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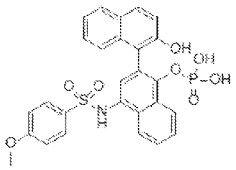

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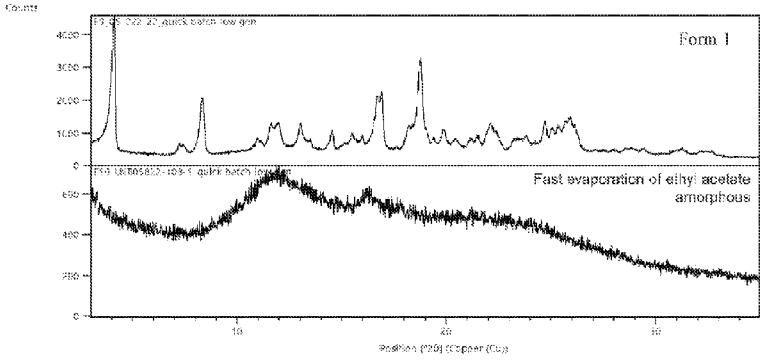

FIG. 1

(57) Abstract: Provided herein, in some embodiments, are solid-state forms of a compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof, pharmaceutical compositions comprising one or more solid-state forms of a compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof, and methods of use thereof.

WO 2025/137366 A2

[Continued on next page]

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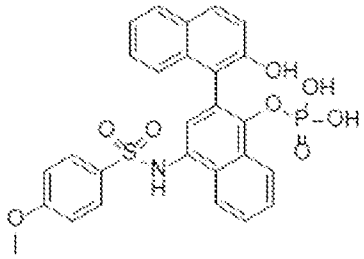
SOLID-STATE FORMS OF STAT3 INHIBITORS AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims priority to U.S. Provisional Application Number 63/612,879 filed December 20, 2023, the contents of which are incorporated herein by reference.

SUMMARY

[0002] Provided herein, in some embodiments, are solid-state forms of a compound represented by Formula (I):



Formula (I),

as free acid or base, or a pharmaceutically acceptable salt or solvate thereof.

[0003] In some embodiments, provided herein are methods of preparing solid-state forms of the compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof.

[0004] In some embodiments, provided herein are pharmaceutical compositions comprising one or more solid-state forms of the compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

[0005] In some embodiments, provided herein are methods that involve the use of (e.g., comprise the administration of) a solid-state form of the compound represented by Formula (I), a STAT3 inhibitor, optionally wherein the solid-state form of the compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof, is formulated in a manner described herein (e.g., is present in a composition as described herein). In some embodiments, provided herein are methods of treating, preventing, or reducing the risk or severity of cancer. In other specific embodiments, provided herein are methods of treating, preventing, or reducing the risk or severity of fibrosis. In still other

specific embodiments, provided herein are methods of treating, preventing, or reducing the risk or severity of an inflammatory disease or disorder.

[0006] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description**, **Examples**, and **Claims**.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIG. 1 shows a comparison of X-ray powder diffraction ("XRPD") diffractograms for the amorphous solid of the compound represented by Formula (I) and Form 1 of the compound represented by Formula (I).

[0008] FIG. 2A shows an XRPD diffractogram of Form 1 of the compound represented by Formula (I).

[0009] FIG. 2B shows an XRPD diffractogram of Form 21 of the compound represented by Formula (I).

[00010] FIG. 3 shows a ^{1}H NMR spectrum of Form 1 of the compound represented by Formula (I).

[00011] FIG. 4 shows a ^{31}P NMR spectrum of Form 1 of the compound represented by Formula (I).

[00012] FIG. 5 shows thermogravimetric analysis ("TGA") and differential scanning calorimetry ("DSC") thermogram traces for Form 1 of the compound represented by Formula (I).

[00013] FIG. 6 shows a DSC thermogram trace for the first heating cycle for Form 1 of the compound represented by Formula (I).

[00014] FIG. 7 shows a dynamic vapor sorption ("DVS") kinetic plot of Form 1 of the compound represented by Formula (I).

[00015] FIG. 8 shows a comparison of XRPD diffractograms of Form 1 of the compound represented by Formula (I) before and after DVS.

[00016] FIG. 9 shows a variable temperature XRPD diffractogram of Form 1 of the compound represented by Formula (I).

[00017] FIG. 10 shows XPRD diffractograms of Form 1 subjected to a seven-day stability test.

[00018] FIG. 11 shows XPRD diffractograms of the compound represented by Formula (I) subjected to maturation cycling and hydration.

[00019] FIG. 12 shows XRPD diffractograms of the compound represented by Formula (I) subjected to temperature cycling.

[00020] FIG. 13 shows XRPD diffractograms of the compound represented by Formula (I) subjected to solvent drop grinding.

[00021] FIG. 14 shows XRPD diffractograms of the compound represented by Formula (I) subjected to vapor diffusion into solids.

[00022] FIG. 15 shows XRPD diffractograms of the compound represented by Formula (I) subjected to vapor diffusion into saturated solutions.

[00023] FIG. 16 shows XPRD diffractograms of the compound represented by Formula (I) subjected to antisolvent additions.

[00024] FIG. 17 shows XRPD diffractograms of the compound represented by Formula (I) subjected to slow solvent evaporation.

[00025] FIGS. 18A, 18B, and 18C show an XPRD diffractogram, TGA/DSC plot, and ^{1}H NMR spectrum, respectively, of Form 2 of the compound represented by Formula (I).

[00026] FIGS. 19A and 19B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 3 of the compound represented by Formula (I).

[00027] FIG. 20 shows an XRPD diffractogram of Form 4 of the compound represented by Formula (I).

[00028] FIGS. 21A and 21B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 5 of the compound represented by Formula (I).

[00029] FIGS. 22A and 22B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 6 of the compound represented by Formula (I).

[00030] FIG. 23 shows an XRPD diffractogram of Form 7 of the compound represented by Formula (I).

[00031] FIGS. 24A and 24B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 8 of the compound represented by Formula (I).

[00032] FIGS. 25A and 25B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 9 of the compound represented by Formula (I).

[00033] FIGS. 26A and 26B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 10 of the compound represented by Formula (I).

[00034] FIGS. 27A and 27B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 11 of the compound represented by Formula (I).

[00035] FIGS. 28A and 28B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 12 of the compound represented by Formula (I).

[00036] FIG. 29 shows an XRPD diffractogram of Form 13 of the compound represented by Formula (I).

[00037] FIG. 30 shows an XRPD diffractogram of Form 14 of the compound represented by Formula (I).

[00038] FIG. 31 shows an XRPD diffractogram of Form 15 of the compound represented by Formula (I).

[00039] FIG. 32 shows an A ^{1}H NMR spectrum of Compound 2 as described in Example 2D.

[00040] FIG. 33 shows Liquid chromatography-mass spectrometry (LCMS) data for Compound 2 as described in Example 2D.

[00041] FIG. 34 shows an A ^{1}H NMR spectrum of Compound 3 as described in Example 2D.

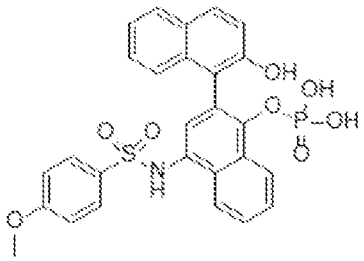
[00042] FIG. 35 shows Liquid chromatography-mass spectrometry (LCMS) data for Compound 3 as described in Example 2D.

[00043] FIG. 36 shows an A ^{1}H NMR spectrum of Compound 4 (compound represented by Formula (I)) as described in Example 2D.

[00044] FIG. 37 shows Liquid chromatography-mass spectrometry (LCMS) data for Compound 4 (compound represented by Formula (I)) as described in Example 2D.

DETAILED DESCRIPTION

[00045] The present disclosure, in some embodiments, provides solid-state forms of the compound represented by Formula (I):



Formula (I),

as free acid or base, or pharmaceutically acceptable salts or solvates thereof, pharmaceutical compositions comprising one or more solid-state forms of the compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. Also provided herein, in some embodiments, are methods of preparing solid-state forms of the compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the solid-state forms of the compound represented by Formula (I) and compositions disclosed

herein are effective at inhibiting signal transducer and activator of transcription 3 (STAT3) and thus are useful in methods of treating, preventing, or reducing the risk or severity of certain diseases or disorders such as cancer, fibrosis, and inflammatory diseases or disorders.

[00046] In some embodiments, provided herein are pharmaceutical compositions comprising one or more solid-state forms of the compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

[00047] In some embodiments, provided herein are methods that involve the use of (e.g., comprise the administration of) a solid-state form of the compound represented by Formula (I), a STAT3 inhibitor, optionally wherein the solid-state form of the compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof, is formulated in a manner described herein (e.g., is present in a composition as described herein). In some embodiments, provided herein are methods of treating, preventing, or reducing the risk or severity of cancer. In other specific embodiments, provided herein are methods of treating, preventing, or reducing the risk or severity of fibrosis. In still other specific embodiments, provided herein are methods of treating, preventing, or reducing the risk or severity of an inflammatory disease or disorder.

Definitions

[0001] The following are definitions of terms used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art.

[0002] As used herein the specification, “a” or “an” may mean one or more. As used herein, when used in conjunction with the word "comprising", the words “a” or “an” may mean one or more than one. As used herein “another” may mean at least a second or more. Still further, the terms “having”, “including”, “containing” and “comprising” are interchangeable and one of skill in the art is cognizant that these terms are open ended terms. Some embodiments of the disclosure may consist of or consist essentially of one or more elements, method steps, and/or methods of the disclosure. It is contemplated that any method, compound, or composition described herein can be implemented with respect to any other method, compound, or composition described herein.

[0003] "About" and "approximately" shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees

of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.

[0004] As used herein, "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0005] As used herein, "solvate" refers to a physical association of a compound with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding and non-hydrogen binding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. 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. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, isopropanolates, and the like.

[0006] As used herein, "pharmaceutically acceptable excipient" refers to any substance in a pharmaceutical formulation other than the active pharmaceutical ingredient(s). Exemplary pharmaceutical excipients include those that aid the manufacturing process; protect, support or enhance stability; increase bioavailability; or increase patient acceptability. They may also assist in product identification or enhance the overall safety or function of the product during storage or use. The terms "excipient" and "carrier" are used interchangeably herein.

[0007] As used herein, a "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle–aged adult or senior adult)) and/or a non-human animal, e.g., a mammal such as primates (e.g., cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In some embodiments, the subject is a human. In some embodiments, the subject is a non-human animal. The terms "human," "patient," "subject," and "individual" are used interchangeably herein. None of these terms require the active supervision of medical personnel.

[0008] Disease, disorder, and condition are used interchangeably herein.

[0009] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or reverses or slows the progression of the disease, disorder or condition (also "therapeutic treatment").

[00010] In general, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the disclosure may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, weight, health, and condition of the subject. A "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit (e.g., treating, preventing, and/or ameliorating cancer in a subject, or inhibiting protein-protein interactions mediated by an SH2 domain in a subject, at

a reasonable benefit/risk ratio applicable to any medical treatment) in the treatment of a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the disease, disorder or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutic agent. A "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease, disorder or condition, or one or more symptoms associated with the disease, disorder or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease, disorder or condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent. A "prophylactic treatment" contemplates an action that occurs before a subject begins to suffer from the specified disease, disorder or condition.

[00011] As used herein, "STAT3 inhibitor" or a compound that "inhibits STAT3" refers to a compound that interferes with the activity of STAT3 to perform one or more activities, including the ability of STAT3 to bind to a molecule such as pY-peptide ligand and/or the ability to be phosphorylated.

[00012] As used herein, the terms "isolated", "isolating", and "isolation", and the like in reference to solid-state forms of the compound represented by Formula (I) correspond to a solid-state form of the compound represented by Formula (I) that is physically separated from a reaction mixture or a slurry comprising the solid-state form of the compound represented by Formula (I).

[00013] Ambient conditions of temperature as used herein refer to temperatures of between about 15 to about 30°C, or about 20 to about 30°C, for example, between about 20 to about 25°C.

[00014] Solid-state forms of the present disclosure include crystalline and amorphous forms of the compounds, including, for example, solvates, hydrates, co-crystals, unsolvated forms (including anhydrates), conformational forms, tautomeric forms, or disordered crystalline forms thereof, as well as mixtures thereof.

[00015] As used herein, and unless otherwise specified, the term “crystalline,” when used to describe a form, solid, or substance means that the form, solid, or substance is substantially crystalline as determined, for example, by X-ray diffraction. The crystalline form, solid, or substance has a highly regular physical arrangement of molecules. The molecules within the form, solid, or substance are arranged in a regular, periodic manner in the 3-dimensional space of the crystalline lattice. In some embodiments, a crystalline form of a compound is substantially free of amorphous forms or other crystalline forms of the compound, or a salt or a solvate thereof.

[00016] Crystalline forms of a compound, in some embodiments, are obtained by a number of methods, such as, without limitation, temperature cycling, melt recrystallization, melt cooling, solvent recrystallization, anti-solvent addition, recrystallization in confined spaces, such as, e.g., in nanopores or capillaries, recrystallization on surfaces or templates, such as, e.g., on polymers, recrystallization in the presence of additives, such as, e.g., co-crystal counter-molecules, desolvation, dehydration, rapid evaporation, rapid cooling, slow cooling, vapor diffusion, sublimation, grinding, solvent-drop grinding, microwave-induced precipitation, sonication-induced precipitation, laser-induced precipitation, or precipitation from a supercritical fluid, or a combination thereof.

[00017] As used herein, and unless otherwise specified, the term "amorphous," when used to describe a form, solid, or substance means that the form, solid, or substance in question is not substantially crystalline as determined, for example, by X-ray diffraction or Differential Scanning Calorimetry (DSC). In some embodiments, an amorphous form of a compound is substantially free of crystalline forms of the compound, or a salt or a solvate thereof.

[00018] Amorphous forms of a compound, in some embodiments, are obtained by several methods, as known in the art. Such methods include, but are not limited to, heating, melt cooling, rapid melt cooling, solvent evaporation, rapid solvent evaporation, desolvation, sublimation, grinding, cryo-grinding, spray drying, and freeze drying.

[00019] As used herein and unless otherwise specified, a solid-state form of a compound described herein that is "substantially free" of a substance (e.g., other form(s) of the compound, or a salt or a solvate thereof) means that the solid-state form comprises less than about 20 percent by weight, less than about 10 percent by weight, less than about 5 percent by weight, less than about 4 percent by weight, less than about 3 percent by weight, less than about 2 percent by weight, less than about 1 percent by weight, less than about 0.5%

by weight, or less than about 0.1 percent by weight of the substance (e.g., other form(s) of the compound, or a salt or a solvate thereof).

[00020] As used herein, and unless otherwise specified, the term "substantially pure" when used to describe a solid-state form of a compound described herein means a solid-state form of the compound that comprises a particular solid-state form the compound and is substantially free of other solid form(s) of the compound, or a salt or a solvate thereof, or other compound(s). A representative substantially pure solid-state form comprises greater than about 80% by weight of one solid-state form of the compound and less than about 20% by weight of other solid forms of the compound or other compounds; greater than about 90% by weight of one solid-state form of the compound and less than about 10% by weight of other solid forms of the compound or other compounds; greater than about 95% by weight of one solid-state form of the compound and less than about 5% by weight of other solid forms of the compound or other compounds; greater than about 97% by weight of one solid-state form of the compound and less than about 3% by weight of other solid forms of the compound or other compounds; or greater than about 99% by weight of one solid-state form of the compound and less than about 1 % by weight of other solid forms of the compound or other compounds.

[00021] Techniques for characterizing crystalline forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), single crystal X-ray diffractometry, vibrational spectroscopy, e.g., infrared (IR) and Raman spectroscopy, solid-state nuclear magnetic resonance (NMR) spectroscopy, optical microscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies, and dissolution studies.

[00022] Generally, a diffraction angle (2θ, “2 theta”) in X-ray powder diffractometry has a variation, for example, in the range of ± 0.5°, ± 0.3°, or ± 0.2°. Accordingly, the diffraction angle values should be understood as including values in the range of about ± 0.5°, ± 0.3°, or ± 0.2°.

[00023] A solid-state form of a compound described herein, in some embodiments, is described by reference to patterns, spectra, or other graphical data as “substantially” shown or “depicted” in a figure, or by one or more data points. It will be appreciated that patterns, spectra, and other graphical data can be shifted in their positions, relative intensities, or other values due to a number of factors known to those of skill in the art. For example, in the crystallographic and powder X-ray diffraction arts, shifts in peak positions or the relative

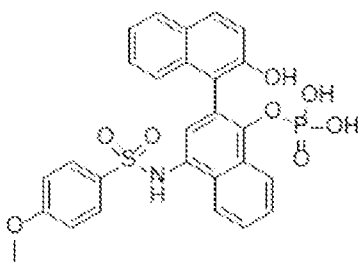
intensities of one or more peaks of a pattern can occur because of, without limitation, the equipment used, the sample preparation protocol, preferred packing and orientations, the radiation source, operator error, method and length of data collection, or the like. However, those of ordinary skill in the art will be able to compare the figures herein with patterns, etc. generated for an unknown form of, in this case, the compound represented by Formula (I), and confirm its identity with the forms disclosed herein. The same holds true for other techniques which may be reported herein.

[00024] As used herein, and unless otherwise specified, the term "peak," when used in connection with the spectra or data presented in graphical form (e.g., XRPD, IR, Raman, and NMR spectra), refers to a peak or other special feature that one skilled in the art would recognize as not attributable to background noise.

Solid-State Forms

[00048] The occurrence of different polymorphs is possible for some compounds. However, the existence and possible number of polymorphic forms for a given compound are not predictable. Different polymorphic forms of the same compound can exhibit different physical, chemical and/or spectroscopic properties. For example, different forms of the compound can have differences in bioavailability, solubility, stability, and/or compressibility that impact the processability of the compound. A particular form of a compound can have improved properties over other forms of the compound such as, but not limited to, ease of handling, ease of processing, ease of purification, improved dissolution profiles, dissolution rates, storage stability, chemical stability, physical stability, bioavailability, storage conditions, shelf-life, purity, process reproducibility, and/or formulation properties.

[00049] Provided herein, in some embodiments, are solid-state forms of a compound represented by Formula (I):



Formula (I),

as free acid or base, or a pharmaceutically acceptable salt or solvate thereof.

Form 1

[00050] Provided herein, in some embodiments, is crystalline Form 1 of a compound represented by Formula (I).

[00051] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 2A. In some embodiments, the crystalline form has an XRPD pattern substantially as shown in Table 1A.

[00052] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 18.8°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 4.2°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 16.7°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 16.9°.

[00053] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 18.8°±0.2°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 4.2°±0.2°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 16.7°±0.2°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 16.9°±0.2°.

[00054] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 18.8°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 4.2°, 16.7°, or 16.9°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 8.4°, 11.6°, 12.0°, 14.6°, or 19.9°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 7.3°, 8.3°, 11.1°, 13.0°, 15.5°, 19.4°, 20.4°, or 21.5°.

[00055] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 18.8°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 4.2°±0.2°, 16.7°±0.2°, or 16.9°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 8.4°±0.2°, 11.6°±0.2°, 12.0°±0.2°, 14.6°±0.2°, or 19.9°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 7.3°±0.2°, 8.3°±0.2°, 11.1°±0.2°, 13.0°±0.2°, 15.5°±0.2°, 19.4°±0.2°, 20.4°±0.2°, or 21.5°±0.2°.

[00056] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 4.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 18.8°, 16.7°, or 16.9°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 8.4°, 11.6°, 12.0°, 14.6°, or

19.9°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 7.3°, 8.3°, 11.1°, 13.0°, 15.5°, 19.4°, 20.4°, or 21.5°.

[00057] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 4.2°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 18.8°±0.2°, 16.7°±0.2°, or 16.9°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 8.4°±0.2°, 11.6°±0.2°, 12.0°±0.2°, 14.6°±0.2°, or 19.9°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 7.3°±0.2°, 8.3°±0.2°, 11.1°±0.2°, 13.0°±0.2°, 15.5°±0.2°, 19.4°±0.2°, 20.4°±0.2°, or 21.5°±0.2°.

[00058] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 4.2°, 18.8°, 16.7°, and 16.9°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 8.4°, 11.6°, 12.0°, 14.6°, or 19.9°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 7.3°, 8.3°, 11.1°, 13.0°, 15.5°, 19.4°, 20.4°, or 21.5°.

[00059] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 4.2°±0.2°, 18.8°±0.2°, 16.7°±0.2°, and 16.9°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 8.4°±0.2°, 11.6°±0.2°, 12.0°±0.2°, 14.6°±0.2°, or 19.9°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 7.3°±0.2°, 8.3°±0.2°, 11.1°±0.2°, 13.0°±0.2°, 15.5°±0.2°, 19.4°±0.2°, 20.4°±0.2°, or 21.5°±0.2°.

[00060] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 4.2°, 18.8°, 16.7°, and 16.9°. In some embodiments, the XRPD pattern further comprises peaks at about 8.4°, 11.6°, 12.0°, 14.6°, and 19.9°. In some embodiments, the XRPD pattern further comprises peaks at about 7.3°, 8.3°, 11.1°, 13.0°, 15.5°, 19.4°, 20.4°, and 21.5°.

[00061] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 4.2°±0.2°, 18.8°±0.2°, 16.7°±0.2°, and 16.9°±0.2°. In some embodiments, the XRPD pattern further comprises peaks at 8.4°±0.2°, 11.6°±0.2°, 12.0°±0.2°, 14.6°±0.2°, and 19.9°±0.2°. In some embodiments, the XRPD pattern further comprises peaks at 7.3°±0.2°, 8.3°±0.2°, 11.1°±0.2°, 13.0°±0.2°, 15.5°±0.2°, 19.4°±0.2°, 20.4°±0.2°, and 21.5°±0.2°.

[00062] In some embodiments, the crystalline form has a DSC thermogram comprising an endothermic event with onset between about 194 °C to 200 °C. In some embodiments, the crystalline form has a DSC thermogram comprising an endothermic peak at about 205 °C. In

some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 5. In some embodiments, the crystalline form has a DSC thermogram comprising an endothermic event with onset between about 190 °C to 196 °C. In some embodiments, the crystalline form has a DSC thermogram comprising an endothermic peak at about 204 °C. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 6. In some embodiments, the crystalline form has a DVS kinetic plot substantially as shown in FIG. 7.

[00063] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

[00064] In some embodiments, the crystalline Form 1 is an anhydrate.

[00065] Also provided herein, in some embodiments, are processes for preparing crystalline Form 1 of a compound represented by Formula (I).

[00066] In some embodiments, the process for preparing crystalline Form 1 of a compound represented by Formula (I) comprises:

(i) providing a mixture of a compound represented by Formula (I) and a first solvent;

(ii) charging the mixture with seed material of crystalline Form 1 of the compound represented by Formula (I) to form a charged mixture;

(iii) further charging the charged mixture with a second solvent to produce a solid precipitate;

(iv) isolating the solid precipitate; and

(v) slurrying the solid precipitate in a third solvent, to produce the crystalline Form 1 of the compound represented by Formula (I).

[00067] In some embodiments, the compound represented by Formula (I) in step (i) comprises solid-state forms of the compound represented by Formula (I) other than Form 1 of the compound represented by Formula (I).

[00068] In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 30% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 25% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 20% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 15% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 10% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 5% w/w of Form 1 of the compound represented by Formula (I).

[00069] In some embodiments, the first solvent is a mixture of ethanol and water or acetic acid and water. In some embodiments, the first solvent is a mixture of ethanol and water. In some embodiments, the first solvent is a mixture of acetic acid and water.

[00070] In some embodiments, after step (ii), the process further comprises cooling the charged mixture to about 0 °C to about 10 °C. In some embodiments, after step (ii), the process further comprises cooling the charged mixture to about 0 °C. In some embodiments, after step (ii), the process further comprises cooling the charged mixture to about 5 °C. In some embodiments, after step (ii), the process further comprises cooling the charged mixture to about 10 °C.

[00071] In some embodiments, the second solvent is water.

[00072] In some embodiments, after step (iv), the process further comprises washing the isolated solid precipitate with a first solvent, a second solvent, or a mixture thereof, and drying the washed solid precipitate.

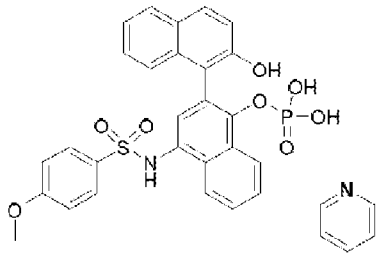
[00073] In some embodiments, in step (v), slurrying the solid precipitate in the third solvent occurs at about 80 °C to about 100 °C. In some embodiments, the slurrying is at about 85 °C to about 95 °C. In some embodiments, the slurrying is at about 80 °C. In some embodiments, the slurrying is at about 85 °C. In some embodiments, the slurrying is at about 90 °C. In some embodiments, the slurrying is at about 95 °C. In some embodiments, the slurrying is at about 100 °C.

[00074] In some embodiments, the third solvent is n-heptane.

[00075] In some embodiments, after step (v), the process further comprises isolating the slurried solid precipitate from the third solvent, and optionally drying the solid precipitate.

[00076] In some embodiments, the process further comprises:

(i) contacting a compound represented by Formula (C):



Formula (C),

with an aqueous solution comprising an acid to produce a first solid precipitate;

(ii) isolating the first solid precipitate;

(iii) contacting the first solid precipitate with a first solvent to form a first mixture;

(iv) contacting the first mixture with an acid to form a second mixture;

(v) contacting the second mixture with a second solvent to form a third mixture;

(vi) contacting the third mixture with a third solvent to produce a second solid precipitate; and

(vii) isolating the second solid precipitate,

thereby preparing a compound represented by Formula (I).

[00077] In some embodiments, in step (i), the acid is hydrochloric acid.

[00078] In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 10 °C to about 50 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 10 °C to about 30 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 30 °C to about 50 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 10 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 15 °C. In some embodiments, in step (i), the contacting

comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 20 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 25 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 30 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 35 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 40 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 45 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 50 °C.

[00079] In some embodiments, after step (ii), the process further comprises washing the first solid precipitate with water.

[00080] In some embodiments, the first solvent is 2-methyltetrahydrofuran.

[00081] In some embodiments, the acid in step (iv) is hydrochloric acid.

[00082] In some embodiments, in step (iv), the second mixture comprises an organic layer and an aqueous layer, and the process further comprises separating the organic layer from the aqueous layer, and optionally adding aqueous hydrochloric acid to the separated organic layer, separating the resulting organic layer from the aqueous layer, and reducing the volume of said organic layer.

[00083] In some embodiments, the second solvent is ethanol.

[00084] In some embodiments, the third solvent is n-heptane.

[00085] In some embodiments, in step (vi), the contacting comprises agitating the third mixture and third solvent at about 20 °C to about 50 °C. In some embodiments, in step (vi), the contacting comprises agitating the third mixture and third solvent at about 20 °C to about 30 °C. In some embodiments, in step (vi), the contacting comprises agitating the third mixture and third solvent at about 40 °C to about 50 °C. In some embodiments, in step (vi), the contacting comprises agitating the third mixture and third solvent at about 20 °C. In some embodiments, in step (vi), the contacting comprises agitating the third mixture and third solvent at about 25 °C. In some embodiments, in step (vi), the contacting comprises agitating the third mixture and third solvent at about 30 °C. In some embodiments, in step (vi), the

contacting comprises agitating the third mixture and third solvent at about 35 °C. In some embodiments, in step (vi), the contacting comprises agitating the third mixture and third solvent at about 40 °C. In some embodiments, in step (vi), the contacting comprises agitating the third mixture and third solvent at about 45 °C. In some embodiments, in step (vi), the contacting comprises agitating the third mixture and third solvent at about 50 °C.

[00086] In some embodiments, after step (vii), the process further comprises washing the second solid precipitate with a second solvent, third solvent, or a mixture thereof, and optionally further comprising washing the second solid precipitate with a third solvent.

[00087] In some embodiments, the process further comprises drying the washed second solid precipitate.

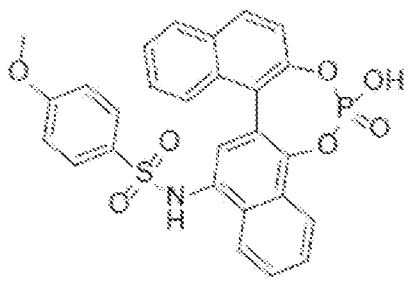
[00088] In some embodiments, the process further comprises slurrying the dried second solid precipitate in a solvent, optionally at about 80 °C to about 100 °C. In some embodiments, the process further comprises slurrying the dried second solid precipitate in a solvent, optionally at about 85 °C to about 95 °C. In some embodiments, the process further comprises slurrying the dried second solid precipitate in a solvent at about 80 °C. In some embodiments, the process further comprises slurrying the dried second solid precipitate in a solvent at about 85 °C. In some embodiments, the process further comprises slurrying the dried second solid precipitate in a solvent at about 90 °C. In some embodiments, the process further comprises slurrying the dried second solid precipitate in a solvent at about 95 °C. In some embodiments, the process further comprises slurrying the dried second solid precipitate in a solvent at about 100 °C.

[00089] In some embodiments, the solvent is n-heptane.

[00090] In some embodiments, the process further comprises isolating the slurried solid precipitate from the solvent.

[00091] In some embodiments, the process further comprises:

(i) contacting a compound represented by Formula (B):



Formula (B)

with an aqueous solution comprising a base to form a first mixture;

(ii) contacting the first mixture with an acid and a solvent to form a second mixture;

(iii) contacting the second mixture with pyridine to produce a solid precipitate; and

(iv) isolating the solid precipitate,

thereby preparing the compound represented by Formula (C).

[00092] In some embodiments, the base is lithium hydroxide.

[00093] In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 65 °C to about 85 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 70 °C to about 80 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 65 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 70 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 75 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 80 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 85 °C.

[00094] In some embodiments, the acid is hydrochloric acid.

[00095] In some embodiments, the solvent is 2-methyltetrahydrofuran.

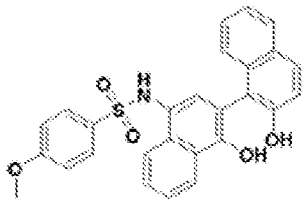
[00096] In some embodiments, in step (ii), the second mixture comprises an organic layer and an aqueous layer, and the process further comprises separating the organic layer from the aqueous layer, and reducing the volume of said organic layer.

[00097] In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 60 °C to about 80 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 65 °C to about 75 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 60 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 65 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 70

°C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 75 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 80 °C.

[00098] In some embodiments, the process further comprises:

(i) contacting a compound of Formula (A):



Formula (A)

in a solvent with phosphorus oxychloride to form a first mixture;

(ii) contacting the first mixture with water and an acid to form a solid precipitate; and

(iii) isolating the solid precipitate,

thereby preparing the compound represented by Formula (B).

[00099] In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about -5 °C to about 35 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 0 °C to about 25 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 0 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 5 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 10 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 15 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 20 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 25 °C.

[000100] In some embodiments, the solvent is pyridine.

[000101] In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 15 °C to about 75 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 25 °C to about 65 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 20 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 25 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 35 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 40 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 45 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 50 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 55 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 60 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 65 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 70 °C.

[000102] In some embodiments, the acid is hydrochloric acid.

[000103] In some embodiments, the process for preparing crystalline Form 1 of a compound represented by Formula (I) comprises:

(i) slurrying a mixture of a compound represented by Formula (I) in a solvent to produce a solid precipitate; and

(ii) isolating the solid precipitate,

thereby preparing the crystalline Form 1 of the compound represented by Formula (I).

[000104] In some embodiments, in step (i), the slurrying occurs at about 80 °C to about 100 °C. In some embodiments, the slurrying is at about 85 °C to about 95 °C. In some embodiments, the slurrying is at about 80 °C. In some embodiments, the slurrying is at about 85 °C. In some embodiments, the slurrying is at about 90 °C. In some embodiments, the slurrying is at about 95 °C. In some embodiments, the slurrying is at about 100 °C.

[000105] In some embodiments, the solvent is n-heptane.

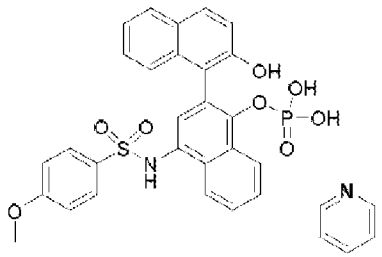
[000106] In some embodiments, after step (ii), the process further comprises drying the solid precipitate.

[000107] In some embodiments, the compound represented by Formula (I) in step (i) comprises solid-state forms of the compound represented by Formula (I) other than Form 1 of the compound represented by Formula (I).

[000108] In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 30% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 25% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 20% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 15% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 10% w/w of Form 1 of the compound represented by Formula (I). In some embodiments, the compound represented by Formula (I) in step (i) comprises less than about 5% w/w of Form 1 of the compound represented by Formula (I).

[000109] In some embodiments, the process further comprises:

(i) contacting a compound represented by Formula (C):



Formula (C),

with an aqueous solution comprising an acid to produce a first solid precipitate;

(ii) isolating the first solid precipitate;

(iii) contacting the first solid precipitate with a first solvent to form a first mixture;

(iv) contacting the first mixture with an acid to form a second mixture;

(v) contacting the second mixture with a second solvent to form a third mixture;

(vi) contacting the third mixture with activated charcoal to form a fourth mixture;

(vii) filtering the fourth mixture to isolate a filtrate;

(viii) contacting the filtrate with a third solvent to form a fifth mixture;

(ix) charging the fifth mixture with seed material of crystalline Form 1 of the compound represented by Formula (I) to form a charged mixture;

(x) further charging the charged mixture with a fourth solvent to produce a solid precipitate; and

(xi) isolating the solid precipitate,

thereby preparing a compound represented by Formula (I).

[000110] In some embodiments, in step (i), the acid is hydrochloric acid.

[000111] In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 5 °C to about 55 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 10 °C to about 50 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 5 °C to about 25 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 35 °C to about 55 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 15 °C to about 35 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 10 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 15 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 20 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 25 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 30 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 35 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 40 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 45 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 50 °C.

[000112] In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 5 °C to about 35 °C, then at about 35 °C to about 55 °C; then about 15 °C to about 35 °C. In some embodiments, in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 10 °C to about 30 °C, then at about 40 °C to about 50 °C; then about 20 °C to about 30 °C.

[000113] In some embodiments, after step (ii), the process further comprises washing the first solid precipitate with water.

[000114] In some embodiments, wherein the first solvent is 2-methyltetrahydrofuran.

[000115] In some embodiments, wherein the acid in step (iv) is hydrochloric acid.

[000116] In some embodiments, in step (iv), wherein the second mixture comprises an organic layer and an aqueous layer, and the process further comprises separating the organic layer from the aqueous layer, and optionally adding aqueous hydrochloric acid to the separated organic layer, separating the resulting organic layer from the aqueous layer, and reducing the volume of said organic layer.

[000117] In some embodiments, the second solvent is ethanol.

[000118] In some embodiments, the third solvent is water.

[000119] In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 15 °C to about 70 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 25 °C to about 60 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 15 °C to about 35 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 50 °C to about 70 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 15 °C to about 35 °C then at about 50 °C to about 70 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 20 °C to about 30 °C then at about 55 °C to about 65 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 20 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 25 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 30 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 35 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating

the filtrate and the third solvent at about 40 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 45 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 50 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 55 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 60 °C. In some embodiments, in step (viii), wherein the contacting comprises agitating the filtrate and the third solvent at about 65 °C.

[000120] In some embodiments, after step (viii), the process further comprises adding additional volume of third solvent. In some embodiments, the third solvent is water.

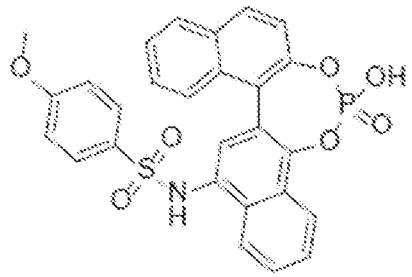
[000121] In some embodiments, the fourth solvent is water.

[000122] In some embodiments, after step (xi), the process further comprises drying the solid precipitate.

[000123] In some embodiments, the solid precipitate is crystalline Form 21 of the compound represented by Formula (I).

[000124] In some embodiments, the process further comprises:

(i) contacting a compound represented by Formula (B):



Formula (B)

with an aqueous solution comprising a base to form a first mixture;

(ii) contacting the first mixture with an acid and a solvent to form a second mixture;

(iii) contacting the second mixture with pyridine to produce a solid precipitate; and

(iv) isolating the solid precipitate,

thereby preparing the compound represented by Formula (C).

[000125] In some embodiments, the base is lithium hydroxide.

[000126] In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about

65 °C to about 85 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 70 °C to about 80 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 65 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 70 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 75 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 80 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 85 °C.

[000127] In some embodiments, the acid is hydrochloric acid.

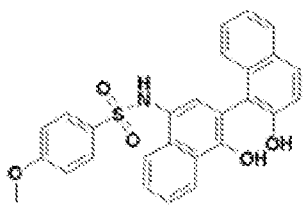
[000128] In some embodiments, the solvent is 2-methyltetrahydrofuran.

[000129] In some embodiments, in step (ii), the second mixture comprises an organic layer and an aqueous layer, and the process further comprises separating the organic layer from the aqueous layer, and reducing the volume of said organic layer.

[000130] In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 60 °C to about 80 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 65 °C to about 75 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 60 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 65 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 70 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 75 °C. In some embodiments, the contacting in step (iii) comprises agitating the second mixture and pyridine at about 80 °C.

[000131] In some embodiments, the process further comprises:

(i) contacting a compound of Formula (A):



Formula (A)

in a solvent with phosphorus oxychloride to form a first mixture;

(ii) contacting the first mixture with water and an acid to form a solid precipitate; and

(iii) isolating the solid precipitate,

thereby preparing the compound represented by Formula (B).

[000132] In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about -5 °C to about 35 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 0 °C to about 25 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 0 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 5 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 10 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 15 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 20 °C. In some embodiments, the contacting in step (i) comprises agitating the compound represented by Formula (A) in the solvent with phosphorous oxychloride at about 25 °C.

[000133] In some embodiments, the solvent is pyridine.

[000134] In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 15 °C to about 75 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 25 °C to about 65 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 20 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 25 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 35 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 40 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 45 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an

acid at about 50 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 55 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 60 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 65 °C. In some embodiments, the contacting step (ii) comprises agitating the first mixture with water and an acid at about 70 °C.

[000135] In some embodiments, the acid is hydrochloric acid.

[000136] Provided herein, in some embodiments, are crystalline Form 1 of the compound represented by Formula (I), prepared according to the processes described herein.

Form 2

[000137] Provided herein, in some embodiments, is crystalline Form 2 of a compound represented by Formula (I).

[000138] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 18A. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 18B.

[000139] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

[000140] In some embodiments, the crystalline Form 2 is a solvate. In some embodiments, the crystalline Form 2 is a THF solvate.

Form 3

[000141] Provided herein, in some embodiments, is crystalline Form 3 of a compound represented by Formula (I).

[000142] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 19A. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 19B.

[000143] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 4

[000144] Provided herein, in some embodiments, is crystalline Form 4 of a compound represented by Formula (I).

[000145] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 20. In some embodiments, the crystalline form has an XRPD pattern substantially as shown in Table 1C.

[000146] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 7.4°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 3.7°, 11.5°, 12.0°, 16.7°, or 19.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 8.3°, 18.6°, 19.5°, 20.1°, 20.7°, 21.8°, 24.4°, 25.2°, or 25.7°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 10.5°, 12.3°, 12.7°, 14.9°, 15.9°, or 20.3°.

[000147] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 7.4°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 3.7°±0.2°, 11.5°±0.2°, 12.0°±0.2°, 16.7°, or 19.2°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 8.3°±0.2°, 18.6°±0.2°, 19.5°±0.2°, 20.1°±0.2°, 20.7°±0.2°, 21.8°±0.2°, 24.4°±0.2°, 25.2°±0.2°, or 25.7°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 10.5°±0.2°, 12.3°±0.2°, 12.7°±0.2°, 14.9°±0.2°, 15.9°±0.2°, or 20.3°±0.2°.

[000148] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 5

[000149] Provided herein, in some embodiments, is crystalline Form 5 of a compound represented by Formula (I).

[000150] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 21A. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 21B.

[000151] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 6

[000152] Provided herein, in some embodiments, is crystalline Form 6 of a compound represented by Formula (I).

[000153] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 22A. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 22B.

[000154] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 7

[000155] Provided herein, in some embodiments, is crystalline Form 7 of a compound represented by Formula (I).

[000156] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 23.

[000157] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 8

[000158] Provided herein, in some embodiments, is crystalline Form 8 of a compound represented by Formula (I).

[000159] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 24A. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 24B.

[000160] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 9

[000161] Provided herein, in some embodiments, is crystalline Form 9 of a compound represented by Formula (I).

[000162] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 25A. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 25B.

[000163] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula

(I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 10

[000164] Provided herein, in some embodiments, is crystalline Form 10 of a compound represented by Formula (I).

[000165] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 26A. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 26B.

[000166] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 11

[000167] Provided herein, in some embodiments, is crystalline Form 11 of a compound represented by Formula (I).

[000168] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 27A. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 27B.

[000169] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the

compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 12

[000170] Provided herein, in some embodiments, is crystalline Form 12 of a compound represented by Formula (I).

[000171] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 28A. In some embodiments, the crystalline form has a DSC thermogram substantially as shown in FIG. 28B.

[000172] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 13

[000173] Provided herein, in some embodiments, is crystalline Form 13 of a compound represented by Formula (I).

[000174] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 29.

[000175] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments,

the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 14

[000176] Provided herein, in some embodiments, is crystalline Form 14 of a compound represented by Formula (I).

[000177] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 30.

[000178] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 15

[000179] Provided herein, in some embodiments, is crystalline Form 15 of a compound represented by Formula (I).

[000180] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 31.

[000181] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments,

the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Form 21

[000182] Provided herein, in some embodiments, is crystalline Form 21 of a compound represented by Formula (I).

[000183] In some embodiments, the crystalline form has an XRPD pattern substantially as shown in FIG. 2B. In some embodiments, the crystalline form has an XRPD pattern substantially as shown in Table 1B.

[000184] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 9.6°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 8.5°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at about 20.8°. In some embodiments, the crystalline form has an XRPD pattern comprising one or more peaks, in terms of 2-theta, at about 8.5°, about 9.6°, or about 20.8°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 12.6°, about 14.5°, or about 22.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at about 9.9°, about 14.2°, about 16.4°, about 17.0°, about 17.5°, about 25.0°, or about 27.1°. In some embodiments, the XPRD pattern further comprises one or more peaks at about 11.8°, about 14.9°, about 18.7°, or about 26.9°.

[000185] In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 9.6°±0.2°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 8.5°±0.2°. In some embodiments, the crystalline form has an XRPD pattern comprising peaks, in terms of 2-theta, at 20.8°±0.2°. In some embodiments, the crystalline form has an XRPD pattern comprising one or more peaks, in terms of 2-theta, at 8.5°±0.2°, 9.6°±0.2°, or 20.8°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 12.6°±0.2°, 14.5°±0.2°, or 22.2°±0.2°. In some embodiments, the XRPD pattern further comprises one or more peaks at 9.9°±0.2°, 14.2°±0.2°, 16.4°±0.2°, 17.0°±0.2°, 17.5°±0.2°, 25.0°±0.2°, or 27.1°±0.2°. In some embodiments, the XPRD pattern further comprises one or more peaks at 11.8°±0.2°, 14.9°±0.2°, 18.7°±0.2°, or 26.9°±0.2°.

[000186] In some embodiments, the crystalline form is substantially pure. In some embodiments, the crystalline form has a chemical purity of greater than 80% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 90% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 95% by weight. In some embodiments, the crystalline form has a chemical purity of greater than 99% by weight. In some embodiments, the crystalline form has no more than about 10 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I). In some embodiments, the crystalline form has no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).

Pharmaceutical Compositions, Administration, and Dosages

[000187] In some embodiments, provided herein are pharmaceutical compositions comprising a solid-state form of a compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or a solvate thereof, and a pharmaceutically acceptable carrier.

[000188] This disclosure therefore provides pharmaceutical compositions that contain, as the active ingredient, one or more solid-state forms of the compound represented by Formula (I), as free acid or base, or a pharmaceutically acceptable salt or a solvate thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. The pharmaceutical compositions is administered alone or in combination with other therapeutic agents. Such compositions are prepared in a manner well known in the pharmaceutical art (see, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G. S. Banker & C. T. Rhodes, Eds.).

[000189] The pharmaceutical compositions are administered in either single or multiple doses by any of the accepted modes of administration of agents, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

[000190] One mode for administration is parenteral, particularly by injection. The forms in which the novel compositions of the present disclosure are incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. Aqueous solutions in saline are also conventionally used for injection, but less preferred in the context of the present disclosure. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[000191] Sterile injectable solutions are prepared by incorporating a solid-state form of a compound according to the present disclosure in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[000192] Oral administration is another route for administration of the solid-state forms of a compound represented by Formula (I) in accordance with the disclosure. Administration may be via capsule or enteric coated tablets, or the like. In making the pharmaceutical compositions that include at least one a solid-state form of a compound described herein, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[000193] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[000194] The solid-state forms of the disclosure can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Another formulation for use in the methods of the present disclosure employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present disclosure in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[000195] The compositions are preferably formulated in a unit dosage form. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient (e.g., a tablet, capsule, ampoule). The solid-state forms of the disclosure are generally administered in a pharmaceutically effective amount. Preferably, for oral administration, each dosage unit contains from 1 mg to 2 g of a solid-state form of a compound described herein, and for parenteral administration, preferably from 0.1 to 1000 mg of a solid-state form of a compound described herein. It will be understood, however, that the amount of the solid-state form of a compound actually administered usually will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[000196] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation

composition containing a homogeneous mixture of a compound of the present disclosure. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[000197] The tablets or pills of the present disclosure, in some embodiments, is coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[000198] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[000199] In some embodiments, compositions comprising a solid-state form of a compound represented by Formula (I) are administered to the subject as oral dosage forms. In some embodiments, the oral dosage form is in the form of a tablet. In some embodiments, the oral dosage form is in the form of a capsule.

[000200] The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics"). Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular subject will depend upon a variety of factors, including the activity of the specific compound

employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the subject's disposition to the disease, condition or symptoms, and the judgment of the treating physician. A course of therapy can comprise one or more separate administrations of a compound as described herein.

Methods of Use

[000201] Solid-state forms and compositions described herein are utilized in methods for treating, preventing, or reducing the risk or severity of a disease or disorder mediated by STAT3, or a disease or disorder that is otherwise treatable with a STAT3 inhibitor. For example, the compounds and compositions are useful for treating, preventing, or reducing the risk or severity of certain diseases or disorders characterized by excessive STAT3 protein expression. Such diseases and disorders include, for example, certain cancers, fibrosis, and inflammatory diseases or disorders.

[000202] In some embodiments, the methods involve the use of (e.g., comprise the administration of) a solid-state form of a compound of formula (I), a STAT3 inhibitor, wherein the solid-state form of the compound of formula (I), as free acid or base, or a pharmaceutically acceptable salt or solvate thereof, is formulated in a manner described herein (e.g., is present in a composition as described herein). In specific embodiments, provided herein are methods of treating, preventing, or reducing the risk or severity of cancer. In other specific embodiments, provided herein are methods of treating, preventing, or reducing the risk or severity of fibrosis. In still other specific embodiments, provided herein are methods of treating, preventing, or reducing the risk or severity of an inflammatory disease or disorder.

[000203] Signal transducer and activator of transcription 3 (STAT3) is central in regulating the anti-tumor immune response. STAT3 is broadly hyperactivated both in cancer and non-cancerous cells within the tumor ecosystem and plays important roles in inhibiting the expression of crucial immune activation regulators and promoting the production of immunosuppressive factors. Methods provided herein are contemplated as being useful for the treatment of a cancer, including for example, solid tumors, soft tissue tumors, and metastases thereof.

[000204] Provided in some embodiments herein are methods of treating, preventing, or reducing the risk or severity of a cancer in an individual in need thereof, the method comprising administering to the individual a solid-state form of a compound or a composition

described herein. In some embodiments, the cancer treated according to a method provided herein is a liver cancer, lung cancer, head and neck cancer, breast cancer, skin cancer, kidney cancer, testicular cancer, colon cancer, rectal cancer, gastric cancer, skin cancer, metastatic melanoma, prostate cancer, ovarian cancer, cervical cancer, bone cancer, spleen cancer, gall bladder cancer, brain cancer, pancreatic cancer, stomach cancer, anal cancer, prostate cancer, multiple myeloma, post-transplant lymphoproliferative disease, restenosis, myelodysplastic syndrome, leukemia, lymphoma, or acute myelogenous leukemia. In some embodiments, a cancer treated according to a method provided herein is a liver cancer, lung cancer, liver carcinoma, hepatocellular carcinoma, head and neck squamous cell carcinoma, non-small cell lung cancer, or estrogen receptor-positive breast cancer. In some embodiments, a cancer treated according to a method provided herein is head and neck cancer, lung cancer, liver cancer, breast cancer, ovarian cancer, colon cancer, multiple myeloma, leukemia, or pancreatic cancer. In some embodiments, the leukemia is acute myelogenous leukemia.

[000205] Moreover, STAT3 is essential for Th17 lymphocyte development and cytokine production, and its activation has been linked to the development of airway inflammation. Upon activation, STAT3 is recruited to cytokine-activated receptor complexes and becomes phosphorylated at Tyr (Y) 705. Phosphotyrosylated (p) STAT3 homodimerizes through reciprocal SH2-pY705 interactions, translocates to the nucleus, and binds to promoters to transcriptionally activate genes that drive Th17 differentiation and production of multiple cytokines. STAT3 activation also is involved in Th2 cytokine production, making it an attractive target for asthma treatment. In addition, several genes have been implicated as risk factors for inflammatory bowel disease (IBD) in genome-wide association studies (GWAS), including *ATG16L, NOD2/CARD15, IBD5, CTLA4, TNFSF15, JAK2, STAT3, IL23R,* and *ORMDL3*, which implicate antimicrobial peptides, innate and adaptive immune cell function, Th17 cells, regulatory T cells (Tregs), and cytokines (tumor necrosis factor, interleukins 17, 23, 12, 22, and IL-6). Many of these cytokines serve as ligands for cell surface receptors that activate STAT3. STAT3 within three cell lineages—myeloid cells, enterocytes, and T cells—has been demonstrated to contribute to colitis in mice and humans. Thus, targeting STAT3 may represent an effective means of treating, preventing, or reducing the risk or severity of inflammatory disease/disorder.

[000206] Provided in some embodiments herein are methods of treating, preventing, or reducing the risk or severity of an inflammatory disease or disorder in an individual in need thereof, the method comprising administering to the individual a solid-state form of a compound or a composition described herein. In some embodiments, the inflammatory

disease/disorder treated herein is inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, asthma, anaphylaxis, cancer cachexia, chronic kidney disease cachexia, nonalcoholic steatohepatitis (NASH), psoriasis, uveitis, scleritis, multiple sclerosis, or pancreatitis. In some embodiments, inflammation treated herein is inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, asthma, anaphylaxis, cancer cachexia, chronic kidney disease cachexia, or nonalcoholic steatohepatitis (NASH). In some embodiments, the anaphylaxis comprises anaphylactic shock.

[000207] Fibrosis is a pathological process involving the accumulation of excessive extra-cellular matrix in tissues, leading to tissue damage and organ dysfunction, which can progress to organ failure and death. In systemic sclerosis, an idiopathic fibrosis disease, the trigger is postulated to be an autoimmune response that leads to tissue injury, production of growth factors, pro-inflammatory and pro-fibrotic cytokines, and accumulation of myofibroblasts. Two potential sources of myofibroblasts are the differentiation of local fibroblasts and the process of epithelial-to-mesenchymal transition (EMT). IL-6 is a proinflammatory and profibrotic cytokine increasingly recognized as an important mediator of fibrosis that may contribute to the accumulation of myofibroblasts. After engaging its receptor, IL-6 signals through the STAT3. Thus, STAT3 represents a potentially important protein to target to treat fibrosis.

[000208] Provided in some embodiments herein are methods of treating, preventing, or reducing the risk or severity of fibrosis in an individual in need thereof, the method comprising administering to the individual a solid-state form of a compound or a composition described herein. In some embodiments, the fibrosis is associated with a disorder or disease such as skin fibrosis (or dermal fibrosis), cardiac fibrosis, cirrhosis, pulmonary fibrosis, bone marrow fibrosis, intestine fibrosis, pancreatic fibrosis, joint fibrosis, liver fibrosis, retroperitoneum, renal fibrosis, myelofibrosis, non-alcoholic fatty liver disease, steatohepatitis, systemic sclerosis (including diffuse systemic sclerosis or limited systemic sclerosis), endomyocardial fibrosis, myocardial infarction, atrial fibrosis, mediastinal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, Keloid, arthrofibrosis, adhesive capsulitis, or cystic fibrosis. In some embodiments, the fibrosis is associated with skin fibrosis (scleroderma), cardiac fibrosis, cirrhosis, pulmonary fibrosis, bone marrow fibrosis, intestine fibrosis, pancreatic fibrosis, joint fibrosis, liver fibrosis, retroperitoneum, myelofibrosis, non-alcoholic fatty liver disease, steatohepatitis, or systemic sclerosis. In some embodiments, the fibrosis is associated with skin fibrosis (scleroderma), cardiac fibrosis, cirrhosis, or pulmonary fibrosis.

[000209] In some embodiments, the fibrosis is associated with exposure to certain drugs such as chemotherapy, fibrosis following exposure to environmental or other toxins or allergens, fibrosis occurring after an ischemia/reperfusion injury such as myocardial infarction or hypotension, fibrosis occurring after radiation, fibrosis following hepatitis induced by alcohol, toxins, drugs or infections, primary biliary cirrhosis, fibrosis following viral infections involving the heart, liver, or lung, and/or idiopathic retroperitoneal fibrosis.

[000210] Muscle wasting is a debilitating complication of catabolic conditions including chronic kidney disease (CKD), diabetes, cancer, or serious infections. For example, in mice with CKD, inhibition of myostatin reduced circulating levels of IL-6 and TNFα, suggesting a link between inflammation and muscle wasting as reported in clinical studies. STAT3 was found to be activated by the IL-6 family of cytokines, thus suggesting that the STAT3 pathway is linked to loss of muscle mass.

[000211] Provided in some embodiments herein are methods of treating, preventing, or reducing the risk or severity of a muscle wasting disease/disorder, muscle weakness disease/disorder, or cachexia in an individual in need thereof, the method comprising administering to the individual a solid-state form of a compound or a composition described herein. The muscle weakness and/or muscle wasting and/or cachexia may have an unknown cause or it may be associated with an underlying condition. The underlying condition may be a catabolic condition. In some embodiments, the underlying medical condition associated with cachexia is least renal disease or failure, cancer, AIDS, HIV infection, chronic obstructive lung disease (including emphysema), multiple sclerosis, congestive heart failure, tuberculosis, familial amyloid polyneuropathy, acrodynia, hormonal deficiency, metabolic acidosis, infectious disease, chronic pancreatitis, autoimmune disorder, celiac disease, Crohn's disease, electrolyte imbalance, Addison's disease, sepsis, burns, trauma, fever, long bone fracture, hyperthyroidism, prolonged steroid therapy, surgery, bone marrow transplant, atypical pneumonia, brucellosis, endocarditis, Hepatitis B, lung abscess, mastocytosis, paraneoplastic syndrome, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, myositis, polymyositis, dermatomyositis, rheumatological diseases, autoimmune disease, collagen-vascular disease, visceral leishmaniasis, prolonged bed rest, and/or addiction to drugs, such as amphetamine, opiates, or barbiturates.

[000212] In addition, STAT3 signaling has been implicated in gap junction intercellular communication, IL-6- and IL11-induced vascular leakage, down-regulation of VE-cadherin concomitant with phosphorylation of STAT3, and the STAT3/mir17-92/E2F1 dependent

regulation of β-catenin nuclear translocation and transcriptional activity. Thus, STAT3 inhibition is useful to reduce vascular permeability in the setting of anaphylaxis.

[000213] Provided in some embodiments herein are methods of treating, preventing, or reducing the risk or severity of an allergic reaction in an individual in need thereof, the method comprising administering to the individual a solid-state form of a compound or a composition described herein. In some embodiments, the allergic reaction is induced following an exposure to an allergen. In some embodiments, the allergen is a food allergen (such as milk, legumes, shellfish, tree nuts, eggs, fish, soy, and wheat), an environmental allergen or seasonal allergen (such as pollen or mold), a venom allergen (such as from wasp, bee, ant, hornet, yellow jacket, or asp), a medication allergen (such as anesthetics, β-lactam antibiotics, aspirin, non-steroidal anti-inflammatory drug, chemotherapy, vaccine, protamine, or herbal preparations), or latex. In some embodiments, the allergic reaction is anaphylaxis, anaphylactic shock, allergic rhinitis, urticaria, food allergy, drug allergy, hymenoptera allerga, bronchial constriction, asthma, or eczema.

[000214] STAT3 also plays an important role in viral infection and pathogenesis. Provided in some embodiments herein are methods of treating, preventing, or reducing the risk or severity of a viral infection in an individual in need thereof, the method comprising administering to the individual a solid-state form of a compound or a composition described herein. In some embodiments, the viral infection is a chronic viral infection. In some embodiments, the chronic viral infection is AIDS, HIV infection, Hepatitis B infection, Hepatitis C virus infection, or Epstein-Barr virus infection.

[000215] In addition, reactive astrocytes in neurodegenerative diseases including Alzheimer's disease are implicated in STAT3 phosphorylation. Pathophysiological roles of astrocytes in the reactive state are thought to have important significance in the pathogenesis of neurodegenerative diseases. Provided in some embodiments herein are methods of treating, preventing, or reducing the risk or severity of a neurodegenerative disease in an individual in need thereof, the method comprising administering to the individual a solid-state form of a compound or a composition described herein. In some embodiments, the neurodegenerative disease is chemotherapy-induced peripheral neuropathy, diabetic neuropathy, or chemobrain. Provided in some embodiments herein are methods of treating, preventing, or reducing the risk or severity of pain in an individual in need thereof, the method comprising administering to the individual a solid-state form of a compound or a composition described herein. In some embodiments, pain is neuropathic pain. Provided in

some embodiments herein are methods of treating, preventing, or reducing the risk or severity of graft-versus-host diseases, pulmonary lymphangioleiomyomatosis, chagasic cardiomyopathy, age-related macular degeneration, amyloidosis, astrogliosis in Alzheimer's or other neurodegenerative diseases, or familial amyloid polyneuropathy.

[000216] STAT3 is involved in cytokine- and nutrient-induced insulin resistance, and excessive STAT3 signaling is implicated in the development of insulin resistance such as skeletal muscle insulin resistance in type 2 diabetes. Provided in some embodiments herein are methods of treating, preventing, or reducing the risk or severity of insulin resistance in an individual in need thereof, the method comprising administering to the individual a solid-state form of a compound or a composition described herein. In some embodiments, the insulin resistance is a result of an underlying condition. In some embodiments, the insulin resistance is associated with muscle of the individual being treated. In some embodiments, the insulin resistance is caused by any reason for the individual, such as elevated free fatty acids in the blood, obesity, being overweight, having visceral fat, having a high fructose intake, having inflammation, being inactive, dysbiosis of the gut microbiota, and/or being genetically predisposed. In some embodiments, any method provided herein is a method of treating, preventing, or reducing the risk or severity of medical conditions associated with insulin resistance or that are complications of insulin resistance at least in part, such as severe high blood sugar; severe low blood sugar; heart attack; stroke; kidney disease (including chronic, for example, chronic kidney disease (CKD)); eye problems; cancer; non-alcoholic fatty liver disease (NAFLD); polycystic ovarian syndrome (PCOS); metabolic syndrome; diabetes; or Alzheimer's disease, for example. In some embodiments, the insulin resistance is a hallmark of metabolic syndrome and type 2 diabetes. Metabolic syndrome is a group of risk factors associated with type 2 diabetes and heart disease. Its symptoms include high blood triglycerides, blood pressure, belly fat, and blood sugar, as well as low HDL (good) cholesterol levels.

[000217] In some embodiments, the methods comprise administering a therapeutically effective amount of a composition disclosed herein to the individual. In some embodiments, the method comprises administering at least 1 mg/kg/day of one or more solid-state forms of the compound of formula (I) to the individual. In some embodiments, the method comprises administering at least 10 mg/kg/day of one or more solid-state forms of the compound of formula (I) to the individual. In some embodiments, the method comprises administering at least 20 mg/kg/day of one or more solid-state forms of the compound of formula (I) to the

individual. In some embodiments, the method comprises administering at least 25 mg/kg/day of one or more solid-state forms of the compound of formula (I) to the individual.

EXAMPLES

Instrumental Analysis

X-ray Powder Diffraction (XRPD)

[000218] XRPD analysis was carried out on a PANalytical X'pert Pro® with PIXcel® detector (128 channels), scanning the samples between 3 and 35° 2θ. The material was gently ground to release any agglomerates and loaded onto a multi-well plate with Mylar polymer film to support the sample. The multi-well plate was then placed into the diffractometer and analyzed using Cu K radiation (α1 λ = 1.54060 Å; α2 = 1.54443 Å; β = 1.39225 Å; α1: α2 ratio = 0.5) running in transmission mode (step size 0.0130° 2θ, step time 18.87s) using 40 kV / 40 mA generator settings.

Polarized Light Microscopy (PLM)

[000219] The presence of crystallinity (birefringence) was determined using an Olympus® BX53 microscope, equipped with cross-polarizing lenses and a Motic® camera. All images were recorded using the 20x objective, unless otherwise stated.

Nuclear Magnetic Resonance (NMR)

[000220] NMR experiments were performed on a Bruker® AVIIIHD spectrometer equipped with a DCH cryoprobe operating at 500.12MHz for protons. Experiments were performed in deuterated dimethyl sulfoxide (DMSO) and each sample was prepared to approximately 10 mM concentration. Spectra were referenced against the solvent peak were analyzed using the Topspin® software package.

Thermogravimetric Analysis/ Differential Scanning Calorimetry (TGA/DSC)

[000221] Approximately, 5-10 mg of material was added into a pre-tared open aluminum pan and loaded i–to a TA Instruments® Discovery SDT 650 Auto - Simultaneous DSC and held at room temperature. The sample was then heated at a rate of 10 °C/min from 30 °C to 400 °C during which time the change in sample weight was recorded along with the heat flow response (DSC). Nitrogen was used as the sample purge gas, at a flow rate of 200 cm^3/min.

Differential Scanning Calorimetry (DSC)

[000222] Approximately, 1-5 mg of material was weighed into an aluminum DSC pan and sealed nonhermetically with an aluminum lid. The sample pan was then loaded into a TA Instruments® Discovery DSC 2500 differential scanning calorimeter equipped with a RC90

cooler. The sample and reference were heated to 170 °C at a scan rate of 10°C/min and the resulting heat flow response monitored. The sample was re-cooled to 20°C and then reheated again to 170 °C all at 10 °C/min. Nitrogen was used as the purge gas, at a flow rate of 50 cm^3/min.

Karl Fischer Coulometric Titration (KF)

[000223] Approximately 10-15 mg of solid material was accurately weighed into a vial. The solid was then manually introduced into the titration cell of a Mettler Toledo C30 Compact Titrator®. The vial was back weighed after the addition of the solid and the weight of the added solid entered on the instrument. Titration was initiated once the sample had fully dissolved in the cell. The water content was calculated automatically by the instrument as a percentage and the data printed.

Infrared Spectroscopy (IR)

[000224] Infrared spectroscopy was carried out on a Bruker® ALPHA P spectrometer. Sufficient material was placed onto the center of the plate of the spectrometer and the spectra were obtained using the following parameters: Resolution: 4 cm-1; Background Scan Time: 16 scans; Sample Scan Time: 16 scans; Data Collection: 4000 to 400 cm-1; Result Spectrum: Transmittance; Software: OPUS version 6

Dynamic Vapor Sorption (DVS)

[000225] Approximately, 10-20 mg of sample was placed into a mesh vapor sorption balance pan and loaded into a DVS Advantage dynamic vapor sorption balance by Surface Measurement Systems. The sample was subjected to a ramping profile from 40 – 90% relative humidity (RH) at 10% increments, maintaining the sample at each step until a stable weight had been achieved (dm/dt 0.004%, minimum step length 30 minutes, maximum step length 500 minutes) at 25°C. After completion of the sorption cycle, the sample was dried using the same procedure to 0% RH and then a second sorption cycle back to 40% RH. Two cycles were performed. The weight change during the sorption/desorption cycles were plotted, allowing for the hygroscopic nature of the sample to be determined. XRPD analysis was then carried out on any solid retained.

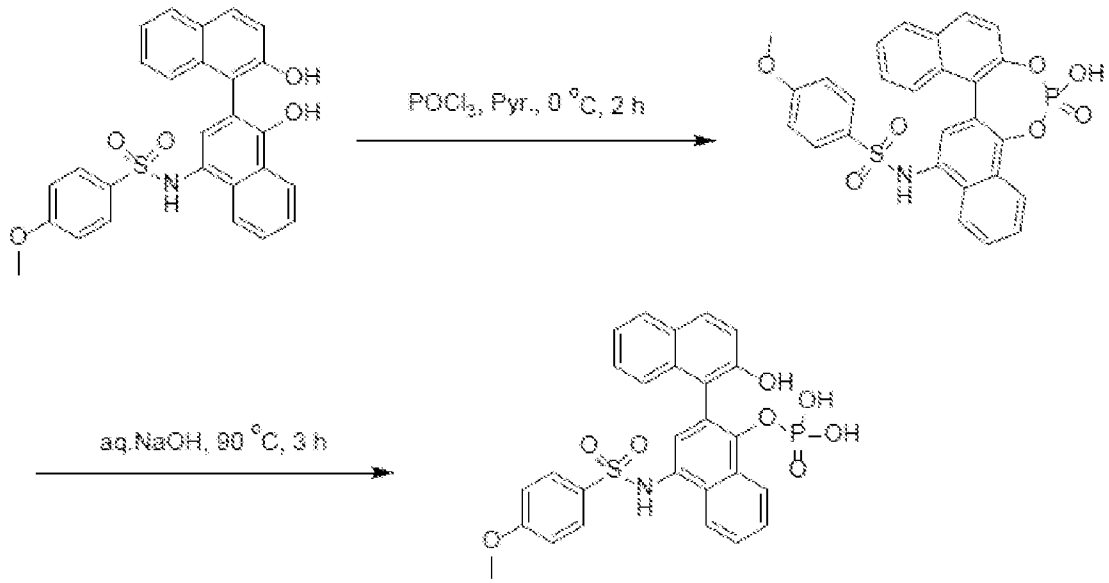
High Performance Liquid Chromatography-Ultraviolet Detection (HPLC-UV)

[000226] HPLC-UV conditions were as follows: Column Cortecs® UPLC C18 1.6μm 2.1 x 100 mm; Column Temperature (°C) 40; Flow Rate (mL/min) 0.35; Column Pressure at start of Run (Bar) 660; Injection Volume (μL) 2; Autosampler Temperature (°C) Ambient; Detection parameters 220 nm; Mobile Phase A 0.2% trifluoroacetic acid (TFA) in water; Mobile Phase B 0.2% TFA in acetonitrile (ACN); Diluent 50:50 ACN: Water

Variable temperature X-ray powder diffraction (VT-XRPD)

[000227] VT-XRPD analysis was carried out on a Philips X'Pert Pro Multipurpose® diffractometer equipped with a temperature chamber. The samples were scanned between 4 and 35.99 °2θ using Cu K radiation (α1 λ = 1.54060 Å; α2 = 1.54443 Å; β = 1.39225 Å; α1 : α2 ratio = 0.5) running in Bragg-Brentano geometry (step size 0.008 °2θ) using 40 kV / 40 mA generator–settings. Measurements were performed at 30 - 205°C.

Example 1. Exemplary process of preparing an amorphous form of a compound represented by Formula (I)



Preparation of N-((6)-6-hydroxy-6-oxidodinaphtho[1,2-d:1',2'-f][1,3,2]dioxaphosphepin-15-yl)-4- methoxybenzenesulfonamide.

[000228] To a solution of *N*-(1',2-dihydroxy-[1,2'-binaphthalen]-4'-yl)-4-methoxybenzenesulfonamide (TTI-101) (3.0 g, 6.36 mmol, 1.0 eq) in pyridine (30 mL) at 0°C was added $POCl_3$ (975 mg, 6.36 mmol, 591 µL, 1.0 eq). The resulting reaction mixture was stirred at 0°C for 2 hours. The reaction was poured into ice water, and the pH was adjusted to pH of about 8 with 1N NaOH. The solution was concentrated under reduced pressure to give a residue. The residue was purified by preparative reverse-phase HPLC to afford the product as a solid. The solid was added into ethanol (EtOH)/acetone (324 mL, 1:5). The resulting slurry was heated to 50 °C for 30 minutes, during which time the solid dissolved to afford a clear solution. The solution was then cooled to 0 °C and stirred for 2 hours, during which time a precipitate formed. The resulting suspension was filtered to collect the solid. The solid was then dried under high vacuum to afford the title compound (578 mg,

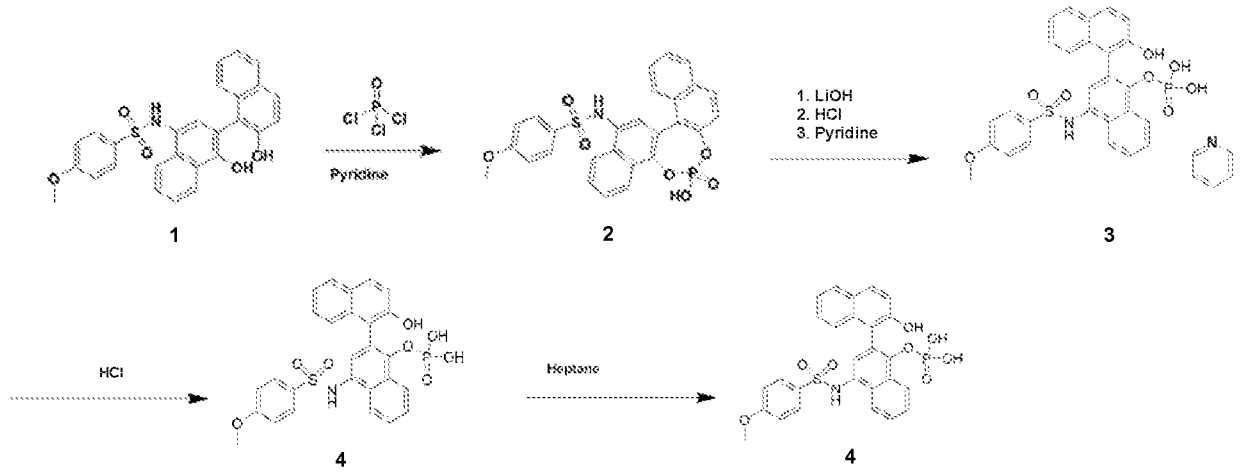
19% yield) as a solid. ^{1}H NMR: (400MHz, Methanol-d4) δ = 10.16 (s, br, 1H), 8.27 (d, 1H), 8.19 (d, 1H), 8.01 (dd, 2H), 7.74 (d, 2H), 7.59 (m, 3H), 7.50 (m, 1H), 7.34-7.24 (m, 4H), 7.16 (s, br, 1H), 7.08 (d, 2H), 3.81 (s, 3H); LCMS calculated for C27H20NO7PS: m/z = 533; found: m/z = 532 (M-H).

Preparation of 2-hydroxy-4'-((4-methoxyphenyl)sulfonamido)-[1,2'-binaphthalen]-1'-yl dihydrogen phosphate.

[000229] A solution of *N*-((6)-6-hydroxy-6-oxidodinaphtho[1,2-d:1',2'-f][1,3,2]dioxaphosphepin-15-yl)-4- methoxybenzenesulfonamide (2 g, 3.75 mmol, 1.0 eq) in NaOH (1 M, 11.25 mL, 3.0 eq) was heated to 80°C with stirring for 3 hours. The reaction mixture was then concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC to afford 650 mg of the product. The product was added into EtOH/isopropanol (*i*-PrOH) (5 mL, 1:3). The resulting slurry was stirred and heated to 50 °C for 30 minutes, during which time the solid dissolved completely to form a clear solution. The solution was then cooled to 0 °C and stirred for 2 hours, during which time a precipitate formed. The resulting suspension was filtered to collect the solid. The solid was then dried under high vacuum to afford the title compound (160 mg, 22% yield) as a solid. ^{1}H NMR: (400MHz, Methanol-d4) δ = 8.62 (d, 1H), 8.19 (d, 1H), 7.79 (d, 1H), 7.74 (d, 1H), 7.49 (m, 4H), 7.24 (m, 2H), 7.11 (d, 1H), 6.77 (d, 2H), 6.59 (d, 1H), 6.40 (s, 1H), 3.62 (m, 3H). LCMS calculated for C27H22NO8PS: m/z = 551, found: m/z = 552 (M+H). The title compound was amorphous as determined by characterization methods, such as XRPD.

[000230] Amorphous form of the compound represented by Formula (I) was also prepared from the fast evaporation of a clear solution of Form 1 (see Example 2) in ethyl acetate. Approximately 400 mg of Form 1 was fully dissolved in about 30 mL of warm ethyl acetate to yield a clear solution. The ethyl acetate was distilled using a rotary evaporator under reduced atmosphere with the bath set at about 30-40 °C. The resulting solid was analyzed by XRPD, which indicated the resulting solid was amorphous (**FIG. 1**).

Example 2A. Exemplary process of preparing Form 1 of a compound represented by Formula (I)



Preparation of Compound 2:

[000231] A mixture of Compound 1 (15 kg) and pyridine (45 L) in a vessel was agitated at about 0 °C. Phosphorus oxychloride (5 kg) was added to the mixture while maintaining a temperature of about 0 °C during the addition. The temperature was adjusted to about 25 °C and the mixture was agitated for at least 1 hour (e.g., at least 2 hours). Water (22.5 L) was added to the mixture and the mixture was agitated at about 25 °C for at least 1 hour (e.g., at least 6 hours). The mixture was transferred to a second vessel containing hydrochloric acid (36%; 135 L). Pyridine and water (1:1) were added to the first vessel to rinse the vessel then the rinse was transferred to the second vessel. The combined mixture was agitated at about 65 °C for at least 1 hour (e.g., at least 2 hours). The temperature was adjusted to about 25 °C. Resulting solid was collected by filtration and the filter cake was washed with water. The solid was dried under a nitrogen stream and at about 50 °C under reduced pressure.

Preparation of Compound 3:

[000232] A mixture of Compound 2 (17 kg) in an aqueous solution of lithium hydroxide (3N; 86 L) was agitated in a vessel at about 75 °C for at least 1 hour (e.g., at least 5 hours). The temperature was adjusted to about 25 °C. 2-MethylTHF (255 L) and hydrochloric acid (36%; 23 L) were added to the mixture. The phases were allowed to separate and the aqueous layer was discarded. The organic layer was washed with brine and the aqueous layer was discarded. The volume of the organic layer was reduced then was added acetonitrile and water. A solution of pyridine (5 L) in acetonitrile (34 L) was added to the mixture and the temperature was adjusted to about 22 °C and agitated for at least 1 hour followed by adjusting the temperature to about 70 °C and agitated at about 70 °C for at least 1 hour (e.g.,

at least 2 hours). The mixture was cooled to about 25 °C and agitated at about 25 °C for at least 1 hour (e.g., at least 12 hours). The resulting solid was collected by filtration. The vessel was rinsed with acetonitrile and filtered over the collected solid. The rinsing step was repeated. The solid was dried under a nitrogen stream followed by drying in a tray dryer under reduced pressure.

Preparation of Compound 4:

[000233] A mixture of Compound 3 (13 kg), hydrochloric acid (12M; 130 L) and water (260 L) in a vessel was agitated at about 15 °C for at least 1 hour followed by adjusting the temperature to about 45 °C and agitated for at least 1 hour (e.g., at least 12 hours). The mixture was cooled to about 25 °C and agitated for at least 1 hour (e.g., at least 2 hours). The resulting solid was collected by filtration and the vessel was rinsed with water and filtered over the collected solid. A mixture of the solid in 2-MethylTHF (195 L), hydrochloric acid (12N; 6 L) and water (65 L) was agitated at about 25 °C for at least 1 hour. The phases were allowed to separate, and the volume of the organic layer was reduced then was added ethanol (130 L). The volume of the mixture was reduced then was added ethanol (130 L). The mixture was added to activated charcoal and agitated for at least 1 hour (e.g., at least 4 hours) at about 45 °C. The mixture was filtered over Celite®. The vessel was rinsed with ethanol over the Celite®. The volume of the combined filtrate was reduced then water was added. The temperature of the mixture was adjusted to about 60 °C and agitated then cooled to 25 °C. Water was added through an inline filter (0.45 μm) to the mixture. Seeds of Form 1 of the compound represented by Formula (I) (e.g., as prepared by Example 2B) (0.2 kg) were added to the mixture and the mixture was stirred for at least 1 hour (e.g., at least 2 hours). The mixture was cooled to about 5 °C. Additional water was added through an inline filter then the mixture was agitated for at least 1 hour. The temperature was adjusted to about 25 °C. The resulting solid was collected by filtration. The vessel was rinsed with ethanol/water and filtered over the collected solid. The solid was dried under a nitrogen stream followed by drying in a tray dryer. An exemplary XRPD pattern of the resulting solid showed that the solid was primarily crystalline Form 21 of the compound represented by Formula (I) with a trace amount of Form 4 of the compound represented by Formula (I).

[000234] The solid (9.5 kg) in n-heptane (95 L) was agitated at about 90 °C in a vessel for at least 1 hour (e.g., at least 12 hours, at least 24 hours, at least 30 hours). The mixture was cooled to about 25 °C. The solid was collected by filtration. The vessel was rinsed with heptane and filtered over the collected solid. The solid was dried under reduced pressure for at least 1 hour (e.g., at least 2 hours, at least 12 hours, at least 24 hours, at least 48 hours). An

exemplary XRPD pattern of the resulting solid showed that the solid was crystalline Form 1 of the compound represented by Formula (I).

Example 2B. Exemplary process of preparing Form 1 of a compound represented by Formula (I)

Preparation of Compound 4:

[000235] A mixture of Compound 3 in hydrochloric acid and water in a vessel was agitated at about 15 °C for at least 1 hour followed by adjusting the temperature to about 45 °C and agitated for at least 1 hour (e.g., at least 20 hours). The mixture was cooled to about 25 °C and agitated for at least 1 hour (e.g., at least 2 hours). The resulting solid was collected by filtration and the vessel was rinsed with water and filtered over the collected solid. A mixture of the solid in 2-MethylTHF was mixed with aqueous hydrochloric acid, phases separated, and the organic layer was transferred to a vessel through a 0.45 μm filter. Water and hydrochloric acid were added, and the mixture was adjusted to about 25 °C and agitated for at least 1 hour. The phases were allowed to separate, and the aqueous phase was discarded. The organic layer was concentrated and was added ethanol. The temperature was adjusted to about 45 °C and n-heptane was added while maintaining a temperature of about 45 °C then agitated for at least 1 hour (e.g., at least 12 hours) then cooled to about 25 °C and agitated at about 25 °C for at least 1 hour (e.g., 2 hours). The resulting solid was collected by filtration and the filter cake was rinsed with ethanol/n-heptane followed by n-heptane. The solid was dried on the filter for at least 1 hour (e.g., at least 2 hours) followed by drying in a tray dryer for at least 1 hour (e.g., at least 12 hours, at least 24 hours, at least 48 hours). The resulting solid in n-heptane was agitated and the temperature was adjusted to about 90 °C and agitated for at least 1 hour (e.g., at least 12 hours, at least 24 hours, at least 30 hours). The mixture was cooled to about 25 °C and agitated for at least 1 hour (e.g., 12 hours). The solid was collected by filtration. The vessel was rinsed with n-heptane and filtered over the collected solid. The combined solids were dried on the filter followed by drying in a tray dryer. An exemplary XRPD pattern of the resulting solid showed that the solid was crystalline Form 1 of the compound represented by Formula (I).

Example 2C. Characterization of crystalline Form 1, Form 21, and Form 4 of a compound represented by Formula (I)

[000236] The XRPD pattern of Form 1 is shown in **FIG. 2A**. Table 1A shows the peak listing and relative intensities (%) of Form 1. ^{1}H NMR and ^{31}P NMR are shown in **FIG. 3** and **FIG. 4**, respectively. The thermal analysis of the compound represented by Formula (I) displayed the following properties by TGA/DSC. From the TGA trace, there was a weight

loss of 1.83 wt% (20-120 °C), weight loss of 0.94% wt% (190-210 °C) and decomposition at about 230 °C (**FIG. 5**). The DSC trace showed two endothermic events at an onset of about 197 °C and peak at about 205 °C; and a second peak at about 231 °C (**FIG. 5**). Thermal analysis by standalone DSC shows in the first heating (**FIG. 6**), an endothermic event at an onset of about 193 °C and peak at about 204 °C; an exothermic event at an onset of about 208 °C and peak at about 211 °C; in the first cooling, a possible glass transition at about 141 °C; and in the second heating, a glass transition at about 151 °C. Karl Fisher titration showed an average water content of 0.70%. DVS analysis (**FIG. 7**) showed a moisture uptake of about 1.5 wt% at 90% RH. The XRPD of the material post DVS showed that Form 1 was retained after DVS analysis (**FIG. 8**). Variable temperature XRPD showed that Form 1 was retained from ambient to 190 °C. At 205 °C, the material became amorphous (**FIG. 9**). The recovered amorphous material was analyzed by HPLC and showed that the compound was degraded.

Table 1A. Representative XRPD peaks of Form 1

Position [°2θ]	**d-spacing [Å]**	**Relative Intensity [%]**
4.2	21.2	33
7.3	12.2	8
8.3	10.6	15
8.4	10.5	24
11.1	8.0	4
11.6	7.6	21
12.0	7.3	27
13.0	6.8	15
14.6	6.1	26
15.5	5.7	6
16.7	5.3	32
16.9	5.2	32
18.8	4.7	100
19.4	4.6	13
19.9	4.5	27
20.4	4.3	10
21.5	4.1	14

[000237] The XRPD pattern of Form 21 is shown in **FIG. 2B**. Table 1B shows the peak listing and relative intensities (%) of Form 21.

Table 1B. Representative XRPD peaks of Form 21

Position [°2θ]	d-spacing [Å]	Relative Intensity [%]
8.5	10.4	90
9.6	9.2	100
9.9	8.9	39
11.8	7.5	12
12.6	7.0	55
14.2	6.2	31
14.5	6.1	44
14.9	5.9	21
16.4	5.4	36
17.0	5.2	40
17.5	5.1	33
18.7	4.7	21
20.8	4.3	85
22.2	4.0	45
25.0	3.6	32
26.9	3.3	22
27.1	3.3	31

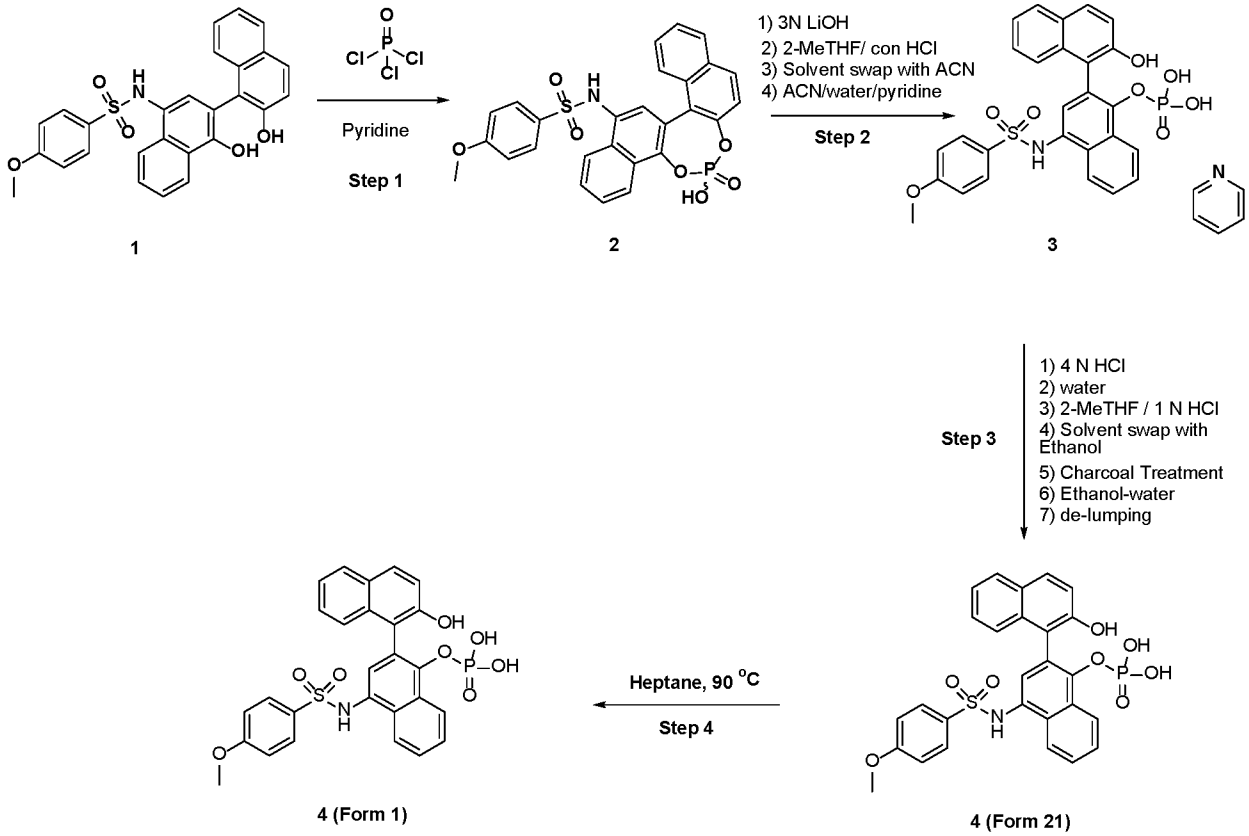
[000238] The XRPD pattern of Form 4 is shown in **FIG. 20**. Table 1C shows the peak listing and intensities of Form 4.

Table 1C. Representative XRPD peaks of Form 4

Position [°2θ]	d-spacing [Å]	Relative Intensity [%]
3.7	23.8	42
7.4	11.9	100
8.3	10.6	25
10.5	8.4	3
11.5	7.7	59
12.0	7.4	48
12.3	7.2	17
12.7	7.0	7
14.9	5.9	10
15.9	5.6	14
16.7	5.3	46
18.6	4.8	32
19.2	4.6	77

19.5	4.6	35
20.1	4.4	31
20.3	4.4	21
20.7	4.3	28
21.8	4.1	31
24.4	3.6	36
25.2	3.5	49
25.7	3.5	30

Example 2D. Exemplary process of preparing Form 1 of a compound represented by Formula (I)



Preparation of Compound 2:

[000239] Compound 1 (16 Kg) was charged to reactor A followed by pyridine (3 volume (vol)). The temperature was adjusted to 0 ± 5 °C. Phosphorus oxychloride (1.05 equivalents) was charged while maintaining the temperature at 0 ± 5 °C during the addition. The reaction temperature was adjusted to 25 ± 5 °C over 1 hour and the mixture was agitated at 25 ± 5 °C for 2 hours. After the reaction was deemed complete by liquid chromatography (LC) analysis (Compound 1: 0.06%), water (1.5 vol) was charged while maintaining a temperature ≤ 60 °C. The temperature was adjusted to 25 ± 5 °C and the mixture was agitated at 25 ± 5 °C for 15 hours. The mixture in reactor A was transferred to reactor B which contained hydrochloric acid

(9 vol). Reactor A was rinsed with a mixture of pyridine/water (0.5 vol / 0.5 vol), and the rinse was transferred to reactor B. The mixture in reactor B was agitated at 65 ± 5 °C at least 2 hours. The temperature was adjusted to 25 ± 5 °C over 3 hours, the solids were collected by filtration, and the filter cake was washed with water (2×5 vol). The solids were dried in a vacuum oven at 48 °C for 90 hours. 18.8 Kg of Compound 2 was obtained in 104% yield and 98.6% purity. The material contained ~0.8 equivalents of pyridine by weight (estimated by ^{1}H NMR). A ^{1}H NMR spectrum of Compound 2 (DMSO-d6) is shown in FIG. 32. Liquid chromatography-mass spectrometry (LCMS) data are shown in FIG. 33.

Preparation of Compound 3:

[000240] Compound 2 (18.7 Kg) was charged to reactor C followed by an aqueous solution of lithium hydroxide (3 N, 5 vol, 8 equivalents). The mixture was agitated at 75 ± 5 °C for at least 5 hours. After the reaction was deemed complete by liquid chromatography (LC) analysis (Compound 2: 1%), the temperature was adjusted to 15 ± 5 °C. 2-MeTHF (15 vol) was charged, and hydrochloric acid (8.2 equivalents) was charged while maintaining a temperature of ≤ 37 °C. The phases were allowed to separate and the aqueous layer was discarded. The organic layer was washed with 10% brine (5 vol), and the aqueous layer was discarded. The organic layer was distilled to 3 vol, and acetonitrile (15 vol) was charged followed by distilling to 3 vol. Water (1 vol) was charged followed by acetonitrile (15 vol). A solution of pyridine (2 equivalents) in acetonitrile (2 vol) was charged and the temperature was adjusted to 25 ± 5 °C. The mixture was agitated at 25 ± 5 °C for 4 hours post pyridine addition followed by adjusting the temperature to 70 ± 5 °C over at least 2 hours. The mixture was agitated at 70 ± 5 °C for 2.5 hours followed by adjusting the temperature to 25 ± 5 °C over 2 hours and held for 5 hours. The solids were collected by filtration. The reactor was rinsed with acetonitrile (2×5 vol) sending the rinse through the filter cake. The product was dried on the filter for at least 1 h followed by drying in a tray dryer at 46 °C for 24 hours. 14.5 Kg of Compound 3 was obtained in 65% yield and 98.8% purity. The material contained 0.41% acetonitrile by weight (estimated by ^{1}H NMR). A ^{1}H NMR spectrum of Compound 3 (DMSO-d6) is shown in FIG. 34. Liquid chromatography-mass spectrometry (LCMS) data are shown in FIG. 35.

Preparation of Compound 4:

[000241] Compound 3 (14.4 Kg) was charged to reactor C followed by an aqueous solution of hydrochloric acid (4 N, 30 vol). The mixture was agitated at 15 ± 5 °C at least 1 hour followed by adjusting the temperature to 45 ± 5 °C and agitated for 20 hours. The mixture was then cooled to 25 ± 5 °C over 2 hours and agitated 2 hours. The solids were collected by

filtration and the filter cake was rinsed with water (20 vol). The solids were charged to reactor C followed by 2-MeTHF (15 vol) and aqueous hydrochloric acid solution (1 N, 5 vol). The mixture was agitated at 25± 5 °C for 1 hour. After the phase cut, the organic layer was distilled to 2.5 vol. Ethanol (10 vol) was charged and the mixture was distilled to 2.5 vol. Ethanol (10 vol) was charged to reactor C. The reactor D was cleaned and charged with charcoal (1.44 Kg). The contents of R-302 were transferred to reactor D. The temperature of reactor D was adjusted to 45 ± 5 °C and agitated at 45 ± 5 °C for 13 hours. The contents in reactor D were filtered through a pad of celite, and the filtrate was transferred to the cleaned reactor C through a 0.45 µm polish filter. Reactor D was rinsed with ethanol (2 vol). The celite cake was rinsed with the ethanol rinse, which was directed to reactor C through the 0.45 µm polish filter. The filtrate in reactor C was distilled to 3 vol. The temperature was adjusted to 25 ± 5 °C. Water (2.1 vol) was charged followed by a temperature change to 60 ± 5 °C and agitated for at least 15 minutes. The temperature was adjusted to 25 ± 5 °C. Water (0.85 vol) was charged through a 0.45 µm filter followed by adding Compound 4 seed. The temperature was then adjusted to 25 ± 5 °C and the mixture was agitated at 25 ± 5 °C for 8.5 hours. The mixture was cooled to 6 ± 3 °C over at least 3 hours before more water (3.4 vol) was charged through a 0.45 µm filter over 1 hour. The mixture was agitated for 1 hour at 6 ± 3 °C. The temperature was adjusted to 25 ± 5 °C over 2 hours and held 2 hours. The solids were collected by filtration and the filter cake was rinsed with a pre-mixed ethanol solution. The solids were dried in the filter for 16.5 hours followed by drying in tray dryer at 50 °C for at least 24 hours. The loss-on-drying (LOD) was 0.85%. The product was de-lumped using a conical screen mill. A screen size of 024R (600 µm) was used. 11.8 Kg of crude Compound 4 was obtained in 99.9% purity and 93% yield. X-ray power diffraction (XRPD) indicated the material was Form 21. The residual pyridine was 14 ppm (HSGC).

[000242] Crude Compound 4 (Form 21, 11.7 Kg) was charged to reactor C followed by heptane (15 vol) through a 0.45 µm filter. The mixture was agitated, and the temperature was adjusted to 90 ± 5 °C over at least 2 hours. The mixture was agitated (rpm: 80) at 90 ± 5 °C for 31 hours. The temperature was adjusted to 55 ± 5 °C over 1 hour. X-ray power diffraction (XRPD) was checked and failed. The temperature was adjusted to 90 ± 5 °C. The mixture in reactor C was agitated at 90 ± 5 °C for an additional 7 hours. The temperature was adjusted to 55 ± 5 °C. X-ray power diffraction (XRPD) was checked and failed. Processing continued under a deviation. The mixture was cooled to 25 ± 5 °C over 2 hours before the solids were collected by filtration. reactor C was rinsed with heptane (3 vol). The filter cake was rinsed with the rinse. The solids were dried in the filter for 5 h followed

by drying in a tray dryer for 36 hours at 54 °C. The loss-on-drying (LOD) was 0.38%. The solids were de-lumped using a conical screen mill and the product was packaged and stored at 5 °C. Compound 4 Form 1 (10.5 kg) was obtained in 98.7% purity and 89% yield.

[000243] A ^{1}H NMR spectrum of Compound 4 (DMSO-d6) is shown in FIG. 36. Liquid chromatography-mass spectrometry (LCMS) data are shown in FIG. 37.

Example 3. Stability study of Form 1 of a compound represented by Formula (I)

[000244] A seven-day stability test was performed on Form 1 to evaluate any changes to the physical form or chemical purity when the material was held under different conditions: 40°C/75 % RH, 80°C, and ambient (25°C). After 7 days, XRPD analysis showed that Form 1 was maintained (**FIG. 10**). HPLC of Form 1 used for the stability testing showed purity of 99.77%. The purities of the material post 7 days at 40°C/75 % RH, 80°C, and ambient (25°C) conditions were 99.46%, 99.59%, and 99.41%, respectively.

Example 4. Maturation cycling and hydration study of Form 1

[000245] Slurries of Form 1 were prepared in water/THF mixtures (Table 2) and thermally cycled to investigate hydration over solvation by THF. Form 1 and solvent system according to Table 2 were slurried and thermally cycled between 20-40 °C. The slurries were filtered by centrifugation and analyzed by XRPD. The solids were dried at 40 °C under vacuum for 24 hours then characterized. In neat water, Form 1 was maintained. In water:THF solvent systems, XRPD showed the solvated form of the compound represented by Formula (I) (Form 2) (**FIG. 11**).

Table 2. Experimental details for maturation cycling and hydration study

Sample	Solvent system	Volume added (µL)	Thermal cycling length (h)	XRPD analysis
1	Water	340	120	Form 1
2	Water:THF 0.1 a_w	80	72	Form 2
3	Water:THF 0.3 a_w	80	72	Form 2
4	Water:THF 0.5 a_w	80	72	Form 2

5	Water:THF 0.7 a_w	80	72	Form 2
6	Water:THF 0.9 a_w	100	72	Form 2

Example 5. Polymorph screening of a compound represented by Formula (I)

Temperature cycling

[000246] To solutions of Form 1, an antisolvent was added until a slurry was formed, then the mixture was temperature cycled between 40 °C and 5 °C for 72 hours. The mixtures were held at each temperature (40 °C and 5 °C) for 1 hour and the temperature ramp rate was 0.1 °C/min. The solids were separated from the mother liquor. The mother liquor was split into three aliquots for further studies at different conditions (see vapor diffusion, antisolvent addition, and slow solvent evaporation below). The solids were analyzed by XRPD while the solids were damp. XRPD analysis of the solids after drying at 40 °C under vacuum for 16 hours was also carried out. Table 3 and **FIG. 12** summarize the results from the temperature cycling.

Table 3. Experimental details of the temperature cycling experiment

Sample	Solvent system	XRPD pattern (damp)	XRPD pattern (dry)
1	MeTHF:Heptane (87:13 %v/v)	Form 7	Form 7
2	2-Propanol:Water (51:49 %v/v)	Form 5	Form 5
3	Acetonitrile:Water (66:34 %v/v)	No solid (oil)	No solid (oil)
4	Acetone:Water (30:70 %v/v)	No solid (oil)	No solid (oil)
5	Acetic acid:Water (28:72 %v/v)	Form 4	Form 1
6	Ethanol:Water (29:71 %v/v)	Form 4	Form 1
7	Ethyl Acetate:Heptane (92:8 %v/v)	Form 8	Form 8
8	Acetone:Heptane (38:62 %v/v)	Form 9	Form 9
9	TBME	Form 10	Form 10
10	2- Propanol:Heptane (92:8 %v/v)	Form 6	Form 6

[000247] Form 1 and Form 4 were obtained from ethanol:water and acetic acid:water systems. Upon drying Form 4 at 40 °C under vacuum, Form 4 converted to Form 1: after drying for about 16 hours, Form 4 was still observed by PXRD; longer drying time (additional 48 hours) showed the full conversion to Form 1.

[000248] Form 5 and Form 6 were obtained from 2-propanol based solvent system. In 2-propanol:water, Form 5 was favored while in 2-propanol:heptane, Form 6 was favored.

Solvent drop grinding

[000249] Amorphous solid of the compound represented by Formula (I) and solvent (Table 4) were milled for 4 cycles of 15 minutes at 5000 rpm. The isolated solids were analyzed by XRPD while the solids were damp. XRPD analysis of the solids after drying at 40 °C under vacuum for 16 hours was also carried out. Table 4 and **FIG. 13** summarize the results from solvent drop grinding.

Table 4. Solvents for solvent drop grinding

Sample	Solvent system	XRPD pattern (damp)	XRPD pattern (dry)
1	MeTHF:Heptane (80:20 %v/v)	Amorphous	Amorphous
2	2-Propanol:Water (50:50 %v/v)	Amorphous	Amorphous
3	Acetonitrile:Water (50:50 %v/v)	No solid (gum)	No solid (gum)
4	Acetone:Water (50:50 %v/v)	No solid (gum)	No solid (gum)
5	Acetic acid:Water (50:50 %v/v)	Form 4	Form 1
6	Ethanol:Water (50:50 %v/v)	Form 4	Form 1
7	Ethyl Acetate:Heptane (80:20 %v/v)	Amorphous	Amorphous
8	Acetone:Heptane (80:20 %v/v)	Amorphous	Amorphous
9	TBME	Amorphous	Amorphous
10	2- Propanol:Heptane (80:20 %v/v)	Form 5	Form 5

[000250] Form 4 and Form 1 were obtained from ethanol:water and acetic acid:water solvent systems. Form 4 converted to Form 1 upon drying. Form 5 was obtained from 2-propanol:heptane.

Vapor diffusion into a solid of a compound represented by Formula (I)

[000251] Amorphous solid of a compound represented by Formula (I) in a smaller vial was placed in a larger vial containing a solvent (Table 5) such that the solid did not come in direct contact with the solvent. The larger vial was closed and left for 7 days at ambient temperature. The isolated solids were analyzed by XRPD while the solids were damp. XRPD

analysis of the solids after drying at 40 °C under vacuum for 16 hours was also carried out. Table 5 and **FIG. 14** summarize the results from vapor diffusion into solids.

Table 5. Experimental details for vapor diffusion into solids

Sample	Solvent system	XRPD pattern (damp)	XRPD pattern (dry)
1	MeTHF:Heptane (50:50 %v/v)	Form 11	Form 11
2	2-Propanol:Water (50:50 %v/v)	Form 5	Form 5
3	Acetonitrile:Water (50:50 %v/v)	No solid (oil)	No solid (oil)
4	Acetone:Water (50:50 %v/v)	No solid (gum)	No solid (gum)
5	Acetic acid:Water (50:50 %v/v)	Form 4	Form 1
6	Ethanol:Water (50:50 %v/v)	Form 4	Form 1
7	Ethyl Acetate:Heptane (50:50 %v/v)	Amorphous	Amorphous
8	Acetone:Heptane (50:50 %v/v)	Form 9	Form 9
9	TBME	Form 10	Form 10
10	2- Propanol:Heptane (80:20 %v/v)	Form 12	Form 12

[000252] Form 4 and Form 1 were obtained from ethanol:water and acetic acid:water solvent systems. Form 4 converted to Form 1 upon drying. Form 5 was obtained from 2-propanol:water and Form 12 was obtained from 2-propanol:heptane. Form 9 and Form 10 were obtained from acetone:heptane and TBME, respectively. Form 11 was obtained from MeTHF:heptane.

Vapor diffusion into a saturated solution of a compound represented by Formula (I)

[000253] Aliquots of a saturated solution of the compound represented by Formula (I) from the mother liquor of the temperature cycling experiment was placed in a larger vial containing an antisolvent, such that the antisolvent did not come directly in contact with the saturated solution. See Table 6. The larger vial was closed and left for 7 days at ambient temperature. The isolated solids were analyzed by XRPD while the solids were damp. XRPD analysis of the solids after drying at 40 °C under vacuum for 16 hours was also carried out. N/A in Table 6 indicates insufficient material obtained for XRPD analysis. Table 6 and **FIG. 15** summarize the results from vapor diffusion into saturated solutions.

Table 6. Experimental details for the vapor diffusion into saturated solutions

Sample	Solvent system	Antisolvent	Observation after 7 days	XRPD pattern (damp)	XRPD pattern (dry)
1	MeTHF:Heptane	Heptane	Crystalline needles	Form 13	Form 13
2	2-Propanol:Water	Water	Solids	N/A	N/A
3	Acetonitrile:Water	Water	Thick gel	No solid (gel)	No solid (gel)
4	Acetone:Water	Water	Thick gel	No solid (gel)	No solid (gel)
5	Acetic acid:Water	Water	Thick gel	No solid (gel)	No solid (gel)
6	Ethanol:Water	Water	Solids	Form 4	Form 1
7	Ethyl Acetate:Heptane	Heptane	Solids	N/A	N/A
8	Acetone:Heptane	Heptane	Oil	No solid (gel)	No solid (gel)
9	TBME	Heptane	Solids	N/A	N/A
10	2- Propanol:Heptane	Heptane	Crystalline needles	Form 6	Form 6

[000254] Form 4 and Form 1 were obtained from ethanol:water. Form 4 converted to Form 1 upon drying. Form 6 was obtained from 2-propanol:heptane. Form 13 formed from MeTHF:heptane.

Antisolvent addition

[000255] An antisolvent (Table 7) was added to aliquots of a saturated solution of the compound represented by Formula (I) from the mother liquor of the temperature cycling experiment until a precipitate was formed or until a total of 0.8 mL was added. When precipitation did not occur immediately upon addition of antisolvent, the mixtures were stored at ambient temperature for 24 hours. The isolated solids were analyzed by XRPD while the solids were damp. XRPD analysis of the solids after drying at 40 °C under vacuum

for 16 hours was also carried out. Table 7 and **FIG. 16** summarize the results from antisolvent additions.

Table 7. Experimental details for the antisolvent addition

Sample	Solvent system	Antisolvent	Volume of antisolvent added (µL)	Observation after antisolvent addition	Observation after 24 hours after antisolvent addition
1	MeTHF:Heptane	Heptane	800	Clear solution	Crystalline needles
2	2-Propanol:Water	Water	800	Clear solution	Clear solution
3	Acetonitrile:Water	Water	800	Oil/haze	Gel
4	Acetone:Water	Water	800	Oil/haze	Gel
5	Acetic acid:Water	Water	800	Thin slurry	Solids
6	Ethanol:Water	Water	800	Thin slurry	Solids
7	Ethyl Acetate:Heptane	Heptane	800	Clear solution	Solids
8	Acetone:Heptane	Heptane	800	Clear solution	Solids
9	TBME	Heptane	800	Thin slurry	Crystalline needles
10	2-Propanol:Heptane	Heptane	800	Thin slurry	Crystalline needles

[000256] Form 14 was observed from MeTHF:heptane when damp and converted to Form 15 upon drying. Form 6 was observed from 2-propanol:heptane when damp and upon drying. There was insufficient material for XRPD analysis for Samples 5-9.

Slow solvent evaporation

[000257] Aliquots of a saturated solution of the compound represented by Formula (I) from the mother liquor of the temperature cycling experiment was left for 7 days with a needle piercing the septum of the lid (of the vial containing the aliquot). For samples where a lot of solvent remained after 5 days, the lid of the sample was removed. The isolated solids

were analyzed by XRPD while the solids were damp. XRPD analysis of the solids after drying at 40 °C under vacuum for 16 hours was also carried out (Table 8). N/A in Table 8 indicates insufficient material obtained for XRPD analysis. Table 8 and **FIG. 17** summarize the results from slow solvent evaporation.

Table 8. Results of slow solvent evaporation experiment

Sample	Solvent system	XRPD pattern (damp)	XRPD pattern (dry)
1	MeTHF:Heptane	No solids (oil)	No solids (oil)
2	2-Propanol:Water	Amorphous	Amorphous
3	Acetonitrile:Water	Amorphous	Amorphous
4	Acetone:Water	Amorphous	Amorphous
5	Acetic acid:Water	Form 4	Form 1
6	Ethanol:Water	Form 4	Form 1
7	Ethyl Acetate:Heptane	N/A	N/A
8	Acetone:Heptane	No solids (oil)	No solids (oil)
9	TBME	N/A	N/A
10	2- Propanol:Heptane	Form 5	Form 5

[000258] Form 4 and Form 1 were obtained from ethanol:water and acetic acid:water. Form 4 converted to Form 1 upon drying. Form 5 was obtained from 2-propanol:heptane.

[000259] Table 9 summarizes exemplary solid-state forms of the compound represented by Formula (I) based at least on the above experiments. In Table 9, TC refers to temperature cycling; SE refers to solvent evaporation; ASA refers to anti-solvent addition; SDG refers to solvent drop grinding; VDS refers to vapor diffusion into a solid; and VDL refers to vapor diffusion into a saturated solution.

[000260] In addition, surprisingly, improvements to morphology and particle size for Form 1 was observed upon drying Form 4 (obtained, e.g., from acetic acid:water or ethanol:water solvent systems). Also, based on the above experiments, Form 1 was a non-solvated crystalline form (anhydrate).

Table 9. Summary of exemplary solid-state forms of the compound represented by Formula (I).

Form	Experiment
1	Upon drying Form 4; from acetic acid:water and ethanol:water (TC, SDG, VDS, VDL, SE)

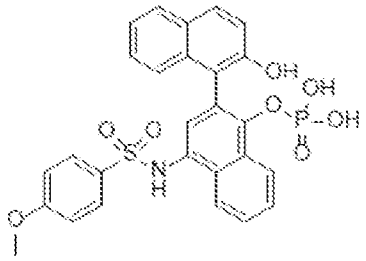
2	From THF during maturation/hydration study
3	From isopropyl acetate
4	From acetic acid:water and ethanol:water (TC, SDG, VDS, VDL, SE)
5	From 2-propanol based solvent systems (TC, SDG, VDS, SE)
6	From 2-propanol:heptane (TC, VDL, ASA)
7	From MeTHF:heptane (TC)
8	From ethyl acetate:heptane (TC)
9	From acetone:heptane (TC, VDS)
10	From TBME (TC, VDS)
11	From MeTHF:heptane (VDS)
12	From 2-propanol:heptane (VDS)
13	From MeTHF:heptane (VDL)
14	From MeTHF:heptane, damp (ASA)
15	From MeTHF:heptane, dry

[000261] FIG. 18A, 18B, and 18C show an XPRD diffractogram, TGA/DSC plot, and ^{1}H NMR spectrum, respectively, of Form 2 of the compound represented by Formula (I). FIG. 19A and 19B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 3 of the compound represented by Formula (I). FIG. 20 shows an XRPD diffractogram of Form 4 of the compound represented by Formula (I). FIG. 21A and 21B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 5 of the compound represented by Formula (I). FIG. 22A and 22B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 6 of the compound represented by Formula (I). FIG. 23 shows an XRPD diffractogram of Form 7 of the compound represented by Formula (I). FIG. 24A and 24B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 8 of the compound represented by Formula (I). FIG. 25A and 25B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 9 of the compound represented by Formula (I). FIG. 26A and 26B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 10 of the compound represented by Formula (I). FIG. 27A and 27B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form 11 of the compound represented by Formula (I). FIG. 28A and 28B show an XRPD diffractogram and TGA/DSC plot, respectively, of Form

12 of the compound represented by Formula (I). FIG. 29 shows an XRPD diffractogram of Form 13 of the compound represented by Formula (I). FIG. 30 shows an XRPD diffractogram of Form 14 of the compound represented by Formula (I). FIG. 31 shows an XRPD diffractogram of Form 15 of the compound represented by Formula (I).

CLAIMS

1. Crystalline Form 1 of a compound represented by Formula (I):



Formula (I).

2. The crystalline form of claim 1, having an XRPD pattern substantially as shown in FIG. 2A.

3. The crystalline form of claim 1, having an XRPD pattern substantially as shown in Table 1A.

4. The crystalline form of claim 1, having an XRPD pattern comprising a peak, in terms of 2-theta, at about 18.8°.

5. The crystalline form of claim 4, wherein the XRPD pattern further comprises one or more peaks, in terms of 2-theta, at about 4.2°, about 16.7°, and about 16.9°.

6. The crystalline form of claim 1, having a DSC thermogram comprising an endothermic event with onset between about 194 °C to 200 °C.

7. The crystalline form of claim 1, having a DSC thermogram comprising an endothermic peak at about 205 °C.

8. The crystalline form of claim 1, having a DSC thermogram substantially as shown in FIG. 5.

9. The crystalline form of claim 1, having a DSC thermogram comprising an endothermic event with onset between about 190 °C to 196 °C.

10. The crystalline form of claim 1, having a DSC thermogram comprising an endothermic peak at about 204 °C.

11. The crystalline form of claim 1, having a DSC thermogram substantially as shown in FIG. 6.
12. The crystalline form of claim 1, having a DVS kinetic plot substantially as shown in FIG. 7.
13. The crystalline form of any one of claims 1-12, which is substantially pure.
14. The crystalline form of any one of claims 1-12, having a chemical purity of greater than 90% by weight.
15. The crystalline form of any one of claims 1-12, having a chemical purity of greater than 95% by weight.
16. The crystalline form of any one of claims 1-12, having a chemical purity of greater than 99% by weight.
17. The crystalline form of any one of claims 1-12, having no more than about 5 mol% of other solid-state forms of the compound represented by Formula (I).
18. The crystalline form of any one of claims 1-12, having no more than about 3 mol% of other solid-state forms of the compound represented by Formula (I).
19. The crystalline form of any one of claims 1-12, having no more than about 1 mol% of other solid-state forms of the compound represented by Formula (I).
20. The crystalline form of any one of claims 1-19, wherein Form 1 is an anhydrate.
21. A process for preparing a crystalline Form 1 of a compound represented by Formula (I), comprising:

    (i) slurrying a mixture of a compound represented by Formula (I) in a solvent to produce a solid precipitate; and
    (ii) isolating the solid precipitate,
    thereby preparing the crystalline Form 1 of the compound represented by Formula (I).
22. The process of claim 21, wherein in step (i), the slurrying occurs at about 80 °C to about 100 °C.
23. The process of claim 22, wherein in step (i), the slurrying occurs at about 90 °C.
24. The process of any one of claims 21-23, wherein the solvent is n-heptane.

25. The process of any one of claims 21-24, wherein after step (ii), the process further comprises drying the solid precipitate.

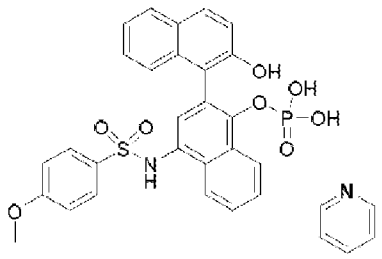
26. The process of any one of claims 21-25, wherein the compound represented by Formula (I) in step (i) comprises less than about 30% w/w of Form 1 of the compound represented by Formula (I).

27. The process of any one of claims 21-25, wherein the compound represented by Formula (I) in step (i) comprises less than about 20% w/w of Form 1 of the compound represented by Formula (I).

28. The process of any one of claims 21-25, wherein the compound represented by Formula (I) in step (i) comprises less than about 10% w/w of Form 1 of the compound represented by Formula (I).

29. The process of any one of claims 21-28, further comprising:

(i) contacting a compound represented by Formula (C):



Formula (C),

with an aqueous solution comprising an acid to produce a first solid precipitate;

(ii) isolating the first solid precipitate;

(iii) contacting the first solid precipitate with a first solvent to form a first mixture;

(iv) contacting the first mixture with an acid to form a second mixture;

(v) contacting the second mixture with a second solvent to form a third mixture;

(vi) contacting the third mixture with activated charcoal to form a fourth mixture;

(vii) filtering the fourth mixture to isolate a filtrate;

(viii) contacting the filtrate with a third solvent to form a fifth mixture;

(ix) charging the fifth mixture with seed material of crystalline Form 1 of the compound represented by Formula (I) to form a charged mixture;

(x) further charging the charged mixture with a fourth solvent to produce a solid precipitate; and

(xi) isolating the solid precipitate,

thereby preparing a compound represented by Formula (I).

30. The process of claim 29, wherein in step (i), the acid is hydrochloric acid.

31. The process of claim 29 or 30, wherein in step (i), the contacting comprises agitating the compound represented by Formula (C) in the aqueous solution comprising the acid at about 10 °C to about 50 °C.

32. The process of any one of claims 29-31, further comprising after step (ii), washing the first solid precipitate with water.

33. The process of any one of claims 29-32, wherein the first solvent is 2-methyltetrahydrofuran.

34. The process any one of claims 29-33, wherein the acid in step (iv) is hydrochloric acid.

35. The process of any one of claims 29-34, wherein in step (iv), the second mixture comprises an organic layer and an aqueous layer, and the process further comprises separating the organic layer from the aqueous layer, and optionally adding aqueous hydrochloric acid to the separated organic layer, separating the resulting organic layer from the aqueous layer, and reducing the volume of said organic layer.

36. The process of any one of claims 29-35, wherein the second solvent is ethanol.

37. The process of any one of claims 29-36, wherein the third solvent is water.

38. The process of any one of claims 29-37, wherein in step (viii), the contacting comprises agitating the filtrate and the third solvent at about 25 °C to about 60 °C.

39. The process of any one of claims 29-38, wherein in step (viii), the contacting comprises agitating the filtrate and the third solvent at about 20 °C to about 30 °C then at about 55 °C to about 65 °C.

40. The process of any one of claims 29-39, wherein after step (viii), the process further comprises adding additional volume of third solvent.

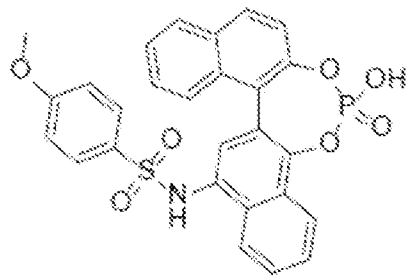
41. The process of any one of claims 29-40, wherein the fourth solvent is water.

42. The process of any one of claims 29-41, wherein after step (xi), the process further comprises drying the solid precipitate.

43. The process of any one of claims 29-42, wherein the solid precipitate is substantially crystalline Form 21 of the compound represented by Formula (I).

44. The process of any one of claims 29-43, further comprising:

(i) contacting a compound represented by Formula (B):



Formula (B)

with an aqueous solution comprising a base to form a first mixture;

(ii) contacting the first mixture with an acid and a solvent to form a second mixture;

(iii) contacting the second mixture with pyridine to produce a solid precipitate;

(iv) isolating the solid precipitate,

thereby preparing the compound represented by Formula (C).

45. The process of claim 44, wherein the base is lithium hydroxide.

46. The process of claim 44 or 45, wherein the contacting in step (i) comprises agitating the compound represented by Formula (B) in the aqueous solution comprising the base at about 65 °C to about 85 °C.

47. The process of any one of claims 44-46, wherein the acid is hydrochloric acid.

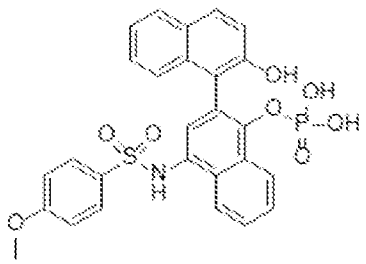
48. The process of any one of claims 44-47, wherein the solvent is 2-methyltetrahydrofuran.

49. The process of any one of claims 44-48, wherein in step (ii), the second mixture comprises an organic layer and an aqueous layer, and the process further comprises separating the organic layer from the aqueous layer, and reducing the volume of said organic layer.

50. The process of any one of claims 44-49, wherein the contacting in step (iii) comprises agitating the second mixture and pyridine at about 60 °C to about 80 °C.

51. Crystalline Form 1 of the compound represented by Formula (I), prepared according to the process of any one of claims 21-50.

52. Crystalline Form 2 of a compound represented by Formula (I):

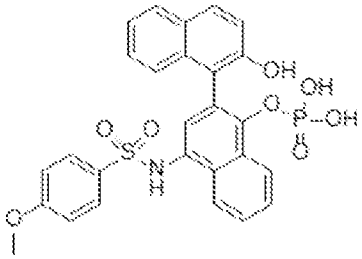


Formula (I).

53. The crystalline form of claim 52, having an XRPD pattern substantially as shown in FIG. 18A.

54. The crystalline form of claim 52, having a DSC thermogram substantially as shown in FIG. 18B.

55. Crystalline Form 3 of a compound represented by Formula (I):

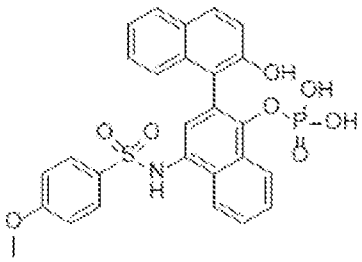


Formula (I).

56. The crystalline form of claim 55, having an XRPD pattern substantially as shown in FIG. 19A.

57. The crystalline form of claim 52, having a DSC thermogram substantially as shown in FIG. 19B.

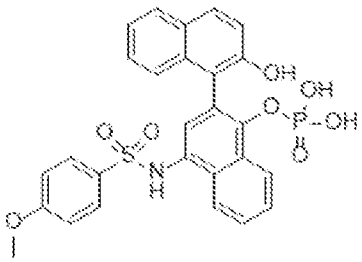
58. Crystalline Form 4 of a compound represented by Formula (I):



Formula (I).

59. The crystalline form of claim 58, having an XRPD pattern substantially as shown in FIG. 20 or Table 1C.

60. Crystalline Form 5 of a compound represented by Formula (I):

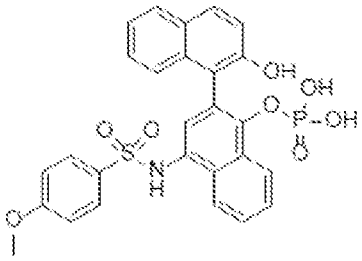


Formula (I).

61. The crystalline form of claim 60, having an XRPD pattern substantially as shown in FIG. 21A.

62. The crystalline form of claim 60, having a DSC thermogram substantially as shown in FIG. 21B.

63. Crystalline Form 6 of a compound represented by Formula (I):

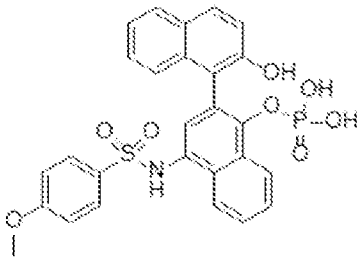


Formula (I).

64. The crystalline form of claim 63, having an XRPD pattern substantially as shown in FIG. 22A.

65. The crystalline form of claim 63, having a DSC thermogram substantially as shown in FIG. 22B.

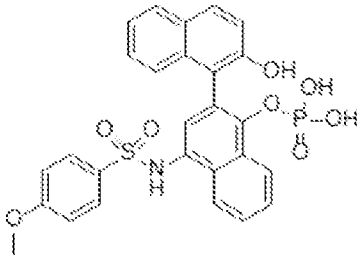
66. Crystalline Form 7 of a compound represented by Formula (I):



Formula (I).

67. The crystalline form of claim 66, having an XRPD pattern substantially as shown in FIG. 23A.

68. Crystalline Form 8 of a compound represented by Formula (I):

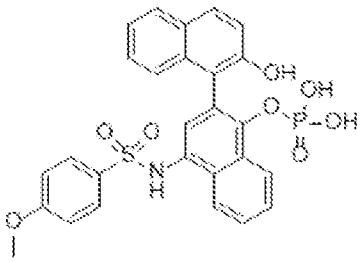


Formula (I).

69. The crystalline form of claim 68, having an XRPD pattern substantially as shown in FIG. 24A.

70. The crystalline form of claim 68, having a DSC thermogram substantially as shown in FIG. 24B.

71. Crystalline Form 9 of a compound represented by Formula (I):

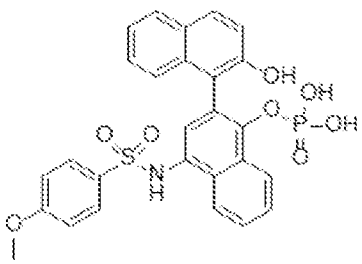


Formula (I).

72. The crystalline form of claim 71, having an XRPD pattern substantially as shown in FIG. 25A.

73. The crystalline form of claim 71, having a DSC thermogram substantially as shown in FIG. 25B.

74. Crystalline Form 10 of a compound represented by Formula (I):

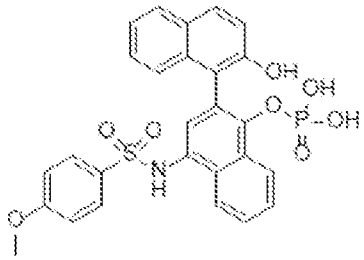


Formula (I).

75. The crystalline form of claim 74, having an XRPD pattern substantially as shown in FIG. 25A.

76. The crystalline form of claim 74, having a DSC thermogram substantially as shown in FIG. 25B.

77. Crystalline Form 11 of a compound represented by Formula (I):

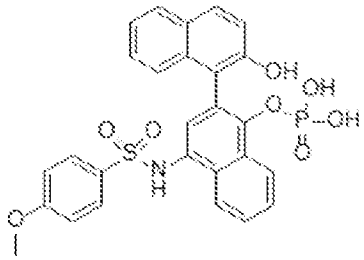


Formula (I).

78. The crystalline form of claim 77, having an XRPD pattern substantially as shown in FIG. 26A.

79. The crystalline form of claim 77, having a DSC thermogram substantially as shown in FIG. 26B.

80. Crystalline Form 11 of a compound represented by Formula (I):

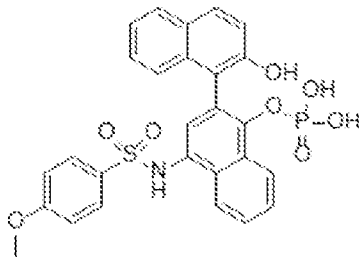


Formula (I).

81. The crystalline form of claim 80, having an XRPD pattern substantially as shown in FIG. 27A.

82. The crystalline form of claim 80, having a DSC thermogram substantially as shown in FIG. 27B.

83. Crystalline Form 12 of a compound represented by Formula (I):

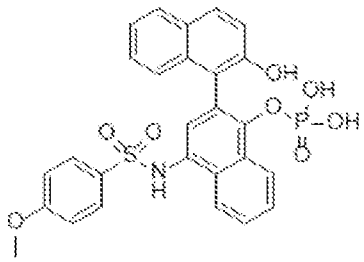


Formula (I).

84. The crystalline form of claim 83, having an XRPD pattern substantially as shown in FIG. 28A.

85. The crystalline form of claim 83, having a DSC thermogram substantially as shown in FIG. 28B.

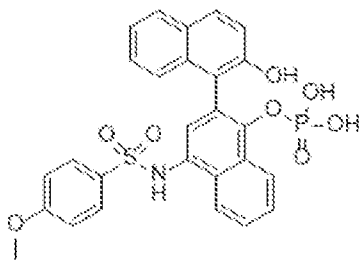
86. Crystalline Form 13 of a compound represented by Formula (I):



Formula (I).

87. The crystalline form of claim 86, having an XRPD pattern substantially as shown in FIG. 29.

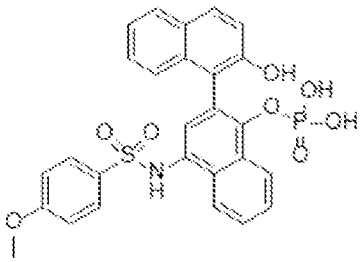
88. Crystalline Form 14 of a compound represented by Formula (I):



Formula (I).

89. The crystalline form of claim 88, having an XRPD pattern substantially as shown in FIG. 30.

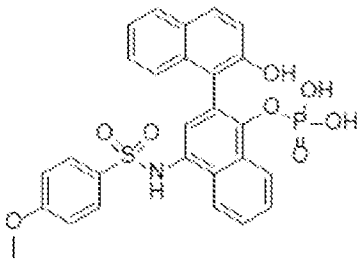
90. Crystalline Form 15 of a compound represented by Formula (I):



Formula (I).

91. The crystalline form of claim 90, having an XRPD pattern substantially as shown in FIG. 31.

92. Crystalline Form 21 of a compound represented by Formula (I):



Formula (I).

93. The crystalline form of claim 92, having an XRPD pattern substantially as shown in FIG. 2B or Table 1B.

94. A pharmaceutical composition comprising: a) a crystalline form of any one of claims 1-20 and 51-93, and b) a pharmaceutically acceptable carrier.

95. A method of treating cancer in an individual in need thereof, comprising administering to the subject an effective amount of a crystalline form of any one of claims 1-20 and 51-93 or a composition of claim 94.

96. The method of claim 95, wherein the cancer is head and neck cancer, lung cancer, liver cancer, breast cancer, skin cancer, kidney cancer, testicular cancer, colon cancer, rectal cancer, gastric cancer, metastatic melanoma, prostate cancer, ovarian cancer, cervical cancer, bone cancer, spleen cancer, gall bladder cancer, brain cancer, pancreatic cancer, stomach cancer, anal cancer, multiple myeloma, post-transplant lymphoproliferative disease, restenosis, myelodysplastic syndrome, leukemia, or lymphoma.

97. The method of claim 95, wherein the cancer is head and neck cancer, lung cancer, liver cancer, breast cancer, ovarian cancer, colon cancer, multiple myeloma, leukemia, or pancreatic cancer.

98. A method of treating fibrosis in an individual in need thereof, comprising administering to the subject an effective amount of a crystalline form of any one of claims 1-20 and 51-93 or a composition of claim 94.

99. The method of claim 98, wherein fibrosis is pulmonary fibrosis, bone marrow fibrosis, intestine fibrosis, pancreatic fibrosis, joint fibrosis, liver fibrosis, retroperitoneum fibrosis, renal fibrosis, myelofibrosis, dermal fibrosis, or systemic sclerosis.

100. A method of treating inflammatory disease or disorder in an individual in need thereof, comprising administering to the subject an effective amount of a crystalline form of any one of claims 1-20 and 51-93 or a composition of claim 94.

101. The method of claim 100, wherein the inflammatory disease or disorder is inflammatory bowel disease, ulcerative colitis, psoriasis, uveitis, scleritis, multiple sclerosis, pancreatitis, or asthma.

102. A method of treating neurodegenerative disease or disorder in an individual in need thereof, comprising administering to the subject an effective amount of a crystalline form of any one of claims 1-20 and 51-93 or a composition of claim 94.

103. The method of claim 102, wherein the neurodegenerative disease or disorder is chemotherapy-induced peripheral neuropathy, diabetic neuropathy, or familial amyloid polyneuropathy.

104. A method of treating cachexia in an individual in need thereof, comprising administering to the subject an effective amount of a crystalline form of any one of claims 1-20 and 51-93 or a composition of claim 94.

105. A method of treating anaphylaxis in an individual in need thereof, comprising administering to the subject an effective amount of a crystalline form of any one of claims 1-20 and 51-93 or a composition of claim 94.

106. A method of treating non-alcoholic fatty liver disease or steatohepatitis in an individual in need thereof, comprising administering to the individual an effective amount of a crystalline form of any one of claims 1-20 and 51-93 or a composition of claim 94.

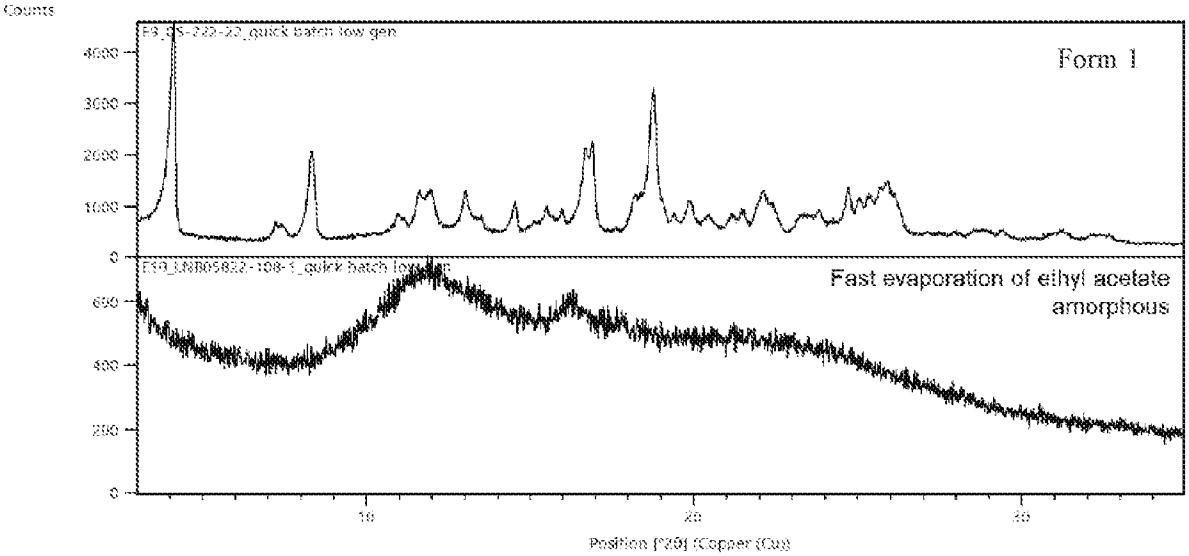

Counts
Form 1
Fast evaporation of ethyl acetate
amorphous
Position [°2θ] (Copper (Cu))

FIG. 1

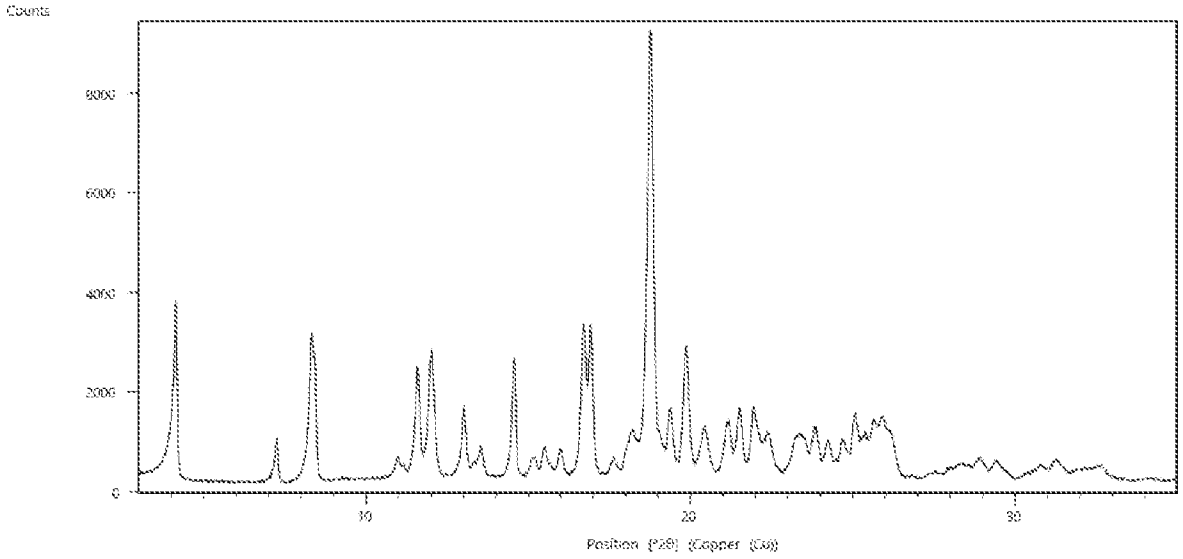

Counts
8000
6000
4000
2000
0
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 2A

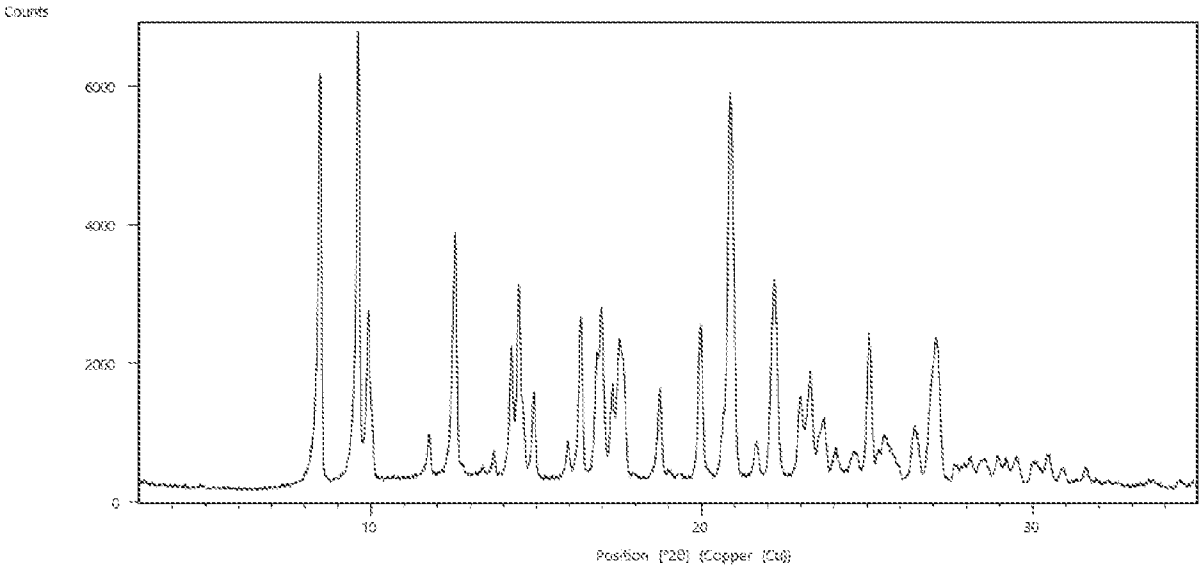

Counts
6000
4000
2000
0
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 2B

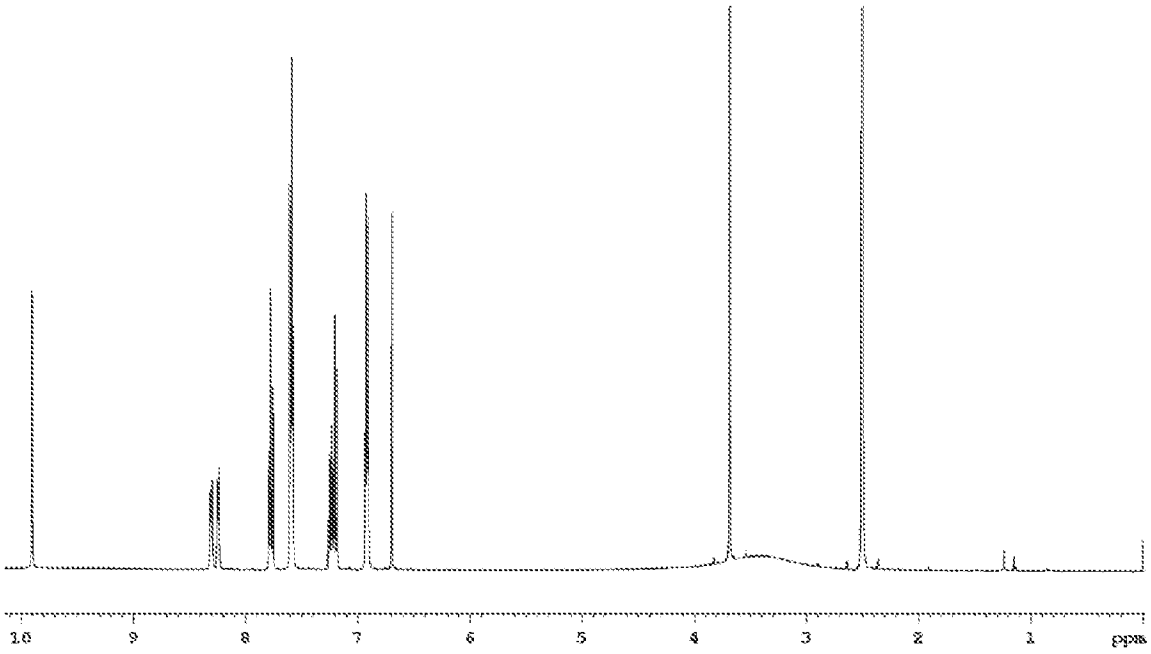

10
9
8
7
6
5
4
3
2
1
ppm

FIG. 3

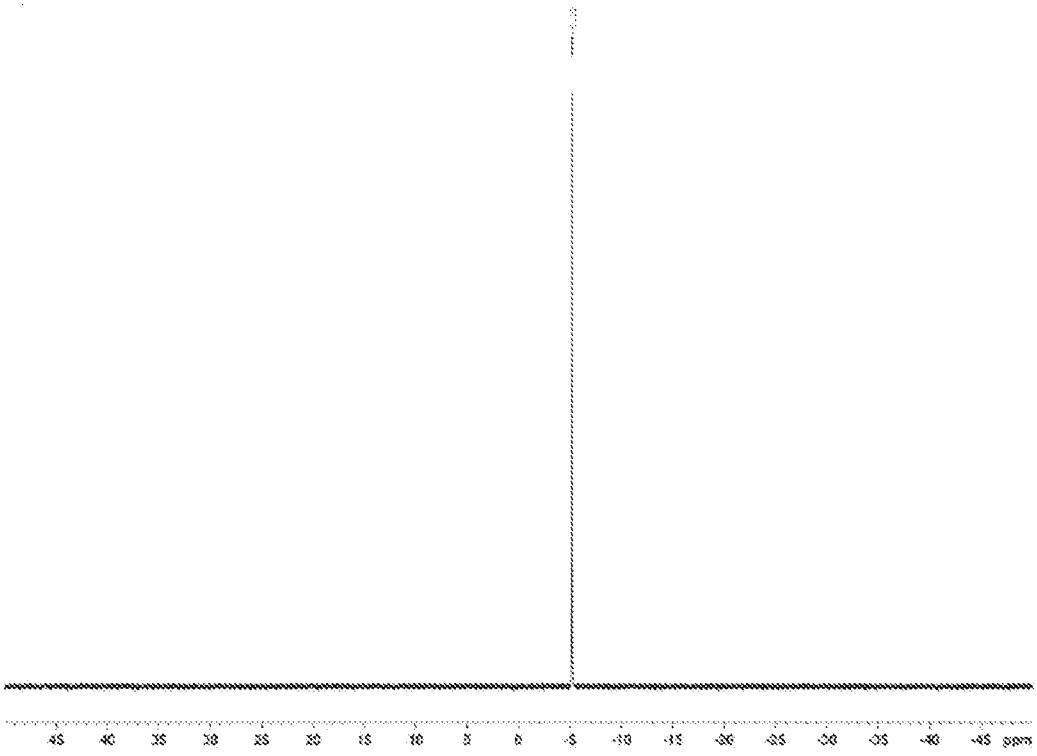

45
40
35
30
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
ppm

FIG. 4

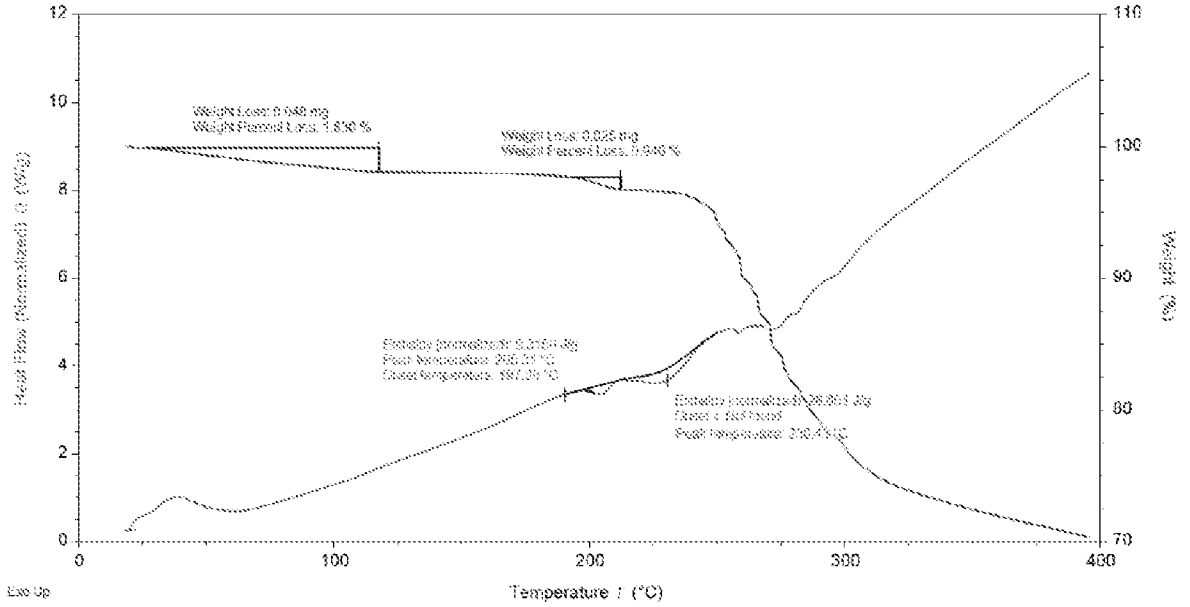

Heat Flow (Normalized) Q (W/g)
Exo Up
Temperature T (°C)
(%) Weight
0
100
200
300
400
70
80
90
100
110
0
2
4
6
8
10
12

FIG. 5

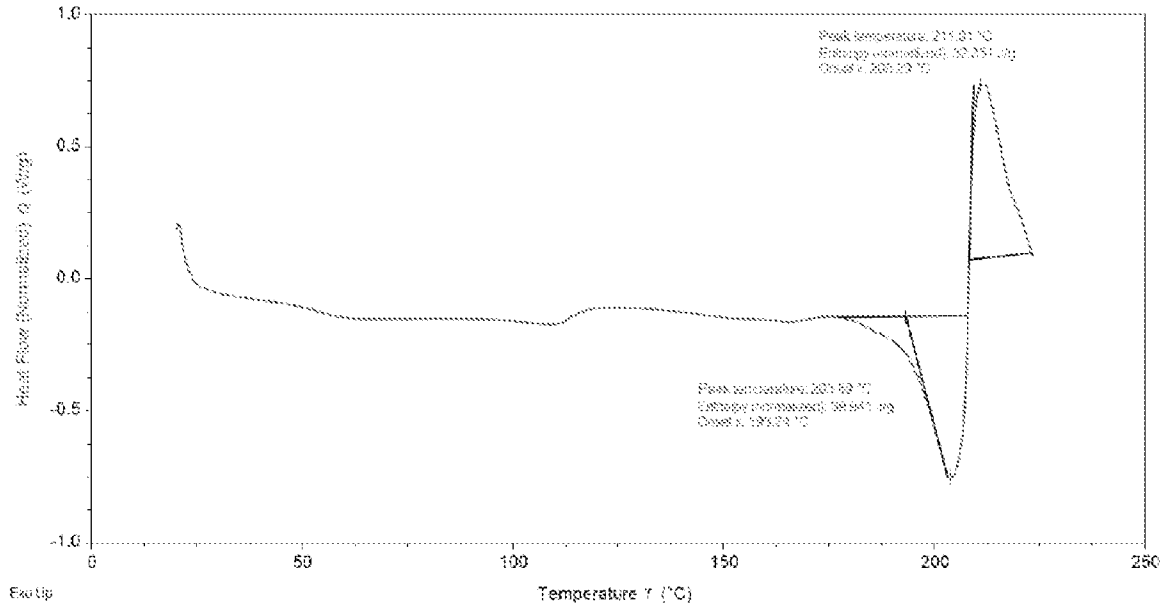

Heat Flow (Normalized) Q (W/g)
Exo Up
Temperature T (°C)
0
50
100
150
200
250
-1.0
-0.5
0.0
0.5
1.0

FIG. 6

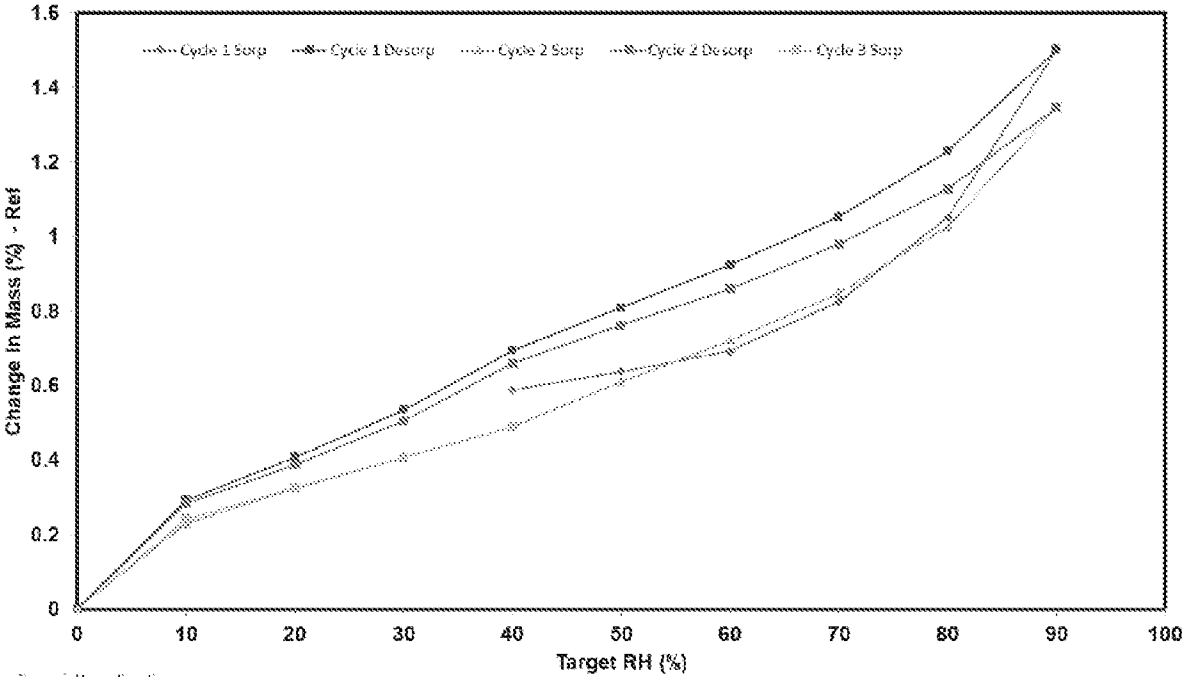

Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Cycle 3 Sorp
Change in Mass (%) - Ref
Target RH (%)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
0
10
20
30
40
50
60
70
80
90
100

FIG. 7

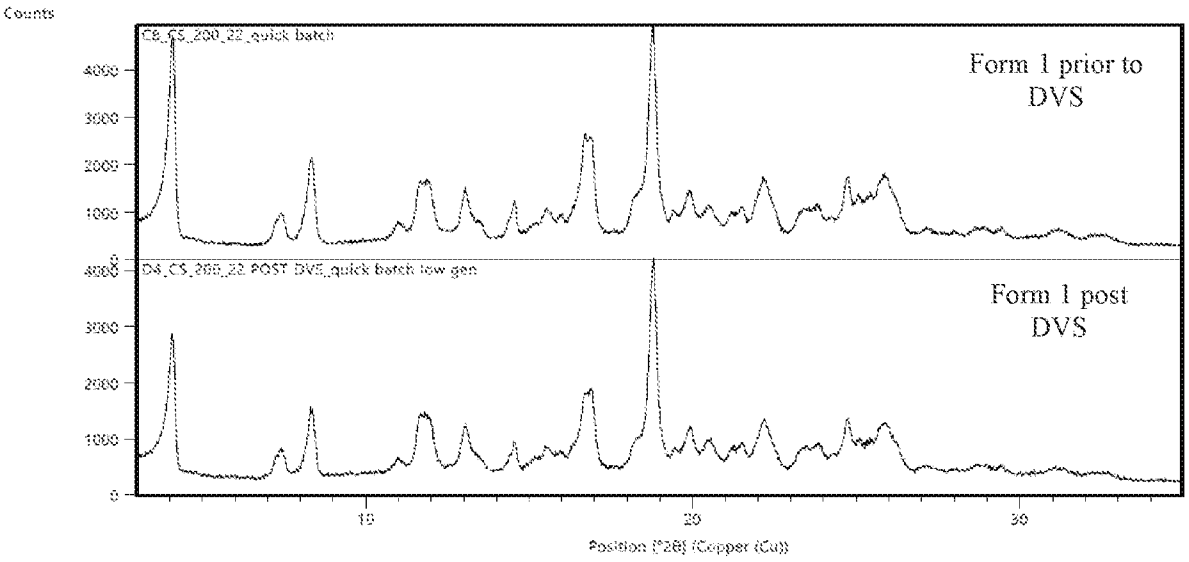

Counts
Form 1 prior to DVS
Form 1 post DVS
Position [°2θ] (Copper (Cu))
10
20
30

FIG. 8

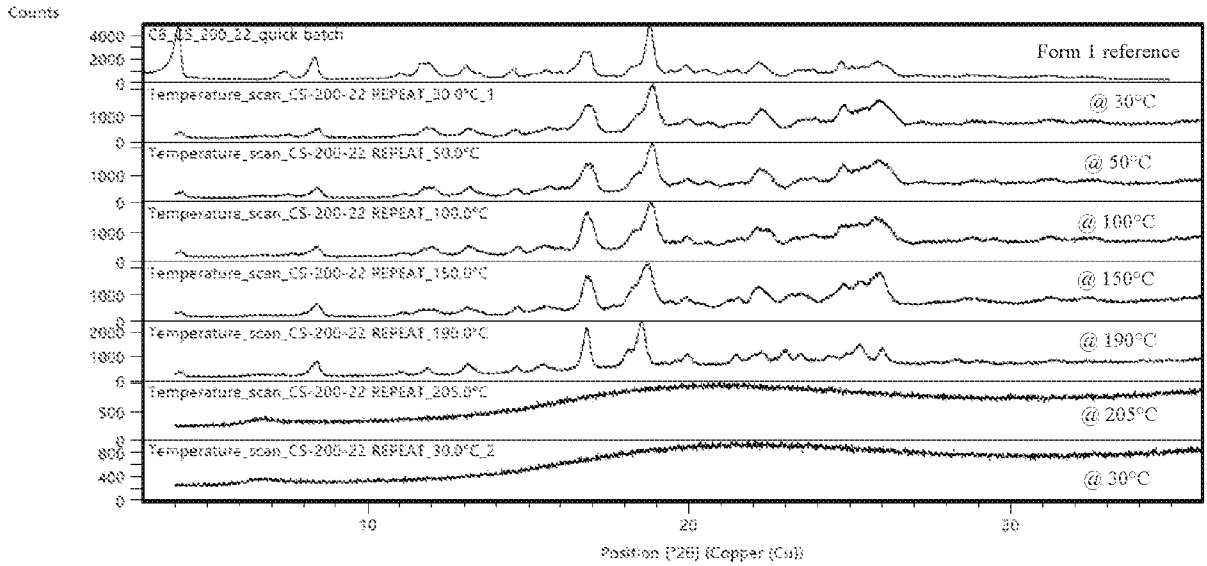

Counts
CS_SS_200_22_quick batch
Form 1 reference
Temperature_scan_CS-200-22 REPEAT_30.0°C_1
@ 30°C
Temperature_scan_CS-200-22 REPEAT_50.0°C
@ 50°C
Temperature_scan_CS-200-22 REPEAT_100.0°C
@ 100°C
Temperature_scan_CS-200-22 REPEAT_150.0°C
@ 150°C
Temperature_scan_CS-200-22 REPEAT_190.0°C
@ 190°C
Temperature_scan_CS-200-22 REPEAT_205.0°C
@ 205°C
Temperature_scan_CS-200-22 REPEAT_30.0°C_2
@ 30°C
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 9

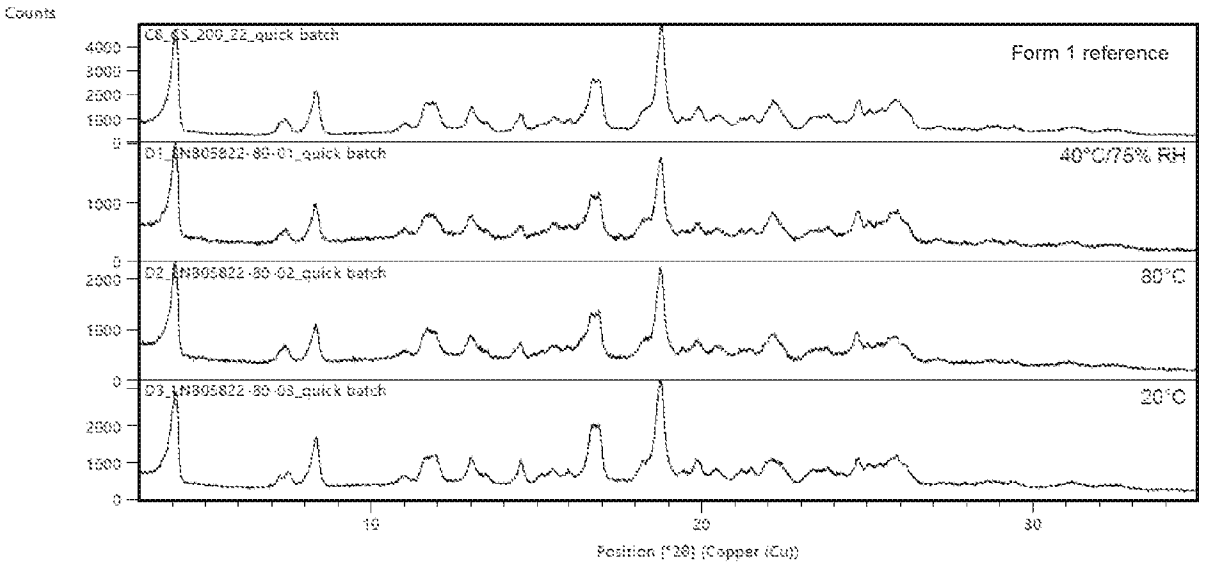

Counts
CS_SS_200_22_quick batch
Form 1 reference
D1_SN805822-80-01_quick batch
40°C/75% RH
D2_SN805822-80-02_quick batch
80°C
D3_SN805822-80-03_quick batch
20°C
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 10

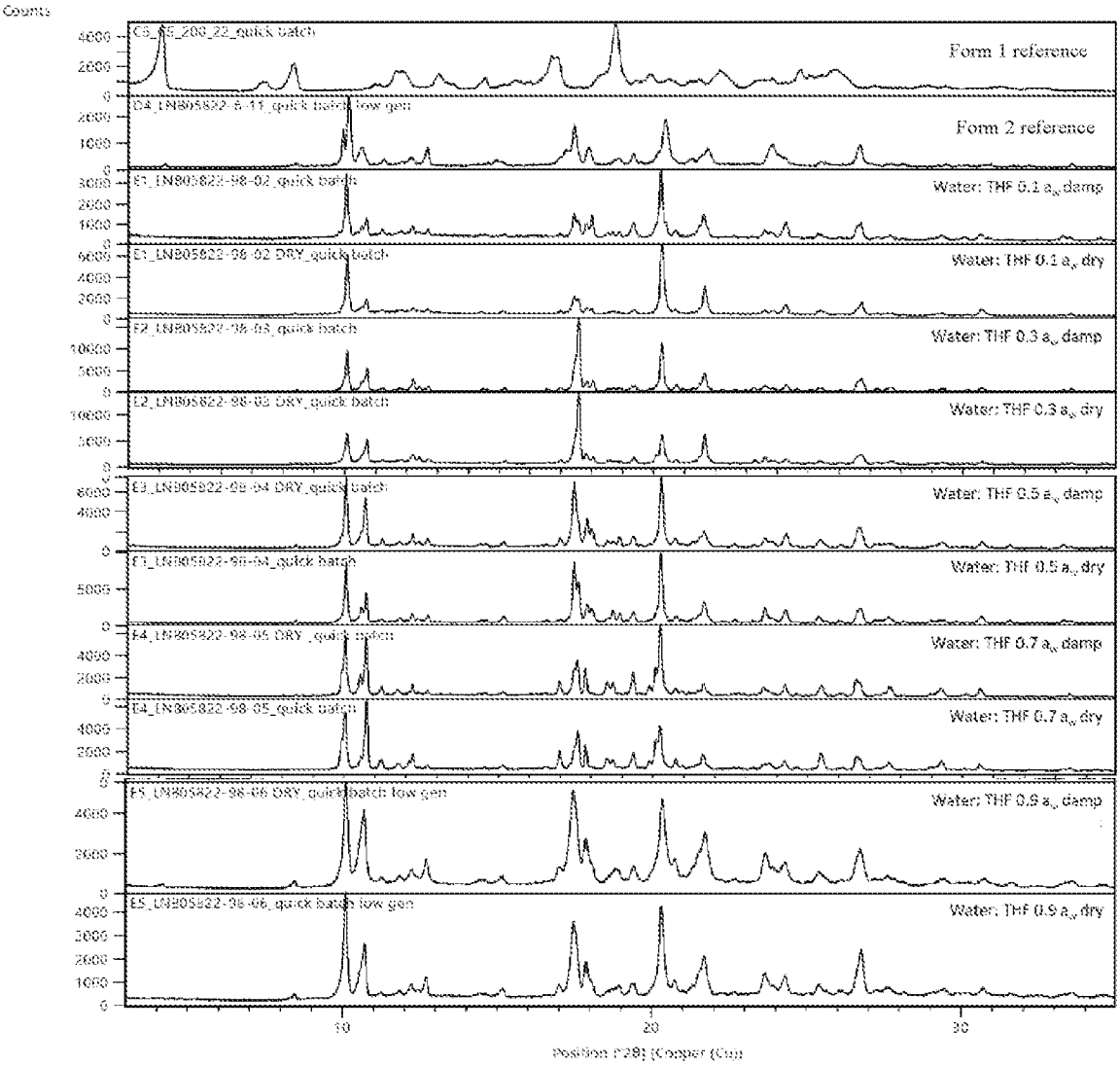

Counts
Form 1 reference
Form 2 reference
Water: THF 0.1 a_w damp
Water: THF 0.1 a_w dry
Water: THF 0.3 a_w damp
Water: THF 0.3 a_w dry
Water: THF 0.5 a_w damp
Water: THF 0.5 a_w dry
Water: THF 0.7 a_w damp
Water: THF 0.7 a_w dry
Water: THF 0.9 a_w damp
Water: THF 0.9 a_w dry
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 11

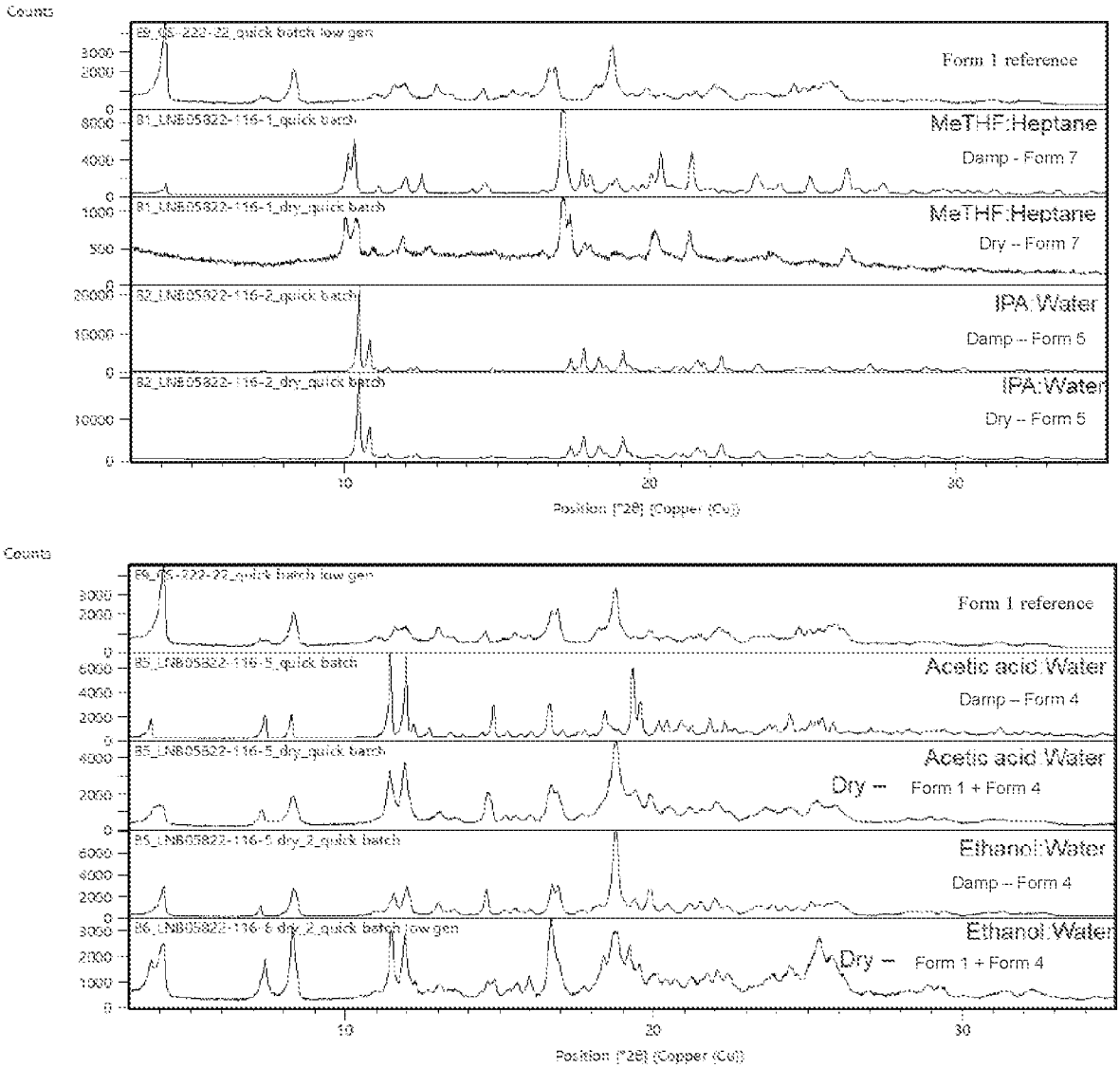

Counts
Form 1 reference
MeTHF:Heptane
Damp - Form 7
MeTHF:Heptane
Dry -- Form 7
IPA:Water
Damp -- Form 5
IPA:Water
Dry -- Form 5
Position [°2θ] (Copper (Cu))
Counts
Form 1 reference
Acetic acid:Water
Damp – Form 4
Acetic acid:Water
Dry – Form 1 + Form 4
Ethanol:Water
Damp – Form 4
Ethanol:Water
Dry – Form 1 + Form 4
Position [°2θ] (Copper (Cu))

FIG. 12

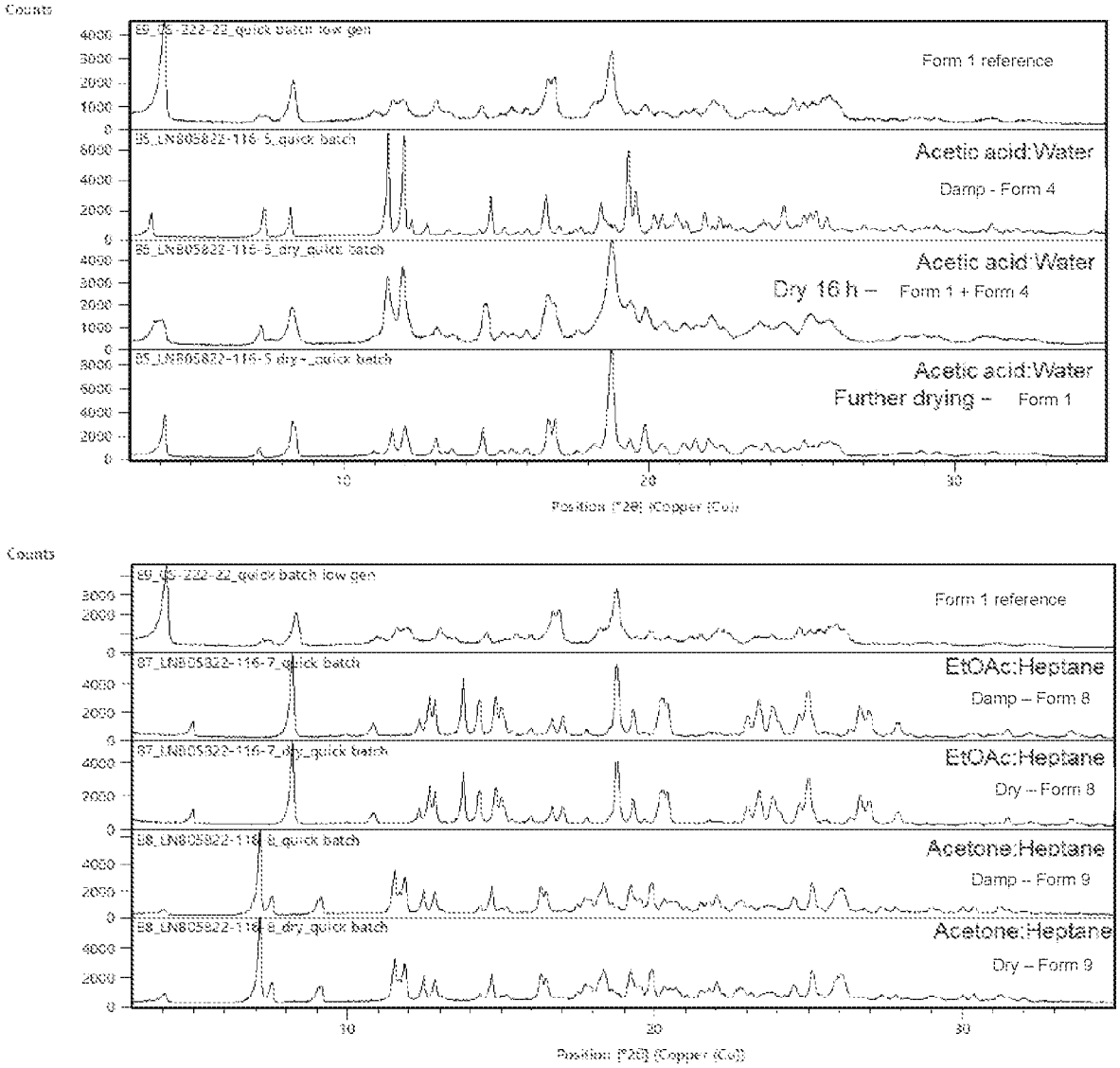

Counts
Form 1 reference
Acetic acid:Water
Damp - Form 4
Acetic acid:Water
Dry 16 h – Form 1 + Form 4
Acetic acid:Water
Further drying – Form 1
Position [°2θ] (Copper (Cu))
Counts
Form 1 reference
EtOAc:Heptane
Damp – Form 8
EtOAc:Heptane
Dry – Form 8
Acetone:Heptane
Damp – Form 9
Acetone:Heptane
Dry – Form 9
Position [°2θ] (Copper (Cu))

FIG. 12 cont'd

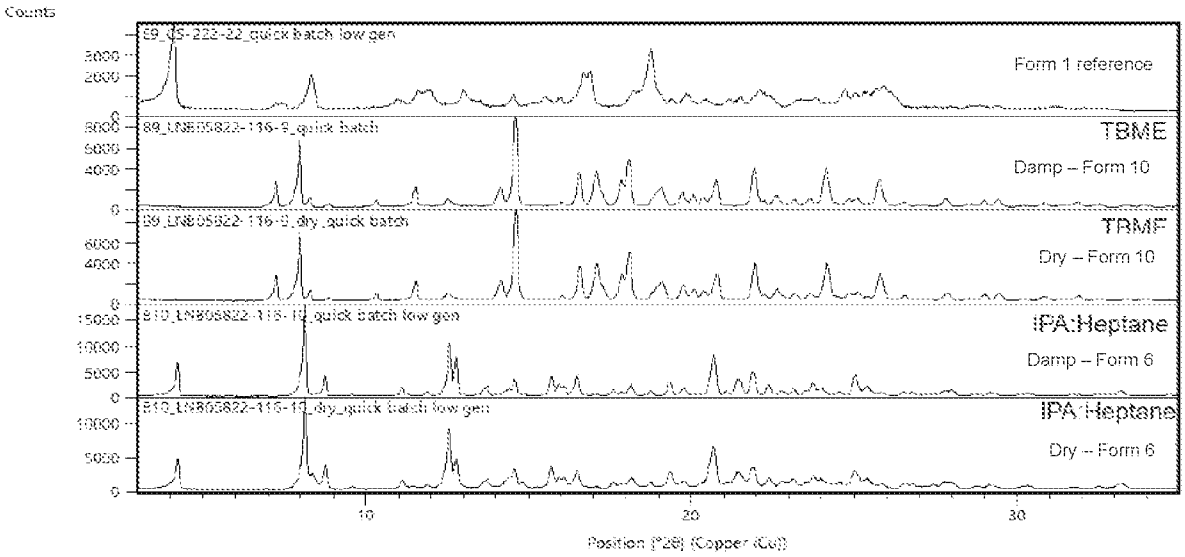

Counts
Form 1 reference
TBME
Damp – Form 10
TBMF
Dry – Form 10
IPA:Heptane
Damp – Form 6
IPA:Heptane
Dry – Form 6
Position [°2θ] (Copper (Cu))

FIG. 12 cont'd

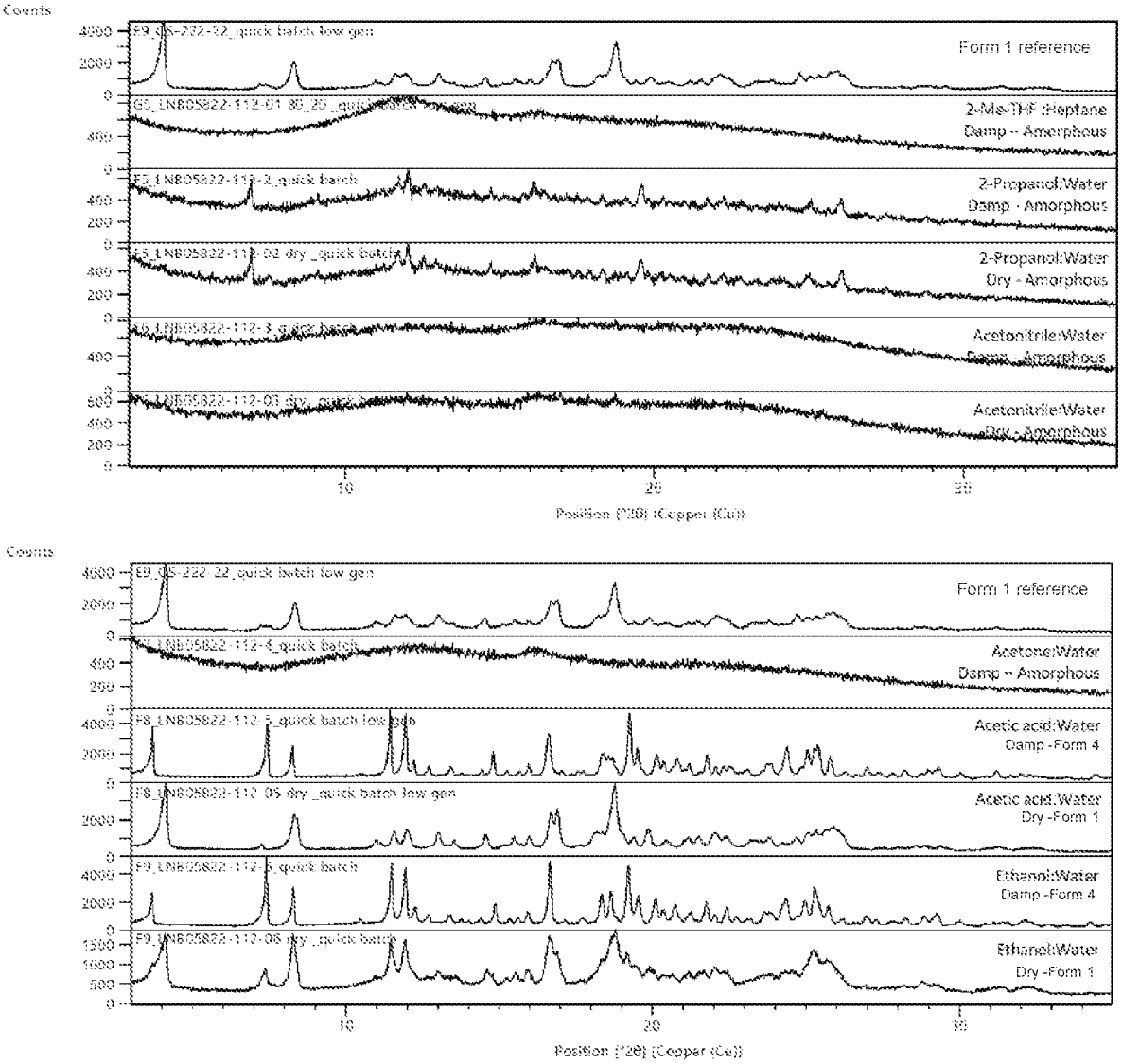

Counts
Form 1 reference
2-Me-THF:Heptane
Damp - Amorphous
2-Propanol:Water
Damp - Amorphous
2-Propanol:Water
Dry - Amorphous
Acetonitrile:Water
Damp - Amorphous
Acetonitrile:Water
Dry - Amorphous
Position [°2θ] (Copper (Cu))
Counts
Form 1 reference
Acetone:Water
Damp - Amorphous
Acetic acid:Water
Damp - Form 4
Acetic acid:Water
Dry - Form 1
Ethanol:Water
Damp - Form 4
Ethanol:Water
Dry - Form 1
Position [°2θ] (Copper (Cu))

FIG. 13

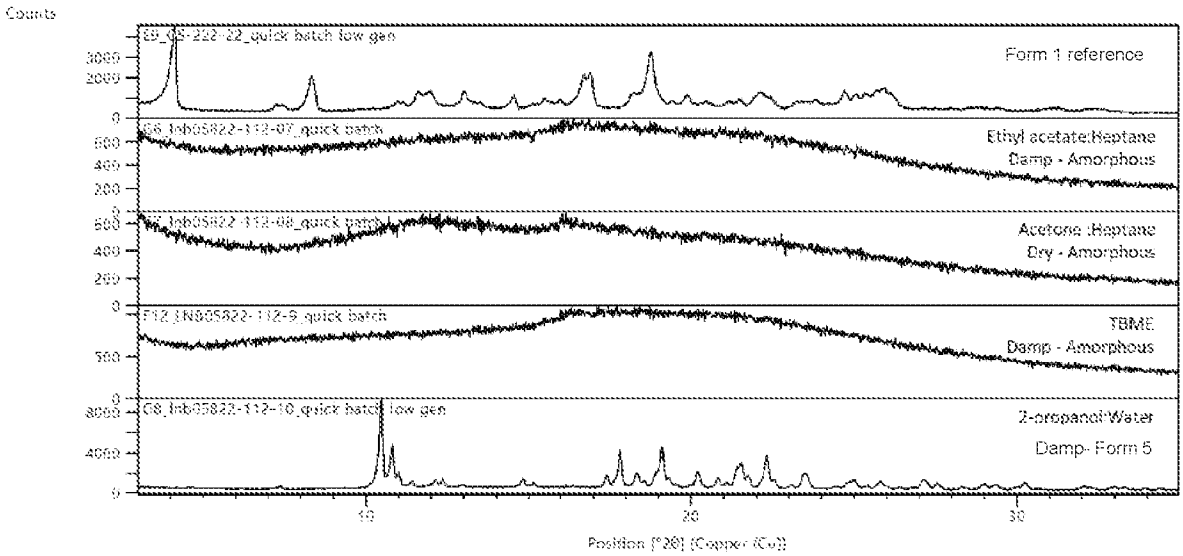

Counts
Form 1 reference
Ethyl acetate:Heptane
Damp - Amorphous
Acetone :Heptane
Dry - Amorphous
TBME
Damp - Amorphous
2-propanol:Water
Damp- Form 5
Position [°2θ] (Copper (Cu))

FIG. 13 cont'd

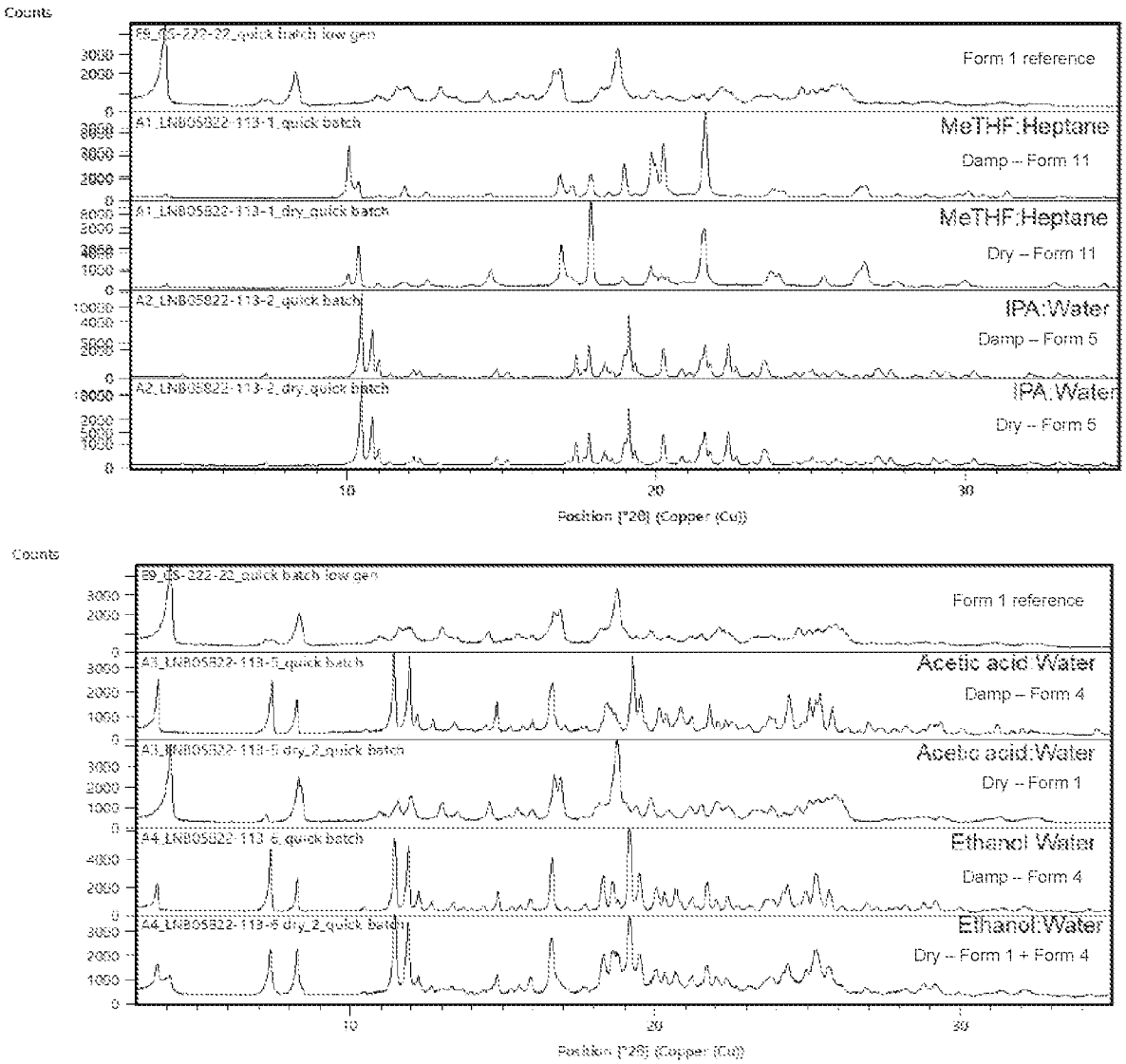

Counts
Form 1 reference
MeTHF:Heptane
Damp – Form 11
MeTHF:Heptane
Dry – Form 11
IPA:Water
Damp – Form 5
IPA:Water
Dry – Form 5
Position [°2θ] (Copper (Cu))
Counts
Form 1 reference
Acetic acid:Water
Damp – Form 4
Acetic acid:Water
Dry – Form 1
Ethanol:Water
Damp – Form 4
Ethanol:Water
Dry – Form 1 + Form 4
Position [°2θ] (Copper (Cu))

FIG. 14

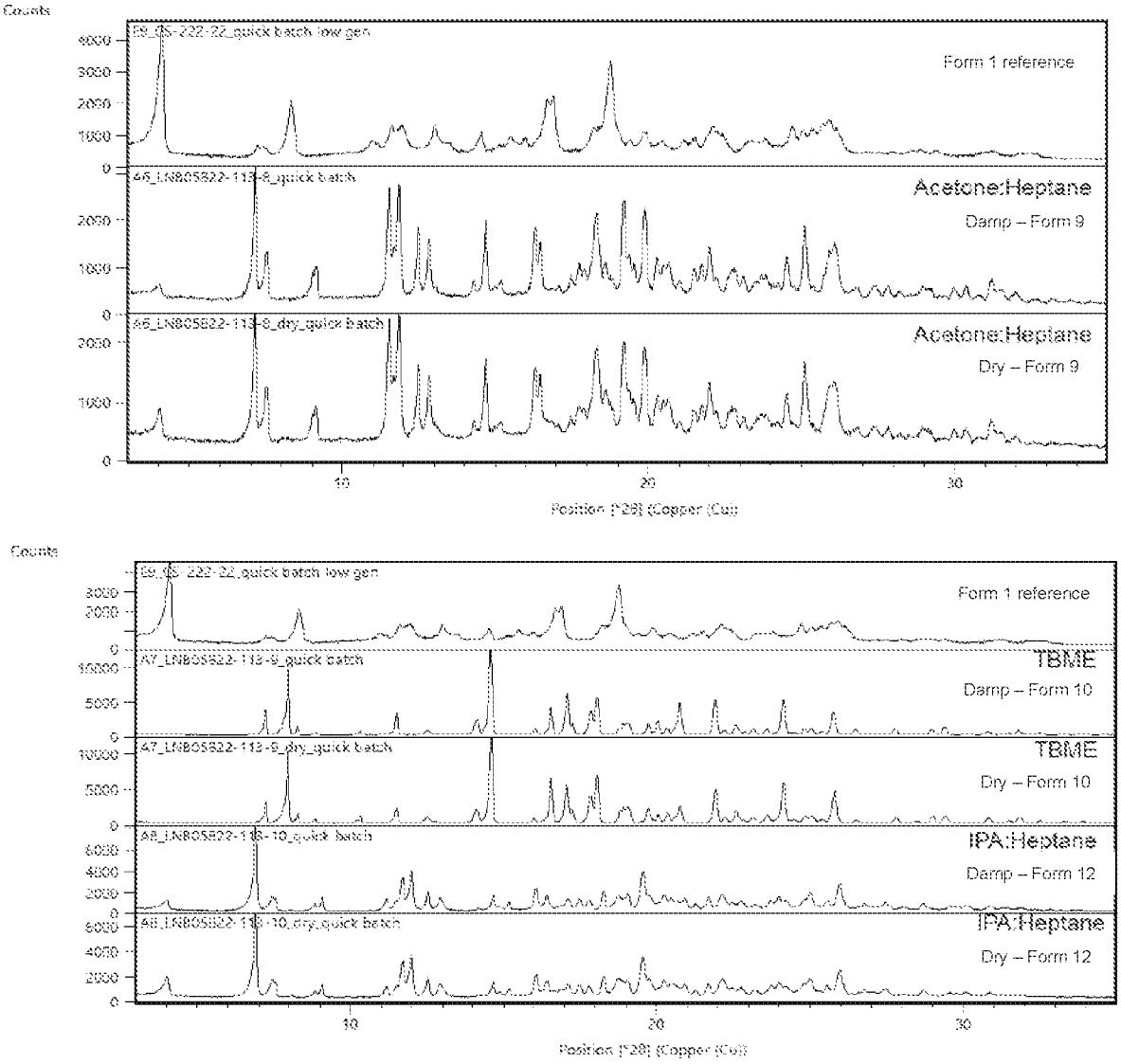

Counts
Form 1 reference
Acetone:Heptane
Damp – Form 9
Acetone:Heptane
Dry – Form 9
Position [°2θ] (Copper (Cu))
Counts
Form 1 reference
TBME
Damp – Form 10
TBME
Dry – Form 10
IPA:Heptane
Damp – Form 12
IPA:Heptane
Dry – Form 12
Position [°2θ] (Copper (Cu))

FIG. 14 cont'd

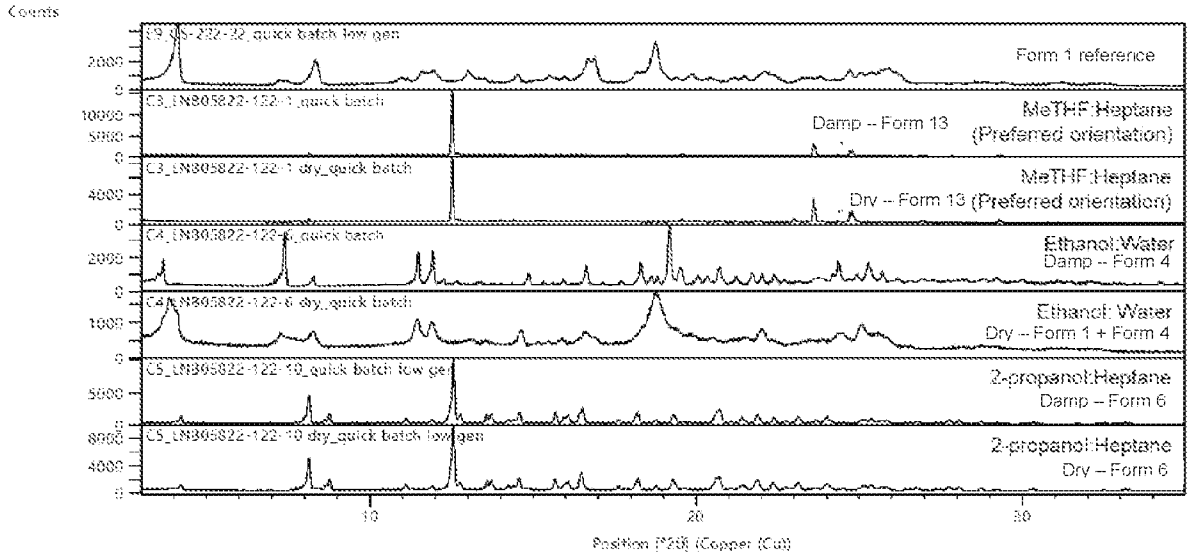

Counts
Form 1 reference
MeTHF:Heptane
(Preferred orientation)
Damp -- Form 13
MeTHF:Heptane
Dry -- Form 13 (Preferred orientation)
Ethanol:Water
Damp -- Form 4
Ethanol: Water
Dry -- Form 1 + Form 4
2-propanol:Heptane
Damp – Form 6
2-propanol:Heptane
Dry – Form 6
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 15

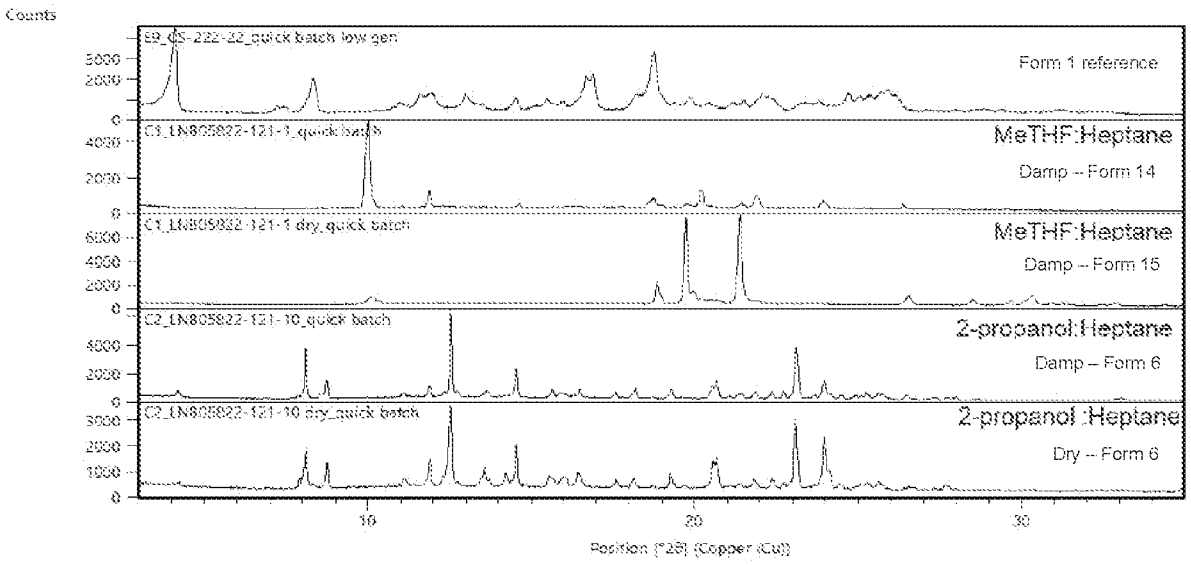

Counts
Form 1 reference
MeTHF:Heptane
Damp -- Form 14
MeTHF:Heptane
Damp -- Form 15
2-propanol:Heptane
Damp – Form 6
2-propanol :Heptane
Dry -- Form 6
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 16

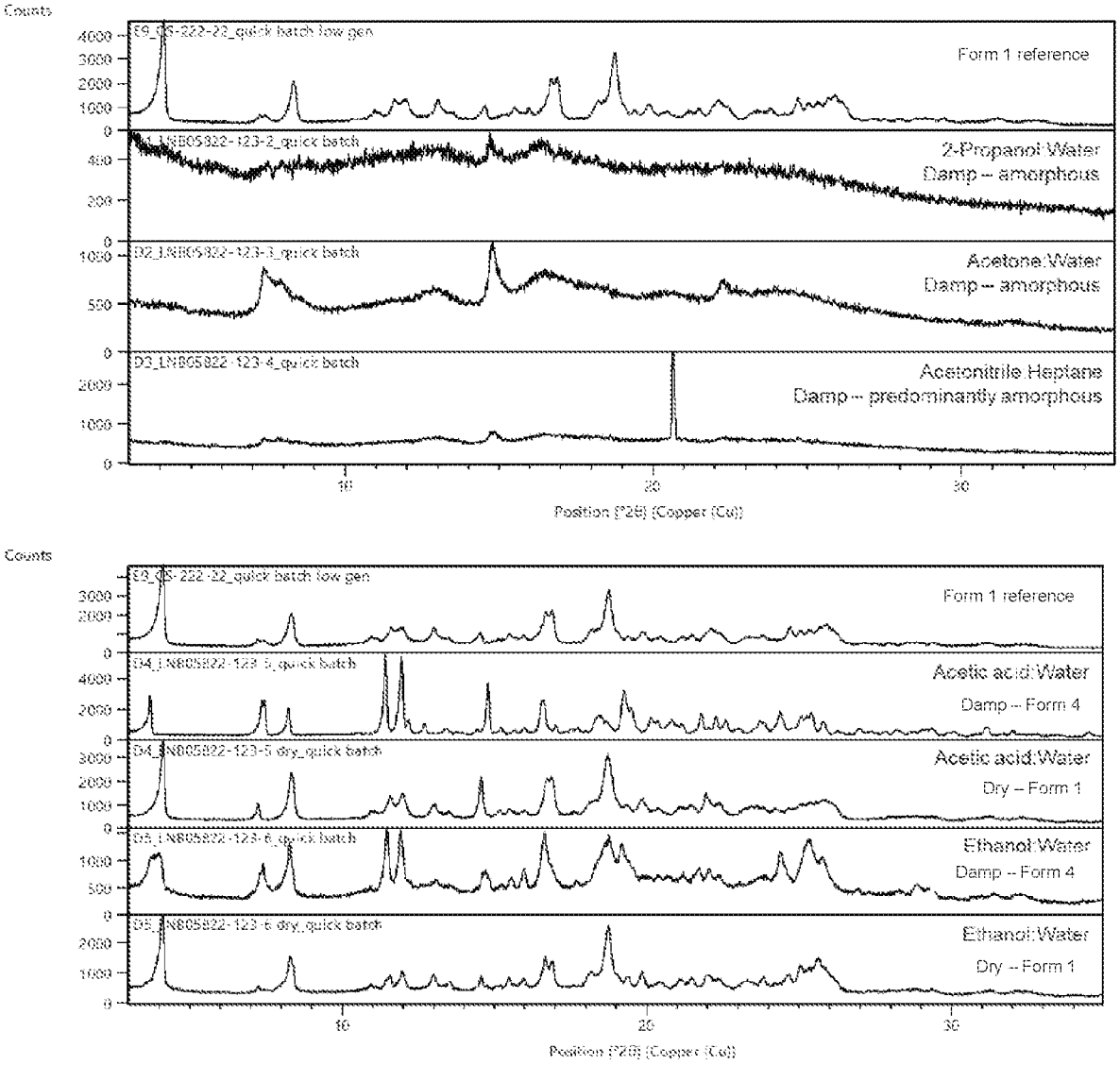

Counts
Form 1 reference
2-Propanol:Water
Damp -- amorphous
Acetone:Water
Damp -- amorphous
Acetonitrile Heptane
Damp -- predominantly amorphous
Position [°2θ] (Copper (Cu))
Counts
Form 1 reference
Acetic acid:Water
Damp -- Form 4
Acetic acid:Water
Dry -- Form 1
Ethanol:Water
Damp -- Form 4
Ethanol:Water
Dry -- Form 1
Position [°2θ] (Copper (Cu))

FIG. 17

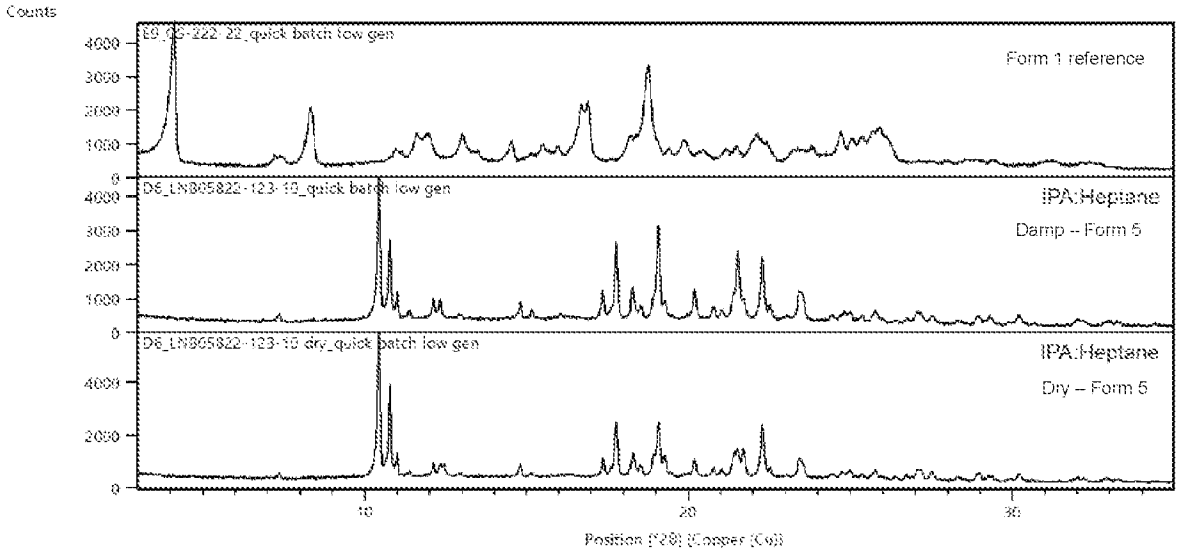

Counts
4000
3000
2000
1000
0
Form 1 reference
IPA:Heptane
Damp – Form 5
IPA:Heptane
Dry – Form 5
10
20
30
Position [°2θ] (Cooper (Cu))

FIG. 17 cont'd

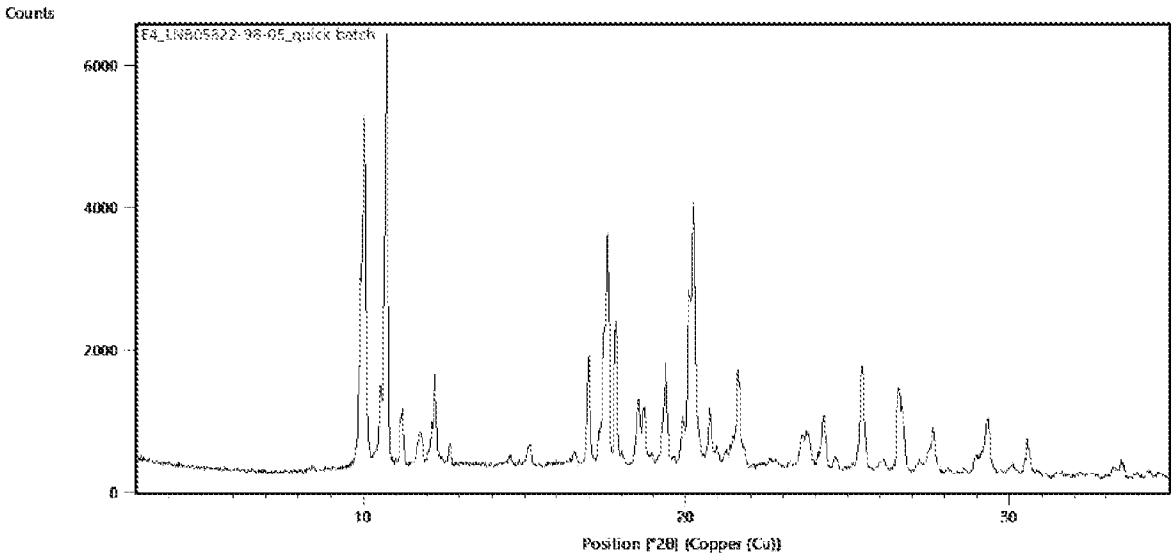


FIG. 18A

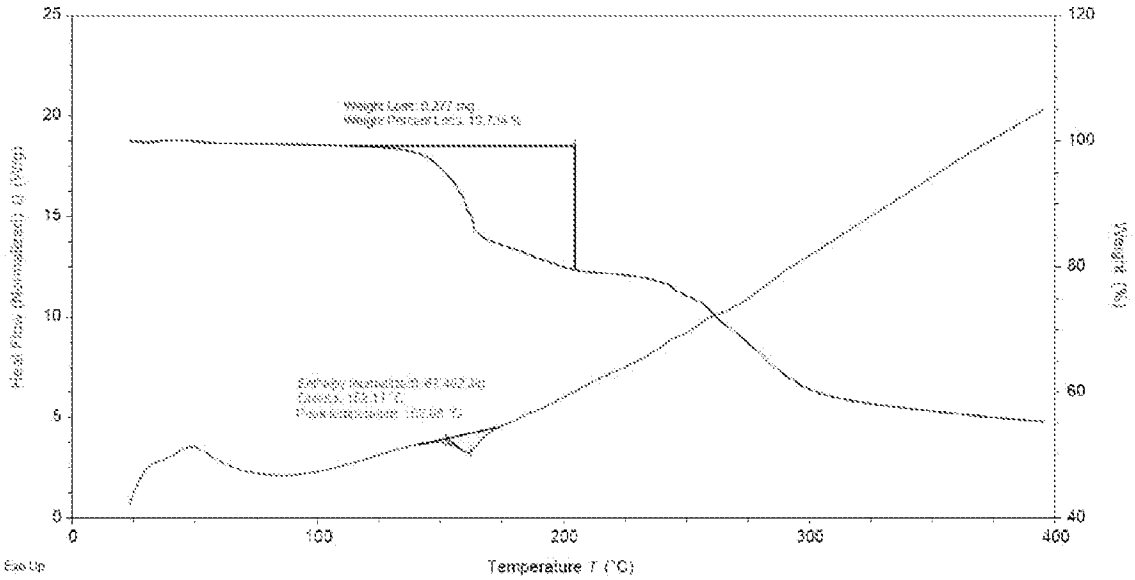


FIG. 18B

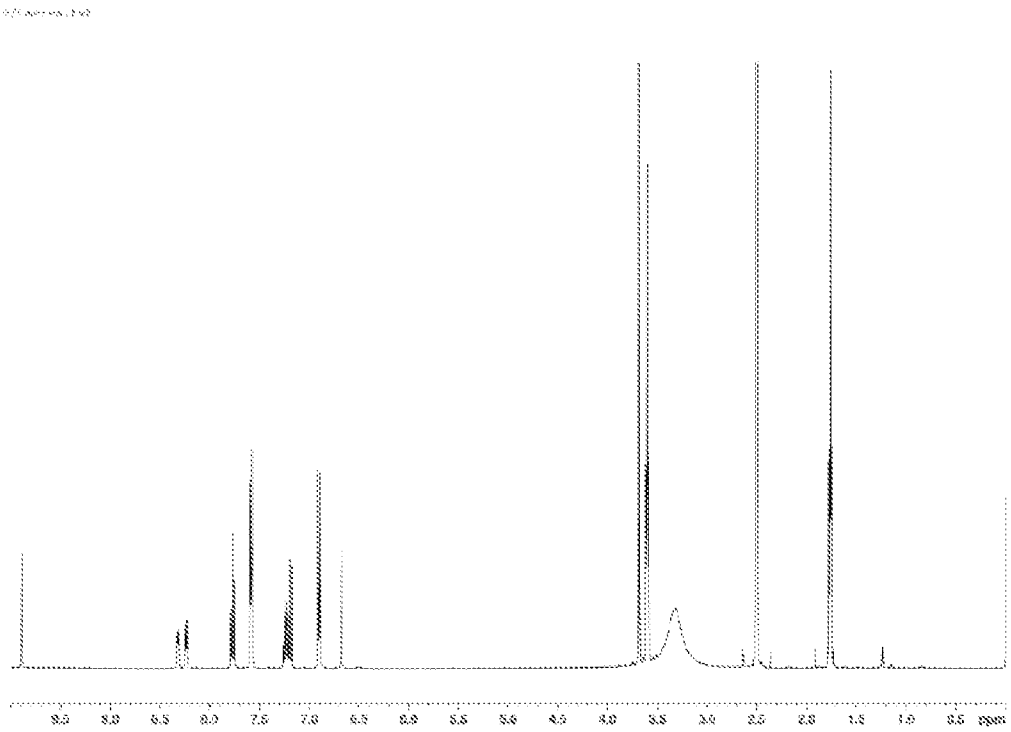


FIG. 18C

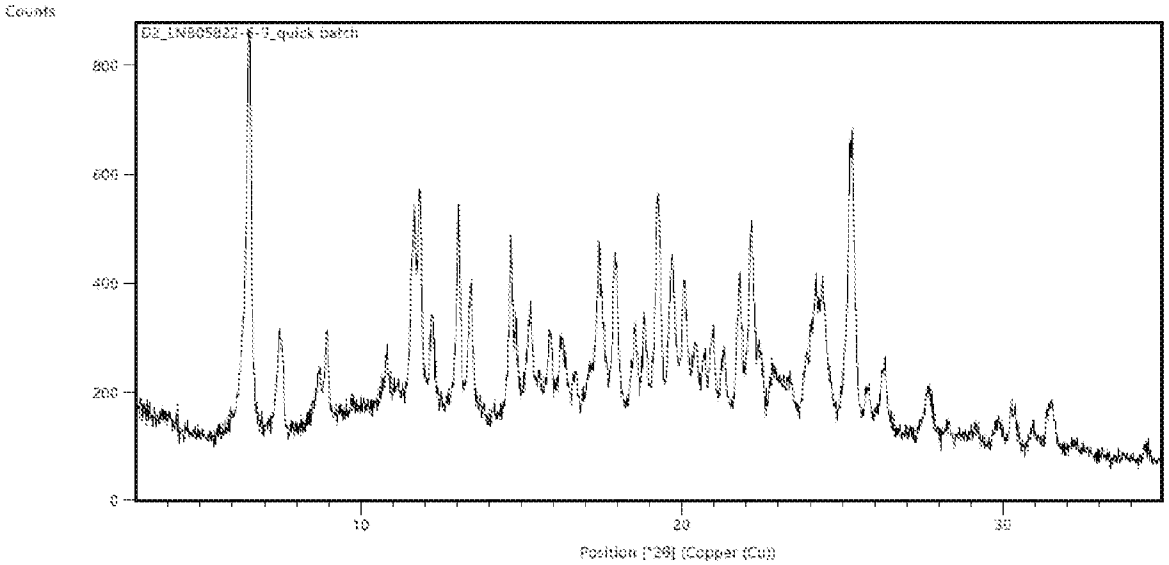


FIG. 19A

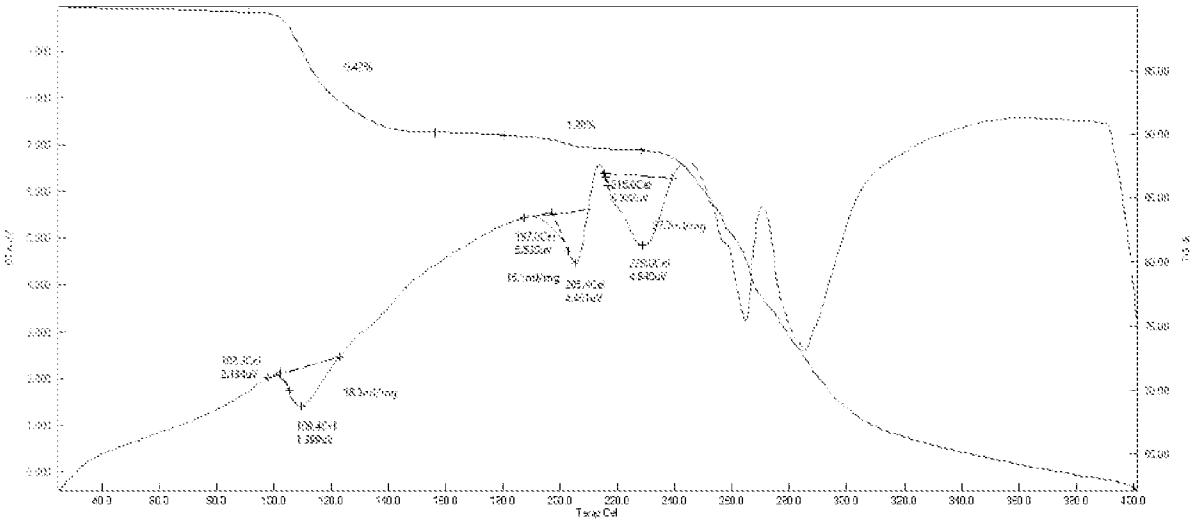


FIG. 19B

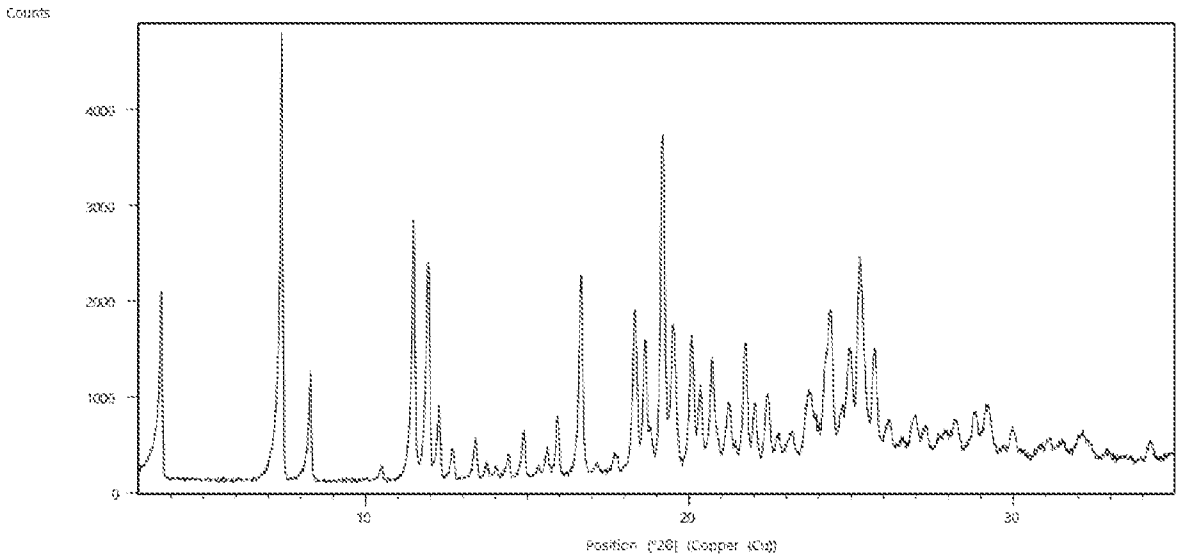


FIG. 20

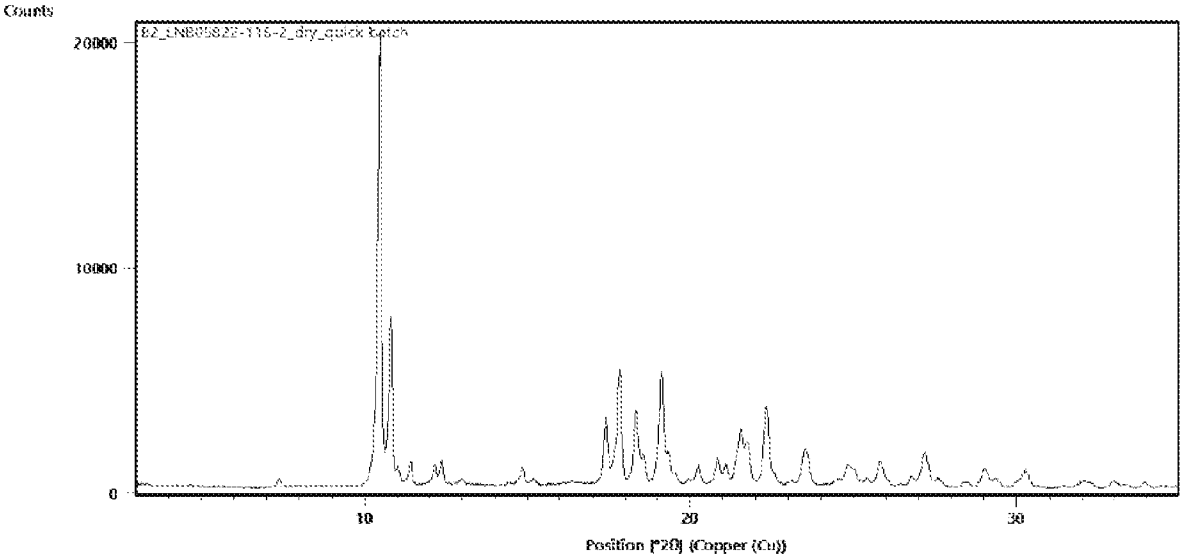


FIG. 21A

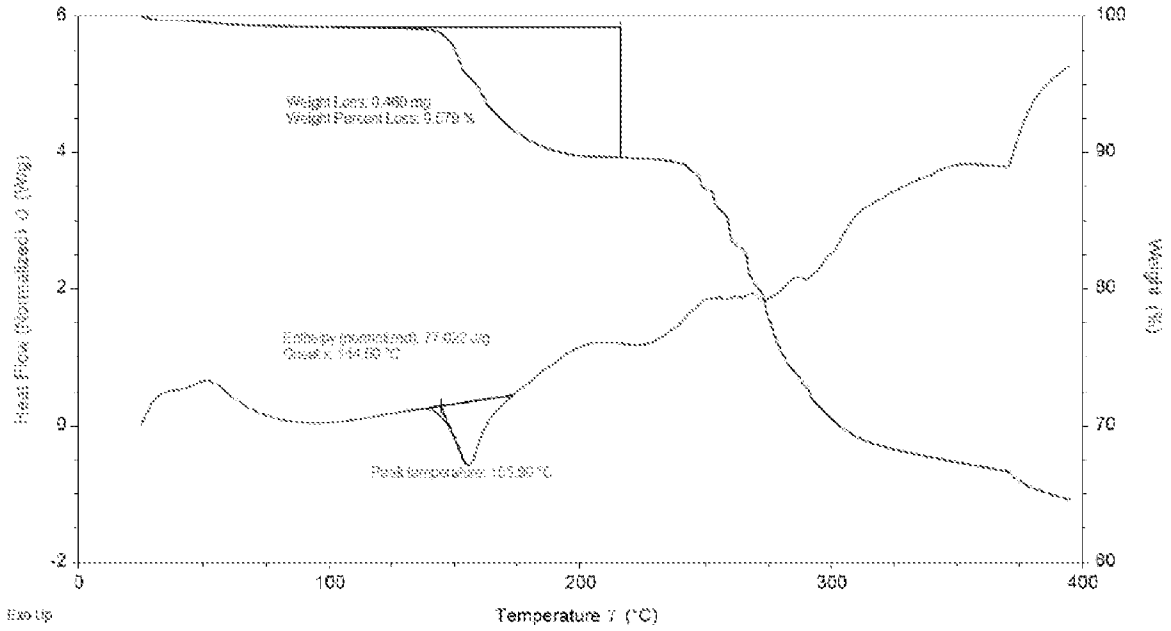


FIG. 21B

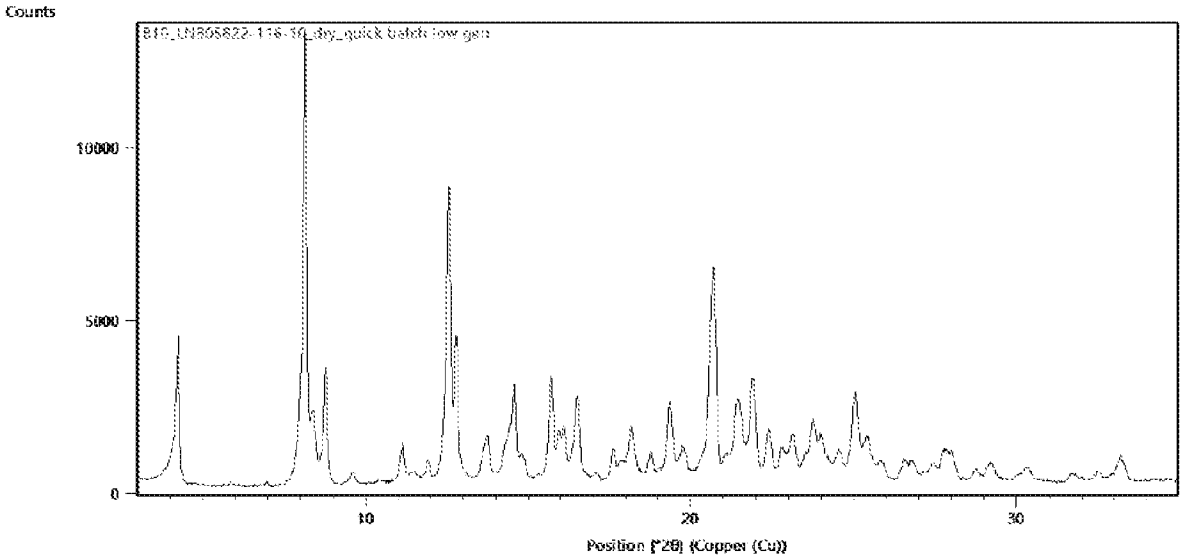


FIG. 22A

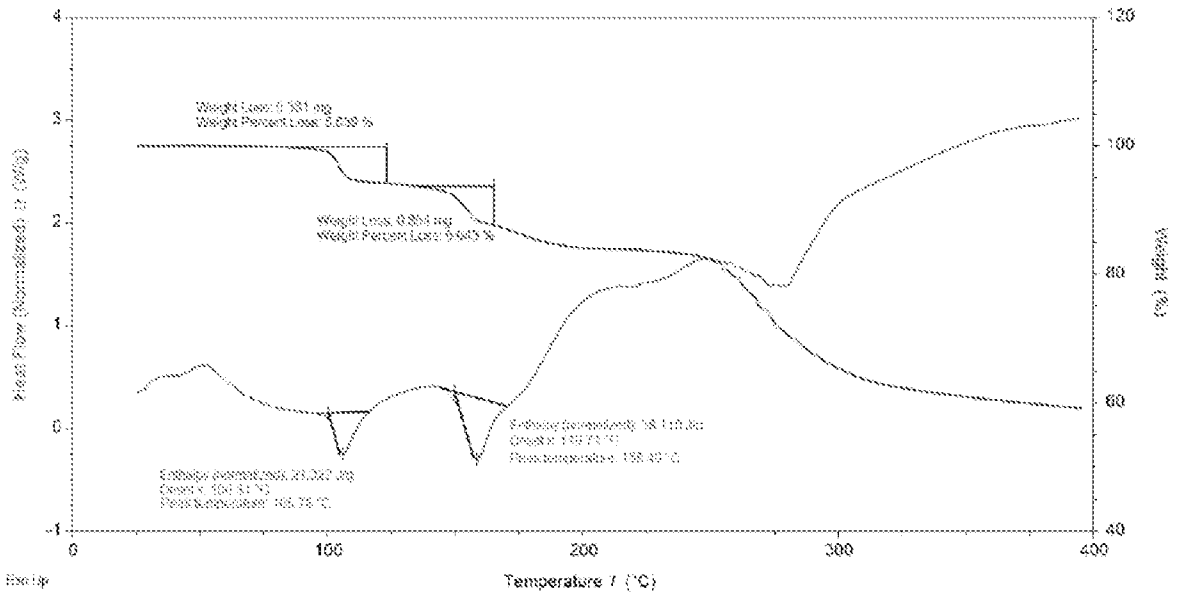


FIG. 22B

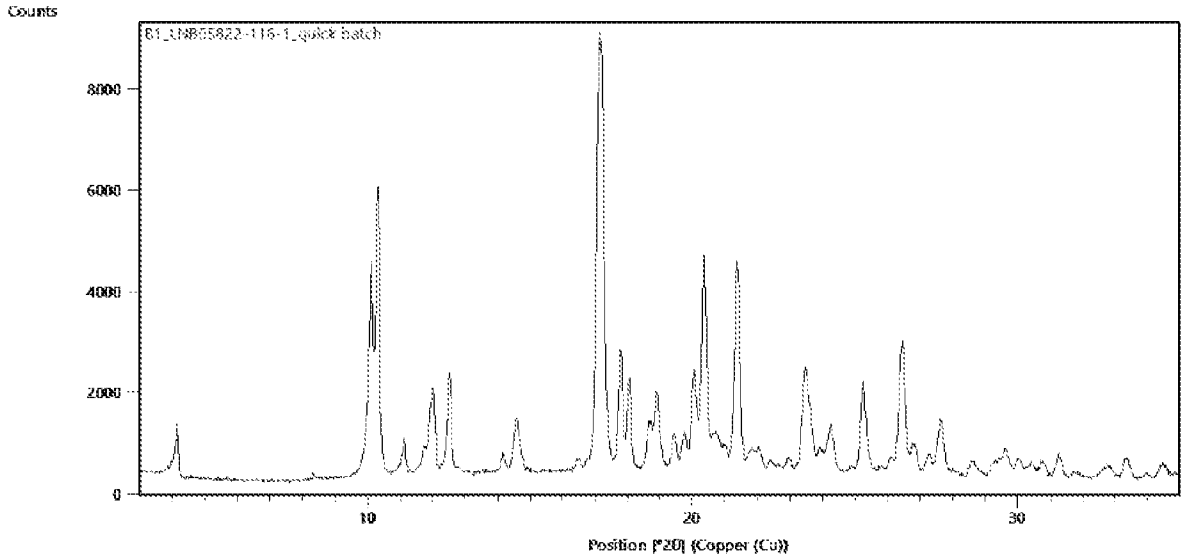


FIG. 23

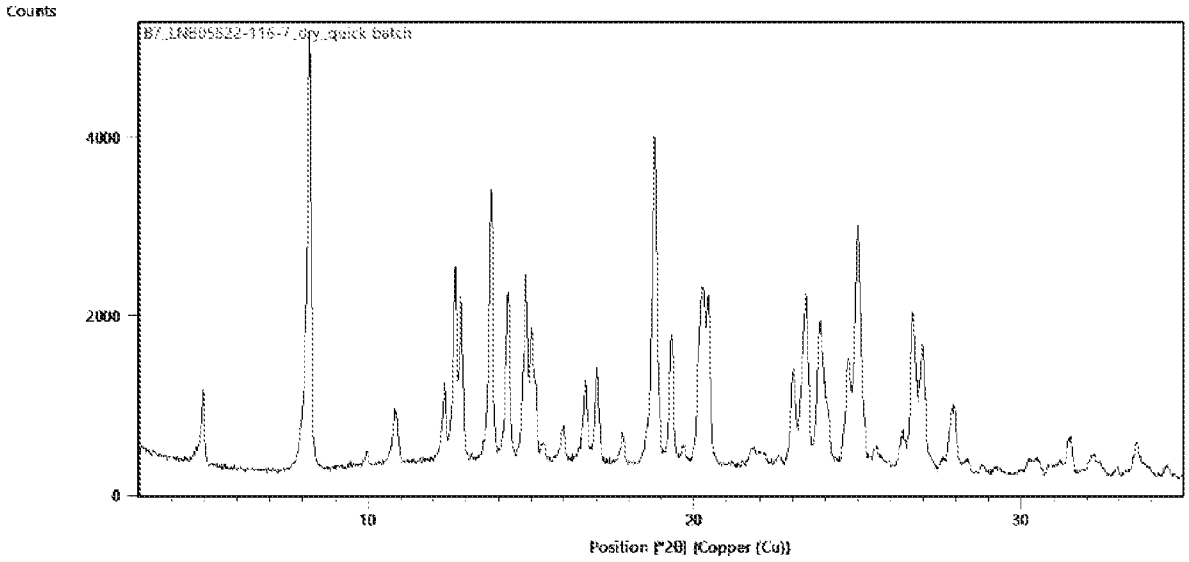


FIG. 24A

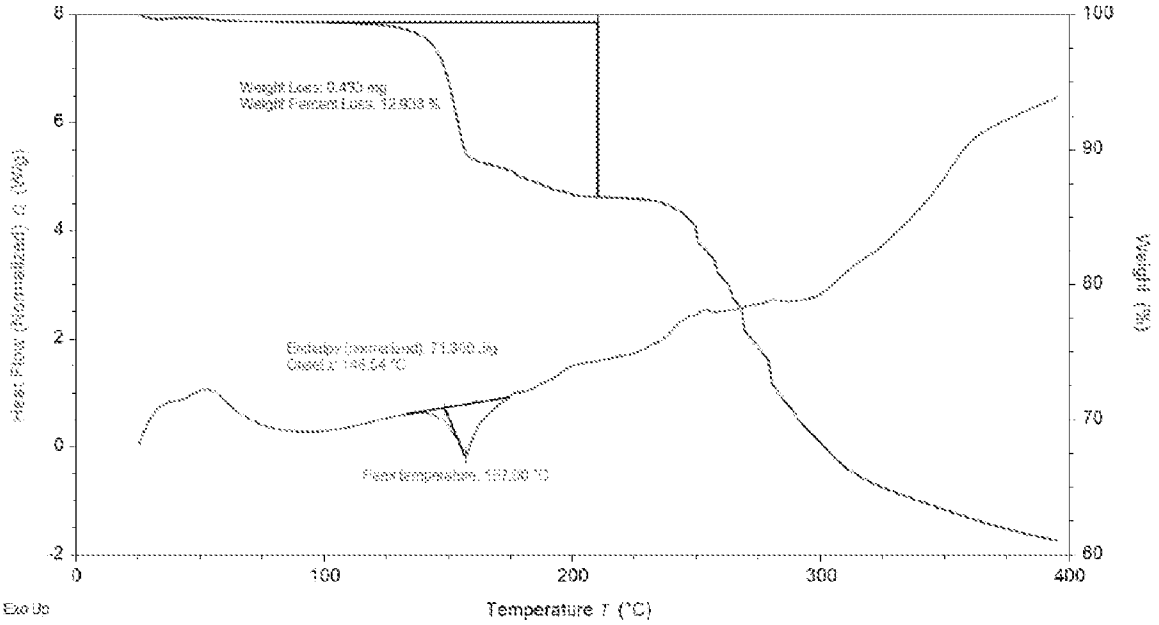


FIG. 24B

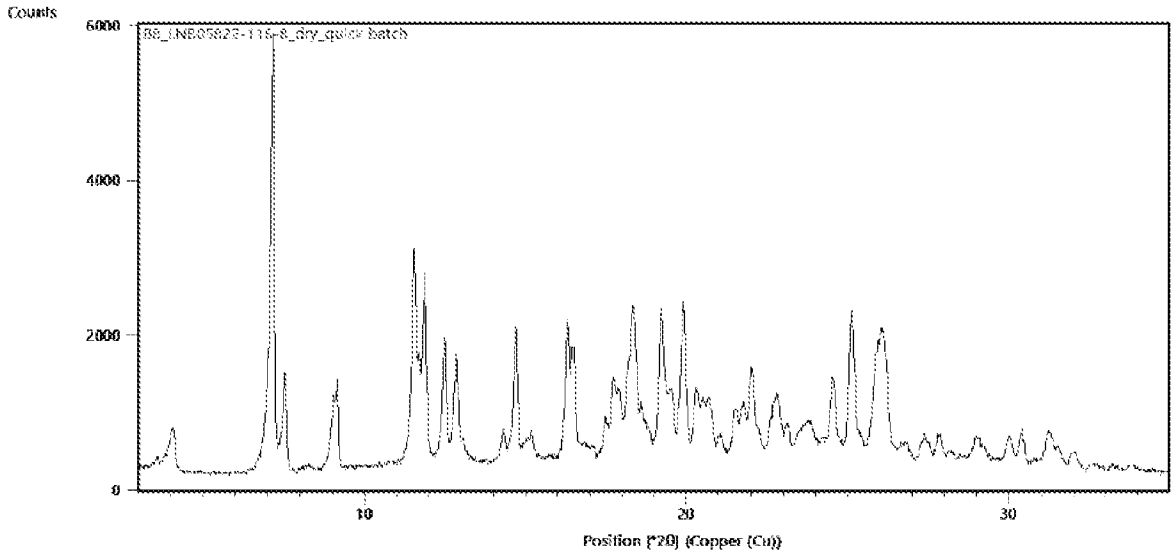


FIG. 25A

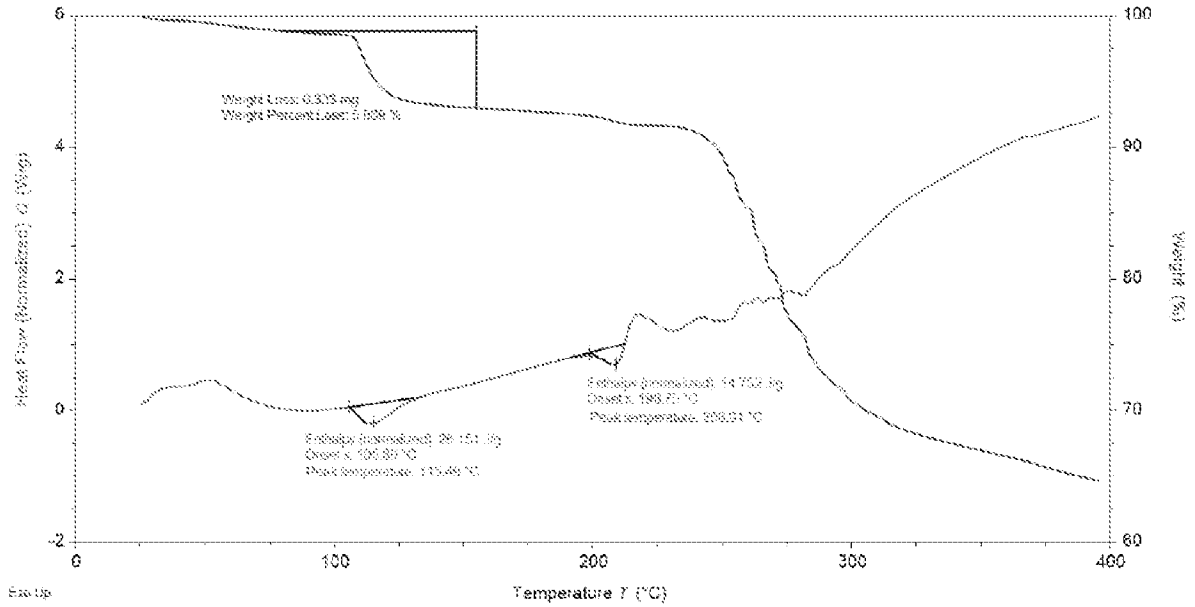


FIG. 25B

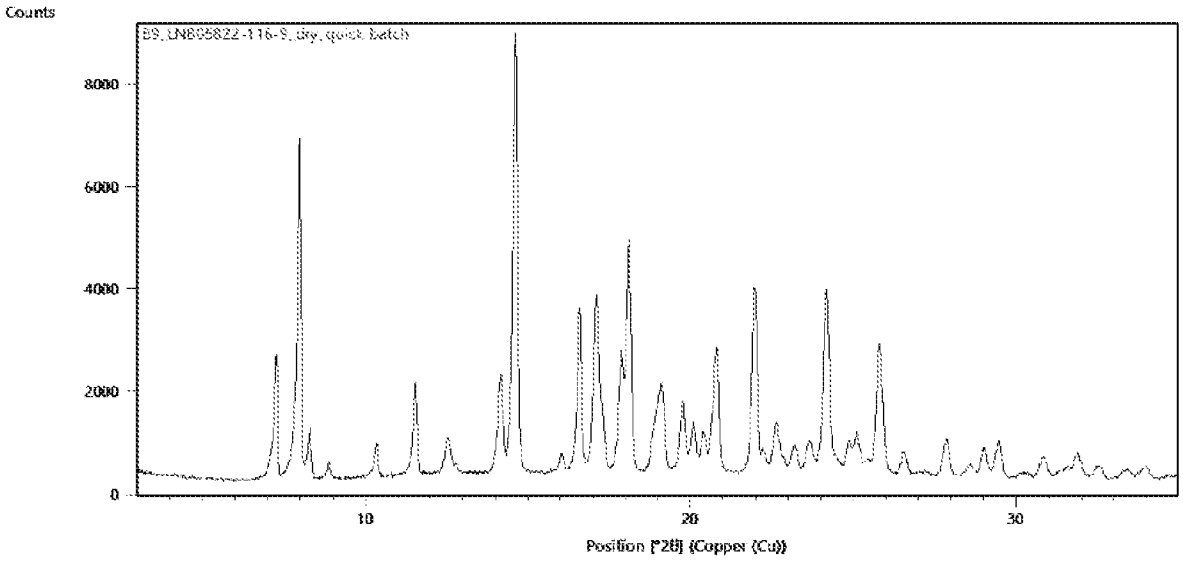


FIG. 26A

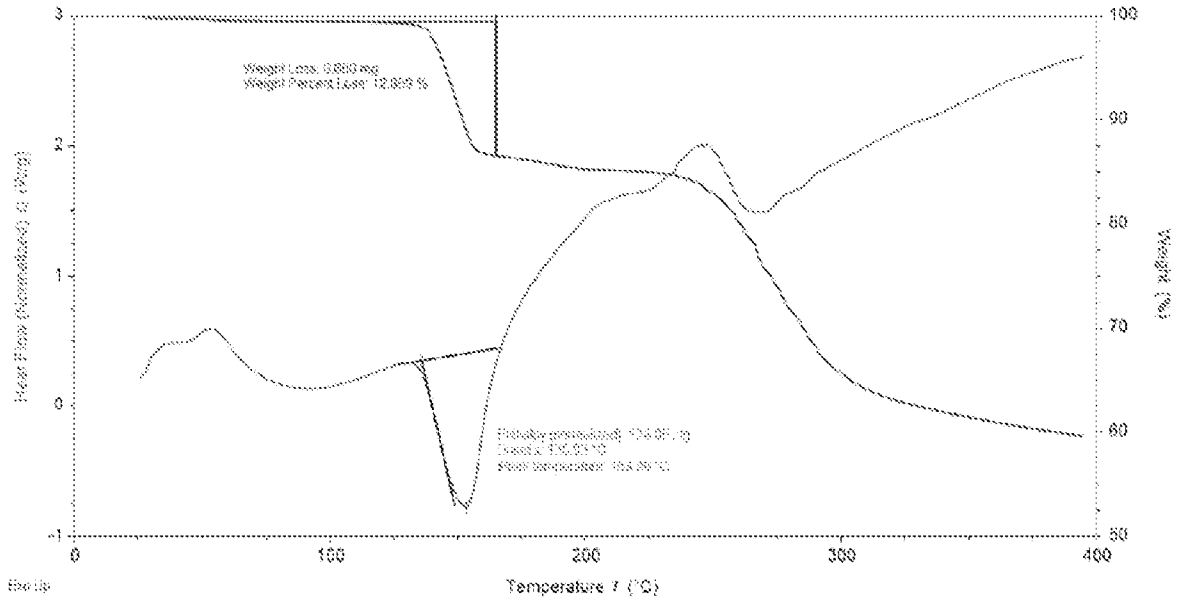


FIG. 26B

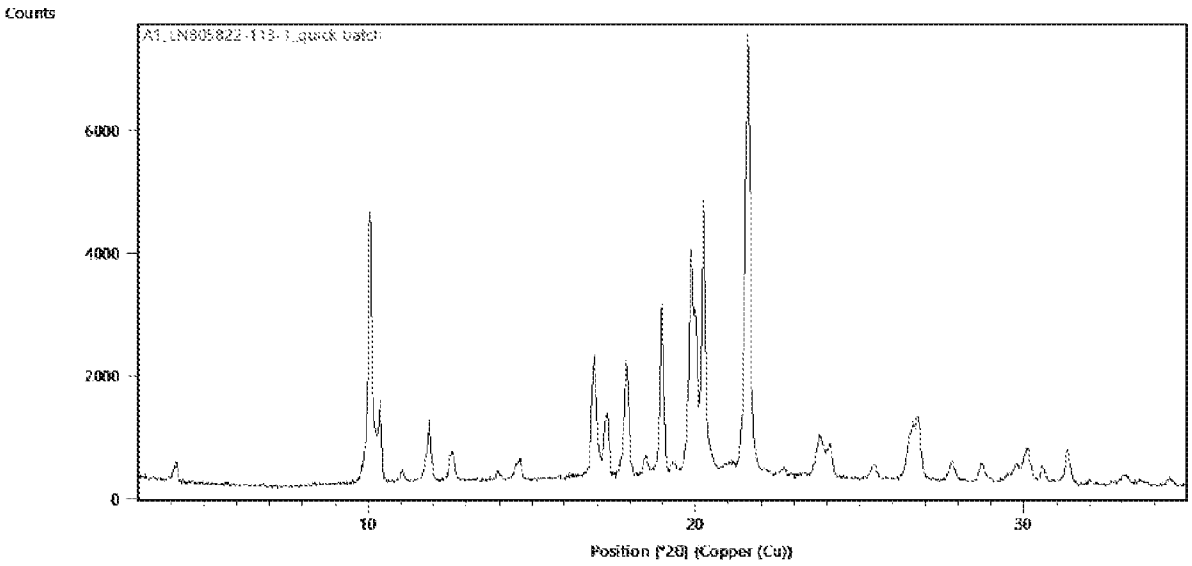


FIG. 27A

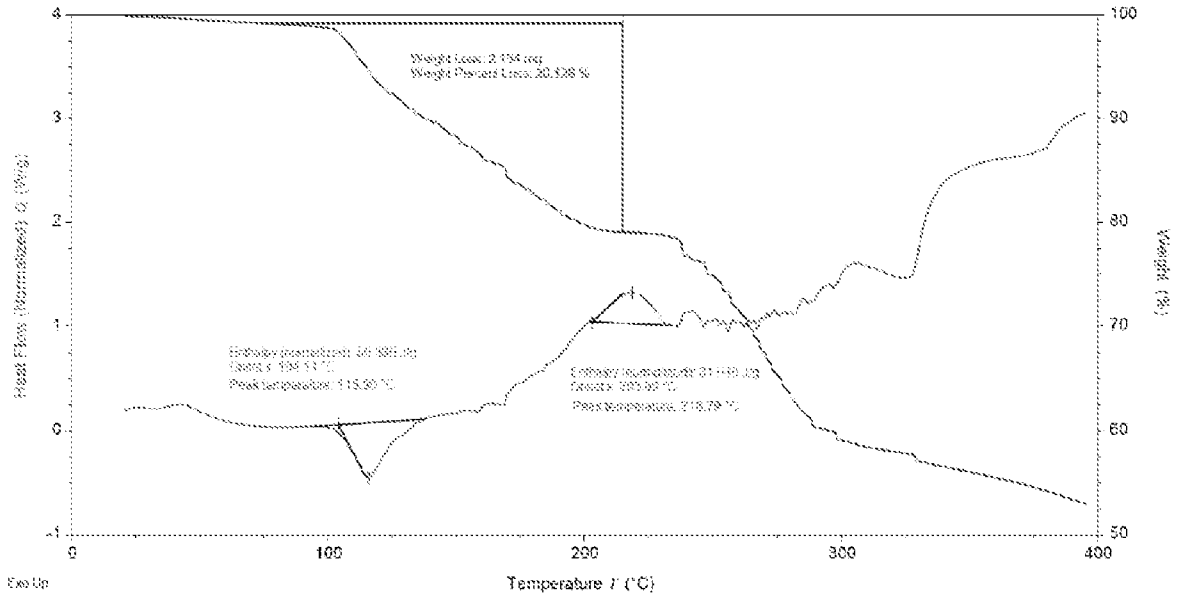


FIG. 27B

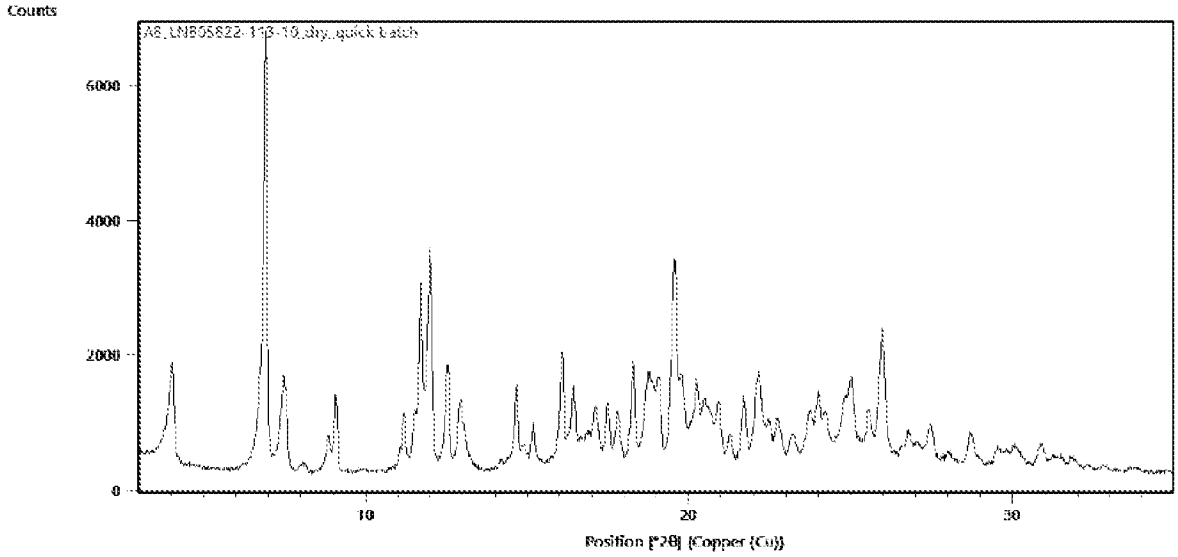


FIG. 28A

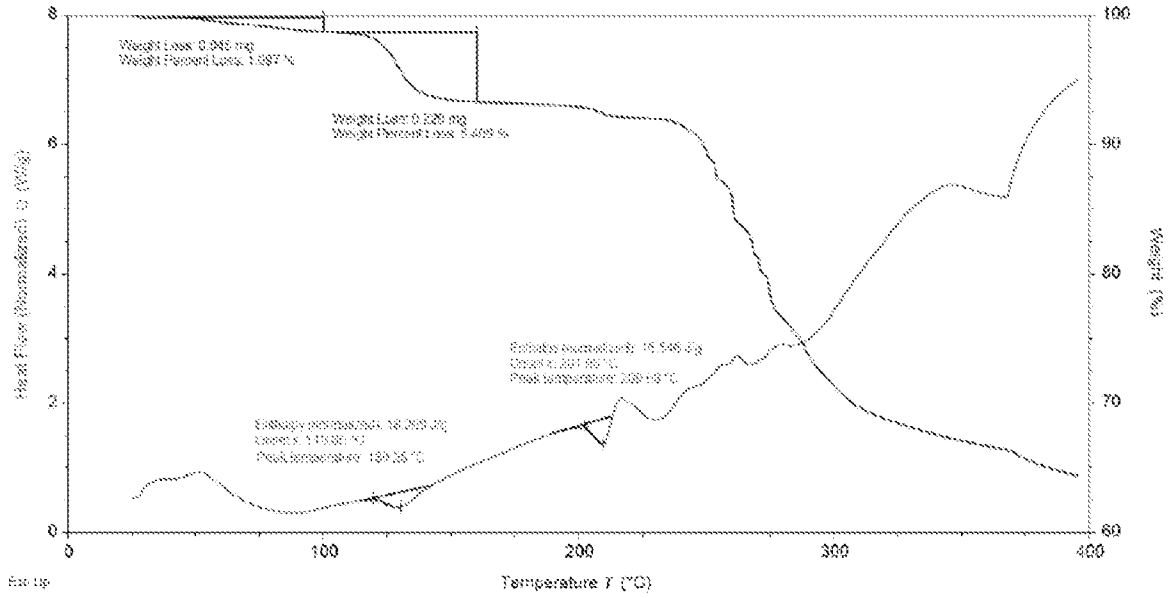


FIG. 28B

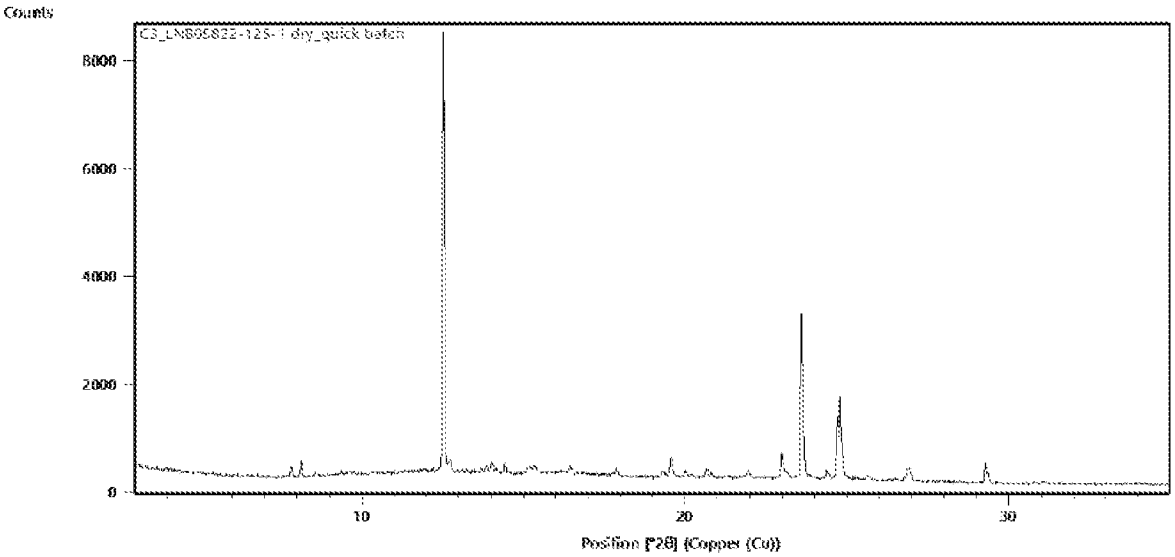

Counts
CS_LN8005822-125-1 dry_quick bean
8000
6000
4000
2000
0
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 29

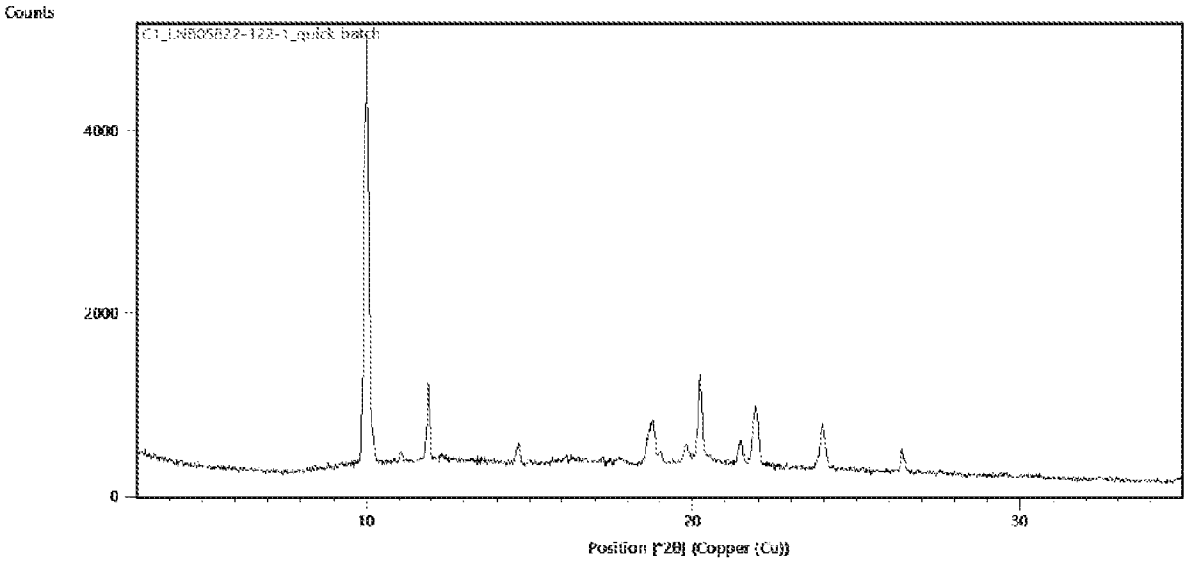


FIG. 30

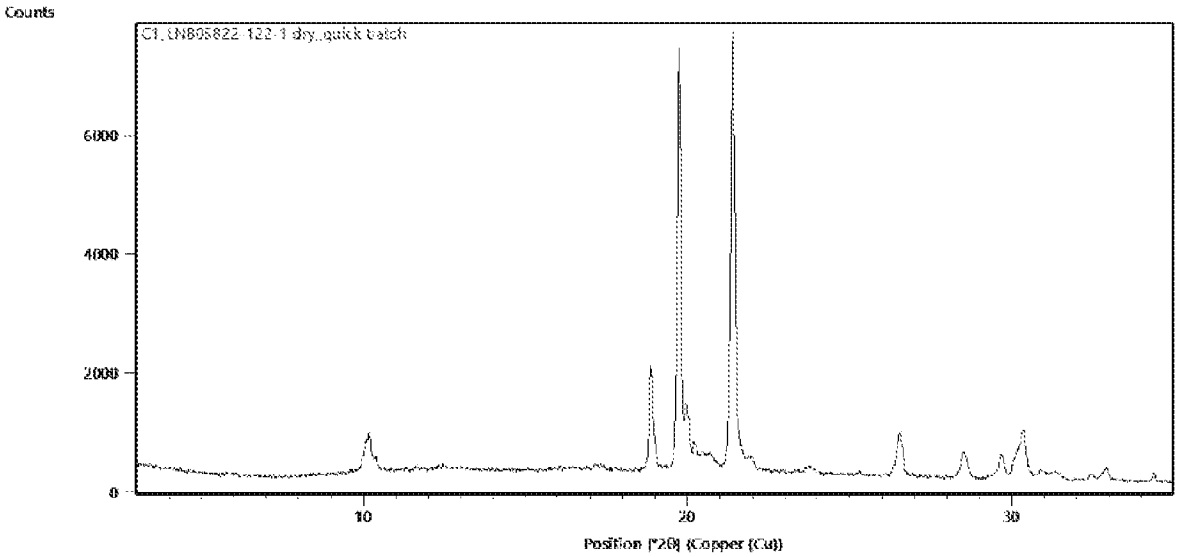

Counts
C1_UNB05822_122-1 dry_quick batch
6000
4000
2000
0
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 31

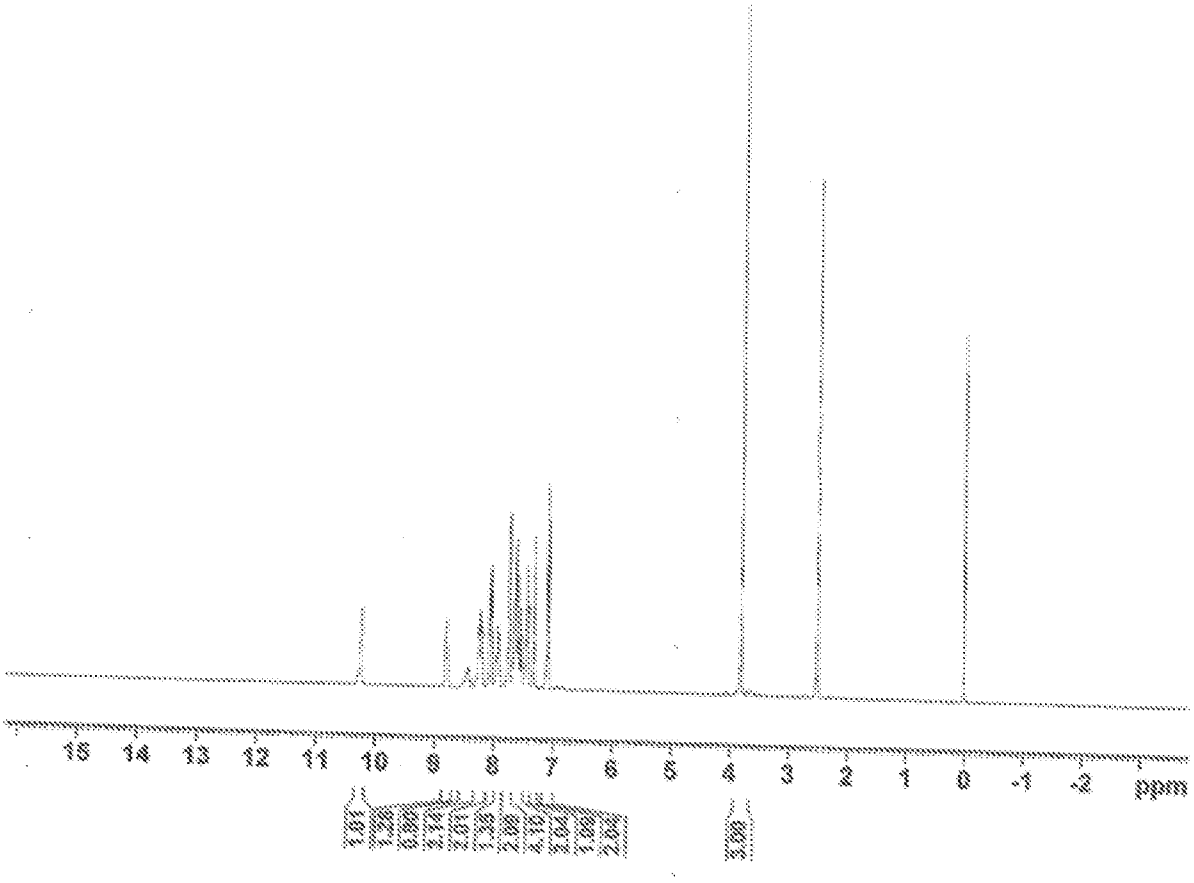


FIG. 32

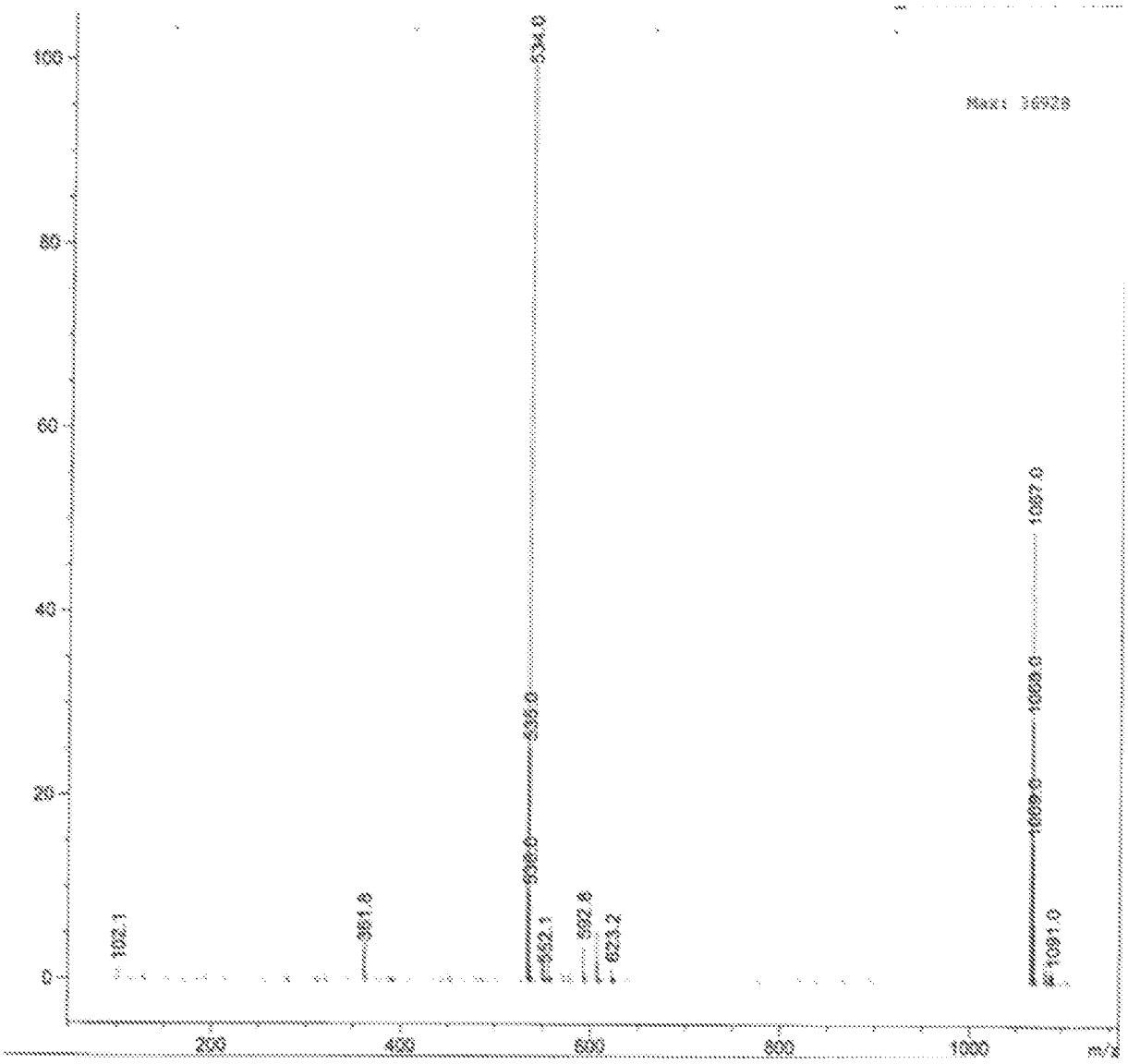


FIG. 33

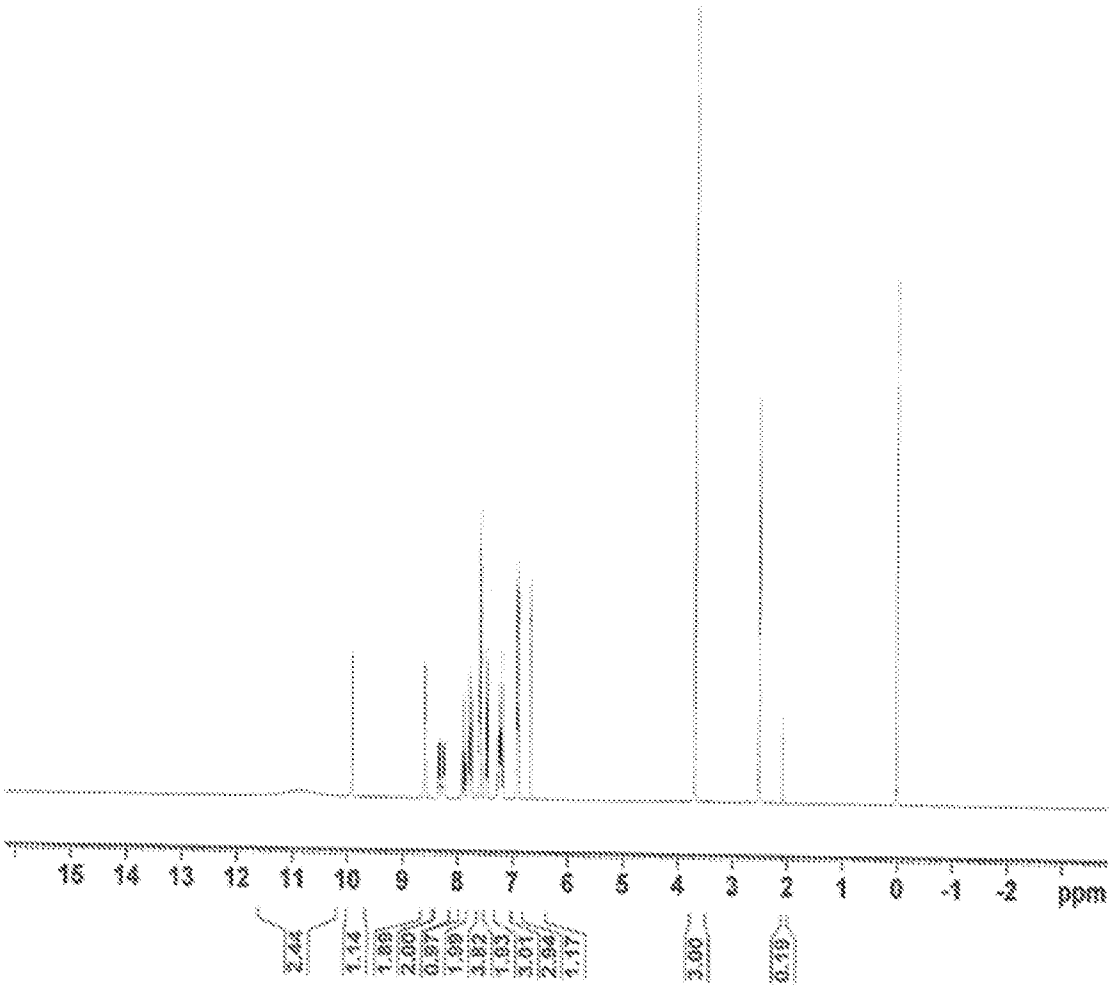


FIG. 34

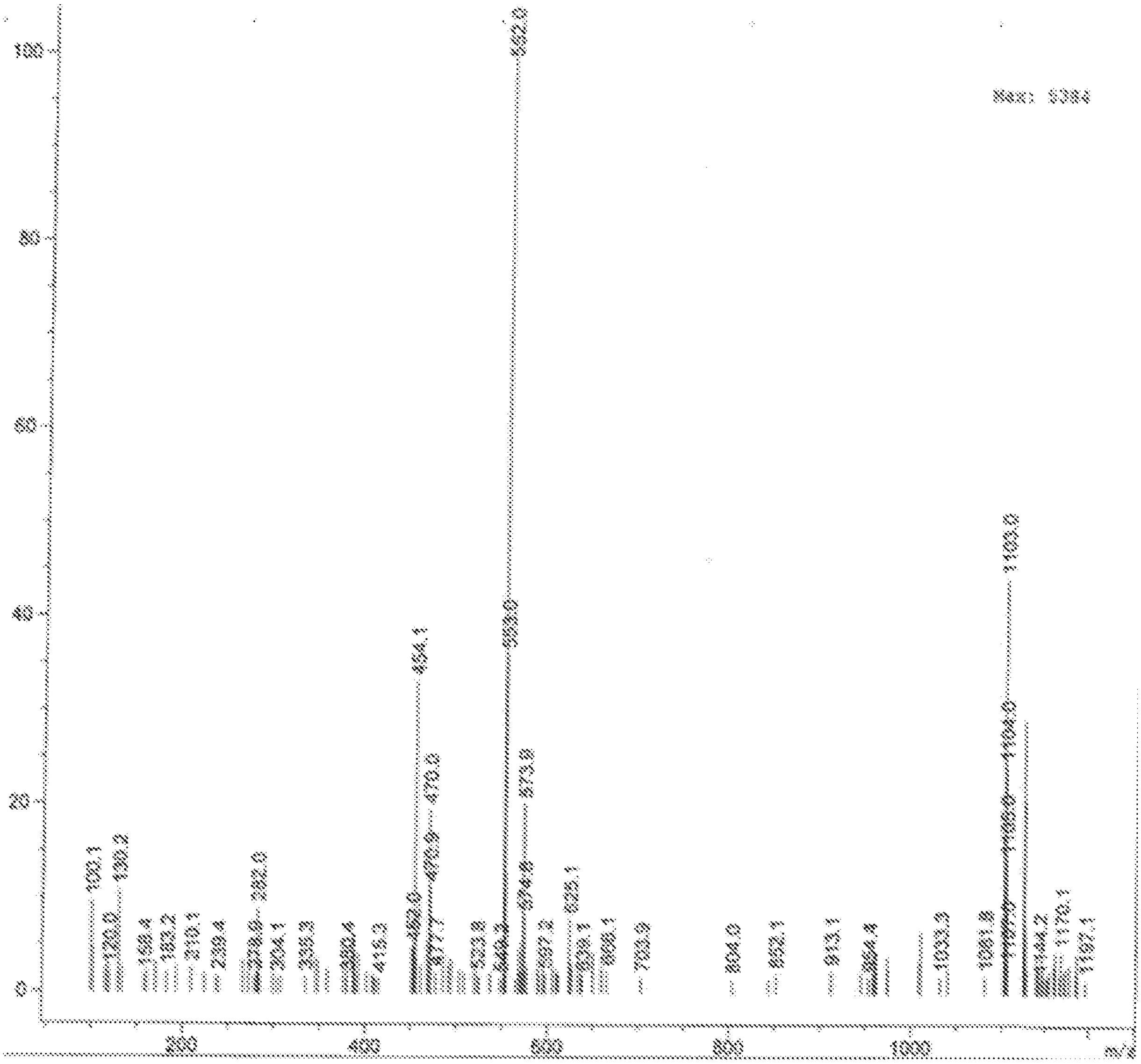


FIG. 35

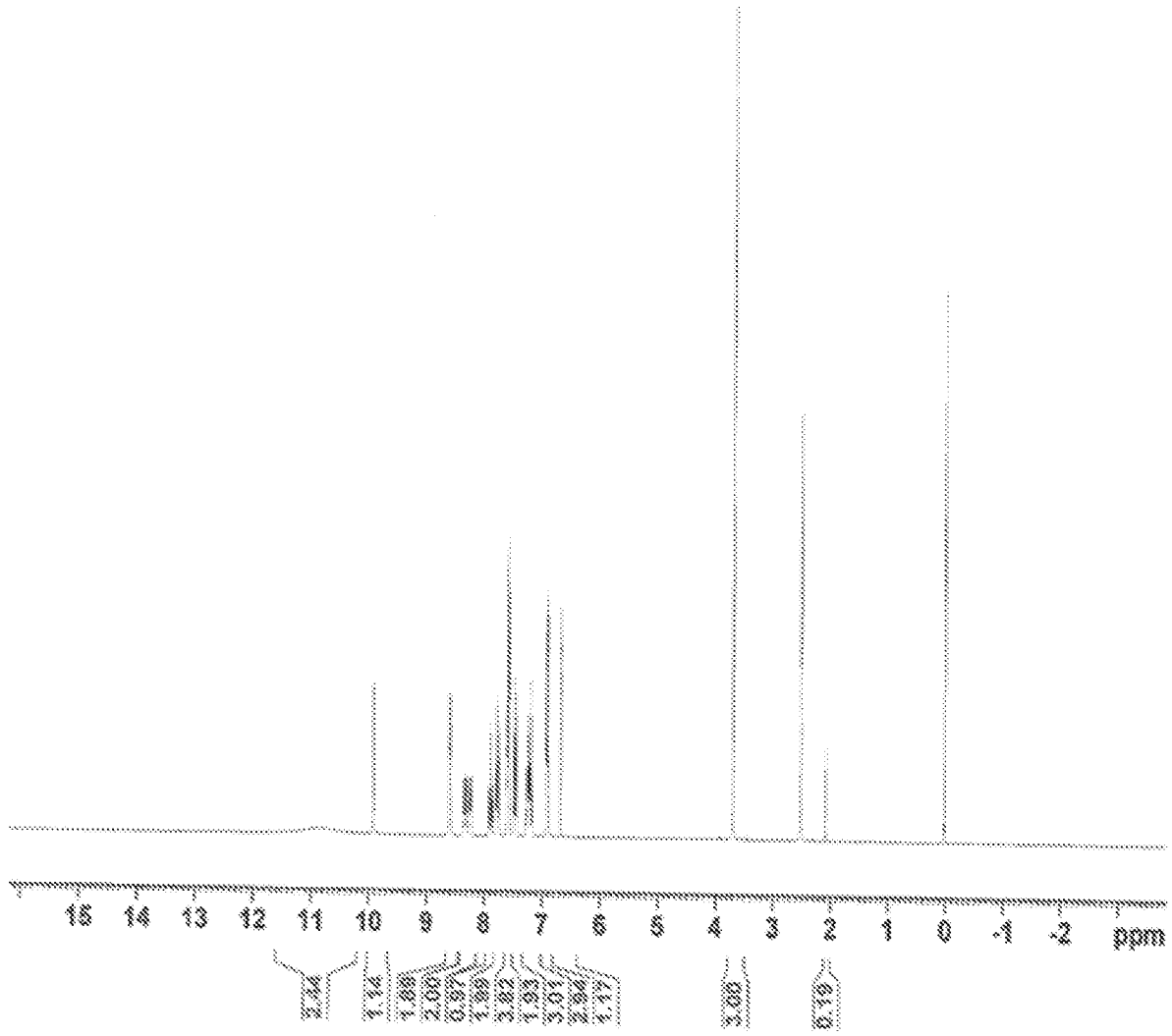


FIG. 36

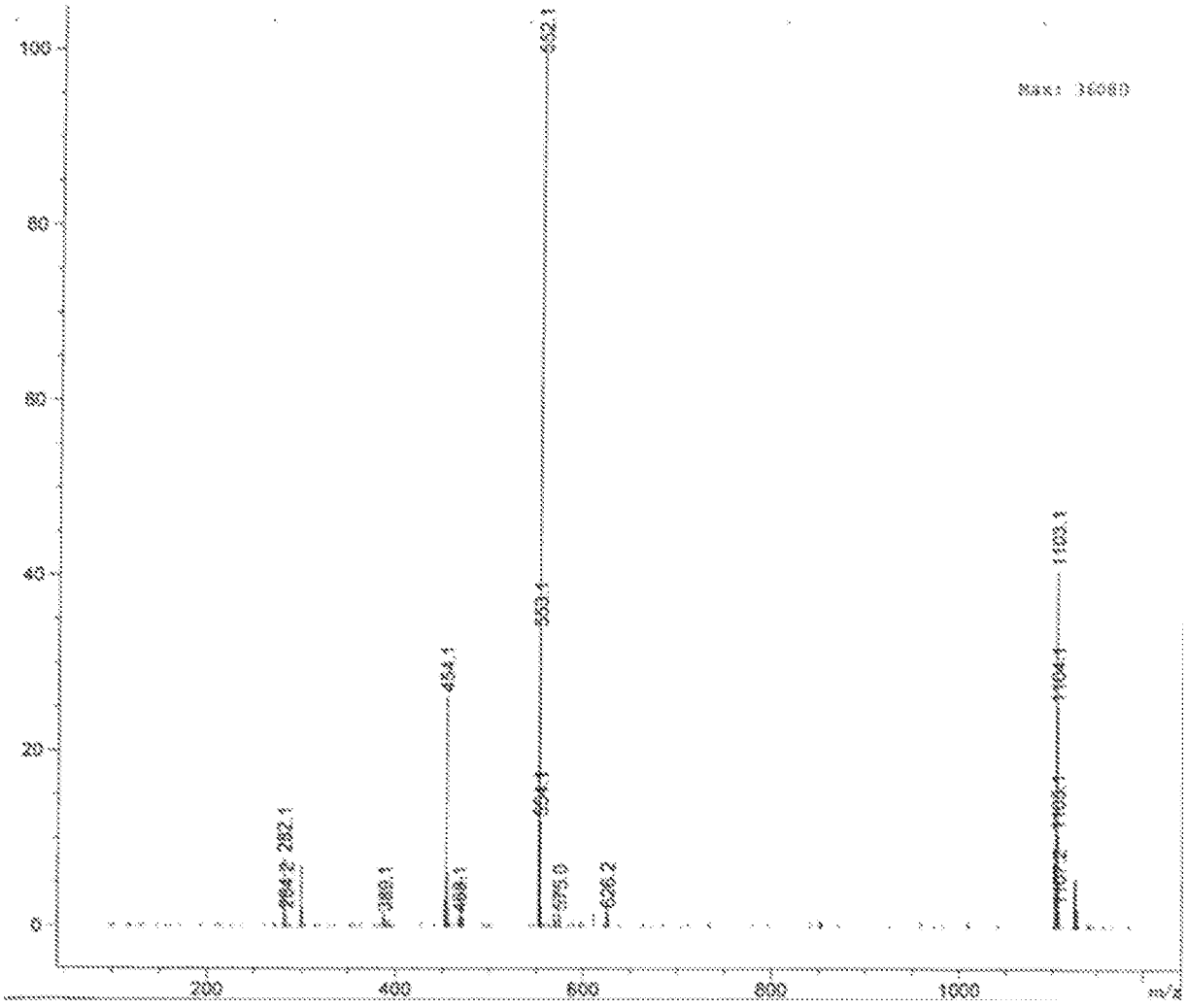

100
80
60
40
20
0
282.1
288.1
454.1
488.1
652.1
494.1
975.0
626.2
1103.1
1104.1
200
400
600
800
1000
m/z

FIG. 37