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(71) Applicant: **CELGENE CORPORATION** [US/US]; 86 Morris Avenue, Summit, NJ 07901 (US).

(72) Inventors: **COHEN, Benjamin, M.;** 32 Hillcrest Avenue, Cranford, NJ 0701 6 (US). **LI, Ying;** 401 Briant Park Drive, Springfield, NJ 07081 (US). XU, **Jean;** 2 Cherry Tree Lane, Warren, NJ 07059 (US). **LEONG, William, W.;** 342 Edgewood Avenue, Westfield, NJ 07090 (US). **MAN, Hon-wah;** 27 Grant Way, Princeton, NJ 08540 (US).

(74) Agents: **POISSANT, Brian, M.** et al; Jones Day, 222 East 41st Street, New York, NY 10017-6702 (US).

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(54) **Title:** SOLID FORMS OF 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-l,3-DIONE, COMPOSITIONS AND METHODS OF USE THEREOF

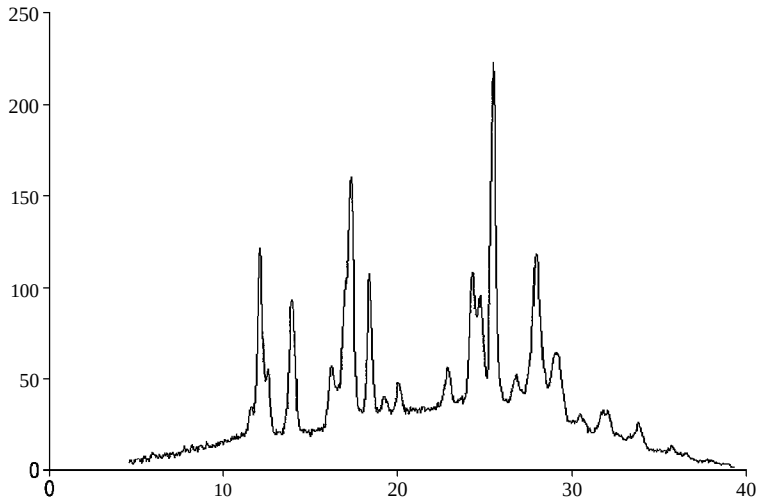

FIG. 1

(57) **Abstract:** Provided herein are solid forms comprising 4-amino-2-(2,6- dioxopiperidine-3-yl)isomdolme-l,3-dione. Pharmaceutical compositions comprising the solid forms and methods for treating, preventing and managing various disorders are also disclosed.

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SOLID FORMS OF 4-AMiNO-2-(2,6-DiOXOPiPERIDI]NE-3-YL)ISOiNDOLiNE-1,3-DIONE, COMPOSITIONS AND METHODS OF USE THEREOF

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 61/601,497, filed Febmary 21, 2012, which is incorporated herein by reference in its entirety.

1. FIELD

[0002] Provided herein are solid forms comprising 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-l ,3-dione. Pharmaceutical compositions comprising the solid forms and methods of use for treating, preventing, and managing various disorders are also provided herein.

2, BACKGROUND

2.1 Solid Forms of Pharmaceutical Compounds

[0003] The identification and selection of a solid form of a pharmaceutical compound are 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, formulation, stability, bioavailability, storage, handling *(e.g.,* shipping), among other important pharmaceutical characteristics. Useful pharmaceutical solids include crystalline solids and amorphous solids, depending on the product and its mode of administration. Amoiphous 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. *Y-a, Adv. Drug. Deliv. Rev.,* (2001) 48:27-42).

[0004] Whether crystalline or amorphous, solid forms of a pharmaceutical compound include single-component and multiple-component solids. Single-component solids

consist essentially of the pharmaceutical compound or active ingredient 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 may be 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.,* 8. 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.

[0006] The variety of possible solid forms creates potential diversity in physical and chemical properties for a given pharmaceutical compound. The discovery and selection of solid forms are of great importance in the development of an effective, stable and marketable pharmaceutical product.

2,2 Pomalidomide

[0007] Pomalidomide, which was previously referred to as CC-4047, and has a chemical name of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline- 1,3-dione. Pomalidomide is a compound that inhibits, for example, LPS induced monocyte TNFa, IL-1β, IL-12, IL-6, MIP-1, MCP-1, GM-CSF, G-CSF, and COX-2 production, and may

be used in treating various disorders. *See, e.g.*, U.S. Patent Nos. 5,635,517, 6,316,471, 6,476,052, 7,393,863, 7,629,360, and 7,863,297; and U.S. Patent Application Publication Nos. 2.005/0143420, 2006/0166932, 2006/0188475, 2007/0048327, 2007/0066512, 2007/0155791, 2008/0051431, 2008/0317708, 2009/0087407, 2009/0088410, 2009/013 17385, 2009/0148853, 2009/0232776, 2009/0232796, 2010/0098657, 2010/0099711, and 201 1/0184025, the entireties of which are incorporated herein by reference. The compound is also known to co-stimulate the activation of T-eells. Pomalidomide has direct anti-myeloma tumoricidal activity, immunomodulatory activities and inhibits stromal cell support for multiple myeloma tumor cell growth. Specifically, pomalidomide inhibits proliferation and induces apoptosis of hematopoietic tumor cells. *Id.* Additionally, pomalidomide inhibits the proliferation of lenaiidomide-resistant multiple myeloma cell lines and synergizes with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity, and inhibits production of pro-inflammatory cytokines *(e.g.*, TNF-αt and XL-6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells. Due to its diversified pharmacological properties, pomalidomide is useful in treating, preventing, and/or managing various diseases or disorders.

[0008] Pomalidomide and methods of synthesizing the compound are described, *e.g.*, in U.S. Patent Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327; and U.S. Patent Application Publication Nos. 2006/0178402 and 201 1/0224440; the entireties of which are incorporated herein by reference.

[0009] Citation of any references in this Section is not to be construed as an admission that such references are prior art to the present application.

3. SUMMARY

[0010] Provided herein are solid forms *(e.g.*, crystal forms or amorphous forms, or mixtures thereof) comprising pomalidomide, or pharmaceutically acceptable salts, stereoisomers, solvates (including, hydrates), co-crystals, prodrugs, or elathrates thereof. Also provided are methods of preparing, isolating, and characterizing the solid forms.

[0011] Also provided herein are pharmaceutical compositions and single unit dosage forms, which comprise one or more solid forms provided herein.

[0012] Also provided herein are methods of treating and managing various diseases or disorders. The methods comprise administering to a patient in need of such treatment or management a therapeutically effective amount of a solid form provided herein.

[0013] Also provided herein are methods of preventing various diseases and disorders, which comprise administering to a patient in need of such prevention a prophylactically effective amount of a solid form provided herein.

[0014] The various diseases and disorders include, but are not limited to: cancer, including hematologic cancer or solid tumor, for example, multiple myeloma, leukemia, lymphoma, sarcoma, prostate cancer, or small cell lung cancer; scleroderma; amyloidosis; pain; myelofibrosis; myeloproliferative disease, for example, myelofibrosis with myeloid metaplasia (MMM); myelodysplastic syndromes; diffuse systemic sclerosis; macular degeneration; a skin disease; a pulmonary disorder; an asbestos-related disorder; a parasitic disease; an immunodeficiency disorder; a CNS disorder; a CNS injury; atherosclerosis; hemoglobinopathy; anemia, for example, sickle cell anemia; an inflammatory disease; an autoimmune disease; a viral disease; a genetic disease; an allergic disease; a bacterial disease; an ocular neovascular disease; a choroidal neovascular disease; a retina neovascular disease; and rubeosis.

4, BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Fig. 1 provides a representative X-ray Powder Diffraction (XRPD) pattern of one embodiment of a solid form of pomalidomide.

[0016] Fig. 2 provides a representative XRPD pattern of one embodiment of a solid form of pomalidomide.

[0017] Fig. 3 provides a representative XRPD pattern of one embodiment of a solid form of pomalidomide.

[0018] Fig. 4 provides a representative XRPD pattern of one embodiment of a solid form of pomalidomide.

[0019] Fig. 5 provides a representative XRPD pattern of one embodiment of a solid form of pomalidomide.

[0020] Fig. 6 provides a representative XRPD pattern of one embodiment of a solid form of pomalidomide.

[0021] Fig. 7 provides a birefringence image (at 5x magnification) of representative crystals of one embodiment of a solid form of pomalidomide.

[0022] Fig. 8 provides a birefringence image (at 5x magnification) of representative crystals of one embodiment of a solid form of pomalidomide.

[0023] Fig. 9 provides a birefringence image (at 5x magnification) of representative crystals of one embodiment of a solid form of pomalidomide.

[0024] Fig. 10 provides a representative Differential Scanning Calorimetry (DSC) thermogram of one embodiment of a solid form of pomalidomide.

[0025] Fig. 11 provides a representative DSC thermogram of one embodiment of a solid form of pomalidomide.

[0026] Figs. 12a and 12b provide representative DSC cycHne thermograms of embodiments of solid forms of pomalidomide.

[0027] Fig. 13 provides a representative DSC thermogram of one embodiment of a solid form of pomalidomide.

[0028] Fig. 14 provides a representative DSC thermogram of one embodiment of a solid form of pomalidomide.

[0029] Fig. 15 provides a representative DSC thermogram of one embodiment of a solid form of pomalidomide.

[0030] Fig. 16 provides a representative DSC thermogram of one embodiment of a solid form of pomalidomide.

[0031] Fig. 17 provides a representative Thermal Gravimetric Analysis (TGA) thermogram of one embodiment of a solid form of pomalidomide.

[0032] Fig. 18 provides a representative XRPD pattern of one embodiment of an amorphous form of pomalidomide.

[0033] Fig. 19 provides one embodiment of a representative single X-ray structure of pomalidomide.

[0034] Fig. 20 provides one embodiment of a representative single X-ray structure of pomalidomide.

[0035] Fig. 21 provides a simulated XRPD pattern, based on the single X-ray data of pomalidomide.

[0036] Fig. 22 provides a representative infrared (IR) spectrum of one embodiment of a solid form of pomalidomide.

[0037] Fig. 23 provides a dynamic vapor sorption (DVS) isotherm plot of one embodiment of a solid form of pomalidomide.

[0038] Fig. 24 provides a DVS isotherm plot of one embodiment of a solid form of pomalidomide.

[0039] Fig. 25 provides a representative XRPD pattern of one embodiment of a solid form of pomalidomide.

[0040] Fig. 26 provides a representative XRPD pattern of one embodiment of a solid form of pomalidomide.

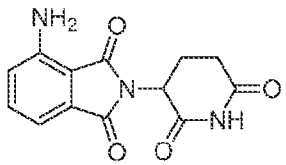
[0041] Fig. 27 provides a representative XRPD pattern of one embodiment of a solid form of pomalidomide after compression test.

5. DETAILED DESCRIPTION

5.1 Definitions

[0042] As used herein, and in the specification and the accompanying claims, the indefinite articles "a" and "an" and the definite article "the" include plural as well as single referents, unless the context clearly indicates otherwise.

[0043] As used herein, and unless otherwise specified, the compound referred to herein by the name pomalidomide, 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoliRe-l ,3-dione, or CC-4047, corresponds to chemical structure (I), depicted below. In certain embodiments, the term pomalidomide, 4-ammo-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, or CC-4047 may be used herein to refer to either a free base form or an ionized form of a compound of formula (I) *(e.g.,* the molecule is protonated at one or more basic centers).



(I)

[0044] Unless otherwise specified, the terms "solid form," "solid forms," and related terms, when used herein to refer to pomalidomide, refer to apliysical form comprising

pomalidomide, which is not predominantly in a liquid or a gaseous state. As used herein, the terms "solid form" and "solid forms" encompass semi-solids. Solid forms may be crystalline, amorphous, partially crystalline, partially amorphous, or mixtures of forms. A "single-component" solid form comprising pomalidomide consists essentially of pomalidomide. A "multiple-component" solid form comprising pomalidomide comprises a significant quantity of one or more additional species, such as ions and/or molecules, within the solid form. For example, in particular embodiments, a crystalline multiple-component solid form comprising pomalidomide further comprises one or more species non-covalenily bonded at regular positions in the crystal lattice.

[0045] Unless otherwise specified, the term "crystalline" and related terms used herein, when used to describe a substance, component, product, or form, mean that the substance, component, product, or form is substantially crystalline, for example, as determined by X-ray diffraction. *(see, e.g., Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA, 173 (1990); *The United States Pharmacopeia*, 23rd ed., 1843-1844 (1995)).

|0046] Unless otherwise specified, the term "crystal form," "crystal forms," and related terms herein refer to crystalline modifications comprising a given substance, including single-component crystal forms and multiple-component crystal forms, and including, but not limited to, polymorphs, solvates, hydrates, co-crystals, other molecular complexes, salts, solvates of salts, hydrates of salts, co-crystals of salts, and other molecular complexes of salts, and polymorphs thereof. In some embodiments, a crystal form of a substance may be substantially free of amorphous forms and/or other crystal forms. In other embodiments, a crystal form of a substance may contain less than about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of one or more amorphous form(s) and/or other crystal form(s) on a weight basis. Crystal forms of a substance may be obtained by a number of methods. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, recrystallization in confined spaces such as, *e.g.*, in nanopores or capillaries, recrystallization on surfaces or templates such as, *e.g.*, on polymers, recrystallization in the presence of additives, such as, *e.g.*, co-crystal counter-molecules, desolvation, dehydration, rapid evaporation, rapid cooling, slow cooling, vapor diffusion, sublimation, grinding, and solvent-drop grinding.

[0047] Unless otherwise specified, the terms "polymorph," "polymorphic form," "polymorphs," "polymorphic forms," and related terms herein refer to two or more crystal forms that consist essentially of 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 a different arrangement or conformation of the molecules or ions in the crystal lattice. The differences in physical properties exhibited by polymorphs may 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 a 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).

[0048] Unless otherwise specified, the term "co-crystal," as used herein, refers to a crystal form of a substance which contains at least one additional ingredient. The substance and the additional ingredient(s) interact through non-covalent forces in a crystal lattice.

[0049] Unless otherwise specified, the term "amorphous," "amorphous form," and related terms used herein mean that the substance, component, or product referred to is not substantially crystalline as determined by X-ray diffraction. In certain embodiments, an amorphous form of a substance may be substantially free of crystal forms. In other embodiments, an amorphous form of a substance may contain less than about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% or 50% of one or more crystal forms on a weight basis. In other embodiments, an amorphous form of a

substance may comprise additional components or ingredients (for example, an additive, a polymer, or an excipient that may serve to further stabilize the amorphous form). In some embodiments, amorphous form may be a solid solution. Amorphous forms of a substance can be obtained by a number of methods. Such methods include, but are not limited to, heating, melt cooling, rapid melt cooling, solvent evaporation, rapid solvent evaporation, desolvation, sublimation, grinding, ball-milling, cryo-grinding, spray drying, and freeze drying.

[0050] As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with doses, amounts, or weight percents of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by one of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. In certain embodiments, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 30%, within 20%, within 15%, within 10%, or within 5%, of the specified dose, amount, or weight percent.

[0051] Techniques for characterizing crystal forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), differential scanning caiorimetry (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, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies, and dissolution studies.

[0052] 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 describes 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, for example, 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 solid form. In certain embodiments, the terms "about" and "approximately," when used in this context, indicate that the numeric value or range of values may vary within 30%, 20%, 15%, 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. For example, in some embodiments, the value of an XRPD peak position may vary by up to ±0.2 degrees two theta while still describing the particular XRPD peak.

[0053] As used herein, and unless otherwise specified, a crystalline or amorphous form that is "pure," *i.e.,* substantially free of other crystalline or amorphous forms, contains less than about 10% by weight of one or more other crystalline or amorphous forms, less than about 5% by weight of one or more other crystalline or amorphous forms, less than about 3% by weight of one or more other crystalline or amorphous forms, or less than about 1% by weight of one or more other crystalline or amorphous forms.

[0054] 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 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 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.

[0055] 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 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 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.

[0056J 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 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 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.

[0057] As used herein, and unless otherwise specified, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable, relatively non-toxic acids, including inorganic acids and organic acids. in some embodiments, suitable acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, carbonic, citric, dihydrogenphosphoric, ethenesulfonic, fumaric, galactunoric, gluconic, glucuronic, glutamic, hydrobromic, hydrochloric, hydriodic, isobutyric, isethionic, lactic, maleic, malic, malonic, mandelic, methanesulfonic, monohydrogencarbonic, monohydrogen-phosphoric, monohydrogensulfuric, mucic, nitric, pamoic, pantothenic, phosphoric, phthalic, propionic, suberic, succinic, sulfuric, tartaric, toluenesulfonic acid (including *p*-toluenesulfonic, zn-ioluenesulfonic, and *o*-toluenesulfonic acids), and the like *(see, e.g.,* S. M. Berge *et al, J. Pharm. Set,* 66:1-19 (1977); and *Handbook of Pharmaceutical Salts: Properties, Selection and Use,* P. **H.** Stahl and C. G. Wermuth, Eds., (2002), Wiley, Weinheim). In some embodiments, suitable acids are strong acids *(e.g.,* with pKa less than about 1), including, but not limited to, hydrochloric, hydrobromic, sulfuric, nitric, methanesulfonic, benzene sulfonic, toluene sulfonic, naphthalene sulfonic, naphthalene disuifonic, pyridine-sulfonic, or other substituted sulfonic acids. Also included are salts of other relatively non-toxic compounds that possess acidic character, including amino acids, such as aspartic acid and the like, and other compounds, such as aspirin, ibuprofen, saccharin, and the like. Acid addition salts can be obtained by contacting the neutral form of a compound with a sufficient amount of the desired acid, either neat or in a suitable solvent. As solids, salts can exist in crystalline or amorphous forms, or mixtures thereof. Salts can also exist in polymorphic forms.

[0058] Unless otherwise specified, the terms "solvate" and "solvated," as used herein, refer to a solid form of a substance which contains solvent. The terms "hydrate" and "hydrated" refer to a solvate wherein the solvent is water. "Polymorphs of solvates"

refer to the existence of more than one solid form for a particular solvate composition. Similarly, "polymorphs of hydrates" refer to the existence of more than one solid form for a particular hydrate composition. The term "desolvated solvate," as used herein, refers to a solid form of a substance which can be made by removing the solvent from a solvate. The terms "solvate" and "solvated," as used herein, can also refer to a solvate of a salt, co-crystal, or molecular complex. The terms "hydrate" and "hydrated," as used herein, can also refer to a hydrate of a salt, co-crystal, or molecular complex.

[0059] As used herein, and unless otheiwise specified, the terms "treat," "treating" and "treatment" refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more prophylactic or therapeutic agents to a subject with such a disease or disorder. In some embodiments, the terms refer to the administration of a compound provided herein, with or without other additional active agent, after the onset of symptoms of a particular disease.

[0060] As used herein, and unless otherwise specified, the terms "prevent," "preventing" and "prevention" refer to the prevention of the onset, recurrence or spread of a disease or disorder, or of one or more symptoms thereof. In certain embodiments, the terms refer to the treatment with or administration of a compound provided herein, with or without other additional active compound, prior to the onset of symptoms, particularly to patients at risk of a disease or disorder provided herein. The terms encompass the inhibition or reduction of a symptom of a particular disease. Patients with familial history of a disease in particular are candidates for preventive regimens in certain embodiments. In addition, patients who have a history of recurring symptoms are also potential candidates for the prevention. In this regard, the term "prevention" may be interchangeably used with the term "prophylactic treatment."

[0061] As used herein, and unless otherwise specified, the terms "manage," "managing" and "management" refer to preventing or slowing the progression, spread, or worsening of a disease or disorder, or of one or more symptoms thereof. Often, the beneficial effects that a subject derives from a prophylactic and/or therapeutic agent do not result in a cure of the disease or disorder. In this regard, the term "managing"

encompasses treating a patient who had suffered from the particular disease in an attempt to prevent or minimize the recurrence of the disease or one or more symptoms thereof.

[0062] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or disorder, or to delay or minimize one or more symptoms associated with the disease or disorder. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, that provides a therapeutic benefit in the treatment or management of the disease or disorder. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or disorder, or enhances the therapeutic efficacy of another therapeutic agent.

[0063] As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease or disorder, or one or more symptoms thereof, or prevent the recurrence of the disease or disorder, or one or more symptoms thereof. A prophylactically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other agents, that provides a prophylactic benefit in the prevention of the disease or disorder. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0064] Unless otherwise specified, the term "composition" as used herein is intended to encompass a product comprising the specified ingredient(s) (and in the specified amountis), if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredient(s) in the specified amouni(s). By "pharmaceutically acceptable," it is meant a diluent, exeipient, or carrier in a formulation must be compatible with the other ingredient(s) of the formulation and not deleterious to the recipient thereof.

[0065] Unless otherwise specified, the term "therapeutically and prophylactically effective amount" refers to the amount of the subject solid form that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician or that is sufficient to prevent development of or alleviate to some extent one or more of the symptoms of the disease being treated.

[0066J Unless otherwise specified, the term "subject" is 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 subject is a human.

[0067] As used herein, and unless otherwise specified, the terms "symptom of a hemoglobinopathy" and "symptom of anemia" mean any physiological or biological symptom associated with any hemoglobinopathy or anemia, including, but not limited to, dizziness, shortness of breath, loss of consciousness, tiredness, weakness, hemolysis, pains associated with abnormal hemoglobin, reduced erythrocyte counts *(i.e.*, reduced hematocrit), a reduced ability of a given volume of blood to cany oxygen, as compared with a volume of normal blood, deformities of erythrocytes visible under a microscope, etc. The terms also include negative psychological symptoms such as depression, low self-esteem, perception of illness, perception of limited physical capability, etc.

[0068] The compounds provide herein may also contain an unnatural proportion of an atomic isotope at one or more of the atoms that constitute such a compound. For example, the compound may be radiolabeled with radioacti ve isotopes, such as for example tritium (^{3}H), iodine- 125 (^{125}Γ) sulfur-35 (^{35}S), or carbon- 14 (^{14}C). Radiolabeled compounds are useful as therapeutic agents, *e.g.*, cancer therapeutic agents, research reagents, *e.g.*, binding assay reagents, and diagnostic agents, *e.g.*, *in vivo* imaging agents. All isotopic variations of the compounds provided herein, whether radioactive or not, are intended to be encompassed herein. In certain embodiments, a compound provided herein contains unnatural proportion(s) of one or more isotopes, including, but not limited to, hydrogen (^{1}H), deuterium (^{2}H), tritium (^{3}1T), carbon- 11 (^{11}C), carbon- 12 (^{12}C), carbon- 13 {^{13}C), carbon- 14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen- 15 (^{15}N), oxygen- 14 (^{14}0), oxygen- 15 (^{15}0), oxygen-16 (^{16}0), oxygen- 17 (^{17}0), oxygen- 18 (^{18}O), fluorine- 17 (^{17}¥), fluorine- 18 (^{18}F), phosphorus-3 1 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sultur-32 (^{32}S), sultur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}C1), chlorine-36 (^{36}C1), chlorine-37 (^{37}C1), bromine-79 (^{79}Br), bromine-81 (^{8},Br), iodine-123 (^{123}l), iodine-125 (^{125}I), iodine- 127 (^{127}I), iodine-129 (^{129}I), and iodine-13 1 (^{13},^{1}l). In certain embodiments, a compound provided herein contains unnatural proportion(s) of one or more isotopes in a stable form, that is, non-radioactive, including, but not limited to, hydrogen (^{1}H), deuterium (^{2}H), carbon- 12

(^{12}C), carbon-13 (^{13}C), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-16 (^{16}0), oxygen-17 (^{17}0), oxygen-18 (^{18}0), fluorine-17 (^{17}F), phosphorus-31 (^{31}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), suifur-36 (^{36}S), chlorine-35 (^{35}C1), chlorine-37 (^{37}C1), bromine-79 (^{79}Br), bromine-81 (^{81}Br), and iodine-127 (^{127}I). In certain embodiments, a compound provided herein contains unnatural proportion(s) of one or more isotopes in an unstable form, that is, radioactive, including, but not limited to, tritium (^{3}H), carbon-11 (^{11}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), oxygen-14 (^{14}0), oxygen-15 (^{15}0), fluorine-18 (^{18}F), phosphorus-32 (^{32}P), phosphorus-33 (^{32}P), sulfur-35 (^{35}S), chlorine-36 (^{36}Ci), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). In certain embodiments, in a compound as provided herein, any hydrogen can be ^{2}H, for example, or any carbon can be ^{13}C, for example, or any nitrogen can be ^{15}N, for example, or any oxygen can be ^{18}0 , for example, where feasible according to the judgment of one of skill. In certain embodiments, a compound provided herein contains unnatural proportions of deuterium (D). In exemplary embodiments, provided herein are isotopologues of pomalidomide, as disclosed in U.S. Provisional Application No. 61/500,053, filed June 22, 2011, which is incorporated by reference herein in its entirety. In one embodiment, provided herein are solid forms *(e.g.,* crysial forms, amorphous forms, or mixtures thereof) of isotopologues of pomalidomide provided herein.

[0069] Unless otherwise specified, to the extent that there is a discrepancy between a depicted chemical structure of a compound provided herein and a chemical name of a compound provided herein, the chemical structure shall control.

5.2 Solid Forms Comprising Pomalidomide

[0070] In one embodiment, provided herein are single-component or multiple-component solid forms *(e.g.,* crystal forms, amorphous forms, or mixtures thereof) comprising pomalidomide, *e.g.,* a solid form of pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, stereoisomer, prodrug, or clathrate thereof. In one embodiment, provided herein are solid forms *(e.g.,* crystal forms, amorphous forms, or mixtures thereof) of a free base of pomalidomide, or a solvate, hydrate, co-crystal, stereoisomer, prodrug, or clathrate thereof. Pomalidomide can be synthesized or obtained according to a method known in the literature or based upon the teachings herein, including the methods described in detail in the examples herein.

[0071] In one embodiment, pomalidomide can be prepared according to methods described in, for example, U.S. Patent Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327; and U.S. Patent Application Publication Nos. 2006/0178402 and 2011/0224440; the entireties of which are incorporated herein by reference.

[0072] In one embodiment, solid forms provided herein may be a crystal form or an amorphous form or mixtures thereof (e.g., mixtures of crystal forms, or mixtures of crystal and amorphous forms), which comprises pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, stereoisomer, prodrug, or clathraie thereof. In one embodiment, provided herein is a crystal form comprising pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, stereoisomer, prodrug, or clathraie thereof. In one embodiment, provided herein is an amorphous form comprising pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, stereoisomer, prodrug, or elathratc thereof. In one embodiment, provided herein is a mixture comprising two or more crystal forms of pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, stereoisomer, prodrug, or clathraie thereof. In one embodiment, provided herein is a mixture comprising a crystal form and an amorphous form of pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, stereoisomer, prodrug, or clathrate thereof.

[0073] Solid forms comprising pomalidomide include: single-component and multiple-component forms, crystal forms comprising pomalidomide, amorphous forms comprising pomalidomide, mixtures of crystal forms comprising pomalidomide, mixtures of crystal and amorphous forms comprising pomalidomide, including, but not limited to, polymorphs, salts, solvates, hydrates, co-crystals, stereoisomers, prodrugs, and clathrates of pomalidomide.

[0074] In one embodiment, provided herein is an unsolvated solid form comprising pomalidomide. In one embodiment, provided herein is an anhydrous solid form comprising pomalidomide. In one embodiment, provided herein is an unsolvated crystal form comprising pomalidomide. In one embodiment, provided herein is an anhydrous crystal form comprising pomalidomide. In one embodiment, provided herein is an unsolvated amorphous form comprising pomalidomide. In one embodiment, provided herein is an anhydrous amorphous form comprising pomalidomide. In one embodiment,

provided herein is a solvated solid form comprising pomalidomide. In one embodiment, provided herein is a hydrated solid form comprising pomalidomide *(e.g.,* a hydrate having a stoichiometric or non-stoichiometric amount of water). Irs one embodiment, provided herein is a hydrated form of pomalidomide, including, but not limited to, a hemihydrate, a monohydrate, a dihydrate, a trihydrate, and the like. In one embodiment, the hydrated form is substantially crystalline. In one embodiment, the hydrated form is substantially amorphous. In one embodiment, the anhydrous form is substantially crystalline. In one embodiment, the anhydrous form is substantially amorphous.

[0075] Solid forms provided herein can be prepared by the methods described herein, or by techniques, including, but not limited to, heating, cooling, freeze drying, spray drying, lyophiiization, quench cooling the melt, rapid solvent evaporation, slow solvent evaporation, solvent recrystaliization, antisolvent addition, slurry recrystaliization, crystallization from the melt, desolvation, recrystaliization in confined spaces, such as, *e.g.,* in nanopores or capillaries, recrystaliization on surfaces or templates, such as, *e.g.,* on polymers, recrystaliization in the presence of additives, such as, *e.g.,* co-crystal counter-molecules, desolvation, dehydration, rapid cooling, slow cooling, exposure to solvent and/or water, drying, including, *e.g.,* vacuum drying, vapor diffusion, sublimation, grinding (including, *e.g.,* cryo-grinding and solvent-drop grinding), microwave-induced precipitation, sonication-mduced precipitation, laser-induced precipitation, and precipitation from a supercritical fluid. The particle size of the resulting solid forms, which can vary *(e.g.,* from nanometer dimensions to millimeter dimensions), can be controlled, *e.g.,* by varying crystallization conditions, such as, *e.g.,* the rate of crystallization and/or the crystallization solvent system, or by particle-size reduction techniques, *e.g.,* grinding, milling, micronizing, or sonication.

[0076] In another embodiment, provided herein are compositions comprising one or more solid form(s) comprising pomalidomide, for example, a solid form of pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, stereoisomer, prodrug, or clathrate thereof. Also provided herein are compositions comprising: (i) one or more solid form(s) provided herein *(e.g.,* one or more crystal forms, one or more amorphous forms, and mixtures thereof), and (ii) other active ingredient(s). Also provided herein are methods of using these compositions in the treatment, prevention, or management of conditions and disorders including, but not

limited to: cancer, including hematologic cancer or solid tumor, for example, multiple myeloma, leukemia, lymphoma, sarcoma, prostate cancer, or small cell lung cancer; scleroderma; amyloidosis; pain; myelofibrosis; myeloproliferative disease, *e.g.,* MMM; myelodysplastic syndromes; diffuse systemic sclerosis; macular degeneration; a skin disease; a pulmonary disorder; an asbestos-related disorder; a parasitic disease; an immunodeficiency disorder; a CNS disorder; a CNS injury; atherosclerosis; hemoglobinopathy; anemia, *e.g.,* sickle cell anemia; an inflammatory disease; an autoimmune disease; a viral disease; a genetic disease; an allergic disease; a bacterial disease; an ocular neovascular disease; a choroidal neovascular disease; a retina neovascular disease; and mbeosis.

[0077] While not intending to be bound by any particular theory, certain solid forms provided herein exhibit physical properties, *e.g.,* stability, solubility and/or dissolution rate, appropriate for use in clinical and therapeutic dosage forms. Moreover, while not wishing to be bound by any particular theory, certain solid forms provided herein exhibit physical properties, *e.g.,* crystal morphology, compressibility and/or hardness, suitable for manufacture of a solid dosage form. In some embodiments, such properties can be determined using techniques such as X-ray diffraction, microscopy, IR spectroscopy and thermal analysis, as described herein and known in the art.

5.2.1 Form A of Pomaiidomide

[0078] Certain embodiments herein provide solid forms comprising pomaiidomide. In one embodiment, provided herein is a solid form of pomaiidomide that is substantially crystalline. In one embodiment, provided herein is a crystal form of pomaiidomide. In one embodiment, provided herein is a solid form of pomaiidomide comprising crystalline pomaiidomide. In one embodiment, provided herein is a solid form of pomaiidomide comprising an amorphous form of pomaiidomide. In one embodiment, provided herein is a solid form of pomaiidomide comprising a crystal form and an amorphous form of pomaiidomide. In one embodiment, provided herein is a solid form of pomaiidomide comprising two or more crystal forms of pomaiidomide.

[0079] In certain embodiments, provided herein are solid forms of pomaiidomide that can be designated herein as Form A. Provided herein are various embodiments, preparations, or modifications of Form A.

[0080] In certain embodiments, Form A can be obtained by crystallization from certain solvent systems, for example, solvent systems comprising one or more of the following solvents or solvent combinations: acetonitrife, methyl ethyl ketone (MEK), tetrahydrofuran (THF), and tetrahydrofuraMieptane. Other examples of solvent systems are provided herein elsewhere. In certain embodiments, a solid form provided herein *(e.g.* . Form A) can be obtained by slurry crystallization, evaporation crystallization, cooling crystallization, and precipitation crystallization.

[0081] In certain embodiments, slurry crystallization is effected by adding solvent or solvent mixtures to a solid substrate, and the slurry is stirred, and optionally heated to various temperatures. In certain embodiments, the slurry is heated at about 25 °C, about 50 °C, about 80 °C, or about 100 °C. In certain embodiments, upon heating and cooling, the residual solvents of the slurry can be removed by wicking, or other suitable methods, such as filtration, centrifugation, or decantation, and the crystals can be dried in air or under vacuum.

[0082] In certain embodiments, evaporation crystallization is effected by adding a solvent or solvent mixture to a solid substrate, and allowing the solvent or solvent mixture to evaporate under ambient conditions. In certain embodiments, the residual solvent can be removed by wicking, or other suitable methods, such as filtration, centrifugation, or decantation, and the crystals can be dried in air or under vacuum.

[0083] In certain embodiments, precipitation crystallization is effected by adding a solvent or solvent mixture to a solid substrate, and subsequently adding an anti-solvent. In certain embodiments, the resultant mixture stands for a period of time, *e.g.* , overnight, and under certain conditions, for example at room temperature. In certain embodiments, the residual solvent can be removed by wicking, or other suitable methods, such as filtration, centrifugation, or decantation, and the crystals can be dried in air or under vacuum.

[0084] In certain embodiments, cooling crystallization is effected by adding a solvent or solvent mixture to a solid substrate at elevated temperature, and allowing the resultant mixture to stand for a period of time at a reduced temperature. In certain embodiments, the elevated temperature is, for example, about 30 °C, about 40 °C, about 50 °C, about 60 °C, about 70 °C, or about 80 °C. In certain embodiments, the reduced temperature is, for example, about 15 °C, about 10 °C, about 5 °C, about 0 °C, about -5 °C, about

-10 °C, about -15 °C, or about -20 °C. The residual solvent can be removed by wicking, or other suitable methods, such as filtration, centrifugation, or decantation, and the crystals can be dried in air or under vacuum.

[0085] 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, representative XRPD patterns of various embodiments of Form A are provided in FIGS, 1-6 and 25-27. In one embodiment, provided herein is a crystalline pomalidomide having an XRPD pattern corresponding substantially to the representative XRPD pattern depicted in Figure 1. In one embodiment, provided herein is a crystalline pomalidomide having an XRPD pattern corresponding substantially to the representative XRPD pattern depicted in Figure 2. In one embodiment, provided herein is a crystalline pomalidomide having an XRPD pattern corresponding substantially to the representative XRPD pattern depicted in Figure 3. In one embodiment, provided herein is a crystalline pomalidomide having an XRPD pattern corresponding substantially to the representative XRPD pattern depicted in Figure 4. In one embodiment, provided herein is a crystalline pomalidomide having an XRPD pattern corresponding substantially to the representative XRPD pattern depicted in Figure 5. In one embodiment, provided herein is a crystalline pomalidomide having an XRPD pattern corresponding substantially to the representative XRPD pattern depicted in Figure 6. In one embodiment, provided herein is a crystalline pomalidomide having an XRPD pattern corresponding substantially to the representative XRPD pattern depicted in Figure 2.5. In one embodiment, provided herein is a crystalline pomalidomide having an XRPD pattern corresponding substantially to the representative XRPD pattern depicted in Figure 26. In one embodiment, provided herein is a crystalline pomalidomide having an XRPD pattern corresponding substantially to the representative XRPD pattern depicted in Figure 27.

[0086] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, seven, eight, nine, ten, or greater than ten peaks) selected from peaks located at the following approximate positions: 12.1, 14.0, 16.2, 17.4, 18.4, 19.3, 20.1, 23.0, 24.4, 24.8, 25.6, 26.9, 28.1, and 29.2 degrees 2Θ. In some embodiments, provided herein is a crystalline pomalidomide characterized by any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of XRPD peaks

selected from peaks located at the following approximate positions: 12.1, 14.0, 16.2, 17.4, 18.4, 19.3, 20.1, 23.0, 24.4, 24.8, 25.6, 26.9, 28.1, and 29.2 degrees 2Θ.

[0087] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, seven, eight, nine, ten, or greater than ten peaks) selected from peaks located at the following approximate positions: 12.15, 14.0, 16.25, **17.4,** 18.45, 19.25, 20.05, 22.95, 24.4, 24.85, 25.6, 26.95, 28.05, and 29.2 degrees 2Θ. In some embodiments, provided herein is a crystalline pomalidomide characterized by any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of XRPD peaks selected from peaks located at the following approximate positions: 12.15, 14.0, 16.25, 17.4, 18.45, 19.25, 20.05, 22.95, 24.4, 24.85, 25.6, 26.95, 28.05, and 29.2 degrees 2Θ.

[0088] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, seven, or eight peaks) selected from peaks located at the following approximate positions: 12.1, 14.0, 17.4, 18.4, 24.4, 24.8, 25.6, and 28.1 degrees 2Θ. In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, seven, or eight peaks) selected from peaks located at the following approximate positions: 12.15, 14.0, 17.4, 18.45, 24.4, 24.85, 25.6, and 28.05 degrees 2Θ.

[0089] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, seven, or eight peaks) selected from peaks located at the following approximate positions: 12.1, 14.0, 17.4, 18.4, 23.0, 24.4, 25.6, and 28.1 degrees 2Θ. **In** some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, seven, or eight peaks) selected from peaks located at the following approximate positions: 12.15, 14.0, 17.4, 18.45, 22.95, 24.4, 25.6, and 28.05 degrees 2Θ.

[0090] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, or seven peaks) selected from peaks located at the following approximate positions: 12.1, 14.0, 17.4, 18.4, 24.4, 25.6, and 28.1 degrees 2Θ. In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two,

three, four, five, six, or seven peaks) selected from peaks located at the following approximate positions: 12.15, 14.0, 17.4, 18.45, 24.4, 25.6, and 28.05 degrees 2Θ.

[0091] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, or seven peaks) selected from peaks located at the following approximate positions: 12.1, 14.0, 17.4, 18.4, 23.0, 24.4, and 25.6 degrees 2Θ. Irs some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks (e.g., one, two, three, four, five, six, or seven peaks) selected from peaks located at the following approximate positions: 12.15, 14.0, 17.4, 18.45, 22.95, 24.4, and 25.6 degrees 2Θ.

[0092] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, or four peaks) selected from peaks located at the following approximate positions: 12.1, 17.4, 24.4, and 25.6 degrees 20. In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, or four peaks) selected from peaks located at the following approximate positions: 12.15, 17.4, 24.4, and 25.6 degrees 2Θ.

[0093] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, or four peaks) selected from peaks located at the following approximate positions: 12.1, 17.4, 25.6, and 28.1 degrees 20. In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, or four peaks) selected from peaks located at the following approximate positions: 12.15, 17.4, 25.6, and 28.05 degrees 2Θ.

[0094] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, or three peaks) selected from peaks located at the following approximate positions: 12.1, 17.4, and 25.6 degrees 2Θ. In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, or three peaks) selected from peaks located at the following approximate positions: 12.15, 17.4, and 25.6 degrees 2Θ.

[0095] In some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, or three peaks) selected from peaks located at the following approximate positions: 12.1, 17.4, and 24.4 degrees 2Θ. In

some embodiments, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, or three peaks) selected from peaks located at the following approximate positions: 12.15, 17.4, and 24.4 degrees 2Θ.

[0096] In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 12, 17, and 26 degrees 2Θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 12.1, 17.4, and 25.6 degrees 2Θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 14, 18, and 24 degrees 2Θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 14, 18, and 25 degrees 2Θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 14.0, 18.4, and 24.4 degrees 2Θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 14.0, 18.4, and 24.8 degrees 2Θ. In certain embodiments, provided herein is a crysialline pomalidomide characterized by XRPD peaks located at the following approximate positions: 14, 18, 24, and 25 degrees 2Θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 14.0, 18.4, 24.4, and 24.8 degrees 2Θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 12, 14, 17, 18, 24, and 26 degrees 2Θ. In certain embodiments, provided herein is a crysialline pomalidomide characterized by XRPD peaks located at the following approximate positions: 12, 14, 17, 18, 25, and 26 degrees 2Θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 12.1, 14.0, 17.4, 18.4, 24.4, and 25.6 degrees 2θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 12.1, 14.0, 17.4, 18.4, 24.8, and 25.6 degrees 2Θ. In certain embodiments, provided herein is a crysialline pomalidomide characterized by XRPD peaks located at the following approximate positions: 12.1, 14.0, 17.4, 18.4, 24.4, 24.8, and 25.6 degrees 2Θ. In certain

embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 12.1, 14.0, 17.4, 18.4, 24.4, 24.8, 25.6, and 28.1 degrees 2Θ. In certain embodiments, provided herein is a crystalline pomalidomide characterized by XRPD peaks located at the following approximate positions: 12.1, 14.0, 17.4, 18.4, 20.1, 23.0, 24.4, 24.8, 25.6, 28.1, and 29.2 degrees 2Θ.

[0097] In one embodiment, provided herein is a crystalline pomalidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, seven, eight, nine, ten, or greater than ten peaks) selected from peaks located at the approximate positions *(e.g.,* ± 0.2 degrees 2Θ) as listed in Table 1.

Table 1

Peak No.	Approximate Peak Position (° 2θ)	Peak Intensity
1	12.15	121.995
2	14.00	93.465
3	16.25	57.345
4	17.40	160.614
5	18.45	107.439
6	19.25	40.401
7	20.05	48.110
8	22.95	56.442
9	24.40	108.833
10	24.85	95.511
11	25.60	223.093
12	26.95	52.851
13	28.05	118.675
14	29.20	64.837

[0098] Certain embodiments of Form A exhibit an XRPD pattern corresponding to the representative XRPD of any one of FIGS. 1, 2, 3, 4, 5, 6, 25, 26, and 27.

[0099] In one embodiment, provided herein is a crystalline pomalidomide *(e.g.,* Form A) having a particular crystal morphology. In one embodimeni, birefringence

images depicting certain pomalidomide crystals are provided in FIGS. 7-9. In one embodiment, birefringence images depicting various embodiments of Form A are provided in FIGS. 7-9. In one embodiment, pomalidomide crystals have a morphology substantially similar to that of the crystals depicted in any one of FIGS. 7, 8, and 9. In some embodiments, pomalidomide crystals are of approximately the same size as the crystals depicted in any one of **FIGS.** 7, 8, and 9.

[00100] In one embodiment, provided herein is a crystalline pomalidomide having thermal characteristics corresponding substantially to the representative thermal characteristics depicted in FIGS. 10, 11, 12, 13, 14, **15,** 16, and **17.** In one embodiment, representative thermal characteristics of various embodiments of Form A are provided in FIGS. 10, 11, 12, 13, 14, 15, 16, and 17.

[00101] In one embodiment, provided herein is a crystalline pomalidomide having a DSC thermograms corresponding substantially to the representative DSC thermograms depicted in FIGS. 10, 11, 12, 13, 14, 15, and 16. In one embodiment, representative DSC thermograms of various embodiments of Form A are presented in FIGS. **10,** 11, 12, 13, 14, 15, and 16.

[00102] In one embodiment, provided herein is a crystalline pomalidomide having a DSC thermogram comprising an endothermic event with a maximum at about 320 °C when heated from approximately 25 °C to approximately 350 °C *(e.g.,* a DSC thermogram comprising an endotherm with a maximum at about 317.60 °C, about 318.62 °C, about 319.16 °C, about 319.35 °C, about 319.87 °C, about 320.02 °C, about 320.08 °C, about 320.46 °C, or about 320.83 °C). In one embodiment, provided herein is a crystalline pomalidomide having a DSC thermogram comprising an endothermic event with a maximum at about 318 °C *(e.g.,* when heated from approximately 25 °C to approximately 350 °C). In one embodiment, provided herein is a crystalline pomalidomide having a DSC thermogram comprising an endothermic event with a maximum at about 319 °C *(e.g.,* when heated from approximately 25 °C to approximately 350 °C). In one embodiment, provided herein is a crystalline pomalidomide having a DSC thermogram comprising an endothermic event with a maximum at about 320 °C *(e.g.,* when heated from approximately 25 °C to approximately 350 °C). In one embodiment, provided herein is a crystalline pomalidomide having a DSC thermogram comprising an endothermic event with a

maximum at about 321 °C *(e.g.,* when heated from approximately 25 °C to approximately 350 °C). In one embodiment, provided herein is a crystalline pomalidomide having a DSC thermogram comprising an onset of melting at about 319 °C. In one embodiment, provided herein is a crystalline pomalidomide having a DSC thermogram indicative of a crystalline, unsolvaied material.

[00103] In one embodiment, provided herein is a crystalline pomalidomide having a TGA thermograph corresponding substantially to the representative TGA thermogram depicted in FIG. **17.** In one embodiment, a representative TGA thermogram of one embodiment of Form A is presented in FIG. **17.** In certain embodiments, provided herein is a crystalline pomalidomide having a mass loss of less than approximately 1% of the total mass of the sample between the temperatures of approximately 25 °C to approximately 200 °C when heated from approximately 25 °C to approximately 350 °C. In certain embodiments, provided herein is a crystalline pomalidomide having a mass loss of less than about 0.001% of the total mass of the sample between the temperatures of approximately 25 °C to approximately 150 °C when heated from approximately 25 °C to approximately 300 °C. In certain embodiments, provided herein is a crystalline pomalidomide having a mass loss of less than 1%, less than 0.9%, less than 0.8%, less than 0.7%, less than 0.5%, less than 0.4%, less than 0.3%, less than 0.2%, less than 0.1%, less than 0.05%, less than 0.01%, less than 0.005%, or less than 0.001% of the total mass of the sample between the temperatures of approximately 25 °C to approximately 200 °C when heated from approximately 25 °C to approximately 350 °C. In one embodiment, provided herein is a crystalline pomalidomide *(e.g.,* Form A) that does not contain substantial amounts of solvent *(e.g.,* water). In one embodiment, provided herein is a crystalline pomalidomide *(e.g.,* Form A) that does not contain substantial amounts of solvent *(e.g.,* water) in the crystal lattice.

[00104] In certain embodiments, provided herein is a crystalline pomalidomide substantially free of solvent and water in the crystal lattice, as determined, *e.g.,* via thermal analysis (such as, *e.g.,* TG Analysis, TG-IR analysis, or TG-MS analysis), titration analysis for water content (such as, *e.g.,* via volumetric or coulometric Karl Fischer titration), spectroscopic analysis (such as, *e.g.,* NMRj, elemental analysis (such as, *e.g.,* combustion analysis), or crystal structure analysis (such as, *e.g.,* single-crystal X-ray diffraction). In certain embodiments, provided herein is an anhydrous crystal form

comprising pomaiidomide. In certain embodiments, provided herein is an unsolvated crystal form comprising pomaiidomide.

[00105] In one embodiment, provided herein is a crystalline pomaiidomide having a structure corresponding substantially to the representative single-crystal X-ray structure depicted in FIGS. 19 and 20. In one embodiment, provided herein is one embodiment of Form A having a structure corresponding substantially to the representative single-crystal X-ray structure depicted in **FIGS. 19** and **20.** In one embodiment, the single X-ray data of a crystalline pomaiidomide provided herein may be used to simulate a representative XRPD pattern of crystalline pomaiidomide, as depicted in **FIG. 21.** In one embodiment, provided herein is a crystalline pomaiidomide characterized by one or more XRPD peaks *(e.g.,* one, two, three, four, five, six, seven, eight, nine, or greater than nine peaks) selected from peaks located at the approximate positions as listed in Table 2.

Table 2

Peak No.	Approximate Peak Position (° 2θ)	Relative Peak Intensity
C	12.379	50.843
I	12.791	19.074
D	14.109	44.921
H	17.028	29.767
B	17.489	60.259
G	24.503	36.754
F	24.904	37.803
A	25.738	100.000
E	28.254	43.584

[00106] In one embodiment, provided herein is a crystalline pomaiidomide having an IR spectrum corresponding substantially to the representative IR spectrum depicted in FIG. 22. In one embodiment, provided herein is one embodiment of Form A having an IR spectrum corresponding substantially to the representative IR spectrum depicted in **FIG. 22.**

[00107] In one embodiment, provided herein is a crystalline pomaiidomide having a DVS isotherm plot corresponding substantially to the representative DVS isotherm plot

depicted in FIGS. 23 and 24. In one embodiment, provided lierein is one embodiment of Form A having a DVS isotherm plot corresponding substantially to the representative DVS isotherm plot depicted in FIGS. 23 and 24.

[00108] In certain embodiments, provided herein is an anhydrous crystal form comprising pomalidomide, characterized by one or more XRPD peaks as provided herein elsewhere. In certain embodiments, provided herein is an anhydrous crystal form comprising pomalidomide, having one or more representative XRPD patterns as provided herein elsewhere. In certain embodiments, provided herein is an unsolvated crystal form comprising pomalidomide, characterized by one or more XRPD peaks as provided herein elsewhere. In certain embodiments, provided herein is an unsolvated crystal form comprising pomalidomide, having one or more representative XRPD patterns as provided herein elsewhere.

[00109] In certain embodiments, provided herein is a crystalline pomalidomide *(e.g.* , Form A) that is substantially physically pure. For example, in certain embodiments, a crystalline pomalidomide provided herein *(e.g.* , Form A) is substantially free of other solid forms, including other solid forms comprising pomalidomide *(e.g.* , crystal forms or amorphous forms comprising pomalidomide), as determined, *e.g.* , using methods of solid-state analysis including, but not limited to, diffraction analysis, thermal analysis, elemental combustion analysis and/or spectroscopic analysis. In certain embodiments, provided herein is a crystalline pomalidomide *(e.g.,* Form A) that is substantially chemically pure. For example, in certain embodiments, a crystalline pomalidomide provided herein *(e.g.* , Form A) is substantially free of other chemical compounds, as determined, *e.g.* , using methods of chemical analysis including, but not limited to, mass spectrometry analysis, spectroscopic analysis, thermal analysis, elemental combustion analysis, and/or chromatographic analysis. In certain embodiments, a crystalline pomalidomide provided herein *(e.g.,* Form A) is substantially free of solvent. In certain embodiments, a crystalline pomalidomide provided herein *(e.g.,* Form A) is substantially free of water. In certain embodiments, provided herein is a crystalline pomalidomide *(e.g.* , Form A) that is substantially chemically pure and substantially physically pure.

[00110] In one embodiment, provided herein is a mixture comprising a crystalline pomalidomide *(e.g.* , Form A) and an amorphous pomalidomide. In one embodiment, provided herein is a solid form of pomalidomide comprising a crystalline pomalidomide

(e.g., Form A) and amorphous pomalidomide. In certain embodiment, provided herein is a solid form of pomalidomide comprising a crystalline pomalidomide *(e.g.,* Form A) and amorphous pomalidomide, which is about 1%, about *2%,* about 3%, about 4%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, or about 99% by weight crystalline. In certain embodiment, provided herein is a solid form of pomalidomide comprising a crystalline pomalidomide *(e.g.,* Form A) and amorphous pomalidomide, which is greater than about 1%, greater than about 2%, greater than about 3%, greater than about 4%, greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 25%, greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99% by weight crystalline. In certain embodiment, provided herein is a solid form of pomalidomide comprising a crystalline pomalidomide *(e.g..* Form A) and amorphous pomalidomide, which is greater than about 95% by weight crystalline. In certain embodiment, provided herein is a solid form of pomalidomide comprising a crystalline pomalidomide *(e.g.,* Form A) and amorphous pomalidomide, which is greater than about 97%> by weight crystalline. In certain embodiment, provided herein is a solid form of pomalidomide comprising a crystalline pomalidomide *(e.g.,* Form A) and amorphous pomalidomide, which is greater than about 99% by weight crystalline.

[00111] In certain embodiments, provided herein is a mixture of solid forms comprising a crystalline form provided herein *(e.g.* , Form A) and one or more other crystalline form(s) of pomalidomide. In certain embodiments, provided herein is a mixture of solid forms comprising a crystalline form provided herein *(e.g.,* Form A) and amorphous pomalidomide.

[00112] In one embodiment, provided herein is a Form A that is greater than 50% by weight crystalline. In certain embodiments, Form A is greater than 50%, greater than

60%, greater than 70%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 97%, greater than 98%», or greater than 99% by weight crystalline.

[00113] In one embodiment, provided herein is a crystalline pomalidomide that is prepared by a method described herein. In one embodiment, provided herein is a Form A that is prepared by a method described herein.

5.2.2 Amorphous Forms **of Pomalidomide**

[00114] In certain embodiments, provided herein is pomalidomide in an amorphous form. In certain embodiments, provided herein are stable amorphous forms of pomalidomide *(e.g.,* does not undergo significant physical form change after storage for a certain period of time or after formulation processing or handling).

[00115] In certain embodiments, an amorphous form of pomalidomide can be obtained from certain aqueous and/or organic solvent systems, as exemplified herein elsewhere. In certain embodiments, an amorphous form of pomalidomide can be obtained by slurry methods, evaporation methods, cooling methods, and precipitation methods.

[0Θ116] In one embodiment, an amorphous form of pomalidomide provided herein is a stable amorphous form *(e.g.,* does not undergo significant change in physical form after storage over a certain period of time, *e.g.,* after 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, or more weeks, under conditions, including, but not limited to, humidity, heat, exposure to light, or combinations thereof; or after formulation processing or handling; as measured by a method for characterizing solid forms described herein).

[00117] In one embodiment, provided herein is a solid form of pomalidomide that is substantially amorphous *(i.e.,* an amorphous form), as indicated by, *e.g.,* X-ray powder diffraction measurements. In one embodiment, a representati ve XRPD pattern of an amorphous form is provided in FIG. 18. In certain embodiments, an amorphous form of pomalidomide is characterized by no sharp or distinguishable XRPD peaks. In some embodiments, an amorphous form of pomalidomide is characterized by a broad hump. In some embodiments, an amorphous form of pomalidomide is characterized by a broad hump with a global maximum at approximately 26 degrees 20. In some embodiments, an amorphous form of pomalidomide is characterized by a broad hump with a global

maximum at approximately 26 degrees 2Θ, and optionally a local maximum at approximately 12 degrees 2Θ.

[00118] In certain embodiments, an amorphous form of pomalidomide provided herein is substantially physically pure. For example, in certain embodiments, an amorphous form is substantially free from other solid forms, including other solid forms comprising pomalidomide *(e.g.,* crystal forms), as determined, *e.g.,* using methods of solid-state analysis including, but not limited to, diffraction analysis, thermal analysis, elemental combustion analysis and/or spectroscopic analysis. In certain embodiments, an amorphous form provided herein is substantially chemically pure. For example, in certain embodiments, an amorphous form provided herein is substantially free from other chemical compounds, as determined, *e.g.,* using methods of chemical analysis including, but not limited to, mass spectrometry analysis, spectroscopic analysis, thermal analysis, elemental combustion analysis, and/or chromatographic analysis. In certain embodiments, an amorphous form provided herein is substantially free of water. In certain embodiments, an amorphous form provided herein is substantially free of solvent. In certain embodiments, an amorphous form provided herein is substantially chemically pure and substantially physically pure.

[00119] In one embodiment, provided herein is a mixture comprising an amorphous form comprising pomalidomide and one or more solid form(s) comprising pomalidomide. In one embodiment, provided herein is a solid form of pomalidomide comprising amorphous pomalidomide and one or more crystal form(s) of pomalidomide. In certain embodiment, provided herein is a solid form of pomalidomide comprising amorphous pomalidomide, wherein the solid form is about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, or about 99% by weight amorphous *(e.g.,* non-crystalline). In certain embodiment, provided herein is a solid form of pomalidomide comprising amorphous pomalidomide, wherein the solid form is greater than about 50%, greater than about 55%, greater than about 60%, greater than about 65%, greater than about 70%, greater than about 75%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99% by weight amorphous. In certain embodiment, provided herein is a solid form of pomalidomide comprising

amorphous pomalidomide, wherein the solid form is greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, or greater than about 99%> by weight amorphous.

[00120] In certain embodiments, provided herein is a mixture of solid forms of pomalidomide comprising amorphous pomalidomide.

[00121] In one embodiment, provided herein is an amorphous pomalidomide that is greater than 50% by weight amorphous. In certain embodiments, an amorphous pomalidomide provided herein is greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 97%, greater than 98%, or greater than 99% by weight amorphous.

[00122] In one embodiment, provided herein is an amorphous form of pomalidomide that is prepared by a method described herein.

5.3 Methods of Treatment, Prevention and Management

[00123] Provided herein are methods of treating, preventing, and/or managing various diseases or disorders using a solid form provided herein. In certain embodiments, provided are methods of treating, managing, and preventing various diseases and disorders, which comprise administering to a patient in need of such treatment, prevention or management a therapeutically or propliylacticaily effective amount of a solid form provided herein. Examples of diseases and disorders are described herein.

[00124] Examples of diseases or disorders include, but are not limited to: cancer, including hematologic cancer or solid tumor, for example, multiple myeloma, leukemia, lymphoma, sarcoma, prostate cancer, or lung cancer *(e.g.,* small ceil lung cancer); scleroderma; amyloidosis; pain, for example, complex regional pain syndrome (CRPS); myelofibrosis; myeloproliferative disease, for example, MMM; myelodysplastic syndromes (MDS); diffuse systemic sclerosis; macular degeneration; a skin disease; a pulmonary disorder; an asbestos-related disorder; a parasitic disease; an immunodeficiency disorder; a CNS disorder; a CNS injury; atherosclerosis; hemoglobinopathy; anemia, for example, sickle cell anemia; an inflammatory disease; an autoimmune disease; a viral disease; a genetic disease; an allergic disease; a bacterial disease; an ocular neovascular disease; a choroidal neovascular disease; a retina

neovascular disease; rubeosis; a sleep disorder; disorders associated with angiogenesis; and TNFa related disorders.

[00125] Examples of cancer and precancerous conditions include, but are not limited to, those described in U.S. patent nos. 6,281,230 and 5,635,517 to Muller *et ah,* in various U.S. patent publications to Zeidis, including publication nos. 2004/0220 144A1, published November 4, 2004 (Treatment of Myelodysplastic Syndrome); 2004/0029832A1, published February 12, 2004 (Treatment of Various Types of Cancer); and 2004/0087546, published May 6, 2004 (Treatment of Myeloproliferative Diseases). Examples also include those described in WO 2004/103274, published December 2, 2004. All of these references are incorporated herein in their entireties by reference.

[00126] Other examples of diseases or disorders include, but are not limited to, those described in U.S. Patent Nos. 5,712,291, 7,393,863, and 7,863,297; and U.S. Patent Application Publication Nos. 2005/0143420, 2006/0166932, 2006/0188475, 2007/0048327, 2007/0066512, 2007/0155791, 2008/0051431, 2008/0317708, 2009/0087407, 2009/0088410, 2009/0148853, 2009/0232776, 2009/0232796, 2009/0317385, 2010/0098657, 2010/009971 1, and 2011/0184025; ail of which are incorporated herein by reference in their entireties.

[00127] In one embodiment is provided a method of treating, preventing and/or managing a disease provided herein, comprising administering to a patient in need of such treatment, prevention and/or management a therapeutically or prophylactically effective amount of a solid form of pomalidomide as described herein and a therapeutically or prophylactically effective amount of a second active agent.

[00128] Examples of second active agents include, but are not limited to, cytokines, corticosteroids, ribonucleotide reductase inhibitors, platelet inhibitors, all-trans retinoic acids, kinase inhibitors, topoisomerase inhibitors, farnesyl transferase inhibitors, antisense oligonucleotides, vaccines, anti-cancer agents, anti-fungal agents, anti-inflammatory agents, immunosuppressive or myelosuppressive agents, and conventional therapies for MPD *(e.g.,* prednisone). Specific second active agents include, but are not limited to, 2-methoxyestradiol, telomestatin, inducers of apoptosis in mutiple myeloma cells (such as, for example, TRAIL), statins, semaxanib, cyclosporin, etanercept, doxycycline, bortezomib, oblimersen (Genasense*), remicade, docetaxel, celecoxib, rnelphalan, dexamethasone (Decadron ®), steroids, gemcitabine, cisplatinum,

temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadei, tamoxifen, topotecan, methotrexate, Ansa*', taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha *(e.g.,* PEG 1NTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxoi, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), pacfitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emeyt®), sulindac, etoposide, and a mixture thereof. In one embodiment, specific second active agent is dexamethasone.

[00129] Certain examples of cancer include, but are not limited to, cancers of the skin, such as melanoma; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectum; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal passages; and AIDS-related cancers. The solid forms are also useful for treating cancers of the blood and bone marrow, such as multiple myeloma and acute and chronic leukeniias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukeniias. The solid forms provided herein can be used for treating, preventing, or managing either primary or metastatic tumors.

[00130] Other cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastases, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B~ Cell lymphoma, low grade follicular lymphoma, metastatic melanoma, focalized melanoma (including, but not limited to, ocular melanoma), malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive,

hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unresectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistance to chemotherapy or radiation.

[00131] In one embodiment is provided a method of treating, preventing, or managing myeloproliferative disease (MPD), comprising administering to a patient in need of such treatment, prevention, or management a therapeutically or prophyketieaily effective amount of a solid form of pomalidomide as described herein. The embodiment encompasses the treatment, prevention or management of specific sub-types of MPD such as, but not limited to, polycythemia rubra vera (PRV), primary t!irornoboeythemia (PT), myelofibrosis with myeloid metaplasia. (MMM) and agnogenic myeloid metaplasia (AMM). In one embodiment, MPD includes: polycythemia rubra vera (PRV), primary thromobocythemia (PT), and agnogenic myeloid metaplasia (AMM). In a specific embodiment, MPD excludes leukemia. In one embodiment, particular types of MPD are MMM, PRV, PT, and AMM.

[00132] In one embodiment, a solid form of pomalidomide is administered to patients who are refractor}' to conventional treatments for myeloproliferative diseases as well as treatments using thalidomide. As used herein, the term "refractory" means the patient's response to a MPD treatment is not satisfactory by clinical standards, *e.g.,* showing no or little improvement of symptoms or laboratory findings.

[00133] In one embodiment is provided a method of reversing, reducing, or avoiding an adverse effect associated with the administration of an active agent used to treat MPD in a patient suffering from MPD, comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of a solid form of pomalidomide as described herein. Examples of active agents include, but are not limited to, the second active agents described herein *(see* paragraph [00128] *supra).*

[00134] Examples of adverse effects associated with active agents used to treat MPD include, but are not limited to: conversion to acute leukemia; severe myelosuppression;

gastrointestinal toxicity such as, but not limited to, early and late-forming diarrhea and flatulence; gastrointestinal bleeding; nausea; vomiting; anorexia; leukopenia; anemia; neutropenia; asthenia; abdominal cramping; fever; pain; loss of body weight; dehydration; alopecia; dyspnea; insomnia; dizziness; mucositis; xerostomia; mucocutaneous lesions; and kidney failure.

[00135] In one embodiment, provided herein is a method of treating, preventing, or managing MPD, comprising administering to a patient *(e.g.,* a human) a solid form of pomalidomide as described herein, before, during, or after transplantation therapy.

[00136] In one embodiment, provided herein are pharmaceutical compositions, single unit dosage forms, and kits, comprising a solid form of pomalidomide as described herein, a second active ingredient, and/or blood or cells for transplantation therapy. For example, a kit may comprise a solid form of pomalidomide as described herein, stem cells for transplantation, an immunosuppressive agent, and an antibiotic or other drug.

[00137] In one embodiment, provided herein is a method of modulating the differentiation of $CD34^+$ stem, precursor, or progenitor ceils to a predominantly erythroid lineage, comprising administering to a patient an effective amount of a solid form of pomalidomide as described herein.

[00138] In one embodiment, provided herein is a method of modulating differentiation of a $CD34^+$ cell to an erythroid lineage comprising differentiating said cell under suitable conditions and in the presence of pomalidomide.

[00139] The $CD34^+$ cell may be any stem, progenitor, or committed cell able to differentiate into an eiythroid cell. Such cells may be totipotent or pluripotent, or may be committed to a hematopoietic lineage. The $CD34^+$ ceil may be derived from any source; in particular embodiments, "embryonic-like" stem cells derived from the placenta. For a description of such embryonic-like stem cells and methods of obtaining them, see U.S. application publication no. LIS 2003/0180269 Al, published September 25, 2003, which is incorporated by reference herein in its entirety. Other $CD34^+$ cells useful for the methods provided herein include stem cells obtained from any tissue (such as, for example, hematopoietic stem ceils or embryonic stem cells) and non-committed progenitor cells from any tissue. Such $CD34^+$ cells may be heterologous or autologous with reference to the intended recipient, when such cells, the differentiation of which is

modulated according to the methods provided herein, are used to treat anemia or a hemoglobinopathy.

[00140] Differentiation of the $CD34^+$ cells may typically take place over the course of 3-6 days. In *in vitro* assays in which $CD34^+$ cells are cultured in the presence of pomalidomide, changes in gene expression indicating differentiation along an erythroid pathway may be evident by the third day of culture. In one embodiment, erytbroid-specific gene expression is significantly increased, and phenotypic characteristics of erythroid cells are present in the $CD34^+$ cells by day 6 of culture.

[00141] In one embodiment, therefore, $CD34^+$ cells may be cultured *in vitro* in the presence of pomalidomide, for a period of days sufficient for erythroid-speeific gene expression, particularly fetal hemoglobin gene expression, and/or cell characteristics to appear. In various embodiments, the $CD34^+$ cells may be cultured for 3, 6, 9, or 12 days, or more. A solid form of pomalidomide or a solution thereof may be introduced once at the start of culture, and culturing continued until differentiation is substantially complete, or for 3, 6, 9, 12 or more days. Alternatively, a solid form of pomalidomide or a solution thereof may be administered to a culture of $CD34^+$ cells a plurality of times during culture. The $CD34^+$ cells may be cultured and differentiated in the presence pomalidomide.

[00142] In one embodiment, a solid form of pomalidomide may be used as a solution at any concentration from 0.01 μM to 10 mM. In certain embodiments, the concentration is between 0.01 μM and 10 μM.

[00143] In addition to differentiating $CD34^+$ cells *in vitro*, such cells may be differentiated within an individual, *in vivo*. In one embodiment, such an individual is a mammal, for example a human. As with *in vitro* differentiation of $CD34^+$ cells, $CD34^+$ cells within an individual may be differentiated by administration of a solid form of pomalidomide as described herein. Such administration may be in the form of a single dose. Alternatively, the individual may be administered a solid form of pomalidomide as described herein a plurality of times. Such administration may be performed, for example, over a period of 3, 6, 9, 12, or more days.

[00144] Where differentiation of $CD34^+$ cells is to be accomplished *in vivo*, differentiation may be accomplished using pomalidomide alone, or a combination with a second active agent. For example, for an individual having a hemoglobinopathy such as

sickle ceil anemia or a thalassemia, who has a higher than normal level of SCF and/or erythropoietin, *in vivo* differentiation may be accomplished by administration of a solid form of pomalidomide as described herein. Conversely, where an individual suffers an anemia that is the result of, or is characterized by, a lower-than-normal level of erythropoietic cytokines *(e.g.,* SCF or erythropoietin), such cytokines may be administered along with, or prior to, administration of a solid form of pomalidomide. For example, an individual suffering from chemotherapy-induced anemia may be administered one or more cytokines *(e.g.,* a combination of SCF, Flt-3L, and/or IL-3) for, *e.g.,* 3-6 days, followed by administration for, *e.g.,* 3-6 days, of the solid form of pomalidomide, particularly with SCF and erythropoietin, in an amount sufficient to cause a detectable increase in fetal hemoglobin expression in CD34+ cells of said individual Alternatively, CD34+ cells may be contacted with one or more cytokines *in vitro (e.g.,* SCF, Flt-3L, and/or IL-3) for, *e.g.,* 3-6 days, followed by administration of the cells to an individual, along with SCF and erythropoietin in an amount sufficient to cause a detectable increase in fetal hemoglobin expression in the CD34+ ceils. Such administration may be performed a single time or multiple times, and any one or more of such administrations may be accompanied by the administration of a solid form of pomalidomide, a second active agent, or a combination thereof.

[00145] In one embodiment is provided a method of inducing one or more genes associated with or essential for erythropoiesis or hematopoiesis, comprising contacting an hematopoietic stem, progenitor or precursor cell with pomalidomide in the presence of erythropoietin and stem ceil factor, wherein said pomalidomide is present in a sufficient amount to cause said hematopoietic stem, progenitor or precursor cell to express one or more genes encoding fetal hemoglobin. In a specific embodiment, said hematopoietic stem, progenitor or precursor cell is a $CD34^{+}$ cell. In another specific embodiment, said one or more genes associated with or essential for erythropoiesis or hematopoiesis are genes encoding Kruppel-like factor I erythroid; rhesus blood group-associated glycoprotein; glycophorin B; integrin alpha 2b; erythroid-assoeiated factor; giycophorin A; Kell blood group precursor; hemoglobin a2; solute carrier 4, anion exchanger; carbonic anhydrase hemoglobin γA; hemoglobin yG; hemoglobin ε1; or any combination of the foregoing.

[00146] In some embodiments, the $CD34^+$ cells are additionally differentiated, either *in vivo* or *in vitro,* in the presence of one or more cytokines. Cytokines useful to direct $CD34^+$ cells along an erythroid differentiation pathway include, but are not limited to, erythropoietin (Epo), TNFa, stem cell factor (SCF), Flt-3L, and granulocyte macrophage-colony stimulating factor (GM-CSF). Epo and SCF are known to be erythropoietic cytokines. Thus, in one embodiment, $CD34^+$ cells are differentiated in the presence of Epo or SCF. In another embodiment, the $CD34^+$ cells are differentiated in the presence of Epo and SCF. In another embodiment, the $CD34^+$ cells are differentiated in the presence of a combination of TNFa, SCF, Flt-3L, and/or GM-CSF. In another embodiment, said cells that are differentiated are one or more cells in cell culture. In another embodiment, said cells that are differentiated are cells within an individual. In an embodiment of *in vitro* differentiation, one or more of Epo, TNFa, SCF, Fit-3L and GM-CSF is contacted with pomalidomide. In an embodiment of *in vivo* differentiation, one or more of Epo, TNFa, SCF, Flt-3L and GM-CSF is administered to an individual in the same treatment regimen a the solid form of pomalidomide as provided herein.

|00147] The cytokines used in the methods provided herein may be naturally-occurring cytokines, or may be an artificial derivative or analog of the cytokines. For example, analogs or derivatives of erythropoietin that may be used in combination with a solid form or compound provided herein include, but are not limited to, Aranesp™ and Darbopoietin™.

[0Θ148] Cytokines used may be purified from natural sources or recombinantly produced. Examples of recombinant cytokines that may be used in the methods provided herein include filgrastim, or recombinant granulocyte-colony stimulating factor (G-CSF), which is sold in the United States under the trade name Neupogen® (Amgen, Thousand Oaks, CA); sargramostim, or recombinant GM-CSF, which is sold in the United States under the trade name Leukine© (Immunex, Seattle, WA); recombinant Epo, which is sold in the United States under the trade name Epogen® (Amgen, Thousand Oaks, CA); and methionyl stem cell factor (SCF), which is sold in the United States under the trade name Ancestim™. Recombinant and mutated forms of GM-CSF can be prepared as described in U.S. patent nos. 5,391,485; 5,393,870; and 5,229,496; all of which are incorporated herein by reference. Recombinant and mutated forms of G-CSF can be

prepared as described in U.S. patent nos. 4,810,643; 4,999,291; 5,528,823; and 5,580,755; all of which are **incorporated** herein by reference.

[00149] Other cytokines may be used which encourage the survival and/or proliferation of hematopoietic precursor ceils and immunologically active poietic cells *in vitro* or *in vivo,* or which stimulate the division and differentiation of committed erythroid progenitors **in** cells *in vitro* or *in vivo.* Such cytokines include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-II ("rIL2") and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa~2a, interferon **alfa-2b**, interferon alfa-nl, interferon alfa-n3, interferon **beta-**I a, and interferon gamma-I b; and G-C8F.

[00150] When administered to a person having a hemoglobinopathy, a solid form of pomalidomide as described herein, particulariy in the presence of Epo, particularly in the presence of the combination of TNFa, SCF, **Flt-3L** and GM-CSF, or more particularly in the presence **of Epo** and SCF, induces the production of erythrocytes, and the production of fetal hemoglobin as well as the production of AHSP. As noted above, cytokines used may include purified or recombinant forms, or analogs or derivatives of specific cytokines.

[00151] A solid form of pomalidomide as described herein may also be administered in conjunction with one or more second compounds known to have, or suspected **of** having, a beneficial effect on a hemoglobinopathy. In this context, "beneficial effect" means any reduction of any symptom of a hemoglobinopathy or anemia.

[00152] For example, with specific reference to the hemoglobinopathy sickle cell anemia, the second compound can be a compound, other than a pomalidomide or a derivative thereof, that is known or suspected **to** induce the production of fetal hemoglobin. Such compounds include hydroxyurea, and butyrates or butyrate derivatives. The second compound may also be a compound that relaxes blood vessels, such as nitrous oxide, *e.g.,* exogenously-applied or administered nitrous oxide. The second compound may also be a compound that binds directly to hemoglobin S, preventing it from assuming the sickle-inducing conformation. For example, the plant extract known as HEMOX1N™ (NIPRISAN™; *see* United States Patent No. 5,800,819), which is an extract **of a mixture** of about 12 to about 17 parts by weight *of Piper guineense* seeds, from about 15 to about 19 parts by weight of *Pterocarpus osun* stem,

from about 12 to about 18 parts by weight of *Eugenia caryophyllata* fruit, and from about 25 to about 32 parts by weight of *Sorghum bicolor* leaves, and optionally 15-22 parts by weight potash, wherein the mixture is extracted with cold water, has antisickling activity. The second compound may also be a Gardos channel antagonist. Examples of Gardos channel antagonists include clotrimazole and triaryl methane derivatives. The second compound may also be one that reduces red blood cell adhesion, thereby reducing the amount of clotting pervasive in sickle cell anemia.

[00153] Other hemoglobinopathies may be treated with a second compound known or suspected to be efficacious for the specific condition. For example, β thalassemia may additionally be treated with the second compound Deferoxamine, an iron chelator that helps prevent the buildup of iron in the blood, or folate (vitamin B9). Thalassemia or sickle cell anemia may also be treated with protein C as the second compound (U.S. Patent No. 6,372,213). There is some evidence that herbal remedies can ameliorate symptoms of hemoglobinopathies, *e.g.*, thalassemia; such remedies, and any of the specific active compounds contained therein, may also be used as a second compound in the method provided herein. *See, e.g.*, Wu Zhikui *et al.* "The Effect of Bushen Shengxue Fang on β-thalassemia at the Gene Level," *Journal of Traditional Chinese Medicine* 18(4): 300-303 (1998); U.S. Patent No. 6,538,023 "Therapeutic Uses of Green Tea Polyphenols for Sickle Cell Disease". Treatment of autoimmune hemolytic anemia can include corticosteroids as the second compound.

[00154] Second compounds that are proteins may also be derivatives or analogs of other proteins. Such derivatives may include, but are not limited to, proteins that lack carbohydrate moieties normally present in their naturally occurring forms *(e.g.*, nonglycosylated forms), pegylated derivatives, and fusion proteins, such as proteins formed by fusing IgG1 or IgG3 to the protein or active portion of the protein of interest. *See, e.g.*, Penichei, MX. and Morrison, S.L., *J. Immunol. Methods* 248:91-101 (2001).

[00155] Cytokines and/or other compounds potentially useful in the treatment of anemia or a hemoglobinopathy may be administered at the same time as pomalidomide or a derivative thereof. In this regard, the cytokines or other compounds may be administered as formulations separate from a solid form of pomalidomide, or, where possible, may be compounded with a solid form of pomalidomide for administration as a single pharmaceutical composition. Alternatively, the cytokines, the other compounds,

or both, may be administered separately from a solid form of pomalidomide used in the methods provided herein, and may follow the same or different dosing schedules. In one embodiment, a solid form of pomalidomide, cytokines, and/or any other compound useful to treat anemia or a hemoglobinopathy, are administered at the same time, but in separate pharmaceutical formulations for flexibility in administration.

[00156] In addition to the treatment combinations outlined herein, the treated individual may be given transfusions. Such transfusions may be of blood, for example matched blood, or of a blood substitute such as Hemospan™ or Hemospan™ PS (Sangart).

[00157] In any of the treatment combinations described herein, the treated individual is eukaryotie. In one embodiment, the treated individual is a mammal, for example a human.

[00158] The methods described herein may be used to treat any anemia, including anemia resulting from a hemoglobinopathy. Hemoglobinopathies and anemias treatable by the methods provided herein may be genetic in origin, such as sickle-cell anemia or thalassemias. The hemoglobinopathy may be due to a disease, such as cancer, including, but not limited to, cancers of the hematopoietic or lymphatic systems. Other conditions treatable using the methods provided herein include Hypersplenism, splenectomy, bowel resection, and bone marrow infiltration. The methods described herein may also be used to treat anemia resulting from the deliberate or accidental introduction of a poison, toxin, or drug. For example, anemias resulting from cancer chemotherapies may be treated using the methods and solid forms provided herein. As such, the methods described herein may be employed when anemia or a hemoglobinopathy is the primary condition to be treated, or is a secondary condition caused by an underlying disease or treatment regimen.

[00159] In one embodiment, the diseases or disorders are various forms of ieukemias such as chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, and acute myeloblastic leukemia, including Ieukemias that are relapsed, refractory, or resistant, as disclosed in U.S. publication no. 2006/0030594, published February 9, 2006, which is incorporated in its entirety by reference.

[00160] The term 'leukemia" refers malignant neoplasms of the blood-forming tissues. The leukemia includes, but is not limited to, chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, and acute myeloblastic leukemia. The leukemia can be relapsed, refractory or resistant to conventional therapy. The term "relapsed" refers to a situation where patients who have had a remission of leukemia after therapy have a return of leukemia cells in the marrow and a decrease in normal blood cells. The term "refractory or resistant" refers to a circumstance where patients, even after intensive treatment, have residual leukemia cells in their marrow.

[00161] In another embodiment, the diseases or disorders are various types of lymphomas, including Non-Hodgkin's lymphoma (NHL). The term "lymphoma" refers a heterogenous group of neoplasms arising in the reticuloendothelial and lymphatic systems. "NHL" refers to malignant monoclonal proliferation of lymphoid cells in sites of the immune system, including lymph nodes, bone marrow, spleen, fiver, and gastrointestinal tract. Examples of NHL include, but are not limited to, mantle cell lymphoma (MCL), lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma (ILL), diffuse poorly differentiated lymphocytic lymphoma (PDL), centrocytic lymphoma., diffuse small-cleaved cell lymphoma (DSCCL), follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, biastic and mentle zone lymphoma).

[00162] Examples of diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, inflammatory diseases, autoimmune diseases, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle). Specific examples of the diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, arthritis, endometriosis, Crohn's disease, heart failure, advanced heart failure, renal impairment, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractor}' anemia, and 5q-deietion syndrome.

[00163] Other disease or disorders treated, prevented, or managed include, but not limited to, viral, genetic, allergic, and autoimmune diseases. Specific examples include, but are not limited to, HIV, hepatitis, adult respiratory distress syndrome, bone resorption diseases, chronic pulmonary inflammatory diseases, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock, sepsis syndrome, post ischemic reperfusion injur)', meningitis, psoriasis, fibrotic disease, cachexia, graft versus host disease, graft rejection, auto-immune disease, rheumatoid spondylitis, Crohn's disease, ulcerative colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythrematosus, ENL in leprosy, radiation damage, cancer, asthma, or hyperoxic alveolar injury.

[00164] In certain embodiments, a solid form provided herein, or a composition comprising a solid form provided herein, is administered orally, parenterally, topically, or mucosaliy. Examples of such dosage forms can be found in section 5.5, *infra.*

[00165] In certain embodiments, a solid form provided herein, or a composition comprising a solid form provided herein, is administered at a dosing frequency of once, twice, thrice, or four times daily. In certain embodiments, solid form provided herein, or a composition comprising a solid form provided herein, comprises pomalidomide in an amount of from about 0.1 to about 100 mg, from about 0.5 to about 50 mg, from, about 0.5 to about 25 mg, from about 1 mg to about 10 mg, from about 0.5 to about 5 mg, or from about 1 mg to about 5 mg. In certain embodiments, provided herein is a single unit dosage form suitable for oral administration to a human comprising: an amount equal to or greater than about 1, 2, 3, 4, or 5 mg of a solid form of pomalidomide provided herein; and a pharmaceutically acceptable excipient. In one embodiment, the amount of the active ingredient is about 0.5 mg. In another embodiment, the amount of the active ingredient is about 1 mg. In another embodiment, the amount of the active ingredient is about 2 mg. In another embodiment, the amount of the active ingredient is about 4 mg.

[00166] In one embodiment, the second active agent is administered intravenously or subcutaneously and once or twice daily, once every other day, once every week, once every two weeks, or once eveiy three weeks, in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. In one embodiment, the second active agent is administered orally and once or twice daily, once every other day, once every week, once even,' two weeks, or

once every three weeks, in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, from about 10 to about 200 mg, from about 10 to about 100 mg, or from about 20 to about 50 mg. In specific embodiments, the second active agent is administered once eveiy week in an amount of about 40 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount(s) of compounds provided herein and any optional additional active agents concurrently administered to the patient.

[00167] As discussed elsewhere herein, also encompassed is a method of reducing, treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. Compounds provided herein and other active ingredients can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

5.4 Cycling Therapy

[00168] In certain embodiments, the prophylactic or therapeutic agents provided herein are cyclically administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest *(i.e.,* discontinuation of the administration) for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

[00169] Consequently, in one embodiment, a compound provided herein is administered daily in a single or divided doses in a four to six week cycle with a rest period of about a week or two weeks. Cycling therapy further allows the frequency, number, and length of dosing cycles to be increased. Thus, another embodiment encompasses the administration of a compound provided herein for more cycles than are typical when it is administered alone. In yet another embodiment, a compound provided herein is administered for a greater number of cycles than would typically cause dose-limiting toxicity in a patient to whom a second active ingredient is not also being administered.

[00170] In one embodiment, a compound provided herein is administered daily and continuously for three or four weeks at a dose of from about 0.1 mg to about 5 mg per day, followed by a rest of one or two weeks. In other embodiments, the dose can be from about 1 mg to about 5 mg per day *(e.g.,* 1, 2, 3, or 4 mg/day), given on Days 1-21 of each 28-day cycle until disease progression , followed by a rest of 7 days on Days 22-28 of each 28-day cycle, for example, in patients with relapsed and refractory multiple myeloma who are refractory to their last myeloma therapy and have received at least 2 prior therapies that included lenaiidomide and bortezomib.

[00171] In one embodiment, a compound provided herein and a second active ingredient are administered orally, with administration of the compound provided herein occurring 30 to 60 minutes prior to the second active ingredient, during a cycle of four to six weeks. In anoiher embodiment, the combination of a compound provided herein and a second active ingredient is administered by intravenous infusion over about 90 minutes every cycle.

[00172] In one embodiment, a compound provided herein is administered at a dose of about 4 mg per day given on Days 1-21, followed by a rest of 7 days on Days 22-28 of each 28-day cycle, alone or in combination with low dose dexamethasone *(e.g.,* 40 mg/day given on Days 1, 8, 15 and 22 of each 28-day cycle), for example, in patients with relapsed and refractory multiple myeloma who are refractory to their last myeloma therapy and have received at least 2 prior therapies that included lenaiidomide and bortezomib.

5.5 **Pharmaceutical Compositions** and Dosage Forms

[00173] Pharmaceutical compositions can be used in the preparation of single unit dosage forms comprising one or more solid forms provided herein. In one embodiment, provided herein are pharmaceutical compositions and dosage forms comprising one or more solid forms comprising a compound provided herein, or a pharmaceutically acceptable salt, solvate *(e.g.,* hydrate), stereoisomer, co-crystal, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms provided herein can further comprise one or more pharmaceutically acceptable excipients or carriers.

[00174] In some embodiments, pharmaceutical compositions and dosage forms provided herein can also comprise one or more additional active ingredients. Examples of optional second, or additional, active ingredients are disclosed herein elsewhere.

[00175] In one embodiment, single unit dosage forms provided herein are suitable for oral, parenteral *(e.g.,* subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical *(e.g.,* eye drops or other ophthalmic preparations), mucosal *(e.g.,* nasal, sublingual, vaginal, buccal, or rectal), or **transdermal** administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules or hard gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols *(e.g.,* nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration **to** a patient, including suspensions *(e.g.,* aqueous or non-aqueous liquid suspensions, **oil-in-water** emulsions, or **water-m-oil** liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to **a** patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids *(e.g.,* crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration **to** a patient. In one embodiment, the single dosage forms provided herein are tablets, caplets, or capsules comprising one or more solid forms provided herein. In one embodiment, the single dosage forms provided herein are tablets or capsules comprising one or more solid forms provided herein.

[00176] The composition, shape, and type of dosage forms **will** typically **vary** depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms are used will vary from one another **will** be readily apparent **to** those skilled in the art. *See, e.g., Remington's Pharmaceutical Sciences,* 18th ed., Mack Publishing, Easton PA (1990).

[00177] In one embodiment, pharmaceutical compositions and dosage forms comprise one or more excipients or carriers. Suitable excipients are 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 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. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, in one embodiment, provided are pharmaceutical compositions and dosage forms that contain little, if any, lactose or other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient. Lactose-free compositions provided herein can comprise excipients which are known in the art and are listed in the *U.S. Pharmacopeia* (USP) 25-NF20 (2002), which is incorporated herein in its entirety.

[00178] Also provided are anhydrous pharmaceutical compositions and dosage forms comprising active ingredient(s), since water may facilitate the degradation of some compounds. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, in one embodiment, anhydrous compositions are 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.

[00179] 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.

|00180] 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. In one embodiment,

dosage forms comprise the active ingredient or solid form of pomalidomide provided herein in an amount of from about 0.10 to about 10 mg, or from about 0.10 to about 5 mg. In other embodiments, dosage forms comprise a compound provided herein in an amount of about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 2.5, 3, 4, or 5 mg.

[00181] In other embodiments, dosage forms comprise a second active ingredient in an amount from about 1 mg to about 1000 mg, from about 5 mg to about 500 mg, from about 10 mg to about 350 mg, from about 5 mg to about 250 mg, from about 5 mg to about 100 mg, from about 10 mg to about 100 mg, from about 10 mg to about 50 mg, or from about 50 mg to about 200 mg. In one embodiment, the specific amount of the second active agent will depend on the specific agent used, the diseases or disorders being treated or managed, and the amount(s) of a compound provided herein, and any optional additional active agents concurrently administered to the patient.

[00182] In particular embodiments, provided herein is a pharmaceutical composition comprising a solid form of pomalidomide provided herein and a pharmaceutically acceptable excipient or carrier. In particular embodiments, provided herein is a pharmaceutical composition comprising a crystalline pomalidomide provided herein and a pharmaceutically acceptable excipient or carrier. In particular embodiments, provided herein is a pharmaceutical composition comprising an amorphous pomalidomide provided herein and a pharmaceutically acceptable excipient or carrier. Exemplary embodiments of formulations of pomalidomide are described in, for example, U.S. Patent Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, and 7,709,502; and U.S. Patent Application Publication No. 2011/0045064; the entireties of which are incorporated herein by reference.

5.5.1 Oral Dosage Forms

[00183] Pharmaceutical compositions that are suitable for oral administration can be provided as discrete dosage forms, such as, but not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In one embodiment, such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy known to those skilled in the art. *See generally, Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing,

Easton PA (1990). As used herein, oral administration also includes buccal, lingual, and sublingual administration.

[00184] In one embodiment, the oral dosage form provided herein is a tablet. In one embodiment, the oral dosage form provided herein is a capsule. In one embodiment, the oral dosage form provided herein is a caplet. In particular embodiments,

[00185] In one embodiment, oral dosage forms provided herein are prepared by combining the active ingredients in an intimate admixture with one or more pharmaceutically acceptable earner or excipient, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide, 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 capiets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[00186] In one embodiment, oral dosage forms are tablets or capsules, in which case solid excipients are employed. In specific embodiments, capsules comprising one or more solid forms of pomalidomide *(e.g.,* Form A or an amorphous form) provided herein can be used for oral administration. In one embodiment, the total amount of pomalidomide in the capsule is about 1 mg, about 2 mg, about 3 mg, about 4 mg, or about 5 mg. In one embodiment, the total amount of pomalidomide in the capsule is about 1 mg, about 2 mg, or about 4 mg. In one embodiment, the total amount of pomalidomide in the capsule is about I mg or about 2 mg. Each capsule can contain pomalidomide as the active ingredient and one or more of the following inactive ingredients: mannitoi, pregelatinized starch and sodium stearyl fumarate. In specific embodiments, the 1 mg capsule shell can contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink and black ink. In specific embodiments, the 2 mg capsule shell can contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3

and white ink. In another embodiment, tablets can be coated by standard aqueous or nonaqueous 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.

[00187] In certain embodiments, the dosage form is a tablet, wherein the tablet is manufactured using standard, art-recognized tablet processing procedures and equipment. In certain embodiments, the method for forming the tablets is direct compression of a powdered, crystalline and/or granular composition comprising a solid form provided herein, alone or in combination with one or more excipients, such as, for example, carriers, additives, polymers, or the like. In certain embodiments, as an alternative to direct compression, the tablets may be prepared using wet granulation or dry granulation processes. In certain embodiments, the tablets are molded rather than compressed, starting with a moist or otherwise tractable material In certain embodiments, compression and granulation techniques are used.

[00188] In certain embodiments, the dosage form is a capsule, wherein the capsules may be manufactured using standard, art-recognized capsule processing procedures and equipments. In certain embodiments, soft gelatin capsules may be prepared in which the capsules contain a mixture comprising a solid form provided herein and vegetable oil or non-aqueous, water miseible materials, such as, for example, polyethylene glycol and the like. In certain embodiments, hard gelatin capsules may be prepared containing granules of solid forms provided herein in combination with a solid pulverulent carrier, such as, for example, lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin. In certain embodiments, a hard gelatin capsule shell may be prepared from a capsule composition comprising gelatin and a small amount of plasticizer such as glycerol. In certain embodiments, as an alternative to gelatin, the capsule shell may be made of a carbohydrate material. In certain embodiments, the capsule composition may additionally include polymers, colorings, flavorings and opaeifiers as required. In certain embodiments, the capsule comprises TiPMC.

[00189] Examples of excipients or carriers that can be used in oral dosage forms provided herein include, but are not limited to, diluents (bulking agents), lubricants, disintegrants, fillers, stabilizers, surfactants, preservatives, coloring agents, flavoring agents, binding agents (binders), excipient supports, glidants, permeation enhancement excipients, plasticizers and the like, *e.g.,* as known in the art. It will be understood by those in the art that some substances serve more than one purpose in a pharmaceutical composition. For instance, some substances are binders that help hold a tablet together after compression, yet are also disintegrants that help break the tablet apart once it reaches the target delivery site. Selection of excipients and amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works available in the art.

[00190] In certain embodiments, dosage forms provided herein comprise one or more binders. Binders may be used, *e.g.,* to impart cohesive qualities to a tablet or a capsule, and thus ensure that the formulation remains intact after compression. Suitable binders include, but are not limited to, starch (including potato starch, corn starch, and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, propylene glycol, waxes, and natural and synthetic gums, *e.g.,* acacia sodium alginate, polyvinylpyrrolidone (PVP), celiulosic polymers (including hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), methyl cellulose, ethyl cellulose, hydroxyethyl cellulose (HEC), carboxymethyl cellulose and the like), veegum, carbomer *(e.g.,* carbopol), sodium, dextrin, guar gum, hydrogenated vegetable oil, magnesium aluminum silicate, maltodextrin, polymethacryiates, povidone *(e.g.,* KOLLIDON, PLASDONE), macrocrystalline cellulose, among others. Binding agents also include, *e.g.,* acacia, agar, aiginic acid, cabomers, carrageenan, cellulose acetate phthalate, ceratonia, chitosan, confectioner's sugar, copovidone, dextrates, dextrin, dextrose, ethylceilulose, gelatin, glyceryl behenate, guar gum, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hydroxypropyl starch, hypromeflose, inulin, lactose, magnesium aluminum silicate, maltodextrin, maltose, methylcellulose, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethylacrylates, povidone, sodium alginate, sodium carboxymethylcellulose, starch, pregelatinized starch, stearic acid, sucrose, and zein. In one embodiment, the binding agent can be, relative to the weight of the dosage form, in an amount of from about 50%

to about 99% w/w. In certain embodiments, a suitable amount of a particular binder is determined by one of ordinary skill in the art.

[00191] 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 (FMC Corporation, Marcus Hook, PA), and mixtures thereof. In one embodiment, a specific binder is a mixture of microcrystalline cellulose and sodium carboxymetbyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

[00192] Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms provided herein include, but are not limited to, talc, calcium carbonate *(e.g.,* granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitoi, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in a pharmaceutical composition is, in one embodiment, present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[00193] In certain embodiments, dosage forms provided herein comprise one or more diluents. Diluents may be used, *e.g.,* to increase bulk so that a practical size tablet or capsule is ultimately provided. Suitable diluents include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitoi, sodium chloride, dry starch, microcrystalline cellulose *(e.g.,* AVICEL), microfine cellulose, pregelitinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitoi, polymeihacrylates *(e.g.,* EUDRAGIT), potassium chloride, sodium chloride, sorbitol and talc, among others. Diluents also include, *e.g.,* ammonium alginate, calcium carbonate, calcium phosphate, calcium sulfate, cellulose acetate, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, erythritol, ethylcellulose, fructose, fumaric acid, glyceryl palraitostearate, isomalt, kaolin, lacitol, lactose, mannitoi, magnesium carbonate, magnesium oxide, maltodextrin, maltose, medium-chain triglycerides, microcrystalline cellulose, microcrystalline siiieified cellulose, powered cellulose, polydextrose, polymethylacrylates, simethicone, sodium alginate, sodium chloride, sorbitol, starch, pregelatinized starch, sucrose, sulfobutylether-β-cyclodextrin, talc, tragaeanth, trehalose, and xylitol. Diluents may be used in amounts

calculated to obtain a desired volume for a tablet or capsule. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[00194] Disintegrants may be used in the compositions to provide tablets or capsules that disintegrate when exposed to an aqueous environment. Dosage forms 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 1 to about 5 weight percent of disintegrant.

[00195] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methyiceliulose and carboxymethylceilulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-finked polymers, such as crospovidone; cross-linked starches; calcium carbonate; mierocrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[00196] 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, mannitof, polyethylene glycol, other glycols, stearic acid, 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 lubricants include, for example, a syloid silica gel (AERGSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a

coagulated aerosol of synthetic silica (marketed by Degussa Co. of Piano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[00197] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monoofeate (TWEEN® 2.0), polyoxyethylene sorbitan monooieate 80 (TWEEN® 80), and triethanoiamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymefhylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxy-propyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooieate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[00198] In one embodiment, a solid oral dosage form comprises a compound provided herein, and one or more excipients selector from anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin. In

one embodiment, capsules comprise one or more solid forms of pomalidomide provided herein, and one or more of the following inactive ingredients: mannitol, pregelatinized starch, sodium stearyl fumarate, gelatin, titanium dioxide, FD&C bine 2, yellow iron oxide, white ink, black ink, FD&C red 3, and a combination thereof.

[00199] The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly-dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcelSulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00200] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrates, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00201] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcelluiose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth

of microorganisms. Suitable preservatives are those as described herein, including methyl- and propylparabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00202] The pharmaceutical compositions provided herein for oral administration can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetai, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, e.g., acetaldehyde diethyl acetai; and a water-miscible solvent having one or more hydroxy! groups, such as propylene glycol and efhanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.,* water, to be measured conveniently for administration.

[00203] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poiy-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glyeol-350-dimethyl ether, polyethylene glycol-550-dimethyi ether, polyethylene glycol-750-dimetliyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BUT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol,

phosphoric acid, bisulfite, sodium meiabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00204] The pharmaceutical compositions provided herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00205] The pharmaceutical compositions provided herein for oral administration can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00206] Coloring and flavoring agents can be used in all of the above dosage forms.

[00207] The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

6, EXAMPLES

[00208] Certain embodiments provided herein are illustrated by the following non-limiting examples.

[00209] In one embodiment, pomalidomide may be synthesized using methods described in U.S. Patent Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327, all of which are incorporated herein in their entireties.

6.1 Pomalidomide Polymorph Preparations

[00210] A weighed sample of pomalidomide (about 100 mg) was treated with 2 mL of a test solvent. The solvents used were either reagent or HPLC grade. The resulting mixture was agitated for at least 24 hours at 25 °C. When all of the solids were dissolved by visual inspection, the estimated solubilities were calculated. The solubility was estimated from these experiments based on the total volume of solvent used to give a solution. The actual solubility may be greater than those calculated due to the use of a large amount of solvent or to a slow rate of dissolution. If dissolution did not occur

during the experiment, the solubility was measured gravimetrically. A known volume of filtrate was evaporated to dryness and the weight of the residue was measured.

[00211] Equilibration and evaporation experiments were carried out by adding an excess of pomalidomide to 4 mL of a test solvent. The resulting mixture was agitated for at least 24 hours at 25 °C and 50 °C separately. Upon reaching equilibrium, the saturated solution was removed and allowed to evaporate slowly in an open vial under nitrogen at 25 °C and 50 °C respectively. The slurry resulting from the equilibration was filtered and dried in the air.

[00212] Crystallizations using cooling methods were performed. The solid was dissolved in a solvent at an elevated temperature, approximately 80 °C and allowed to cool to room temperature. Samples that did not crystallize at room temperature were placed in a refrigerator (0-5 °C). Solids were isolated by decantation and allowed to dry in the air.

[00213] Precipitation studies were carried out by solvent/anti-solvent combinations. The solid was dissolved in a solvent in which pomalidomide solubility was high, and then a selected solvent in which pomalidomide was highly insoluble (anti-solvent) was added to the solution. A precipitate formed immediately in some solvent/anti-solvent systems. If the precipitation did not occur immediately, the resulting mixture was allowed to cool in a refrigerator until a precipitate formed. The precipitate was then isolated by decantation and allowed to dry in the air.

[00214] All of the samples generated as described in the polymorph preparation study were analyzed by XRPD. XRPD was conducted on a Thermo ARL X'TRA X-ray powder diffractometer using Cu Kα radiation at 1.54 A. The instrument was equipped with a fine focus X-ray tube. The voltage and amperage of X-ray generator were set at 45 kV and 40 mA, respectively. The divergence slices were set at 4 mm and 2 mm and the measuring slices were set at 0.5 mm and 0.2 mm. Diffracted radiation was detected by peitier-cooled Si(Li) solid state detector. A theta-two theta continuous scan at 2.40°/min (0.5 sec/0.02° step) from 1.5° 2Θto 40° 2.Θwas used. **A** sintered alumina standard was used to check the peak position.

[00215] DSC analyses were performed on a TA instrument Q1000. Indium was used as calibration standards. Approximately 2-5 mg of sample was placed into a DSC pan and the weight was accurately recorded. The sample was heated under nitrogen at a rate

of 10 °C/min, up to a final temperature of 350 °C. Melting points were reported as extrapolated onset temperature.

[00216] TG analyses were performed on a TA instrument Q500. Calcium oxalate was used for performance check. Approximately 10-25 mg of sample was placed on a pan, accurately weighed and loaded into the TG furnace. The sample was heated under nitrogen at a rate of 10 °C/min, up to a final temperature of 350 °C.

[00217] Morphology and particle size analysis of the samples were carried out on an Olympus microscope. The instrument was calibrated with USP standards.

[00218] Hygroscopicity was determined on a Surface Measurement Systems DVS. Typically a sample size of 10-50 mg was loaded into the DVS instrument sample pan and the sample was analyzed on a DVS automated sorption analyzer at 25 °C. The relative humidity was increased in 10% increments from 0% to 95% RH. The relative humidity was then decreased in a similar mariner to accomplish a full adsosption/desorption cycle.

[00219] Solubility of pomalidomide in various solvents at ambient temperature was determined and is shown in Table 3. Pomalidomide was found to be most soluble in THF (5.26 mg/mL) followed by acetone (1.99 mg/mL). It was also found to have low solubility in certain solvents (< 1 mg/mL), including heptane, n-butanol, n-butyl acetate, ethanol, methanol, ethyl acetate, methyl t-butyl ether 2-propanoi, toluene, and water.

Table 3: Solubility of Pomalidomide

Solvent	Solubility (mg/mL)
Acetone	1.99
Acetonitrile	1.27
n-Butanol	0.08
n-Butyl acetate	0.10
Absolute ethanol	0.14
Ethyl acetate	0.63
Heptane	0.36
Methylene chloride	1.45
Methyl ethyl ketone	1.26
Methanol	0.41
Methyl t-butyl ether	1.03
2-Propanol	0.32
Tetrahydrofuran	5.26
Toluene	0.36
Water	0.19
Ethanol/Water (1:1)	0.54

[00220] Various embodiments of Form A of pomalidomide were prepared from evaporation study at 50 °C, in methyl ethyl ketone or in tetrahydrofiiran; slurry at 25 °C in certain solvent *(e.g.* , acetone, acetonitrile, n-butanol, n-butyl acetate, ethanol, ethyl acetate, heptane, methylene chloride, methyl ethyl ketone, methanol, methyl t-butyl ether, 2-propanoi, tetrahydrofiiran, toluene, water, or ethanol/water (1:1)), or slurry at 50 °C in certain solvent *(e.g.* , acetone, acetonitrile, n-butanol, n-butyl acetate, ethanol, ethyl acetate, heptane, methyl ethyl ketone, methanol, 2-propanoi, tetrahydrofuran, toluene, water, or ethanol/water (1:1)).

[00221] Crystalline material was also obtained from crystallization from solvent, such as acetomtrile, methyl ethyl ketone, or tetrahydrofuran, under conditions summarized in Table 4, to generate samples with XRPD patterns consistent with Form A.

Table 4: Crystallization of Pomalidomide

Solvent	Method	XRPD Result
Acetonitrile	Dissolved at ~80 °C Cooled in refrigerator	Form A
Methyl Ethyl Ketone	Dissolved at 80 °C Cooled in refrigerator	Form A
Tetrahydrofuran	Dissolved at ~80 °C Cooled in refrigerator	Form A

[00222] The results of precipitation studies are summarized in Table 5. When toluene, methyl t-butyl ether, or water was added to a pomalidomide in TITF solution at 60 °C, clear solutions were obtained. After the solutions were cooled in a refrigerator, no crystalline materials precipitated. When heptane was added to a pomalidomide in THF solution at 60 °C, a cloudy mixture was obtained. The mixture was then placed in a refrigerator. The crystalline material obtained after 24 hours was identified as one preparation of Form A by XRPD.

Table 5: Precipitation with Solvent/Anti-Solvent

Solvent	Anti-solvent	Ratio of Solvent and Anti-solvent	XRPD Result
Tetrahydrofuran	Heptane	1:3	Form A
Tetrahydrofuran	Toluene	1:3	
Tetrahydrofuran	Water	1:3	
Tetrahydrofuran	Methyl t-butyl ether	1:3	

6.2 Pomalidomide Solid Form Preparations

[00223] Preparation of solid form of pomalidomide was conducted by equilibrating pomalidomide in 96 solvent compositions at 50 °C and subjected to four conditions: slurry, evaporation, cooling, and precipitation.

[00224] For the slurry experiment, approximately 3 mg of a solid sample of pomalidomide *(e.g.*. Form A) was delivered to each position of the plate. Solvents were then added, as binary gradients consisting of main solvent and co-solvent, to give a total of 150 μL in each of the 96 vials (see Table 6 for the exact composition of each vial). The sealed plate was then magnetically stirred at 50 °C for 8 hours, then at 25 °C for 8 hours. The lid of the crystal lizer assembly was then removed, the residual solvents removed by wicking, and the samples dried in air. Each sample was analyzed by XRPD and birefringence.

[00225] For each of the evaporation, precipitation, and cooling experiments, approximately 8 mg of a solid sample of pomalidomide *(e.g.,* Form A) was delivered to each position of the plate. Solvents were added to the master plate, as binary gradients consisting of main solvent and co-solvent, to give a total volume of 800 μL in each of the 96 vials (see Table 7 for the exact composition of each vial). The master plate, containing pomalidomide and solvents, was then equilibrated by stirring for 2 hours at 50 °C. Upon completion of the equilibration cycle, the supernatant was aspirated into a four-tipped needle assembly and transferred to a sealed parallel filtration assembly. The mixtures were forced through the filtration assembly using positive pressure and the filtrates were collected in an array of glass vials. The filtered solutions were subsequently aspirated into the four-tipped assembly and aliquots were dispensed to an array of glass vials for subsequent LC analysis to determine approximate concentrations of pomalidomide in each solvent composition at the beginning of the experiments (Table **8).** Both the four-tipped needle assembly and filtration assembly were maintained at the equilibration temperature of 50 °C throughout the entire transfer process.

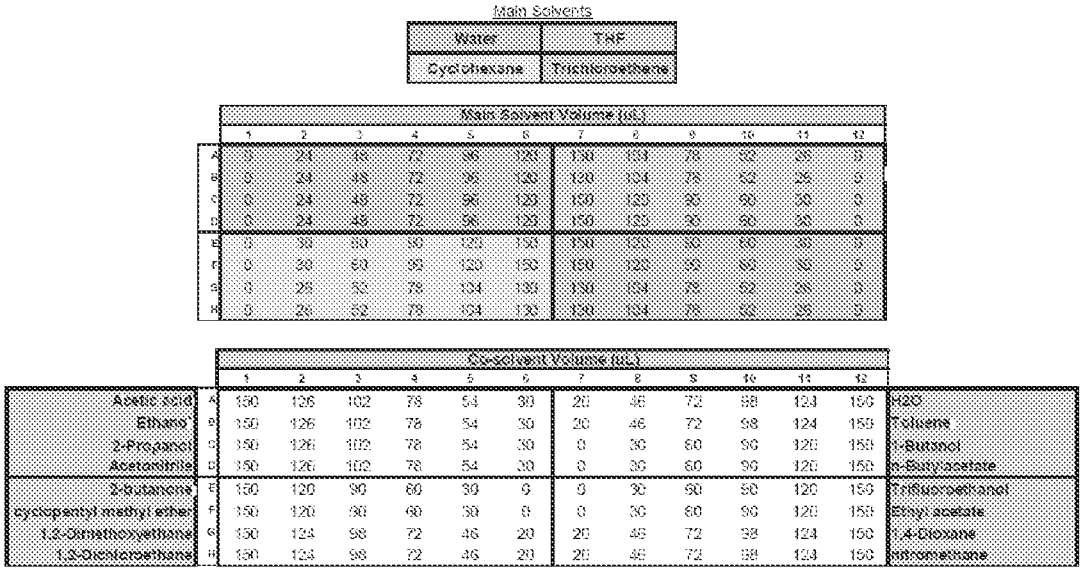


Table 6. Solvents, **Co-Solvents,** and Amounts Thereof for the **Slurry** Experiment

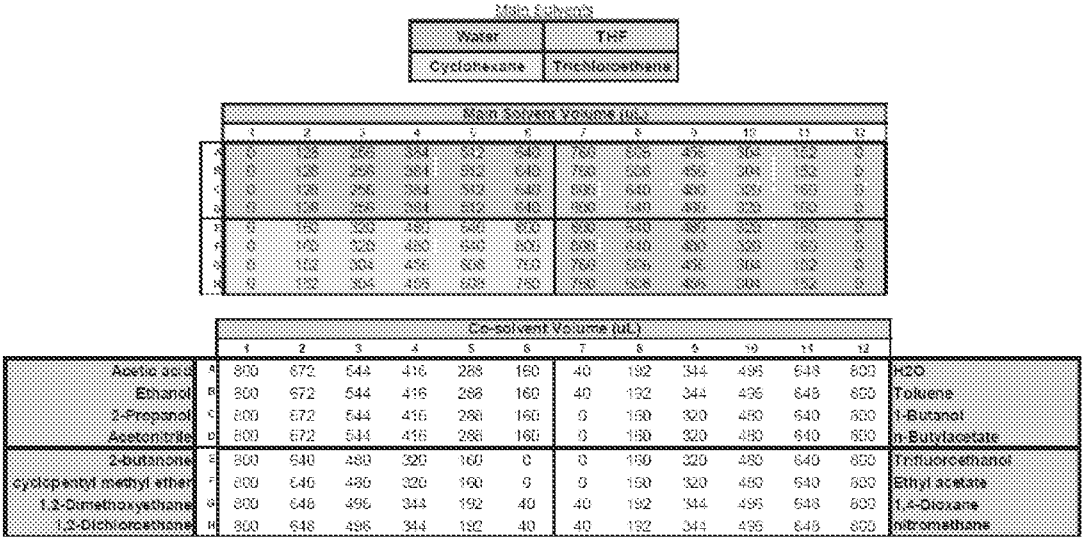


Table 7. Solvents, Co-Solveots, and Amounts Thereof for the Evaporation, **Precipitation, and Cooling Experiments**

[00226] For the evaporation experiments, 200 µL filtrate aliquots were dispensed into each well of an unsealed erystaliizer assembly and allowed to evaporate under ambient conditions.

[00227] For the precipitation experiments, 100 \tL filtrate aliquots were dispensed into a sealed crystallizer assembly containing 300 LtL of anti-solvent. The plate stood at room

temperature overnight. Water was the anti-solvent for cells A1-A12, B1-B6, C1-C6, and D1-D6 of Table **7;** heptanes was the anti-solvent for the remainder.

[00228] For the cooling experiments, 200 μL filtrate aliquots were dispensed into each well of a sealed crysiallizer assembly and cooled slowly over 8 hours from 50 °C to 5 °C, then held at 5 °C for several hours.

[00229] Afterwards, in each of the evaporation, precipitation, and cooling experiments, the lids of the crystallizer assemblies were removed, the residual solvents removed by wicking, and the samples dried in air for several hours. Each sample was analyzed by XRPD and birefringence.

[00230] The results of the solubility study are set forth in Table **8,** below. The results correspond to the solvent systems described in Table **7,** equilibrated at 50 °C for 2 hours. The maximum concentration of pomalidomide when completely dissolved was about 10.0 mg/mL. The approximate concentrations were determined by LC.

	1	2	3	4	5	6	7	8	9	10	11	12
A	2.24	3.19	2.43	1.44	0.80	0.28	6.66	7.84	4.41	1.83	0.29	0.03
B	0.29	0.73	1.00	0.22	0.36	0.16	3.16	1.72	0.32	0.48	0.18	ND
C	0.62	1.41	1.87	0.46	0.47	0.26	3.71	2.97	1.84	1.09	0.49	0.34
D	1.39	0.67	0.45	2.50	1.34	0.40	3.70	2.31	1.83	0.36	1.16	0.67
E	1.65	0.69	0.52	0.13	0.02	ND	0.02	0.73	1.83	2.31	2.48	0.66
F	0.13	0.06	0.03	0.01	ND	ND	0.04	0.04	0.13	0.13	0.38	0.65
G	2.69	1.69	0.70	0.23	0.06	ND	0.01	0.41	0.85	2.01	5.18	6.98
H	0.38	0.24	0.11	0.04	ND	ND	0.05	0.40	0.36	1.53	3.96	2.68

Table **8.** Approximate Measured Solubility of Pomalidomide at **50 °C**

6.3 Preparation and Characterization of Solid Forms of Pomalidomide

6.3.1 Preparations of Form A of Pomalidomide

[00231] In one embodiment, various preparations of Form A were obtained via crystallization in certain solvent systems. The pomalidomide starting material used in these experiments was first characterized by XRPD (FIG. **2)** and DSC (FIG. **11).**

[00232] In one embodiment, 20 mg of pomalidomide was heated in 10 mL of nitromethane at 50 °C with magnetic stirring for 2 hours. The resulting homogenous solution was allowed to slowly evaporate under ambient conditions. The isolated solid was characterized by XRPD (FIG. **3,** one embodiment of Form A), DSC (FIG. **13,** single endotherm at 318.6 °C), and TGA (0.6 **wt** % lost up to 200 °C), which was

consistent with an unsolvated form. This experiment resulted in large crystals, as shown in the birefringence image of FIG. 7.

[00233] In one embodiment, Form A was prepared from 20 mg of pomaiidomide slurried in 0.8 mL of water and 0.2 mL of acetonitrile at 50 °C with magnetic stirring for 20 hours. After cooling to room temperature, the solvent was removed by decanting and the isolated solid was further dried by wicking onto filter paper. The isolated solid was characterized by XRPD (FiG, 4, one embodiment of Form A), DSC (FIG, **14,** single endotherm at 320 °C), and TGA (FIG. 17, 0.3 wt % gained up to 200 °C), which was consistent with an unsolvated form. The birefringence image of the resultant crystalline material is shown in FiG, **8.**

[00234] In one embodiment, Form A was prepared from 40 mg of pomaiidomide slurried in 2 mL of acetonitrile at 80 °C with magnetic stirring for 3 days. After cooling to room temperature, the solvent was removed by decanting and the isolated solid was further dried by wicking onto filter paper. The isolated solid was characterized by XRPD (FIG. **1,** one embodiment of Form A) and DSC (FiG. 10, single endotherm at 320.1 °C), which was consistent with an unsolvated form.

[00235] In one embodiment, Form A was prepared from 40 mg of pomaiidomide slurried in 2 mL of water at 100 °C with magnetic stirring for 3 days. After cooling to room temperature, the solvent was removed by decanting and the isolated solid was further dried by wicking onto filter paper. The isolated solid was characterized by XRPD (FIG. 5, one embodiment of Form A) and DSC (FiG. 15, single endotherm at 320.5 °C), which was consistent with an unsolvated form.

[00236] In one embodiment. Form A was prepared from 100 mg of pomaiidomide slurried in 4 mL of water and 1 mL of acetonitrile at 100 °C with magnetic stirring for 20 hours. After cooling to room temperature, the solvent was removed by decanting and the isolated solid was further dried by wicking onto filter paper. The isolated solid was characterized by XRPD (FIG, 6, one embodiment of Form A), DSC (FIG. 16, single endotherm at 319.2 °C), and TGA (0.3 wt. % gained up to 200 °C), and was consistent with an unsolvated form. The birefringence image of the resultant crystalline material is shown in FIG. **9.**

[00237] In one embodiment, solid forms of pomaiidomide comprising Form A may be prepared via crystallization in solvent systems, such as: water/ethanol, water/2-propanol,

water/acetonitriie, cyclohexane/2-butanone, cyclohexane/cyclopentyl methyl ether, cyclohexane/1 ,2-dimethoxyethane, cyclohexane/1 ,2-dichloroethane, THF/toluene, THF/l-butanol, THF/n-butylacetate, l,l,2-trichloroethene/trifluoroethanof, 1,1,2-tricholoethene/ethyl acetate, l,l,2-trieholoethene/l,4-dioxane, and 1,1,2-tricholoethene/nitromethane.

[00238] DSC cycling experiments were performed on certain samples comprising Form A to determine if thermal conversion or melt crystallization would generate a form change. Form A remained the only form detected after DSC cycling experiments (FIGS. 12a and 12b).

[00239] Figures 1-17 provide representative XRPD patterns, birefringence images, DSC thermograms, and TGA thermogram, of various preparations of Form A of pomalidomide.

6.3.2 Amorphous Forms of Pomalidomide

[00240] In certain embodiments, an amorphous form of pomalidomide can be obtained from certain aqueous and/or organic solvent systems, for example, water/acetic acid, THF/water, water/ethanol, THF/toluene, and water/2-propanol, using a method described herein.

[00241] In one embodiment, amorphous forms were prepared in the slurry experiment described in Section 6.2 and Table 6, for example, including the following cells of the 96-well plate: A1-A10, B3, C2, C3, C11, E4, F8, F10, F11, and G12.

[00242] In one embodiment, amorphous forms were prepared in the evaporation experiment described in Section 6.2 and Table 4, for example, including the following cells of the 96-well plate: A11, A12, B6, C1-C3, C5, C6, C9-C11, D3, D4, D8, El, E9, Ell, and G12.

[00243] In one embodiment, amorphous forms were prepared in the precipitation experiment described in Section 6.2 and Table 4, for example, including the following cells of the 96-well plate: A8, B7, C7, C8, D1-D5, D7, El, G10, G12, and H11.

[00244] In one embodiment, amorphous forms were prepared in the cooling experiment described in Section 6.2 and Table 4, for example, including the following cells of the 96-well plate: A10, All, B2, B6, CI, C2, C6-C8, C10, C12, D2, D5, D6, E1, E2, E10, E12, and H12.

63.3 Characterization Methods

[00245] X-ray powder diffraction (XRPD) data were obtained with a Bruker D8 Discover equipped with a xyz translation stage (with x, y, z travel of 100 mm, 150 mm, and 100 mm, respectively). The X-ray detector was a high-performance HI-STAR two-dimensional detector which was set to 30 cm from the center of the goniometer. At this distance, the detector had a typical FWHM of 0.15-0.2 degrees in 2Θ. The X-ray generator was typically set to 40 kV and 40 mA. The data was collected in one frame with a typical data acquisition time of 3 minutes. The 2Θrange covered by the HI-STAR detector was from 4.5 to 39.5 degrees. The sample was typically oscillated in the y direction (perpendicular to the x-ray travel direction) with oscillation amplitude of ± 2-3 mm. Omega-scan (rocking the x-ray source and the detector synchronously) was also used occasionally to reduce preferred orientation in samples that were producing very spotty diffraction patterns. Crystals grown on Universal Substrate were analyzed either uncrushed or crashed. Epoch software was used to facilitate the translation of the stage to the elements of interest and a joystick to control translation and a knob to adjust the Z height were used to focus the beam on the samples of interest. Epoch then stored the images and coordinates of each of the user specified locations to the database. Epoch was also used to control the data acquisition parameters, area plots, and 2Θplots to the database as an XRPD experiment.

[00246] Differential Scanning Calorimetry (DSC) analyses were made on a DSC 2920 differential scanning calorimeter by TA Instruments with a dual sample ceil. Samples (0.1 - 2 mg) were loaded in an aluminum pan with an aluminum lid set on top (not crimp sealed). The prepared samples and an inert reference were placed in the device to measure the differential heat flow from 50 to 350 °C at 10 °C /minute. Universal analysis software from TA Instruments was used for data analysis.

[00247] Thermogravimetric (TG) analyses were performed on a TGA 2950 Thermogravimetrix analyzer by TA Instruments. Samples (0.1 - 2 mg) were placed in an aluminum pan and placed in the device. The data were collected from 50 to 350 °C at 10 °C /minute.

[00248] Birefringence microscopy measurements were made on an Inverted Microscope Axiovert 200M by Carl Zeiss Inc. equipped with a Bioprecision Inverted

Stage from Ludi which had a total travel of 120 mm x 100 mm with a resolution of 0.2 μm, a repeatability of i μm, ars accuracy of 6 μη, and was controlled by a MAC 5000 controller. The light source for the microscope system was a Hal 100W system. The light was passed through a polarizing filter, the sample, and then a second polarizing filter set perpendicular to the first so that only materials that rotate plane polarized light are observed. AxioVision controlled the microscope, camera, light, XY stage, shutter, and filter wheels. A 2.5X microscope objective was used to ensure that the entire area of each element on the Universal Substrate could be captured in a single image. A transiational sequence was set up to obtain birefringence images for all 96 elements. Epoch software interfaced with AxioVision software and controlled the acquisition of birefringence images and stored the images and intensities to the da.taba.se. A 10X microscope objective was used to obtain higher resolution images of selected samples. Higher magnification images of user selected samples were subsequently recorded and saved to the database using Epoch.

[00249] The general characterization methods described herein are non-limiting, and are intended merely as examples of parameters, methods and techniques which can be used to analyze certain embodiments provided herein. Other standard parameters, methods and techniques for chemical, biological, physiological and solid-state analysis are contemplated herein as means of characterizing various embodiments provided herein.

6.4 Additional Data on Form A of **Pomalidomide**

6.4.1 DSC **and TGA**

[00250] In one embodiment, TG and DSC thermograms of one preparation of Form A were obtained. In this preparation, Form A was found to lose about 0.13% volatiles before decomposition, indicative of an unsolvated material. The DSC thermogram exhibited an endotherm at about 317.60 °C.

6.4.2 Elemental Analysis

[00251] The results of the determined and the theoretical values of %carbon, %hydrogen and %nitrogen of one sample of pomalidomide are given in Table 9. The experimental results were consistent with theory.

Table 9: Elemental Analysis of Pomalidomide

	% Carbon	% Hydrogen	% Nitrogen
Theoretical values	57.14%	4.06%	15.38%
Results	57.13%	4.12%	15.41%

6.4.3 Single Crystal X-Ray Analysis

[00252] The molecular structure and representative solid state conformation of pomalidomide were determined by a single crystal X-ray study at 173 K. Single crystal intensities were measured dififractometrically using radiation wavelength of 1.54178 A. The structure is shown in Figure 19. Figure 20 shows a drawing of the packing along the a-axis where the dotted lines represent potential hydrogen bonding. The unit cell dimensions were determined to be a = 7.0046(2) A, b = 7.8130(2) A, c = 11.2541(4) A. Atomic coordinates are shown in Tables 10 and 12. Bond length (A) and bond angles (°) are shown in Tables 11 and 13.

[00253] XRPD powder diffraction data was simulated using the single crystal intensity data using the program XPOW1. Key parameters for the calculation include the wavelength (used copper wavelength of 1.54 Á), and the cell parameters retrieved from the final refinements. The simulated XRPD pattern is shown in Figure 21, with peak position and peak intensity values listed at the bottom of the Figure.

[00254] Experimental: Pomalidomide was dissolved in warm DMF, and then placed in the refrigerator. The initial crystals were small, allowing these to sit in mother liquor produced larger crystals. A yellow needle crystal with dimensions of 0.26 x 0.14 x 0.07 mm was mounted on a Nylon loop using very small amount of paratone oil. Data were collected using a Bruker CCD (charge coupled device) based diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at 173 K. Data were measured using omega and phi scans of 0.5° per frame for 45 s. The total number of images was based on results from the program COSMO where redundancy was expected to be 4.0 and completeness to 100% out to 0.83 A. Cell parameters were retrieved using APEX II software and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software which corrects for Lp. Scaling and absorption corrections were applied using SADABS multi-scan technique. The structures are

solved by the direct method using the SHELXS-97 program and refined by least squares method on F^2, SHELXL-97, which were incorporated in SHELXTL-PC V 6.10.

[00255] The structure was solved in the space group $P\bar{1}$ (# 2). All non-hydrogen atoms were refined anisotropically. Hydrogens were found by difference Fourier methods and refined isotropically. The crystal used for the diffraction study showed no decomposition during data collection. All drawings were done at 50% ellipsoids.

Table 10: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3).

	x	y	z	U(eq)
0(1)	2909(3)	9805(3)	4402(2)	31(1)
0(2)	5972(3)	5099(3)	6544(2)	40(1)
0(3)	2202(3)	898(3)	6783(2)	39(1)
0(4)	3084(4)	4673(3)	9 119(2)	44(1)
N(l)	4314(4)	7461(3)	5590(2)	29(1)
N(2)	2609(3)	3134(3)	7703(2)	29(1)
N(3)	2941(5)	1983(5)	11692(3)	47(1)
C(l)	2731(4)	831 1(4)	5115(3)	25(1)
C(2)	860(4)	7282(4)	5491(3)	34(1)
C(3)	798(4)	5775(4)	6682(3)	33(1)
C(4)	2566(4)	4624(4)	6604(3)	29(1)
C(5)	4437(4)	5718(4)	6287(3)	28(1)
C(6)	2813(4)	3265(4)	8892(3)	30(1)
C(7)	2662(4)	1450(4)	9715(3)	26(1)
C(8)	2744(4)	829(4)	10995(3)	30(1)
C(9)	2585(4)	-1017(4)	1 1510(3)	35(1)
C(10)	2369(4)	-2144(5)	10794(3)	36(1)
C(ll)	2253(4)	-1523(4)	9513(3)	33(1)
C(12)	2411(4)	288(4)	901 1(3)	26(1)
C(13)	2383(4)	1368(4)	7698(3)	28(1)

Table 11. Bond lengths [Å] and angles [°].

0(1)-C{1)	1.216(3)
0(2)-C(5)	1.211(3)
0(3)-C(13)	1.21 1(4)
0(4)-C(6)	1.222(4)
[illegible]	1.378(4)
N(l)-C(l)	1.379(4)
N(l)-H(l)	0.85(4)
N(2)-C(13)	1.395(4)
N(2)-C(6)	1.400(4)
N(2)-C(4)	1.448(4)
N(3)-C(8)	1.371(4)
N(3)-H(3A)	1.02(5)
N(3)-H(3B)	0.88(5)
C(l)-C(2)	1.496(4)
C(2)-C(3)	1.514(4)
C(2)-H(2A)	0.98(4)
C(2)-H(2B)	0.97(4)
C(3)-C(4)	1.516(4)
C(3)-H(3C)	0.95(3)
C(3)-H(3D)	0.99(4)
C(4)-C(5)	1.523(4)
C(4)-H(4)	1.01(3)
C(6)-C(7)	1.459(4)
C(7)-C(12)	1.391(4)
C(7)-C(8)	1.397(4)
C(8)-C(9)	1.398(4)
C(9)-C(10)	1.374(5)
C(9)-H(9)	0.94(4)
C(10)-C(l 1)	1.403(5)
C(10)-H(10)	0.84(3)

C(ll)-C(12)	1.371(4)
C(ll)-H(ll)	1.01(3)
C(12)-C(13)	1.488(4)
C(5)-N(l)-C(l)	128.0(3)
C(5)-N(l)-H(l)	l 15(3)
C(l)-N(l)-H(l)	117(3)
C(13)-N(2)-C(6)	111.8(2)
C(13)-N(2)-C(4)	122.8(3)
C(6)-N(2)-C(4)	125.4(2)
C(8)-N(3)-H(3A)	l 15(3)
C(8)-N(3)-H(3B)	116(3)
H(3A)-N(3)-H(3B)	122(4)
0(1)-C(1)-N(1)	120.0(3)
O(1)-C(1)-C(2)	123.2(3)
N(l)-C(l)-C(2)	116.7(2)
C(l)-C(2)-C(3)	113.3(2)
C(1)-C(2)-H(2A)	108(2)
C(3)-C(2)-H(2A)	107(2)
C(1)-C(2)-H(2B)	109(2)
C(3)-C(2)-H(2B)	113(2)
H(2A)-C(2)-H(2B)	106(3)
C(2)-C(3)-C(4)	110.5(3)
C(2)-C(3)-Hi3C)	109.7(19)
C(4)-C(3)-H(3C)	109.7(19)
C(2)-C(3)-H(3D)	107(2)
C(4)-C(3)-H(3D)	111(2)
H(3C)-C(3)-H(3D)	109(3)
N(2)-C(4)-C(3)	114.0(3)
N(2)-C(4)-C(5)	110.6(2)
C(3)-C(4)-C(5)	111.9(3)
N(2)-C(4)-H(4)	107.1(18)
C(3)-C(4)-H(4)	108.6(18)

C(5)-C(4)-H(4)	103.8(18)
0(2)-C(5)-N(l)	120.9(3)
0(2)-C(5)-C(4)	123.5(3)
N(l)-C(5)-C(4)	115.4(2)
0(4)-C(6)-N(2)	123.6(3)
0(4)-C(6)-C(7)	130.2(3)
N(2)-C(6)-C(7)	106.2(2)
C(12)-C(7)-C(8)	121.5(3)
C(12)-C(7)-C(6)	108.7(2)
C(8)-C(7)-C(6)	129.9(3)
N(3)-C(8)-C(7)	121.3(3)
N(3)-C(8)-C(9)	122.9(3)
C(7)-C(8)-C(9)	115.9(3)
C(10)-C(9)-C(8)	121.7(3)
C(10)-C(9)-H(9)	121(2)
C(8)-C(9)-H(9)	117(2)
C(9)-C(10)-C(l l)	122.5(3)
C(9)-C(10)-H(10)	122(2)
C(ll)-C(10)-H(10)	116(2)
C(12)-C(l l)-C(10)	115.6(3)
C(12)-C(l l)-H(l l)	119.5(18)
C(10)-C(l l)-H(l l)	124.9(19)
C(11)-C(12>C(7)	122.8(3)
C(ll)-C(12)-C(13)	129.3(3)
C(7)-C(12)-C(13)	107.9(2)
0(3)-C(13)-N(2)	124.7(3)
0(3)-C(13)-C(12)	129.8(3)
N(2)-C(13)-C(!2)	105.5(2)

Table **12.** Hydrogen coordinates fx 1O^4) and isotropic displacement parameters (A¾ 10)^3)

	x	y	z	Ufeq)
H(l)	5370(60)	8050(50)	5390(40)	50(1 l)
H(3A)	3360(70)	3240(70)	11 180(50)	85(15)
H(3B)	3260(70)	1500(60)	12440(50)	76(14)
H(2A)	700(50)	6750(50)	4820(40)	44(10)
H(2B)	-200(60)	8090(50)	5540(40)	56(l l)
H(3C)	-340(50)	5070(40)	6810(30)	30(8)
H(3D)	750(50)	6330(50)	7380(40)	53(1 1)
H(4)	2590(40)	4110(40)	5870(30)	33(8)
H(9)	2650(50)	-1460(40)	12370(30)	39(9)
H(10)	2310(40)	-3250(50)	11090(30)	27(8)
H(H)	2090(50)	-2310(40)	8960(30)	33(8)

Table **13.** Torsion angles [°]

C(5)-N(l)-C(l)-0(1)	-172.1(3)
C(5)-N(l)-C(l)-C(2)	6.0(4)
0(1)-C(1)-C(2)-C(3)	-160.4(3)
N(l)-C(l)-C(2)-C(3)	21.6(4)
C(l)-C(2)-C(3)-C(4)	-50.9(4)
C(13)-N(2)-Cf4)-C(3)	110.6(3)
C(6)-N(2)-C(4)-C(3)	-67.2(4)
C(13)-N(2)-C(4)-C(5)	-122.2(3)
C(6)-Nf2)-C(4)-C(5)	60.0(4)
C(2)-C(3)-C(4)-N(2)	-179.3(3)
C(2)-C(3)-C(4)-C(5)	54.2(4)
C(l)-N(l)-C(5)-0(2)	173.0(3)
C(l)-N(l)-C(5)-C(4)	-2.2(4)
N(2)-C(4)-C(5)-0(2)	28.0(4)

C(3)-C(4)-C(5)-0(2)	156.3(3)
N(2)-C(4)-C(5)-N(l)	-157.0(3)
C(3)-C(4)-C(5)-N(l)	-28.6(4)
C(13)-N(2)-C(6)-0(4)	177.9(3)
C(4)-N(2)-C(6)-0(4)	-4.1(4)
C(13)-N(2)-C(6)-C(7)	-1.4(3)
C(4)-N(2)-C(6)-C(7)	176.7(2)
0(4)-C(6)-C(7)-C(12)	-178.1(3)
N(2)-C(6)-C(7)-C(12)	1.0(3)
0(4)-C(6)-C(7)-C(8)	1.6(5)
N(2)-C(6)-C(7)-C(8)	-179.2(3)
C(12)-C(7)-C(8)-N(3)	-178.3(3)
C(6)-C(7)-C(8)-N(3)	2.1(5)
C(12)-C(7)-C(8)-C(9)	0.8(4)
C(6)-C(7)-C(8)-C(9)	-178.9(3)
N(3)-C(8)-C(9)-C(10)	179.3(3)
C(7)-C(8)-C(9)-C(10)	0.2(4)
C(8)-C(9)-C(10)-C(ll)	-1.4(5)
C(9)-C(10)-C(l l)-C(12)	1.3(4)
C(10)-C(l l)-C(12)-C(7)	-0.2(4)
C(10)-C(l l)-C(12)-C(13)	178.9(3)
C(8)-C(7)-C(12)-C(ll)	-0.9(4)
C(6)-C(7)-C(12)-C(ll)	178.9(3)
C(8)-C(7)-C(12)-C(13)	179.9(2)
C(6)-C(7)-C(12)-C(13)	-0.4(3)
C(6)-N(2)-C(13)-0(3)	-179.1(3)
C(4)-N(2>C(13)-0(3)	2.8(4)
C(6)-N(2)-C(13)-C(12)	1.1(3)
C(4)-N(2)-C(13)-C(12)	-177.0(2)
C(l l)-C(12>C(13)-0(3)	0.6(5)
C(7)-C(12)-C(13)-0(3)	179.8(3)
C(ll)-C(12)-C(13)-N(2)	-179.6(3)
C(7)-C(12)-C(13)-N(2)	-0.4(3)

6,4.4 Infrared Spectrum **(FT-IR** Spectrum)

[00256] A representative FT-IR spectrum of pomalidomide was obtained as per USP <197K> in diffuse reflectance mode from KBr pellet. The FT-IR spectrum and its spectral assignments are shown in Figure 22 and Table **14,** respectively.

Table **14:** Infrared Spectral Assignments of Pomalidomide

Wave Number (cm^{-1})	Functional Group
3482, 3378	Aniline N-H stretching
3250	Imide N-H stretch
3115	Aromatic C-H stretch
2900	Aliphatic C-H stretch
1701, 1634	Imide C=O stretching
1595, 1480, 1409	Aromatic C=C stretching
1260	Aniline C-N stretch
470 – 1200	Fingerprint region

6.4.5 Hygroscopicity

[00257] Dynamic vapor sorption (DVS) analysis was carried out for two preparations of Form A using Surface Measurement Systems DVS. Representative DVS isotherm plots are presented in Figure 23 and Figure 24. In one study, the moisture uptake was less than about 0.14 % (wv'w) up to 95% relative humidity, indicative that pomalidomide Form A is not hygroscopic. In another study, Form A exhibited less than about 0.11% mass change over the dry mass when relative humidity was increased from 0 to 95%. At the end of desorption, the sample lost all of the weight it gained during the process of moisture sorption. After undergoing a full adsorption/desorption cycle, the sample had an XRPD pattern consistent with Form A.

6.4.6 X-Ray Powder Diffraction

[00258] XRPD of two preparations of Form A of poraalklomide was measured. The X-ray powder diffraetograrns are shown in Figure 25 and Figure 26.

6.4.7 Stability

[00259] The stability of Form A was demonstrated by exposing the sample to a 40 °C/75% RH environment for four weeks. The physical properties of the exposed form A were unchanged as compared to at the start of the study.

|00260] Form A also appeared to be stable in acetone, acetonitriie, ethanol, ethyl acetate, methyl ethyl ketone, THF, toluene, ethanoi-water (1:1) or water at 40 °C for at least 4 weeks.

6.4.8 Compression Test

[00261] A compression test for Form A was carried out by applying 2000-psi pressure to the sample for 1 minute and then analyzing the sample by XRPD. The XRPD pattern revealed thai Form A was unchanged after compression (Figure 27).

6.4.9 Particle Size Distribution

[00262] In some embodiments, Form A was prepared as a white, irregular plate crystalline with a particle size D90 < 12 μη. Particle size distribution was determined for various lots of pomalidomide. Particle size data for representative lots are listed in Table 15.

Table 15: Particle Size Data for Pomalidomide Lots

Lot Number	D (v, 0.5)	< 10μm	< Iμm
1	11	46%	0.0%
2	15	31%	0.0%
3	17	31%	0.0%
4	11	43%	0.0%
5	9	57%	0.0%

6.5 Assays

6,5.1 TNFα Inhibition Assay *in* PBMC

[00263] Peripheral blood mononuclear cells (PBMC) from normal donors are obtained by Ficoll Hypaque (Pharmacia, Piscatawav, NJ, USA) density centnfugation. Cells are cultured in RPMl 1640 (Life Technologies, Grand Island, NY, USA) supplemented with 10% AB+human serum (Gemini Bio-products, Woodland, CA, USA), 2 mM L~ glutamine, 100 U/ml penicillin, and 100 ^tg/ml streptomycin (Life Technologies).

[00264] PBMC (2 x 10^5 cells) are plated in 96-well flat-bottom Costar tissue culture plates (Corning, NY, USA) in triplicate. Cells are stimulated with LPS (from Salmonella abortus equi, Sigma cat. no. L-1887, St. Louis, MO, USA) at 1 ng/mL final in the absence or presence of compounds. Compounds provided herein are dissolved in DMSO (Sigma) and further dilutions are done in culture medium immediately before use. The final DMSO concentration in all assays can be about 0.25%. Compounds are added to cells 1 hour before LPS stimulation. Ceils are then incubated for 18-20 hours at 37 °C in 5 % CO_2, and supernatants are then collected, diluted with culture medium and assayed for TNFα levels by ELISA (Endogen, Boston, MA, USA). IC_{53S} are calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100% and bottom to 0%, allowing variable slope (GraphPad Prism v3.02).

6.5.2 IL-2 and MIP-3a Production by T Ceils

[00265] PBMC are depleted of adherent monocytes by placing 1 x 10^8 PBMC in 10 ml complete medium (RPMl 1640 supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, 100 U/ml penicillin, and 100 ^tg/ml streptomycin) per 10 cm tissue culture dish, in 37°C, 5 % $C0_2$ incubator for 30-60 minutes. The dish is rinsed with medium to remove all non-adherent PBMC. T cells are purified by negative selection using the following antibody (Pharmingen) and Dynabead (Dynai) mixture for every 1 x 10^8 non-adherent PBMC: 0.3 ml Sheep anti-mouse IgG beads, 15 μl anti-CD16, 15 μï anti-CD33, 15 μï anti-CD56, 0.23 ml anti-CD19 beads, 0.23 ml anti-HLA class II beads, and 56 μl anti-CD 14 beads. The cells and bead/antibody mixture is rotated end-over-end for 30-60 minutes at 4°C. Purified T cells are removed from beads

using a Dynal magnet. Typical yield is about 50% T cells, 87-95% $CD3^+$ by flow cytometry.

[00266] Tissue culture 96-well flat-bottom plates are coated with anti-CD3 antibody OKT3 at 5 μg/ml in PBS, 100 μl per well, incubated at 37°C for 3-6 hours, then washed four times with complete medium 100 μl/well just before T cells are added. Compounds are diluted to 20 times of final in a round bottom tissue culture 96-well plate. Final concentrations are about 10 μM to about 0.00064 μM. A 10 mM stock of compounds provided herein is diluted 1:50 in complete for the first 20x dilution of 200 μM in 2 % DMSO and serially diluted 1:5 into 2 % DMSO. Compound is added at 10 μl per 200 μl culture, to give a final DMSO concentration of 0.1 %. Cultures are incubated at 37°C, 5 % $C0_2$ for 2-3 days, and supernatants analyzed for IL-2 and MTP-3<¾ by ELISA (R&D Systems). IL-2 and MIP-3α levels are normalized to the amount produced in the presence of an amount of a compound provided herein, and EC50S calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100 % and bottom to 0 %, allowing variable slope (GraphPad Prism v3.02).

6.5.3 Cell Proliferation **Assay**

|00267] Cell lines Namalwa, MUTZ-5, and UT-7 are obtained from the Deutsche Sammlung von Mikroorganismen und Zellkuituren GmbH (Braunschweig, Germany). The cell line KG-l is obtained from the American Type Culture Collection (Manassas, VA, LISA). Cell proliferation as indicated by ^{3}H-thymidine incorporation is measured in all cell lines as follows.

[00268] Cells are plated in 96-well plates at 6000 cells per well in media. The cells are pre-treated with compounds at about 100, 10, 1, 0.1, 0.01, 0.001, 0.0001 and 0 μM in a final concentration of about 0.25 % DMSO in triplicate at 37°C in a humidified incubator at 5 % $C0_2$ for 72 hours. One microcurie of ^{3}H-thymidine (Amersham) is then added to each well, and cells are incubated again at 37°C in a humidified incubator at 5 % $C0_2$ for 6 hours. The cells are harvested onto UniFilter GF/C filter plates (Perkin Elmer) using a cell harvester (Tomtec), and the plates are allowed to dry overnight. Microscint 20 (Packard) (25 μl/well) is added, and plates are analyzed in TopCount NXT (Packard). Each well is counted for one minute. Percent inhibition of cell proliferation

is calculated by averaging all triplicates and normalizing to the DMSO control (0 % inhibition). Each compound is tested in each cell line in three separate experiments. Final IC_{50}s are calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100 % and bottom to 0 %, allowing variable slope. (GraphPad Prism v3.02).

6.5.4 Immunoprecipitation and Immunoblot

[00269] Namalwa cells are treated with DMSO or an amount of a compound provided herein for 1 hour, then stimulated with 10 U/ml of Epo (R&D Systems) for 30 minutes. Cell lysates are prepared and either immunoprecipitated with Epo receptor Ab or separated immediately by SDS-PAGE. Immunoblots are probed with Akt, phospo-Akt (Ser473 or Thr308), phospho-Gabl (Y627), Gabl , IRS2, actin and IRF-1 Abs and analyzed on a Storm 860 Imager using ImageQuant software (Molecular Dynamics).

6.5.5 Cell Cycle Analysis

[00270] Cells are treated with DMSO or an amount of a compound provided herein overnight. Propidiurn iodide staining for cell cycle is performed using CycleTEST PLUS (Beeton Dickinson) according to manufacturer's protocol Following staining, cells are analyzed by a FACSCalibur flow cytometer using ModFit LT software (Becton Dickinson).

6.5.6 Apoptosis Analysis

[00271] Cells are treated with DMSO or an amount of a compound provided herein at various time points, then washed with armexin-V wash buffer (BD Biosciences). Cells are incubated with annexin-V binding protein and propidiurn iodide (BD Biosciences) for 10 minutes. Samples are analyzed using flow cytometry.

6.5.7 Luciferase Assay

[00272] Namalwa cells are transfected with 4 μg of AP1-luciferase (Stratagene) per 1 x 10^6 cells and 3 μl Lipofectamine 2000 (Invitrogen) reagent according to manufacturer's instructions. Six hours post-transfeciion, cells are treated with DMSO or an amount of a compound provided herein. Luciferase activity is assayed using

luciferase lysis buffer and substrate (Promega) and measured using a luminometer (Turner Designs).

[00273] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the disclosure and are encompassed by the appended claims.

[00274] All of the patents, patent applications and publications referred to herein are incorporated herein in their entireties. Citation or identification of any reference in this application is not an admission that such reference is available as prior art. The full scope of the disclosure is better understood with reference to the appended claims.

CLAIMS

What is claimed is:

1. A solid form of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione having an X-ray powder diffraction pattern comprising peaks at approximately 12, 17, and 26 degrees 2Θ.

2. The solid form of claim 1, wherein the X-ray powder diffraction pattern further comprises peaks at approximately 14, 18, and 24 degrees 2Θ.

3. The solid form of claim 1, having an X-ray powder diffraction pattern comprising peaks at approximately 12.1, 14.0, 17.4, 18.4, 24.4, and 25.6 degrees 2Θ.

4. The solid form of claim 3, wherein the X-ray powder diffraction pattern further comprises peaks at approximately 24.8 and 28.1 degrees 2Θ.

5. The solid form of claim 1, having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction pattern of any one of Figures 1, 2, 3, 4, 5, 6, 25, 26, and 27.

6. The solid form of claim 1, having a thermogravimetric analysis thermogram exhibiting a total mass loss of less than about 1% between about 25 °C and about 200 °C, when heated from about 25 °C to about 350 °C.

7. The solid form of claim 1, having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at approximately 320 °C, when heated from about 25 °C to about 350 °C.

8. The solid form of claim 1, which is substantially crystalline.

9. The solid form of claim 1, which is greater than 80% by weight, greater than 90% by weight, greater than 95% by weight, greater than 97% by weight, or greater than 99% by weight crystalline.

10. The solid form of claim 1, which is substantially physically pure.

11. The solid form of claim 10, which is substantially free of other solid forms of 4-amino-2-(2,6-dioxopiperidine-3-y3)isoindo3ine-l,3-dione.

12. The solid form of claim 1, which is substantially chemically pure.

13. The solid form of claim 1, which is substantially free of solvent.

14. The solid form of claim 1, which is substantially free of water.

15. The solid form of claim 1, further comprising amorphous 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione.

16. The solid form of claim 1, which is stable.

17. The solid form of claim 1, which is substantially crystalline and thermally stable.

18. A solid form of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-3,3-dione comprising amorphous 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindolirie-l ,3-dione.

19. The solid form of claim 18, having an X-ray powder diffraction pattern comprising no sharp peaks.

20. The solid form of claim 19, wherein the X-ray powder diffraction pattern comprises a global maximum at approximately 26 °2Θ.

21. The solid form of claim 20, further comprising a local maximum at approximately 12 °2Θ.

22. The solid form of claim 18, which is greater than 50% by weight, greater than 60% by weight, greater than 70% by weight, greater than 80% by weight, greater than 90% by weight, greater than 95% by weight, greater than 97% by weight, or greater than 99% by weight amorphous.

23. The solid form of claim 18, which is substantially physically pure.

24. The solid form of claim 23, which is substantially free of other solid forms of 4-amino-2-(2,6-dioxopiperidine-3-y3)isoindo3ine-l,3-dione.

25. The solid form of claim 18, which is substantially chemically pure.

26. The solid form of claim 18, which is stable.

27. A pharmaceutical composition comprising the solid form of any one of claims 1 to 26.

28. The pharmaceutical composition of claim 27, further comprising a pharmaceutically acceptable excipient or carrier.

29. The pharmaceutical composition of claim 27, which is a single unit dosage form.

30. The pharmaceutical composition of claim 27, which is a tablet.

31. The pharmaceutical composition of claim 27, which is a capsule.

32. The pharmaceutical composition of claim 27, wherein the pomalidomide is in an amount of from about 0.1 to about 5 mg.

33. A method of treating a disease, comprising administering the solid form of any one of claims 1 to 26 or the pharmaceutical composition of any one of claims 27 to 31 to a subject in need thereof.

34. The method of claim 33, wherein the disease is multiple myeloma.

35. The method of claim 33, wherein the disease is myeloproliferative disease.

36. The method of claim 33, wherein the disease is anemia.

37. The method of claim 33, wherein the disease is scleroderma.

38. The method of claim 33, wherein the disease is amyloidosis.

39. The method of claim 33, further comprising administering a second active agent.

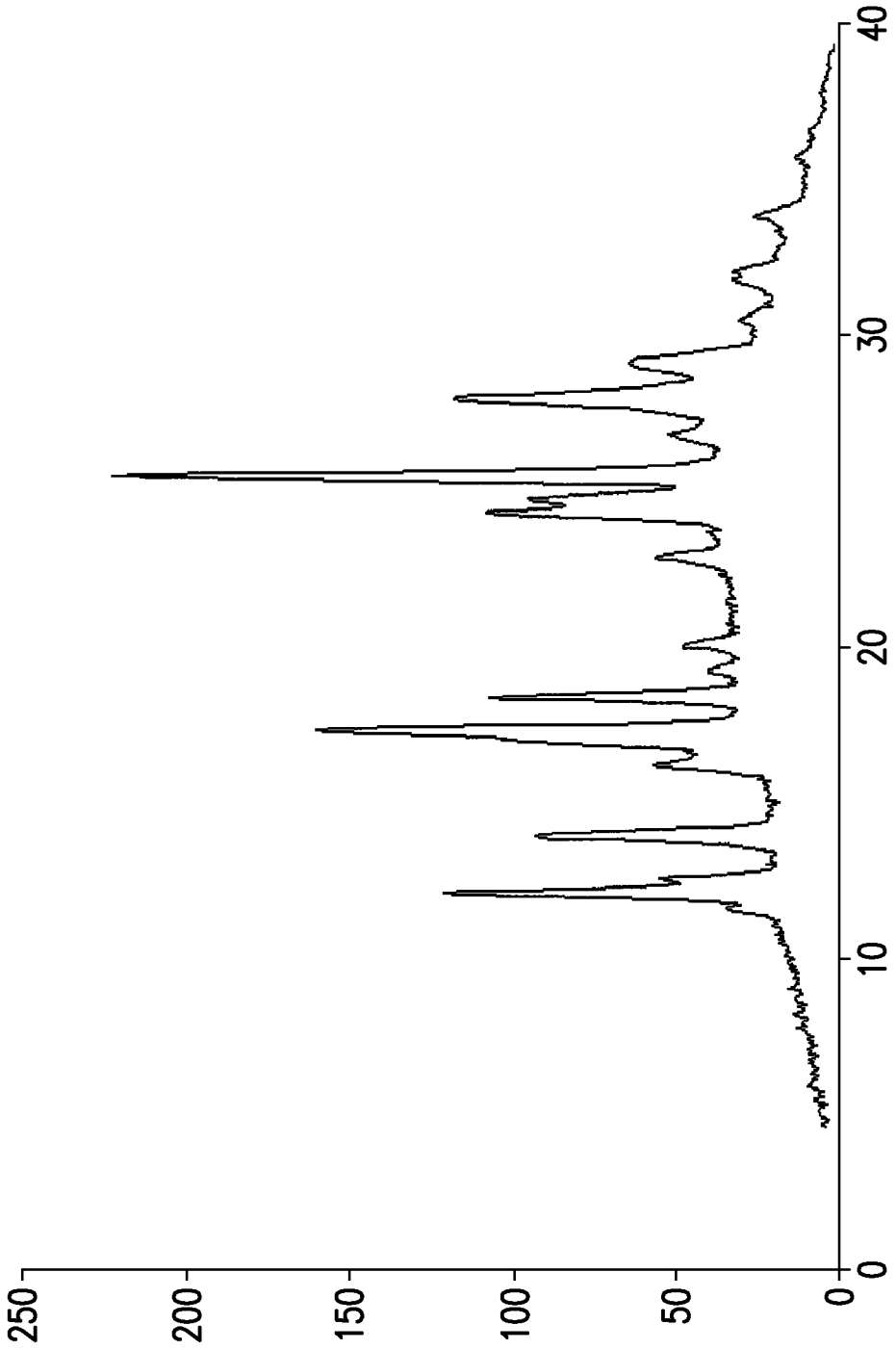


FIG. 1

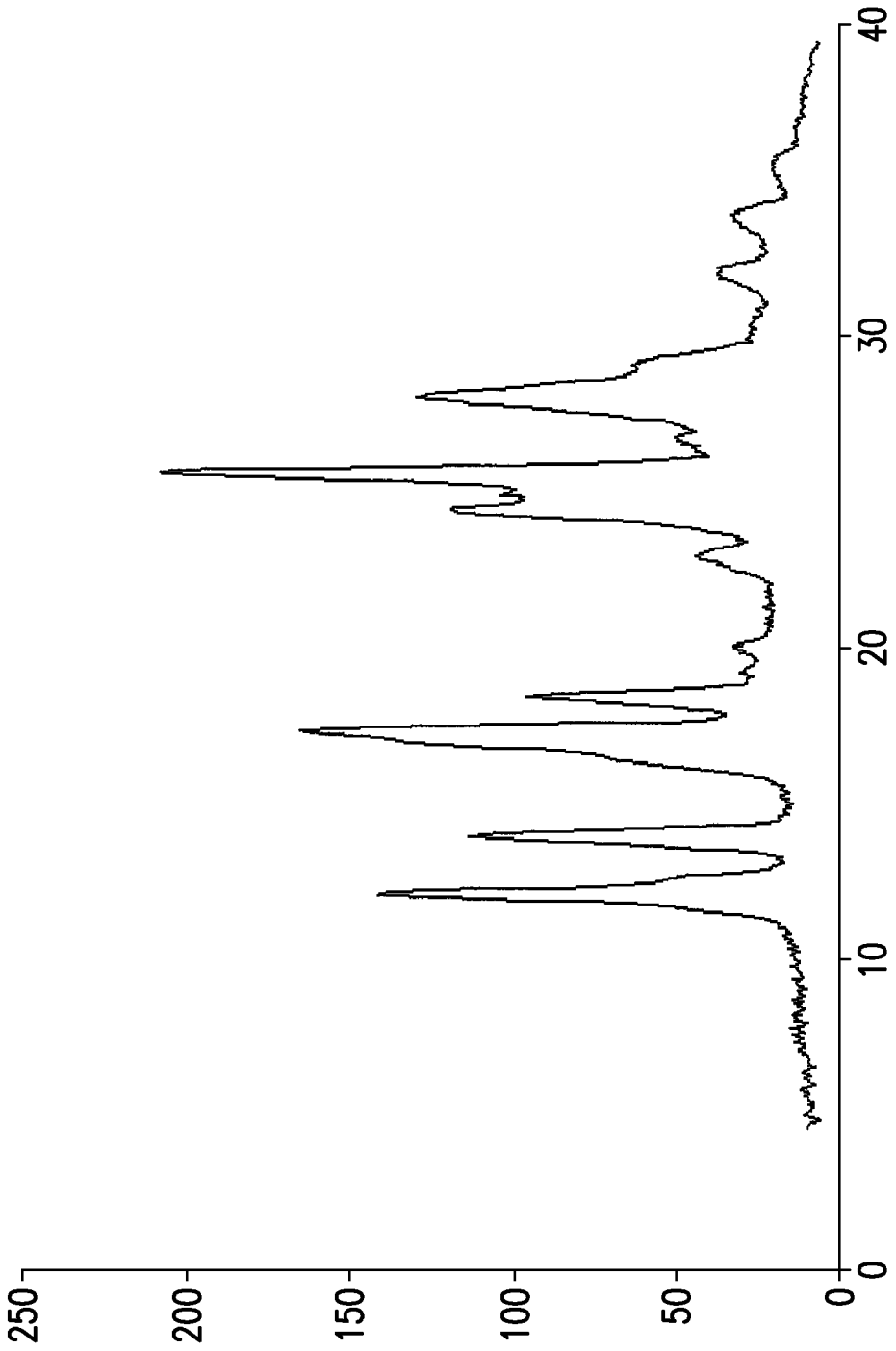


FIG. 2

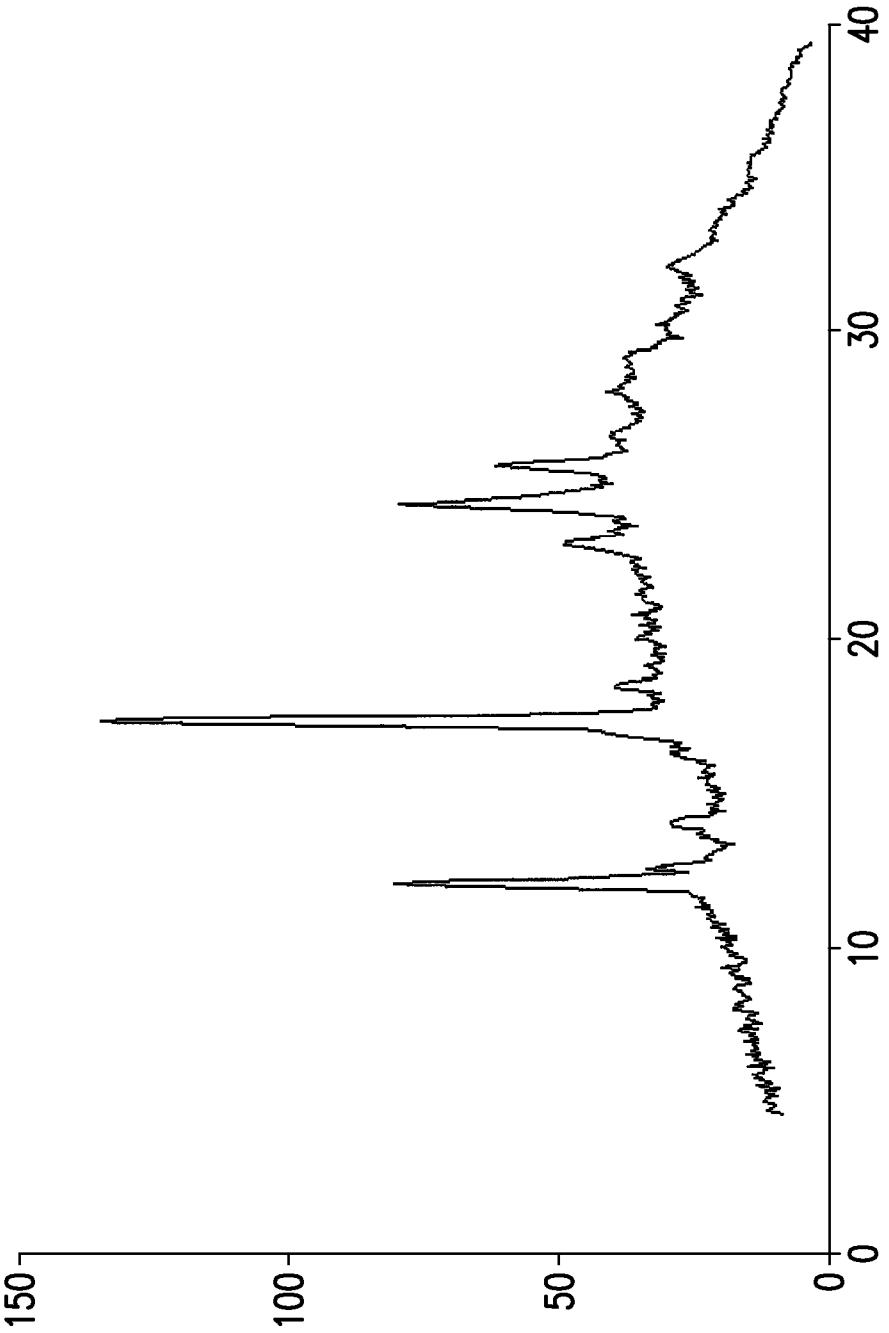


FIG. 3

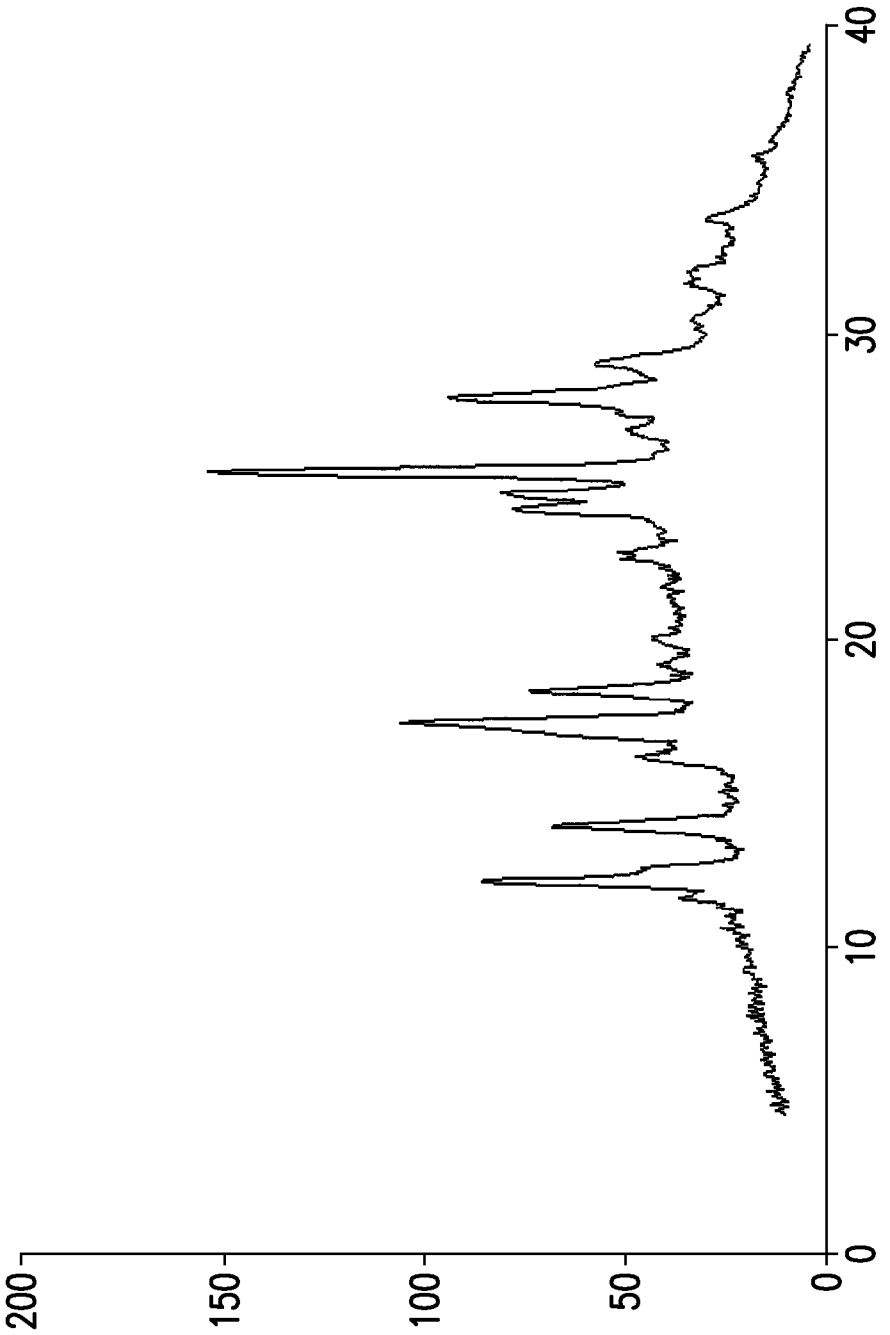


FIG. 4

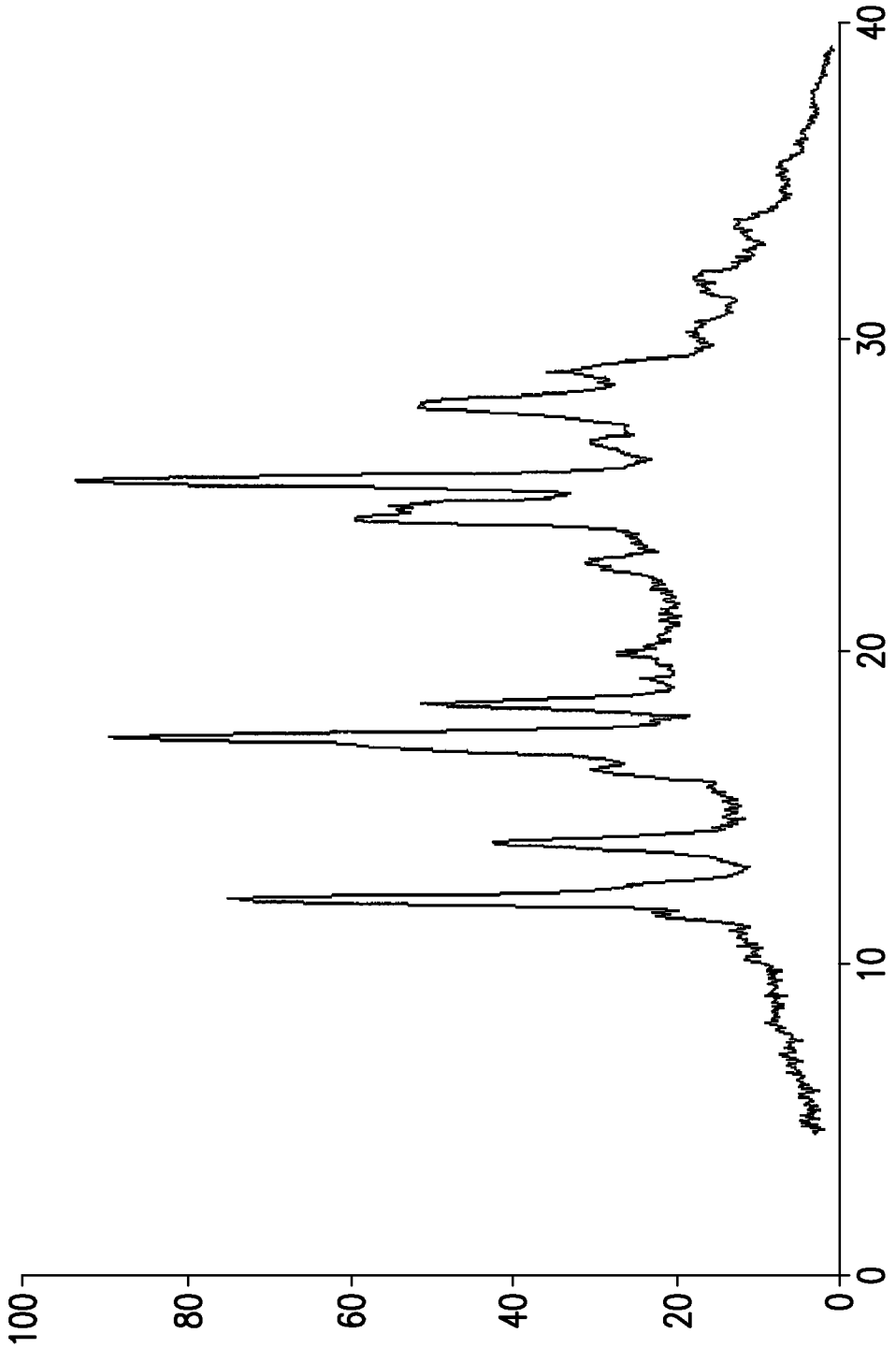


FIG. 5

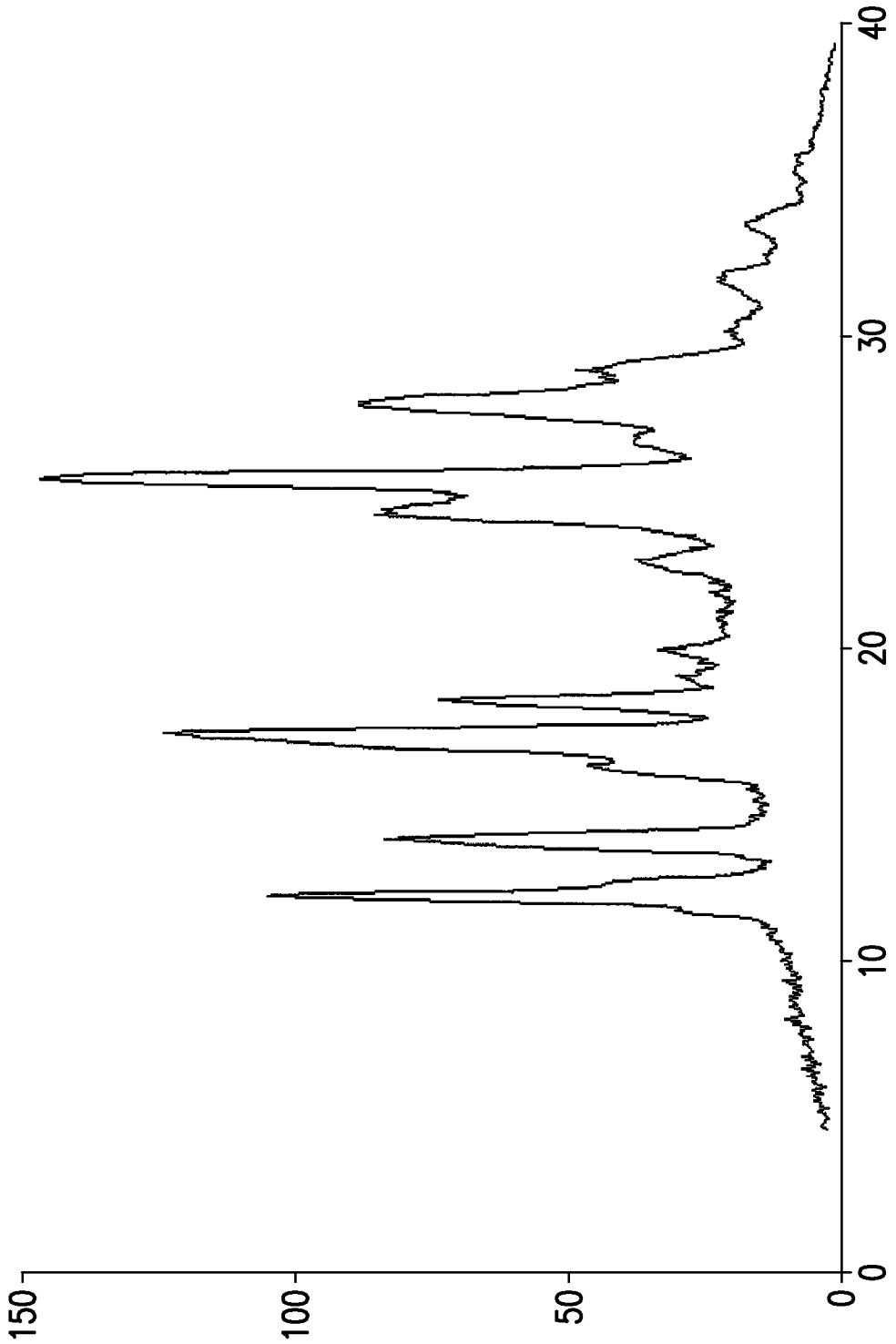


FIG. 6

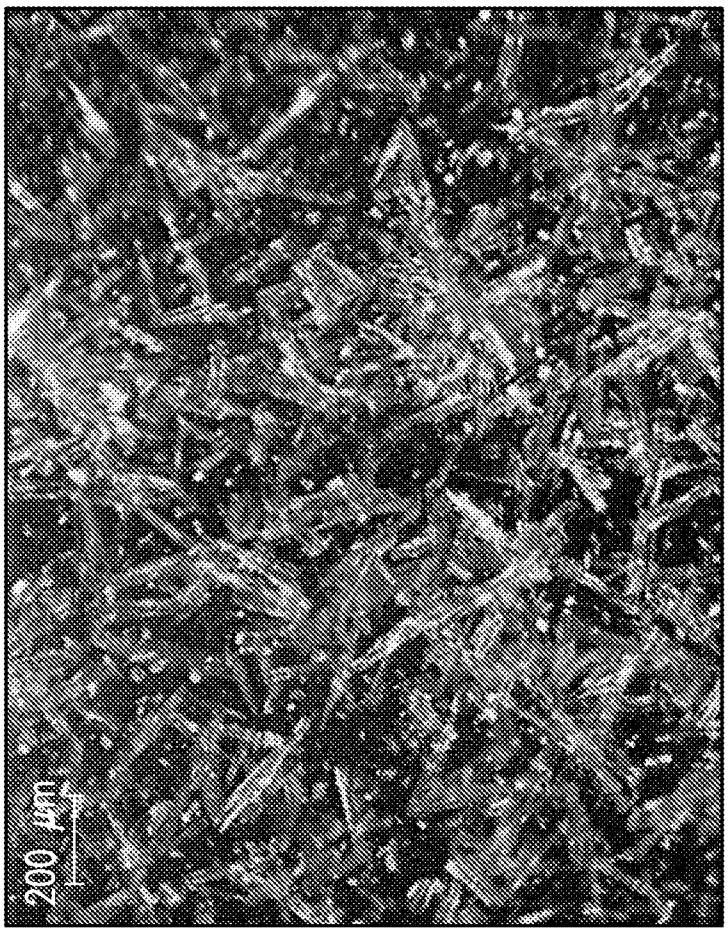


FIG. 7

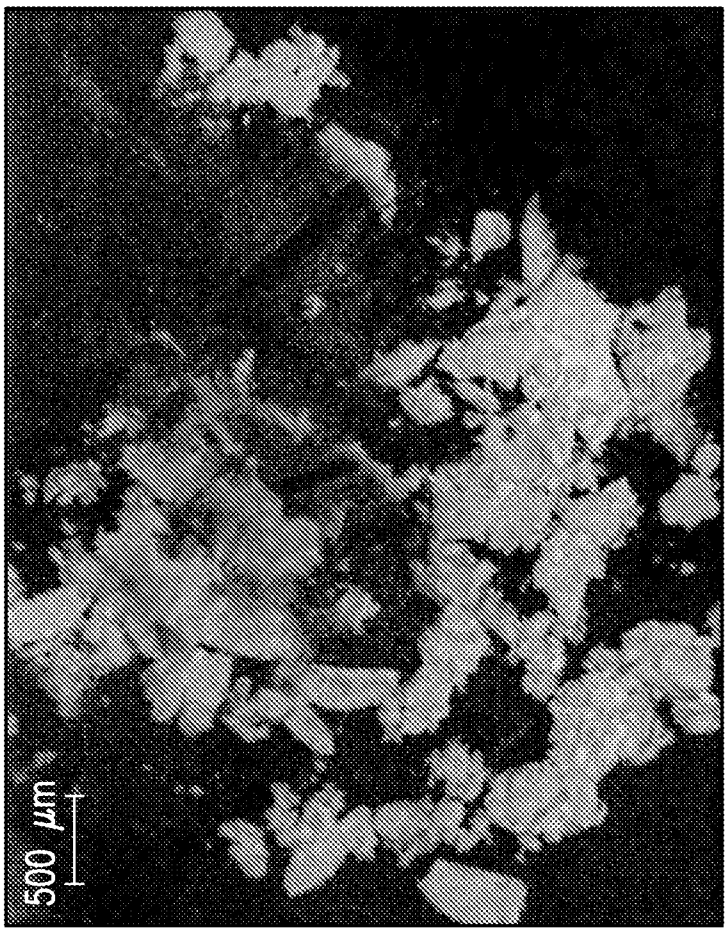


FIG. 8

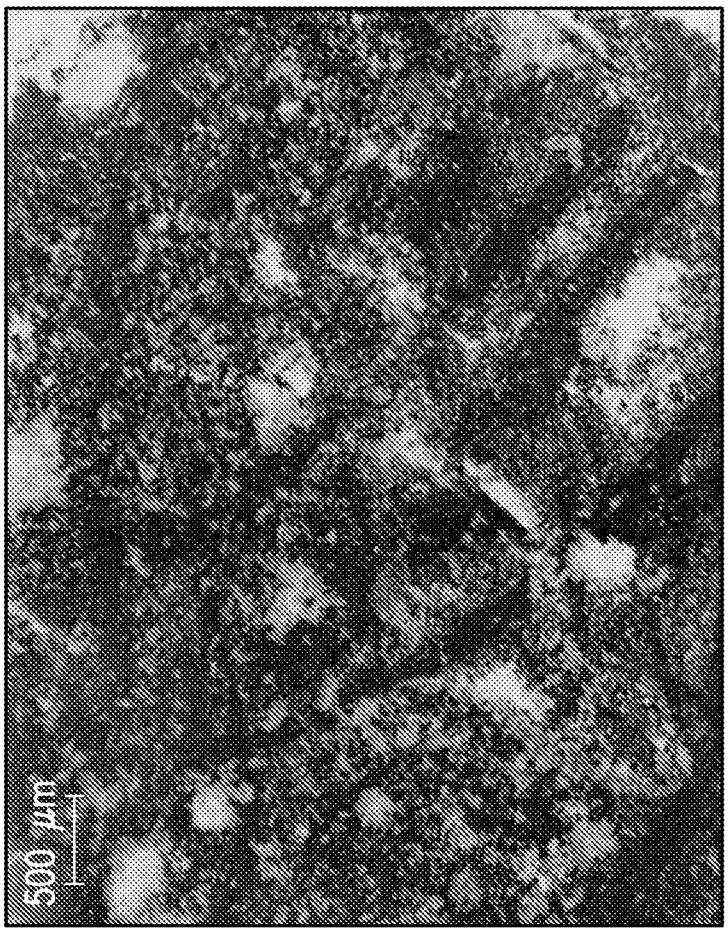


FIG. 9

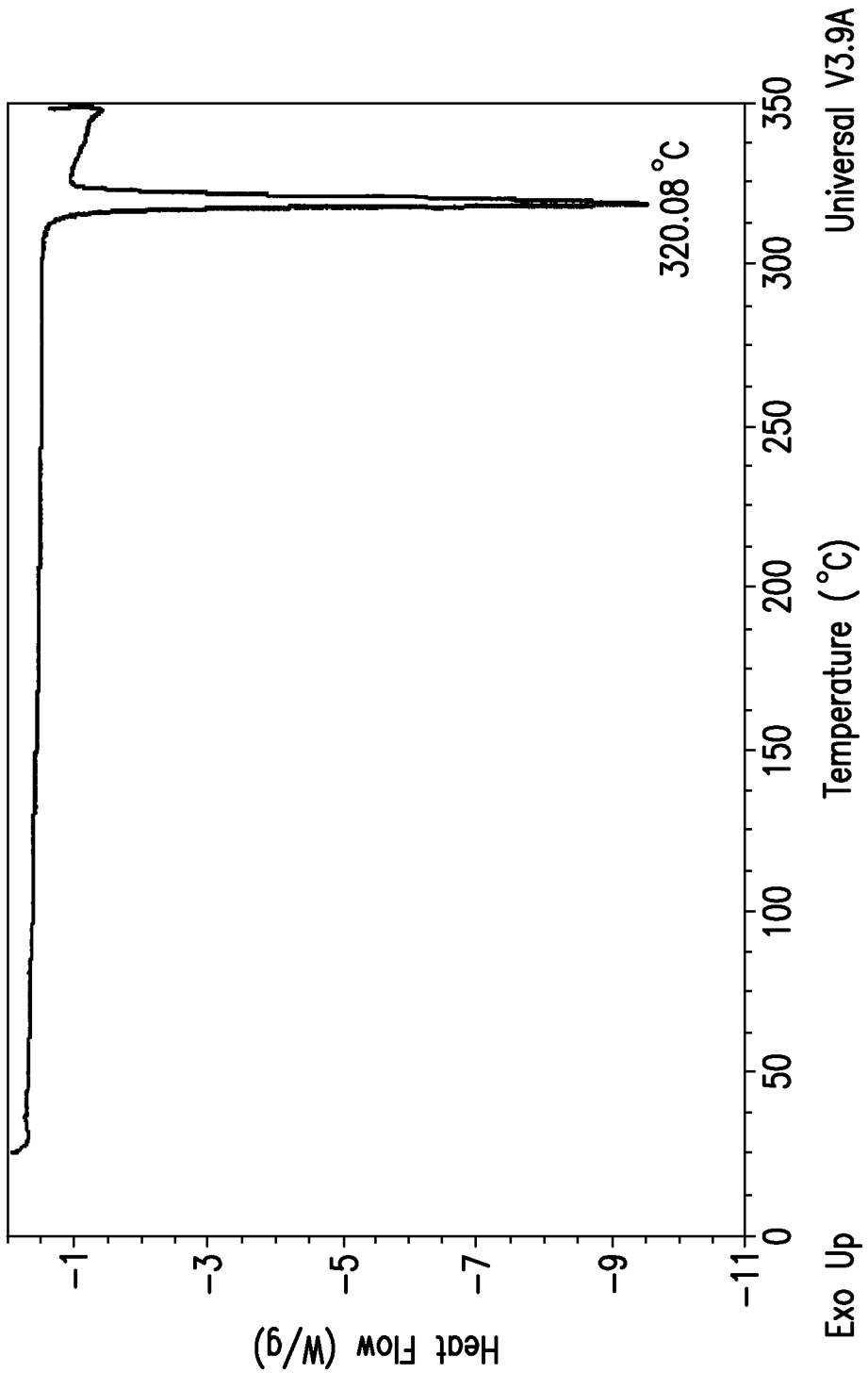

320.08 °C
Universal V3.9A
Temperature (°C)
Exo Up
Heat Flow (W/g)
-1
-3
-5
-7
-9
-11
0
50
100
150
200
250
300
350

FIG. 10

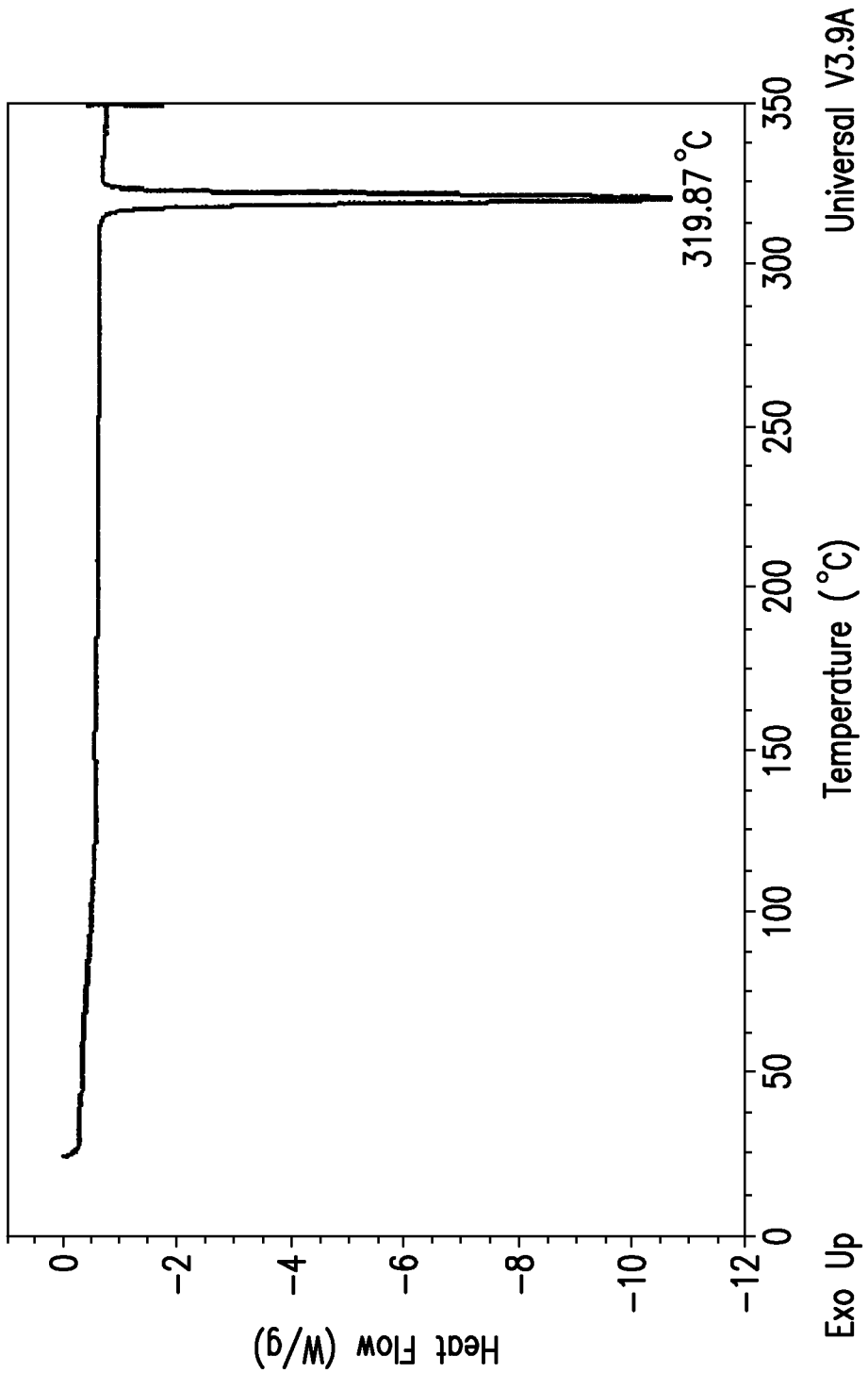

319.87°C
Universal V3.9A
Temperature (°C)
Heat Flow (W/g)
Exo Up
0
50
100
150
200
250
300
350
0
-2
-4
-6
-8
-10
-12

FIG. 11

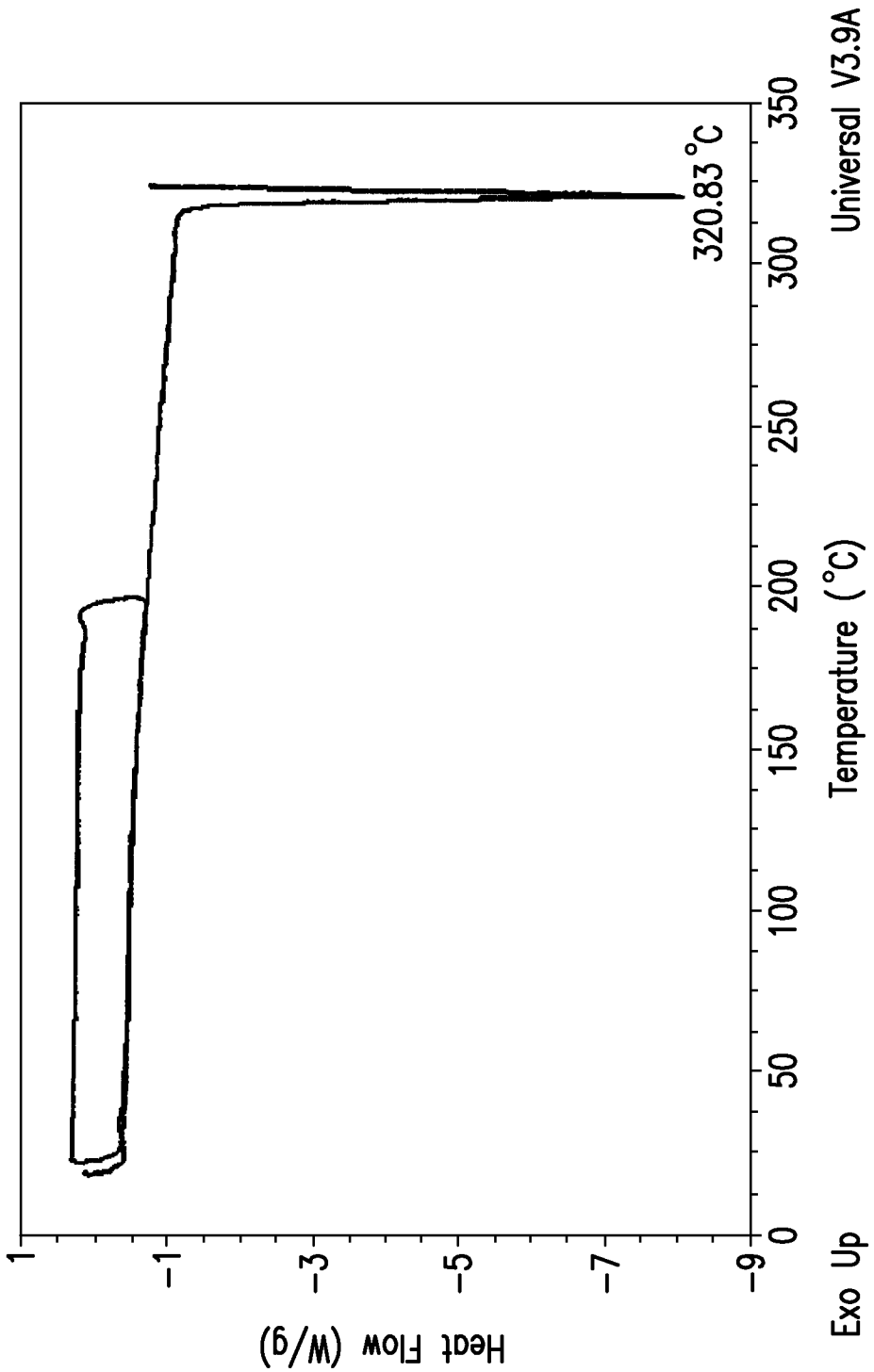

320.83 °C
Universal V3.9A
Temperature (°C)
Heat Flow (W/g)
Exo Up
1
-1
-3
-5
-7
-9
0
50
100
150
200
250
300
350

FIG. 12A

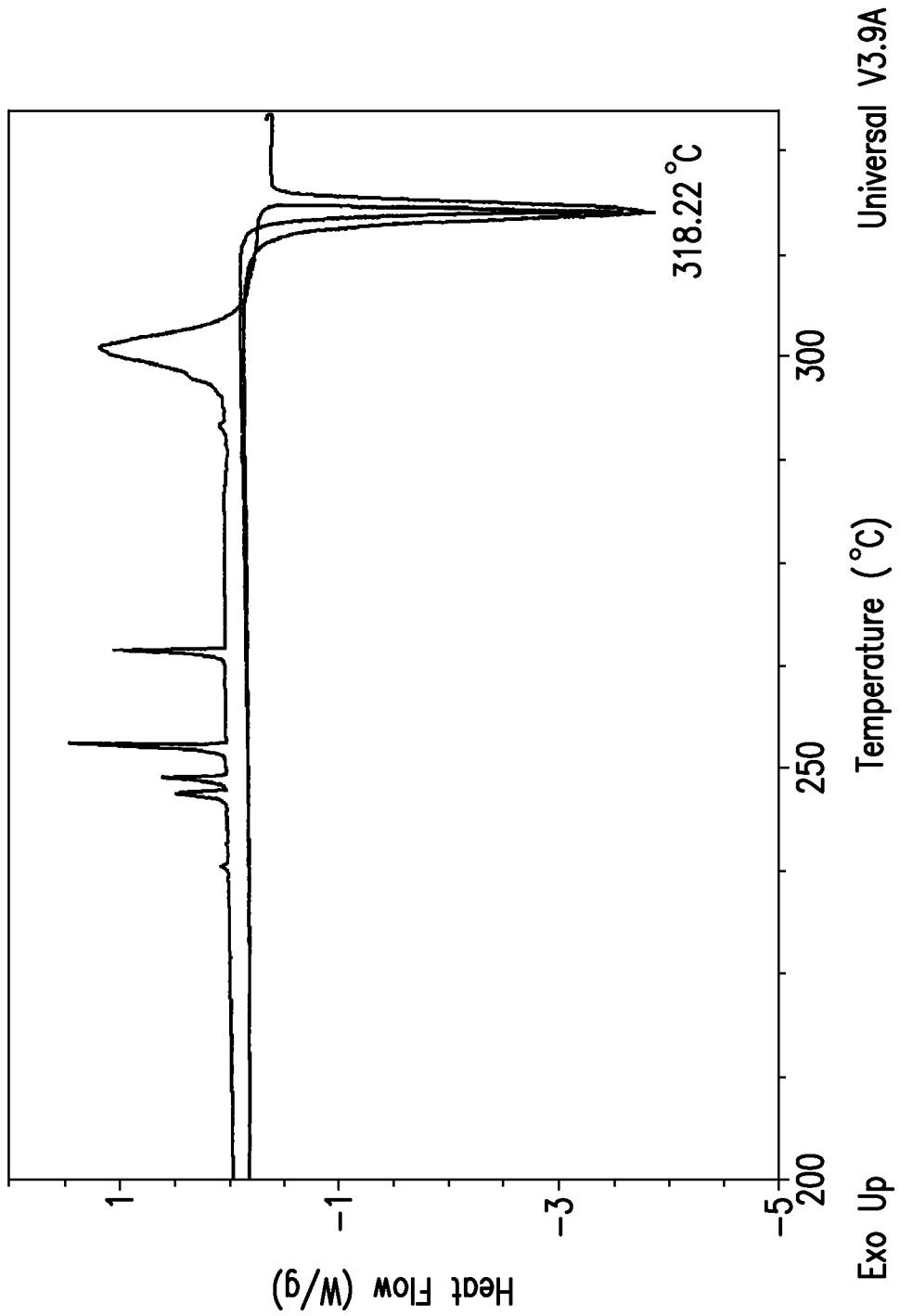

318.22 °C
Universal V3.9A
Heat Flow (W/g)
1
-1
-3
-5
200
250
300
Temperature (°C)
Exo Up

FIG. 12B

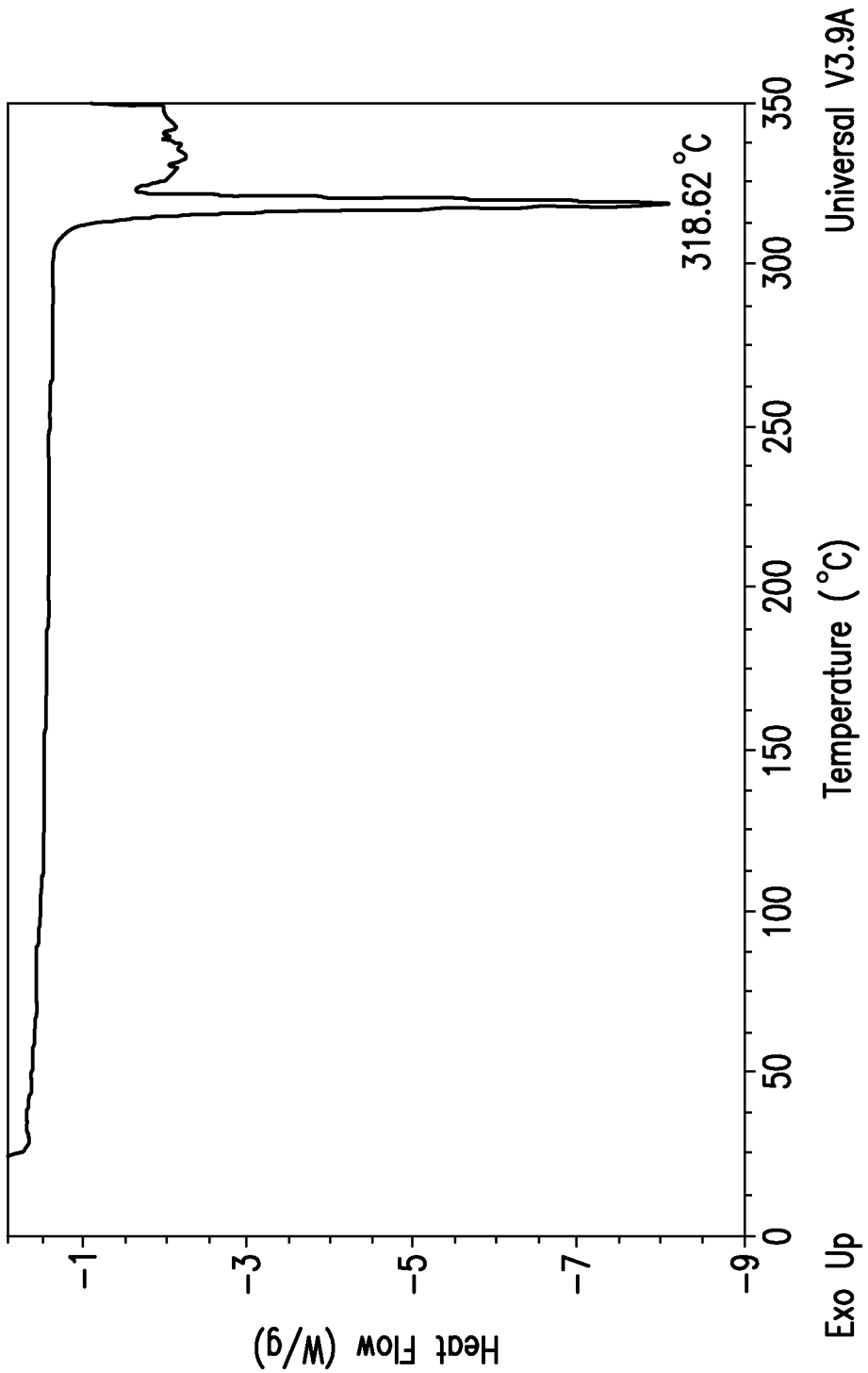

318.62 °C
Universal V3.9A
Temperature (°C)
Exo Up
Heat Flow (W/g)
-1
-3
-5
-7
-9
0
50
100
150
200
250
300
350

FIG. 13

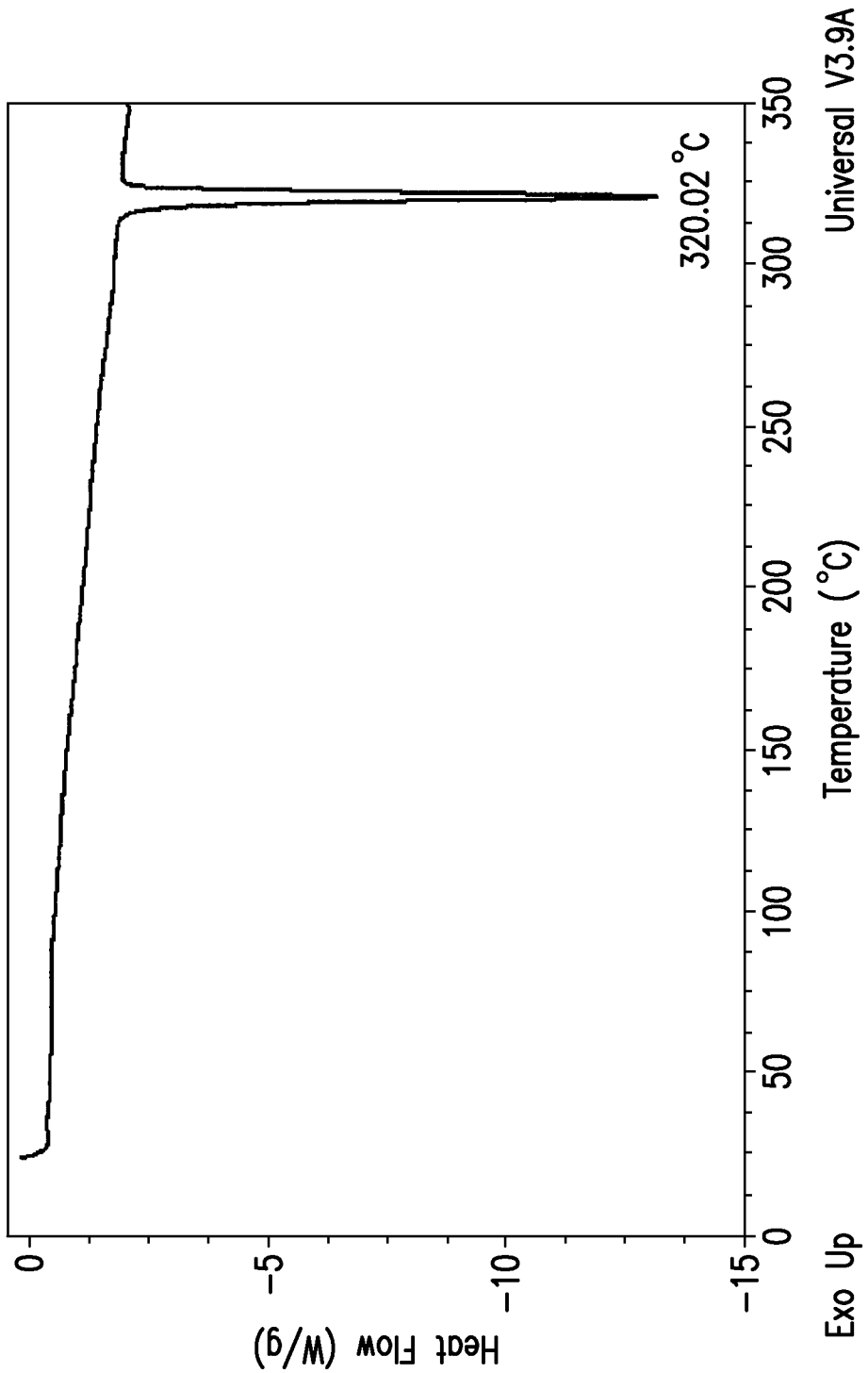
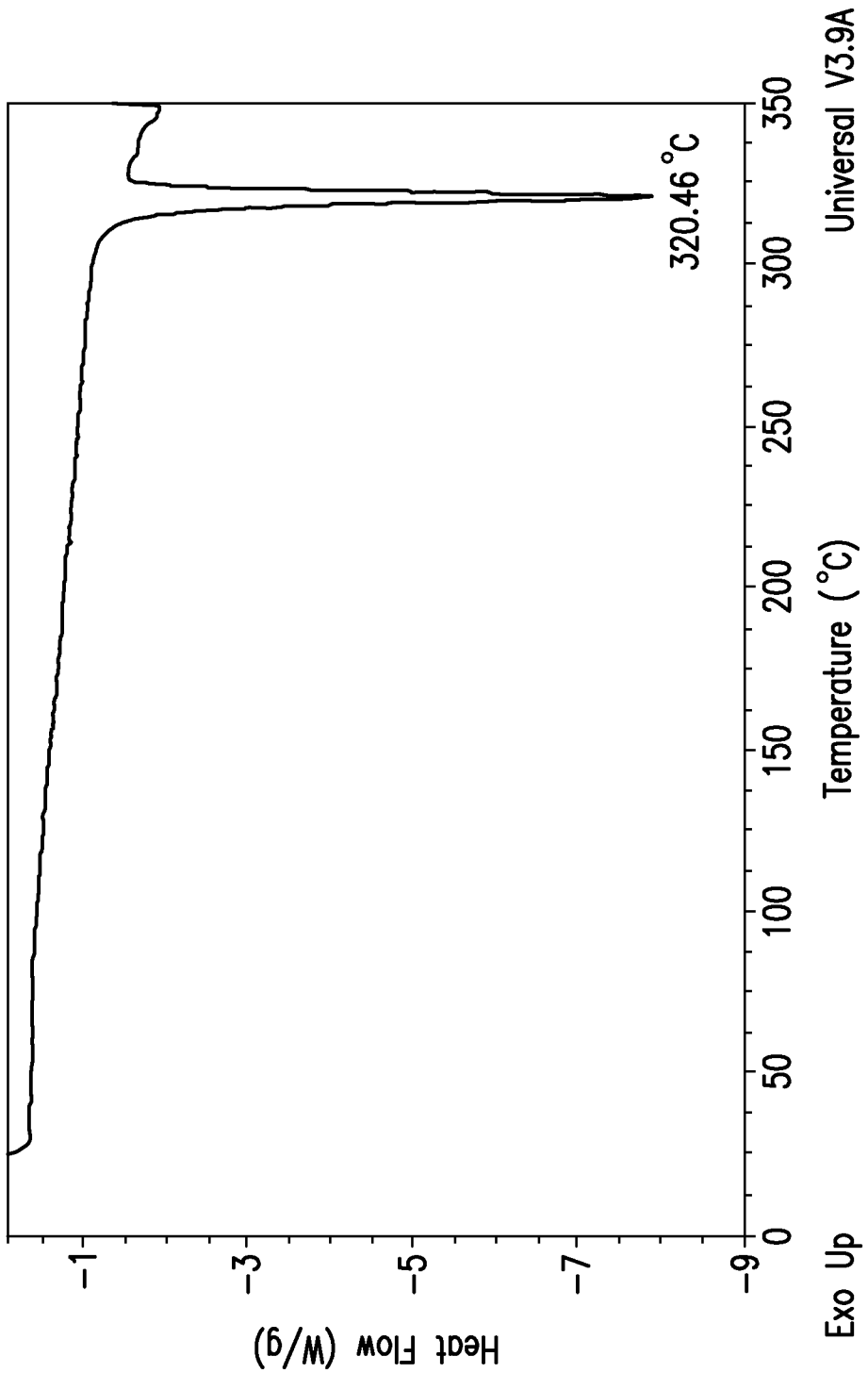

320.02 °C
Universal V3.9A
Temperature (°C)
Heat Flow (W/g)
Exo Up
0
50
100
150
200
250
300
350
0
−5
−10
−15

FIG. 14


320.46°C
Universal V3.9A
Temperature (°C)
Heat Flow (W/g)
Exo Up
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150
200
250
300
350
-1
-3
-5
-7
-9

FIG. 15

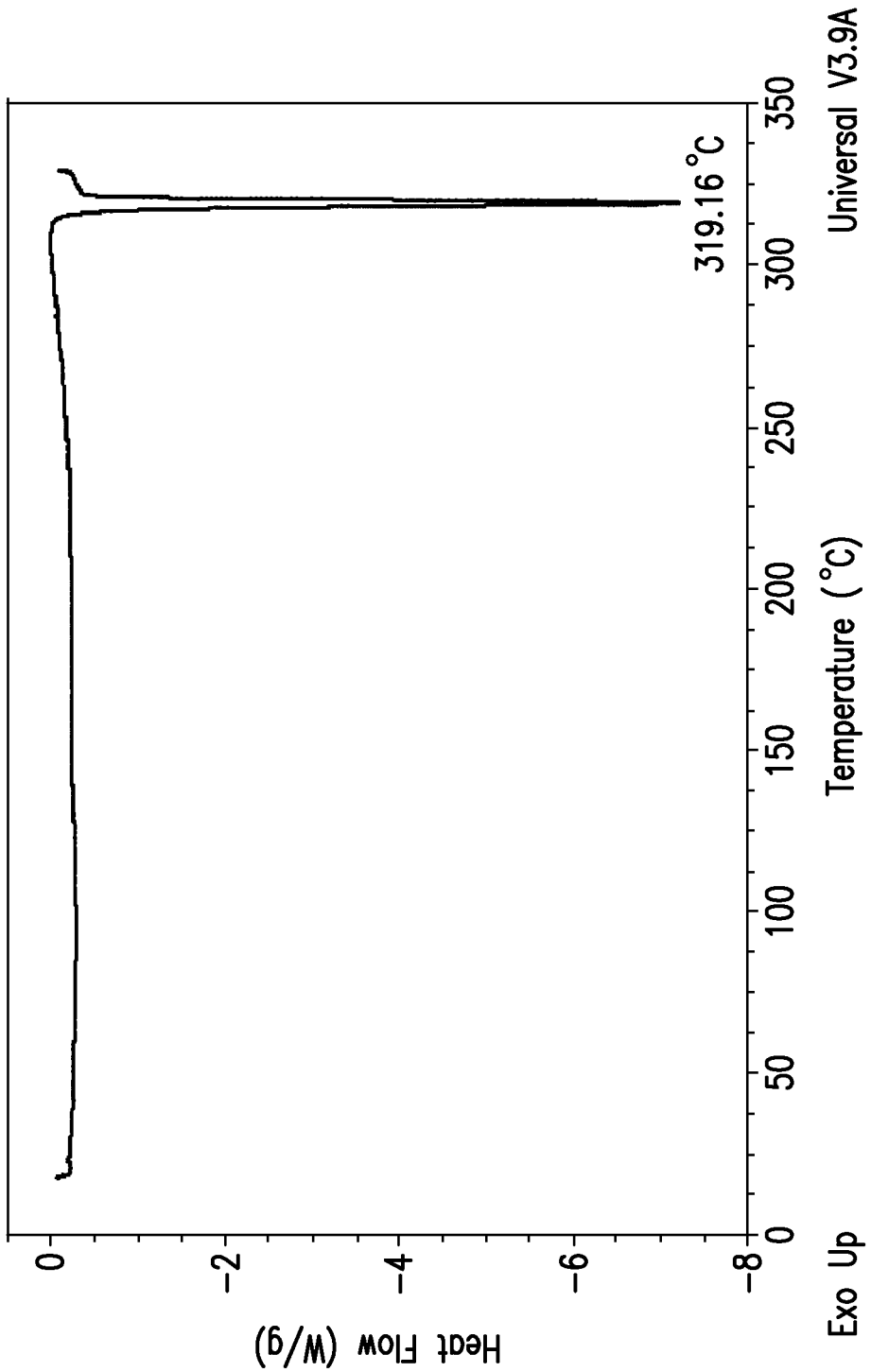
319.16°C
Universal V3.9A
Temperature (°C)
Heat Flow (W/g)
Exo Up
0
50
100
150
200
250
300
350
0
-2
-4
-6
-8

FIG. 16

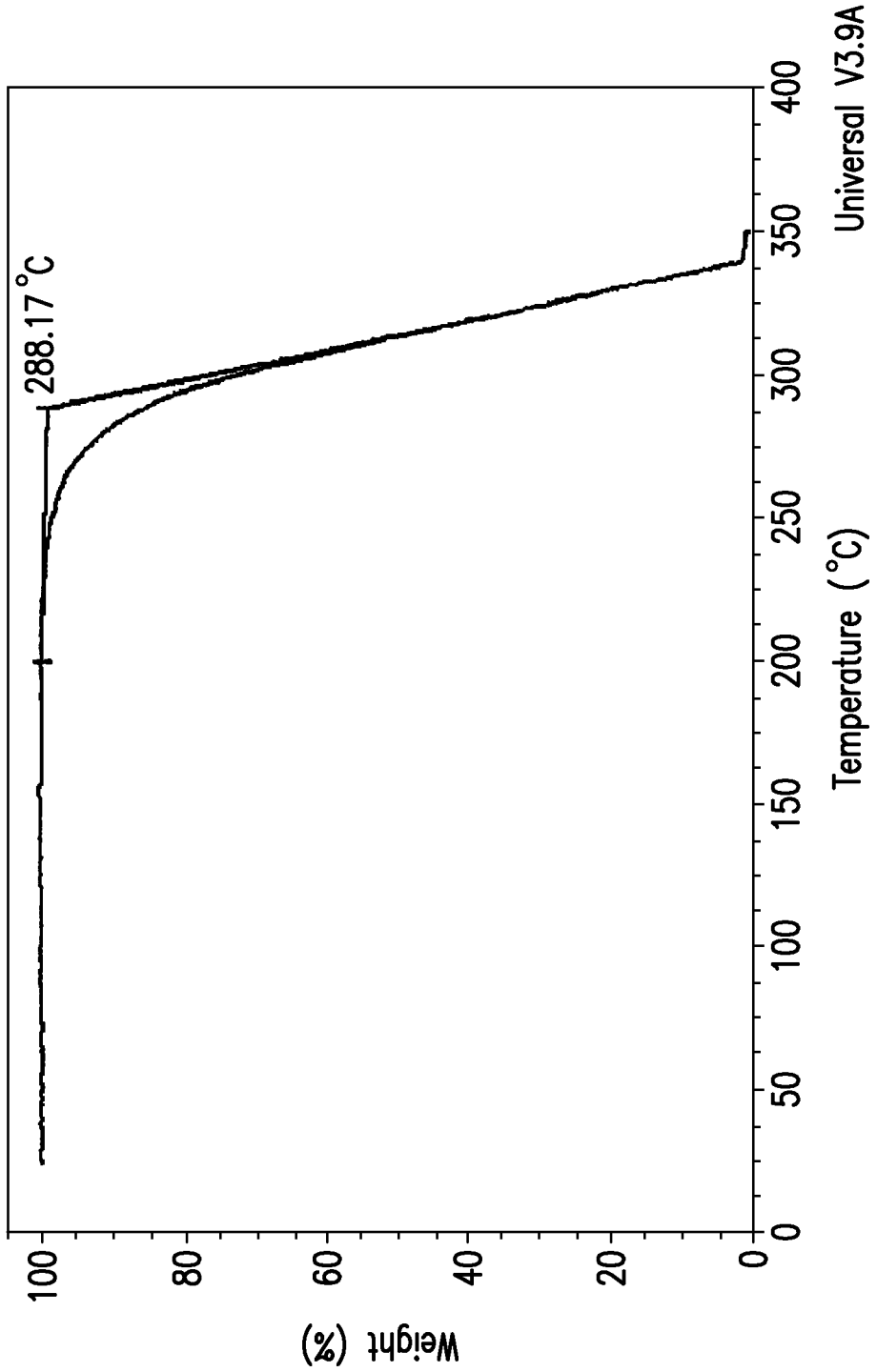
288.17°C
Weight (%)
100
80
60
40
20
0
0
50
100
150
200
250
300
350
400
Temperature (°C)
Universal V3.9A

FIG. 17

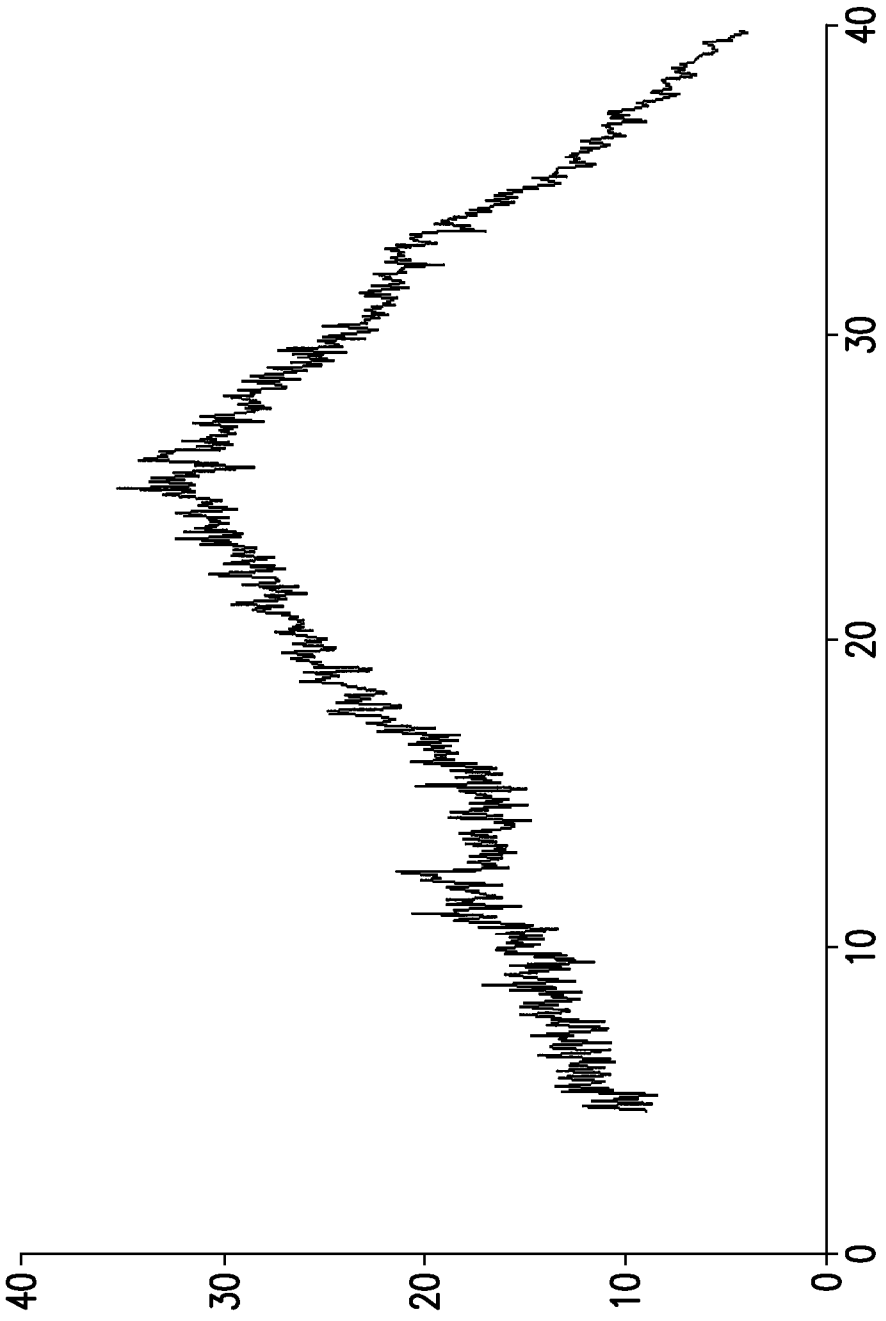

FIG. 18

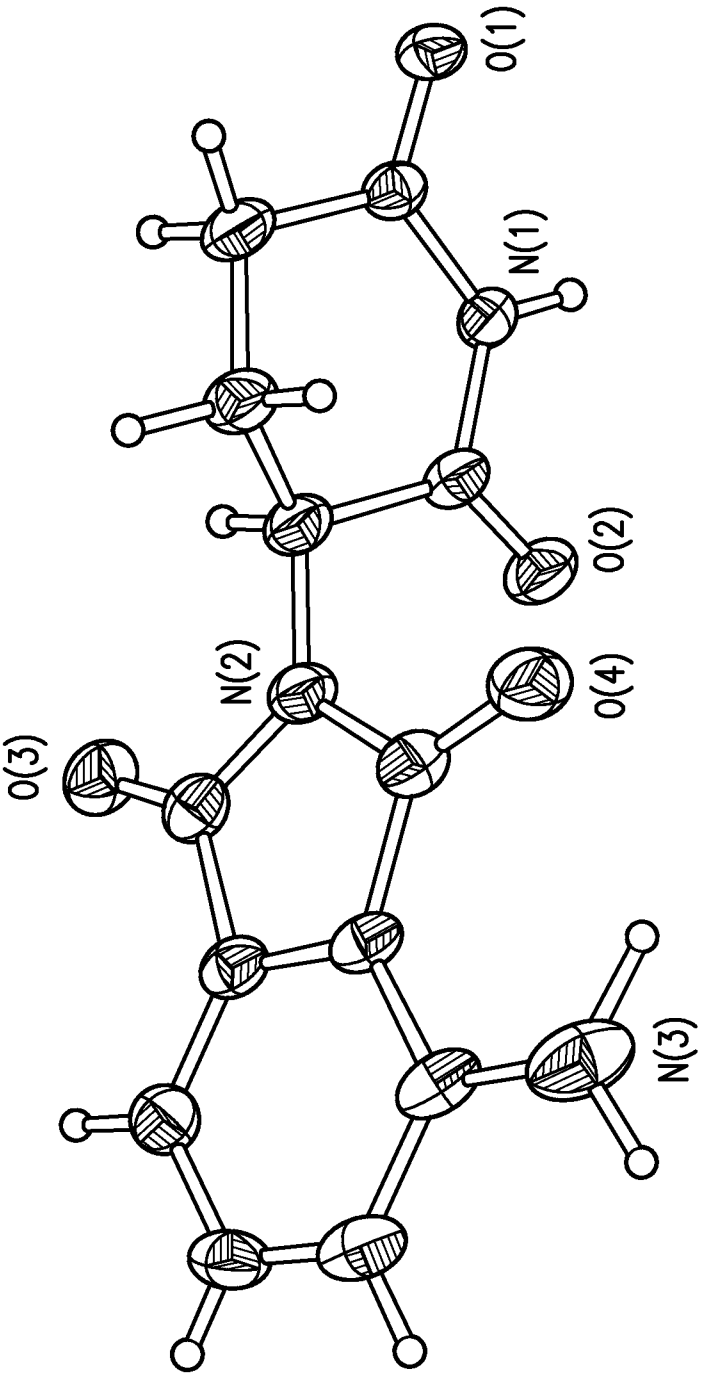

FIG. 19

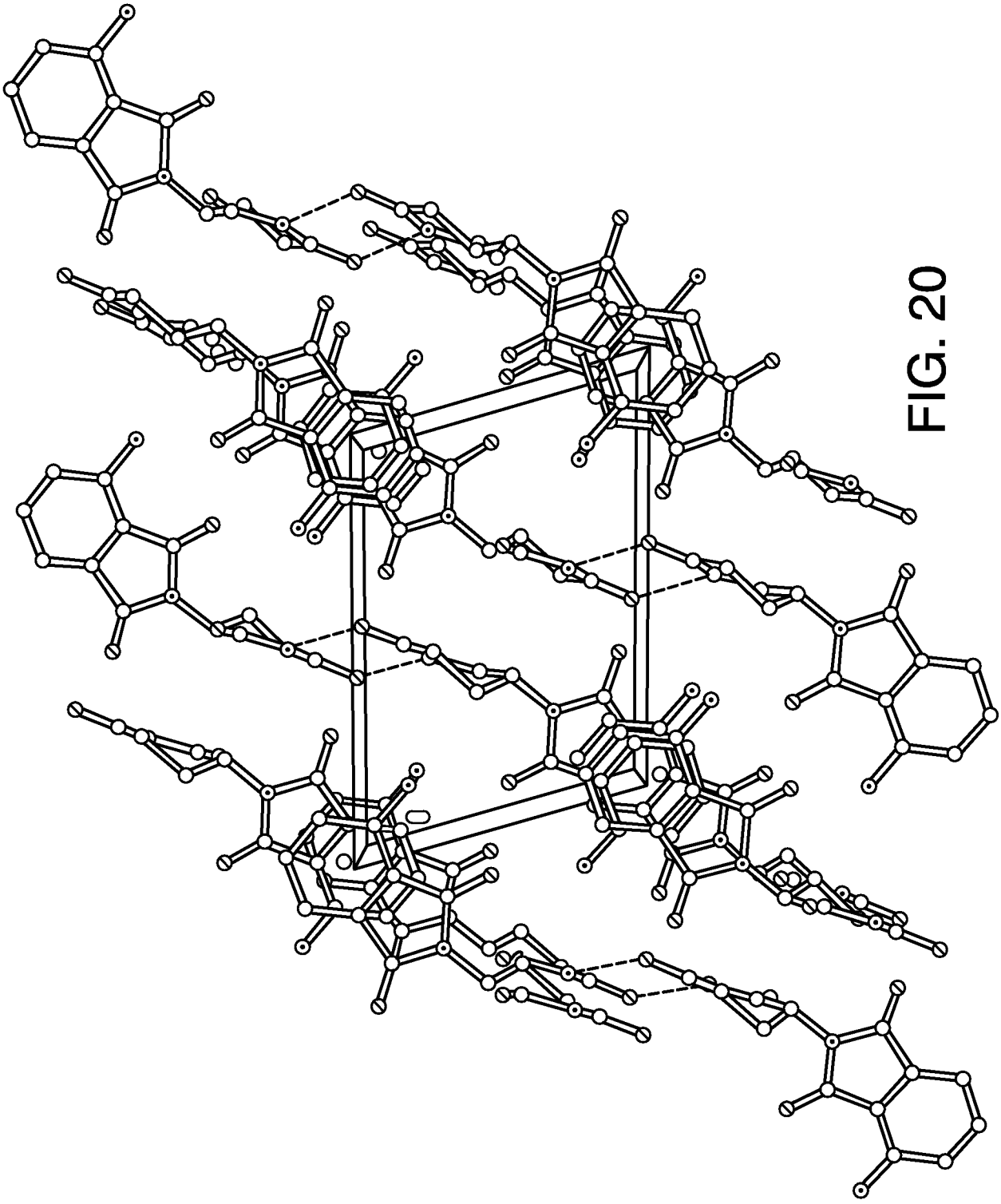

FIG. 20

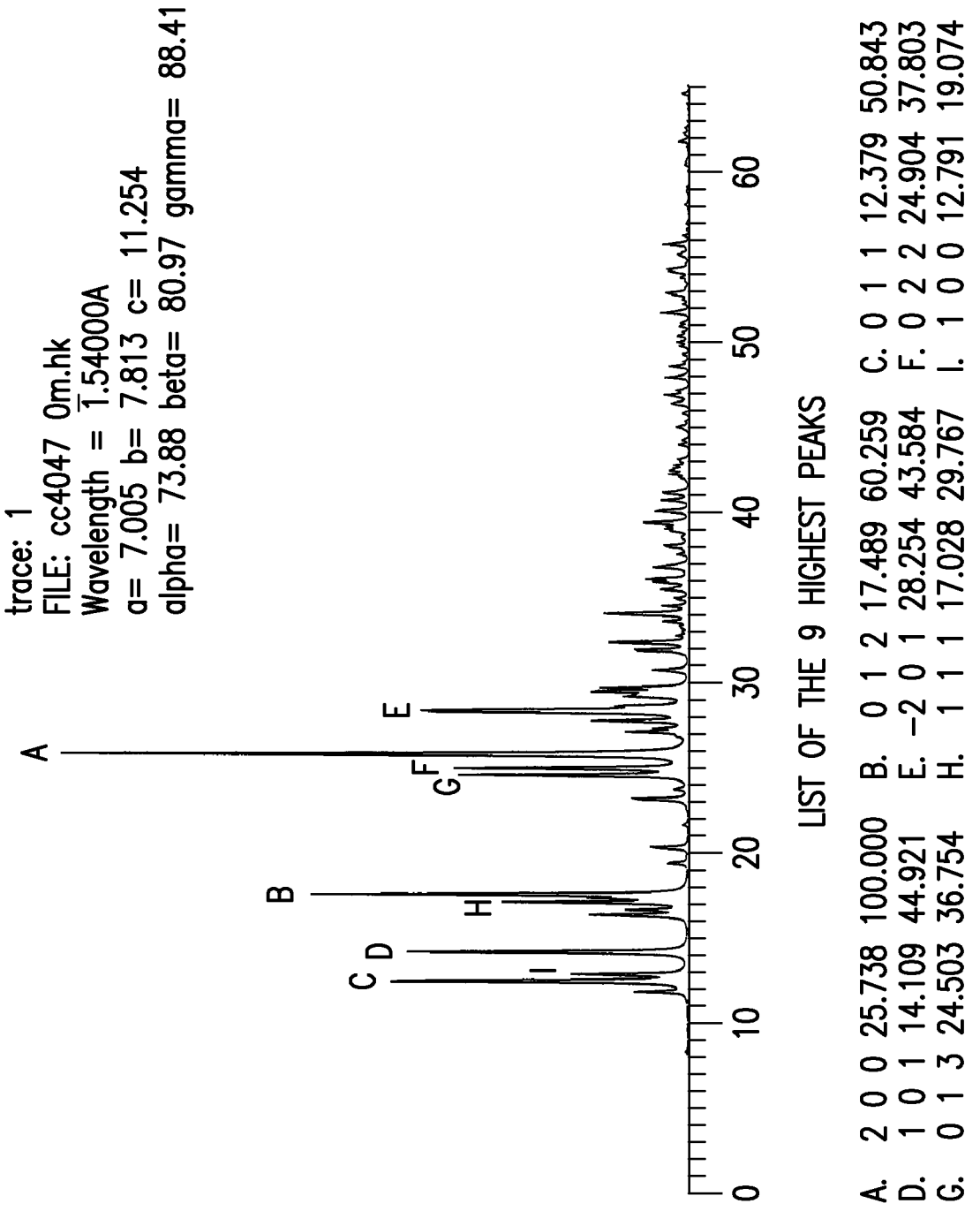
trace: 1
FILE: cc4047 0m.hk
Wavelength = 1.54000A
a= 7.005 b= 7.813 c= 11.254
alpha= 73.88 beta= 80.97 gamma= 88.41
A
B
C
D
E
F
G
H
I
0
10
20
30
40
50
60
LIST OF THE 9 HIGHEST PEAKS
A. 2 0 0 25.738 100.000 B. 0 1 2 17.489 60.259 C. 0 1 1 12.379 50.843
D. 1 0 1 14.109 44.921 E. −2 0 1 28.254 43.584 F. 0 2 2 24.904 37.803
G. 0 1 3 24.503 36.754 H. 1 1 1 17.028 29.767 I. 1 0 0 12.791 19.074

FIG. 21

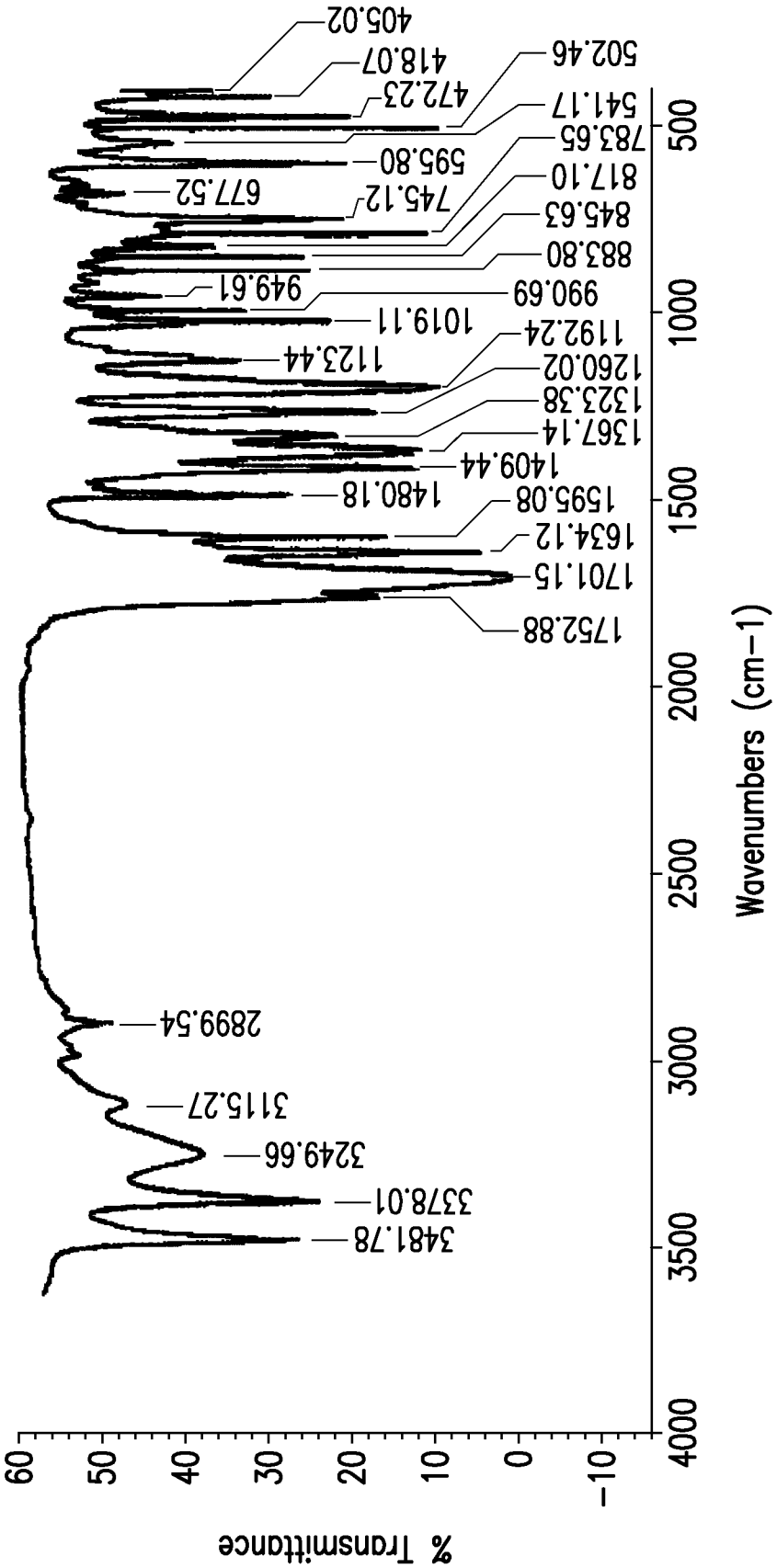
% Transmittance
60
50
40
30
20
10
0
−10
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm−1)
3481.78
3378.01
3249.66
3115.27
2899.54
1752.88
1701.15
1634.12
1595.08
1480.18
1409.44
1367.14
1323.38
1260.02
1192.24
1123.44
1019.11
990.69
949.61
883.80
845.63
817.10
783.65
745.12
677.52
595.80
541.17
502.46
472.23
418.07
405.02

FIG. 22

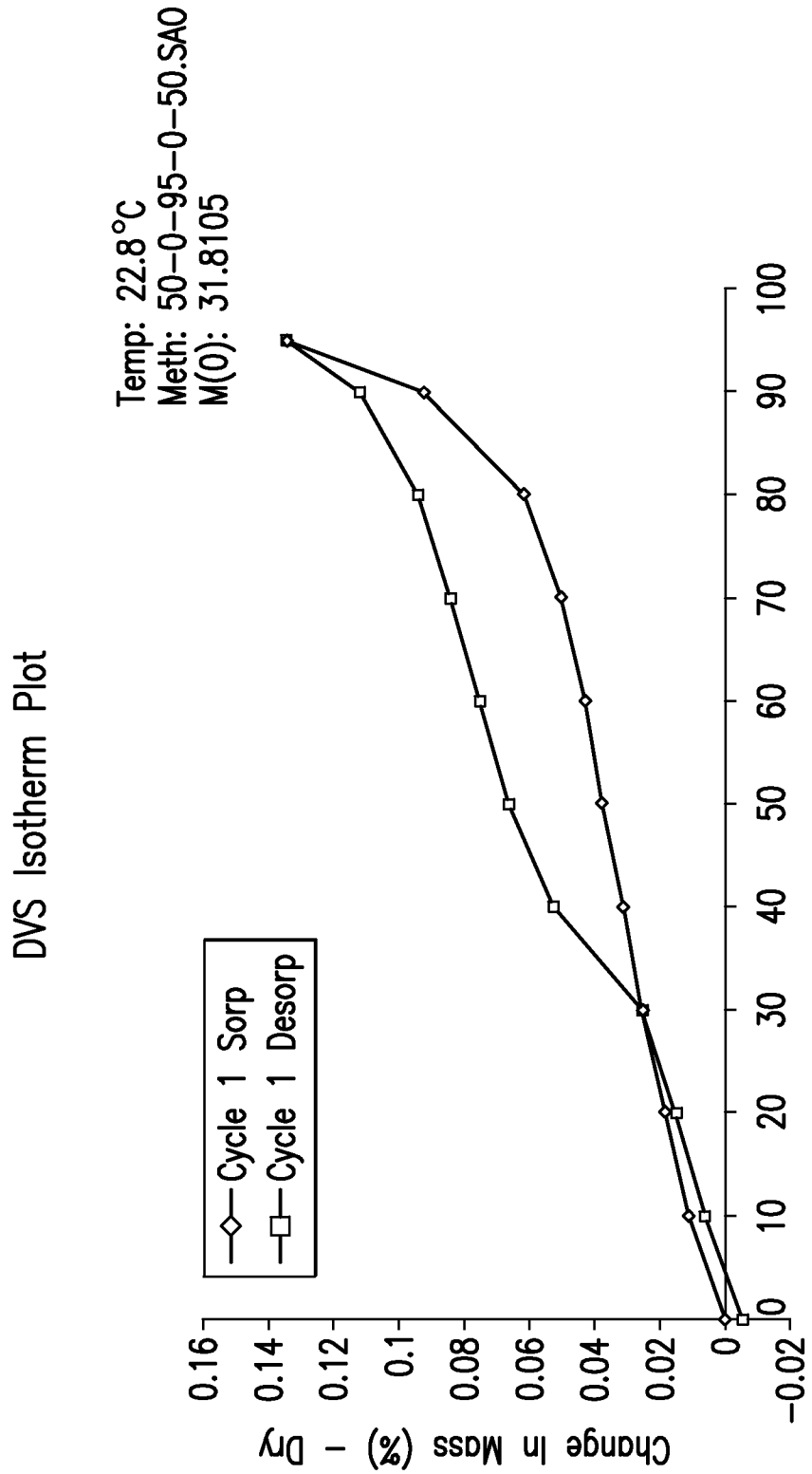
DVS Isotherm Plot
Temp: 22.8°C
Meth: 50–0–95–0–50.SAO
M(0): 31.8105
Cycle 1 Sorp
Cycle 1 Desorp
Change In Mass (%) – Dry
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
-0.02
0
10
20
30
40
50
60
70
80
90
100
Target RH (%)

FIG. 23

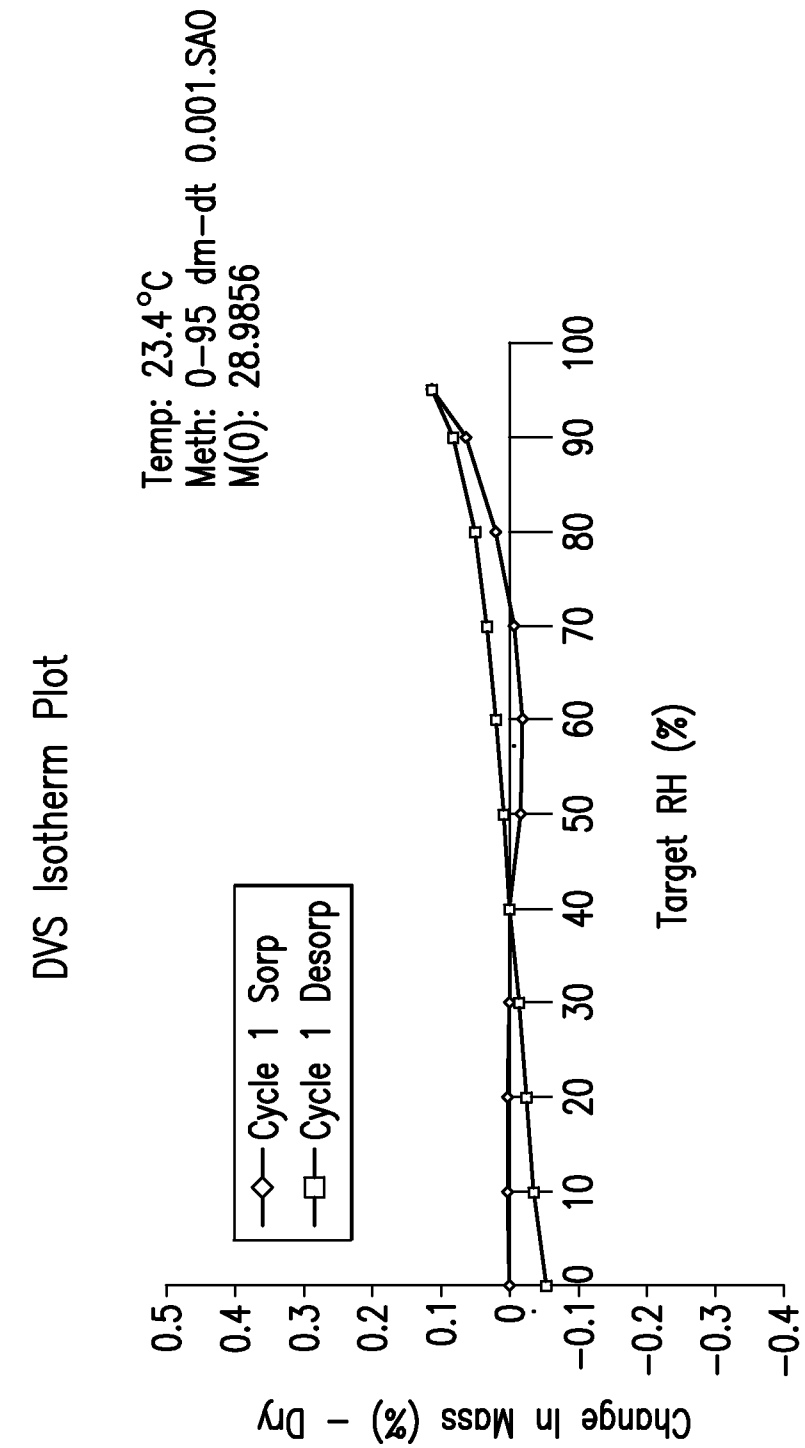
DVS Isotherm Plot
Temp: 23.4°C
Meth: 0-95 dm-dt 0.001.SAO
M(0): 28.9856
Cycle 1 Sorp
Cycle 1 Desorp
Change In Mass (%) - Dry
Target RH (%)
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
0
10
20
30
40
50
60
70
80
90
100

FIG. 24

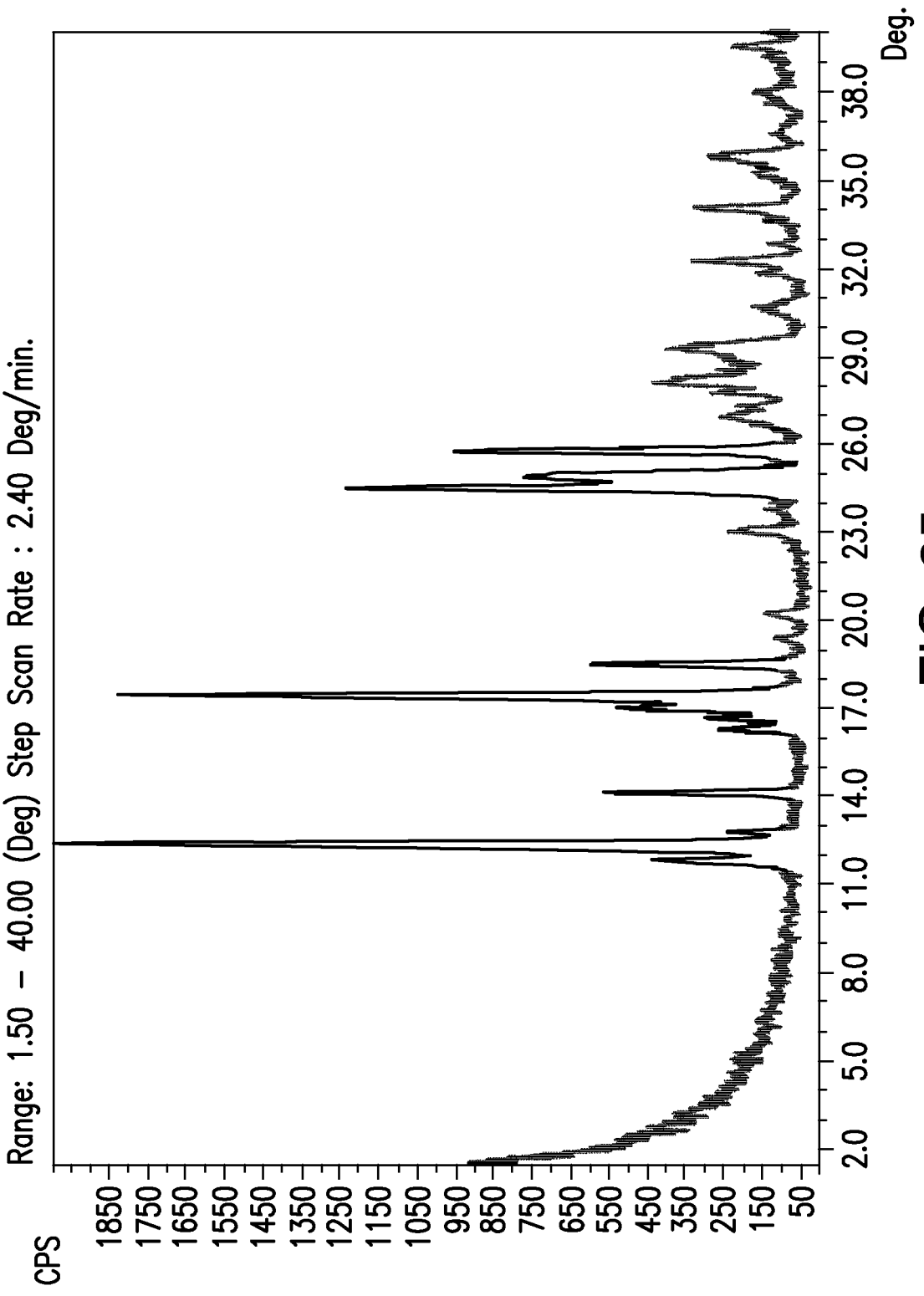
Range: 1.50 - 40.00 (Deg) Step Scan Rate : 2.40 Deg/min.
CPS
1850
1750
1650
1550
1450
1350
1250
1150
1050
950
850
750
650
550
450
350
250
150
50
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

FIG. 25

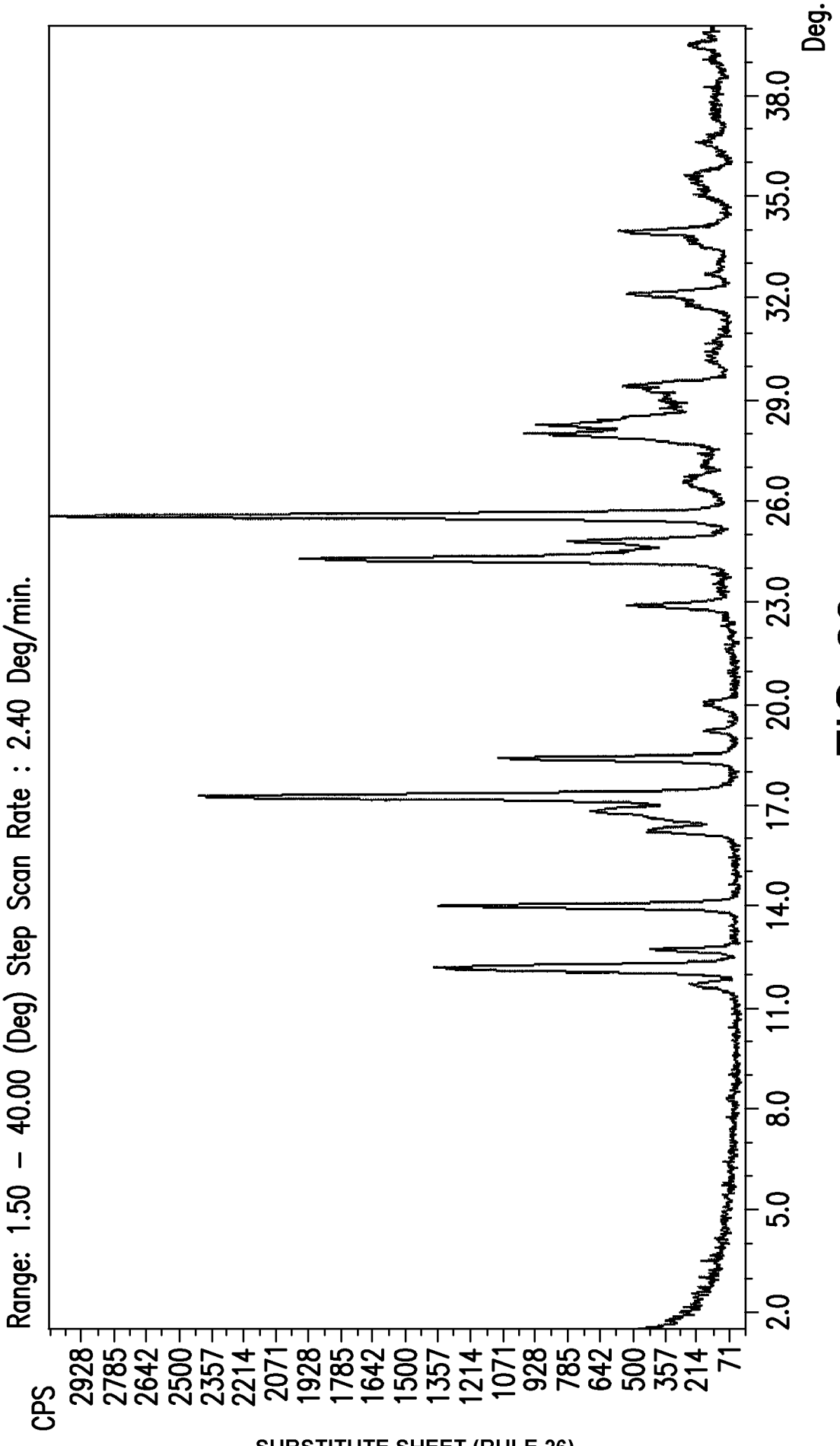
Range: 1.50 - 40.00 (Deg) Step Scan Rate : 2.40 Deg/min.
CPS
2928
2785
2642
2500
2357
2214
2071
1928
1785
1642
1500
1357
1214
1071
928
785
642
500
357
214
71
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

FIG. 26

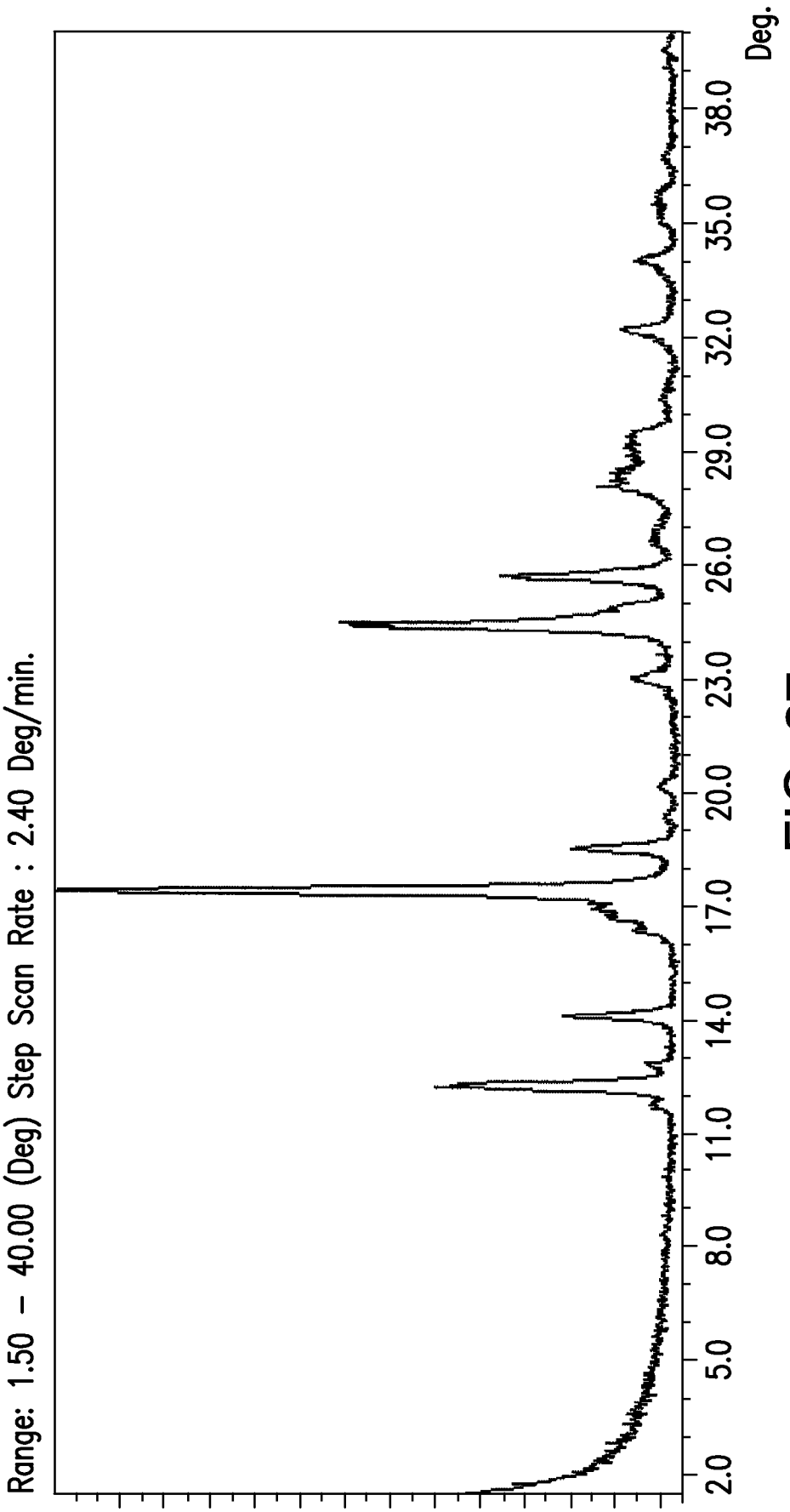
Range: 1.50 - 40.00 (Deg) Step Scan Rate : 2.40 Deg/min.
CPS
3333
3066
2800
2533
2266
2000
1733
1466
1200
933
666
400
133
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

FIG. 27

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/026662

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 A61K31/45
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7 994 327 B2 (GE CHUANSHEN [US] ET AL GE CHUANSHENG [US] ET AL) 9 August 2011 (2011-08-09) cited in the application	18-39
Y	column 1, line 15 - line 17 column 24 - column 25; example 13 column 25 - column 26; example 17 column 19	1-17

A	US 2008/051431 Al (VERHELLE DOMINIQUE [US] ET AL) 28 February 2008 (2008-02-28) cited in the application page 10, paragraph 162 page 15, paragraph 240 - page 16, paragraph 241	1-39

	-/-	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* 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" documentwhich may throw doubts on priority claim(s) orwhich 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
17 May 2013	05/06/2013

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/026662

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 addi tional sheet

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

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

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paaiidd wwiitthhiinn tthhee ttiimmee lliimmiitt ssppeecoiiffiied in the invitation.

☒ No protest accompanied the payment of additional search fees .

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/026662

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 635 517 A (MULLER GEORGE W [US] ET AL) 3 June 1997 (1997-06-03) cited in the application column 7, line 47 - line 53; example 1	1-39
X	US 2006/160854 A1 (MULLER GEORGE W [US] ET AL) 20 July 2006 (2006-07-20) cited in the application	18-39
A	page 1, paragraph 1 page 9, paragraph 78	1-17
Y	CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 ISBN: 978-3-540-36760-4	1-17
A	page 165, paragraph 2.1	18-39

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/026662

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 7994327 B2	09-08-2011	AU 2006265019 A1	11-01-2007
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		US 2006178402 A1	10-08-2006
		US 2006183910 A1	17-08-2006
		US 2010093799 A1	15-04-2010
		US 2013030021 A1	31-01-2013

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: l-17 (completely) ; 27-39 (partially)

a solid form of
4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione
having an X-ray powder diffraction pattern comprising peaks
at 12, 17 and 26 degrees

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2. claims: 18-26(completely) ; 27-39 (partially)

a solid form of
4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione
comprising amorphous
4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione