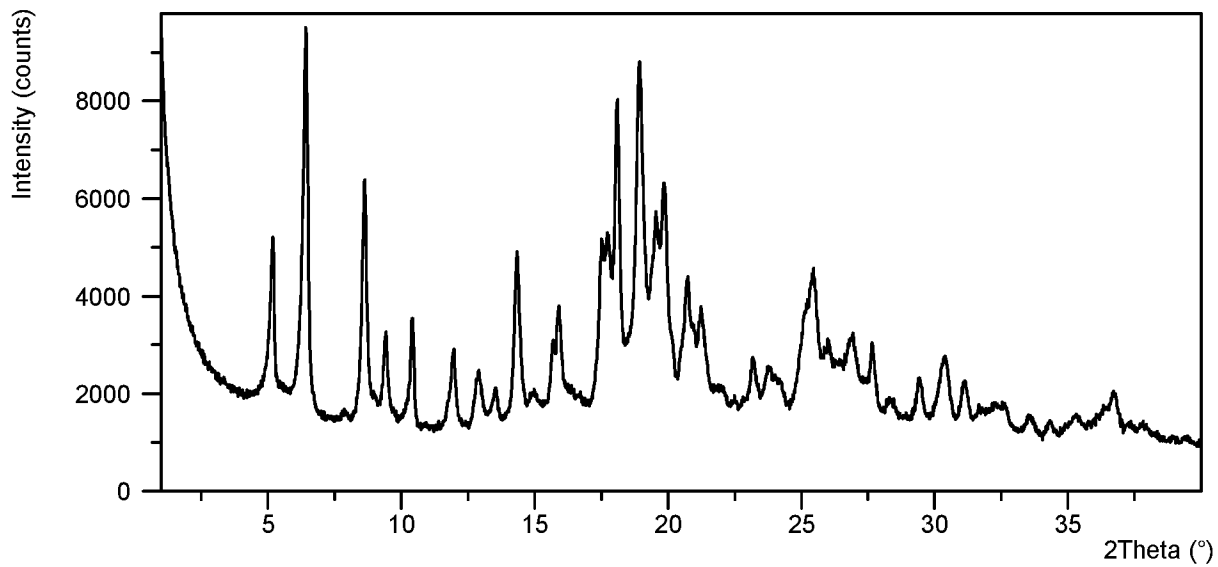


FIGURE 58

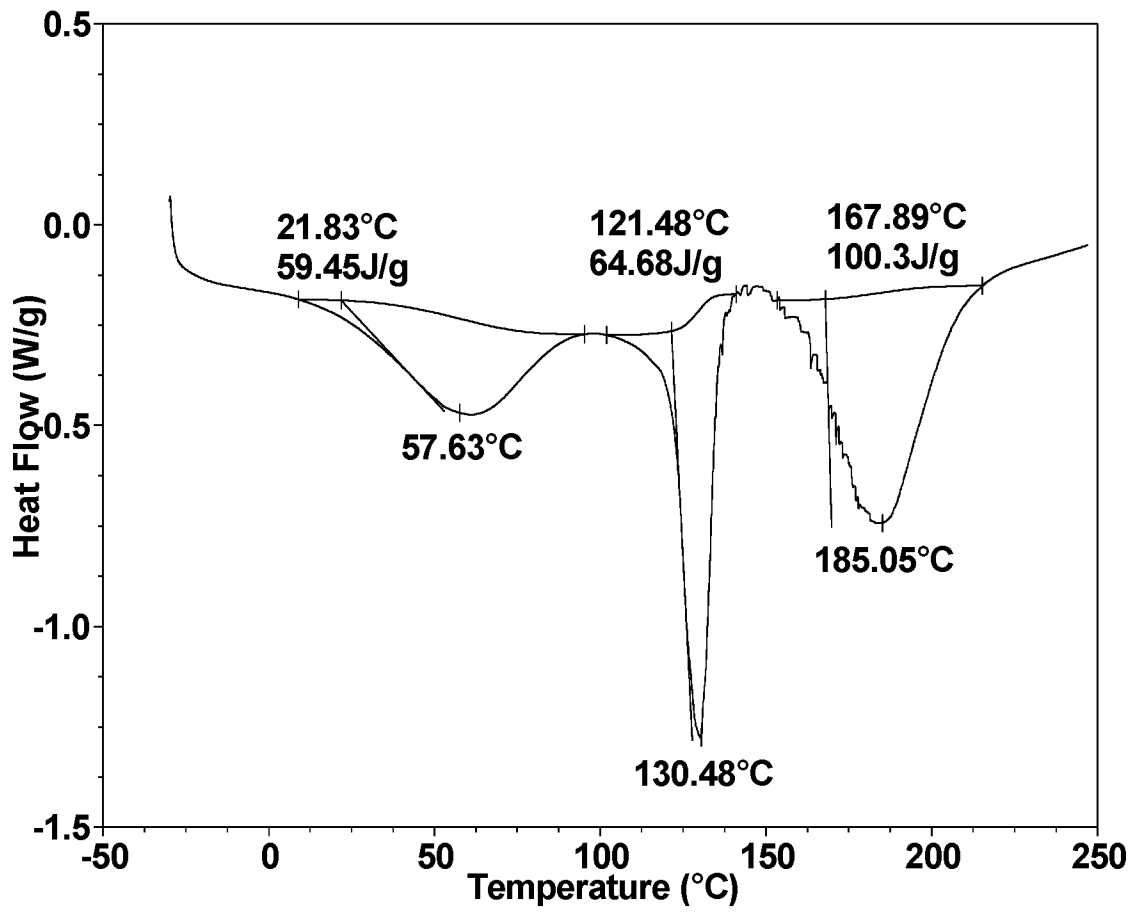


FIGURE 59

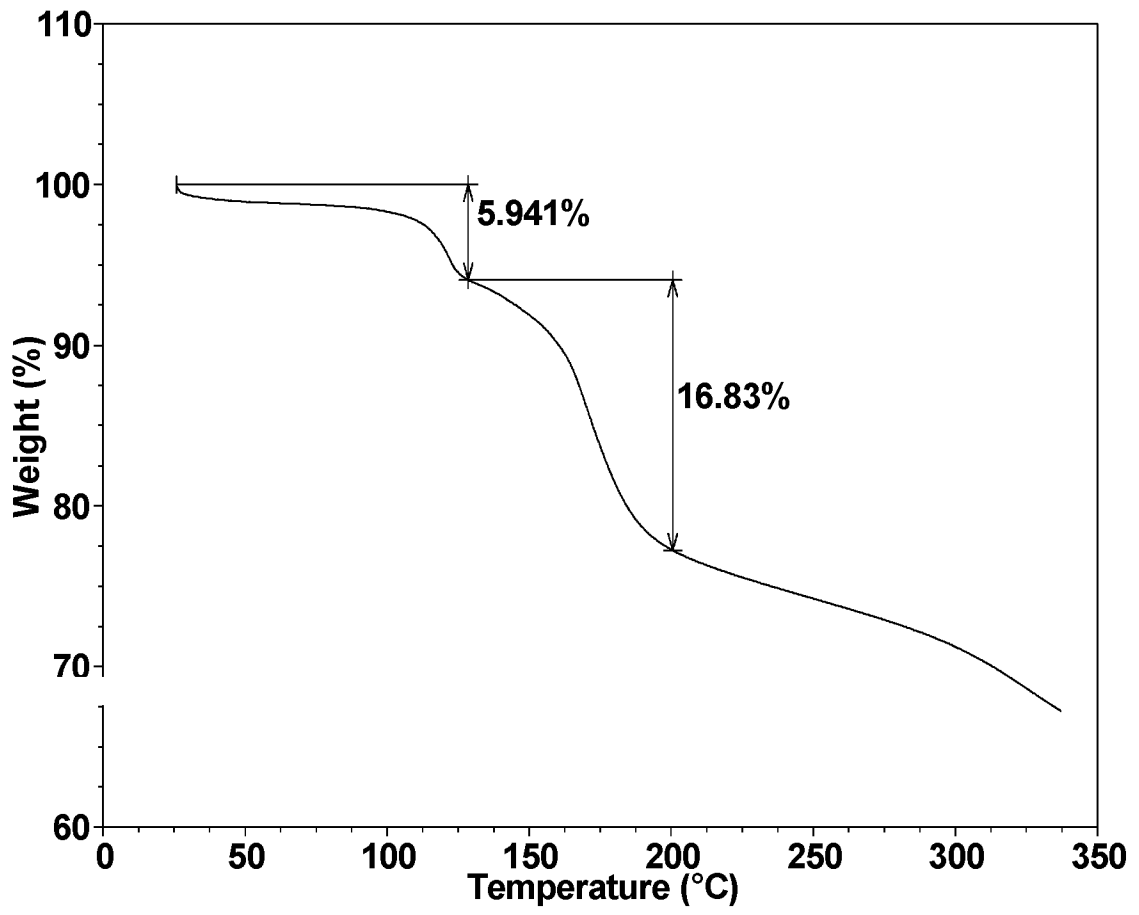


FIGURE 60

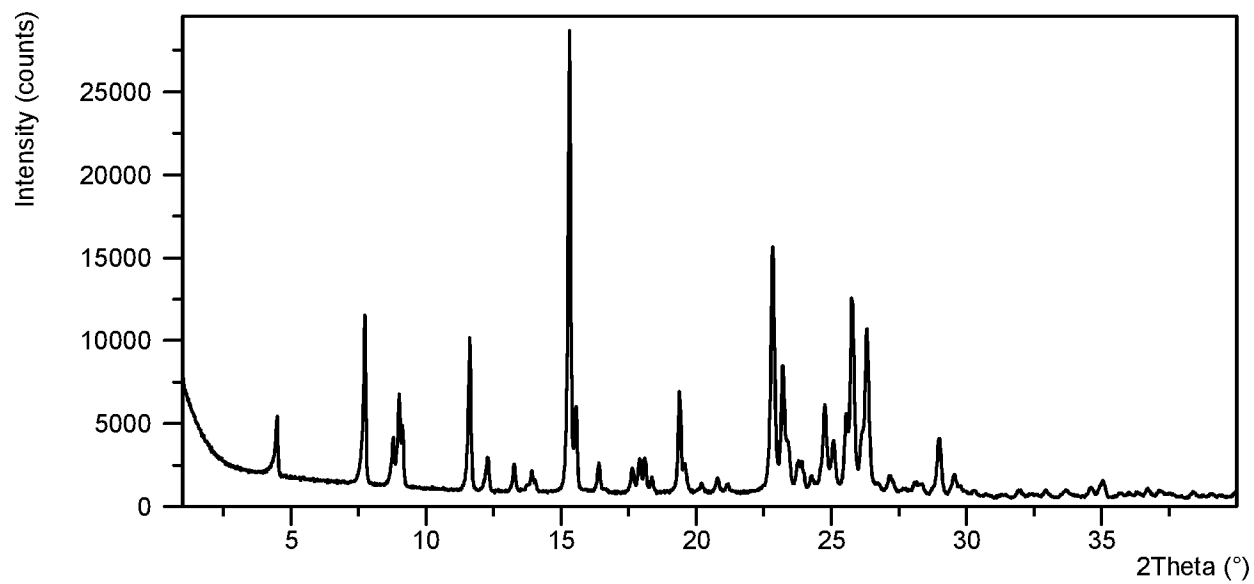


FIGURE 61

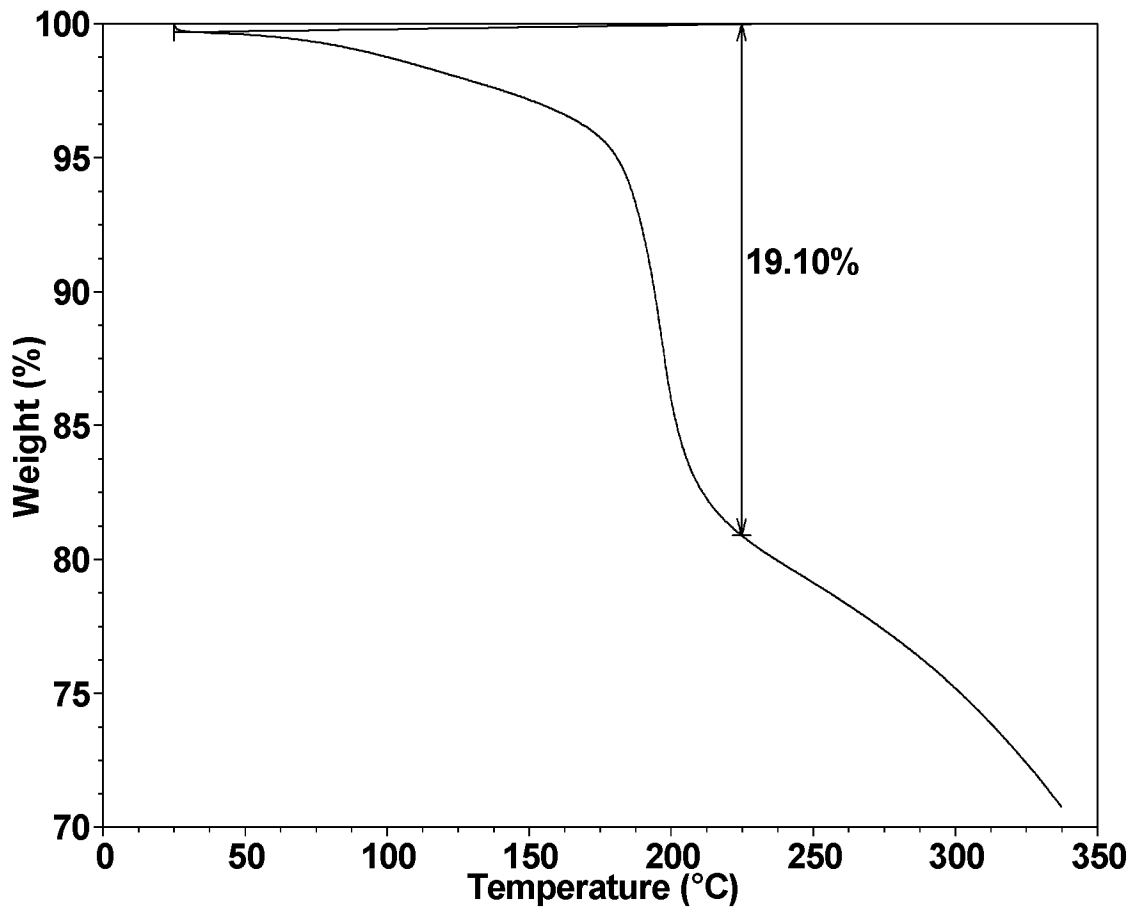


FIGURE 62

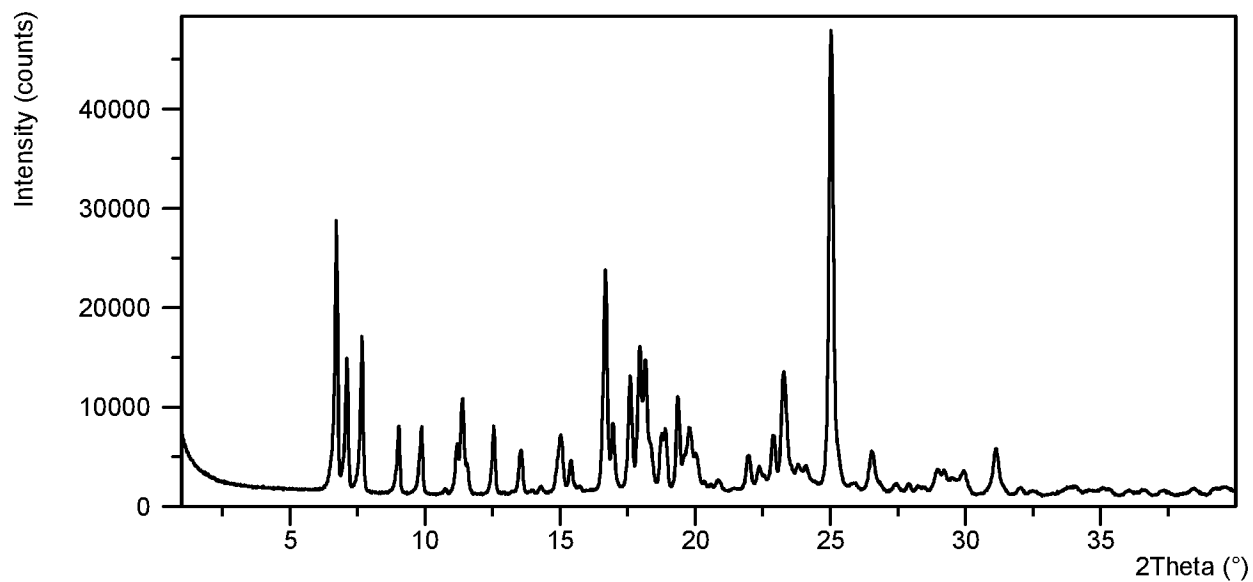


FIGURE 63

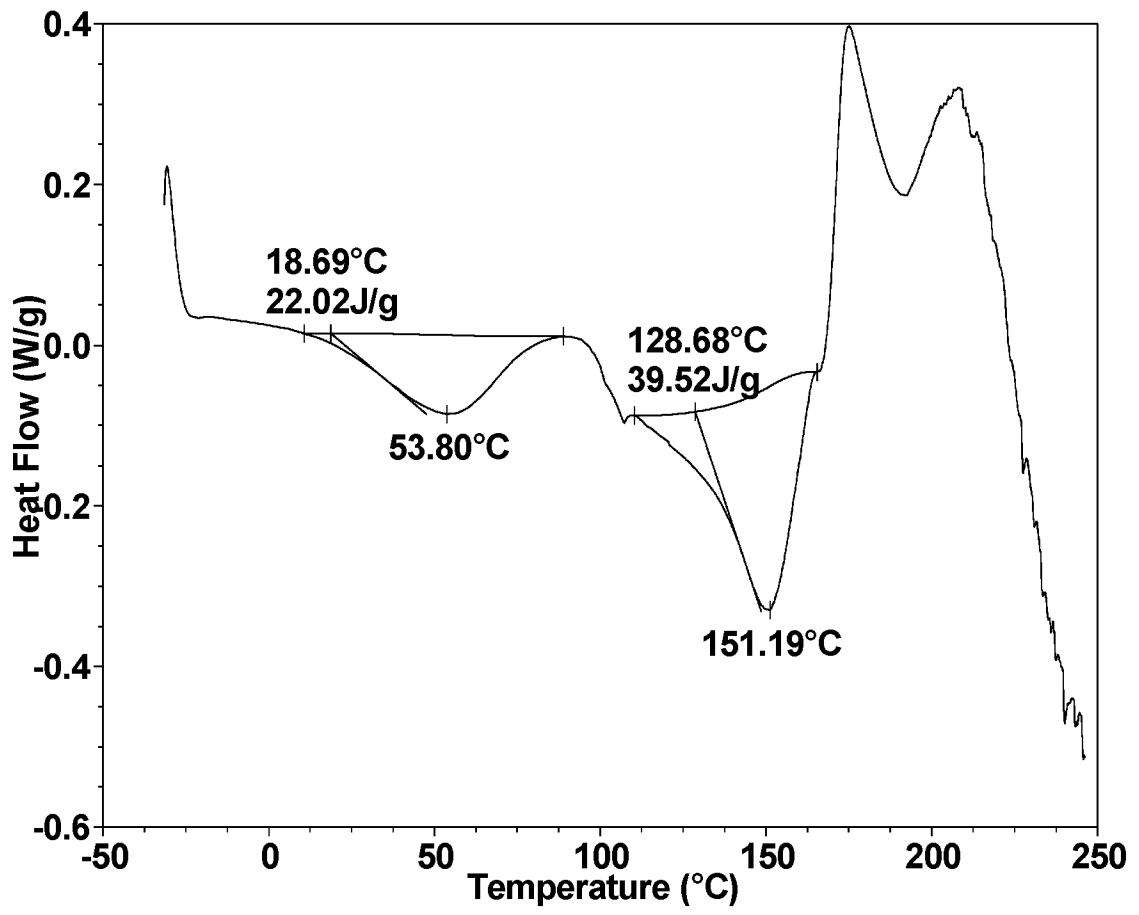


FIGURE 64

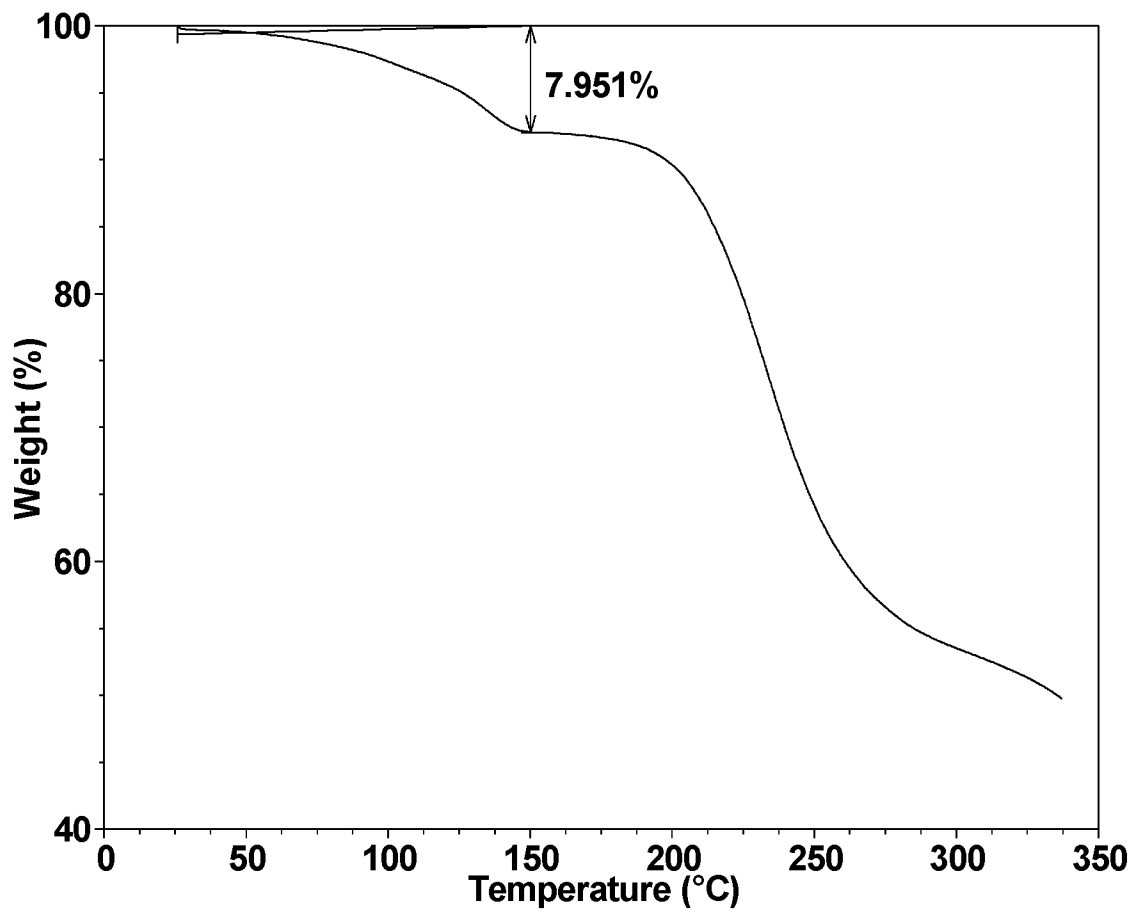


FIGURE 65

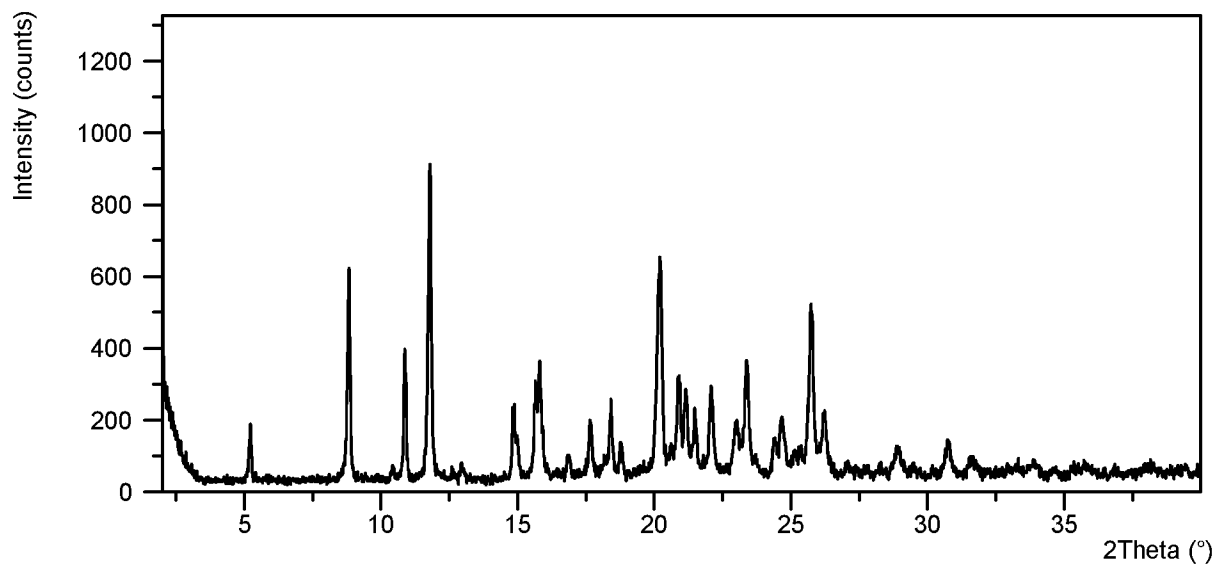


FIGURE 66

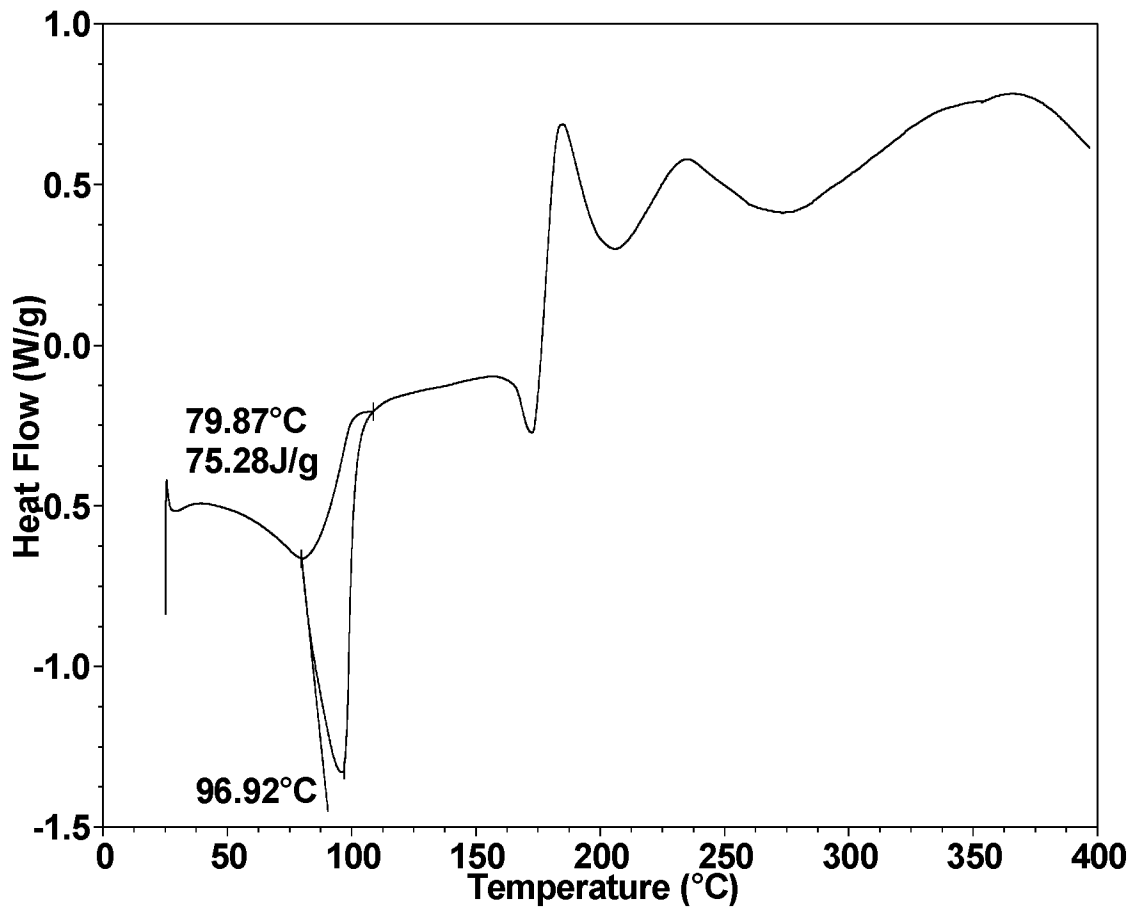


FIGURE 67

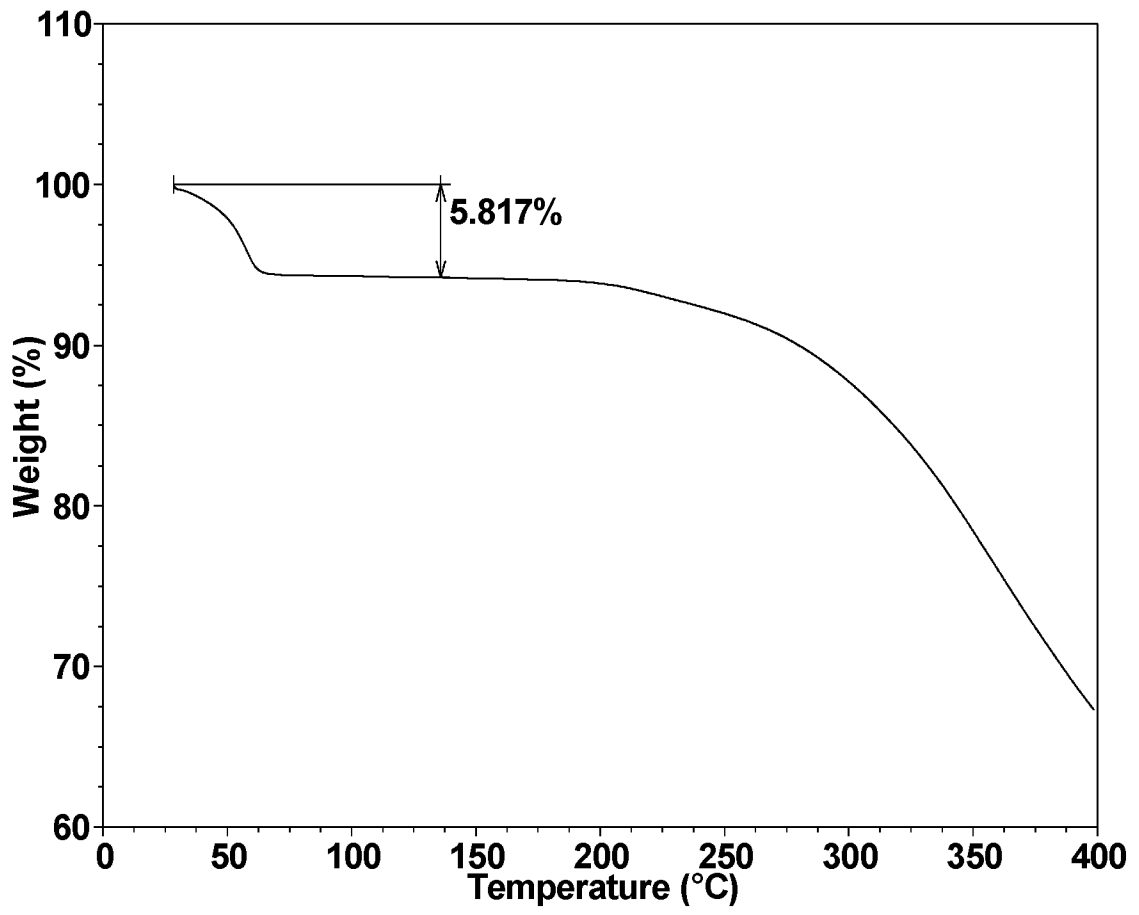


FIGURE 68

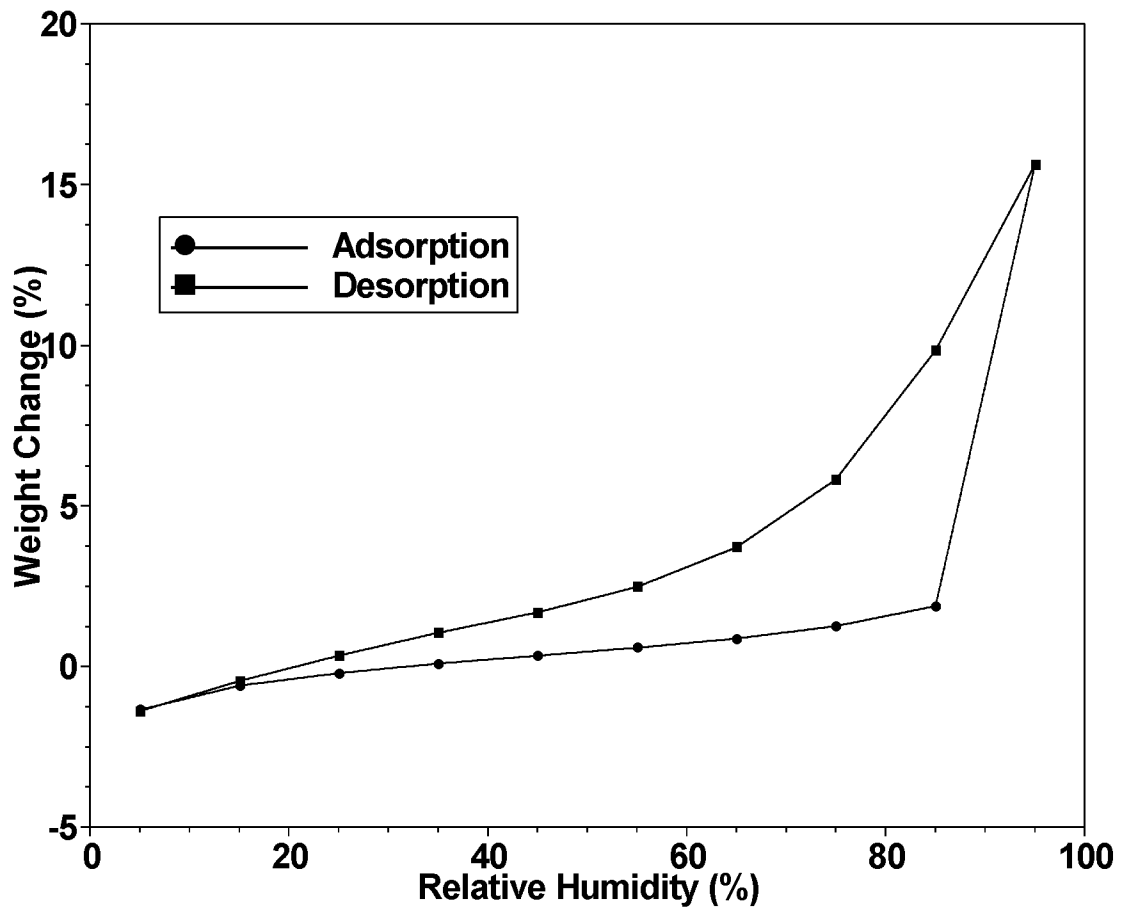


FIGURE 69

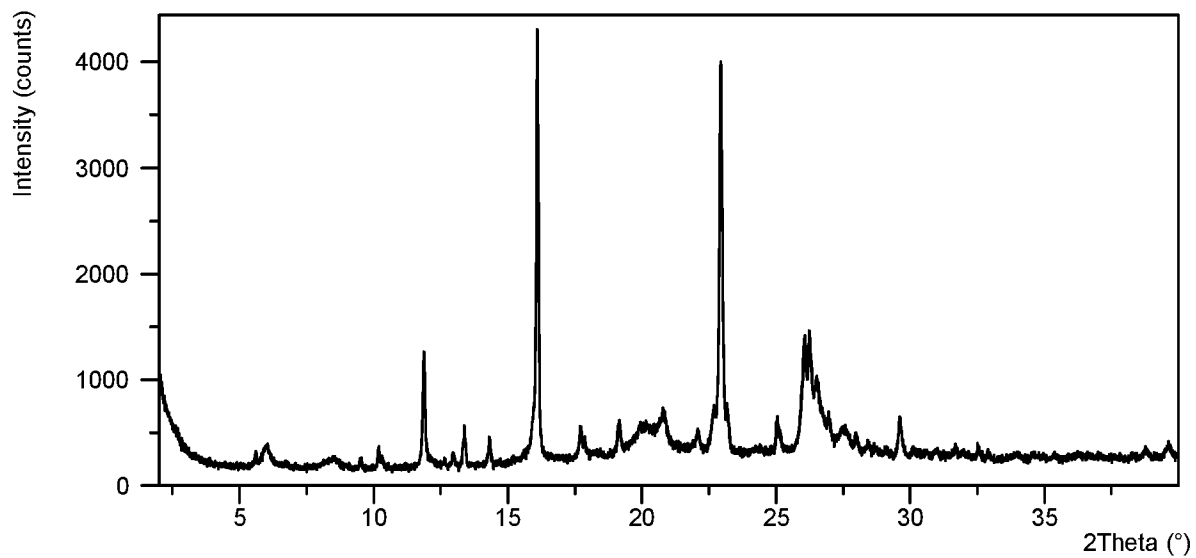


FIGURE 70

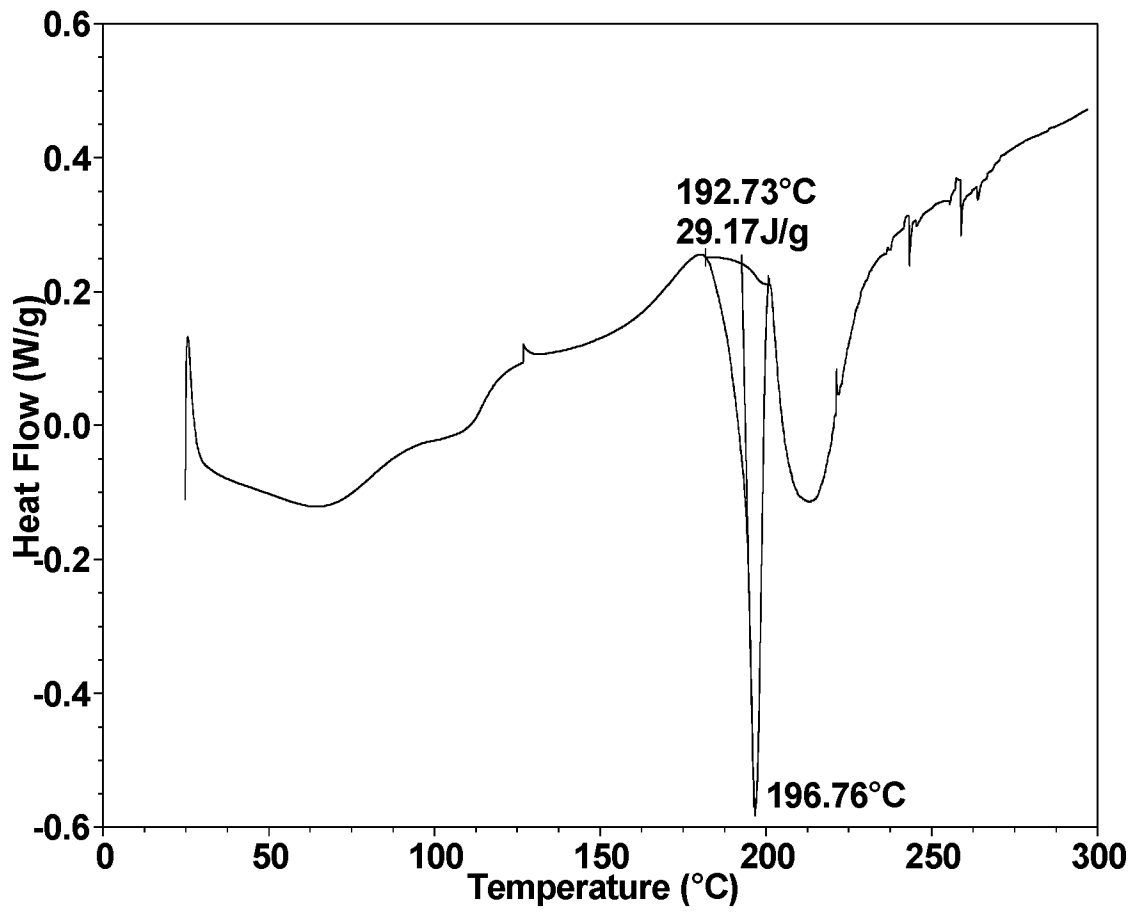


FIGURE 71

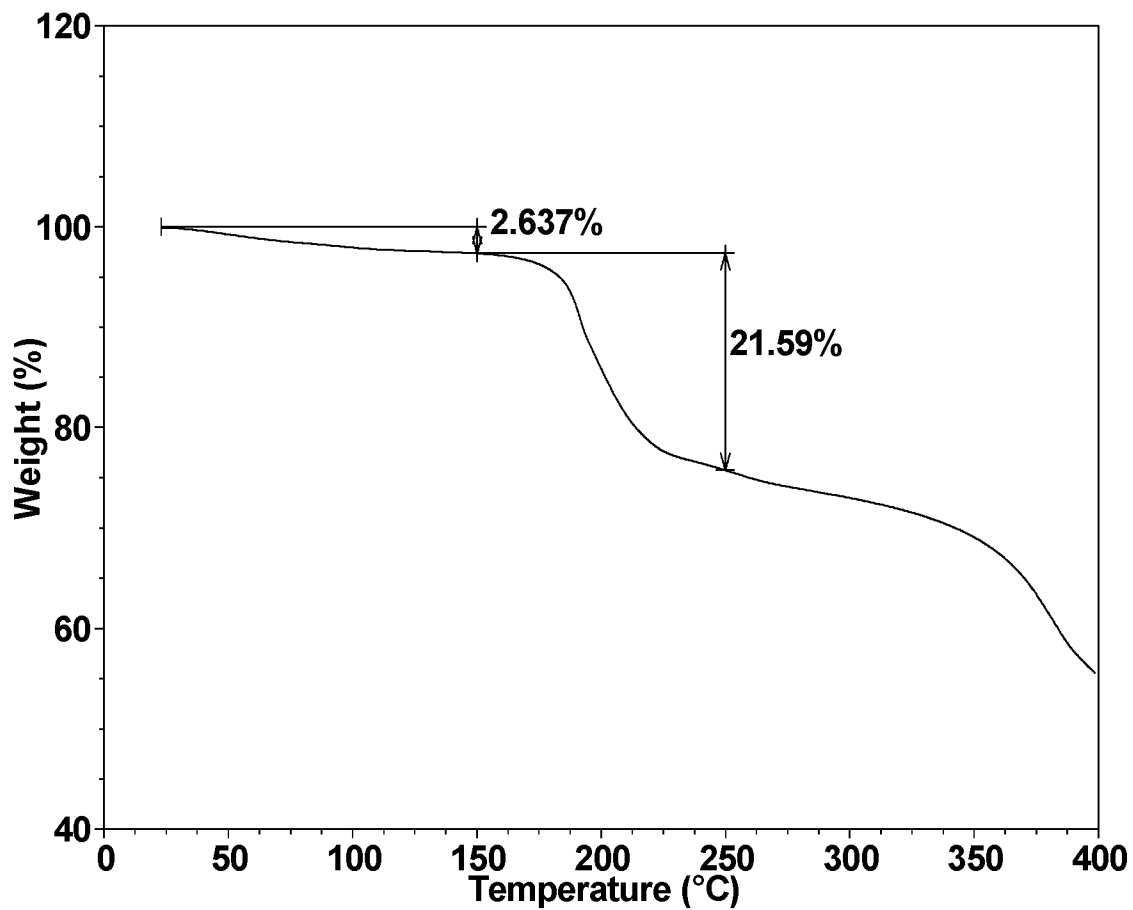


FIGURE 72

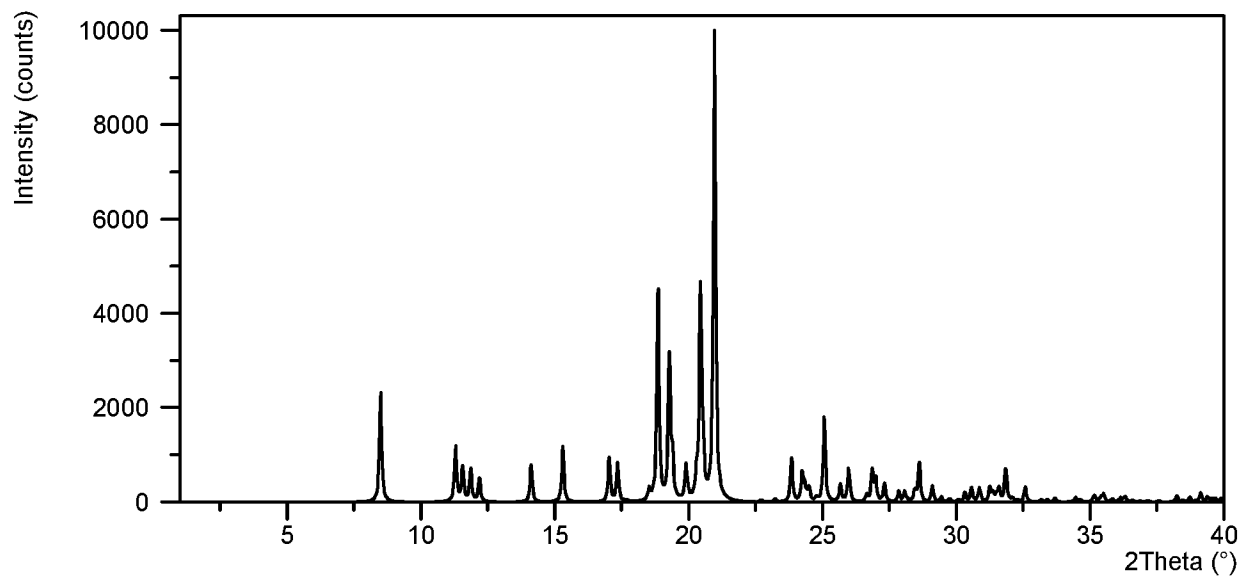


FIGURE 73

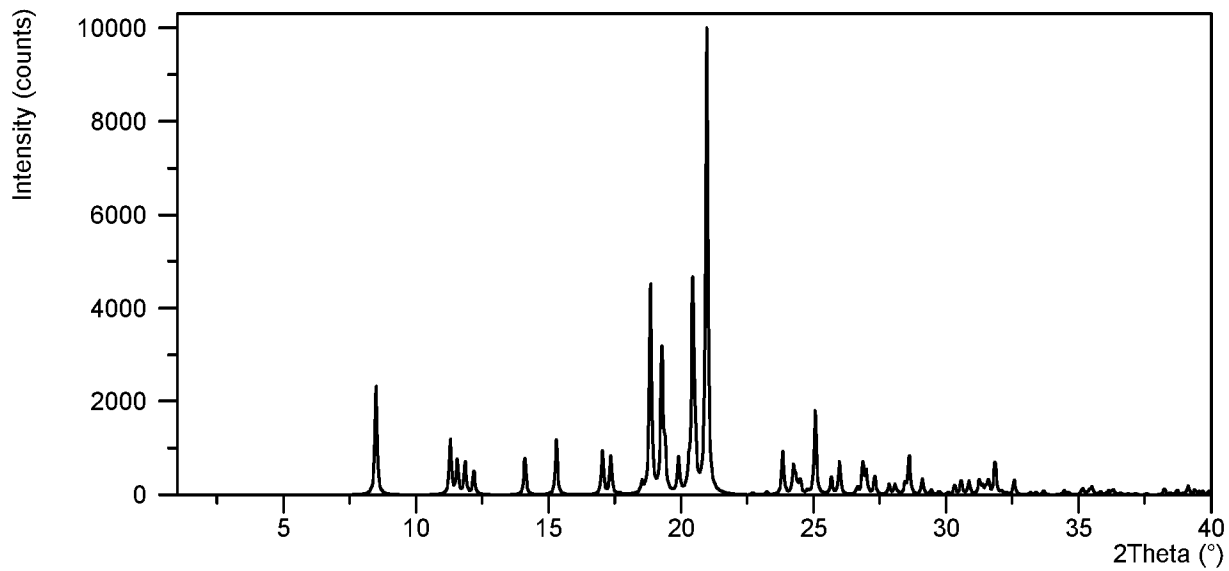


FIGURE 74

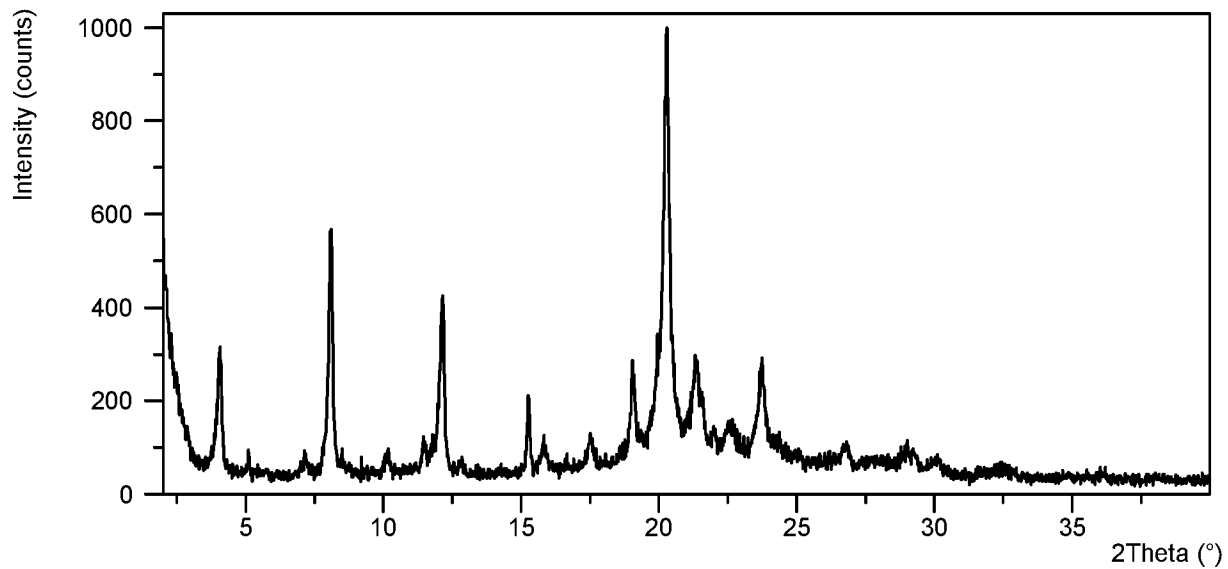


FIGURE 75

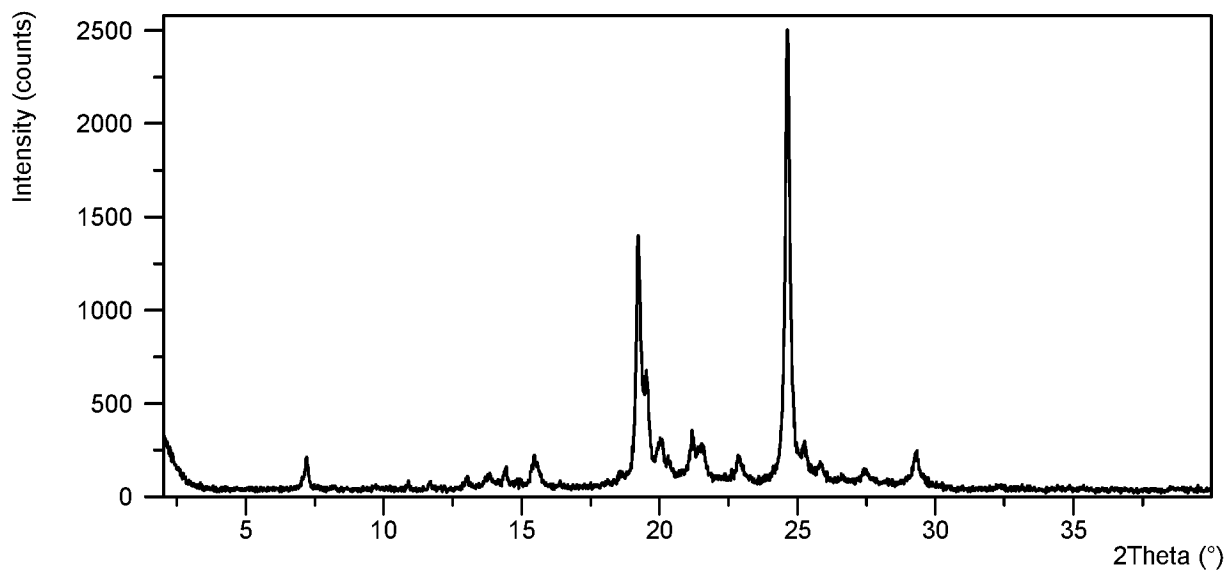


FIGURE 76

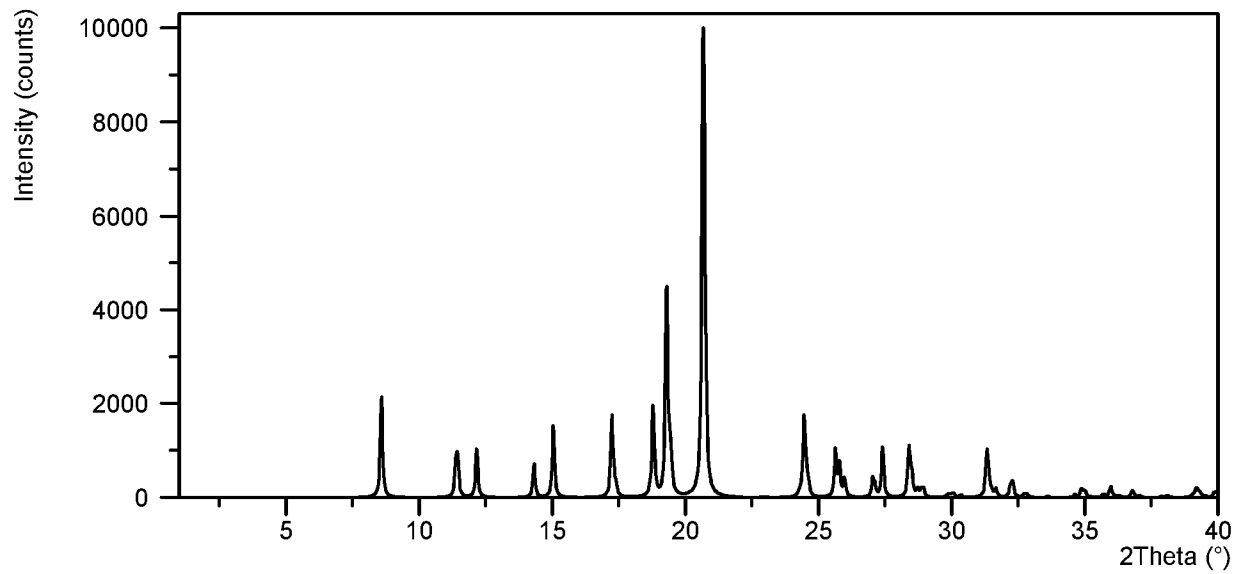


FIGURE 77

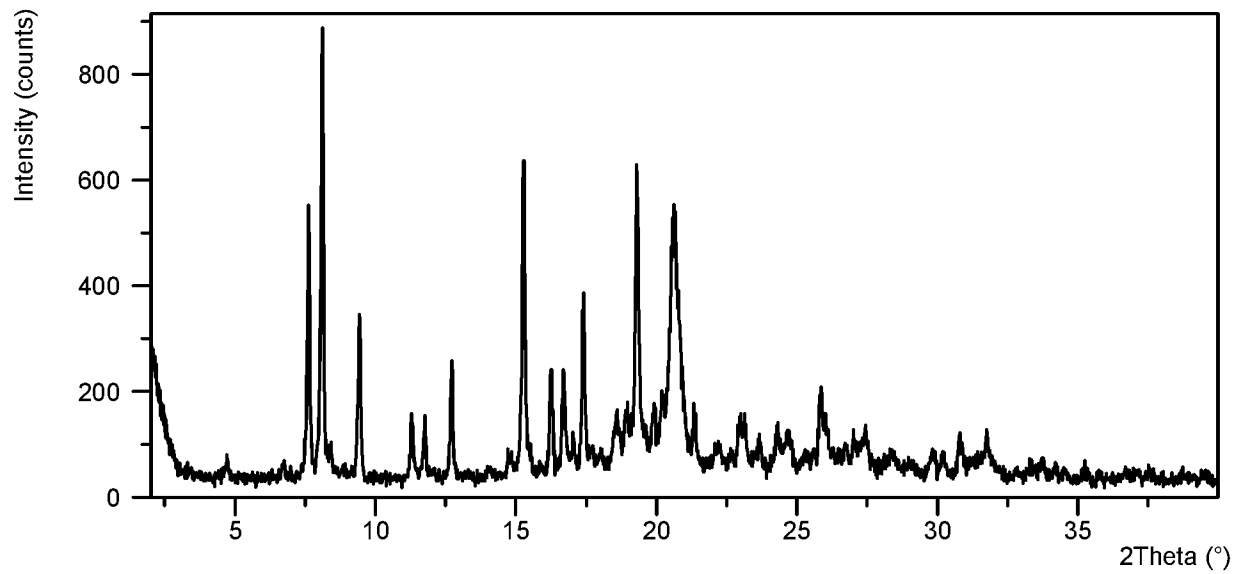


FIGURE 78

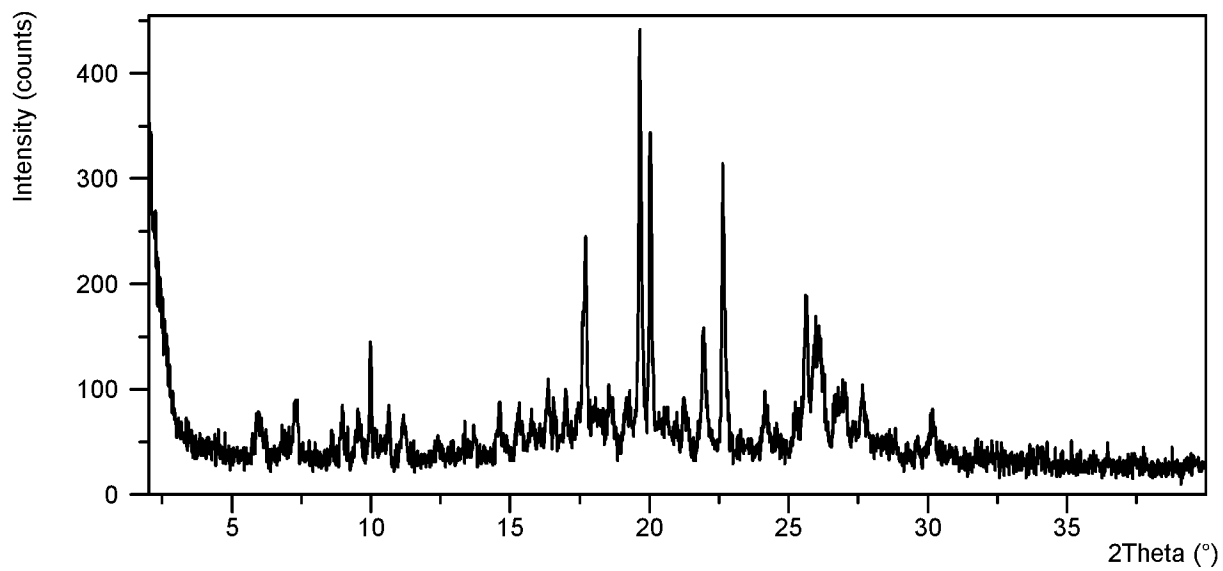


FIGURE 79

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/019071

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61P35/00 A61P37/00 A61K31/4985
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/100217 A1 (GILEAD SCIENCES INC [US]) 2 July 2015 (2015-07-02) cited in the application abstract page 106 - page 108; example 2 page 124 - page 125 page 127 page 129 - page 130 examples claims figures 9,13 ----- -/--	1-188

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
---	---

Date of the actual completion of the international search 28 July 2020	Date of mailing of the international search report 05/08/2020
---	--

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Stix-Malaun, Elke
--	---

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/019071

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MINO R CAIRA ED - MONTCHAMP JEAN-LUC: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY; [TOPICS IN CURRENT CHEMISTRY], SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 [retrieved on 1999-02-26] page 165, last paragraph - page 166, paragraph 1 Chapter 3</p> <p style="text-align: center;">-----</p>	1-9,73, 95-101, 170-188

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/019071

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 2-9, 95-106, 119-169(completely); 1, 73, 170-188(partially)

Crystalline form (I) of compound (I)

2. claims: 10-16, 107-111(completely); 1, 73, 170-188(partially)

Crystalline form (II) of compound (I)

3. claims: 17-24, 74-80, 112-118(completely); 1, 73, 170-188(partially)

Crystalline form (III) of compound (I)

4. claims: 81-87(completely); 73, 170-188(partially)

Crystalline form (IV) of salt of compound (I)

5. claims: 25-33, 88-94(completely); 1, 73, 170-188(partially)

Crystalline form (V) of compound (I)

6. claims: 34-41(completely); 1, 73, 170-188(partially)

Crystalline form (VII) of compound (I)

7. claims: 42-49(completely); 1, 73, 170-188(partially)

Crystalline form (VIII) of compound (I)

8. claims: 50-59(completely); 1, 73, 170-188(partially)

Crystalline form (IX) of compound (I)

9. claims: 60-64(completely); 1, 73, 170-188(partially)

Crystalline form (XIII) of compound (I)

10. claims: 65-72(completely); 1, 73, 170-188(partially)

Crystalline form (XIV) of compound (I)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2020/019071

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015100217	A1	02-07-2015	
		AR 098912 A1	22-06-2016
		AU 2014370010 A1	30-06-2016
		AU 2017228612 A1	05-10-2017
		AU 2019236696 A1	17-10-2019
		CA 2875877 A1	23-06-2015
		CL 2016001537 A1	02-12-2016
		CN 105934434 A	07-09-2016
		CN 107746405 A	02-03-2018
		CR 20160287 A	19-09-2016
		CU 20160097 A7	02-02-2017
		CY 1120104 T1	12-12-2018
		DK 3087075 T3	19-03-2018
		DO P2016000140 A	30-06-2016
		EA 201690989 A1	30-11-2016
		EA 201891553 A1	30-04-2019
		EP 3087075 A1	02-11-2016
		EP 3342773 A1	04-07-2018
		ES 2664799 T3	23-04-2018
		GT 201600123 A	01-12-2017
		HK 1251563 A1	01-02-2019
		HK 1256999 A1	11-10-2019
		HR P20180460 T1	01-06-2018
		HU E037662 T2	28-09-2018
		IL 245846 A	31-10-2018
		JP 6243062 B2	06-12-2017
		JP 6530792 B2	12-06-2019
		JP 2017501229 A	12-01-2017
		JP 2018021063 A	08-02-2018
		JP 2019172680 A	10-10-2019
		KR 20160102041 A	26-08-2016
		KR 20180130598 A	07-12-2018
		LT 3087075 T	10-04-2018
		MD 20160078 A2	31-01-2017
		ME 03001 B	20-10-2018
		NO 3183247 T3	28-04-2018
		NZ 721175 A	26-05-2017
		PE 20160995 A1	23-10-2016
		PH 12016501204 A1	15-08-2016
		PL 3087075 T3	29-03-2019
		PT 3087075 T	09-04-2018
		SG 10201707432S A	30-10-2017
		SG 10201912586U A	27-02-2020
		SG 11201604491V A	28-07-2016
		SI 3087075 T1	29-06-2018
		SV 2016005229 A	28-07-2017
		TW 201609735 A	16-03-2016
		TW 201940488 A	16-10-2019
		US 2016310490 A1	27-10-2016
		US 2018325896 A1	15-11-2018
		US 2019388419 A1	26-12-2019
		UY 35898 A	31-07-2015
		WO 2015100217 A1	02-07-2015