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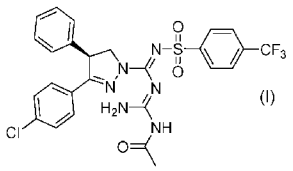
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(54) Title: CRYSTALLINE FORMS OF N-{[(S)-{[3-(4-CHLOROPHENYL)-4-PHENYL-4,5-DIHYDRO-1H-PYRAZOL-1-YL][4-(TRIFLUOROMETHYL)BENZENE SULFONAMIDO]METHYLIDENE}AMINO] METHANIMIDOYL}ACETAMIDE

(57) Abstract: Crystalline Forms of a compound of Formula I are provided: (I) Crystalline Form C is among the crystalline Forms identified. Form C has an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86, and a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset at 157.1°C.



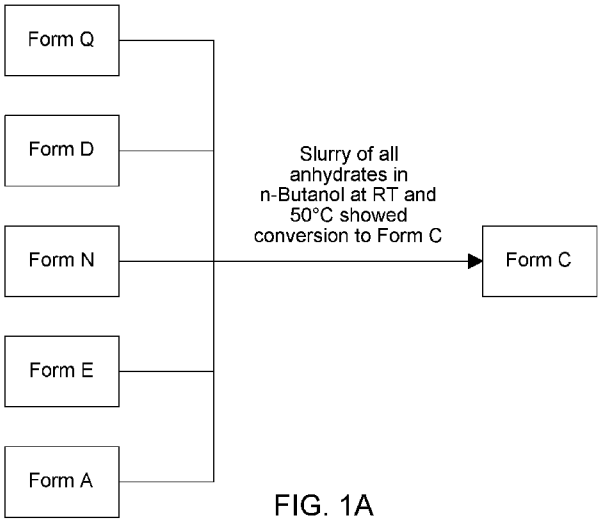


FIG. 1A

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[Continued on next page]

SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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CRYSTALLINE FORMS OF N-{[(S)-{[3-(4-CHLOROPHENYL)-4-PHENYL-4,5-DIHYDRO-1H-PYRAZOL-1-YL][4-(TRIFLUOROMETHYL)BENZENE SULFONAMIDO]METHYLIDENE}AMINO] METHANIMIDOYL}ACETAMIDE

TECHNICAL FIELD

The technical field relates to crystalline forms of the compound N-N'-((S)-3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(((4-(trifluoromethyl)phenyl)sulfonyl) imino)methyl)carbamimidoyl)acetamide, as well as pharmaceutical compositions, therapeutic uses thereof and processes of manufacture.

BACKGROUND

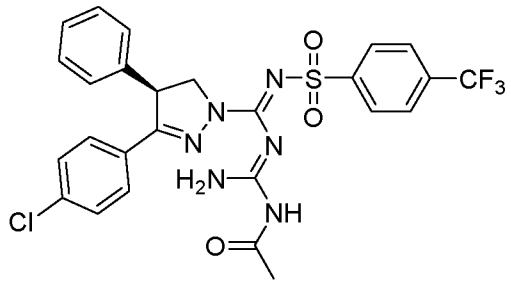
It is generally known that activation of the cannabinoid CB_1 receptor increases appetite, increases the biosynthesis and storage of lipids, inhibits the actions of insulin and leptin, and promotes inflammation and fibrosis. Research was thus focused on developing CB_1 receptor inhibitors for the potential treatment of obesity and the metabolic disorder associated therewith, referred to as metabolic syndrome. Rimonabant was shown effective in treating metabolic syndrome but caused neuropsychiatric (i.e. CNS-related) side effects, which resulted in its withdrawal from the market.

Compounds preferentially targeting the CB_1 receptor in peripheral tissues (e.g. adipose tissue, liver, muscle, lung, kidney, macrophages, pancreatic beta cells and gastrointestinal tract), while not interacting with CB_1 receptors in brain tissue, thereby avoiding or reducing CNS-related side effects, were disclosed by George Kunos et al. in U.S. Patent 9,765,031.

One of the compounds is N-{[(S)-{[3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazol-1-yl][4-(trifluoromethyl)benzenesulfonamido]methylidene}amino]methanimidoyl}acetamide, for which it is desirable to identify stable crystalline forms, that may be suitable for therapeutic use.

SUMMARY

In one aspect, there is provided a compound of Formula I:



(I)

which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86.

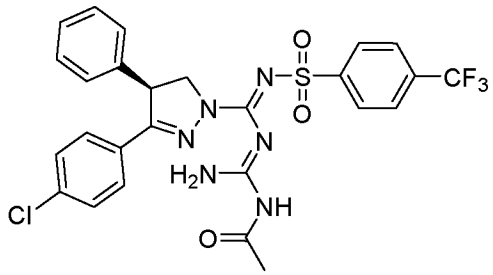
In some embodiments, the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 7.46, 22.15 and 26.24.

In some embodiments, the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 9.85, 19.07, 22.77.

In some embodiments, the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 3.81, 17.17 and 20.84.

In some embodiments, the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 17.95, 15.43 and 24.24.

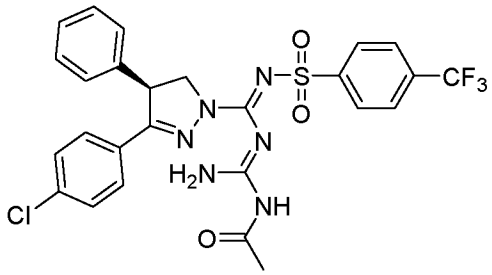
In another aspect, there is provided a compound of Formula I:



(I)

which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset of about 157.1°C.

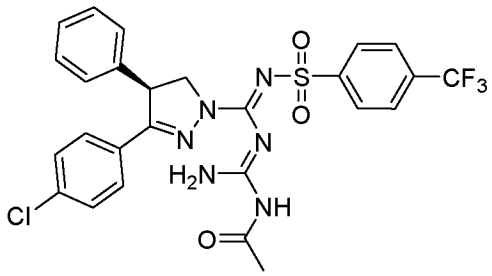
In another aspect, there is provided a compound of Formula I:



(I)

which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having a peak temperature of about 167.9°C.

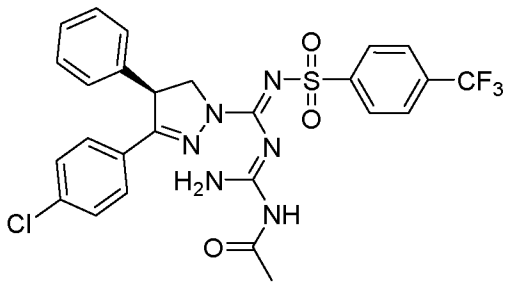
In another aspect, there is provided a compound of Formula I:



(I)

which has an X-ray powder diffraction pattern substantially the same as shown in Figure 4A-Form C.

In another aspect, there is provided a compound of Formula I:



(I)

which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.89 and 17.39.

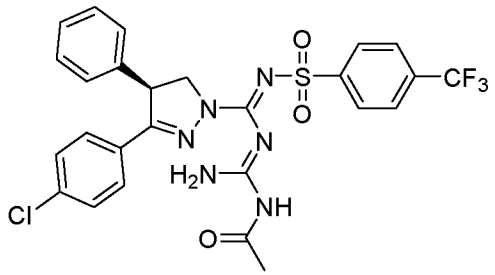
In some embodiments, the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 9.39 and 17.80.

In some embodiments, the XRPD pattern further has a characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 12.96.

In some embodiments, the XRPD pattern further has a characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 19.85.

In some embodiments, the XRPD pattern further has a characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 16.96.

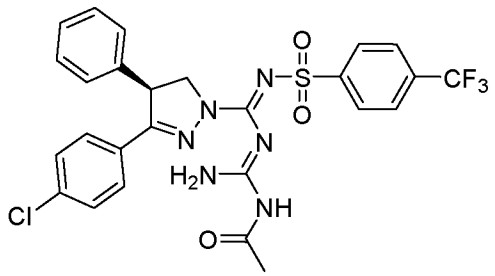
In another aspect, there is provided a compound of Formula I:



(I)

which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset of about 152.2°C.

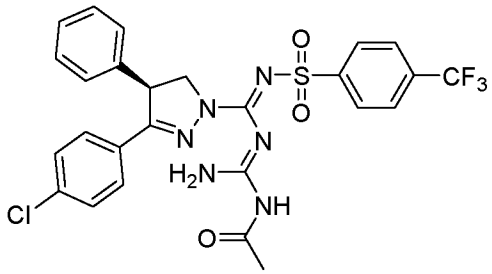
In another aspect, there is provided a compound of Formula I:



(I)

which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having a peak temperature of about 162.3°C.

In another aspect, there is provided a compound of Formula I:



(I)

which has an X-ray powder diffraction pattern substantially the same as shown in Figure 2A.

In some embodiments, the compound of Formula I comprises one crystalline form at a purity of 95% or higher.

In some embodiments, the purity is of 99% or higher.

In some embodiments, the purity is of 99.8% or higher.

In some embodiments, the compound of Formula I is substantially pure.

In another aspect, there is provided a pharmaceutical composition, comprising the compound of Formula I as described herein, and a pharmaceutically acceptable carrier or excipient.

In some embodiments, the pharmaceutical composition is formulated as an oral dosage form.

In some embodiments, the oral dosage form is a tablet, a capsule, a lozenge, a pastille or a granule.

In some embodiments, the pharmaceutical composition is formulated as an oral suspension.

In another aspect, there is provided the use of the compound of Formula I as described herein or the pharmaceutical composition as described herein, for the treatment of a disease or disorder selected from the group consisting of: obesity (type 1 or 2), non-

alcoholic and alcoholic fatty liver disease (a risk factor for insulin resistance), a co-morbidity of obesity, a co-morbidity of diabetes, Prader-Willi Syndrome (PWS), Pro-opiomelanocortin (POMC) deficiency obesity, LepR deficiency obesity, POMC heterozygous deficiency obesity, POMC epigenetic disorders, Bardet-Biedl syndrome, Alström syndrome, dyslipidemia predisposing to arteriosclerotic heart disease, diabetic nephropathy, fibrosis and fibrotic diseases such as Idiopathic Pulmonary Fibrosis (IPF) and Hermansky-Pudlak Syndrome pulmonary fibrosis (HPS-PF), and gout.

In another aspect, there is provided the use of the compound of Formula I as described herein or the pharmaceutical composition as described herein, for the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of: obesity (type 1 or 2), non-alcoholic and alcoholic fatty liver disease (a risk factor for insulin resistance), a co-morbidity of obesity, a co-morbidity of diabetes, Prader-Willi Syndrome (PWS), Pro-opiomelanocortin (POMC) deficiency obesity, LepR deficiency obesity, POMC heterozygous deficiency obesity, POMC epigenetic disorders, Bardet-Biedl syndrome, Alström syndrome, dyslipidemia predisposing to arteriosclerotic heart disease, diabetic nephropathy, fibrosis and fibrotic diseases such as Idiopathic Pulmonary Fibrosis (IPF) and Hermansky-Pudlak Syndrome pulmonary fibrosis (HPS-PF), and gout.

In another aspect, there is provided a method for the treatment of a disease or disorder selected from the group consisting of obesity, diabetes (type 1 or 2), non-alcoholic and alcoholic fatty liver disease (a risk factor for insulin resistance), a co-morbidity of obesity, a co-morbidity of diabetes, Prader-Willi Syndrome (PWS), Pro-opiomelanocortin (POMC) deficiency obesity, LepR deficiency obesity, POMC heterozygous deficiency obesity, POMC epigenetic disorders, Bardet-Biedl syndrome, Alström syndrome, dyslipidemia predisposing to arteriosclerotic heart disease, diabetic nephropathy, fibrosis and fibrotic diseases such as Idiopathic Pulmonary Fibrosis (IPF) and Hermansky-Pudlak Syndrome pulmonary fibrosis (HPS-PF), and gout, comprising administering the compound of Formula I as defined herein or the pharmaceutical composition as defined herein, to a subject in need thereof.

In some embodiments, the co-morbidity of obesity is selected from metabolic syndrome, dementia, heart disease, hypertension, gallbladder disease, gastrointestinal disorders, menstrual irregularities, degenerative arthritis, venous statis ulcer, pulmonary hypoventilation syndrome, sleep apnea, snoring, coronary artery disease, arterial sclerotic

disease, pseudotumor cerebri, osteoarthritis, high cholesterol, and increased incidence of malignancies of the liver, ovaries, cervix, uterus, breasts, prostate, or gallbladder.

In some embodiments, the co-morbidity of diabetes (e.g. type 1) is selected from diabetic nephropathy, chronic kidney disease, diabetic retinopathy, and peripheral and autonomic neuropathy.

In some embodiments, the disease or disorder is selected from diabetes (type 1 or 2), obesity, and non-alcoholic fatty liver disease (e.g. non-alcoholic steatohepatitis).

In another aspect, there is provided a process for preparing the compound of Formula I, Form C as defined herein, comprising:

suspending a first crystalline form of Formula I in water, the first crystalline form exhibiting an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.89 and 17.39;

subjecting the suspension to temperature cycling, between a first temperature and a second temperature lower than the first temperature; and

retrieving the compound of Formula I as a second crystalline form exhibiting an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86.

In some embodiments, the first temperature is between 45°C and 65°C.

In some embodiments, the first temperature is between 50°C and 60°C.

In some embodiments, the second temperature is between 5°C and 35°C.

In some embodiments, the second temperature is between 5°C and 25°C.

In some embodiments, the first temperature is of about 60°C and the second temperature is of about 25°C.

In some embodiments, the process further comprises between the temperature cycling and the retrieval of the second crystalline form: stirring and maintaining the suspension at the second temperature.

In some embodiments, stirring and maintaining the suspension at the second temperature is performed for about 1 hour to about 12 hours.

In some embodiments, stirring and maintaining the suspension at the second temperature is performed for about 3 hours to about 6 hours.

In some embodiments, retrieving the compound of Formula I as the second crystalline form comprising filtering the suspension.

In another aspect, there is provided a process for preparing the compound of Formula I, Form C as described herein, comprising:

solubilizing a compound of Formula I in a solvent selected from the group consisting of methanol, ethanol, n-propanol and isopropanol, to obtain a solution;

adding water to the solution until a solid precipitates; and

retrieving the compound of Formula I as a crystalline form exhibiting an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86.

In some embodiments, the solvent is selected from the group consisting of methanol, ethanol and n-propanol.

In some embodiments, the solvent is ethanol.

In some embodiments, solubilizing the compound of Formula I in the solvent comprises solubilizing the compound of Formula I as a crystalline form exhibiting an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.89 and 17.39.

In some embodiments, solubilizing the compound of Formula I in the solvent is performed at a first temperature between about 30°C and a boiling point of the solvent.

In some embodiments, the first temperature is between about 35°C and about 60°C.

In some embodiments, adding water is performed at the first temperature.

In some embodiments, the process further comprises cooling the solvent / water mixture to a second temperature that is lower than the first temperature.

In some embodiments, the second temperature is between about 5°C and about 30°C.

In some embodiments, the second temperature is between about 20°C and about 30°C.

In some embodiments, the solvent : water ratio (by volume) is between about 1:1 and about 3:1.

In some embodiments, the solvent : water ratio is between about 2:1 and about 3:1.

In some embodiments, retrieving the compound of Formula I comprises filtering and drying the compound of Formula I.

In another aspect, there is provided a process for preparing the compound of Formula I, Form C as defined herein, comprising:

providing a slurry of a first crystalline form of Formula I in a solvent selected from the group consisting of water, n-butanol and an MIBK/n-heptane mixture, the first crystalline form exhibiting an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.89 and 17.39;

stirring the slurry; and

retrieving the compound of Formula I as a crystalline form exhibiting an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86.

In some embodiments, the solvent is water.

In some embodiments, the solvent is a 1:4 (v/v) MIBK:n-heptane mixture.

In some embodiments, stirring the slurry is performed at a temperature between about 50°C and about 70°C.

In some embodiments, the temperature is between about 55°C and about 65°C.

In some embodiments, the process further comprises adding a seed of the compound of Formula I, Form C, to the mixture.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A is a phase map of the anhydrate crystalline forms of the compound of Formula I;

Figure 1B is a phase interconversion map of solvate and hydrate crystalline forms of the compound of Formula I;

Figure 2A is an XRPD of the compound of Formula I, Form A;

Figure 2B is a graph including TGA and DSC thermograms of Form A;

Figure 2C is an XRPD overlay of Form A and Form J;

Figure 3A is an XRPD overlay of Form A with Form I and Form B from temperature cycling in IPA;

Figure 3B is a graph including TGA and DSC thermograms of Form B;

Figure 4A is an XRPD overlay of Form A and Form C obtained from temperature cycling in H_2O;

Figure 4B is a graph including TGA and DSC thermograms of Form C;

Figure 5A is an XRPD overlay of Form A with Form D and Form H obtained from temperature cycling in toluene;

Figure 5B is a graph including TGA and DSC thermograms of Form D;

Figure 6A is an XRPD overlay of Form A with Form E and Form P obtained from temperature cycling in IPAc/MTBE (1:3 v/v);

Figure 6B is a graph including TGA and DSC thermograms of Form E;

Figure 6C is a graph including a cycle DSC thermogram of Form E;

Figure 7A is an XRPD overlay of Form A with Form G and Form F from RT slurry in THF/H_2O (0.92/0.08 v/v Aw=0.2 and 0.83/0.17 v/v Aw=0.4, respectively);

Figure 7B is a graph including TGA and DSC thermograms of Form F;

Figure 8A is an XRPD overlay of Form A and Form K from crash cooling in anisole;

Figure 8B is a graph including TGA and DSC thermograms of Form K;

Figure 8C is an XRPD overlay of Form K and Form K heated to 90 °C and cooled back to RT;

Figure 9A is an XRPD overlay of Form A and Form L from crash cooling in anisole;

Figure 9B is a graph including TGA and DSC thermograms of Form L;

Figure 10A is an XRPD overlay of Form A and Form M from crash cooling in IPAc;

Figure 10B is a graph including TGA and DSC thermograms of Form M;

Figure 11A is an XRPD overlay of Form A and Form N obtained from temperature cycling in CHCl3/n-Heptane (1:3 v/v);

Figure 11B is a graph including TGA and DSC thermograms of Form N;

Figure 12A is an XRPD overlay of Form A and Form O from slow evaporation in MeOH;

Figure 12B is a graph including TGA and DSC thermograms of Form O;

Figure 13A is an XRPD overlay of Form A and Form Q from slow evaporation in slurrying Form A in n-Butanol at 100 °C;

Figure 13B is a graph including TGA and DSC thermograms of Form Q;

Figure 14 is an XRPD overlay of the 5-gram scale up batch showing that Form C is obtained; and

Figure 15 is an overlay of a simulated XRPD from single crystal X-ray diffraction data and the experimental XRPD pattern of Form B.

DETAILED DESCRIPTION

Definitions

The term "stable", as used herein, includes chemical stability and/or solid-state stability. A compound is considered chemically stable when the compound can be stored in an isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, without any significant degree of chemical degradation or decomposition.

A compound is considered to have solid-state stability when the compound can be stored in an isolated solid form, or in the form of a solid formulation in which it may be provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants, under normal storage conditions, without any significant degree of solid state transformation (e.g. crystallisation, recrystallisation, loss of crystallinity, solid state phase transition, hydration, dehydration, deliquescence, solvation or desolvation).

Crystalline forms of solid chemical compounds influence not only their dissolution behavior (i.e. bioavailability) but also their solid-state stability. One way of comparing the solid-state stability of crystalline forms is to evaluate the relative "thermodynamic stability" of the crystalline forms. To evaluate the thermodynamic stability of crystalline forms, typical techniques include, but are not limited to, slurrying, slow evaporation, slow cooling, slow antisolvent addition, or a combination of these methods. Calorimetry techniques (e.g., Differential Scanning Calorimetry) can also be used to measure thermal events and phase transitions across a wide temperature range, and a comparison between the crystalline forms can give an indication as to their relative thermodynamic stability.

The expression "pharmaceutically acceptable carrier or excipient", as used herein, includes without limitation any adjuvant, carrier, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent or emulsifier which is known as being acceptable for pharmaceutical use in humans or domestic animals.

The expression "pharmaceutical composition", as used herein, refers to the formulation of a compound and a pharmaceutically acceptable carrier or excipient.

The term “about”, as used herein, generally means within an acceptable standard error of the mean, when considered by a person skilled in the art. For example, depending on the value or range considered, the term “about” can mean within 10%, within 5%, or within 1% of the value or range.

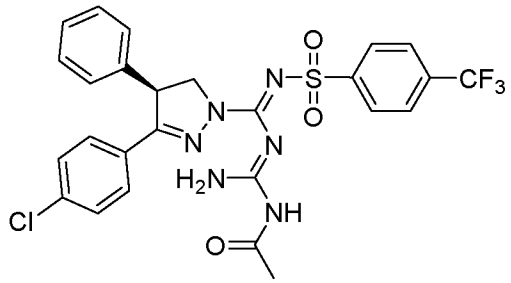
As used herein, the term "hydrate" refers to a crystalline form of a molecule that further comprises molecules of water incorporated into the crystalline lattice structure. The water molecules in the hydrate may be present in a regular arrangement and/or a non-ordered arrangement. The hydrate may comprise either a stoichiometric or nonstoichiometric amount of the water molecules. For example, a hydrate with a nonstoichiometric amount of water molecules may result from partial loss of water from the hydrate.

As used herein, the terms “anhydrate” or "anhydrous" refer to a crystalline form of a molecule *per se* that does not further comprise molecules of water incorporated into the crystalline lattice structure.

As used herein, the term "solvate" refers to a crystalline form of a molecule that further comprises molecules of a solvent or solvents incorporated into the crystalline lattice structure. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. For example, a solvate with a nonstoichiometric amount of solvent molecules may result from partial loss of solvent from the solvate. The solvent can include various organic solvents. It should also be understood that a “solvate” can include a single solvent, a mixture of solvents or a mixture of a solvent (or solvents) and water.

The term “substantially the same”, used herein to describe X-ray diffraction patterns, is meant to include patterns in which peaks are within a standard deviation of ±0.2° 2Θ or an X-ray diffraction pattern comprising least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 peaks in common with the referenced pattern. Further, a person skilled in the art will appreciate that relative peak intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, prepared sample surface, and other factors. As such, the relative peak intensities should be taken as a qualitative measure.

The present description provides crystalline Forms of the compound of Formula I:



(I)

The structure depicted for the compound of Formula I is also meant to include all tautomeric forms of the compound of Formula I. Additionally structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the structure of the compound of Formula I except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of the present description.

The term "substantially pure", when used in reference to a crystalline form of the compound of Formula I, is meant to include a crystalline form which has a purity that is greater than about 90%. This means that the crystalline form may not contain more than about 10% of any other compound, and in particular, does not contain more than about 10% of any other crystalline form of the compound of Formula I. Preferably, the term "substantially pure" means a crystalline form which has a purity that is greater than about 95%. This means that the crystalline form may not contain more than about 5% of any other compound, and in particular, does not contain more than about 5% of any other crystalline form of the compound of Formula I. More preferably, the term "substantially pure" means a crystalline form which has a purity that is greater than about 99%. This means that the crystalline form may not contain more than about 1% of any other compound, and in particular, does not contain more than about 1% of any other crystalline form of the compound of Formula I.

The term "solid" or "solid mixture" when used in reference to the compound of Formula I, refers to a mixture of crystalline forms. For example, a solid or solid mixture can include at least two different crystalline forms of the compound of Formula I. For example, a solid

mixture can include crystalline Form C and one or more additional crystalline form(s) such as Form A, Form B, Form D, Form E, Form F, Form G, Form H, Form I, Form J, Form K, Form L, Form M, Form N, Form O, Form P and/or Form Q.

XRPD data were obtained using Panalytical™ X-ray powder diffractometers, used in reflection mode. The radiation used was Cu Kα (λ = 1.540598 Å). It should be understood that the 2Θ values listed herein are dependent on the Form of radiation used, and that a person skilled in the art would understand that the XRPD of a given crystalline form will exhibit different 2Θ values if a different radiation is used (e.g., a molybdenum radiation).

The term “optically pure”, as used herein, refers to compounds which include a proportion of the desired enantiomer that is greater than that of the other enantiomer. An optically pure compound is generally made up of at least about 90%, 95% or 99% of the desired enantiomer, based upon 100 wt% total weight of the compound.

As used herein the terms “crystalline Form” or "polymorph" refers to crystal structure of a compound, having the same chemical composition but different spatial arrangements of the molecules, atoms, and/or ions forming the crystal structure.

17 crystalline Forms are obtained from polymorph screening of the compound of Formula I, including Forms A to Q. Some of the crystalline Forms can convert to other crystalline Forms, as will be described in detail herein.

Form A

Crystalline Form A is an anhydrate. According to DSC, Form A has an endotherm that has an onset of about 152.2°C and a peak temperature at about 162.3°C. The TGA analysis of Form A shows a weight loss of about 0.01% up to 200°C.

Form A has an XRPD pattern substantially the same to that shown at Figure 2A. Form A exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.89 and 17.39. The XRPD pattern of Form A can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 9.39 and 17.80. The XRPD pattern of Form A can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 12.96. The XRPD pattern of Form A can also exhibit a further characteristic peak

expressed in degrees 2Θ (±0.2° 2Θ) at 19.85. The XRPD pattern of Form A can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 16.96.

Form A can be prepared by anti-solvent addition of water into a solution of the compound of Formula I in acetonitrile. Form A can also be prepared by anti-solvent addition of water into a solution of the compound of Formula I in acetone. Form A can also be prepared by anti-solvent addition of heptane into a solution of the compound of Formula I in acetone. Form A can be prepared by anti-solvent addition of MTBE into a solution of the compound of Formula I in acetonitrile.

Form A can be prepared by dissolving the compound of Formula I into a solvent and evaporating the solvent until crystalline material forms (e.g., slow evaporation crystallization). The solvent can for example be selected from the group consisting of DCM, $CHCl_3$, MEK and acetonitrile.

Form A can also be prepared by slow cooling of a solution of the compound of Formula I in a solvent or solvent mixture selected from the group consisting of IPA, toluene, MTBE, EtOH/n-heptane and $CHCl_3$/MTBE. For example, the solvent mixtures can have the following ratios (v:v): EtOH/n-heptane (1:4) and $CHCl_3$/MTBE (1:4).

Form A can also be prepared by triturating the compound of Formula I in DCM/n-heptane (e.g., 1/1 v/v). The trituration can for example be performed at a temperature between about 25°C and about 35°C.

Form B

Crystalline Form B is an IPA solvate. According to DSC, Form B has an endotherm that has an onset of about 126.4°C and a peak temperature at about 136.3°C. The TGA analysis of Form B shows a weight loss of about 5.34% up to 174.0°C.

Form B has an XRPD pattern substantially the same to that shown at Figure 3A (Form B). Form B exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.60, 6.83 and 15.02. The XRPD pattern of Form B can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 9.09 and 9.73. The XRPD pattern of Form B can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 15.40 and 9.88. The XRPD pattern of Form B can also exhibit further

characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 21.90, 19.84 and 14.32. The XRPD pattern of Form B can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 26.56, 15.82 and 23.39.

Form C

Crystalline Form C is an anhydrate. According to DSC, Form C has an endotherm that has an onset of about 157.1°C and a peak temperature at about 167.9°C. The TGA analysis of Form C shows a weight loss of about 0.32% up to 175.0°C.

Form C has an XRPD pattern substantially the same to that shown at Figure 4A (Form C). Form C exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 7.46, 22.15 and 26.24. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 3.81, 17.17 and 20.84. The XRPD pattern of Form C can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 17.95, 15.43 and 24.24. The XRPD pattern of Form C can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 21.53, 25.11 and 23.34. The XRPD pattern of Form C can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 14.94, 27.38 and 28.41. The XRPD pattern of Form C can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 30.57, 12.94 and 14.50.

Form C can be prepared by suspending the compound of Formula I, Form A in water; subjecting the suspension to temperature cycling, between a first temperature and a second temperature lower than the first temperature; and retrieving Form C. In some embodiments, the first temperature is between 45°C and 65°C., or between about 50°C and about 60°C. In some embodiments, the second temperature is between about 5°C and about 35°C, or between about 5°C and about 25°C. In some embodiments, the first temperature is of about 60°C and the second temperature is of about 25°C. In some embodiments, preparing Form C further includes stirring and maintaining the suspension at the second temperature between the temperature cycling and the retrieval of Form C. In some embodiments, stirring and maintaining the suspension at the second temperature is performed for about 1 hour to about 12 hours, or for about 3 hours to about 6 hours., or for about 4.5 hours. In some embodiments, preparing Form C further includes retrieving

the compound of Formula I as the second crystalline form comprising filtering the suspension.

Form C can also be prepared by solubilizing a compound of Formula I in a solvent selected from the group consisting of methanol, ethanol, n-propanol and isopropanol, to obtain a solution; adding water to the solution until a solid precipitates; and retrieving the precipitated solid as Form C. In some embodiments, the solvent is selected from the group consisting of methanol, ethanol and n-propanol. In some embodiments, the solvent is ethanol. In some embodiments, wherein solubilizing the compound of Formula I in the solvent comprises solubilizing the compound of Formula I as Form A. In some embodiments, solubilizing the compound of Formula I in the solvent is performed at a first temperature between about 30°C and a boiling point of the solvent. In some embodiments, the first temperature is between about 35°C and about 60°C. In some embodiments, adding water is performed at the first temperature. In some embodiments, preparing Form C further includes cooling the solvent / water mixture to a second temperature that is lower than the first temperature. In some embodiments, the second temperature is between about 5°C and about 30°C, or between about 20°C and about 30°C. In some embodiments, the solvent : water ratio (v/v) is between about 1:1 and about 3:1, or between about 2:1 and about 3:1. In some embodiments, retrieving the compound of Formula I, Form C includes filtering and drying.

Form C can also be prepared by providing a slurry of the Compound of Formula I, Form A in a solvent selected from the group consisting of water and an MIBK/n-heptane mixture; stirring the slurry; and retrieving the compound of Formula I as Form C. In some embodiments, the solvent in water. In other embodiments, the solvent a a 1:4 (v/v) MIBK:n-heptane mixture. In some embodiments, stirring the slurry is performed at a temperature between about 50°C and about 70°C, or between about 55°C and about 65°C.

As shown at Figure 1A, Form C can also be prepared by slurrying any one of the anhydrate crystalline Forms A, D, E, N and Q in n-butanol at 25°C or at 50°C converts the respective anhydrate crystalline forms to Form C.

In some embodiments, a seed of Form C can be added to any one of the manufacturing process of Form C described herein.

Form D

Crystalline Form D is an anhydrate. According to DSC, Form D has an endotherm that has an onset of about 155.9°C and a peak temperature at about 163.9°C. The TGA analysis of Form D shows a weight loss of about 0.07% up to 180.0°C.

Form D has an XRPD pattern substantially the same to that shown at Figure 5A (Form D). Form D exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.94, 11.27 and 11.86. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 20.75, 8.82 and 24.74. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 4.43, 22.79 and 19.66. The XRPD pattern of Form D can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 19.41, 12.34 and 26.91. The XRPD pattern of Form D can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 12.08 and 20.98. The XRPD pattern of Form D can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 18.53 and 16.89.

Form E

Crystalline Form E is an anhydrate. According to DSC, Form E has two endotherms, with onsets of 120.6°C and 146.0°C and peak temperatures of 129.5°C and 154.6°C respectively. The TGA analysis of Form E shows a weight loss of about 0.317% up to 177.9°C.

Form E has an XRPD pattern substantially the same to that shown at Figure 6A (Form E). Form E exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.62, 8.95 and 8.01. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 17.94, 22.30 and 24.31. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 16.29, 12.82 and 18.83. The XRPD pattern of Form E can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 23.45, 26.11 and 20.62. The XRPD pattern of Form E can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 15.95 and 13.86. The XRPD pattern of Form E

can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 25.65 and 10.22.

Form F

Crystalline Form F is a THF solvate. According to DSC, Form F has a broad endotherm that has an onset of about 119.5°C and a peak temperature at about 132.4°C. The TGA analysis of Form F shows a weight loss of about 1.85% up to 165.0°C.

Form F has an XRPD pattern substantially the same to that shown at Figure 7A (Form F). Form F exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 7.51, 22.37 and 7.89. The XRPD pattern of Form F can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 18.95, 20.25, 17.62 and 11.22. The XRPD pattern of Form F can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 11.73, 23.13, 9.26 and 5.66. The XRPD pattern of Form F can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 12.53, 9.64, 15.69 and 4.17. The XRPD pattern of Form F can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 19.91, 14.32, 12.22 and 13.51.

Form G

Crystalline Form G is a labile solvate that converts to Form F upon drying.

Form G has an XRPD pattern substantially the same to that shown at Figure 7A (Form G). Form G exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 18.86, 25.22 and 6.28. The XRPD pattern of Form G can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 38.23, 31.67 and 21.95. The XRPD pattern of Form G can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 10.88 and 8.36. The XRPD pattern of Form G can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 19.75 and 12.56. The XRPD pattern of Form G can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 20.51 and 22.74.

Form H

Crystalline Form H is a labile solvate that converts to Form D upon drying.

Form H has an XRPD pattern substantially the same to that shown at Figure 5A (Form H). Form H exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.73, 10.90, and 11.45. The XRPD pattern of Form H can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 19.12, 16.68 and 18.86. The XRPD pattern of Form H can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 20.35, 23.96, 26.36 and 22.03. The XRPD pattern of Form H can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 24.18, 12.02, 22.62 and 15.90. The XRPD pattern of Form H can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 16.43, 6.01, 8.73, 20.84 and 4.36.

Form I

Crystalline Form I is a labile solvate that converts to Form B upon drying.

Form I has an XRPD pattern substantially the same to that shown at Figure 3A (Form I). Form I exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.28, 8.43 and 18.77. The XRPD pattern of Form I can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 17.18, 7.78 and 21.51. The XRPD pattern of Form I can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 11.77, 19.40 and 17.96. The XRPD pattern of Form I can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 10.39, 25.55 and 15.56. The XRPD pattern of Form I can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 9.00, 14.23, 23.00 and 15.25. The XRPD pattern of Form I can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 20.84, 16.47, 21.02 and 26.47.

Form J

Crystalline Form J is a labile solvate that converts to Form J upon drying.

Form J has an XRPD pattern substantially the same to that shown at Figure 2C (Form J). Form J exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.59 and 16.76. The XRPD pattern of Form J can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 9.35 and 22.43. The XRPD pattern of Form J can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 22.75, 21.63 and 26.63. The XRPD pattern of Form J can also exhibit further

characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 18.78, 21.11 and 24.05. The XRPD pattern of Form J can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 18.10, 24.62 and 16.17.

Form K

Crystalline Form K is a hemi-hydrate. According to DSC, Form K shows two endothermic events with onsets of 53.6°C and 106.3°C and peak temperatures at 68.7°C and 125.9°C, respectively. The TGA analysis of Form K shows a weight loss of about 1.35% up to 160.0°C.

Form K has an XRPD pattern substantially the same to that shown at Figure 8A (Form K). Form K exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.65 and 6.92. The XRPD pattern of Form K can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 26.74 and 20.02. The XRPD pattern of Form K can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 15.55 and 27.75. The XRPD pattern of Form K can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 15.13, 9.94 and 17.89. The XRPD pattern of Form K can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 13.79, 30.57 and 9.13.

Form L

Crystalline Form L is a partly desolvated anisole solvate having a stoichiometry API:Anisole of about 0:0.26. According to DSC, Form L shows a single endothermic event with an onset of 126.4°C and a peak temperature of 133.8°C in the DSC curve that occurs after the solvent is driven. The TGA analysis of Form L shows a weight loss of about 4.56% up to 165°C.

Form L has an XRPD pattern substantially the same to that shown at Figure 9A (Form L). Form L exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.07 and 6.65. The XRPD pattern of Form L can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 5.24. The XRPD pattern of Form L can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ)

at 20.64. The XRPD pattern of Form L can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 8.03. The XRPD pattern of Form L can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 22.38. The XRPD pattern of Form L can also exhibit a further characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 17.99.

Form M

Crystalline Form M is an IPAc mono-solvate. According to DSC, Form M shows 2 overlapping endothermic events with an onset of 109 °C, and peak temperatures at 116.7°C and 128.2°C that occur concurrently with the TGA weight loss step. The TGA analysis of Form M shows a weight loss of 13.33% up to 165.0 °C.

Form M has an XRPD pattern substantially the same to that shown at Figure 10A (Form M). Form M exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.59, 8.26 and 19.79. The XRPD pattern of Form M can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 22.71 and 26.49. The XRPD pattern of Form M can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 17.84 and 14.38. The XRPD pattern of Form M can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 4.73, 24.57 and 12.25. The XRPD pattern of Form M can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 20.69, 13.29 and 16.40.

Form N

Crystalline Form N is an anhydrate. According to DSC, Form N shows a single endotherm with an onset of 141.9 °C and a peak temperature of 152.1°C. The TGA analysis of Form N shows a weight loss of 0.46% up to 179.0°C.

Form N has an XRPD pattern substantially the same to that shown at Figure 11A (Form N). Form N exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.12, 4.16 and 19.29. The XRPD pattern of Form N can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 3.32 and 16.65. The XRPD pattern of Form N can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) a 4.63 and 3.11. The XRPD pattern of Form N can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 21.81, 22.45 and 26.20. The

XRPD pattern of Form N can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 9.93, 9.12 and 18.05.

Form O

Crystalline Form O is a methanol mono-solvate. According to DSC, Form O shows a broad endotherm with an onset of 107.4 °C and a peak temperature of 110.6°C. The TGA analysis of Form O shows a weight loss of 5.11% up to 160.0°C.

Form O has an XRPD pattern substantially the same to that shown at Figure 12A (Form O). Form O exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.59 and 16.76. The XRPD pattern of Form O can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 28.10 and 6.63. The XRPD pattern of Form O can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 11.16 and 22.41. The XRPD pattern of Form O can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 33.87 and 25.38. The XRPD pattern of Form O can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 11.89 and 16.20.

Form P

Crystalline Form P is a labile solvate that converts to Form E upon drying.

Form P has an XRPD pattern substantially the same to that shown at Figure 6A (Form P). Form P exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.38, 16.69 and 6.93. The XRPD pattern of Form P can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 11.61, 21.89 and 8.95. The XRPD pattern of Form P can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 19.84 and 17.85. The XRPD pattern of Form P can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 20.82 and 15.86. The XRPD pattern of Form P can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 12.35 and 22.99.

Form Q

Crystalline Form Q is an anhydrate. According to DSC, Form Q shows a single broad endotherm with an onset of 101.4°C and a peak temperature of 130.1°C. The TGA analysis of Form N shows a weight loss 0.63% up to 160.0°C.

Form Q has an XRPD pattern substantially the same to that shown at Figure 13A (Form N). Form Q exhibits an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 13.58, 5.61 and 16.82. The XRPD pattern of Form Q can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 12.34, 21.73 and 19.39. The XRPD pattern of Form Q can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 14.95, 20.94 and 18.73. The XRPD pattern of Form Q can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 12.78, 23.31, 26.25 and 28.21. The XRPD pattern of Form Q can also exhibit further characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 17.69, 8.37, 24.47 and 31.84.

Formulations, Methods and Uses

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

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.

The term "patient or subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be either a patient or a healthy human.

The compound of Formula I is useful for the treatment of diseases and disorders where inhibition of the cannabinoid receptor CB_1 is indicated, for instance such as those described in U.S. Patent No. 9,765,031. Such diseases and disorders are generally related to diabetes and metabolic disorders (e.g. metabolic syndrome). Preferably, the active ingredient selective targets the CB_1 receptor in peripheral tissue (e.g. adipose tissue, liver, muscle, lung, kidney, macrophages, pancreatic beta cells and gastrointestinal tract), while not interacting with CB_1 receptors in brain tissue, thereby avoiding or reducing CNS-related side effects.

The effect of the compound of Formula I may include reduced food intake, reduced body weight, reversed insulin and leptin resistance, reverse hepatic steatosis (fatty liver) and improved dyslipidemia. Examples of diseases and disorders to be treated include obesity, diabetes (type 1 or 2), non-alcoholic and alcoholic fatty liver disease (a risk factor for insulin resistance), a co-morbidity of obesity, a co-morbidity of diabetes, Prader-Willi Syndrome (PWS), Pro-opiomelanocortin (POMC) deficiency obesity, LepR deficiency obesity, POMC heterozygous deficiency obesity, POMC epigenetic disorders, Bardet-Biedl syndrome, Alström syndrome, dyslipidemia predisposing to arteriosclerotic heart disease, diabetic nephropathy, fibrosis and fibrotic diseases such as Idiopathic Pulmonary Fibrosis (IPF) and Hermansky-Pudlak Syndrome pulmonary fibrosis (HPS-PF), and gout. For instance, the co-morbidity of obesity is selected from metabolic syndrome, dementia, heart disease, hypertension, gallbladder disease, gastrointestinal disorders, menstrual irregularities, degenerative arthritis, venous statis ulcer, pulmonary hypoventilation syndrome, sleep apnea, snoring, coronary artery disease, arterial sclerotic disease, pseudotumor cerebri, osteoarthritis, high cholesterol, and increased incidence of malignancies of the liver, ovaries, cervix, uterus, breasts, prostate, or gallbladder. In preferred examples, the disease or disorder include diabetes (type 1 or 2), obesity, and non-alcoholic fatty liver disease (e.g. non-alcoholic steatohepatitis). Examples of co-morbidities of diabetes (e.g. type 1) include diabetic nephropathy, chronic kidney disease, diabetic retinopathy, and peripheral and autonomic neuropathy.

The compound of Formula I and pharmaceutical compositions including the compound of Formula I may also be used in a method for preventing or reversing the deposition of adipose tissue in a subject, which is expected to contribute to a reduction of incidence or severity of obesity, which in turn would reduce the incidence or severity of associated co-morbidities.

The present description provides a method of treating a disorder (as described herein) in a subject, comprising administering to the subject identified as in need thereof, the compound of Formula I. The identification of those patients who are in need of treatment for the disorders described above is well within the ability and knowledge of one skilled in the art. Certain of the methods for identification of patients which are at risk of developing the above disorders which can be treated by the subject method are appreciated in the medical arts, such as family history, and the presence of risk factors associated with the development of that disease state in the subject patient. A clinician skilled in the art can readily identify such candidate patients, by the use of, for example, clinical tests, physical examination, medical/family history, and genetic determination.

A method of assessing the efficacy of a treatment in a subject includes determining the pre-treatment symptoms of a disorder by methods well known in the art and then administering a therapeutically effective amount of a compound of the present description, to the subject. After an appropriate period of time following the administration of the compound (e.g., 1 week, 2 weeks, one month, six months), the symptoms of the disorder are determined again. The modulation (e.g., decrease) of symptoms and/or of a biomarker of the disorder indicates efficacy of the treatment. The symptoms and/or biomarker of the disorder may be determined periodically throughout treatment. For example, the symptoms and/or biomarker of the disorder may be checked every few days, weeks or months to assess the further efficacy of the treatment. A decrease in symptoms and/or biomarker of the disorder indicates that the treatment is efficacious.

Compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

Injectable formulations can be sterilized, for example, by filtration through a bacterial -retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a provided compound, it may be desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made

by forming micro-encapsulated matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled.

Examples of other biodegradable polymers include poly(orthoesters) and poly-(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of the present description with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar Form may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, lozenges, capsules, pastilles, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that

they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar Form may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

Provided compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, lozenges, capsules, pastilles, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of the present description include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of the present description. Additionally, the description contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Pharmaceutically acceptable compositions provided herein may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promotors to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

Pharmaceutically acceptable compositions provided herein may be formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this disclosure are administered without food. In other embodiments, pharmaceutically acceptable compositions of this disclosure are administered with food.

Pharmaceutically acceptable compositions provided herein may be formulated for oral administration. Such formulations may be administered with or without food. The compositions are formulated in unit dosage forma for ease of administration and uniformity of dosage. The expression "unit dosage form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment.

The amount of the compound of Formula I that may be included in a single dosage form will vary depending upon the patient to be treated (e.g. child vs adult, etc.). Provided compositions may be formulated such that a total daily dosage of, for instance, between 0.01 and 20 mg/kg body weight/day of the compound can be administered to a patient receiving these compositions. Single dose compositions may contain such an amount, or the total daily dose may be divided in multiple dosage forms to be taken, for instance, one, two or three times a day. For instance, a single dose may include between 5 and 500 mg of the active ingredient, or between 20 and 200 mg. Treatment regimens may comprise administration to a patient a total amount of from about 10 mg to about 1000 mg of the compound(s) of the present description per day in a single dose or divided in multiple doses.

It will be understood, that the total daily dose of the compound of Formula I will be decided by the attending physician within the scope of sound medical judgment. For instance, a

specific dosage or treatment regimen for any particular patient will depend upon a variety of factors, including age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician, and the severity of the symptoms associated with the disease or disorder.

Depending upon the disease or disorder to be treated, additional therapeutic agents may also be present in the compositions of this disclosure or co-administered separately. Non-limiting examples of additional therapeutic agents which could be used in combination with the compound of Formula I include antidiabetic agents, cholesterol-lowering agents, anti-inflammatory agents, antimicrobial agents, matrix metalloproteinase inhibitors, lipoxygenase inhibitors, cytokine antagonists, immunosuppressants, anti-cancer agents, anti-viral agents, cytokines, growth factors, immunomodulators, prostaglandins, or anti-vascular hyperproliferation compound. The treatment may also be complemented with other treatments or interventions such as surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), a biologic response modifier (e.g., an interferon, an interleukin, tumor necrosis factor (TNF)), and agents used to attenuate an adverse effect of the present compound or of a co-administered ingredient.

The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

In some embodiments, the therapeutically effective amount of a compound as defined herein, or a pharmaceutically acceptable salt thereof, can be administered to a patient alone or admixed with a pharmaceutically acceptable carrier.

The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or

electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of the present description that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of the present description or an inhibitory active metabolite or residue thereof.

EXPERIMENTS AND EXAMPLES

Materials and instruments

Polarized light microscopic (PLM) pictures were captured on a Nikon™ DS-Fi2 upright microscope at room temperature.

Powder X-ray Diffraction (XRPD) was performed with a Panalytical™ XPert Powder XRPD on a Si zero-background. The XRPD parameters used were as follows:

	Parameters for Reflection Mode
X-Ray wavelength	Cu, kα, Kα1 (Å): 1.540598, Kα2 (Å): 1.544426 Kα2/Kα1 intensity ratio: 0.50
X-Ray tube setting	45 kV, 40 mA
Divergence slit	Automatic
Scan mode	Continuous
Scan range (°2TH)	3° - 40°
Step size (°2TH)	0.0131
Scan speed (°/s)	0.16
Experiment time	~4min

Differential Scanning Calorimetry (DSC) was performed on a TA Q2000 DSC from TA Instruments™. The DSC method was as follows: ramp from RT to desired temperature at a heating rate of 10 °C/min using N_2 as the purge gas, with crimped pan having a pin hole in the lid. The DSC parameters were as follows:

Parameters	DSC
Pan Type	Aluminum pan, closed
Temperature	RT-300 °C
Ramp rate	10 °C/min

Thermogravimetric Analysis (TGA) was performed on a TA Q500 TGA from TA Instruments. The TGA method was as follows: ramp from RT to desired temperature

(300°C) at a heating rate of 10 °C/min using N_2 as the purge gas. The TGA parameters were as follows:

Parameters	TGA
Pan Type	Platinum plate, open
Temperature	300 °C
Ramp rate	10 °C/min
Purge gas	N_2
Sample purge flow	15 mL/min
Balance purge flow	25 mL/min

Karl Fisher (KF) was performed on a Mettler Toledo™ volumetric KF titrator, to determine the water content in the samples.

The solvent abbreviations are as follows:

Abbreviation	Solvent	Abbreviation	Solvent
MeOH	Methanol	THF	Tetrahydrofuran
EtOH	Ethanol	2-MeTHF	2-Methyltetrahydrofuran
IPA	Isopropyl alcohol	DCM	Dichloromethane
MIBK	4-Methyl-2-pentanone	ACN	Acetonitrile
EtOAc	Ethyl acetate	DMSO	Dimethylsulfoxide
IPAc	Isopropyl acetate	DMF	Dimethylformamide
MTBE	Methyl tert-butyl ether	MEK	Methyl ethyl ketone

Summary of the Experimental Results

A polymorph screening of the compound of Formula I was performed, to identify the most stable crystalline form.

A first crystalline form of the compound of Formula I was obtained through the method described in Example 2. This crystalline form was characterized by X-Ray Powder Diffraction (XRPD), Polarized Light Microscopy (PLM), Thermo-Gravimetric Analysis

(TGA) and Differential Scanning Calorimetry (DSC). The characterization results indicated that the starting material was an anhydrous crystalline material with rod-like particles. DSC showed a single melting endotherm with an onset of 152.2 °C. This crystalline Form was designated as Form A.

Starting with Form A, a polymorph screening was performed under 100 different conditions, using methods of slurry conversion at room-temperature (RT) and 60 ºC, temperature cycling, anti-solvent addition, slow cooling, slow evaporation, polymer induced crystallization, crash cooling, bulky solvent slurry, and reverse anti-solvent addition. The screening produced 17 crystalline forms (Forms A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, and Q):

- Forms A, C, D, E, N, and Q were found to be anhydrates;
- Forms A, D and E were found to products of desolvation of the labile solvates Forms J, H, and P, respectively;
- Forms C, N, and Q were found to be true anhydrates where no change in XRPD pattern was observed between wet and dry cake samples;
- Form K was found to be a hemi-hydrate (1:0.5 API:H_2O ratio);
- Forms B, F, L, M, and O were found to be solvates; and
- Wet cake XRPD analysis of the solvates produced 2 new crystalline patterns, Forms I and G, which upon ambient drying produced Forms B and F, respectively.

A thermodynamic assessment of the six anhydrates (Forms A, C, D, E, N, Q) was performed in a non-solvating solvent, *n*-butanol to determine the most stable phase at RT and 50 °C. Both experiments showed full conversion to Form C, indicating that Form C is the thermodynamically most stable anhydrous form under those conditions.

Example 1: Polymorph Screening

Polymorph screening experiments were performed using different solution crystallization or solid phase transition methods starting with Form A. The methods used and crystal forms identified are summarized in Table 1-1

Table 1-1: Summary of polymorph screening experiments

Method	No. of Experiment	Crystal Form Identified
Anti-solvent addition	20	Type A, C, E, G, J, N, P
Slow evaporation	10	Type A, J, O,
Crash Cooling	4	Type K, M, L
Slurry at RT	20	Type A, B, E, F, G, I, N, P
Slurry at High Temperature	10	Type B, C, D, H, I, K, N,
Bulky Solvent Slurry	6	Type N, Q
Slow Cooling	5	Type D, H, I, K, L
Polymer induced crystallization	5	Type A, K
Temperature Cycling	10	Type A, B, C, D, E, F, H, I, P
Reverse Anti-Solvent	10	Type A, J, N
Total	100	17

Anti-Solvent Addition

About 20-50 mg of Form A was dissolved in appropriate solvent to obtain a clear solution. The solution was magnetically stirred followed by addition of 0.2 mL anti-solvent stepwise until precipitate appeared or the total amount of anti-solvent reached 15.0 mL. The obtained precipitate was isolated for XRPD analysis. A total of 20 experiments were conducted. Results in Table 1-2 showed that Form A, C, E, G, J, N, and P were obtained.

Table 1-2: Summary of anti-solvent addition experiments

Solvent	**Anti-solvent**	**Solid Form**
ACN	H_2O	A/J
EtOH	H_2O	C
Acetone	H_2O	A
2-MeTHF	H_2O	E/P
DMF	H_2O	Amorphous
THF	H_2O	Amorphous
Acetone	n-Heptane	A/J

Chloroform	n-Heptane	N
DCM	n-Heptane	N
EtOAc	n-Heptane	N
MEK	n-Heptane	N
MIBK	n-Heptane	N
IPAc	n-Heptane	N
MEK	MTBE	Amorphous
ACN	MTBE	A/J
2-MeTHF	MTBE	Amorphous
Acetone	MTBE	Amorphous
THF	MTBE	Amorphous
EtOAc	MTBE	Amorphous
1,4-Dioxane	MTBE	G/F

Slow Evaporation

Slow evaporation experiments were performed under 10 conditions. About 20 mg of Form A was dissolved in 1.0 mL of solvent in a 3-mL glass vial. The visually clear solutions were allowed a slow evaporation at RT. The solids were isolated for XRPD analysis. The results summarized in Table 1-3 indicated that Form A, E, F, G, J, and K were obtained.

Table 1-3: Summary of slow evaporation experiments

Solvent	Solid Form
DCM	A/J
CHCl3	A/J
MEK	A/J
IPAc	Amorphous
THF	Amorphous
EtOAc	Amorphous
ACN	A/J
Dioxane	G/F

EtOH	K
DMF	E

Crash cooling

About 25-50 mg of Form A dissolved in 0.2-0.6 mL solvent to get a suspension. The suspension was then heated to 60°C using magnetic stirring and equilibrated for two hours and filtered using a PTFE membrane (pore size of 0.20 µm). Filtrates were immediately transferred to an environment of 5°C. A total of 4 experiments were conducted. Results in Table 1-4 showed that Form E, K, L, M, and P were obtained.

Table 1-4: Summary of crash cooling experiments

Solvent (v:v)	Solid Form
EtOH	K
IPAc	M
Anisole	L
Toluene	E/P

Slurry at RT

Slurry conversion experiments were conducted at RT in 20 solvent systems. About 15-20 mg of Form A was suspended in 0.5 mL-1.0 mL of solvent at RT. The remaining solids were isolated for XRPD analysis. Result summarized in Table 1-5 indicated that Form A, B, E, F, G, I, N, and P were obtained.

Table 1-5: Summary of slurry conversion experiments at RT

Solvent (v/v)	Solid Form
MIBK/IPA (1:9)	B/I
EtOH/IPA (1:9)	B/I
DMSO/IPA (1:9)	Amorphous
ACN/IPA (1:9)	B/I

2-MeTHF/MTBE (1:9)	E/P
Acetone/MTBE (1:9)	E/P
IPAc/MTBE (1:9)	E/P
DCM/MTBE (1:9)	A/J
CHCl3/Heptane (1:9)	N
Dioxane/Heptane (1:9)	N
Toluene	A/J
Anisole	E/P
IPA	B/I
MTBE	E/P
DMF	Gel
H2O	Amorphous
THF/H2O (Aw=0.2, 0.92/0.08)	F/G
THF/H2O (Aw =0.4, 0.83/0.17)	F/G
THF/H2O (Aw =0.6, 0.73/0.27)	F/G
THF/H2O (Aw =0.8, 0.6/0.4)	Amorphous

Slurry at 60°C

Slurry conversion experiments were conducted at 60°C in 10 solvent systems. About ~25-75 mg of Form A was suspended in 0.5 mL of solvent at 60°C for 3 days. The remaining solids were isolated for XRPD analysis. Result summarized in Table 1-6 indicated that Form B, C, D, H, I, K, and N were obtained from all experiments.

Table 1-6: Summary of slurry conversion experiments at 60°C

Solvent (v/v)	Solid Form
Toluene	D/H
Water	C
Heptane	N
IPA	B/I
DMF/Toluene (1:9)	Amorphous

MIBK/Heptane (1:4)	C
MEK/Heptane (1:4)	N
EtOH/Toluene (1:5)	K
EtOAC/Toluene (1:5)	D/H
2Me-THF/IPA (1:4)	B/I

Slurry in bulky solvents

Slurry conversion experiments were conducted at 60°C and 100°C in 6 different bulky solvent systems. About ~25-75 mg of Form A was suspended in 0.5 mL of bulky solvent at the corresponding temperature and magnetically stirred. The remaining solids were isolated for XRPD analysis. Result summarized in Table 1-7 indicated that Form N and Q were obtained from all experiments.

Table 1-7: Summary of slurry conversion experiments in bulky solvents

Solvent (v/v)	Temperature	Solid Form
Iso-Octane	60°C	N
Iso-Butanol	100°C	Q
Propylene Glycol	100°C	Q
Ethylene Glycol	100°C	Q
n-Butanol	100°C	Q
n-Pentanol	100°C	Q

Slow cooling

About 25-50 mg of Form A was dissolved in 0.2-0.6 mL solvent to get a suspension. The suspension was then heated to 50°C using magnetic stirring and equilibrated for two hours and filtered using a PTFE membrane (pore size of 0.20 µm). Filtrates were slowly cooled down to 5°C at a rate of 0.1°C/min. A total of 5 experiments were conducted. Results in Table 1-8 showed that Form D, H, K, and L were obtained.

Table 1-8: Summary of slow cooling experiments

Solvent (v:v)	Solid Form
EtOH	K
IPAc	Amorphous
Anisole	L
Toluene	D/H
n-Heptane	No Solids

Polymer Induced Crystallization

Polymer induced crystallization experiments were performed with two different polymers in 5 solvents. About 20 mg of Form A was dissolved in 0.5~2.0 mL of appropriate solvent to obtain a clear solution in a 3-mL vial. About 2 mg of polymer mixture was added into 3-mL glass vial. All the samples were subjected to evaporate at RT to induce precipitation. The solids were isolated for XRPD analysis. Results summarized in Table 1-9 showed that Form A, J, and K were obtained.

Table 1-9: Summary of polymer induced crystallization experiments

Solvent (v:v)	Polymer	Solid Form
H_2O	polyvinylchloride (PVC)	Amorphous
EtOH	polyvinylchloride (PVC)	K
DCM	polyvinylchloride (PVC)	A/J
EtOAc	sodium alginate (SA)	Amorphous
n-Heptane	sodium alginate (SA)	Low crystallinity

Temperature cycling

Suspensions of Form A about 50-100 mg/ml in 0.5ml of solvent were magnetically stirred and exposed to high (50°C) and low (5°C) temperature in cycles. Solids were isolated at day 1 and day 3 and analyzed by XRPD. A total of 10 experiments were conducted as summarized in Table 7-15 and Form A, B, C, D, E, F, G, H, I, J, and N were obtained.

Table 1-10: Summary of temperature cycling experiments between 50°C and 5°C

Solvent (v/v)	Solid Form Day 1	Solid Form Day 3
n-Heptane	A/J	N
IPA	B/I	B/I
H_2O	C	C
Toluene	D/H	D/H
IPAc/MTBE (1:3)	E/P	E/P
Acetone/Heptane (1:4)	A/J	A/J
$CHCl_3$/Heptane (1:3)	N	N
THF/H_2O (1:3)	F/G	F/G
2-MeTHF/H_2O (1:4)	Amorphous	Amorphous
2-MeTHF/n-Heptane	A/J	N

Reverse Anti-Solvent Addition

About 20-50 mg of Form A was dissolved in appropriate solvent to obtain a clear solution. The solution was then added dropwise into the corresponding anti-solvent with magnetic stirring. The obtained precipitate was isolated for XRPD analysis. A total of 10 experiments were conducted. Results in Table 1-11 showed that Form A, J, and N were obtained.

Table 1-11: Summary of reverse anti-solvent addition experiments

Solvent	**Anti-solvent**	**Solid Form**
ACN	H_2O	Amorphous
EtOH	H_2O	Amorphous
MeOH	H_2O	Amorphous
DMF	H_2O	Amorphous
Dioxane	H_2O	Amorphous
THF	H_2O	Amorphous
Acetone	n-Heptane	A/J
Chloroform	n-Heptane	N (gel)

DCM	n-Heptane	N (gel)
EtOAc	n-Heptane	N

XRPD of the isolatable forms is can be seen in the Figures. The characterization results are summarized in Table 1. A phase map of the six anhydrates is shown at Figure 1A. A phase interconversion map of all solvates and hydrates is shown at Figure 1B.

Table 1: Characterization of crystalline forms of the compound of Formula I.

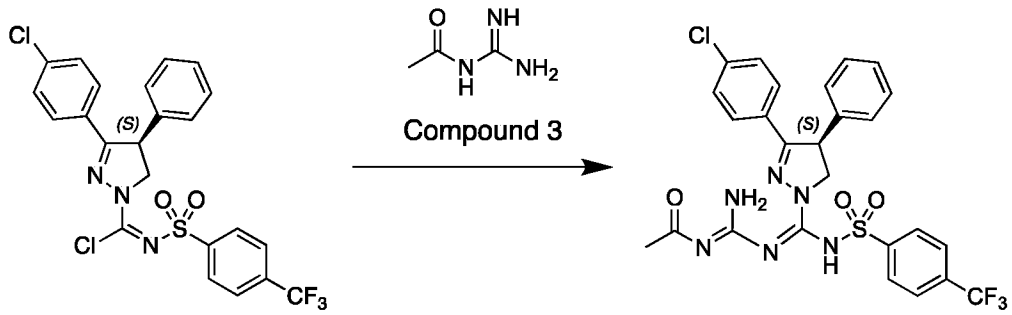
Form/Sample ID	Preparation condition	TGA (weight %)	KF (H_2O%)	DSC (onset or peak* °C)	Form Identification based on TGA & KF	Stoichiometry API:Solvent based on TGA & KF
Form A	Obtained from synthesis (see Example 2)	0.01	NA	152.2	Anhydrate	NA
Form B	Temperature Cycling in IPA (Air Dry XRPD)	5.34	0.5	126.4	Solvate	1:0.55
Form C	Temperature cycling in H_2O or Anti-solvent addition EtOH/H_2O (XRPD wet solids)	0.32	NA	157.1	Anhydrate	NA
Form D	Temperature Cycling in Toluene (Air Dry XRPD)	0.07	NA	155.9	Anhydrate	NA
Form E	Temperature Cycling in IPAc/MTBE (1:3) (Air Dry)	0.43	NA	120.9, 146.1	Anhydrate	NA

Form F	RT slurry in THF/H2O (0.92/0.08; Aw=0.2) (Air Dry XRPD)	1.85	0.6	119.5	Partially desolvated	1:0.15 (THF)
Form G	RT slurry in THF/H2O (0.92/0.08; Aw=0.2) (Wet XRPD)	NA	NA	NA	Labile Solvate	NA
Form H	Temperature Cycling in Toluene (Wet XRPD)	NA	NA	NA	Labile Solvate	NA
Form I	Temperature Cycling in IPA (Wet XRPD)	NA	NA	NA	Labile Solvate	NA
Form J	Anti-Solvent Addition ACN/H2O (Wet XRPD)	NA	NA	NA	Labile Solvate	NA
Form K	Crash Cooling in EtOH	1.35	1.4	53.6, 106.3	Hemi-Hydrate	1:0.47
Form L	Crash Cooling in Anisole	4.56	0.21	126.4	Solvate	1:0.26
Form M	Crash Cooling in IPAc	13.33	0.17	108.9, 116.7*, 128.2*	Solvate	1:0.89

Form N	Temperature Cycling in CHCl3/n-Heptane (1:3)	0.46	NA	142.0	Anhydrate	NA
Form O	Slow Evaporation in MeOH	5.11	Minimal solids produced	107.4	Very Likely Solvate	1:0.99
Form P	Temperature Cycling in IPAc/MTBE (1:3) (Air Dry)	NA	NA	NA	Labile Solvate	NA
Form Q	100 0C slurry in n-Butanol	0.63	NA	101.4	Anhydrate	NA

Example 2: Form A and Form J

Form A was obtained via the following synthesis step:



1) 7.75 L of DMF was pumped into a 50 L enamel jacket kettle by reduced pressure agitated.

2) 1.58 kg of Compound 2 was added to the solution at 25-30°C in one portion.

3) 0.595 kg of Compound 3 was added to the solution at 25-30°C in one portion.

4) The reaction mixture was stirred at 20-30°C for 0.5 h.

5) 1.49 kg of TEA was added to the solution at 25-30°C under nitrogen.

6) The reaction mixture was stirred at 20-30°C for 1.0 h.

7) The reaction was monitored by HPLC until completion.

8) After completion, the reaction mixture was slowly added into 31 L of water and stirred at 10-15°C for 30 min.

9) The reaction mixture was then filtered, and the filter cake was washed with water (2000 mL). The washed filter cake was dissolved in DCM (4000 mL) and water (1000 mL) was added.

10) The organic layers were washed with brine (3000 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude compound having a purity of 93.1% (by HPLC).

11) The crude compound of Formula I was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=3/1 to 2/1, TLC: PE:EA=1:1,p1:Rf=0.5).

12) The collected fractions were concentrated under reduced pressure to give a residue.

13) The residue was triturated with DCM (5.0 L) and n-heptane (5.0 L) at 30°C for 1.0 h.

14) The mixture was then filtered, and the filter cake was dried under reduced pressure at 45°C.

15) Crystalline compound of Formula I, Form A (1.48 kg, 85% yield, purity 99.8%) was obtained as a white solid, which was confirmed by HPLC, LCMS and H/FNMR.

Form A was characterized by XRPD (Figure 2A) and PLM. Form A was shown to be crystalline and possess small rod-like particles with agglomeration.

Thermal analysis conducted on Form A showed a weight loss of 0.01% up to 200 °C, and a single endothermic peak with an onset of 152.2°C and a peak temperature of 162.3°C as displayed in Figure 2B.

Form A obtained from anti-solvent addition in ACN/H_2O was further investigated by analyzing the wet solids by XRPD. The sample was covered with 3511 Kapton film to minimize the solvent evaporation from the wet cake. A unique pattern, different from Form A was observed indicating a labile solvate phase forms in this solvent system. This crystalline form was designated as Form J. Upon ambient drying, Form J converted to Form A. XRPD overlay of Form A and Form J is shown in Figure 2C.

Approximate solubility of Form A was determined in 20 single solvents at RT, respectively. Approximately 2 mg of Form A was added into a 3-mL glass vial. Corresponding solvents were added stepwise (50 µL- 50 µL - 200 µL - 700 µL) into the vials until the solids were dissolved visually or a total volume of 1 mL was reached. The ranges of approximate solubility were calculated according to the mass of sample, volume of solvent and observation. The results summarized in Table 2 were used to guide the solvent selection in polymorph screening.

Form A had high solubility (>10mg/mL) in most solvents including MeOH, EtOH, Acetone, MIBK, MEK, EtOAc, IPAc, THF, 2-MeTHF, 1,4-Dioxane, Anisole, ACN, $CHCl_3$, DMSO, and DCM. Moderate solubility (2.0<S<10.0) was observed in Toluene. Low solubility (<3.0 mg/mL) was observed in IPA, MTBE, n-Heptane, and H_2O.

Table 2: Solubility of the compound of Formula I, Form A

Solvent	**Solubility (mg/mL)**	**Solvent**	**Solubility (mg/mL)**
MeOH	S>36.0	Dioxane	S>64.0
EtOH	18.0<S<36.0	MTBE	S<2.4
IPA	S<3.1	Anisole	7.7<S<23.0
Acetone	S>42.0	n-heptane	S<2.7
MIBK	S>44.0	ACN	S>70.0
MEK	S>40.0	Water	S<2.9
EtOAc	S>40.0	Toluene	2.8<S<9.3
IPAc	33.0<S<66.0	CHCl3	S>40.0
THF	S>34.0	DMSO	S>52.0
2-MeTHF	S>54.0	DCM	S>42.0

Example 3: Form B and Form I

Form B was obtained by temperature cycling in IPA. The formation of Form B was also observed in IPA slurry at RT and 60°C. Form B was further characterized by analyzing the wet cake by XRPD. The sample on the XRPD sample holder was covered by 3511 Kapton Film to minimize the solvent evaporation from the sample. A unique pattern, different from Form A and Form B, was observed, and was designated as Form I. Upon ambient drying, Form I converted to Form B, indicating that Form I is a labile solvate. Comparison of Form A, Form B, and Form I XRPD patterns is displayed in Figure 3A. PLM showed small irregularly shaped birefringent particles. Thermal analysis in Figure 3B showed a weight loss of 5.34% up to 174.0 °C by TGA, and a broad endotherm with an onset of 126.4°C and a peak temperature of 136.3°C by DSC. KF analysis of Form B and showed 0.5% water content. Comparing the KF and TGA results, it was concluded that Form B is an IPA solvate, more specifically, a hemi-solvate determined by calculating the API:Solvent stoichiometry from the TGA weight loss to be 1:0.6.

Example 4: Form C

Form C was obtained by temperature cycling in H_2O from 60°C to 25°C. The formation of Form C was also observed in anti-solvent addition and 60°C screening experiments. Comparison of Form A and Form C XRPD patterns is shown in Figure 4A. PLM image of Form C showed small irregularly shaped birefringent particles. Thermal analysis in Figure 4B showed a weight loss 0.32% up to 175.0°C and a single endotherm with an onset of 157.1°C and a peak temperature of 167.9°C. The minimal weight loss observed indicated an anhydrous phase.

Example 5: Form D and Form H

Form D was obtained by temperature cycling in toluene. The formation of Form D was also observed in 60 ^{0}C slurry and slow cooling using toluene. Form D was further characterized by analyzing the wet solids by XRPD. The sample on the XRPD sample holder was covered by 3511 Kapton Film to minimize the solvent evaporation from the sample. A unique pattern, different from Form A and Form D, was observed indicating a

labile solvate phase, and was designated as Form H. Upon ambient drying, Form H converted to Form D. Comparison of Form A, Form D, and Form H XRPD patterns is displayed in Figure 5A. PLM image of Form D showed small irregular needles with agglomeration. Thermal analysis in Figure 5B showed a weight loss 0.07% up to 180.0 ^{0}C and a single endotherm with an onset of 155.9°C and an enthalpy of 23.5 J/g, and a peak temperature of 163.9°C. The minimal weight loss observed indicated an anhydrous phase.

Example 6: Form E and Form P

Form E was obtained by temperature cycling in IPAc/MTBE (1:3 v/v). The formation of Form E was also observed in anti-solvent addition, crash cooling, and slurry at RT experiments using MTBE, 2-MeTHF, or toluene. Form E was further characterized by analyzing the wet solids by XRPD. The sample on the XRPD sample holder was covered by 3511 Kapton Film to minimize the solvent evaporation from the sample. A unique pattern, different from Form A and Form E, was observed indicating a labile solvate phase, and was designated as Form P. Upon ambient drying, Form P converted to Form E. Comparison of Form A, Form E, and Form P XRPD patterns is displayed in Figure 6A. PLM image of Form E showed small irregularly shaped birefringent particles. Thermal analysis in Figure 6B showed a weight loss 0.31% up to 177.9°C and two endotherms, with onsets of 120.6°C and 146.0°C and peak temperatures of 129.5°C and 154.6°C respectively. The minimal weight loss observed indicated an anhydrous phase.

The first small endotherm was further investigated to determine if a conversion to another form occurred upon heating past the first small endotherm and before the final melting endotherm, and then cooling back down to room temperature. Cycle DSC shown in Figure 6C was performed by heating to 135 °C in cycle 1, cooling to RT in cycle 2, then heating to 300 °C (past the final melt) in cycle 3. In cycle 2, the endothermic event that occurred in cycle 1 (onset 122.1 °C) was observed upon cooling indicating that it is a reversible event. In the final cycle, the first endotherm is again observed. This indicates Form E converts to a high temperature melting point that cannot be isolated, because it converts back to Form E upon cooling. This is an indication that Form E and the high temperature melting form are enantiotropically related, with Form E being more stable at temperatures <122 °C. The melting endotherm at 147.4°C does not match the melting of any of the other forms observed in the screening providing additional evidence that a new form exists at

the elevated temperature. XRPD of this new form can be obtained by in situ hot stage XRPD.

Example 7: Form F and Form G

Form F was obtained by temperature cycling in THF/H_2O (0.92/0.08 v/v A_w=0.2). The formation of Form F was also observed in RT slurry in THF/H_2O at A_w= 0.4 and 0.6, and in temperature cycling in THF/H_2O (1:3). Form F was further characterized by analyzing the wet solids by XRPD. The sample on the XRPD sample holder was covered by 3511 Kapton film to minimize the solvent evaporation. A unique pattern, different from Form A and Form F, was observed indicating a labile solvate phase, which was designated as Form G. Upon ambient drying, Form G converted to Form F. Comparison of Form A, Form F, and Form G XRPD patterns is displayed in Figure 7A. PLM image showed small irregularly shaped birefringent particles. Thermal analysis in Figure 7B showed a weight loss of 1.85% up to 165.0 ^{0}C by TGA, and a broad endotherm with an onset of 119.5°C and a peak temperature of 132.4°C. KF was obtained of Form F and resulted in a water content of 0.6%. Comparing the KF and TGA results, it was concluded that Form F is likely a THF solvate.

Example 8: Form K

Form K was obtained by crash cooling from EtOH solution. The formation of Form K was also observed in slow evaporation, 60 °C slurry, slow cooling, and polymer induced crystallization using EtOH. Comparison of Form A and Form K XRPD patterns is displayed in Figure 8A. PLM image showed small irregularly shaped birefringent single particles and agglomerates. Thermal analysis in Figure 8B showed a weight loss of 1.35% up to 160.0 °C by TGA, and two endothermic events with onsets of 53.6°C and 106.3°C and peak temperatures at 68.7°C and 125.9°C respectively. Form K was heated to 90 °C and cooling back down. XRPD of the resulting material showed a change in compared patterns as shown in Figure 8C due to the driving off of the water by heating resulting in the dehydrated phase. The water content of the solids was determined by KF to be 1.4%. The weight loss in TGA and water content obtained by KF were complimentary and Form K was concluded to be a hemi-hydrate.

Example 9: Form L

Form L was obtained by crash cooling of anisole solution. The formation of Form L was also observed in slow cooling experiments using anisole. Comparison of Form A and Form L XRPD patterns is displayed in Figure 9A. PLM image showed small irregularly shaped birefringent primary particles and agglomerates. Thermal analysis in Figure 9B showed a weight loss of 4.56% up to 165.0 ^{0}C by TGA, and a single endothermic event with an onset of 126.4°C and a peak temperature of 133.8°C in the DSC curve that occurs after the solvent is driven. KF was obtained of Form L and resulted in a water content of 0.2%. Comparing the KF and TGA results, it was concluded that Form L is a partially desolvated anisole solvate as the stoichiometry of API:Anisole is 0:0.26.

Example 10: Form M

Form M was obtained by crash cooling of IPAc solution. Comparison of Form A and Form M XRPD patterns is displayed in Figure 10A. PLM image showed small irregular shaped birefringent particles. Thermal analysis in Figure 10B showed a weight loss of 13.33% up to 165.0 °C by TGA, and 2 overlapping endothermic events in the DSC curve with an onset of 109 °C, and peak temperatures at 116.7°C and 128.2°C that occur concurrently with the TGA weight loss step. KF was obtained of Form M and resulted in a water content of 0.2%. Comparing the KF and TGA results, it was concluded that Form M is an IPAc solvate, more specifically, a mono-solvate determined by calculating the API:Solvent stoichiometry from TGA weight loss.

Example 11: Form N

Form N was obtained by temperature cycling n $CHCl_3$/n-Heptane (1:3 v/v). The formation of Form N was also observed in anti-solvent addition, RT and 60 °C slurry, bulky solvent slurry, and reverse anti-solvent addition experiments using n-Heptane. Comparison of Form A and Form N patterns is displayed in Figure 11A. PLM image of Form N showed small irregularly birefringent particles. Thermal analysis in Figure 11B showed a weight loss 0.46% up to 179.0 °C and a single endotherm with an onset of 141.9 °C and a peak temperature of 152.1°C. The minimal weight loss observed indicated an anhydrous phase.

Example 12: Form O

Form O was obtained only by slow evaporation in MeOH. Comparison of Form A and Form O XRPD patterns is displayed in Figure 12A. PLM image showed crystals with a large plate-like morphology. Thermal analysis in Figure 12B showed a weight loss of 5.11% up to 160.0°by TGA, and a broad endotherm with an onset of 107.4 °C and a peak temperature of 110.6°C. Due to the method in which Form O was produced, minimal solids were isolated. Scaling up of Form O was attempted by cooling crystallization and using the remaining solids as seeds. This was unsuccessful and KF was not performed for this Form. However, calculating the stoichiometry of API:MeOH from the TGA weight loss shows 1:0.99 providing some evidence that Form O is a MeOH mono-solvate.

Example 13: Form Q

Form Q was obtained by slurrying Form A in n-Butanol at 100 °C. The formation of Form Q was also observed in 100 °C bulky solvent slurry using iso-butanol, propylene glycol, ethylene glycol, and n-pentanol. Comparison of Form A and Form Q XRPD patterns is displayed in Figure 13A. PLM image of Form Q showed very small irregularly shaped birefringent particles. Thermal analysis in Figure 13B showed a weight loss 0.63% up to 160.0°C and a single broad endotherm with an onset of 101.4°C and a peak temperature of 130.1°C. The minimal weight loss observed indicated an anhydrous phase.

Example 14: Slurry Competition Experiments

Anhydrates:

A total of six anhydrates, Forms A, C, D, E, N, and Q were observed. A thermodynamic assessment of all anhydrates was performed by slurrying all anhydrates in equal mass ratios in a non-solvating solvent, n-Butanol, at RT and 50 °C. At both RT and 50 °C, conversion of all anhydrates to Form C was observed indicating that it is the most stable anhydrate.

Hydrates:

One hydrate (Form K) was observed and found to be a hemi-hydrate. A thermodynamic assessment of Form K was performed by creating a slurry of Form K and Form C (the

most stable anhydrate) in equal mass ratios at various water activities using a non-solvating solvent. Initially, EtOH/H_2O was used, and results indicated that from the range, 0.1<Aw<0.9, Form K was more stable. However, in this experiment Form C was found to be more stable at Aw≥0.9. It was suspected that EtOH may be forming a solvate that favors the formation of Form K because at higher water activities, the hydrate should be more thermodynamically stable. The values and results for obtaining the critical water activity follows the laws of thermodynamics and the results obtained from this experiment can be transferred to another solvent/H_2O system. Additional critical water activity experiments were performed in acetone/H_2O at A_w= 0.5 and 0.9 using Form K and Form C. At both water activities, conversion to Form C was observed. These results indicate that Form K is not a stable hydrate and that the formation of Form K is influenced by the presence of EtOH.

Example 15: Scale up of Form C

Form C was successfully scaled up to 5 grams. Starting with Form A, ~5 grams were weighed and transferred to a 100 mL bottle. 50 mL of EtOH was added to create a suspension and the mixture was magnetically stirred at 65 °C. Once a clear solution was obtained, the solution was slowly cooled to 50 °C. Once the sample reached 50 °C, H_2O was at added at a rate of ~1 mL/min to the solution until a 1:1 ratio (v/v) of EtOH/H_2O was obtained. The sample was filtered, and the wet solids were evenly distributed onto a large weigh boat breaking apart any large clumps. A sample was extracted from the bulk solids to perform in house baseline characterization. XRPD of wet solids confirmed the formation of Form C as shown in Figure 14. PLM image of the material showed needle-like morphology with some agglomeration. The extracted sample was vacuum dried at 40 °C for several hours, then analyzed by TGA/DSC. TGA results confirmed the anhydrous nature of Form C, and an increase in enthalpy (AH) was observed. The remaining bulk solids were then vacuum dried over a weekend.

Example 16: Comparison of simulated XRPD and experimental XRPD data

Single-crystal data of a compound of Formula I is disclosed in Liu et al., Functional Selectivity of a Biased Cannabinoid-1 Receptor (CB_1R) Antagonist, ACS Pharmacology & Translational Science, 2021, which is hereby incorporated by reference in its entirety.

This single crystal data was matched to experimental XRPD data through simulation, and was shown to correspond to Form B. An overlay of the simulated XRPD data and of the experimental XRPD data of Form B is shown at Figure 15.

The simulated XRPD pattern shows a strong match with the experimentally obtained pattern for Form B at low angles with minor adjustments (0.1° 2θ). There is noticeable drift across the peak locations across the two spectra, but the peak intensity ratios and relative locations when considered as groups is an excellent match. The single-crystal data was noted in the CIF to have been collected at 100 K while the XRPD data was collected at ambient conditions. The displacement on the x-axis is due to thermal contraction and expansion and is to be expected with a temperature disparity this great. It is significant that the peak patterns retain their similarity to the simulation so well, inferring that the temperature change causes a near-uniform shift in the unit cell parameters, and indicates that there is no polymorphic transition across the temperature range. In addition to the crystallographic evidence, the single-crystal data indicates that the crystal is a monosolvate of isopropyl alcohol and hemihydrate. While the ratios are not consistent with those reported for Form B, the solvent identified is consistent.

Example 17: Other experimental conditions to obtain Form C

Form C was obtained by temperature cycling in water:

- 3g of the compound of Formula I, Form A were added to a flask;
- 10vol water were added to the flask;
- Temperature cycling was conducted from 60°C to 25°C;
- The mixture was stirred for 4.5h at 25°C;
- The precipitated crystalline solids were filtered and dried under nitrogen at 20-25°C and identified as Form C by XRPD.

Form C was also obtained by water addition to an ethanol solution:

- 0.5g of the compound of Formula I, Form A was dissolved in 6vol EtOH at 60°C;
- 2vol water were added to the mixture;
- 0.5% seed Form C was added to the mixture;
- The mixture was stirred for 1h at 60°C;
- The mixture was then cooled to 25°C over 4h;

- The mixture was then stirred for 8h at 25°C;
- The precipitated crystalline solids were filtered and dried under nitrogen at 20-25°C and identified as Form C by XRPD. The yield was of 81%.

Form C was also obtained by water addition to a methanol solution:

- 0.5g of the compound of Formula I, Form A was dissolved in 5vol MeOH at 60°C;
- 0.2vol water were added to the mixture;
- 0.5% seed Form C was added to the mixture;
- The mixture was stirred for 1h at 60°C;
- 2.3vol water were added to the mixture;
- The mixture was stirred for 1h at 60°C;
- The mixture was then cooled to 25°C over 4h;
- The mixture was then stirred for 8h at 25°C;
- The precipitated crystalline solids were filtered and dried under nitrogen at 20-25°C and identified as Form C by XRPD. The yield was of 74%.

Form C was also obtained by water addition to a n-propanol solution:

- 0.5g of the compound of Formula I, Form A was dissolved in 10vol n-PrOH at 60°C;
- 3.2vol water were added to the mixture;
- 0.5% seed Form C was added to the mixture;
- The mixture was stirred for 1h at 53°C;
- 1.8vol water were added to the mixture;
- The mixture was stirred for 1h at 53°C;
- The mixture was then cooled to 25°C over 4h;
- The mixture was then stirred for 13h at 25°C;
- The precipitated crystalline solids were filtered and dried under nitrogen at 20-25°C and identified as Form C by XRPD. The yield was of 82%.

Form C was also obtained in 5g, 18g and 115g-scale crystallization experiments starting from by dissolving Form A in Ethanol at 40°C, adding water, cooling to 25°C, and collecting crystalline compound of Formula I, Form C (yield 92%).

XRPD peak lists

Form A :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.086090	183.494200	0.076752	28.62961	0.45
3.707256	169.922600	0.102336	23.83388	0.42
4.519086	154.441900	0.153504	19.55390	0.38
4.767668	95.149730	0.127920	18.53492	0.24
5.895159	40344.720000	0.204672	14.99228	100.00
9.390182	1958.212000	0.230256	9.41854	4.85
10.059180	151.920000	0.127920	8.79360	0.38
10.648700	479.452900	0.153504	8.30807	1.19
11.634810	54.030360	0.307008	7.60604	0.13
12.381600	137.328200	0.153504	7.14892	0.34
12.959010	1182.441000	0.255840	6.83165	2.93
14.120070	74.544290	0.153504	6.27241	0.18
14.384260	89.043460	0.076752	6.15779	0.22
15.362120	106.397700	0.102336	5.76796	0.26
15.886470	431.711300	0.179088	5.57874	1.07
16.167840	654.325000	0.153504	5.48228	1.62
16.959060	850.349500	0.255840	5.22825	2.11
17.395840	2363.185000	0.153504	5.09795	5.86
17.804300	1452.938000	0.153504	4.98190	3.60
18.353340	243.036700	0.179088	4.83409	0.60
18.616340	181.817200	0.102336	4.76639	0.45
19.504140	618.851400	0.179088	4.55139	1.53
19.853480	877.906900	0.204672	4.47208	2.18
20.248410	223.899100	0.127920	4.38574	0.55
21.097250	78.173740	0.102336	4.21116	0.19
21.822750	254.780300	0.307008	4.07277	0.63
22.916980	266.261600	0.102336	3.88073	0.66
23.997590	178.567200	0.102336	3.70837	0.44
24.344500	248.531300	0.102336	3.65631	0.62
25.001850	401.287800	0.204672	3.56164	0.99
25.368100	127.185200	0.102336	3.51105	0.32
25.661320	185.998300	0.102336	3.47159	0.46
26.780970	36.757570	0.153504	3.32894	0.09
27.523320	28.599570	0.307008	3.24082	0.07
28.202270	69.732460	0.307008	3.16432	0.17
29.155480	74.018680	0.204672	3.06300	0.18
29.812190	46.653190	0.076752	2.99701	0.12
30.211580	44.721800	0.204672	2.95829	0.11
33.151900	29.172220	0.409344	2.70233	0.07
33.555400	6.709808	0.076752	2.67075	0.02
34.322070	60.547740	0.358176	2.61283	0.15
35.097970	81.229270	0.204672	2.55683	0.20
35.834360	20.889450	0.076752	2.50596	0.05
36.803920	33.269680	0.307008	2.44214	0.08

Form B :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.081334	53.230170	0.076752	28.67379	0.34
3.249706	168.982500	0.076752	27.18853	1.07

4.759403	70.288630	0.409344	18.56709	0.45
5.590357	219.460400	0.076752	15.80900	1.39
6.595675	15774.250000	0.102336	13.40146	100.00
6.827613	3869.795000	0.102336	12.94672	24.53
8.450346	628.405000	0.102336	10.46383	3.98
9.089335	3421.267000	0.127920	9.72960	21.69
9.727601	3338.140000	0.102336	9.09259	21.16
9.884985	1988.280000	0.076752	8.94817	12.60
10.866150	524.915400	0.102336	8.14229	3.33
11.516460	130.023300	0.076752	7.68394	0.82
11.963940	258.657900	0.127920	7.39753	1.64
12.960680	103.954800	0.102336	6.83078	0.66
13.647040	240.041800	0.102336	6.48874	1.52
14.317250	882.790200	0.127920	6.18646	5.60
15.017310	3571.110000	0.127920	5.89961	22.64
15.403460	2891.514000	0.153504	5.75257	18.33
15.819520	797.909400	0.127920	5.60220	5.06
16.725450	527.029900	0.127920	5.30074	3.34
17.257070	565.594500	0.102336	5.13863	3.59
17.542590	615.927200	0.179088	5.05563	3.90
18.201460	424.163000	0.076752	4.87408	2.69
18.561580	200.214100	0.076752	4.78032	1.27
18.884760	75.524100	0.102336	4.69924	0.48
19.837210	1155.661000	0.127920	4.47571	7.33
20.669110	182.399200	0.127920	4.29741	1.16
21.106720	374.324600	0.153504	4.20929	2.37
21.900850	1810.287000	0.153504	4.05843	11.48
22.338730	73.347710	0.127920	3.97986	0.46
22.779130	6.581588	0.153504	3.90390	0.04
23.387450	692.068500	0.230256	3.80371	4.39
24.268100	146.559900	0.204672	3.66764	0.93
24.716470	389.913900	0.153504	3.60212	2.47
25.215700	340.009100	0.153504	3.53192	2.16
25.528630	100.247600	0.102336	3.48933	0.64
26.555510	851.397900	0.127920	3.35669	5.40
27.495570	346.388400	0.102336	3.24402	2.20
28.492430	151.165100	0.153504	3.13275	0.96
29.042300	127.460400	0.127920	3.07468	0.81
29.493730	31.629500	0.102336	3.02864	0.20
30.031030	264.662000	0.127920	2.97567	1.68
30.281130	477.097800	0.153504	2.95166	3.02
30.807330	72.322240	0.153504	2.90243	0.46
31.997810	60.348350	0.153504	2.79711	0.38
35.225640	18.970190	0.102336	2.54785	0.12
36.879590	55.833400	0.307008	2.43730	0.35
38.025720	55.632700	0.204672	2.36643	0.35
39.081850	40.755120	0.102336	2.30488	0.26

Form C :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.194969	35.615380	0.204672	27.65420	0.70
3.812396	716.015100	0.230256	23.17681	14.14
5.856102	1436.277000	0.179088	15.09218	28.37
6.456882	5063.125000	0.230256	13.68922	100.00

7.459860	1033.798000	0.204672	11.85080	20.42
9.850815	810.558400	0.179088	8.97913	16.01
11.187440	62.419810	0.153504	7.90917	1.23
12.939770	245.169100	0.102336	6.84177	4.84
13.494440	75.203870	0.102336	6.56177	1.49
14.497570	232.105300	0.102336	6.10992	4.58
14.937460	329.660100	0.204672	5.93096	6.51
15.433590	461.171900	0.179088	5.74141	9.11
15.879330	2886.998000	0.153504	5.58123	57.02
17.171920	689.987900	0.204672	5.16392	13.63
17.945050	496.922600	0.204672	4.94315	9.81
19.074500	798.566900	0.127920	4.65292	15.77
19.441190	2391.910000	0.204672	4.56598	47.24
20.837700	578.154500	0.204672	4.26303	11.42
21.534950	368.731800	0.102336	4.12655	7.28
22.148020	940.696900	0.204672	4.01369	18.58
22.774290	749.816500	0.204672	3.90472	14.81
23.338800	350.197500	0.127920	3.81153	6.92
24.235250	408.793000	0.179088	3.67254	8.07
25.108530	363.560800	0.179088	3.54675	7.18
26.236280	811.929100	0.179088	3.39680	16.04
27.380220	312.011300	0.204672	3.25743	6.16
28.411830	311.342200	0.153504	3.14146	6.15
29.612520	95.846000	0.409344	3.01676	1.89
30.077750	88.930350	0.179088	2.97115	1.76
30.567640	270.615100	0.153504	2.92464	5.34
31.335150	50.665160	0.153504	2.85473	1.00
31.715630	111.390500	0.204672	2.82135	2.20
32.610040	93.354220	0.255840	2.74598	1.84
33.141310	70.288350	0.204672	2.70317	1.39
33.990470	56.458010	0.307008	2.63756	1.12
35.198830	96.069080	0.204672	2.54973	1.90
35.775650	67.623210	0.255840	2.50993	1.34
37.471480	26.640010	0.614016	2.40015	0.53
38.903870	83.803490	0.204672	2.31502	1.66
39.217410	57.555520	0.153504	2.29723	1.14

Form D :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.153332	169.307800	0.204672	28.01926	0.50
4.431448	2658.429000	0.127920	19.94041	7.86
5.941830	33835.610000	0.127920	14.87462	100.00
8.426903	1065.092000	0.102336	10.49289	3.15
8.816577	3616.264000	0.102336	10.02998	10.69
9.383790	375.809400	0.127920	9.42494	1.11
10.439640	807.970000	0.102336	8.47397	2.39
11.271880	7283.616000	0.127920	7.85011	21.53
11.857220	5193.201000	0.102336	7.46387	15.35
12.078650	1768.847000	0.076752	7.32753	5.23
12.338430	2233.939000	0.127920	7.17383	6.60
12.987940	115.890800	0.127920	6.81650	0.34
13.219940	357.182200	0.102336	6.69739	1.06
13.618540	13.893700	0.409344	6.50225	0.04
13.900400	467.011200	0.102336	6.37103	1.38
14.725480	569.724400	0.153504	6.01586	1.68

15.152470	487.087300	0.102336	5.84729	1.44
15.353710	286.600400	0.076752	5.77110	0.85
15.777290	323.654600	0.102336	5.61710	0.96
16.110340	1169.031000	0.102336	5.50172	3.46
16.886170	1272.457000	0.102336	5.25065	3.76
17.196420	328.858300	0.102336	5.15662	0.97
17.812720	513.725300	0.153504	4.97957	1.52
18.528180	1350.473000	0.102336	4.78887	3.99
18.743030	261.212500	0.076752	4.73445	0.77
19.213330	756.393700	0.102336	4.61961	2.24
19.414990	2298.519000	0.102336	4.57208	6.79
19.657140	2311.595000	0.127920	4.51630	6.83
20.031570	756.401100	0.102336	4.43272	2.24
20.246710	175.839200	0.076752	4.38611	0.52
20.747560	4468.067000	0.102336	4.28134	13.21
20.976770	1522.862000	0.102336	4.23508	4.50
21.834720	531.257800	0.153504	4.07057	1.57
22.393390	266.612300	0.102336	3.97026	0.79
22.792050	2442.323000	0.127920	3.90171	7.22
23.315150	266.353400	0.076752	3.81535	0.79
23.609490	121.638500	0.076752	3.76844	0.36
24.051330	255.356300	0.102336	3.70020	0.75
24.739830	2664.119000	0.179088	3.59877	7.87
25.164060	436.465200	0.127920	3.53905	1.29
25.661990	87.449390	0.153504	3.47150	0.26
25.967390	142.152200	0.102336	3.43136	0.42
26.553990	365.973800	0.127920	3.35688	1.08
26.913950	1881.958000	0.153504	3.31279	5.56
27.307290	314.477400	0.127920	3.26596	0.93
28.303020	72.745290	0.076752	3.15329	0.21
28.565290	561.713000	0.127920	3.12493	1.66
29.083400	35.792210	0.127920	3.07043	0.11
29.601760	255.646800	0.179088	3.01783	0.76
29.877580	151.904800	0.127920	2.99060	0.45

Form E :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.223808	254.574600	0.179088	27.40688	2.75
4.545509	66.329070	0.307008	19.44030	0.72
6.624407	9269.059000	0.127920	13.34340	100.00
8.007524	4108.179000	0.153504	11.04147	44.32
8.949897	4742.364000	0.102336	9.88087	51.16
9.678118	69.981640	0.102336	9.13897	0.76
10.222920	298.882400	0.127920	8.65312	3.22
11.003670	14.221230	0.409344	8.04084	0.15
11.635970	43.491710	0.102336	7.60528	0.47
11.970480	44.075680	0.076752	7.39350	0.48
12.365720	106.049700	0.076752	7.15806	1.14
12.819600	1294.077000	0.102336	6.90563	13.96
13.205330	103.229400	0.204672	6.70477	1.11
13.857730	368.166600	0.153504	6.39056	3.97
15.944810	423.062300	0.153504	5.55846	4.56
16.288310	1540.268000	0.127920	5.44201	16.62
17.265660	31.821440	0.076752	5.13609	0.34
17.939710	2597.920000	0.102336	4.94460	28.03

18.832640	1204.338000	0.179088	4.71213	12.99
19.469820	105.158300	0.307008	4.55933	1.13
20.616500	993.015900	0.204672	4.30826	10.71
22.296370	2354.107000	0.153504	3.98732	25.40
23.448510	1027.299000	0.153504	3.79395	11.08
24.312890	1658.200000	0.127920	3.66099	17.89
25.050100	92.009680	0.153504	3.55489	0.99
25.649440	343.220300	0.127920	3.47317	3.70
26.110090	1003.525000	0.230256	3.41293	10.83
26.588660	86.151680	0.153504	3.35258	0.93
26.968050	120.633700	0.204672	3.30627	1.30
27.560610	105.635400	0.255840	3.23652	1.14
28.575280	141.872600	0.102336	3.12386	1.53
29.730410	64.201560	0.255840	3.00506	0.69
30.309700	54.688740	0.230256	2.94894	0.59
30.942090	18.423020	0.307008	2.89010	0.20
31.864190	66.645730	0.153504	2.80854	0.72
32.386040	193.558800	0.153504	2.76446	2.09
33.072680	71.152350	0.153504	2.70862	0.77
33.849360	65.444690	0.127920	2.64823	0.71
34.437140	88.265690	0.204672	2.60436	0.95
36.312720	22.743430	0.153504	2.47403	0.25
37.628940	8.127533	0.409344	2.39047	0.09
38.771420	25.264060	0.307008	2.32262	0.27
39.366760	34.209900	0.204672	2.28885	0.37

Form F :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.178694	45.813100	0.076752	27.79576	4.64
3.325501	29.859660	0.076752	26.56901	3.02
4.168773	63.817540	0.076752	21.19625	6.46
4.434412	45.639750	0.102336	19.92709	4.62
4.965300	46.610870	0.076752	17.79762	4.72
5.658827	174.513200	0.358176	15.61786	17.67
6.419788	45.377340	0.063960	13.76823	4.60
7.512460	987.422200	0.230256	11.76794	100.00
7.891961	525.677400	0.127920	11.20289	53.24
9.262142	177.934000	0.102336	9.54845	18.02
9.638004	105.897100	0.051168	9.17691	10.72
9.789849	41.722350	0.102336	9.03491	4.23
11.222670	223.954900	0.153504	7.88442	22.68
11.735000	202.417800	0.255840	7.54133	20.50
12.110230	39.485890	0.038376	7.30850	4.00
12.220780	55.438760	0.051168	7.24263	5.61
12.529300	118.171200	0.102336	7.06497	11.97
13.365880	44.173050	0.051168	6.62459	4.47
13.505930	48.023010	0.102336	6.55621	4.86
14.321600	58.829660	0.102336	6.18459	5.96
15.690800	66.869320	0.038376	5.64787	6.77
16.914250	63.279140	0.063960	5.24200	6.41
17.199370	38.307210	0.038376	5.15574	3.88
17.625100	249.335100	0.127920	5.03215	25.25
18.952340	404.319200	0.358176	4.68264	40.95
20.252680	312.856600	0.614016	4.38483	31.68

21.896730	3.386084	0.051168	4.05918	0.34
22.367480	530.229800	0.127920	3.97480	53.70
23.129520	179.857100	0.255840	3.84554	18.21
23.804160	44.651970	0.102336	3.73806	4.52
25.040020	27.817500	0.153504	3.55630	2.82
25.723530	39.814260	0.127920	3.46334	4.03
27.160890	28.098980	0.076752	3.28323	2.85
28.114280	23.322130	0.153504	3.17402	2.36
29.388560	30.545480	0.051168	3.03924	3.09
30.289680	33.744010	0.076752	2.95084	3.42
31.931690	26.935100	0.063960	2.80275	2.73
33.508710	9.988585	0.051168	2.67437	1.01
37.127620	36.166680	0.046800	2.41958	3.66
38.118730	35.280220	0.051168	2.36087	3.57

Form G :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.057389	29.327710	0.102336	28.89831	1.12
3.320305	12.952490	0.102336	26.61058	0.50
4.125527	22.215040	0.102336	21.41835	0.85
4.673285	19.682430	0.127920	18.90905	0.75
6.283435	600.213900	0.051168	14.06669	22.97
7.780389	52.321620	0.204672	11.36329	2.00
8.357451	104.135600	0.153504	10.57993	3.99
9.034883	15.194670	0.153504	9.78812	0.58
10.884600	128.167800	0.179088	8.12854	4.91
12.336040	30.377210	0.076752	7.17522	1.16
12.563210	93.844090	0.038376	7.04598	3.59
13.789700	10.633010	0.307008	6.42193	0.41
14.497210	7.484401	0.409344	6.11007	0.29
15.563210	15.552420	0.511680	5.69388	0.60
16.632960	70.214870	0.102336	5.33001	2.69
17.603200	39.619290	0.307008	5.03836	1.52
18.389760	53.215650	0.127920	4.82460	2.04
18.855700	2612.816000	0.051168	4.70642	100.00
19.746090	101.330000	0.204672	4.49616	3.88
20.512260	86.700270	0.102336	4.32992	3.32
21.214370	64.815360	0.127920	4.18818	2.48
21.952470	137.321300	0.102336	4.04900	5.26
22.737490	78.777340	0.255840	3.91095	3.02
23.399160	29.378910	0.127920	3.80184	1.12
23.925380	24.954240	0.153504	3.71940	0.96
24.494490	40.232560	0.307008	3.63426	1.54
25.224590	689.014000	0.038376	3.53070	26.37
25.864670	23.144240	0.153504	3.44476	0.89
26.462280	13.818680	0.307008	3.36830	0.53
28.208050	21.898060	0.204672	3.16369	0.84
29.011920	37.525020	0.127920	3.07783	1.44
29.599420	12.601030	0.153504	3.01806	0.48
30.217880	16.616070	0.307008	2.95769	0.64
31.673660	249.517600	0.038376	2.82499	9.55
32.620170	6.461364	0.409344	2.74515	0.25
38.226000	350.608600	0.046800	2.35254	13.42

Form H :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.099136	19.949290	0.204672	28.50912	1.47
3.646530	16.577460	0.076752	24.23065	1.23
4.363048	73.752250	0.127920	20.25286	5.45
5.727725	1352.822000	0.076752	15.43015	100.00
6.008395	81.391620	0.076752	14.70998	6.02
6.655096	8.122511	0.307008	13.28194	0.60
8.232493	13.942910	0.153504	10.74024	1.03
8.725933	76.479350	0.127920	10.13397	5.65
10.322960	50.104050	0.127920	8.56948	3.70
10.898240	446.715400	0.076752	8.11839	33.02
11.446050	388.088200	0.076752	7.73105	28.69
12.022070	104.122300	0.051168	7.36189	7.70
12.817090	20.923400	0.076752	6.90698	1.55
13.508090	46.248000	0.076752	6.55517	3.42
14.360230	20.274310	0.204672	6.16804	1.50
15.895580	97.727670	0.089544	5.57556	7.22
16.426840	95.441180	0.127920	5.39642	7.05
16.675810	316.096300	0.089544	5.31641	23.37
17.245350	52.702640	0.127920	5.14209	3.90
18.071070	18.371720	0.204672	4.90896	1.36
18.430560	32.563690	0.153504	4.81401	2.41
18.857260	237.783200	0.076752	4.70603	17.58
19.119920	321.130500	0.089544	4.64197	23.74
19.562450	23.032940	0.153504	4.53795	1.70
19.864540	63.697700	0.102336	4.46962	4.71
20.352290	234.578600	0.076752	4.36359	17.34
20.837090	74.304350	0.102336	4.26315	5.49
21.254610	54.243780	0.127920	4.18034	4.01
22.027940	143.167800	0.076752	4.03530	10.58
22.619560	98.559720	0.051168	3.93107	7.29
22.892640	60.932400	0.102336	3.88480	4.50
23.226790	60.662960	0.127920	3.82966	4.48
23.955300	157.354500	0.127920	3.71482	11.63
24.175430	106.334500	0.127920	3.68149	7.86
24.811950	23.558100	0.102336	3.58847	1.74
25.974150	29.833640	0.127920	3.43048	2.21
26.357980	154.997100	0.102336	3.38139	11.46
27.694480	7.210134	0.307008	3.22118	0.53
28.735050	34.483060	0.102336	3.10685	2.55
28.977000	39.221290	0.153504	3.08146	2.90
29.376030	34.110350	0.102336	3.04050	2.52
30.272620	35.313870	0.153504	2.95247	2.61
33.063500	21.608550	0.127920	2.70935	1.60
33.698660	37.710240	0.153504	2.65972	2.79
38.960580	10.923690	0.409344	2.31178	0.81

Form I :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.781225	26.785220	0.051168	23.36780	2.08
4.760598	11.119640	0.153504	18.56244	0.86
5.401361	51.423460	0.153504	16.36173	4.00
6.277009	1286.643000	0.063960	14.08108	100.00

7.782325	365.825000	0.063960	11.36046	28.43
8.430950	885.338700	0.063960	10.48786	68.81
8.998234	108.646500	0.051168	9.82790	8.44
9.893166	12.216860	0.102336	8.94079	0.95
10.390060	141.699500	0.102336	8.51429	11.01
11.774070	289.927200	0.076752	7.51639	22.53
12.477330	14.584140	0.076752	7.09428	1.13
13.787140	23.490670	0.153504	6.42311	1.83
14.235030	89.408000	0.063960	6.22201	6.95
15.254360	77.687270	0.153504	5.80846	6.04
15.558040	121.010100	0.076752	5.69576	9.41
16.472210	62.644770	0.076752	5.38166	4.87
17.179380	560.647900	0.063960	5.16169	43.57
17.961650	188.601000	0.076752	4.93861	14.66
18.774440	792.503100	0.063960	4.72661	61.59
19.403260	199.829000	0.102336	4.57482	15.53
20.842530	68.443550	0.102336	4.26205	5.32
21.021690	57.874100	0.127920	4.22613	4.50
21.514130	345.837500	0.076752	4.13050	26.88
22.996520	88.302530	0.102336	3.86748	6.86
25.552010	135.955100	0.102336	3.48619	10.57
26.471860	51.841460	0.204672	3.36711	4.03
27.026890	14.750680	0.204672	3.29921	1.15
29.237340	22.381110	0.179088	3.05461	1.74
30.129540	24.333990	0.307008	2.96616	1.89
36.834370	6.560548	0.614016	2.44019	0.51

Form J :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.060036	20.107240	0.076752	28.87331	1.24
3.546805	12.909750	0.063960	24.91171	0.80
5.589293	1623.410000	0.038376	15.81200	100.00
7.172551	30.510520	0.076752	12.32485	1.88
9.346706	151.934600	0.127920	9.46225	9.36
10.228600	12.634670	0.255840	8.64833	0.78
11.157600	30.001350	0.153504	7.93026	1.85
12.433120	28.395290	0.179088	7.11941	1.75
14.807790	9.132507	0.818688	5.98261	0.56
16.174290	33.692260	0.127920	5.48011	2.08
16.761260	488.234000	0.076752	5.28950	30.07
18.104100	39.459320	0.153504	4.90007	2.43
18.779020	58.463190	0.179088	4.72546	3.60
19.593020	17.123870	0.307008	4.53094	1.05
20.545190	8.742917	0.204672	4.32305	0.54
21.112540	49.452260	0.153504	4.20815	3.05
21.638240	70.180120	0.255840	4.10708	4.32
22.429600	95.639860	0.153504	3.96394	5.89
24.051750	48.808610	0.204672	3.70014	3.01
24.619970	39.523670	0.153504	3.61602	2.43
25.750420	74.033410	0.153504	3.45978	4.56
26.302590	24.439390	0.051168	3.38839	1.51
26.634740	59.148650	0.307008	3.34688	3.64
28.131650	13.329710	0.307008	3.17210	0.82
32.319550	16.882490	0.204672	2.77000	1.04
33.918590	12.353660	0.153504	2.64298	0.76

34.822170	11.704460	0.076752	2.57644	0.72
35.180100	5.877381	0.409344	2.55105	0.36

Form K :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.125749	8.088668	0.204672	28.26645	0.20
3.690096	34.221650	0.038376	23.94468	0.86
6.655328	4000.436000	0.102336	13.28147	100.00
6.918468	2274.822000	0.153504	12.77690	56.86
9.126177	78.247190	0.127920	9.69040	1.96
9.939386	170.294900	0.102336	8.89932	4.26
13.794490	148.119900	0.102336	6.41971	3.70
14.462850	9.473206	0.204672	6.12451	0.24
15.134850	287.340900	0.102336	5.85405	7.18
15.552060	388.102900	0.179088	5.69794	9.70
17.277180	38.765110	0.102336	5.13269	0.97
17.892630	169.488900	0.179088	4.95751	4.24
18.715640	17.159640	0.204672	4.74132	0.43
20.016740	395.259800	0.127920	4.43598	9.88
20.708050	26.209950	0.204672	4.28942	0.66
21.277530	47.009900	0.204672	4.17589	1.18
22.016590	40.886010	0.255840	4.03735	1.02
22.500280	11.137440	0.204672	3.95164	0.28
23.319700	15.363510	0.076752	3.81461	0.38
23.819170	14.342480	0.204672	3.73574	0.36
24.886350	38.284170	0.179088	3.57791	0.96
25.802420	18.001050	0.307008	3.45293	0.45
26.744750	587.459500	0.115128	3.33337	14.68
27.751720	378.932300	0.127920	3.21466	9.47
28.685780	14.706780	0.204672	3.11208	0.37
29.261460	10.540700	0.255840	3.05215	0.26
30.570120	118.664600	0.179088	2.92441	2.97
31.603030	55.510100	0.307008	2.83115	1.39
33.571690	29.434850	0.255840	2.66949	0.74
35.121890	19.828520	0.511680	2.55514	0.50
37.437180	28.227860	0.102336	2.40227	0.71
38.211490	10.843290	0.153504	2.35535	0.27
38.760920	23.425870	0.255840	2.32322	0.59

Form L :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.114982	14.554110	0.153504	28.36413	0.35
3.758476	14.447550	0.409344	23.50919	0.35
4.169389	5.237628	0.038376	21.19312	0.13
4.260997	16.627330	0.051168	20.73769	0.40
5.242640	550.946700	0.127920	16.85672	13.32
6.074583	4135.564000	0.191880	14.54985	100.00
6.651309	1421.657000	0.230256	13.28949	34.38
8.033223	54.731720	0.038376	11.00620	1.32
8.987103	33.490450	0.153504	9.84005	0.81
11.092880	10.653230	0.255840	7.97638	0.26
12.662410	6.889622	0.614016	6.99100	0.17
14.958270	14.251120	0.409344	5.92276	0.34
15.403210	14.595950	0.076752	5.75266	0.35

16.002700	31.538320	0.127920	5.53848	0.76
17.989470	35.317420	0.153504	4.93104	0.85
18.896130	12.980740	0.204672	4.69644	0.31
20.636900	528.174400	0.153504	4.30405	12.77
22.379920	35.571950	0.204672	3.97262	0.86
23.203550	23.980560	0.255840	3.83344	0.58
25.413920	9.127674	0.307008	3.50482	0.22
26.798530	21.352080	0.409344	3.32680	0.52
33.827310	8.121967	0.153504	2.64990	0.20

Form M :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
4.728935	13.776310	0.818688	18.68665	4.03
6.588024	341.719900	0.051168	13.41701	100.00
8.261230	75.353040	0.076752	10.70294	22.05
12.250490	9.965623	0.409344	7.22513	2.92
13.289440	6.679496	0.307008	6.66252	1.95
14.378050	17.072970	0.255840	6.16044	5.00
16.397870	6.512505	0.409344	5.40589	1.91
17.840790	24.415730	0.153504	4.97180	7.14
19.791230	48.229930	0.076752	4.48601	14.11
20.690970	7.122862	0.307008	4.29292	2.08
22.710500	36.524030	0.204672	3.91554	10.69
24.566370	12.601660	0.614016	3.62378	3.69
26.487140	24.771800	0.153504	3.36520	7.25

Form N :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.113648	376.837200	0.102336	28.37628	16.12
3.318589	594.056600	0.127920	26.62434	25.41
4.161664	912.430700	0.204672	21.23245	39.03
4.630490	459.210400	0.460512	19.08371	19.64
6.117166	2337.646000	0.460512	14.44866	100.00
9.118856	132.685900	0.614016	9.69817	5.68
9.931746	174.102600	0.511680	8.90615	7.45
11.301470	32.516500	0.127920	7.82962	1.39
12.795170	94.187770	0.716352	6.91876	4.03
14.601680	66.507620	0.204672	6.06659	2.85
16.650740	576.411700	0.204672	5.32436	24.66
18.046860	122.791300	0.614016	4.91549	5.25
19.290020	675.995700	0.409344	4.60142	28.92
21.812730	236.414100	0.818688	4.07462	10.11
22.454700	190.607200	0.614016	3.95956	8.15
24.552440	82.365620	0.409344	3.62581	3.52
25.178850	69.694710	0.076752	3.53701	2.98
26.198530	180.769800	0.614016	3.40161	7.73
26.644090	97.681620	0.076752	3.34573	4.18
27.768210	54.726810	0.076752	3.21279	2.34
29.782660	103.983000	0.409344	2.99991	4.45
31.465190	40.332150	0.076752	2.84323	1.73
32.055110	60.119980	0.102336	2.79224	2.57
32.371410	56.691350	0.409344	2.76568	2.43
33.063660	46.334440	0.127920	2.70934	1.98

34.070330	25.037890	0.153504	2.63156	1.07
34.636520	16.466960	0.255840	2.58983	0.70
36.130640	19.433070	0.614016	2.48608	0.83
37.015120	29.113220	0.076752	2.42869	1.25
37.664140	9.674776	0.614016	2.38831	0.41
38.024600	22.310820	0.102336	2.36650	0.95

Form O :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.118466	24.847240	0.204672	28.33245	0.12
5.589300	21028.510000	0.063960	15.81198	100.00
6.629287	1108.200000	0.140712	13.33359	5.27
11.158960	255.084800	0.076752	7.92929	1.21
11.890180	74.750580	0.102336	7.44325	0.36
12.501050	22.268180	0.153504	7.08088	0.11
12.790830	30.640750	0.127920	6.92110	0.15
13.679850	31.283680	0.102336	6.47325	0.15
13.931390	18.834180	0.051168	6.35693	0.09
14.526300	31.686580	0.127920	6.09790	0.15
15.138950	35.324620	0.063960	5.85248	0.17
16.199310	73.933690	0.127920	5.47170	0.35
16.760720	17539.250000	0.076752	5.28967	83.41
18.091150	58.280900	0.127920	4.90355	0.28
18.491030	20.503230	0.038376	4.79840	0.10
18.779640	25.379980	0.153504	4.72531	0.12
19.183380	18.742030	0.127920	4.62676	0.09
19.476950	12.469360	0.127920	4.55768	0.06
20.014390	13.370590	0.307008	4.43649	0.06
22.408610	223.833400	0.076752	3.96760	1.06
23.419320	10.663080	0.153504	3.79861	0.05
23.792870	25.059040	0.204672	3.73981	0.12
24.280210	24.563670	0.153504	3.66584	0.12
25.380830	84.704150	0.127920	3.50932	0.40
26.594250	4.398074	0.614016	3.35189	0.02
28.098140	1146.925000	0.076752	3.17581	5.45
29.862670	40.787540	0.127920	2.99206	0.19
33.452210	28.497950	0.153504	2.67875	0.14
33.873600	219.748600	0.153504	2.64639	1.05
39.717160	39.621590	0.127920	2.26947	0.19

Form P :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.529689	27.888510	0.038376	25.03247	1.18
3.662600	23.476020	0.076752	24.12437	0.99
4.400123	35.489730	0.038376	20.08230	1.50
5.382416	2372.071000	0.115128	16.41928	100.00
6.063667	11.157090	0.102336	14.57602	0.47
6.932938	221.108600	0.102336	12.75027	9.32
7.198101	32.781830	0.038376	12.28116	1.38
7.833931	49.410480	0.038376	11.28574	2.08
8.951140	142.715800	0.063960	9.87950	6.02
9.657990	31.260630	0.076752	9.15797	1.32
10.403560	56.011520	0.127920	8.50328	2.36

11.610730	160.530200	0.127920	7.62176	6.77
12.350530	86.125170	0.102336	7.16683	3.63
13.032840	36.368250	0.204672	6.79312	1.53
13.307100	30.614840	0.038376	6.65372	1.29
13.707020	29.934460	0.307008	6.46048	1.26
14.332740	22.274910	0.089544	6.17981	0.94
14.490940	17.291070	0.076752	6.11270	0.73
15.112550	19.244290	0.127920	5.86264	0.81
15.859560	90.625380	0.102336	5.58815	3.82
16.064370	58.597610	0.102336	5.51736	2.47
16.688640	238.859300	0.140712	5.31235	10.07
17.130230	54.009750	0.204672	5.17639	2.28
17.496240	35.200040	0.051168	5.06892	1.48
17.847610	129.373800	0.127920	4.96991	5.45
18.156050	23.965910	0.409344	4.88617	1.01
18.676350	51.434760	0.153504	4.75121	2.17
19.843090	129.746400	0.102336	4.47440	5.47
20.598120	42.555630	0.038376	4.31206	1.79
20.819570	121.577300	0.153504	4.26670	5.13
21.889910	143.646000	0.127920	4.06043	6.06
22.991970	85.011130	0.179088	3.86824	3.58
23.998440	65.841820	0.127920	3.70824	2.78
24.321900	58.779780	0.153504	3.65965	2.48
24.829690	53.545770	0.102336	3.58595	2.26
25.930430	46.740940	0.179088	3.43617	1.97
26.469120	13.342160	0.307008	3.36745	0.56
29.441520	13.563290	0.307008	3.03389	0.57
32.238140	10.968090	0.409344	2.77681	0.46
36.180110	6.661629	0.614016	2.48280	0.28

Form Q :

Pos.[°2Th.]	Height [cts]	FWHMLeft[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.260787	12.693460	0.102336	27.09616	1.11
5.608259	908.625200	0.115128	15.75857	79.68
8.367888	72.985470	0.179088	10.56676	6.40
10.418170	44.613940	0.153504	8.49139	3.91
11.246690	24.166920	0.153504	7.86763	2.12
12.344520	561.072400	0.115128	7.17031	49.20
12.777440	153.379900	0.102336	6.92832	13.45
13.576850	1140.351000	0.102336	6.52212	100.00
14.947770	188.392700	0.076752	5.92690	16.52
16.820880	820.353500	0.115128	5.27089	71.94
17.692630	73.823840	0.204672	5.01309	6.47
18.728990	157.793900	0.153504	4.73797	13.84
19.388890	217.951200	0.115128	4.57818	19.11
20.147680	41.924150	0.358176	4.40744	3.68
20.937470	159.415700	0.127920	4.24294	13.98
21.732220	221.688000	0.076752	4.08954	19.44
23.310170	134.005500	0.115128	3.81615	11.75
24.474700	52.413970	0.102336	3.63715	4.60
24.825740	48.549210	0.153504	3.58651	4.26
25.196770	14.342530	0.102336	3.53453	1.26
25.474120	12.290820	0.127920	3.49668	1.08
26.251990	115.046000	0.102336	3.39481	10.09
26.838030	16.341230	0.076752	3.32199	1.43

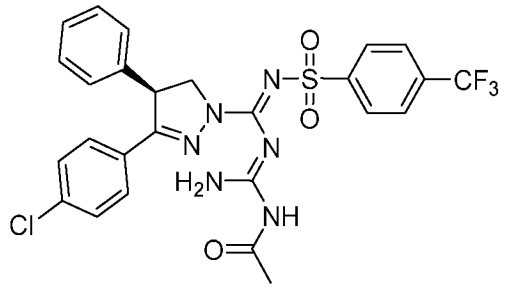
27.203510	32.787080	0.204672	3.27819	2.88
28.207540	94.352190	0.204672	3.16374	8.27
28.915720	23.455230	0.204672	3.08785	2.06
30.220390	39.440030	0.153504	2.95745	3.46
31.844520	50.706460	0.153504	2.81023	4.45
32.409930	25.599560	0.153504	2.76248	2.24
34.063480	8.783975	0.307008	2.63207	0.77
36.838030	9.840682	0.153504	2.43995	0.86
37.636080	12.850160	0.153504	2.39003	1.13

Although the invention has been illustrated and described with respect to one or more implementations, equivalent alterations and modifications will occur to others skilled in the art upon the reading and understanding of this specification. In addition, while a particular feature of the invention may have been disclosed with respect to only one of several implementations, such feature may be combined with one or more other features of the other implementations as may be desired and advantageous for any given or particular application.

Accordingly, it is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. Any publication, document, patent, patent application or publication referred to herein should be construed as incorporated by reference each in their entirety for all purposes.

CLAIMS

1. A compound of Formula I:



(I)

which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86.

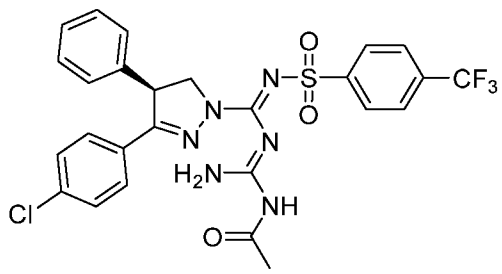
2. The compound of claim 1, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 7.46, 22.15 and 26.24.

3. The compound of claim 1 or 2, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 9.85, 19.07, 22.77.

4. The compound of any one of claims 1 to 3, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 3.81, 17.17 and 20.84.

5. The compound of any one of claims 1 to 4, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 17.95, 15.43 and 24.24.

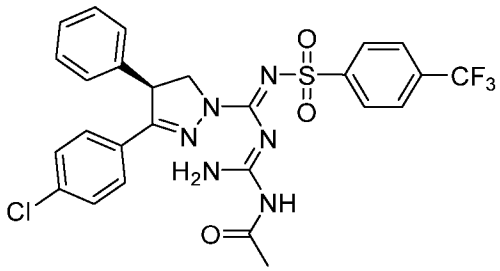
6. A compound of Formula I:



(I)

which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset of about 157.1°C.

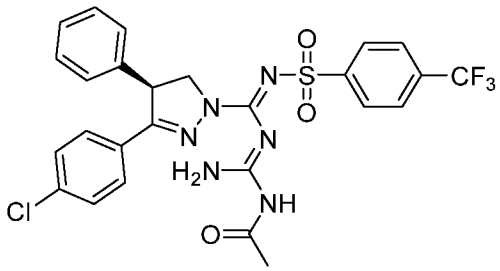
7. A compound of Formula I:



(I)

which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having a peak temperature of about 167.9°C.

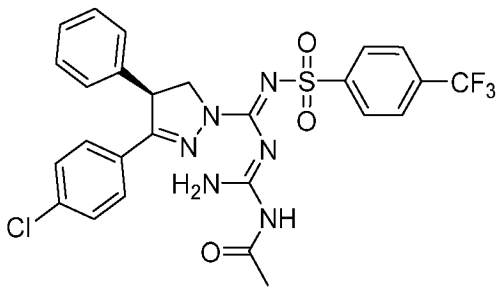
8. A compound of Formula I:



(I)

which has an X-ray powder diffraction pattern substantially the same as shown in Figure 4A-Form C.

9. A compound of Formula I:



(I)

which is crystalline and exhibits an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.89 and 17.39.

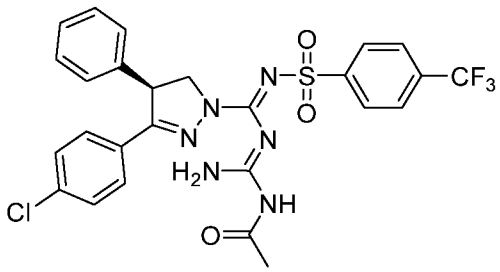
10. The compound of claim 9, wherein the XRPD pattern further has characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 9.39 and 17.80.

11. The compound of claim 9 or 10, wherein the XRPD pattern further has a characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 12.96.

12. The compound of any one of claims 9 to 11, wherein the XRPD pattern further has a characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 19.85.

13. The compound of any one of claims 9 to 12, wherein the XRPD pattern further has a characteristic peak expressed in degrees 2Θ (±0.2° 2Θ) at 16.96.

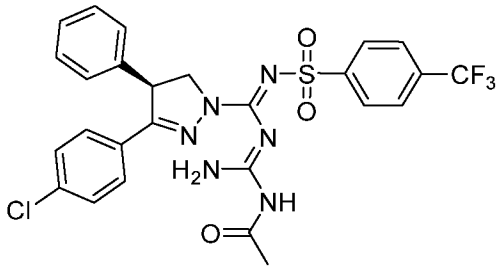
14. A compound of Formula I:



(I)

which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having an onset of about 152.2°C.

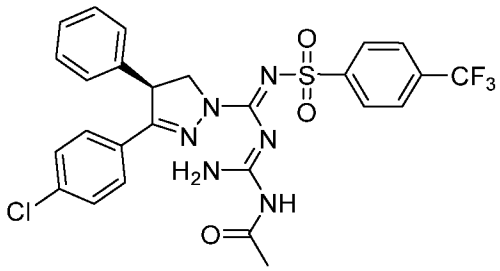
15. A compound of Formula I:



(I)

which is crystalline and has a Differential Scanning Calorimetry (DSC) thermogram that exhibits an endotherm having a peak temperature of about 162.3°C.

16. A compound of Formula I:



(I)

which has an X-ray powder diffraction pattern substantially the same as shown in Figure 2A.

17. The compound of any one of claims 1 to 16, that comprises one crystalline form at a purity of 95% or higher.

18. The compound of claim 17, wherein the purity is of 99% or higher.

19. The compound of claim 17, wherein the purity is of 99.8% or higher.

20. The compound of any one of claims 1 to 16, that is substantially pure.

21. A pharmaceutical composition, comprising a compound of any one of claims 1 to 20 and a pharmaceutically acceptable carrier or excipient.

22. The pharmaceutical composition of claim 21, that is formulated as an oral dosage form.

23. The pharmaceutical composition of claim 22, wherein the oral dosage form is a tablet, a capsule, a lozenge, a pastille or a granule.

24. The pharmaceutical composition of claim 22, that is formulated as an oral suspension.

25. Use of the compound of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 21 to 24, for the treatment of a disease or disorder selected from the group consisting of: obesity (type 1 or 2), non-alcoholic and alcoholic fatty liver disease (a risk factor for insulin resistance), a co-morbidity of obesity, a co-morbidity of diabetes, Prader-Willi Syndrome (PWS), Pro-opiomelanocortin (POMC) deficiency obesity, LepR deficiency obesity, POMC heterozygous deficiency obesity, POMC epigenetic disorders, Bardet-Biedl syndrome, Alström syndrome, dyslipidemia predisposing to arteriosclerotic heart disease, diabetic nephropathy, fibrosis and fibrotic diseases such as Idiopathic Pulmonary Fibrosis (IPF) and Hermansky-Pudlak Syndrome pulmonary fibrosis (HPS-PF), and gout.

26. The use of claim 25, wherein the co-morbidity of obesity is selected from metabolic syndrome, dementia, heart disease, hypertension, gallbladder disease, gastrointestinal disorders, menstrual irregularities, degenerative arthritis, venous statis ulcer, pulmonary hypoventilation syndrome, sleep apnea, snoring, coronary artery disease, arterial sclerotic disease, pseudotumor cerebri, osteoarthritis, high cholesterol, and increased incidence of malignancies of the liver, ovaries, cervix, uterus, breasts, prostate, or gallbladder.

27. The use of claim 25, wherein the co-morbidity of diabetes (e.g. type 1) is selected from the group consisting of: diabetic nephropathy, chronic kidney disease, diabetic retinopathy, and peripheral and autonomic neuropathy.

28. The use of claim 25, wherein said disease or disorder is selected from diabetes (type 1 or 2), obesity, and non-alcoholic fatty liver disease (e.g. non-alcoholic steatohepatitis).

29. Use of the compound of any one of claims 1 to 20 or the pharmaceutical composition of any one of claims 21 to 24, for the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of: obesity (type 1 or 2), non-alcoholic and alcoholic fatty liver disease (a risk factor for insulin resistance), a co-morbidity of obesity, a co-morbidity of diabetes, Prader-Willi Syndrome (PWS), Pro-opiomelanocortin (POMC) deficiency obesity, LepR deficiency obesity, POMC heterozygous deficiency obesity, POMC epigenetic disorders, Bardet-Biedl syndrome, Alström syndrome, dyslipidemia predisposing to arteriosclerotic heart disease, diabetic

nephropathy, fibrosis and fibrotic diseases such as Idiopathic Pulmonary Fibrosis (IPF) and Hermansky-Pudlak Syndrome pulmonary fibrosis (HPS-PF), and gout.

30. The use of claim 29, wherein the co-morbidity of obesity is selected from metabolic syndrome, dementia, heart disease, hypertension, gallbladder disease, gastrointestinal disorders, menstrual irregularities, degenerative arthritis, venous statis ulcer, pulmonary hypoventilation syndrome, sleep apnea, snoring, coronary artery disease, arterial sclerotic disease, pseudotumor cerebri, osteoarthritis, high cholesterol, and increased incidence of malignancies of the liver, ovaries, cervix, uterus, breasts, prostate, or gallbladder.

31. The use of claim 29, wherein the co-morbidity of diabetes (e.g. type 1) is selected from the group consisting of: diabetic nephropathy, chronic kidney disease, diabetic retinopathy, and peripheral and autonomic neuropathy.

32. The use of claim 29, wherein said disease or disorder is selected from diabetes (type 1 or 2), obesity, and non-alcoholic fatty liver disease (e.g. non-alcoholic steatohepatitis).

33. A method for the treatment of a disease or disorder selected from the group consisting of obesity, diabetes (type 1 or 2), non-alcoholic and alcoholic fatty liver disease (a risk factor for insulin resistance), a co-morbidity of obesity, a co-morbidity of diabetes, Prader-Willi Syndrome (PWS), Pro-opiomelanocortin (POMC) deficiency obesity, LepR deficiency obesity, POMC heterozygous deficiency obesity, POMC epigenetic disorders, Bardet-Biedl syndrome, Alström syndrome, dyslipidemia predisposing to arteriosclerotic heart disease, diabetic nephropathy, fibrosis and fibrotic diseases such as Idiopathic Pulmonary Fibrosis (IPF) and Hermansky-Pudlak Syndrome pulmonary fibrosis (HPS-PF), and gout, comprising administering the compound as defined in any one of claims 1 to 20 or the pharmaceutical composition as defined in any one of claims 21 to 24, to a subject in need thereof.

34. The method of claim 33, wherein the co-morbidity of obesity is selected from metabolic syndrome, dementia, heart disease, hypertension, gallbladder disease, gastrointestinal disorders, menstrual irregularities, degenerative arthritis, venous statis ulcer, pulmonary hypoventilation syndrome, sleep apnea, snoring, coronary artery disease, arterial sclerotic disease, pseudotumor cerebri, osteoarthritis, high cholesterol,

and increased incidence of malignancies of the liver, ovaries, cervix, uterus, breasts, prostate, or gallbladder.

35. The method of claim 33, the co-morbidity of diabetes (e.g. type 1) is selected from diabetic nephropathy, chronic kidney disease, diabetic retinopathy, and peripheral and autonomic neuropathy.

36. The method of claim 33, wherein the disease or disorder is selected from diabetes (type 1 or 2), obesity, and non-alcoholic fatty liver disease (e.g. non-alcoholic steatohepatitis).

37. A process for preparing the compound of any one of claims 1 to 8, comprising:

suspending a first crystalline form of Formula I in water, the first crystalline form exhibiting an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.89 and 17.39;

subjecting the suspension to temperature cycling, between a first temperature and a second temperature lower than the first temperature; and

retrieving the compound of Formula I as a second crystalline form exhibiting an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86.

38. The process of claim 37, wherein the first temperature is between 45°C and 65°C.

39. The process of claim 38, wherein the first temperature is between 50°C and 60°C.

40. The process of any one of claims 37 to 39, wherein the second temperature is between 5°C and 35°C.

41. The process of claim 40, wherein the second temperature is between 5°C and 25°C.

42. The process of any one of claims 37 to 41, wherein the first temperature is of about 60°C and the second temperature is of about 25°C.

43. The process of any one of claims 37 to 42, further comprising between the temperature cycling and the retrieval of the second crystalline form: stirring and maintaining the suspension at the second temperature.

44. The process of claim 43, wherein stirring and maintaining the suspension at the second temperature is performed for about 1 hour to about 12 hours.

45. The process of claim 43, wherein stirring and maintaining the suspension at the second temperature is performed for about 3 hours to about 6 hours.

46. The process of any one of claims 37 to 45, wherein retrieving the compound of Formula I as the second crystalline form comprising filtering the suspension.

47. A process for preparing the compound of any one of claims 1 to 8, comprising:

solubilizing a compound of Formula I in a solvent selected from the group consisting of methanol, ethanol, n-propanol and isopropanol, to obtain a solution;

adding water to the solution until a solid precipitates; and

retrieving the compound of Formula I as a crystalline form exhibiting an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86.

48. The process of claim 47, wherein the solvent is selected from the group consisting of methanol, ethanol and n-propanol.

49. The process of claim 47, wherein the solvent is ethanol.

50. The process of any one of claims 47 to 49, wherein solubilizing the compound of Formula I in the solvent comprises solubilizing the compound of Formula I as a crystalline form exhibiting an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.89 and 17.39.

51. The process of any one of claims 47 to 50, wherein solubilizing the compound of Formula I in the solvent is performed at a first temperature between about 30°C and a boiling point of the solvent.

52. The process of claim 51, wherein the first temperature is between about 35°C and about 60°C.

53. The process of claim 50, adding water is performed at the first temperature.

54. The process of claim 50, further comprising cooling the solvent / water mixture to a second temperature that is lower than the first temperature.

55. The process of claim 54, wherein the second temperature is between about 5°C and about 30°C.

56. The process of claim 54, wherein the second temperature is between about 20°C and about 30°C.

57. The process of any one of claims 47 to 56, wherein the solvent : water ratio (by volume) is between about 1:1 and about 3:1.

58. The process of claim 57, wherein the solvent : water ratio is between about 2:1 and about 3:1.

59. The process of any one of claims 47 to 58, wherein retrieving the compound of Formula I comprises filtering and drying the compound of Formula I.

60. A process for preparing the compound of any one of claims 1 to 8, comprising:

providing a slurry of a first crystalline form of Formula I in a solvent selected from the group consisting of water, n-butanol and an MIBK/n-heptane mixture, the first crystalline form exhibiting an X-ray powder diffraction (XRPD) pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 5.89 and 17.39;

stirring the slurry; and

retrieving the compound of Formula I as a crystalline form exhibiting an XRPD pattern having characteristic peaks expressed in degrees 2Θ (±0.2° 2Θ) at 6.46, 15.88, 19.44 and 5.86.

61. The process of claim 60, wherein the solvent is water.

62. The process of claim 60, wherein the solvent is a 1:4 (v/v) MIBK:n-heptane mixture.

63. The process of any one of claims 60 to 62, wherein stirring the slurry is performed at a temperature between about 50°C and about 70°C.

64. The process of claim 63, wherein the temperature is between about 55°C and about 65°C.

65. The process of any one of claims 37 to 64, further comprising adding a seed of the compound as defined in any one of claims 1 to 8, to the mixture.

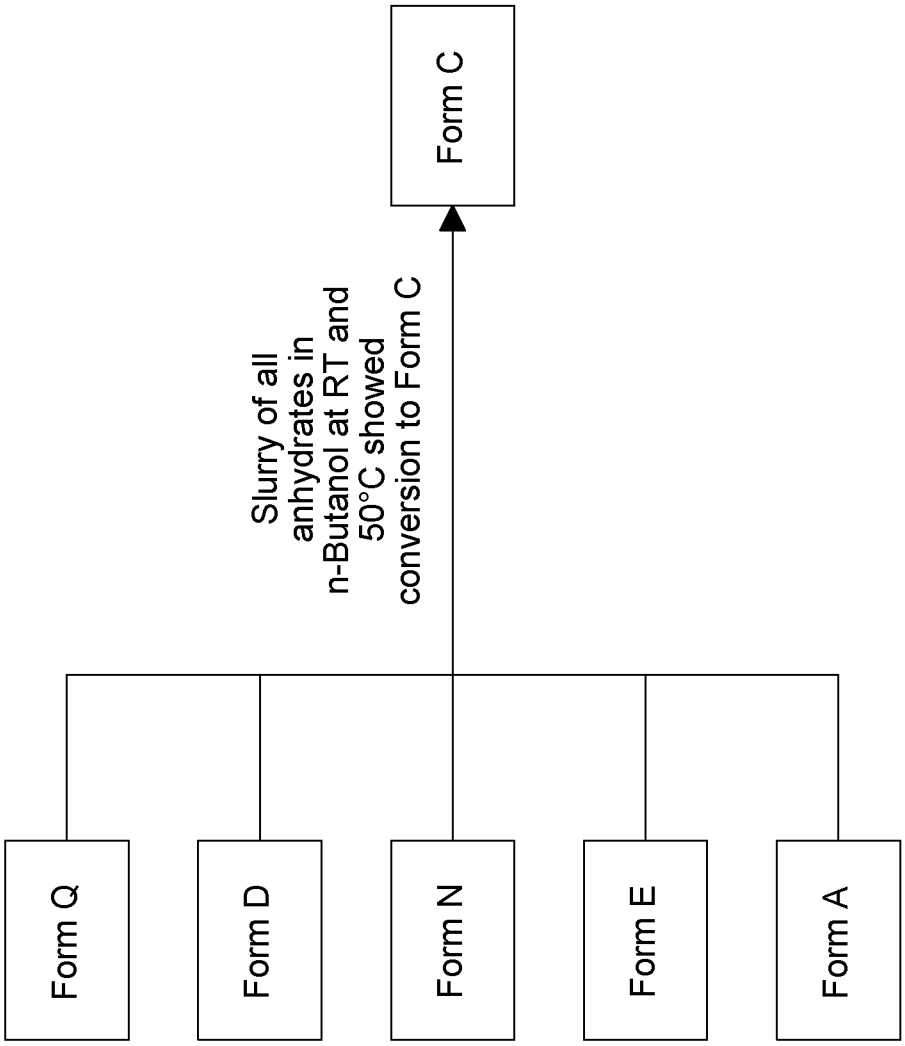

Form C
Slurry of all anhydrates in n-Butanol at RT and 50°C showed conversion to Form C
Form Q
Form D
Form N
Form E
Form A

FIG. 1A

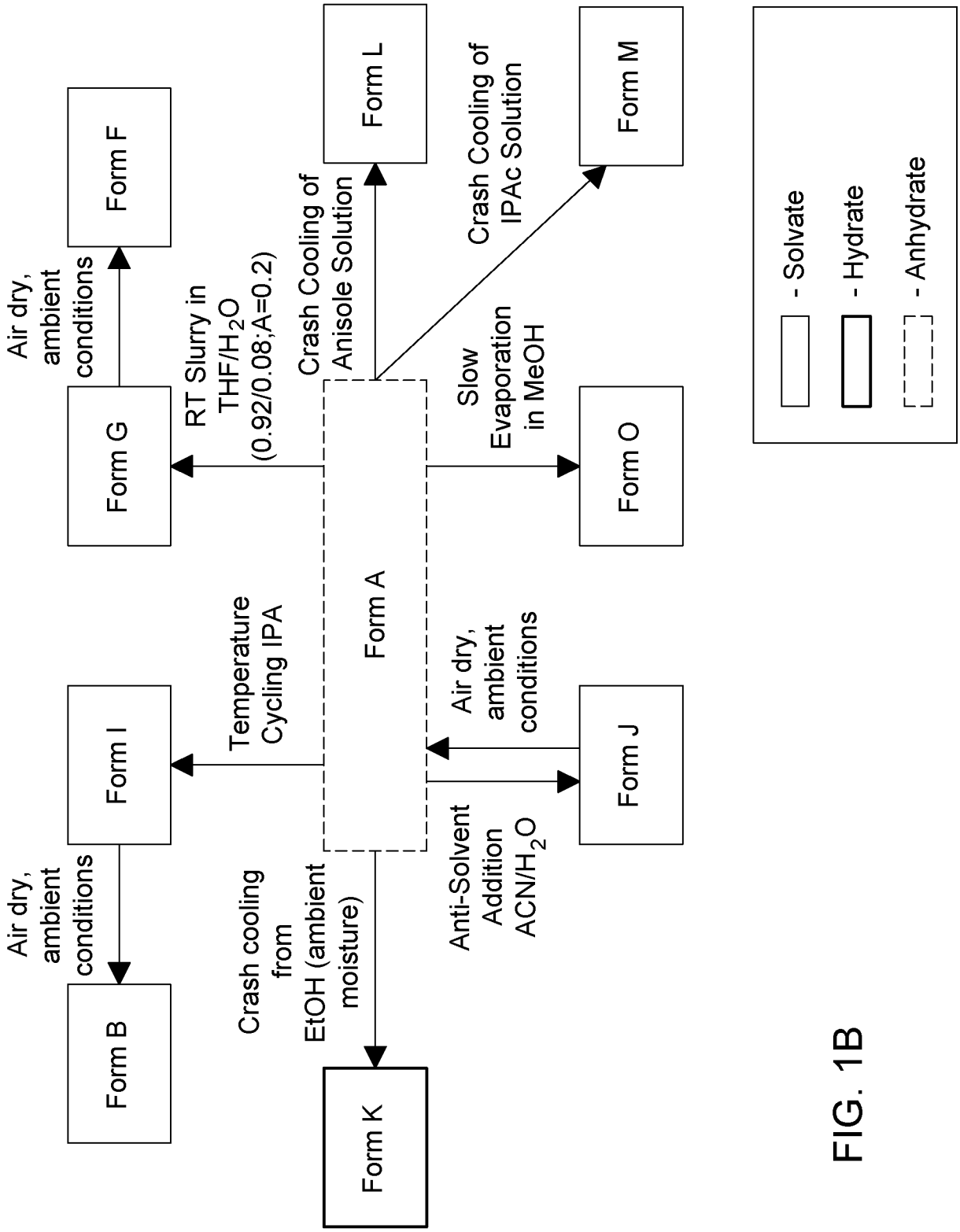

Form F
Form L
Form M
Air dry, ambient conditions
RT Slurry in THF/H2O (0.92/0.08;A=0.2)
Crash Cooling of Anisole Solution
Crash Cooling of IPAc Solution
Form G
Slow Evaporation in MeOH
Form O
Form A
Temperature Cycling IPA
Air dry, ambient conditions
Form I
Form J
Air dry, ambient conditions
Crash cooling from EtOH (ambient moisture)
Anti-Solvent Addition ACN/H2O
Form B
Form K
- Solvate
- Hydrate
- Anhydrate

FIG. 1B

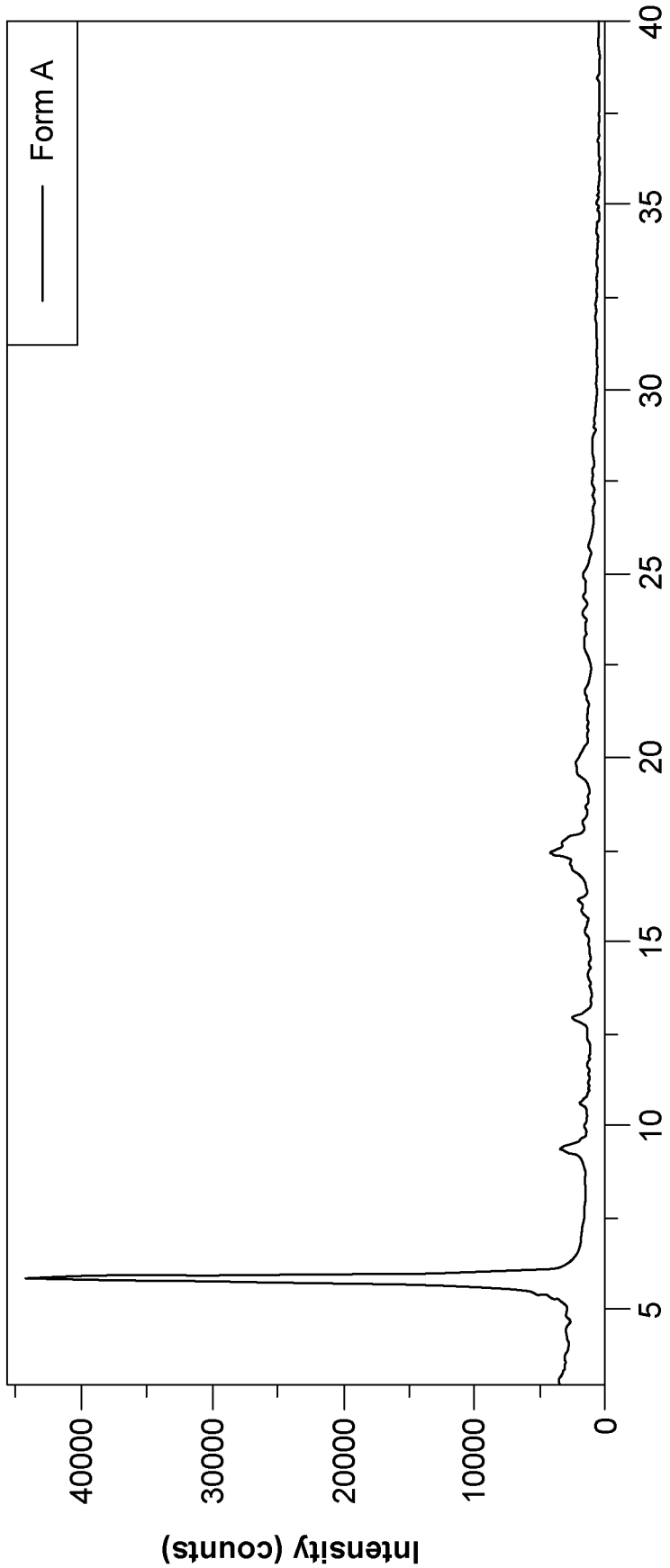

Form A
Intensity (counts)
40000
30000
20000
10000
0
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 2A

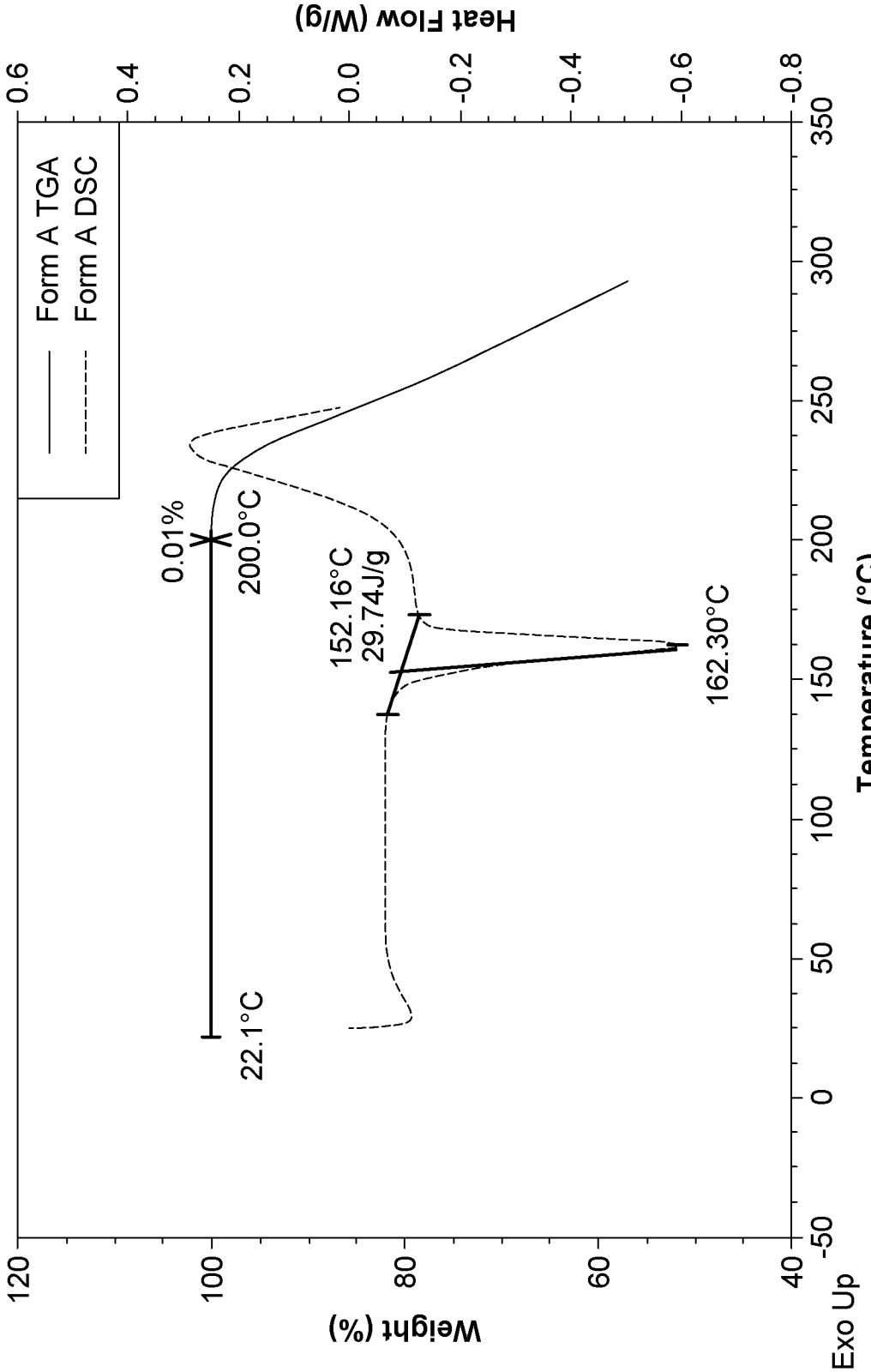

Form A TGA
Form A DSC
0.01%
200.0°C
152.16°C
29.74J/g
162.30°C
22.1°C
Weight (%)
Heat Flow (W/g)
Temperature (°C)
Exo Up

FIG. 2B

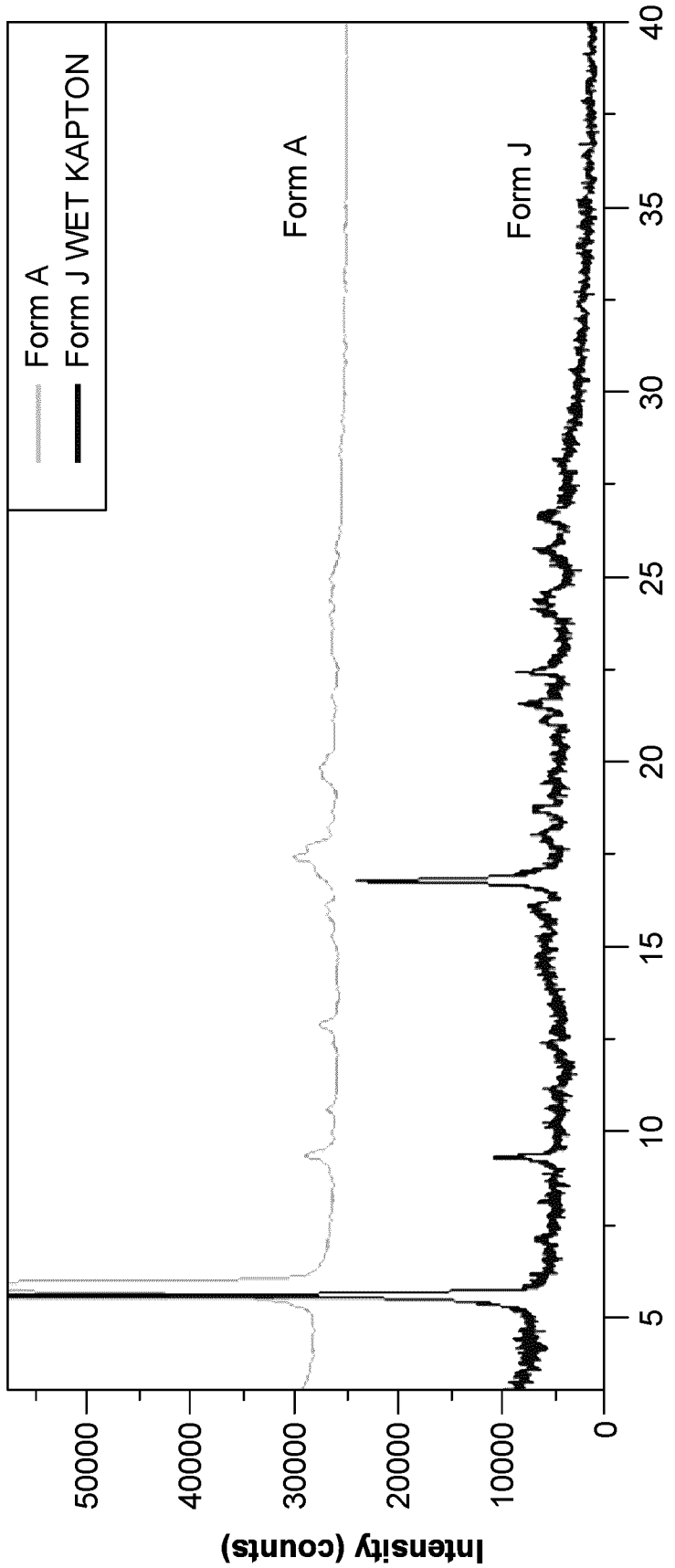

Form A
Form J WET KAPTON
Form A
Form J
Intensity (counts)
2Theta (deg)
0
10000
20000
30000
40000
50000
5
10
15
20
25
30
35
40

FIG. 2C

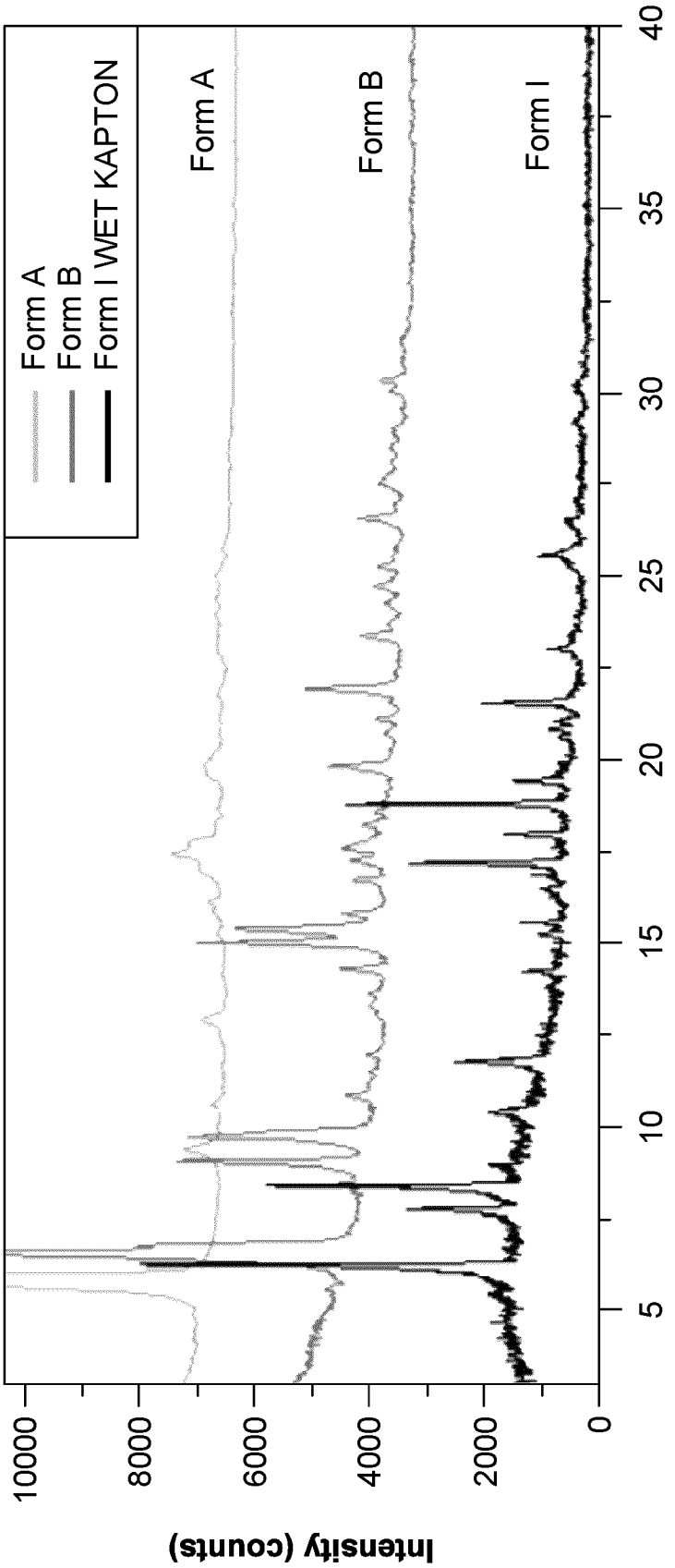

Form A
Form B
Form I WET KAPTON
Form A
Form B
Form I
Intensity (counts)
0
2000
4000
6000
8000
10000
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 3A

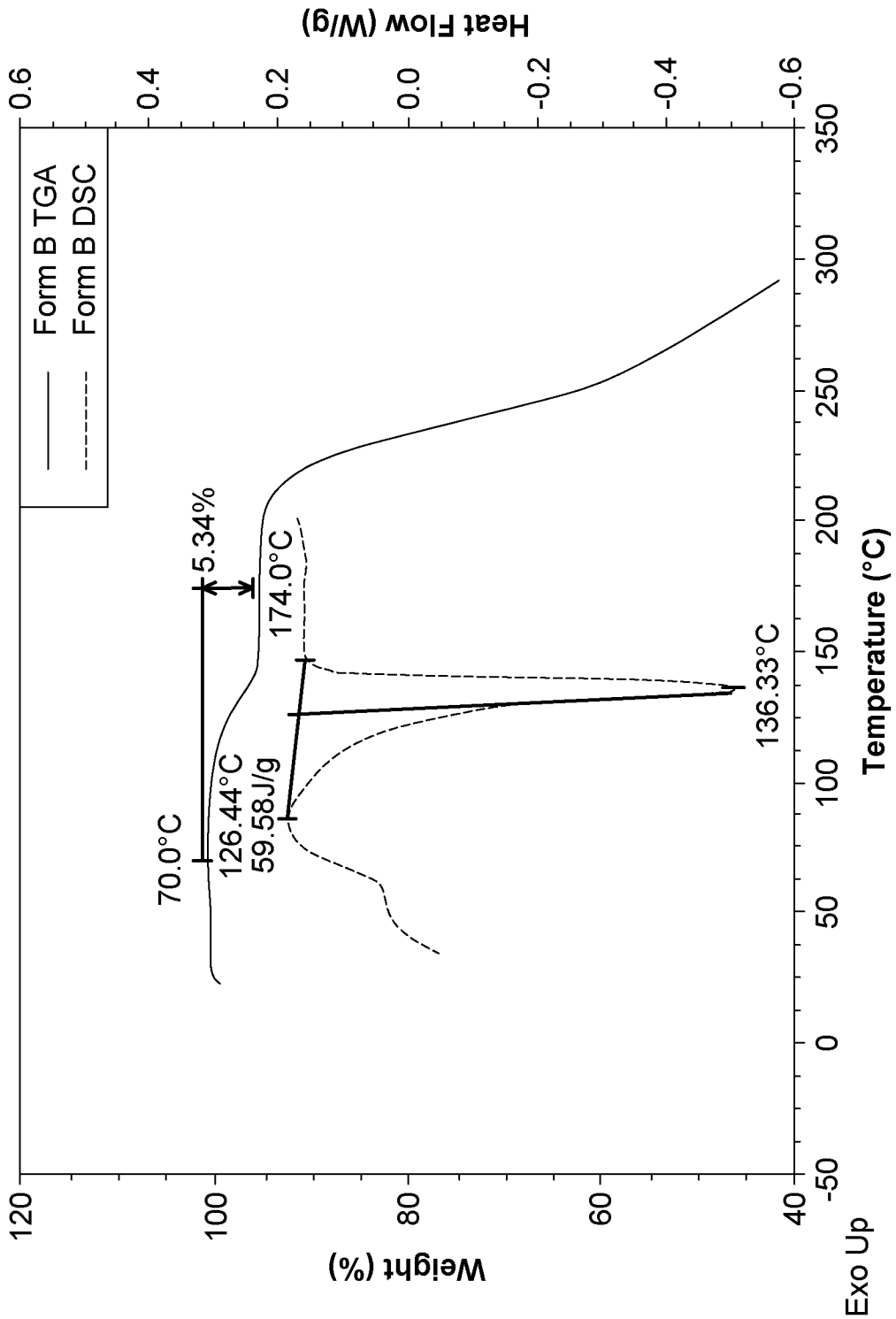

Form B TGA
Form B DSC
5.34%
174.0°C
136.33°C
70.0°C
126.44°C
59.58J/g
Weight (%)
Heat Flow (W/g)
Temperature (°C)
Exo Up
120
100
80
60
40
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-50
0
50
100
150
200
250
300
350

FIG. 3B

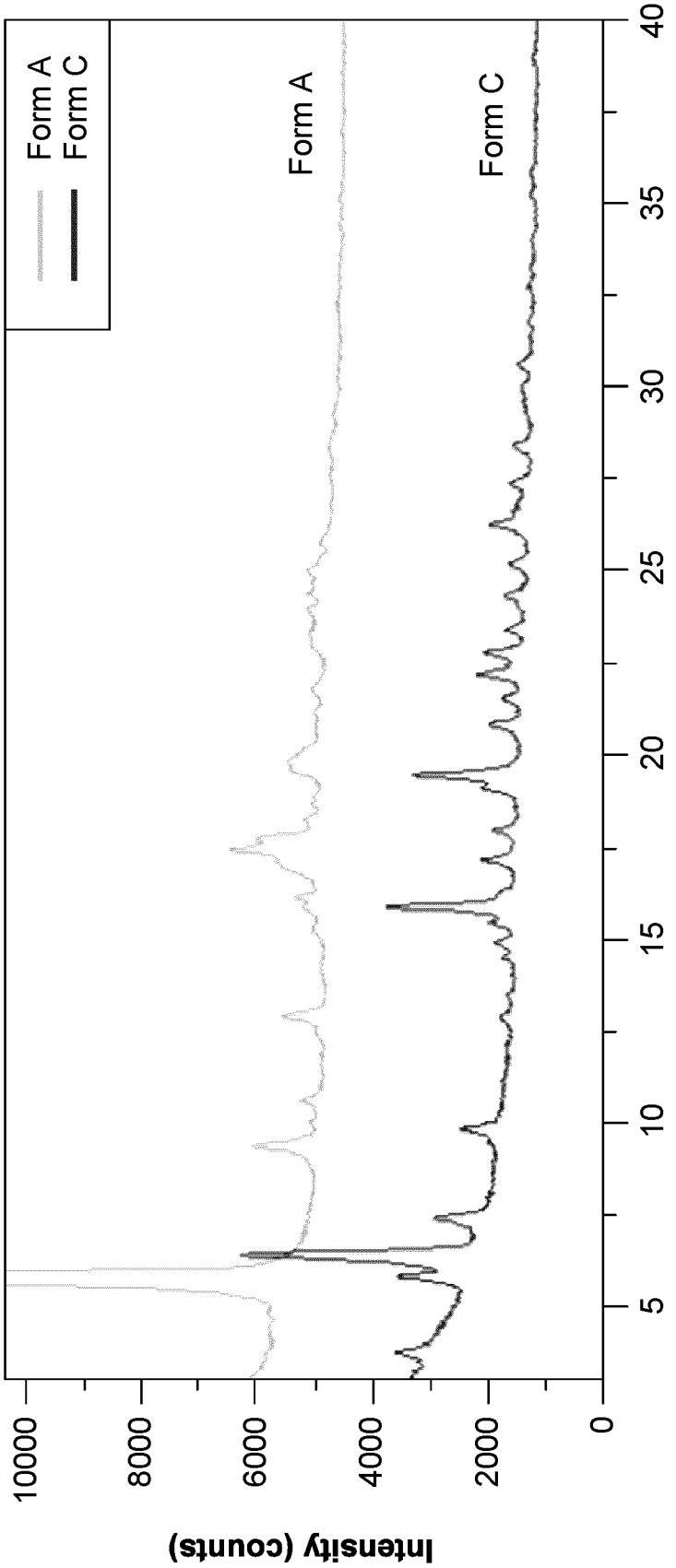

Form A
Form C
Form A
Form C
Intensity (counts)
10000
8000
6000
4000
2000
0
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 4A

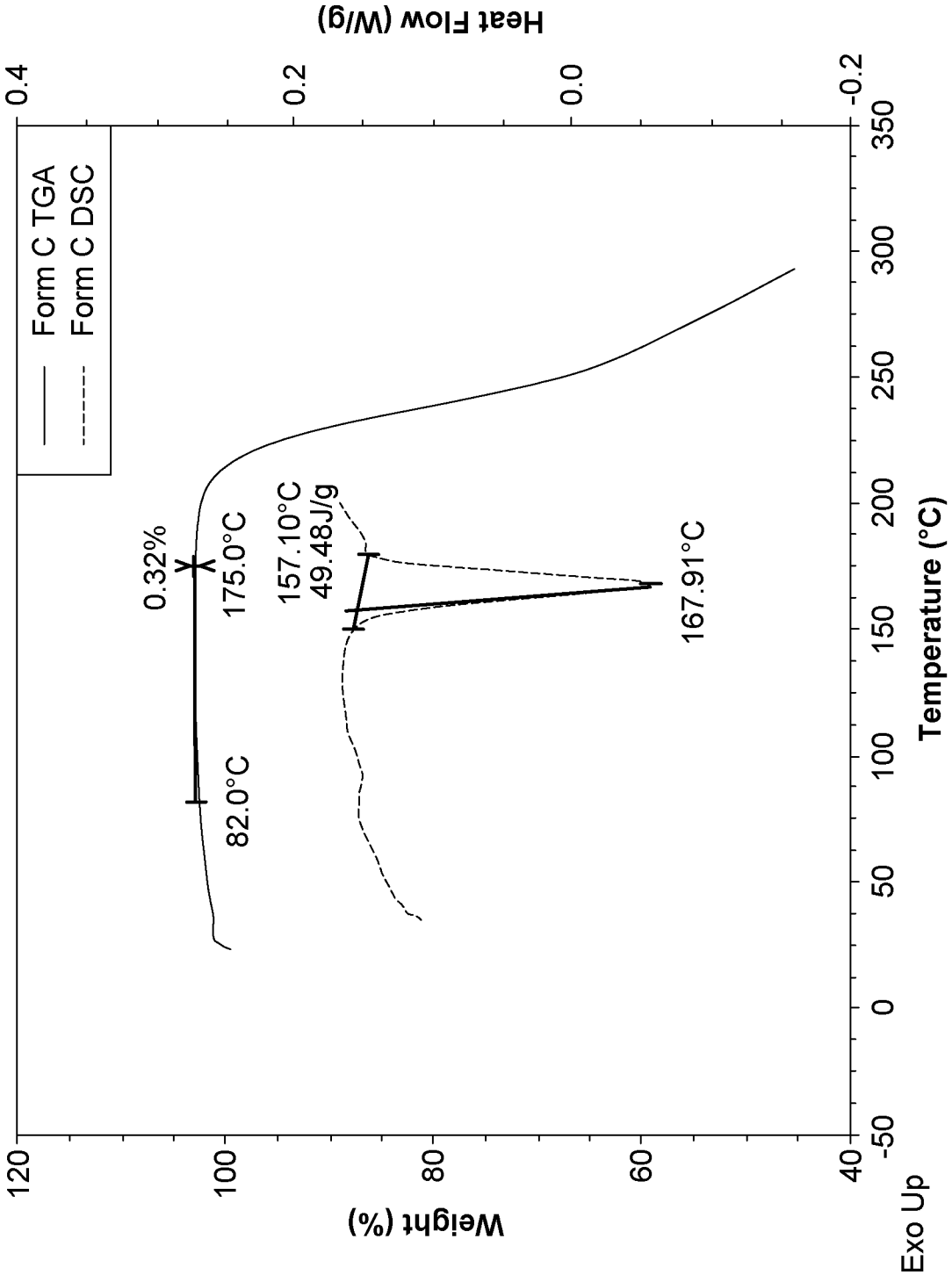

Heat Flow (W/g)
0.4
0.2
0.0
-0.2
Form C TGA
Form C DSC
0.32%
175.0°C
82.0°C
157.10°C
49.48J/g
167.91°C
120
100
80
60
40
Weight (%)
-50
0
50
100
150
200
250
300
350
Temperature (°C)
Exo Up

FIG. 4B

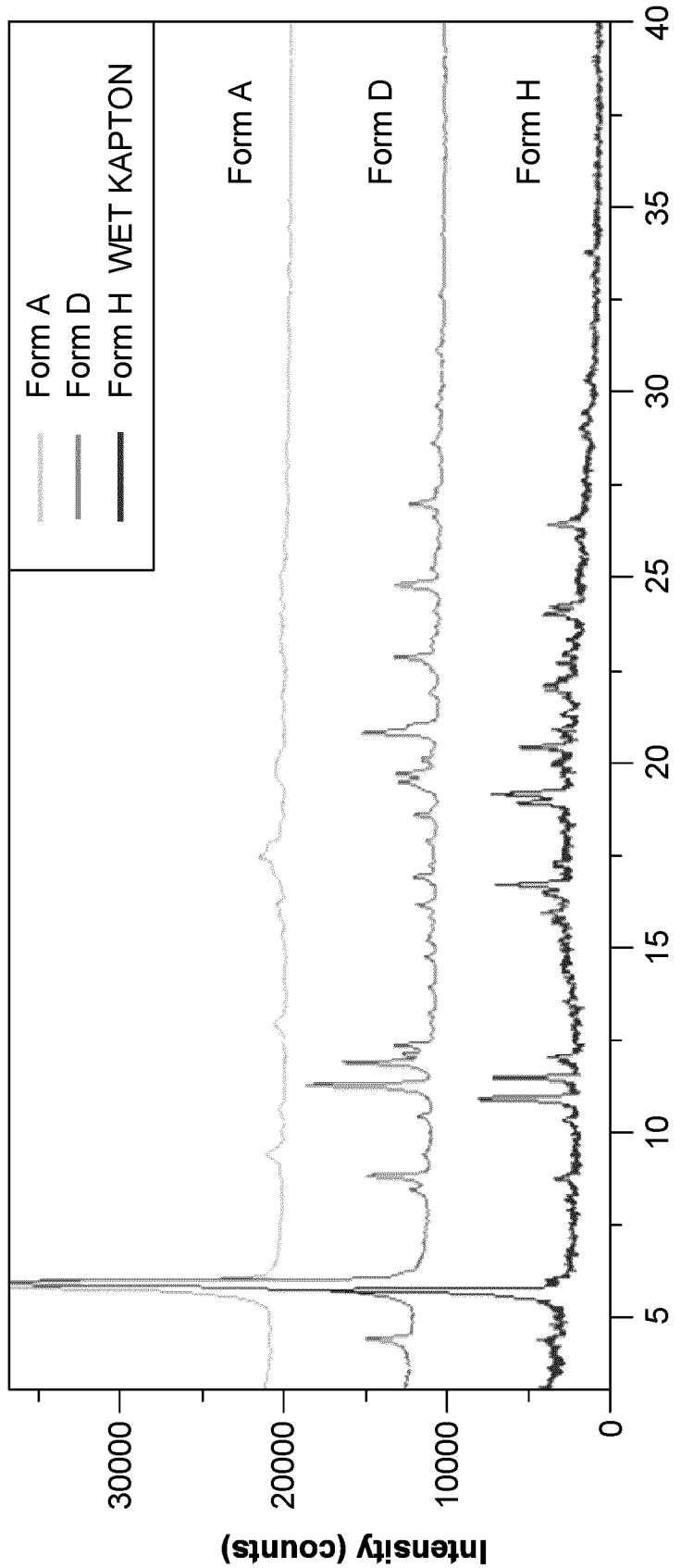

Form A
Form D
Form H WET KAPTON
Form A
Form D
Form H
Intensity (counts)
0
10000
20000
30000
2Theta (deg)
5
10
15
20
25
30
35
40

FIG. 5A

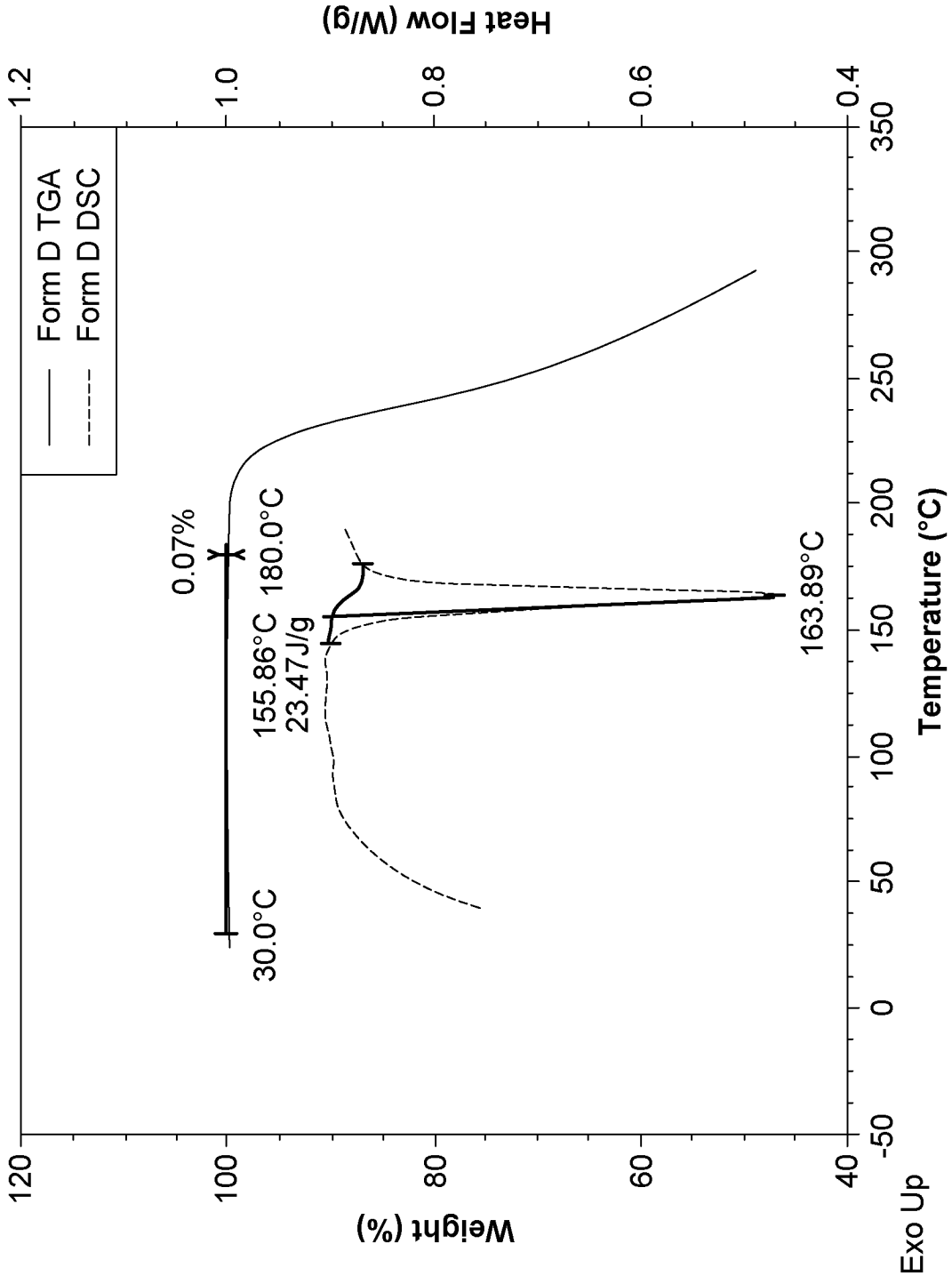

Form D TGA
Form D DSC
0.07%
180.0°C
155.86°C
23.47J/g
30.0°C
163.89°C
Weight (%)
Heat Flow (W/g)
Temperature (°C)
Exo Up
120
100
80
60
40
1.2
1.0
0.8
0.6
0.4
-50
0
50
100
150
200
250
300
350

FIG. 5B

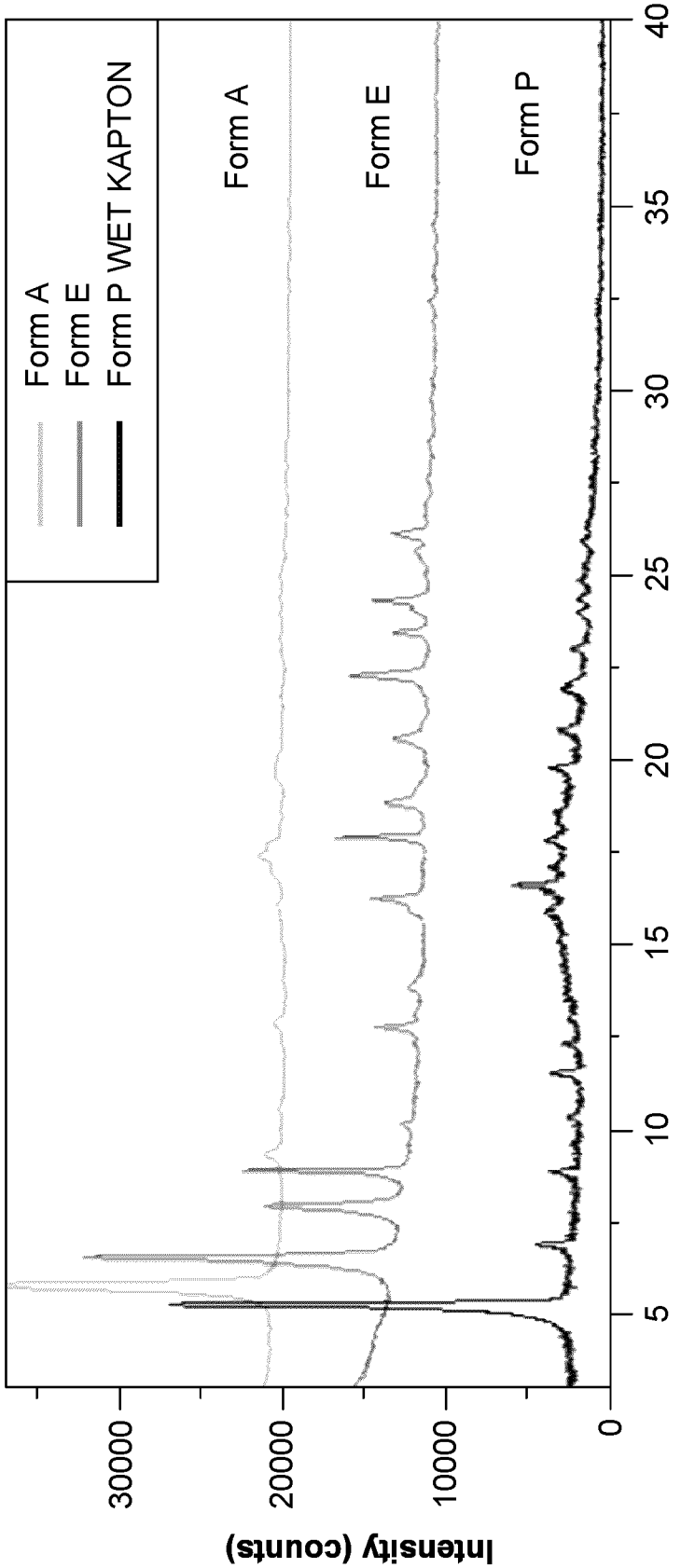

Form A
Form E
Form P WET KAPTON
Form A
Form E
Form P
Intensity (counts)
30000
20000
10000
0
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 6A

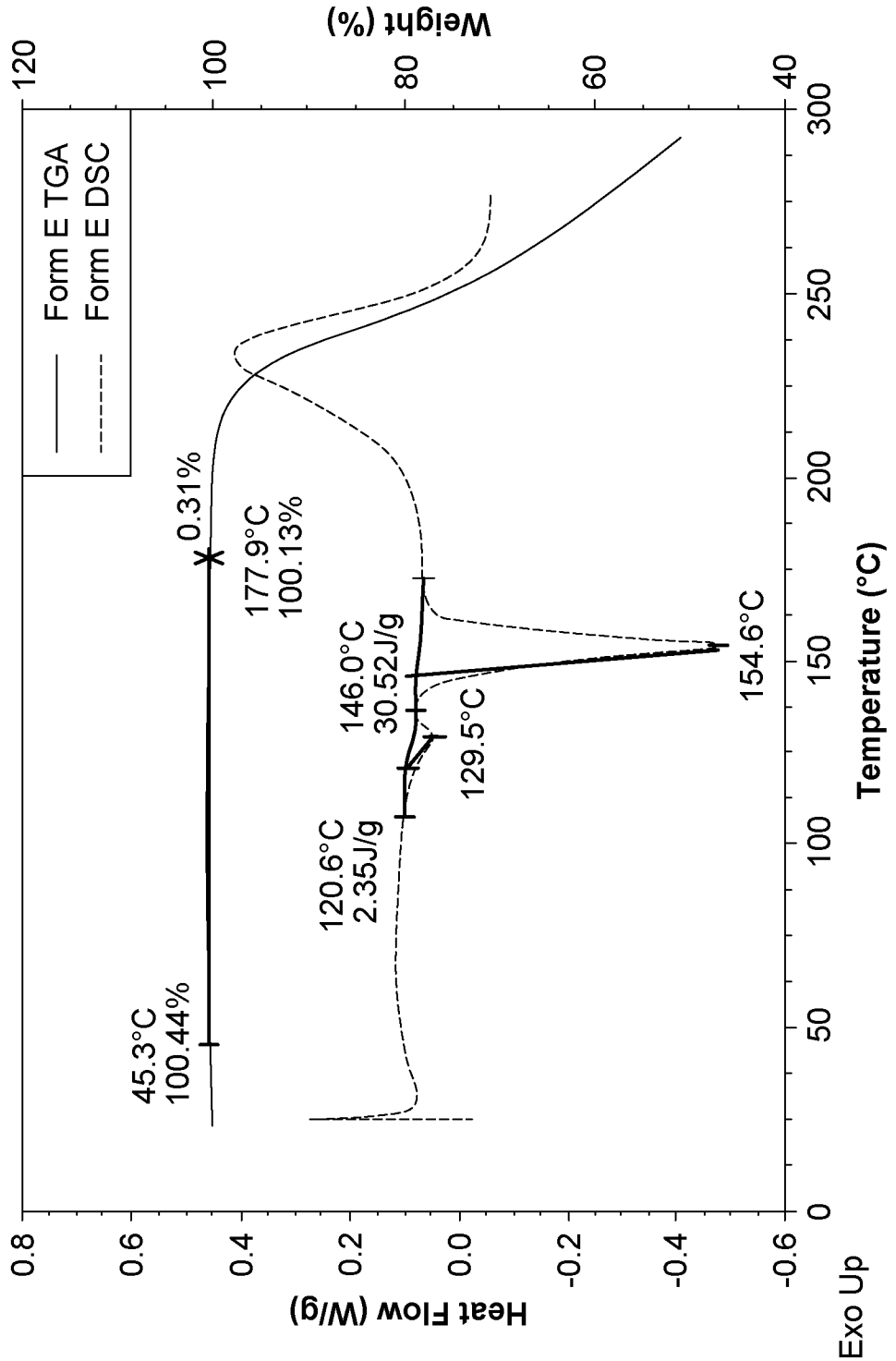

Form E TGA
Form E DSC
Weight (%)
Heat Flow (W/g)
Temperature (°C)
Exo Up
45.3°C
100.44%
0.31%
177.9°C
100.13%
120.6°C
2.35J/g
146.0°C
30.52J/g
129.5°C
154.6°C

FIG. 6B

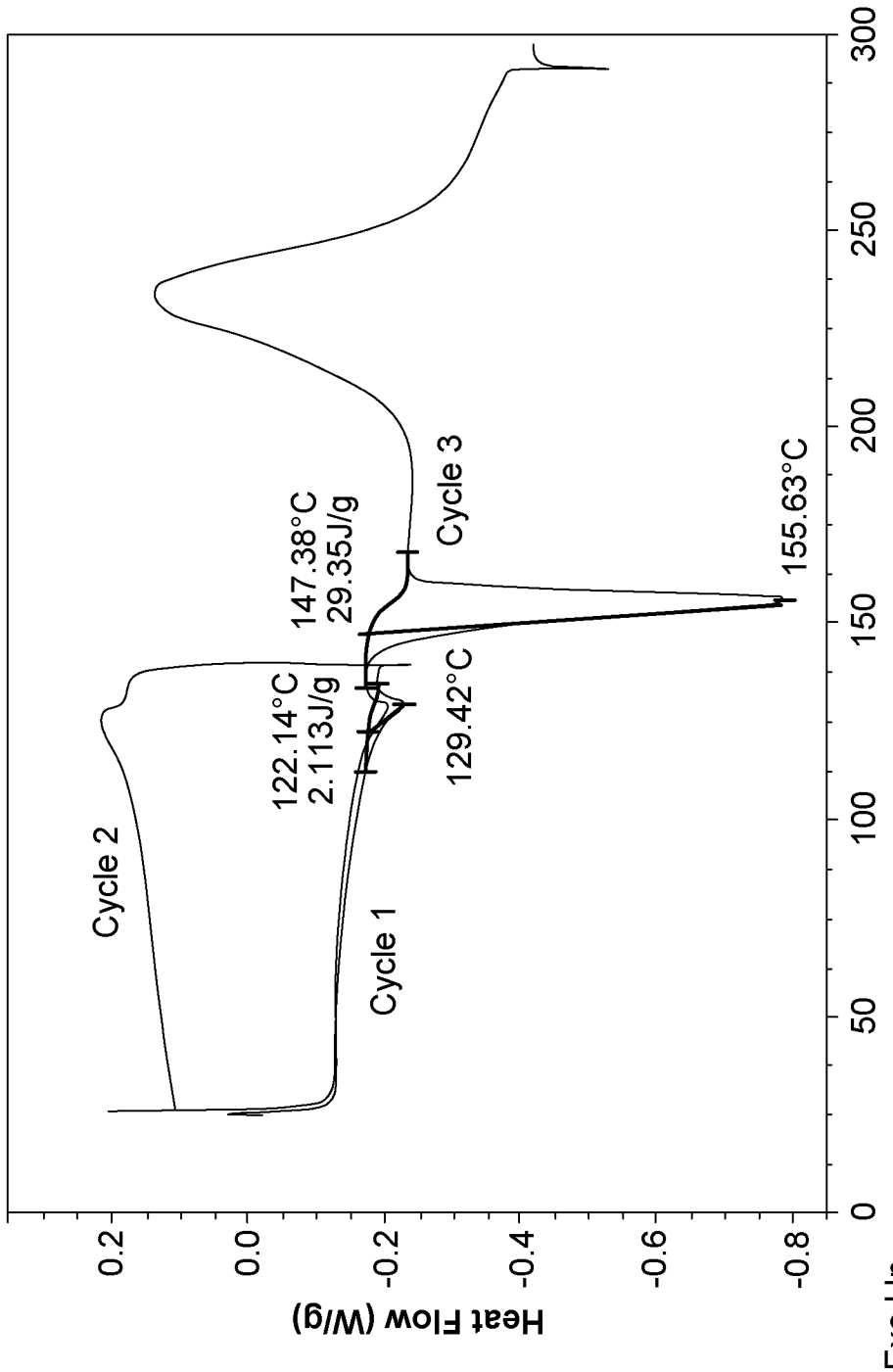

Heat Flow (W/g)
Exo Up
0.2
0.0
-0.2
-0.4
-0.6
-0.8
0
50
100
150
200
250
300
Temperature (°C)
Cycle 2
Cycle 1
Cycle 3
122.14°C
2.113J/g
129.42°C
147.38°C
29.35J/g
155.63°C

FIG. 6C

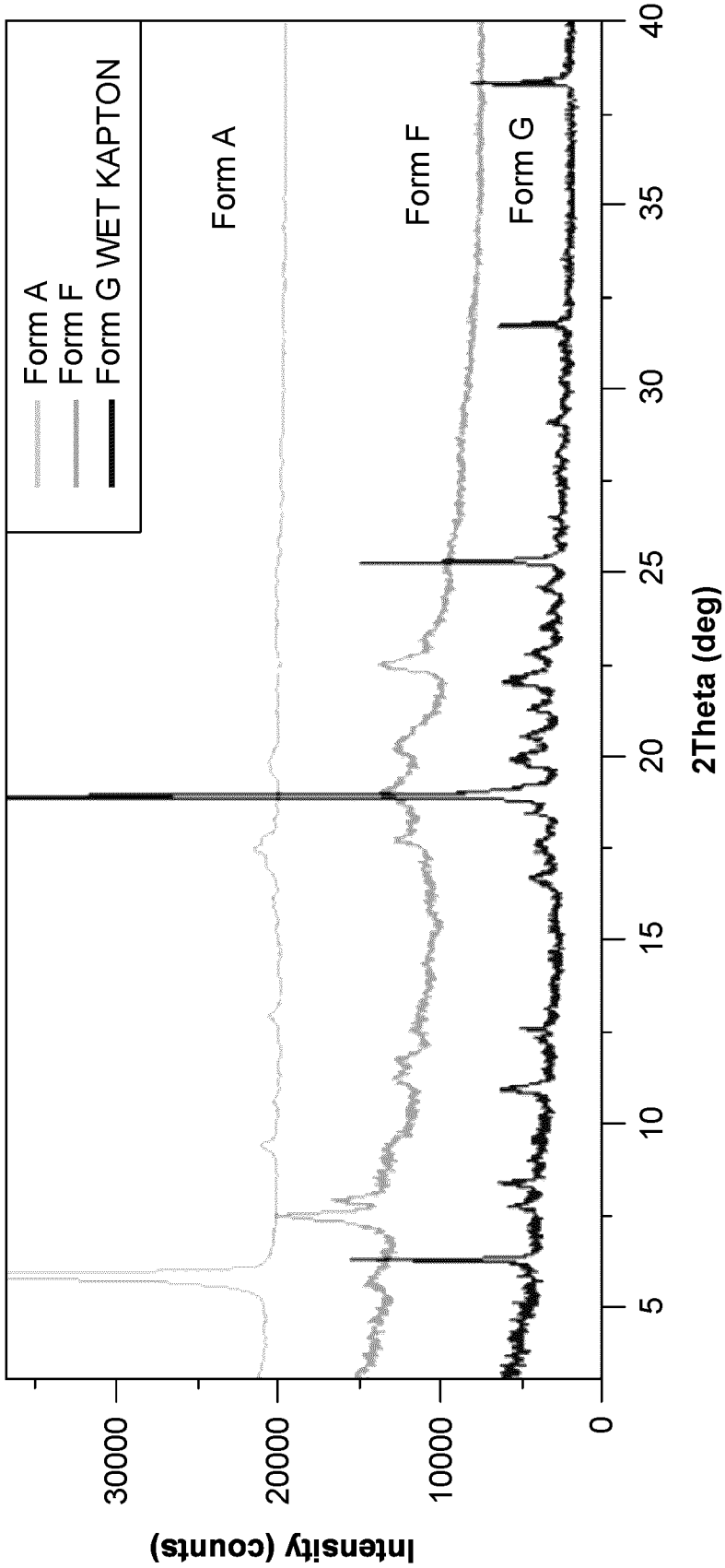

Form A
Form F
Form G WET KAPTON
Form A
Form F
Form G
Intensity (counts)
30000
20000
10000
0
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 7A

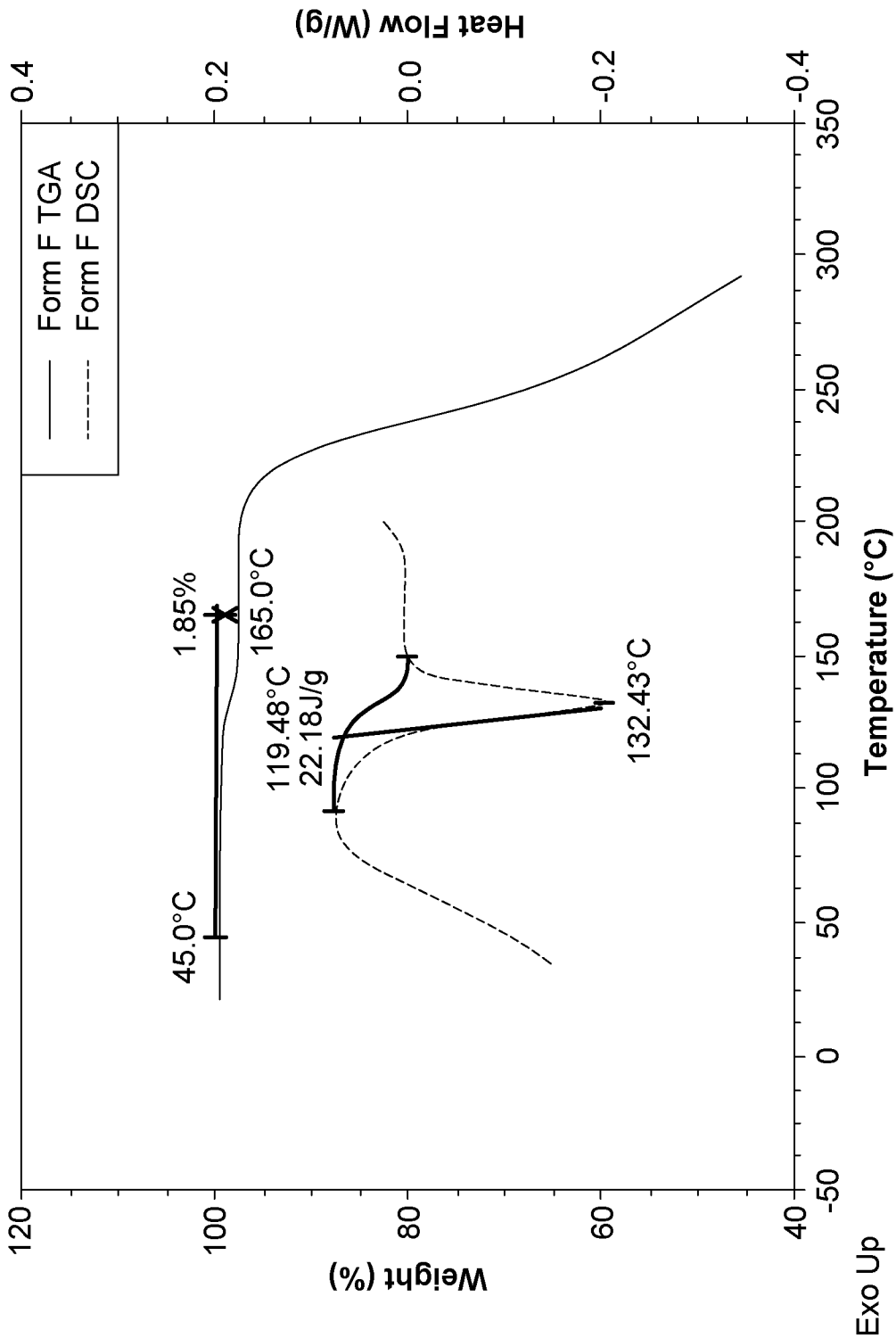

Heat Flow (W/g)
0.4
0.2
0.0
-0.2
-0.4
Form F TGA
Form F DSC
1.85%
165.0°C
119.48°C
22.18J/g
132.43°C
45.0°C
Weight (%)
120
100
80
60
40
-50
0
50
100
150
200
250
300
350
Temperature (°C)
Exo Up

FIG. 7B

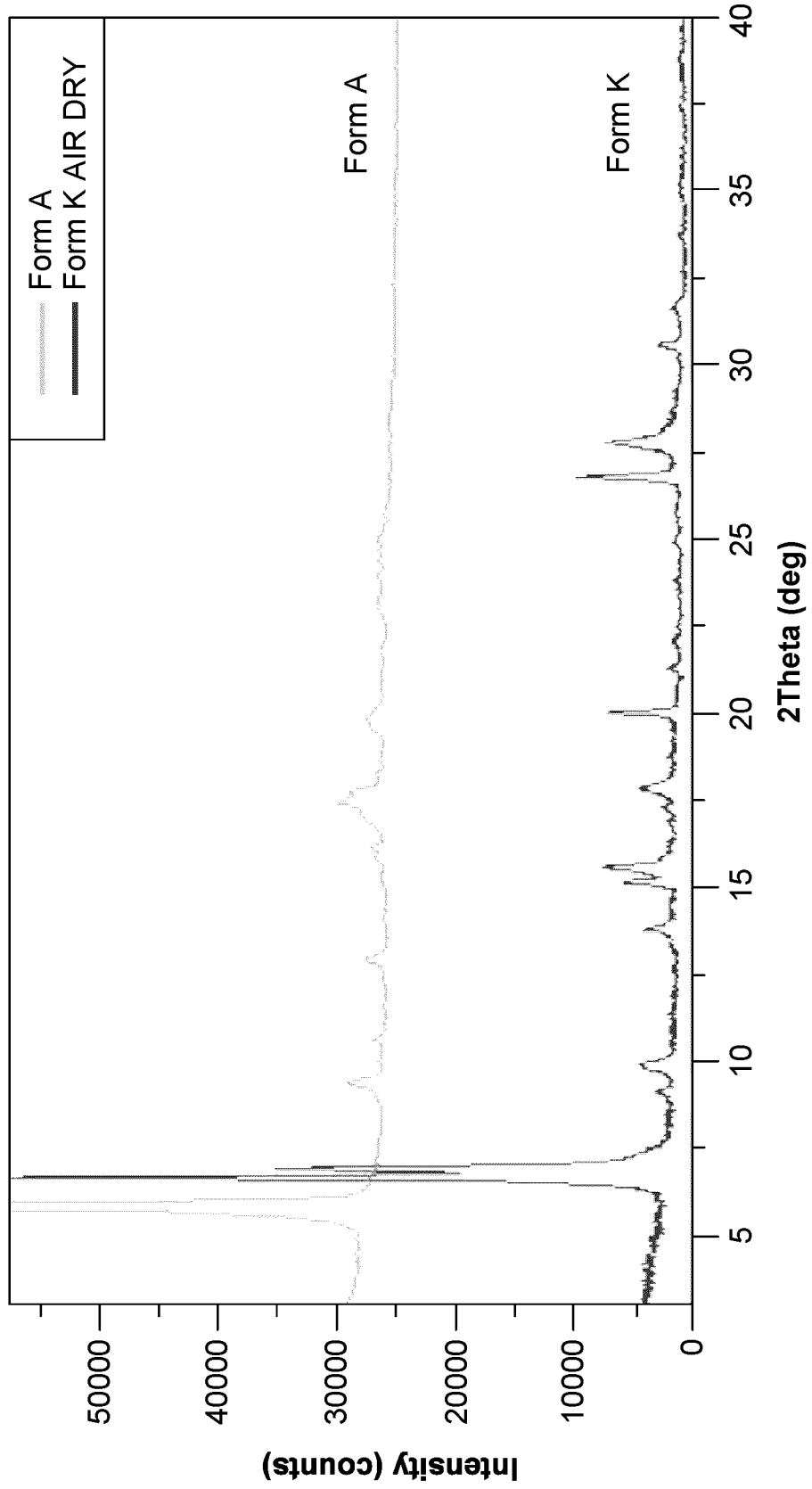

Form A
Form K AIR DRY
Form A
Form K
Intensity (counts)
50000
40000
30000
20000
10000
0
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 8A

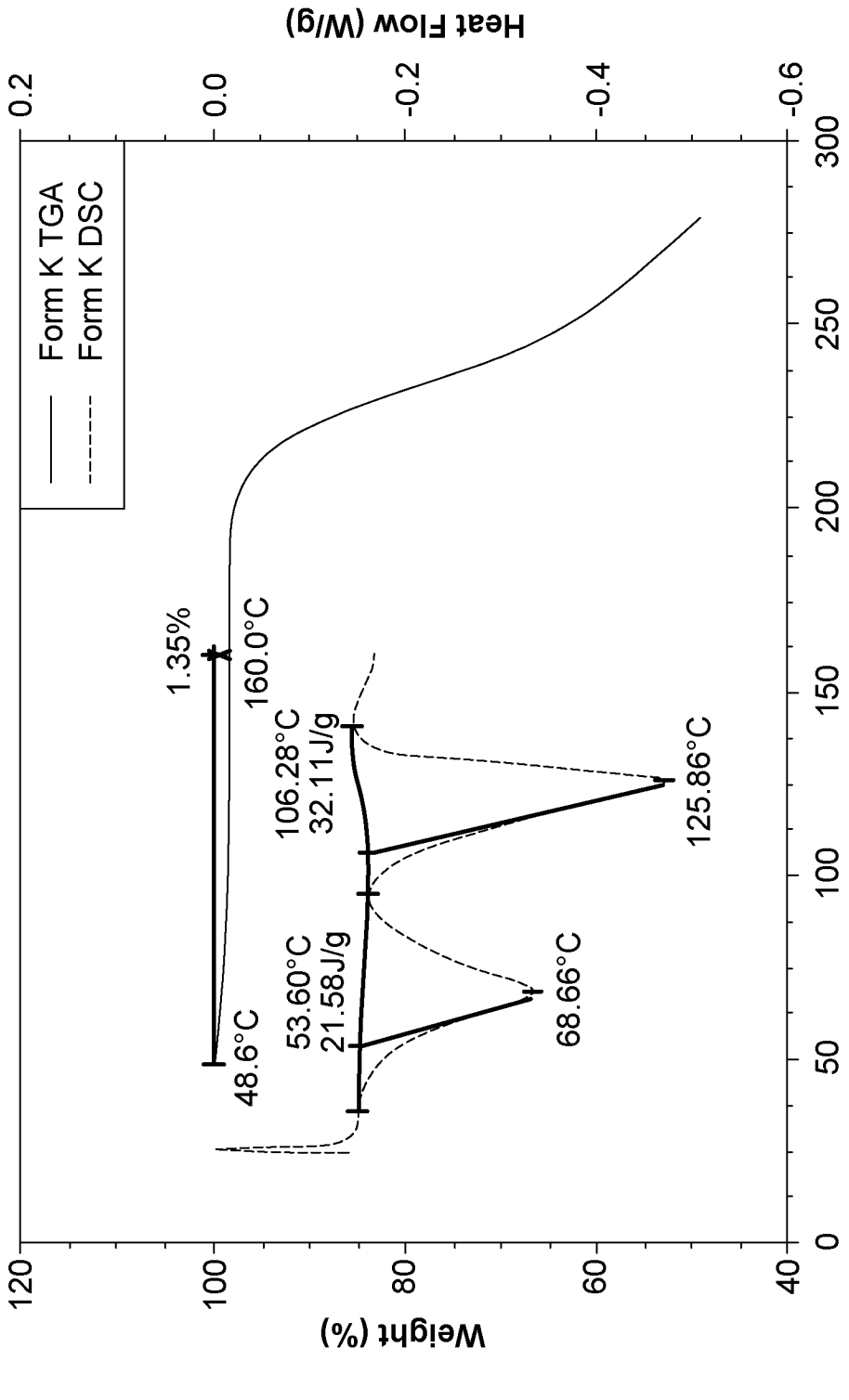

Heat Flow (W/g)
0.2
0.0
-0.2
-0.4
-0.6
Form K TGA
Form K DSC
1.35%
160.0°C
106.28°C
32.11J/g
125.86°C
53.60°C
21.58J/g
68.66°C
48.6°C
Weight (%)
120
100
80
60
40
0
50
100
150
200
250
300
Temperature (°C)
Exo Up

FIG. 8B

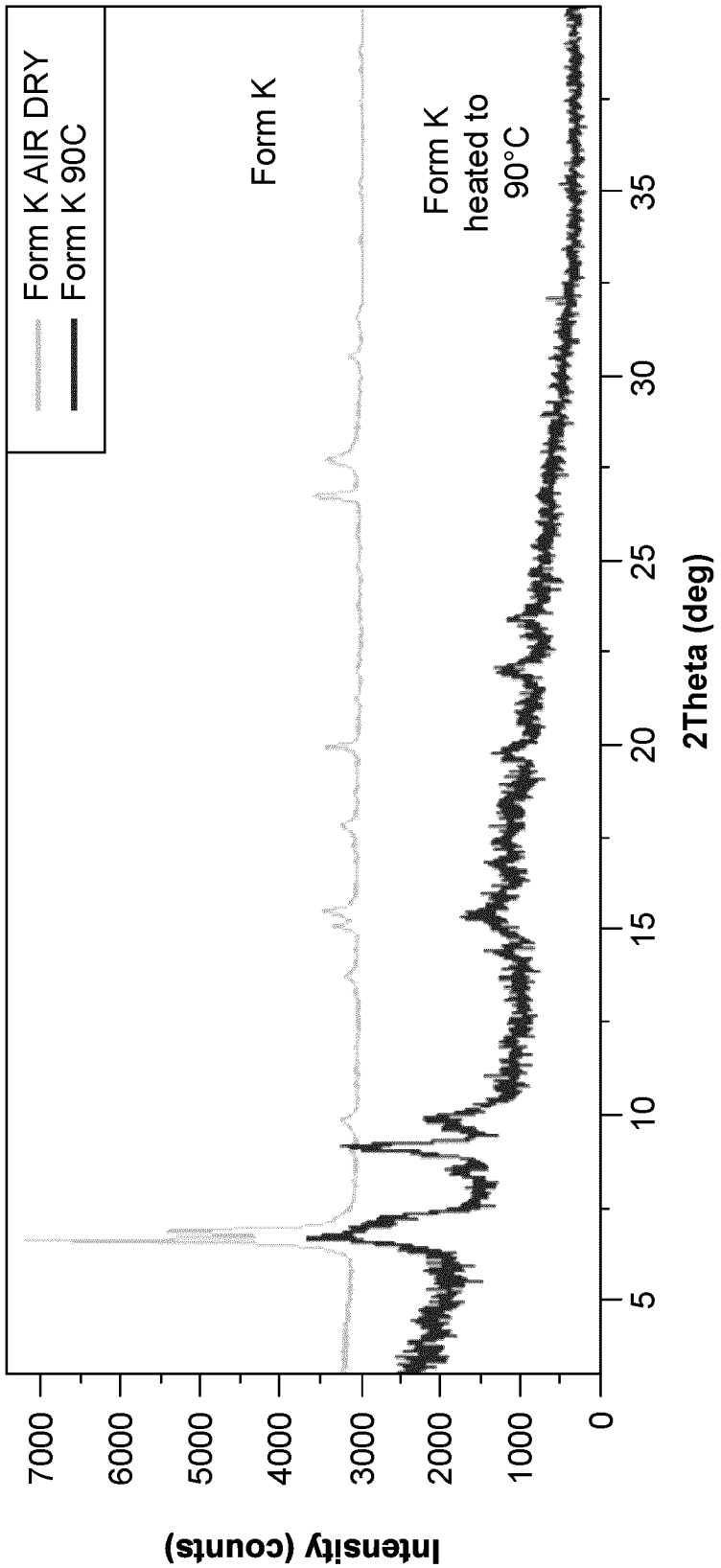

Form K AIR DRY
Form K 90C
Form K
Form K heated to 90°C
Intensity (counts)
2Theta (deg)
0
1000
2000
3000
4000
5000
6000
7000
5
10
15
20
25
30
35

FIG. 8C

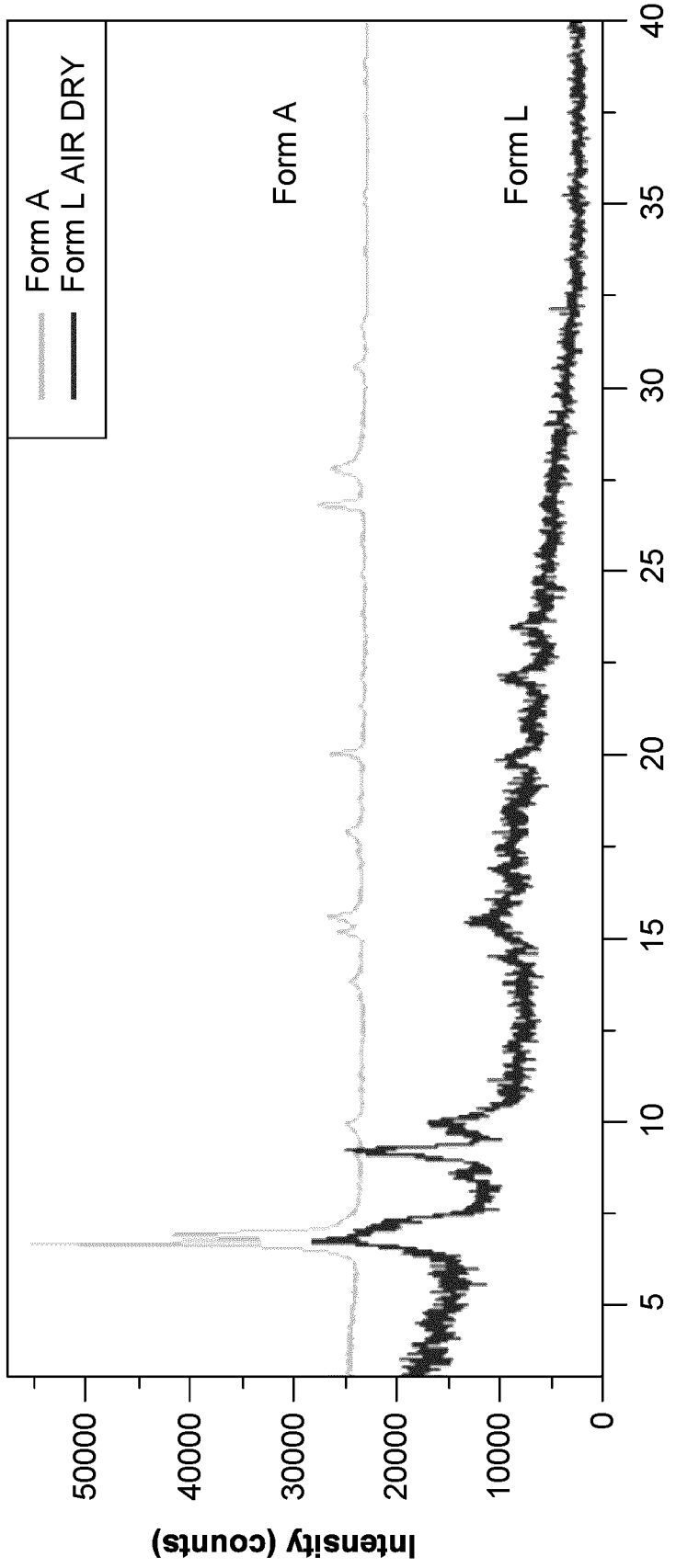

Form A
Form L AIR DRY
Form A
Form L
Intensity (counts)
50000
40000
30000
20000
10000
0
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 9A

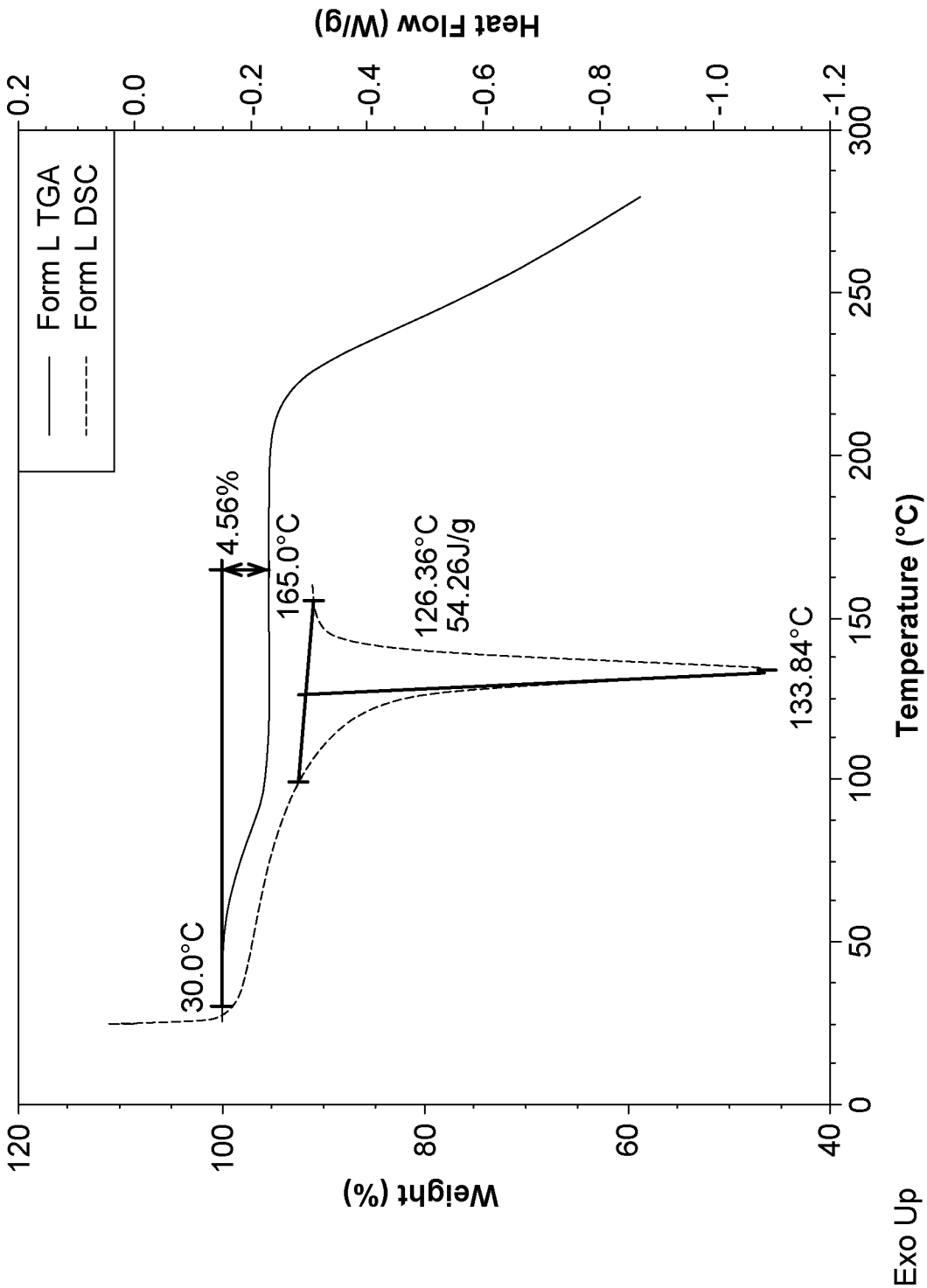

Heat Flow (W/g)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
Form L TGA
Form L DSC
4.56%
165.0°C
126.36°C
54.26J/g
133.84°C
30.0°C
120
100
80
60
40
Weight (%)
0
50
100
150
200
250
300
Temperature (°C)
Exo Up

FIG. 9B

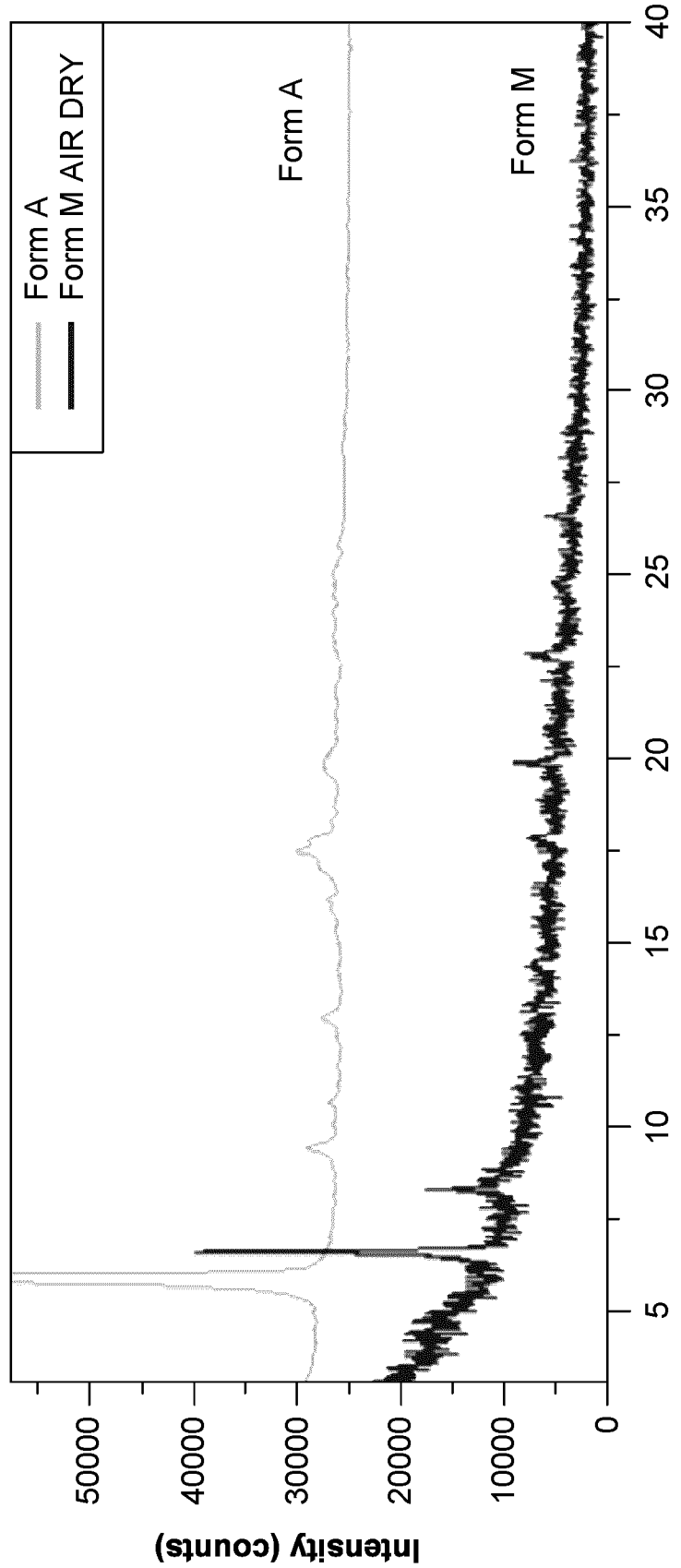

Form A
Form M AIR DRY
Form A
Form M
Intensity (counts)
0
10000
20000
30000
40000
50000
2Theta (deg)
5
10
15
20
25
30
35
40

FIG. 10A

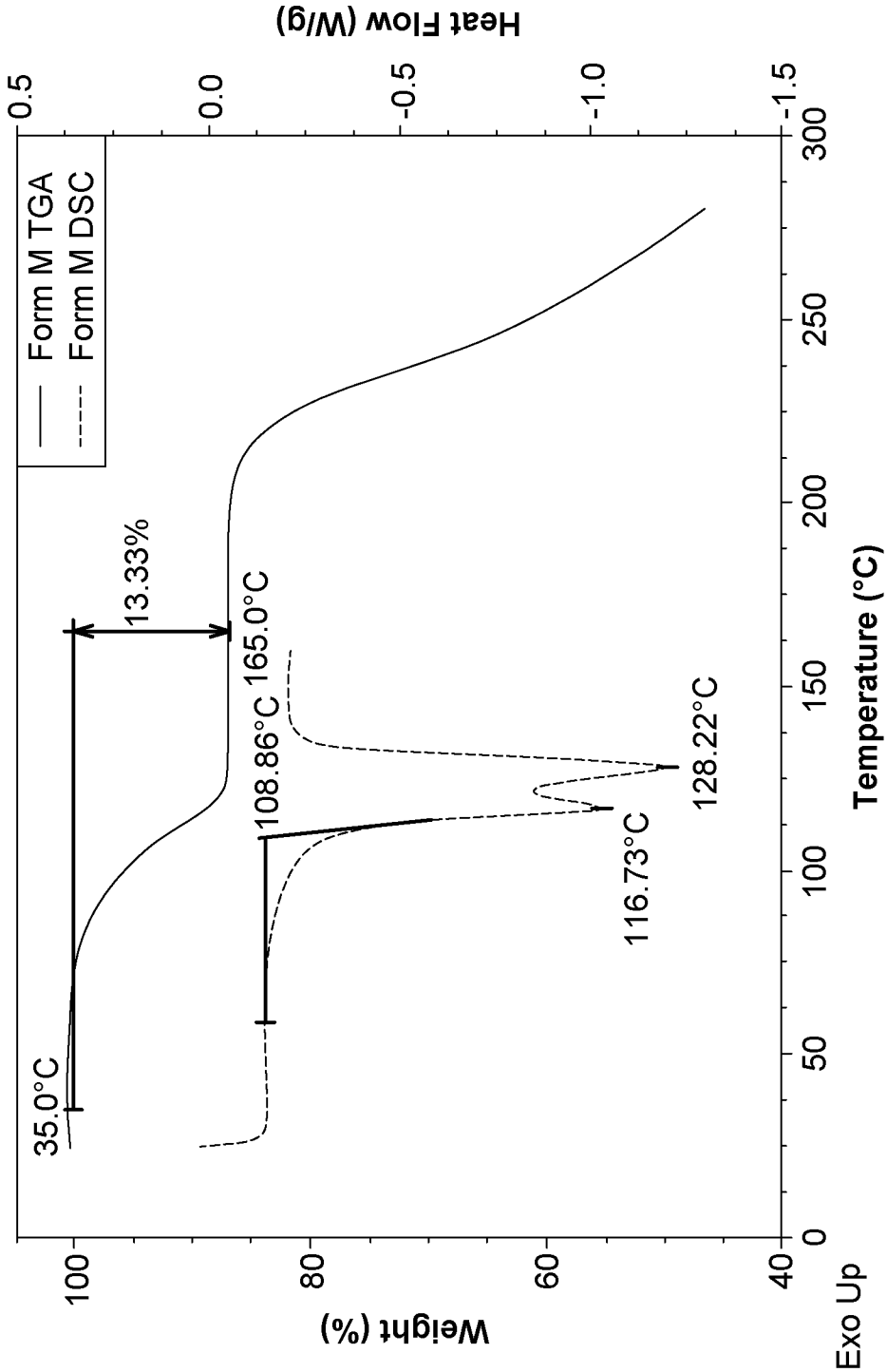

Heat Flow (W/g)
0.5
0.0
-0.5
-1.0
-1.5
Form M TGA
Form M DSC
13.33%
35.0°C
108.86°C
165.0°C
116.73°C
128.22°C
Weight (%)
100
80
60
40
0
50
100
150
200
250
300
Temperature (°C)
Exo Up

FIG. 10B

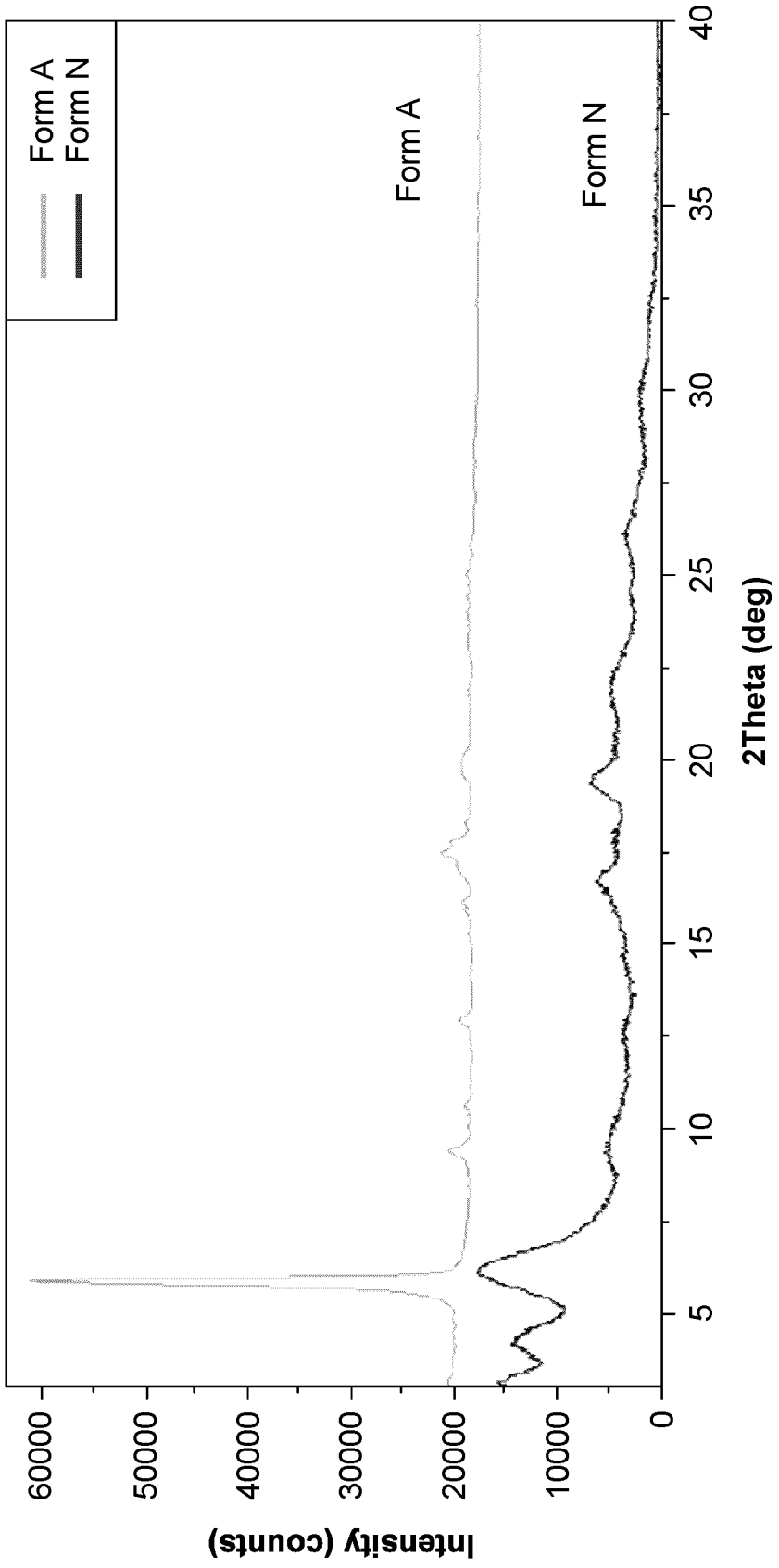

Form A
Form N
Form A
Form N
Intensity (counts)
60000
50000
40000
30000
20000
10000
0
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 11A

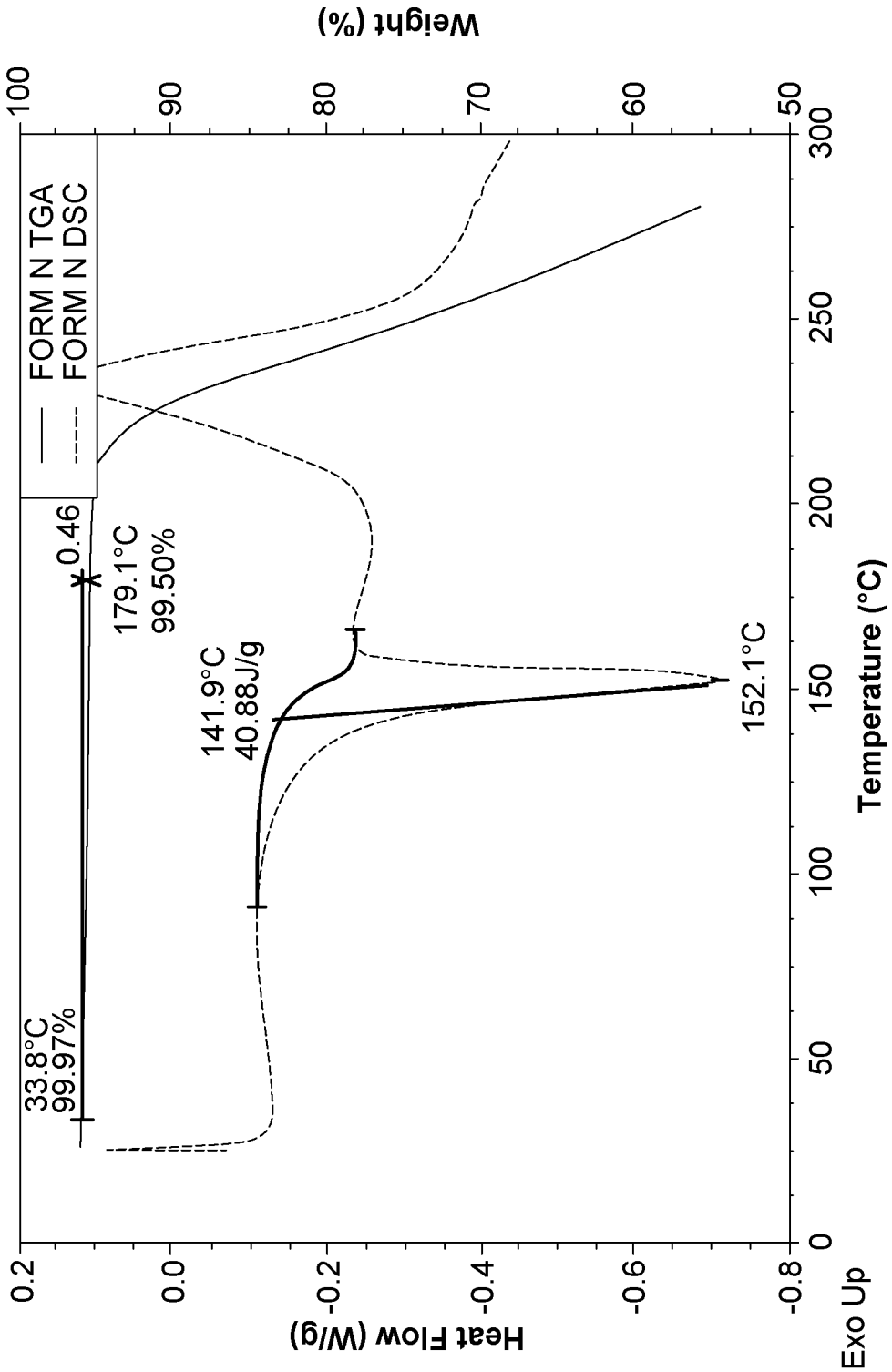

Weight (%)
100
90
80
70
60
50
FORM N TGA
FORM N DSC
0.46
179.1°C
99.50%
141.9°C
40.88J/g
152.1°C
33.8°C
99.97%
0.2
0.0
-0.2
-0.4
-0.6
-0.8
Heat Flow (W/g)
Exo Up
0
50
100
150
200
250
300
Temperature (°C)

FIG. 11B

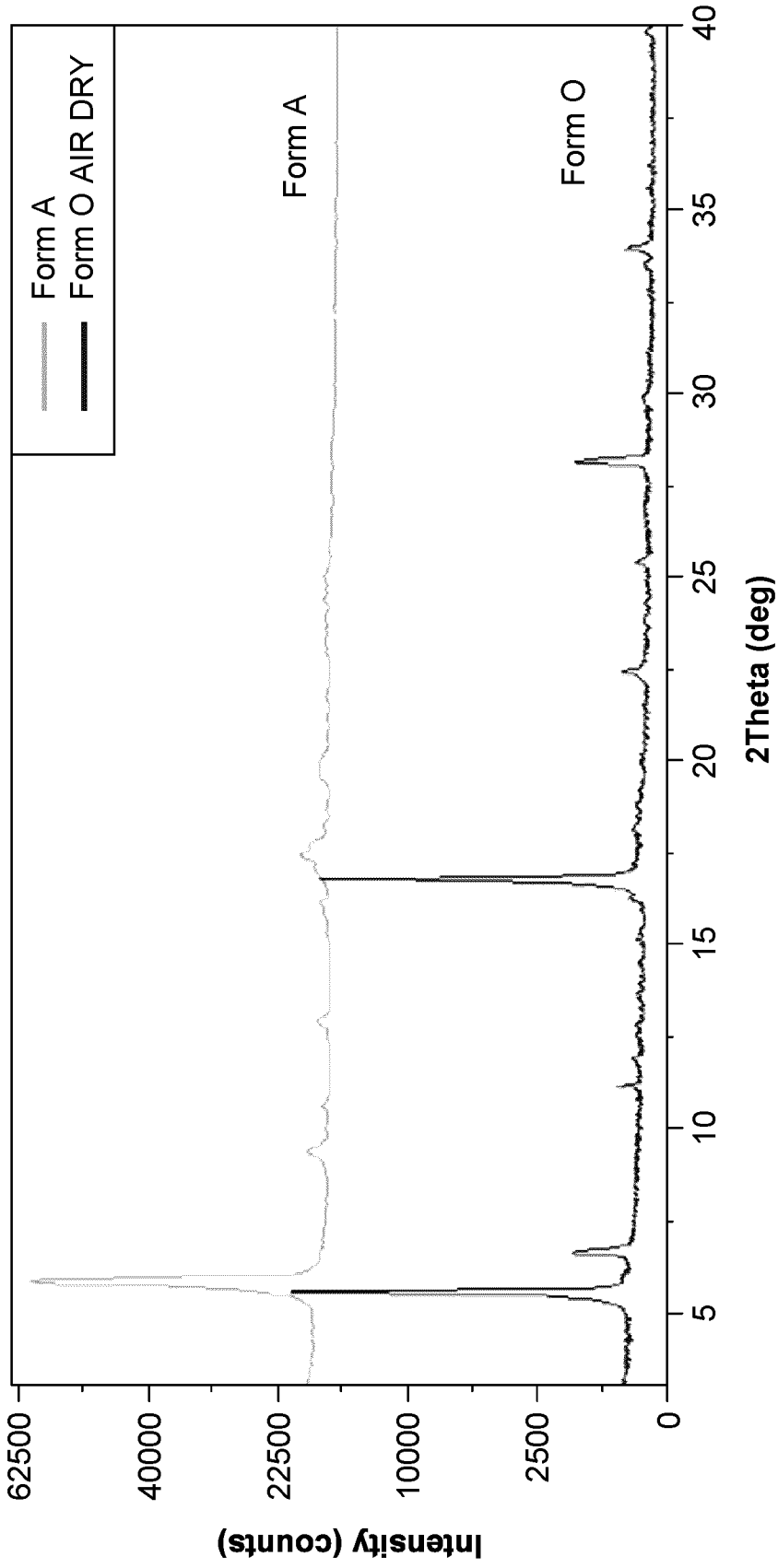

Form A
Form O AIR DRY
Form A
Form O
Intensity (counts)
62500
40000
22500
10000
2500
0
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 12A

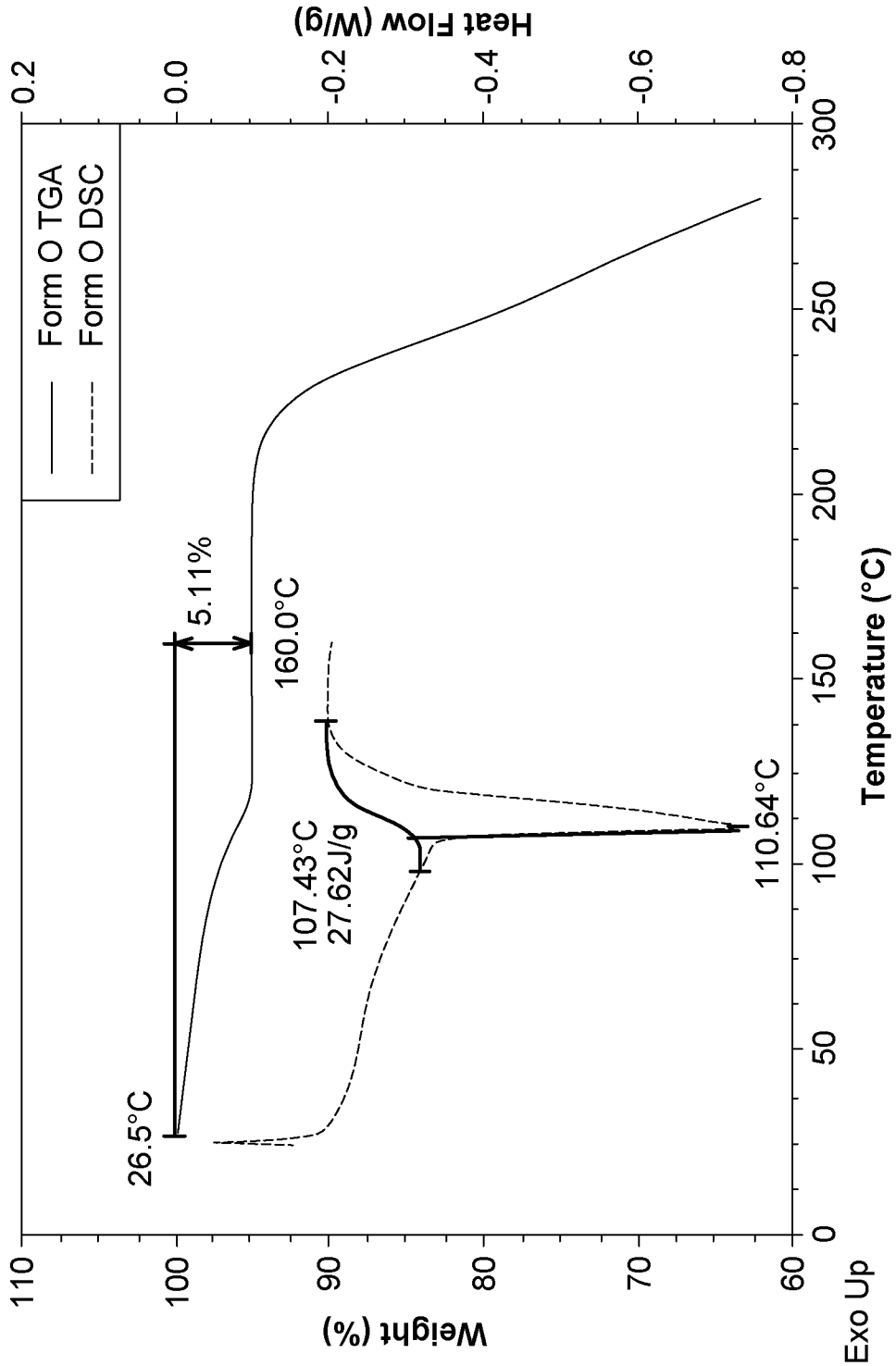

Form O TGA
Form O DSC
5.11%
160.0°C
107.43°C
27.62J/g
110.64°C
26.5°C
Weight (%)
Heat Flow (W/g)
Temperature (°C)
Exo Up

FIG. 12B

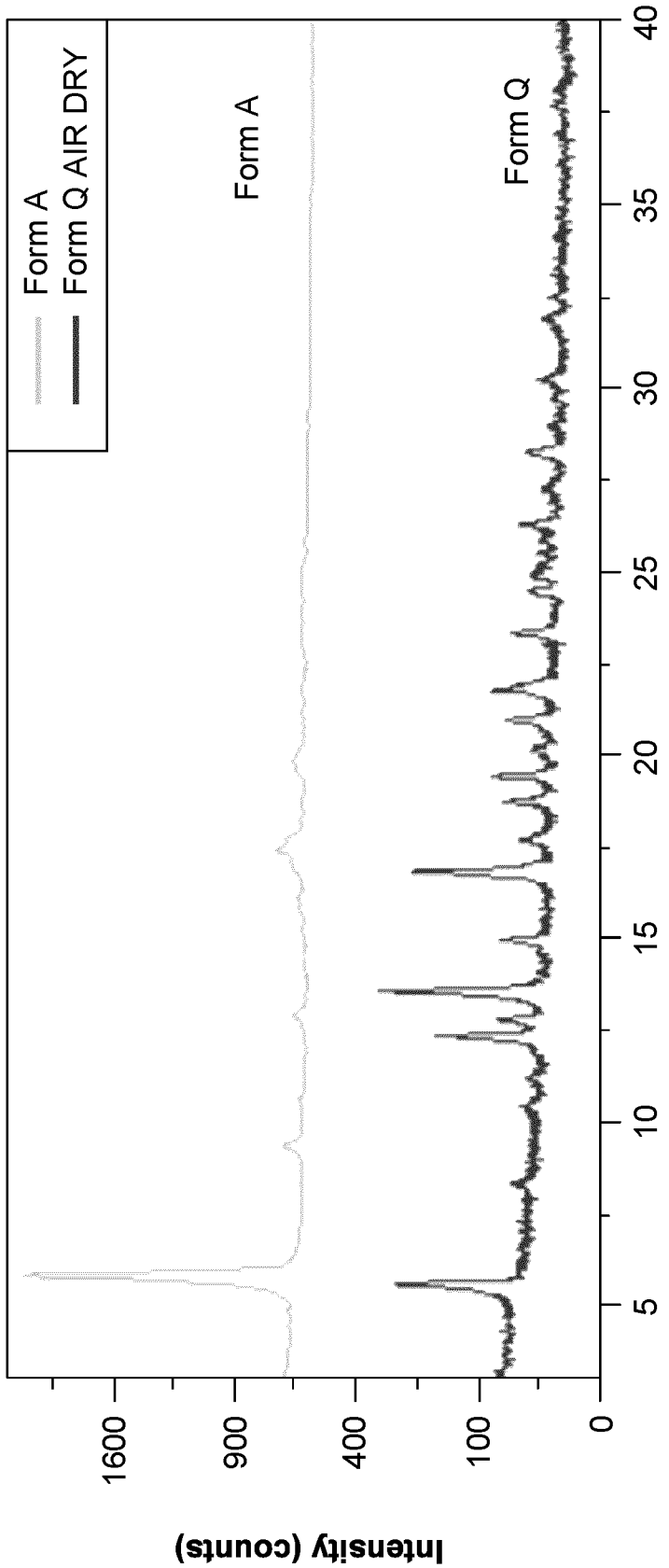

Form A
Form Q AIR DRY
Form A
Form Q
Intensity (counts)
0
100
400
900
1600
5
10
15
20
25
30
35
40
2Theta (deg)

FIG. 13A

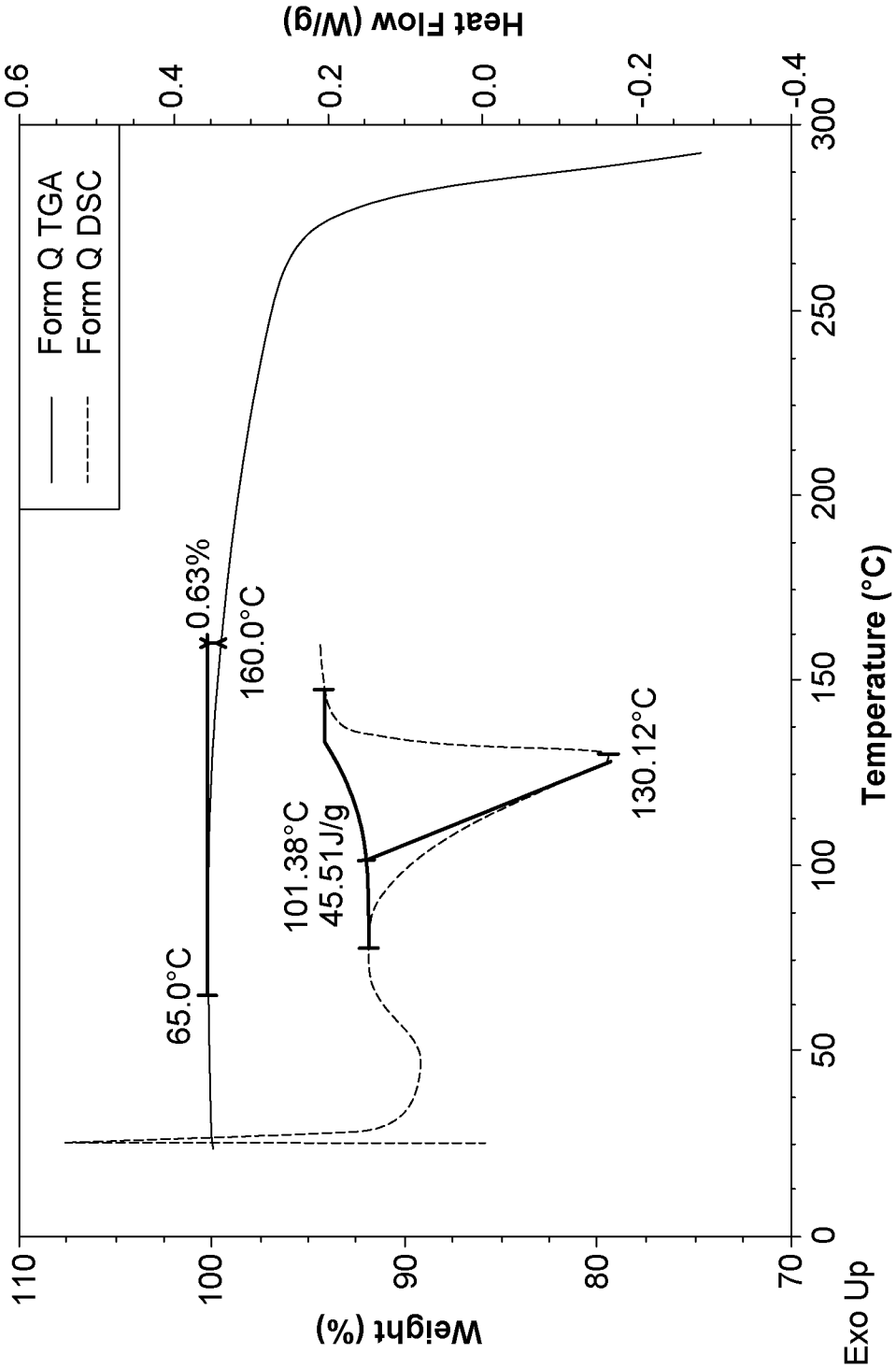

Heat Flow (W/g)
0.6
0.4
0.2
0.0
-0.2
-0.4
Form Q TGA
Form Q DSC
0.63%
160.0°C
65.0°C
101.38°C
45.51J/g
130.12°C
Weight (%)
110
100
90
80
70
Temperature (°C)
0
50
100
150
200
250
300
Exo Up

FIG. 13B

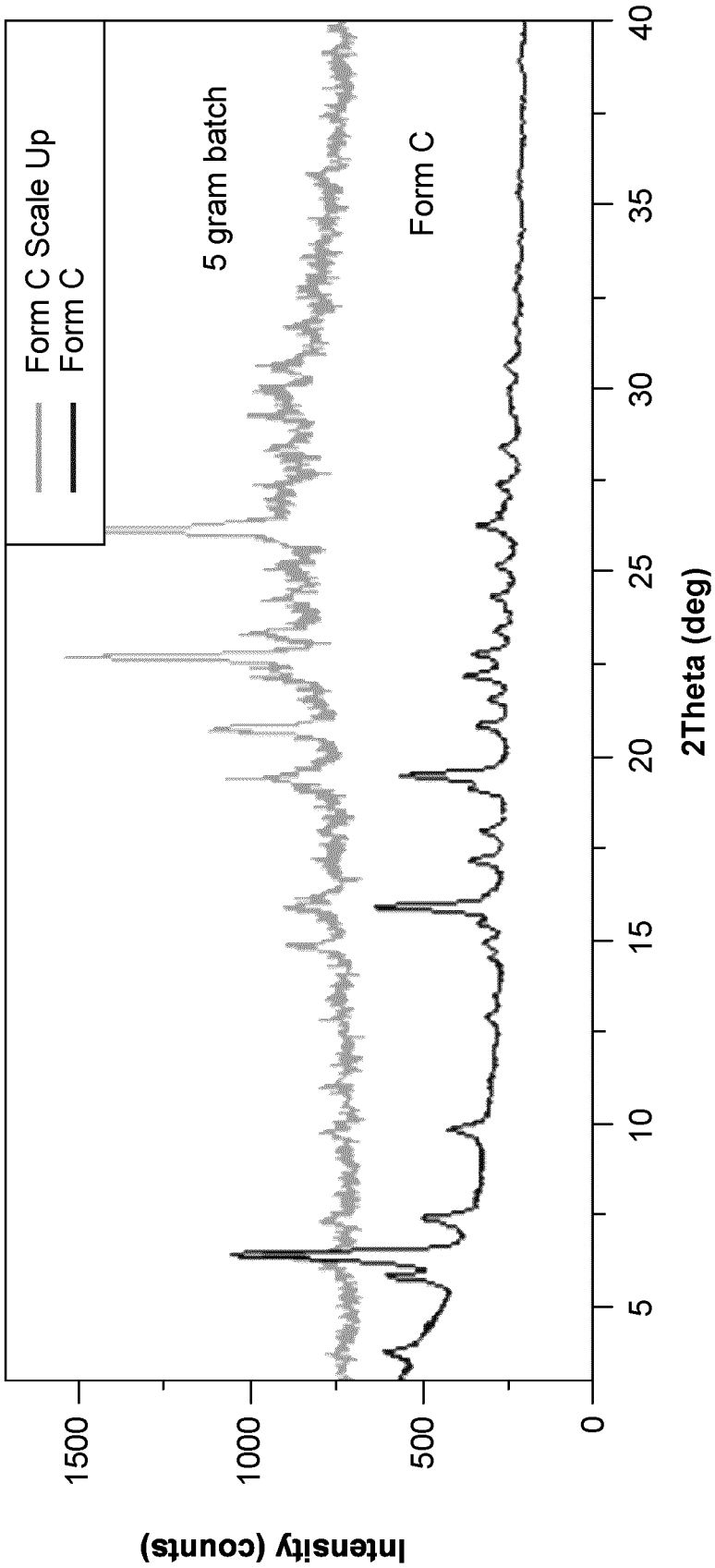

Form C Scale Up
Form C
5 gram batch
Form C
Intensity (counts)
0
500
1000
1500
2Theta (deg)
5
10
15
20
25
30
35
40

FIG. 14

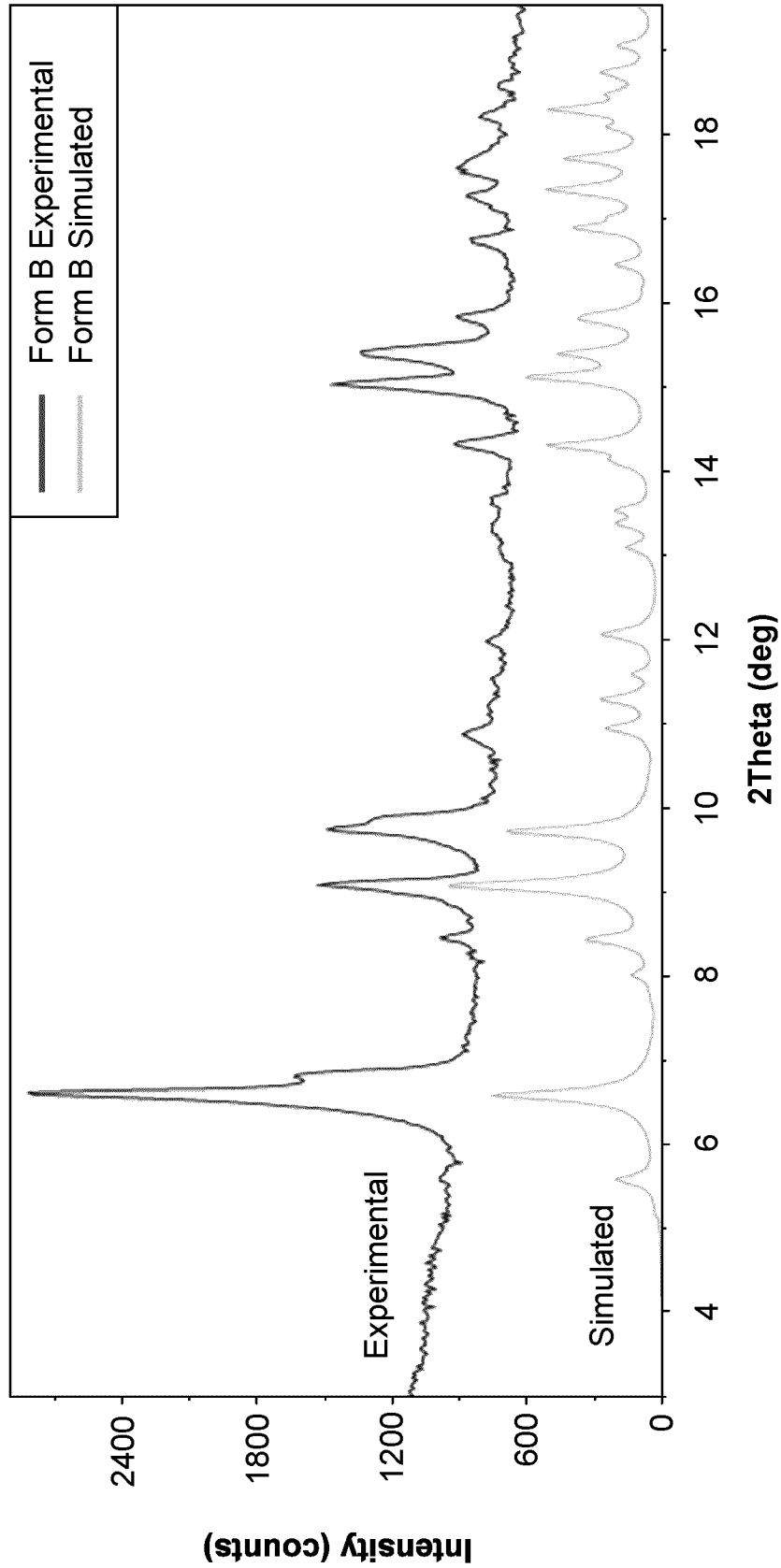

Form B Experimental
Form B Simulated
Experimental
Simulated
Intensity (counts)
2400
1800
1200
600
0
4
6
8
10
12
14
16
18
2Theta (deg)

FIG. 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2023/050163

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07D 231/06*** (2006.01), ***A61K 31/415*** (2006.01), ***A61P 1/16*** (2006.01), ***A61P 3/04*** (2006.01), ***A61P 3/10*** (2006.01)

CPC: **C07D 231/06** (2022.08), A61K 31/415 (2020.01), A61P 1/16 (2020.01), A61P 3/04 (2020.01), A61P 3/10 (2020.01)

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)
CPC: C07D 231/06 (2022.08), A61K 31/415 (2020.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN (CAS Registry, CAPlus); Questel-Orbit; Scopus; Medline; Google Scholar
Search terms: MRI-1891, cannabinoid, crystalline, polymorph

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, D	Liu, Ziyi et al. "Functional Selectivity of a Biased Cannabinoid-1 Receptor (CB1R) Antagonist" ACS Pharmacology and Translational Science, 4(3):1175-1187, 11 June 2021 (11-06-2021) American Chemical Society DOI: 10.1021/acsptsci.1c00048 Supporting Information: https://pubs.acs.org/doi/suppl/10.1021/acsptsci.1c00048/suppl_file/pt1c00048_si_001.pdf	1-65
A	WO 2016/196646 A1 (KUNOS, George et al.) 8 December 2016 (08-12-2016) (page 54, compound 72; Figure 10D)	1-65

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"D"	document cited by the applicant in the international application	"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
"E"	earlier application or patent but published on or after the international filing date	"&"	document member of the same patent family
"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)		
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 06 April 2023 (06-04-2023)	Date of mailing of the international search report 04 May 2023 (04-05-2023)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer May Ling Nung (819) 639-9347

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2023/050163

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2016196646A1	08 December 2016 (08-12-2016)	WO2016196646A8	05 January 2017 (05-01-2017)
		CA2889697A1	22 May 2014 (22-05-2014)
		CA2889697C	14 March 2023 (14-03-2023)
		CN104884057A	02 September 2015 (02-09-2015)
		CN104884057B	20 August 2019 (20-08-2019)
		CN108699043A	23 October 2018 (23-10-2018)
		EP2919779A1	23 September 2015 (23-09-2015)
		EP2919779B1	06 January 2021 (06-01-2021)
		EP3303325A1	11 April 2018 (11-04-2018)
		EP3423448A1	09 January 2019 (09-01-2019)
		IN3733DEN2015A	18 September 2015 (18-09-2015)
		JP2015536997A	24 December 2015 (24-12-2015)
		JP6272626B2	31 January 2018 (31-01-2018)
		US2016039766A1	11 February 2016 (11-02-2016)
		US9765031B2	19 September 2017 (19-09-2017)
		US2018022706A1	25 January 2018 (25-01-2018)
		US10683270B2	16 June 2020 (16-06-2020)
		US2018022705A1	25 January 2018 (25-01-2018)
		US10787419B2	29 September 2020 (29-09-2020)
		US2016257654A1	08 September 2016 (08-09-2016)
		US11155521B2	26 October 2021 (26-10-2021)
		US2020331861A1	22 October 2020 (22-10-2020)
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		US2018273485A1	27 September 2018 (27-09-2018)
		US2019352268A1	21 November 2019 (21-11-2019)
		WO2014078309A1	22 May 2014 (22-05-2014)
		WO2014078309A8	21 May 2015 (21-05-2015)
		WO2017151802A1	08 September 2017 (08-09-2017)