(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 July 2016 (28.07.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/118858 A1

(51) International Patent Classification:
A61K 31/4439 (2006.01) *A61K 31/444* (2006.01)
A61K 31/4415 (2006.01) *A61K 31/513* (2006.01)

(21) International Application Number:
PCT/US2016/014517

(22) International Filing Date:
22 January 2016 (22.01.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/106,765 23 January 2015 (23.01.2015) US
62/205,096 14 August 2015 (14.08.2015) US

(71) Applicant: AKEBIA THERAPEUTICS, INC. [US/US]; 245 First Street, Suite 1100, Cambridge, MA 02142 (US).

(72) Inventors: HANSELMANN, Roger; 311 Field Point Road, Branford, CT 06405 (US). LUONG, Anne; 6151 Rowers Crescent, Mississauga, Ontario, L5V 3A1 (CA).

(74) Agents: BRUNER, Michael J. et al.; Jones Day, 222 East 41st Street, New York, NY 10017-6702 (US).

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

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

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: SOLID FORMS OF 2-(5-(3-FLUOROPHENYL)-3-HYDROXYPICOLINAMIDO)ACETIC ACID, COMPOSITIONS, AND USES THEREOF

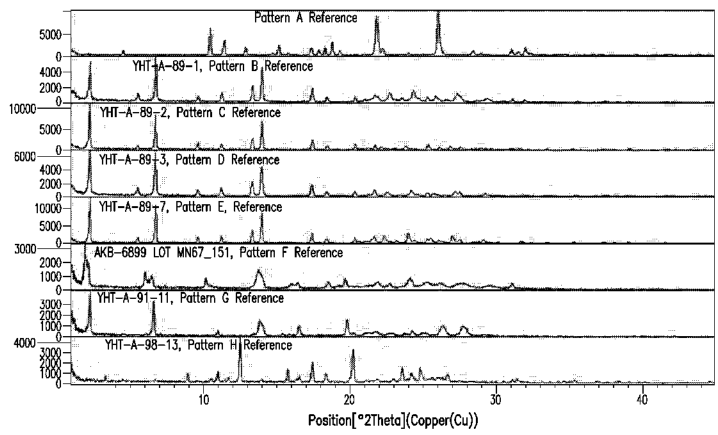


FIG. 1

(57) Abstract: Provided herein are solid forms comprising 2-(5-(3-fluorophenyl)-3- hydroxypicolinamido)acetic acid, methods of making the solid forms, methods of their use for the treatment of various diseases and/or disorders and pharmaceutical compositions comprising the solid forms.

WO 2016/118858 A1

SOLID FORMS OF 2-(5-(3-FLUOROPHENYL)-3-HYDROXYPICOLINAMIDO)ACETIC ACID, COMPOSITIONS, AND USES THEREOF

[0001] This application claims the benefit of U.S. Provisional Application No. 62/205,096, filed August 14, 2015, and U.S. Provisional Application No. 62/106,765, filed January 23, 2015, the entire contents of each of which are incorporated herein by reference.

1. FIELD OF THE INVENTION

[0002] Provided herein are solid forms of 2-(5-(3-fluorophenyl)-3-hydroxypicolinamido)acetic acid, methods of making the solid forms, methods of their use for the treatment of various diseases or symptoms thereof, and pharmaceutical compositions thereof.

2. BACKGROUND OF THE INVENTION

[0003] The identification and selection of a solid form for making a pharmaceutical composition is complex, given that a change in solid form may affect a variety of physical and chemical properties, which may provide benefits or drawbacks in processing, maintaining, storage, formulation, stability and bioavailability, among other important pharmaceutical characteristics. Potential pharmaceutical solids include crystalline solids, amorphous solids, and mixtures thereof. Amorphous solids are characterized by a lack of long-range structural order, whereas crystalline solids are characterized by structural periodicity. The desired class of pharmaceutical solid depends upon the specific application; amorphous solids are sometimes selected on the basis of, *e.g.*, an enhanced dissolution profile, while crystalline solids may be desirable for properties such as, *e.g.*, physical or chemical stability (*See*, *e.g.*, S. R. Vippagunta *et al.*, *Adv. Drug. Deliv. Rev.*, (2001) 48:3-26; L. Yu, *Adv. Drug. Deliv. Rev.*, (2001) 48:27-42).

[0004] Whether crystalline or amorphous, potential solid forms for making a pharmaceutical composition include single-component and multiple-component solids. Single-component solids consist essentially of the pharmaceutical Compound 1 in the absence of other compounds. Variety among single-component crystalline materials may potentially arise from the phenomenon of polymorphism, wherein multiple three-dimensional arrangements exist for a particular pharmaceutical compound (*See*, *e.g.*, S. R. Byrn *et al.*, Solid State Chemistry of Drugs,

(1999) SSCI, West Lafayette). The importance of discovering polymorphs was underscored by the case of Ritonavir, an HIV protease inhibitor that was formulated as soft gelatin capsules. About two years after the product was launched, the unanticipated precipitation of a new, less soluble polymorph in the formulation necessitated the withdrawal of the product from the market until a more consistent formulation could be developed (*See* S. R. Chemburkar *et al., Org. Process Res. Dev.*, (2000) 4:413-417).

[0005] Additional diversity among the potential solid forms of a pharmaceutical compound may arise from the possibility of multiple-component solids. Crystalline solids comprising two or more ionic species are termed salts (*See, e.g.*, Handbook of Pharmaceutical Salts: Properties, Selection and Use, P. H. Stahl and C. G. Wermuth, Eds., (2002), Wiley, Weinheim). Additional types of multiple-component solids that may potentially offer other property improvements for a pharmaceutical compound or salt thereof include, *e.g.*, hydrates, solvates, co-crystals and clathrates, among others (*See, e.g.*, S. R. Byrn *et al.*, Solid State Chemistry of Drugs, (1999) SSCI, West Lafayette). Moreover, multiple-component crystal forms may potentially be susceptible to polymorphism, wherein a given multiple-component composition may exist in more than one three-dimensional crystalline arrangement. The discovery of solid forms is of great importance in the development of a safe, effective, stable and marketable pharmaceutical compound.

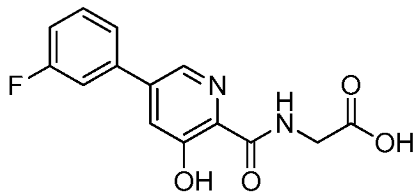
[0006] Nobel Prize winner Dr. Judah Folkman first proposed in 1971 that all cancer tumors were angiogenesis-dependent and therefore targeting angiogenesis was a potential means for treating cancer. Angiogenesis is the growth of new capillaries from pre-existent microvasculature. A wide range of pathological conditions, from atherosclerosis to cancer, are associated with either excessive or deficient angiogenesis.

[0007] It is now widely accepted that tumor growth beyond a few cubic millimeters cannot occur without the induction of a new vascular supply. Therefore, inhibition of new vasculature (antiangiognesis) can provide a non-chemotherapy or non-radiation therapy approach to the treatment of cancer by denying tumors the nutrient supply necessary for the tumors to grow. Although normally quiescent, endothelial cells are responsible for the formation of new vasculature in response to various stimuli. These stimuli can have their genesis in many forms.

[0008] The endothelial cells which form new vascular networks in tumors respond to angiogenic stimuli produced by the tumor itself. The best known of these stimuli is vascular endothelial growth factor (VEGF). Found to be ubiquitous in human tumors, increasing levels of VEGF correlate with an increasing rate of tumor growth. Therefore, suppression of VEGF represents a method for controlling the growth rate of tumors (primary and metastatic) and offers a possible means for shrinking existing tumors.

3. SUMMARY OF THE INVENTION

[0009] Provided herein are solid forms of Compound 1:



1

[0010] having the name 2-(5-(3-fluorophenyl)-3-hydroxypicolinamido)acetic acid, including tautomers thereof. Also provided are methods of preparing, isolating and characterizing the solid forms. 2-(5-(3-fluorophenyl)-3-hydroxypicolinamido)acetic acid ("Compound 1") is disclosed in United States Patent Application Publication No. 2007/0299086, published December 27, 2007, United States Patent Application Publication No. 2012/0329836, published December 27, 2012 and International Patent Application Publication No. WO 2012/170442, published December 13, 2012, the entireties of which are incorporated by reference herein.

[0011] Provided herein are pharmaceutical compositions and dosage units comprising a solid form of Compound 1. In certain embodiments, the pharmaceutical compositions and dosage units comprise a solid form of Compound 1 and a pharmaceutically acceptable diluent, excipient or carrier.

[0012] Provided herein are methods for treating or preventing cancer, compromising administering an effective amount of a solid form of Compound 1 to a patient having cancer.

[0013] Provided herein are methods for decreasing vascular endothelial growth factor (VEGF) in a cell in vitro, in vivo or ex vivo, comprising contacting the cell with an effective amount of a solid form of Compound 1.

[0014] Provided herein are methods for increasing secretion of soluble vascular endothelial growth factor receptor-1 (sVEGF-1) in a cell in vitro, in vivo or ex vivo, comprising contacting the cell with an effective amount of a solid form of Compound 1.

[0015] Provided herein are methods for stabilizing hypoxia inducible factor-2 alpha (HIF-2a) in a cell in vitro, in vivo or ex vivo, comprising contacting the cell with an effective amount of a solid form of Compound 1.

4. BRIEF DESCRIPTION OF THE FIGURES

[0016] Figure 1 depicts an overlay of X-ray powder diffractogram (XRPD) patterns of Forms A, B, C, D, E, F, G and H of Compound 1.

[0017] Figure 2 depicts an XRPD pattern of Form A of Compound 1.

[0018] Figure 3 depicts an XRPD pattern of Form B of Compound 1.

[0019] Figure 4 depicts an XRPD pattern of Form C of Compound 1.

[0020] Figure 5 depicts an XRPD pattern of Form D of Compound 1.

[0021] Figure 6 depicts an XRPD pattern of Form E of Compound 1.

[0022] Figure 7 depicts an XRPD pattern of Form F of Compound 1.

[0023] Figure 8 depicts an XRPD pattern of Form G of Compound 1.

[0024] Figure 9 depicts an XRPD pattern of Form H of Compound 1.

[0025] Figure 10 depicts a ^{1}H NMR spectrum of Form A of Compound 1.

[0026] Figure 11 depicts a DSC thermogram of Form A of Compound 1.

[0027] Figure 12 depicts a TGA thermogram of Form A of Compound 1.

[0028] Figure 13 depicts a DVS analysis of Form A of Compound 1.

[0029] Figure 14 depicts an XRPD pattern of post-DVS Form A of Compound 1.

[0030] Figure 15 depicts a ^{1}H NMR spectrum of Form B of Compound 1.

[0031] Figure 16 depicts a DSC thermogram of Form B of Compound 1.

[0032] Figure 17 depicts a TGA thermogram of Form B of Compound 1.

[0033] Figure 18 depicts a ^{1}H NMR spectrum of Form C of Compound 1.

[0034] Figure 19 depicts a DSC thermogram of Form C of Compound 1.

[0035] Figure 20 depicts a TGA thermogram of Form C of Compound 1.

[0036] Figure 21 depicts a ^{1}H NMR spectrum of Form D of Compound 1.

[0037] Figure 22 depicts a DSC thermogram of Form D of Compound 1.

[0038] Figure 23 depicts a TGA thermogram of Form D of Compound 1.

[0039] Figure 24 depicts a DVS analysis of Form D of Compound 1.

[0040] Figure 25 depicts a XRPD pattern of post-DVS Form D of Compound 1.

[0041] Figure 26 depicts a ^{1}H NMR spectrum of Form E of Compound 1.

[0042] Figure 27 depicts a DSC thermogram of Form E of Compound 1.

[0043] Figure 28 depicts a TGA thermogram of Form E of Compound 1.

[0044] Figure 29 depicts a ^{1}H NMR spectrum of Form F of Compound 1.

[0045] Figure 30 depicts a DSC thermogram of Form F of Compound 1.

[0046] Figure 31 depicts a TGA thermogram of Form F of Compound 1.

[0047] Figure 32 depicts a ^{1}H NMR spectrum of Form G of Compound 1.

[0048] Figure 33 depicts a DSC thermogram of Form G of Compound 1.

[0049] Figure 34 depicts a TGA thermogram of Form G of Compound 1.

[0050] Figure 35 depicts a DVS analysis of Form G of Compound 1.

[0051] Figure 36 depicts a XRPD pattern of post-DVS of Form G of Compound 1.

[0052] Figure 37 depicts a ^{1}H NMR spectrum of Form H of Compound 1.

[0053] Figure 38 depicts a DSC thermogram of Form H of Compound 1.

[0054] Figure 39 depicts a TGA thermogram of Form H of Compound 1.

[0055] Figure 40 depicts a XRPD Diffractogram of Salt I of Compound 1.

[0056] Figure 41 depicts a XRPD Diffractogram of Salt II of Compound 1.

[0057] Figure 42 depicts a XRPD Diffractogram of Salt III of Compound 1.

[0058] Figure 43 depicts a XRPD Diffractogram of Salt IV of Compound 1.

[0059] Figure 44 depicts a XRPD Diffractogram of Salt V of Compound 1.

[0060] Figure 45 depicts a XRPD Diffractogram of Salt VI of Compound 1.

[0061] Figure 46 depicts a XRPD stackplot of Salt I of Compound 1 before (middle) and after DVS (bottom) analysis.

[0062] Figure 47 depicts a ^{1}H NMR spectrum of Salt I of Compound 1.

[0063] Figure 48 depicts a DSC thermogram of Salt I of Compound 1.

[0064] Figure 49 depicts a TGA thermogram of Salt I of Compound 1.

[0065] Figure 50 depicts a DVS thermogram of Salt I of Compound 1.

[0066] Figure 51 depicts a XRPD stackplot of Salt II of Compound 1 before (middle) and after DVS (bottom) analysis.

[0067] Figure 52 depicts a ^{1}H NMR spectrum of Salt II of Compound 1.

[0068] Figure 53 depicts a DSC thermogram of Salt II of Compound 1.

[0069] Figure 54 depicts a TGA thermogram of Salt II of Compound 1.

[0070] Figure 55 depicts a DVS thermogram of Salt II of Compound 1.

[0071] Figure 56 depicts a XRPD stackplot of Salt III of Compound 1 before (middle) and after DVS (bottom) analysis.

[0072] Figure 57 depicts a ^{1}H NMR spectrum of Salt III of Compound 1.

[0073] Figure 58 depicts a DSC thermogram of Salt III of Compound 1.

[0074] Figure 59 depicts a TGA thermogram of Salt III of Compound 1.

[0075] Figure 60 depicts a DVS thermogram of Salt III of Compound 1.

[0076] Figure 61 depicts a XRPD stackplot of Salt IV of Compound 1 before (middle) and after DVS (bottom) analysis.

[0077] Figure 62 depicts a ^{1}H NMR spectrum of Salt IV of Compound 1.

[0078] Figure 63 depicts a DSC thermogram of Salt IV of Compound 1.

[0079] Figure 64 depicts a TGA thermogram of Salt IV of Compound 1.

[0080] Figure 65 depicts a DVS thermogram of Salt IV of Compound 1.

[0081] Figure 66 depicts a XRPD stackplot of Salt V of Compound 1 before (middle) and after DVS (bottom) analysis.

[0082] Figure 67 depicts a ^{1}H NMR spectrum of Salt V of Compound 1.

[0083] Figure 68 depicts a DSC thermogram of Salt V of Compound 1.

[0084] Figure 69 depicts a TGA thermogram of Salt V of Compound 1.

[0085] Figure 70 depicts a DVS thermogram of Salt V of Compound 1.

[0086] Figure 71 depicts a XRPD stackplot of Salt VI of Compound 1 before (top) and after DVS (bottom) analysis.

[0087] Figure 72 depicts a XRPD stackplot (zoom in) of Salt VI of Compound 1 before (top) and after DVS (bottom) analysis.

[0088] Figure 73 depicts a ^{1}H NMR spectrum of Salt VI of Compound 1.

[0089] Figure 74 depicts a DSC thermogram of Salt VI of Compound 1.

[0090] Figure 75 depicts a TGA thermogram of Salt VI of Compound 1.

[0091] Figure 76 depicts a DVS thermogram of Salt VI of Compound 1.

[0092] Figure 77 depicts a ^{1}H NMR spectrum of 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine.

[0093] Figure 78 depicts a ^{1}H NMR spectrum of 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine.

[0094] Figure 79 depicts a ^{1}H NMR spectrum of 5-(3-fluorophenyl)-3-hydroxypyridine-2-carboxylic acid.

[0095] Figure 80 depicts a ^{1}H NMR spectrum of N-carboxymethyl-5-(3-fluorophenyl)-3-hydroxypyridine-2-carboxamide.

[0096] Figure 81 depicts a ^{1}H NMR spectrum of a mixture of 5-(3-fluorophenyl)-3-methoxypicolinamide and 5-(3-fluorophenyl)-3-methoxypicolinic acid.

[0097] Figure 82 depicts a ^{1}H NMR spectrum of 5-(3-fluorophenyl)-2-(2-methoxy-2-oxoethylcarbamoyl)pyridin-3-yl pivalate.

[0098] Figure 83 depicts a ^{1}H NMR spectrum of 2-(5-(3-fluorophenyl)-3-hydroxypicolinamido)acetate.

[0099] Figure 84 depicts a XRPD Diffractogram of Salt VII of Compound 1.

[00100] Figure 85 depicts a ^{1}H NMR spectrum of Salt VII of Compound 1.

[00101] Figure 86 depicts a DSC thermogram of Salt VII of Compound 1.

[00102] Figure 87 depicts a TGA thermogram of Salt VII of Compound 1.

[00103] Figure 88 depicts a microscopy analysis of Salt VII of Compound 1.

[00104] Figure 89 depicts a DVS thermogram of Salt VII of Compound 1.

[00105] Figure 90 depicts a XRPD stackplot of Salt VII of Compound 1 before (top) and after DVS (bottom) analysis.

[00106] Figure 91 depicts a XRPD Diffractogram of Salt VIII of Compound 1.

[00107] Figure 92 depicts a ^{1}H NMR spectrum of Salt VIII of Compound 1.

[00108] Figure 93 depicts a DSC thermogram of Salt VIII of Compound 1.

[00109] Figure 94 depicts a TGA thermogram of Salt VIII of Compound 1.

[00110] Figure 95 depicts a microscopy analysis of Salt VIII of Compound 1.

[00111] Figure 96 depicts a DVS thermogram of Salt VIII of Compound 1.

[00112] Figure 97 depicts a XRPD stackplot of Salt VIII of Compound 1 before (top) and after DVS (bottom) analysis.

[00113] Figure 98 depicts a XRPD Diffractogram of Salt IX of Compound 1.

[00114] Figure 99 depicts a ^{1}H NMR spectrum of Salt IX of Compound 1.

[00115] Figure 100 depicts a DSC thermogram of Salt IX of Compound 1.

[00116] Figure 101 depicts a TGA thermogram of Salt IX of Compound 1.

[00117] Figure 102 depicts a DSC thermogram of Salt IX of Compound 1.

[00118] Figure 103 depicts a microscopy analysis of Salt IX of Compound 1.

[00119] Figure 104 depicts a XRPD stackplot of Salt IX of Compound 1 before (top) and after DVS (bottom) analysis.

[00120] Figure 105 depicts a XRPD Diffractogram of Salt X of Compound 1.

[00121] Figure 106 depicts a ^{1}H NMR spectrum of Salt X of Compound 1.

[00122] Figure 107 depicts a DSC thermogram of Salt X of Compound 1.

[00123] Figure 108 depicts a TGA thermogram of Salt X of Compound 1.

[00124] Figure 109 depicts a microscopy analysis of Salt X of Compound 1.

5. DETAILED DESCRIPTION

5.1 Definitions

[00125] As used herein, the terms "prevent", "preventing" and "prevention" are art-recognized, and when used in relation to a condition, such as a local recurrence, a disease or any other medical condition, such as those described herein, is well understood in the art, and includes administration of a compound, such as a solid form of Compound 1, which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a patient relative to a patient which does not receive the composition.

[00126] As used herein, the terms "treat", "treating" and "treatment" refer to the reversing, reducing, or arresting the symptoms, clinical signs, and underlying pathology of a disease condition, such as those described herein, in manner to improve or stabilize a subject's condition. The terms "treat" and "treatment" also refer to the eradication or amelioration of the disease or symptoms associated with the disease. In certain embodiments, such terms refer to minimizing the spread or worsening of the disease by the administration of a solid form of Compound 1 to a patient with such a disease.

[00127] As used herein, the term "hydrate" means 5-(3-fluorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[00128] As used herein, the term "solvate" means 5-(3-fluorophenyl)-3-hydroxypyridine-2-carbonyl]amino}acetic acid or a pharmaceutically acceptable salt thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent, other than water, bound by non-covalent intermolecular forces.

[00129] As used herein, the term "HIF prolyl hydroxylase" is art-recognized and may be abbreviated as "PHD". HIF prolyl hydroxylase is also known as "prolyl hydroxylase domain-containing protein" which may be abbreviated as "PHD". In this regard, there are three different PHD isoforms, PHD1, PHD2, and PHD3, also referred to as EGLN2, EGLN1, and EGLN3, or HPH3, HPH2, and HPH1, respectively.

[00130] The terms "solid form," "solid forms" and related terms, when used herein to refer to Compound 1, refer to a physical form comprising Compound 1 which is not predominantly in a liquid or a gaseous state. Crystal forms are examples of solid forms. In one embodiment, the solid form is Form A. In another embodiment, the solid form is Form B. In another embodiment, the solid form is Form C. In another embodiment, the solid form is Form D. In another embodiment, the solid form is Form E. In another embodiment, the solid form is Form F. In another embodiment, the solid form is Form G. In another embodiment, the solid form is Form H. In one embodiment, the solid form is Salt I. In one embodiment, the solid form is Salt II. In one embodiment, the solid form is Salt III. In one embodiment, the solid form is Salt IV. In one embodiment, the solid form is Salt V. In one embodiment, the solid form is Salt VI.

[00131] The term "crystalline" and related terms used herein, when used to describe a substance, component, product, or form, means that the substance, component or product is substantially crystalline as determined by X-ray diffraction. *See, e.g.*, Remington's Pharmaceutical Sciences, 22nd ed., Pharmaceutical Press, (2012).; *The United States Pharmacopoeia,* 30th ed., (2011).

[00132] The term "crystal form," "crystalline form" and related terms herein refer to a crystalline solid form comprising a chemical compound, and may refer to a particular single-component or multiple-component crystal form, including, but not limited to, a polymorph, a solvate, a hydrate or other molecular complex, a salt, a solvate of a salt, a hydrate of a salt, or other molecular complex of a salt, or a polymorph thereof.

[00133] The terms “polymorphs,” “polymorphic forms” and related terms herein refer to two or more crystal forms that comprise the same molecule, molecules or ions. Different polymorphs may have different physical properties such as, for example, melting temperatures, heats of fusion, solubilities, dissolution rates and/or vibrational spectra as a result of the arrangement or conformation of the molecules or ions in the crystal lattice. The differences in physical properties exhibited by polymorphs affect pharmaceutical parameters such as storage stability, compressibility and density (important in formulation and product manufacturing), and dissolution rate (an important factor in bioavailability). Differences in stability can result from changes in chemical reactivity (*e.g.*, differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical changes (*e.g.*, tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (*e.g.*, tablets of one polymorph are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some polymorphic transitions may result in lack of potency or, at the other extreme, toxicity. In addition, the physical properties of the crystal may be important in processing; for example, one polymorph might be more likely to form solvates or might be difficult to filter and wash free of impurities (*e.g.*, particle shape and size distribution might be different between polymorphs).

[00134] Techniques for characterizing crystal forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), melting point, 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 and solution nuclear magnetic resonance (NMR) spectroscopy, optical microscopy (*e.g.*, polaraized light microscopy), hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography, dynamic vapor sorption (DVS), and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies and dissolution studies.

[00135] As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. Specifically, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 15%, more specifically within 10%, more specifically within 5%, of the specified dose, amount, or weight percent.

[00136] As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with a numeric value or range of values, which is provided to characterize a particular solid form, *e.g.*, a specific temperature or temperature range, such as, for example, that describing a melting, dehydration, desolvation or glass transition temperature; a mass change, such as, for example, a mass change as a function of temperature or humidity; a solvent or water content, in terms of, for example, mass or a percentage; or a peak position, such as, for example, in analysis by IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the particular solid form. Specifically, the terms "about" and "approximately," when used in this context, indicate that the numeric value or range of values may vary, in particular embodiments, within 20%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. With respect to XRPD, values given are ±0.2 degrees 2 theta.

[00137] As used herein, and unless otherwise specified, a crystalline that is "pure," *i.e.*, substantially free of other crystalline or amorphous solids, contains less than about 10% by weight of one or more other crystalline or amorphous solids, less than about 5% by weight of one or more other crystalline or amorphous solids, less than about 3% by weight of one or more other crystalline or amorphous solids, or less than about 1% by weight of one or more other crystalline or amorphous solids.

[00138] As used herein, and unless otherwise specified, a solid form that is "substantially physically pure" is substantially free from other solid forms. In certain embodiments, a crystal form that is substantially physically pure contains less than about 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other solid forms on a weight basis. The detection of other solid forms can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, diffraction analysis, thermal analysis, elemental combustion analysis and/or spectroscopic analysis.

[00139] As used herein, and unless otherwise specified, a solid form that is "substantially chemically pure" is substantially free from other chemical compounds (*i.e.*, chemical impurities). In certain embodiments, a solid form that is substantially chemically pure contains less than about 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other chemical compounds on a weight basis. The detection of other chemical compounds can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, methods of chemical analysis, such as, *e.g.*, mass spectrometry analysis, spectroscopic analysis, thermal analysis, elemental combustion analysis and/or chromatographic analysis.

[00140] As used herein, and unless otherwise indicated, a chemical compound, solid form, or composition that is "substantially free" of another chemical compound, solid form, or composition means that the compound, solid form, or composition contains, in certain embodiments, less than about 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2% 0.1%, 0.05%, or 0.01% by weight of the other compound, solid form, or composition.

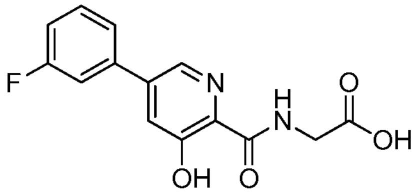
[00141] As used herein, an "effective amount" refers to that amount of Compound 1 or a pharmaceutically acceptable salt, solvate or hydrate thereof sufficient to provide a therapeutic benefit in the treatment of the disease or to delay or minimize symptoms associated with the disease, such as any disease or condition described herein.

[00142] The terms "subject" and "patient," unless otherwise specified, are defined herein to include animals such as mammals, including, but not limited to, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In specific embodiments, the patient or patient is a human. In certain embodiments, the patient has a disease or condition as described herein.

[00143] "VEGF-dependent cancer," "VEGF dependent cancers," "VEGF-dependent tumor" or "VEGF dependent tumors" refers to cancers that rely on VEGF to proliferate.

5.2 Compound 1

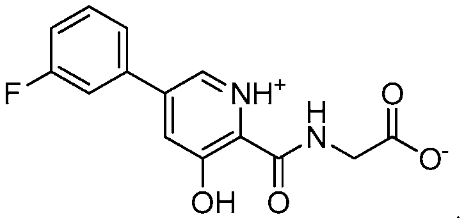
[00144] The solid forms (*e.g.*, Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Salt I, Salt II, Salt III, Salt IV, Salt V, Salt VI, Salt VII, Salt VIII, Salt IX and Salt X), formulations and methods of use provided herein relate to Compound 1:



1

[00145] having the name 2-(5-(3-fluorophenyl)-3-hydroxypicolinamido)acetic acid, including tautomers thereof.

[00146] In certain embodiments, Form A, Form B, Form C, Form D, Form E, Form F, Form G and Form H of Compound 1 exist in the following zwitterionic form:



[00147] Compound 1 can be prepared using reagents and methods known in the art, including the methods provided in United States Patent Application Publication No. 2007/0299086, published December 27, 2007, United States Patent Application Publication 2012/0329836, published December 27, 2012 and International Patent Application Publication No. WO 2012/170442, published December 13, 2012, the entireties of which are incorporated by reference herein.

[00148] It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

5.3 Solid Forms of Compound 1

[00149] In certain embodiments, provided herein are solid forms of Compound 1. In certain embodiments, the solid form is crystalline. In certain embodiments, the solid form is a single-component solid form. In certain embodiments, the solid form is a solvate. In certain embodiments, the solid form is anhydrous. In certain embodiments, the solid form is Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Salt I, Salt II, Salt III, Salt IV, Salt V, Salt VI, Salt VII, Salt VIII, Salt IX or Salt X.

[00150] While not intending to be bound by any particular theory, certain solid forms are characterized by physical properties, *e.g.*, stability, solubility and dissolution rate, appropriate for pharmaceutical and therapeutic dosage forms. Moreover, while not wishing to be bound by any particular theory, certain solid forms are characterized by physical properties (*e.g.*, density, compressibility, hardness, morphology, cleavage, stickiness, solubility, water uptake, electrical properties, thermal behavior, solid-state reactivity, physical stability, and chemical stability) affecting particular processes (*e.g.*, yield, filtration, washing, drying, milling, mixing, tableting, flowability, dissolution, formulation, and lyophilization) which make certain solid forms suitable for the manufacture of a solid dosage form. Such properties can be determined using particular analytical chemical techniques, including solid-state analytical techniques (*e.g.*, X-ray diffraction, microscopy, spectroscopy and thermal analysis), as described herein and known in the art.

[00151] The solid forms provided herein (*e.g.*, Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Salt I, Salt II, Salt III, Salt IV, Salt V, Salt VI, Salt VII, Salt VIII, Salt IX and Salt X of Compound 1) may be characterized using a number of methods known to a person skilled in the art, including, but not limited to, X-ray powder diffraction (XRPD), microscopy (*e.g.*, scanning electron microscopy (SEM)) and thermal analysis (*e.g.*, thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC)). The particle size and size distribution of the solid form provided herein may be determined by conventional methods, such as laser light scattering technique.

[00152] It should be understood that the numerical values of the peaks of an X-ray powder diffraction pattern may vary slightly from one machine to another or from one sample to another, and so the values quoted are not to be construed as absolute, but with an allowable variability, such as $\pm 0.2\ ^{\circ}\ 2\theta$ (*see* United State Pharmacopoeia, page 2228 (2003)).

5.3.1 **Form A of Compound 1**

[00153] In certain embodiments, provided herein is Form A of Compound 1.

[00154] In one embodiment, Form A is a solid form of Compound 1. In one embodiment, Form A is anhydrous. In another embodiment, Form A is crystalline.

[00155] In certain embodiments, Form A is prepared by single solvent fast cooling crystallization, single solvent slow cooling crystallization, binary solvent fast cooling crystallization or binary solvent slow cooling crystallization experiments (*see* Table 1-Table 10).

[00156] In one embodiment, provided herein are methods for preparing Form A of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the solution to a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is THF, MIBK or MTBE.

[00157] In one embodiment, provided herein are methods for preparing Form A of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (*e.g.*, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) cooling the solution to a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is THF, MIBK or MTBE.

[00158] In one embodiment, provided herein are methods for preparing Form A of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (e.g, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is THF or MTBE.

[00159] In one embodiment, provided herein are methods for preparing Form A of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (e.g, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is THF or MTBE.

[00160] In one embodiment, provided herein are methods for preparing Form A of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form. *See* Table 3, Table 5, Table 7 and Table 9. In certain embodiments, the solvent is MeOH, EtOH, IPA, acetone, DMSO, DMF, NMP, IPAc, MIBK or MTBE. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00161] In one embodiment, provided herein are methods for preparing Form A of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form. *See* Table 3, Table 5, Table 7 and Table 9. In certain embodiments, the solvent is MeOH, EtOH, IPA, acetone, DMSO, DMF, NMP, IPAc, MIBK or MTBE. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00162] In one embodiment, provided herein are methods for preparing Form A of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form. *See* Table 4, Table 6, Table 8 and Table 10. In certain embodiments, the solvent is acetone, DMF, NMP, MeCN, IPAc, MIBK or MTBE. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00163] In one embodiment, provided herein are methods for preparing Form A of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form. *See* Table 4, Table 6, Table 8 and Table 10. In certain embodiments, the solvent is acetone, DMF, NMP, MeCN, IPAc, MIBK or MTBE. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00164] In one embodiment, provided herein is Form A prepared by stirring Form G in a solvent for a period of time. *See* Table 13. In one embodiment, the solvent is IPAc/heptane (*e.g.*, about 1:2 (V:V)) or toluene. In one embodiment, the solvent is acetone/water (*e.g.*, about 1:2 (V:V)). In one embodiment, the period of time is from about 1 day to about 7 days (*e.g.*, about 1 day or about 7 days).

[00165] In one embodiment, provided herein is Form A having a DSC thermogram substantially as depicted in Figure 11. In certain embodiments, the crystalline form exhibits a DSC thermogram comprising an endothermic event with a maximum at about 186 °C when heated from approximately 30 °C to approximately 230 °C.

[00166] In one embodiment, provided herein is Form A having a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 12. In certain embodiments, the crystalline form exhibits a TGA thermogram comprising no mass loss before about 155 °C when heated from approximately 30 °C to approximately 300 °C. The TGA thermogram further comprises a decomposition event with an onset temperature at approximately 249.2 °C when heated from approximately 30 °C to approximately 300 °C. Thus, in certain embodiments, the crystalline form has no mass loss at a temperature lower than about 100 °C.

[00167] In one embodiment, provided herein is moderately hygroscopic Form A having about 0% weight moisture uptake at 60% RH and about 6.1% weight moisture uptake at 90% RH. *See* Figure 13.

[00168] In certain embodiments, a solid form provided herein, *e.g.*, Form A, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form A has an X-ray powder diffraction pattern substantially as shown in Figure 2. In one embodiment, Form A has one or more characteristic X-ray powder diffraction peaks at approximately 3.73, 3.86, 4.24, 4.39, 5.46, 5.58, 5.77, 6.01, 6.49, 6.86, 7.27, 7.40, 7.83, 8.13, 8.56, 8.67, 8.80, 8.93, 9.91, 10.09, 10.23, 10.41, 11.07, 12.14, 13.05, 14.45, 15.67, 16.20, 16.60, 17.21, 17.70, 18.71, 19.19, 19.59, 20.08, 20.54, 21.60, 22.15, 22.97, 23.34, 24.37, 25.02, 25.55, 25.93, 26.92, 27.55, 29.20, 29.70, 30.10, 31.68, 32.13, 32.59, 33.00, 33.77, 34.18, 34.67, 35.19, 35.88, 36.40, 36.99, 37.46, 38.08, 39.74, 40.38, 40.96, 41.76, 42.12, 42.45, 43.26, 43.87 or 44.52 ° 2θ as depicted in Figure 2. In a specific embodiment, Form A has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 12.14, 13.05, 14.45, 16.60, 19.59, 20.08, 22.97 or 26.92 ° 2θ. In another embodiment, Form A has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 12.14, 13.05, 22.97 or 26.92 ° 2θ. In another embodiment, Form A has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three, sixty-four, sixty-five, sixty-six, sixty-seven, sixty-eight, sixty-nine, seventy or seventy-one characteristic X-ray powder diffraction peaks as set forth in Table 20.

[00169] In certain embodiments, a solid form provided herein, *e.g.*, Form A, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form A has an X-ray powder diffraction pattern substantially as shown in Figure 2. In one embodiment, Form A has one or more characteristic X-ray powder diffraction peaks at approximately 3.7, 3.9, 4.2, 4.4, 5.5, 5.6, 5.8, 6.0, 6.5, 6.9, 7.3, 7.4, 7.8, 8.1, 8.6, 8.7, 8.8, 8.9, 9.9, 10.1, 10.2, 10.4, 11., 12.1, 13., 14.5, 15.7, 16.2, 16.6, 17.2, 17.7, 18.7, 19.2, 19.6, 20.1, 20.5, 21.6, 22.2, 23.0, 23.3, 24.4, 25.0, 25.6, 25.9, 26.9, 27.6, 29.2, 29.7, 30.1, 31.7, 32.1, 32.6, 33.0, 33.8, 34.2, 34.7, 35.2, 35.9, 36.4, 37.0, 37.5, 38.1, 39.7, 40.4, 41.0, 41.8, 42.1, 42.5, 43.3, 43.9 or 44.5 ° 2θ as depicted in Figure 2. In a specific embodiment, Form A has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 12.1, 13.1, 14.5, 16.6, 19.6, 20.1, 23.0 or 26.9 ° 2θ. In another embodiment, Form A has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 12.1, 13.1, 23.0 or 26.9 ° 2θ. In another embodiment, Form A has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 12.1, 13.1, 16.6, 20.1, 23.0 or 26.9 ° 2θ. In another embodiment, Form A has one, two or three characteristic X-ray powder diffraction peaks at approximately 12.1, 23.0 or 26.9 ° 2θ. In another embodiment, Form A has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three, sixty-four, sixty-five, sixty-six, sixty-seven, sixty-eight, sixty-nine, seventy or seventy-one characteristic X-ray powder diffraction peaks as set forth in Table 20.

[00170] In still another embodiment, Form A is substantially pure. In certain embodiments, the substantially pure Form A is substantially free of other solid forms, *e.g.*, Forms B, C, D, E, F, G or H. In certain embodiments, the purity of the substantially pure Form A is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

5.3.2 **Form B of Compound 1**

[00171] In certain embodiments, provided herein is Form B of Compound 1.

[00172] In one embodiment, Form B is a solid form of Compound 1. In one embodiment, Form B is anhydrous. In one embodiment, Form B is an anhydrous solid form of Compound 1 retaining residual solvent. In one embodiment, Form B is an anhydrous solid form of Compound 1 retaining residual MEK. In another embodiment, Form B is crystalline.

[00173] In certain embodiments, Form B is prepared by single solvent fast cooling crystallization, single solvent slow cooling crystallization, binary solvent fast cooling crystallization or binary solvent slow cooling crystallization experiments (*see* Table 1-Table 10).

[00174] In one embodiment, provided herein are methods for preparing Form B of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the solution to a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is MeOH, THF or acetone.

[00175] In one embodiment, provided herein are methods for preparing Form B of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (*e.g.*, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) cooling the solution to a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is MeOH, THF or acetone.

[00176] In one embodiment, provided herein are methods for preparing Form B of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (e.g, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is MeOH, MeCN, THF, acetone or MIBK.

[00177] In one embodiment, provided herein are methods for preparing Form B of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (e.g, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is MeOH, MeCN, THF, acetone or MIBK.

[00178] In one embodiment, provided herein are methods for preparing Form B of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1)

dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3). In certain embodiments, the solvent is THF. In certain embodiments, the co-solvent is water.

[00179] In one embodiment, provided herein are methods for preparing Form B of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 µm syringe filter); (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3). In certain embodiments, the solvent is THF. In certain embodiments, the co-solvent is water.

[00180] In one embodiment, provided herein are methods for preparing Form B of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 4 and Table 6). In certain embodiments, the solvent is MeOH, MEK, MIBK or DMF. In certain embodiments, the co-solvent is water or toluene.

[00181] In one embodiment, provided herein are methods for preparing Form B of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 µm syringe filter); (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 4 and Table 6). In certain embodiments, the solvent is MeOH, MEK, MIBK or DMF. In certain embodiments, the co-solvent is water or toluene.

[00182] In one embodiment, provided herein is Form B having a DSC thermogram substantially as depicted in Figure 16. In certain embodiments, the crystalline form exhibits a DSC thermogram comprising an endothermic event with a maximum at about 141.5 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at about 185.2 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an exothermic event with a maximum at about 146.9 °C when heated from approximately 30 °C to approximately 230 °C.

[00183] In one embodiment, provided herein is Form B having a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 17. In certain embodiments, the crystalline form exhibits a TGA thermogram comprising about 0.64% mass loss before about 155 °C when heated from approximately 30 °C to approximately 300 °C. The TGA thermogram further comprises a decomposition event with an onset temperature at approximately 258.0 °C when heated from approximately 30 °C to approximately 300 °C.

[00184] In one embodiment, provided herein is Form B that can be converted to Form A after being stirred in a solvent for a period of time. *See* Table 13. In one embodiment, the solvent is IPAc/heptane (*e.g.*, about 1:2 (V:V)) or toluene. In one embodiment, the period of time is from about 1 day to about 7 days (*e.g.*, about 1 day or about 7 days).

[00185] In certain embodiments, a solid form provided herein, *e.g.*, Form B, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form B has an X-ray powder diffraction pattern substantially as shown in Figure 3. In one embodiment, Form B has one or more characteristic X-ray powder diffraction peaks at approximately 4.34, 7.46, 8.61, 11.37, 12.90, 14.89, 15.50, 18.76, 19.71, 21.52, 22.15, 22.81, 23.03, 23.77, 24.60, 25.29, 25.73, 26.23, 26.76, 27.49, 28.17, 30.10, 31.76, 32.57, 34.34, 35.94, 37.74, 38.63, 39.27, 41.75, 42.20 or 44.45 ° 2θ as depicted in Figure 3. In a specific embodiment, Form B has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.34, 8.61, 12.90, 14.89, 15.50, 18.76, 23.77 or 25.29 ° 2θ. In another embodiment, Form B has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.34, 8.61, 14.89 or 15.50 ° 2θ. In another embodiment, Form B has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one or thirty-two characteristic X-ray powder diffraction peaks as set forth in Table 21.

[00186] In certain embodiments, a solid form provided herein, *e.g.*, Form B, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form B has an X-ray powder diffraction pattern substantially as shown in Figure 3. In one embodiment, Form B has one or more characteristic X-ray powder diffraction peaks at approximately 4.3, 7.5, 8.6, 11.4, 12.9, 14.9, 15.5, 18.8, 19.7, 21.5, 22.2, 22.8, 23.0, 23.8, 24.6, 25.3, 25.7, 26.2, 26.8, 27.5, 28.2, 30.1, 31.8, 32.6, 34.3, 35.9, 37.7, 38.6, 39.3, 41.8, 42.2 or 44.5 ° 2θ as depicted in Figure 3. In a specific embodiment, Form B has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 12.9, 14.9, 15.5, 18.8, 23.8 or 25.3 ° 2θ. In another embodiment, Form B has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 14.9 or 15.5 ° 2θ. In another embodiment, Form B has one, two, three, four, five, six or seven characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 12.9, 14.9, 15.5, 18.8 or 25.3 ° 2θ. In another embodiment, Form B has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 14.9, 15.5, 18.8 or 25.3 ° 2θ. In another embodiment, Form B has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 15.5 or 25.3 ° 2θ. In another embodiment, Form B has one, two or three characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6 or 15.5 ° 2θ. In another embodiment, Form B has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one or thirty-two characteristic X-ray powder diffraction peaks as set forth in Table 21.

[00187] In still another embodiment, Form B is substantially pure. In certain embodiments, the substantially pure Form B is substantially free of other solid forms, *e.g.*, Forms A, C, D, E, F, G or H. In certain embodiments, the purity of the substantially pure Form B is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

5.3.3 **Form C of Compound 1**

[00188] In certain embodiments, provided herein is Form C of Compound 1.

[00189] In one embodiment, Form C is a solid form of Compound 1. In one embodiment, Form C is anhydrous. In one embodiment, Form C is an anhydrous solid form of Compound 1 retaining residual solvent. In one embodiment, Form C is an anhydrous solid form of Compound 1 retaining residual EtOH. In another embodiment, Form C is crystalline.

[00190] In certain embodiments, Form C is prepared by single solvent fast cooling crystallization, single solvent slow cooling crystallization, binary solvent fast cooling crystallization or binary solvent slow cooling crystallization experiments (*see* Table 1-Table 10).

[00191] In one embodiment, provided herein are methods for preparing Form C of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the solution to a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is EtOH or IPAc.

[00192] In one embodiment, provided herein are methods for preparing Form C of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (*e.g.*, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) cooling the solution to a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is EtOH or IPAc.

[00193] In one embodiment, provided herein are methods for preparing Form C of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (e.g, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is EtOH or IPAc.

[00194] In one embodiment, provided herein are methods for preparing Form C of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (e.g, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is EtOH or IPAc.

[00195] In one embodiment, provided herein are methods for preparing Form C of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3, Table 5 and Table 9). In certain embodiments, the solvent is EtOH. In certain embodiments, the co-solvent is water, toluene or cyclohexane.

[00196] In one embodiment, provided herein are methods for preparing Form C of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3, Table 5 and Table 9). In certain embodiments, the solvent is EtOH. In certain embodiments, the co-solvent is water, toluene or cyclohexane.

[00197] In one embodiment, provided herein are methods for preparing Form C of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 10). In certain embodiments, the solvent is EtOH, EtOAc or IPAc. In certain embodiments, the co-solvent is cyclohexane.

[00198] In one embodiment, provided herein are methods for preparing Form C of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1)

dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 10). In certain embodiments, the solvent is EtOH, EtOAc or IPAc. In certain embodiments, the co-solvent is cyclohexane.

[00199] In one embodiment, provided herein is Form C having a DSC thermogram substantially as depicted in Figure 19. In certain embodiments, the crystalline form exhibits a DSC thermogram comprising an endothermic event with a maximum at about 63.5 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at about 77.6 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at about 134.9 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at about 185.8 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an exothermic event with a maximum at about 143.0 °C when heated from approximately 30 °C to approximately 230 °C.

[00200] In one embodiment, provided herein is Form C having a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 20. In certain embodiments, the crystalline form exhibits a TGA thermogram comprising about 1.08% mass loss before about 150.0 °C when heated from approximately 30 °C to approximately 300 °C. The TGA thermogram further comprises a decomposition event with an onset temperature at approximately 269.1 °C when heated from approximately 30 °C to approximately 300 °C.

[00201] In one embodiment, provided herein is Form C that can be converted to Form A after being stirred in a solvent for a period of time. *See* Table 13. In one embodiment, the solvent is IPAc/heptane (*e.g.*, about 1:2 (V:V)) or toluene. In one embodiment, the period of time is from about 1 day to about 7 days (*e.g.*, about 1 day or about 7 days).

[00202] In certain embodiments, a solid form provided herein, *e.g.*, Form C, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form C has an X-ray powder diffraction pattern substantially as shown in Figure 4. In one embodiment, Form C has one or more characteristic X-ray powder diffraction peaks at approximately 3.09, 4.35, 7.46, 8.63, 11.41, 12.93, 14.94, 15.55, 18.80, 19.78, 21.60, 22.51, 22.89, 23.31, 24.10, 24.87, 25.25, 26.34, 27.07, 27.77, 28.10, 28.45, 29.09, 29.43, 29.75, 30.37, 30.73, 31.77, 32.24, 32.86, 34.02, 35.67, 37.86, 38.39, 39.35, 41.85, 42.35, 43.28, 43.74 or 44.24 ° 2θ as depicted in Figure 4. In a specific embodiment, Form C has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.35, 8.63, 11.41, 12.93, 14.94, 15.55, 18.80 or 21.60 ° 2θ. In another embodiment, Form C has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.35, 8.63, 14.94 or 15.55 ° 2θ. In another embodiment, Form C has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine or forty characteristic X-ray powder diffraction peaks as set forth in Table 22.

[00203] In certain embodiments, a solid form provided herein, *e.g.*, Form C, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form C has an X-ray powder diffraction pattern substantially as shown in Figure 4. In one embodiment, Form C has one or more characteristic X-ray powder diffraction peaks at approximately 3.1, 4.4, 7.5, 8.6, 11.4, 12.9, 14.9, 15.6, 18.8, 19.8, 21.6, 22.5, 22.9, 23.3, 24.1, 24.9, 25.3, 26.3, 27.1, 27.8, 28.1, 28.5, 29.1, 29.4, 29.8, 30.4, 30.7, 31.8, 32.2, 32.9, 34.0, 35.7, 37.9, 38.4, 39.4, 41.9, 42.4, 43.3, 43.7 or 44.2 ° 2θ as depicted in Figure 4. In a specific embodiment, Form C has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.4, 8.6, 11.4, 12.9, 14.9, 15.6, 18.8 or 21.6 ° 2θ. In another embodiment, Form C has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.4, 8.6, 14.9 or 15.6 ° 2θ. In another embodiment, Form C has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 4.4, 8.6, 11.4, 14.9, 15.6 or 18.8 ° 2θ. In another embodiment, Form C has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.4, 8.6, 11.4 or 15.6 ° 2θ. In another embodiment, Form C has one, two or three characteristic X-ray powder diffraction peaks at approximately 4.4, 8.6 or 15.6 ° 2θ. In another embodiment, Form C has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine or forty characteristic X-ray powder diffraction peaks as set forth in Table 22.

[00204] In still another embodiment, Form C is substantially pure. In certain embodiments, the substantially pure Form C is substantially free of other solid forms, *e.g.*, Forms A, B, D, E, F, G or H. In certain embodiments, the purity of the substantially pure Form C is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

5.3.4 **Form D of Compound 1**

[00205] In certain embodiments, provided herein is Form D of Compound 1.

[00206] In one embodiment, Form D is a solid form of Compound 1. In one embodiment, Form D is anhydrous. In another embodiment, Form D is crystalline.

[00207] In certain embodiments, Form D is prepared by single solvent fast cooling crystallization, single solvent slow cooling crystallization, binary solvent fast cooling crystallization or binary solvent slow cooling crystallization experiments (*see* Table 1-Table 10).

[00208] In one embodiment, provided herein are methods for preparing Form D of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the solution to a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is IPA, 1-BuOH, MeCN or EtOAc.

[00209] In one embodiment, provided herein are methods for preparing Form D of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (*e.g.*, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 µm syringe filter); (3) cooling the solution to a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is IPA, 1-BuOH, MeCN or EtOAc.

[00210] In one embodiment, provided herein are methods for preparing Form D of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (e.g, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is IPA, EtOAc or MEK.

[00211] In one embodiment, provided herein are methods for preparing Form D of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (e.g, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 µm syringe filter); (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is IPA, EtOAc or MEK.

[00212] In one embodiment, provided herein are methods for preparing Form D of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3, Table 5, Table 7 and Table 9). In certain embodiments, the solvent is MeOH, MeCN, n-Propanol, 1-BuOH, THF, 2-MeTHF, EtOAc, IPA, IPAc, acetone, MEK or MIBK. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00213] In one embodiment, provided herein are methods for preparing Form D of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3, Table 5, Table 7 and Table 9). In certain embodiments, the solvent is MeOH, MeCN, n-Propanol, 1-BuOH, THF, 2-MeTHF, EtOAc, IPA, IPAc, acetone, MEK or MIBK. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00214] In one embodiment, provided herein are methods for preparing Form D of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5)

isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form. (*see* Table 4, Table 6, Table 8 and Table 10). In certain embodiments, the solvent is n-propanol, 1-BuOH, MeOH, MeCN, THF, acetone, MEK or MIBK. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00215] In one embodiment, provided herein are methods for preparing Form D of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 4, Table 6, Table 8 and Table 10). In certain embodiments, the solvent is n-propanol, 1-BuOH, MeOH, MeCN, THF, acetone, MEK or MIBK. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00216] In one embodiment, provided herein is Form D having a DSC thermogram substantially as depicted in Figure 11. In certain embodiments, the crystalline form exhibits a DSC thermogram comprising an endothermic event with a maximum at about 185.2 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an exothermic event with a maximum at about 118.7 °C when heated from approximately 30 °C to approximately 230 °C.

[00217] In one embodiment, provided herein is Form D having a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 12. In certain embodiments, the crystalline form exhibits a TGA thermogram comprising no mass loss before about 155 °C when heated from approximately 30 °C to approximately 300 °C. The TGA thermogram further comprises a decomposition event with an onset temperature at approximately 259.8 °C when heated from approximately 30 °C to approximately 300 °C. Thus, in certain embodiments, the crystalline form has no mass loss at a temperature lower than about 100 °C.

[00218] In one embodiment, provided herein is slightly hygroscopic Form D having about 0.7% weight moisture uptake at 60% RH and about 1.0% weight moisture uptake at 90% RH. *See* Figure 24.

[00219] In one embodiment, provided herein is Form D that can be converted to Form A after being stirred in a solvent for a period of time. *See* Table 13. In one embodiment, the solvent is IPAc/heptane (*e.g.*, about 1:2 (V:V)) or toluene. In one embodiment, the period of time is from about 1 day to about 7 days (*e.g.*, about 1 day or about 7 days).

[00220] In certain embodiments, a solid form provided herein, *e.g.*, Form D, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form D has an X-ray powder diffraction pattern substantially as shown in Figure 5. In one embodiment, Form D has one or more characteristic X-ray powder diffraction peaks at approximately 4.32, 7.44, 8.59, 11.31, 12.85, 14.85, 15.49, 18.72, 19.71, 21.51, 22.40, 22.75, 23.62, 24.48, 25.17, 26.19, 26.68, 26.96, 27.32, 27.98, 28.35, 29.34, 29.98, 30.30, 32.44, 34.07, 35.81, 37.16, 37.69, 38.44, 39.25, 41.71, 42.19 or 44.35 ° 2θ as depicted in Figure 5. In a specific embodiment, Form D has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.32, 7.44, 8.59, 11.31, 12.85, 14.85, 15.49 or 18.72 ° 2θ. In another embodiment, Form D has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.32, 8.59, 14.85 or 15.49 ° 2θ. In another embodiment, Form D has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three or thirty-four characteristic X-ray powder diffraction peaks as set forth in Table 23.

[00221] In certain embodiments, a solid form provided herein, *e.g.*, Form D, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form D has an X-ray powder diffraction pattern substantially as shown in Figure 5. In one embodiment, Form D has one or more characteristic X-ray powder diffraction peaks at approximately 4.3, 7.4, 8.6, 11.3, 12.9, 14.9, 15.5, 18.7, 19.7, 21.5, 22.4, 22.8, 23.6, 24.5, 25.2, 26.2, 26.7, 27.0, 27.3, 28.0, 28.4, 29.3, 30.0, 30.3, 32.4, 34.1, 35.8, 37.2, 37.7, 38.4, 39.3, 41.7, 42.2 or 44.4 ° 2θ as depicted in Figure 5. In a specific embodiment, Form D has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.3, 7.4, 8.6, 11.3, 12.9, 14.9, 15.5 or 18.7 ° 2θ. In another embodiment, Form D has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 14.9 or 15.5 ° 2θ. In another embodiment, Form D has one, two, three, four, five, six or seven characteristic X-ray powder diffraction peaks at approximately 4.3, 7.4, 8.6, 12.9, 14.9, 15.5 or 18.7 ° 2θ. In another embodiment, Form D has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 12.8, 14.9, 15.5 or 18.7 ° 2θ. In another embodiment, Form D has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.3, 7.4, 8.6 or 15.5 ° 2θ. In another embodiment, Form D has one, two or three characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6 or 15.5 ° 2θ. In another embodiment, Form D has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three or thirty-four characteristic X-ray powder diffraction peaks as set forth in Table 23.

[00222] In still another embodiment, Form D is substantially pure. In certain embodiments, the substantially pure Form D is substantially free of other solid forms, *e.g.*, Forms A, B, C, E, F, G and H. In certain embodiments, the purity of the substantially pure Form D is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

5.3.5 **Form E of Compound 1**

[00223] In certain embodiments, provided herein is Form E of Compound 1.

[00224] In one embodiment, Form E is a solid form of Compound 1. In one embodiment, Form E is anhydrous. In one embodiment, Form E is an anhydrous solid form of Compound 1 retaining residual solvent. In one embodiment, Form E is an anhydrous solid form of Compound 1 retaining residual EtOAc. In another embodiment, Form E is crystalline.

[00225] In certain embodiments, Form E is prepared by single solvent fast cooling crystallization, single solvent slow cooling crystallization, binary solvent fast cooling crystallization or binary solvent slow cooling crystallization experiments (*see* Table 1-Table 10).

[00226] In one embodiment, provided herein are methods for preparing Form E of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the solution to a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is 2-MeTHF, MEK or n-Propanol.

[00227] In one embodiment, provided herein are methods for preparing Form E of Compound 1 comprising single solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (*e.g.*, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) cooling the solution to a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 1. In certain embodiments, the solvent is 2-MeTHF, MEK or n-Propanol.

[00228] In one embodiment, provided herein are methods for preparing Form E of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 10-55 mg) with a minimum amount of solvents (e.g, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, from about 6 hours to about 72 hours); (4) isolating the resulting solids; and (5) evaporating the samples without precipitation to dryness and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is 1-BuOH, 2-MeTHF or n-Propanol.

[00229] In one embodiment, provided herein are methods for preparing Form E of Compound 1 comprising single solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, approximately 30-35 mg) with a minimum amount of solvents (e.g, up to about 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) cooling the hot solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature over a period of time (*e.g.*, about 24 hours); (4) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (5) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen) and collecting the resulting solids. *See* Table 2. In certain embodiments, the solvent is 1-BuOH, 2-MeTHF or n-Propanol.

[00230] In one embodiment, provided herein are methods for preparing Form E of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3, Table 5, Table 7 and Table 9). In certain embodiments, the solvent is IPA, MEK, n-Propanol, EtOH, 1-BuOH, IPA, THF, 2-MeTHF or EtOAc. In certain embodiments, the co-solvent is toluene, heptane or cyclohexane.

[00231] In one embodiment, provided herein are methods for preparing Form E of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3, Table 5, Table 7 and Table 9). In certain embodiments, the solvent is IPA, MEK, n-Propanol, EtOH, 1-BuOH, IPA, THF, 2-MeTHF or EtOAc. In certain embodiments, the co-solvent is toluene, heptane or cyclohexane.

[00232] In one embodiment, provided herein are methods for preparing Form E of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 4, Table 6, Table 8 and Table 10). In certain embodiments, the solvent is EtOH, THF, IPA, 2-MeTHF, EtOAc, n-Propanol, 1-BuOH or MIBK. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00233] In one embodiment, provided herein are methods for preparing Form E of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 4, Table 6, Table 8 and Table 10). In certain embodiments, the solvent is EtOH, THF, IPA, 2-MeTHF, EtOAc, n-Propanol, 1-BuOH or MIBK. In certain embodiments, the co-solvent is water, toluene, heptane or cyclohexane.

[00234] In one embodiment, provided herein is Form E having a DSC thermogram substantially as depicted in Figure 27. In certain embodiments, the crystalline form exhibits a

DSC thermogram comprising an endothermic event with a maximum at about 154.8 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at about 185.6 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an exothermic event with a maximum at about 156.7 °C when heated from approximately 30 °C to approximately 230 °C.

[00235] In one embodiment, provided herein is Form E having a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 28. In certain embodiments, the crystalline form exhibits a TGA thermogram comprising about 1.96% mass loss before about 165.0 °C when heated from approximately 30 °C to approximately 300 °C. The TGA thermogram further comprises a decomposition event with an onset temperature at approximately 261.6 °C when heated from approximately 30 °C to approximately 300 °C.

[00236] In one embodiment, provided herein is Form E that can be converted to Form A after being stirred in a solvent for a period of time. *See* Table 13. In one embodiment, the solvent is IPAc/heptane (*e.g.*, about 1:2 (V:V)) or toluene. In one embodiment, the period of time is from about 1 day to about 7 days (*e.g.*, about 1 day or about 7 days).

[00237] In certain embodiments, a solid form provided herein, *e.g.*, Form E, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form E has an X-ray powder diffraction pattern substantially as shown in Figure 6. In one embodiment, Form E has one or more characteristic X-ray powder diffraction peaks at approximately 4.33, 4.66, 5.42, 5.73, 5.99, 6.16, 6.29, 6.50, 7.46, 8.61, 9.32, 10.07, 10.78, 10.93, 11.37, 12.17, 12.89, 13.45, 14.45, 14.89, 15.50, 16.66, 18.74, 19.73, 20.04, 20.56, 21.53, 21.80, 22.19, 22.57, 22.81, 23.45, 23.87, 24.23, 24.97, 25.35, 26.24, 26.47, 26.96, 27.24, 27.85, 28.36, 29.19, 29.57, 29.85, 30.30, 30.81, 31.25, 32.34, 32.93, 34.10, 34.77, 35.74, 36.36, 37.23, 37.71, 38.36, 39.28, 40.74, 41.66, 42.19, 42.61, 43.29, 43.71 or 44.18 ° 2θ as depicted in Figure 6. In a specific embodiment, Form E has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.33, 8.61, 14.89, 15.50, 18.74, 23.45, 24.97 or 27.85 ° 2θ. In another embodiment, Form E has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.33, 8.61, 14.89 or 15.50 ° 2θ. In another embodiment, Form E has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three, sixty-four or sixty-five characteristic X-ray powder diffraction peaks as set forth in Table 24.

[00238] In certain embodiments, a solid form provided herein, *e.g.*, Form E, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form E has an X-ray powder diffraction pattern substantially as shown in Figure 6. In one embodiment, Form E has one or more characteristic X-ray powder diffraction peaks at approximately 4.3, 4.7, 5.4, 5.7, 6.0, 6.2, 6.3, 6.5, 7.5, 8.6, 9.3, 10.1, 10.8, 10.9, 11.4, 12.2, 12.9, 13.5, 14.5, 14.9, 15.5, 16.7, 18.7, 19.7, 20.0, 20.6, 21.5, 21.8, 22.2, 22.6, 22.8, 23.5, 23.9, 24.2, 25.0, 25.4, 26.2, 26.5, 27.0, 27.2, 27.9, 28.4, 29.2, 29.6, 29.9, 30.3, 30.8, 31.3, 32.3, 32.9, 34.1, 34.8, 35.7, 36.4, 37.2, 37.7, 38.4, 39.3, 40.7, 41.7, 42.2, 42.6, 43.3, 43.7 or 44.2 ° 2θ as depicted in Figure 6. In a specific embodiment, Form E has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 14.9, 15.5, 18.7, 23.5, 25.0 or 27.9 ° 2θ. In another embodiment, Form E has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 14.9 or 15.5 ° 2θ. In another embodiment, Form E has one, two, three, four, five, six or seven characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 14.9, 15.5 18.7, 25.0 or 27.9 ° 2θ. In another embodiment, Form E has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 14.9, 15.5 18.7 or 25.0 ° 2θ. In another embodiment, Form E has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6, 15.5 or 27.9 ° 2θ. In another embodiment, Form E has one, two or three characteristic X-ray powder diffraction peaks at approximately 4.3, 8.6 or 15.5 ° 2θ. In another embodiment, Form E has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three, sixty-four or sixty-five characteristic X-ray powder diffraction peaks as set forth in Table 24.

[00239] In still another embodiment, Form E is substantially pure. In certain embodiments, the substantially pure Form E is substantially free of other solid forms, *e.g.*, Forms A, B, C, D, F, G and H. In certain embodiments, the purity of the substantially pure Form E is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

5.3.6 **Form F of Compound 1**

[00240] In certain embodiments, provided herein is Form F.

[00241] In one embodiment, Form F is a solid form of Compound 1. In one embodiment, Form F is a hydrate solid form of Compound 1. In another embodiment, Form F is crystalline.

[00242] In certain embodiments, Form F is prepared by binary solvent fast cooling crystallization or binary solvent slow cooling crystallization experiments (*see* Table 3 and Table 4).

[00243] In one embodiment, provided herein are methods for preparing Form F of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3). In certain embodiments, the solvent is THF, n-Propanol or MIBK. In certain embodiments, the co-solvent is water.

[00244] In one embodiment, provided are methods for preparing Form F of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3). In certain embodiments, the solvent is THF, n-Propanol or MIBK. In certain embodiments, the co-solvent is water.

[00245] In one embodiment, provided herein are methods for preparing Form F of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 4). In certain embodiments, the solvent is THF. In certain embodiments, the co-solvent is water.

[00246] In one embodiment, provided herein are methods for preparing Form F of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 4). In certain embodiments, the solvent is THF. In certain embodiments, the co-solvent is water.

[00247] In one embodiment, provided herein is Form F having a DSC thermogram substantially as depicted in Figure 30. In certain embodiments, the crystalline form exhibits a DSC thermogram comprising an endothermic event with a maximum at about 64.1 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at about 91.3 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at about 185.9 °C when heated from approximately 30 °C to approximately 230 °C.

[00248] In one embodiment, provided herein is Form F having a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 31. In certain embodiments, the crystalline form exhibits a TGA thermogram comprising about 1.86% mass loss before about 110.0 °C when heated from approximately 30 °C to approximately 300 °C. The TGA thermogram further comprises a decomposition event with an onset temperature at approximately 268.3 °C when heated from approximately 30 °C to approximately 300 °C.

[00249] In one embodiment, provided herein is Form F that can be converted to Form A after being stirred in a solvent for a period of time. *See* Table 13. In one embodiment, the solvent is IPAc/heptane (*e.g.*, about 1:2 (V:V)) or toluene. In one embodiment, the period of time is from about 1 day to about 7 days (*e.g.*, about 1 day or about 7 days).

[00250] In certain embodiments, a solid form provided herein, *e.g.*, Form F, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form F has an X-ray powder diffraction pattern substantially as shown in Figure 7. In one embodiment, Form F has one or more characteristic X-ray powder diffraction peaks at approximately 3.99, 4.23, 7.89, 8.36, 11.81, 15.21, 15.44, 17.39, 17.79, 19.78, 20.87, 22.98, 23.83, 25.17, 26.10, 27.15, 28.53, 30.30, 31.71 or 34.06 ° 2θ as depicted in Figure 7. In a specific embodiment, Form F has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.99, 4.23, 7.89, 8.36, 15.21, 15.44, 20.87 or 25.17 ° 2θ. In another embodiment, Form F has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.99, 4.23, 7.89 or 15.21 ° 2θ. In another embodiment, Form F has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen or twenty characteristic X-ray powder diffraction peaks as set forth in Table 25.

[00251] In certain embodiments, a solid form provided herein, *e.g.*, Form F, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form F has an X-ray powder diffraction pattern substantially as shown in Figure 7.

In one embodiment, Form F has one or more characteristic X-ray powder diffraction peaks at approximately 4.0, 4.2, 7.9, 8.4, 11.8, 15.2, 15.4, 17.4, 17.8, 19.8, 20.9, 23.0, 23.8, 25.2, 26.1, 27.2, 28.5, 30.3, 31.7 or 34.1 ° 2θ as depicted in Figure 7. In a specific embodiment, Form F has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.0, 4.2, 7.9, 8.4, 15.2, 15.4, 20.9 or 25.2 ° 2θ. In another embodiment, Form F has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.0, 4.2, 7.9 or 15.2 ° 2θ. In another embodiment, Form F has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 4.0, 4.2, 7.9, 8.4, 15.2 or 15.4 ° 2θ. In another embodiment, Form F has one, two or three characteristic X-ray powder diffraction peaks at approximately 4.0, 4.2 or 15.2 ° 2θ. In another embodiment, Form F has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen or twenty characteristic X-ray powder diffraction peaks as set forth in Table 25.

[00252] In still another embodiment, Form F is substantially pure. In certain embodiments, the substantially pure Form F is substantially free of other solid forms, *e.g.*, Forms A, B, C, D, E, G and H. In certain embodiments, the purity of the substantially pure Form F is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

5.3.7 **Form G of Compound 1**

[00253] In certain embodiments, provided herein is Form G.

[00254] In one embodiment, Form G is a solid form of Compound 1. In one embodiment, Form G is anhydrous. In another embodiment, Form G is crystalline.

[00255] In certain embodiments, Form G is prepared by binary solvent fast cooling crystallization or binary solvent slow cooling crystallization experiments (*see* Table 3 and Table 4).

[00256] In one embodiment, provided herein are methods for preparing Form G of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3). In certain embodiments, the solvent is MEK, MIBK or 2-MeTHF. In certain embodiments, the co-solvent is water.

[00257] In one embodiment, provided herein are methods for preparing Form G of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) cooling the solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 4). In certain embodiments, the solvent is IPA or 2-MeTHF. In certain embodiments, the co-solvent is water.

[00258] In one embodiment, provided herein is Form G having a DSC thermogram substantially as depicted in Figure 33. In certain embodiments, the crystalline form exhibits a DSC thermogram comprising an endothermic event with a maximum at about 90.5 °C when heated from approximately 30 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at about 184.9 °C when heated from approximately 30 °C to approximately 230 °C.

[00259] In one embodiment, provided herein is Form G having a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 34. In certain embodiments, the crystalline form exhibits a TGA thermogram comprising no mass loss before about 110.0 °C when heated from approximately 30 °C to approximately 300 °C. The TGA thermogram further comprises a decomposition event with an onset temperature at approximately 263.5 °C when heated from approximately 30 °C to approximately 300 °C.

[00260] In one embodiment, provided herein is Form G that can be converted to Form A after being stirred in a solvent for a period of time. *See* Table 13. In one embodiment, the solvent is IPAc/heptane (*e.g.*, about 1:2 (V:V)) or toluene. In one embodiment, the period of time is from about 1 day to about 7 days (*e.g.*, about 1 day or about 7 days).

[00261] In one embodiment, provided herein is slightly hygroscopic Form G having about 0.4% weight moisture uptake at 60% RH and about 7.1% weight moisture uptake at 90% RH. *See* Figure 35.

[00262] In certain embodiments, a solid form provided herein, *e.g.*, Form G, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form G has an X-ray powder diffraction pattern substantially as shown in Figure 8. In one embodiment, Form G has one or more characteristic X-ray powder diffraction peaks at approximately 4.19, 8.33, 12.47, 15.19, 15.44, 16.67, 17.81, 19.26, 20.87, 21.33, 22.18, 22.86, 23.71, 24.59, 25.09, 25.89, 27.00, 28.36, 28.63, 29.87, 32.45, 34.70, 39.53 or 42.08 ° 2θ as depicted in Figure 8. In a specific embodiment, Form G has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.19, 8.33, 15.19, 15.44, 17.81, 20.87, 27.00 or 28.36 ° 2θ. In another embodiment, Form G has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.19, 8.33, 15.19 or 20.87 ° 2θ. In another embodiment, Form G has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three or twenty-four characteristic X-ray powder diffraction peaks as set forth in Table 26.

[00263] In certain embodiments, a solid form provided herein, *e.g.*, Form G, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form G has an X-ray powder diffraction pattern substantially as shown in Figure 8. In one embodiment, Form G has one or more characteristic X-ray powder diffraction peaks at approximately 4.2, 8.3, 12.5, 15.2, 15.4, 16.7, 17.8, 19.3, 20.9, 21.3, 22.2, 22.9, 23.7, 24.6, 25.1, 25.9, 27.0, 28.4, 28.6, 29.9, 32.5, 34.7, 39.5 or 42.1 ° 2θ as depicted in Figure 8. In a specific embodiment, Form G has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.2, 8.3, 15.2, 15.4, 17.8, 20.9, 27.0 or 28.4 ° 2θ. In another embodiment, Form G has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.2, 8.3, 15.2 or 20.9 ° 2θ. In another embodiment, Form G has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 4.2, 8.3, 15.2, 15.4, 17.8 or 20.9 ° 2θ. In another embodiment, Form G has one, two or three characteristic X-ray powder diffraction peaks at approximately 4.2, 8.3 or 15.2 ° 2θ. In another embodiment, Form G has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three or twenty-four characteristic X-ray powder diffraction peaks as set forth in Table 26.

[00264] In still another embodiment, Form G is substantially pure. In certain embodiments, the substantially pure Form G is substantially free of other solid forms, *e.g.*, Forms A, B, C, D, E, F and H. In certain embodiments, the purity of the substantially pure Form G is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

5.3.8 **Form H of Compound 1**

[00265] In certain embodiments, provided herein is Form H.

[00266] In one embodiment, Form H is a solid form of Compound 1. In one embodiment, Form H is a solvate of Compound 1. In one embodiment, Form H is a DMSO solvate of Compound 1. In one embodiment, Form H is a mono-DMSO solvate of Compound 1. In another embodiment, Form H is crystalline.

[00267] In certain embodiments, Form H is prepared by binary solvent fast cooling crystallization or binary solvent slow cooling crystallization experiments (*see* Table 3 and Table 4).

[00268] In one embodiment, provided herein are methods for preparing Form H of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, from about -5 °C to about 10 °C) for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by

XRPD to determine the solid form (*see* Table 3 and Table 5). In certain embodiments, the solvent is DMSO. In certain embodiments, the co-solvent is toluene.

[00269] In one embodiment, provided herein are methods for preparing Form H of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) placing the solution at a second temperature (*e.g.*, about 4 °C) for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3 and Table 5). In certain embodiments, the solvent is DMSO. In certain embodiments, the co-solvent is toluene.

[00270] In one embodiment, provided herein are methods for preparing Form H of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 10-55 mg) with a minimum amount of solvents (*e.g.*, from about 0.25 mL to about 14.0 mL) at a first temperature (*e.g.*, from about 30 °C to about 90 °C); (2) filtering the hot solution; (3) adding a co-solvent; (4) cooled the solution to ambient temperature at a rate (*e.g.*, from about 5 °C/hr to about 40 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, from about 6 hours to about 72 hours); (5) isolating the resulting solids; and (6) evaporating the samples without precipitation to dryness and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 6). In certain embodiments, the solvent is DMSO. In certain embodiments, the co-solvent is toluene.

[00271] In one embodiment, provided herein are methods for preparing Form H of Compound 1 comprising binary solvent slow cooling crystallization comprising the steps of: (1) dissolving Compound 1 (*e.g.*, about 30-35 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) filtering the hot solution (*e.g.*, filtering through a 0.45 μm syringe filter); (3) adding a co-solvent; (4) cooled the solution to ambient temperature at a rate (*e.g.*, about 20 °C/hr) and allowing to equilibrate at ambient temperature for a period of time (*e.g.*, about 24 hours); (5) isolating the resulting solids (*e.g.*, isolating by vacuum filtration); and (6) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 6). In certain embodiments, the solvent is DMSO. In certain embodiments, the co-solvent is toluene.

[00272] In one embodiment, provided herein is Form H having a DSC thermogram substantially as depicted in Figure 38. In certain embodiments, the crystalline form exhibits a DSC thermogram comprising an endothermic event with a maximum at about 88.0 °C when heated from approximately 30 °C to approximately 230 °C.

[00273] In one embodiment, provided herein is Form H having a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 39. In certain embodiments, the crystalline form exhibits a TGA thermogram comprising about 6.4% mass loss before about 140 °C when heated from approximately 30 °C to approximately 300 °C. In certain embodiments, the TGA thermogram further comprises about 9.8% mass loss before about 240 °C when heated from approximately 30 °C to approximately 300 °C. The TGA thermogram further comprises a decomposition event with an onset temperature at approximately 268.1 °C when heated from approximately 30 °C to approximately 300 °C.

[00274] In one embodiment, provided herein is Form H that can be converted to Form A after being stirred in a solvent for a period of time. *See* Table 13. In one embodiment, the solvent is IPAc/heptane (*e.g.*, about 1:2 (V:V)) or toluene. In one embodiment, the period of time is from about 1 day to about 7 days (*e.g.*, about 1 day or about 7 days).

[00275] In certain embodiments, a solid form provided herein, *e.g.*, Form H, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form H has an X-ray powder diffraction pattern substantially as shown in Figure 9. In one embodiment, Form H has one or more characteristic X-ray powder diffraction peaks at approximately 3.07, 5.35, 8.56, 10.69, 12.20, 12.62, 13.08, 13.32, 14.08, 15.46, 16.04, 17.18, 17.69, 17.93, 18.76, 19.69, 20.14, 21.19, 21.40, 22.22, 22.99, 24.02, 24.59, 25.18, 25.75, 26.55, 26.93, 27.53, 28.32, 29.07, 31.19, 31.72, 32.05, 33.70, 35.09, 35.76, 37.23, 37.94, 38.67, 39.26, 39.96, 40.36, 43.14 or 44.56 ° 2θ as depicted in Figure 9. In a specific embodiment, Form H has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.07, 12.62, 14.08, 17.18, 18.76, 21.40, 24.59 or 25.75 ° 2θ. In another embodiment, Form H has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 14.08, 18.76, 21.40 or 24.59 ° 2θ. In another embodiment, Form H has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three or forty-four characteristic X-ray powder diffraction peaks as set forth in Table 27.

[00276] In certain embodiments, a solid form provided herein, *e.g.*, Form H, is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Form H has an X-ray powder diffraction pattern substantially as shown in Figure 9. In one embodiment, Form H has one or more characteristic X-ray powder diffraction peaks at approximately 3.1, 5.4, 8.6, 10.7, 12.2, 12.6, 13.1, 13.3, 14.1, 15.5, 16.0, 17.2, 17.7, 17.9, 18.8, 19.7, 20.1, 21.2, 21.4, 22.2, 23.0, 24.0, 24.6, 25.2, 25.8, 26.6, 26.9, 27.5, 28.3, 29.1, 31.2, 31.7, 32.1, 33.7, 35.1, 35.8, 37.2, 37.9, 38.7, 39.3, 40.0, 40.4, 43.1 or 44.6 ° 2θ as depicted in Figure 9. In a specific embodiment, Form H has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.1, 12.6, 14.1, 17.2, 18.8, 21.4, 24.6 or 25.8 ° 2θ. In another embodiment, Form H has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 14.1, 18.8, 21.4 or 24.6 ° 2θ. In another embodiment, Form H has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 14.1, 17.2, 18.8, 21.4, 24.6 or 25.7 ° 2θ. In another embodiment, Form H has one, two or three characteristic X-ray powder diffraction peaks at approximately 14.1, 18.8 or 21.4 ° 2θ. In another embodiment, Form H has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three or forty-four characteristic X-ray powder diffraction peaks as set forth in Table 27.

[00277] In still another embodiment, Form H is substantially pure. In certain embodiments, the substantially pure Form H is substantially free of other solid forms, *e.g.*, Forms A, B, C, D, E, F and G. In certain embodiments, the purity of the substantially pure

Form H is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

5.4 **Salts of Compound 1**

[00278] In certain embodiments, provided herein are salts of Compound 1. In one embodiment, the salt is crystalline.

[00279] The salts provided herein (*e.g.*, Salt I, Salt II, Salt III, Salt IV, Salt V and Salt VI of Compound 1) may be characterized using a number of methods known to a person skilled in the art, including, but not limited to, single crystal X-ray diffraction, X-ray powder diffraction (XRPD), microscopy (*e.g.*, scanning electron microscopy (SEM)), thermal analysis (*e.g.*, differential scanning calorimetry (DSC), dynamic vapor sorption (DVS), thermal gravimetric analysis (TGA), and hot-stage microscopy), spectroscopy (*e.g.*, infrared, Raman, and solid-state nuclear magnetic resonance), high performance liquid chromatography (HPLC), and proton nuclear magnetic resonance (^{1}H NMR) spectrum. The particle size and size distribution of the salt provided herein may be determined by conventional methods, such as laser light scattering technique.

[00280] It should be understood that the numerical values of the peaks of an X-ray powder diffraction pattern may vary slightly from one machine to another or from one sample to another, and so the values quoted are not to be construed as absolute, but with an allowable variability, such as $\pm 0.2°$ 2θ (*see* United State Pharmacopoeia, page 2228 (2003)).

[00281] In certain embodiments, provided herein is a method for making a salt of Compound 1, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, CH_3OH, CH_3CN or acetone) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 30-70 °C or about 50 °C); 3) filtering the mixture at the elevated temperature to yield a solution; 4) adding a basic counter-ion solution (*e.g.*, about 1 or 3 equivalents); 5) cooling the resulting mixture to a temperature (*e.g.*, about 10-30 °C or about 25°C); 6) collecting precipitation by filtration; and 7) evaporating the solution to yield a solid if no precipitation and collecting the solid. In certain embodiments, the solvent is CH_3OH, CH_3CN or acetone. In certain embodiments, the basic counter-ion is provided by calcium acetate hydrate, choline hydroxide, potassium hydroxide, sodium hydroxide in, l-arginine, n-methyl-d-glucamine (meglumine), a mixture of magnesium nitrate and sodium hydroxide or a mixture of calcium nitrate and sodium hydroxide. In certain embodiments, the solvent of the basic counter-ion solution is water, CH_3OH or a mixture of water and CH_3OH.

5.4.1 Hemi-Calcium Salt of Compound 1 (Salt I)

[00282] In one embodiment, provided herein is a calcium salt of Compound 1. In one embodiment, provided herein is a hemi-calcium salt of Compound 1 ("Salt I"). In one embodiment, Salt I is crystalline. In one embodiment, Salt I is moderately hydroscopic. In one embodiment, Salt I is chemically stable.

[00283] In certain embodiments, provided herein is a method for making Salt I, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, CH_3OH) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 30-70 °C); 3) filtering the mixture at the elevated temperature to yield a solution; 4) contacting the mixture with a calcium acetate solution (*e.g.*, about 0.5-1.5 equivalents); 5) cooling the resulting mixture (*e.g.*, to about 10-30 °C); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the calcium acetate solution is a solution of calcium acetate hydrate in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00284] In certain embodiments, provided herein is a method for making Salt I, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, CH_3OH) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 50 °C); 3) filtering the mixture at the elevated temperature with a 0.45 μm syringe filter to yield a solution; 4) contacting the mixture with a calcium acetate solution (*e.g.*, about 1 equivalent); 5) cooling the resulting mixture (*e.g.*, to about 25 °C) (*e.g.*, at a speed of about 20 °C/hour); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the calcium acetate solution is a solution of calcium acetate hydrate in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00285] In one embodiment, Salt I has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 49. In certain embodiments, Salt I exhibits a TGA thermogram comprising a total mass loss of approximately 0.34% of the total mass of the sample between approximately 65 °C and approximately 105 °C when heated from approximately 25 °C to approximately 230 °C. In one embodiment, the TGA thermogram further comprises a total mass loss of approximately 1.41% of the total mass of the sample between approximately 140 °C and approximately 190 °C when heated from approximately 25 °C to approximately 230 °C. In one embodiment, the TGA thermogram further comprises a decomposition event with onset temperature at approximately 213.8 °C when heated from approximately 25 °C to approximately 230 °C.

[00286] In one embodiment, Salt I has a DSC thermogram as depicted in Figure 48 comprising an endothermic event with a maximum at approximately 104.0 °C when heated from approximately 25 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 170.6 °C when heated from approximately 25 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 179.1 °C when heated from approximately 25 °C to approximately 230 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 210.6 °C when heated from approximately 25 °C to approximately 230 °C.

[00287] In certain embodiments, Salt I is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt I has an X-ray powder diffraction pattern substantially as shown in Figure 40. In one embodiment, Salt I has one or more characteristic X-ray powder diffraction peaks at approximately 3.20, 4.09, 4.51, 4.85, 4.99, 5.19, 5.43, 5.69, 6.01, 6.49, 6.92, 7.21, 8.29, 8.47, 9.17, 9.53, 10.39, 10.58, 11.30, 11.87, 12.10, 12.23, 12.73, 13.23, 14.23, 15.60, 15.97, 17.21, 17.49, 18.08, 18.88, 19.15, 22.00, 22.41, 23.92, 25.25, 25.60, 26.35, 26.67, 27.76, 28.21, 29.29, 31.08, 31.46, 31.82, 33.44, 34.63, 35.58, 37.97, 38.65, 38.96, 41.35, 42.29 or 43.31 ° 2θ as depicted in Figure 40. In a specific embodiment, Salt I has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.20, 5.43, 9.53, 13.23, 15.60, 15.97, 19.15 or 22.41 ° 2θ. In another embodiment, Salt I has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.20, 9.53, 15.97 or 22.41 ° 2θ. In another embodiment, Salt I has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three or fifty-four characteristic X-ray powder diffraction peaks as set forth in Table 38.

[00288] In certain embodiments, Salt I is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt I has an X-ray powder diffraction pattern substantially as shown in Figure 40. In one embodiment, Salt I has one or more characteristic X-ray powder diffraction peaks at approximately 3.2, 4.1, 4.5, 4.9, 5.0, 5.2, 5.4, 5.7, 6.0, 6.5, 6.9, 7.2, 8.3, 8.5, 9.2, 9.5, 10.4, 10.6, 11.3, 11.9, 12.1, 12.2, 12.7, 13.2, 14.2, 15.6, 16.0, 17.2, 17.5, 18.1, 18.9, 19.2, 22.0, 22.4, 23.9, 25.3, 25.6, 26.4, 26.7, 27.8, 28.2, 29.3, 31.1, 31.5, 31.8, 33.4, 34.6, 35.6, 38.0, 38.7, 39.0, 41.4, 42.3 or 43.3 ° 2θ as depicted in Figure 40. In a specific embodiment, Salt I has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.2, 5.4, 9.5, 13.2, 15.6, 16.0, 19.2 or 22.4 ° 2θ. In another embodiment, Salt I has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.2, 9.5, 16.0 or 22.4 ° 2θ. In another embodiment, Salt I has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 3.2, 9.5, 15.6, 16.0, 19.2 or 22.4 ° 2θ. In another embodiment, Salt I has one, two or three characteristic X-ray powder diffraction peaks at approximately 3.2, 9.5 or 16.0 ° 2θ. In another embodiment, Salt I has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three or fifty-four characteristic X-ray powder diffraction peaks as set forth in Table 38.

5.4.2 **Dihydrate Hemi-Calcium Salt of Compound 1 (Salt II)**

[00289] In one embodiment, provided herein is a calcium salt of Compound 1. In one embodiment, provided herein is a hemi-calcium salt of Compound 1. In one embodiment, the hemi-calcium salt is a hydrate. In one embodiment, the hemi-calcium salt is a dihydrate ("Salt II"). In one embodiment, Salt II is crystalline. In one embodiment, Salt II is moderately hydroscopic. In one embodiment, Salt II is chemically stable.

[00290] In certain embodiments, provided herein is a method for making Salt II, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetone) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 30-70 °C); 3) filtering the mixture at the elevated temperature to yield a solution; 4) contacting the mixture with a calcium acetate solution (*e.g.*, about 0.5-1.5 equivalents); 5) cooling the resulting mixture (*e.g.*, to about 10-30 °C); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the calcium acetate solution is a solution of calcium acetate hydrate in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00291] In certain embodiments, provided herein is a method for making Salt II, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetone) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 50 °C); 3) filtering the mixture at the elevated temperature with a 0.45 μm syringe filter to yield a solution; 4) contacting the mixture with a calcium acetate solution (*e.g.*, about 1 equivalent); 5) cooling the resulting mixture (*e.g.*, to about 25 °C) (*e.g.*, at a speed of about 20 °C/hour); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the calcium acetate solution is a solution of calcium acetate hydrate in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00292] In one embodiment, Salt II has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 54. In one embodiment, Salt II exhibits a TGA thermogram comprising a total mass loss of approximately 10.98% of the total mass of the sample between approximately 65 °C and approximately 140 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the TGA thermogram further comprises a total mass loss of approximately 0.33% of the total mass of the sample between approximately 150 °C and approximately 180 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the TGA thermogram further comprises a decomposition event with onset temperature at approximately 298 °C when heated from approximately 25 °C to approximately 350 °C.

[00293] In one embodiment, Salt II has a DSC thermogram as depicted in Figure 53 comprising an endothermic event with a maximum at approximately 115.5 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 127.0 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an exothermic event with a maximum at approximately 200.5 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 220.8 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 311.3 °C when heated from approximately 25 °C to approximately 350 °C.

[00294] In certain embodiments, Salt II is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt II has an X-ray powder diffraction pattern substantially as shown in Figure 41. In one embodiment, Salt II has one or more characteristic X-ray powder diffraction peaks at approximately 3.37, 3.81, 3.94, 4.15, 4.33, 4.59, 4.77, 5.12, 5.51, 6.07, 6.25, 7.27, 7.45, 7.82, 8.03, 8.56, 8.83, 10.07, 10.39, 10.71, 11.32, 11.56, 11.70, 13.21, 13.46, 14.10, 14.36, 15.32, 15.58, 16.86, 19.28, 19.51, 20.23, 20.68, 21.32, 22.41, 22.95, 23.71, 24.27, 24.90, 25.87, 26.21, 26.83, 27.15, 27.57, 27.85, 28.12, 28.95, 29.24, 29.53, 29.95, 31.08, 31.47, 31.90, 32.59, 32.97, 33.42, 34.73, 34.97, 35.25, 36.09, 38.09, 39.69, 41.35, 42.56, 42.94 or 44.06 ° 2θ as depicted in Figure 41. In a specific embodiment, Salt II has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.37, 10.07, 13.21, 16.86, 20.23, 23.71, 31.47 or 38.09 ° 2θ. In another embodiment, Salt II has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.37, 10.07, 16.86 or 23.71 ° 2θ. In another embodiment, Salt II has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three, sixty-four, sixty-five, sixty-six or sixty-seven characteristic X-ray powder diffraction peaks as set forth in Table 39.

[00295] In certain embodiments, Salt II is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt II has an X-ray powder diffraction pattern substantially as shown in Figure 41. In one embodiment, Salt II has one or more characteristic X-ray powder diffraction peaks at approximately 3.4, 3.8, 3.9, 4.2, 4.3, 4.6, 4.8, 5.1, 5.5, 6.1, 6.3, 7.3, 7.5, 7.8, 8.0, 8.6, 8.8, 10.1, 10.4, 10.7, 11.3, 11.6, 11.7, 13.2, 13.5, 14.1, 14.4, 15.3, 15.6, 16.9, 19.3, 19.5, 20.2, 20.7, 21.3, 22.4, 23.0, 23.7, 24.3, 24.9, 25.9, 26.2, 26.8, 27.2, 27.6, 27.9, 28.1, 29.0, 29.2, 29.5, 30.0, 31.1, 31.5, 31.9, 32.6, 33.0, 33.4, 34.7, 35.0, 35.3, 36.1, 38.1, 39.7, 41.4, 42.6, 42.9 or 44.1 ° 2θ as depicted in Figure 41. In a specific embodiment, Salt II has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.4, 10.1, 13.2, 16.9, 20.2, 23.7, 31.5 or 38.1 ° 2θ. In another embodiment, Salt II has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.4, 10.1, 16.9 or 23.7 ° 2θ. In another embodiment, Salt II has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 3.4, 10.1, 13.2, 16.9, 20.2 or 23.7 ° 2θ. In another embodiment, Salt II has one, two or three characteristic X-ray powder diffraction peaks at approximately 10.1, 16.9 or 23.7 ° 2θ. In another embodiment, Salt II has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three, sixty-four, sixty-five, sixty-six or sixty-seven characteristic X-ray powder diffraction peaks as set forth in Table 39.

5.4.3 **Mono-Potassium Salt of Compound 1 (Salt III)**

[00296] In one embodiment, provided herein is a potassium salt of Compound 1. In one embodiment, provided herein is a mono-potassium salt of Compound 1 ("Salt III"). In one embodiment, Salt III is crystalline. In one embodiment, Salt III is moderately hydroscopic. In one embodiment, Salt III is chemically stable. In one embodiment, Salt III has a tendency to form hydrates.

[00297] In certain embodiments, provided herein is a method for making Salt III, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetonitrile) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 30-70 °C); 3) filtering the mixture at the elevated temperature to yield a solution; 4) contacting the mixture with a potassium hydroxide solution (*e.g.*, about 0.5-1.5 equivalents); 5) cooling the resulting mixture (*e.g.*, to about 10-30 °C); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the potassium hydroxide solution is a solution of potassium hydroxide in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00298] In certain embodiments, provided herein is a method for making Salt III, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetonitrile) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 50 °C); 3) filtering the mixture at the elevated temperature with a 0.45 µm syringe filter to yield a solution; 4) contacting the mixture with a potassium hydroxide solution (*e.g.*, about 1 equivalent); 5) cooling the resulting mixture (*e.g.*, to about 25 °C) (*e.g.*, at a speed of about 20 °C/hour); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the potassium hydroxide solution is a solution of potassium hydroxide in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00299] In one embodiment, Salt III has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 59. In one embodiment, Salt III exhibits a TGA thermogram comprising a total mass loss of approximately 0.91% of the total mass of the sample between approximately 40 °C and approximately 70 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the TGA thermogram further comprises a total mass loss of approximately 0.25% of the total mass of the sample between approximately 100 °C and approximately 120 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the TGA thermogram further comprises a decomposition event with onset temperature at approximately 297.2 °C when heated from approximately 25 °C to approximately 350 °C.

[00300] In one embodiment, Salt III has a DSC thermogram as depicted in Figure 58 comprising an endothermic event with a maximum at approximately 54.3 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 109.3 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 314.4 °C when heated from approximately 25 °C to approximately 350 °C.

[00301] In certain embodiments, Salt III is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt III has an X-ray powder diffraction pattern substantially as shown in Figure 42. In one embodiment, Salt III has one or more characteristic X-ray powder diffraction peaks at approximately 4.18, 4.71, 4.98, 5.61, 6.06, 6.41, 6.73, 7.14, 7.39, 8.01, 8.55, 8.78, 9.03, 9.73, 9.88, 10.72, 10.89, 11.76, 11.89, 12.48, 12.97, 13.29, 13.97, 14.54, 14.65, 15.18, 15.29, 16.35, 16.49, 17.01, 17.17, 18.09, 19.70, 21.78, 22.62, 23.13, 23.99, 24.44, 25.16, 25.44, 25.88, 27.37, 28.88, 29.93, 32.09, 34.55, 37.21, 40.15, 40.86 or 41.95 ° 2θ as depicted in Figure 42. In a specific embodiment, Salt III has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.71, 10.72, 10.89, 14.54, 14.65, 15.18, 15.29 or 16.35 ° 2θ. In another embodiment, Salt III has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.71, 14.54, 14.65 or 15.29 ° 2θ. In another embodiment, Salt III has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine or fifty characteristic X-ray powder diffraction peaks as set forth in Table 40.

[00302] In certain embodiments, Salt III is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt III has an X-ray powder diffraction pattern substantially as shown in Figure 42. In one embodiment, Salt III has one or more characteristic X-ray powder diffraction peaks at approximately 4.2, 4.7, 5.0, 5.6, 6.1, 6.4, 6.7, 7.1, 7.4, 8.0, 8.6, 8.8, 9.0, 9.7, 9.9, 10.7, 10.9, 11.8, 11.9, 12.5, 13.0, 13.3, 14.0, 14.5, 14.7, 15.2, 15.3, 16.4, 16.5, 17.0, 17.2, 18.1, 19.7, 21.8, 22.6, 23.1, 24.0, 24.4, 25.2, 25.4, 25.9, 27.4, 28.9, 29.9, 32.1, 34.6, 37.2, 40.2, 40.9 or 42.0 ° 2θ as depicted in Figure 42. In a specific embodiment, Salt III has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 4.7, 10.7, 10.9, 14.5, 14.6, 15.2, 15.3 or 16.4 ° 2θ. In another embodiment, Salt III has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 4.7, 14.5, 14.7 or 15.3 ° 2θ. In another embodiment, Salt III has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 4.7, 10.9, 14.5, 14.7, 15.2 or 15.3 ° 2θ. In another embodiment, Salt III has one, two or three characteristic X-ray powder diffraction peaks at approximately 14.5, 14.7 or 15.3 ° 2θ. In another embodiment, Salt III has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine or fifty characteristic X-ray powder diffraction peaks as set forth in Table 40.

5.4.4 **Monohydrate Mono-Sodium Salt of Compound 1 (Salt IV)**

[00303] In one embodiment, provided herein is a sodium salt of Compound 1. In one embodiment, provided herein is a mono-sodium salt of Compound 1. In one embodiment, the mono-sodium salt is a hydrate. In one embodiment, the mono-sodium salt is a mono-hydrate ("Salt IV"). In one embodiment, Salt IV is crystalline. In one embodiment, Salt IV is moderately hydroscopic. In one embodiment, Salt IV is chemically stable. In one embodiment, Salt IV is a stable hydrate.

[00304] In certain embodiments, provided herein is a method for making Salt IV, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetone) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 30-70 °C); 3) filtering the mixture at the elevated temperature to yield a solution; 4) contacting the mixture with a sodium hydroxide solution (*e.g.*, about 0.5-1.5 equivalents); 5) cooling the resulting mixture (*e.g.*, to about 10-30 °C); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the sodium hydroxide solution is a solution of sodium hydroxide in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00305] In certain embodiments, provided herein is a method for making Salt IV, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetone) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 50 °C); 3) filtering the mixture at the elevated temperature with a 0.45 μm syringe filter to yield a solution; 4) contacting the mixture with a sodium hydroxide solution (*e.g.*, about 1 equivalent); 5) cooling the resulting mixture (*e.g.*, to about 25 °C) (*e.g.*, at a speed of about 20 °C/hour); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the sodium hydroxide solution is a solution of sodium hydroxide in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00306] In one embodiment, Salt IV has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 64. In one embodiment, Salt IV exhibits a TGA thermogram comprising a total mass loss of approximately 5% of the total mass of the sample between approximately 60 °C and approximately 120 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, Salt IV exhibits a TGA thermogram comprising a total mass loss of approximately 5.43% of the total mass of the sample between approximately 60 °C and approximately 120 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the TGA thermogram further comprises a decomposition event with onset temperature at approximately 302.5 °C when heated from approximately 25 °C to approximately 350 °C.

[00307] In one embodiment, Salt IV has a DSC thermogram as depicted in Figure 63 comprising an endothermic event with a maximum at approximately 107.9 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an exothermic event with a maximum at approximately 217.2 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 307.4 °C when heated from approximately 25 °C to approximately 350 °C.

[00308] In certain embodiments, Salt IV is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt IV has an X-ray powder diffraction pattern substantially as shown in Figure 43. In one embodiment, Salt IV has one or more characteristic X-ray powder diffraction peaks at approximately 3.18, 4.17, 4.78, 5.23, 5.62, 5.86, 5.93, 6.29, 6.44, 6.74, 7.43, 9.45, 9.66, 9.94, 10.63, 11.83, 12.03, 12.62, 13.24, 13.61, 14.57, 14.85, 15.05, 15.80, 16.17, 16.68, 16.98, 17.37, 18.31, 19.00, 19.43, 19.94, 20.72, 22.20, 22.69, 23.63, 24.22, 25.42, 26.01, 26.70, 27.54, 28.35, 28.67, 29.39, 31.24, 31.97, 32.69, 33.18, 34.29, 34.73, 35.82, 37.41, 37.84, 38.27, 38.67, 39.65, 40.64, 41.02, 41.48, 41.90, 42.80, 43.80, 44.32 or 44.59 ° 2θ as depicted in Figure 43. In a specific embodiment, Salt IV has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.18, 6.29, 9.45, 15.80, 16.17, 19.00, 19.43 or 25.42 ° 2θ. In another embodiment, Salt IV has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.18, 9.45, 15.80 or 19.00 ° 2θ. In another embodiment, Salt IV has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three or sixty-four characteristic X-ray powder diffraction peaks as set forth in Table 41.

[00309] In certain embodiments, Salt IV is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt IV has an X-ray powder diffraction pattern substantially as shown in Figure 43. In one embodiment, Salt IV has one or more characteristic X-ray powder diffraction peaks at approximately 3.2, 4.2, 4.8, 5.2, 5.6, 5.9, 6.3, 6.4, 6.7, 7.4, 9.5, 9.7, 9.9, 10.6, 11.8, 12.0, 12.6, 13.2, 13.6, 14.6, 14.9, 15.1, 15.8, 16.2, 16.7, 17.0, 17.4, 18.3, 19.00, 19.4, 19.9, 20.7, 22.2, 22.7, 23.6, 24.2, 25.4, 26.0, 26.7, 27.5, 28.4, 28.7, 29.4, 31.2, 32.0, 32.7, 33.2, 34.3, 34.7, 35.8, 37.4, 37.8, 38.3, 38.7, 39.7, 40.6, 41.0, 41.5, 41.9, 42.8, 43.8, 44.3 or 44.6 ° 2θ as depicted in Figure 43. In a specific embodiment, Salt IV has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.2, 6.3, 9.5, 15.8, 16.2, 19.0, 19.4 or 25.4 ° 2θ. In another embodiment, Salt IV has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.2, 9.5, 15.8 or 19.0 ° 2θ. In another embodiment, Salt IV has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 3.2, 6.3, 9.5, 15.8, 19.0 or 19.4 ° 2θ. In another embodiment, Salt IV has one, two or three characteristic X-ray powder diffraction peaks at approximately 3.2, 9.5 or 19.0 ° 2θ. In another embodiment, Salt IV has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three or sixty-four characteristic X-ray powder diffraction peaks as set forth in Table 41.

5.4.5 Monohydrate Bis-Sodium Salt of Compound 1 (Salt V)

[00310] In one embodiment, provided herein is a sodium salt of Compound 1. In one embodiment, provided herein is a bis-sodium salt of Compound 1. In one embodiment, the bis-sodium salt is a hydrate. In one embodiment, the bis-sodium salt is a mono-hydrate ("Salt V"). In one embodiment, Salt V is crystalline. In one embodiment, Salt V is moderately hydroscopic. In one embodiment, Salt V is an unstable hydrate.

[00311] In certain embodiments, provided herein is a method for making Salt V, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetone) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 30-70 °C); 3) filtering the mixture at the elevated temperature to yield a solution; 4) contacting the mixture with a sodium hydroxide solution (*e.g.*, about 2-4 equivalents); 5) cooling the resulting mixture (*e.g.*, to about 10-30 °C); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the sodium hydroxide solution is a solution of sodium hydroxide in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00312] In certain embodiments, provided herein is a method for making Salt V, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetone) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 50 °C); 3) filtering the mixture at the elevated temperature with a 0.45 μm syringe filter to yield a solution; 4) contacting the mixture with a sodium hydroxide solution (*e.g.*, about 3 equivalents); 5) cooling the resulting mixture (*e.g.*, to about 25 °C) (*e.g.*, at a speed of about 20 °C/hour); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the sodium hydroxide solution is a solution of sodium hydroxide in water, methanol or a mixture of methanol and water (*e.g.*, about 1:1).

[00313] In one embodiment, Salt V has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 69. In one embodiment, Salt V exhibits a TGA thermogram comprising a total mass loss of approximately 5.85% of the total mass of the sample between approximately 40 °C and approximately 130 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the TGA thermogram further comprises a decomposition event with onset temperature at approximately 344.77 °C when heated from approximately 25 °C to approximately 350 °C.

[00314] In one embodiment, Salt V has a DSC thermogram as depicted in Figure 68 comprising an endothermic event with a maximum at approximately 93.3 °C when heated from approximately 25 °C to approximately 350 °C.

[00315] In certain embodiments, Salt V is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt V has an X-ray powder diffraction pattern substantially as shown in Figure 44. In one embodiment, Salt V has one or more characteristic X-ray powder diffraction peaks at approximately 3.15, 3.33, 3.51, 3.65, 4.19, 4.45, 4.74, 5.09, 5.24, 5.40, 5.75, 6.00, 6.24, 6.43, 6.64, 7.29, 7.45, 7.58, 7.92, 8.57, 9.21, 9.39, 9.97, 13.02, 13.31, 13.64, 13.97, 16.69, 17.13, 17.65, 18.09, 18.65, 19.51, 20.06, 22.15, 22.50, 22.87, 23.41, 24.54, 25.01, 25.70, 26.29, 26.87, 27.81, 28.89, 29.06, 29.90, 30.29, 30.60, 31.08, 31.97, 32.21, 33.85, 34.24, 35.73, 37.31, 38.39, 39.71, 40.87, 42.01 or 44.30 ° 2θ as depicted in Figure 44. In a specific embodiment, Salt V has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.15, 9.97, 13.31, 13.64, 13.97, 16.69, 20.06 or 26.87 ° 2θ. In another embodiment, Salt V has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 9.97, 13.64, 13.97 or 16.69 ° 2θ. In another embodiment, Salt V has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty or sixty-one characteristic X-ray powder diffraction peaks as set forth in Table 42.

[00316] In certain embodiments, Salt V is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt V has an X-ray powder diffraction pattern substantially as shown in Figure 44. In one embodiment, Salt V has one or more characteristic X-ray powder diffraction peaks at approximately 3.2, 3.3, 3.5, 3.7, 4.2, 4.5, 4.7, 5.1, 5.2, 5.4, 5.8, 6.0, 6.2, 6.4, 6.6, 7.3, 7.5, 7.6, 7.9, 8.6, 9.2, 9.4, 10.0, 13.0, 13.3, 13.6, 14.0, 16.7, 17.1, 17.7, 18.1, 18.7, 19.5, 20.1, 22.2, 22.5, 22.9, 23.4, 24.5, 25.0, 25.7, 26.3, 26.9, 27.8, 28.9, 29.1, 29.9, 30.3, 30.6, 31.1, 32.0, 32.2, 33.9, 34.2, 35.7, 37.3, 38.4, 39.7, 40.9, 42.0 or 44.3 ° 2θ as depicted in Figure 44. In a specific embodiment, Salt V has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.2, 10.0, 13.3, 13.6, 14.0, 16.7, 20.1 or 26.9 ° 2θ. In another embodiment, Salt V has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 10.0, 13.6, 14.0 or 16.7 ° 2θ. In another embodiment, Salt V has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 3.2, 10.0, 13.3, 13.6, 14.0 or 16.7 ° 2θ. In another embodiment, Salt V has one, two or three characteristic X-ray powder diffraction peaks at approximately 10.0, 13.6 or 16.7 ° 2θ. In another embodiment, Salt V has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty or sixty-one characteristic X-ray powder diffraction peaks as set forth in Table 42.

5.4.6 **Anhydrous Mono-Sodium Salt of Compound 1 (Salt VI)**

[00317] In one embodiment, provided herein is a sodium salt of Compound 1. In one embodiment, provided herein is a mono-sodium salt of Compound 1. In one embodiment, the mono-sodium salt is anhydrous ("Salt VI"). In one embodiment, Salt VI is crystalline. In one embodiment, Salt VI is slightly hydroscopic. In one embodiment, Salt VI is chemically stable.

[00318] In certain embodiments, provided herein is a method for making Salt VI, comprising 1) heating Salt IV of Compound 1 from a first temperature (*e.g.*, about 160-200 °C) to a second temperature (*e.g.*, about 240-280 °C) at a speed (*e.g.*, about 10 °C/minute); 2) holding the solid at the second temperature for a period of time (*e.g.*, about 1-10 minutes); and 3) collecting the resulting solids.

[00319] In certain embodiments, provided herein is a method for making Salt VI, comprising 1) heating Salt IV of Compound 1 from a first temperature (*e.g.*, about 180 °C) to a second temperature (*e.g.*, about 260 °C) at a speed (*e.g.*, about 10 °C/minute); 2) holding the solid at the second temperature for a period of time (*e.g.*, about 2 minutes); and 3) collecting the resulting solids.

[00320] In one embodiment, Salt VI has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 75. In one embodiment, Salt VI exhibits a TGA thermogram comprising a decomposition event with onset temperature at approximately 305.7 °C when heated from approximately 25 °C to approximately 350 °C.

[00321] In one embodiment, Salt VI has a DSC thermogram as depicted in Figure 74 comprising an endothermic event with a maximum at approximately 282.4 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an exothermic event with a maximum at approximately 283.9 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 308.4 °C when heated from approximately 25 °C to approximately 350 °C.

[00322] In certain embodiments, Salt VI is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt VI has an X-ray powder diffraction pattern substantially as shown in Figure 45. In one embodiment, Salt VI has one or more characteristic X-ray powder diffraction peaks at approximately 3.03, 3.39, 4.42, 4.63, 5.01, 5.40, 5.81, 6.23, 6.42, 7.06, 7.66, 8.96, 10.06, 10.68, 11.53, 11.89, 12.42, 13.40, 13.73, 14.04, 14.91, 15.22, 15.67, 16.33, 16.74, 17.10, 17.82, 18.11, 18.48, 19.07, 20.15, 20.94, 21.47, 22.05, 23.37, 24.03, 24.96, 26.38, 26.96, 28.88, 30.07, 31.04, 31.61, 33.20, 33.94, 34.87, 37.20, 38.13, 39.72, 40.29, 40.97, 42.35, 43.41 or 44.38 ° 2θ as depicted in Figure 45. In a specific embodiment, Salt VI has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.03, 3.39, 10.06, 11.89, 13.40, 15.22, 16.74 or 18.11 ° 2θ. In another embodiment, Salt VI has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.03, 3.39, 10.06 or 11.89 ° 2θ. In another embodiment, Salt VI has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three or forty-four characteristic X-ray powder diffraction peaks as set forth in Table 43.

[00323] In certain embodiments, Salt VI is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt VI has an X-ray powder diffraction pattern substantially as shown in Figure 45. In one embodiment, Salt VI has one or more characteristic X-ray powder diffraction peaks at approximately 3.0, 3.4, 4.4, 4.6, 5.0, 5.4, 5.8, 6.2, 6.4, 7.1, 7.7, 9.0, 10.1, 10.7, 11.5, 11.9, 12.4, 13.4, 13.7, 14.0, 14.9, 15.2, 15.7, 16.3, 16.7, 17.1, 17.8, 18.1, 18.5, 19.1, 20.2, 20.9, 21.5, 22.1, 23.4, 24.0, 25.0, 26.4, 27.0, 28.9, 30.1, 31.0, 31.6, 33.2, 33.9, 34.9, 37.2, 38.1, 39.7, 40.3, 41.0, 42.4, 43.4 or 44.4 ° 2θ as depicted in Figure 45. In a specific embodiment, Salt VI has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.0, 3.4, 10.1, 11.9, 13.4, 15.2, 16.7 or 18.1 ° 2θ. In another embodiment, Salt VI has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.0, 3.4, 10.1 or 11.9 ° 2θ. In another embodiment, Salt VI has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 3.0, 3.4, 10.1, 11.9, 16.7 or 18.1 ° 2θ. In another embodiment, Salt VI has one, two or three characteristic X-ray powder diffraction peaks at approximately 3.0, 3.4 or 10.1 ° 2θ. In another embodiment, Salt VI has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three or forty-four characteristic X-ray powder diffraction peaks as set forth in Table 43.

5.4.7 **Hydrated Mono-Sodium Salt of Compound 1 (Salt VII)**

[00324] In one embodiment, provided herein is a sodium salt of Compound 1. In one embodiment, provided herein is a mono-sodium salt of Compound 1. In one embodiment, the mono-sodium salt is a hydrate ("Salt VII"). In one embodiment, Salt VII is crystalline. In one embodiment, Salt VII is moderately hydroscopic. In one embodiment, Salt VII is chemically stable. In one embodiment, Salt VII is a stable hydrate.

[00325] In certain embodiments, provided herein is a method for making Salt VII, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, methanol) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 30-70 °C); 3) filtering the mixture at the elevated temperature to yield a solution; 4) contacting the mixture with a sodium hydroxide solution (*e.g.*, about 0.5-1.5 equivalents); 5) cooling the resulting mixture (*e.g.*, to about 10-30 °C); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the sodium hydroxide solution is a solution of sodium hydroxide in water, methanol or a mixture of methanol and water.

[00326] In certain embodiments, provided herein is a method for making Salt VII, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, methanol) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 50 °C); 3) filtering the mixture at the elevated temperature with a 0.45 μm syringe filter to yield a solution; 4) contacting the mixture with a sodium hydroxide solution (*e.g.*, about 1 equivalent); 5) cooling the resulting mixture (*e.g.*, to about 25 °C) (*e.g.*, at a speed of about 20 °C/hour); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the sodium hydroxide solution is a solution of sodium hydroxide in water, methanol or a mixture of methanol and water.

[00327] In one embodiment, Salt VII has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 87. In one embodiment, the TGA thermogram comprises a decomposition event with onset temperature at approximately 290.6 °C when heated from approximately 25 °C to approximately 350 °C.

[00328] In one embodiment, Salt VII has a DSC thermogram as depicted in Figure 86 comprising a broad transition event before approximately 90 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises a glass transition event at approximately 160 °C when heated from approximately 25 °C to approximately 350 °C.

[00329] In certain embodiments, Salt VII is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt VII has an X-ray powder diffraction pattern substantially as shown in Figure 43. In one embodiment, Salt VII has one or more characteristic X-ray powder diffraction peaks at approximately 3.40, 3.71, 4.08, 4.31, 4.95, 5.07, 5.33, 5.59, 6.11, 6.55, 6.95, 7.27, 7.60, 7.79, 8.49, 8.62, 9.54, 9.96, 10.87, 11.53, 11.88, 12.53, 12.78, 13.28, 13.64, 13.97, 14.31, 14.90, 15.48, 15.73, 16.37, 16.66, 18.02, 18.68, 20.03, 20.76, 20.96, 21.58, 22.15, 24.89, 25.46, 25.82, 26.83, 28.73, 29.35, 31.10, 32.28, 32.84, 33.75, 34.30, 37.27, 38.29, 38.86, 39.67, 40.80 or 44.33 ° 2θ as depicted in Figure 43. In a specific embodiment, Salt VII has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.40, 3.71, 9.96, 10.87, 14.90, 15.48, 15.73 or 16.66 ° 2θ. In another embodiment, Salt VII has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.40, 9.96, 14.90 or 16.66 ° 2θ. In another embodiment, Salt VII has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, or fifty-six characteristic X-ray powder diffraction peaks as set forth in Table 44.

[00330] In certain embodiments, Salt VII is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt VII has an X-ray powder diffraction pattern substantially as shown in Figure 43. In one embodiment, Salt VII has one or more characteristic X-ray powder diffraction peaks at approximately 3.4, 3.7, 4.1, 4.3, 5.0, 5.1, 5.3, 5.6, 6.1, 6.6, 7.0, 7.3, 7.6, 7.8, 8.5, 8.6, 9.5, 10.0, 10.9, 11.5, 11.9, 12.5, 12.8, 13.3, 13.6, 14.0, 14.3, 14.9, 15.5, 15.7, 16.4, 16.7, 18.0, 18.7, 20.0, 20.8, 21.0, 21.6, 22.2, 24.9, 25.5, 25.8, 26.8, 28.7, 29.4, 31.1, 32.3, 32.8, 33.8, 34.3, 37.3, 38.3, 38.9, 39.7, 40.8 or 44.3 ° 2θ as depicted in Figure 43. In a specific embodiment, Salt VII has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.4, 3.7, 10.0, 10.9, 14.9, 15.5, 15.7 or 16.7 ° 2θ. In another embodiment, Salt VII has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.4, 10.0, 14.9 or 16.7 ° 2θ. In another embodiment, Salt VII has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 3.4, 10.0, 10.9, 14.9, 15.5 or 16.7 ° 2θ. In another embodiment, Salt VII has one, two or three characteristic X-ray powder diffraction peaks at approximately 3.4, 10.0 or 14.9 ° 2θ. In another embodiment, Salt VII has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, or fifty-six characteristic X-ray powder diffraction peaks as set forth in Table 44.

5.4.8 **Anhydrous Mono-Sodium Salt of Compound 1 (Salt VIII)**

[00331] In one embodiment, provided herein is a sodium salt of Compound 1. In one embodiment, provided herein is a mono-sodium salt of Compound 1. In one embodiment, the mono-sodium salt is anhydrous ("Salt VIII"). In one embodiment, Salt VIII is crystalline. In one embodiment, Salt VIII is moderately hydroscopic. In one embodiment, Salt VIII is chemically stable.

[00332] In certain embodiments, provided herein is a method for making Salt VIII, comprising 1) stirring Salt IV of Compound 1 in a solvent (*e.g.*, methanol) for a period of time (*e.g.*, about 12 hours to about 48 hours) at a temperature (*e.g.*, about 5 °C to about 45 °C); 2) collecting precipitation by filtration; and 3) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid.

[00333] In certain embodiments, provided herein is a method for making Salt VIII, comprising 1) stirring Salt IV of Compound 1 in a solvent (*e.g.*, methanol) for a period of time (*e.g.*, about 24 hours) at a temperature (*e.g.*, about 25 °C); 2) collecting precipitation by filtration; and 3) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid.

[00334] In one embodiment, Salt VIII has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 94. In one embodiment, the TGA thermogram comprises a decomposition event with onset temperature at approximately 291.2 °C when heated from approximately 25 °C to approximately 350 °C.

[00335] In one embodiment, Salt VIII has a DSC thermogram as depicted in Figure 93 comprising a decomposition event with onset temperature at approximately 294.0 °C when heated from approximately 25 °C to approximately 350 °C.

[00336] In certain embodiments, Salt VIII is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt VIII has an X-ray powder diffraction pattern substantially as shown in Figure 91. In one embodiment, Salt VIII has one or more characteristic X-ray powder diffraction peaks at approximately 3.06, 3.39, 3.64, 3.79, 3.95, 4.54, 4.94, 5.07, 5.21, 5.40, 6.02, 6.27, 6.65, 7.18, 8.00, 8.37, 9.32, 10.00, 10.43, 11.04, 11.94, 12.72, 13.01, 13.71, 13.97, 14.66, 15.01, 15.65, 15.73, 16.34, 16.69, 17.14, 17.37, 18.31, 18.91, 19.57, 20.13, 22.17, 24.68, 25.02, 26.92, 28.96, 29.53, 31.12, 32.42, 33.47, 33.76, 34.58, 35.75, 37.25, 39.65, 40.87, 42.36, 43.42 or 44.34 ° 2θ as depicted in Figure 91. In a specific embodiment, Salt VIII has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.06, 3.39, 3.64, 13.71, 13.97, 15.01, 15.65 or 15.73 ° 2θ. In another embodiment, Salt VIII has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.06, 3.39, 15.01 or 15.65 ° 2θ. In another embodiment, Salt VIII has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four or fifty-five characteristic X-ray powder diffraction peaks as set forth in Table 45.

[00337] In certain embodiments, Salt VIII is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt VIII has an X-ray powder diffraction pattern substantially as shown in Figure 91. In one embodiment, Salt VIII has one or more characteristic X-ray powder diffraction peaks at approximately 3.1, 3.4, 3.6, 3.8, 4.0, 4.5, 4.9, 5.1, 5.2, 5.4, 6.0, 6.3, 6.7, 7.2, 8.0, 8.4, 9.3, 10.0, 10.4, 11.0, 11.9, 12.7, 13.0, 13.7, 14.0, 14.7, 15.0, 15.7, 15.7, 16.3, 16.7, 17.1, 17.4, 18.3, 18.9, 19.6, 20.1, 22.2, 24.7, 25.0, 26.9, 29.0, 29.5, 31.1, 32.4, 33.5, 33.8, 34.6, 35.8, 37.3, 39.7, 40.9, 42.4, 43.4 or 44.3 ° 2θ as depicted in Figure 91. In a specific embodiment, Salt VIII has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.1, 3.4, 3.6, 13.7, 14.0, 15.0, 15.7 or 15.7 ° 2θ. In another embodiment, Salt VIII has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.1, 3.4, 15.0 or 15.7 ° 2θ. In another embodiment, Salt VIII has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 3.1, 3.4, 13.7, 15.0, 15.6 or 15.7 ° 2θ. In another embodiment, Salt VIII has one, two or three characteristic X-ray powder diffraction peaks at approximately 3.1, 3.4 or 15.0 ° 2θ. In another embodiment, Salt VIII has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four or fifty-five characteristic X-ray powder diffraction peaks as set forth in Table 45.

5.4.9 **Anhydrous Mono-Sodium Salt of Compound 1 (Salt IX)**

[00338] In one embodiment, provided herein is a sodium salt of Compound 1. In one embodiment, provided herein is a mono-sodium salt of Compound 1. In one embodiment, the mono-sodium salt is anhydrous ("Salt IX"). In one embodiment, Salt IX is crystalline. In one embodiment, Salt IX is moderately hydroscopic. In one embodiment, Salt IX is chemically stable.

[00339] In certain embodiments, provided herein is a method for making Salt IX, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetone) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 30-70 °C); 3) filtering the mixture at the elevated temperature to yield a solution; 4) contacting the mixture with a sodium hydroxide solution (*e.g.*, about 0.5-1.5 equivalents); 5) cooling the resulting mixture (*e.g.*, to about 10-30 °C); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the sodium hydroxide solution is a solution of sodium hydroxide in water, acetone or a mixture of acetone and water.

[00340] In certain embodiments, provided herein is a method for making Salt IX, comprising 1) dissolving Compound 1 in a solvent (*e.g.*, acetone) to yield a mixture; 2) heating the mixture to an elevated temperature (*e.g.*, about 50 °C); 3) filtering the mixture at the elevated temperature with a 0.45 μm syringe filter to yield a solution; 4) contacting the mixture with a sodium hydroxide solution (*e.g.*, about 1 equivalent); 5) cooling the resulting mixture (*e.g.*, to about 25 °C) (*e.g.*, at a speed of about 20 °C/hour); 6) collecting precipitation by filtration; and 7) in the absence of precipitation, evaporating the solution to yield a solid and collecting the solid. In one embodiment, the sodium hydroxide solution is a solution of sodium hydroxide in water, acetone or a mixture of acetone and water.

[00341] In one embodiment, Salt IX has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 101. In one embodiment, the TGA thermogram comprises a decomposition event with onset temperature at approximately 301.8 °C when heated from approximately 25 °C to approximately 350 °C.

[00342] In one embodiment, Salt IX has a DSC thermogram as depicted in Figure 100 comprising an endothermic event with a maximum at approximately 82.8 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an exothermic event with a maximum at approximately 229.5 °C when heated from approximately 25 °C to approximately 350 °C.

[00343] In certain embodiments, Salt IX is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt IX has an X-ray powder diffraction pattern substantially as shown in Figure 98. In one embodiment, Salt IX has one or more characteristic X-ray powder diffraction peaks at approximately 3.05, 3.19, 4.33, 4.57, 5.11, 5.25, 5.71, 6.32, 7.68, 7.88, 9.47, 9.93, 10.04, 12.63, 13.06, 13.69, 14.01, 14.89, 15.83, 16.31, 16.68, 17.39, 18.33, 19.01, 19.94, 20.72, 20.88, 22.12, 22.27, 22.60, 23.58, 24.21, 24.69, 25.47, 26.26, 26.62, 27.63, 28.42, 28.73, 29.44, 31.25, 31.90, 32.51, 33.23, 34.35, 35.85, 37.39, 38.30, 39.79, 40.61, 41.44, 41.96 or 44.56 ° 2θ as depicted in Figure 98. In a specific embodiment, Salt IX has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.05, 3.19, 6.32, 9.47, 13.69, 15.83, 19.01 or 25.47 ° 2θ. In another embodiment, Salt IX has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.05, 3.19, 9.47 or 19.01 ° 2θ. In another embodiment, Salt IX has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two or fifty-three characteristic X-ray powder diffraction peaks as set forth in Table 46.

[00344] In certain embodiments, Salt IX is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt IX has an X-ray powder diffraction pattern substantially as shown in Figure 98. In one embodiment, Salt IX has one or more characteristic X-ray powder diffraction peaks at approximately 3.1, 3.2, 4.3, 4.6, 5.1, 5.3, 5.7, 6.3, 7.7, 7.9, 9.5, 9.9, 10.0, 12.6, 13.1, 13.7, 14.0, 14.9, 15.8, 16.3, 16.7, 17.4, 18.3, 19.0, 19.9, 20.7, 20.9, 22.1, 22.3, 22.6, 23.6, 24.2, 24.7, 25.5, 26.3, 26.6, 27.6, 28.4, 28.7, 29.4, 31.3, 31.9, 32.5, 33.2, 34.4, 35.9, 37.4, 38.3, 39.8, 40.6, 41.4, 42.0 or 44.6 ° 2θ as depicted in Figure 98. In a specific embodiment, Salt IX has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.1, 3.2, 6.3, 9.5, 13.7, 15.8, 19.0 or 25.5 ° 2θ. In another embodiment, Salt IX has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.1, 3.2, 9.5 or 19.0 ° 2θ. In another embodiment, Salt IX has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 3.1, 3.2, 6.3, 9.5, 15.8 or 19.0 ° 2θ. In another embodiment, Salt IX has one, two or three characteristic X-ray powder diffraction peaks at approximately 3.2, 9.5 or 19.0 ° 2θ. In another embodiment, Salt IX has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two or fifty-three characteristic X-ray powder diffraction peaks as set forth in Table 46.

5.4.10 **Hydrated Mono-Sodium Salt of Compound 1 (Salt X)**

[00345] In one embodiment, provided herein is a sodium salt of Compound 1. In one embodiment, provided herein is a mono-sodium salt of Compound 1. In one embodiment, the mono-sodium salt is a hydrate ("Salt X"). In one embodiment, Salt X is crystalline. In one embodiment, Salt X is moderately hydroscopic. In one embodiment, Salt X is chemically unstable. In one embodiment, Salt X is an unstable hydrate.

[00346] In one embodiment, provided herein are methods for preparing Salt X of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Salt IV of Compound 1 (*e.g.*, about 100-300 mg) with a minimum amount of solvents (*e.g.*, up to 7.0 mL) at a first temperature (*e.g.*, about 50 or 70 °C); (2) adding a co-solvent (*e.g.*, about 5-25 mL); (3) placing the solution at a second temperature (*e.g.*, about 15-35 °C) for a period of time (*e.g.*, about 12-48 hours); and (4) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 47). In certain embodiments, the solvent is water. In certain embodiments, the co-solvent is THF.

[00347] In one embodiment, provided herein are methods for preparing Salt X of Compound 1 comprising binary solvent fast cooling crystallization comprising the steps of: (1) dissolving Salt IV of Compound 1 (*e.g.*, about 168 mg) with a minimum amount of solvents (*e.g.*, about 4.3 mL) at a first temperature (*e.g.*, about 60 °C); (2) adding a co-solvent (*e.g.*, about 12.8 mL); (3) placing the solution at a second temperature (*e.g.*, about 25 °C) for a period of time (*e.g.*, about 24 hours); and (4) evaporating the samples without precipitation to dryness (*e.g.*, evaporating under a gentle stream of nitrogen gas) and collecting the resulting solids. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 47). In certain embodiments, the solvent is water. In certain embodiments, the co-solvent is THF.

[00348] In one embodiment, Salt X has a TGA thermogram corresponding substantially to the representative TGA thermogram as depicted in Figure 108. In one embodiment, Salt X exhibits a TGA thermogram comprising a total mass loss of approximately 1.3% of the total mass of the sample between approximately 60 °C and approximately 120 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, Salt X exhibits a TGA thermogram comprising a total mass loss of approximately 2.3% of the total mass of the sample between approximately 120 °C and approximately 180 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the TGA thermogram further comprises a decomposition event with onset temperature at approximately 296.7 °C when heated from approximately 25 °C to approximately 350 °C.

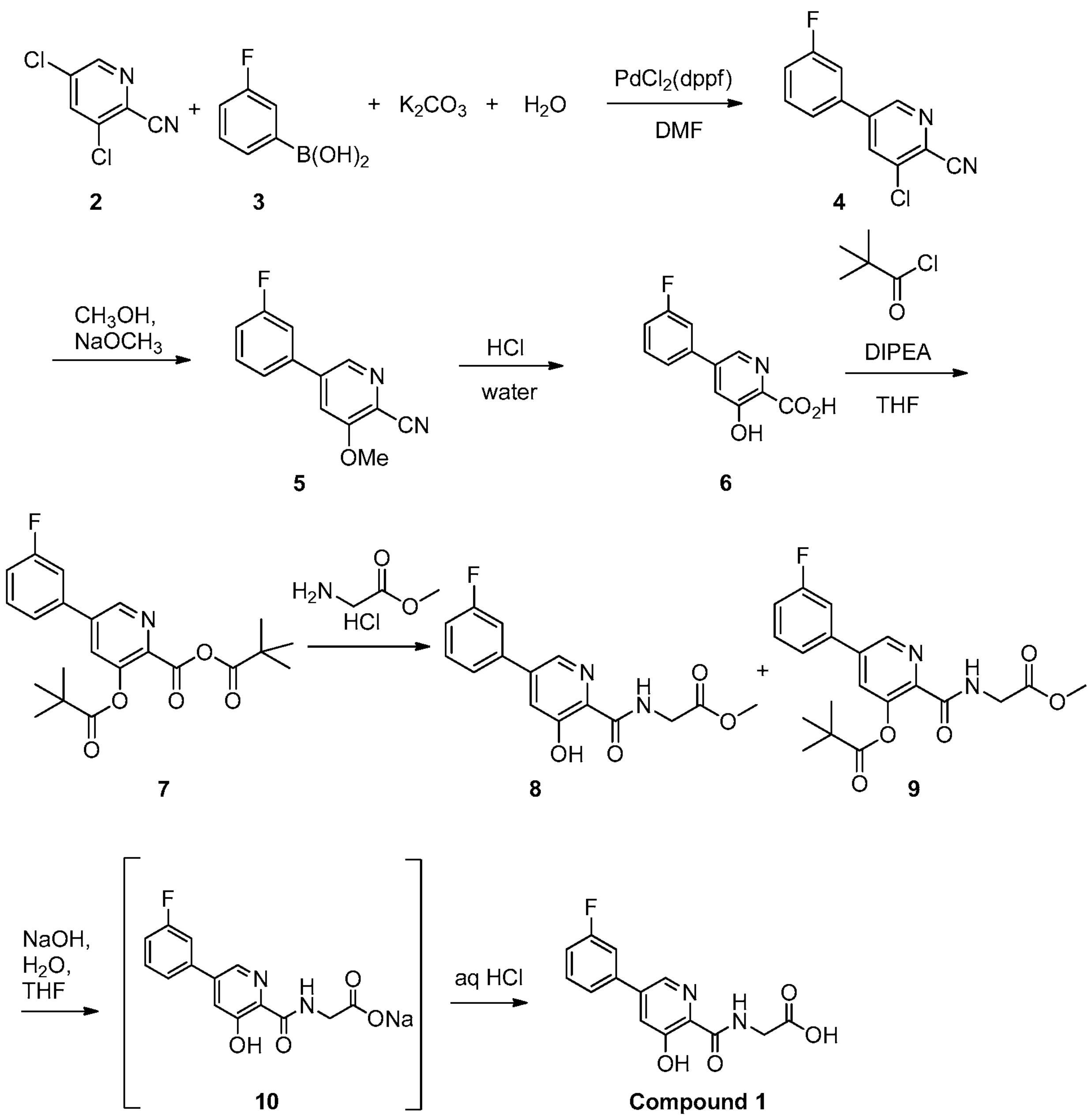
[00349] In one embodiment, Salt IX has a DSC thermogram as depicted in Figure 107 comprising an endothermic event with a maximum at approximately 91.3 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an endothermic event with a maximum at approximately 149.3 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, the DSC thermogram further comprises an exothermic event with a maximum at approximately 230.6 °C when heated from approximately 25 °C to approximately 350 °C.

[00350] In certain embodiments, Salt X is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt X has an X-ray powder diffraction pattern substantially as shown in Figure 105. In one embodiment, Salt X has one or more characteristic X-ray powder diffraction peaks at approximately 3.20, 3.74, 4.11, 4.23, 4.36, 4.59, 4.78, 5.03, 5.22, 5.43, 5.62, 5.88, 6.06, 6.28, 6.76, 7.24, 7.41, 7.83, 8.01, 9.50, 10.37, 11.01, 11.15, 11.38, 12.12, 12.75, 13.58, 14.37, 14.87, 15.06, 15.41, 15.78, 16.65, 18.71, 19.70, 20.35, 20.88, 22.16, 22.49, 23.83, 24.73, 25.62, 26.38, 27.11, 28.71, 29.79, 30.65, 31.15, 32.80, 34.52, 35.81, 37.64, 38.77, 41.35, 42.26, 43.70 or 44.25 ° 2θ as depicted in Figure 105. In a specific embodiment, Salt X has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.20, 3.74, 15.41, 18.71, 19.70, 22.16, 23.83 or 25.62 ° 2θ. In another embodiment, Salt X has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.20, 3.74, 15.41 or 25.62 ° 2θ. In another embodiment, Salt X has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three or sixty-four characteristic X-ray powder diffraction peaks as set forth in Table 47.

[00351] In certain embodiments, Salt X is substantially crystalline, as indicated by, *e.g.*, X-ray powder diffraction measurements. In one embodiment, Salt X has an X-ray powder diffraction pattern substantially as shown in Figure 105. In one embodiment, Salt X has one or more characteristic X-ray powder diffraction peaks at approximately 3.2, 3.7, 4.1, 4.2, 4.4, 4.6, 4.8, 5.0, 5.2, 5.4, 5.6, 5.9, 6.1, 6.3, 6.8, 7.2, 7.4, 7.8, 8.0, 9.5, 10.4, 11.0, 11.2, 11.4, 12.1, 12.8, 13.6, 14.4, 14.9, 15.0, 15.4, 15.8, 16.7, 18.7, 19.7, 20.4, 20.9, 22.1, 22.5, 23.8, 24.7, 25.6, 26.4, 27.1, 28.7, 29.8, 30.7, 31.2, 32.8, 34.5, 35.8, 37.6, 38.8, 41.4, 42.3, 43.7 or 44.3 ° 2θ as depicted in Figure 105. In a specific embodiment, Salt X has one, two, three, four, five, six, seven or eight characteristic X-ray powder diffraction peaks at approximately 3.2, 3.7, 15.4, 18.7, 19.7, 22.2, 23.8 or 25.6 ° 2θ. In another embodiment, Salt X has one, two, three or four characteristic X-ray powder diffraction peaks at approximately 3.2, 3.7, 15.4 or 25.6 ° 2θ. In another embodiment, Salt X has one, two, three, four, five or six characteristic X-ray powder diffraction peaks at approximately 3.2, 3.7, 15.4, 18.7, 23.8 or 25.6 ° 2θ. In another embodiment, Salt X has one, two or three characteristic X-ray powder diffraction peaks at approximately 3.2, 3.7 or 25.6 ° 2θ. In another embodiment, Salt X has one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty-five, twenty-six, twenty-seven, twenty-eight, twenty-nine, thirty, thirty-one, thirty-two, thirty-three, thirty-four, thirty-five, thirty-six, thirty-seven, thirty-eight, thirty-nine, forty, forty-one, forty-two, forty-three, forty-four, forty-five, forty-six, forty-seven, forty-eight, forty-nine, fifty, fifty-one, fifty-two, fifty-three, fifty-four, fifty-five, fifty-six, fifty-seven, fifty-eight, fifty-nine, sixty, sixty-one, sixty-two, sixty-three or sixty-four characteristic X-ray powder diffraction peaks as set forth in Table 47.

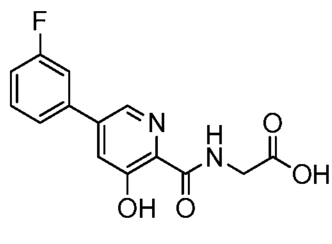
5.5 Methods for Making Compound 1

[00352] By way of example and not limitation, Compound 1 can be prepared as outlined in Scheme 1, as well as in the examples set forth herein.



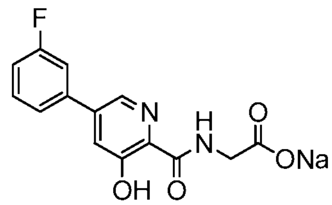
Scheme 1

[00353] Provided are methods of preparing Compound 1



1,

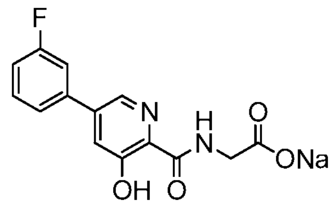
comprising contacting compound 10



10

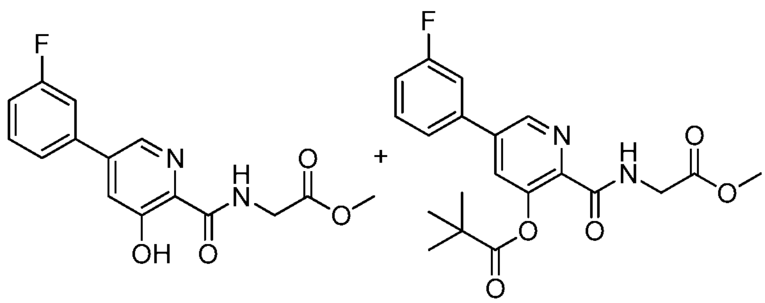
with an acid (*e.g.*, aq. HCl) in a solvent (*e.g.*, tetrahydrofuran (THF), water or a mixture of THF and water) at about 10 °C to about 35 °C. In one embodiment, the solvent is THF, water or a mixture thereof. In one embodiment, the acid is 37% HCl aqueous solution. In one embodiment, the contacting proceeds at about 22 °C. In one embodiment, the contacting lasts for about 15 minutes to about 2 hours.

[00354] Also provided are methods of preparing compound 10



10

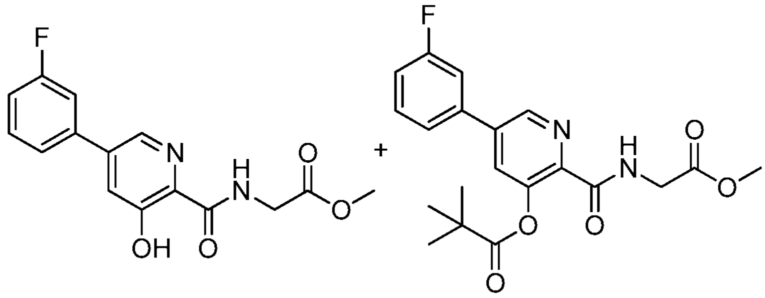
comprising contacting a mixture of compound 8 and compound 9



8 9

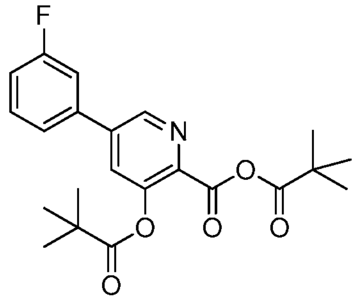
with a base (*e.g.*, NaOH) in a solvent (*e.g.*, tetrahydrofuran (THF), water or THF/water) at about 10 °C to about 35 °C. In some embodiments, the solvent is THF, water or a mixture thereof. In one embodiment, the base is NaOH. In one embodiment, the contacting proceeds at about 22 °C. In one embodiment, the contacting lasts for about 1 hour to about 5 hours.

[00355] Also provided are methods of preparing a mixture of compound 8 and compound 9



8 9

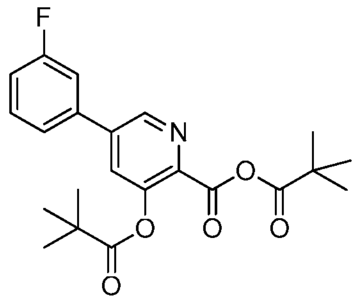
comprising contacting compound 7



7

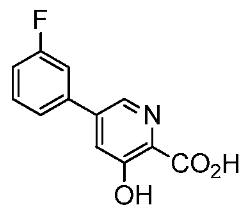
with glycine methyl ester HCl salt in a solvent (*e.g.*, tetrahydrofuran (THF)) in the presence of a base (*e.g.*, diisopropylethylamine) at about 10 °C to about 35 °C. In some embodiments, the solvent is THF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the contacting proceeds at about 22 °C. In one embodiment, the contacting lasts for about 4 hours to about 16 hours.

[00356] Also provided are methods of preparing compound 7



7

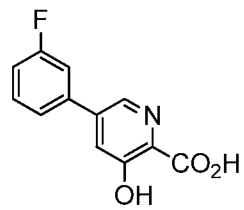
comprising contacting compound 6



6

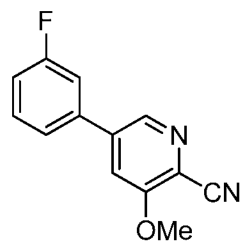
with trimethylacetyl chloride in a solvent (*e.g.*, tetrahydrofuran (THF)) in the presence of a base (*e.g.*, diisopropylethylamine) at about -10 °C to about 10 °C. In some embodiments, the solvent is THF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the contacting proceeds at about 3 °C. In one embodiment, the contacting lasts for about 1 hours to about 3 hours.

[00357] Also provided are methods of preparing compound 6



6

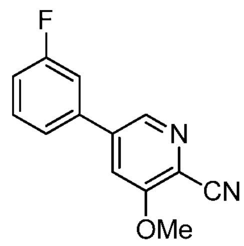
comprising contacting compound 5



5

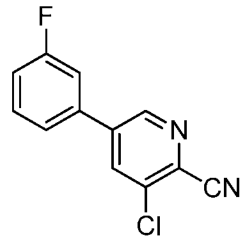
with an acid (*e.g.*, 37% HCl aqueous solution) in a solvent (*e.g.*, water) at about 60 °C to about 110 °C. In one embodiment, the acid is 37% HCl aqueous solution. In one embodiment, the contacting proceeds at about 100 °C. In one embodiment, the contacting lasts for about 10 hours to about 60 hours.

[00358] Also provided are methods of preparing compound 5



5

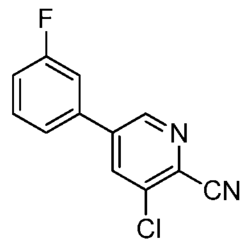
comprising contacting compound 4



4

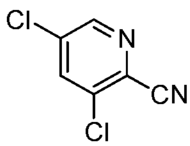
with a methoxide (*e.g.*, sodium methoxide) in a solvent (*e.g.*, methanol) at about 50 °C to about 90 °C. In one embodiment, the methoxide is sodium methoxide. In one embodiment, the solvent is methanol. In one embodiment, the contacting proceeds at about 68 °C. In one embodiment, the contacting lasts for about 6 hours to about 36 hours.

[00359] Also provided are methods of preparing compound 4



4

comprising contacting compound 2



2

with (3-fluorophenyl)boronic acid and a catalyst (*e.g.*, DCM adduct $PdCl_2$(dppf) and $PdCl_2$(dppf)) in a solvent (*e.g.*, DMF, water or DMF/water) in the presence of a base (*e.g.*, potassium carbonate) at about 25 °C to about 75 °C. In certain embodiments, the catalyst is

DCM adduct $PdCl_2$(dppf) or $PdCl_2$(dppf). In some embodiments, the solvent is DMF, water or a mixture thereof. In some embodiments, the base is potassium carbonate. In one embodiment, the contacting proceeds at about 50 °C. In one embodiment, the contacting lasts for about 6 hours to about 36 hours.

5.6 Methods of Use

[00360] Provided herein are methods for treating or preventing cancer, comprising administering an effective amount of a solid form of Compound 1 to a patient having cancer.

[00361] Further provided herein are methods for preventing metastasis of malignant tumors or other cancerous cells, comprising administering an effective amount of a solid form of Compound 1 to a patient having a malignant tumor or cancerous cells.

[00362] Further provided herein are methods for reducing the rate of tumor growth or cancer cell growth, comprising administering an effective amount of a solid form of Compound 1 to a patient having a malignant tumor or cancerous cells.

[00363] Further provided herein are methods for decreasing tumor angiogenesis, comprising administering an effective amount of a solid form of Compound 1 to a patient having cancer.

[00364] Further provided herein are methods for stabilizing hypoxia inducible factor-2 alpha (HIF-2α), comprising administering an effective amount of a solid form of Compound 1 to a patient in need thereof.

[00365] Further provided herein are methods for decreasing vascular endothelial growth factor (VEGF) in a cell in vitro, in vivo or ex vivo, by inhibiting the binding of VEGF to vascular endothelial growth factor receptors (VEGFRs), comprising contacting the cell with an effective amount of a solid form of Compound 1. In one embodiment, the cell is a cancer cell. In another embodiment, the cell is a human cell. In as still further embodiment, the cell is a human cancer cell.

[00366] Further provided herein are methods for increasing secretion of soluble vascular endothelial growth factor receptor-1 (sVEGF-1) from a cell in vitro, in vivo or ex vivo, comprising contacting the cell with an effective amount of a solid form of Compound 1. In one embodiment, the cell is a tumor associated cell. In another embodiment, the cell is a human tumor associated cell. In as still further embodiment, the cell is a human cancer cell.

[00367] Further provided herein are methods for the treatment or prevention of cancer treatable or preventable by decreasing vascular endothelial growth factor (VEGF), comprising administering an effective amount of a solid form of Compound 1 to a patient having cancer treatable or preventable by decreasing VEGF.

[00368] Further provided herein are methods for the treatment or prevention of cancer treatable or preventable by increasing secretion of soluble vascular endothelial growth factor receptor-1 (sVEGF-1), comprising administering effective amount of a solid form of Compound 1 to a patient having cancer treatable or preventable by increasing sVEGF-1.

[00369] Further provided herein are methods for the treatment or prevention of cancer treatable or preventable by stabilizing hypoxia inducible factor-2 alpha (HIF-2a), comprising administering an effective amount of a solid form of Compound 1 to a patient having cancer treatable or preventable by stabilizing HIF-2a.

[00370] Further provided are methods for controlling, inhibiting or decreasing tumor growth in a patient, comprising administering effective amount of a solid form of Compound 1 to a patient having a tumor.

[00371] Further provided herein is the use of a solid form of Compound 1 for making a medicament for treating cancer.

[00372] Further provided herein is the use of a solid form of Compound 1 for making a medicament for the uses provided herein.

[00373] Provided herein is the use of a solid form of Compound 1 for treating or preventing cancer.

[00374] Further provided herein is the use of a solid form of Compound 1 for preventing metastasis of malignant tumors or other cancerous cells and for slowing tumor growth.

[00375] Further still provided herein is the use of a solid form of Compound 1 for decreasing tumor angiogenesis.

[00376] Further provided herein are methods for treating or preventing cancer, comprising administering to a patient having cancer an effective amount of a solid form of Compound 1 and an effective amount of one or more chemotherapeutic agents, wherein a solid form of Compound 1 and the one or more chemotherapeutic agents are administered in any order. Non-limiting examples of chemotherapeutic agents include taxol, IL-2, gemcitabine, erlotinib, doxil, irinortecan, and bevacizumab.

[00377] Further provided herein are methods for preventing metastasis of cancer cells, comprising administering to a patient having cancer an effective amount of a solid form of Compound 1 and an effective amount of one or more chemotherapeutic agents, wherein a solid form of Compound 1 and the one or more chemotherapeutic agents are administered in any order. Non-limiting examples of chemotherapeutic agents include taxol, IL-2, gemcitabine, erlotinib, doxil, irinortecan, and bevacizumab.

[00378] Further provided herein are methods for treating a patient diagnosed with cancer, comprising administering to a patient diagnosed with cancer an effective amount of a solid form of Compound 1 and an effective amount of one or more chemotherapeutic agents, wherein a solid form of Compound 1 and the one or more chemotherapeutic agents are administered in any order. Non-limiting examples of chemotherapeutic agents include taxol, IL-2, gemcitabine, erlotinib, doxil, irinortecan, and bevacizumab.

[00379] The following are non-limiting examples of cancers that can be treated by the disclosed methods and compositions: Acute Lymphoblastic; Acute Myeloid Leukemia; Adrenocortical Carcinoma; Adrenocortical Carcinoma, Childhood; Appendix Cancer; Basal Cell Carcinoma; Bile Duct Cancer, Extrahepatic; Bladder Cancer; Bone Cancer; Osteosarcoma and Malignant Fibrous Histiocytoma; Brain Stem Glioma, Childhood; Brain Tumor, Adult; Brain Tumor, Brain Stem Glioma, Childhood; Brain Tumor, Central Nervous System Atypical Teratoid/Rhabdoid Tumor, Childhood; Central Nervous System Embryonal Tumors; Cerebellar Astrocytoma; Cerebral Astrocytoma/Malignant Glioma; Craniopharyngioma; Ependymoblastoma; Ependymoma; Medulloblastoma; Medulloepithelioma; Pineal Parenchymal Tumors of Intermediate Differentiation; Supratentorial Primitive Neuroectodermal Tumors and Pineoblastoma; Visual Pathway and Hypothalamic Glioma; Brain and Spinal Cord Tumors; Breast Cancer; Bronchial Tumors; Burkitt Lymphoma; Carcinoid Tumor; Carcinoid Tumor, Gastrointestinal; Central Nervous System Atypical Teratoid/Rhabdoid Tumor; Central Nervous System Embryonal Tumors; Central Nervous System Lymphoma; Cerebellar Astrocytoma; Cerebral Astrocytoma/Malignant Glioma, Childhood; Cervical Cancer; Chordoma, Childhood; Chronic Lymphocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloproliferative Disorders; Colon Cancer; Colorectal Cancer; Craniopharyngioma; Cutaneous T-Cell Lymphoma; Esophageal Cancer; Ewing Family of Tumors; Extragonadal Germ Cell Tumor; Extrahepatic Bile Duct Cancer; Eye Cancer, Intraocular Melanoma; Eye Cancer, Retinoblastoma; Gallbladder

Cancer; Gastric (Stomach) Cancer; Gastrointestinal Carcinoid Tumor; Gastrointestinal Stromal Tumor (GIST); Germ Cell Tumor, Extracranial; Germ Cell Tumor, Extragonadal; Germ Cell Tumor, Ovarian; Gestational Trophoblastic Tumor; Glioma; Glioma, Childhood Brain Stem; Glioma, Childhood Cerebral Astrocytoma; Glioma, Childhood Visual Pathway and Hypothalamic; Hairy Cell Leukemia; Head and Neck Cancer; Hepatocellular (Liver) Cancer; Histiocytosis, Langerhans Cell; Hodgkin Lymphoma; Hypopharyngeal Cancer; Hypothalamic and Visual Pathway Glioma; Intraocular Melanoma; Islet Cell Tumors; Kidney (Renal Cell) Cancer; Langerhans Cell Histiocytosis; Laryngeal Cancer; Leukemia, Acute Lymphoblastic; Leukemia, Acute Myeloid; Leukemia, Chronic Lymphocytic; Leukemia, Chronic Myelogenous; Leukemia, Hairy Cell; Lip and Oral Cavity Cancer; Liver Cancer; Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphoma, AIDS-Related; Lymphoma, Burkitt; Lymphoma, Cutaneous T-Cell; Lymphoma, Hodgkin; Lymphoma, Non-Hodgkin; Lymphoma, Primary Central Nervous System; Macroglobulinemia, Waldenstrom; Malignant Fibrous Histiocytoma of Bone and Osteosarcoma; Medulloblastoma; Melanoma; Melanoma, Intraocular (Eye); Merkel Cell Carcinoma; Mesothelioma; Metastatic Squamous Neck Cancer with Occult Primary; Mouth Cancer; Multiple Endocrine Neoplasia Syndrome, (Childhood); Multiple Myeloma/Plasma Cell Neoplasm; Mycosis Fungoides; Myelodysplastic Syndromes; Myelodysplastic/:Myeloproliferative Diseases; Myelogenous Leukemia, Chronic; Myeloid Leukemia, Adult Acute; Myeloid Leukemia, Childhood Acute; Myeloma, Multiple; Myeloproliferative Disorders, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer; Neuroblastoma; Non-Small Cell Lung Cancer; Oral Cancer; Oral Cavity Cancer; Oropharyngeal Cancer; Osteosarcoma and Malignant Fibrous Histiocytoma of Bone; Ovarian Cancer; Ovarian Epithelial Cancer; Ovarian Germ Cell Tumor; Ovarian Low Malignant Potential Tumor; Pancreatic Cancer; Pancreatic Cancer, Islet Cell Tumors; Papillomatosis; Parathyroid Cancer; Penile Cancer; Pharyngeal Cancer; Pheochromocytoma; Pineal Parenchymal Tumors of Intermediate Differentiation; Pineoblastoma and Supratentorial Primitive Neuroectodermal Tumors; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary Blastoma; Primary Central Nervous System Lymphoma; Prostate Cancer; Rectal Cancer; Renal Cell (Kidney) Cancer; Renal Pelvis and Ureter, Transitional Cell Cancer; Respiratory Tract Carcinoma Involving the NUT Gene on Chromosome 15; Retinoblastoma; Rhabdomyosarcoma; Salivary Gland Cancer; Sarcoma, Ewing Family of Tumors; Sarcoma, Kaposi; Sarcoma, Soft Tissue; Sarcoma, Uterine; Sezary Syndrome; Skin Cancer (Nonmelanoma); Skin Cancer (Melanoma); Skin Carcinoma, Merkel Cell; Small Cell Lung Cancer; Small Intestine Cancer; Soft Tissue Sarcoma; Squamous Cell Carcinoma, Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Supratentorial Primitive Neuroectodermal Tumors; T-Cell Lymphoma, Cutaneous; Testicular Cancer; Throat Cancer; Thymoma and Thymic Carcinoma; Thyroid Cancer; Transitional Cell Cancer of the Renal Pelvis and Ureter; Trophoblastic Tumor, Gestational; Urethral Cancer; Uterine Cancer, Endometrial; Uterine Sarcoma; Vaginal Cancer; Vulvar Cancer; Waldenstrom Macroglobulinemia; and Wilms Tumor.

[00380] The cancer can be any cancer described herein, including VEGF-dependent cancers.

[00381] In certain embodiments, provided herein are methods of treating and/or preventing conditions of the eye wherein the methods comprise administering to a subject in need of treatment and/or prevention a solid form of Compound 1. Illustrative conditions of the eye include, but are not limited to, retinopathy (including diabetic retinopathy), radiation retinopathy, macular degeneration, age-related macular degeneration (including early, intermediate, and advanced stage age-related macular degeneration), Wet (exudative) age-related macular degeneration, specific genotypes associated with macular degeneration, cancer, solid or blood borne tumors, choroidal melanoma, sickle cell retinopathy, neovascularization, ocular neovascularization, subretinal neovascularization, vein occlusion, retinopathy of prematurity, chronic uveitis/vitritis, ocular trauma, ocular ischemia, retinal ischemia, Best's disease, chronic retinal detachment, diseases associated with rubeosis, Eales' disease proliferative vitreoretinopathy, familial exudative vitreoretinopathy, Stargardt's disease, presumed ocular histoplasmosis, hyperviscosity syndromes, myopia, post-laser complications, retinopathy of prematurity, infections causing a retinitis or choroiditis, optic pits, pars planitis, toxoplasmosis, choroidal neovascularization (including Type 1, 2, and 3 choroidal neovascularization), macular edema, cystoid macular edema, diabetic macular edema, ocular edema, glaucoma, neovascular glaucoma, surgery-induced edema, surgery-induced neovascularization, retinoschisis, retinal capillary occlusions, retinal angiomatous proliferation, vitreous hemorrhage, retinal neovascularization, polypoidal choroidal vasculopathy (juxtafoveal and subfovial), vitreomacular adhesion, geographic atrophy, retinal hypoxia, pathological myopia, dysregulated para-inflammation, chronic inflammation, chronic wound healing environment in the aging eye, carotid vacernous fistula, idiopathic occlusive arteriolitis, birdshot retinochoroidopathy, retinal vasculitis, incontinentia pigmenti, retinitis pigmentosa, tachyphylaxis, and limbal stem cell deficiency.

5.7 **Pharmaceutical Compositions**

[00382] Pharmaceutical compositions may be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms provided herein comprise a solid form of Compound 1.

[00383] In certain embodiment, pharmaceutical compositions and dosage forms comprise a solid form of Compound 1 and one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water.

[00384] Lactose-free compositions can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopeia (USP) 25 NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. In one embodiment, lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

[00385] Also provided are anhydrous pharmaceutical compositions and dosage forms since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See*, *e.g.*, Jens T. Carstensen, Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[00386] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are, in one embodiment, packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

[00387] Also provided are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[00388] Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients.

5.7.1 **Oral Dosage Forms**

[00389] Pharmaceutical compositions that are suitable for oral administration can be provided as discrete dosage forms, such as, but not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, suspensions and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. *See* generally, Remington's The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (2005).

[00390] Oral dosage forms provided herein are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[00391] In one embodiment, oral dosage forms are tablets or capsules, in which case solid excipients are employed. In another embodiment, tablets can be coated by standard aqueous or non-aqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[00392] For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient.

[00393] Examples of excipients that can be used in oral dosage forms provided herein include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[00394] Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM. Other suitable forms of microcrystalline cellulose include, but are not limited to, silicified microcrystalline cellulose, such as the materials sold as PROSOLV 50, PROSOLV 90, PROSOLV HD90, PROSOLV 90 LM, and mixtures thereof.

[00395] Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms provided herein include, but are not limited to, talc, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions is, in one embodiment, present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form. The binder or filler in pharmaceutical compositions is, in another embodiment, present in from about 20 to about 30 weight percent of the pharmaceutical composition or dosage form. The binder or filler in pharmaceutical compositions is, in another embodiment, present in about 24 weight percent of the pharmaceutical composition or dosage form.

[00396] In certain embodiments, fillers may include, but are not limited to block copolymers of ethylene oxide and propylene oxide. Such block copolymers may be sold as POLOXAMER or PLURONIC, and include, but are not limited to POLOXAMER 188 NF, POLOXAMER 237 NF, POLOXAMER 338 NF, POLOXAMER 437 NF, and mixtures thereof. In certain embodiments, POLOXAMER or PLURONIC, including, but not limited to POLOXAMER 188 NF, POLOXAMER 237 NF, POLOXAMER 338 NF, POLOXAMER 437 NF, and mixtures thereof, are surfactants.

[00397] In certain embodiments, fillers may include, but are not limited to isomalt, lactose, lactitol, mannitol, sorbitol xylitol, erythritol, and mixtures thereof.

[00398] Disintegrants may be used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients may be used to form solid oral dosage forms. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. In one embodiment, pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, or from about 5 to about 9 weight percent of disintegrant, or from about 1 to about 5 weight percent of disintegrant, or from about 1 to about 7 weight percent of disintegrant, or about 7 weight percent of disintegrant.

[00399] Disintegrants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, povidone, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

[00400] Glidants and/or lubricants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium stearyl fumarate, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional glidants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic colloidal silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, glidants and/or lubricants may be used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

[00401] In certain embodiments, an oral dosage form comprises the compound, silicified microcrystalline cellulose, sodium starch glycolate, a block copolymer of ethylene oxide and propylene oxide, sodium stearyl fumarate and colloidal silicon dioxide. In certain embodiments, an oral dosage form comprises a solid form of Compound 1 in an amount of about 5% to about 75% by weight, silicified microcrystalline cellulose in an amount of about 15% to about 85%, sodium starch glycolate in an amount of about 2% to about 10%, block copolymer of ethylene oxide and propylene oxide in an amount of about 2% to about 10%, sodium stearyl fumarate in an amount of 0.2% to about 2%, and colloidal silicon dioxide in an amount of about 0.2% to about 2% by weight of the oral dosage form.

[00402] In certain embodiments, an oral dosage form comprises the solid form of Compound 1, microcrystalline cellulose, isomalt, sodium starch glycolate, sodium lauryl sulfate, povidone, colloidal silicon dioxide, and magnesium stearate. In certain embodiments, an oral dosage form comprises a solid form of Compound 1 in an amount of about 40% to about 50%, microcrystalline cellulose in an amount of about 40% to about 50%, isomalt in an amount of 0% to about 5%, sodium starch glycolate in an amount of about 5% to about 10%, sodium lauryl sulfate in an amount of 0.2% to about 2%, povidone in an amount of about 2% to about 10%, colloidal silicon dioxide in an amount of 0.1% to about 1%, and magnesium stearate in an amount of about 0.1% to about 1% by weight of the oral dosage form.

[00403] In certain embodiments, the invention relates to unit dosage forms that comprise between about 100 mg and about 1,200 mg, about 200 mg and about 1,000 mg, about 400 mg and about 800 mg, or about 450 mg and about 600 mg of a solid form of Compound 1.

[00404] In certain embodiments, the invention relates to unit dosage forms that comprise about 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1,000 mg, 1,050 mg, 1,100 mg, 1,150, or even about 1,200 mg of a solid form of Compound 1. In certain such embodiments, the unit dosage form is a capsule comprising about 40 mg, about 120 mg, about 185 mg, about 200 mg, about 250 mg, or about 400 mg of a solid form of Compound 1.

[00405] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents, and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1 ,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan, and mixtures thereof.

[00406] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

[00407] Suspensions, in addition to the active inhibitor(s) may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

6. Examples

[00408] The following examples are presented by way of illustration, not limitation. The following abbreviations are used in descriptions and examples:

ACN:	Acetonitrile
AUC:	Area under the curve
CI:	Counter Ion
DMF:	*N*,*N*-Dimethylformide
DMSO:	Dimethylsulfoxide
DSC:	Differential Scanning Calorimetry
DVS:	Dynamic Vapor Sorption
EtOH:	Ethanol
Evp:	Evaporation
HPLC:	High performance liquid chromatography
IC:	Ion Chromatography
IPA:	2-Propanol
IPAc:	Isopropyl Acetate
LCMS:	Liquid Chromatography with Mass Spectroscopy
MEK:	Methyl Ethyl Ketone
MeCN:	Acetonitrile
MeOH:	Methanol
MIBK:	Methyl isoButyl Ketone
mp:	Melting point
MS:	Mass spectrometry
MTBE:	tert-Butyl methyl ether
NMP:	*N*-Methyl-2-pyrrolidone
NMR:	Nuclear magnetic resonance
ppt:	Precipitation

RH:	Relative Humidity
RT:	Room Temperature
SM:	Compound 1
TGA:	Thermogravimetric Analysis
THF:	Tetrahydrofuran
XRPD:	X-Ray Powder Diffraction

6.1 SUMMARY OF POLYMORPH SCREEN OF COMPOUND 1

[00409] Eight unique crystal forms (Forms A, B, C, D, E, F, G, and H) were prepared in the polymorph screen, including single solvent and binary solvent crystallization experiments, based on XRPD analysis. The characterization data indicated that Form A is a stable anhydrate polymorph. Forms B, C, D, and E showed high similarity with each other, with small differences between approximately 15 and 30 °2θ. Based on the DSC analysis, all four forms (B, C, D and E) showed similar endotherms at low temperature and recrystallization events at ~150.0 °C. Characterization data showed that Form D is likely a metastable anhydrate polymorph. Forms B, C and E are likely either metastable anhydrate polymorph or solvent inclusion complexes, in which variable amount and type of organic solvents are retained and cause minor changes in crystal lattice. Form F is likely a metastable hydrate polymorph. Although Form G showed similarity to Form F, its TGA analysis did not show significant weight loss so it is possibly a metastable anhydrate polymorph. Form H is a mono-DMSO solvate, harvested when DMSO was used as primary solvent during re-crystallization experiment. Form A was found to be thermodynamically the most stable anhydrate polymorph.

6.1.1 Crystallization Experiments

[00410] Both fast cooling (refrigerating at 4 °C, 24 hrs) and slow cooling (20 °C/hr) approaches were used in attempt to generate crystals via single-solvent and binary solvent crystallization steps. Solvent crystallization experiments were performed as described in Sections 6.1.1.1 and 6.1.1.2 and summarized in Table 1-Table 10.

[00411] Table 1. Compound 1 single solvent fast cooling crystallization experiments (refrigerate at 4 °C, 24 hrs), no precipitation formed.

Cmpd 1 amount. (mg)	Solvent	Solvent Vol. (mL)	Temp. (°C)	Solid form determined by XRPD
33.0	MeOH	2.25	50.0	B
33.6	EtOH	2.63	50.0	C
32.5	IPA	4.81	50.0	D
31.2	1-BuOH	4.91	50.0	D + minor additional peaks
32.8	MeCN	5.06	50.0	D
30.2	THF	3.08	50.0	A+B
32.2	2-MeTHF	5.10	50.0	E
32.1	EtOAc	4.61	50.0	D
35.8	IPAc	4.50	50.0	C
32.9	Acetone	3.85	50.0	B
34.2	MEK	4.64	50.0	E + minor additional peaks
32.7	MIBK	6.00	50.0	A + minor additional peaks
35.1	MTBE	6.13	50.0	A
30.3	DMSO	1.04	50.0	--
31.6	n-Propanol	3.72	50.0	E

[00412] Table 2. Compound 1 single solvent slow cooling crystallization experiments (20 °C/hr) , no precipitation formed.

Cmpd 1 amount. (mg)	Solvent	Solvent Vol. (mL)	Temp. (°C)	Solid form by XRPD
35.6	MeOH	2.25	50.0	B
32.8	EtOH	2.63	50.0	C
31.1	IPA	4.81	50.0	D
31.0	1-BuOH	4.91	50.0	E
31.2	MeCN	5.06	50.0	B
34.7	THF	3.08	50.0	A+B
33.1	2-MeTHF	5.10	50.0	E
32.0	EtOAc	4.61	50.0	D
33.2	IPAc	4.50	50.0	C
30.7	Acetone	3.85	50.0	B
32.1	MEK	4.64	50.0	D

30.0	MIBK	6.00	50.0	B
35.8	MTBE	6.13	50.0	A + minor peak
33.2	DMSO	1.04	50.0	--
35.3	n-Propanol	3.72	50.0	E

[00413] Table 3. Compound 1 binary solvent fast cooling crystallization experiments, water as co-solvent (refrigerate at 4 °C, 24 hrs).

Cmpd 1 amnt. (mg)	Primary Solvent	Temp. (°C)	1° solvent Vol. (mL)	Co-solvent Vol. (mL)	Precipitation / Evaporation	Yield (mg)	Solid form by XRPD
36.5	MeOH	50.0	2.5	3.0	Precipitation	3.99	A + D
32.8	EtOH	70.0	2.6	5.0	Precipitation	12.13	A + C
33.4	IPA	70.0	4.9	10.0	Precipitation	20.6	A
35.0	MeCN	70.0	5.4	10.0	Precipitation	13.49	D
31.3	THF	50.0	3.2	7.5	Evaporation with N_2	-	B + F
32.5	Acetone	50.0	3.8	8.0	Precipitation	13.06	A
35.5	DMSO	70.0	1.2	1.0	Precipitation	20.86	A
30.1	DMF	70.0	1.1	2.0	Precipitation	7.86	A
33.9	NMP	70.0	1.3	2.0	Precipitation	15.46	A
34.2	n-Propanol	70.0	4.0	8.0	Precipitation	4.91	D + F
30.2	MEK	70.0	4.1	2.0	Evaporation with N_2	-	G
31.5	MIBK	70.0	5.7	1.0	Evaporation with N_2	-	F + G
31.8	2-MeTHF	70.0	5.0	1.0	Evaporation with N_2	-	G
32.5	1-BuOH	70.0	5.1	5.0	Evaporation with N_2	-	D

[00414] Table 4. Compound 1 binary solvent slow cooling crystallization experiments, water as co-solvent (20 °C/hr).

Cmpd 1 amnt. (mg)	Primary Solvent	Temp. (°C)	1° solvent Vol. (mL)	Co-solvent Vol. (mL)	Precipitation / Evaporation	Yield (mg)	Solid form by XRPD
32.6	MeOH	50.0	2.2	3.0	Precipitation	14.35	A + B
35.9	EtOH	70.0	2.8	5.0	Precipitation	12.1	E
35.1	IPA	70.0	5.2	10.0	Evaporation	-	G

					with N_2		
34.8	MeCN	70.0	5.4	10.0	Precipitation	12.86	A
36.7	THF	50.0	3.7	7.5	Evaporation with N_2	-	E + F
36.3	Acetone	50.0	4.2	8.0	Precipitation	16.96	A
30.7	DMSO	70.0	1.1	1.0	Evaporation with N_2	-	Oily material
32.2	DMF	70.0	1.2	2.0	Precipitation	2.66	A
33.5	NMP	70.0	1.3	2.0	Precipitation	11.16	A
34.0	n-Propanol	70.0	4.0	8.0	Evaporation with N_2	-	D
31.6	MEK	70.0	4.3	2.0	Evaporation with N_2	-	B
33.4	MIBK	70.0	6.0	1.0	Evaporation with N_2	-	B
30.1	2-MeTHF	70.0	4.8	1.0	Evaporation with N_2	-	G
31.9	1-BuOH	70.0	5.0	5.0	Evaporation with N_2	-	D

[00415] Table 5. Compound 1 binary solvent fast cooling crystallization experiments, toluene as co-solvent (refrigerate at 4 °C, 24 hrs), no precipitation formed.

Cmpd 1 amnt. (mg)	Primary Solvent	Temp. (°C)	1° solvent Vol. (mL)	Co-solvent Vol. (mL)	Solid form by XRPD
30.0	MeOH	50.0	2.0	4.0	D + extra peak (5.475° 2θ)
32.0	EtOH	70.0	2.5	5.0	C
35.0	IPA	70.0	5.2	10.0	E
31.3	1-BuOH	70.0	4.9	9.5	E + extra peak (4.984° 2θ)
35.0	MeCN	70.0	5.4	10.8	D
31.0	THF	50.0	3.2	6.4	D
31.5	2-MeTHF	70.0	5.0	10.0	D
33.2	EtOAc	70.0	4.7	9.6	D
31.1	IPAc	70.0	3.9	7.6	D
32.8	Acetone	50.0	3.9	7.6	D

32.6	MEK	70.0	4.4	8.8	E
31.2	MIBK	70.0	5.9	11.6	D
32.8	DMSO	70.0	1.1	2.2	H
31.1	DMF	70.0	1.1	2.2	A + extra peaks (4.32, 15.4° 2θ)
33.1	NMP	70.0	1.3	2.5	Oily material
32.0	n-Propanol	70.0	3.8	7.4	E

[00416] Table 6. Compound 1 binary solvent slow cooling crystallization experiments, toluene as co-solvent (20 °C/hr), no precipitation formed.

Cmpd 1 amnt. (mg)	Primary Solvent	Temp. (°C)	1° solvent Vol. (mL)	Co-solvent Vol. (mL)	Solid form by XRPD
33.2	MeOH	50.0	2.3	4.4	D
31.1	EtOH	70.0	2.4	4.8	E
30.0	IPA	70.0	4.4	8.8	E
32.4	1-BuOH	70.0	5.1	10.0	E + extra peak (4.984° 2θ)
30.4	MeCN	70.0	4.7	9.3	D
31.5	THF	50.0	3.2	6.4	D
30.4	2-MeTHF	70.0	4.8	9.6	E
34.3	EtOAc	70.0	4.9	9.8	E
32.3	IPAc	70.0	4.0	8.0	A
30.0	Acetone	50.0	3.5	7.0	D
33.9	MEK	70.0	4.6	9.2	D
33.1	MIBK	70.0	6.0	12.0	D
34.3	DMSO	70.0	1.2	2.2	H
31.2	DMF	70.0	1.1	2.2	A + B
34.6	NMP	70.0	1.3	2.6	Oily material
33.5	n-Propanol	70.0	3.9	7.8	E

[00417] Table 7. Compound 1 binary solvent fast cooling crystallization experiments, heptane as co-solvent (refrigerate at 4 °C, 24 hrs), no precipitation formed.

Cmpd 1 amnt. (mg)	Primary Solvent	Temp. (°C)	1° solvent Vol. (mL)	Co-solvent Vol. (mL)	Solid form by XRPD

32.0	EtOH	70.0	2.5	5.0	E
34.7	IPA	70.0	5.1	10.0	D
32.5	1-BuOH	70.0	5.1	10.0	E
32.9	THF	50.0	3.4	6.7	D
33.8	2-MeTHF	70.0	5.4	10.8	D
32.1	EtOAc	70.0	4.6	9.0	D
34.3	IPAc	70.0	4.3	8.6	C
32.1	Acetone	50.0	3.8	7.4	D
33.8	MEK	70.0	4.6	9.0	D
35.7	MIBK	70.0	6.5	12.5	A + D
32.7	MTBE	70.0	5.7	11.4	A (with strong preferred orientation)
34.0	NMP	70.0	1.3	2.5	Oily material
35.8	n-Propanol	70.0	4.2	8.4	E

[00418] Table 8. Compound 1 binary solvent slow cooling crystallization experiments, heptane as co-solvent (20 °C/hr).

Cmpd 1 amnt. (mg)	Primary Solvent	Temp. (°C)	1° solvent Vol. (mL)	Co-solvent Vol. (mL)	Precipitation / Evaporation	Yield (mg)	Solid form by XRPD
32.4	EtOH	70.0	2.5	5.0	Evaporation with N_2	-	E
30.9	IPA	70.0	4.5	9.0	Evaporation with N_2	-	E
33.9	1-BuOH	70.0	5.3	10.5	Evaporation with N_2	-	E + extra peak (5.07° 2θ)
30.4	THF	50.0	3.1	6.2	Evaporation with N_2	-	E
33.0	2-MeTHF	70.0	5.2	10.4	Evaporation with N_2	-	E
31.9	EtOAc	70.0	4.6	9.0	Evaporation with N_2	-	E
33.6	IPAc	70.0	4.2	8.4	Precipitation	20.57	A
32.6	Acetone	50.0	3.8	7.6	Evaporation with N_2	-	D
35.2	MEK	70.0	4.8	9.4	Evaporation with	-	D

					N_2		
34.8	MIBK	70.0	6.3	12.6	Precipitation	13.01	A
33.1	MTBE	70.0	5.8	11.6	Precipitation	15.49	A
31.3	NMP	70.0	1.2	2.4	Evaporation with N_2	-	Oily material
30.8	n-Propanol	70.0	3.6	7.2	Evaporation with N_2	-	E

[00419] Table 9. Compound 1 binary solvent fast cooling crystallization experiments, cyclohexane as co-solvent (refrigerate at 4 °C, 24 hrs), no precipitation formed.

Cmpd 1 amnt. (mg)	Primary Solvent	Temp. (°C)	1° solvent Vol. (mL)	Co-solvent Vol. (mL)	Solid form by XRPD
30.5	EtOH	70.0	2.4	4.8	C
33.0	IPA	70.0	4.9	9.8	E
33.4	1-BuOH	70.0	5.2	10.4	E
31.2	THF	50.0	3.2	6.4	E
34.9	2-MeTHF	70.0	5.5	11.0	E
30.4	EtOAc	70.0	4.4	8.8	E
30.5	IPAc	70.0	3.8	7.6	A
35.6	Acetone	50.0	4.2	8.4	D
30.1	MEK	70.0	4.1	8.2	D
32.4	MIBK	70.0	5.9	11.8	D
30.3	NMP	70.0	1.1	2.2	Oily material
30.0	n-Propanol	70.0	3.5	7.0	E

[00420] Table 10. Compound 1 binary solvent slow cooling crystallization experiments, cyclohexane as co-solvent (20 °C/hr), no precipitation formed.

Cmpd 1 amnt. (mg)	Primary Solvent	Temp. (°C)	1° solvent Vol. (mL)	Co-solvent Vol. (mL)	Solid form by XRPD
34.2	EtOH	70.0	2.7	5.4	C
34.2	IPA	70.0	5.0	10.0	E
34.5	1-BuOH	70.0	5.4	10.8	E + extra peak (5.05° 2θ)
33.5	THF	50.0	3.4	6.8	E

32.6	2-MeTHF	70.0	5.2	10.4	E
31.9	EtOAc	70.0	4.6	9.2	C
32.6	IPAc	70.0	4.1	8.2	A + C
32.8	Acetone	50.0	3.9	7.8	D
30.8	MEK	70.0	4.2	8.4	D
30.0	MIBK	70.0	5.5	11.0	E
31.5	NMP	70.0	1.2	2.4	Oily material
31.3	n-Propanol	70.0	3.7	7.4	E

6.1.1.1 Single Solvent Crystallization

[00421] Single solvent crystallizations were conducted at 30 - 35 mg scale using the primary solvents listed in Table 1 and Table 2. The experiments employed fast and slow cooling profiles as described in Table 1 and Table 2. No precipitates were obtained for all single-solvent crystallization experiments. All 30 crystallization samples had to be evaporated to dryness under a gentle stream of nitrogen to obtain solid for XRPD analysis (Table 1 and Table 2). Five unique XRPD patterns (Forms A, B, C, D, and E, Figure 1) were observed from 28 crystallization experiments. Forms A, B, C, D, and E were prepared. The remaining two experiments produced an oily material that was not suitable for XRPD analysis.

[00422] The method of single solvent fast cooling crystallization comprised the steps of: (1) placing approximately 30-35 mg of Compound 1 into 8 mL clear glass vials equipped with stir bars; (2) dissolving with a minimum amount of solvents (starting with 500 µL increment) at 50 °C (up to 7.0 mL); (3) filtering the hot solution through a 0.45 µm syringe filter into a clean preheated vial; (4) placing the vial in a refrigerator (4 °C) without stirring over 24 hours; (5) isolating the resulting solids by vacuum filtration; and (6) evaporating the samples without precipitation to dryness under a gentle stream of nitrogen. All obtained solids were analyzed by XRPD to determine the solid form. *See* Table 1.

[00423] The method of single solvent slow cooling crystallization comprised the steps of: (1) placing approximately 30-35 mg of Compound 1 into 8 mL clear glass vials equipped with stir bars; (2) dissolving with a minimum amount of solvents (starting with 500 µL increment) at 50 °C (up to 7.0 mL); (3) filtering the hot solution through a 0.45 µm syringe filter into a clean preheated vial; (4) cooling to ambient temperature at a rate of 20 °C/hr and allowing to equilibrate with stirring at ambient temperature over 24 hours; (5) isolating the resulting solids by vacuum filtration; and (6) evaporating the samples without precipitation to dryness under a gentle stream of nitrogen. All obtained solids were analyzed by XRPD to determine the solid form. *See* Table 2.

6.1.1.2 Binary Solvent Crystallization

[00424] Binary solvent crystallizations were conducted at ~30 mg scale. A list of the chosen primary solvent systems is presented in Table 3-Table 10, respectively, to dissolve the Compound 1 at 50 or 70 °C. Solvents such as H_2O, toluene, heptane and cyclohexane were used as co-solvents as described in Table 3-Table 10. Besides the six patterns (Forms A, B, C, D, E and F), two additional unique XRPD patterns (Forms G and H) were obtained from 110 binary solvent crystallization experiments. Forms A, B, C, D, E, F, G and H were prepared. A representative overlay of XRPD patterns of all eight forms is shown in Figure 1.

[00425] The method of binary solvent fast cooling crystallization comprised the steps of: (1) placing approximately 30.0-35.0 mg of Compound 1 into 8 mL clear glass vials equipped with stir bars; (2) dissolving with a minimum amount of solvents (starting with 500 mL increment) at 50 or 70 °C (up to 7.0 mL); (3) filtering the hot solution through a 0.45 μm syringe filter into a clean preheated vial; (4) adding a co-solvent drop-wise; (5) placing the vials in a refrigerator (4 °C) without stirring over 24 hours; (6) isolating the resulting solids by vacuum filtration; and (7) evaporating the samples without precipitation to dryness under a gentle stream of nitrogen gas. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 3, Table 5, Table 7 and Table 9).

[00426] The method of binary solvent slow cooling crystallization comprised the steps of: (1) placing approximately 30.0-35.0 mg of Compound 1 into 8 mL clear glass vials equipped with stir bars; (2) dissolving with a minimum amount of solvents (starting with 500 mL increment) at 50 or 70 °C (up to 7.0 mL); (3) filtering the hot solution through a 0.45 μm syringe filter into a clean preheated vial; (4) adding a co-solvent drop-wise; (5) cooling the vial to ambient temperature at a rate of 20 °C/hr and allowing to equilibrate with stirring at ambient temperature over 24 hours; (6) isolating the resulting solids by vacuum filtration; and (7) evaporating the samples without precipitation to dryness under a gentle stream of nitrogen gas. All obtained solids were analyzed by XRPD to determine the solid form (*see* Table 4, Table 6, Table 8 and Table 10).

[00427] Water as co-solvent:

[00428] Precipitations were isolated by filtration from 15 experiments out of 28 crystallization experiments (Table 3 and Table 4). For the remaining crystallization experiments, solids were obtained in most experiments after the solutions were evaporated to dryness under a gentle stream of nitrogen, followed by XRPD analysis. Five unique XRPD patterns (Forms A, B, D, E and G) and seven XRPD pattern mixtures were observed. Forms A, B, D, E and G were prepared.

[00429] Toluene as co-solvent:

[00430] No precipitates were obtained for all binary-solvent crystallizations in toluene (Table 5 and Table 6). All the solutions were evaporated to dryness under a gentle stream of nitrogen to obtain solids for XRPD analysis. In 32 crystallization experiments, five unique XRPD patterns (Forms A, C, D, E and H) and one pattern mixture were observed. Forms A, C, D, and E were prepared. New unique Form H was observed and prepared from DMSO/Toluene via both fast and slow cooling methods.

[00431] Heptane as co-solvent:

[00432] Precipitations were isolated by filtration from 3 experiments out of 26 crystallization experiments (Table 7 and Table 8). For the remaining crystallization samples, solids were obtained in most experiments after the solutions were evaporated to dryness under a gentle stream of nitrogen, followed by XRPD analysis. Four unique XRPD patterns (Forms A, C, D, and E) and one XRPD pattern mixture were observed. Forms A, C, D, and E were prepared.

[00433] Cyclohexane as co-solvent:

[00434] No precipitates were obtained for all binary-solvent crystallizations in cyclohexane (Table 9 and Table 10). All the solutions were evaporated to dryness under a gentle stream of nitrogen to obtain solids for XRPD analysis. In 24 crystallization experiments, four unique XRPD patterns (Forms A, C, D, and E) and one pattern mixture was observed. Forms A, C, D, and E were prepared.

6.1.2 **Scale up of crystalline Forms D and G**

[00435] Forms A, D and G were identified as potential anhydrate polymorphs and prepared for full characterization. The starting material was Form A. A series of experiments were performed to generate a sufficient quantity of Forms D and G materials for further characterization. Details of the experiments are summarized in Table 11.

[00436] Table 11. Scale up of crystalline Forms D and G with the slow cooling method (20 °C/hr).

Cmpd 1 amnt. (mg)	Primary Solvent	Temp. (°C)	1° solvent Vol. (mL)	Co-solvent	Co-solvent Vol. (mL)	Precipitation / Evaporation	Yield (mg)	Solid form by XRPD
60.7	THF	50.0	6.2	Toluene	12.0	Evaporation with N_2	-	D
62.5	MEK	70.0	8.5	Toluene	17.0	Evaporation with N_2	-	D
59.7	IPA	70.0	8.8	Water	17.5	Precipitation	30.2	G
61.4	2-MeTHF	70.0	9.8	Water	12.0	Evaporation with N_2	-	G

[00437] Form D material was scaled up using the binary solvent crystallizations method and conducted at ~60 mg scale (Table 11). Two batches of Form D materials were generated. Procedures utilized to generate these Form D materials followed the methods used for the two batches in intermediate scale experiments (Table 5 and Table 6).

[00438] The scale-up method of binary solvent slow cooling crystallization for preparation of Form D comprised the steps of: (1) placing approximately 60 mg of Compound 1 into 20 mL clear glass vials equipped with stir bars; (2) dissolving with a minimum amount of solvents (THF or MEK, starting with 500 mL increment) at 50 or 70 °C; (3) filtering the hot solution through a 0.45 μm syringe filter into a clean preheated vial; (4) adding a co-solvent (toluene); (5) cooling the vial to ambient temperature at a rate of 20 °C/hr and allowing to equilibrate with stirring at ambient temperature over 5 hours; (6) isolating the resulting solids by vacuum filtration; and (7) evaporating the samples without precipitation to dryness under a gentle stream of nitrogen gas. All obtained solids were analyzed by XRPD to determine the solid form (Table 11).

[00439] Form G material was scaled up using binary solvent crystallizations method and conducted at ~60 mg scale (Table 11). Two batches of Form G materials were generated. Procedures utilized to generate these Form G materials followed the methods used for the two batches in intermediate scale experiments (Table 3 and Table 4).

[00440] The scale-up method of binary solvent slow cooling crystallization for preparation of Form G comprised the steps of: (1) placing approximately 60 mg of Compound 1 into 20 mL clear glass vials equipped with stir bars; (2) dissolving with a minimum amount of solvents (IPA or 2-MeTHF, starting with 500 mL increment) at 70 °C; (3) filtering the hot solution through a 0.45 µm syringe filter into a clean preheated vial; (4) adding a co-solvent (water); (5) cooling the vial to ambient temperature at a rate of 20 °C/hr and allowing to equilibrate with stirring at ambient temperature over 5 hours; (6) isolating the resulting solids by vacuum filtration; and (7) evaporating the samples without precipitation to dryness under a gentle stream of nitrogen gas. All obtained solids were analyzed by XRPD to determine the solid form (Table 11).

6.1.3 **Competitive Slurry experiment of Forms A, D and G**

[00441] To evaluate relative stability of the anhydrate polymorphs, competitive slurry experiments of Forms A, D and G were conducted as described in below and summarized in Table 12. In all three solvent systems, water, 1:2 v/v IPAc/heptane, and toluene, Form A was the final polymorph after equilibration for 8 days. Therefore, Form A is the most stable anhydrate polymorph among the three polymorphs at ambient temperature.

[00442] Table 12. Competitive slurry experiment of Forms A, D and G.

Parent Materials	Weight (mg)	Solvent	Vol. (mL)	Tempt. (°C)	Aliquot time point		Aliquot time point	
					Day	XRPD	Day	XRPD
Form A	12.54	Water	1.0	RT	1	A+D	8	A
Form D	11.06							
Form G	12.00							
Form A	12.45	IPAc /Heptane (1:2 V/V)	1.0	RT	1	A	8	A
Form D	12.88							
Form G	12.34							

Form A	15.20	Toluene	1.0	RT	1	A	8	A
Form D	16.70							
Form G	14.75							

[00443] Slurry experiments were performed using the following procedure: a mixture of Form A (~12.0 mg, Compound 1), Form D (~12.0 mg) and Form G (~12.0 mg) were weighed into a 20.0 mL clear vial equipped with magnetic stir bars (Table 12). Water, IPAc/Heptane (1:2 V/V) and toluene were used as the solvent systems for these competitive slurry experiments. Three selected solvents, 1.0 mL, were added to achieve free-flowing slurry and allowed to equilibrate at room temperature.

6.1.4 **Competitive Slurry experiment of Forms A through H**

[00444] Competitive slurry experiment of all unique Forms A through H were also conducted as described below and summarized in Table 13. Again Form A was detected after one day and seven days equilibration, indicating that it is the most stable polymorph.

[00445] Table 13. Competitive slurry experiment of Forms A to H.

Parent Materials	Weight (mg)	Solvent	Vol. (mL)	Tempt. (°C)	Aliquot time point		Aliquot time point	
					Day	XRPD	Day	XRPD
Form A	4.72	IPAc/Heptane (1:2, V/V)	1.0	RT	1	A	7	A
Form B	3.01							
Form C	1.13, 1.91							
Form D	1.65 or 1.70							
Form E	3.23							
Form F	3.45							
Form G	3.43							
Form H	3.52							
Form A	4.95	Toluene	1.0	RT	1	A	7	A
Form B	3.32							
Form C	1.97, 1.80							

Form D	1.64 or 1.72							
Form E	3.60							
Form F	3.22							
Form G	3.25							
Form H	3.61							

[00446] Approximately 2 to 3 mg of materials from Forms A to H were weighed into a 20.0 mL clear vial equipped with magnetic stir bars (Table 13). IPAc/Heptane (1:2 V/V) and toluene were used as the solvent systems for these competitive slurry experiments. Two selected solvents, 1.0 mL, were added to achieve free-flowing slurry and allowed to equilibrate at room temperature. All slurries will be isolated via centrifuge filtration after one day and seven days of equilibration.

6.1.5 **Single form slurry experiments**

[00447] Single form slurry experiments were conducted for Forms A, D and G in three solvents stems, water, 1:2 v/v IPAc/heptane, and toluene to evaluate their physical form stability as a single polymorph (Table 14). Form A remained unchanged at six day time point. Form G converted to Form A after three day time points. Form D remained unchanged for three days in water but converted to a mixture A and D at six days. In 1:2 IPAc/heptane and toluene, Form D converted to a mixture of A and D at three days and then Form A at six days. These results showed that Form G is a metastable polymorph and readily converts to Form A under slurry conditions at ambient temperature. Form D is also a metastable polymorph but its conversion to Form A is kinetically slower than Form G. The conversion was the slowest in water partly due to low solubility.

[00448] Table 14. Single form slurry experiment of Forms A, D and G

Parent Materials	Weight (mg)	Solvent	Vol. (mL)	Tempt. (°C)	Aliquot time point		Aliquot time point	
					Day	XRPD	Day	XRPD
Form A	16.33	Water	1.0	RT	3	A	6	A
Form A	17.80	IPAc/Heptane (1:2 V/V)	1.0	RT	3	A	6	A

Form A	16.28	Toluene	1.0	RT	3	A	6	A
Form D	10.01	Water	1.0	RT	3	D	6	A + D
Form D	11.70	IPAc/Heptane (1:2 V/V)	1.0	RT	3	A + D	6	A
Form D	10.90	Toluene	1.0	RT	3	A + D	6	A
Form G	27.01	Water	1.0	RT	3	A	6	A
Form G	21.32	IPAc/Heptane (1:2 V/V)	1.0	RT	3	A	6	A
Form G	21.29	Toluene	1.0	RT	3	A	6	A

[00449] Approximately 10 - 20 mg of Forms A, D and G were weighed into 8 mL clear vials equipped with magnetic stir bars (Table 14). Water, IPAc/Heptane (1:2 V/V) and toluene were used as the solvent systems for these competitive slurry experiments. Three selected solvents, 1.0 mL, were added to achieve free-flowing slurry and allowed to equilibrate at room temperature. All slurries will be isolated via centrifuge filtration after three day and six days of equilibration.

[00450] Thermal stability experiments of Forms A, D and G were conducted and summarized in Table 15.

[00451] Table 15. Thermal Stability Experiments

Parent Material	Weight (mg)	Tempt. (°C)	Aliquot time point		Aliquot time point		Parent Material HPLC (%AUC)	HPLC (%AUC)
			Day	XRPD	Day	XRPD		
Form A	27.0	60.0	1	A	7	A	>99.9	>99.9
Form D	26.5	60.0	1	D	7	D	>99.9	>99.9
Form G	27.3	60.0	1	A + G	7	A	>99.3	>99.9

6.1.6 **Aqueous Solubility**

[00452] Approximately 14 - 25 mg of Forms A, D and G were transferred to 20 mL vials equipped with magnetic stir bars. 1.0 mL of deionized water was added and the resulting free flowing slurry was allowed to equilibrate over 1 and 7 days period with stirring at room temperature. The slurries were filtered through 0.45 micron centrifuge filters and the resulting solids analyzed by XRPD (Table 16). The filtrates were analyzed by HPLC to determine solubility.

[00453] Table 16. Aqueous solubility of Forms A, D and G

Initial form	Mass (mg)	DI H_2O vol. (mL)	Condition	Solid form by XRPD after 1 day	Solid form by XRPD after 7 day	Solubility (mg/mL)
A	25.93	1.0	free flowing slurry was allowed to equilibrate with stirring at room temperature	A	A	(0.0026)*
D	13.88	1.0		A	A	(0.49)*
G	21.94	1.0		A	A	0.061

*Extrapolated values based on the standard curve (0.008 – 0.2 mg/mL).

6.2 **Instrumentation**

[00454] The vendor and model information of the instruments used for analysis are provided below in Table 17.

[00455] Table 17. Instrument vendors and models

Instrument	**Vendor/Model #**
Differential Scanning Calorimeter	Mettler DSC1
Thermal Gravimetric Analyzer	Mettler 851^e TGA
X-Ray Powder Diffractometer	CubiX-Pro
Nuclear Magnetic Resonance Spectrometer	Bruker 500 MHz AVANCE

6.2.1 **Differential Scanning Calorimetry (DSC)**

[00456] DSC analysis was performed on the sample "as is." Sample was weighed in an aluminum pan, covered with a pierced lid, and then crimped and analyzed from 30-230 °C at 10 °C/min.

6.2.2 **Thermal Gravimetric Analysis (TGA)**

[00457] TGA was carried out on the sample "as is." Sample was weighed in an alumina crucible and analyzed from 30-300 °C at 10 °C/min.

6.2.3 **X-Ray Powder Diffraction**

[00458] Samples were analyzed "as is." Sample was placed on Si zero-return ultra-micro sample holders. Analysis was performed using a 10 mm irradiated width and the following parameters were set within the hardware/software:

[00459]	X-ray tube:	Cu Kα, 45 kV, 40 mA
[00460]	Detector:	X'Celerator
[00461]	ASS Primary Slit:	Fixed 1°
[00462]	Divergence Slit (Prog):	Automatic - 5 mm irradiated length
[00463]	Soller Slits:	0.02 radian
[00464]	Scatter Slit (PASS):	Automatic - 5 mm observed length
[00465]	Scan Range:	3.0-45.0°
[00466]	Scan Mode:	Continuous
[00467]	Step Size:	0.02°
[00468]	Time per Step:	10 s
[00469]	Active Length:	2.54°

[00470] Following analysis the data was converted from adjustable to fixed slits using the X'Pert HighScore Plus software with the following parameters:

[00471] Fixed Divergence Slit Size: 1.00°, 1.59 mm

6.2.4 **Nuclear Magnetic Resonance**

[00472] Samples were dissolved in DMSO-*d*6 with 0.05% tetramethylsilane (TMS) for internal reference. ^{1}H-NMR spectra were acquired at 500 MHz using 5 mm broadband (1H-X) Z gradient probe. A 30 degree pulse with 20 ppm spectral width, 1.0 s repetition rate, and 64 transients were utilized in acquiring the spectra.

[00473] Weight percent purity determination by ^{1}H NMR using 1,4 Dimethoxybenzene in DMSO-d6 with 0.05% tetramethylsilane (TMS). Sample preparation, ^{1}H-NMR spectra acquiring and sample purity was calculated accordingly.

6.2.5 **Dynamic Vapour Sorption (DVS)**

[00474] Dynamic vapour sorption experiment was carried out by first holding the sample at 40% RH and 25.0 °C until an equilibrium weight was reached or for a maximum of four hours. The sample was then subjected to an isothermal (at 25.0 °C) adsorption scan from 40 to 90% RH in steps of 10%. The sample was allowed to equilibrate to an asymptotic weight at each point for a maximum of four hours. Following adsorption, a desorption scan from 85 to 5% RH (at 25.0 °C) was run in steps of 10% again allowing a maximum of four hours for equilibration to an asymptotic weight. An adsorption scan was then performed from 0 to 40% RH in steps of 10%. The sample was then dried for no less than two hours at 60.0 °C and the resulting solid analyzed by XRPD.

6.2.6 **HPLC**

[00475] HPLC conditions are listed in Table 18.

[00476] Table 18. HPLC conditions

System:	Agilent 1100 Series HPLC
Column:	Agilent Zorbax SB-C18, (SN: USEG012031) 4.6 mm × 150 mm, 3.5 µm
Column Temperature:	30.0 °C
Auto Sampler Temp:	Ambient
Flow Rate:	1.0 mL/min.
Injection Volume:	15.0 µL
Run Time:	40 minutes

Detection:	263 nm
Sample Preparation:	*Standard reference:* 1.0 mg/mL Dissolved 2.333 mg of Compound 1 in 2.333 mL of diluent and stirred at 25.0 °C for 10 minutes *API aqueous solubility samples*: Filtrates from aqueous solubility experiments *Thermal Stability Experiments:* API weight (mg) Diluent volume (mL) Compound 1, Form A 3.284 3.284 Compound 1, Form D 3.549 3.549 Compound 1, Form G 2.586 2.586 Dissolved polymorphs in diluent and stirred at 25.0 °C for 10 minutes
Mobile Phases:	A – 0.1% TEA and TFA in H_2O, adjusted pH to 1.3 using HCl solution
	B – 100% ACN
Diluent:	50:50 (V/V) ACN : H_2O

6.2.7 **Characterization of Compound 1 Polymorphs**

[00477] All unique XRPD forms of Compound 1 were characterized to evaluate their physical form and stability. Table 19 summarizes the characterization results for each polymorph of Compound 1. A stackplot of representative XRPD Patterns of Forms A, B, C, D, E, F, G and H is shown in Figure 1. X-ray powder diffraction pattern and peak list of each unique polymorph are shown in Figure 2-Figure 9.

[00478] Table 19. Summary of Compound 1 Polymorphs.

Solid form	DSC (°C)	TGA (Weight loss)	NMR	Moisture Sorption	Comments
A	Endotherm at 186.0	onset of decomposition at 249.2 °C	No detectable solvent, no degradation	60% RH: 0% 90% RH: 6.1 wt%	Anhydrate

B	Endotherm at 141.5, 185.2 Exotherm at 146.9	0.64% @ 135-155 °C, onset decomposition at 258.0 °C	No degradation, 0.48 wt% MEK	N/A	Metastable anhydrate (or possible inclusion complex)
C	Endotherm at 63.5, 77.6, 134.9, 185.8 Exotherm at 143.0	1.08% @ 120-150 °C, onset decomposition at 269.1 °C	Additional NMR peaks 1.98 wt% EtOH	N/A	Metastable anhydrate (or possible inclusion complex)
D	Endotherm at 185.2 Exotherm at 118.7	onset of decomposition at 259.8 °C	No detectable solvent, no degradation	60% RH: 0.7% 90% RH: 1.0 wt%	Metastable anhydrate
E	Endotherm at 154.8, 185.6 Exotherm at 156.7	1.96% @ 130-165 °C, onset decomposition at 261.6 °C	1.66 wt% EtOAc, no degradation	N/A	Metastable anhydrate (or possible inclusion complex)
F	Endotherm at 64.1, 91.3, 185.9	1.86% @ 50-110 °C, onset decomposition at 268.3 °C	No detectable solvent, no degradation	N/A	metastable hydrate
G	Endotherm at 90.5, 184.9	onset of decomposition at 263.5 °C	No detectable solvent, no degradation	60% RH: 0.4% 90% RH: 7.1 wt%	metastable anhydrate
H	Endotherm at 88.0	6.4% @ 70-140 °C, 9.8% @ 145-240 °C, onset decomposition at 268.1 °C	18.9 wt% DMSO, no degradation	N/A	mono-DMSO solvate

6.2.8 **Form A of Compound 1**

[00479] Form A was harvested from the binary solvent recrystallization experiment using acetone as primary solvent and water as co-solvent (Table 3 and Table 4). Form A was also isolated in other single solvent and binary solvents recrystallization experiments in multiple solvent systems (Table 1-Table 10). The ^{1}H NMR (d_6-DMSO) spectrum of Form A is provided in Figure 10. Thermal analysis by DSC showed a single endothermic transition at 186.0 °C (Figure 11). Further analysis by TGA indicated no weight loss before the onset of decomposition at 249.2 °C (Figure 12). The material adsorbed 0 wt% moisture at 60% RH and 6.1 wt% moisture at 90% RH (Figure 13). Although the material is moderately hygroscopic, no deliquescence was observed. The XRPD analysis of the post-DVS material after drying at 60 °C for 2 hours, recorded an XRPD pattern consistent with the starting material (Figure 14). Aqueous solubility of Form A was determined to be 0.0026 mg/mL, which is extrapolated value based on the standard curve (Table 16).

[00480] In the single form and competitive slurry experiments, Form A was found to be the most stable polymorph at ambient temperature under all tested conditions. In addition, DSC did not show any noticeable endothermic event prior to 186 °C and TGA did not show any weight loss at low temperature range (< 100.0 °C). No chemical and physical form changes were observed for Form A after storing the material at 60 °C for seven days (Table 15).

[00481] Characterization results of Form A are consistent with a stable anhydrate polymorph.

[00482] Figure 2 provides an XRPD pattern of Form A. A list of X-Ray Diffraction Peaks for Form A is provided below in Table 20.

[00483] Table 20. X-Ray Diffraction Peaks for Form A

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.73	23.68	0.99
3.86	22.92	1.14
4.24	20.86	2.46
4.39	20.13	1.24
5.46	16.19	1.25
5.58	15.85	0.78
5.77	15.31	1.04
6.01	14.70	1.21
6.49	13.61	11.74
6.86	12.89	0.62
7.27	12.16	0.63
7.40	11.94	0.26
7.83	11.29	0.77
8.13	10.88	0.98

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
8.56	10.34	0.85
8.67	10.20	0.57
8.80	10.05	0.44
8.93	9.91	1.18
9.91	8.92	1.34
10.09	8.76	0.79
10.23	8.65	0.01
10.41	8.50	0.17
11.07	7.99	1.37
12.14	7.29	58.99
13.05	6.78	33.11
14.45	6.13	17.61
15.67	5.66	0.64
16.20	5.47	4.48
16.60	5.34	19.83
17.21	5.15	4.65
17.70	5.01	2
18.71	4.74	15.15
19.19	4.63	12.76
19.59	4.53	19
20.08	4.42	28.19
20.54	4.33	9.63
21.60	4.11	1.1
22.15	4.01	2.09
22.97	3.87	84.6
23.34	3.81	15.95
24.37	3.65	1.22
25.02	3.56	6.03
25.55	3.49	0.72
25.93	3.44	1.66
26.92	3.31	100
27.55	3.24	1.69
29.20	3.06	10.29
29.70	3.01	3.15
30.10	2.97	1.34
31.68	2.82	11.82
32.13	2.79	8.52
32.59	2.75	16.15
33.00	2.71	2.88
33.77	2.65	1.79
34.18	2.62	0.43

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
34.67	2.59	0.64
35.19	2.55	3.41
35.88	2.50	1.01
36.40	2.47	0.33
36.99	2.43	1.57
37.46	2.40	1.86
38.08	2.36	0.68
39.74	2.27	0.84
40.38	2.23	0.39
40.96	2.20	0.79
41.76	2.16	1.44
42.12	2.15	1.48
42.45	2.13	0.83
43.26	2.09	0.54
43.87	2.06	1.84
44.52	2.03	0.81

6.2.9 **Form B of Compound 1**

[00484] Form B was prepared in the binary solvent recrystallization experiment using MEK as primary solvent and water as co-solvent, (Table 3 and Table 4). Form B was also isolated in other single solvent and binary solvents recrystallization experiments in multiple solvent systems (Table 1-Table 4). An estimated 0.48 wt% of MEK and no degradation were observed by ^{1}H NMR (d_6-DMSO) (Figure 15). DSC analysis presented two endotherms at 141.5 and 185.2 °C, and an exotherm at 146.9 °C (Figure 16). TGA analysis indicated a weight loss of 0.64%, attributed to loss of MEK, before 155 °C and onset decomposition at 258.0 °C (Figure 17). In the competitive slurry experiment, Form B converted to Form A (Table 13).

[00485] Characterization results of Form B are mostly consistent with a metastable anhydrate polymorph retaining residual solvent. The residual solvents was not released until melt and Form B showed similarity to several other forms (i.e., Forms C, D and E), indicating that Form B might be an inclusion complex in which non-stoichiometry amount of solvent was retained and caused minor changes in crystal lattice.

[00486] Figure 3 provides an XRPD pattern of Form B. A list of X-Ray Diffraction Peaks for Form B is provided below in Table 21.

[00487] Table 21. X-Ray Diffraction Peaks for Form B

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
4.34	20.37	82.64
7.46	11.86	17.24
8.61	10.27	100
11.37	7.78	12.06
12.90	6.86	19.52
14.89	5.95	34.65
15.50	5.72	78.65
18.76	4.73	28.42
19.71	4.50	10.4
21.52	4.13	11.25
22.15	4.01	4.18
22.81	3.90	13.48
23.03	3.86	8.41
23.77	3.74	19.1
24.60	3.62	6.72
25.29	3.52	22.84
25.73	3.46	5.58
26.23	3.40	7.14
26.76	3.33	10.88
27.49	3.24	3.85
28.17	3.17	18.3
30.10	2.97	7.77
31.76	2.82	6.67
32.57	2.75	5.14
34.34	2.61	1.74
35.94	2.50	2.24
37.74	2.38	1.68
38.63	2.33	1.36
39.27	2.29	2.07
41.75	2.16	1.36
42.20	2.14	0.81
44.45	2.04	0.87

6.2.10 **Form C of Compound 1**

[00488] Form C was prepared in the binary solvent recrystallization experiment using EtOH as primary solvent and cyclohexane as co-solvent (Table 9 and Table 10). Form C was also isolated in other single solvent and binary solvents recrystallization experiments usually

when EtOH and IPAc were used (Table 1-Table 10). An estimated 1.98 wt% of EtOH and additional peaks were observed by ^{1}H NMR (d_6-DMSO) (Figure 18). Additional peaks indicated by asterisk in Figure 18 were noted in the ^{1}H NMR. These resonances are likely attributed to a degradation product due to esterification of the carboxylic acid group. Therefore, alcoholic solvents may present the risk of degradation through ester formation. DSC analysis presented four endotherms at 63.5, 77.6, 134.9 and 185.8 °C, and an exotherm at 143.0 °C (Figure 19). TGA analysis indicated a weight loss of 1.08%, attributed to loss of EtOH, before 150.0 °C and onset decomposition at 269.1 °C (Figure 20). In the competitive slurry experiment, Form C converted to Form A (Table 13).

[00489] Characterization results of Form C are mostly consistent with a metastable anhydrate polymorph retaining residual solvent. The residual solvents was not released until melt and Form C showed similarity to several other forms (i.e., Forms B, D and E), indicating that Form C might be an inclusion complex in which non-stoichiometry amount of solvent was retained and caused minor changes in crystal lattice.

[00490] Figure 4 provides an XRPD pattern of Form C. A list of X-Ray Diffraction Peaks for Form C is provided below in Table 22.

[00491] Table 22. X-Ray Diffraction Peaks for Form C

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.09	28.62	5.24
4.35	20.32	100
7.46	11.85	8.25
8.63	10.25	76.25
11.41	7.76	15.09
12.93	6.85	10.8
14.94	5.93	23.35
15.55	5.70	62.12
18.80	4.72	19.03
19.78	4.49	8.2
21.60	4.11	11.12
22.51	3.95	2.83
22.89	3.89	8.58
23.31	3.82	5.08
24.10	3.69	1.43
24.87	3.58	6.48

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
25.25	3.53	1.75
26.34	3.38	10.28
27.07	3.29	4.33
27.77	3.21	7.03
28.10	3.18	1.59
28.45	3.14	5.36
29.09	3.07	0.87
29.43	3.04	1.09
29.75	3.00	3.84
30.37	2.94	1.5
30.73	2.91	0.36
31.77	2.82	2.07
32.24	2.78	1.97
32.86	2.73	0.55
34.02	2.64	1.66
35.67	2.52	1.44
37.86	2.38	0.98
38.39	2.34	0.8
39.35	2.29	1.72
41.85	2.16	1.01
42.35	2.13	0.61
43.28	2.09	0.68
43.74	2.07	0.55
44.24	2.05	0.73

6.2.11 **Form D of Compound 1**

[00492] Form D was prepared in the binary solvent recrystallization experiment using THF as primary solvent and toluene as co-solvent (Table 5 and Table 6). Form D was also isolated in other single solvent and binary solvents recrystallization experiments in multiple solvent systems (Table 1-Table 10). No detectable solvent or degradation was observed by ^{1}H NMR (d_6-DMSO) (Figure 21). DSC analysis presented an endotherm at 185.2 °C, and an exotherm at 118.7 °C (Figure 22). Further analysis by TGA indicated no weight loss before the onset of decomposition at 259.8 °C (Figure 23). The material adsorbed 0.7 wt% moisture at 60% RH and 1.0 wt% moisture at 90% RH (Figure 24). This material is considered slightly hygroscopic. The XRPD analysis of the post-DVS material, after drying at 60 °C for 2 hours, recorded an XRPD pattern consistent with the starting material (Figure 25). Once formed, Form

D maintained its chemical and physical form even after storing the material at 60 °C for seven days (Table 15). Aqueous solubility of Form D was not achieved because Form D converted to Form A in aqueous equilibrium (Table 16). The obtained solubility of 0.49 mg/mL represents solubility of Form A. The discrepancy compared to the Form A solubility value described in Table 16 (0.0026 mg/mL) was possibly due to insufficient equilibrium or different residual solvent/impurity profile. In the single form and competitive slurry experiments, Form D converted to Form A at ambient temperature under all tested conditions.

[00493] Characterization results of Form D are mostly consistent with metastable anhydrate polymorph.

[00494] Figure 5 provides an XRPD pattern of Form D. A list of X-Ray Diffraction Peaks for Form D is provided below in Table 23.

[00495] Table 23. X-Ray Diffraction Peaks for Form D

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
4.32	20.45	92.9
7.44	11.88	17.03
8.59	10.30	100
11.31	7.82	13.88
12.85	6.89	17.13
14.85	5.96	34.18
15.49	5.72	68.51
18.72	4.74	27.1
19.71	4.50	10.18
21.51	4.13	10.6
22.40	3.97	3.16
22.75	3.91	13.28
23.62	3.77	7.61
24.48	3.64	1.81
25.17	3.54	11.43
26.19	3.40	6.39
26.68	3.34	6.01
26.96	3.31	2.19
27.32	3.27	1.33
27.98	3.19	9.25
28.35	3.15	8.91
29.34	3.04	1.4
29.98	2.98	5.45

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
30.30	2.95	2.44
32.44	2.76	3.55
34.07	2.63	0.75
35.81	2.51	1.34
37.16	2.42	1.12
37.69	2.39	2.33
38.44	2.34	1.07
39.25	2.30	2.46
41.71	2.17	1.41
42.19	2.14	0.91
44.35	2.04	0.88

6.2.12 **Form E of Compound 1**

[00496] Form E was prepared in the binary solvent recrystallization experiment using EtOAc as primary solvent and toluene as co-solvent (Table 5 and Table 6). Form E was also isolated in other single solvent and binary solvents recrystallization experiments in multiple solvent systems (Table 1-Table 10). An estimated 1.66 wt% of EtOAc and no degradation were observed by ^{1}H NMR (d_6-DMSO) (Figure 26). DSC analysis presented two endotherms at 154.8 and 185.6 °C, and an exotherm at 156.7 °C (Figure 27). Further analysis by TGA indicated a weight loss of 1.96%, attributed to loss of EtOAc, before 165.0 °C and onset of decomposition at 261.6 °C (Figure 28). In the competitive slurry experiment, Form E converted to Form A (Table 13).

[00497] Characterization results of Form E are mostly consistent with a metastable anhydrate polymorph retaining residual solvent. The residual solvents was not released until melt and Form E showed similarity to several other forms (i.e., Forms B, C and D), indicating that Form E might be an inclusion complex in which non-stoichiometry amount of solvent was retained and caused minor changes in crystal lattice.

[00498] Figure 6 provides an XRPD pattern of Form E. A list of X-Ray Diffraction Peaks for Form E is provided below in Table 24.

[00499] Table 24. X-Ray Diffraction Peaks for Form E

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
4.33	20.40	100
4.66	18.96	1.11
5.42	16.31	0.89
5.73	15.43	0.2
5.99	14.76	0.67
6.16	14.36	0.78
6.29	14.06	0.27
6.50	13.59	0.76
7.46	11.85	11.12
8.61	10.27	90.7
9.32	9.49	1.07
10.07	8.78	0.37
10.78	8.21	0.49
10.93	8.09	0.33
11.37	7.78	14.51
12.17	7.27	0.99
12.89	6.87	13.92
13.45	6.58	0.54
14.45	6.13	0.44
14.89	5.95	27.33
15.50	5.72	66.57
16.66	5.32	0.78
18.74	4.74	22.56
19.73	4.50	9.11
20.04	4.43	0.58
20.56	4.32	0.47
21.53	4.13	11.42
21.80	4.08	3.21
22.19	4.01	2.72
22.57	3.94	5.03
22.81	3.90	13.03
23.45	3.79	14.55
23.87	3.73	1.37
24.23	3.67	4.18
24.97	3.57	18.47
25.35	3.51	4.98
26.24	3.40	8.36
26.47	3.37	8.99
26.96	3.31	4.6
27.24	3.27	2.52

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
27.85	3.20	15.23
28.36	3.15	7.68
29.19	3.06	2.43
29.57	3.02	2.49
29.85	2.99	6.95
30.30	2.95	2.02
30.81	2.90	1.47
31.25	2.86	0.42
32.34	2.77	4.49
32.93	2.72	0.8
34.10	2.63	1.64
34.77	2.58	0.22
35.74	2.51	2.35
36.36	2.47	0.37
37.23	2.41	0.48
37.71	2.39	1.97
38.36	2.35	1.17
39.28	2.29	2.17
40.74	2.21	0.39
41.66	2.17	1.45
42.19	2.14	0.82
42.61	2.12	0.43
43.29	2.09	0.4
43.71	2.07	0.63
44.18	2.05	1.05

6.2.13 **Form F of Compound 1**

[00500] Form F was prepared in binary solvent crystallization using water as an anti-solvent (Table 3 and Table 4). Form F was not isolated from single solvent and binary solvent crystallization experiments but a mixture of Forms F and B, or D, or E, or G was encountered in binary solvent crystallization. The ^{1}H NMR (DMSO-d_6) spectrum was consistent with the structure of Compound 1 with no significant residual solvent (Figure 29). DSC analysis presented three endotherms at 64.1, 91.3 and 185.9 °C (Figure 30). Further analysis by TGA indicated a weight loss of 1.86% before 110.0 °C and onset of decomposition at 268.3 °C (Figure 31). In the competitive slurry experiment, Form F converted to Form A (Table 13).

[00501] Characterization results of Form F are mostly consistent with a metastable hydrate polymorph.

[00502] Figure 7 provides an XRPD pattern of Form F. A list of X-Ray Diffraction Peaks for Form F is provided below in Table 25.

[00503] Table 25. X-Ray Diffraction Peaks for Form F

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.99	22.15	100
4.23	20.91	42.6
7.89	11.20	35.92
8.36	10.58	30.55
11.81	7.50	19.52
15.21	5.82	37.6
15.44	5.74	33.4
17.39	5.10	10.19
17.79	4.99	12.96
19.78	4.49	13.97
20.87	4.26	22.28
22.98	3.87	12.77
23.83	3.73	11.45
25.17	3.54	20.19
26.10	3.41	12.71
27.15	3.28	8.58
28.53	3.13	10.53
30.30	2.95	5.79
31.71	2.82	12.17
34.06	2.63	1.29

6.2.14 **Form G of Compound 1**

[00504] Form G was prepared in the binary solvent recrystallization experiment using IPA as primary solvent and water as co-solvent (Table 3 and Table 4). Form G showed a high degree of similarity to Form F (Figure 1). No detectable solvent or degradation was observed by ^{1}H NMR (d_6-DMSO) (Figure 32). DSC analysis presented two endotherms at 90.5 and 184.9 °C (Figure 33). Analysis by TGA indicated no weight loss before the onset of decomposition at 263.5 °C (Figure 34). The material adsorbed 0.4 wt% moisture at 60% RH and 7.1 wt% moisture at 90% RH (Figure 35). This material is considered as moderately hygroscopic. The

XRPD analysis of the post-DVS material after drying at 60 °C for 2 hours, afforded Form A (Figure 36). Since no apparent hysteresis was observed on DVS, Form G is not a hydrate form. Because it converted to Form A after the DVS experiment and drying, it is likely a metastable anhydrate polymorph. Aqueous slurry experiment also supported that Form G is not a hydrate form because Form G converted to Form A after one day in water (Table 12). When storing Form G at 60 °C for 24 hours a form mixture was observed at day 1, and at day 7 only Form A was obtained (Table 15). Aqueous solubility of Form G was not achieved because Form G converted to Form A in aqueous equilibrium (Table 16). The obtained solubility of 0.061 mg/mL represents solubility of Form A. The discrepancy compared to the Form A solubility value described in Table 16 (0.0026 mg/mL) was possibly due to insufficient equilibrium or different residual solvent/impurity profile. In the single form and competitive slurry experiments, Form G converted to Form A at ambient temperature under all tested conditions.

[00505] Characterization results of Form G are mostly consistent with a metastable anhydrate polymorph.

[00506] Figure 8 provides an XRPD pattern of Form G. A list of X-Ray Diffraction Peaks for Form G is provided below in Table 26.

[00507] Table 26. X-Ray Diffraction Peaks for Form G

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
4.19	21.07	100
8.33	10.61	80.94
12.47	7.10	11.24
15.19	5.83	36.87
15.44	5.74	22.1
16.67	5.32	4.11
17.81	4.98	24.01
19.26	4.61	1.69
20.87	4.26	34.66
21.33	4.17	4.01
22.18	4.01	5.07
22.86	3.89	7.24
23.71	3.75	4.57
24.59	3.62	3.4
25.09	3.55	9.73
25.89	3.44	4.8

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
27.00	3.30	19.8
28.36	3.15	20.89
28.63	3.12	16.14
29.87	2.99	2.25
32.45	2.76	1.52
34.70	2.59	1.57
39.53	2.28	1.34
42.08	2.15	1.27

6.2.15 **Form H of Compound 1**

[00508] Form H was prepared in the binary solvent recrystallization experiment using DMSO as primary solvent and toluene as co-solvent (Table 5 and Table 6). Form H was isolated from conditions where DMSO was used. An estimated 18.9 wt% of DMSO and no degradation were observed by ^{1}H NMR (MeOD) (Figure 37). DSC analysis presented an endotherm at 88.0 °C (Figure 38). Analysis by TGA indicated two weight losses of 6.4% before 140 °C and 9.8% before 240 °C, and the onset of decomposition at 268.1 °C (Figure 39).

[00509] Based on characterization results, Form H is consistent with a mono-DMSO solvate polymorph.

[00510] Figure 9 provides an XRPD pattern of Form H. A list of X-Ray Diffraction Peaks for Form H is provided below in Table 27.

[00511] Table 27. X-Ray Diffraction Peaks for Form H

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.07	28.81	20.05
5.35	16.53	12.44
8.56	10.33	2.24
10.69	8.28	18.25
12.20	7.26	6.45
12.62	7.01	21.51
13.08	6.77	5.27
13.32	6.65	10.86
14.08	6.29	100
15.46	5.73	3.68

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
16.04	5.53	2.76
17.18	5.16	29.96
17.69	5.01	4.89
17.93	4.95	15.41
18.76	4.73	44.25
19.69	4.51	17.85
20.14	4.41	2.51
21.19	4.19	10.15
21.40	4.15	72.29
22.22	4.00	3.08
22.99	3.87	6.26
24.02	3.70	5.81
24.59	3.62	31.18
25.18	3.54	18.49
25.75	3.46	29.33
26.55	3.36	7.81
26.93	3.31	8.85
27.53	3.24	17.48
28.32	3.15	2.33
29.07	3.07	1.97
31.19	2.87	1.53
31.72	2.82	6.13
32.05	2.79	6.34
33.70	2.66	1.26
35.09	2.56	3.94
35.76	2.51	6.55
37.23	2.42	2.48
37.94	2.37	1.06
38.67	2.33	2.67
39.26	2.29	1.16
39.96	2.26	0.82
40.36	2.23	1.88
43.14	2.10	0.79
44.56	2.03	3.62

6.2.16 **Conclusion**

[00512] During the polymorph study, eight unique polymorphs (Forms A, B, C, D, E, F, G and H) were observed. Form A is characterized as a moderately hygroscopic, anhydrate polymorph and was determined to be the most stable polymorph from slurry experiments, thermal stability and aqueous solubility. Forms B, C, D and E shared many common XRPD diffraction peaks between 15 and 30 °2θ. The small variation in diffraction patterns is probably due to minor changes in crystal lattice due to presence of variable amount of residual solvents. Forms F and G also shared some similarity. Based on NMR and TGA analysis, Forms D and G are likely metastable anhydrate polymorphs. Form H was found to be a DMSO solvate. All the polymorphs converted to Form A in competitive and single form slurry experiments. All four polymorphs showed similar endotherm/exotherm at low temperature, attributed to a melt/recrystallization event, followed by an endothermic event at ~150.0 °C in the DSC analysis. Forms A, D and G were found to be chemically stable over storage as solid at 60 °C for 7 days. However, potential ester degradation product was detected in the solid isolated from EtOH, indicating that alcoholic solvents should be avoided to reduce the potential risk of degradation.

6.3 POLYMORPH CONVERSION

[00513] The conversion of Form G to Form A was conducted initially on a 2.0 g scale of Compound 1 in seven volumes of 33% acetone in water (2.3 vol of acetone and 4.7 vol of water) with 5.4% w/w of form A seeds of Compound 1. The desired Form A of Compound 1 was recovered in 97% yield. Following this successful trial experiment, a 72.4 g conversion of Form G to Form A was completed in seven volumes of 33% acetone in water and seeding with 2.3% w/w of Form A. The scale up experiment yielded 73.9 g in 97% yield (including added seeds) of Form A.

6.3.1 2.0 g Trial Experiment

[00514] To a 25-mL, three-neck, round-bottom flask equipped with an overhead stirrer were charged Form G of Compound 1 (2.0 g, 6.9 mmol), acetone (4.6 mL, 2.3 vol), and H_2O (9.4 mL, 4.7 vol) at 18 °C (room temperature). The slurry was stirred for 10 min at which Form A seeds (0.107 g, 5.4% w/w, lot # 1150-041) were added. After 24 h of stirring at 17–18 °C, the mixture was filtered in a Buchner funnel and washed with H_2O (4 mL, 2 vol). The wet cake was dried in vacuum oven at 20–25 °C for 16 h to afford 1.90 g of Form A of Compound 1 in 97% yield as a white solid.

6.3.2 **74.2 g Scale Up Experiment**

[00515] To a 1-L, three-neck, round-bottom flask equipped with an overhead stirrer were charged Form G of Compound 1 (74.2 g, 0.26 mol), acetone (171 mL, 2.3 vol), and H_2O (349 mL, 4.7 vol) at 18–20 °C (room temperature). The slurry was stirred for 10 min at which Form A seeds (1.71 g, 2.3% w/w) were added. After 28 h of stirring at 18–20 °C, the mixture was filtered in a Buchner funnel and washed with H_2O (140 mL, 2 vol). The wet cake was dried in vacuum oven at 20–25 °C for 42 h to afford 73.9 g of Form A in 97% yield as a white solid.

6.4 **SUMMARY OF SALT SCREEN OF COMPOUND 1**

[00516] Following counterions were selected for initial salt formation experiments, based on the pKa of Compound 1 and safety/acceptance in pharmaceutical drug products: Calcium acetate, choline hydroxide, potassium hydroxide, sodium hydroxide, arginine, meglumine, magnesium hydroxide and calcium hydroxide. Solids isolated from the salt formation experiments were characterized. Based on the salt stoichiometry and preliminary stability evaluation by thermal analysis and competitive slurry, five salts (Salt I, Salt II, Salt III, Salt IV and Salt V) were selected for scale up and full characterization. Salt I and Salt II provided poor aqueous solubility at 0.01 mg/mL and 0.03 mg/mL, respectively. All sodium and potassium salts (Salt III, Salt IV and Salt V) showed good solubility (>19 mg/mL). The five salts all had endothermic events at low temperature. Salt II, Salt IV and Salt V exhibited 5-10% weight loss which started below 100 °C. DVS of Salt IV showed that it is a stable hydrate throughout humidity range at 25 °C. Therefore Salt IV has good solubility and relative stability. Although some endothermic events were observed, Salt III also showed good stability. From thermal holding experiment, Salt VI was discovered. Salt VI was found to be an anhydrate form and only slightly hygroscopic. This form showed more favorable physical property than Salt IV. However, preparation of Salt VI involved thermal holding at 260 °C.

6.4.1 **Salt Formation on 30 mg Scale**

[00517] Approximately 30 mg of Compound 1 was weight into 4 mL glass vials equipped with stir bar. Solvent (1.0 or 2.0 mL) was added and the mixture was heated to elevated temperatures 50 °C, and then the acetone and MeCN solution was polish filtered through a 0.45 µm syringe filter into a clean preheated vial. After hot filtration, basic counterion solution was added drop-wise as summarized in Table 28 and the resulting mixture was cooled to RT at 20 °C/h. The vial was inspected for precipitation. If no precipitation or very little precipitation was discovered, the content was evaporated under nitrogen. All precipitates were isolated by filtration.

[00518] Table 28. Counterion lists

Name	M.W.	Solvent	Safety Class
Calcium acetate hydrate	176.18	Water	1
Choline hydroxide	121.18	Water	1
Potassium hydroxide	56.11	Water/MeOH	1
Sodium hydroxide in	40	Water/MeOH or Water	1
l-Arginine	174.2	Water	1
n-methyl-d-glucamine (meglumine)	195.21	Water/MeOH	1
Magnesium nitrate+Sodium hydroxide	256.41	Water	1
Calcium nitrate+ Sodium hydroxide	236.15	Water	1

[00519] The details of 30 mg scale salt formation experiments are summarized in Table 29, Table 30, Table 31, Table 32, Table 33 and Table 34. The reaction was performed at elevated temperature and filtered to ensure complete dissolution of the free acid. If precipitation did not occur instantaneously, crystallization of the potential salts was attempted by cooling or evaporation crystallization. The majority of experiments afforded solids isolable by filtration. The solids from filtration or evaporation were analyzed by XRPD for crystallinity and form. Salt stoichiometry was examined by NMR or IC. The results are summarized in Table 35.

[00520] Table 29. Salt formation experiments (1:1 equiv.) part 1

SM (mg)	CI Solution	CI Actual Conc. (M)	CI Amt (mL)	After CI Addition	After Cooling	Isolation
32.5	Calcium acetate hydrate in water	0.25	0.41	ppt	ppt	Filtration, white solid

29.9	Choline hydroxide in water	0.5	0.21	Clear	Clear	Evaporation, gel solid
30.1	Potassium hydroxide in water	0.5	0.21	ppt	ppt	Filtration, white solid
29.7	Potassium hydroxide in MeOH	0.5	0.21	ppt	ppt	Filtration, white solid
29.8	Sodium hydroxide in water	0.5	0.21	Clear	ppt	Filtration, white solid
29.7	Sodium hydroxide in MeOH:water (3/2)	0.5	0.21	ppt	ppt	Filtration, white solid
29.3	l-Arginine in water	0.5	0.21	Clear	Clear	Evaporation, white solid
30	Meglumine in water	0.5	0.21	Clear	Clear	Evaporation, gel solid
30.2	Meglumine in MeOH:water (1/1)	0.5	0.21	Clear	ppt, small quant.	Evaporation, white solid
30.7	Magnesium itrate+Sodium hydroxide in water	0.5	0.21/0.21	ppt	ppt	Filtration, white solid
30.8	Calcium nitrate+ Sodium hydroxide in water	0.5	0.21/0.21	ppt	ppt	Filtration, white solid

[00521] Solvent=CH_3OH; Solvent Amount=1 mL; Temperature=50°C; Equivalent=1.

[00522] Table 30. Salt formation experiments (1:1 equiv.) part 2

SM (mg)	CI Solution	CI Actual Conc. (M)	CI Amt (mL)	After CI Addition	After Cooling	Isolation
30.5	Calcium acetate hydrate in water	0.25	0.41	ppt	ppt	Filtration, white solid
28.8	Choline hydroxide in water	0.5	0.21	ppt	ppt, small quant.	Evaporation, gel solid

30.6	Potassium hydroxide in water	0.5	0.21	Clear	ppt	Filtration, white solid
31	Potassium hydroxide in MeOH	0.5	0.21	ppt	ppt	Filtration, white solid
28.7	Sodium hydroxide in water	0.5	0.21	ppt	ppt	Filtration, white solid
30.7	Sodium hydroxide in MeOH:water (3/2)	0.5	0.21	ppt	ppt	Filtration, white solid
30.4	l-Arginine in water	0.5	0.21	ppt	ppt, small quant.	Filtration, not enough solid
31.3	Meglumine in water	0.5	0.21	Clear	Clear	Evaporation, gel solid
29.9	Meglumine in MeOH:water (1/1)	0.5	0.21	Clear	ppt	Filtration, white solid
31.7	Magnesium nitrate+Sodium hydroxide in water	0.5	0.21/0.21	ppt	ppt	Filtration, white solid
29.6	Calcium nitrate+ Sodium hydroxide in water	0.5	0.21/0.21	ppt	ppt	Filtration, white solid

[00523] Solvent= Acetone; Solvent Amount=1 mL; Temperature=50°C; Equivalent=1.

[00524] Table 31. Salt formation experiments (1:1 equiv.) part 3

SM (mg)	CI Solution	CI Actual Conc. (M)	CI Amt (mL)	After CI Addition	After Cooling	Isolation
31.1	Calcium acetate hydrate in water	0.25	0.41	ppt	ppt	Filtration, white solid
31	Choline hydroxide in water	0.5	0.21	ppt	ppt, small quant	Evaporation, gel solid
29.6	Potassium hydroxide in water	0.5	0.21	ppt	ppt	Filtration, white solid

31.3	Potassium hydroxide in MeOH	0.5	0.21	ppt	ppt	Filtration, white solid
30.7	Sodium hydroxide in water	0.5	0.21	ppt	ppt	Filtration, white solid
29.8	Sodium hydroxide in MeOH:water (3/2)	0.5	0.21	ppt	ppt	Filtration, white solid
30.8	l-Arginine in water	0.5	0.21	ppt	ppt, gel solid	Evaporation, white solid
30.6	Meglumine in water	0.5	0.21	ppt	ppt, gel solid	Evp, gel solid
31.4	Meglumine in MeOH:water (1/1)	0.5	0.21	ppt	ppt	Filtration, white solid
30.4	Magnesium nitrate+Sodium hydroxide in water	0.5	0.21/0.21	ppt	ppt	Filtration, white solid
30.1	Calcium nitrate+ Sodium hydroxide in water	0.5	0.21/0.21	ppt	ppt	Filtration, white solid

[00525] Solvent= CH_3CN; Solvent Amount=2 mL; Temperature=50°C; Equivalent=1.

[00526] Table 32. Salt formation experiments (2:1 or 1:2 equiv.) part 1

SM (mg)	**CI Solution**	**CI Actual Conc. (M)**	**Equiv.**	**CI Amt (mL)**	**After CI addition**	**After cooling**	**Isolation**
29.2	Calcium acetate hydrate in water	0.25	2.1	0.87	ppt	ppt	Filtration, white solid
32.3	Choline hydroxide in water	0.5		0.43	Clear	Clear	Evaporation, gel solid
31.3	Potassium hydroxide in water	0.5		0.43	Clear	Clear	Evaporation, yellow solid
33.0	Potassium hydroxide in MeOH	0.5		0.43	ppt	ppt	Filtration, white solid

29.9	Sodium hydroxide in water	0.5		0.43	ppt	ppt	Filtration, white solid
32.9	Sodium hydroxide in MeOH:water (3/2)	0.5		0.43	ppt	ppt	Filtration, white solid
30.6	l-Arginine in water	0.5		0.43	Clear	Clear	Evaporation, white solid
30.2	Meglumine in water	0.5		0.43	Clear	Clear	Evaporation, gel solid
32.2	Meglumine in MeOH:water (1/1)	0.5		0.43	Clear	Clear	Evaporation, gel solid
30.8	Magnesium nitrate+Sodium hydroxide in water	0.5		0.43/0.87	ppt	ppt	Filtration, white solid
31.5	Calcium nitrate+ Sodium hydroxide in water	0.5		0.43/0.87	ppt	ppt	Filtration, white solid
32.4	Calcium acetate hydrate in water	0.25	0.51	0.21	ppt	ppt	Filtration, white solid
30.7	Calcium nitrate+ Sodium hydroxide in water	0.5		0.11/0.21	ppt	ppt	Filtration, white solid

[00527] Solvent= CH_3OH; Solvent Amount=1 mL; Temperature=50°C

[00528] Table 33. Salt formation experiments (2:1 or 1:2 equiv.) part 2

SM (mg)	CI Solution	CI Actual Conc. (M)	Equiv.	CI Amt (mL)	After CI addition	After cooling	Isolation
30.3	Calcium acetate hydrate in water	0.25	2.1	0.87	ppt	ppt	Filtration, white solid
29.7	Choline hydroxide in water	0.5		0.43	Clear	Clear	Evaporation, gel solid

28.8	Potassium hydroxide in water	0.5		0.43	Clear	Clear	Evaporation, yellow solid
30.7	Potassium hydroxide in MeOH	0.5		0.43	ppt	ppt	Filtration, white solid
29.3	Sodium hydroxide in water	0.5		0.43	ppt	ppt	Filtration, white solid
31.4	Sodium hydroxide in MeOH:water (3/2)	0.5		0.43	ppt	ppt	Filtration, white solid
31.5	l-Arginine in water	0.5		0.43	Clear	Clear	Evaporation, white solid
28.8	Meglumine in water	0.5		0.43	Clear	Clear	Evaporation, gel solid
29.3	Meglumine in MeOH:water (1/1)	0.5		0.43	Clear	Clear	Evaporation, gel solid
29.3	Magnesium nitrate+Sodium hydroxide in water	0.5		0.43/0.87	ppt	ppt	Filtration, white solid
28.8	Calcium nitrate+ Sodium hydroxide in water	0.5		0.43/0.87	ppt	ppt	Filtration, white solid
31.3	Calcium acetate hydrate in water	0.25	0.51	0.21	ppt	ppt	Filtration, white solid
29.7	Calcium nitrate+ Sodium hydroxide in water	0.5		0.11/0.21	ppt	ppt	Filtration, white solid

[00529] Solvent= Acetone; Solvent Amount=1 mL; Temperature=50°C

[00530] Table 34. Salt formation experiments (2:1 or 1:2 equiv.) part 3

SM (mg)	CI Solution	CI Actual Conc. (M)	Equiv.	CI Amt (mL)	After CI addition	After cooling	Isolation

33.9	Calcium acetate hydrate in water	0.25		0.87	ppt	ppt	Filtration, white solid
32.5	Choline hydroxide in water	0.5		0.43	Clear	Clear	Evaporation, gel solid
30.1	Potassium hydroxide in water	0.5		0.43	Clear	Clear	Evaporation, yellow solid
31.1	Potassium hydroxide in MeOH	0.5		0.43	ppt	ppt	Filtration, white solid
30.4	Sodium hydroxide in water	0.5		0.43	ppt	ppt	Filtration, white solid
30.7	Sodium hydroxide in MeOH:water (3/2)	0.5	2.1	0.43	ppt	ppt	Filtration, white solid
30.5	l-Arginine in water	0.5		0.43	ppt	ppt	Evaporation, white solid
33.2	Meglumine in water	0.5		0.43	Clear	Clear	Evaporation, gel solid
29.7	Meglumine in MeOH:water (1/1)	0.5		0.43	ppt	ppt	Evaporation, white solid
32.4	Magnesium nitrate+Sodium hydroxide in water	0.5		0.43/0.87	ppt	ppt	Filtration, white solid
29.7	Calcium nitrate+ Sodium hydroxide in water	0.5		0.43/0.87	ppt	ppt	Filtration, white solid
29.5	Calcium acetate hydrate in water	0.25	0.51	0.21	ppt	ppt	Filtration, white solid
30.0	Calcium nitrate+ Sodium hydroxide in water	0.5		0.11/0.21	ppt	ppt	Filtration, white solid

[00531] Solvent= CH_3CN; Solvent Amount=2 mL; Temperature=50°C

[00532] Table 35. Salt formation experiments – characterization summary (1:1 equiv.)

Solvent	CI Solution (0.5 M unless specified)	XRPD	NMR	API: CI Ratio by IC
MeOH	calcium acetate in water	Salt I	No degradation	1:0.56
	calcium nitrate+ sodium hydroxide in water		No degradation	1:0.52
	calcium acetate hydrate in water		-	-
acetone	calcium acetate in water	Salt II	No degradation	1:0.50
	calcium nitrate+ Sodium hydroxide in water		No degradation	1:0.51
	Calcium acetate in water		-	-
	Calcium acetate in water		-	-
	Calcium nitrate+ Sodium hydroxide in water	Salt II + impurity	-	-
MeOH	Calcium acetate in water	Salt II	-	-
MeCN	calcium acetate in water		-	-
	calcium nitrate+ sodium hydroxide in water		-	-
	Calcium acetate hydrate in water		-	-
	Calcium acetate hydrate in water		-	-
MeCN	Calcium nitrate+ Sodium hydroxide in water	Salt II+ impurity	-	-
MeOH	potassium hydroxide in MeOH	Salt III	-	-
MeCN	potassium hydroxide in water	Salt III	No degradation	1:0.65
	potassium hydroxide in MeOH		-	-
acetone	Sodium hydroxide in water	Salt IV	No degradation	1:1

Solvent	CI Solution (0.5 M unless specified)	XRPD	NMR	API: CI Ratio by IC
	Sodium hydroxide in MeOH	Salt IV	-	-
MeCN	Sodium hydroxide in water	Salt IV	-	-
	Sodium hydroxide in MeOH	Salt IV + impurity	No degradation	1:0.84
MeOH	Sodium hydroxide in water	Salt V	No degradation	1 : 1.48
	Sodium hydroxide in MeOH		-	-
acetone	Sodium hydroxide in water		-	-
	Sodium hydroxide in MeOH		-	-
MeCN	Sodium hydroxide in water		-	-
	Sodium hydroxide in MeOH		-	-

[00533] Overall salt formation was confirmed with counterion ratio of approximately 0.5 to 1.5 equivalents. Most salts exhibited polymorphism with observation of multiple unique XRPD patterns: four for calcium salts, two for choline salts, seven for potassium salts, and eight for sodium salts. A crystalline salt was obtained using meglumine but only 0.38 equivalents of meglumine were detected. Magnesium also afforded a crystalline mono-salt.

6.4.2 **Slurry Experiments**

[00534] Calcium, sodium, and potassium salts were used to setup different competitive slurry experiments. For competitive slurry of calcium salts (~5 – 6 mg of Salt I and Salt II) were weighed into a 5.0 mL clear vial equipped with magnetic stir bars. These steps were repeated for potassium salt material (~5 – 6.5 mg of Salt III) and sodium salt materials (~2.6 – 6.4 mg of Salt IV and Salt V). Acetone, 1.0 mL, was added to each vial to achieve free-flowing slurry and allowed to equilibrate at room temperature. 50 µL of water was added to the potassium and sodium salt mixtures to increase solubility. All slurries, 400 µL, were filtered through 0.45 micron centrifuge filters after one and seven days of equilibration. The solids were analyzed by XRPD to check for salt conversion (Table 36).

[00535] It was found that Salt I, Salt III and Salt V were the most stable polymorphs in these solvent systems. These three salts were selected for scale up and full characterization.

[00536] Table 36. Competitive Slurry

Salt	Parent Materials	Weight (mg)	Solvent	Vol. (mL)	Temp. (°C)	Aliquot time point		Aliquot time point	
						Day	XRPD	Day	XRPD
Ca^{2+}	Salt I, (filtration)	5.36	Acetone	1.0	RT	1	Salt I	7	Salt I
	Salt II, (filtration)	6.53							
K^+	Salt III, (filtration)	6.57	Acetone Water	1.5 0.05	RT	1	Salt III	7	Salt III
Na^+	Salt IV, (filtration)	6.36	Acetone Water	1.0 0.05	RT	1	Salt V + impurity	7	Salt V
	Salt V, (filtration)	6.31							

6.4.3 Characterization Summary of Salts I, II, III, IV, V, VI, VII, VIII, IX and X

[00537] Salt I, Salt II, Salt III, Salt IV, Salt V, Salt VI, Salt VII, Salt VIII, Salt IX and Salt X were characterized to evaluate its physical form and stability. Since all these salt forms showed low temperature endothermic events, except Salt VIII, thermal holding experiments were performed in an attempt to isolate high melting salt form. Salt VI was obtained from the thermal holding experiments (Table 50) and characterized. Table 37 summarizes the characterization results for each salt.

[00538] Table 37. Characterization summary of Salts I, II, III, IV, V, VI, VII, VIII, IX and X

Salt	Salt I	Salt II	Salt III
DSC (°C)	Endotherm at 104.0, 170.6, 179.1 and 210.6	Endotherm at 115.5, 127.0, 220.8, 311.3 Exotherm at 200.5	Endotherm at 54.3, 109.3, 314.4

TGA (Weight loss)	0.34% @ 65-105 °C 1.41% @ 140-190 °C onset of decomposition at 213.8 °C	10.98% @ 65-140 °C, 0.33% @ 150-180 °C onset decomposition at 298.0 °C	0.91% @ 40-70 °C, 0.25% @ 100-120 °C, onset decomposition at 297.2 °C
NMR	0.24 wt% MeOH	0.32 wt% Acetone	0.24 wt% MeCN
Cmpd 1:CI ratio by IC	1 : 0.37	1 : 0.69	1 : 0.94
Moisture Sorption	60% RH: 1.0 wt% 90% RH: 4.1 wt% (moderately hygroscopic)	60% RH: 11.9 wt% 90% RH: 12.0 wt% (moderately hygroscopic)	60% RH: 2.1 wt% 90% RH: 4.5 wt% (moderately hygroscopic)
Aqueous Solubility — **Solubility (mg/mL)**	0.01	0.03	35.8
	Standard curve linear range 0.008 to 0.2 mg/mL.		
Aqueous Solubility — **XRPD (1 day)**	Salt I + Extra peaks	Salt II	Salt IX
hydration property	anhydrate (60 %RH) to monohydrate (90% RH)	di-hydrate	hemi- (60% RH) to mono-hydrate (90% RH)
Comment	Hemi-calcium Salt	Hemi-calcium Salt	Mono-potassium Salt
Salt	**Salt IV**	**Salt V**	**Salt VI**
DSC (°C)	Endotherm at 107.9, 307.4 Exotherm at 217.2	Endotherm at 93.3 (no melting was observed between 70 - 320 °C)	Endotherm at 282.4 and 308.4, Exotherm at 283.9
TGA (Weight loss)	5.43% @ 60-120 °C onset of decomposition at 302.5 °C	5.85% @ 40-130 °C, onset decomposition at 344.77 °C	onset decomposition at 305.7 °C
NMR	0.29 wt% Acetone	2.26 wt% Acetone	No degradation
Cmpd 1:CI ratio by IC	1 : 1.12	1 : 1.86	N/A
Moisture Sorption	60% RH: 6.1 wt% 90% RH: 6.5 wt% (moderately	60% RH: 6.0 wt% 90% RH: 6.4 wt% (moderately	60% RH: 0.3 wt% 90% RH: 0.7 wt%

		hygroscopic)	hygroscopic)	
Aqueous Solubility	**Solubility (mg/mL)**	19	79.8	N/A
		Standard curve linear range 0.008 to 0.2 mg/mL.		
	XRPD (1 day)	Salt IV + Extra peaks	Salt V + Extra peaks	N/A
hydration property		monohydrate	monohydrate	anhydrate
Comment		Mono-sodium Salt	Bis-sodium Salt	Mono-sodium Salt
Salt		**Salt VII**	**Salt VIII**	**Salt IX**
DSC (°C)		Broad transition before 90 (might be water loss), Possible glass transition at 160, onset decomposition at 294.9	No thermic change before onset decomposition at 294.1	Endothermic at 82.8; Exotherm at 229.5; Onset decomposition at 293.9
TGA (Weight loss)		onset decomposition at 290.6	onset decomposition at 291.2	onset decomposition at 301.8
NMR		No detectable solvent, no degradation	No detectable solvent, no degradation	0.01 wt% Acetone
Cmpd 1:Cl ratio by IC		1 : 1.15	1 : 1.09	1 : 1.09
Moisture Sorption		60% RH: 0.9 wt% 90% RH: 2.9 wt%	60% RH: 1.0 wt% 90% RH: 2.7 wt%	60% RH: 0.3 wt% 90% RH: 0.3 wt%
Aqueous Solubility	**Solubility (mg/mL)**			
	XRPD (1 day)			
hydration property				
Comment		Mono-sodium Salt	Mono-sodium Salt	Mono-sodium Salt
Salt		**Salt X**		
DSC (°C)		Endothermic at 91.3 and 149.3; Exotherm at 230.6; Onset decomposition at		

	294.7		
TGA (Weight loss)	onset 1.3 wt% loss at 79.2; onset 2.3 wt% loss at 135.1; onset decomposition at 296.7		
NMR	3.5 wt% of 4-hydroxybutanoic acid		
Cmpd 1:Cl ratio by IC	1 : 1.00		
Moisture Sorption			
Aqueous Solubility — **Solubility (mg/mL)**			
Aqueous Solubility — **XRPD (1 day)**			
hydration property			
Comment	Mono-sodium Salt		

6.4.4 **Salt I of Compound 1**

[00539] Salt I of Compound 1 is a hemi-calcium salt. Salt I was obtained in filtration from the salt formation experiment using methanol as primary solvent (Table 48, Figure 40). An estimated 0.24 wt% of MeOH was observed by ^{1}H NMR (d_6-DMSO) (Table 37, Figure 47). From IC analysis, Compound 1 free acid:calcium ratio was determined to be 1.0:0.4, consistent with a hemi-calcium salt. DSC analysis presented four endotherms at 104.0, 170.6, 179.1 and 210.6 °C (Figure 48). TGA analysis indicated a two weight losses: 0.34% at 65–105 °C (attributed to loss of residual MeOH), and 1.41% at 140–190 °C and onset decomposition at 213.8 °C (Figure 49). To further investigate the material's moisture sorption behavior, DVS analysis was carried out. The material adsorbed 1.0 wt% moisture at 60% RH, and 4.1 wt% moisture at 90% RH, indicating that it is moderately hygroscopic (Figure 50). The XRPD analysis of the post-DVS material after drying at 60.0 °C for two hours, recorded a consistent XRPD pattern as the starting material (Figure 46).

[00540] Salt I exhibited no change in physical form upon exposure to 60 °C for a period of seven days (Table 49). It was also chemically stable based on HPLC analysis. It was found that

Salt I is sparingly soluble in the aqueous solubility study, where a solubility of 0.01 mg/mL was obtained.

[00541] Figure 40 provides an XRPD pattern of Salt I. A list of XRPD Peaks for Salt I is provided below in Table 38.

[00542] Table 38. X-Ray Diffraction Peaks for Salt I

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.20	27.61	90.18
4.09	21.60	1.21
4.51	19.58	7.6
4.85	18.23	4.2
4.99	17.70	4.19
5.19	17.04	8
5.43	16.27	9.32
5.69	15.54	6.49
6.01	14.71	5.98
6.49	13.61	5.32
6.92	12.77	2.72
7.21	12.27	3.38
8.29	10.67	5.25
8.47	10.44	3.08
9.17	9.64	2.21
9.53	9.28	32.9
10.39	8.51	4.58
10.58	8.37	5.32
11.30	7.83	2.4
11.87	7.45	3.31
12.10	7.31	4.51
12.23	7.23	4.1
12.73	6.95	5.94
13.23	6.69	17.06
14.23	6.22	5.17
15.60	5.68	23.52
15.97	5.55	100
17.21	5.15	2.21
17.49	5.07	3.54
18.08	4.91	3.02
18.88	4.70	4.87
19.15	4.63	18.36
22.00	4.04	3.38
22.41	3.97	31.57

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
23.92	3.72	7.89
25.25	3.53	5.93
25.60	3.48	6.38
26.35	3.38	3.02
26.67	3.34	2.1
27.76	3.21	4.32
28.21	3.16	5.53
29.29	3.05	9.13
31.08	2.88	2.7
31.46	2.84	2.95
31.82	2.81	3.11
33.44	2.68	2.71
34.63	2.59	1.81
35.58	2.52	3.51
37.97	2.37	1.24
38.65	2.33	3.26
38.96	2.31	5.02
41.35	2.18	6.64
42.29	2.14	4.11
43.31	2.09	0.84

6.4.5 **Salt II of Compound 1**

[00543] Salt II of Compound 1 is a dihydrated hemi-calcium salt. Salt II was obtained in filtration from the salt formation experiment using acetone as primary solvent (Table 48, Figure 51). An estimated 0.32 wt% of acetone was observed by ^{1}H NMR (d_6-DMSO) (Table 37, Figure 52). The ratio of Compound 1 free acid to calcium counterion was 1.0:0.69, indicating it is a hemi-calcium salt.

[00544] DSC analysis presented four endotherms at 115.5, 127.0, 220.8, 311.3 °C and an exotherm at 220.5 °C (Figure 53). TGA analysis indicated a two weight losses: 10.98% at 65-140 °C (attributed to water loss), 0.33% at 150-180 °C and onset decomposition at 298.0 °C (Figure 54). The material adsorbed 11.9 wt% moisture at 60% RH, and 12.0 wt% moisture at 90% RH, indicating that it is moderately hygroscopic (Figure 55). Slight hysteresis was observed at 0–40% RH. The XRPD analysis of the post-DVS material after drying at 60.0 °C for two hours, recorded a new XRPD pattern (bottom) (Figure 51). TGA and DVS results indicated that Salt II is a dihydrate, which is stable above 40% RH.

[00545] Salt II exhibited no change in physical form upon exposure to 60 °C for a period of seven days (Table 49). Chemical purity of the thermally stressed solid was assessed by HPLC and no significant reduction in purity was observed. It was found that Salt II remained sparingly soluble in the aqueous solubility study, where a solubility of 0.03 mg/mL was obtained.

[00546] Figure 41 provides an XRPD pattern of Salt II. A list of XRPD Peaks for Salt II is provided below in Table 39.

[00547] Table 39. X-Ray Diffraction Peaks for Salt II

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
3.37	26.19	23.10
3.81	23.16	0.13
3.94	22.45	2.32
4.15	21.28	4.74
4.33	20.43	4.51
4.59	19.25	1.91
4.77	18.54	2.30
5.12	17.28	1.77
5.51	16.03	1.14
6.07	14.55	2.22
6.25	14.15	1.09
7.27	12.16	1.77
7.45	11.86	1.82
7.82	11.31	1.77
8.03	11.01	1.75
8.56	10.32	0.22
8.83	10.02	2.15
10.07	8.78	100.00
10.39	8.52	3.22
10.71	8.26	1.84
11.32	7.82	1.04
11.56	7.66	0.73
11.70	7.56	1.49
13.21	6.70	7.45
13.46	6.58	3.58
14.10	6.28	1.43
14.36	6.17	0.80
15.32	5.78	0.93
15.58	5.69	0.44
16.86	5.26	27.14
19.28	4.60	2.06

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
19.51	4.55	3.28
20.23	4.39	9.96
20.68	4.29	0.15
21.32	4.17	2.82
22.41	3.97	1.76
22.95	3.88	1.05
23.71	3.75	26.87
24.27	3.67	2.66
24.90	3.58	1.19
25.87	3.44	3.47
26.21	3.40	0.61
26.83	3.32	2.54
27.15	3.28	3.24
27.57	3.24	0.57
27.85	3.20	2.38
28.12	3.17	2.44
28.95	3.08	0.53
29.24	3.05	0.64
29.53	3.02	0.48
29.95	2.98	1.62
31.08	2.88	0.60
31.47	2.84	6.68
31.90	2.81	2.70
32.59	2.75	1.65
32.97	2.72	0.47
33.42	2.68	3.66
34.73	2.58	2.95
34.97	2.57	2.37
35.25	2.55	1.08
36.09	2.49	0.62
38.09	2.36	4.79
39.69	2.27	0.70
41.35	2.18	0.91
42.56	2.12	1.54
42.94	2.11	2.32
44.06	2.05	0.86

6.4.6 **Salt III of Compound 1**

[00548] Salt III of Compound 1 is a mono-potassium salt. Salt III was obtained in filtration from the salt experiment using acetonitrile as primary solvent (Table 36, Figure 56). An estimated 0.24 wt% of CH_3CN was observed by ^{1}H NMR (Table 50, Figure 52). The ratio of Compound 1 free acid : potassium was determined by IC analysis to be 1.0:0.9 indicating it is a mono-potassium salt. DSC analysis presented three endotherms at 54.3, 109.3 and 314.4 °C (Figure 58). TGA analysis indicated two weight losses: 0.91% at 40–70 °C, and 0.25% at 100–120 °C and onset decomposition at 297.2 °C (Figure 59). The material adsorbed 2.1 wt% moisture at 60% RH, and 4.5 wt% moisture at 90% RH, indicating it is moderately hygroscopic (Figure 60). Mild hysteresis was observed indicating presence of potential hydrate form. The XRPD analysis of the post-DVS material after drying at 60.0 °C for two hours, recorded a similar XRPD pattern as the starting material (Figure 56).

[00549] Salt III exhibited no change in physical form upon exposure to 60 °C for a period of seven days (Table 48). Chemical purity of the thermally stressed solid was assessed by HPLC and no reduction in purity was observed. Aqueous solubility measurement of potassium salt in deionized water was carried out in room temperature. The materials after 24 hour equilibrium converted from Salt III to Salt IX, and remained as Salt IX on day seven. Collected filtrate was subjected to HPLC analysis and a solubility of 35.8 mg/mL was attained.

[00550] Multiple thermal transitions (endothermic) were observed on DSC analysis with some occur at low temperature. In an effort to isolate a high melt crystal form, the material was held at 130 °C for 2 minutes followed by cooling to ambient temperature. XRPD analysis of the resulting solid was consistent with Salt III.

[00551] Based on the characterization results, Salt III showed a tendency to form hydrate form. Although several low temperature thermal events were observed, the material appeared to be stable under thermal stress.

[00552] Figure 42 provides an XRPD pattern of Salt III. A list of XRPD Peaks for Salt III is provided below in Table 40.

[00553] Table 40. X-Ray Diffraction Peaks for Salt III

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
4.18	21.14	2.11
4.71	18.77	65.00
4.98	17.76	18.65
5.61	15.75	17.46
6.06	14.60	34.64
6.41	13.80	11.03
6.73	13.14	7.69
7.14	12.39	7.87
7.39	11.96	12.77
8.01	11.04	11.19
8.55	10.34	4.72
8.78	10.07	5.16
9.03	9.80	9.46
9.73	9.09	20.42
9.88	8.95	34.85
10.72	8.26	39.75
10.89	8.12	50.42
11.76	7.53	8.26
11.89	7.44	9.01
12.48	7.09	25.58
12.97	6.83	8.88
13.29	6.66	4.99
13.97	6.34	27.99
14.54	6.09	90.90
14.65	6.05	100.00
15.18	5.84	62.41
15.29	5.79	66.49
16.35	5.42	49.40
16.49	5.37	37.96
17.01	5.21	2.87
17.17	5.16	6.63
18.09	4.90	22.64
19.70	4.51	4.56
21.78	4.08	6.45
22.62	3.93	6.14
23.13	3.85	3.58
23.99	3.71	6.61
24.44	3.64	7.47
25.16	3.54	2.65
25.44	3.50	4.44
25.88	3.44	2.22

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
27.37	3.26	6.45
28.88	3.09	16.07
29.93	2.99	3.52
32.09	2.79	2.50
34.55	2.60	7.41
37.21	2.42	1.67
40.15	2.25	3.75
40.86	2.21	4.58
41.95	2.16	1.21

6.4.7 **Salt IV of Compound 1**

[00554] Salt IV of Compound 1 is a monohydrated mono-sodium salt. Salt IV was obtained in filtration from the recrystallization experiment using acetone as primary solvent (Table 36, Figure 61). IC analysis of this material indicated the material had a Compound 1 free acid : sodium ratio of 1.0:1.1, consistent with a mono-sodium salt. An estimated 0.29 wt% of acetone was observed by ^{1}H NMR (Table 50, Figure 62). DSC analysis presented two endotherms at 107.9, 307.4 °C and an exotherm at 217.2 °C (Figure 63). TGA analysis indicated a weight loss of 5.43% at 60–120 °C attributed to water loss followed by an onset decomposition at 302.5 °C (Figure 64). The material adsorbed 6.1 wt% moisture at 60% RH, and 6.5 wt% moisture at 90% RH, indicating it is moderately hygroscopic (Figure 65). The XRPD analysis of the post-DVS material after drying at 60.0 °C for two hours, recorded a consistent XRPD pattern as the starting material (Figure 61). DVS analysis showed that Salt IV is a stable hydrate.

[00555] In an effort to isolate a high melt crystal form through a dehydration/ recrystallization process, Salt IV was held at 130 °C for 2 minutes followed by cooling to ambient temperature. XRPD analysis of the resulting solid was consistent with Salt IV. The holding experiment was repeated by holding the material at 260 °C, a temperature higher than the exothermic event at 217.2 °C. A conversion to a new salt (Salt VI) was observed.

[00556] In the aqueous solubility study, no form change was observed after slurring Salt IV in water for 13 days (Table 49). A solubility of 19.0 mg/mL was attained. When storing Salt IV at 60 °C, no polymorph conversion or degradation of the material was observed at day 1, and 7 (Table 48).

[00557] Figure 43 provides an XRPD pattern of Salt IV. A list of XRPD Peaks for Salt IV is provided below in Table 41.

[00558] Table 41. X-Ray Diffraction Peaks for Salt IV

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.18	27.83	100.00
4.17	21.18	0.82
4.78	18.50	0.36
5.23	16.91	0.58
5.62	15.74	0.54
5.86	15.08	0.21
5.93	14.91	0.36
6.29	14.04	9.51
6.44	13.73	5.33
6.74	13.11	0.33
7.43	11.90	0.15
9.45	9.36	30.33
9.66	9.16	5.46
9.94	8.90	1.64
10.63	8.33	0.56
11.83	7.48	0.30
12.03	7.36	0.07
12.62	7.01	1.03
13.24	6.68	0.45
13.61	6.50	0.86
14.57	6.08	0.13
14.85	5.97	0.32
15.05	5.89	0.07
15.80	5.61	26.27
16.17	5.48	6.01
16.68	5.32	0.55
16.98	5.22	0.03
17.37	5.11	0.69
18.31	4.85	0.85
19.00	4.67	30.80
19.43	4.57	7.57
19.94	4.45	0.92
20.72	4.29	0.55
22.20	4.00	2.92
22.69	3.92	1.22
23.63	3.77	0.28
24.22	3.68	0.26

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
25.42	3.50	6.32
26.01	3.43	1.49
26.70	3.34	0.73
27.54	3.24	1.09
28.35	3.15	0.53
28.67	3.11	2.01
29.39	3.04	1.15
31.24	2.86	0.43
31.97	2.80	1.32
32.69	2.74	0.75
33.18	2.70	0.20
34.29	2.61	0.79
34.73	2.58	0.32
35.82	2.51	0.33
37.41	2.40	1.04
37.84	2.38	0.12
38.27	2.35	1.51
38.67	2.33	0.46
39.65	2.27	0.13
40.64	2.22	1.05
41.02	2.20	0.41
41.48	2.18	0.47
41.90	2.16	0.40
42.80	2.11	0.10
43.80	2.07	0.23
44.32	2.04	0.65
44.59	2.04	0.92

6.4.8 **Salt V of Compound 1**

[00559] Salt V of Compound 1 is a monohydrated bis-sodium salt. Salt V was obtained in filtration from the recrystallization experiment using acetone as primary solvent (Table 36, Figure 66). IC analysis of this material indicated the material had a Compound 1 free acid : sodium ratio of 1.0:1.9, consistent with a bis-sodium salt. An estimated 2.26 wt% of acetone was observed by ^{1}H NMR (Table 50, Figure 67). DSC analysis presented an endotherm at 93.3 °C (Figure 68). TGA analysis indicated a weight loss of 5.85% at 40–130 °C attributed to water loss, followed by an onset of decomposition at 344.8 °C (Figure 69). The material adsorbed 6.0 wt% moisture at 60% RH, and 6.4 wt% moisture at 90% RH, indicating it is moderately hygroscopic (Figure 70). Significant hysteresis was observed at 0–40% RH, indicating it is not a stable hydrate that may lose water at low humidity. The XRPD analysis of the post-DVS material after drying at 60.0 °C for two hours, recorded a XRPD pattern mostly consistent with Salt V with a few missing peaks (Figure 66).

[00560] No melting event was observed for this bis-sodium salt when subject to heating between 70 – 410 °C at the rate of 1 °C/min on melting apparatus. The white crystalline Salt V remained unchanged until it reached the decomposition temperature (> 320 °C) as shown in Table 51. The material showed a high solubility at 80.0 mg/mL.

[00561] Figure 44 provides an XRPD pattern of Salt V. A list of XRPD Peaks for Salt V is provided below in Table 42.

[00562] Table 42. X-Ray Diffraction Peaks for Salt V

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.15	28.01	33.88
3.33	26.55	20.18
3.51	25.19	3.70
3.65	24.18	1.01
4.19	21.10	1.34
4.45	19.86	0.31
4.74	18.66	1.46
5.09	17.35	2.23
5.24	16.87	1.10
5.40	16.37	2.15
5.75	15.38	2.50
6.00	14.73	1.57
6.24	14.18	1.74
6.43	13.75	1.73
6.64	13.32	2.14
7.29	12.13	1.51
7.45	11.87	1.27
7.58	11.66	1.44
7.92	11.16	1.53
8.57	10.32	1.38
9.21	9.61	1.32
9.39	9.42	0.71
9.97	8.87	100.00
13.02	6.80	12.96
13.31	6.65	33.72

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
13.64	6.49	39.41
13.97	6.34	37.17
16.69	5.31	63.51
17.13	5.18	3.63
17.65	5.03	1.29
18.09	4.90	0.97
18.65	4.76	0.53
19.51	4.55	2.67
20.06	4.43	28.05
22.15	4.01	16.77
22.50	3.95	0.78
22.87	3.89	0.48
23.41	3.80	0.40
24.54	3.63	1.23
25.01	3.56	1.99
25.70	3.47	0.20
26.29	3.39	10.34
26.87	3.32	23.31
27.81	3.21	3.07
28.89	3.09	8.62
29.06	3.07	9.74
29.90	2.99	0.54
30.29	2.95	2.38
30.60	2.92	2.03
31.08	2.88	21.52
31.97	2.80	0.89
32.21	2.78	0.56
33.85	2.65	4.03
34.24	2.62	3.76
35.73	2.51	0.64
37.31	2.41	2.39
38.39	2.34	1.09
39.71	2.27	1.60
40.87	2.21	6.46
42.01	2.15	0.67
44.30	2.04	8.24

6.4.9 **Salt VI of Compound 1**

[00563] Salt VI of Compound 1 is an anhydrous mono-sodium salt. Salt VI was isolated from the thermal holding experiment (Table 50, Figure 71). No degradation was observed by ^{1}H NMR (Table 50, Figure 73). DSC analysis presented two endothermic peaks at 282.4 and 308.4 °C and an exothermic peak at 283.9 °C (Figure 74). No weight loss was observed by TGA, and the onset decomposition temperature is 305.7 °C (Figure 75). The material adsorbed 0.3 wt% moisture at 60% RH, and 0.7 wt% moisture at 90% RH, indicating it is slightly hygroscopic material (Figure 76).

[00564] The XRPD analysis of the post-DVS material after drying at 60.0 °C for two hours, recorded a consistent XRPD diffractogram (Figure 72). These results indicated that Salt VI is a stable anhydrate form of mono-sodium salt.

[00565] Figure 45 provides an XRPD pattern of Salt VI. A list of XRPD Peaks for Salt VI is provided below in Table 43.

[00566] Table 43. X-Ray Diffraction Peaks for Salt VI

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.03	29.12	100.00
3.39	26.05	41.75
4.42	19.99	1.12
4.63	19.08	1.77
5.01	17.62	2.09
5.40	16.37	2.37
5.81	15.21	1.21
6.23	14.19	0.78
6.42	13.77	0.58
7.06	12.52	0.74
7.66	11.55	0.95
8.96	9.87	0.82
10.06	8.79	9.02
10.68	8.28	1.75
11.53	7.67	0.14
11.89	7.45	8.37
12.42	7.13	2.13
13.40	6.61	3.37
13.73	6.45	1.19
14.04	6.31	2.74

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
14.91	5.94	2.99
15.22	5.82	4.62
15.67	5.65	0.68
16.33	5.43	2.07
16.74	5.30	6.01
17.10	5.19	0.92
17.82	4.98	2.82
18.11	4.90	7.43
18.48	4.80	0.20
19.07	4.65	3.04
20.15	4.41	2.67
20.94	4.24	1.42
21.47	4.14	0.36
22.05	4.03	1.14
23.37	3.81	0.40
24.03	3.70	0.27
24.96	3.57	0.53
26.38	3.38	0.03
26.96	3.31	2.44
28.88	3.09	0.42
30.07	2.97	2.24
31.04	2.88	1.20
31.61	2.83	0.78
33.20	2.70	0.73
33.94	2.64	0.24
34.87	2.57	0.41
37.20	2.42	0.75
38.13	2.36	0.29
39.72	2.27	0.18
40.29	2.24	0.31
40.97	2.20	0.51
42.35	2.13	0.63
43.41	2.08	0.31
44.38	2.04	0.40

6.4.10 **Salt VII of Compound 1**

[00567] Salt VII of Compound 1 is a mono-sodium salt and a possible hydrate form. It was obtained from the salt formation experiment in MeOH. IC analysis of this material indicated the material had a free acid : sodium ratio of 1.0 : 1.2, consistent with a mono-sodium salt. ^{1}H

NMR (D_2O) analysis was consistent with the chemical structure and no solvent was detected (Figure 85). DSC analysis showed a broad transition before 90 °C, which might be from water loss and a possible glass transition at 160 °C (Figure 86). TGA analysis indicated no weight loss and onset decomposition at 290.6 °C (Figure 87). Polarized microscopy analysis revealed birefringent particles, ~10.0 µm to 80.0 µm (Figure 88).

[00568] In the moisture sorption analysis, the material adsorbed 0.9 wt% moisture at 60% RH, and 2.9 wt% moisture at 90% RH (Figure 89). The XRPD analysis of the post-DVS material after drying at 60.0 °C for two hours, recorded a XRPD pattern consistent with the starting material (Figure 90). DVS analysis showed minor hysteresis indicating that Salt VII of Compound 1 is a possible hydrate with variable water content depending on the environment humidity.

[00569] The polymorph form was stable after seven days of stirring in acetone and no change in XRPD pattern was observed. After seven days of storage at 60 °C, no change in XRPD pattern and no degradation were observed by HPLC.

[00570] Approximately 160 mg of Compound 1 was weighed in a 20.0 mL clear vial equipped with magnetic stir bars and dissolved with minimum amount of methanol at 50 °C. Prior to CI addition, each solution was polish filtered through a 0.45 µm syringe filter into clean preheated vials. After hot filtration, 1.2 mL of 0.5 M aqueous sodium hydroxide was added drop-wise. The vials were cooled to ambient temperature at a rate of 20 °C/hour and allowed to equilibrate with stirring at ambient temperature overnight with slow cooling. The resulting solids were transferred into a Büchner funnel (with grade 1 Whatman paper) and isolated by filtration. All obtained solids were dried under vacuum (~30 inches Hg) and analyzed by XRPD to determine the solid pattern, ^{1}H NMR to confirm structure and IC for salt stoichiometry (Table 37).

[00571] Figure 84 provides an XRPD pattern of Salt VII. A list of XRPD Peaks for Salt VII is provided below in Table 44.

[00572] Table 44. X-Ray Diffraction Peaks for Salt VII

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.40	25.96	100.00
3.71	23.80	48.20

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
4.08	21.67	27.72
4.31	20.50	29.20
4.95	17.86	29.21
5.07	17.43	35.50
5.33	16.58	33.39
5.59	15.82	25.36
6.11	14.46	33.91
6.55	13.49	22.93
6.95	12.72	18.29
7.27	12.15	21.19
7.60	11.64	17.55
7.79	11.35	16.23
8.49	10.42	18.29
8.62	10.26	18.46
9.54	9.27	21.65
9.96	8.88	94.70
10.87	8.14	48.51
11.53	7.67	20.75
11.88	7.45	23.67
12.53	7.06	36.50
12.78	6.92	27.31
13.28	6.67	34.98
13.64	6.49	28.43
13.97	6.34	32.67
14.31	6.19	28.60
14.90	5.94	86.48
15.48	5.72	54.80
15.73	5.63	39.86
16.37	5.41	33.98
16.66	5.32	60.39
18.02	4.92	20.75
18.68	4.75	15.27
20.03	4.43	27.28
20.76	4.28	7.31
20.96	4.24	7.06
21.58	4.12	6.69
22.15	4.01	13.35
24.89	3.58	5.75
25.46	3.50	6.34
25.82	3.45	5.02
26.83	3.32	11.50

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
28.73	3.11	6.55
29.35	3.04	7.21
31.10	2.88	12.92
32.28	2.77	2.27
32.84	2.73	3.85
33.75	2.66	2.21
34.30	2.61	2.49
37.27	2.41	3.03
38.29	2.35	2.09
38.86	2.32	0.56
39.67	2.27	1.86
40.80	2.21	7.08
44.33	2.04	3.68

6.4.11 **Salt VIII of Compound 1**

[00573] Salt VIII of Compound 1 is a mono-sodium salt and a stable anhydrate polymorph. It was obtained from the slurry experiment using MeOH as solvent (Figure 91). IC analysis of this material indicated the material had a free acid : sodium ratio of 1.0 : 1.1, consistent with a mono-sodium salt. No degradation was observed by ^{1}H NMR (D_2O) (Figure 92). DSC analysis showed no thermic change before onset decomposition at 294.0 °C (Figure 93). TGA analysis showed no weight loss and an onset decomposition at 291.2 °C (Figure 94). Polarized microscopy analysis revealed birefringent particles, ~20.0 µm to 80.0 µm (Figure 95).

[00574] Salt VIII of Compound 1 adsorbed 1.0 wt% moisture at 60% RH, and 2.7 wt% moisture at 90% RH (Figure 96). The XRPD analysis of the post-DVS material after drying at 60.0 °C for two hours, showed an XRPD pattern consistent with the starting material (Figure 97).

[00575] Salt VIII of Compound 1 was stable after seven days of stirring in acetone and no change in XRPD pattern was observed. In competitive slurry experiments, Salt VIII of Compound 1 was stable in an acetone slurry after seven days of equilibration. After seven days of storage at 60 °C, no change in XRPD pattern and no degradation were observed by HPLC.

[00576] Approximately 150 mg of Salt IV of Compound 1 was placed into a 20.0 mL clear vial equipped with magnetic stir bars. Methanol (10.0 mL) was added to achieve free-flowing slurry and allowed to equilibrate at room temperature. The slurry was transferred into a

Büchner funnel (with grade 1 Whatman paper) after one day of equilibration. The resulting solid was dried under vacuum (~30 inches Hg) and analyzed by XRPD to determine the solid pattern, ^{1}H NMR to confirm structure and IC for salt stoichiometry (Table 37).

[00577] Figure 91 provides an XRPD pattern of Salt VIII. A list of XRPD Peaks for Salt VIII is provided below in Table 45.

[00578] Table 45. X-Ray Diffraction Peaks for Salt VIII

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.06	28.86	100.00
3.39	26.07	73.24
3.64	24.29	31.30
3.79	23.31	27.13
3.95	22.36	24.85
4.54	19.47	16.91
4.94	17.89	27.50
5.07	17.44	23.21
5.21	16.95	18.18
5.40	16.37	16.87
6.02	14.69	17.08
6.27	14.11	14.06
6.65	13.28	15.61
7.18	12.31	12.13
8.00	11.06	6.23
8.37	10.56	10.79
9.32	9.49	9.06
10.00	8.85	22.09
10.43	8.48	13.83
11.04	8.01	30.28
11.94	7.41	9.98
12.72	6.96	21.11
13.01	6.80	18.85
13.71	6.46	35.02
13.97	6.34	31.38
14.66	6.04	24.16
15.01	5.90	54.69
15.65	5.66	43.71
15.73	5.63	34.23
16.34	5.42	15.36
16.69	5.31	16.66
17.14	5.17	10.36

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
17.37	5.11	6.32
18.31	4.84	16.85
18.91	4.69	8.79
19.57	4.54	5.57
20.13	4.41	13.39
22.17	4.01	10.89
24.68	3.61	3.20
25.02	3.56	3.44
26.92	3.31	5.68
28.96	3.08	6.20
29.53	3.02	6.68
31.12	2.87	6.69
32.42	2.76	1.62
33.47	2.68	1.24
33.76	2.66	0.81
34.58	2.59	1.21
35.75	2.51	1.74
37.25	2.41	2.01
39.65	2.27	1.30
40.87	2.21	1.65
42.36	2.13	1.62
43.42	2.08	1.57
44.34	2.04	1.72

6.4.12 **Salt IX of Compound 1**

[00579] Salt IX of Compound 1 is a mono-sodium salt and an anhydrate polymorph. It was obtained from salt formation experiments in acetone (Figure 98). IC analysis of this material indicated the material had a free acid : sodium ratio of 1.0 : 1.1, consistent with a mono-sodium salt. An estimated 0.01 wt% of acetone was observed by ^{1}H NMR (D_2O) (Figure 99). DSC analysis showed an endotherm at 82.8 °C and exotherm at 229.5 °C (Figure 100). However, DSC analysis of the post thermal holding experiment at 150 °C showed no endothermic change before 180 °C (Figure 102). XRPD analysis of the post thermal holding experiment gave material consistent with the starting material, which indicated the endothermic change was not related to a form change. TGA analysis indicated no weight loss and an onset decomposition of 301.8 °C (Figure 101). Polarized microscopy analysis revealed birefringent particles, ~10.0 µm to 40.0 µm (Figure 103).

[00580] The material adsorbed 0.3 wt% moisture at 60% RH, and 0.3 wt% moisture at 90% RH (Figure 104). The XRPD analysis of the post-DVS material after drying at 60.0 °C for two hours, showed an XRPD pattern consistent with Salt IV of Compound 1.

[00581] After seven days of stirring in water and acetone, all Salt IX of Compound 1 had converted to Salt VIII or Salt IV. After seven days of storage at 60 °C, no change in XRPD pattern and no degradation were observed by HPLC.

[00582] Approximately 1.6 g of Compound 1 was placed into a 250 mL round bottom flask equipped with stir bar and dissolved with 123.0 mL of acetone at 50 °C. The solution was polish filtered through a 0.45 µM syringe filter into clean preheated flask. After hot filtration, 12.7 mL of 0.5 M sodium hydroxide was added drop-wise to generate a white color suspension. After stirred at 50 °C for 10 minutes, the flask was cooled to ambient temperature at a rate of 20 °C/hour and allowed to equilibrate with stirring at ambient temperature overnight with slow cooling. The resulting solids were transferred into a Büchner funnel (with grade 1 Whatman paper) and isolated by filtration. The clear solutions were kept at ambient temperature. The obtained solid was dried under vacuum (~30 inches Hg) and analyzed by XRPD to determine the solid pattern, ^{1}H NMR to confirm structure and IC for salt stoichiometry.

[00583] Figure 98 provides an XRPD pattern of Salt IX. A list of XRPD Peaks for Salt IX is provided below in Table 46.

[00584] Table 46. X-Ray Diffraction Peaks for Salt IX

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.05	28.95	78.75
3.19	27.68	100.00
4.33	20.41	6.91
4.57	19.34	6.24
5.11	17.30	4.92
5.25	16.82	4.17
5.71	15.47	5.57
6.32	13.98	35.72
7.68	11.51	4.25
7.88	11.22	4.40
9.47	9.34	99.14

Two-theta angle (°)	*d* Space (Å)	Relative Intensity (%)
9.93	8.91	7.57
10.04	8.81	9.36
12.63	7.01	4.96
13.06	6.78	6.44
13.69	6.47	21.62
14.01	6.32	13.40
14.89	5.95	3.86
15.83	5.60	65.85
16.31	5.44	4.42
16.68	5.32	4.05
17.39	5.10	5.60
18.33	4.84	2.89
19.01	4.67	79.21
19.94	4.45	4.88
20.72	4.29	4.76
20.88	4.25	2.57
22.12	4.02	7.77
22.27	3.99	6.70
22.60	3.93	5.31
23.58	3.77	2.40
24.21	3.68	2.54
24.69	3.61	2.16
25.47	3.50	17.07
26.26	3.39	2.92
26.62	3.35	4.83
27.63	3.23	10.05
28.42	3.14	4.76
28.73	3.11	5.48
29.44	3.03	5.15
31.25	2.86	2.74
31.90	2.81	3.89
32.51	2.75	1.25
33.23	2.70	1.41
34.35	2.61	3.94
35.85	2.50	1.23
37.39	2.41	4.41
38.30	2.35	6.23
39.79	2.27	0.81
40.61	2.22	4.40
41.44	2.18	2.34
41.96	2.15	1.04

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
44.56	2.03	3.89

6.4.13 **Salt X of Compound 1**

[00585] Salt X of Compound 1 is a mono-sodium salt and an unstable hydrate polymorph. It was obtained from the binary solvent crystallization experiment, using water as primary solvent and THF as anti-solvent (Figure 105). IC analysis of this material indicated the material had a free acid : sodium ratio of 1.0 : 1.0, consistent with a mono-sodium salt. ^{1}H NMR (D_2O) analysis indicated this material contained an estimated 3.5 wt% of 4-hydroxybutanoic acid, which was the contamination of tetrahydrofuran peroxides (Figure 106). DSC analysis showed two endotherms at 91.3 °C and 149.3 °C, respectively and an exotherm at 230.6 °C (Figure 107). TGA analysis indicated a 1.3% weight loss at 60-120 °C and a 2.3% weight loss at 120-180 °C, followed by an onset decomposition at 296.7 °C (Figure 108). Polarized microscopy analysis revealed birefringent particles, ~10.0 µm to 40.0 µm (Figure 109).

[00586] After seven days of stirring in water and acetone, all Salt X converted to Salt VII or Salt IV. After seven days of storage at 60 °C, no change in XRPD pattern and no degradation were observed by HPLC.

[00587] Approximately 168 mg of Salt IV of Compound 1 was placed into a 50.0 mL clear glass vial equipped with stir bar and dissolved in 4.3 mL of water at 60 °C. Tetrahydrofuran, 12.8 mL, was added drop-wise at the same temperature. The vial was cooled to ambient temperature at a rate of 20 °C/hour and allowed to equilibrate with stirring at ambient temperature over 24 hours. The solvent was evaporated to dryness under a gentle stream of nitrogen gas. The obtained solid was dried under vacuum (~30 inches Hg) and analyzed by XRPD to determine the solid form, ^{1}H NMR to confirm structure and IC for salt stoichiometry.

[00588] Figure 105 provides an XRPD pattern of Salt X. A list of XRPD Peaks for Salt X is provided below in Table 47.

[00589] Table 47. X-Ray Diffraction Peaks for Salt X

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
3.20	27.65	60.05
3.74	23.61	100.00
4.11	21.51	11.05
4.23	20.90	8.87
4.36	20.28	6.93
4.59	19.26	5.18
4.78	18.48	7.24
5.03	17.59	6.96
5.22	16.92	5.19
5.43	16.27	5.79
5.62	15.72	5.24
5.88	15.04	8.05
6.06	14.58	7.87
6.28	14.08	10.30
6.76	13.08	5.00
7.24	12.20	5.19
7.41	11.92	4.33
7.83	11.30	4.33
8.01	11.03	4.13
9.50	9.31	14.32
10.37	8.53	3.76
11.01	8.04	3.65
11.15	7.93	7.58
11.38	7.78	3.38
12.12	7.30	2.94
12.75	6.94	3.38
13.58	6.52	7.26
14.37	6.16	7.76
14.87	5.96	5.54
15.06	5.88	7.16
15.41	5.75	44.42
15.78	5.62	11.20
16.65	5.32	4.31
18.71	4.74	31.15
19.70	4.51	15.61
20.35	4.36	11.27
20.88	4.26	13.46
22.16	4.01	14.64
22.49	3.95	10.09
23.83	3.73	20.69
24.73	3.60	9.74

Two-theta angle (°)	***d* Space (Å)**	**Relative Intensity (%)**
25.62	3.48	60.92
26.38	3.38	8.68
27.11	3.29	11.10
28.71	3.11	10.22
29.79	3.00	8.15
30.65	2.92	4.71
31.15	2.87	6.76
32.80	2.73	4.49
34.52	2.60	2.50
35.81	2.51	0.77
37.64	2.39	0.99
38.77	2.32	1.44
41.35	2.18	1.24
42.26	2.14	2.24
43.70	2.07	3.25
44.25	2.05	2.30

6.4.14 **400 mg scale preparation of Salt I, Salt II, Salt III, Salt IV and Salt V**

[00590] Approximately 400 mg of Compound 1 was placed into 20 mL clear glass vials equipped with stir bars and dissolved with a minimum amount of solvents at 50 °C. Methanol was used as the primary solvent to dissolve Compound 1 before addition of counter ion (CI) (0.25 M calcium acetate hydrate/H_2O) to generate Salt I. Acetone was used as primary solvent for dissolving Compound 1 before addition of CI to generate Salt II. Prior to CI addition, each solution was polish filtered through a 0.45 µm syringe filter into clean preheated vials. After hot filtration, 5.8 mL of 0.25 M calcium acetate hydrate was added drop-wise. The vials were cooled to ambient temperature at a rate of 20 °C/hr and allowed to equilibrate with stirring at ambient temperature overnight with slow cooling. The resulting solids were transferred into a Büchner funnel (with grade 1 Whitman paper) and isolated by filtration. The clear solutions were kept in RT. All obtained solids were analyzed by XRPD to characterize the solid (Table 48)

[00591] Approximately 400 mg of Compound 1 was placed into 20 mL clear glass vial equipped with stir bar and dissolved with a minimum amount of solvent at 50 °C. Acetonitrile was used as the primary solvent to dissolve Compound 1 before addition of counter ion (CI) (0.5 M potassium hydroxide/H_2O) to generate Salt III. Prior to CI addition, the solution was polish filtered through a 0.45 μm syringe filter into a clean preheated vial. After hot filtration, 1.9 mL of 0.5 M potassium hydroxide was added drop-wise. The vial was cooled to ambient temperature at a rate of 20 °C/hr and allowed to equilibrate with stirring at ambient temperature overnight with slow cooling. The resulting solid was transferred into a Büchner funnel (with grade 1 Whitman paper) and isolated by filtration. The clear solution was kept in RT. Obtained solid was analyzed by XRPD to characterize the solid (Table 48)

[00592] Approximately ~250 to 400 mg of Compound 1 was placed into 20 mL clear glass vials equipped with stir bars and dissolved with a minimum amount of solvents at 50 °C. Acetone was used as the primary solvent to dissolve Compound 1 before addition of CI (0.5 M sodium hydroxide/H_2O) to generate Salt IV and Salt V. Prior to CI addition, each solution was polish filtered through a 0.45 μm syringe filter into clean preheated vials. After hot filtration, 1.8 mL of 0.5 M sodium hydroxide was added drop-wise to generate Salt IV, and 5.8 mL of 0.5 M sodium hydroxide was added drop-wise to generate Salt V. The vials were cooled to ambient temperature at a rate of 20 °C/hr and allowed to equilibrate with stirring at ambient temperature overnight with slow cooling. The resulting solids were transferred into a Büchner funnel (with grade 1 Whitman paper) and isolated by filtration. The clear solutions were kept in RT. All obtained solids were analyzed by XRPD to characterize the solid (Table 48)

[00593] Details of the experiments are summarized in Table 48.

[00594] Table 48. Scale up of Salts I, II, III, IV and V

Salt	API amnt. (mg)	Primary Solvent	Temp. (°C)	Primary solvent Vol. (mL)	CI Vol. (mL)	Precipitation /Isolation	pH of Filtrate	Recovery (mg)	Yield (%, filtration)	XRPD
Ca^{2+}	398.9	MeOH	50.0	13.3	4.8	PPT formed, Filtration	6.07	407.1	91.9	Salt I
Ca^{2+}	402.3	Acetone	50.0	23.4	5.8	PPT formed, Filtration	6.56	561.8	116.4	Salt II
K^+	396.7	MeCN	50.0	27.7	1.9	PPT formed, Filtratio	9.74	149	32.9	Salt III

						n				
K^+	320.4	MeCN	50.0	22.7	2.3	PPT formed, Filtration	7.50	273.4	74.8	Salt III + H
Na^+	251.2	Acetone	50.0	18.4	1.8	PPT formed, Filtration	8.54	241.4	80.1	Salt IV
Na^+	405.3	Acetone	50.0	23.5	5.8	PPT formed, Filtration	9.24	400.5	82.3	Salt V

*Cooling method - Slow Cooling (20 °C/hr)

[00595] Table 49 provides thermal stability data. Table 50 provides TGA thermal data. Table 51 provides stability of crystalline materials from selected salts in different humidity.

[00596] Table 49. Thermal Stability Experiments

Parent Material	Weight (mg)	Temp (°C)	Aliquot time point		Aliquot time point		Parent Material HPLC (%AUC)	HPLC (%AUC)
			Day	XRPD	Day	XRPD		
Filtration, Salt I	42.4	60.0	1	Salt I	7	Salt I	N/A*	N/A*
Filtration, Salt II	47.2	60.0	1	Salt II	7	Salt II	99.9	99.9
Filtration, Salt III	35.6	60.0	1	Salt III	7	Salt III	99.9	99.9
Filtration, Salt IV	37.8	60.0	1	Salt IV	7	Salt IV	99.9	99.9
Filtration, Salt V	3.6.4	60.0	1	Salt V	7	Salt V	99.9	99.9

*Materials poorly dissolved in D_2O, DMSO, or diluent for HPLC analysis. No degradation of the materials (before and after thermal stress analysis) based on ^1H NMR.

[00597] Table 50. TGA thermal hold experiments of crystalline materials from selected salts

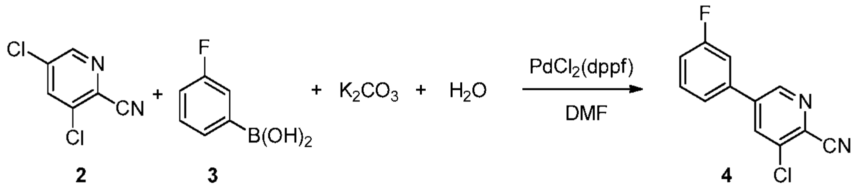
Parent Material	Weight (mg)	Thermal Hold Temperature range, °C	Holding Temp. / time	XRPD		
				Pre-thermal hold	Post thermal hold	Post thermal hold, sample left on bench top, 24 hrs*
Filtration, Salt IV	6.184	30 - 130, at 10 °C/min	130 °C/2 min	Salt IV	Salt IV	Salt IV
Filtration, Salt IV	4.957	180 - 260, at 10 °C/min	260 °C/2 min	Salt IV	Salt VI	Salt VI
Filtration, Salt V	8.84	30 - 160, at 10 °C/min	160 °C/2 min	Salt V	Salt V + missing peaks	Salt V + missing peaks
Filtration, Salt III	8.208	30 - 130, at 10 °C/min	130 °C/2 min	Salt III + Salt IX	Salt III	Salt III

[00598] Table 51. Stability of Crystalline materials from selected salts in different humidity.

Parent Material	Weight (mg)	Humidity condition	XRPD	
			Initial	Post humidity exposure
Filtration, Salt V	4.35	0% RH, RT	Salt V	Salt V + missing peaks
Filtration, Salt V	7.12	65% RH, RT	Salt V	Salt V
Filtration, Salt IV	11.5	65% RH, RT	Salt IV	Salt IV + missing peaks
Filtration, Salt III	19.23	65% RH, RT	Salt III + Salt IX	Salt III + Salt IX

6.5 Synthesis Of Compound 1

6.5.1 Preparation of 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine (4)



[00599] Potassium carbonate (1785 g, 1.49 eq), 3,5-dichloro-2-cyanopyridine (1500 g, 1.0 eq), (3-fluorophenyl)boronic acid (1069.5 g, 1.0 eq), dichloro[1,1'-bis(diphenylphosphino) ferrocene] palladium (II) (DCM adduct $PdCl_2$(dppf)) (30 g, 0.004 eq) and dimethylformamide (10.6 kg) were charged to a 30L reactor equipped with an over-head agitator, condenser, thermocouple and nitrogen sparger. The mixture was agitated and sparged with nitrogen gas through the dip-tube for ca. 30 minutes. Degassed water (969 g) was slowly charged to the mixture while maintaining a temperature of less than 45 °C.

[00600] The reaction mixture was agitated at 20 to 45 °C and sparged with nitrogen gas through the dip-tube for 30 minutes, followed by agitation at 50 °C (between 47 to 53 °C) for 12 to 24 hours until the reaction was determined to be complete due to the disappearance of compound 2 as measured by HPLC.

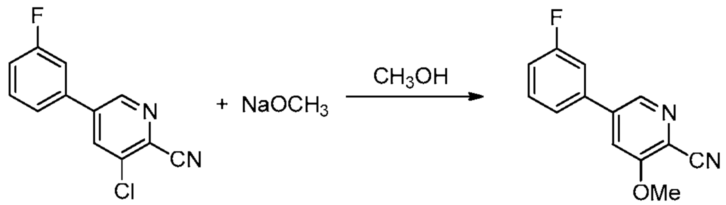
[00601] The reaction mixture was cooled to 22 °C (between 19 to 25 °C). n-Heptane (2.2 kg) and water (12.9 kg) were charged to the reaction mixture while keeping the temperature at no more than 45 °C. After the mixture was agitated at 22 °C (between 19 to 25 °C) for 1 to 2 hours, crude 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine (4) was isolated as a solid by filtration.

[00602] The crude 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine (4) was transferred into an empty reactor with water (12.9 kg). The mixture was agitated at 22 °C (between 19 to 25 °C) for 2 hours. Crude 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine (4) was isolated as a solid by filtration and washed with water (3 kg).

[00603] The crude 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine (4) was transferred into an empty reactor with 2-propanol (14.25 kg). The mixture was agitated at reflux at 82 °C for 1 to 2 hours. After cooling to 22 °C (19 to 25 °C), the mixture was agitated at 22 °C (19 to 25 °C) for 2 to 3 hours. 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine (4) was isolated as a solid by filtration and rinsed with 2-propanol (2.36 kg).

[00604] After being dried under vacuum at 50 °C until the water content was less than 1.5% (~16 hours), 1736.9 g 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine (4) was obtained as a brown solid (yield 86%). Figure 77 depicts the ^{1}H NMR spectrum of 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine (4).

6.5.2 **Preparation of 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine (5)**



4 5

[00605] 5-(3-fluorophenyl)-3-chloro-2-cyanopyridine (1.2 kg, 1.0 eq) and methanol (17.8 kg) were charged to a 30 L reactor equipped with an over-head agitator, condenser, thermocouple and nitrogen bubbler. 25% sodium methoxide in methanol (2.01 kg, 1.8 eq) was charged to the reactor and rinsed with methanol (1.2 kg). The reaction mixture was agitated at reflux (ca. 68 °C) for 12 to 24 hours until the reaction was determined to be complete.

[00606] The reaction mixture was distilled under vacuum to a volume of ca. 12 L with a maximum bath/jacket temperature of 50 °C. After the mixture was cooled to 22 °C (19 to 25 °C), water (12 kg) was charged. After the mixture was agitated at 22 °C (19 to 25 °C) for 1 to 2 hours, crude 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine (5) was isolated as a solid by filtration. The filter cake was washed with methanol (0.95 kg) and pulled dry until no filtrate was observed.

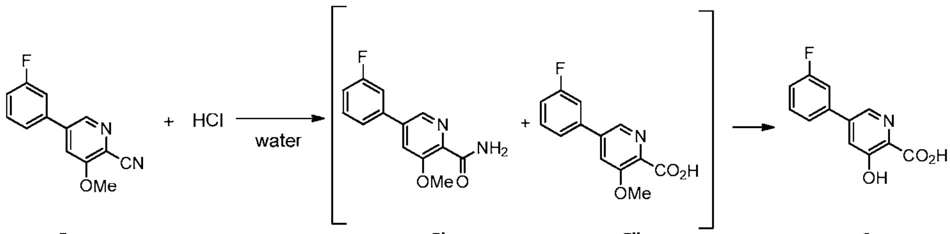
[00607] The crude 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine (5) was transferred into an empty reactor with acetone (19.2 kg) and agitated at 22 °C (between 19 to 25 °C) until all solids dissolved (~1 hour).

[00608] A celite pad (ca. 1") was packed in a 3 L glass Buchner funnel and wetted with acetone. Activated carbon Darco G-60 (0.24 kg) was packed on the top of the celite pad. A second celite pad (ca 1") was packed on the top of the carbon and wetted with acetone. The acetone solution was filtered through the carbon/celite pad and rinsed with acetone (4.8 kg).

[00609] The acetone solution was distilled under vacuum (bath temperature of 50 °C) to a volume of 4.8 L. Methanol (3.6 kg) was charged and the suspension and concentrated to 4.8 L. The acetone chasing was repeated twice. The slurry was agitated at 22 °C (19 to 25 °C) for 2 to 3 hours, 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine (5), filtered and washed with methanol (2.4 kg).

[00610] The isolated 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine (5) was dried under vacuum at 45 °C to give 992.3 g 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine (5) in 84% yield. Figure 78 depicts the ^{1}H NMR spectrum of 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine (5).

6.5.3 Preparation of 5-(3-fluorophenyl)-3-hydroxypyridine-2-carboxylic acid (6)



[00611] 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine (1.35 kg, 1.0 eq) and 37% aqueous HCl (9.72 kg) were charged to a 30 L reactor with condenser, agitator, nitrogen line and scrubber containing ca. 20% aqueous sodium hydroxide. The reaction mixture was heated gradually to 70 °C (67 to 73 °C) over 2 hours.

[00612] After the mixture was agitated at 70 °C (67 to 73 °C) for 3 hours, water (8.1 kg) was charged. The reaction mixture was heated to reflux (108 to 110 °C) and agitated until the reaction was determined to be complete when the total AUC of 5-(3-fluorophenyl)-3-methoxy-2-cyanopyridine 5, 5-(3-fluorophenyl)-3-methoxypicolinamide (5') (*See* ^{1}H NMR in Figure 81) and 5-(3-fluorophenyl)-3-methoxypicolinic acid (5'') (*See* ^{1}H NMR in Figure 81) was less than 1% as measured by HPLC (16 to 48 hr expected).

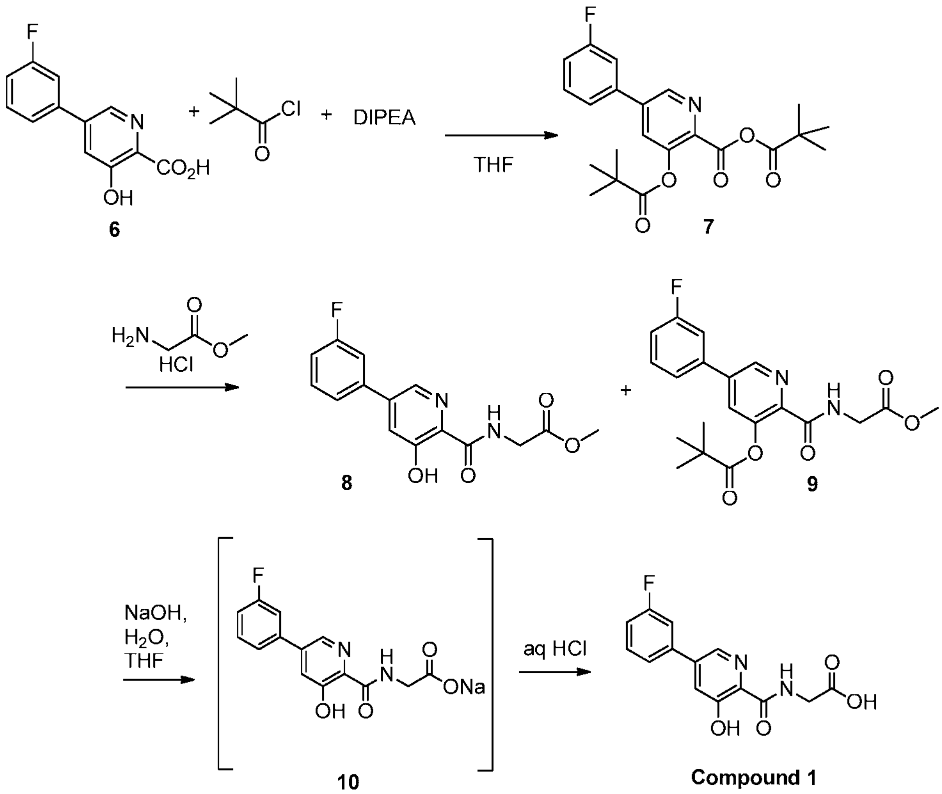
[00613] An alternative procedure after the water is charged comprises of: a) refluxing for ca. 16 hours; b) charging additional concentrated HCl (1.62 kg) to the reaction mixture; c) refluxing for 6 hours; d) charging another portion of concentrated HCl (1.62 kg) to the reaction mixture; and e) refluxing for 12 hours; and f) proceeding to HPLC analysis.

[00614] After the reaction mixture was cooled to 22 °C (19 °C to 25 °C, water (4.05 kg), was charged and the reaction mixture agitated at 22 °C (19 °C to 25 °C) for ca. 3 to 4 hours. The solids were isolated by filtration, rinsed with water (6.75 kg) and dried.

[00615] The solid was transferred into a reactor with acetone (11.75 kg) and agitated at reflux (ca 58 °C) for 2 hours. The mixture was cooled to 22 °C (19 °C to 25 °C) and agitated at 22 °C for 2 hours. The solid was isolated by filtration and rinsed with water (2.13 kg).

[00616] The solid was dried under vacuum at 45 to 50 °C until the water content was less than 0.5% wt. 1200.3 g of 5-(3-fluorophenyl)-3-hydroxypyridine-2-carboxylic acid (6) was obtained as an off-white solid in 84% yield. Figure 79 depicts the ^{1}H NMR spectrum of 5-(3-fluorophenyl)-3-hydroxypyridine-2-carboxylic acid (6).

6.5.4 **Preparation of N-carboxymethyl-5-(3-fluorophenyl)-3-hydroxypyridine-2-carboxamide (1)**



[00617] 5-(3-fluorophenyl)-3-hydroxypyridine-2-carboxylic acid (1.8 kg), THF (7.2 kg) and *N,N*-diisopropylethylamine (2.2 kg) were charged to a 30 L reactor with stirrer, addition funnel, condenser, and nitrogen bubbler. The mixture was cooled to 3 °C (0 to 6 °C).

[00618] Trimethylacetyl chloride (2.05 kg, 2.2 eq) was added via an addition funnel to the reaction mixture while keeping the temperature around 3 °C (0 to 6 °C). The reaction mixture was agitated at 3 °C (0 to 6 °C) until the reaction was determined to be complete by HPLC (1 to 3 hours).

[00619] Glycine methyl ester HCl salt (1.21 kg, 1.25 eq.) was added to the reaction mixture followed by *N,N*-diisopropylethylamine (1.31 kg, 1.30 eq.) while keeping the temperature below 22 °C.

[00620] The reaction mixture was agitated at 22 °C (19 to 25 °C) until deemed complete by HPLC (4 to 12 hours expected).

[00621] Ethanol (4.32 kg) was added and the reaction mixture and agitated for 15 to 30 minutes. The reaction mixture was distilled under reduce pressure at a maximum temperature of 45 °C to ca. 5 volumes. The solvent switch was repeated twice

[00622] Ethanol (4.32 kg) and water (9.0 kg) were added to the reaction mixture and agitated at 22 °C (19 to 25 °C) for 3 hours. The solid was isolated by filtration, rinsed with a mixture of water (1.8 kg) and ethanol (1.42 kg), followed by rinsing with water (1.8 kg). The solid was dried on the filter for ca. 2 hours. The resulting solid was white to off-white and contained 3 to 5% of methyl 2-(5-(3-fluorophenyl)-3-hydroxypicolinamido)acetate (8) (*See* ^{1}H NMR in Figure 83) and 94 to 97% 5-(3-fluorophenyl)-2-(2-methoxy-2-oxoethylcarbamoyl)pyridin-3-yl pivalate (9) (*See* ^{1}H NMR in Figure 82).

[00623] The methyl 2-(5-(3-fluorophenyl)-3-hydroxypicolinamido)acetate (8) and 5-(3-fluorophenyl)-2-(2-methoxy-2-oxoethylcarbamoyl)pyridin-3-yl pivalate (9) mixture, and THF (11.16 kg) were charged to a 30 L reactor with stirrer, addition funnel, thermocouple and nitrogen line. The mixture was agitated at 22 °C (19 to 25 °C) until all solids dissolved, followed by the addition of water (9.0 kg). A solution of 50% NaOH (1.85 kg) in water (1.8 kg) was added to the reaction mixture while keeping the temperature around 3 °C (0 to 5 °C). The reaction mixture was warmed to to 22 °C (19 to 25 °C) and agitated until the reaction was deemed to be complete.

[00624] The reaction mixture was adjusted to ~ pH 2, by adding concentrated HCl (ca. 2.36 kg, 3.1 eq.) while keeping the temperature below 25 °C. The rection mixture was agitated at 22 °C (19 to 25 °C) for ca. 30 minutes to 1 hour. The organic phase was separated and filtered through a one μm filter..

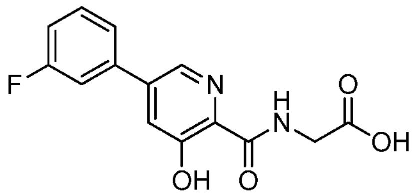
[00625] The solution was distilled under reduced pressure at not more than 45°C to ca. 3 volumes. Acetone (5.65 kg) was charged, followed by distillation under vacuum to ca. 3 volumes. Aftre the solvent chase was twice repeated, water (10.8 kg) was charged to the slurry, followed by agitation at 22 °C (19 to 25 °C) for at least 2 hours. The solid was isolated by filtration, washed with a mixture of acetone (1.42 kg) and water (1.8 kg).

[00626] The solid was dried under vacuum at 50 °C to give 1818.4 g N-carboxymethyl-5-(3-fluorophenyl)-3-hydroxypyridine-2-carboxamide (1) as a white to off white solid in 81%

yield. Figure 80 depicts the ^{1}H NMR spectrum of N-carboxymethyl-5-(3-fluorophenyl)-3-hydroxypyridine-2-carboxamide (1).

What is claimed is:

1. A crystal form comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 12.1, 23.0 and 26.9 °2θ.

2. The crystal form of claim 1 which has an X-ray powder diffraction pattern further comprising peaks at approximately 13.1, 16.6 and 20.1 °2θ.

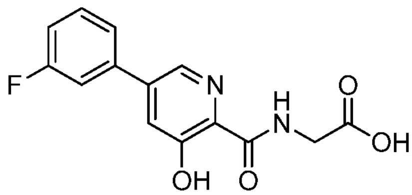
3. The crystal form of claim 1 which has a thermogravimetric analysis thermogram comprising no mass loss of the crystal form before about 155 °C when heated from about 25 °C to about 300 °C.

4. The crystal form of claim 1 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 186 °C when heated from about 25 °C to about 300 °C.

5. The crystal form of claim 1 which is anhydrous.

6. The crystal form of claim 1 which is substantially pure.

7. A crystal form comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 4.3, 8.6, 15.5, and 25.3 °2θ.

8. The crystal form of claim 7 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 0.64% of the total mass of the crystal form before about 155 °C when heated from about 25 °C to about 300 °C.

9. The crystal form of claim 7 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 141.5 °C when heated from about 25 °C to about 300 °C.

10. The crystal form of claim 7 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 185.2 °C when heated from about 25 °C to about 300 °C.

11. The crystal form of claim 7 which has a differential scanning calorimetry thermogram comprising an exotherm event with a maximum at approximately 146.9 °C when heated from about 25 °C to about 300 °C.

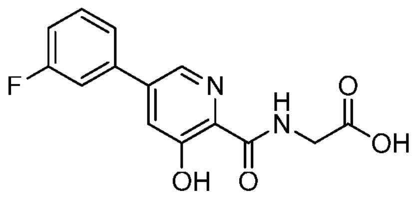
12. The crystal form of claim 7 which is anhydrous.

13. The crystal form of claim 7 which retains a residual solvent.

14. The crystal form of claim 13, wherein the residual solvent is ethanol.

15. The crystal form of claim 7 which is substantially pure.

16. A crystal form comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 4.4, 8.6, 11.4 and 15.6 °2θ.

17. The crystal form of claim 16 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 1.08% of the total mass of the crystal form before about 150 °C when heated from about 25 °C to about 300 °C.

18. The crystal form of claim 16 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 63.5 °C when heated from about 25 °C to about 300 °C.

19. The crystal form of claim 16 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 77.6 °C when heated from about 25 °C to about 300 °C.

20. The crystal form of claim 16 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 134.9 °C when heated from about 25 °C to about 300 °C.

21. The crystal form of claim 16 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 185.8 °C when heated from about 25 °C to about 300 °C.

22. The crystal form of claim 16 which has a differential scanning calorimetry thermogram comprising an exotherm event with a maximum at approximately 143.0 °C when heated from about 25 °C to about 300 °C.

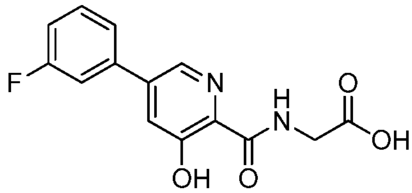
23. The crystal form of claim 16 which is anhydrous.

24. The crystal form of claim 16 which retains a residual solvent.

25. The crystal form of claim 24, wherein the residual solvent is methyl ethyl ketone.

26. The crystal form of claim 16 which is substantially pure.

27. A crystal form comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 4.3, 7.4, 8.6 and 15.5 °2θ.

28. The crystal form of claim 27 which has a thermogravimetric analysis thermogram comprising no mass loss of the crystal form before 155 °C when heated from about 25 °C to about 300 °C.

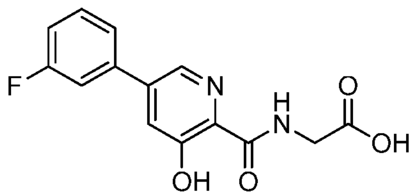
29. The crystal form of claim 27 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 185.2 °C when heated from about 25 °C to about 300 °C.

30. The crystal form of claim 29 which has a differential scanning calorimetry thermogram comprising an exotherm event with a maximum at approximately 118.7 °C when heated from about 25 °C to about 300 °C.

31. The crystal form of claim 27 which is anhydrous.

32. The crystal form of claim 27 which is substantially pure.

33. A crystal form comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 4.3, 8.6, 15.5 and 27.9 °2θ.

34. The crystal form of claim 33 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 1.96 % of the total mass of the crystal form before 165 °C when heated from about 25 °C to about 300 °C.

35. The crystal form of claim 33 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 154.8 °C when heated from about 25 °C to about 300 °C.

36. The crystal form of claim 33 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 185.6 °C when heated from about 25 °C to about 300 °C.

37. The crystal form of claim 33 which has a differential scanning calorimetry thermogram comprising an exotherm event with a maximum at approximately 156.7 °C when heated from about 25 °C to about 300 °C.

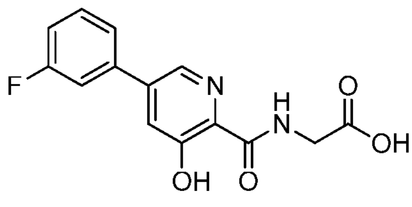
38. The crystal form of claim 33 which is anhydrous.

39. The crystal form of claim 33 which retains a residual solvent.

40. The crystal form of claim 39, wherein the residual solvent is ethyl acetate.

41. The crystal form of claim 33 which is substantially pure.

42. A crystal form comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 4.0, 4.2 and 15.2 °2θ.

43. The crystal form of claim 42 which has an X-ray powder diffraction pattern further comprising peaks at approximately 7.9, 8.4 and 15.4 °2θ.

44. The crystal form of claim 42 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 1.86% of the total mass of the crystal form before 110 °C when heated from about 25 °C to about 300 °C.

45. The crystal form of claim 42 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 64.1 °C when heated from about 25 °C to about 300 °C.

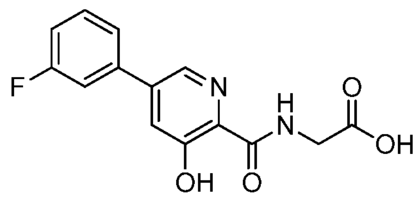
46. The crystal form of claim 42 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 91.3 °C when heated from about 25 °C to about 300 °C.

47. The crystal form of claim 42 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 185.9 °C when heated from about 25 °C to about 300 °C.

48. The crystal form of claim 42 which is a hydrate.

49. The crystal form of claim 42 which is substantially pure.

50. A crystal form comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 4.2, 8.3, 15.2 and 20.9 °2θ.

51. The crystal form of claim 50 which has an X-ray powder diffraction pattern further comprising peaks at approximately 15.4 and 17.8 °2θ.

52. The crystal form of claim 50 which has a thermogravimetric analysis thermogram comprising no mass loss of the crystal form before 110 °C when heated from about 25 °C to about 300 °C.

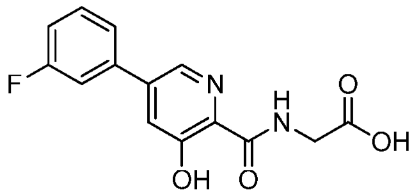
53. The crystal form of claim 50 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 90.5 °C when heated from about 25 °C to about 300 °C.

54. The crystal form of claim 50 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 184.9 °C when heated from about 25 °C to about 300 °C.

55. The crystal form of claim 50 which is anhydrous.

56. The crystal form of claim 50 which is substantially pure.

57. A crystal form comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 14.1, 18.8 and 21.4 °2θ.

58. The crystal form of claim 57 which has an X-ray powder diffraction pattern further comprising peaks at approximately 17.2, 24.6 and 25.7 °2θ.

59. The crystal form of claim 57 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 6.4% of the total mass of the crystal form before 140 °C when heated from about 25 °C to about 130 °C.

60. The crystal form of claim 57 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 9.8% of the total mass of the crystal form before 240 °C when heated from about 25 °C to about 130 °C.

61. The crystal form of claim 57 which has a differential scanning calorimetry thermogram comprising an endotherm event with a maximum at approximately 88.0 °C when heated from about 25 °C to about 300 °C.

62. The crystal form of claim 57 which is a solvate.

63. The crystal form of claim 57 which is a dimethyl sulfoxide solvate.

64. The crystal form of claim 57 which is a mono-dimethyl sulfoxide solvate.

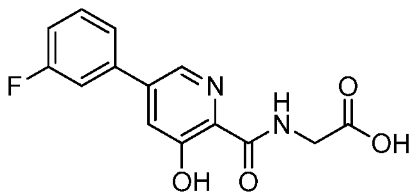
65. The crystal form of claim 57 which is substantially pure.

66. A pharmaceutical composition comprising a solid form of anyone of claims 1-65.

67. A method for treatment or prevention of a cancer, comprising administering to a patient having cancer an effective amount of a solid form of any one of claims 1-65.

68. A method for treatment or prevention of a cancer, comprising administering to a patient having cancer an effective amount of a solid form of any one of claims 1-65 and an effective amount of one or more other chemotherapeutic agents.

69. A hemi-calcium salt comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 3.2, 9.5 and 16.0 °2θ.

70. The salt of claim 69 which has an X-ray powder diffraction pattern further comprising peaks at approximately 15.6, 19.2 and 22.4 °2θ.

71. The salt of claim 70 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 0.34% of the total mass of the salt when heated from about 65 °C to about 105 °C.

72. The salt of claim 71 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 1.41% of the total mass of the salt when heated from about 140 °C to about 190 °C.

73. The salt of claim 72 which has a thermogravimetric analysis thermogram comprising a decomposition event with an onset temperature at about 213.8 °C.

74. The salt of claim 70 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 104.0 °C when heated from about 25 °C to about 230 °C.

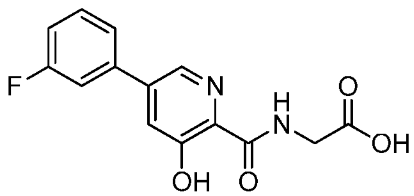
75. The salt of claim 74 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 170.6 °C when heated from about 25 °C to about 230 °C.

76. The salt of claim 75 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 179.1 °C when heated from about 25 °C to about 230 °C.

77. The salt of claim 76 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 210.6 °C when heated from about 25 °C to about 230 °C.

78. The salt of claim 70 which is substantially pure.

79. A dihydrated hemi-calcium salt comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 10.1, 16.9 and 23.7 °2θ.

80. The salt of claim 79 which has an X-ray powder diffraction pattern further comprising peaks at approximately 3.4, 13.2 and 20.2 °2θ.

81. The salt of claim 80 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 10.98% of the total mass of the salt when heated from about 65 °C to about 140 °C.

82. The salt of claim 81 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 0.33% of the total mass of the salt when heated from about 150 °C to about 180 °C.

83. The salt of claim 82 which has a thermogravimetric analysis thermogram comprising a decomposition event with an onset temperature at about 298.0 °C.

84. The salt of claim 80 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 115.5 °C when heated from about 25 °C to about 350 °C.

85. The salt of claim 84 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 127.0 °C when heated from about 25 °C to about 350 °C.

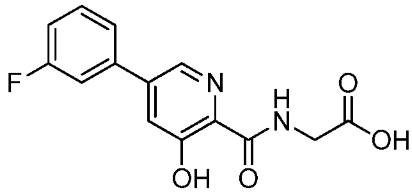
86. The salt of claim 85 which has a differential scanning calorimetry thermogram comprising an exotherm with a maximum at approximately 200.5 °C when heated from about 25 °C to about 350 °C.

87. The salt of claim 86 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 220.8 °C when heated from about 25 °C to about 350 °C.

88. The salt of claim 87 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 311.3 °C when heated from about 25 °C to about 350 °C.

89. The salt of claim 80 which is substantially pure.

90. A mono-potassium salt comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 14.5, 14.7 and 15.3 °2θ.

91. The salt of claim 90 which has an X-ray powder diffraction pattern further comprising peaks at approximately 4.7, 10.9 and 15.2 °2θ.

92. The salt of claim 91 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 0.91% of the total mass of the salt when heated from about 40 °C to about 70 °C.

93. The salt of claim 92 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 0.25% of the total mass of the salt when heated from about 100 °C to about 120 °C.

94. The salt of claim 93 which has a thermogravimetric analysis thermogram comprising a decomposition event with an onset temperature at about 297.2 °C.

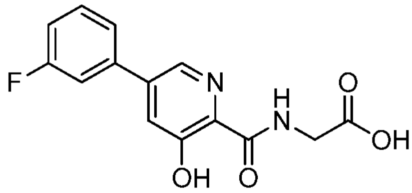
95. The salt of claim 91 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 54.3 °C when heated from about 25 °C to about 350 °C.

96. The salt of claim 95 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 109.3 °C when heated from about 25 °C to about 350 °C.

97. The salt of claim 96 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 314.4 °C when heated from about 25 °C to about 350 °C.

98. The salt of claim 91 which is substantially pure.

99. A monohydrated mono-sodium salt comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 3.2, 9.5 and 19.0 °2θ.

100. The salt of claim 99 which has an X-ray powder diffraction pattern further comprising peaks at approximately 6.3, 15.8 and 19.4 °2θ.

101. The salt of claim 100 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 5% of the total mass of the salt when heated from about 60 °C to about 120 °C.

102. The salt of claim 101 which has a thermogravimetric analysis thermogram comprising a decomposition event with an onset temperature at about 302.5 °C.

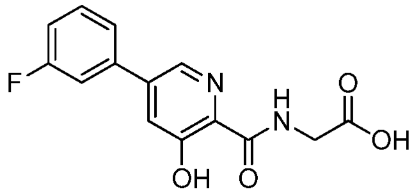
103. The salt of claim 100 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 107.9 °C when heated from about 25 °C to about 350 °C.

104. The salt of claim 103 which has a differential scanning calorimetry thermogram comprising an exotherm with a maximum at approximately 217.2 °C when heated from about 25 °C to about 350 °C.

105. The salt of claim 104 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 307.4 °C when heated from about 25 °C to about 350 °C.

106. The salt of claim 100 which is substantially pure.

107. A monohydrated bis-sodium salt comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 10.0, 13.6 and 16.7 °2θ.

108. The salt of claim 107 which has an X-ray powder diffraction pattern further comprising peaks at approximately 3.2, 13.3 and 14.0 °2θ.

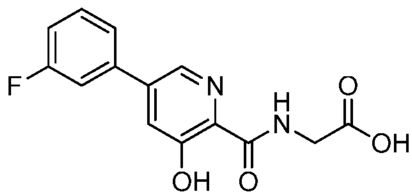
109. The salt of claim 108 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 5.85% of the total mass of the salt when heated from about 40 °C to about 130 °C.

110. The salt of claim 109 which has a thermogravimetric analysis thermogram comprising a decomposition event with an onset temperature at about 344.8 °C.

111. The salt of claim 108 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 93.3 °C when heated from about 25 °C to about 350 °C.

112. The salt of claim 108 which is substantially pure.

113. An anhydrous mono-sodium salt comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 3.0, 3.4 and 10.1 °2θ.

114. The salt of claim 113 which has an X-ray powder diffraction pattern further comprising peaks at approximately 11.9, 16.7 and 18.1 °2θ.

115. The salt of claim 114 which has a thermogravimetric analysis thermogram comprising a decomposition event with an onset temperature at about 305.7 °C.

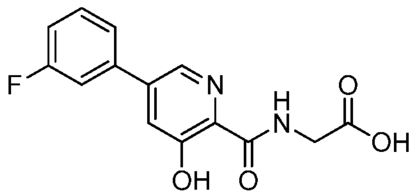
116. The salt of claim 114 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 282.4 °C when heated from about 25 °C to about 350 °C.

117. The salt of claim 116 which has a differential scanning calorimetry thermogram comprising an exotherm with a maximum at approximately 283.9 °C when heated from about 25 °C to about 350 °C.

118. The salt of claim 117 which has a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 308.4 °C when heated from about 25 °C to about 350 °C.

119. The salt of claim 114 which is substantially pure.

120. A hydrated mono-sodium salt comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 3.4, 10.0 and 14.9 °2θ.

121. The salt of claim 120 which has an X-ray powder diffraction pattern further comprising peaks at approximately 10.9, 15.5 and 16.7 °2θ.

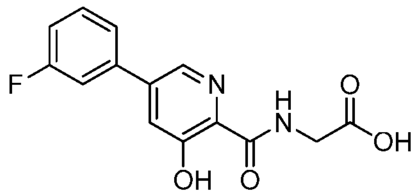
122. The salt of claim 121 which has a thermogravimetric analysis thermogram comprising a decomposition event with an onset temperature at about 290.6 °C.

123. The salt of claim 121 which has a differential scanning calorimetry thermogram comprising a broad transition before approximately 90 °C when heated from about 25 °C to about 350 °C.

124. The salt of claim 123 which has a differential scanning calorimetry thermogram comprising a glass transition at approximately 160 °C when heated from about 25 °C to about 350 °C.

125. The salt of claim 121 which is substantially pure.

126. An anhydrous mono-sodium salt comprising Compound 1, or a tautomer thereof:



1

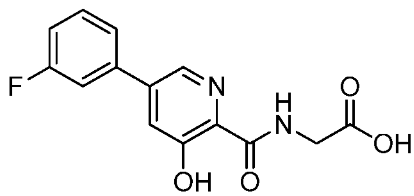
which has an X-ray powder diffraction pattern comprising peaks at approximately 3.1, 3.4 and 15.0 °2θ.

127. The salt of claim 126 which has an X-ray powder diffraction pattern further comprising peaks at approximately 13.7, 15.6 and 15.7 °2θ.

128. The salt of claim 127 which has a thermogravimetric analysis thermogram comprising a decomposition event with an onset temperature at about 291.2 °C.

129. The salt of claim 127 which is substantially pure.

130. An anhydrous mono-sodium salt comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 3.2, 9.5 and 19.0 °2θ.

131. The salt of claim 130 which has an X-ray powder diffraction pattern further comprising peaks at approximately 3.1, 6.3 and 15.8 °2θ.

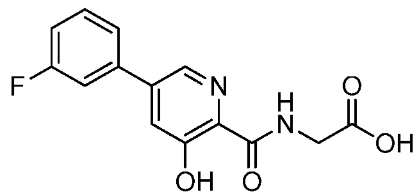
132. The salt of claim 131 which has a thermogravimetric analysis thermogram comprising a decomposition event with an onset temperature at about 301.8 °C.

133. The salt of claim 131 which has a differential scanning calorimetry thermogram comprising an endotherm at approximately 82.8 °C when heated from about 25 °C to about 350 °C.

134. The salt of claim 133 which has a differential scanning calorimetry thermogram comprising an exotherm at approximately 229.5 °C when heated from about 25 °C to about 350 °C.

135. The salt of claim 131 which is substantially pure.

136. A hydrated mono-sodium salt comprising Compound 1, or a tautomer thereof:



1

which has an X-ray powder diffraction pattern comprising peaks at approximately 3.2, 3.7 and 25.6 °2θ.

137. The salt of claim 136 which has an X-ray powder diffraction pattern further comprising peaks at approximately 15.4, 18.7 and 23.8 °2θ.

138. The salt of claim 137 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 1.3% of the total mass of the salt when heated from about 60 °C to about 120 °C.

139. The salt of claim 138 which has a thermogravimetric analysis thermogram comprising a total mass loss of approximately 2.3% of the total mass of the salt when heated from about 120 °C to about 180 °C.

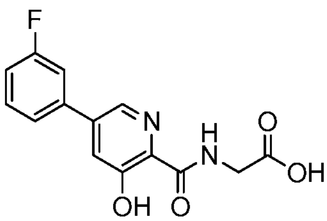
140. The salt of claim 137 which has a differential scanning calorimetry thermogram comprising an endotherm at approximately 91.3 °C when heated from about 25 °C to about 350 °C.

141. The salt of claim 140 which has a differential scanning calorimetry thermogram comprising an endotherm at approximately 149.3 °C when heated from about 25 °C to about 350 °C.

142. The salt of claim 141 which has a differential scanning calorimetry thermogram comprising an exotherm at approximately 230.6 °C when heated from about 25 °C to about 350 °C.

143. The salt of claim 137 which is substantially pure.

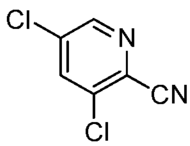
144. A method for preparing Compound 1



1,

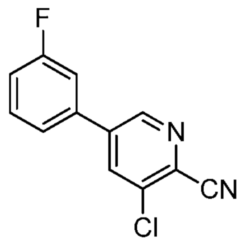
the method comprising

1) contacting compound 2



2

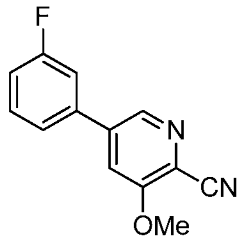
with (3-fluorophenyl)boronic acid and a coupling agent or catalyst in a solvent in the presence of a base at about 25 °C to about 75 °C to yield compound 4



4,

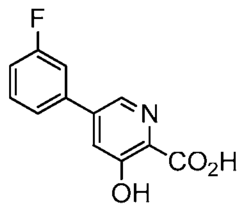
wherein the coupling agent or catalyst is DCM adduct $PdCl_2$(dppf) or $PdCl_2$(dppf));

2) contacting compound 4 with a methoxide in a solvent at about 50 °C to about 90 °C to yield compound 5



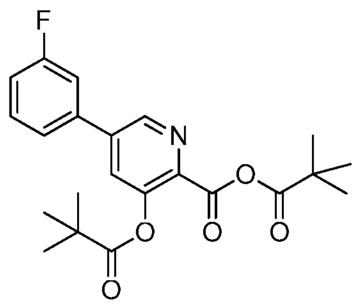
5;

3) contacting compound 5 with an acid in a solvent at about 60 °C to about 110 °C to yield compound 6



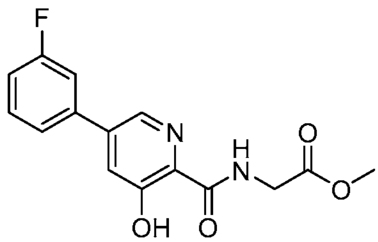
6;

4) contacting compound 6 with trimethylacetyl chloride in a solvent in the presence of a base at about -10 °C to about 10 °C to yield compound 7

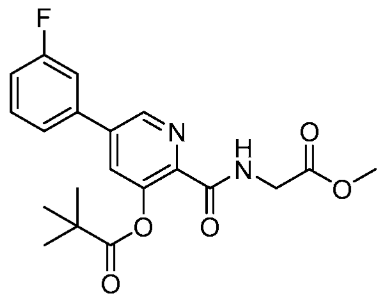


7;

5) contacting compound 7 with glycine methyl ester HCl salt in a solvent in the presence of a base at about 10 °C to about 35 °C to give a mixture of compound 8 and compound 9

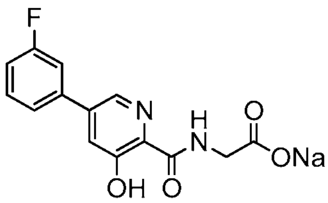


8



9;

6) contacting the mixture of compound 8 and compound 9 with a base in a solvent at about 10 °C to about 35 °C to yield compound 10



10; and

7) contacting compound 10 with an acid in a solvent at about 10 °C to about 35 °C to yield Compound 1.

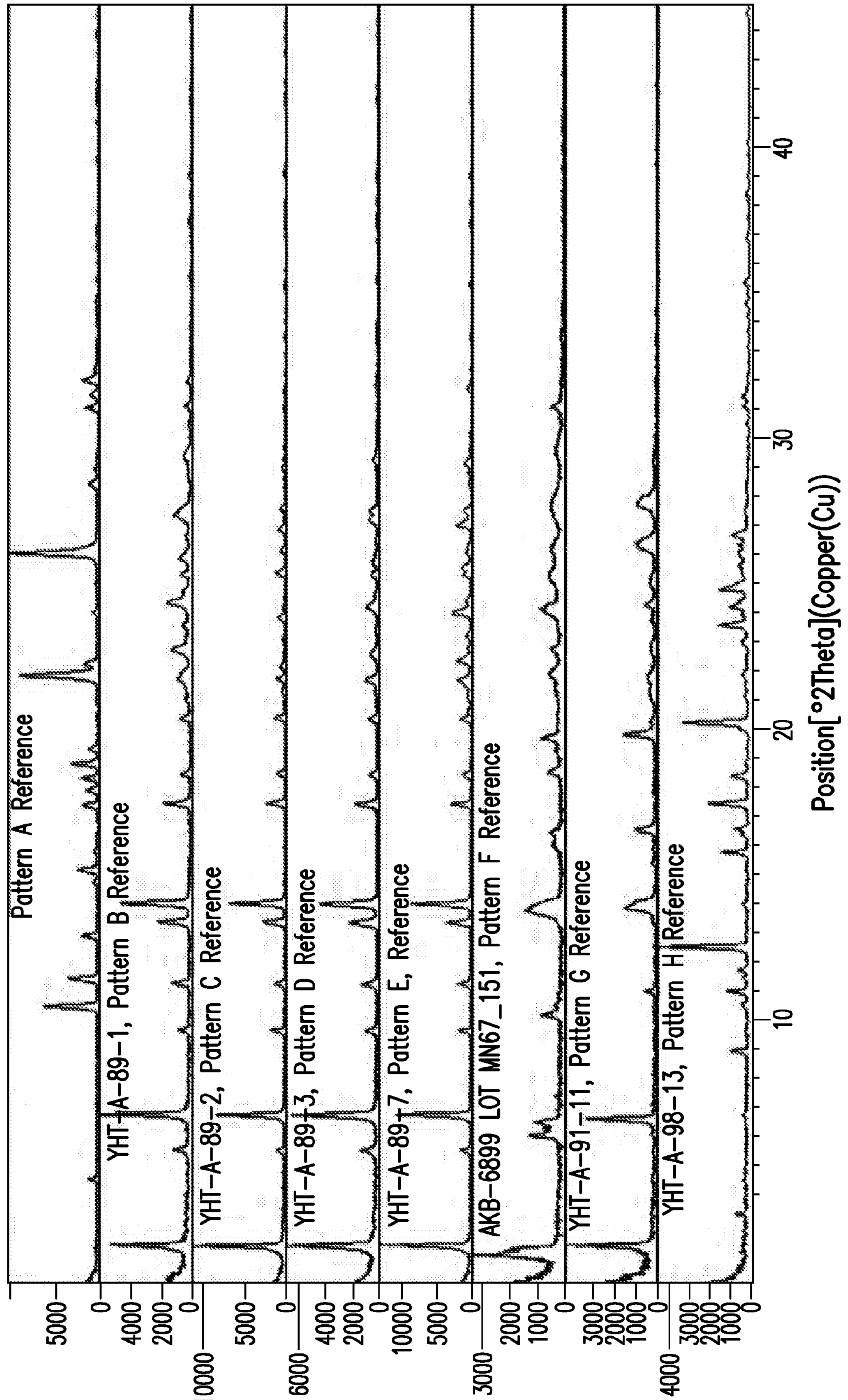
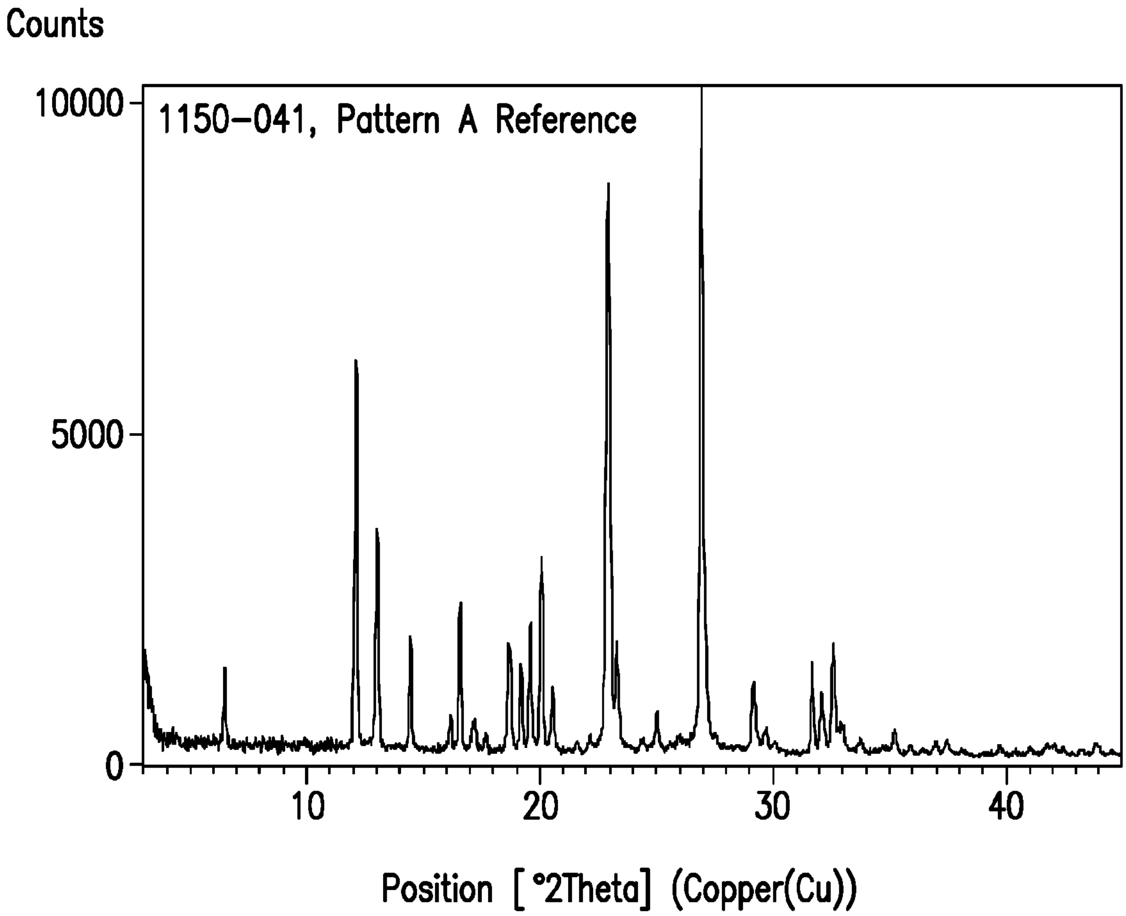

Pattern A Reference
YHT-A-89-1, Pattern B Reference
YHT-A-89-2, Pattern C Reference
YHT-A-89-3, Pattern D Reference
YHT-A-89-7, Pattern E, Reference
AKB-6899 LOT MN67_151, Pattern F Reference
YHT-A-91-11, Pattern G Reference
YHT-A-98-13, Pattern H Reference
Position[°2Theta](Copper(Cu))

FIG. 1



Counts
10000
5000
0
1150-041, Pattern A Reference
10
20
30
40
Position [°2Theta] (Copper(Cu))

FIG. 2

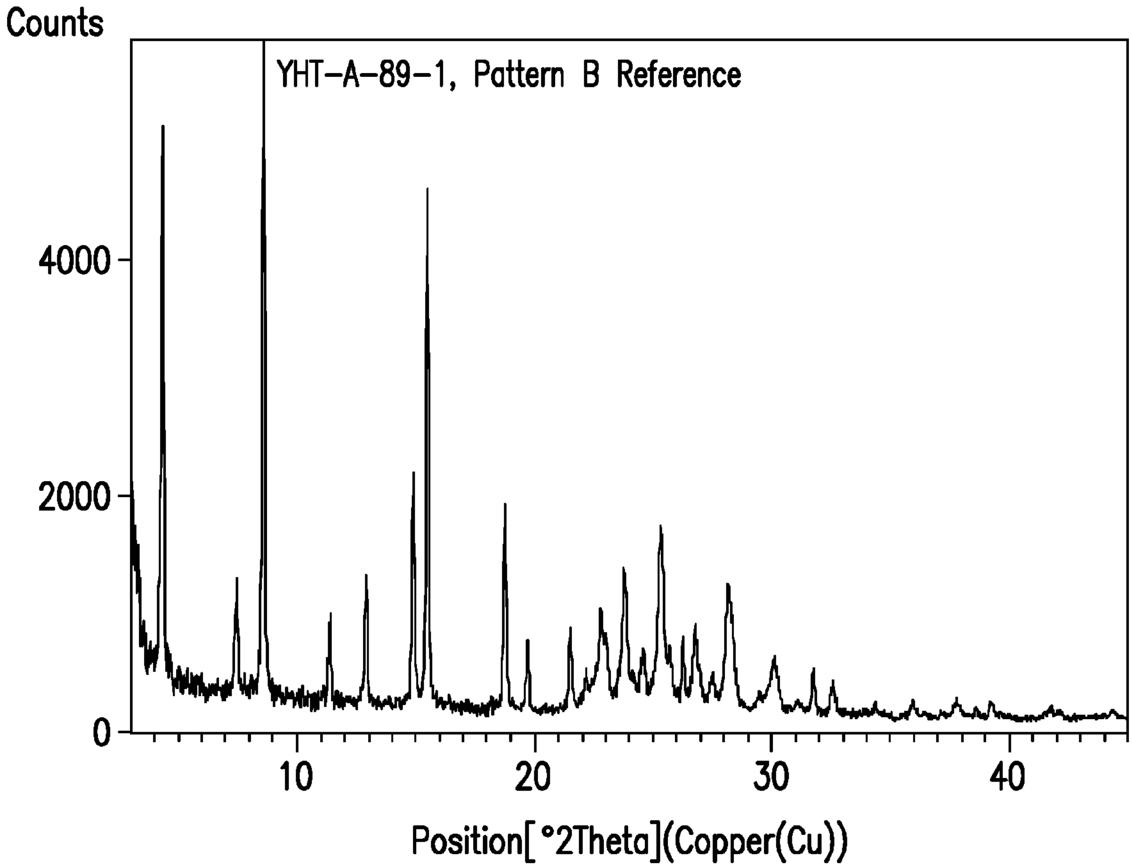

Counts
YHT-A-89-1, Pattern B Reference
4000
2000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 3

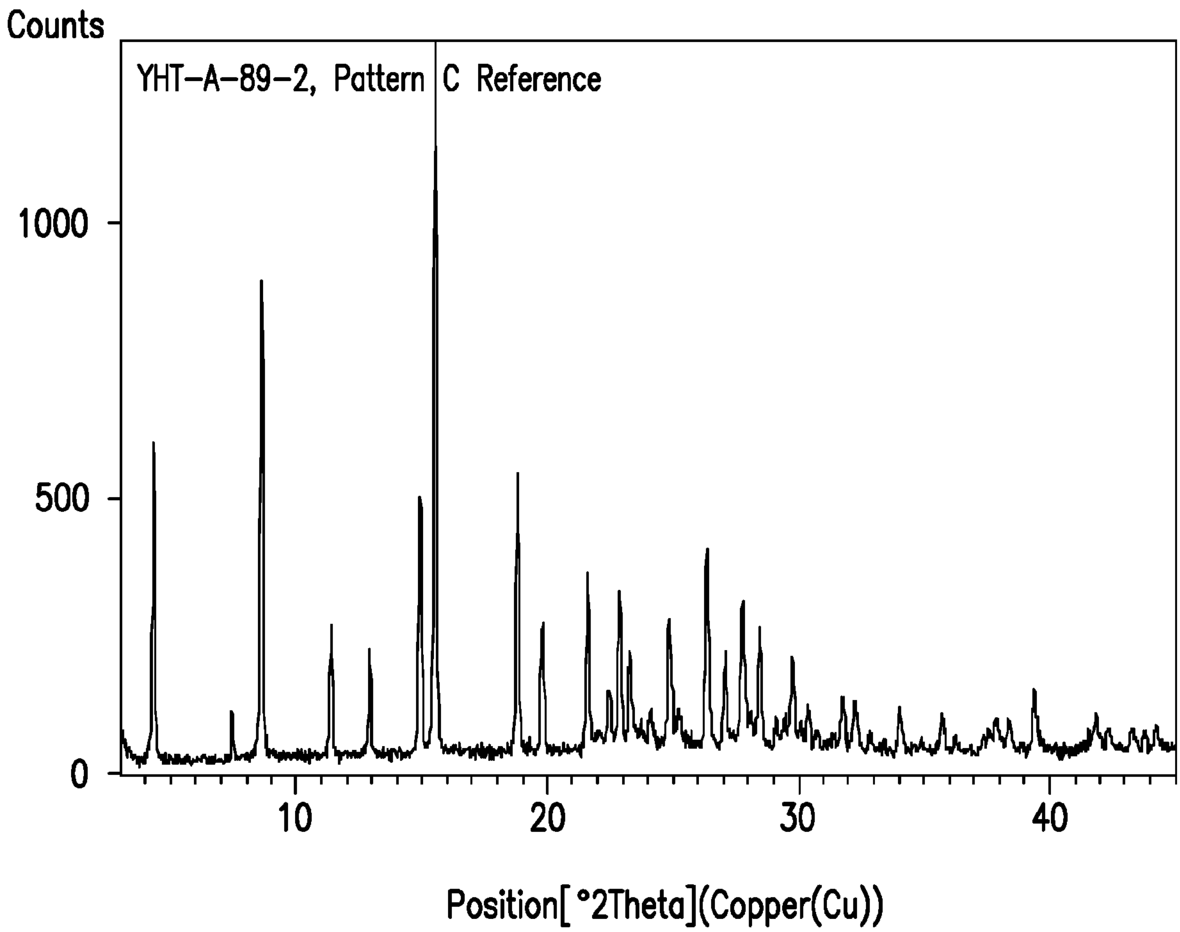

Counts
YHT-A-89-2, Pattern C Reference
1000
500
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 4

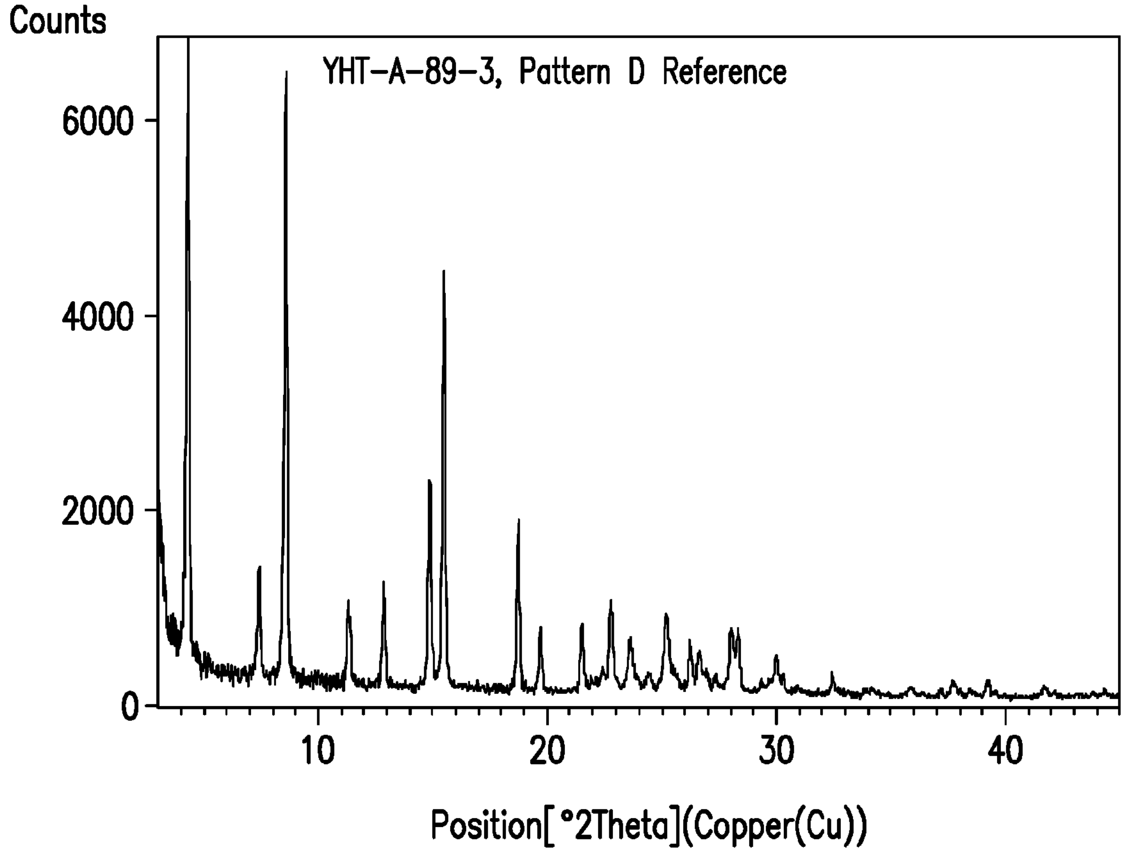

Counts
YHT-A-89-3, Pattern D Reference
6000
4000
2000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 5

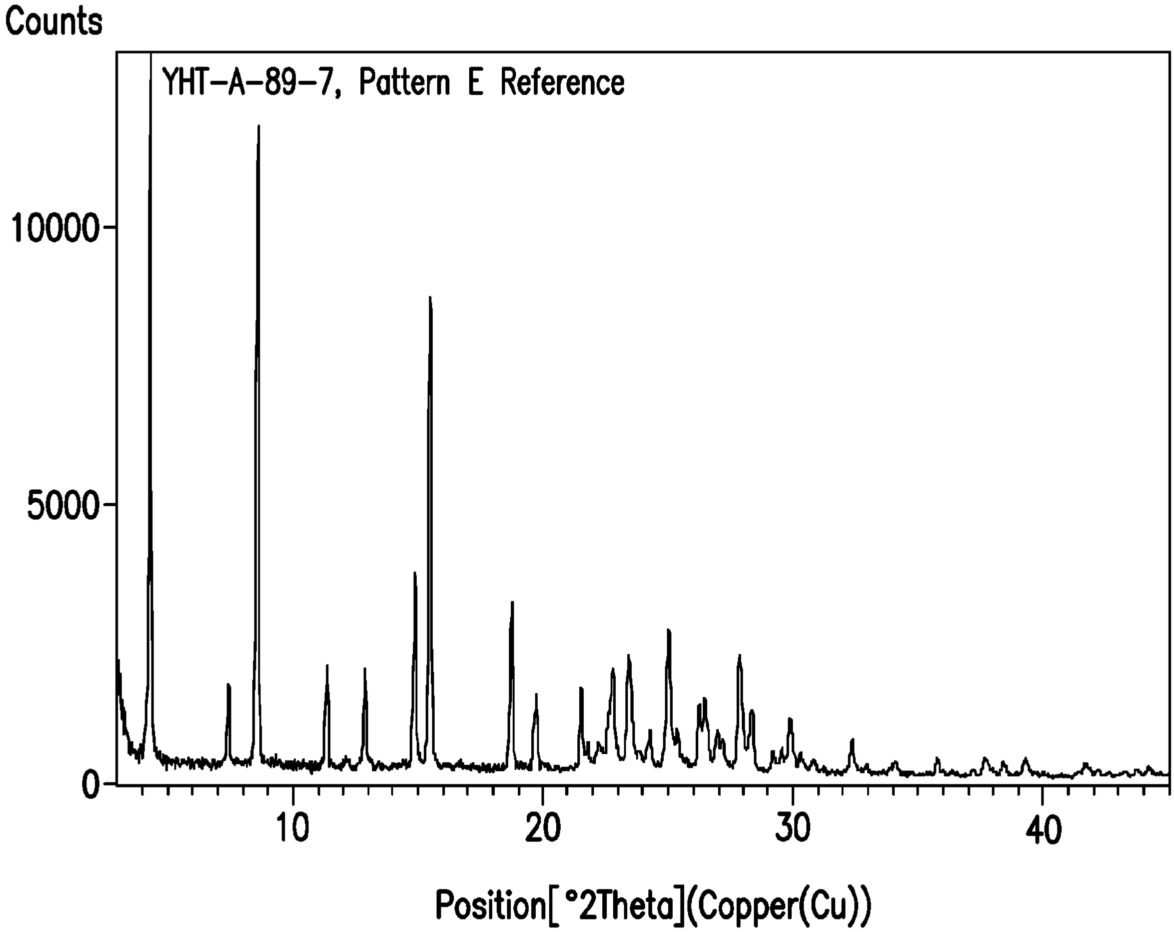

Counts
YHT-A-89-7, Pattern E Reference
10000
5000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 6

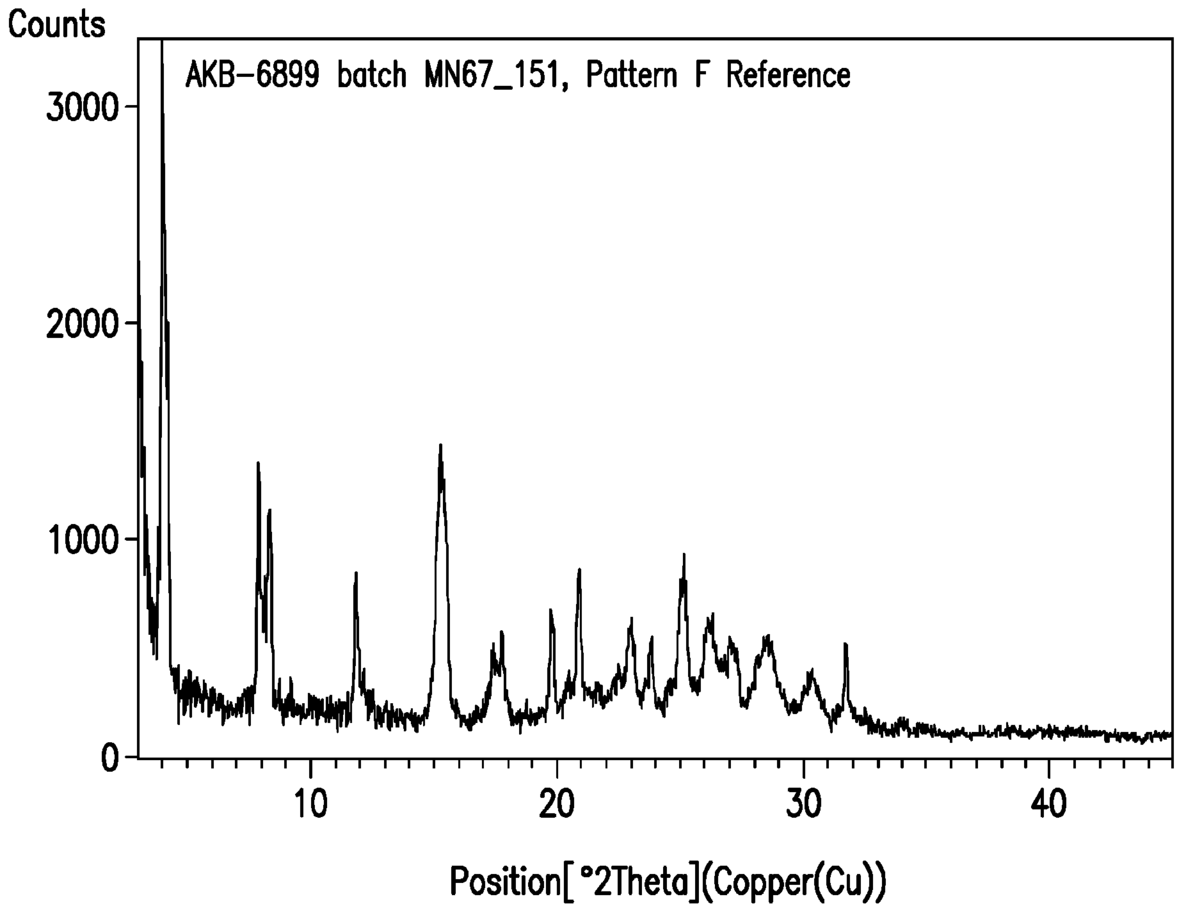

Counts
AKB-6899 batch MN67_151, Pattern F Reference
3000
2000
1000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 7

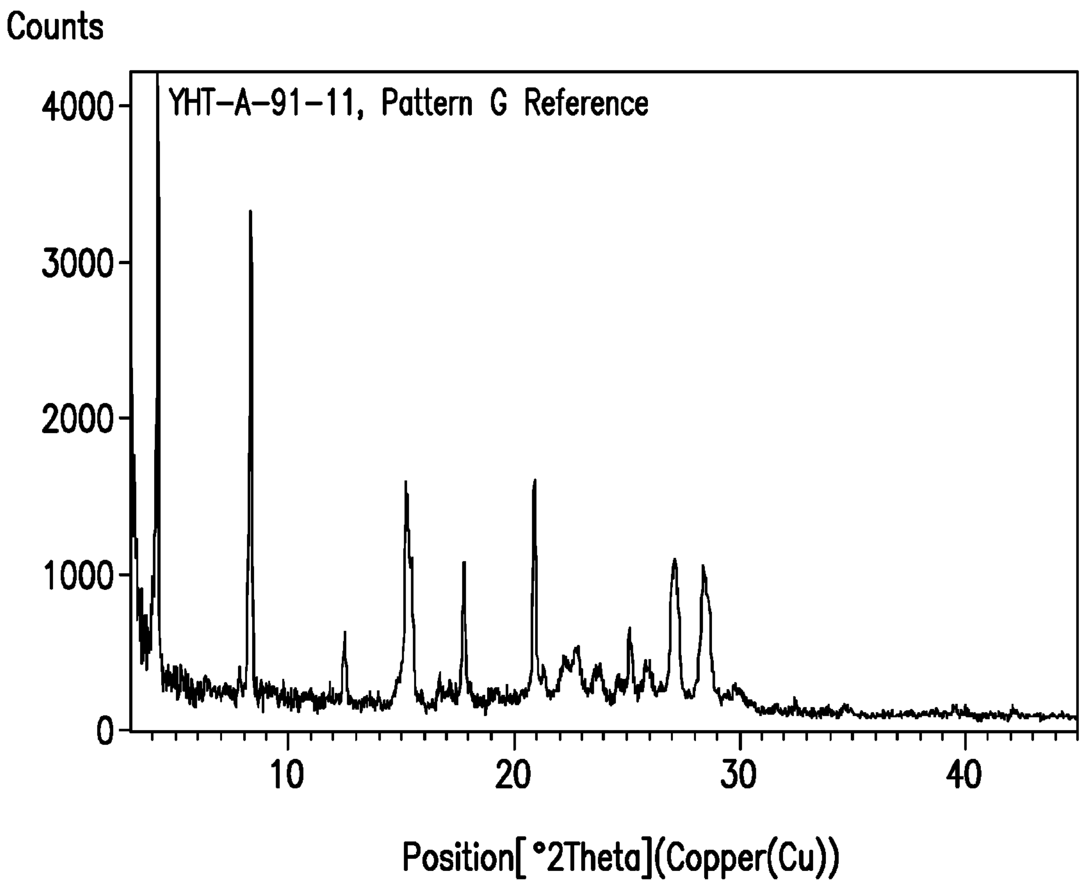

Counts
YHT-A-91-11, Pattern G Reference
4000
3000
2000
1000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 8

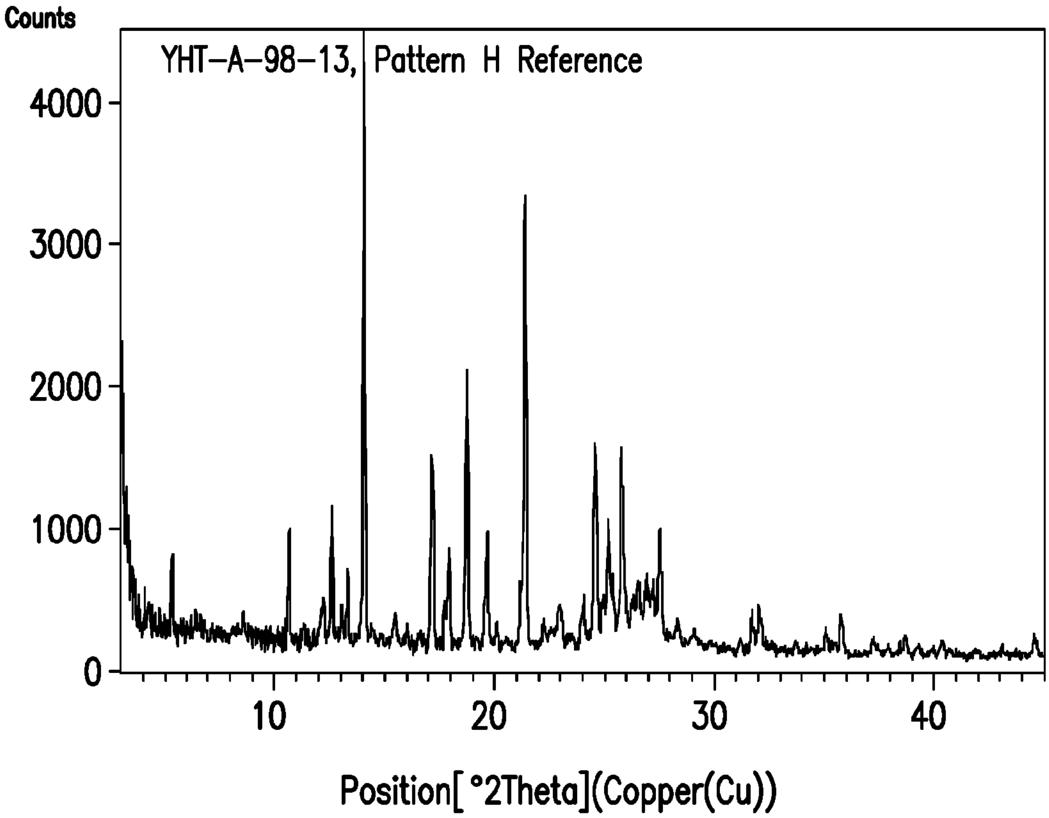

Counts
YHT-A-98-13, Pattern H Reference
4000
3000
2000
1000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 9

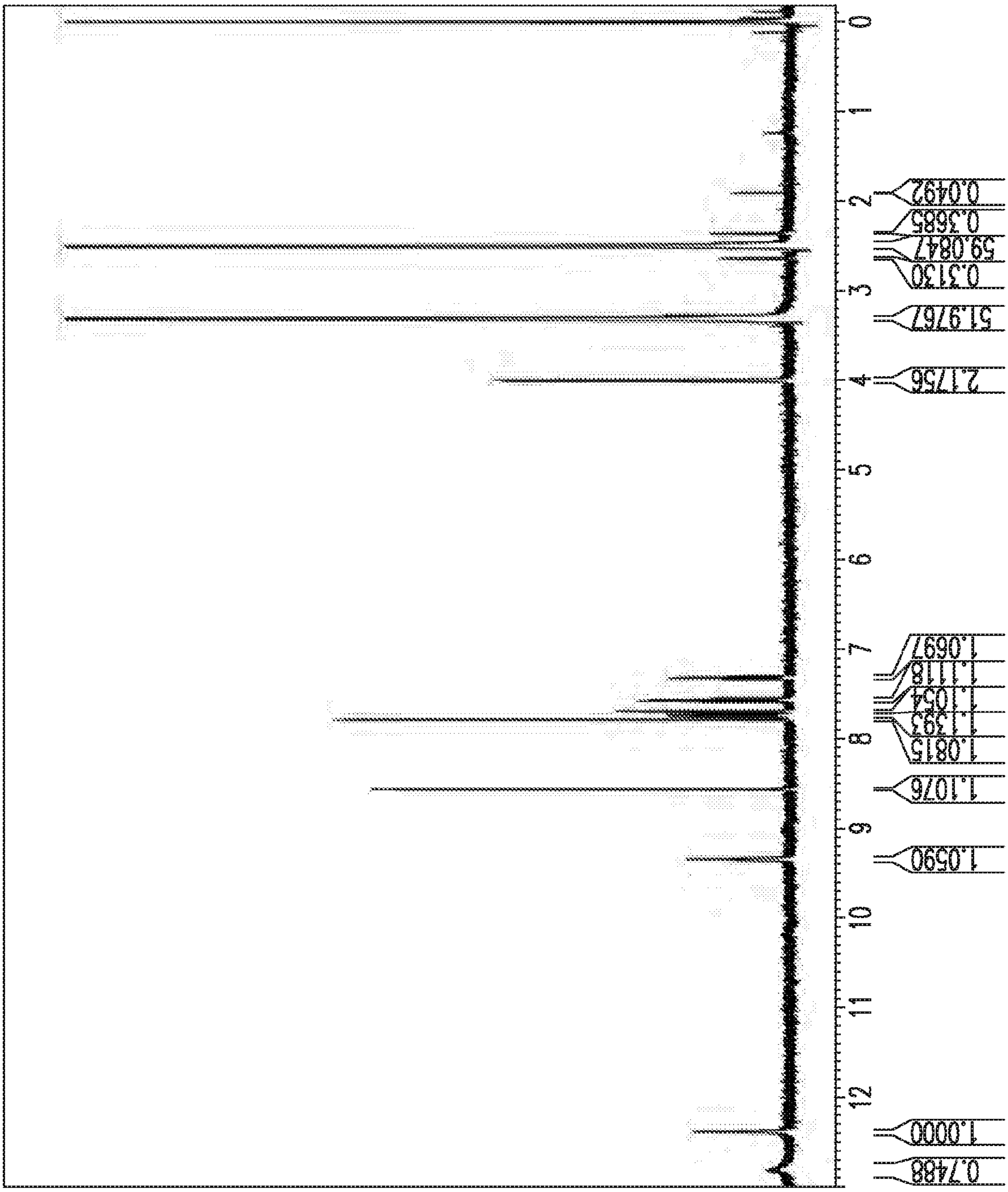
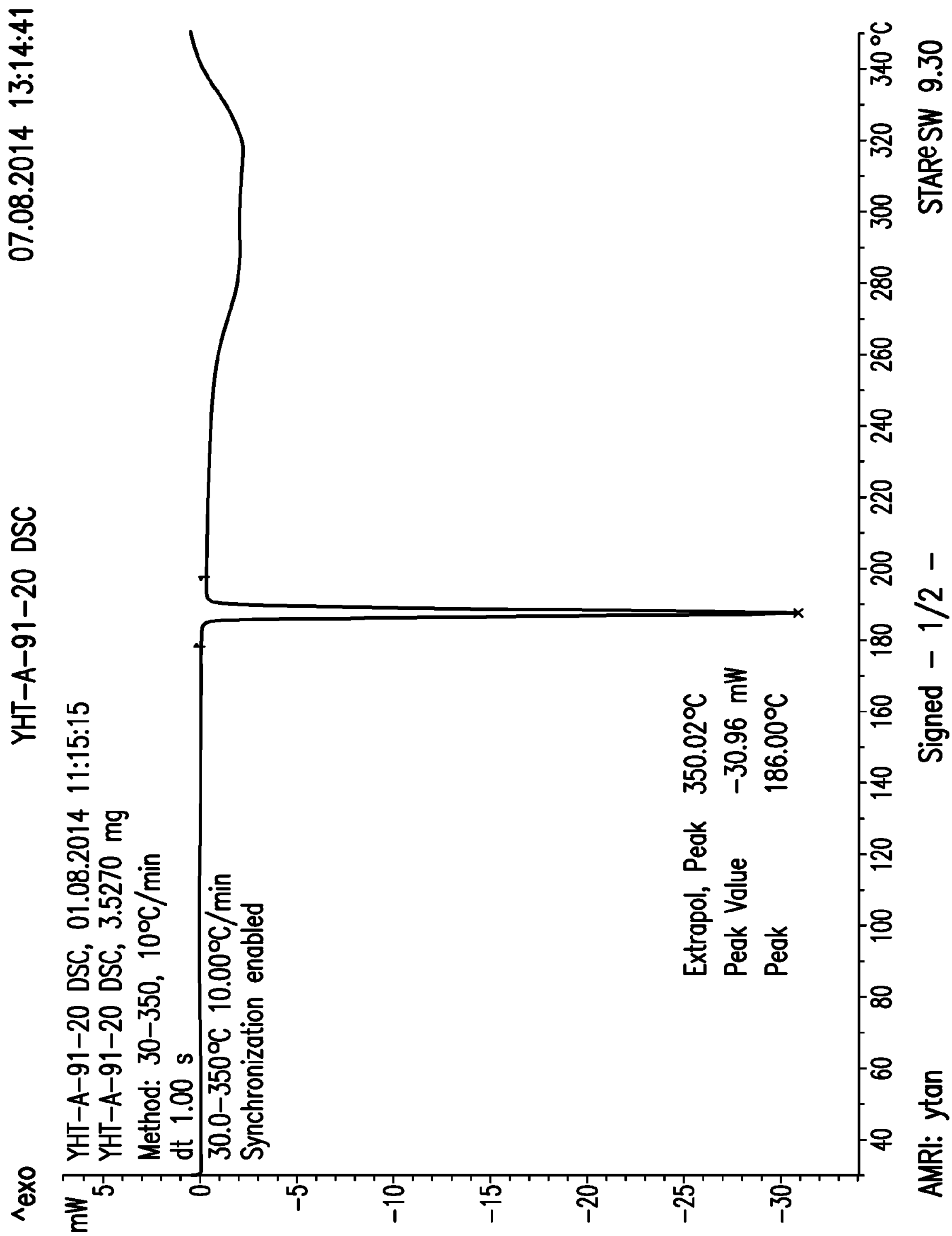

0
1
2
3
4
5
6
7
8
9
10
11
12
0.0492
0.3685
59.0847
0.3130
51.9767
2.1756
1.0697
1.1118
1.1054
1.1393
1.0815
1.1076
1.0590
1.0000
0.7488

FIG. 10



07.08.2014 13:14:41
YHT-A-91-20 DSC
^exo
mW
YHT-A-91-20 DSC, 01.08.2014 11:15:15
YHT-A-91-20 DSC, 3.5270 mg
Method: 30-350, 10°C/min
dt 1.00 s
30.0-350°C 10.00°C/min
Synchronization enabled
Extrapol, Peak 350.02°C
Peak Value -30.96 mW
Peak 186.00°C
5
0
-5
-10
-15
-20
-25
-30
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
AMRI: ytan
Signed - 1/2 -
STARe SW 9.30

FIG. 11

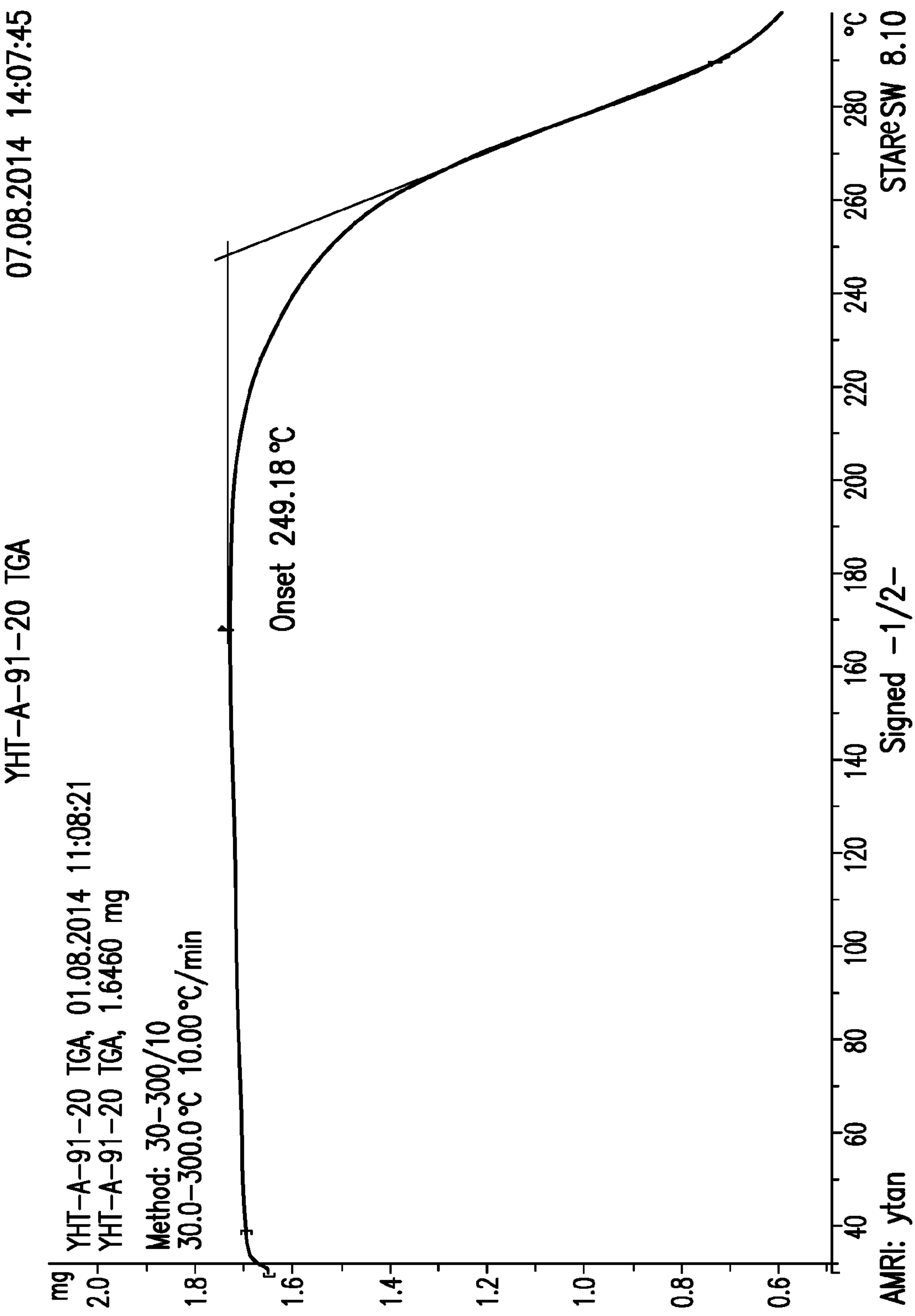

YHT-A-91-20 TGA
07.08.2014 14:07:45
YHT-A-91-20 TGA, 01.08.2014 11:08:21
YHT-A-91-20 TGA, 1.6460 mg
Method: 30-300/10
30.0-300.0 °C 10.00 °C/min
Onset 249.18 °C
mg
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
AMRI: ytan
Signed -1/2-
STARe SW 8.10

FIG. 12

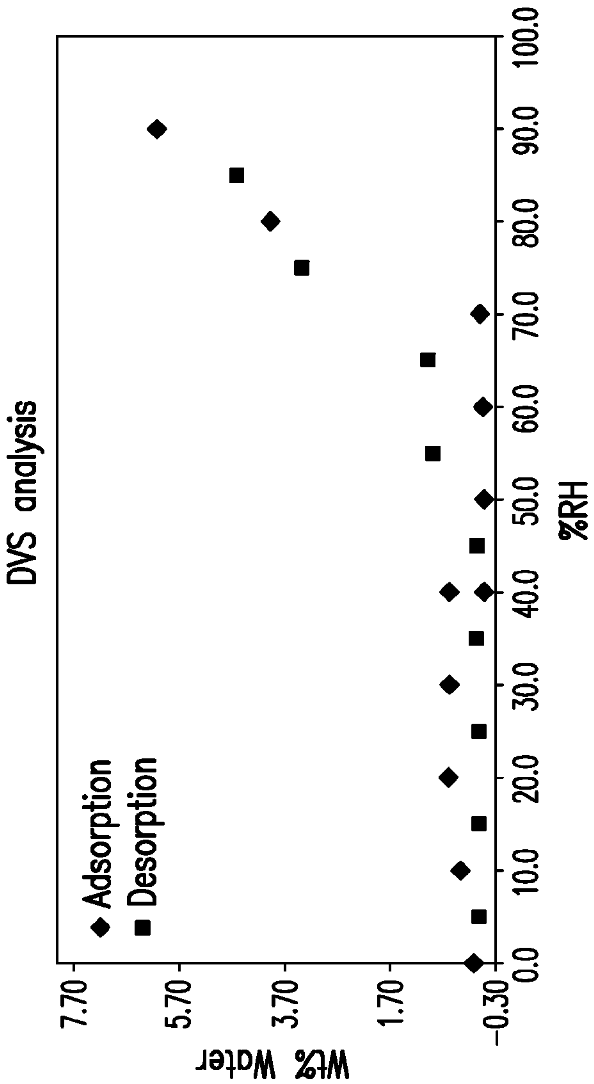

DVS analysis
Adsorption
Desorption
Wt% Water
%RH
7.70
5.70
3.70
1.70
-0.30
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

FIG. 13

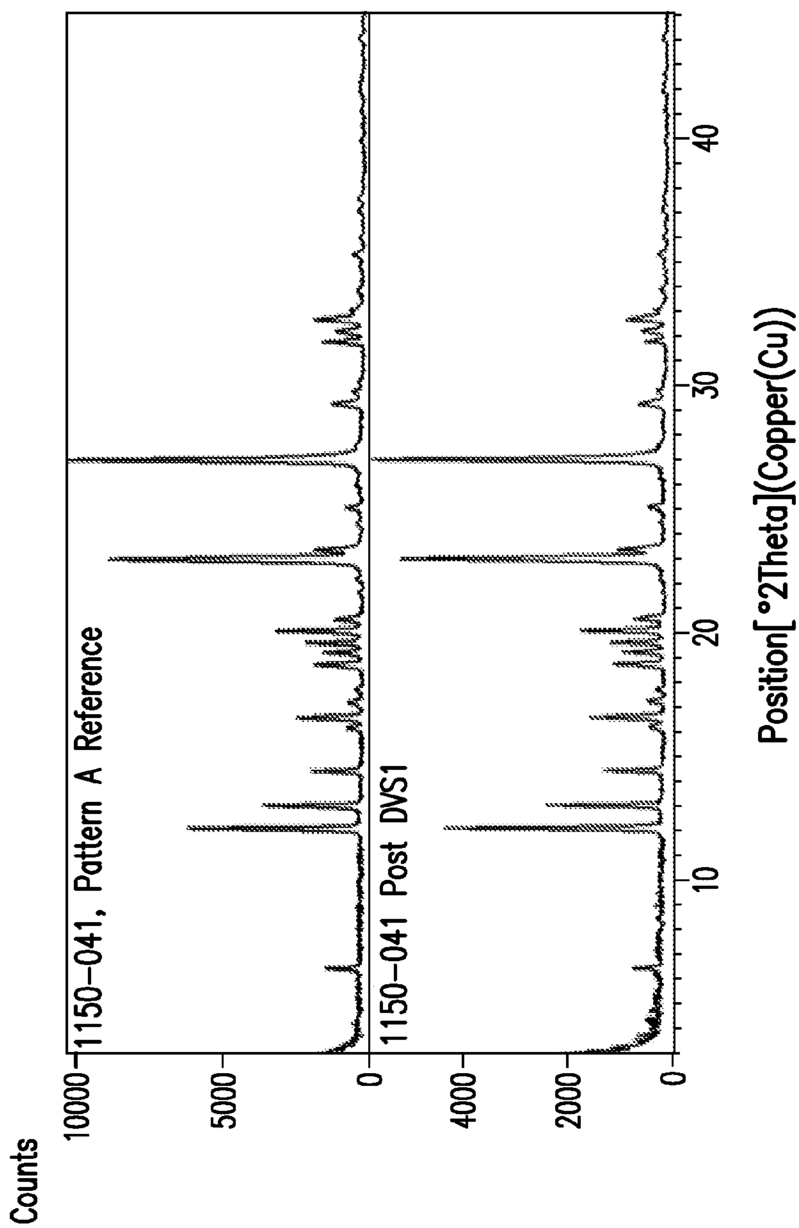
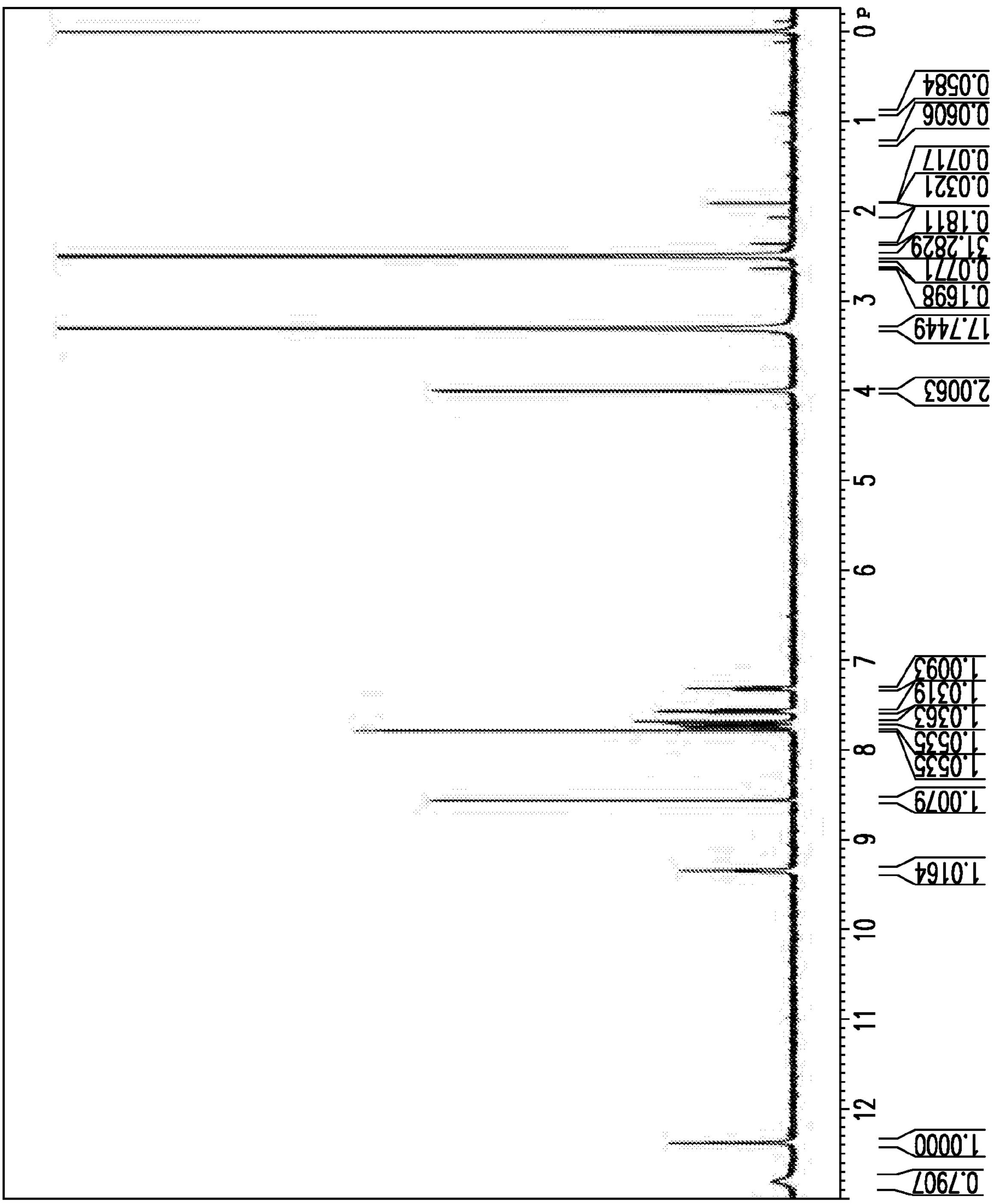

Counts
10000
5000
0
4000
2000
0
1150-041, Pattern A Reference
1150-041 Post DVS1
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 14

FIG. 15


0
1
2
3
4
5
6
7
8
9
10
11
12
ppm
0.0584
0.0606
0.0717
0.0321
0.1811
31.2829
0.0771
0.1698
17.7449
2.0063
1.0093
1.0319
1.0363
1.0535
1.0535
1.0079
1.0164
1.0000
0.7907

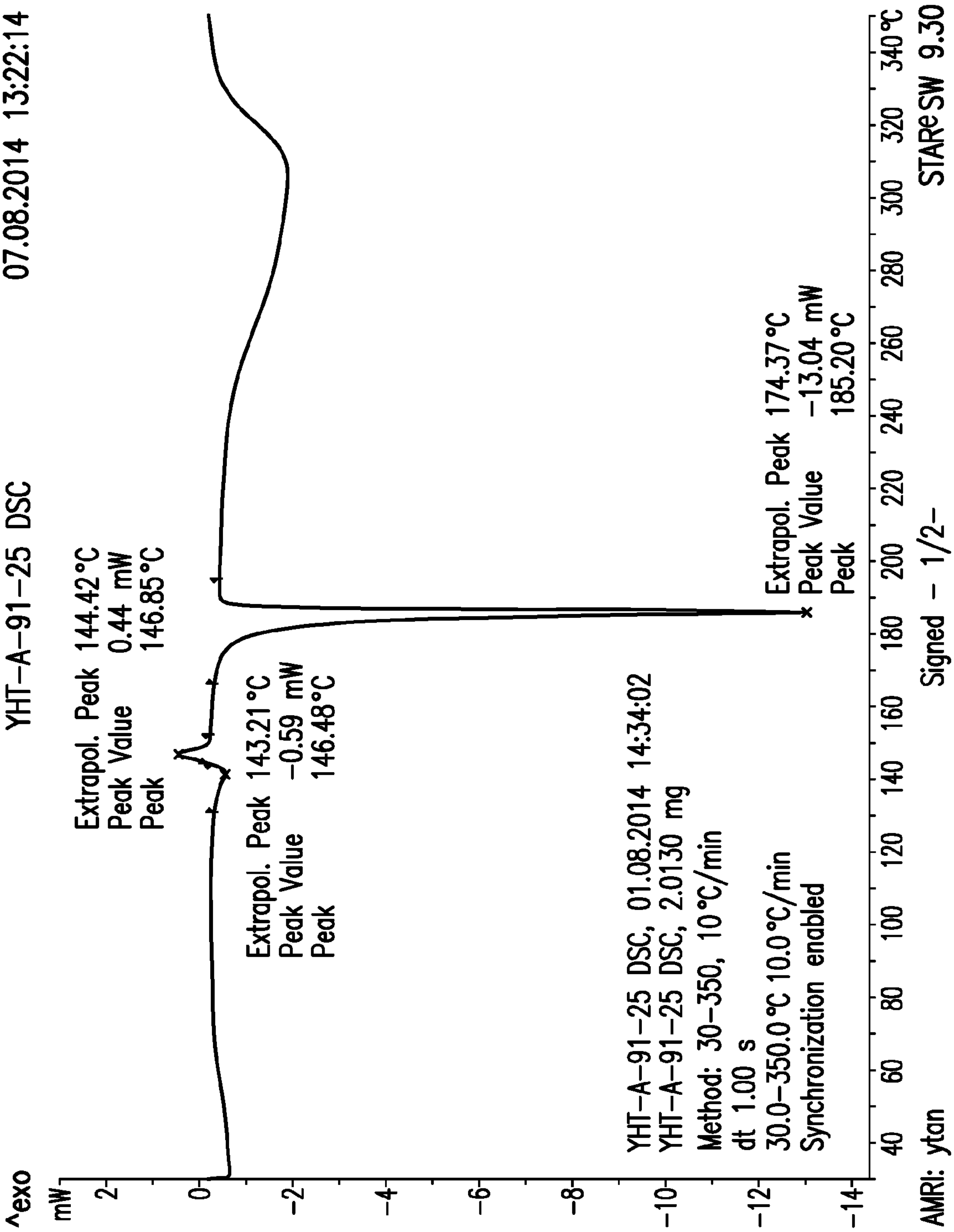
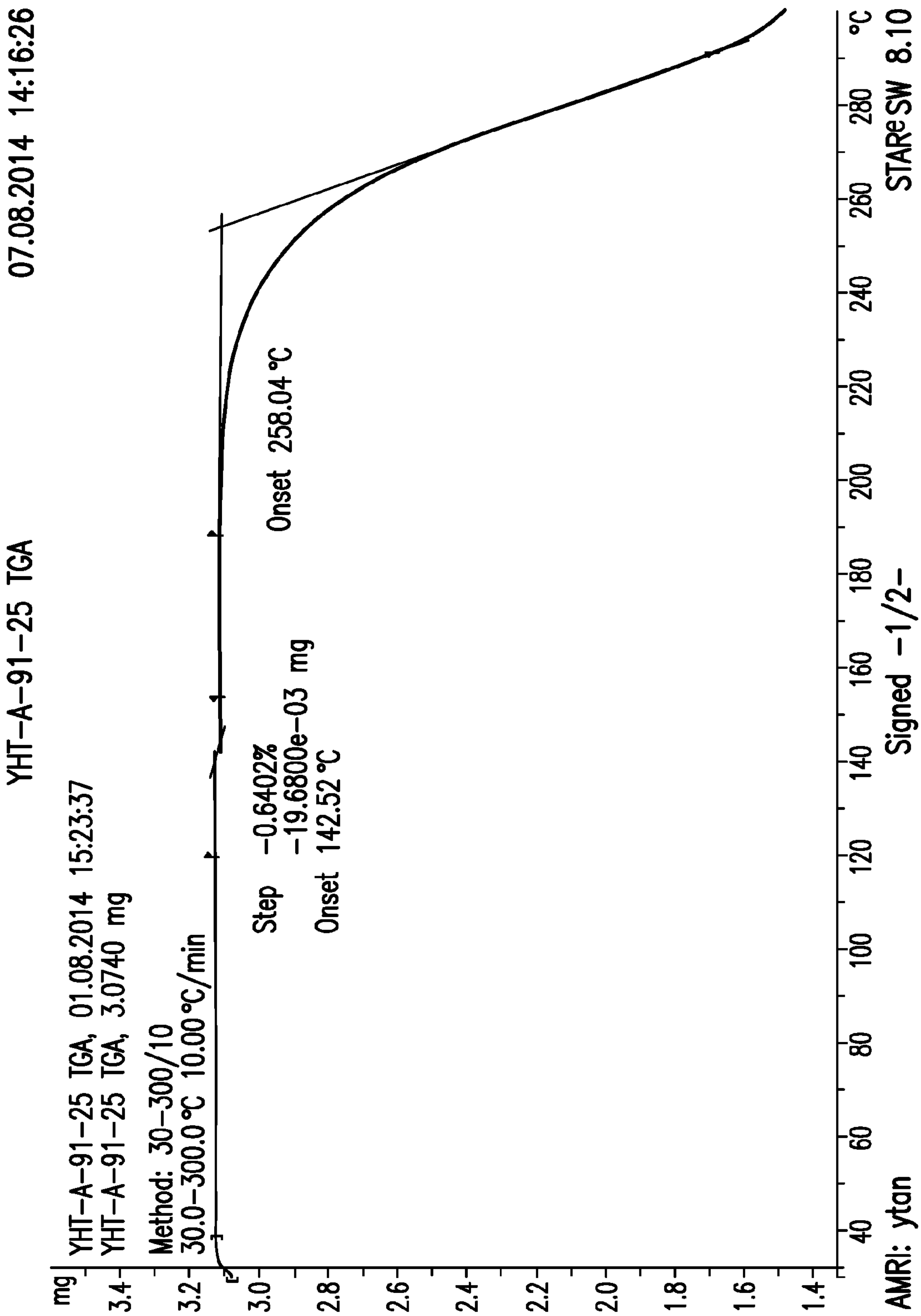

YHT–A–91–25 DSC
07.08.2014 13:22:14
^exo
mW
Extrapol. Peak 144.42°C
Peak Value 0.44 mW
Peak 146.85°C
Extrapol. Peak 143.21°C
Peak Value –0.59 mW
Peak 146.48°C
Extrapol. Peak 174.37°C
Peak Value –13.04 mW
Peak 185.20°C
YHT–A–91–25 DSC, 01.08.2014 14:34:02
YHT–A–91–25 DSC, 2.0130 mg
Method: 30–350, 10°C/min
dt 1.00 s
30.0–350.0°C 10.0°C/min
Synchronization enabled
2
0
–2
–4
–6
–8
–10
–12
–14
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340°C
AMRI: ytan
Signed – 1/2–
STARe SW 9.30

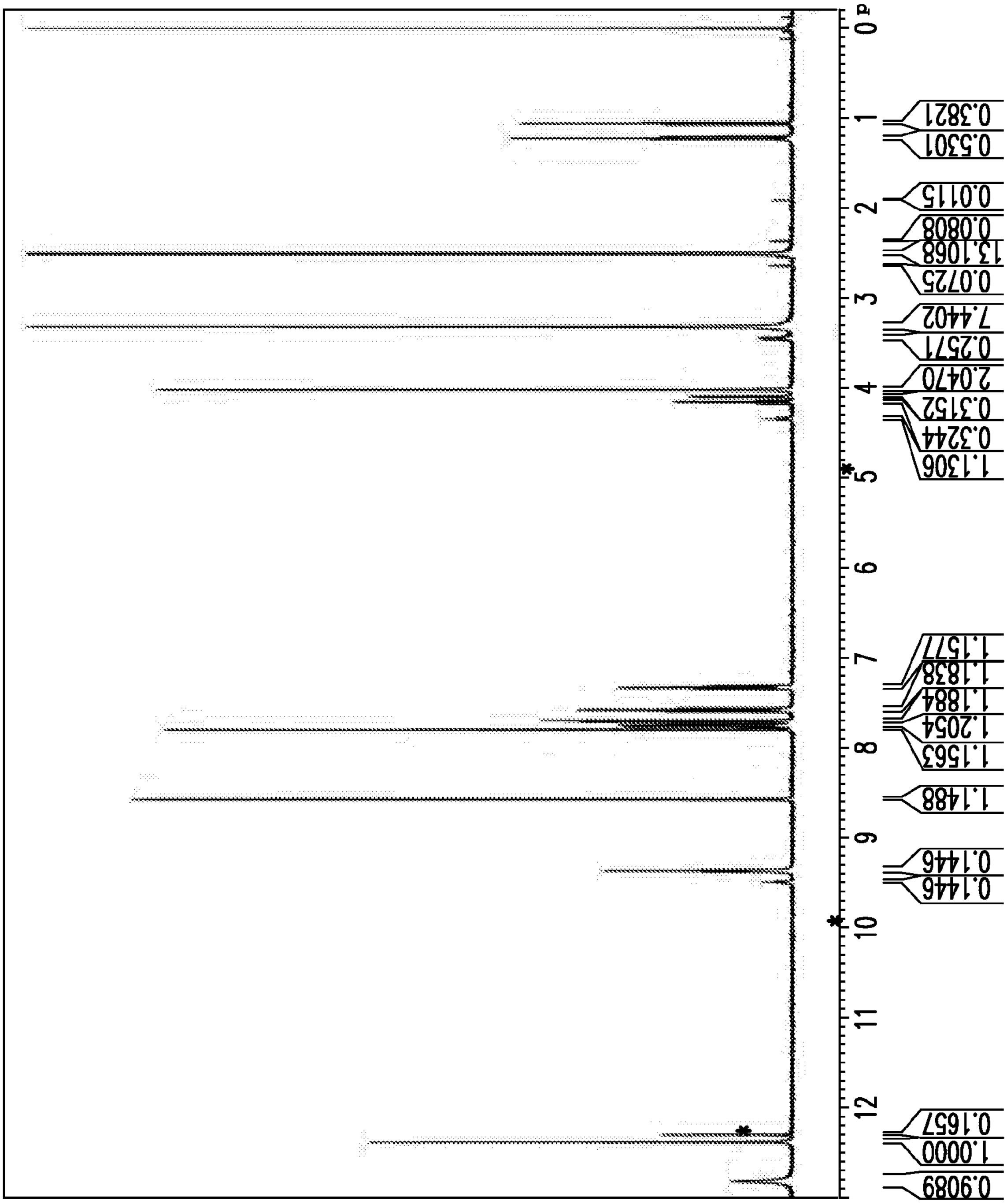
FIG. 16



YHT–A–91–25 TGA
07.08.2014 14:16:26
YHT–A–91–25 TGA, 01.08.2014 15:23:37
YHT–A–91–25 TGA, 3.0740 mg
Method: 30–300/10
30.0–300.0°C 10.00°C/min
Step −0.6402%
−19.6800e–03 mg
Onset 142.52 °C
Onset 258.04 °C
mg
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
AMRI: ytan
Signed –1/2–
STARe SW 8.10

FIG. 17

FIG. 18



0.3821
0.5301
0.0115
0.0808
13.1068
0.0725
7.4402
0.2571
2.0470
0.3152
0.3244
1.1306
1.1577
1.1838
1.1884
1.2054
1.1563
1.1488
0.1446
0.1446
0.1657
1.0000
0.9089

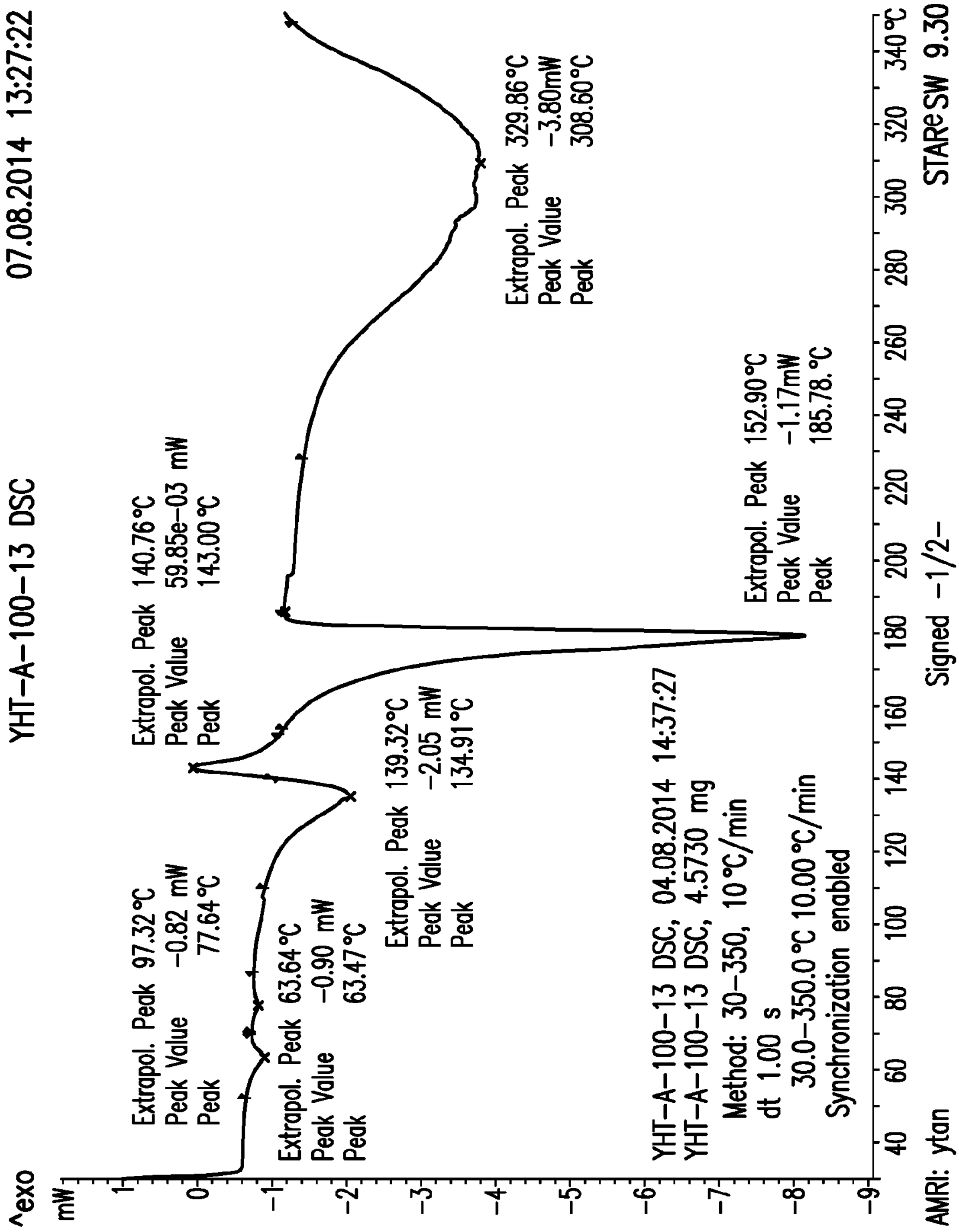

YHT-A-100-13 DSC
07.08.2014 13:27:22
^exo
mW
1
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C
Extrapol. Peak 97.32 °C
Peak Value -0.82 mW
Peak 77.64 °C
Extrapol. Peak 63.64 °C
Peak Value -0.90 mW
Peak 63.47 °C
Extrapol. Peak 140.76 °C
Peak Value 59.85e-03 mW
Peak 143.00 °C
Extrapol. Peak 139.32 °C
Peak Value -2.05 mW
Peak 134.91 °C
Extrapol. Peak 152.90 °C
Peak Value -1.17mW
Peak 185.78 °C
Extrapol. Peak 329.86 °C
Peak Value -3.80mW
Peak 308.60 °C
YHT-A-100-13 DSC, 04.08.2014 14:37:27
YHT-A-100-13 DSC, 4.5730 mg
Method: 30-350, 10 °C/min
dt 1.00 s
30.0-350.0 °C 10.00 °C/min
Synchronization enabled
AMRI: ytan
Signed -1/2-
STARe SW 9.30

FIG. 19

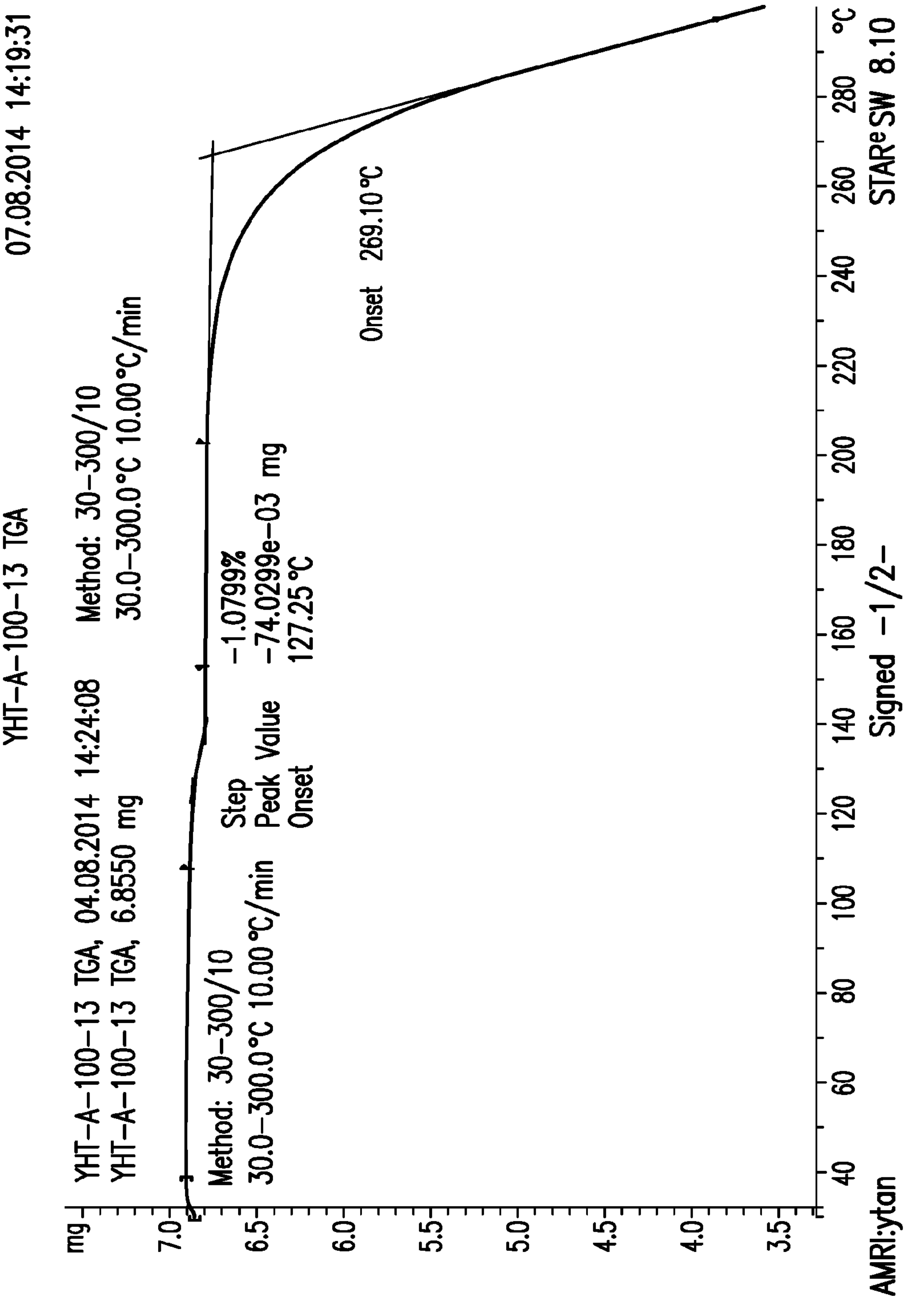

YHT-A-100-13 TGA
07.08.2014 14:19:31
YHT-A-100-13 TGA, 04.08.2014 14:24:08
YHT-A-100-13 TGA, 6.8550 mg
Method: 30-300/10
30.0-300.0°C 10.00°C/min
Method: 30-300/10
30.0-300.0°C 10.00°C/min
Step -1.0799%
Peak Value -74.0299e-03 mg
Onset 127.25°C
Onset 269.10°C
mg
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
AMRI:ytan
Signed -1/2-
STARe SW 8.10

FIG. 20

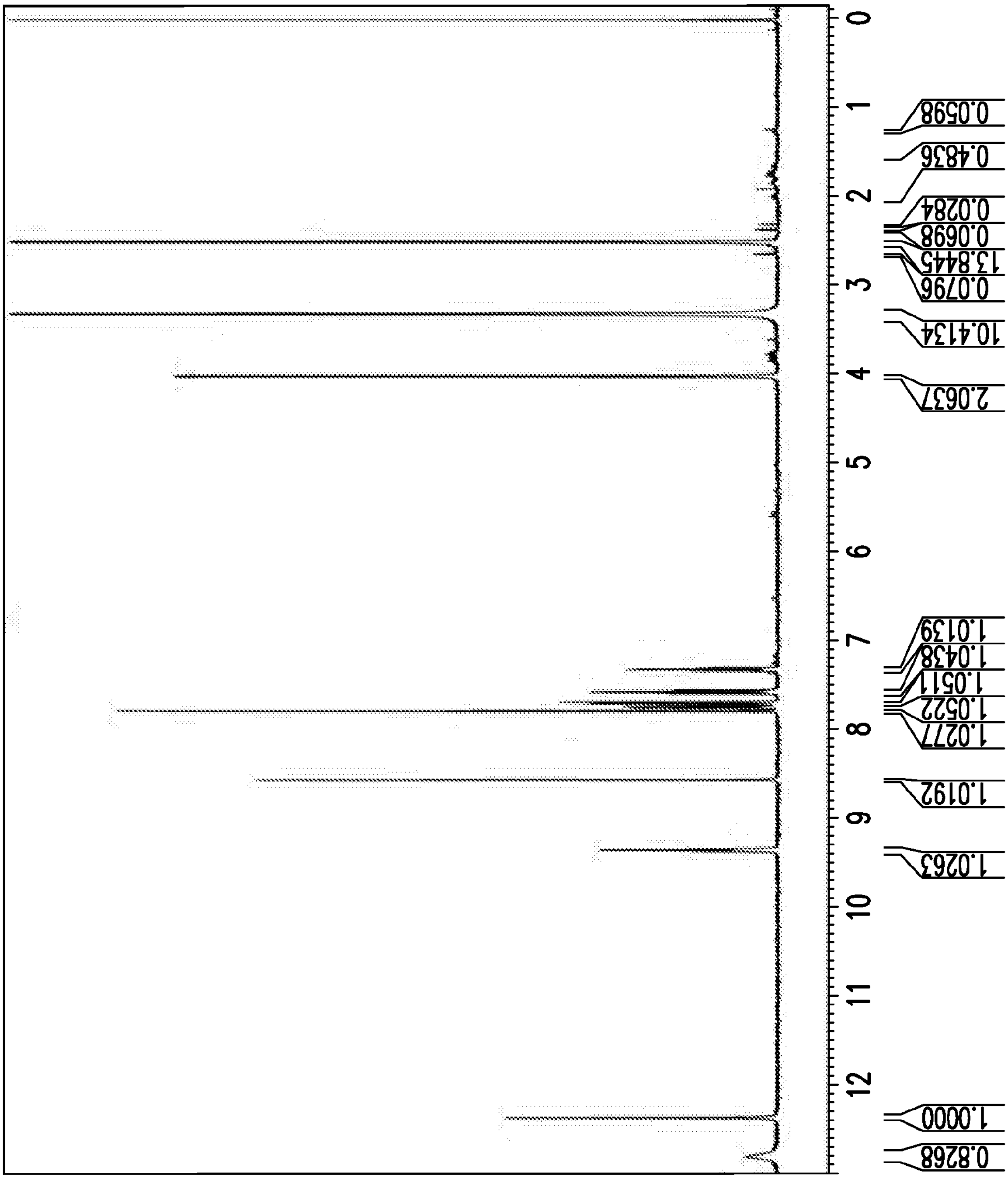

0
1
2
3
4
5
6
7
8
9
10
11
12
0.0598
0.4836
0.0284
0.0698
13.8445
0.0796
10.4134
2.0637
1.0139
1.0438
1.0511
1.0522
1.0277
1.0192
1.0263
1.0000
0.8268

FIG. 21

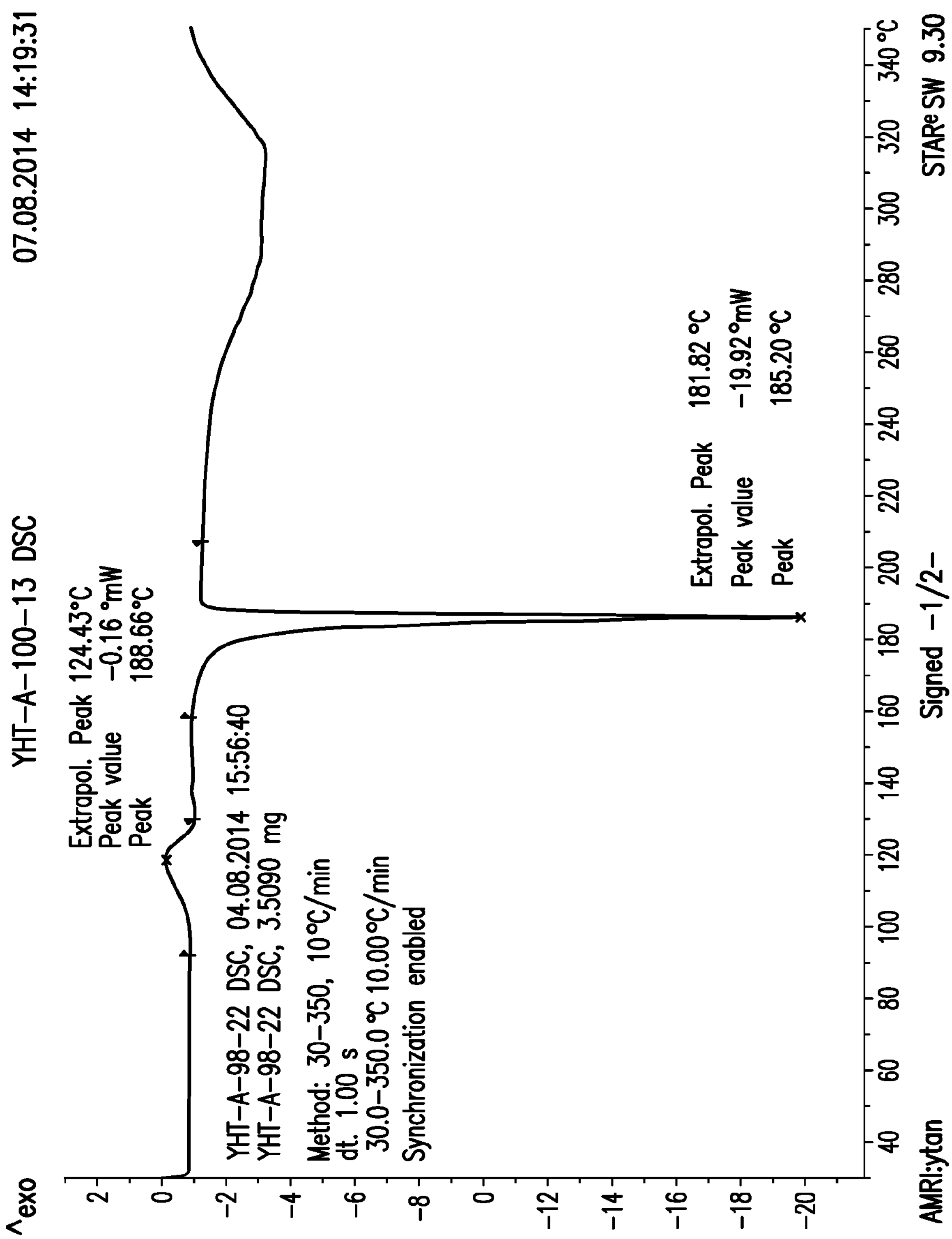

^exo
YHT-A-100-13 DSC
07.08.2014 14:19:31
Extrapol. Peak 124.43°C
Peak value -0.16 °mW
Peak 188.66°C
YHT-A-98-22 DSC, 04.08.2014 15:56:40
YHT-A-98-22 DSC, 3.5090 mg
Method: 30-350, 10°C/min
dt. 1.00 s
30.0-350.0 °C 10.00°C/min
Synchronization enabled
Extrapol. Peak 181.82 °C
Peak value -19.92 °mW
Peak 185.20 °C
2 0 -2 -4 -6 -8 0 -12 -14 -16 -18 -20
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
AMRI:ytan
Signed -1/2-
STARe SW 9.30

FIG. 22

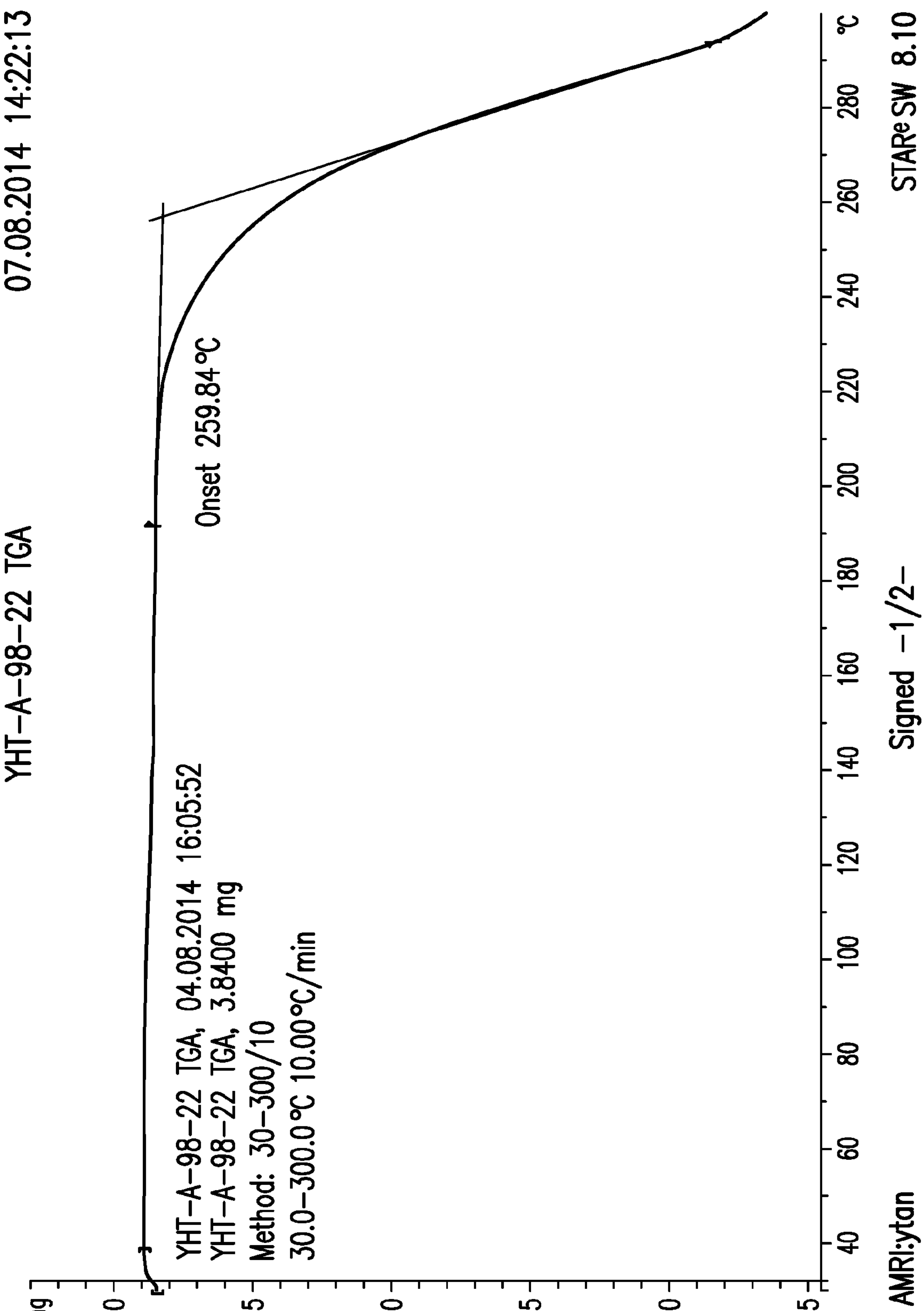

YHT–A–98–22 TGA
07.08.2014 14:22:13
YHT–A–98–22 TGA, 04.08.2014 16:05:52
YHT–A–98–22 TGA, 3.8400 mg
Method: 30–300/10
30.0–300.0°C 10.00°C/min
Onset 259.84°C
mg
4.0
3.5
3.0
2.5
2.0
1.5
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
AMRI:ytan
Signed –1/2–
STARe SW 8.10

FIG. 23

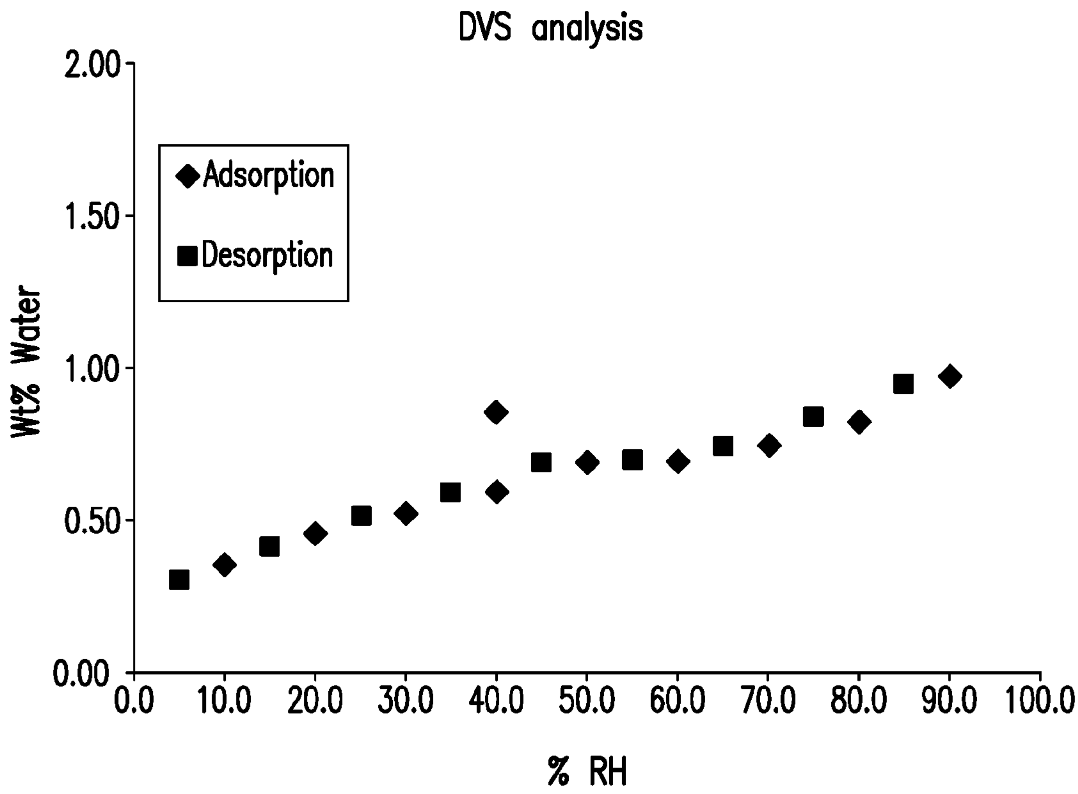

DVS analysis
2.00
1.50
1.00
0.50
0.00
Wt% Water
Adsorption
Desorption
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
% RH

FIG. 24

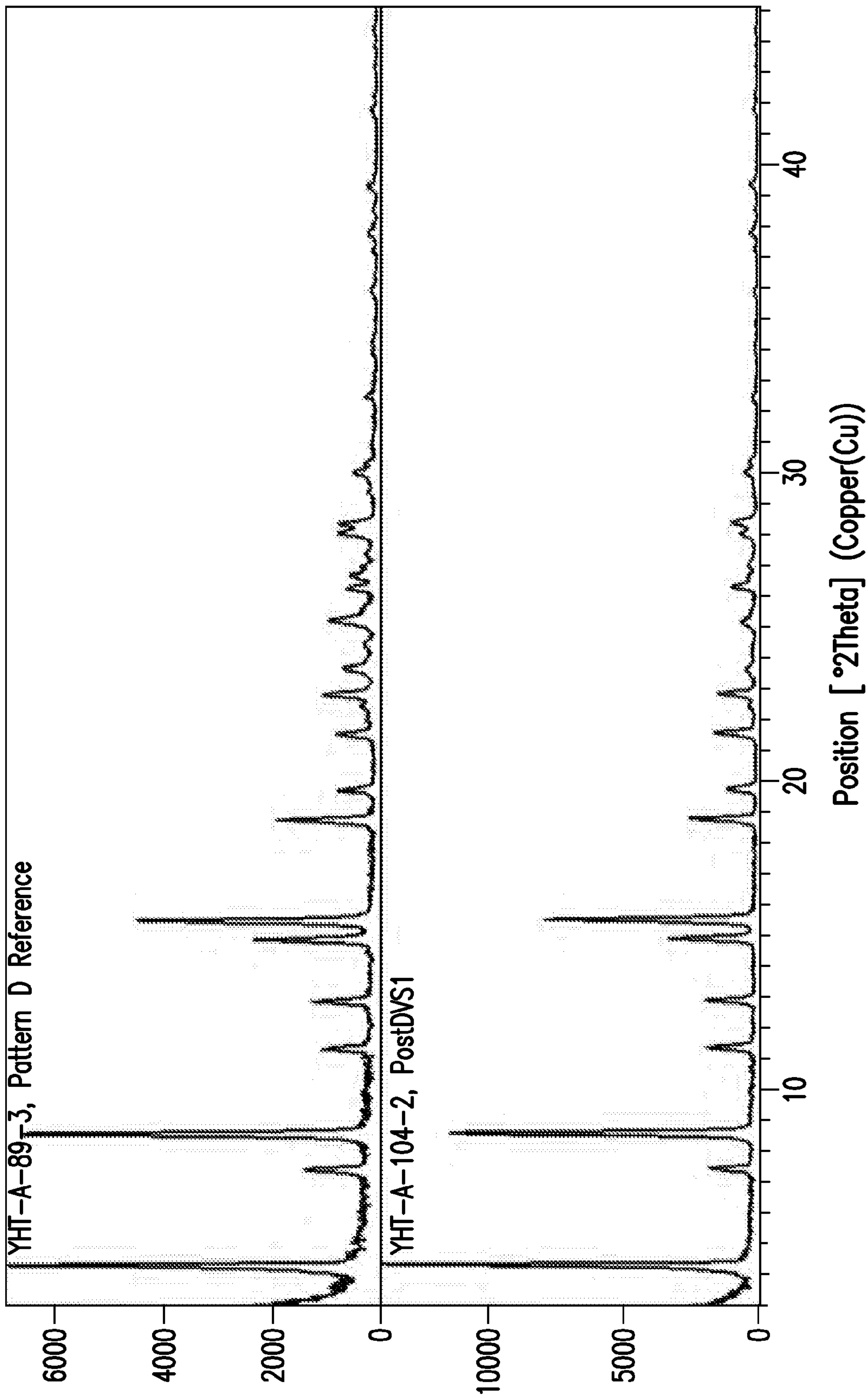

YHT-A-89-3, Pattern D Reference
YHT-A-104-2, PostDVS1
6000
4000
2000
0
10000
5000
0
10
20
30
40
Position [°2Theta] (Copper(Cu))

FIG. 25

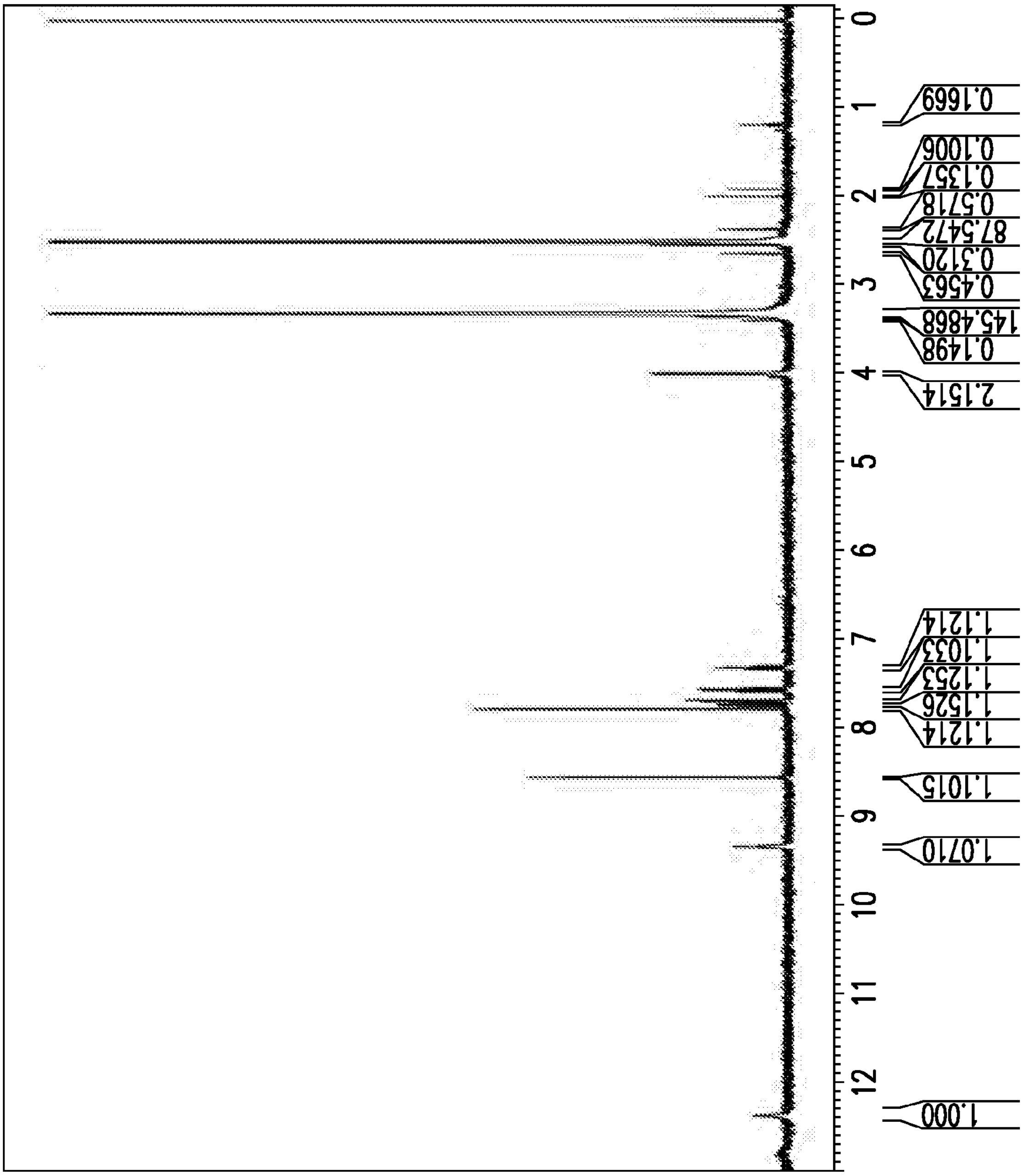

0
1
2
3
4
5
6
7
8
9
10
11
12
0.1669
0.1006
0.1357
0.5718
87.5472
0.3120
0.4563
145.4868
0.1498
2.1514
1.1214
1.1033
1.1253
1.1526
1.1214
1.1015
1.0710
1.000

FIG. 26

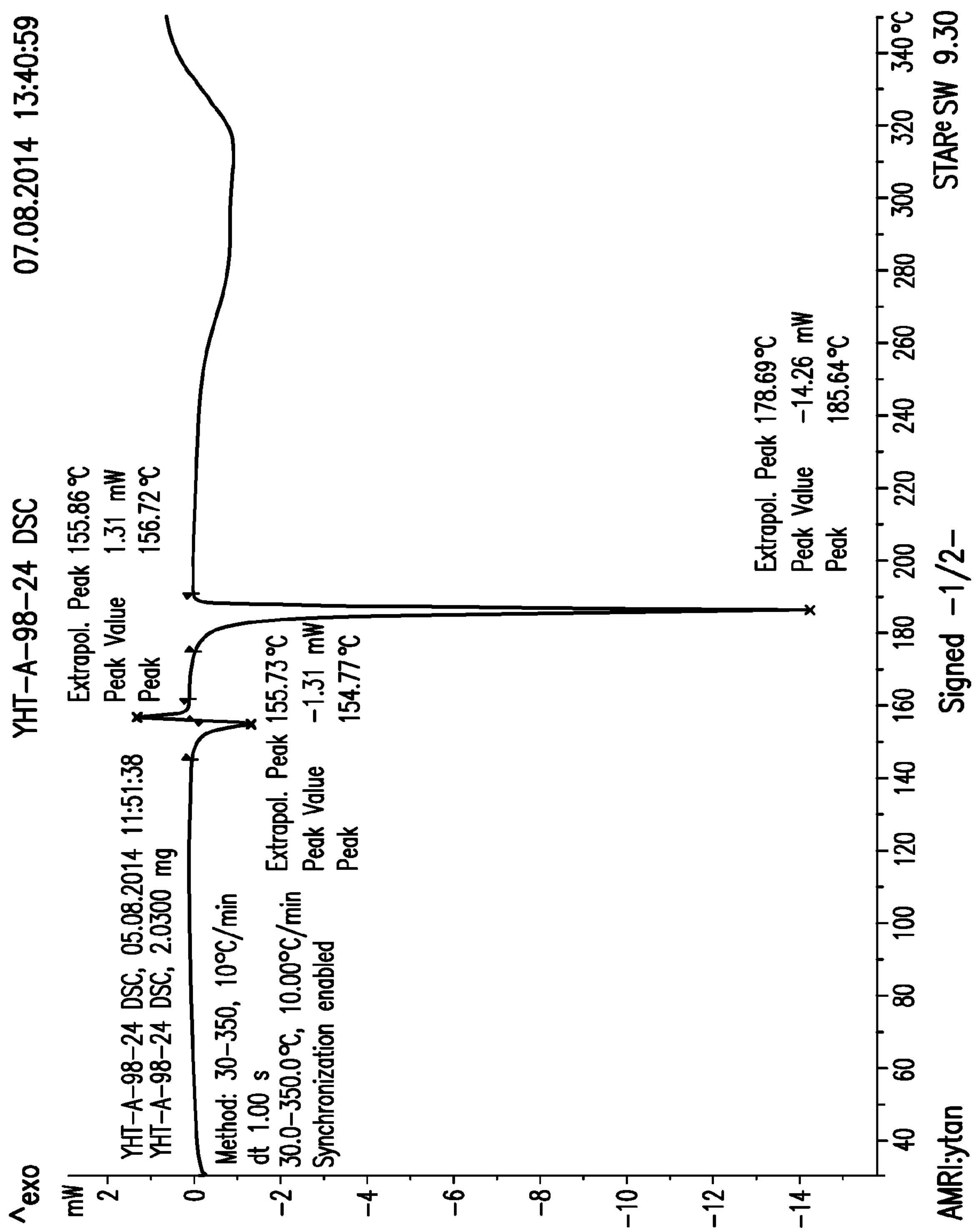
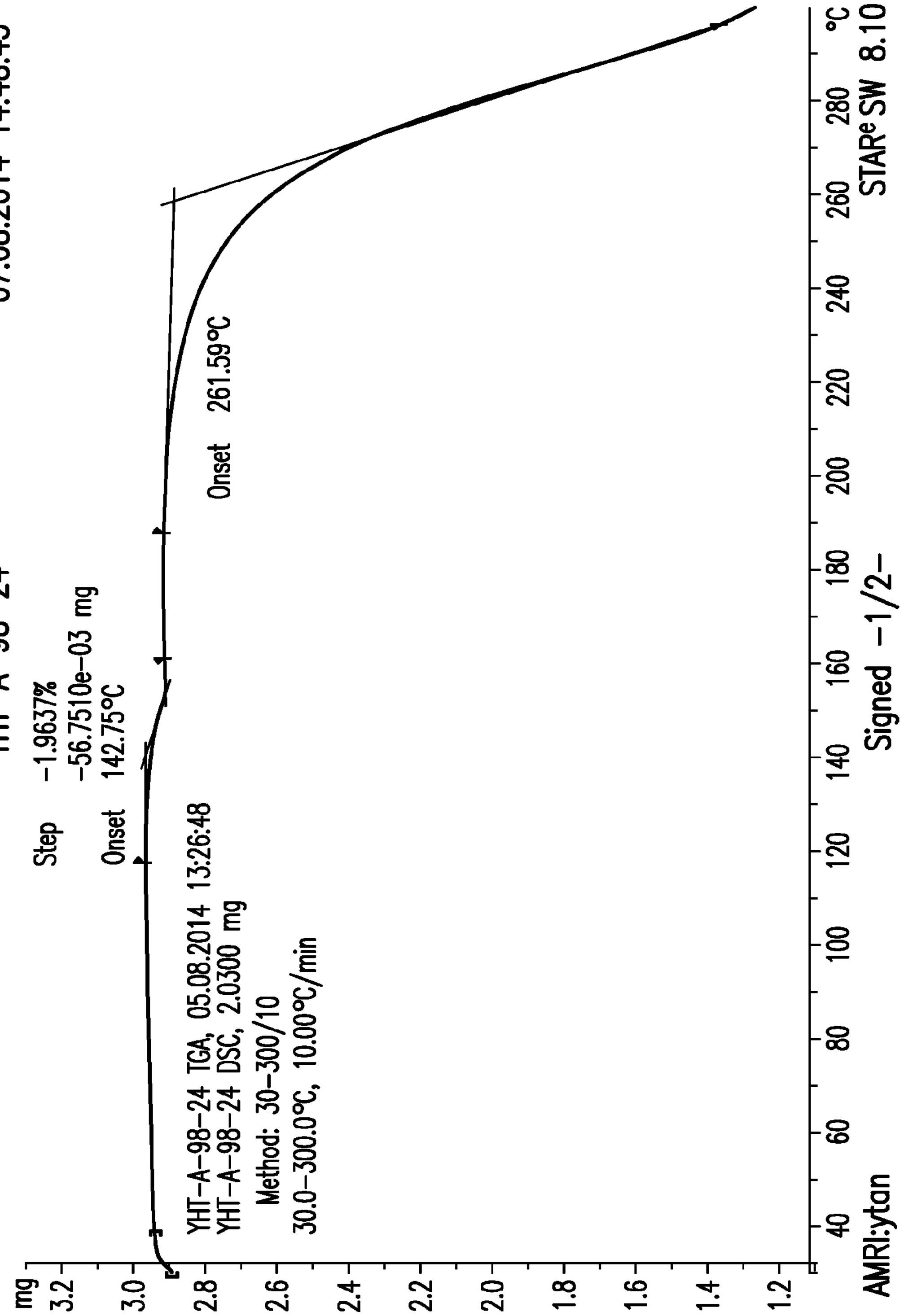

YHT–A–98–24 DSC
07.08.2014 13:40:59
YHT–A–98–24 DSC, 05.08.2014 11:51:38
YHT–A–98–24 DSC, 2.0300 mg
Method: 30–350, 10°C/min
dt 1.00 s
30.0–350.0°C, 10.00°C/min
Synchronization enabled
Extrapol. Peak 155.86°C
Peak Value 1.31 mW
Peak 156.72°C
Extrapol. Peak 155.73°C
Peak Value –1.31 mW
Peak 154.77°C
Extrapol. Peak 178.69°C
Peak Value –14.26 mW
Peak 185.64°C
^exo
mW
2
0
–2
–4
–6
–8
–10
–12
–14
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340°C
AMRI:ytan
Signed –1/2–
STARe SW 9.30

FIG. 27



YHT-A-98-24
07.08.2014 14:48:43
Step -1.9637%
-56.7510e-03 mg
Onset 142.75°C
Onset 261.59°C
YHT-A-98-24 TGA, 05.08.2014 13:26:48
YHT-A-98-24 DSC, 2.0300 mg
Method: 30-300/10
30.0-300.0°C, 10.00°C/min
mg
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
AMRI:ytan
Signed -1/2-
STARe SW 8.10

FIG. 28

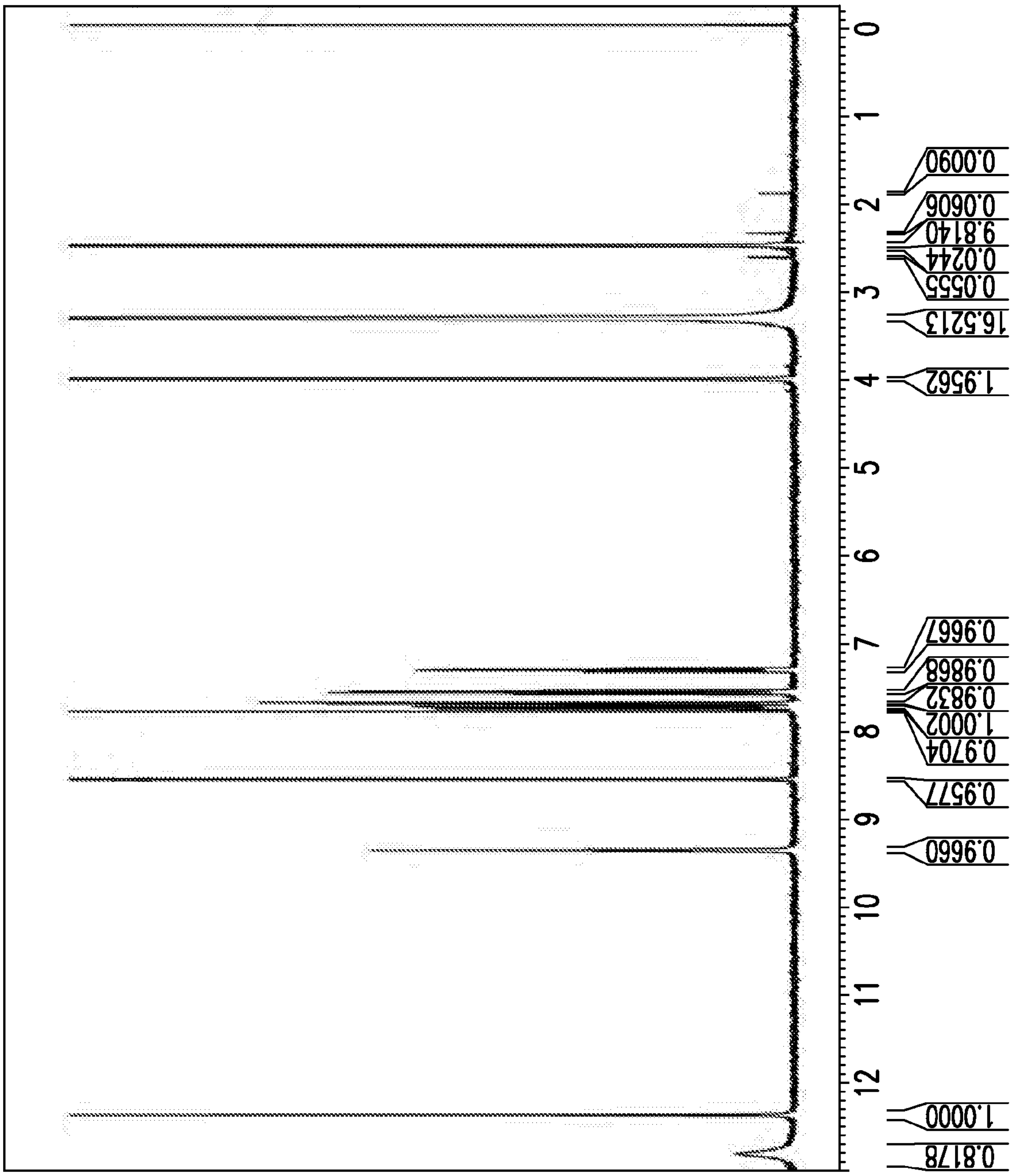


FIG. 29

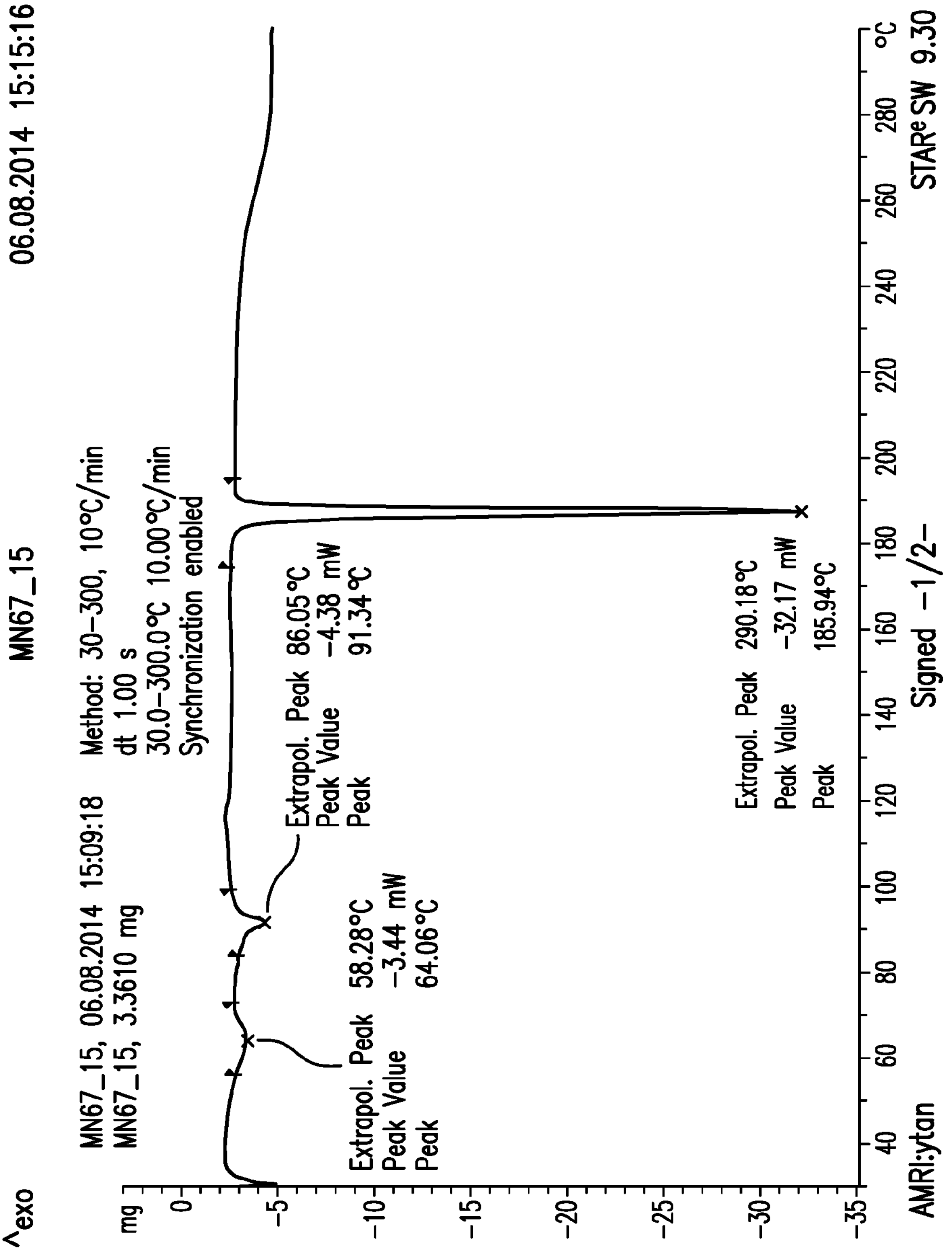

^exo
MN67_15
06.08.2014 15:15:16
MN67_15, 06.08.2014 15:09:18
MN67_15, 3.3610 mg
Method: 30–300, 10°C/min
dt 1.00 s
30.0–300.0°C 10.00°C/min
Synchronization enabled
Extrapol. Peak 58.28°C
Peak Value –3.44 mW
Peak 64.06°C
Extrapol. Peak 86.05°C
Peak Value –4.38 mW
Peak 91.34°C
Extrapol. Peak 290.18°C
Peak Value –32.17 mW
Peak 185.94°C
mg
0
–5
–10
–15
–20
–25
–30
–35
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
AMRI:ytan
Signed –1/2–
STARe SW 9.30

FIG. 30

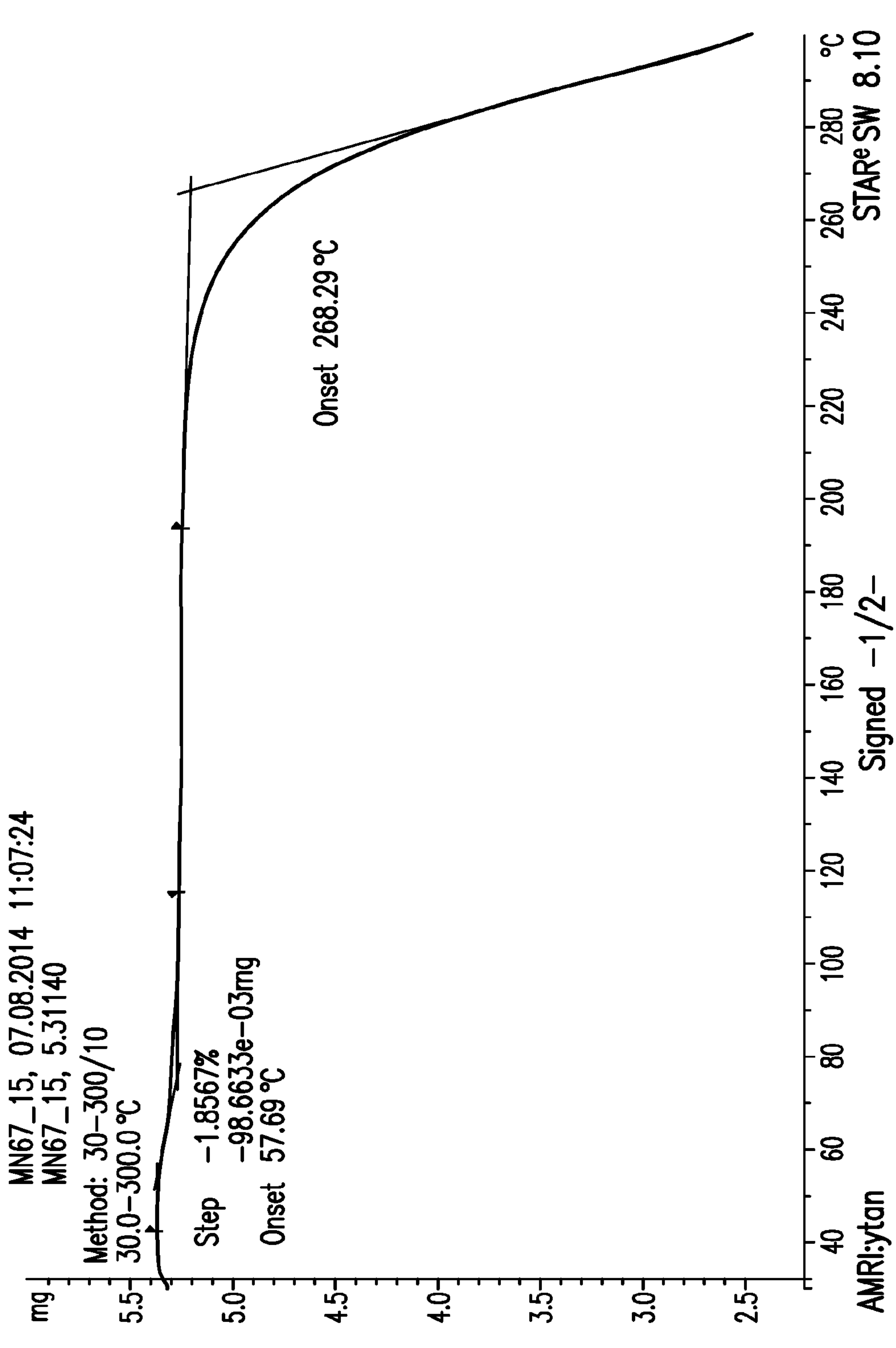

07.08.2014 15:22:58
MN67_15
MN67_15, 07.08.2014 11:07:24
MN67_15, 5.31140
Method: 30–300/10
30.0–300.0 °C
Step −1.8567%
−98.6633e−03mg
Onset 57.69 °C
Onset 268.29 °C
mg
5.5
5.0
4.5
4.0
3.5
3.0
2.5
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
AMRI:ytan
Signed −1/2−
STARe SW 8.10

FIG. 31

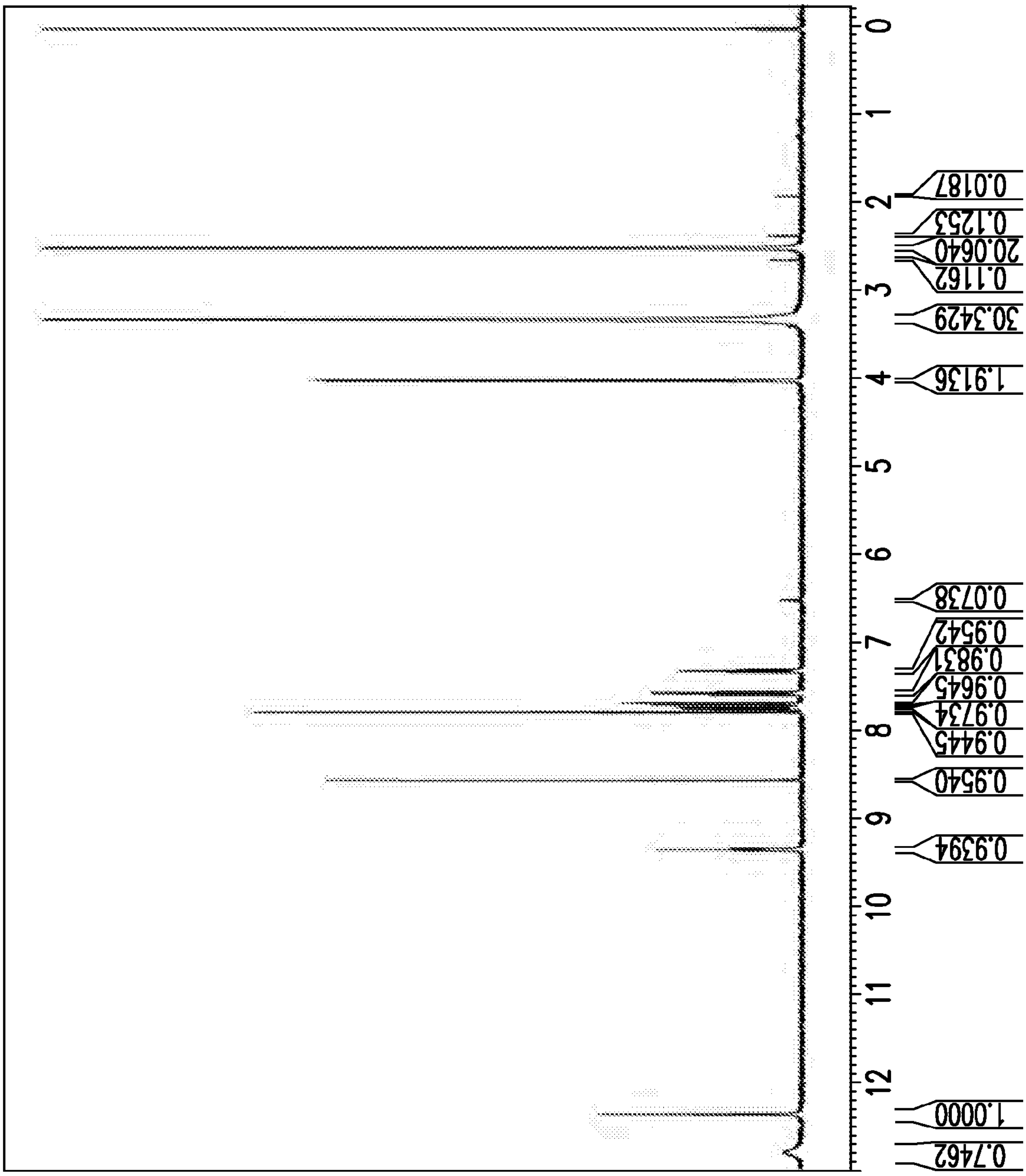

0
1
2
3
4
5
6
7
8
9
10
11
12
0.0187
0.1253
20.0640
0.1162
30.3429
1.9136
0.0738
0.9542
0.9831
0.9645
0.9734
0.9445
0.9540
0.9394
1.0000
0.7462

FIG. 32

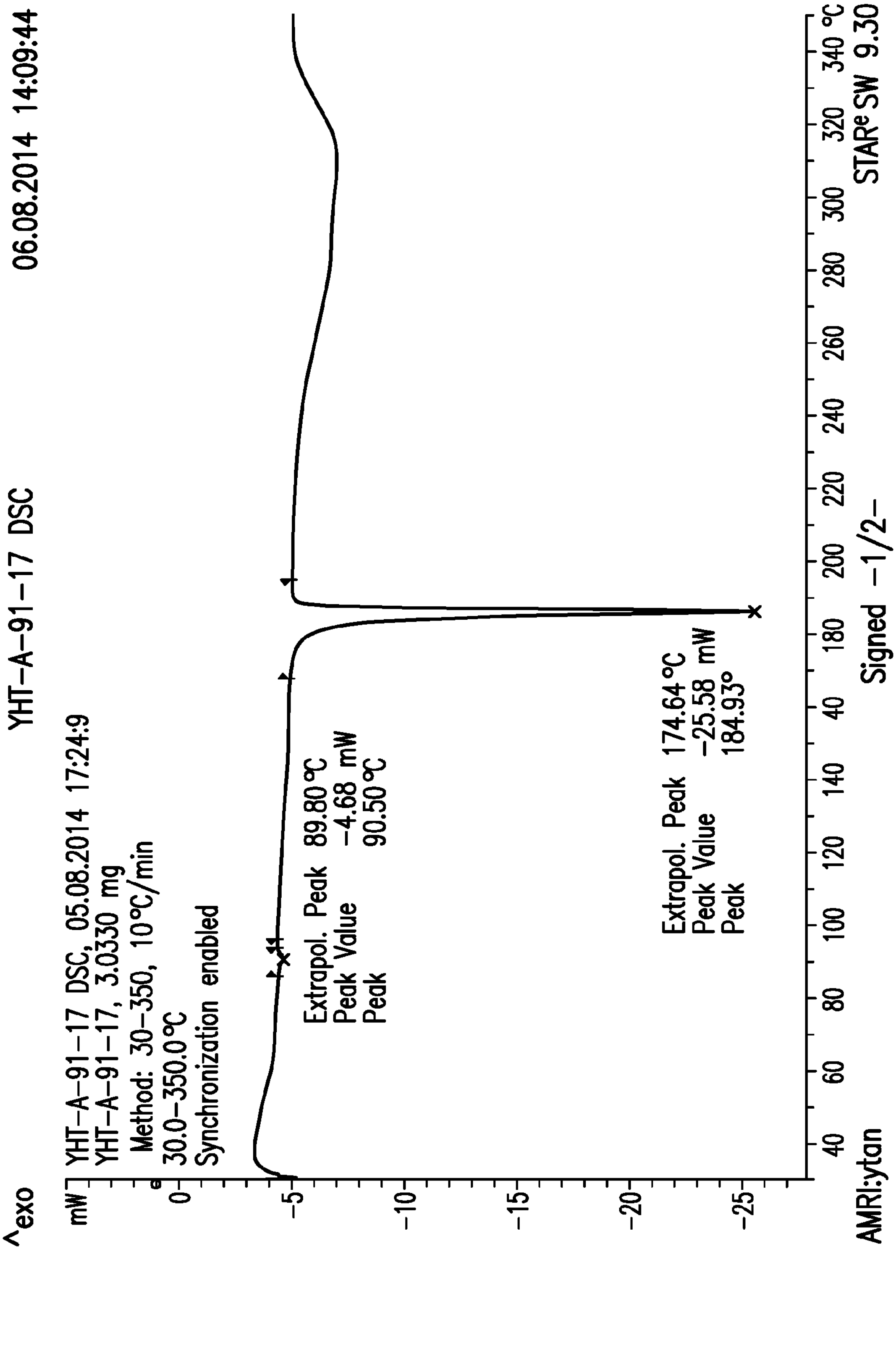
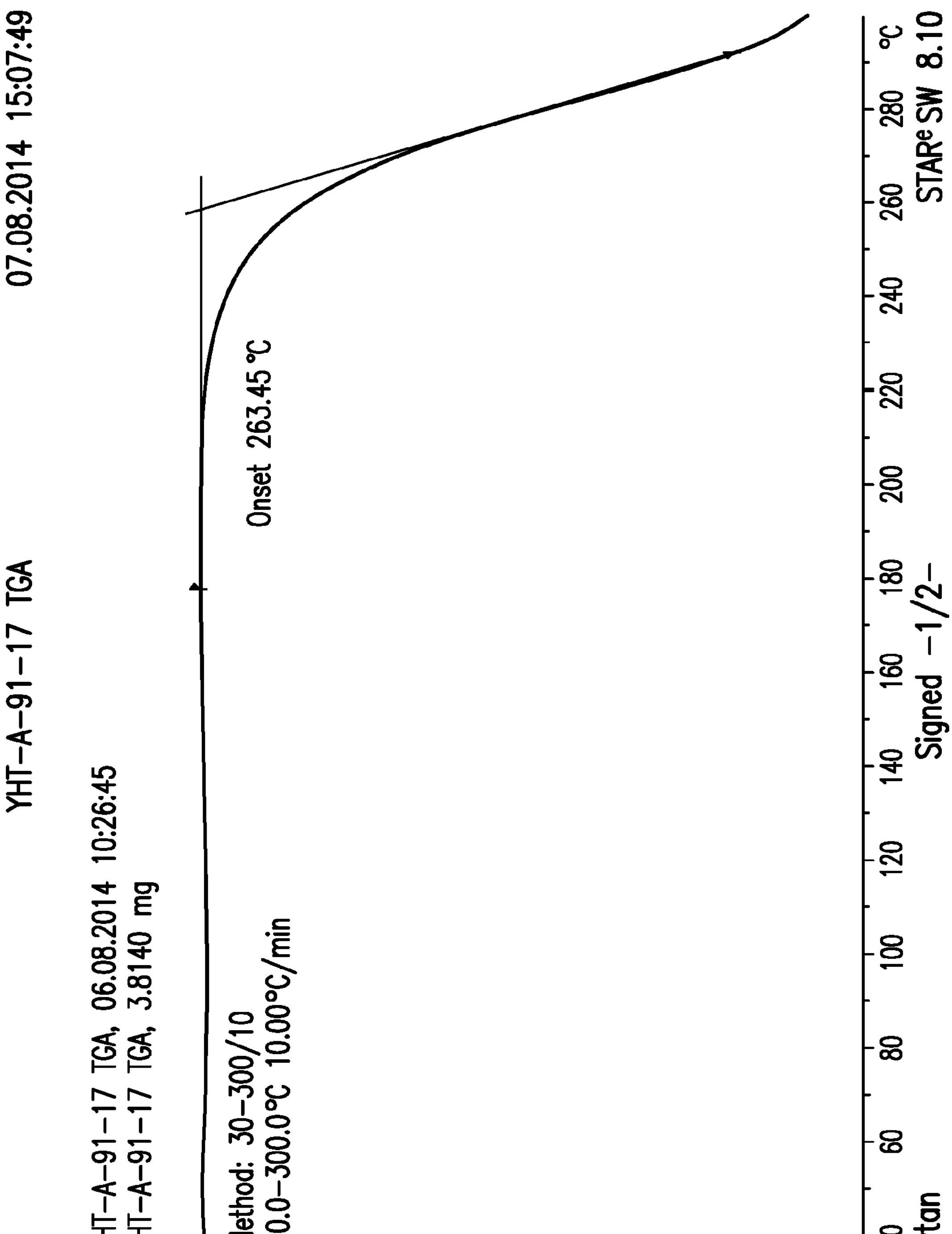

YHT-A-91-17 DSC
06.08.2014 14:09:44
^exo
mW
YHT-A-91-17 DSC, 05.08.2014 17:24:9
YHT-A-91-17, 3.0330 mg
Method: 30-350, 10°C/min
30.0-350.0°C
Synchronization enabled
Extrapol. Peak 89.80°C
Peak Value -4.68 mW
Peak 90.50°C
Extrapol. Peak 174.64°C
Peak Value -25.58 mW
Peak 184.93°
0
-5
-10
-15
-20
-25
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C
AMRI:ytan
Signed -1/2-
STARe SW 9.30

FIG. 33



YHT-A-91-17 TGA
07.08.2014 15:07:49
YHT-A-91-17 TGA, 06.08.2014 10:26:45
YHT-A-91-17 TGA, 3.8140 mg
Method: 30-300/10
30.0-300.0°C 10.00°C/min
Onset 263.45 °C
mg
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
AMRI:ytan
Signed -1/2-
STARe SW 8.10

FIG. 34

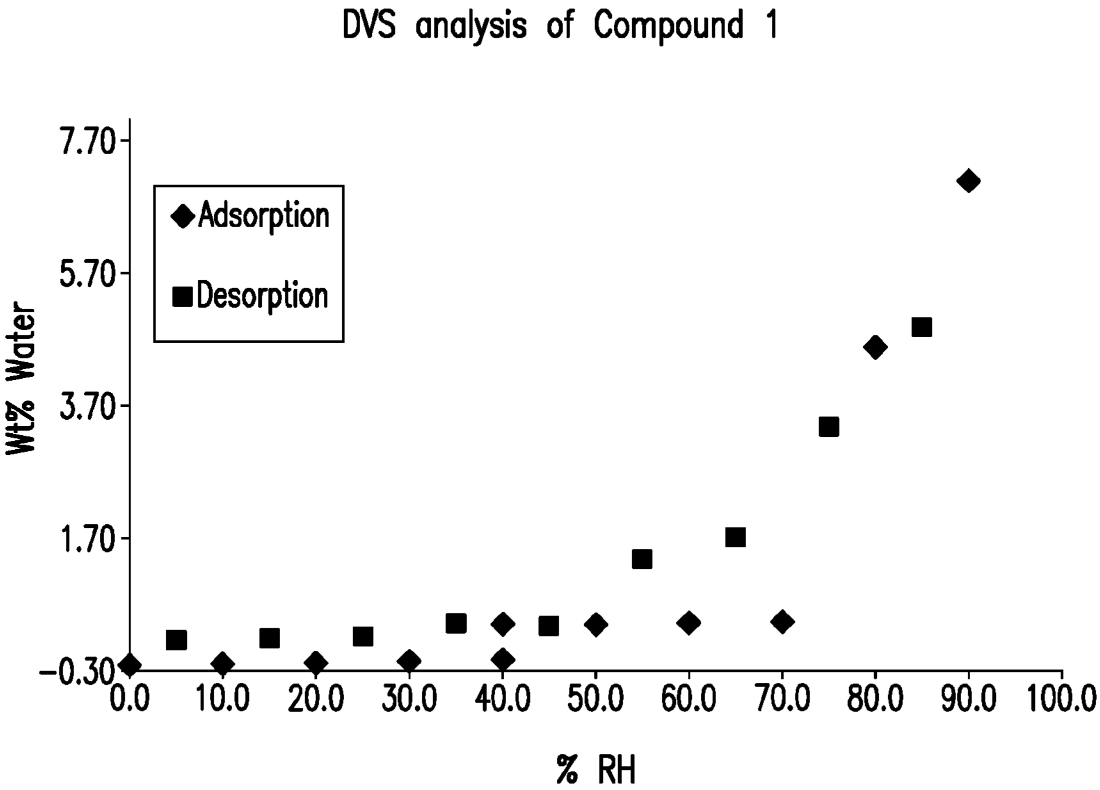

DVS analysis of Compound 1
Adsorption
Desorption
Wt% Water
7.70
5.70
3.70
1.70
−0.30
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
% RH

FIG. 35

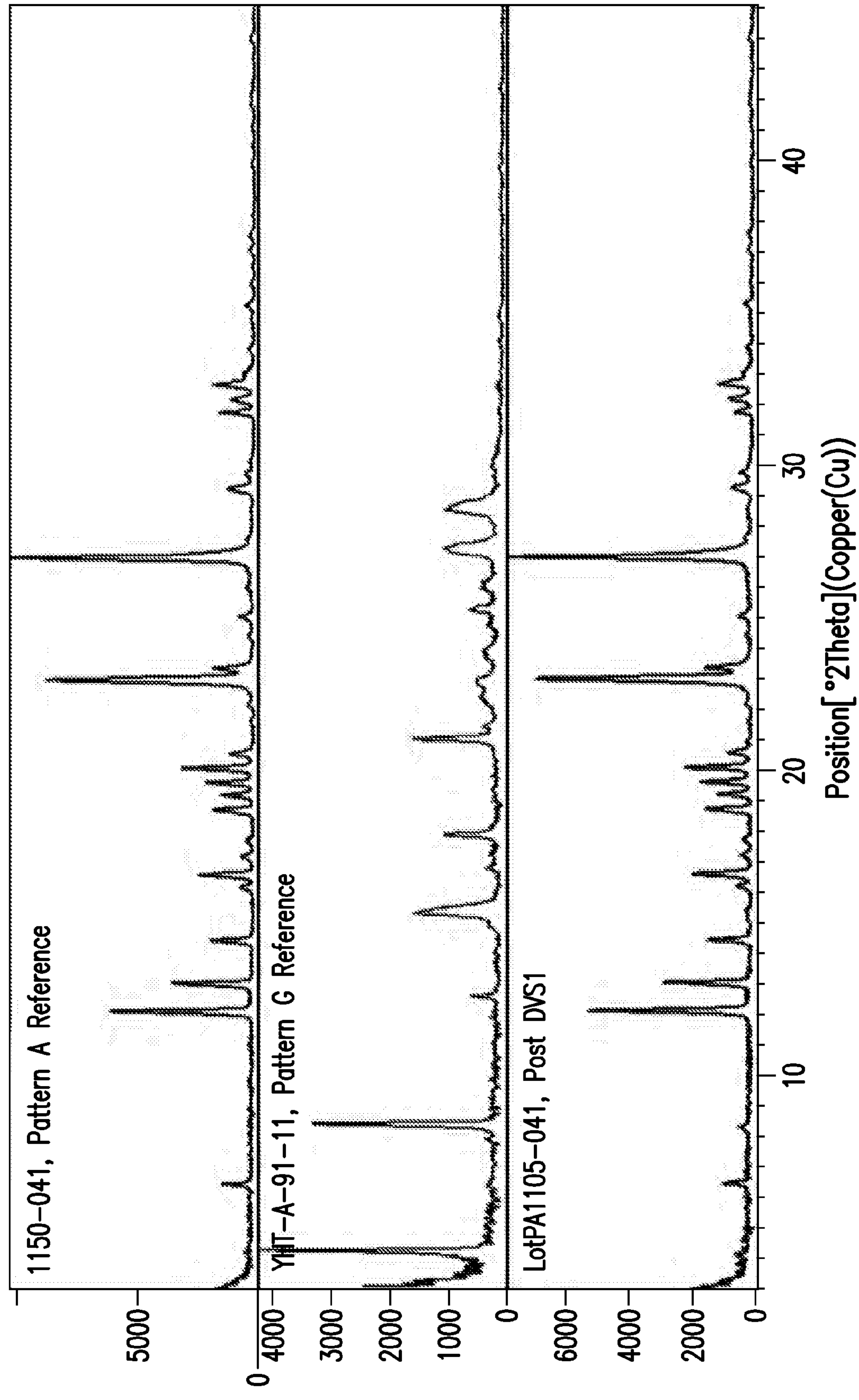

1150-041, Pattern A Reference
YMT-A-91-11, Pattern G Reference
LotPA1105-041, Post DVS1
5000
0
4000
3000
2000
1000
0
6000
4000
2000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 36

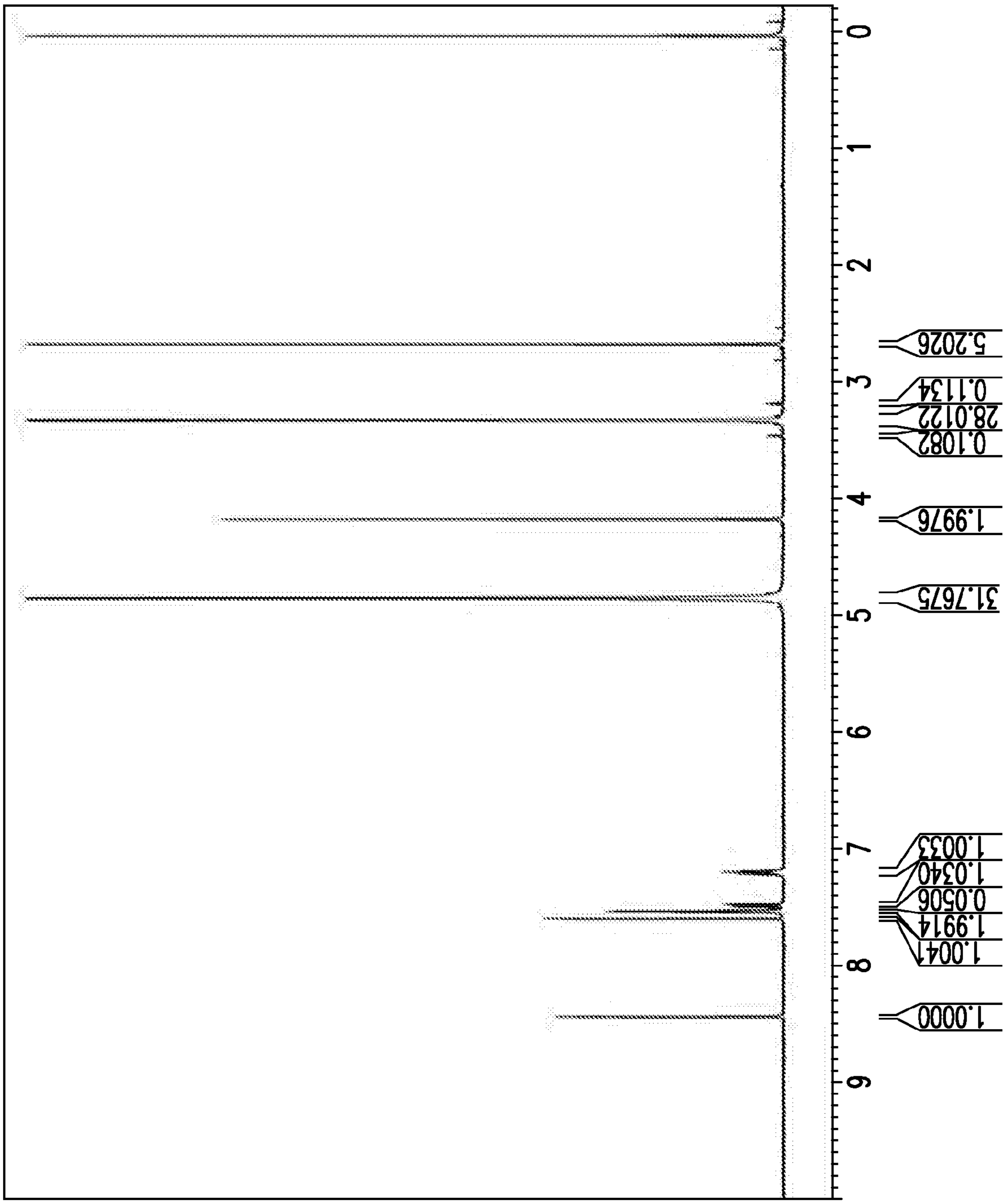

0
1
2
3
4
5
6
7
8
9
5.2026
0.1134
28.0122
0.1082
1.9976
31.7675
1.0033
1.0340
0.0506
1.9914
1.0041
1.0000

FIG. 37

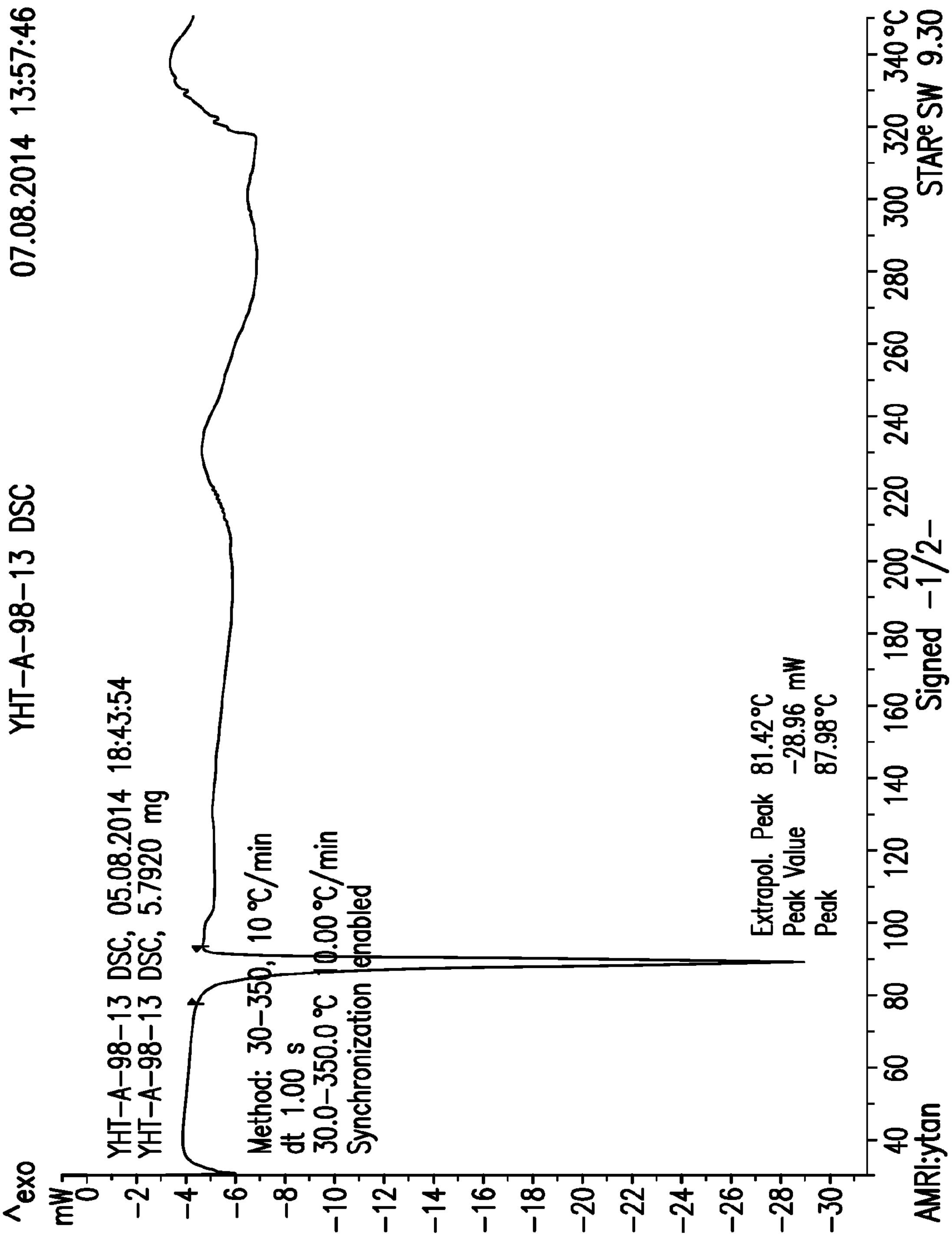

YHT-A-98-13 DSC
07.08.2014 13:57:46
YHT-A-98-13 DSC, 05.08.2014 18:43:54
YHT-A-98-13 DSC, 5.7920 mg
Method: 30-350, 10 °C/min
dt 1.00 s
30.0-350.0 °C 10.00 °C/min
Synchronization enabled
Extrapol. Peak 81.42°C
Peak Value -28.96 mW
Peak 87.98°C
^exo
mW
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
-22
-24
-26
-28
-30
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C
AMRI:ytan
Signed -1/2-
STARe SW 9.30

FIG. 38

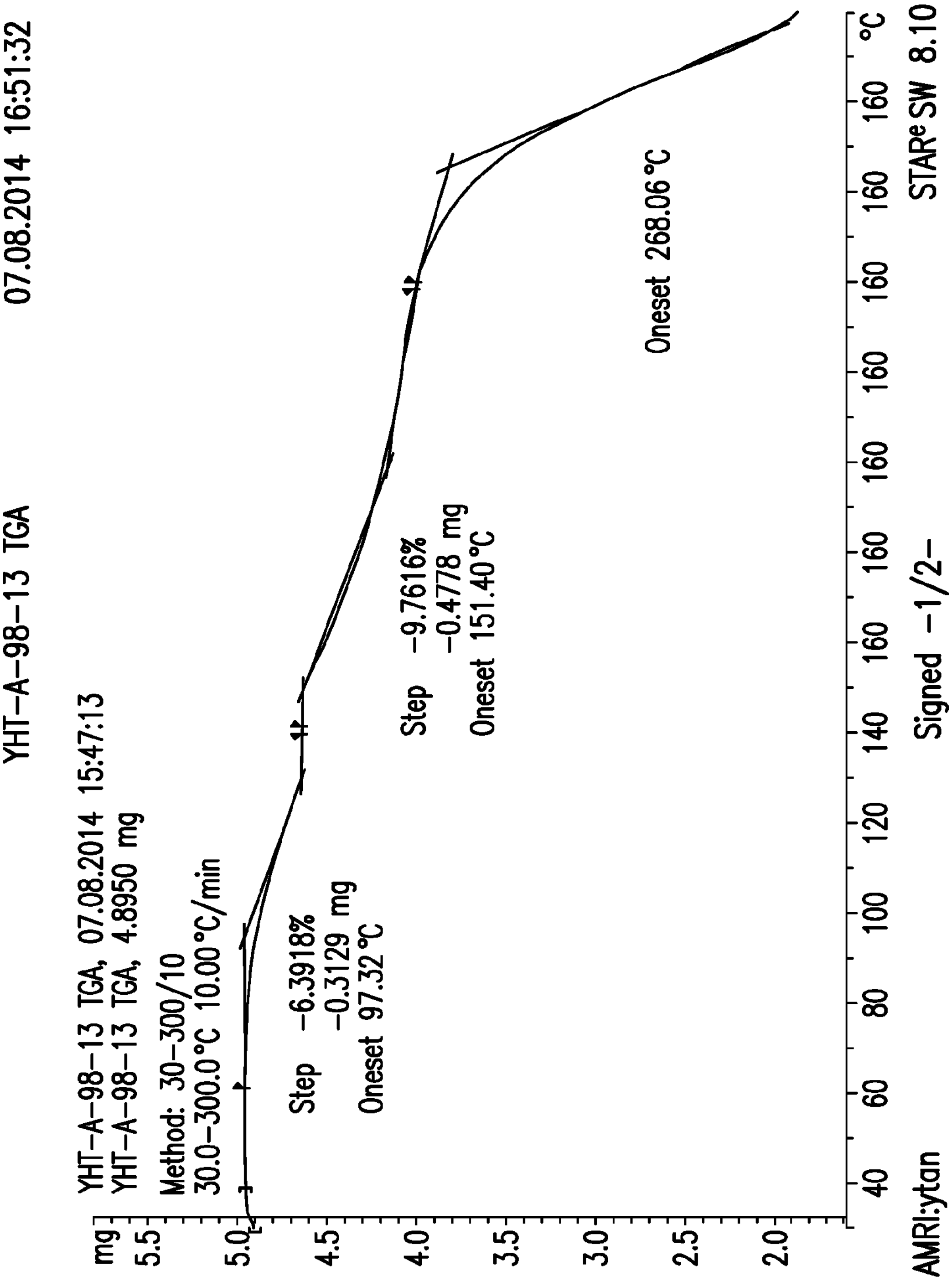

YHT-A-98-13 TGA
07.08.2014 16:51:32
YHT-A-98-13 TGA, 07.08.2014 15:47:13
YHT-A-98-13 TGA, 4.8950 mg
Method: 30-300/10
30.0-300.0°C 10.00°C/min
Step -6.3918%
-0.3129 mg
Oneset 97.32°C
Step -9.7616%
-0.4778 mg
Oneset 151.40°C
Oneset 268.06°C
mg
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
40
60
80
100
120
140
160
160
160
160
160
160
160
°C
AMRI:ytan
Signed -1/2-
STARe SW 8.10

FIG. 39

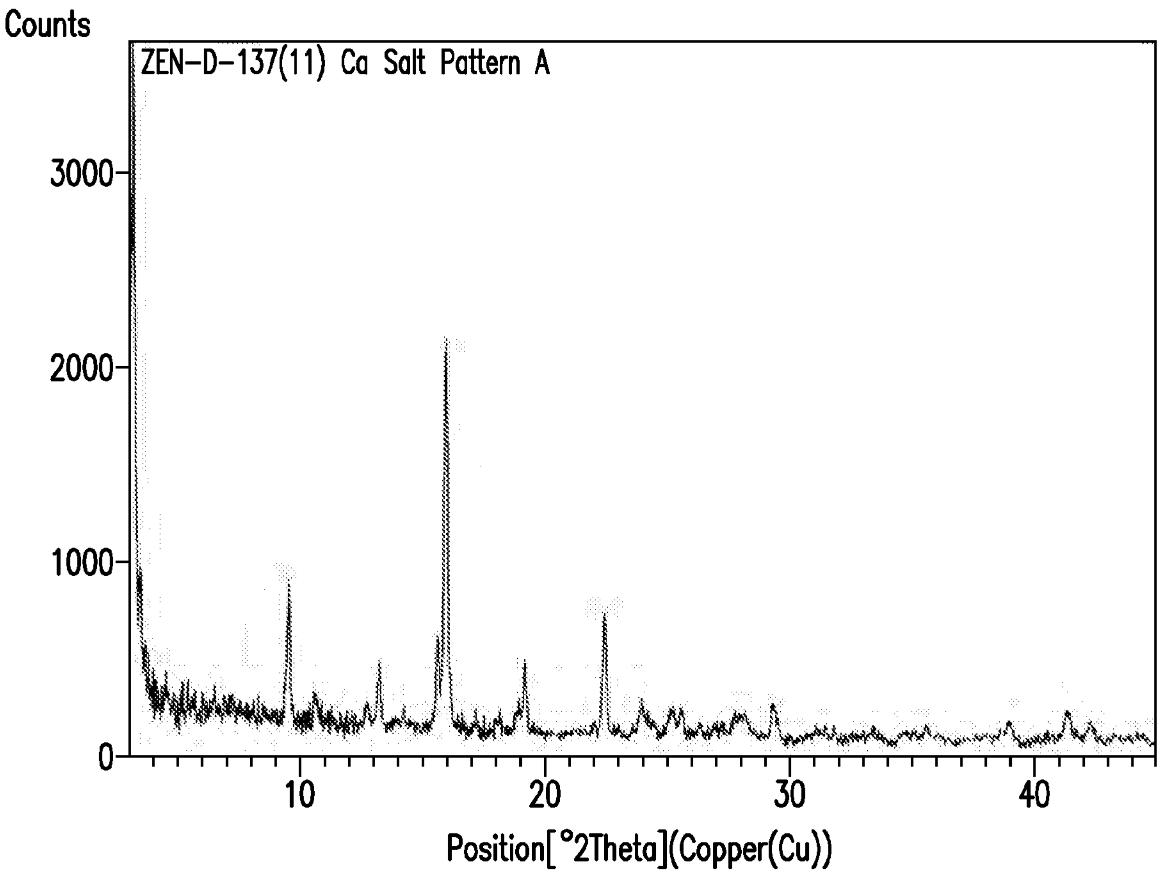

Counts
ZEN-D-137(11) Ca Salt Pattern A
3000
2000
1000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 40

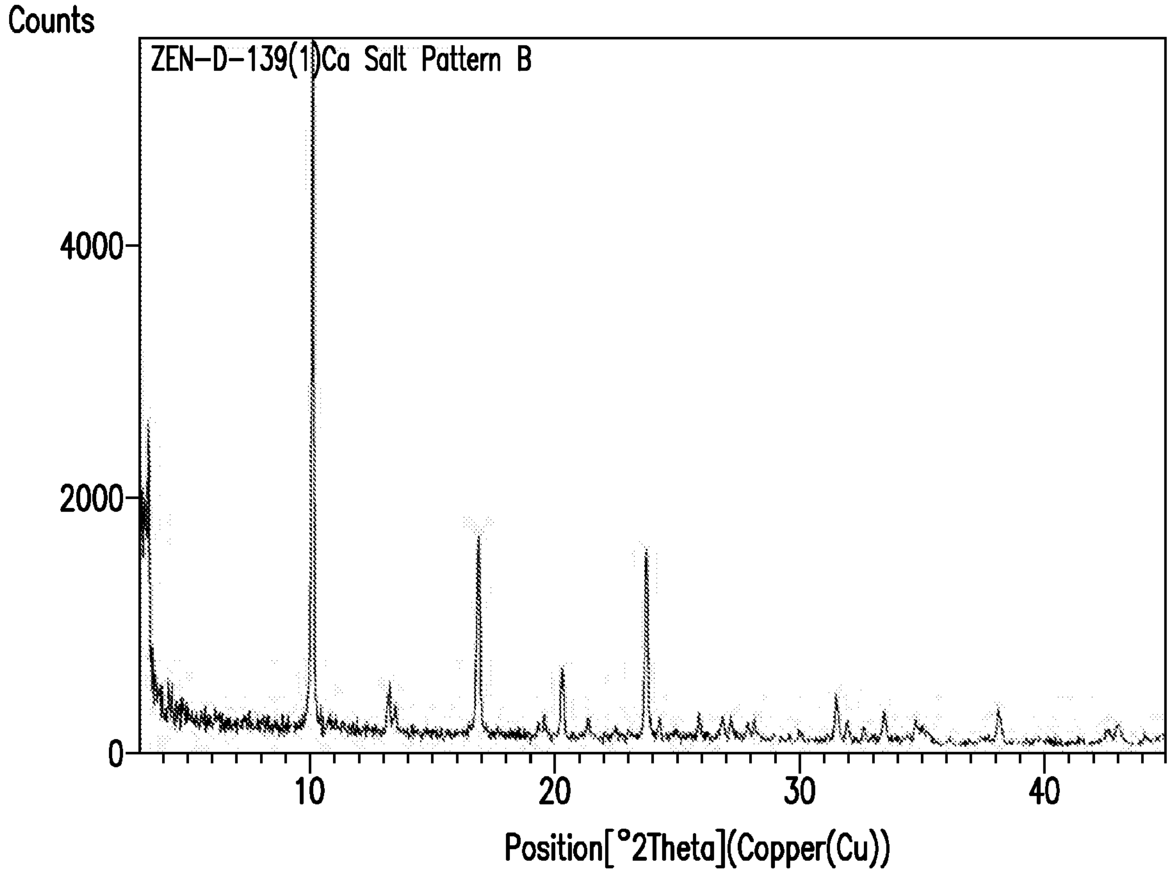

Counts
ZEN-D-139(1)Ca Salt Pattern B
4000
2000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 41

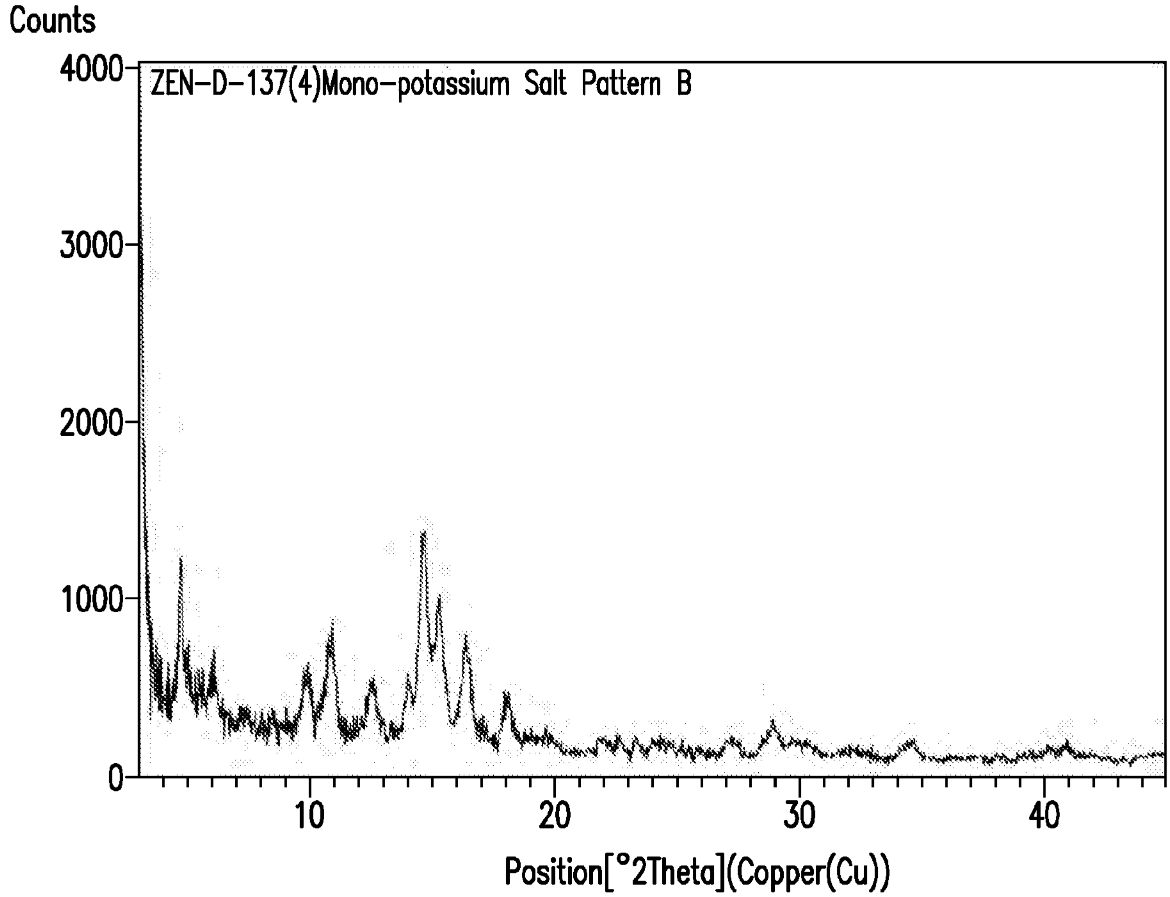

Counts
4000
3000
2000
1000
0
ZEN-D-137(4)Mono-potassium Salt Pattern B
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 42

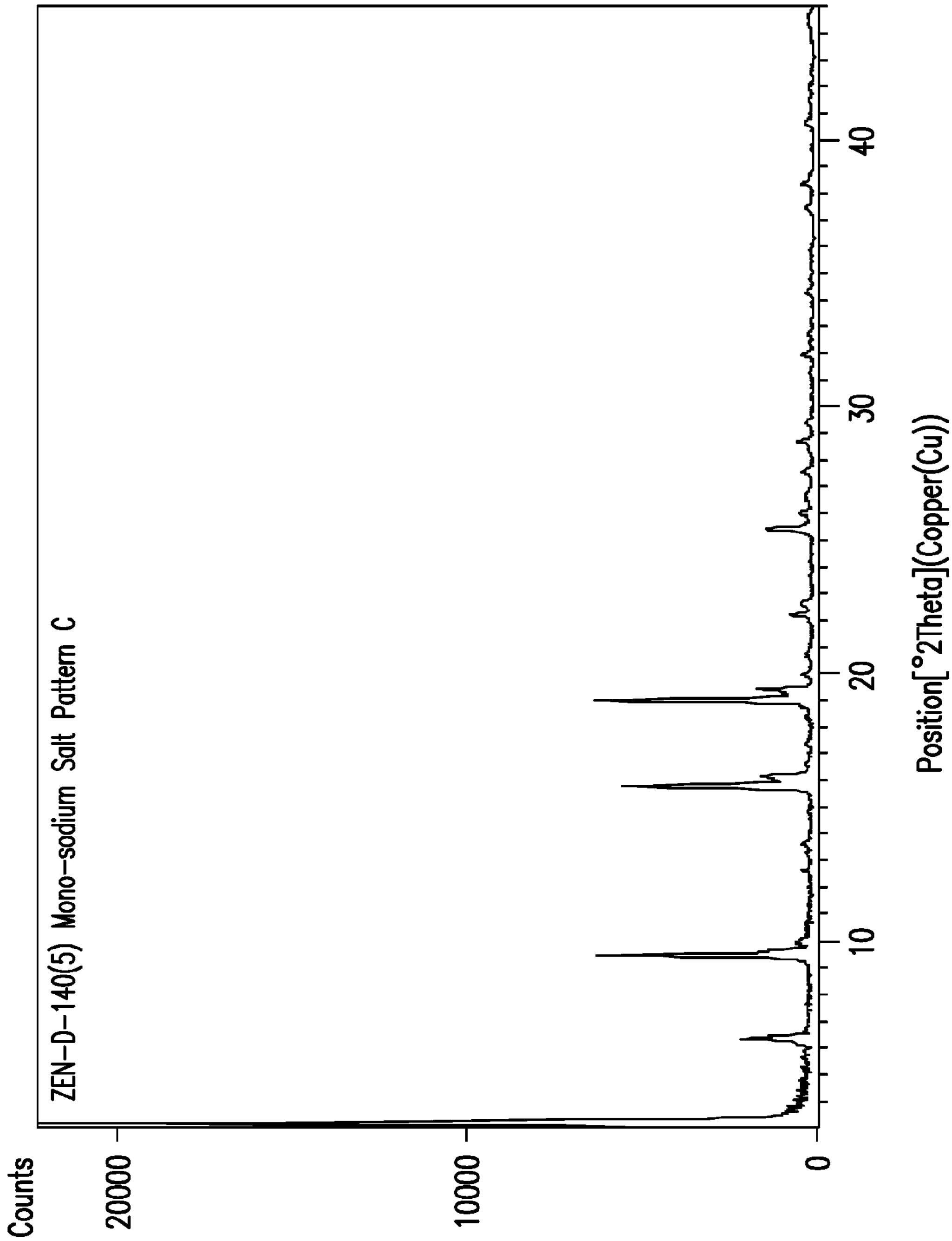

ZEN-D-140(5) Mono-sodium Salt Pattern C
Counts
20000
10000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 43

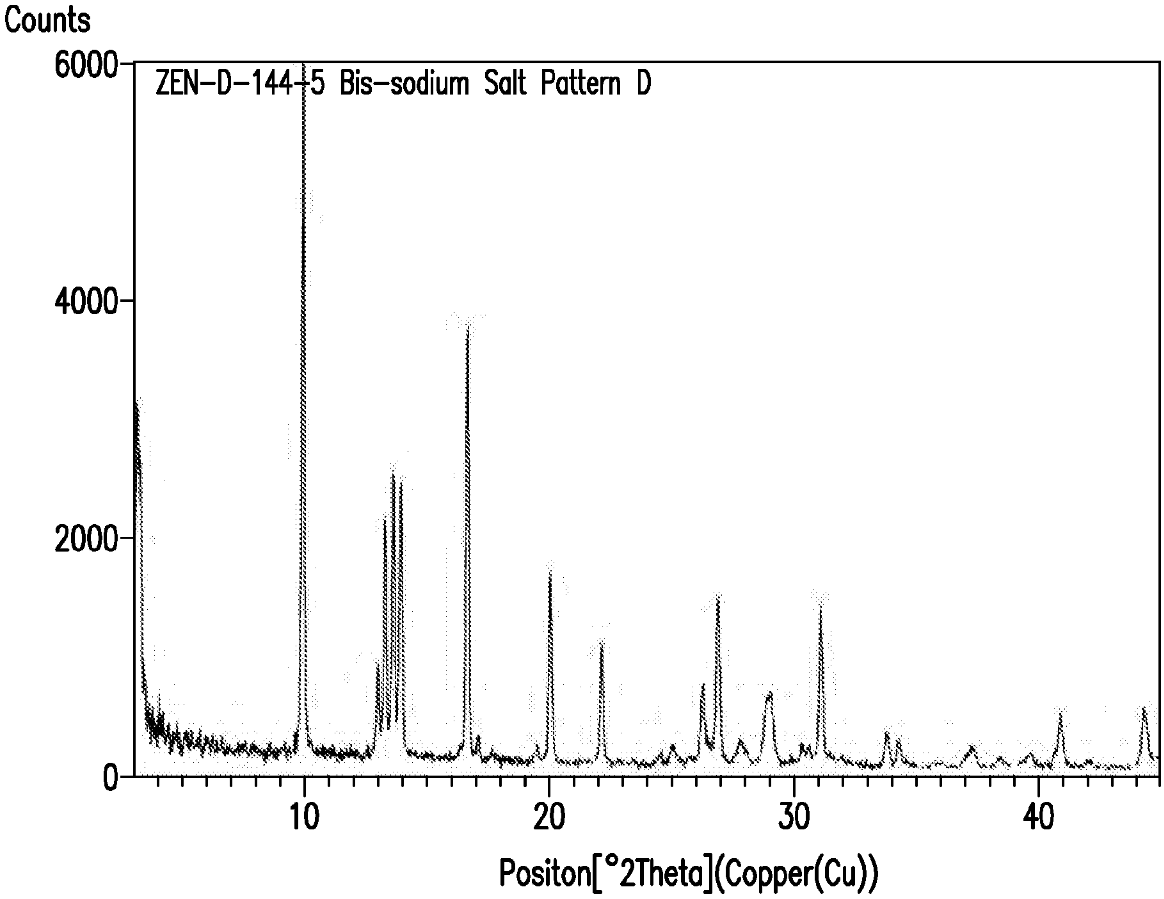

Counts
6000
4000
2000
0
ZEN-D-144-5 Bis-sodium Salt Pattern D
10
20
30
40
Positon[°2Theta](Copper(Cu))

FIG. 44

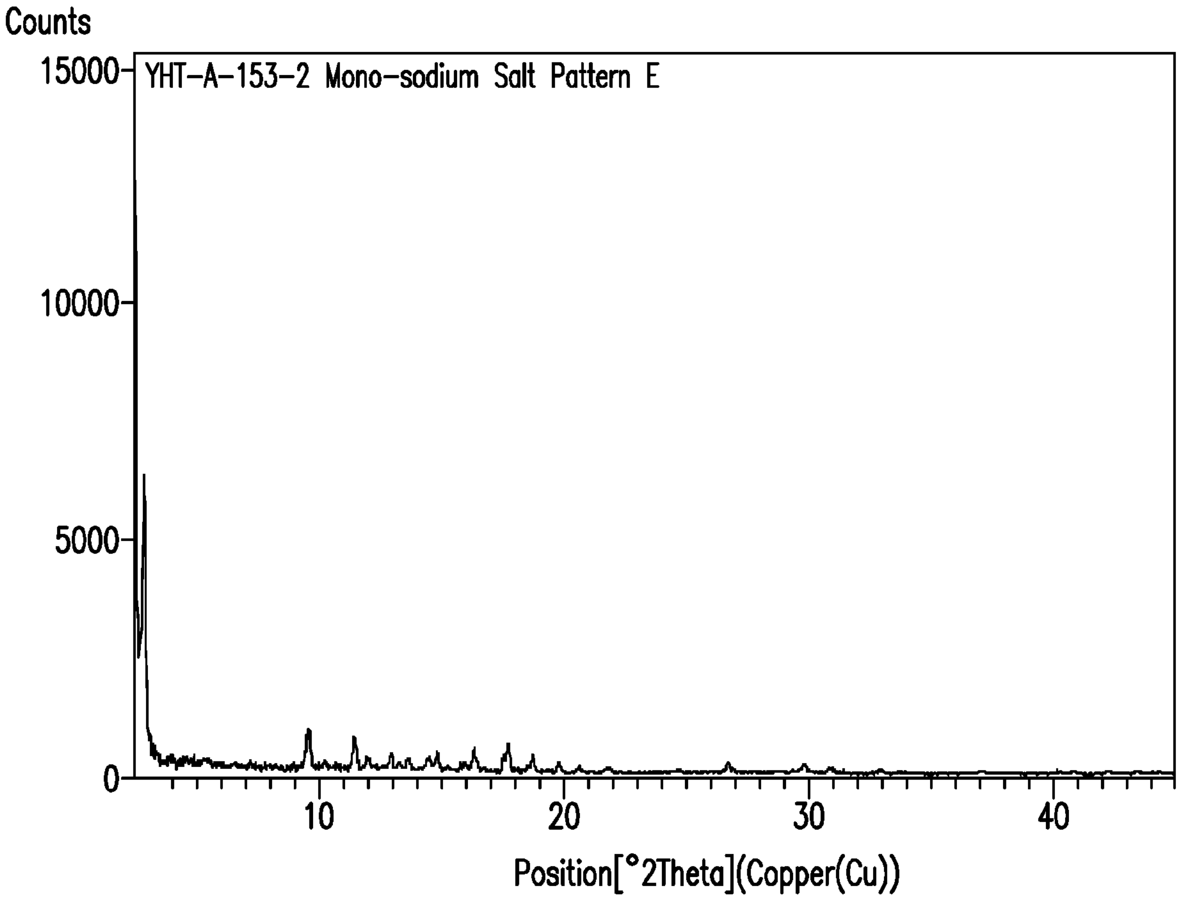

Counts
15000
10000
5000
0
YHT-A-153-2 Mono-sodium Salt Pattern E
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 45

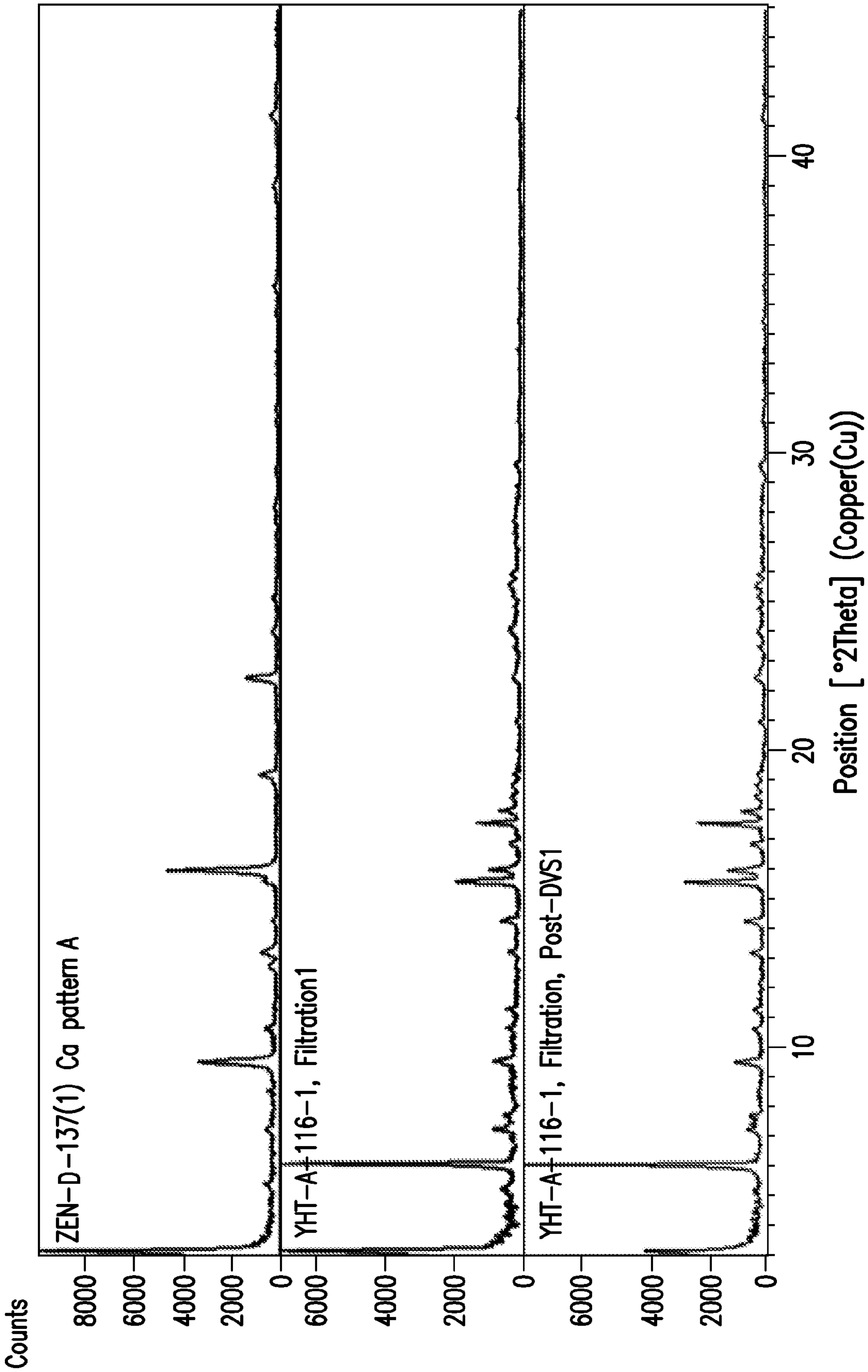

Counts
8000
6000
4000
2000
0
ZEN-D-137(1) Ca pattern A
YHT-A-116-1, Filtration1
YHT-A-116-1, Filtration, Post-DVS1
10
20
30
40
Position [°2Theta] (Copper(Cu))

FIG. 46

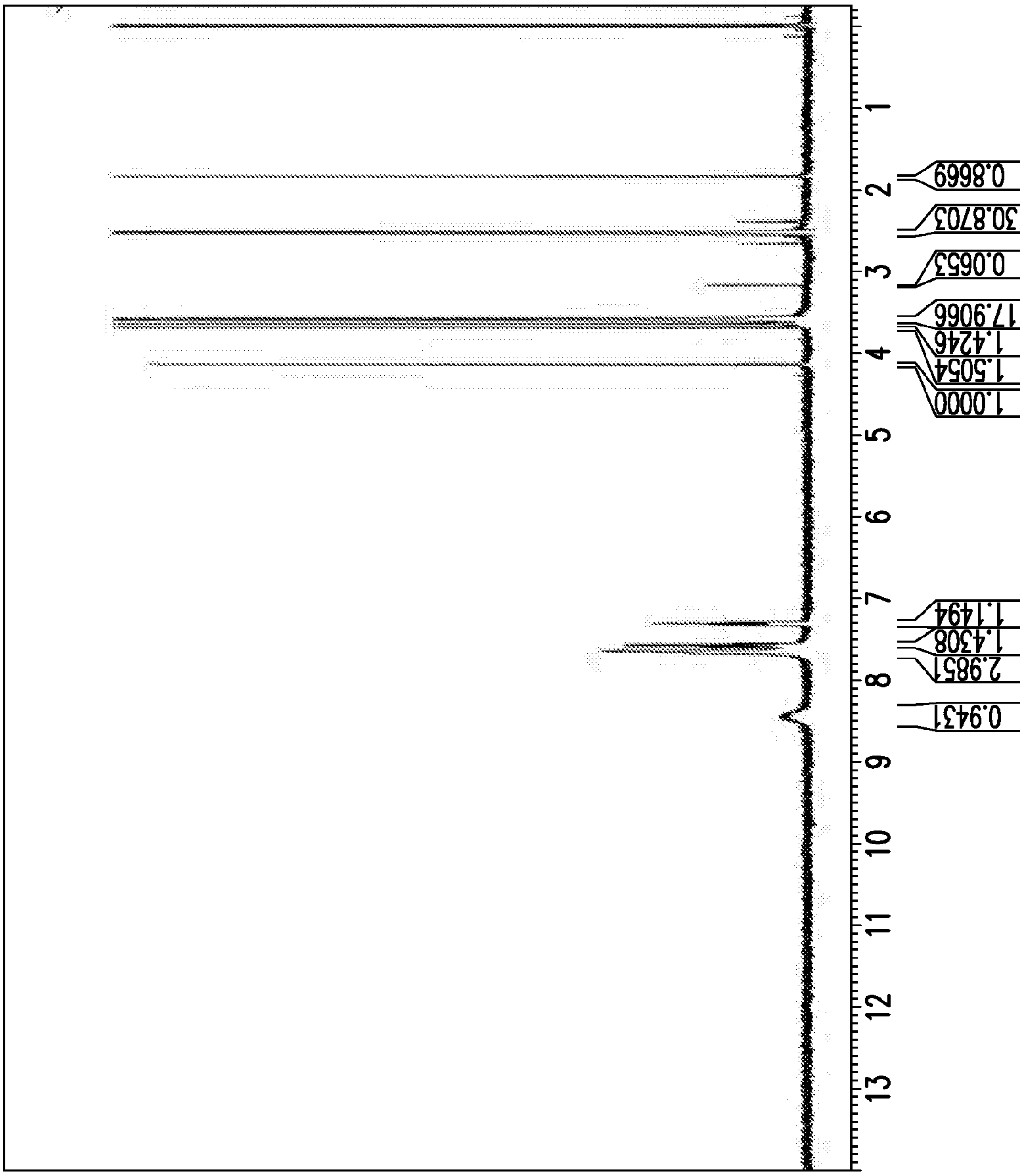
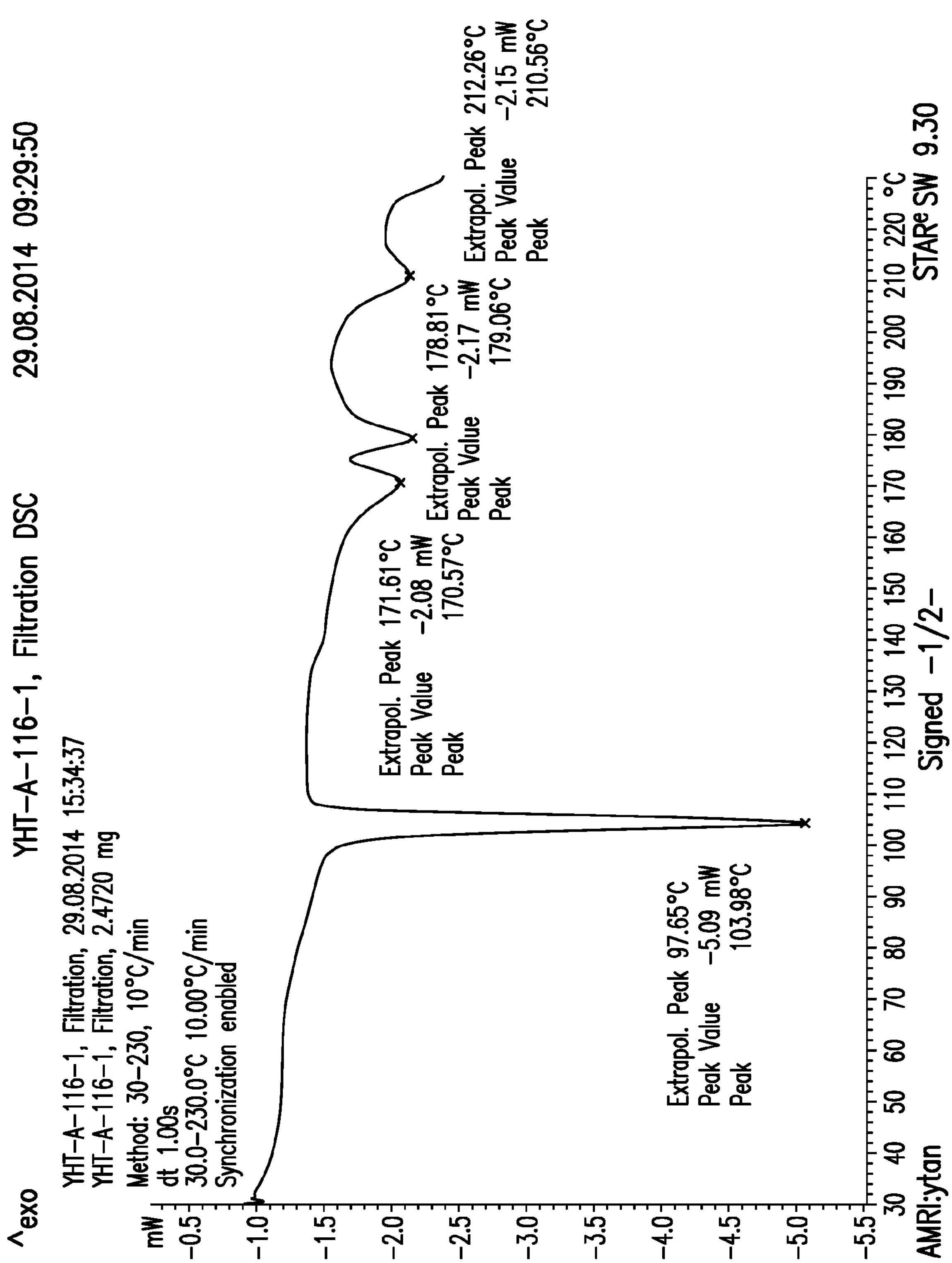

1
2
3
4
5
6
7
8
9
10
11
12
13
0.8669
30.8703
0.0653
17.9066
1.4246
1.5054
1.0000
1.1494
1.4308
2.9851
0.9431

FIG. 47



YHT–A–116–1, Filtration DSC
29.08.2014 09:29:50
^exo
YHT–A–116–1, Filtration, 29.08.2014 15:34:37
YHT–A–116–1, Filtration, 2.4720 mg
Method: 30–230, 10°C/min
dt 1.00s
30.0–230.0°C 10.00°C/min
Synchronization enabled
Extrapol. Peak 97.65°C
Peak Value –5.09 mW
Peak 103.98°C
Extrapol. Peak 171.61°C
Peak Value –2.08 mW
Peak 170.57°C
Extrapol. Peak 178.81°C
Peak Value –2.17 mW
Peak 179.06°C
Extrapol. Peak 212.26°C
Peak Value –2.15 mW
Peak 210.56°C
mW
–0.5
–1.0
–1.5
–2.0
–2.5
–3.0
–3.5
–4.0
–4.5
–5.0
–5.5
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 °C
AMRI:ytan
Signed –1/2–
STARe SW 9.30

FIG. 48

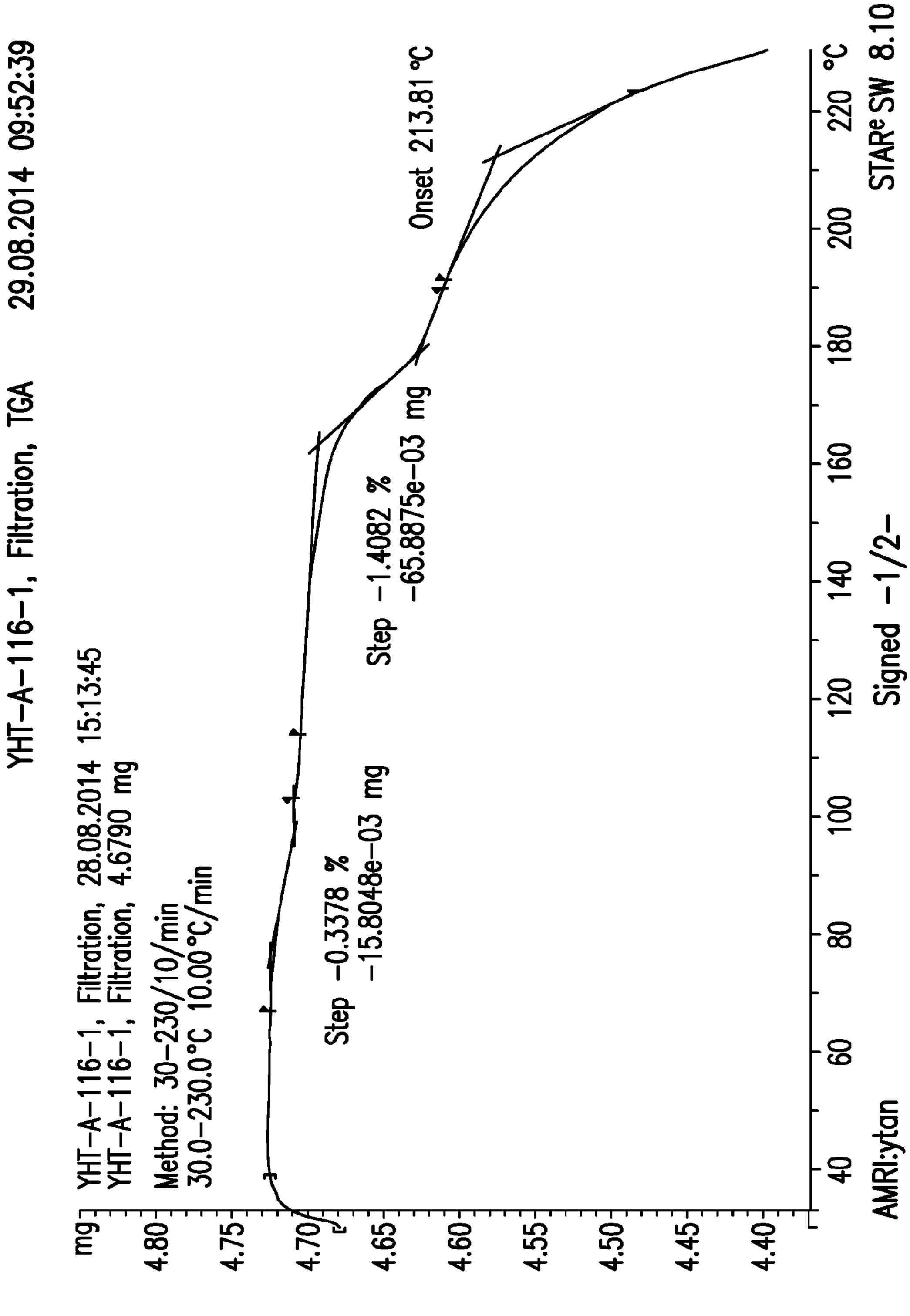

YHT-A-116-1, Filtration, TGA 29.08.2014 09:52:39
YHT-A-116-1, Filtration, 28.08.2014 15:13:45
YHT-A-116-1, Filtration, 4.6790 mg
Method: 30-230/10/min
30.0-230.0°C 10.00°C/min
Step -0.3378 %
-15.8048e-03 mg
Step -1.4082 %
-65.8875e-03 mg
Onset 213.81 °C
mg
4.80
4.75
4.70
4.65
4.60
4.55
4.50
4.45
4.40
40
60
80
100
120
140
160
180
200
220
°C
AMRI:ytan
Signed -1/2-
STARe SW 8.10

FIG. 49

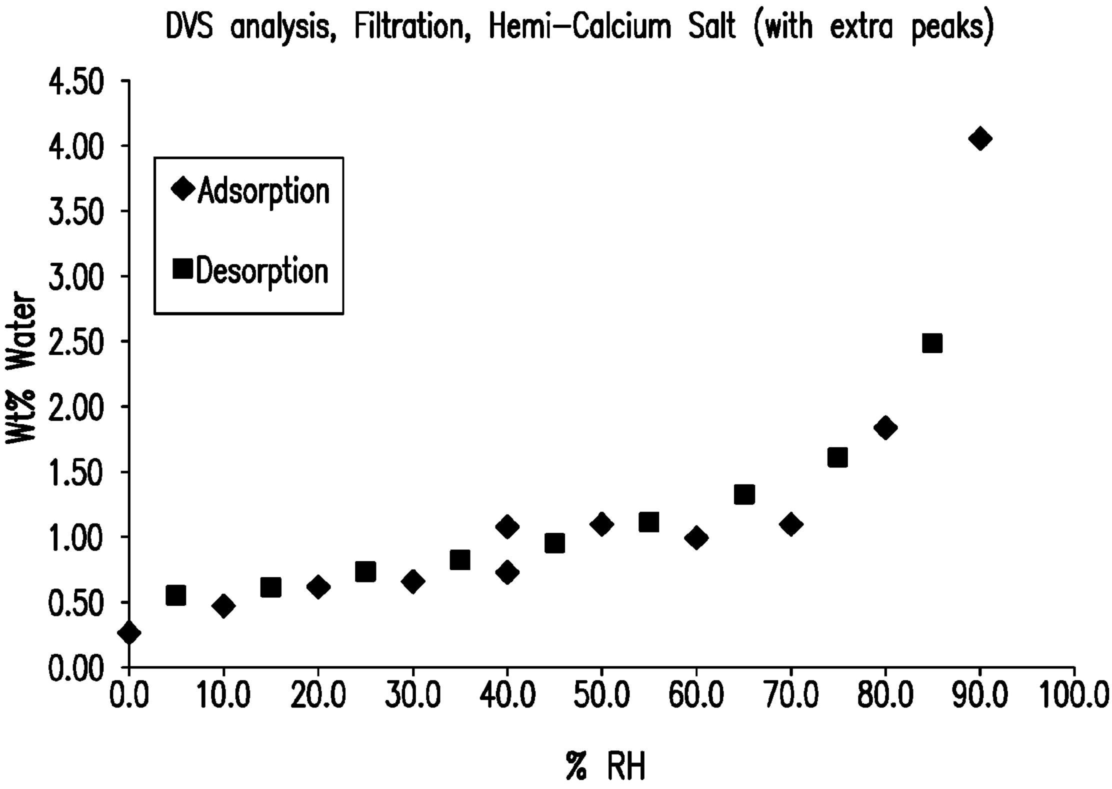

DVS analysis, Filtration, Hemi-Calcium Salt (with extra peaks)
Adsorption
Desorption
Wt% Water
% RH
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

FIG. 50

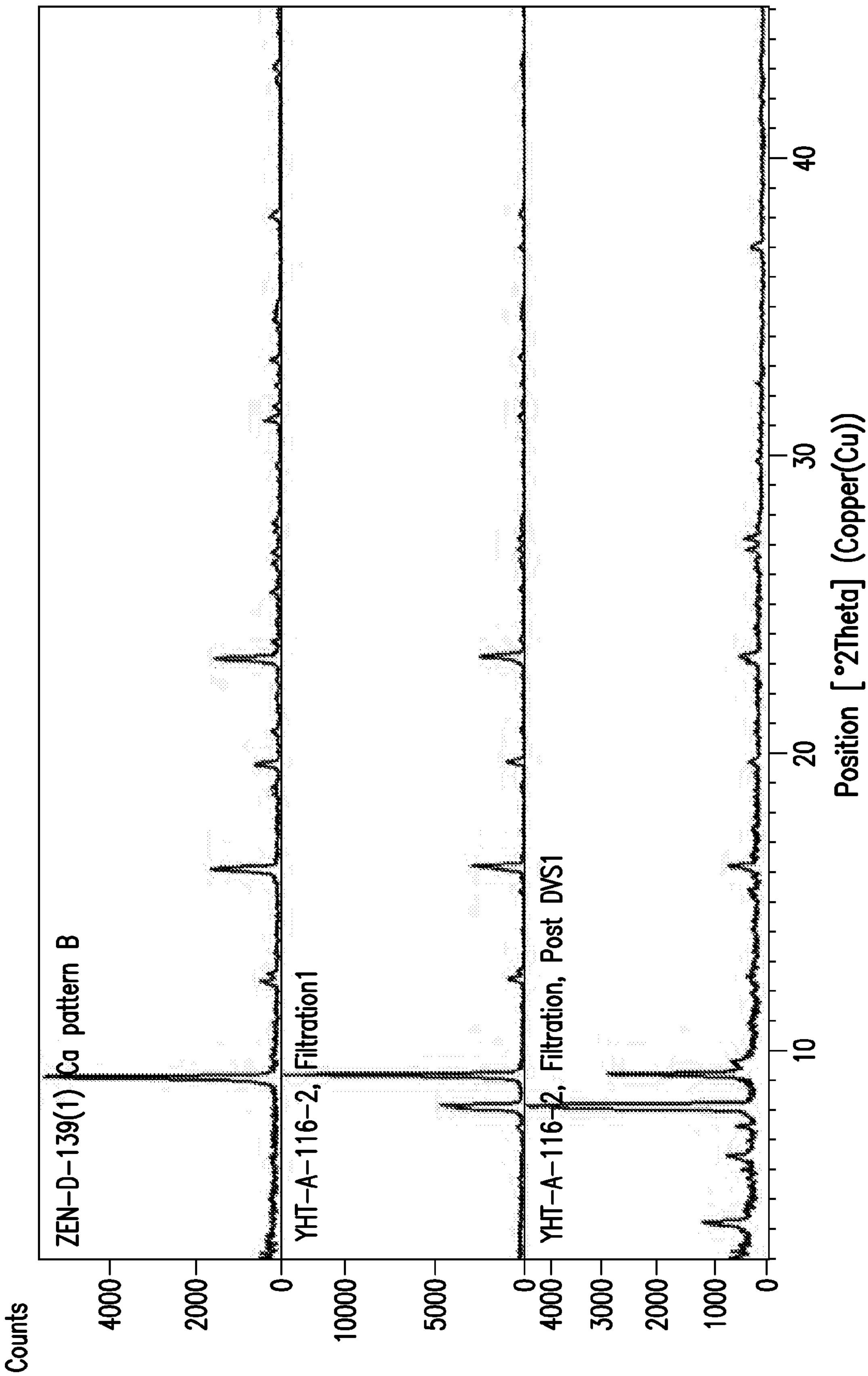

Counts
ZEN-D-139(1) Ca pattern B
YHT-A-116-2, Filtration1
YHT-A-116-2, Filtration, Post DVS1
4000
2000
0
10000
5000
0
4000
3000
2000
1000
0
10
20
30
40
Position [°2Theta] (Copper(Cu))

FIG. 51

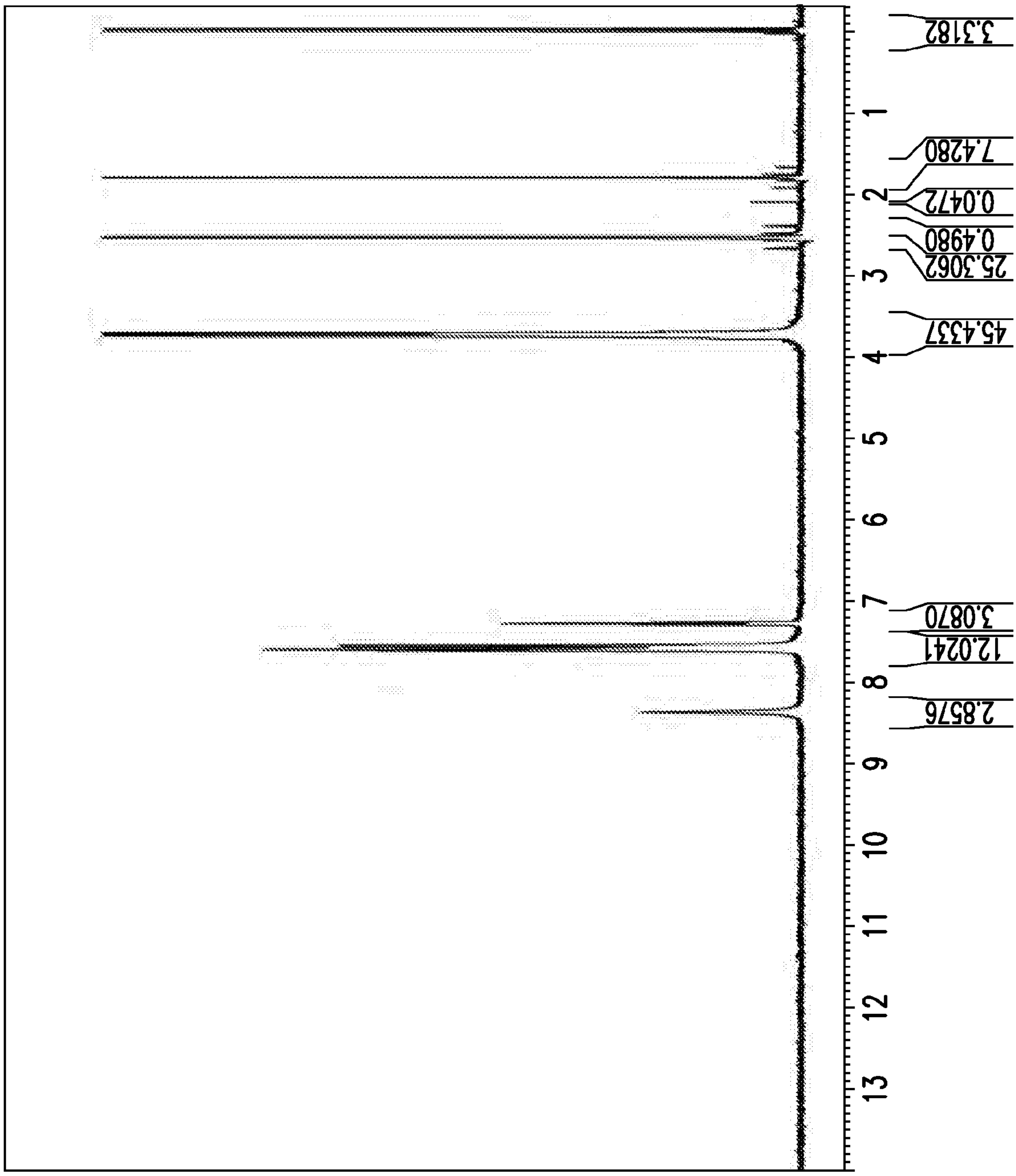
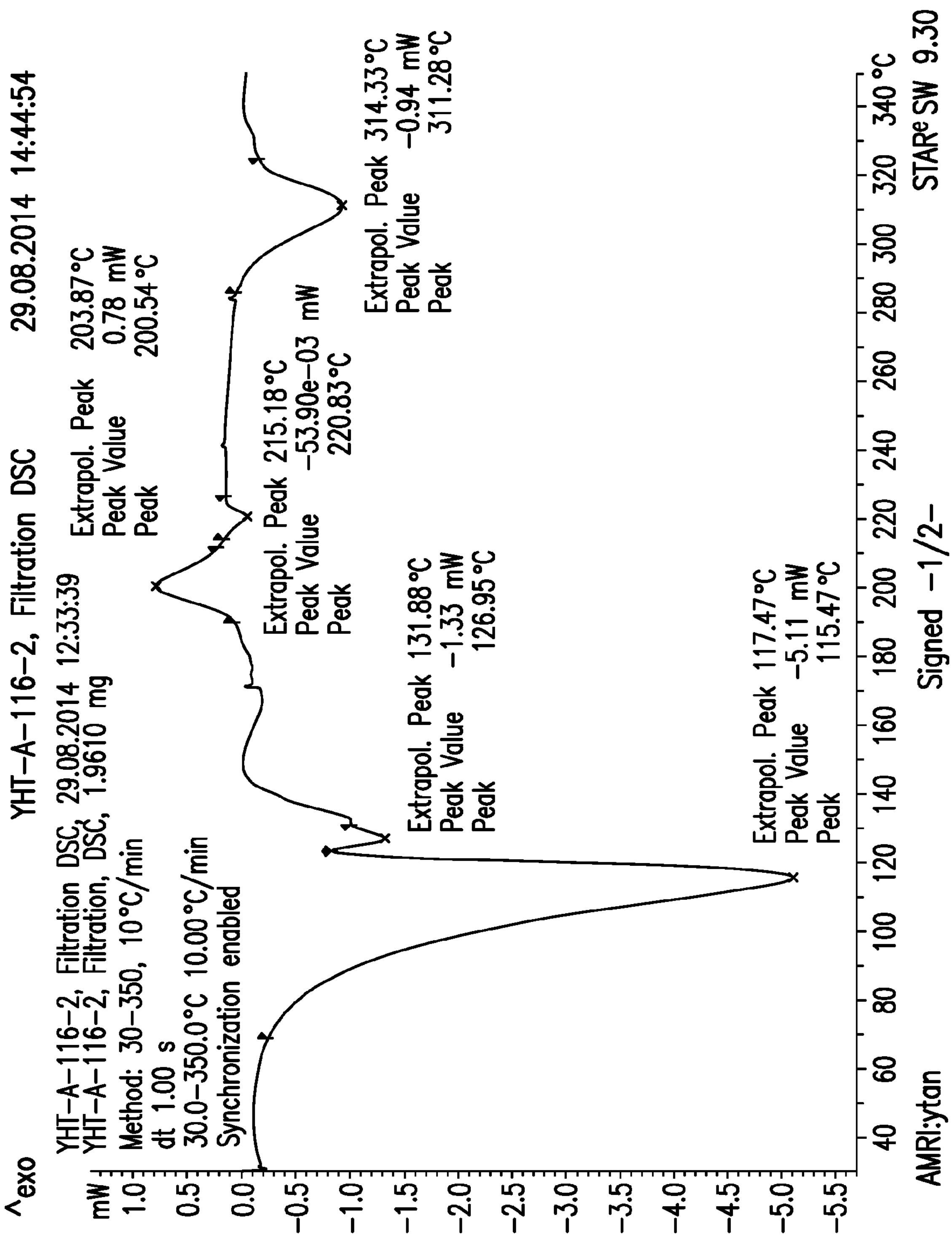
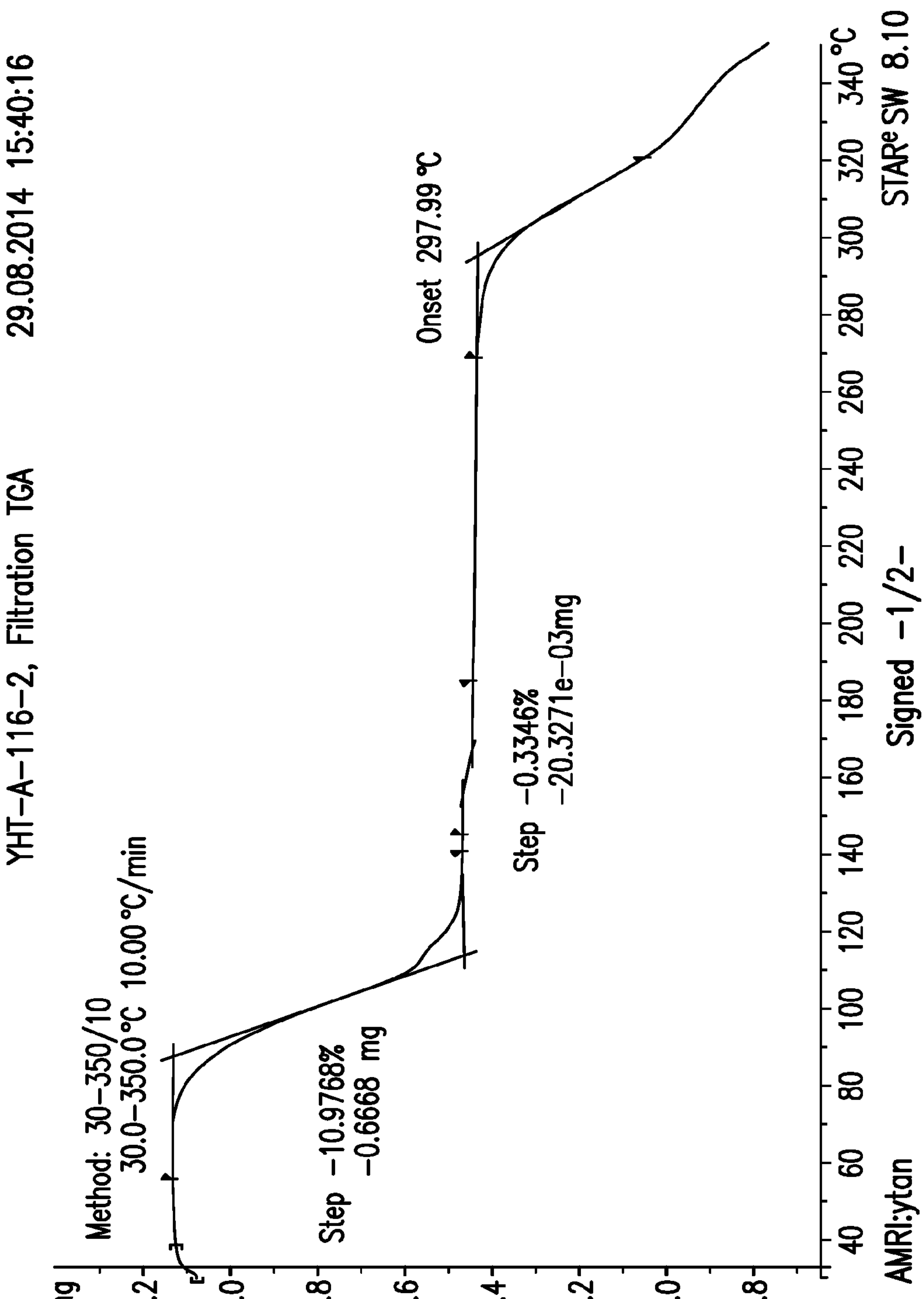

3.3182
7.4280
0.0472
0.4980
25.3062
45.4537
3.0870
12.0241
2.8576
1
2
3
4
5
6
7
8
9
10
11
12
13

FIG. 52



YHT-A-116-2, Filtration DSC
29.08.2014 14:44:54
^exo
YHT-A-116-2, Filtration DSC, 29.08.2014 12:33:39
YHT-A-116-2, Filtration, DSC, 1.9610 mg
Method: 30-350, 10°C/min
dt 1.00 s
30.0-350.0°C 10.00°C/min
Synchronization enabled
Extrapol. Peak 203.87°C
Peak Value 0.78 mW
Peak 200.54°C
Extrapol. Peak 215.18°C
Peak Value -53.90e-03 mW
Peak 220.83°C
Extrapol. Peak 314.33°C
Peak Value -0.94 mW
Peak 311.28°C
Extrapol. Peak 131.88°C
Peak Value -1.33 mW
Peak 126.95°C
Extrapol. Peak 117.47°C
Peak Value -5.11 mW
Peak 115.47°C
mW
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-5.5
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
AMRI:ytan
Signed -1/2-
STAR^e SW 9.30

FIG. 53



YHT–A–116–2, Filtration TGA
29.08.2014 15:40:16
Method: 30–350/10
30.0–350.0°C 10.00°C/min
Step −10.9768%
−0.6668 mg
Step −0.3346%
−20.3271e−03mg
Onset 297.99 °C
mg
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
°C
AMRI:ytan
Signed −1/2−
STARe SW 8.10

FIG. 54

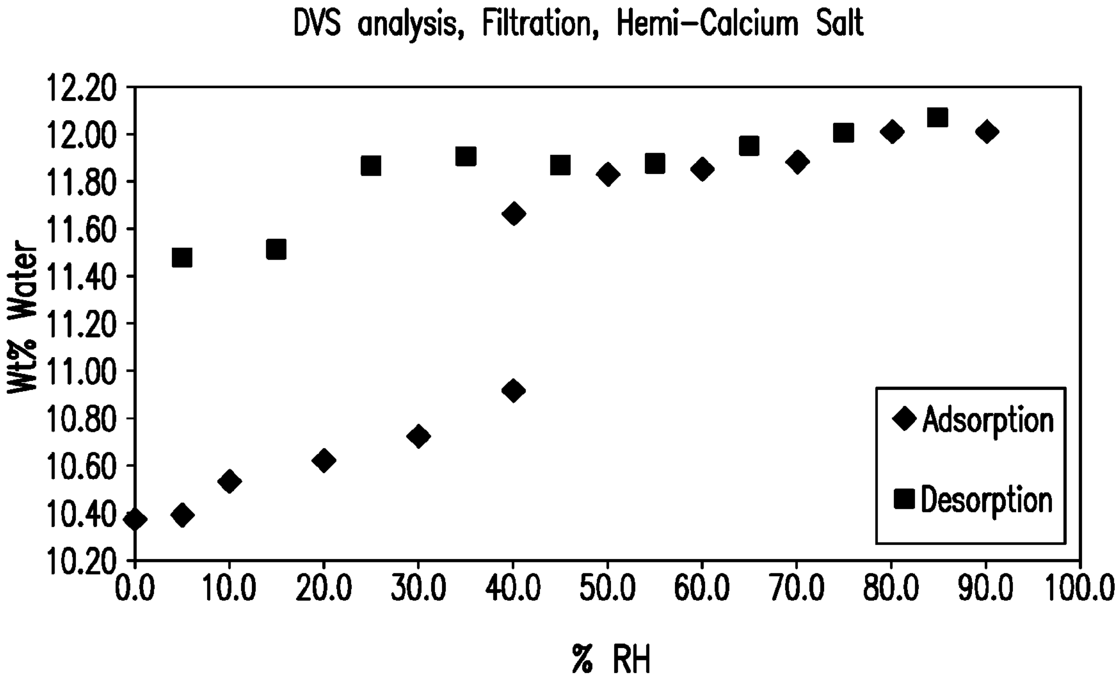

DVS analysis, Filtration, Hemi-Calcium Salt
Wt% Water
12.20
12.00
11.80
11.60
11.40
11.20
11.00
10.80
10.60
10.40
10.20
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
% RH
Adsorption
Desorption

FIG. 55

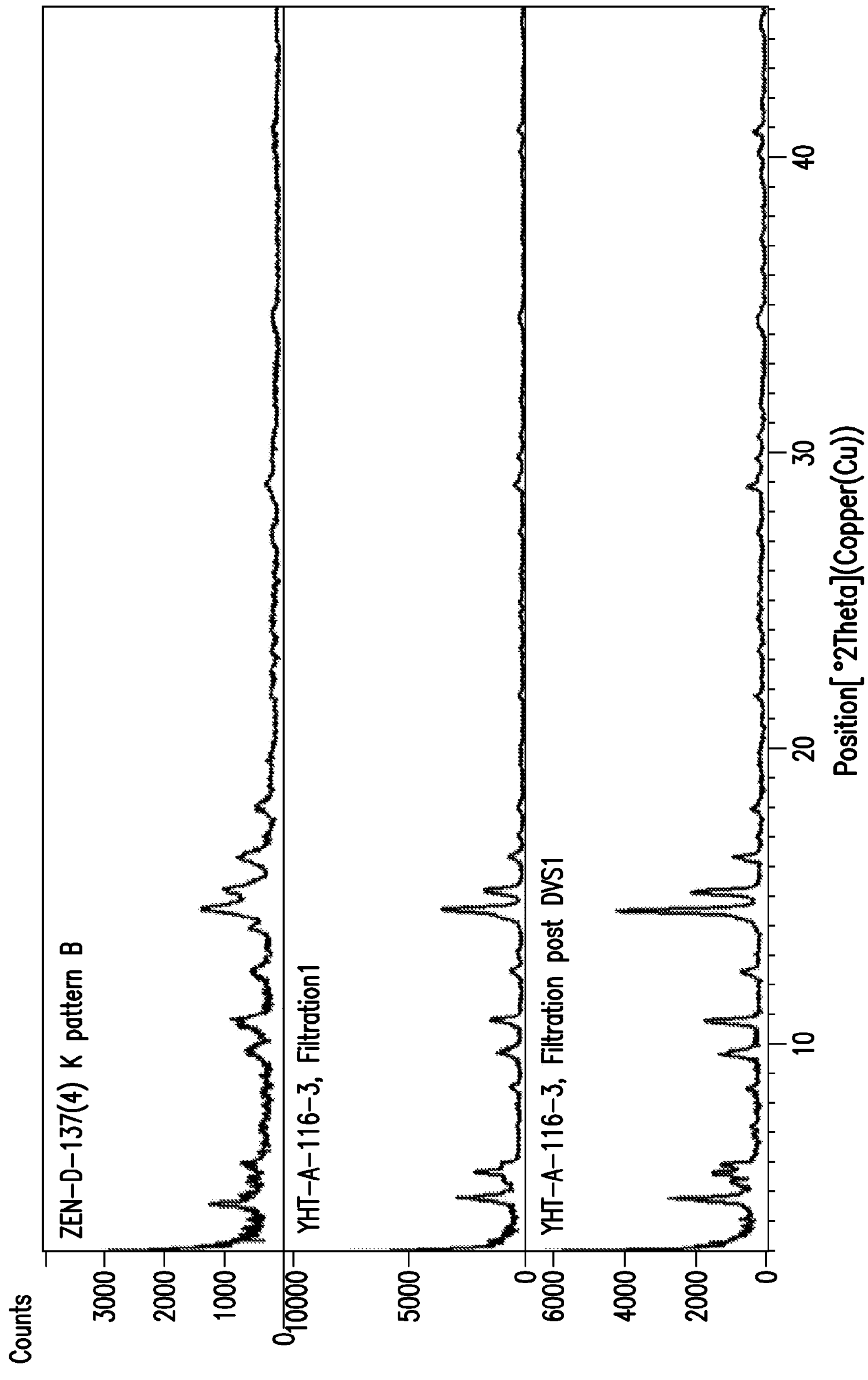

Counts
3000
2000
1000
0
10000
5000
0
6000
4000
2000
0
ZEN-D-137(4) K pattern B
YHT-A-116-3, Filtration1
YHT-A-116-3, Filtration post DVS1
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 56

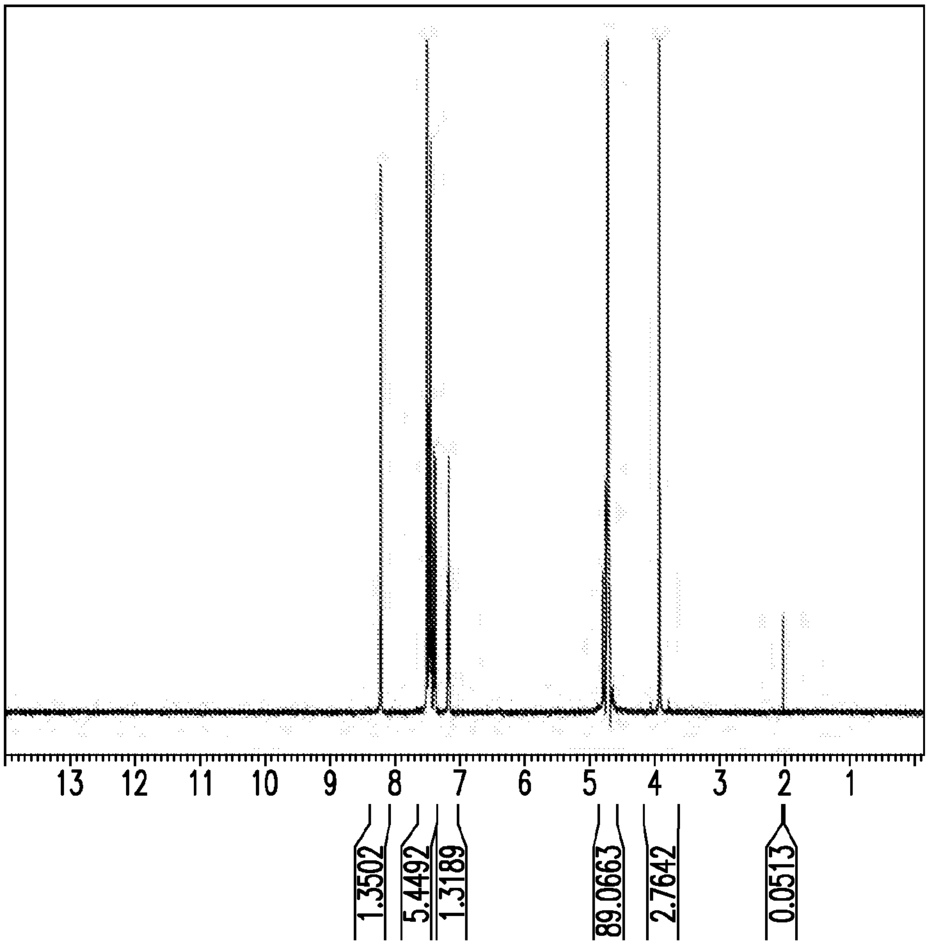


FIG. 57

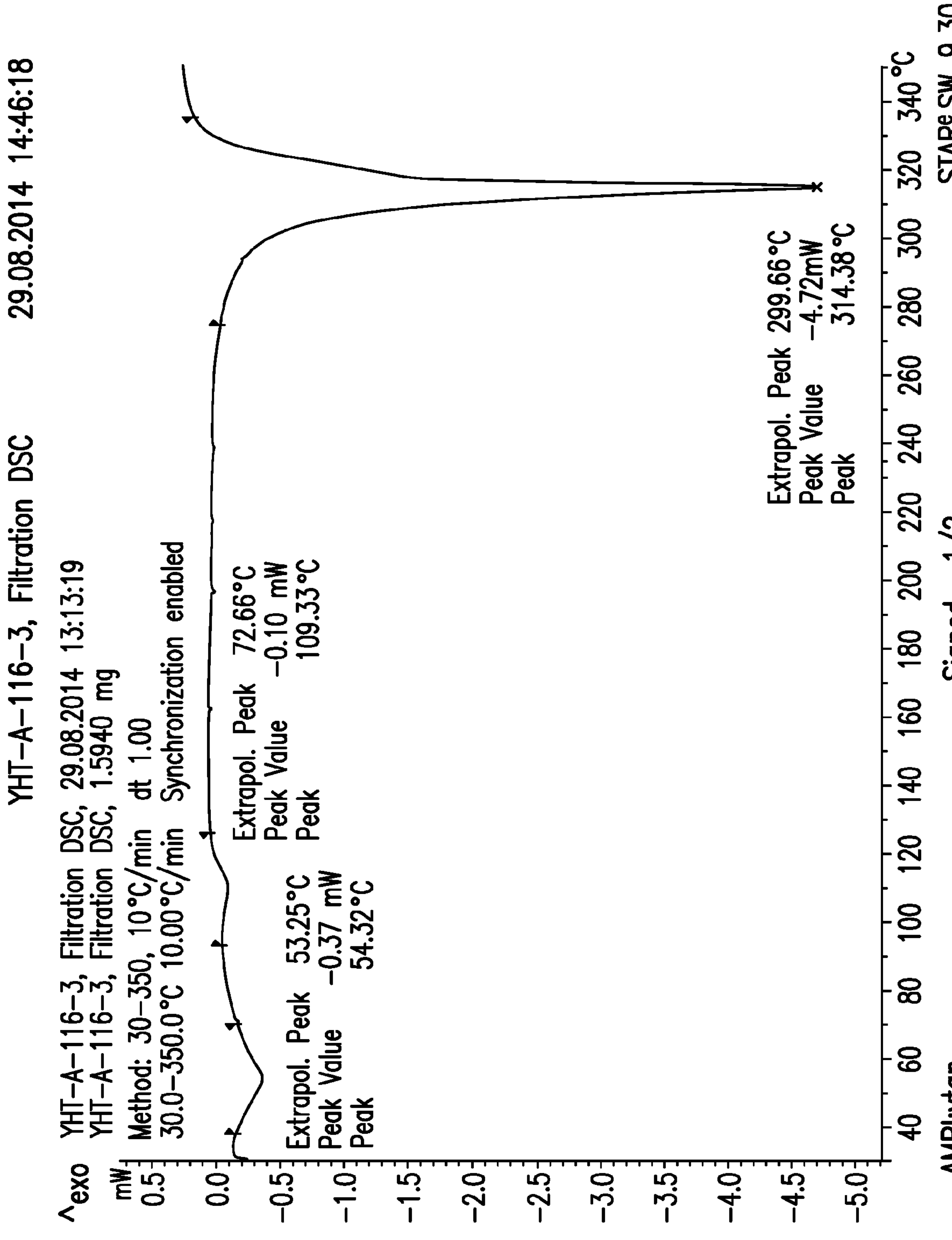

YHT–A–116–3, Filtration DSC
29.08.2014 14:46:18
YHT–A–116–3, Filtration DSC, 29.08.2014 13:13:19
YHT–A–116–3, Filtration DSC, 1.5940 mg
Method: 30–350, 10°C/min dt 1.00
30.0–350.0°C 10.00°C/min Synchronization enabled
^exo
mW
0.5
0.0
–0.5
–1.0
–1.5
–2.0
–2.5
–3.0
–3.5
–4.0
–4.5
–5.0
Extrapol. Peak 53.25°C
Peak Value –0.37 mW
Peak 54.32°C
Extrapol. Peak 72.66°C
Peak Value –0.10 mW
Peak 109.33°C
Extrapol. Peak 299.66°C
Peak Value –4.72mW
Peak 314.38°C
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
AMRI:ytan
Signed –1/2–
STARe SW 9.30

FIG. 58

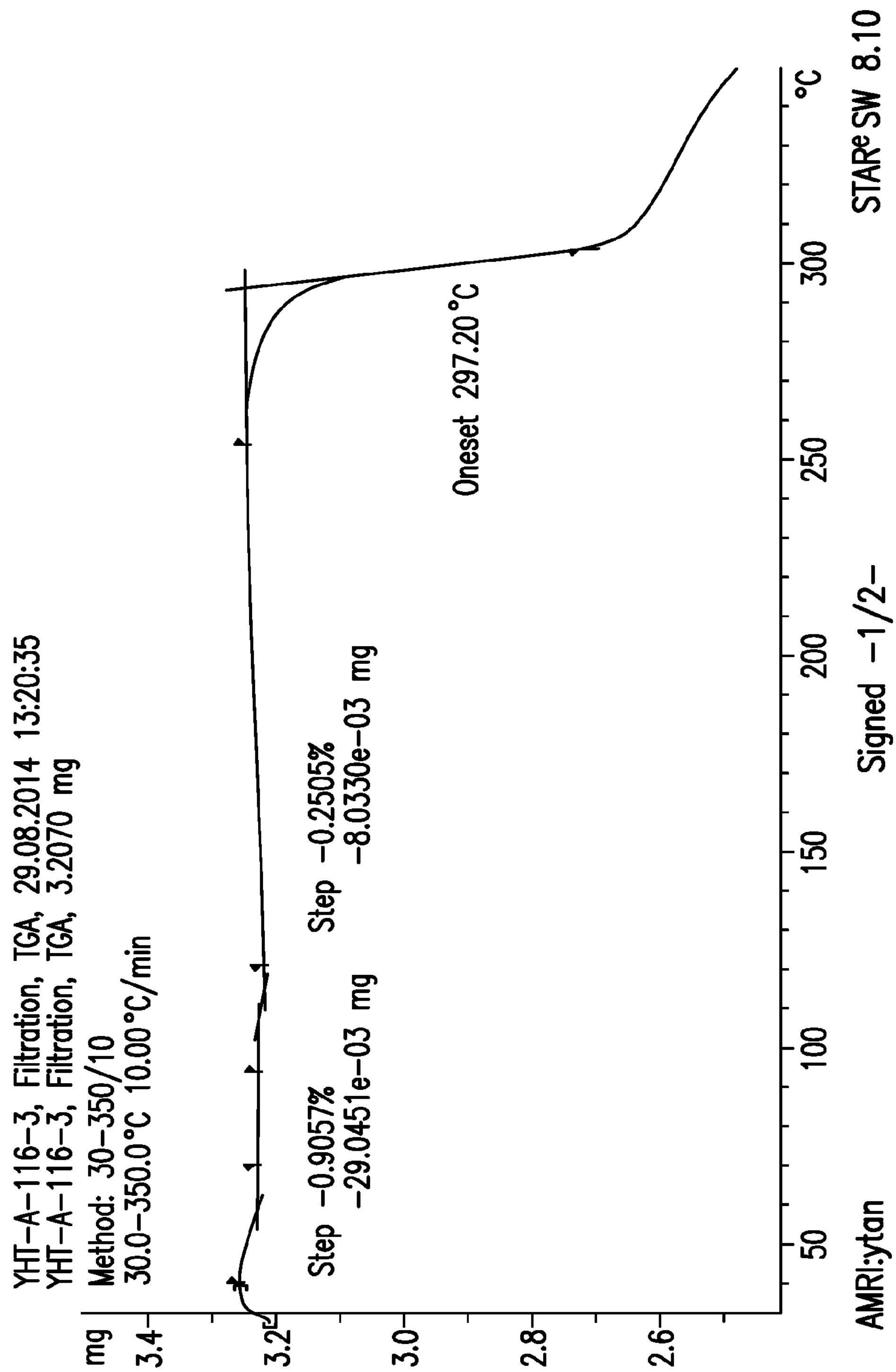

YHT−A−116−3, Filtration TGA
29.08.2014 15:56:53
YHT−A−116−3, Filtration, TGA, 29.08.2014 13:20:35
YHT−A−116−3, Filtration, TGA, 3.2070 mg
Method: 30−350/10
30.0−350.0°C 10.00°C/min
Step −0.9057%
−29.0451e−03 mg
Step −0.2505%
−8.0330e−03 mg
Oneset 297.20°C
mg
3.4
3.2
3.0
2.8
2.6
50
100
150
200
250
300
°C
AMRI:ytan
Signed −1/2−
STARe SW 8.10

FIG. 59

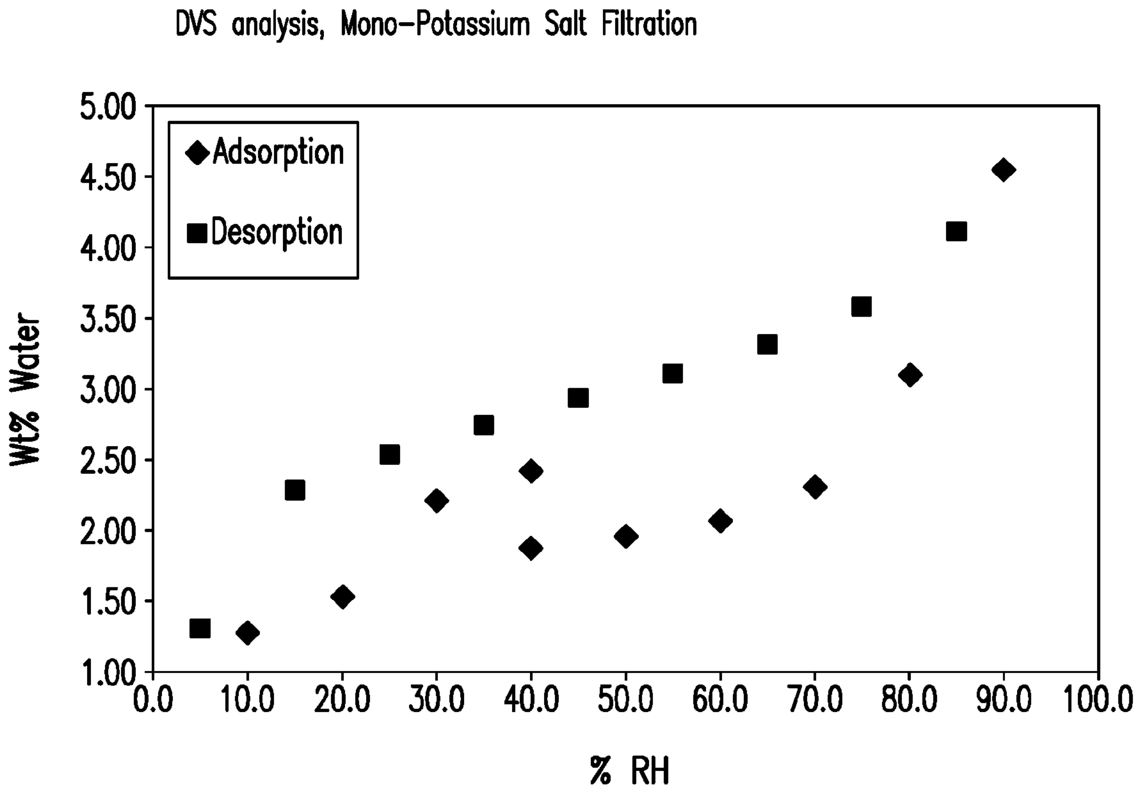

DVS analysis, Mono-Potassium Salt Filtration
Adsorption
Desorption
Wt% Water
% RH
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

FIG. 60

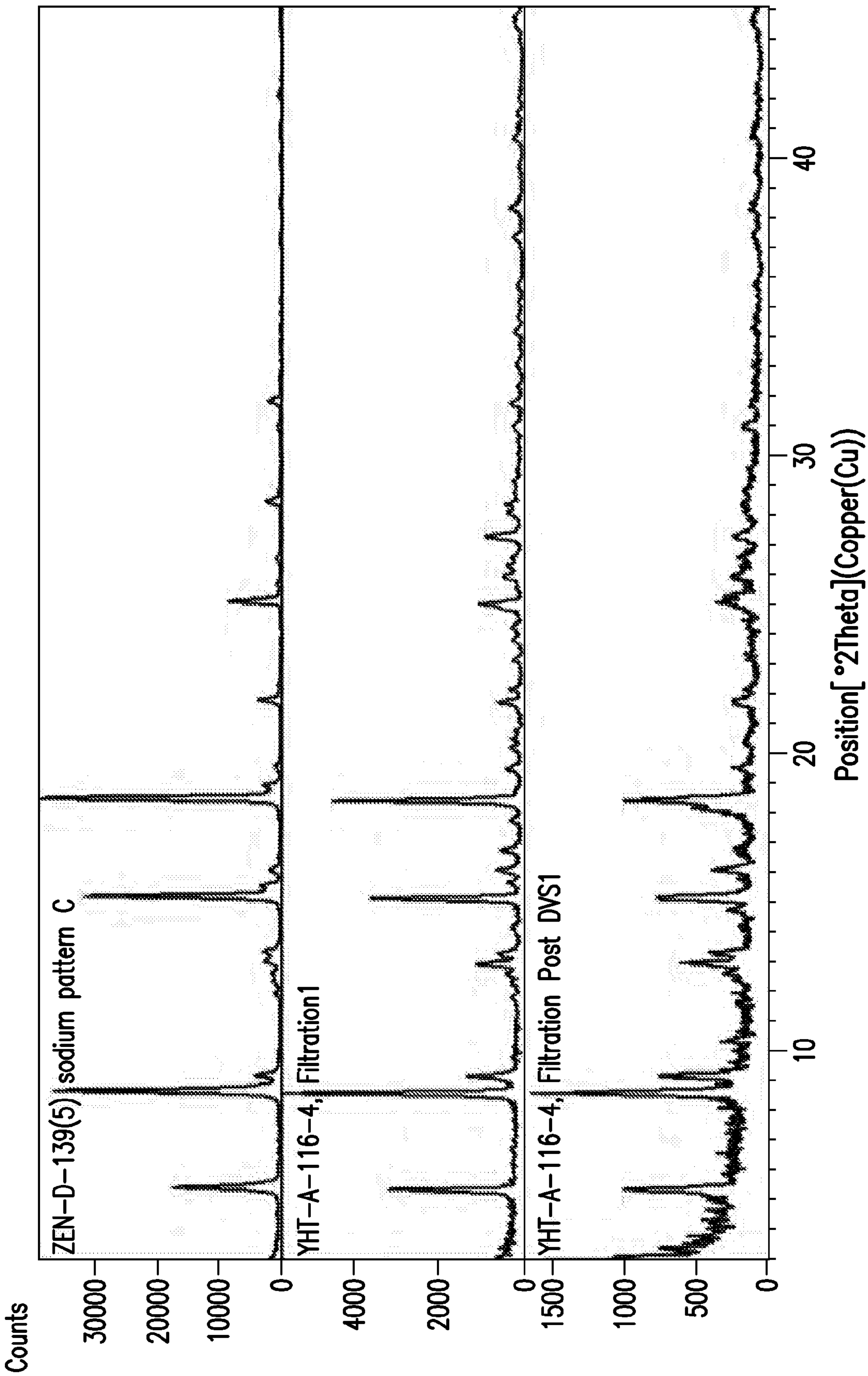

Counts
30000
20000
10000
0
4000
2000
0
1500
1000
500
0
ZEN-D-139(5) sodium pattern C
YHT-A-116-4, Filtration1
YHT-A-116-4, Filtration Post DVS1
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 61

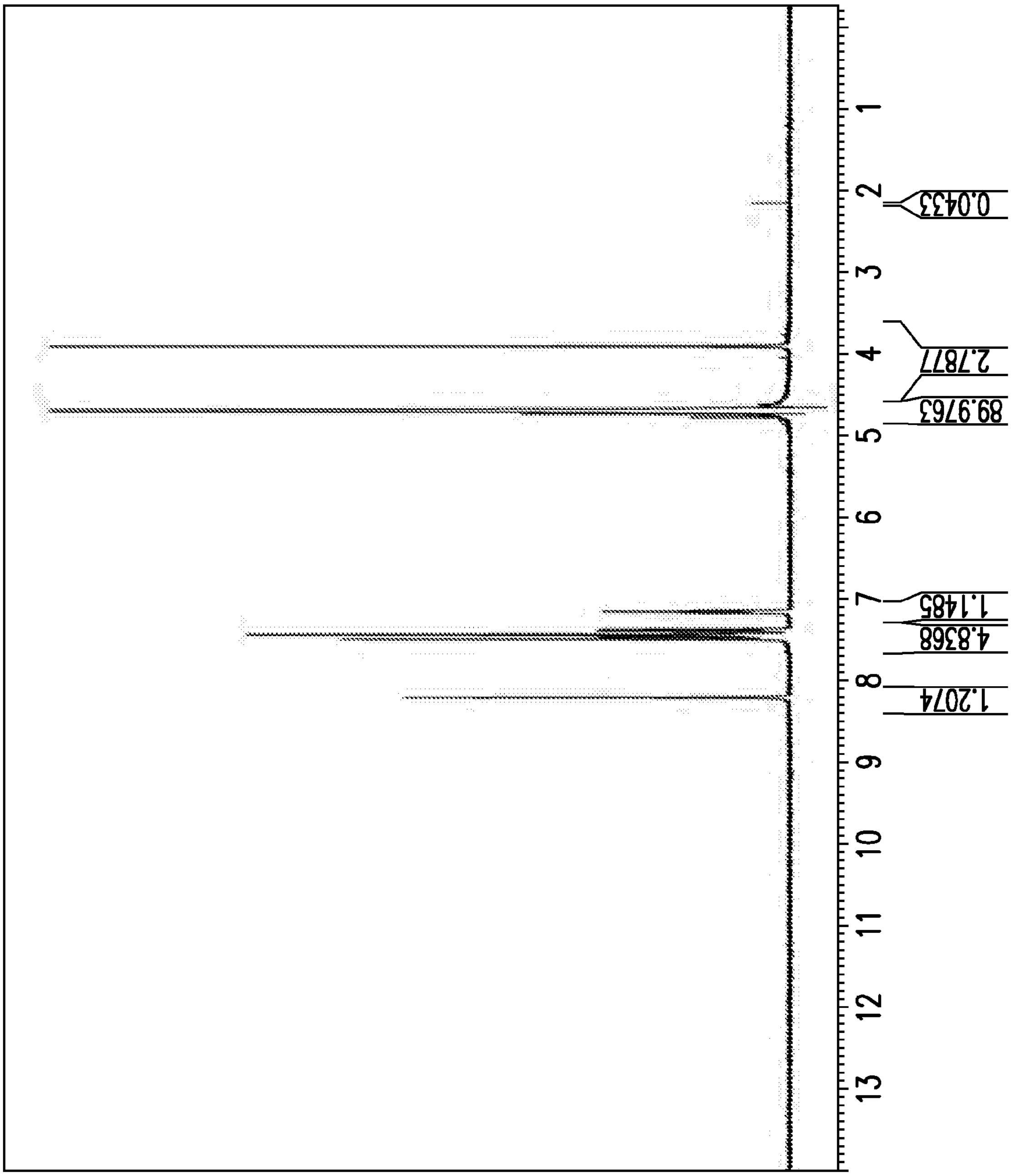


FIG. 62

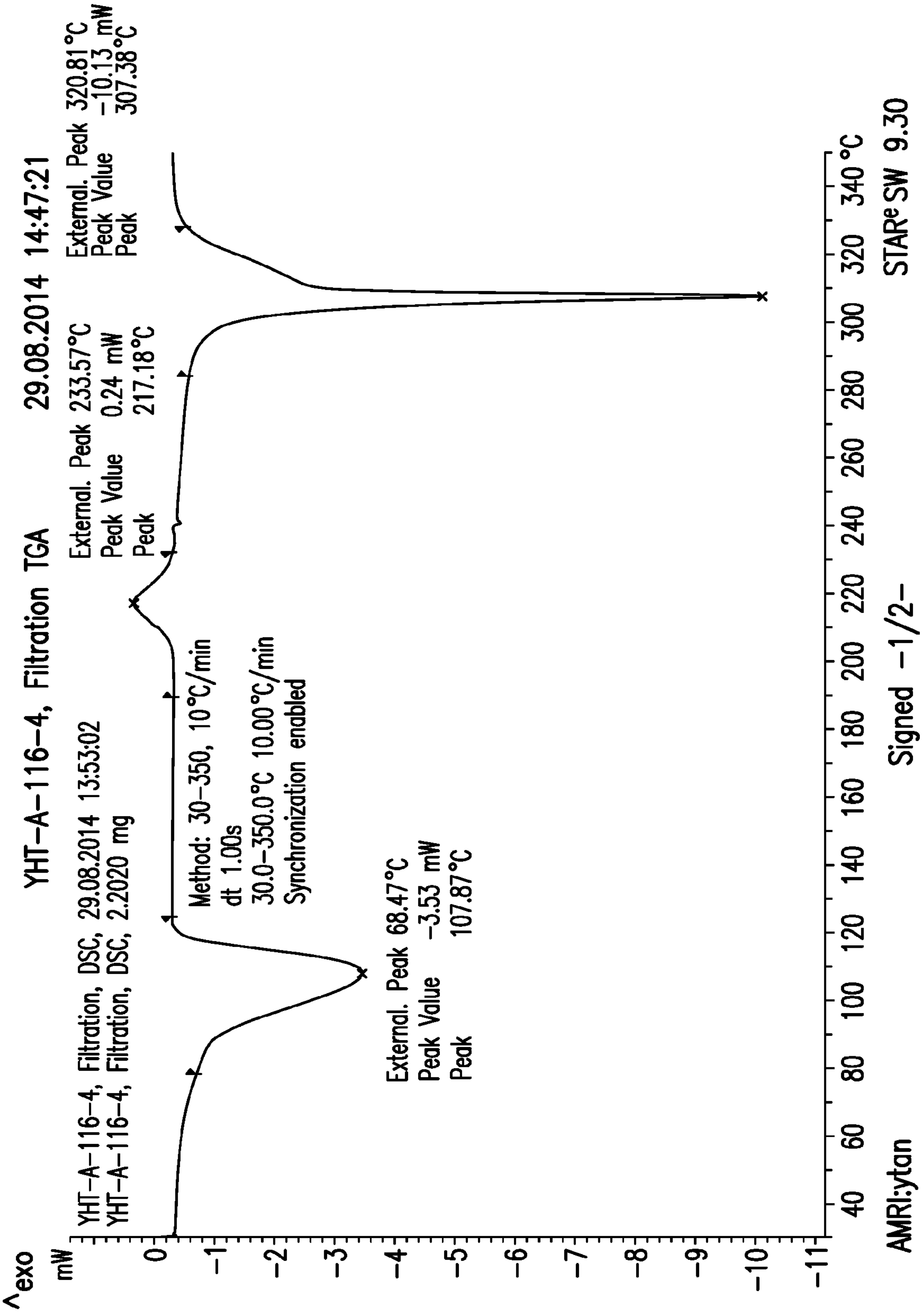
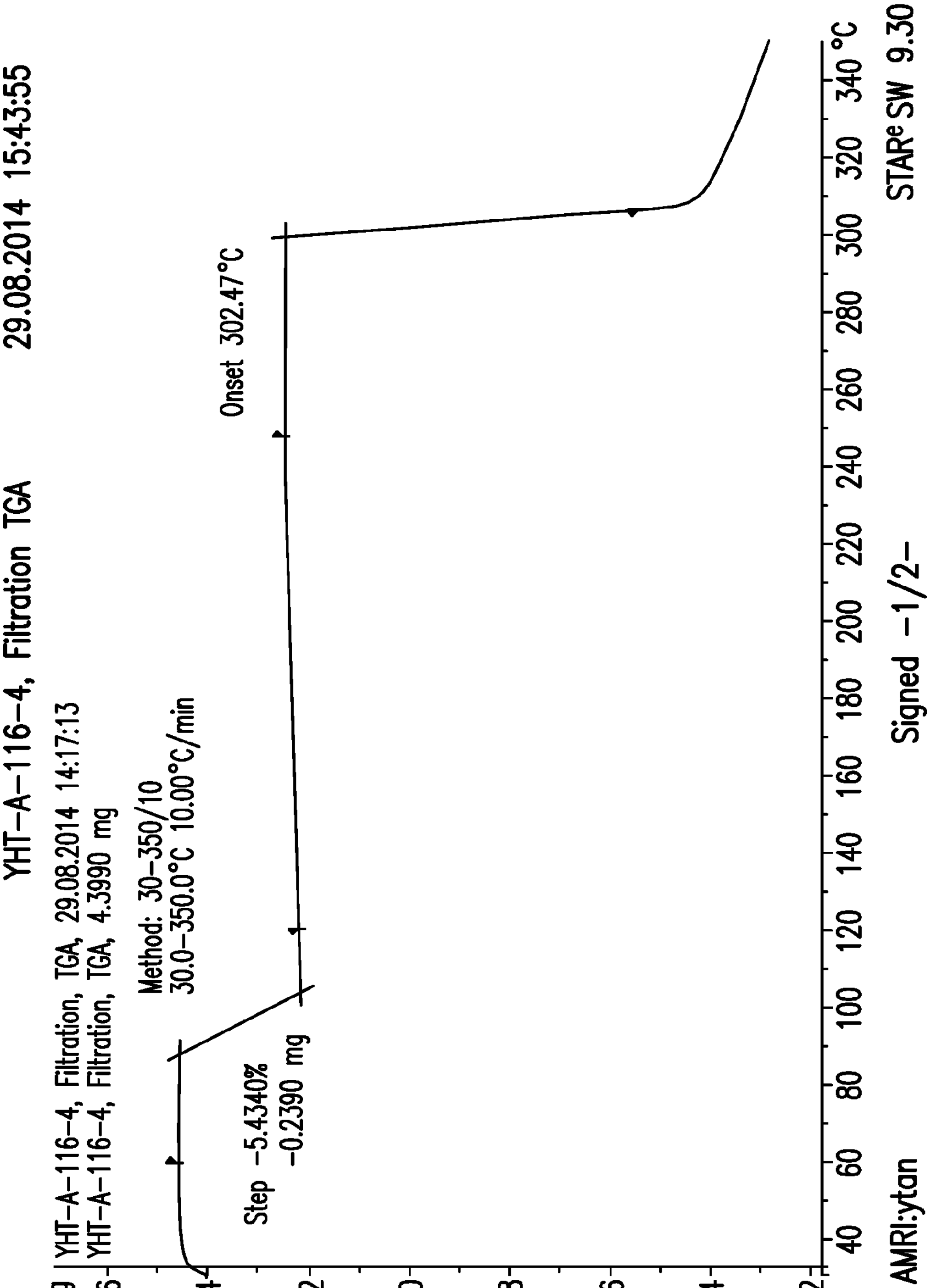
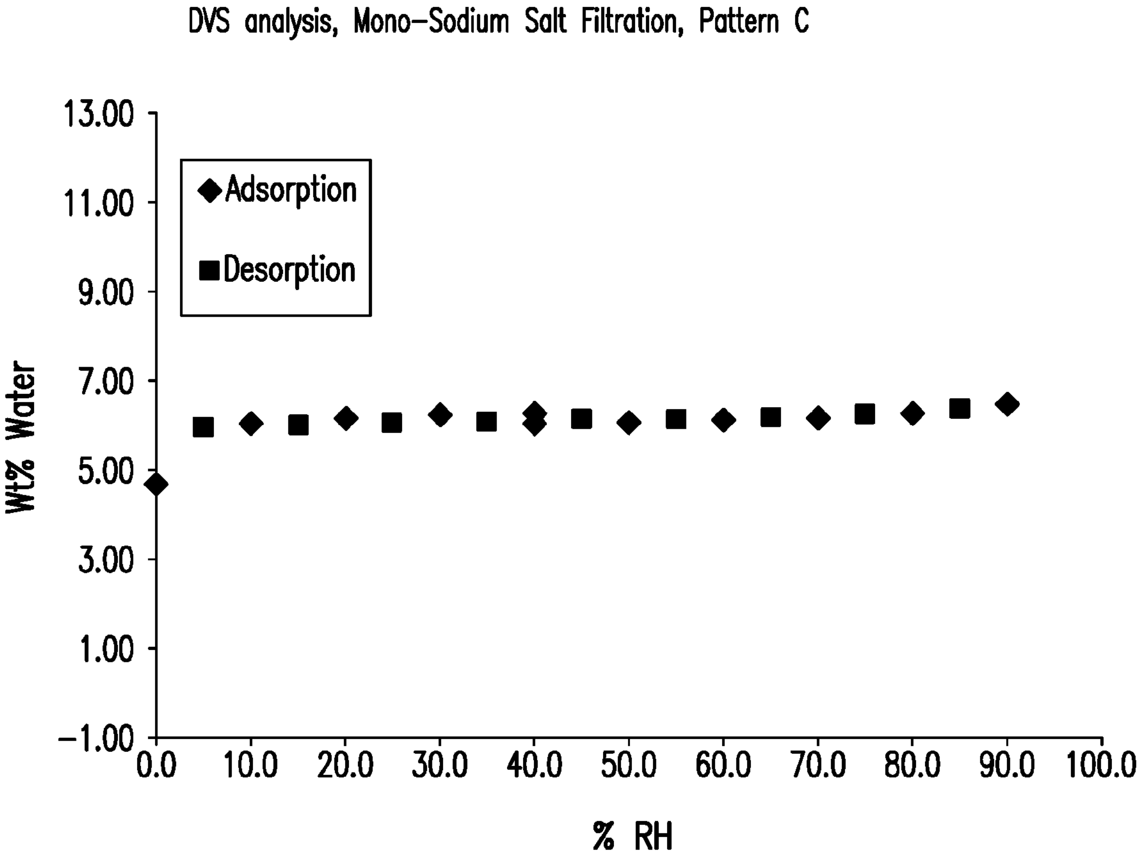

YHT–A–116–4, Filtration TGA 29.08.2014 14:47:21
YHT–A–116–4, Filtration, DSC, 29.08.2014 13:53:02
YHT–A–116–4, Filtration, DSC, 2.2020 mg
Method: 30–350, 10°C/min
dt 1.00s
30.0–350.0°C 10.00°C/min
Synchronization enabled
External. Peak 68.47°C
Peak Value –3.53 mW
Peak 107.87°C
External. Peak 233.57°C
Peak Value 0.24 mW
Peak 217.18°C
External. Peak 320.81°C
Peak Value –10.13 mW
Peak 307.38°C
^exo
mW
0
–1
–2
–3
–4
–5
–6
–7
–8
–9
–10
–11
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
AMRI:ytan
Signed –1/2–
STARe SW 9.30

FIG. 63



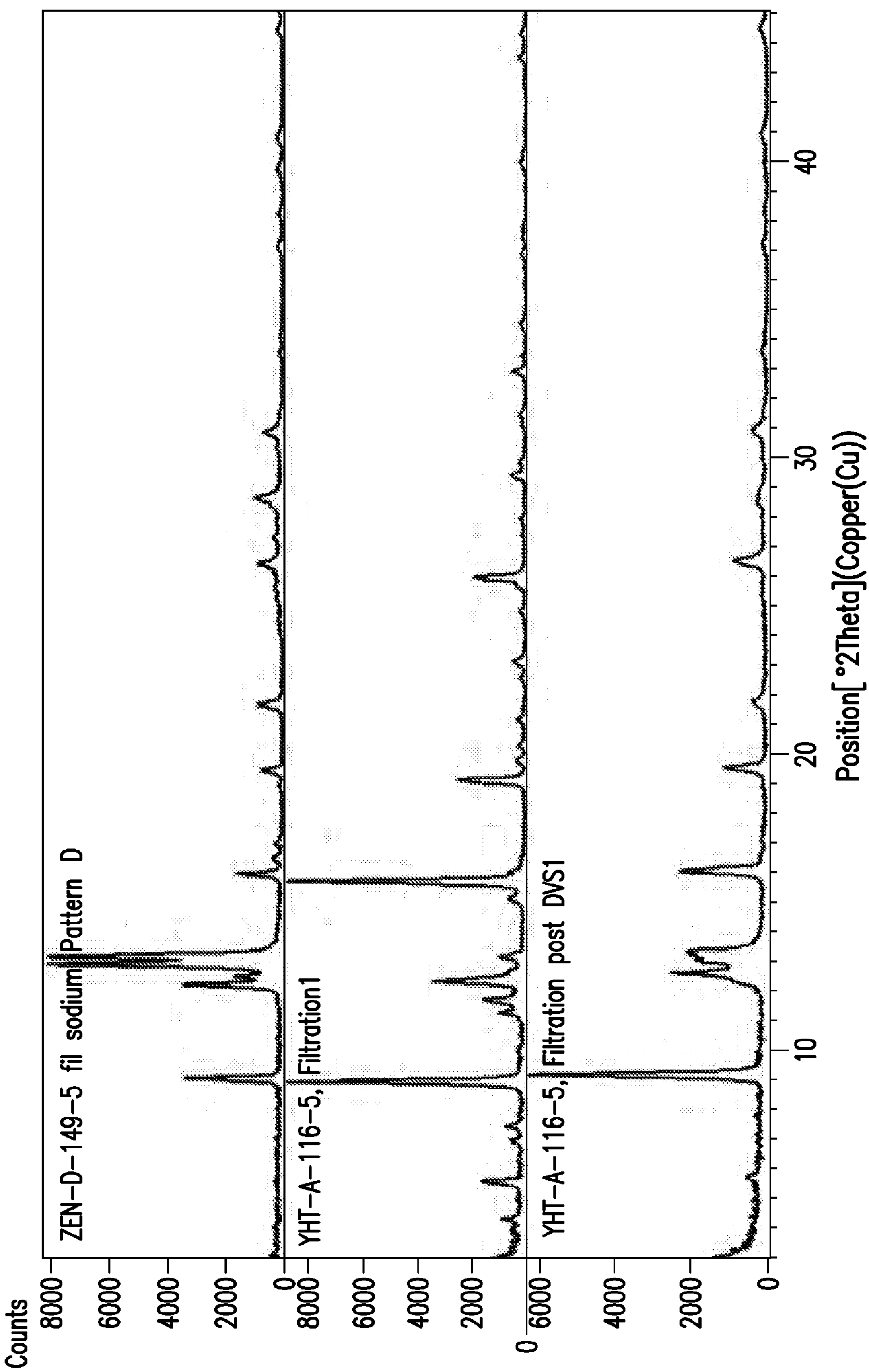
YHT–A–116–4, Filtration TGA
29.08.2014 15:43:55
YHT–A–116–4, Filtration, TGA, 29.08.2014 14:17:13
YHT–A–116–4, Filtration, TGA, 4.3990 mg
Method: 30–350/10
30.0–350.0°C 10.00°C/min
Step –5.4340%
–0.2390 mg
Onset 302.47°C
mg
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C
AMRI:ytan
Signed –1/2–
STARe SW 9.30

FIG. 64



DVS analysis, Mono-Sodium Salt Filtration, Pattern C
Adsorption
Desorption
Wt% Water
13.00
11.00
9.00
7.00
5.00
3.00
1.00
−1.00
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
% RH

FIG. 65



Counts
ZEN-D-149-5 fil sodium Pattern D
YHT-A-116-5, Filtration1
YHT-A-116-5, Filtration post DVS1
8000
6000
4000
2000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 66

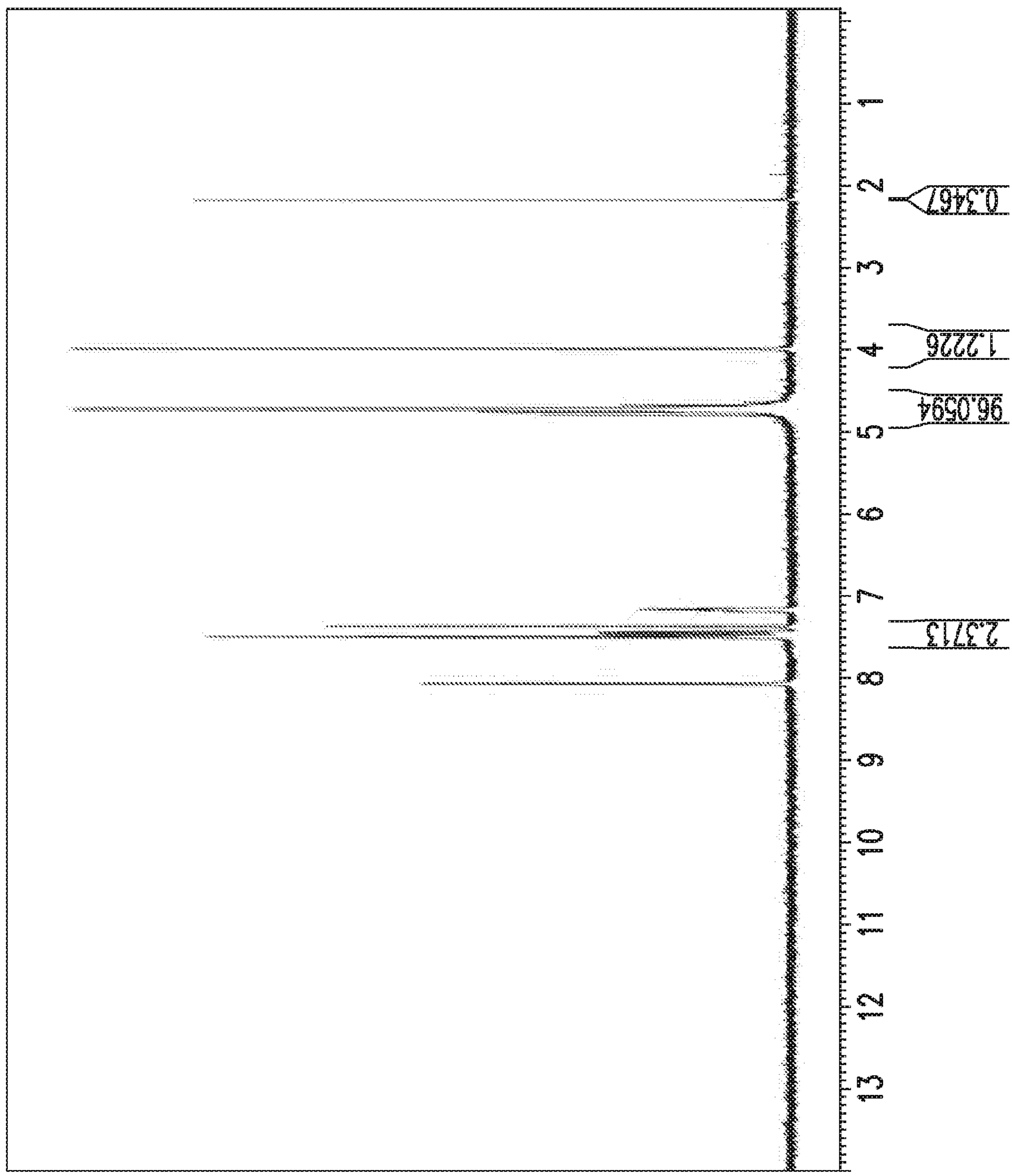


FIG. 67

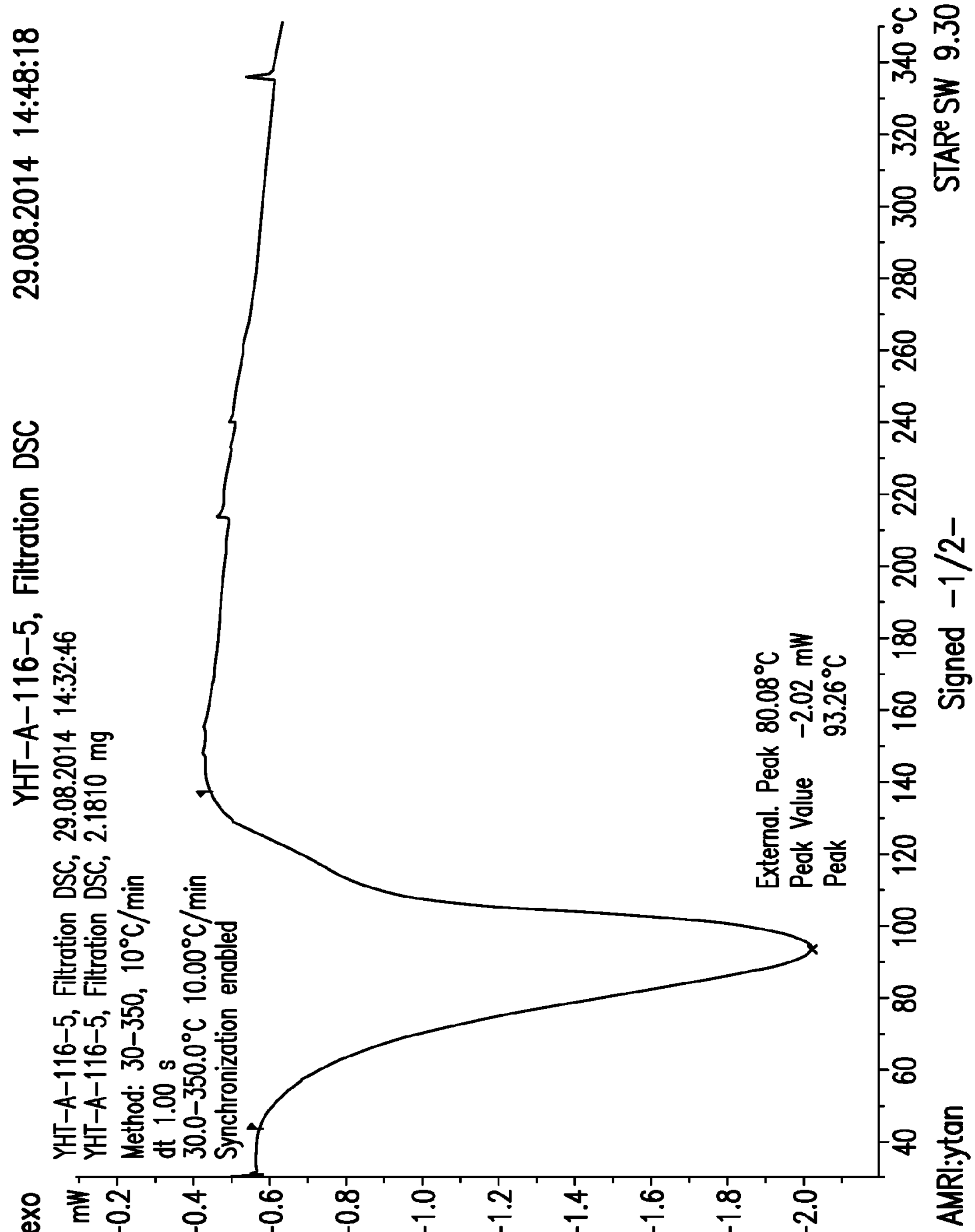
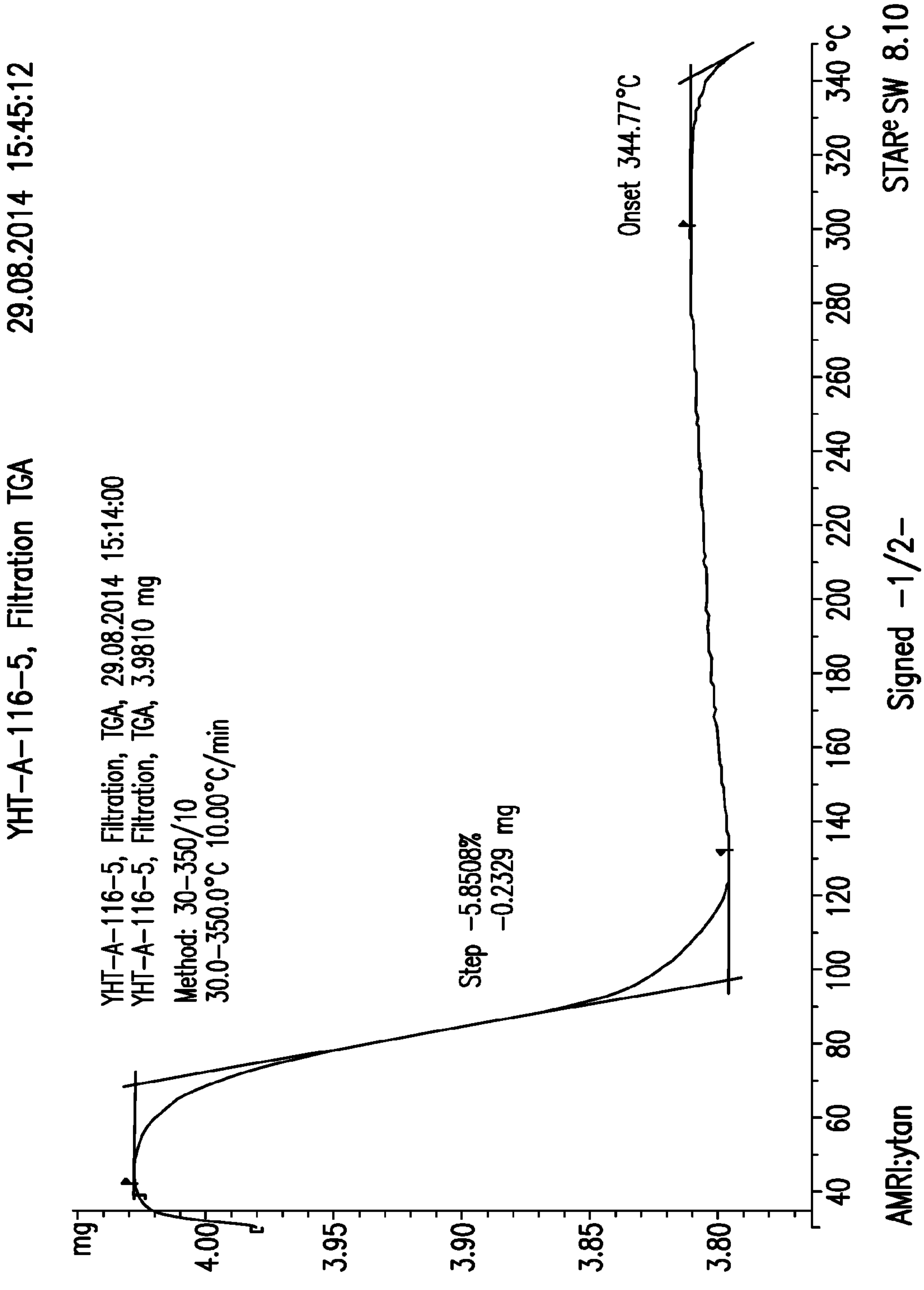

YHT-A-116-5, Filtration DSC
29.08.2014 14:48:18
YHT-A-116-5, Filtration DSC, 29.08.2014 14:32:46
YHT-A-116-5, Filtration DSC, 2.1810 mg
Method: 30-350, 10°C/min
dt 1.00 s
30.0-350.0°C 10.00°C/min
Synchronization enabled
^exo
mW
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-2.0
External. Peak 80.08°C
Peak Value -2.02 mW
Peak 93.26°C
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C
AMRI:ytan
Signed -1/2-
STAR^e SW 9.30

FIG. 68



YHT-A-116-5, Filtration TGA
29.08.2014 15:45:12
YHT-A-116-5, Filtration, TGA, 29.08.2014 15:14:00
YHT-A-116-5, Filtration, TGA, 3.9810 mg
Method: 30-350/10
30.0-350.0°C 10.00°C/min
Step -5.8508%
-0.2329 mg
Onset 344.77°C
mg
4.00
3.95
3.90
3.85
3.80
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C
AMRI:ytan
Signed -1/2-
STARe SW 8.10

FIG. 69

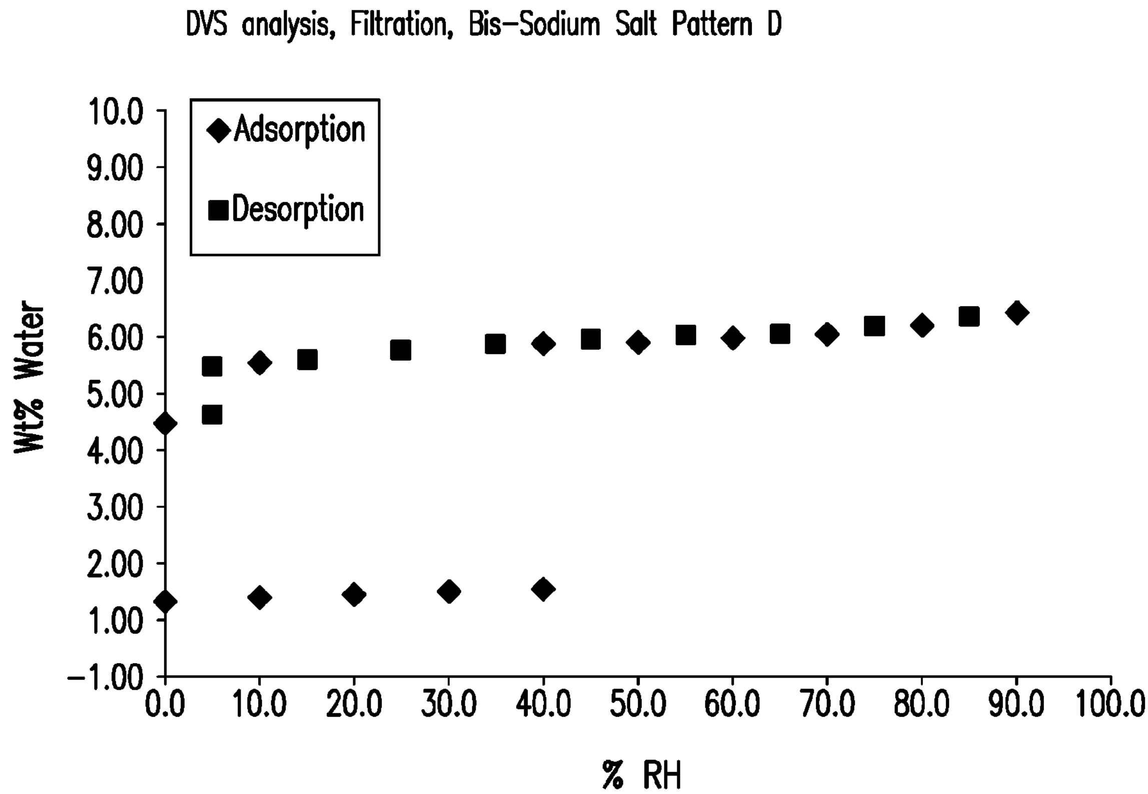

DVS analysis, Filtration, Bis-Sodium Salt Pattern D
Adsorption
Desorption
Wt% Water
10.0
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
-1.00
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
% RH

FIG. 70

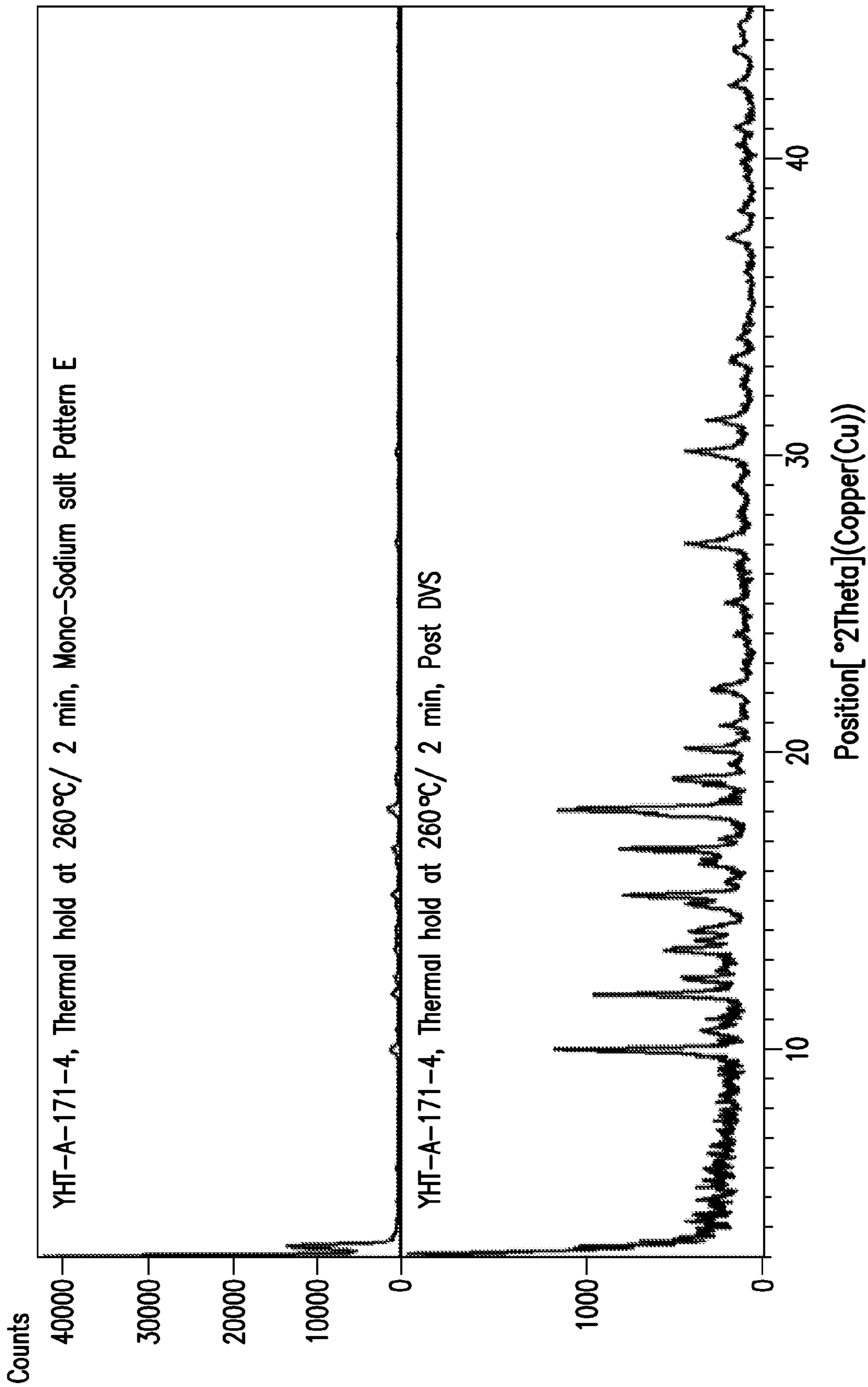
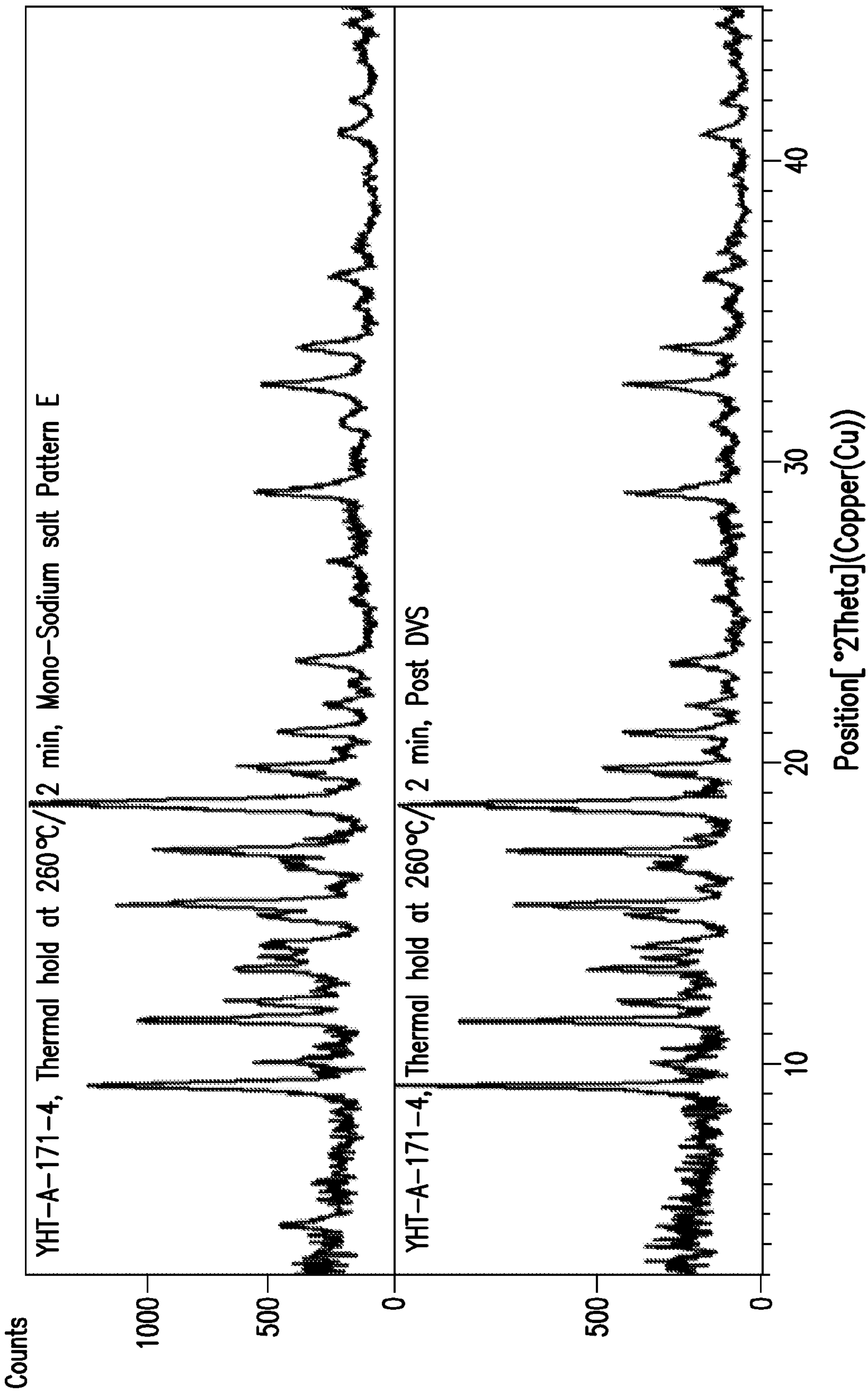

YHT-A-171-4, Thermal hold at 260°C/ 2 min, Mono-Sodium salt Pattern E
YHT-A-171-4, Thermal hold at 260°C/ 2 min, Post DVS
Counts
40000
30000
20000
10000
0
1000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 71



YHT-A-171-4, Thermal hold at 260°C/ 2 min, Mono-Sodium salt Pattern E
YHT-A-171-4, Thermal hold at 260°C/ 2 min, Post DVS
Counts
1000
500
0
500
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 72

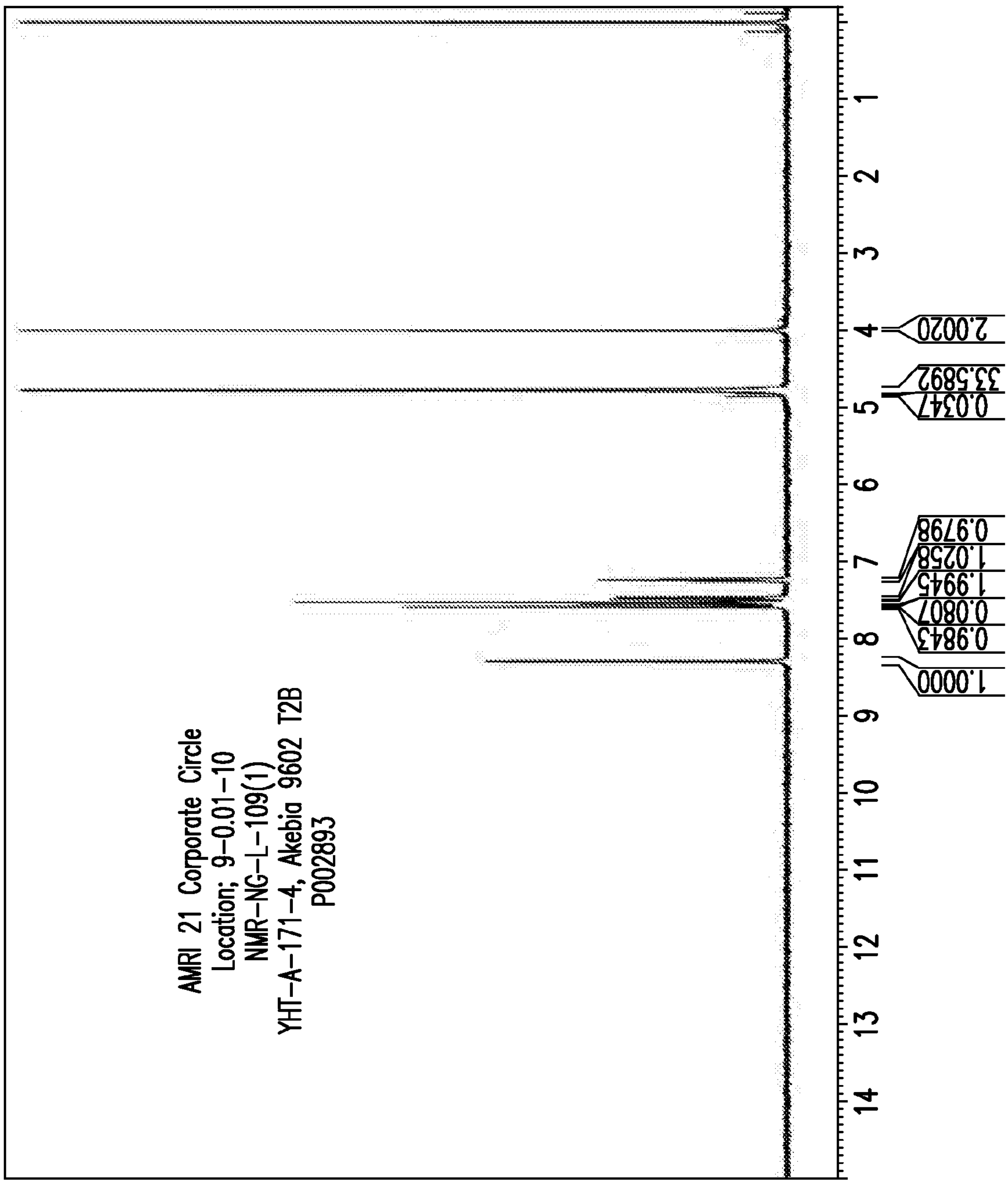

AMRI 21 Corporate Circle
Location; 9-0.01-10
NMR-NG-L-109(1)
YHT-A-171-4, Akebia 9602 T2B
P002893
2.0020
33.5892
0.0347
0.9798
1.0258
1.9945
0.0807
0.9843
1.0000
1
2
3
4
5
6
7
8
9
10
11
12
13
14

FIG. 73

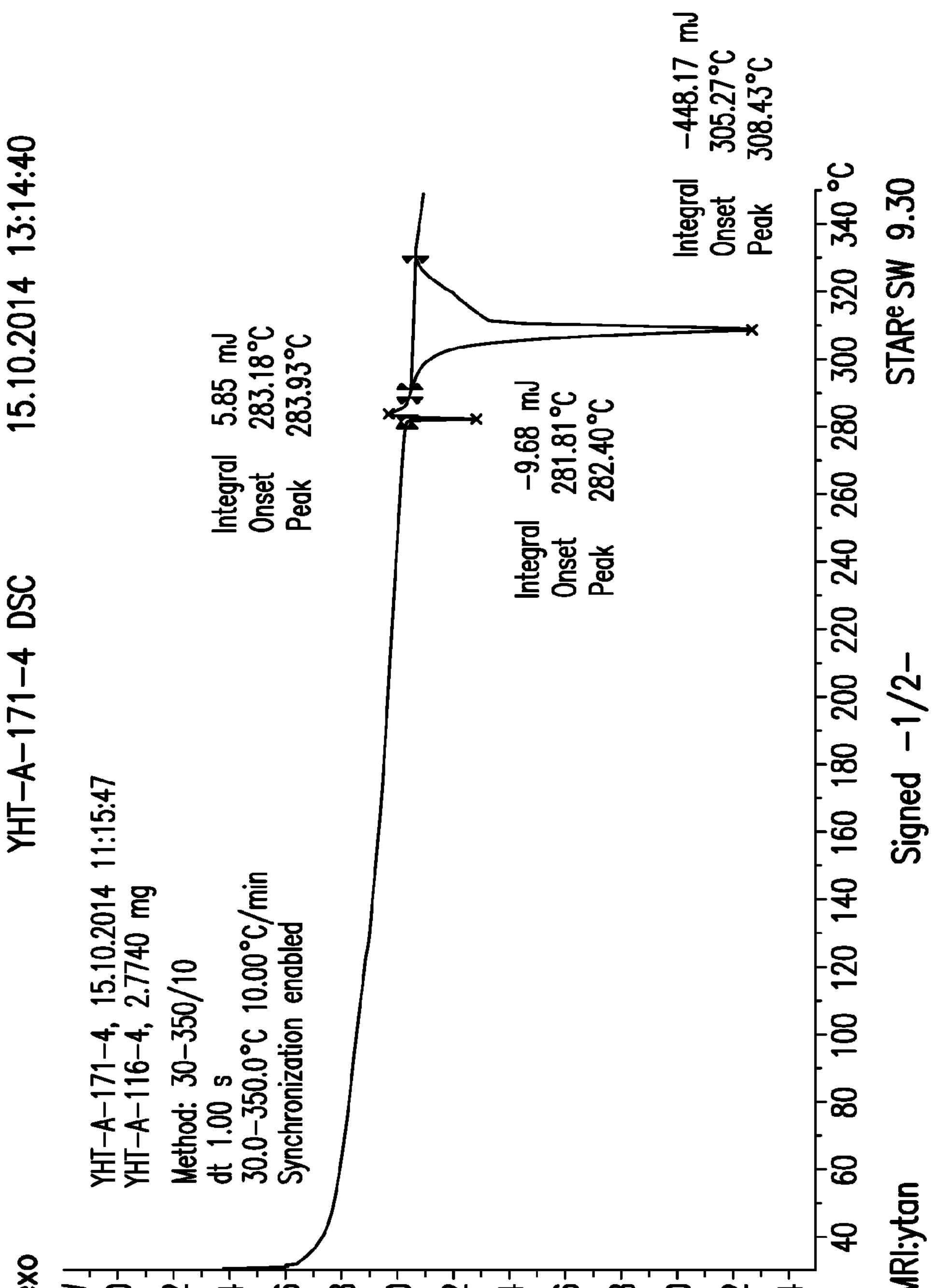

YHT-A-171-4 DSC
15.10.2014 13:14:40
YHT-A-171-4, 15.10.2014 11:15:47
YHT-A-116-4, 2.7740 mg
Method: 30-350/10
dt 1.00 s
30.0-350.0°C 10.00°C/min
Synchronization enabled
Integral 5.85 mJ
Onset 283.18°C
Peak 283.93°C
Integral -9.68 mJ
Onset 281.81°C
Peak 282.40°C
Integral -448.17 mJ
Onset 305.27°C
Peak 308.43°C
^exo
mW
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
-22
-24
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 °C
AMRI:ytan
Signed -1/2-
STARe SW 9.30

FIG. 74

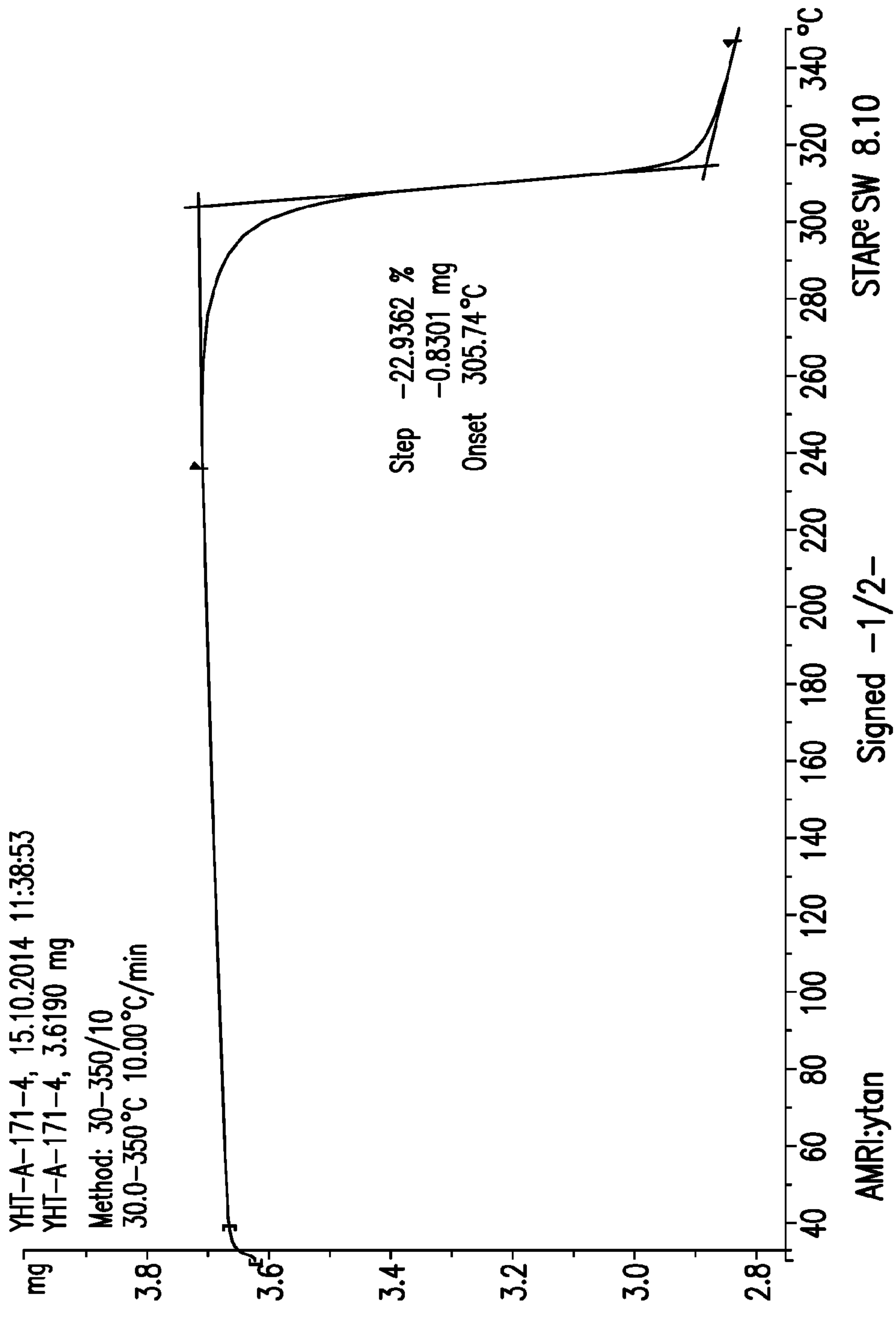

YHT-A-171-4, TGA
15.10.2014 13:18:03
YHT-A-171-4, 15.10.2014 11:38:53
YHT-A-171-4, 3.6190 mg
Method: 30-350/10
30.0-350°C 10.00°C/min
Step -22.9362 %
-0.8301 mg
Onset 305.74°C
mg
3.8
3.6
3.4
3.2
3.0
2.8
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C
AMRI:ytan
Signed -1/2-
STAR^e SW 8.10

FIG. 75

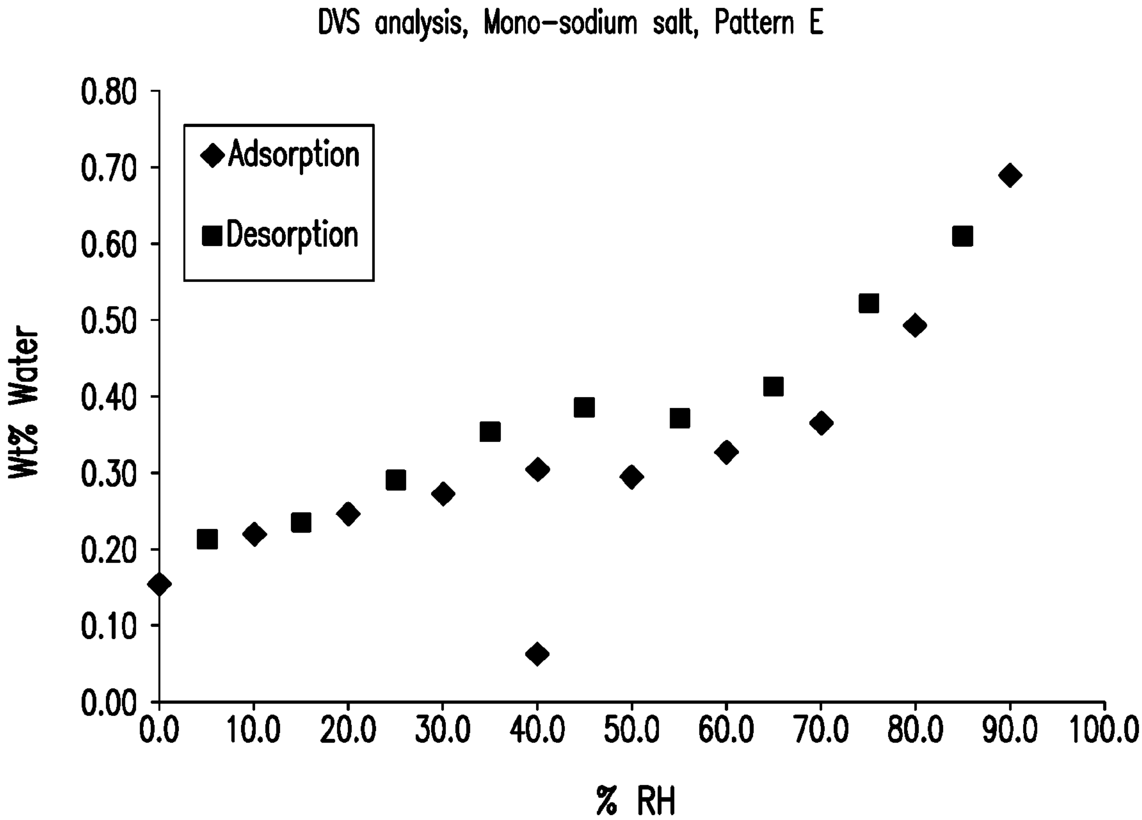

DVS analysis, Mono-sodium salt, Pattern E
Adsorption
Desorption
Wt% Water
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
% RH

FIG. 76

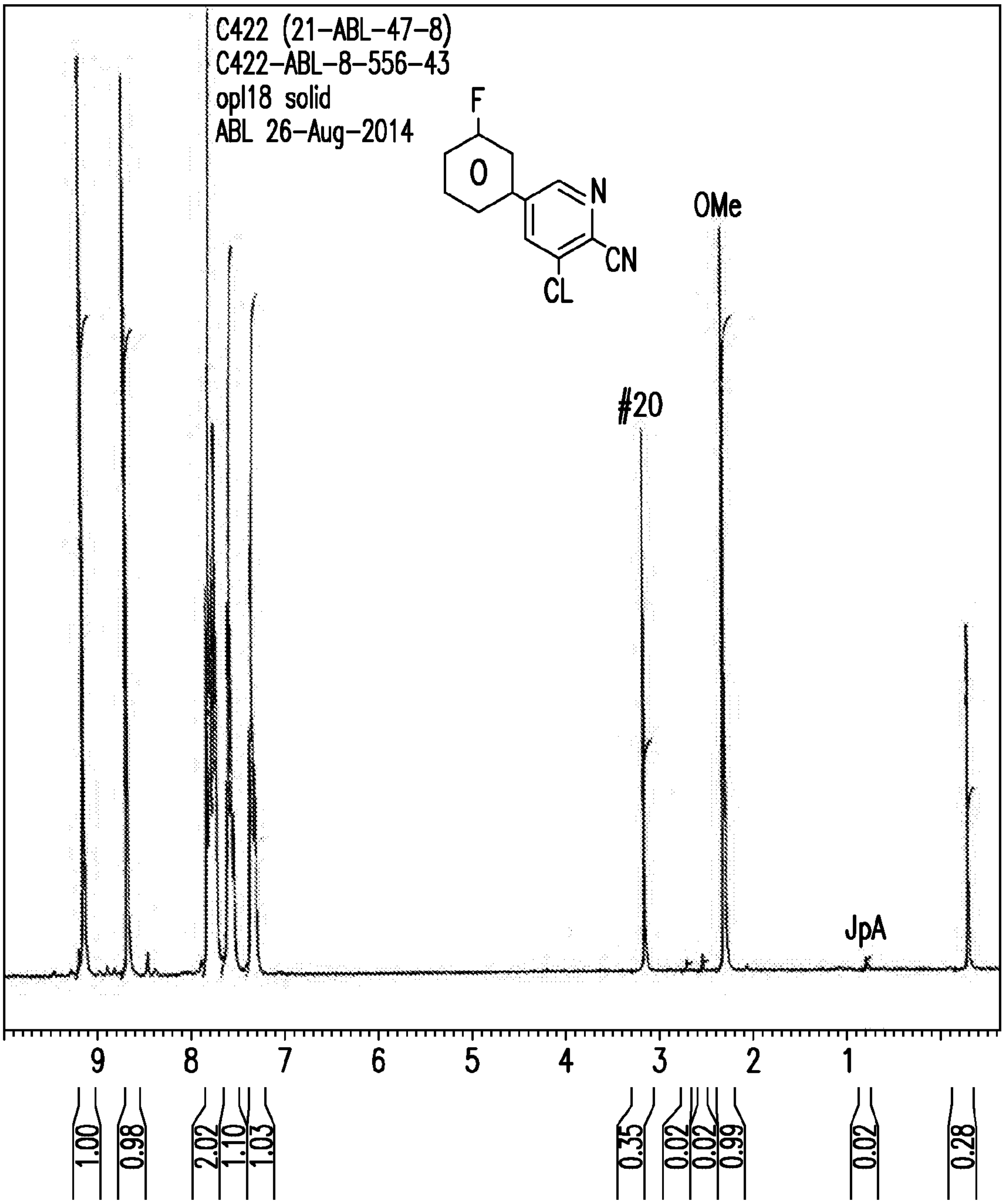

C422 (21-ABL-47-8)
C422-ABL-8-556-43
opl18 solid
ABL 26-Aug-2014
F
O
N
CN
CL
OMe
#20
JpA
9
8
7
6
5
4
3
2
1
1.00
0.98
2.02
1.10
1.03
0.35
0.02
0.02
0.02
0.99
0.02
0.28

FIG. 77

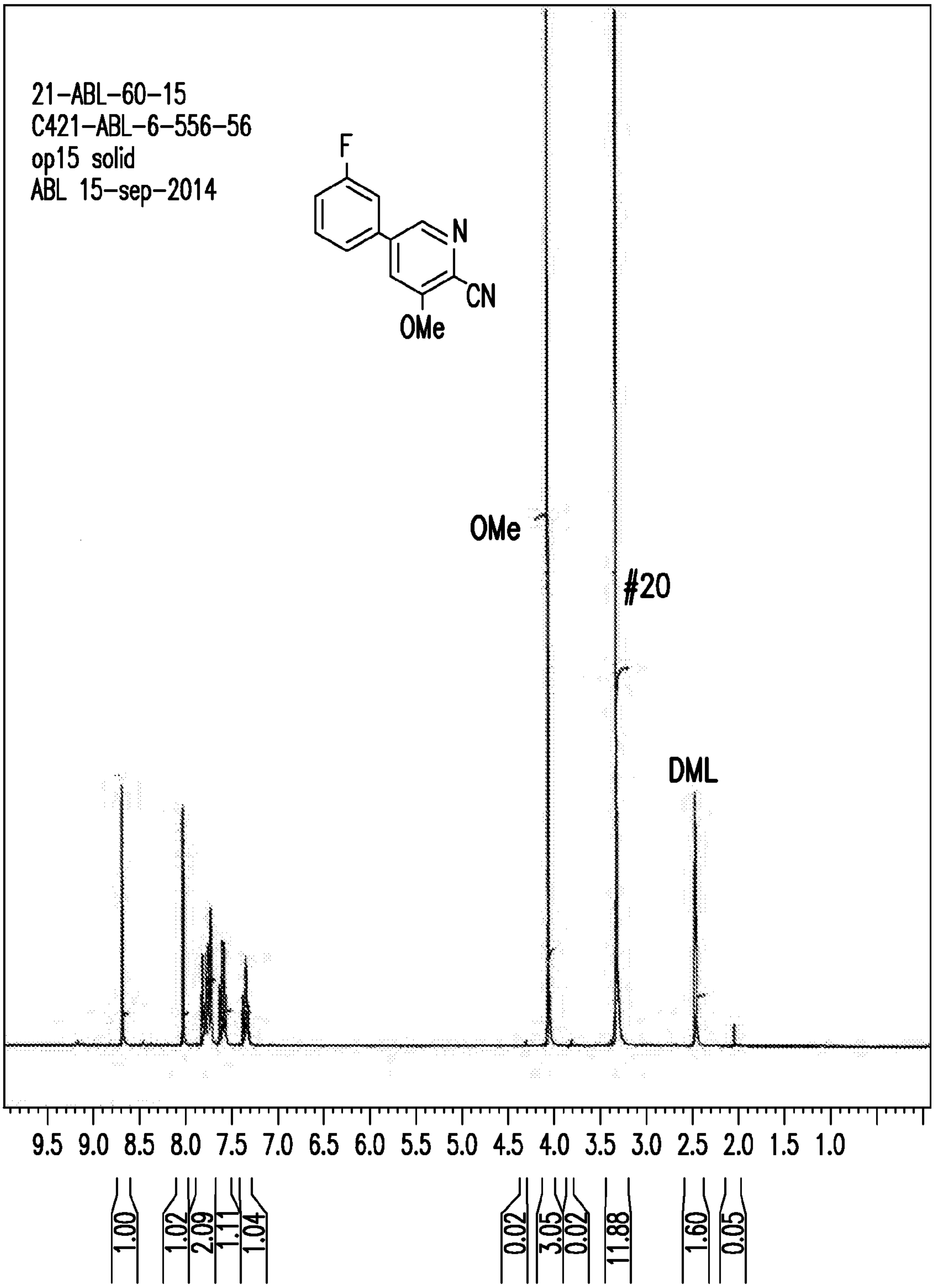
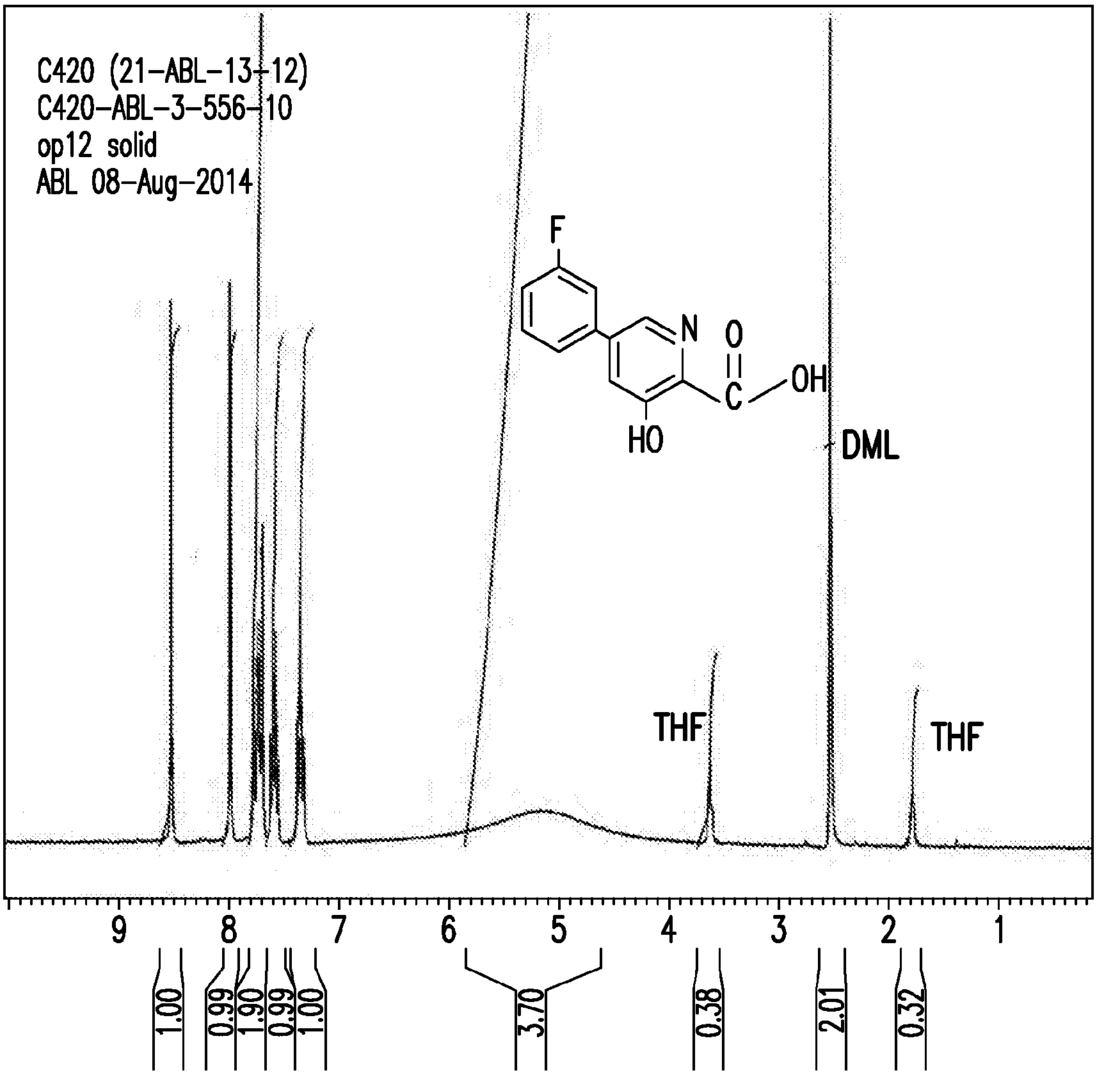

21-ABL-60-15
C421-ABL-6-556-56
op15 solid
ABL 15-sep-2014
F
N
CN
OMe
OMe
#20
DML
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
1.00
1.02
2.09
1.11
1.04
0.02
3.05
0.02
11.88
1.60
0.05

FIG. 78



C420 (21-ABL-13-12)
C420-ABL-3-556-10
op12 solid
ABL 08-Aug-2014
F
N
O
OH
HO
DML
THF
THF
9
8
7
6
5
4
3
2
1
1.00
0.99
1.90
0.99
1.00
3.70
0.38
2.01
0.32

FIG. 79

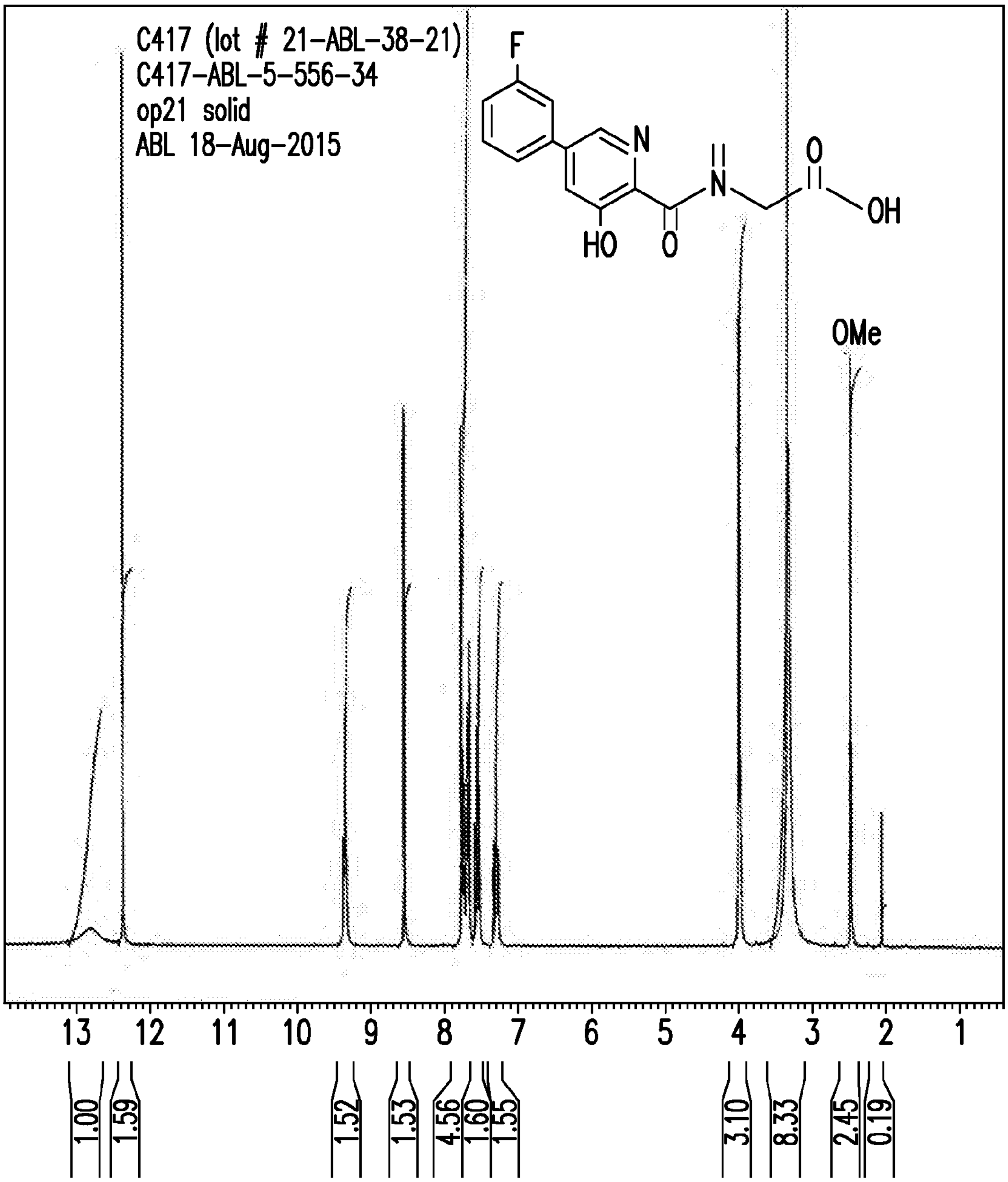

C417 (lot # 21-ABL-38-21)
C417-ABL-5-556-34
op21 solid
ABL 18-Aug-2015
F
N
N
O
OH
HO
O
OMe
13 12 11 10 9 8 7 6 5 4 3 2 1
1.00
1.59
1.52
1.53
4.56
1.60
1.55
3.10
8.33
2.45
0.19

FIG. 80

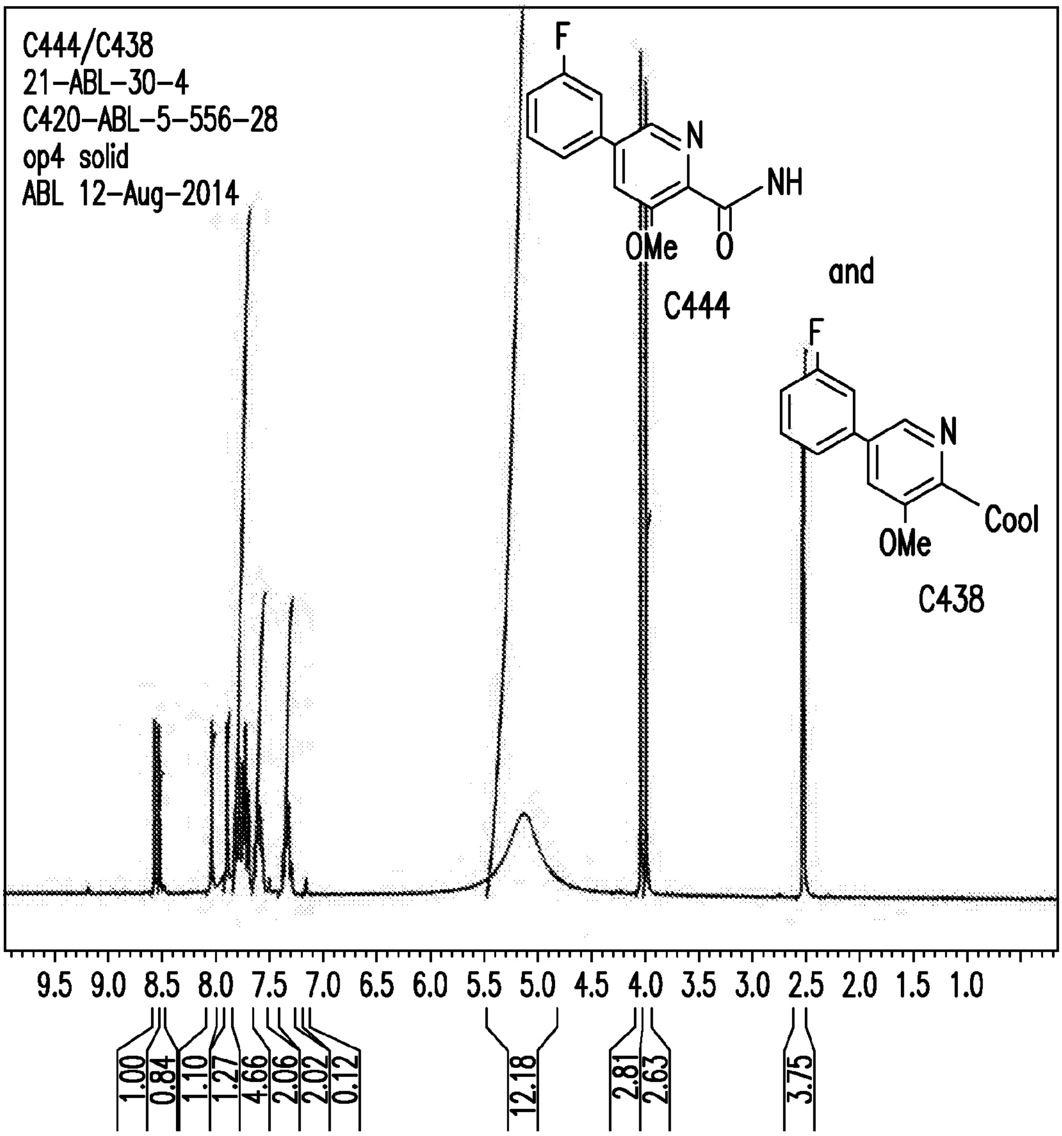

C444/C438
21-ABL-30-4
C420-ABL-5-556-28
op4 solid
ABL 12-Aug-2014
F
N
NH
OMe
O
C444
and
F
N
Cool
OMe
C438
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
1.00
0.84
1.10
1.27
4.66
2.06
2.02
0.12
12.18
2.81
2.63
3.75

FIG. 81

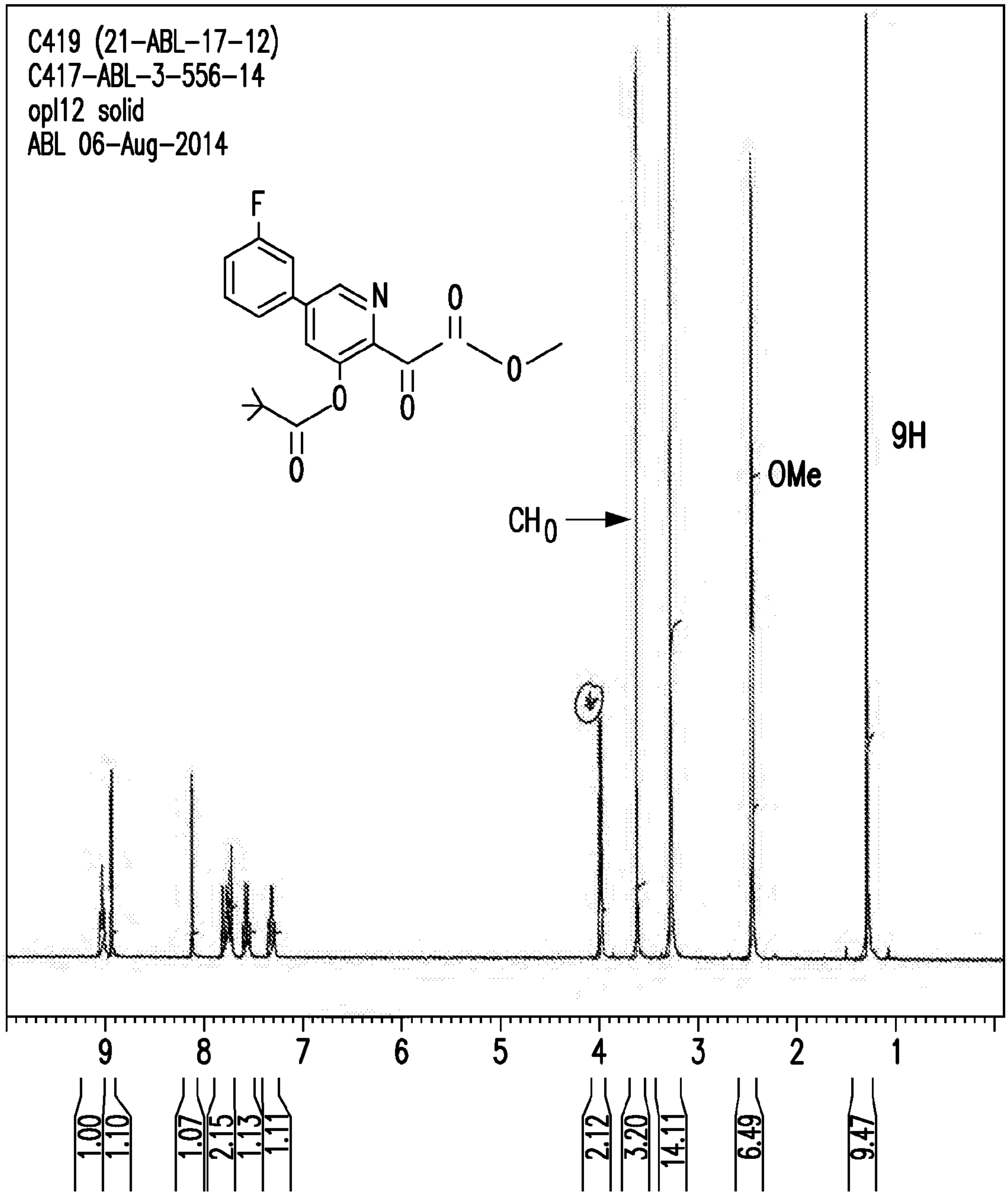

C419 (21-ABL-17-12)
C417-ABL-3-556-14
opl12 solid
ABL 06-Aug-2014
F
N
O
O
O
O
O
CH0
OMe
9H
9
8
7
6
5
4
3
2
1
1.00
1.10
1.07
2.15
1.13
1.11
2.12
3.20
14.11
6.49
9.47

FIG. 82

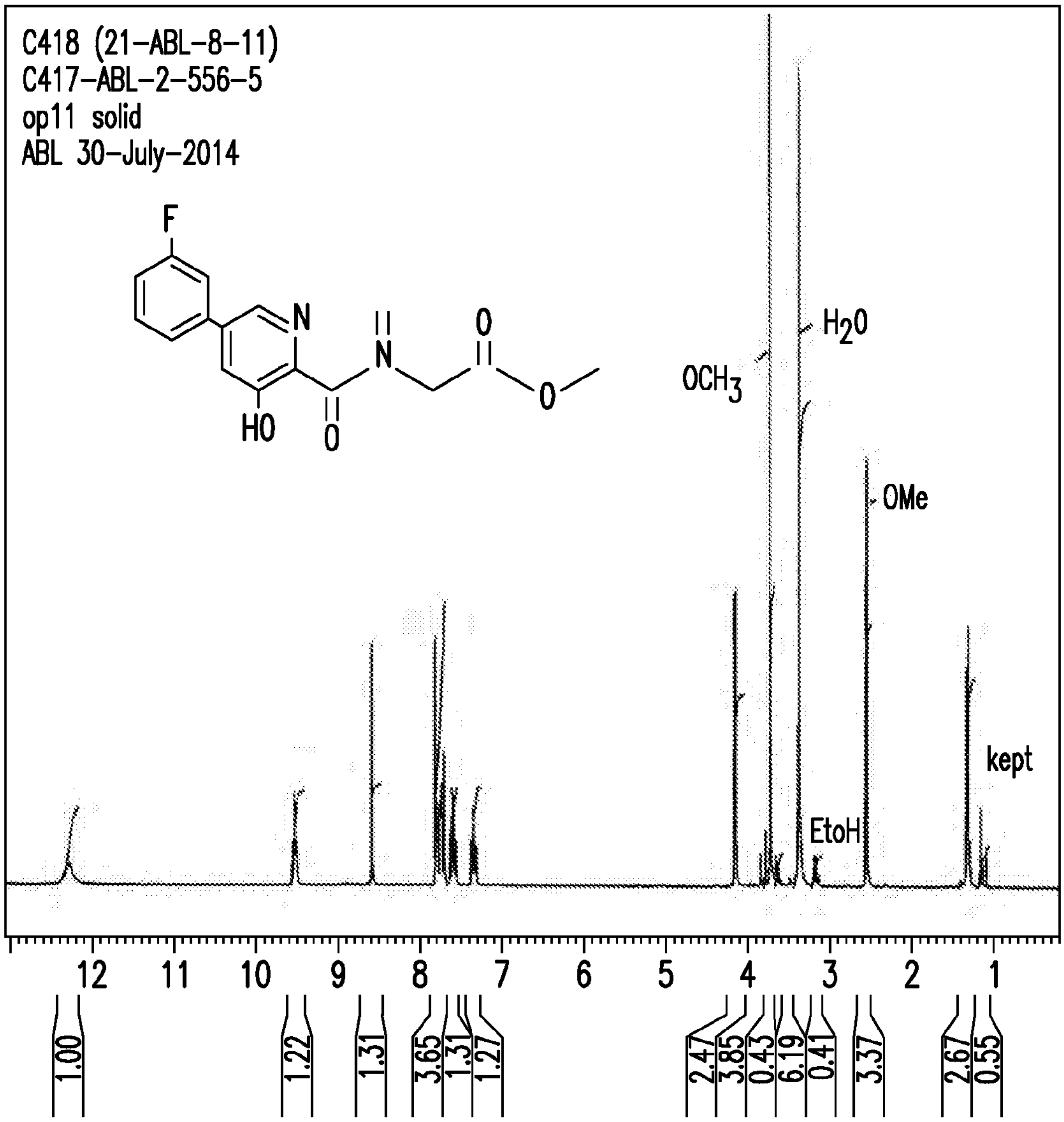
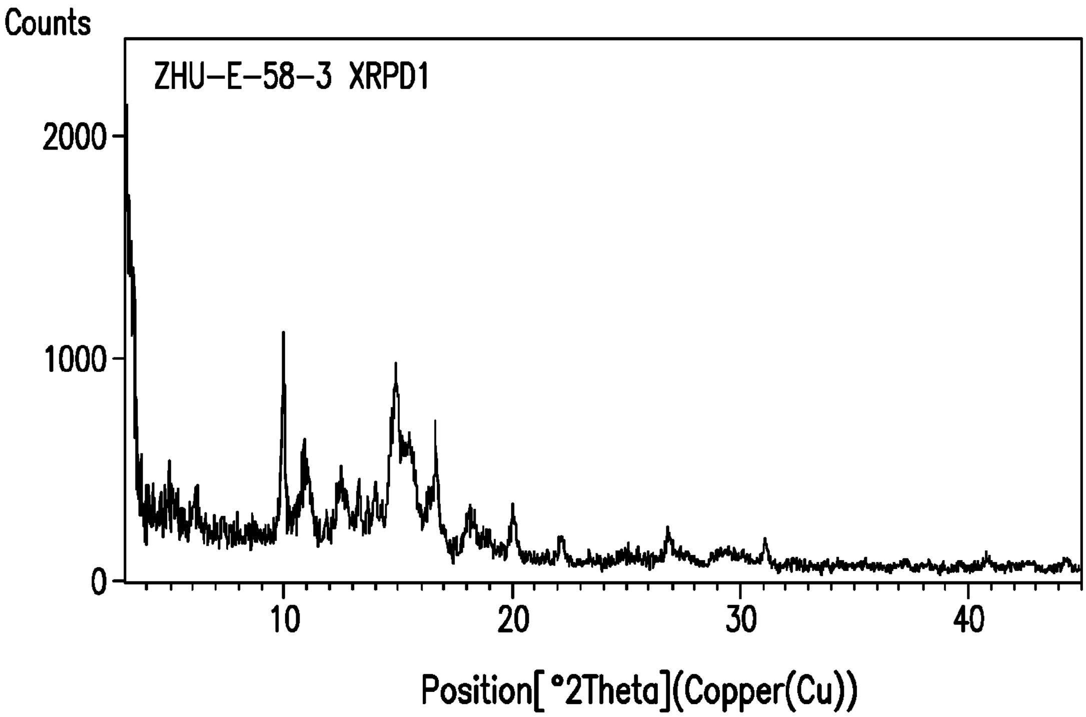

C418 (21-ABL-8-11)
C417-ABL-2-556-5
op11 solid
ABL 30-July-2014
F
N
N
O
O
HO
O
OCH3
H2O
OMe
kept
EtoH
12 11 10 9 8 7 6 5 4 3 2 1
1.00
1.22
1.31
3.65
1.31
1.27
2.47
3.85
0.43
6.19
0.41
3.37
2.67
0.55

FIG. 83



Counts
ZHU-E-58-3 XRPD1
2000
1000
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 84

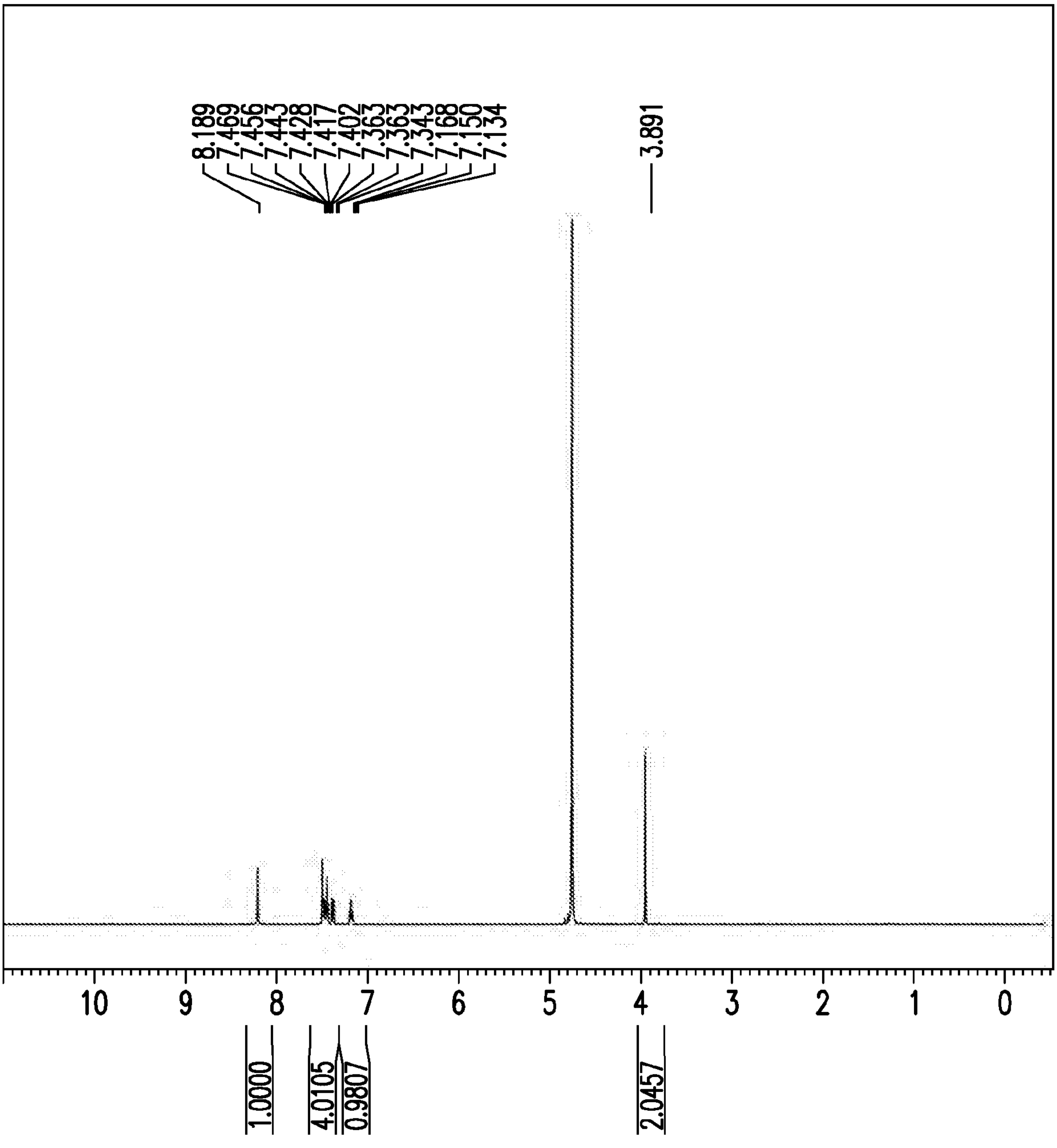

8.189
7.469
7.456
7.443
7.428
7.417
7.402
7.363
7.363
7.343
7.168
7.150
7.134
3.891
10
9
8
7
6
5
4
3
2
1
0
1.0000
4.0105
0.9807
2.0457

FIG. 85

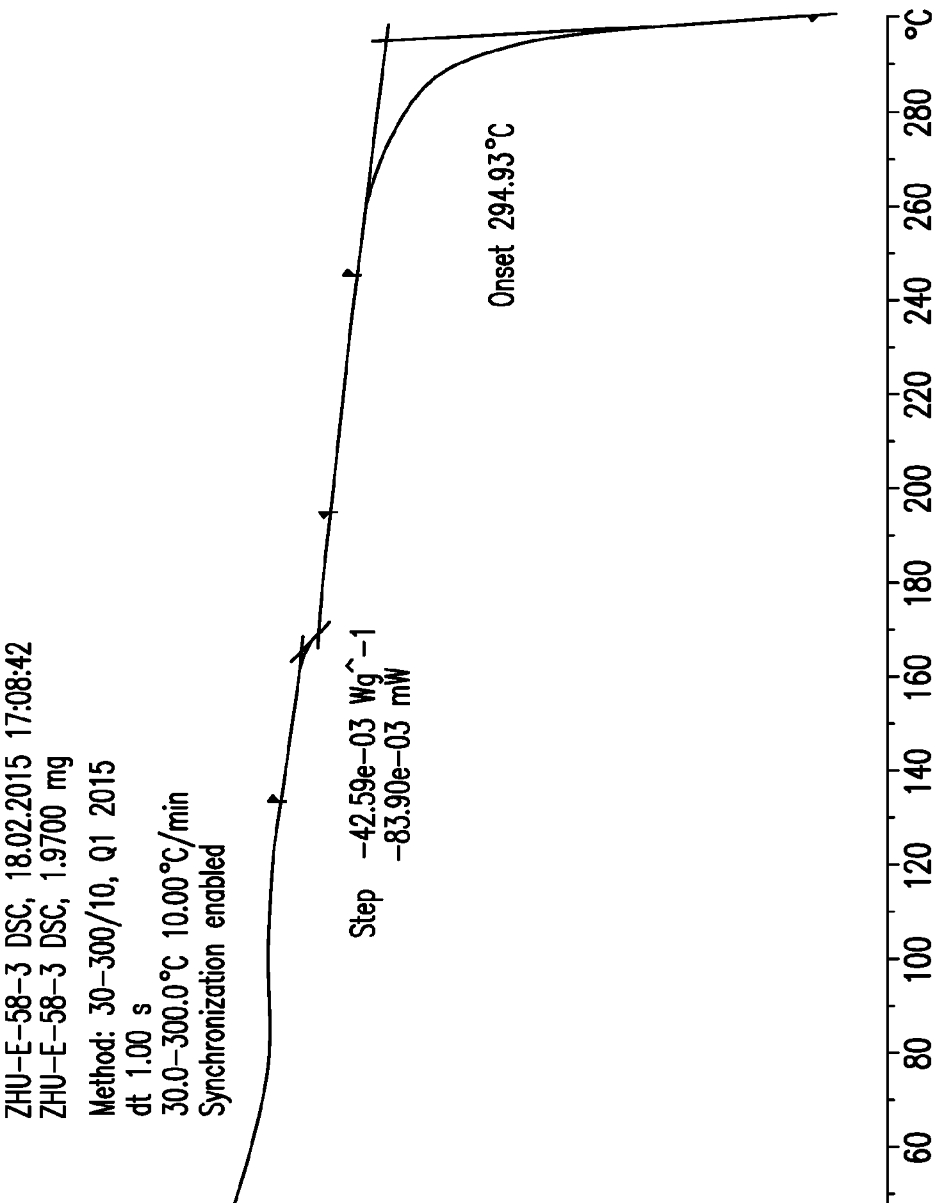

ZHU-E-58-3 DSC, 18.02.2015 17:08:42
ZHU-E-58-3 DSC, 1.9700 mg
Method: 30-300/10, Q1 2015
dt 1.00 s
30.0-300.0°C 10.00°C/min
Synchronization enabled
Step -42.59e-03 Wg^-1
-83.90e-03 mW
Onset 294.93°C
mW
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
40
60
80
100
120
140
160
180
200
220
240
260
280
°C

FIG. 86

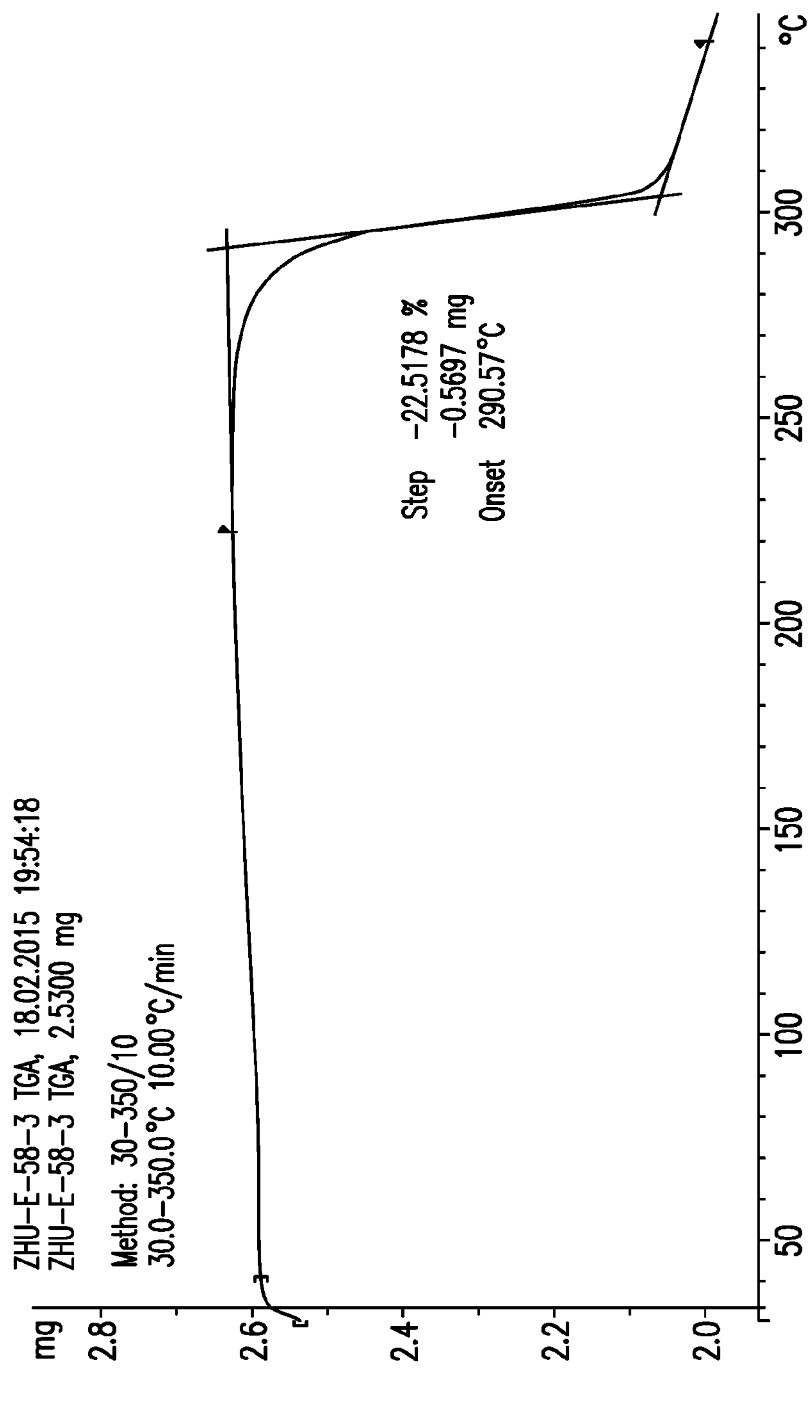

ZHU-E-58-3 TGA, 18.02.2015 19:54:18
ZHU-E-58-3 TGA, 2.5300 mg
Method: 30-350/10
30.0-350.0°C 10.00°C/min
Step -22.5178 %
-0.5697 mg
Onset 290.57°C
mg
2.8
2.6
2.4
2.2
2.0
50
100
150
200
250
300
°C

FIG. 87

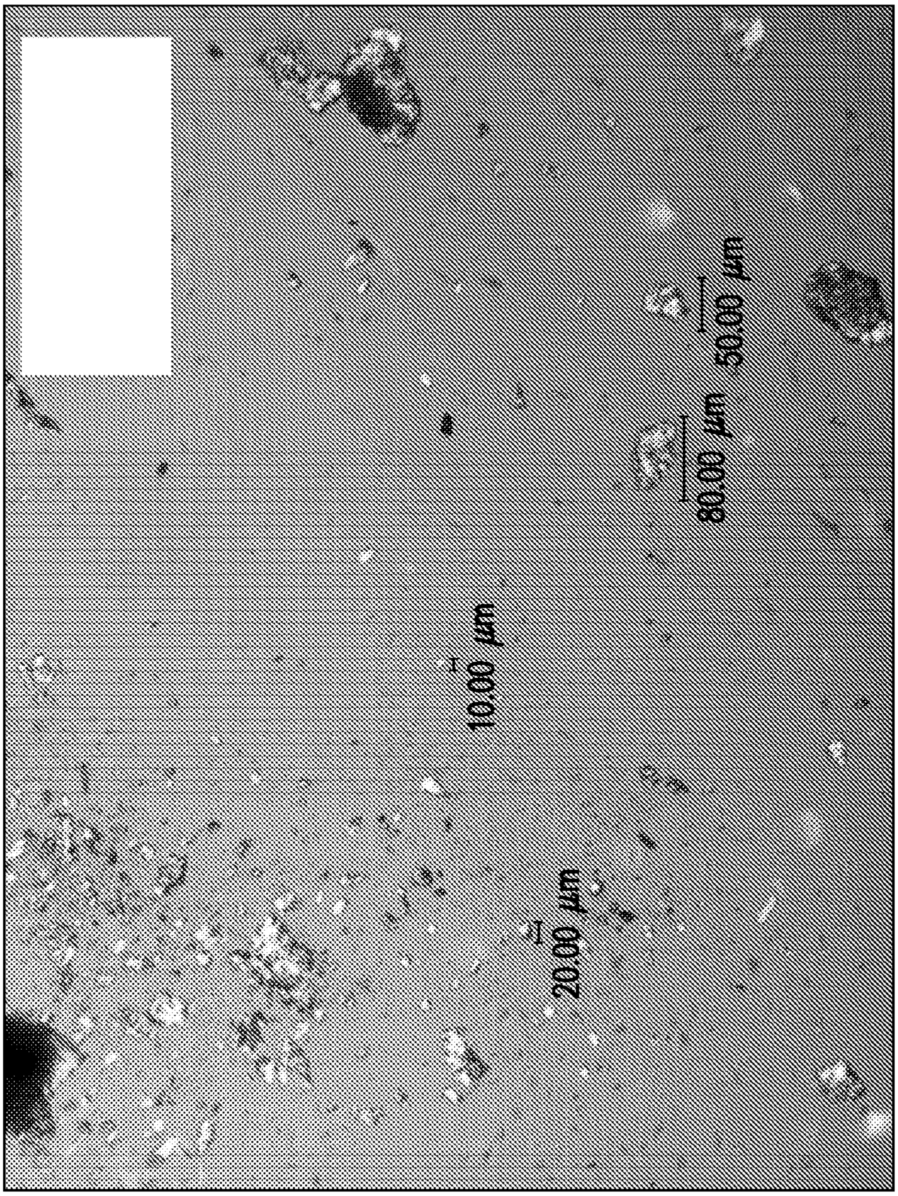


FIG. 88

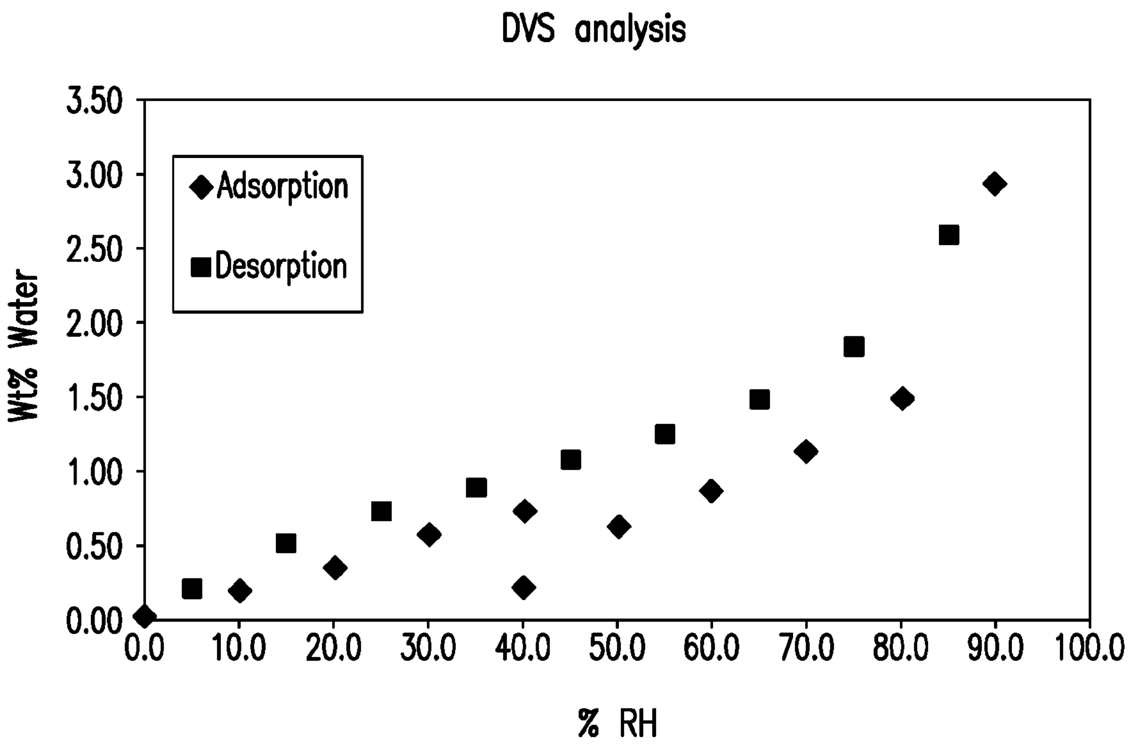

DVS analysis
Adsorption
Desorption
Wt% Water
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
% RH

FIG. 89

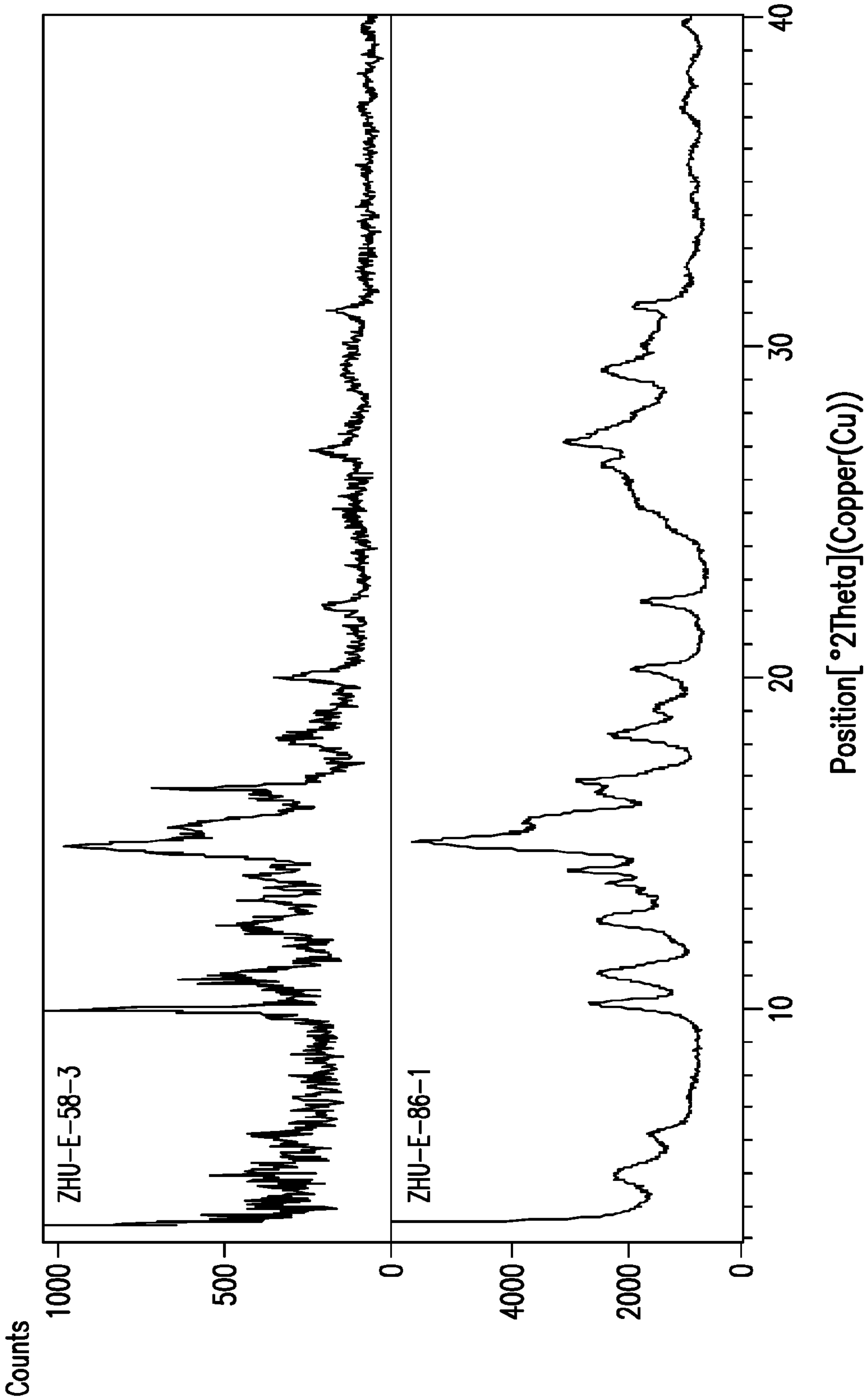

Counts
1000
500
0
4000
2000
0
ZHU-E-58-3
ZHU-E-86-1
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 90

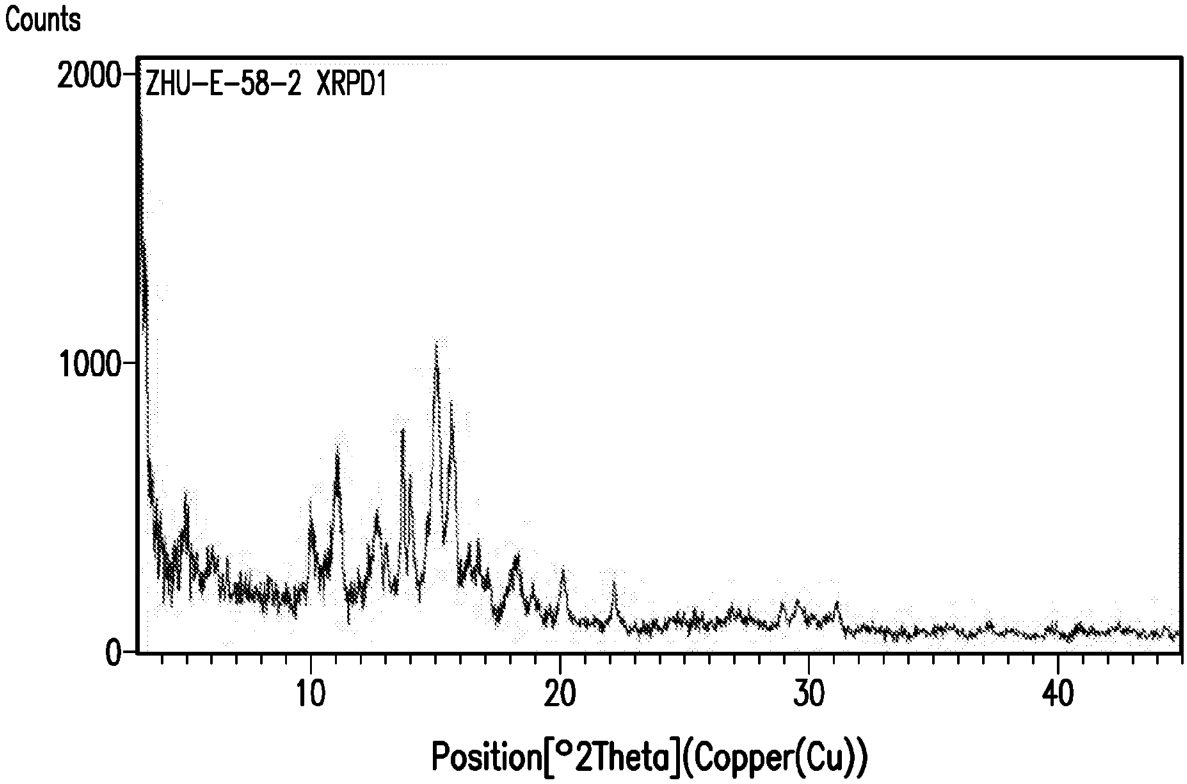

Counts
2000
1000
0
ZHU-E-58-2 XRPD1
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 91

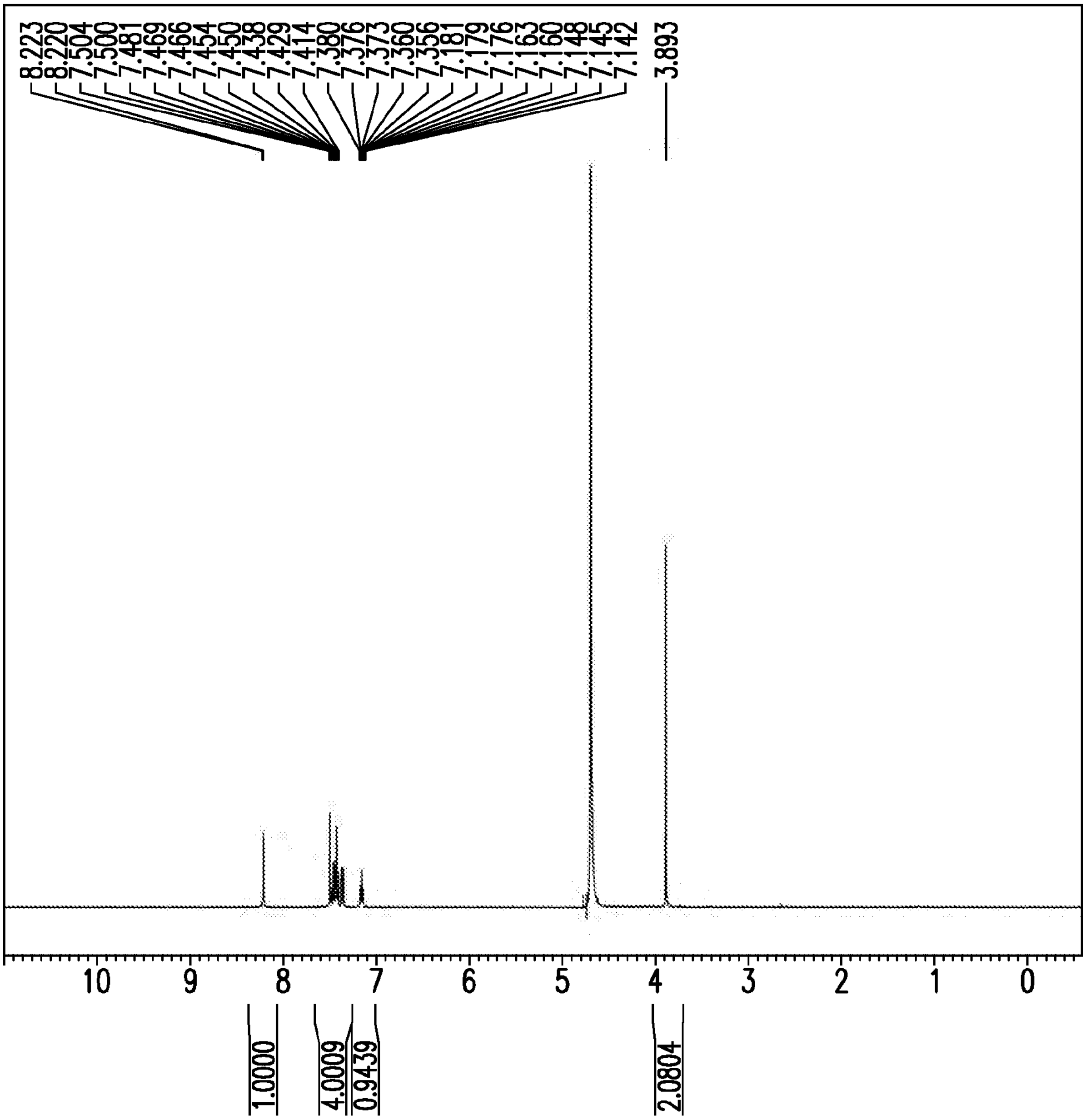

8.223
8.220
7.504
7.500
7.481
7.469
7.466
7.454
7.450
7.438
7.429
7.414
7.380
7.376
7.373
7.360
7.356
7.181
7.179
7.176
7.163
7.160
7.148
7.145
7.142
3.893
10
9
8
7
6
5
4
3
2
1
0
1.0000
4.0009
0.9439
2.0804

FIG. 92

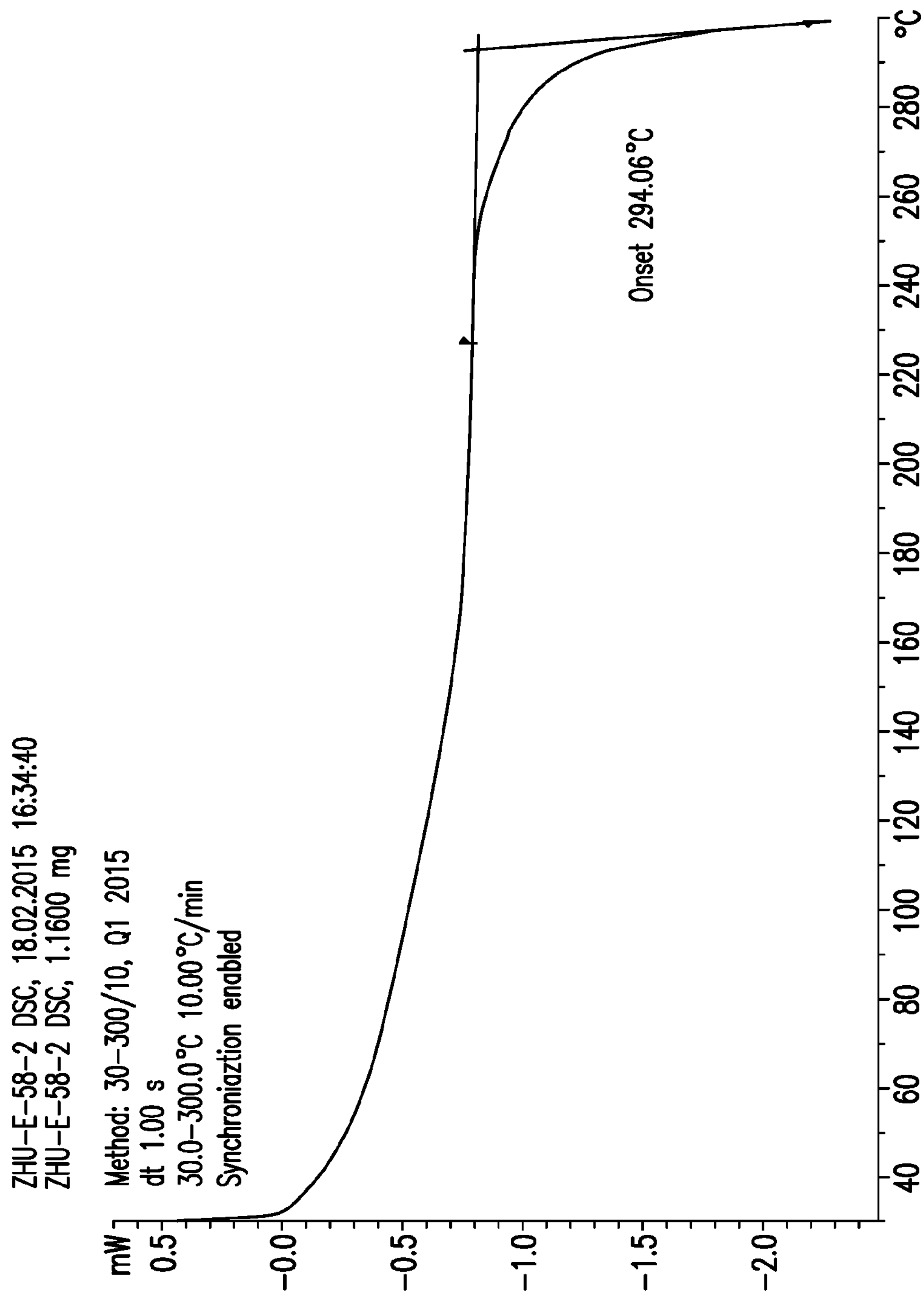

ZHU–E–58–2 DSC, 18.02.2015 16:34:40
ZHU–E–58–2 DSC, 1.1600 mg
Method: 30–300/10, Q1 2015
dt 1.00 s
30.0–300.0°C 10.00°C/min
Synchroniaztion enabled
Onset 294.06°C
mW
0.5
–0.0
–0.5
–1.0
–1.5
–2.0
40
60
80
100
120
140
160
180
200
220
240
260
280
°C

FIG. 93

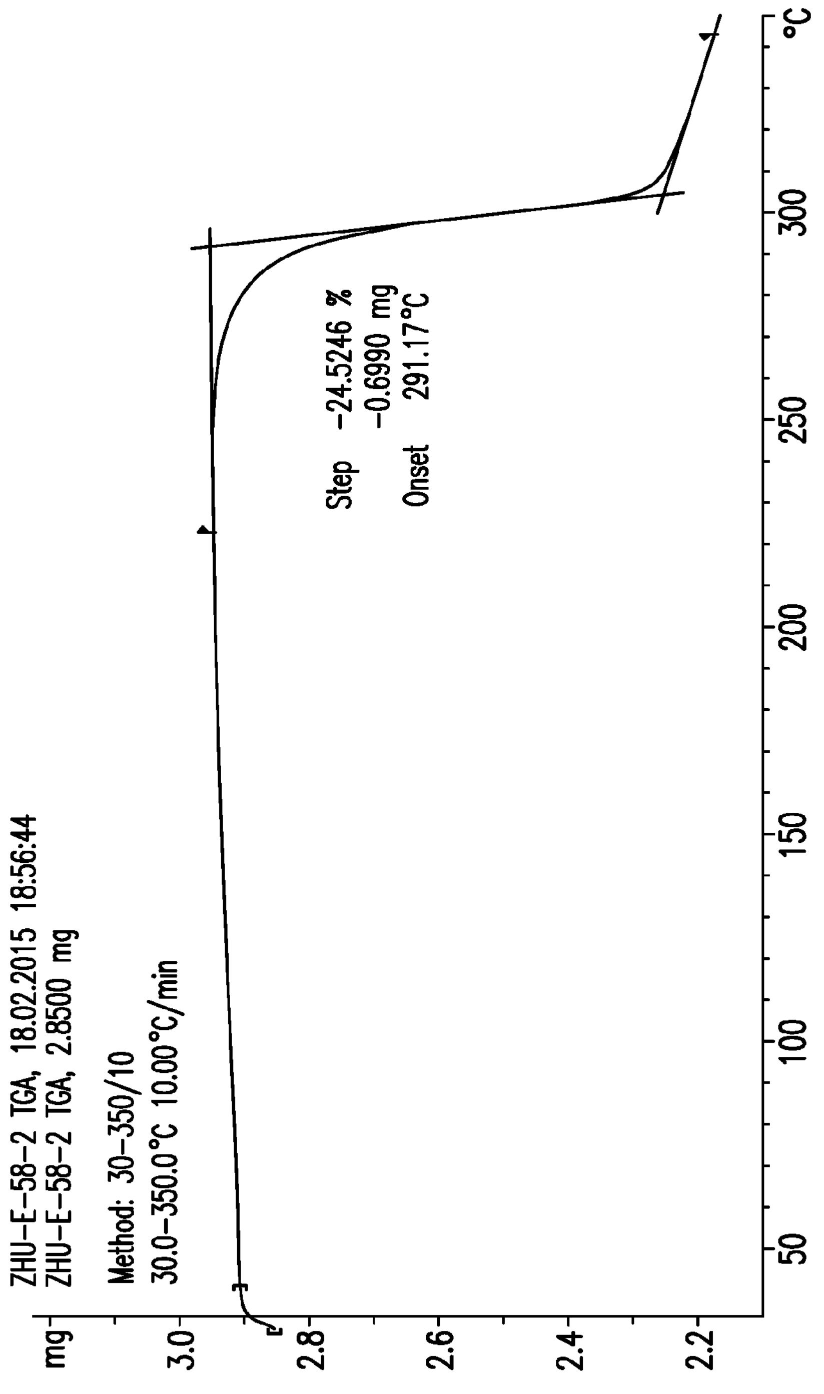

ZHU-E-58-2 TGA, 18.02.2015 18:56:44
ZHU-E-58-2 TGA, 2.8500 mg
Method: 30-350/10
30.0-350.0°C 10.00°C/min
Step −24.5246 %
−0.6990 mg
Onset 291.17°C
mg
3.0
2.8
2.6
2.4
2.2
50
100
150
200
250
300
°C

FIG. 94

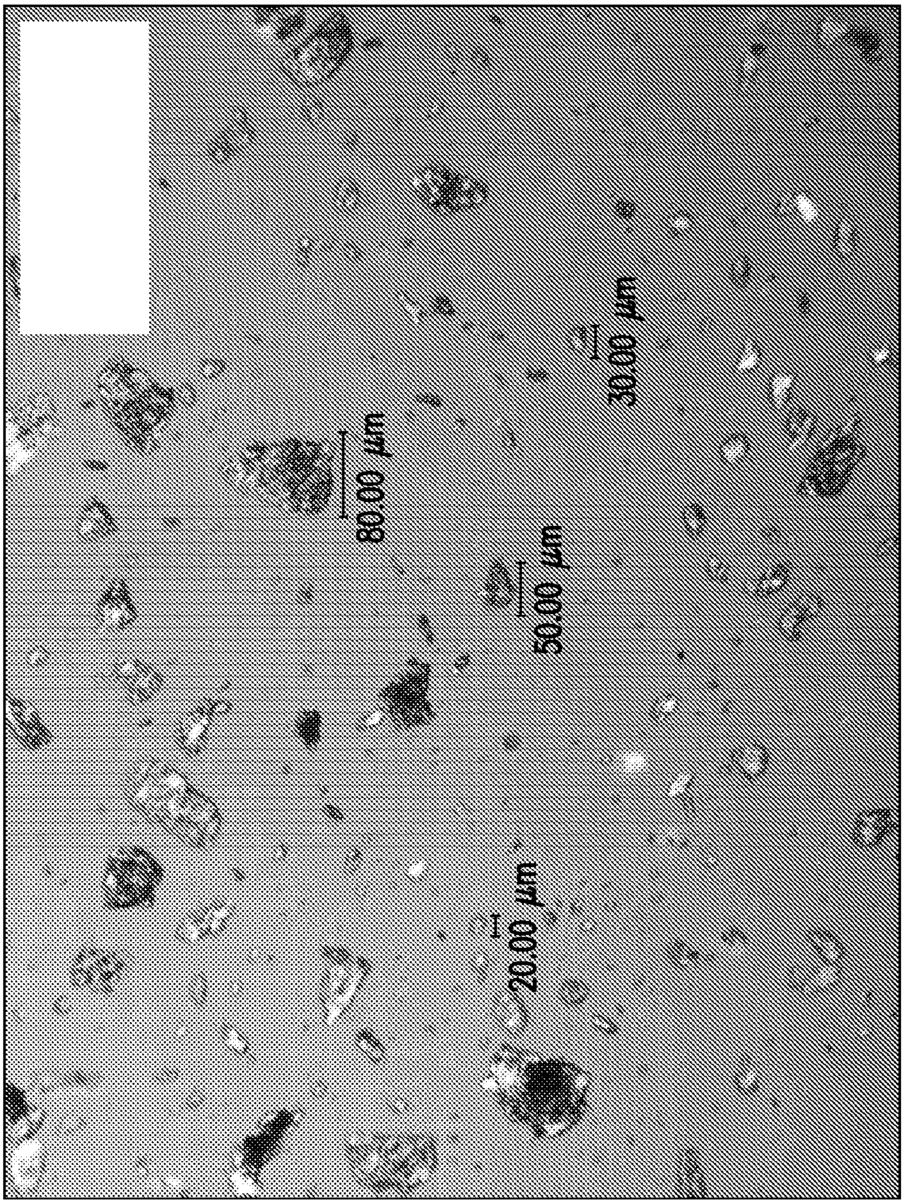


FIG. 95

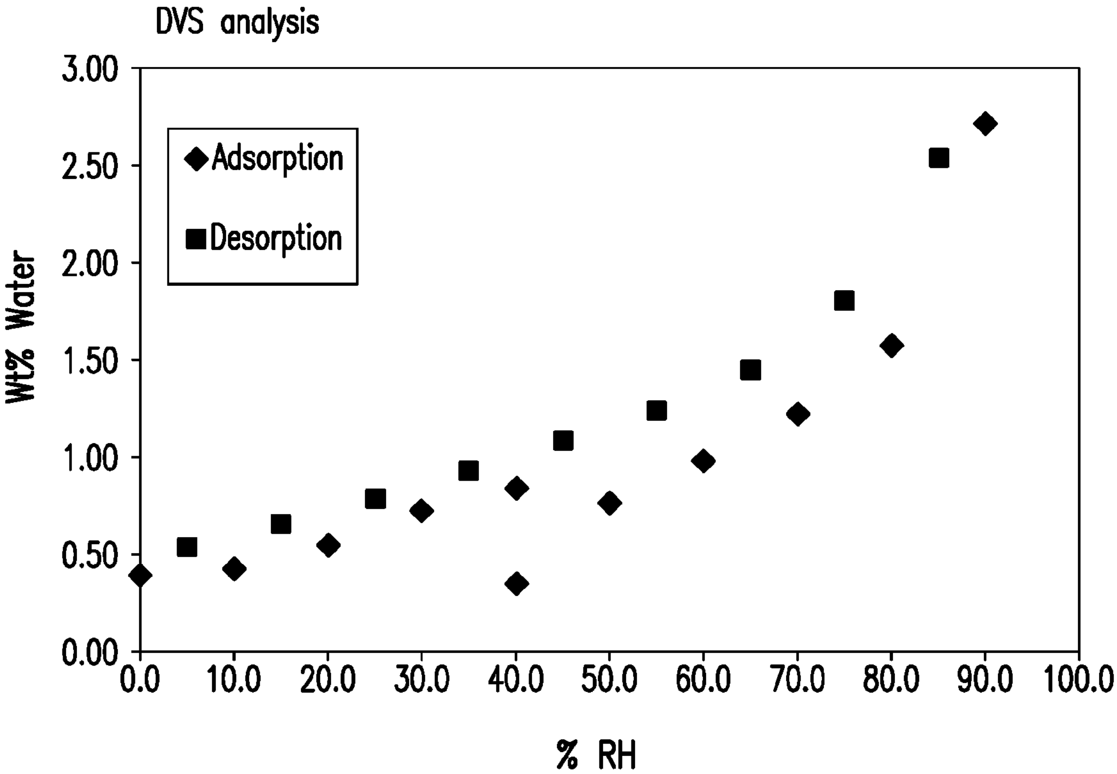

DVS analysis
Wt% Water
% RH
Adsorption
Desorption
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

FIG. 96

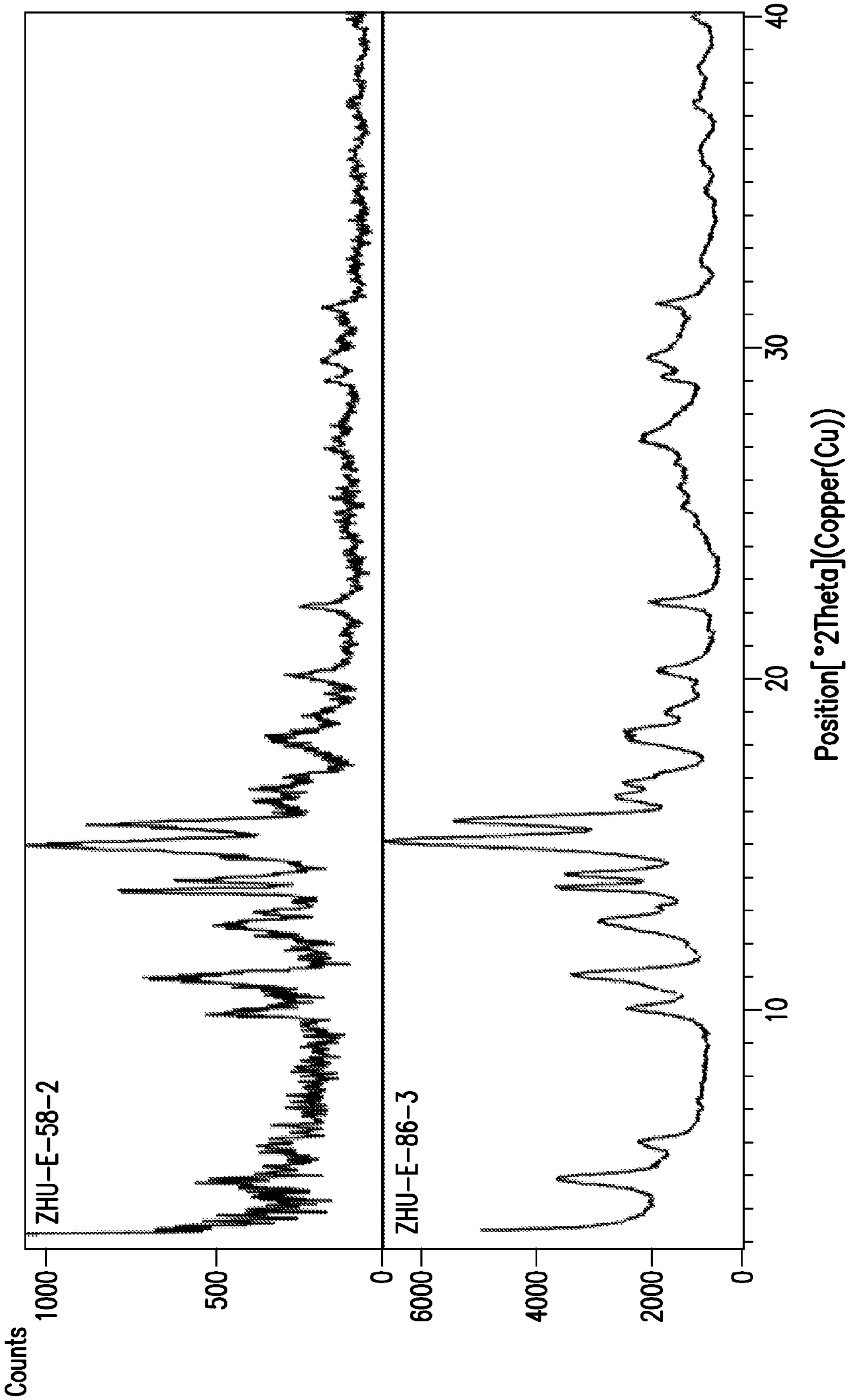

Counts
1000
500
0
6000
4000
2000
0
ZHU-E-58-2
ZHU-E-86-3
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 97

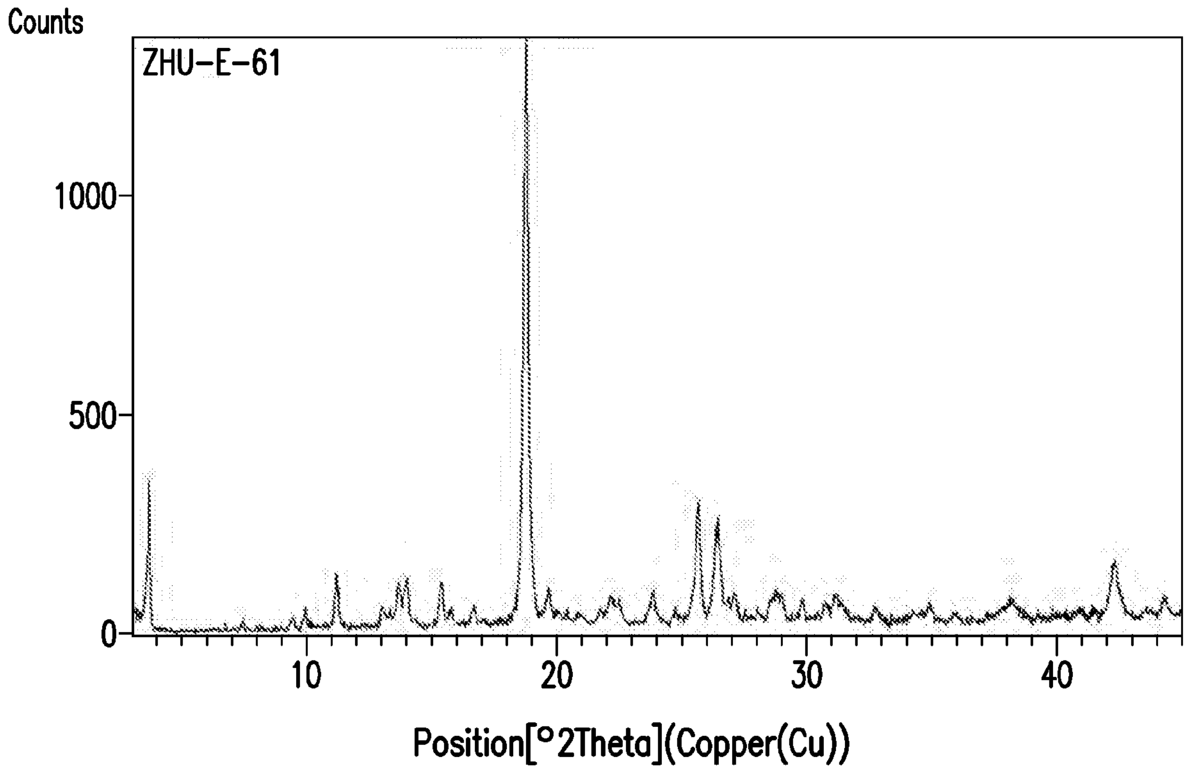

Counts
ZHU-E-61
1000
500
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 98

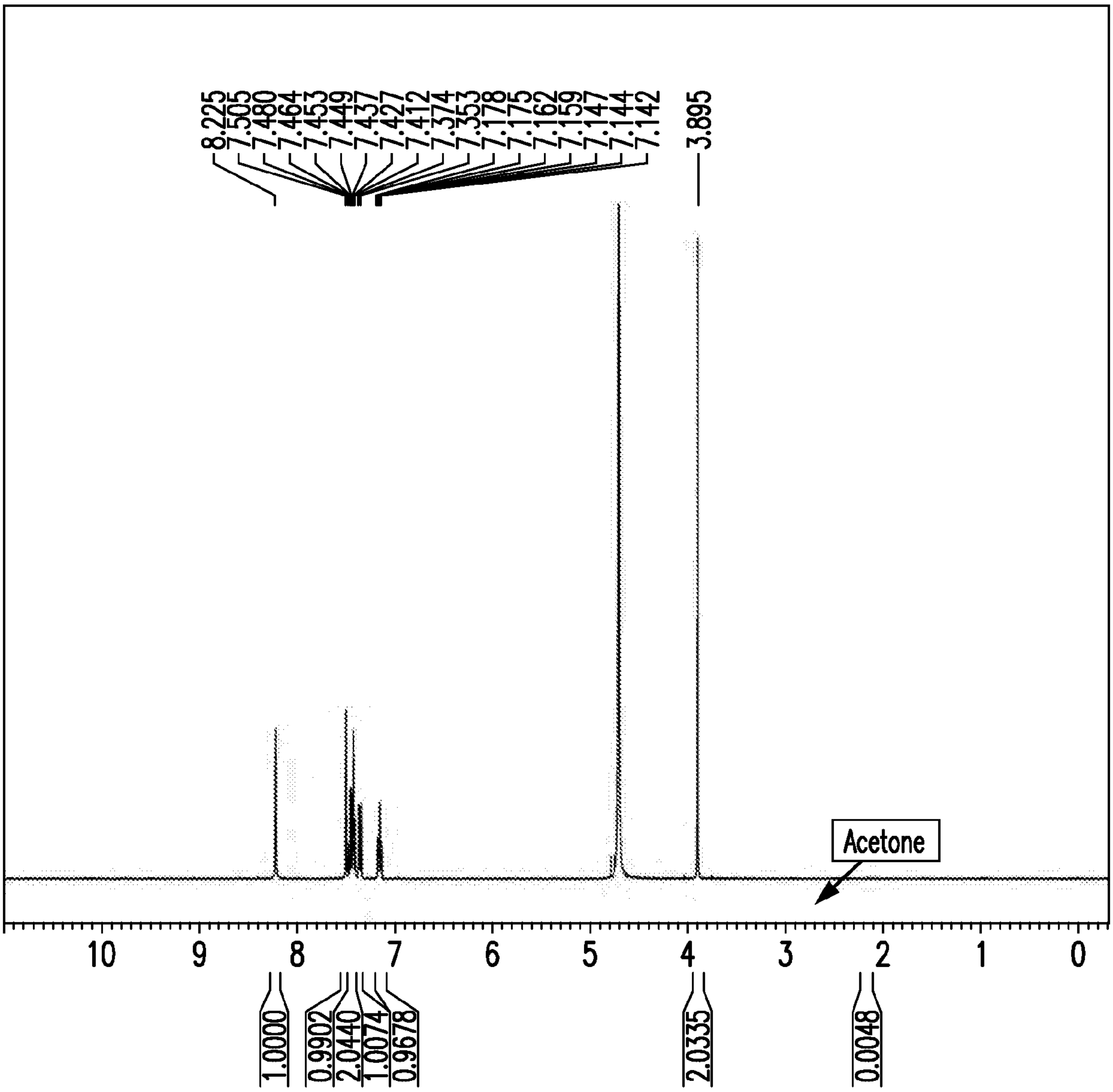

8.225
7.505
7.480
7.464
7.453
7.449
7.437
7.427
7.412
7.374
7.353
7.178
7.175
7.162
7.159
7.147
7.144
7.142
3.895
Acetone
10
9
8
7
6
5
4
3
2
1
0
1.0000
0.9902
2.0440
1.0074
0.9678
2.0335
0.0048

FIG. 99

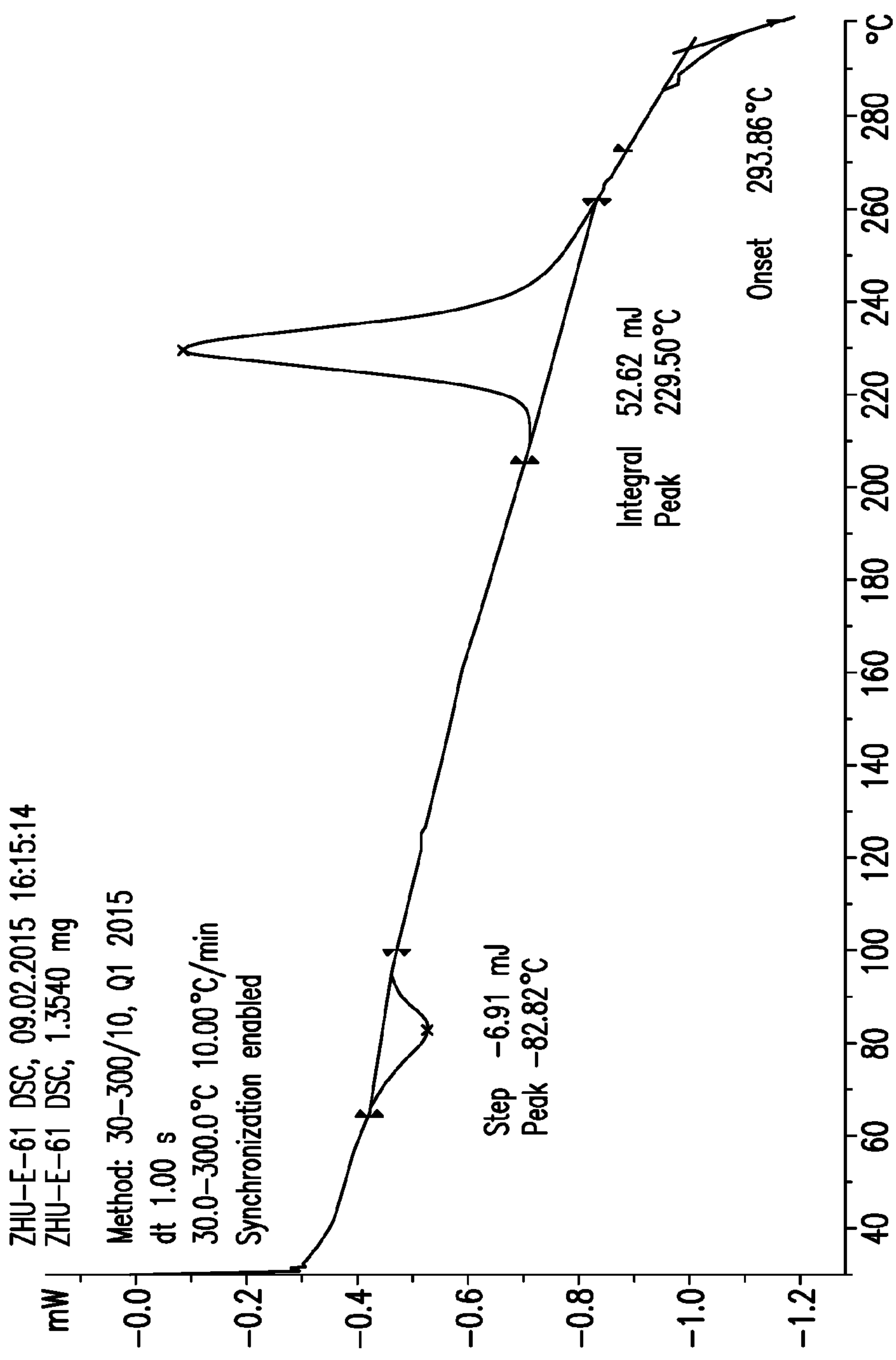

ZHU-E-61 DSC, 09.02.2015 16:15:14
ZHU-E-61 DSC, 1.3540 mg
Method: 30-300/10, Q1 2015
dt 1.00 s
30.0-300.0°C 10.00°C/min
Synchronization enabled
Step -6.91 mJ
Peak -82.82°C
Integral 52.62 mJ
Peak 229.50°C
Onset 293.86°C
mW
-0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
40
60
80
100
120
140
160
180
200
220
240
260
280
°C

FIG. 100

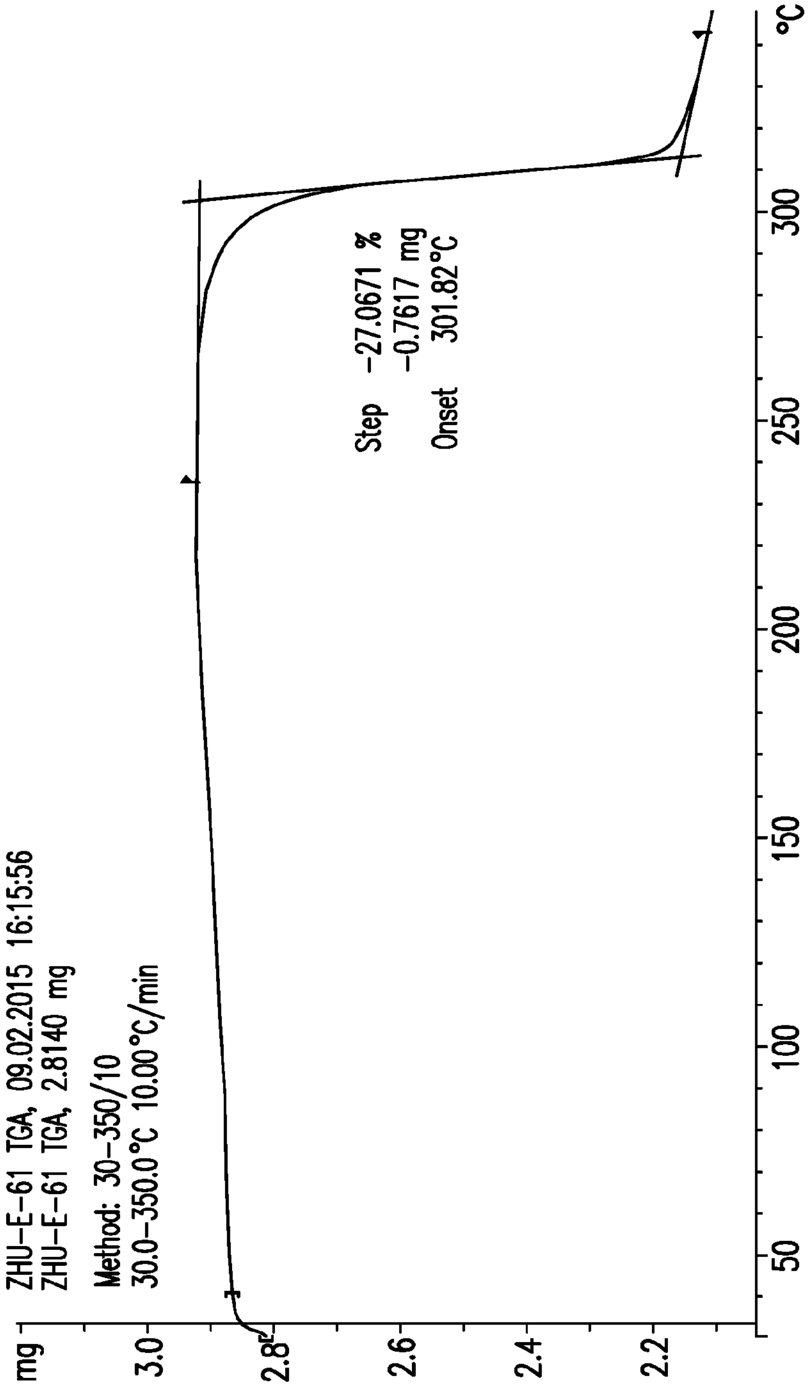

ZHU-E-61 TGA, 09.02.2015 16:15:56
ZHU-E-61 TGA, 2.8140 mg
Method: 30-350/10
30.0-350.0°C 10.00°C/min
Step -27.0671 %
-0.7617 mg
Onset 301.82°C
mg
3.0
2.8
2.6
2.4
2.2
50
100
150
200
250
300
°C

FIG. 101

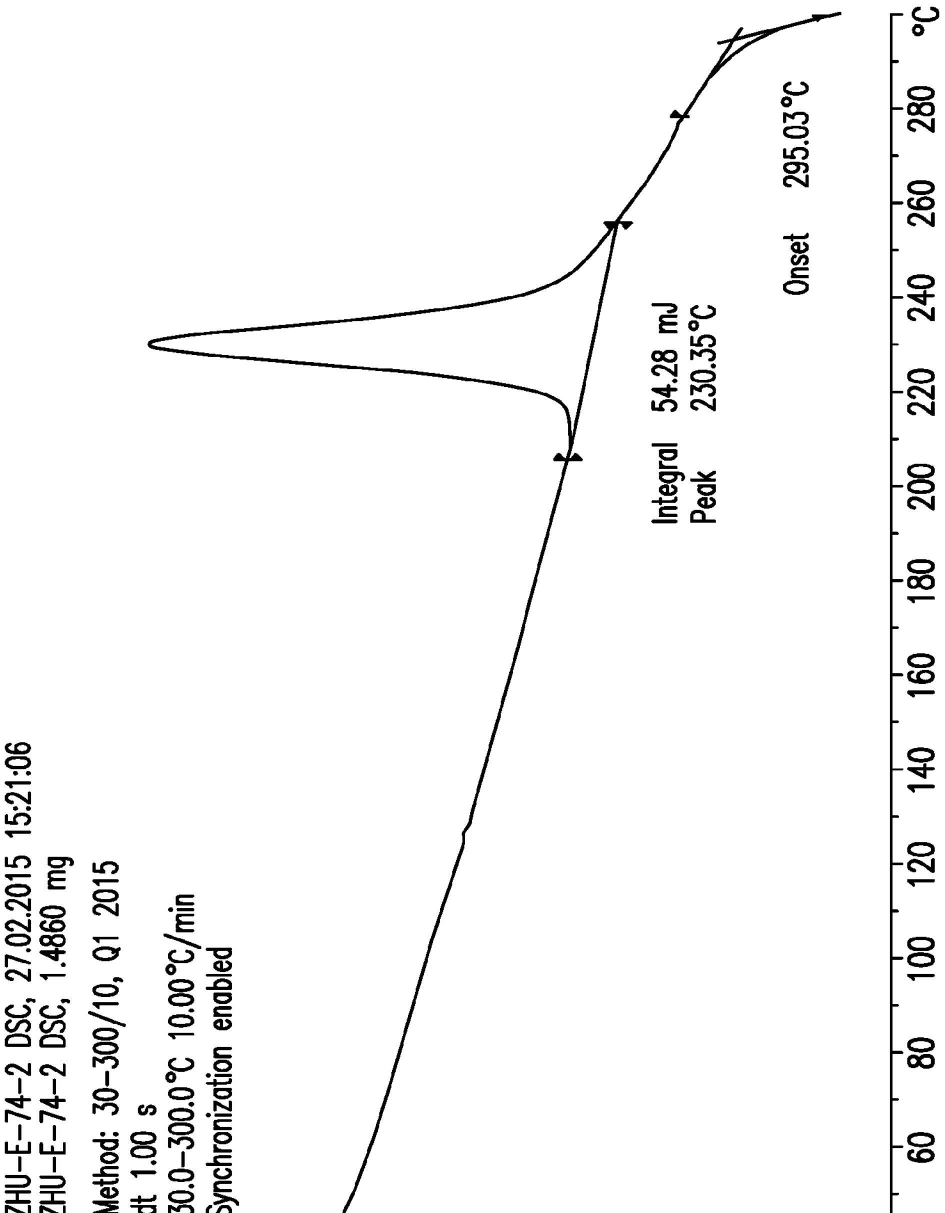

ZHU-E-74-2 DSC, 27.02.2015 15:21:06
ZHU-E-74-2 DSC, 1.4860 mg
Method: 30-300/10, Q1 2015
dt 1.00 s
30.0-300.0°C 10.00°C/min
Synchronization enabled
Integral 54.28 mJ
Peak 230.35°C
Onset 295.03°C
mW
0.2
0.0
-0.2
-0.4
-0.6
-0.8
40
60
80
100
120
140
160
180
200
220
240
260
280
°C

FIG. 102

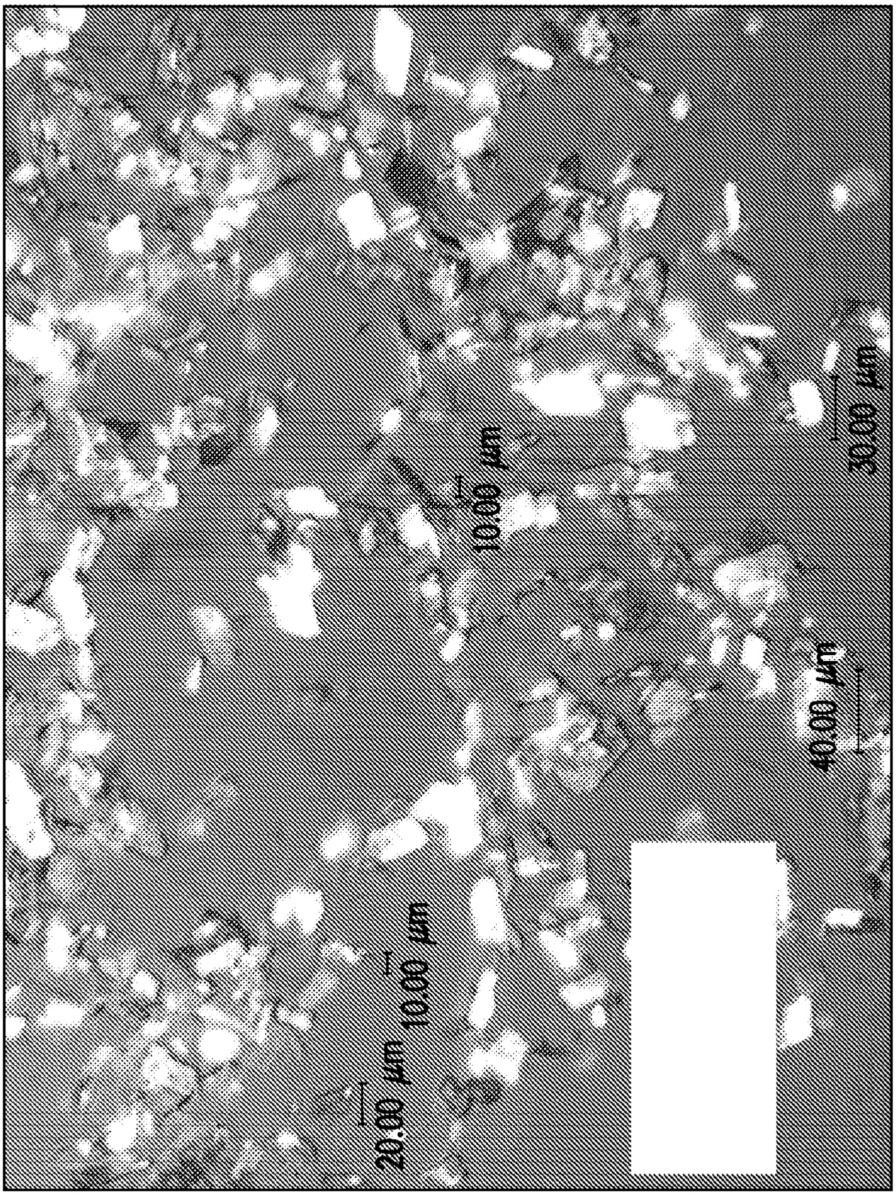


FIG. 103

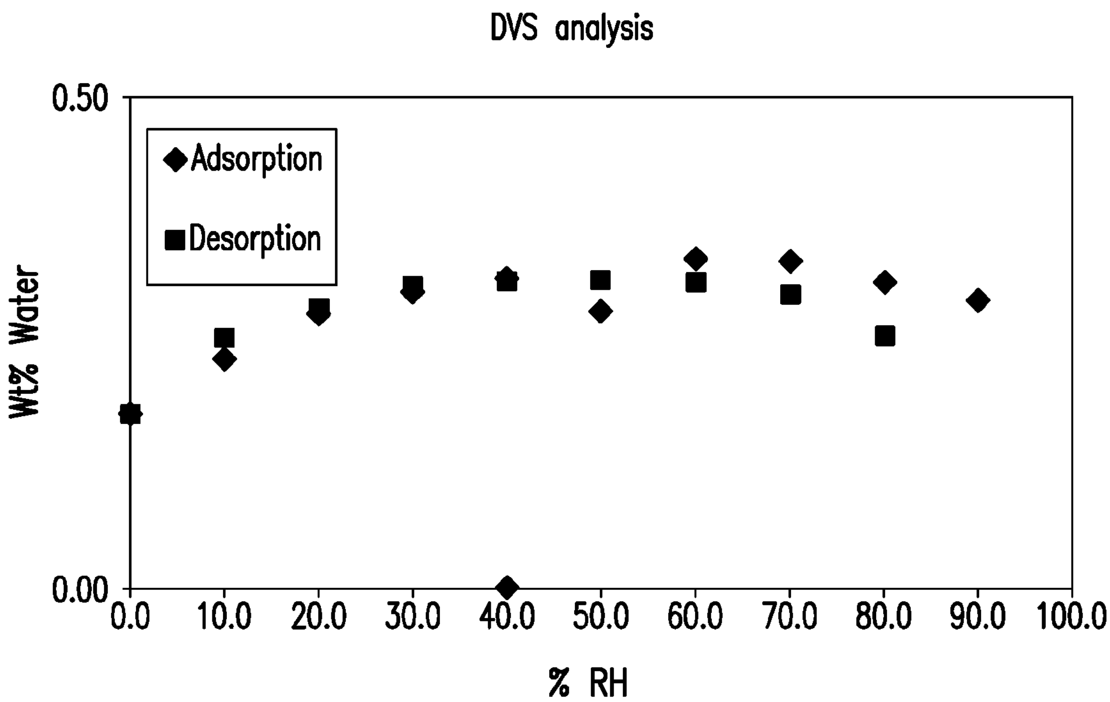

DVS analysis
0.50
0.00
Adsorption
Desorption
Wt% Water
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
% RH

FIG. 104

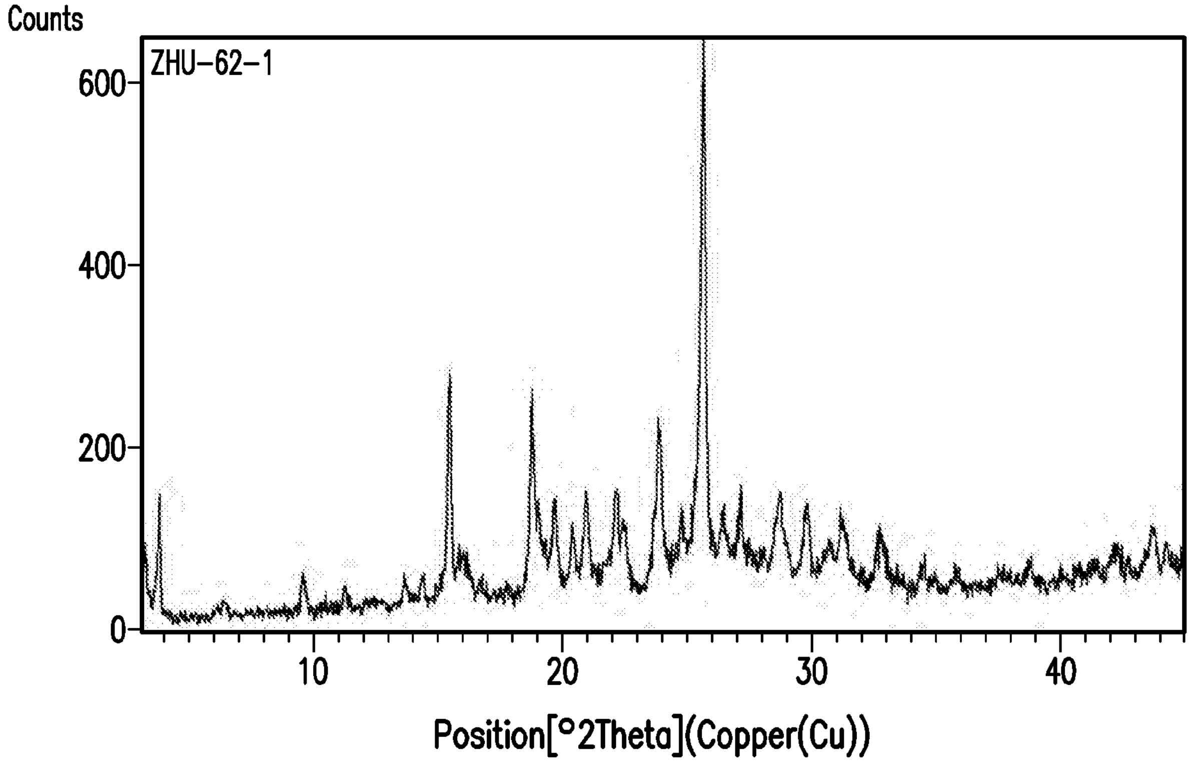

Counts
ZHU-62-1
600
400
200
0
10
20
30
40
Position[°2Theta](Copper(Cu))

FIG. 105

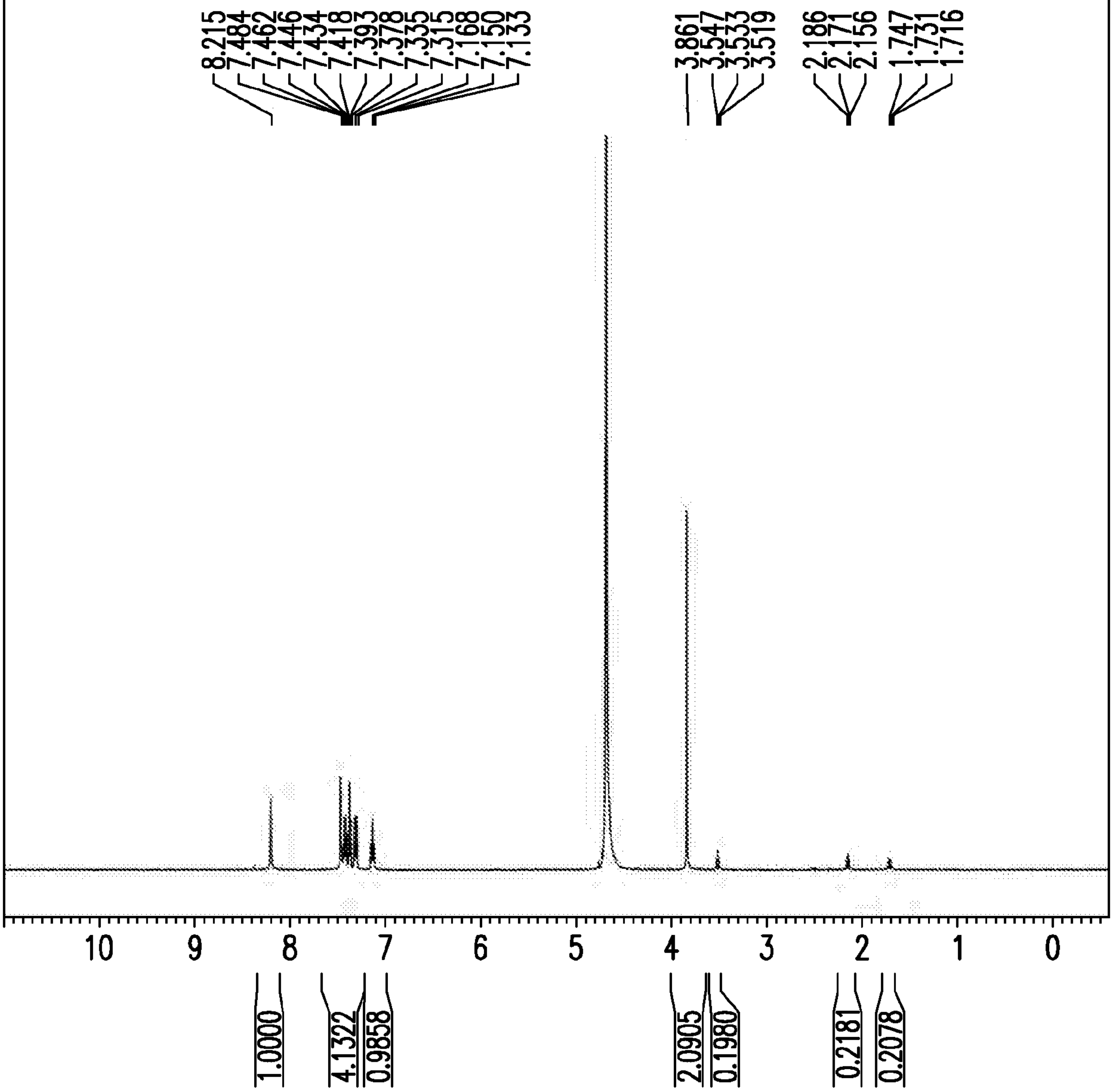
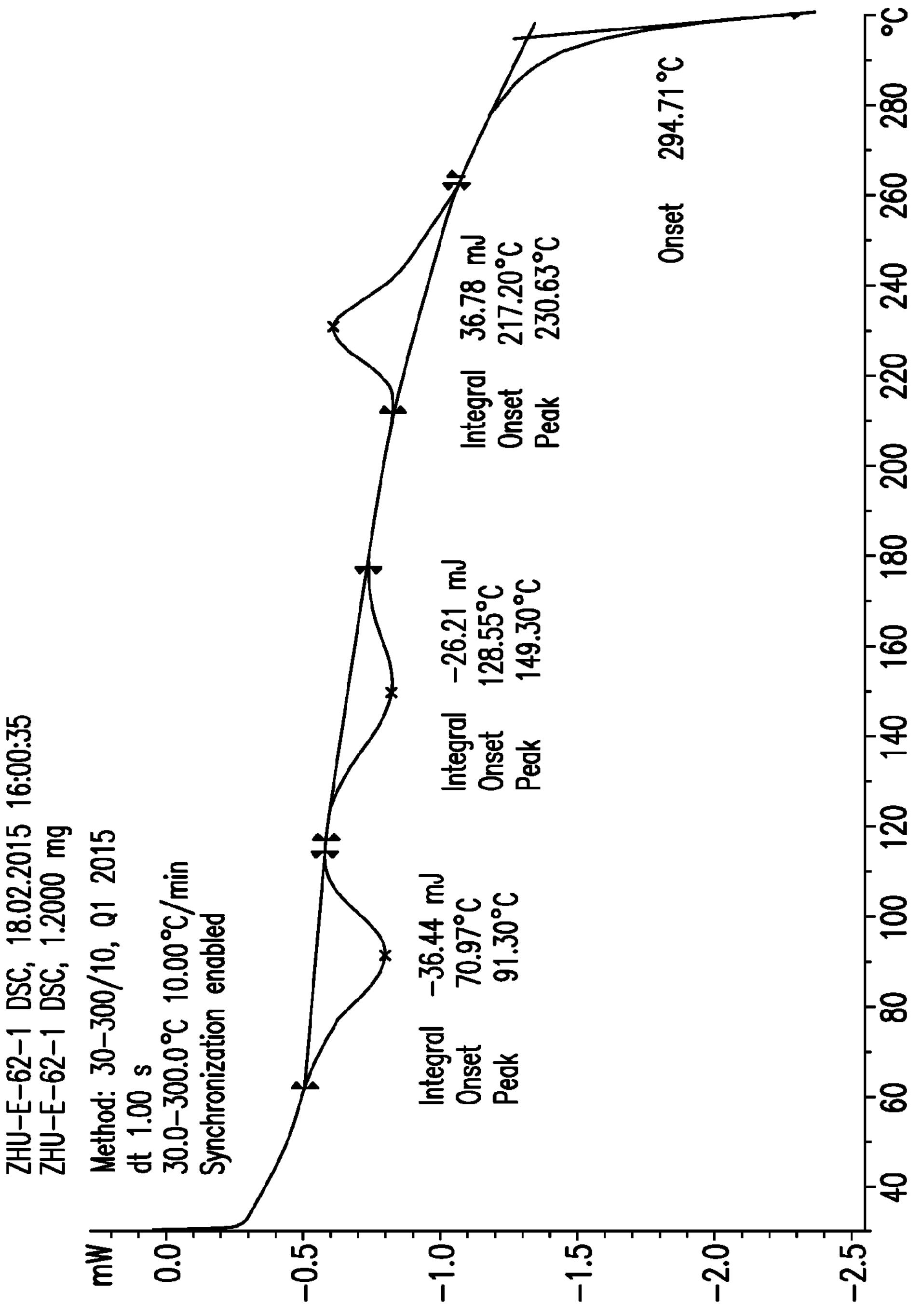

8.215
7.484
7.462
7.446
7.434
7.418
7.393
7.378
7.335
7.315
7.168
7.150
7.133
3.861
3.547
3.533
3.519
2.186
2.171
2.156
1.747
1.731
1.716
10
9
8
7
6
5
4
3
2
1
0
1.0000
4.1322
0.9858
2.0905
0.1980
0.2181
0.2078

FIG. 106



ZHU-E-62-1 DSC, 18.02.2015 16:00:35
ZHU-E-62-1 DSC, 1.2000 mg
Method: 30-300/10, Q1 2015
dt 1.00 s
30.0-300.0°C 10.00°C/min
Synchronization enabled
Integral -36.44 mJ
Onset 70.97°C
Peak 91.30°C
Integral -26.21 mJ
Onset 128.55°C
Peak 149.30°C
Integral 36.78 mJ
Onset 217.20°C
Peak 230.63°C
Onset 294.71°C
mW
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
40
60
80
100
120
140
160
180
200
220
240
260
280
°C

FIG. 107

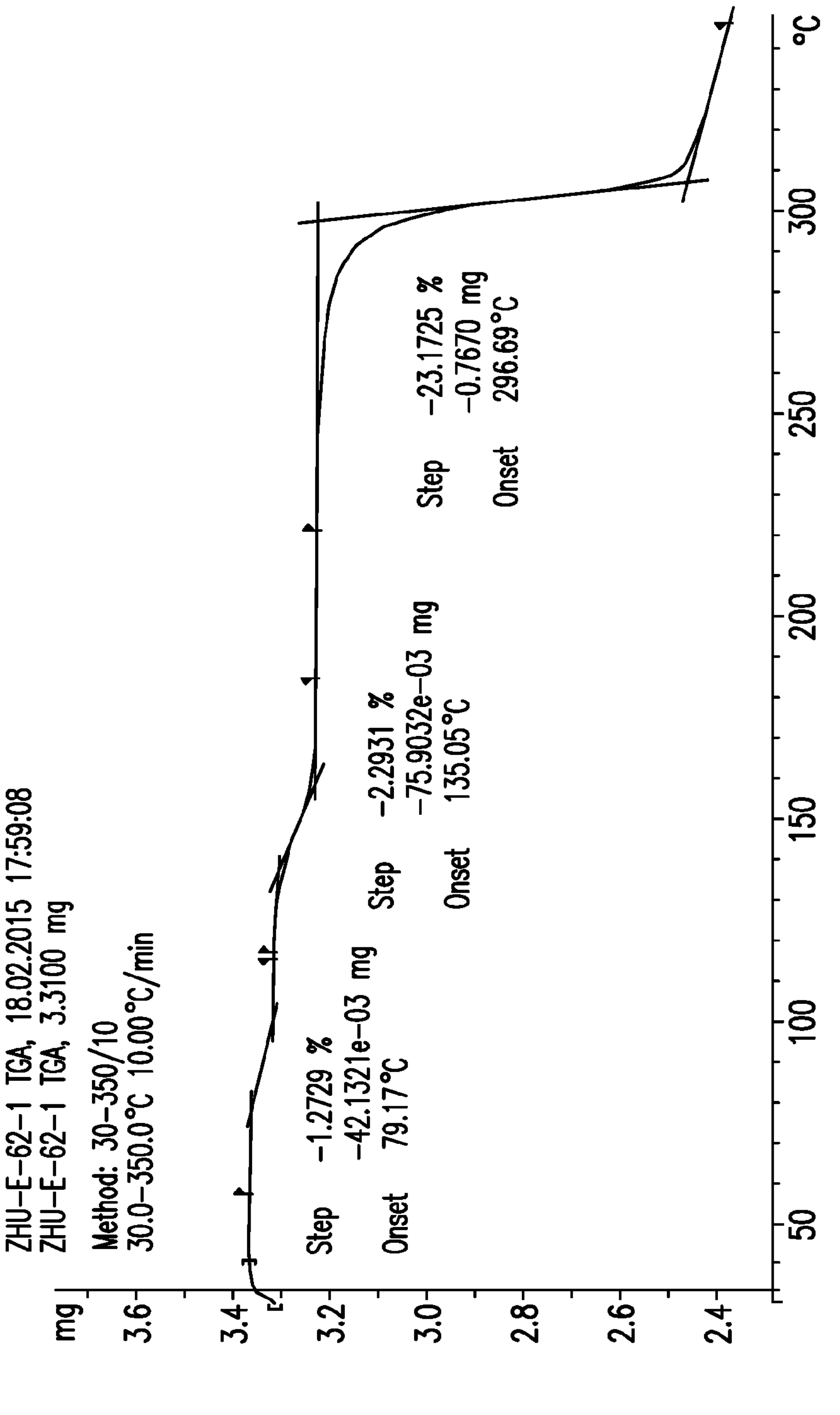

ZHU-E-62-1 TGA, 18.02.2015 17:59:08
ZHU-E-62-1 TGA, 3.3100 mg
Method: 30-350/10
30.0-350.0°C 10.00°C/min
Step -1.2729 %
-42.1321e-03 mg
Onset 79.17°C
Step -2.2931 %
-75.9032e-03 mg
Onset 135.05°C
Step -23.1725 %
-0.7670 mg
Onset 296.69°C
mg
3.6
3.4
3.2
3.0
2.8
2.6
2.4
50
100
150
200
250
300
°C

FIG. 108

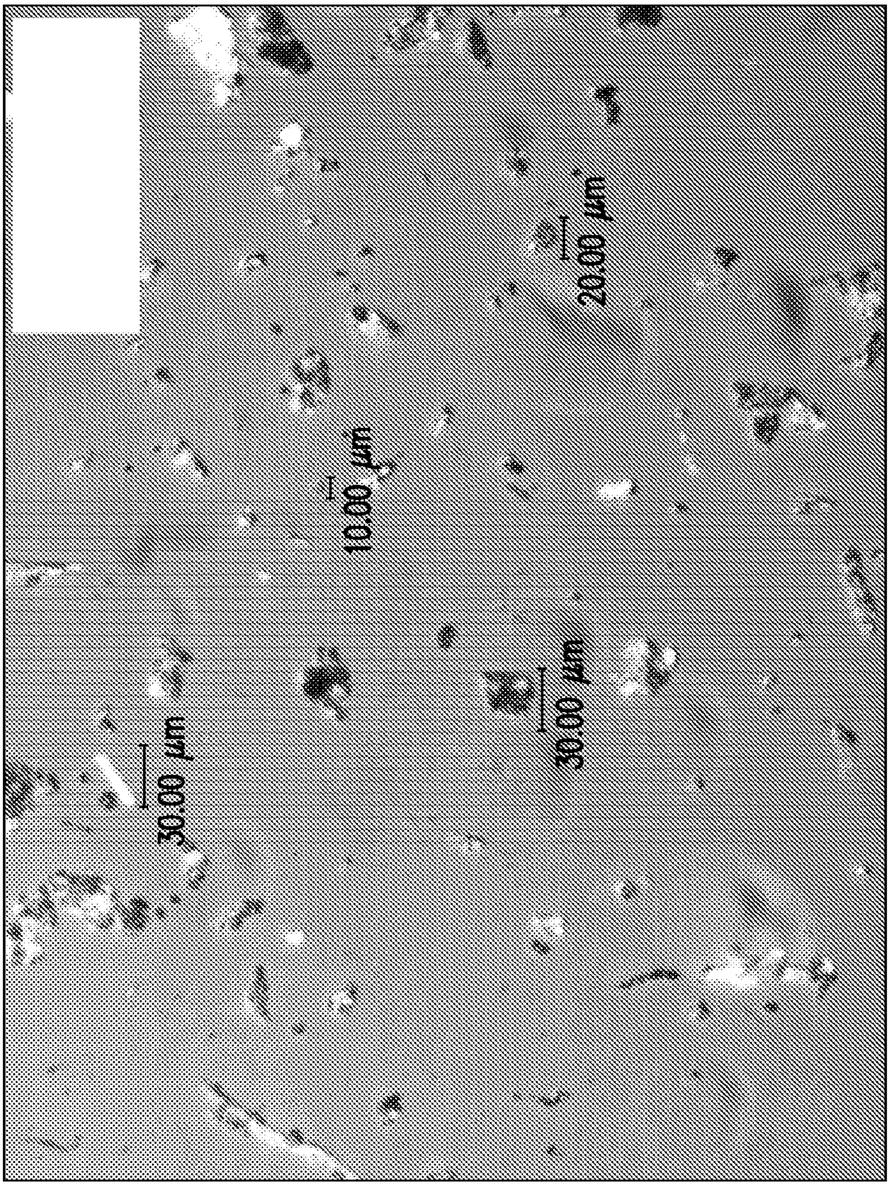


FIG. 109

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/14517

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4439, A61K 31/4415, A61K 31/444, A61K 31/513 (2016.01)
CPC - C07D 213/81, C07D 417/04, C07C 235/60, C07C 255/57, C07C 237/42, C07D 213/65, C07D 405/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/4439, A61K 31/4415, A61K 31/444, A61K 31/513 (2016.01)
CPC: C07D 213/81, C07D 417/04, C07C 235/60, C07C 255/57, C07C 237/42, C07D 213/65, C07D 405/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/256, 514/383, 514/408, 514/447, 514/342

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase; Keyword limited: 2-(5-(3-fluorophenyl)-3-hydroxypicolinamido)acetic acid; solid form; salt; Powder x ray diffraction; X ray powdor diffraction; Pxrd; Xprd; Xrpd; x-ray; x ray; xray; powder; diffraction

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/0316204 A1 (SHAWLITZ et al.) 13 December 2013 (31.12.2013), entire document, especially: (para [0062]).	1-68
A	PubChem-CID-49848485, Create Date: 31 January 2011 (31.01.2011), entire document, especially: pg 3, Fig.	1-68
A	WO 2013/013609 A1 to (ZHEJIANG BETA PHARMA INCORPORATION) 31 January 2013 (31.01.2013) entire document, especially: abstract, Formula I; pg 3, Table 1.	1-68
X, P	WO 2015/073779 A1 (AKEBIA THERAPEUTICS INC) 21 May 2015 (21.05.2015), entire document.	1-68
A	PubChem-CID-71491828, Create Date: 10 June 2013 (10.06.2013), entire document, especially: pg 3, Fig.	1-68

☐ Further documents are listed in the continuation of Box C. ☐

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

Date of the actual completion of the international search	Date of mailing of the international search report
16 May 2016 (16.05.2016)	27 MAY 2016

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/14517

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

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

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

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

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

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

This International Searching Authority found multiple inventions in this international application, as follows:
--See attached extra sheet--

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-68

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

-- Box III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-68 drawn to a crystal form comprising Compound 1.

Group II: Claims 69-78 drawn to a hemi-calcium salt comprising Compound 1.

Group III: Claims 79-89 drawn to a dihydrated hemi-calcium salt comprising Compound 1.

Group IV: Claims 90-98 drawn to a mono-potassium salt comprising Compound 1.

Group V: Claims 99-106 drawn to a monohydrated mono-sodium salt comprising Compound 1.

Group VI: Claims 107-112 drawn to a monohydrated bis-sodium salt comprising Compound 1.

Group VII: Claims 113-119, and 126-135 drawn to an anhydrous mono-sodium salt comprising Compound 1.

Group VIII: Claims 120-125 and 136-143 drawn to a hydrated mono-sodium salt comprising Compound 1.

Group IX: Claim 144 drawn to a method for preparing Compound 1.

The inventions listed as Groups I-IX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
Special Technical Features

Group I includes the technical feature of a crystal form of Compound 1 havng specific PXRD pattern, which is not required by Groups II-IX.

Group II includes the technical feature of a hemi-calcium salt of Compound 1 havng specific PXRD pattern, which is not required by Groups I or III-IX

Group III includes the technical feature of a dihydrated hemi-calcium salt of Compound 1 havng specific PXRD pattern, which is not required by Groups I-II or IV-IX.

Group IV includes the technical feature of a mono-potassium salt of Compound 1 havng specific PXRD pattern, which is not required by Groups I-III or V-IX.

Group V includes the technical feature of a monohydrated mono-sodium salt of Compound 1 havng specific PXRD pattern, which is not required by Groups I-IV or VI-IX.

Group VI includes the technical feature of a monohydrated bis-sodium salt of Compound 1 havng specific PXRD pattern, which is not required by Groups I-V or VII-IX.

Group VII includes the technical feature of an anhydrous mono-sodium salt of Compound 1 havng specific PXRD pattern, which is not required by Groups I-VI or VIII-IX.

Group VIII includes the technical feature of a hydrated mono-sodium salt of Compound 1 havng specific PXRD pattern, which is not required by Groups I-VII or IX.

Group IX includes the technical feature of a method for preparing Compound 1, which is not required by Groups I-VIII.

Shared Common Features

Groups I-IX shar teh technical feature compound of formula I. However, this shared teachical feature does not provide a contribution over the prior art, as being anticipated by the document PubChem-CID-49848485 (hereinaffer 'PubChem-485') teaches Compound 1 (pg 3, Fig).

Groups II-VIII share the technical fetaure of formula I salt. However, this shared teachical feature does not provide a contribution over the prior art, as being anticipated by the document PubChem-CID-71491828 (hereinafter 'PubChem-828') teaches formula I salt (pg 3, Fig).
As the technical feature was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I-IX therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.