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(54) Title: SOLID FORMS OF (R)-11-(METHOXYMETHYL)-12-(3-METHOXYPROPOXY)-3,3-DIMETHYL-8-OXO-2,3,8,13B-TETRAHYDRO-1H-PYRIDO[2,1-A]PYRROLO[1,2-C] PHTHALAZINE-7-C ARBOXYLIC ACID

(57) Abstract: The present invention relates to novel crystalline forms of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2, 3,8,13b-tetrahydro-1H-pyrido[2, 1 -a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid for use in treating viral infections. In some embodiments, the viral infection is caused by a hepatitis B virus.

SOLID FORMS OF (R)-11-(METHOXYMETHYL)-12-(3-METHOXYPROPOXY)-3,3-DIMETHYL-8-OXO-2,3,8,13B-TETRAHYDRO-1H-PYRIDO[2,1-A]PYRROLO[1,2-C]PHTHALAZINE-7-CARBOXYLIC ACID

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This patent application claims the benefit of priority of U.S. Provisional Patent Application Serial No. 62/713,098, filed August 1, 2018. The contents of this application are incorporated herein by reference.

FIELD

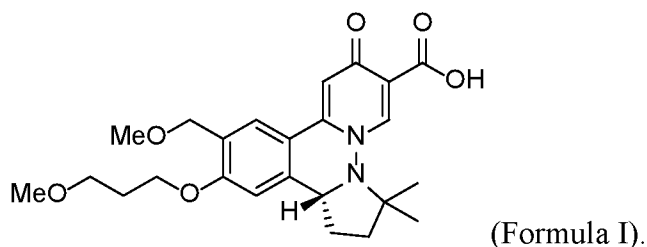
[0002] The present invention relates to novel solid forms of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid, the pharmaceutical formulations, and the therapeutic uses thereof in treating viral infections.

BACKGROUND

[0003] The hepatitis B virus (HBV) is an enveloped, partially double-stranded DNA virus. HBV is an infectious disease that affects the liver. Initial symptoms of infection may include vomiting, jaundice, lethargy, dark urine, and abdominal pain. Chronic HBV infection can result in cirrhosis and liver cancer. Currently available therapies can inhibit replication of the virus and minimize liver damage; however, there are no currently available therapies that can clear an HBV infection.

[0004] The compound (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid, referred herein as Formula I, is known to exhibit antiviral properties against hepatitis B virus as described in co-pending United States patent application no. 15/885,390, filed January 31, 2018.

[0005] (R)-11-(Methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid, (Formula I), has the following structure:



[0006] It is desired to have physically stable forms of the compound that are suitable for the therapeutic use and the manufacturing process.

BRIEF SUMMARY

[0007] In some embodiments, the present disclosure is directed to novel forms of Formula I.

[0008] In some embodiments, the present disclosure is directed to crystalline forms of (R)-11-(Methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid.

[0009] In some embodiments, the present disclosure is directed to (R)-11-(Methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid Form I (Formula I Form I).

[0010] In some embodiments, the present disclosure is directed to (R)-11-(Methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid Form II (Formula I Form II).

[0011] In some embodiments, the present disclosure is directed to an amorphous form of (R)-11-(Methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid.

[0012] In some embodiments, the present disclosure is directed to methods of treating a hepatitis B virus infection by administering a compound of Formula I provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 shows an X-ray powder diffraction (XRPD) pattern of crystalline Form I of Formula I.

[0014] FIG. 2 shows a differential scanning calorimetry (DSC) thermogram of crystalline Form I of Formula I.

[0015] FIG. 3 shows a thermogravimetric analysis (TGA) graph of crystalline Form I of Formula I.

[0016] FIG. 4 shows a dynamic vapor sorption (DVS) plot of crystalline Form I of Formula I.

[0017] FIG. 5 shows an X-ray powder diffraction (XRPD) pattern of crystalline Form II of Formula I.

[0018] FIG. 6 shows a differential scanning calorimetry (DSC) thermogram of crystalline Form II of Formula I.

[0019] FIG. 7 shows a thermogravimetric analysis (TGA) graph of crystalline Form II of Formula I.

[0020] FIG. 8 shows a dynamic vapor sorption (DVS) plot of crystalline Form II of Formula I.

[0021] FIG. 9 shows an X-ray powder diffraction (XRPD) pattern of an amorphous solid form of Formula I.

[0022] FIG. 10 shows a differential scanning calorimetry (DSC) thermogram of an amorphous solid form of Formula I.

[0023] FIG. 11 shows a thermogravimetric analysis (TGA) graph of an amorphous solid form of Formula I.

DETAILED DESCRIPTION

I. GENERAL

[0024] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention. However, one skilled in the art will understand that the invention may be practiced without these details. The description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

II. DEFINITIONS

[0025] Unless the context requires otherwise, throughout the present specification and claims, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is as “including, but not limited to”.

[0026] Reference throughout this specification to “one embodiment” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0027] Embodiments that reference throughout this specification to “a Compound of Formula I” includes the crystalline, amorphous, co-crystal, and solvate, *e.g.*, hydrate, forms of the formulas and/or compounds disclosed herein. Thus, the appearance or the phrase “a Compound of Formula I” comprises crystalline Forms I-II, amorphous, and mixtures of crystalline and/or amorphous forms thereof.

[0028] The invention disclosed herein is also meant to encompass all pharmaceutically acceptable compounds of Formula I being isotopically-labeled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of Formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^3H , and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0029] Substitution with heavier isotopes such as deuterium, *i.e.* ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability. For example, *in vivo* half-life may increase or dosage requirements may be reduced. Thus, heavier isotopes may be preferred in some circumstances.

[0030] Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Formula I can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0031] “Pharmaceutically acceptable excipient” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0032] A “pharmaceutical composition” refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable excipients therefor.

[0033] A “treatment” or “treating” is an approach for obtaining beneficial or desired results. For purposes of the present disclosure, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom associated with a disease or condition. In one embodiment, “treatment” or “treating” includes one or more of the following: a) inhibiting the disease or condition (*e.g.*, decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more symptoms associated with the disease or condition (*e.g.*, stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); and c) relieving the disease or condition, *e.g.*, causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

[0034] A “prevention” or “preventing” refers to a regimen that protects against the onset of the disease or disorder such that the clinical symptoms of the disease do not develop. Thus, “prevention” relates to administration of a therapy (*e.g.*, administration of a therapeutic substance) to a subject before signs of the disease are detectable in the subject (*e.g.*, administration of a therapeutic substance to a subject in the absence of detectable infectious agent (*e.g.*, virus) in the subject). The subject may be an individual at risk of developing the disease or disorder, such as an individual who has one or more risk factors known to be associated with development or onset of the disease or disorder. Thus, in certain embodiments, the term “preventing HBV infection” refers to administering to a subject who does not have a detectable HBV infection an anti-HBV therapeutic substance. It is understood that the subject for anti-HBV preventative therapy may be an individual at risk of contracting the HBV virus.

[0035] The term “therapeutically effective amount” or “effective amount” refers to an amount that is effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The effective amount will vary depending on the particular compound, and characteristics of the subject to be treated, such as age, weight, etc. The effective amount can include a range of amounts. As is understood in the art, an effective amount may be in one or more doses, *i.e.*, a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one

or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any co-administered compounds may optionally be lowered due to the combined action (*e.g.*, additive or synergistic effects) of the compounds.

[0036] As used herein, “co-administration” includes administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound of the present disclosure is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound of the present disclosure within seconds or minutes. In some embodiments, a unit dose of a compound of the present disclosure is administered first, followed, after a period of hours (*e.g.*, 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (*e.g.*, 1-12 hours), by administration of a unit dose of a compound of the present disclosure.

[0037] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”. Also, the singular forms “a” and “the” include plural references unless the context clearly dictates otherwise. Thus, *e.g.*, reference to “the compound” includes a plurality of such compounds and reference to “the assay” includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0038] “Unit dosage forms” are physically discrete units suitable as unitary dosages for subjects (*e.g.*, human subjects and other mammals), each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[0039] The term “substantially as set forth in” when referring, for example, to an XRPD pattern, a DSC thermogram, a DVS plot, or a TGA graph includes a pattern, thermogram or graph that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art.

[0040] In some embodiments, the term “substantially pure” or “substantially free” with respect to a particular solid form of a compound means that the composition comprising the solid form contains less than 99%, less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, or less than 1% by weight of other substances, including other solid forms and/or impurities. In some embodiments, “substantially pure” or “substantially free of” refers to a substance free of other substances, including other solid forms and/or impurities. Impurities may, for example, include by-products or left over reagents from chemical reactions, contaminants, degradation products, other solid forms, water, and solvents.

III. SOLID FORMS

[0041] A solid form may have properties such as bioavailability, stability, purity, and/or manufacturability at certain conditions that may be suitable for medical or pharmaceutical uses. Solid forms of Formula I, including substantially pure forms and mixtures of substantially pure forms, may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the dissolution rate (which may affect bioavailability, *etc.*), manufacturability (*e.g.*, ease of handling, ability to consistently prepare doses of known strength), and stability (*e.g.*, thermal stability, shelf life, *etc.*) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solutions or solid oral dosage form including tablets and capsules. A solid form, *e.g.*, a crystalline form, may provide desired or suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control. Solid forms of Formula I may provide advantages such as: improving the manufacturing process of an active agent, *e.g.*, by enhancing the removal of impurities, or the stability or storability of a drug product form of the compound or an active ingredient, and/or having suitable bioavailability and/or stability as an active agent.

[0042] The use of certain solvents and/or processes have been found to produce different solid forms of Formula I described herein which may exhibit one or more favorable characteristics described above. The processes for the preparation of the solid forms described herein, and characterization of these solid forms are described in greater detail below.

[0043] The compound name provided above is named according to IUPAC rules or using ChemBioDraw Ultra and one skilled in the art understands that the compound structure may be

named or identified using other commonly recognized nomenclature systems and symbols. By way of example, the compound may be named or identified with common names, systematic or non-systematic names. The nomenclature systems and symbols that are commonly recognized in the art of chemistry including but not limited to Chemical Abstract Service (CAS) and International Union of Pure and Applied Chemistry (IUPAC). Accordingly, the compound structure provided above may also be named or identified as (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid, according to ChemBioDraw Ultra.

[0044] In some embodiments, provided is a crystalline form of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid, or a solvate or hydrate thereof. In particular embodiments, crystalline forms of Formula I are disclosed. In some embodiments, the crystalline form is solvated, *e.g.*, by methanol. In some embodiments, the crystalline form is non-solvated.

[0045] In some embodiments, the crystalline form of Formula I is Form I. In some embodiments, the crystalline form of Formula I is Form II.

[0046] In some embodiments, provided is an amorphous solid form of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid, or a solvate or hydrate thereof. In particular embodiments, the amorphous solid form of Formula I is disclosed.

[0047] In some embodiments, the solid forms are characterized by the interlattice plane intervals determined by an X-ray powder diffraction pattern (XRPD). The diffractogram of XRPD is typically represented by a diagram plotting the intensity of the peaks versus the location of the peaks, *i.e.*, diffraction angle 2θ (two-theta) in degrees. The characteristic peaks of a given XRPD can be selected according to the peak locations and their relative intensity to distinguish one crystalline structure from others.

[0048] Those skilled in the art recognize that the measurements of the XRPD peak locations and/or intensity for a given crystalline form of the same compound will vary within a margin of error. The values of degree 2θ allow appropriate error margins. Typically, the error margins are represented by “ $\pm$ ” or “ $+/-$ ”. For example, the degree 2θ of about “ 8.7 ± 0.3 ” denotes a range from about $8.7+0.3$, *i.e.*, about 9.0, to about $8.7-0.3$, *i.e.*, about 8.4. Depending on the sample preparation techniques, the calibration techniques applied to the instruments, human operational variation, and etc., those skilled in the art recognize that the appropriate error of margins for a XRPD can be ± 0.5 ; ± 0.4 ; ± 0.3 ; ± 0.2 ; ± 0.1 ; ± 0.05 ; or less. In some embodiments of the

invention, the XRPD margin of error is ± 0.2 . In some embodiments of the invention, the XRPD margin of error is ± 0.5 .

[0049] Additional details of the methods and equipment used for the XRPD analysis are described in the Examples section.

Formula I Form I

[0050] In some embodiments, provided is a crystalline form of Formula I. In some embodiments, the crystalline form is non-solvated. In some embodiments, the crystalline form is Form I of Formula I (Formula I Form I).

[0051] The XRPD peaks for crystalline Formula I Form I are shown below in Table 1A.

Table 1A: XRPD peaks for crystalline Formula I Form I

Formula I Form I	
Position [°2 θ .]	Relative Intensity [%]
8.0	100.0
16.0	42.4
26.8	40.2
8.7	21.5
24.3	10.2
13.6	4.5
11.4	3.4
12.1	2.8
15.0	2.8
12.9	2.2

[0052] In some embodiments, crystalline Formula I Form I has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, or at least eight of the degree 2 θ -reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 1.

[0053] In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having one or more peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, or 15.0° 2 $\theta \pm 0.2^\circ$ 2 θ . In some embodiments, Form I is characterized by an X-ray powder diffraction (XRPD) pattern having two or more peaks at 8.0°, 8.7°, 16.0°,

11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, or 15.0° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, Form I is characterized by an X-ray powder diffraction (XRPD) pattern having three or more peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, or 15.0° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, Form I is characterized by an X-ray powder diffraction (XRPD) pattern having four or more peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, or 15.0° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, Form I is characterized by an X-ray powder diffraction (XRPD) pattern having five or more peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, or 15.0° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, Form I is characterized by an X-ray powder diffraction (XRPD) pattern having six or more peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, or 15.0° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, Form I is characterized by an X-ray powder diffraction (XRPD) pattern having seven or more peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, or 15.0° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, Form I is characterized by an X-ray powder diffraction (XRPD) pattern having eight or more peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, or 15.0° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, Form I is characterized by an X-ray powder diffraction (XRPD) pattern having nine or more peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, or 15.0° $2\theta \pm 0.2^\circ 2\theta$.

[0054] In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0°, 8.7°, and 16.0° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0°, 8.7°, and 16.0° $2\theta \pm 0.2^\circ 2\theta$ and one or more peaks at 11.4°, 12.1°, 12.9°, or 13.6° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0°, 8.7°, and 16.0° $2\theta \pm 0.2^\circ 2\theta$ and two or more peaks at 11.4°, 12.1°, 12.9°, or 13.6° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0°, 8.7°, and 16.0° $2\theta \pm 0.2^\circ 2\theta$ and three or more peaks at 11.4°, 12.1°, 12.9°, or 13.6° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0°, 8.7°, and 16.0° $2\theta \pm 0.2^\circ 2\theta$ and one peak at 11.4°, 12.1°, 12.9°, or 13.6° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0°, 8.7°, and 16.0° $2\theta \pm 0.2^\circ 2\theta$ and two peaks at 11.4°, 12.1°, 12.9°, or 13.6° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0°, 8.7°, and 16.0° $2\theta \pm 0.2^\circ 2\theta$ and three peaks at 11.4°, 12.1°, 12.9°, or 13.6° $2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern

having peaks at 8.0° , 8.7° , $16.0^\circ 2\theta \pm 0.2^\circ 2\theta$ and further peaks at 11.4° , 12.1° , 12.9° , and $13.6^\circ 2\theta \pm 0.2^\circ 2\theta$.

[0055] In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having further peaks at 26.8° , 24.3° , and $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , and $16.0^\circ 2\theta \pm 0.2^\circ 2\theta$ and one or more peaks at 26.8° , 24.3° , or $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , and $16.0^\circ 2\theta \pm 0.2^\circ 2\theta$ and two or more peaks at 26.8° , 24.3° , or $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , and $16.0^\circ 2\theta \pm 0.2^\circ 2\theta$ and one peak at 26.8° , 24.3° , or $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , and $16.0^\circ 2\theta \pm 0.2^\circ 2\theta$ and two peaks at 26.8° , 24.3° , or $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , $16.0^\circ 2\theta \pm 0.2^\circ 2\theta$ and further peaks at 26.8° , 24.3° , and $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$.

[0056] In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , 16.0° , 11.4° , 12.1° , 12.9° , and $13.6^\circ 2\theta \pm 0.2^\circ 2\theta$ and one or more peaks at 26.8° , 24.3° , or $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , 16.0° , 11.4° , 12.1° , 12.9° , and $13.6^\circ 2\theta \pm 0.2^\circ 2\theta$ and two or more peaks at 26.8° , 24.3° , or $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , 16.0° , 11.4° , 12.1° , 12.9° , and $13.6^\circ 2\theta \pm 0.2^\circ 2\theta$ and one peak at 26.8° , 24.3° , or $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , 16.0° , 11.4° , 12.1° , 12.9° , and $13.6^\circ 2\theta \pm 0.2^\circ 2\theta$ and two peaks at 26.8° , 24.3° , or $15.0^\circ 2\theta \pm 0.2^\circ 2\theta$.

[0057] In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , and $13.6^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , and $13.6^\circ 2\theta \pm 0.2^\circ 2\theta$ and one or more peaks at 8.0° , 8.7° , or $16.0^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , and $13.6^\circ 2\theta \pm 0.2^\circ 2\theta$ and two or more peaks at 8.0° , 8.7° , or $16.0^\circ 2\theta \pm 0.2^\circ 2\theta$.

In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , and 13.6° $2\theta \pm 0.2^\circ$ 2θ and one peak at 8.0° , 8.7° , or 16.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , and 13.6° $2\theta \pm 0.2^\circ$ 2θ and two peaks at 8.0° , 8.7° , or 16.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , 16.0° , 11.4° , 12.1° , 12.9° , and 13.6° $2\theta \pm 0.2^\circ$ 2θ .

[0058] In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , and 13.6° $2\theta \pm 0.2^\circ$ 2θ and one or more peaks at 26.8° , 24.3° , or 15.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , and 13.6° $2\theta \pm 0.2^\circ$ 2θ and two or more peaks at 26.8° , 24.3° , or 15.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , and 13.6° $2\theta \pm 0.2^\circ$ 2θ and one peak at 26.8° , 24.3° , or 15.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , and 13.6° $2\theta \pm 0.2^\circ$ 2θ and two peaks at 26.8° , 24.3° , or 15.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 11.4° , 12.1° , 12.9° , 13.6° , 26.8° , 24.3° , and 15.0° $2\theta \pm 0.2^\circ$ 2θ .

[0059] In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 26.8° , 24.3° , and 15.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 26.8° , 24.3° , and 15.0° $2\theta \pm 0.2^\circ$ 2θ and one or more peaks at 8.0° , 8.7° , or 16.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 26.8° , 24.3° , and 15.0° $2\theta \pm 0.2^\circ$ 2θ and two or more peaks at 8.0° , 8.7° , or 16.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 26.8° , 24.3° , and 15.0° $2\theta \pm 0.2^\circ$ 2θ and one peak at 8.0° , 8.7° , or 16.0° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 26.8° , 24.3° , and 15.0° $2\theta \pm 0.2^\circ$ 2θ and two peaks at 8.0° , 8.7° , or 16.0° $2\theta \pm 0.2^\circ$ 2θ .

[0060] In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, and 15.0° $2\theta \pm 0.2^\circ 2\theta$.

[0061] In some embodiments, the crystalline Formula I Form I is characterized by a unit cell as determined by single crystal X-ray crystallography of the following dimensions: $a = 9.9330(3) \text{ \AA}$; $b = 10.5884(2) \text{ \AA}$; $c = 11.2740(4) \text{ \AA}$; $\alpha = 77.799(2)^\circ$; $\beta = 87.547(3)^\circ$; and $\gamma = 80.283(2)^\circ$.

[0062] In some embodiments, Formula I Form I is characterized by a Differential Scanning Calorimetry (DSC) thermogram peak with an onset at about 131 °C.

[0063] In some embodiments, the crystalline Formula I Form I is characterized by one or more of the following: an X-ray powder diffraction (XRPD) pattern having peaks at 8.0°, 8.7°, 16.0°, 11.4°, 12.1°, 12.9°, 13.6°, 26.8°, 24.3°, and 15.0° $2\theta \pm 0.2^\circ 2\theta$; a Differential Scanning Calorimetry (DSC) thermogram peak with an onset at about 131 °C; and a unit cell as determined by single crystal X-ray crystallography of the following dimensions: $a = 9.9330(3) \text{ \AA}$; $b = 10.5884(2) \text{ \AA}$; $c = 11.2740(4) \text{ \AA}$; $\alpha = 77.799(2)^\circ$; $\beta = 87.547(3)^\circ$; and $\gamma = 80.283(2)^\circ$.

[0064] In some embodiments, crystalline Formula I Form I is characterized by an X-ray powder diffraction (XRPD) pattern substantially as set forth in FIG. 1.

[0065] In some embodiments, crystalline Formula I Form I is characterized by a differential scanning calorimetry (DSC) pattern substantially as set forth in FIG. 2.

[0066] In some embodiments, crystalline Formula I Form I is characterized by a thermogravimetric analysis (TGA) pattern substantially as set forth in FIG. 3.

[0067] In some embodiments, crystalline Formula I Form I is characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in FIG. 4.

[0068] In some embodiments of crystalline Formula I Form I, at least one, at least two, at least three, at least four, at least five, at least six, or all of the following (a)-(g) apply: (a) crystalline Formula I has an XRPD pattern substantially as set forth in FIG. 1; (b) crystalline Formula I Form I has a unit cell, as determined by crystal X-ray crystallography at a temperature of 299 K, of the following dimensions: $a = 9.9330(3) \text{ \AA}$; $b = 10.5884(2) \text{ \AA}$; $c = 11.2740(4) \text{ \AA}$; $\alpha = 77.799(2)^\circ$; $\beta = 87.547(3)^\circ$; and $\gamma = 80.283(2)^\circ$; (c) crystalline Formula I Form I has a triclinic crystal system; (d) crystalline Formula I Form I has a P 1 space group; (e) crystalline Formula I Form I has a volume of $1142.30(6) \text{ \AA}^3$; (f) crystalline Formula I Form I has a Z value of 2; and (g) crystalline Formula I Form I has a calculated density of 1.287 g/cm^3 .

[0069] In some embodiments of crystalline Formula I Form I, at least one, at least two, at least three, at least four, or all of the following (a)-(e) apply: (a) crystalline Formula I Form I has a unit cell, as determined by crystal X-ray crystallography at a temperature of 299 K, of the following dimensions: $a = 9.9330(3) \text{ \AA}$; $b = 10.5884(2) \text{ \AA}$; $c = 11.2740(4) \text{ \AA}$; $\alpha = 77.799(2)^\circ$; $\beta = 87.547(3)^\circ$; and $\gamma = 80.283(2)^\circ$; (b) crystalline Formula I Form I has an XRPD pattern substantially as set forth in FIG. 1; (c) crystalline Formula I Form I has a DSC thermogram substantially as set forth in FIG. 2; (d) crystalline Formula I Form I has a TGA graph substantially as set forth in FIG. 3; (e) crystalline Formula I Form I has a DVS graph substantially as set forth in FIG. 4.

Formula I Form II

[0070] In some embodiments, the crystalline form is solvated. In some embodiments, the crystalline form is a methanol solvate. In some embodiments, the crystalline form is Form II of Formula I (Formula I Form II).

[0071] The XRPD peaks for crystalline Formula I Form II are shown below in Table 1B.

Table 1B: XRPD peaks for crystalline Formula I Form II

Formula I Form II	
Position [2θ .]	Relative Intensity [%]
16.3	100.0
8.1	37.4
9.4	32.5
8.8	31.4
26.5	17.9
19.2	10.5
14.8	7.9
15.4	4.7
12.9	4.1

[0072] In some embodiments, crystalline Formula I Form II has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, or at least eight of the degree 2θ -reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG. 5.

[0073] In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having one or more peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , or 15.4° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, Form II is characterized by an X-ray powder diffraction (XRPD) pattern having two or more peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , or 15.4° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, Form II is characterized by an X-ray powder diffraction (XRPD) pattern having three or more peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , or 15.4° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, Form II is characterized by an X-ray powder diffraction (XRPD) pattern having four or more peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , or 15.4° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, Form II is characterized by an X-ray powder diffraction (XRPD) pattern having five or more peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , or 15.4° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, Form II is characterized by an X-ray powder diffraction (XRPD) pattern having six or more peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , or 15.4° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, Form II is characterized by an X-ray powder diffraction (XRPD) pattern having seven or more peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , or 15.4° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, Form II is characterized by an X-ray powder diffraction (XRPD) pattern having eight or more peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , or 15.4° $2\theta \pm 0.2^\circ$ 2θ .

[0074] In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and 8.8° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and 8.8° $2\theta \pm 0.2^\circ$ 2θ and one or more peaks at 16.3° , 26.5° , or 19.2° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and 8.8° $2\theta \pm 0.2^\circ$ 2θ and two or more peaks at 16.3° , 26.5° , or 19.2° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and 8.8° $2\theta \pm 0.2^\circ$ 2θ and one peak at 16.3° , 26.5° , or 19.2° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and 8.8° $2\theta \pm 0.2^\circ$ 2θ and two peaks at 16.3° , 26.5° , or 19.2° $2\theta \pm 0.2^\circ$ 2θ . In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and 8.8° $2\theta \pm 0.2^\circ$ 2θ and further peaks at 16.3° , 26.5° , and 19.2° $2\theta \pm 0.2^\circ$ 2θ .

[0075] In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having further peaks at 12.9° , 14.8° , and 15.4° $2\theta \pm 0.2^\circ$ 2θ .

In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and $8.8^\circ 2\theta \pm 0.2^\circ 2\theta$ and one or more peaks at 12.9° , 14.8° , or $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and $8.8^\circ 2\theta \pm 0.2^\circ 2\theta$ and two or more peaks at 12.9° , 14.8° , or $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and $8.8^\circ 2\theta \pm 0.2^\circ 2\theta$ and one peak at 12.9° , 14.8° , or $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and $8.8^\circ 2\theta \pm 0.2^\circ 2\theta$ and two peaks at 12.9° , 14.8° , or $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and $8.8^\circ 2\theta \pm 0.2^\circ 2\theta$ and further peaks at 12.9° , 14.8° , and $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$.

[0076] In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$ and one or more peaks at 12.9° , 14.8° , or $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$ and two or more peaks at 12.9° , 14.8° , or $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$ and one peak at 12.9° , 14.8° , or $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$ and two peaks at 12.9° , 14.8° , or $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$ and one peak at 12.9° , 14.8° , or $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$.

[0077] In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$ and one or more peaks at 8.1° , 9.4° , or $8.8^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$ and two or more peaks at 8.1° , 9.4° , or $8.8^\circ 2\theta \pm 0.2^\circ 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$ and one peak at 8.1° , 9.4° ,

or $8.8^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , and $19.2^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$ and two peaks at 8.1° , 9.4° , or $8.8^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , and $19.2^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.

[0078] In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , and $19.2^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$ and one or more peaks at 12.9° , 14.8° , or $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , and $19.2^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$ and two or more peaks at 12.9° , 14.8° , or $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , and $19.2^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$ and one peak at 12.9° , 14.8° , or $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , and $19.2^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$ and two peaks at 12.9° , 14.8° , or $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , and $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.

[0079] In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 12.9° , 14.8° , and $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$, and one or more peaks at 8.1° , 9.4° , or $8.8^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 12.9° , 14.8° , and $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$, and two or more peaks at 8.1° , 9.4° , or $8.8^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 12.9° , 14.8° , and $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$, and one peak at 8.1° , 9.4° , or $8.8^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 12.9° , 14.8° , and $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$, and two peaks at 8.1° , 9.4° , or $8.8^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$. In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , 8.8° , 12.9° , 14.8° , and $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.

[0080] In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , and $15.4^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.

[0081] In some embodiments, crystalline Formula I Form II is characterized by a Differential Scanning Calorimetry (DSC) thermogram peak with an onset at about 174°C .

[0082] In some embodiments, crystalline Formula I Form II is characterized by one or more of the following: an X-ray powder diffraction (XRPD) pattern having peaks at 8.1°, 9.4°, 8.8°, 16.3°, 26.5°, 19.2°, 12.9°, 14.8°, and 15.4° $2\theta \pm 0.2^\circ 2\theta$; and a Differential Scanning Calorimetry (DSC) thermogram peak with an onset at about 174 °C.

[0083] In some embodiments, crystalline Formula I Form II is characterized by an X-ray powder diffraction (XRPD) pattern substantially as set forth in FIG. 5.

[0084] In some embodiments, crystalline Formula I Form II is characterized by a differential scanning calorimetry (DSC) pattern substantially as set forth in FIG. 6.

[0085] In some embodiments, crystalline Formula I Form II is characterized by a thermogravimetric analysis (TGA) pattern substantially as set forth in FIG. 7.

[0086] In some embodiments, crystalline Formula I Form II is characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in FIG. 8.

[0087] In some embodiments of crystalline Formula I Form II, at least one, at least two, at least three, at least four, or all of the following (a)-(e) apply: (a) crystalline Formula I Form II has an X-ray powder diffraction (XRPD) pattern having peaks at 8.1°, 9.4°, 8.8°, 16.3°, 26.5°, 19.2°, 12.9°, 14.8°, and 15.4° $2\theta \pm 0.2^\circ 2\theta$; (b) crystalline Formula I Form II has an XRPD pattern substantially as set forth in FIG. 5; (c) crystalline Formula I Form II has a DSC thermogram substantially as set forth in FIG. 6; (d) crystalline Formula I Form II has a TGA graph substantially as set forth in FIG. 7; and (e) crystalline Formula I Form II has a DVS graph substantially as set forth in FIG. 8.

Amorphous Solid Form of Formula I

[0088] In some embodiments, provided is amorphous solid form of Formula I. In some embodiments, the amorphous form is characterized by an X-ray powder diffraction (XRPD) pattern having an absence of sharp peaks.

[0089] In some embodiments, amorphous Formula I is characterized by a Differential Scanning Calorimetry (DSC) thermogram having a glass transition starting at about 48 °C. In some embodiments, amorphous Formula I is characterized by a Differential Scanning Calorimetry (DSC) thermogram having a shift in baseline beginning at about 48 °C and ending at about 60 °C.

[0090] In some embodiments, amorphous Formula I is characterized by an X-ray powder diffraction (XRPD) pattern substantially as set forth in FIG. 9.

[0091] In some embodiments, amorphous Formula I is characterized by a differential scanning calorimetry (DSC) pattern substantially as set forth in FIG. 10.

[0092] In some embodiments, amorphous Formula I is characterized by a thermogravimetric analysis (TGA) pattern substantially as set forth in FIG. 11.

[0093] In some embodiments of the amorphous Formula I, at least one, at least two, at least three, or all of the following (a)-(d) apply: (a) amorphous Formula I is characterized by a Differential Scanning Calorimetry (DSC) thermogram having a glass transition starting at about 48 °C; (b) amorphous Formula I has an XRPD pattern substantially as set forth in FIG. 9; (c) amorphous Formula I has a DSC thermogram substantially as set forth in FIG. 10; (d) amorphous Formula I has a TGA graph substantially as set forth in FIG. 11.

IV. PHARMACEUTICAL COMPOSITIONS

[0094] In certain embodiments, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition comprises one or more additional therapeutic agents, as described in more detail below.

[0095] Pharmaceutical compositions comprising the compounds disclosed herein may be prepared with one or more pharmaceutically acceptable excipients which may be selected in accord with ordinary practice. "Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0096] In certain embodiments, pharmaceutical compositions are provided as a solid dosage form, including a solid oral dosage form, such as a tablet. Tablets may contain excipients including glidants, fillers, binders and the like. Aqueous compositions may be prepared in sterile form, and when intended for delivery by other than oral administration generally may be isotonic. All compositions may optionally contain excipients such as those set forth in the Rowe et al, Handbook of Pharmaceutical Excipients, 6th edition, American Pharmacists Association, 2009. Excipients can include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

[0097] Pharmaceutical compositions disclosed herein include those suitable for various administration routes, including oral administration. The compositions may be presented in unit

dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient (*e.g.*, a compound of the present disclosure or a pharmaceutical salt thereof) with one or more pharmaceutically acceptable excipients. The compositions may be prepared by uniformly and intimately bringing into association the active ingredient with liquid excipients or finely divided solid excipients or both, and then, if necessary, shaping the product. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams and Wilkins, Philadelphia, Pa., 2006.

[0098] Compositions described herein that are suitable for oral administration may be presented as discrete units (a unit dosage form) including but not limited to capsules, cachets or tablets each containing a predetermined amount of the active ingredient. In one embodiment, the pharmaceutical composition is a tablet.

[0099] Pharmaceutical compositions disclosed herein comprise one or more compounds disclosed herein together with a pharmaceutically acceptable excipient and optionally other therapeutic agents. Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more excipients including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0100] The pharmaceutical compositions of the invention may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be

administered by injection can be prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. Alternatively, a pharmaceutical composition intended to be administered by injection can be prepared by combining a compound of the invention with sterile, reverse osmosis water so as to form a solution. A surfactant or other solubilizing excipient may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

[0101] In other embodiments, a solid pharmaceutical composition intended for oral administration can be prepared by mixing a therapeutically effective amount of a compound of the invention with at least one suitable pharmaceutically acceptable excipient to form a solid preformulation composition, which then may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. Accordingly, in some embodiments, a pharmaceutical composition is provided, which includes a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient.

[0102] The amount of active ingredient that may be combined with the inactive ingredients to produce a dosage form may vary depending upon the intended treatment subject and the particular mode of administration. For example, in some embodiments, a dosage form for oral administration to humans may contain approximately 1 to 1000 mg of active material formulated with an appropriate and convenient amount of a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutically acceptable excipient varies from about 5 to about 95% of the total compositions (weight:weight).

[0103] In some embodiments are provided compositions comprising a crystalline form as described herein, wherein the compound of Formula I within the composition is substantially pure (*i.e.*, substantially pure compound of Formula I described herein). In particular embodiments of compositions comprising a crystalline form of Formula I, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of Formula I present in the composition is one of the crystalline forms disclosed herein. In some embodiments, the composition includes at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of one of the crystalline forms of Formula I.

[0104] In other embodiments of compositions comprising a crystalline form disclosed herein, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of Formula I present in the composition are other amorphous or crystal forms of Formula I and/or impurities.

[0105] In yet other embodiments of compositions comprising the crystalline forms disclosed herein, impurities make up less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of the total mass relative to the mass of the crystalline forms present. Impurities may, for example, include by-products from synthesizing Formula I, contaminants, degradation products, other crystalline forms, amorphous form, water, and solvents. In some embodiments, impurities include by-products from the process of synthesizing Formula I. In some embodiments, impurities include contaminants from the process of synthesizing Formula I. In some embodiments, impurities include degradation products of Formula I. In some embodiments, impurities include other crystalline forms of Formula I. In some embodiments, impurities include water or solvent. In some embodiments of compositions comprising a crystalline form disclosed herein, impurities are selected from the group consisting of by-products from synthesizing Formula I, contaminants, degradation products, other crystalline forms, water, solvents and combinations thereof.

V. METHODS OF TREATING

[0106] In certain embodiments, the present disclosure provides methods of treating or preventing an HBV infection. In certain embodiments, a method of treating or preventing an HBV infection comprises administering to an individual (*e.g.* a human) a therapeutically effective amount a compound disclosed herein, *e.g.*, a compound of Formula I. In certain embodiments, the present disclosure also provides methods for treating an HBV infection comprising administering to an individual (*e.g.* a human) infected with HBV a therapeutically effective amount a compound disclosed herein. In some embodiments, the individual is chronically infected with HBV. In some embodiments, the individual is acutely infected with HBV. In some embodiments, a method of treating an individual (*e.g.* a human) infected with HBV comprises inhibiting HBsAg secretion and/or production.

[0107] In certain embodiments, a compound disclosed herein, *e.g.*, a compound of Formula I, for use in medical therapy is provided. In certain embodiments, the disease or condition is an HBV infection. In certain embodiments, a compound disclosed herein for use in treating or preventing an HBV infection is provided.

[0108] In certain embodiments, the use of a compound of the present disclosure, *e.g.*, a compound of Formula I, for the manufacture of a medicament for treating or preventing HBV infection is provided. In certain embodiments, a compound of the present disclosure for the manufacture of a medicament for treating or preventing an HBV infection is provided.

[0109] As described more fully herein, compounds of the present disclosure can be administered with one or more additional therapeutic agent(s) to an individual (*e.g.* a human) infected with HBV. The additional therapeutic agent(s) can be administered to the infected individual (*e.g.* a human) at the same time as a compound disclosed herein or before or after administration of a compound disclosed herein. For example, in certain embodiments, when used to treat or prevent a HBV infection, a compound disclosed herein is administered with one or more additional therapeutic agent(s) selected from the group consisting of HBV DNA polymerase inhibitors, toll-like receptor 7 modulators, toll-like receptor 8 modulators, Toll-like receptor 7 and 8 modulators, Toll-like receptor 3 modulators, interferon alpha ligands, HBsAg inhibitors, compounds targeting HBcAg, cyclophilin inhibitors, HBV therapeutic vaccines, HBV prophylactic vaccines, HBV viral entry inhibitors, NTCP inhibitors, antisense oligonucleotide targeting viral mRNA, short interfering RNAs (siRNA), hepatitis B virus E antigen inhibitors, HBx inhibitors, cccDNA inhibitors, HBV antibodies including HBV antibodies targeting the surface antigens of the hepatitis B virus, thymosin agonists, cytokines, nucleoprotein inhibitors (HBV core or capsid protein inhibitors), stimulators of retinoic acid-inducible gene 1, stimulators of NOD2, recombinant thymosin alpha-1 and hepatitis B virus replication inhibitors, and combinations thereof. Specific examples are more fully described below.

[0110] In certain embodiments, the present disclosure provides a method for ameliorating a symptom associated with an HBV infection, wherein the method comprises administering to an individual (*e.g.* a human) infected with hepatitis B virus a therapeutically effective amount of a compound of the present disclosure, *e.g.*, a compound of Formula I, wherein the therapeutically effective amount is sufficient to ameliorate a symptom associated with the HBV infection. Such symptoms include the presence of HBV virus particles in the blood, liver inflammation, jaundice, muscle aches, weakness and tiredness.

[0111] In certain embodiments, the present disclosure provides a method for reducing the rate of progression of a hepatitis B viral infection in an individual (*e.g.* a human), wherein the method comprises administering to an individual (*e.g.* a human) infected with hepatitis B virus a therapeutically effective amount of a compound disclosed herein, *e.g.*, a compound of Formula I, wherein the therapeutically effective amount is sufficient to reduce the rate of progression of the

hepatitis B viral infection. The rate of progression of the infection can be followed by measuring the amount of HBV virus particles in the blood.

[0112] In certain embodiments, the present disclosure provides a method for reducing the viral load associated with HBV infection, wherein the method comprises administering to an individual (*e.g.* a human) infected with HBV a therapeutically effective amount of a compound of the present disclosure, *e.g.*, a compound of Formula I, wherein the therapeutically effective amount is sufficient to reduce the HBV viral load in the individual. In some embodiments, a method of treating an individual (*e.g.* a human) infected with hepatitis B virus comprises reducing the viral load associated with HBV infection as measured by PCR testing.

[0113] Compounds disclosed herein can be administered by any route appropriate for use in a method described herein. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like.

[0114] Compounds disclosed herein may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least one week, at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer. In one variation, the compound is administered on a daily or intermittent schedule for the duration of the individual's life.

[0115] The dosage or dosing frequency of a compound of the present disclosure may be adjusted over the course of the treatment, based on the judgment of the administering physician.

[0116] Therapeutically effective amounts of compounds disclosed herein are from about 0.00001 mg/kg body weight per day to about 10 mg/kg body weight per day, such as from about 0.0001 mg/kg body weight per day to about 10 mg/kg body weight per day, or such as from about 0.001 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.01 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.05 mg/kg body weight per day to about 0.5 mg/kg body weight per day, or such as from about 0.3 µg to about 30 mg per day, or such as from about 30 µg to about 300 µg per day.

[0117] A compound of the present disclosure (*e.g.*, a compound of Formula (I)) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of the present disclosure (*e.g.*, from 1 mg to 1000 mg of compound). Therapeutically effective amounts of the compound of Formula (I) can range from about 0.01 mg per dose to about 1000 mg per dose, such as from about 0.01 mg per dose to about 100 mg per dose, or such as from about 0.1 mg per dose to about 100 mg per dose, or such as from about 1 mg per dose to

about 100 mg per dose, or such as from about 1 mg per dose to about 10 mg per dose. Other therapeutically effective amounts of the compound of Formula (I) are about 1 mg per dose, or about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or about 100 mg per dose. Other therapeutically effective amounts of the compound of Formula (I) are about 100 mg per dose, or about 125, 150, 175, 200, 225, 250, 275, 300, 350, 400, 450, or about 500 mg per dose.

[0118] A single dose can be administered hourly, daily, or weekly. For example, a single dose can be administered once every 1 hour, 2, 3, 4, 6, 8, 12, 16 or once every 24 hours. A single dose can also be administered once every 1 day, 2, 3, 4, 5, 6, or once every 7 days. A single dose can also be administered once every 1 week, 2, 3, or once every 4 weeks. In certain embodiments, a single dose can be administered once every week. A single dose can also be administered once every month. In some embodiments, a compound disclosed herein is administered once daily in a method disclosed herein. In some embodiments, a compound disclosed herein is administered twice daily in a method disclosed herein.

[0119] The frequency of dosage of a compound disclosed herein will be determined by the needs of the individual patient and can be, for example, once per day or twice, or more times, per day. Administration of a compound continues for as long as necessary to treat an HBV infection. For example, a compound disclosed herein can be administered to a human being infected with HBV for a period of from 20 days to 180 days or, for example, for a period of from 20 days to 90 days or, for example, for a period of from 30 days to 60 days.

[0120] Administration can be intermittent, with a period of several or more days during which a patient receives a daily dose of a compound disclosed herein, followed by a period of several or more days during which a patient does not receive a daily dose of the compound. For example, a patient can receive a dose of a compound every other day, or three times per week. Again by way of non-limiting example, a patient can receive a dose of a compound each day for a period of from 1 to 14 days, followed by a period of 7 to 21 days during which the patient does not receive a dose of the compound, followed by a subsequent period (*e.g.*, from 1 to 14 days) during which the patient again receives a daily dose of the compound. Alternating periods of administration of the compound, followed by non-administration of the compound, can be repeated as clinically required to treat the patient.

VI. COMBINATION THERAPY FOR HBV

[0121] In certain embodiments, a method for treating or preventing an HBV infection in a human having or at risk of having the infection is provided, comprising administering to the

human a therapeutically effective amount of a compound disclosed herein in combination with a therapeutically effective amount of one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents. In one embodiment, a method for treating an HBV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein in combination with a therapeutically effective amount of one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents.

[0122] In certain embodiments, the present disclosure provides a method for treating an HBV infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein in combination with a therapeutically effective amount of one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents which are suitable for treating an HBV infection.

[0123] In one embodiment, pharmaceutical compositions comprising a compound of the present disclosure, *e.g.*, a compound of Formula I, in combination with one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents, and a pharmaceutically acceptable excipient are provided.

[0124] In certain embodiments, a compound disclosed herein is combined with one, two, three, four, or more additional therapeutic agents. In certain embodiments, a compound disclosed herein is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein is combined with four additional therapeutic agents. The one, two, three, four, or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

Administration of HBV Combination Therapy

[0125] In certain embodiments, when a compound disclosed herein is combined with one or more additional therapeutic agents as described above, the components of the composition are administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0126] Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of each agent are present in the body of the patient.

[0127] Co-administration includes administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents. The compound disclosed herein may be administered within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound disclosed herein is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein within seconds or minutes. In some embodiments, a unit dose of a compound disclosed herein is administered first, followed, after a period of hours (*e.g.*, 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (*e.g.*, 1-12 hours), by administration of a unit dose of a compound disclosed herein.

[0128] In certain embodiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration.

[0129] In certain embodiments a compound of Formula (I) is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HBV. In certain embodiments, the tablet can contain another active ingredient for treating HBV.

[0130] In certain embodiments, such tablets are suitable for once daily dosing.

HBV Combination Therapy

[0131] The compounds described herein may be used or combined with one or more of a chemotherapeutic agent, an immunomodulator, an immunotherapeutic agent, a therapeutic antibody, a therapeutic vaccine, a bispecific antibody and “antibody-like” therapeutic protein (such as DARTs®, Duobodies®, Bites®, XmAbs®, TandAbs®, Fab derivatives), an antibody-drug conjugate (ADC), gene modifiers or gene editors (such as CRISPR Cas9, zinc finger nucleases, homing endonucleases, synthetic nucleases, TALENs), cell therapies such as CAR-T (chimeric antigen receptor T-cell), and TCR-T (an engineered T cell receptor) agent or any combination thereof.

[0132] In certain embodiments, a compound of Formula (I) is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HBV. In certain embodiments, the tablet can contain another active ingredient for treating HBV, such as 3-dioxygenase (IDO) inhibitors, Apolipoprotein A1 modulator, arginase inhibitors, B- and T-

lymphocyte attenuator inhibitors, Bruton's tyrosine kinase (BTK) inhibitors, CCR2 chemokine antagonist, CD137 inhibitors, CD160 inhibitors, CD305 inhibitors, CD4 agonist and modulator, compounds targeting HBcAg, compounds targeting hepatitis B core antigen (HBcAg), core protein allosteric modulators, covalently closed circular DNA (cccDNA) inhibitors, cyclophilin inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ipi4) inhibitors, DNA polymerase inhibitor, Endonuclease modulator, epigenetic modifiers, Farnesoid X receptor agonist, HBsAg inhibitors, HBsAg secretion or assembly inhibitors, HBV DNA polymerase inhibitors, HBV replication inhibitors, HBV RNase inhibitors, HBV viral entry inhibitors, HBx inhibitors, Hepatitis B large envelope protein modulator, Hepatitis B large envelope protein stimulator, Hepatitis B structural protein modulator, hepatitis B surface antigen (HBsAg) inhibitors, hepatitis B surface antigen (HBsAg) secretion or assembly inhibitors, hepatitis B virus E antigen inhibitors, hepatitis B virus replication inhibitors, Hepatitis virus structural protein inhibitor, HIV-1 reverse transcriptase inhibitor, Hyaluronidase inhibitor, IAPs inhibitors, IL-2 agonist, IL-7 agonist, immunomodulators, indoleamine-2 inhibitors, inhibitors of ribonucleotide reductase, Interleukin-2 ligand, ipi4 inhibitors, lysine demethylase inhibitors, histone demethylase inhibitors, KDM1 inhibitors, KDM5 inhibitors, killer cell lectin-like receptor subfamily G member 1 inhibitors, lymphocyte-activation gene 3 inhibitors, lymphotoxin beta receptor activators, modulators of Axl, modulators of B7-H3, modulators of B7-H4, modulators of CD160, modulators of CD161, modulators of CD27, modulators of CD47, modulators of CD70, modulators of GITR, modulators of HEVEM, modulators of ICOS, modulators of Mer, modulators of NKG2A, modulators of NKG2D, modulators of OX40, modulators of SIRPalpha, modulators of TIGIT, modulators of Tim-4, modulators of Tyro, Na⁺-taurocholate cotransporting polypeptide (NTCP) inhibitors, natural killer cell receptor 2B4 inhibitors, NOD2 gene stimulator, Nucleoprotein inhibitor, nucleoprotein modulators, PD-1 inhibitors, PD-L1 inhibitors, Peptidylprolyl isomerase inhibitor, phosphatidylinositol-3 kinase (PI3K) inhibitors, Retinoic acid-inducible gene 1 stimulator, Reverse transcriptase inhibitor, Ribonuclease inhibitor, RNA DNA polymerase inhibitor, SLC10A1 gene inhibitor, SMAC mimetics, Src tyrosine kinase inhibitor, stimulator of interferon gene (STING) agonists, stimulators of NOD1, T cell surface glycoprotein CD28 inhibitor, T-cell surface glycoprotein CD8 modulator, Thymosin agonist, Thymosin alpha 1 ligand, Tim-3 inhibitors, TLR-3 agonist, TLR-7 agonist, TLR-9 agonist, TLR9 gene stimulator, toll-like receptor (TLR) modulators, Viral ribonucleotide reductase inhibitor, and combinations thereof.

HBV Combination Drugs

[0133] Examples of combination drugs for the treatment of HBV include TRUVADA[®] (tenofovir disoproxil fumarate and emtricitabine); ABX-203, lamivudine, and PEG-IFN-alpha; ABX-203 adefovir, and PEG-IFNalpha; and INO-1800 (INO-9112 and RG7944).

Other HBV Drugs

[0134] Examples of other drugs for the treatment of HBV include alpha-hydroxytropolones, amdoxovir, beta-hydroxycytosine nucleosides, AL-034, CCC-0975, elvucitabine, ezetimibe, cyclosporin A, gentiopiricin (gentiopicroside), JNJ-56136379, nitazoxanide, birinapant, NJK14047, NOV-205 (molixan, BAM-205), oligotide, mivotilate, feron, GST-HG-131, levamisole, Ka Shu Ning, alloferon, WS-007, Y-101 (Ti Fen Tai), rSIFN-co, PEG-IIFNm, KW-3, BP-Inter-014, oleanolic acid, HepB-nRNA, cTP-5 (rTP-5), HSK-II-2, HEISCO-106-1, HEISCO-106, Hepbarna, IBPB-006IA, Hepuyinfen, DasKloster 0014-01, ISA-204, Jiangantai (Ganxikang), MIV-210, OB-AI-004, PF-06, picoside, DasKloster-0039, hepulantai, IMB-2613, TCM-800B, reduced glutathione, RO-6864018, RG-7834, UB-551, and ZH-2N, and the compounds disclosed in US20150210682, (Roche), US 2016/0122344 (Roche), WO2015173164, WO2016023877, US2015252057A (Roche), WO16128335A1 (Roche), WO16120186A1 (Roche), US2016237090A (Roche), WO16107833A1 (Roche), WO16107832A1 (Roche), US2016176899A (Roche), WO16102438A1 (Roche), WO16012470A1 (Roche), US2016220586A (Roche), and US2015031687A (Roche).

HBV Vaccines

[0135] HBV vaccines include both prophylactic and therapeutic vaccines. Examples of HBV prophylactic vaccines include Vaxelis, Hexaxim, Heplisav, Mosquirix, DTwP-HBV vaccine, Bio-Hep-B, D/T/P/HBV/M (LBVP-0101; LBVW-0101), DTwP-Hepb-Hib-IPV vaccine, Heberpenta L, DTwP-HepB-Hib, V-419, CVI-HBV-001, Tetrabhay, hepatitis B prophylactic vaccine (Advax Super D), Hepatrol-07, GSK-223192A, ENGERIX B[®], recombinant hepatitis B vaccine (intramuscular, Kangtai Biological Products), recombinant hepatitis B vaccine (Hansensual polymorpha yeast, intramuscular, Hualan Biological Engineering), recombinant hepatitis B surface antigen vaccine, Bimmugen, Euforavac, Eutravac, anrix-DTaP-IPV-Hep B, HBAI-20, Infanrix-DTaP-IPV-Hep B-Hib, Pentabio Vaksin DTP-HB-Hib, Comvac 4, Twinrix, Euvax-B, Tritanrix HB, Infanrix Hep B, Comvac, DTP-Hib-HBV vaccine, DTP-HBV vaccine, Yi Tai, Heberbiovac HB, Trivac HB, GerVax, DTwP-Hep B-Hib vaccine, Bilive, Hepavax-Gene, SUPERVAX, Comvac5, Shanvac-B, Hebsulin, Recombivax HB, Revac B mcf, Revac

B+, Fendrix, DTwP-HepB-Hib, DNA-001, Shan5, Shan6, rhHBsAG vaccine, HBI pentavalent vaccine, LBVD, Infanrix HeXa, and DTaP-rHB-Hib vaccine.

[0136] Examples of HBV therapeutic vaccines include HBsAG-HBIG complex, ARB-1598, Bio-Hep-B, NASVAC, abi-HB (intravenous), ABX-203, Tetrabhay, GX-110E, GS-4774, peptide vaccine (epsilonPA-44), Hepatrol-07, NASVAC (NASTERAP), IMP-321, BEVAC, Revac B mcf, Revac B+, MGN-1333, KW-2, CVI-HBV-002, AltraHepB, VGX-6200, FP-02, FP-02.2, TG-1050, NU-500, HBVax, im/TriGrid/antigen vaccine, Mega-CD40L-adjuvanted vaccine, HepB-v, RG7944 (INO-1800), recombinant VLP-based therapeutic vaccine (HBV infection, VLP Biotech), AdTG-17909, AdTG-17910 AdTG-18202, ChronVac-B, TG-1050, and Lm HBV.

HBV DNA Polymerase Inhibitors

[0137] Examples of HBV DNA polymerase inhibitors include adefovir (HEPSERA[®]), emtricitabine (EMTRIVA[®]), tenofovir disoproxil fumarate (VIREAD[®]), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir dipivoxil, tenofovir dipivoxil fumarate, tenofovir octadecyloxyethyl ester, CMX-157, besifovir, entecavir (BARACLUDE[®]), entecavir maleate, telbivudine (TYZEKA[®]), filocilovir, pradefovir, clevudine, ribavirin, lamivudine (EPIVIR-HBV[®]), phosphazide, famciclovir, fusolin, metacavir, SNC-019754, FMCA, AGX-1009, AR-II-04-26, HIP-1302, tenofovir disoproxil aspartate, tenofovir disoproxil orotate, and HS-10234.

Immunomodulators

[0138] Examples of immunomodulators include rintatolimod, imidol hydrochloride, ingaron, dermaVir, plaquenil (hydroxychloroquine), proleukin, hydroxyurea, mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF), JNJ-440, WF-10, AB-452, ribavirin, IL-12, INO-9112, polymer polyethyleneimine (PEI), Gepon, VGV-1, MOR-22, CRV-431, JNJ-0535, TG-1050, ABI-H2158, BMS-936559, GS-9688, RO-7011785, RG-7854, AB-506, RO-6871765, AIC-649, and IR-103.

Toll-like Receptor (TLR) Modulators

[0139] TLR modulators include modulators of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, TLR11, TLR12, and TLR13. Examples of TLR3 modulators include rintatolimod, poly-ICLC, RIBOXXON[®], Apoxsim, RIBOXXIM[®], IPH-33, MCT-465, MCT-475, and ND-1.1.

[0140] Examples of TLR7 modulators include GS-9620, GSK-2245035, imiquimod, resiquimod, DSR-6434, DSP-3025, IMO-4200, MCT-465, MEDI-9197, 3M-051, SB-9922, 3M-

052, Limtop, D, telratolimod, SP-0509, TMX-30X, TMX-202, RG-7863, RG-7795, LHC-165, RG-7854, and the compounds disclosed in US20100143301 (Gilead Sciences), US20110098248 (Gilead Sciences), and US20090047249 (Gilead Sciences).

[0141] Examples of TLR8 modulators include motolimod, resiquimod, 3M-051, 3M-052, MCT-465, IMO-4200, VTX-763, VTX-1463, GS-9688 and the compounds disclosed in US20140045849 (Janssen), US20140073642 (Janssen), WO2014/056953 (Janssen), WO2014/076221 (Janssen), WO2014/128189 (Janssen), US20140350031 (Janssen), WO2014/023813 (Janssen), US20080234251 (Array Biopharma), US20080306050 (Array Biopharma), US20100029585 (Ventirx Pharma), US20110092485 (Ventirx Pharma), US20110118235 (Ventirx Pharma), US20120082658 (Ventirx Pharma), US20120219615 (Ventirx Pharma), US20140066432 (Ventirx Pharma), US20140088085 (Ventirx Pharma), US20140275167 (Novira Therapeutics), US20130251673 (Novira Therapeutics), US Patent No. 9670205, US20160289229, US Patent Application No. 15/692161, and US Patent Application No. 15/692093.

[0142] Examples of TLR9 modulators include BB-001, BB-006, CYT-003, IMO-2055, IMO-2125, IMO-3100, IMO-8400, IR-103, IMO-9200, agatolimod, DIMS-9054, DV-1079, DV-1179, AZD-1419, leftolimod (MGN-1703), litenimod, and CYT-003-QbG10.

[0143] Examples of TLR7, TLR8 and TLR9 modulators include the compounds disclosed in WO2017047769 (Teika Seiyaku), WO2015014815 (Janssen), WO2018045150 (Gilead Sciences Inc), WO2018045144 (Gilead Sciences Inc), WO2015162075 (Roche), WO2017034986 (University of Kansas), WO2018095426 (Jiangsu Hengrui Medicine Co Ltd), WO2016091698 (Roche), WO2016075661 (GlaxoSmithKline Biologicals), WO2016180743 (Roche), WO2018089695 (Dynavax Technologies), WO2016055553 (Roche), WO2015168279 (Novartis), WO2016107536 (Medshine Discovery), WO2018086593 (Livo (Shanghai Pharmaceutical)), WO2017106607 (Merck), WO2017061532 (Sumitomo Dainippon Pharma), WO2016023511 (Chia Tai Tianqing Pharmaceutical), WO2017076346 (Chia Tai Tianqing Pharmaceutical), WO2017046112 (Roche), WO2018078149 (Roche), WO2017040233 (3M Co), WO2016141092 (Gilead Sciences), WO2018049089 (BristolMyers Squibb), WO2015057655 (Eisai Co Ltd), WO2017001307 (Roche), WO2018005586 (BristolMyers Squibb), WO201704023 (3M Co), WO2017163264 (Council of Scientific and Industrial Research (India)), WO2018046460 (GlaxoSmithKline Biologicals), WO2018047081 (Novartis), WO2016142250 (Roche), WO2015168269 (Novartis), WO201804163 (Roche), WO2018038877 (3M Co), WO2015057659 (Eisai Co Ltd), WO2017202704 (Roche), WO2018026620 (BristolMyers Squibb), WO2016029077 (Janus Biotherapeutics), WO201803143 (Merck),

WO2016096778 (Roche), WO2017190669 (Shanghai De Novo Pharmatech), US09884866 (University of Minnesota), WO2017219931 (Sichuan KelunBiotech Biopharmaceutical), WO2018002319 (Janssen Sciences), WO2017216054(Roche), WO2017202703 (Roche), WO2017184735 (IFM Therapeutics), WO2017184746 (IFM Therapeutics), WO2015088045 (Takeda Pharmaceutical), WO2017038909 (Takeda Pharmaceutical), WO2015095780 (University of Kansas), and WO2015023958 (University of Kansas).

Interferon Alpha Receptor Ligands

[0144] Examples of interferon alpha receptor ligands include interferon alpha-2b (INTRON A[®]), pegylated interferon alpha-2a (PEGASYS[®]), PEGylated interferon alpha-1b, interferon alpha 1b (HAPGEN[®]), Veldona, Infradure, Roferon-A, YPEG-interferon alfa-2a (YPEG-rhIFNalpha-2a), P-1101, Algeron, Alfaferon, Ingaron (interferon gamma), rSIFN-co (recombinant super compound interferon), Ypeginterferon alfa-2b (YPEG-rhIFNalpha-2b), MOR-22, peginterferon alfa-2b (PEG-INTRON[®]), Bioferon, Novaferon, Inmutag (Inferon), MULTIFERON[®], interferon alfa-n1(HUMOFERON[®]), interferon beta-1a (AVONEX[®]), Shaferon, interferon alfa-2b (Axxo), Alfaferone, interferon alfa-2b (BioGeneric Pharma), interferon-alpha 2 (CJ), Laferonum, VIPEG, BLAUFERON-A, BLAUFERON-B, Intermax Alpha, Realdiron, Lanstion, Pegaferon, PDferon-B, interferon alfa-2b (IFN, Laboratorios Bioprofarma), alfainterferona 2b, Kalferon, Pegnano, Feronsure, PegiHep, interferon alfa 2b (Zydus-Cadila), interferon alfa 2a, Optipeg A, Realfa 2B, Reliferon, interferon alfa-2b (Amega), interferon alfa-2b (Virchow), ropeginterferon alfa-2b, rHSA-IFN alpha-2a (recombinant human serum albumin interfereferon alpha 2a fusion protein), rHSA-IFN alpha 2b, recombinant human interferon alpha-(1b, 2a, 2b), peginterferon alfa-2b (Amega), peginterferon alfa-2a , Reaferon-EC, Proquiferon, Uniferon, Urifron, interferon alfa-2b (Changchun Institute of Biological Products), Anterferon, Shanferon, Layfferon, Shang Sheng Lei Tai, INTEFEN, SINOGEN, Fukangtai, Pegstat, rHSA-IFN alpha-2b, SFR-9216, and Interapo (Interapa).

Hyaluronidase Inhibitors

[0145] Examples of hyaluronidase inhibitors include astodrimer.

Hepatitis B Surface Antigen (HBsAg) Inhibitors

[0146] Examples of HBsAg inhibitors include HBF-0259, PBHBV-001, PBHBV-2-15, PBHBV-2-1, REP-9AC, REP-9C, REP-9, REP-2139, REP-2139-Ca, REP-2165, REP-2055, REP-2163, REP-2165, REP-2053, REP-2031 and REP-006, and REP-9AC'.

[0147] Examples of HBsAg secretion inhibitors include BM601.

Cytotoxic T-lymphocyte-associated protein 4 (ipi4) inhibitors

[0148] Examples of Cytotoxic T-lymphocyte-associated protein 4 (ipi4) inhibitors include AGEN-2041, AGEN-1884, ipilimumab, belatacept, PSI-001, PRS-010, Probody mAbs, tremelimumab, and JHL-1155.

Cyclophilin Inhibitors

[0149] Examples of cyclophilin inhibitors include CPI-431-32, EDP-494, OCB-030, SCY-635, NVP-015, NVP-018, NVP-019, STG-175, and the compounds disclosed in US8513184 (Gilead Sciences), US20140030221 (Gilead Sciences), US20130344030 (Gilead Sciences), and US20130344029 (Gilead Sciences).

HBV Viral Entry Inhibitors

[0150] Examples of HBV viral entry inhibitors include Myrcludex B.

Antisense Oligonucleotide Targeting Viral mRNA

[0151] Examples of antisense oligonucleotide targeting viral mRNA include ISIS-HBVRx, IONIS-HBVRx, IONIS-GSK6-LRx, GSK-3389404, RG-6004.

Short Interfering RNAs (siRNA) and ddRNAi

[0152] Examples of siRNA include TKM-HBV (TKM-HepB), ALN-HBV, SR-008, HepB-nRNA, ARC-520, ARC-521, ARB-1740, and ARB-1467.

[0153] Examples of DNA-directed RNA interference (ddRNAi) include BB-HB-331.

Endonuclease Modulators

[0154] Examples of endonuclease modulators include PGN-514.

Ribonucleotide Reductase Inhibitors

[0155] Examples of inhibitors of ribonucleotide reductase include Trimidox.

HBV E Antigen Inhibitors

[0156] Examples of HBV E antigen inhibitors include wogonin.

Covalently Closed Circular DNA (cccDNA) Inhibitors

[0157] Examples of cccDNA inhibitors include BSBI-25, and CHR-101.

Farnesoid X receptor agonist

[0158] Examples of farnesoid x receptor agonist such as EYP-001, GS-9674, EDP-305, MET-409, Tropifexor, AKN-083, RDX-023, BWD-100, LMB-763, INV-3, NTX-023-1, EP-024297 and GS-8670

HBV Antibodies

[0159] Examples of HBV antibodies targeting the surface antigens of the hepatitis B virus include GC-1102, XTL-17, XTL-19, KN-003, IV Hepabulin SN, and fully human monoclonal antibody therapy (hepatitis B virus infection, Humabs BioMed).

[0160] Examples of HBV antibodies, including monoclonal antibodies and polyclonal antibodies, include Zutectra, Shang Sheng Gan Di, Uman Big (Hepatitis B Hyperimmune), Omri-Hep-B, Nabi-HB, Hepatect CP, HepaGam B, igantibe, Niuliva, CT-P24, hepatitis B immunoglobulin (intravenous, pH4, HBV infection, Shanghai RAAS Blood Products), and Fovepta (BT-088).

[0161] Fully human monoclonal antibodies include HBC-34.

CCR2 Chemokine Antagonists

[0162] Examples of CCR2 chemokine antagonists include propagermanium.

Thymosin Agonists

[0163] Examples of thymosin agonists include Thymalfasin, recombinant thymosin alpha 1 (GeneScience).

Cytokines

[0164] Examples of cytokines include recombinant IL-7, CYT-107, interleukin-2 (IL-2, Immunex), recombinant human interleukin-2 (Shenzhen Neptunus), IL-15, IL-21, IL-24, and celmoleukin.

Nucleoprotein modulators

[0165] Nucleoprotein modulators may be either HBV core or capsid protein inhibitors. Examples of nucleoprotein modulators include GS-4882, AB-423, AT-130, GLS4, NVR-1221, NVR-3778, AL-3778, BAY 41-4109, morphothiadin mesilate, ARB-168786, ARB-880, JNJ-379, RG-7907, HEC-72702, AB-506, ABI-H0731, JNJ-440, ABI-H2158 and DVR-23.

[0166] Examples of capsid inhibitors include the compounds disclosed in US20140275167 (Novira Therapeutics), US20130251673 (Novira Therapeutics), US20140343032 (Roche),

WO2014037480 (Roche), US20130267517 (Roche), WO2014131847 (Janssen), WO2014033176 (Janssen), WO2014033170 (Janssen), WO2014033167 (Janssen), WO2015/059212 (Janssen), WO2015118057 (Janssen), WO2015011281 (Janssen), WO2014184365 (Janssen), WO2014184350 (Janssen), WO2014161888 (Janssen), WO2013096744 (Novira), US20150225355 (Novira), US20140178337 (Novira), US20150315159 (Novira), US20150197533 (Novira), US20150274652 (Novira), US20150259324, (Novira), US20150132258 (Novira), US9181288 (Novira), WO2014184350 (Janssen), WO2013144129 (Roche), WO2017198744 (Roche), US 20170334882 (Novira), US 20170334898 (Roche), WO2017202798 (Roche), WO2017214395 (Enanta), WO2018001944 (Roche), WO2018001952 (Roche), WO2018005881 (Novira), WO2018005883 (Novira), WO2018011100 (Roche), WO2018011160 (Roche), WO2018011162 (Roche), WO2018011163 (Roche), WO2018036941 (Roche), WO2018043747 (Kyoto Univ), US20180065929 (Janssen), WO2016168619 (Indiana University), WO2016195982 (The Penn State Foundation), WO2017001655 (Janssen), WO2017048950 (Assembly Biosciences), WO2017048954 (Assembly Biosciences), WO2017048962 (Assembly Biosciences), US20170121328 (Novira), US20170121329 (Novira).

[0167] Examples of transcript inhibitors include the compounds disclosed in WO2017013046 (Roche), WO2017016960 (Roche), WO2017017042 (Roche), WO2017017043 (Roche), WO2017061466 (Toyoma chemicals), WO2016177655 (Roche), WO2016161268 (Enanta), WO2017001853 (Redex Pharma), WO2017211791 (Roche), WO2017216685 (Novartis), WO2017216686 (Novartis), WO2018019297 (Ginkgo Pharma), WO2018022282 (Newave Pharma), US20180030053 (Novartis), WO2018045911 (Zhejiang Pharma).

Retinoic Acid-inducible Gene 1 Stimulators

[0168] Examples of stimulators of retinoic acid-inducible gene 1 include SB-9200, SB-40, SB-44, ORI-7246, ORI-9350, ORI-7537, ORI-9020, ORI-9198, ORI-7170, and RGT-100.

NOD2 Stimulators

[0169] Examples of stimulators of NOD2 include SB-9200.

Phosphatidylinositol 3-kinase (PI3K) Inhibitors

[0170] Examples of PI3K inhibitors include idelalisib, ACP-319, AZD-8186, AZD-8835, buparlisib, CDZ-173, CLR-457, pictilisib, neratinib, rigosertib, rigosertib sodium, EN-3342, TGR-1202, alpelisib, duvelisib, IPI-549, UCB-5857, taselisib, XL-765, gedatolisib, ME-401, VS-5584, copanlisib, CAI orotate, perifosine, RG-7666, GSK-2636771, DS-7423, panulisib, GSK-2269557, GSK-2126458, CUDC-907, PQR-309, INCB-40093, pilaralisib, BAY-1082439,

puquitinib mesylate, SAR-245409, AMG-319, RP-6530, ZSTK-474, MLN-1117, SF-1126, RV-1729, sonolisib, LY-3023414, SAR-260301, TAK-117, HMPL-689, tenalisib, voxalisib, and CLR-1401.

Indoleamine-2, 3-dioxygenase (IDO) Pathway Inhibitors

[0171] Examples of IDO inhibitors include epacadostat (INCB24360), resminostat (4SC-201), indoximod, F-001287, SN-35837, NLG-919, GDC-0919, GBV-1028, GBV-1012, NKTR-218, and the compounds disclosed in US20100015178 (Incyte), US2016137652 (Flexus Biosciences, Inc.), WO2014073738 (Flexus Biosciences, Inc.), and WO2015188085 (Flexus Biosciences, Inc.).

PD-1 Inhibitors

[0172] Examples of PD-1 inhibitors include cemiplimab, nivolumab, pembrolizumab, pidilizumab, BGB-108, STI-A1014, SHR-1210, PDR-001, PF-06801591, IBI-308, GB-226, STI-1110, JNJ-63723283, CA-170, durvalumab, atezolizumab and mDX-400, JS-001, Camrelizumab, Sintilimab, Sintilimab, tislelizumab, BCD-100, BGB-A333 JNJ-63723283, GLS-010 (WBP-3055), CX-072, AGEN-2034, GNS-1480 (Epidermal growth factor receptor antagonist; Programmed cell death ligand 1 inhibitor), CS-1001, M-7824 (PD-L1/TGF- β bifunctional fusion protein), Genolimzumab, BMS-936559

PD-L1 Inhibitors

[0173] Examples of PD-L1 inhibitors include atezolizumab, avelumab, AMP-224, MEDI-0680, RG-7446, GX-P2, durvalumab, KY-1003, KD-033, MSB-0010718C, TSR-042, ALN-PDL, STI-A1014, GS-4224, CX-072, and BMS-936559.

[0174] Examples of PD-1 inhibitors include the compounds disclosed in WO2017112730 (Incyte Corp), WO2017087777 (Incyte Corp), WO2017017624, WO2014151634 (BristolMyers Squibb Co), WO201317322 (BristolMyers Squibb Co), WO2018119286 (Incyte Corp), WO2018119266 (Incyte Corp), WO2018119263 (Incyte Corp), WO2018119236 (Incyte Corp), WO2018119221 (Incyte Corp), WO2018118848 (BristolMyers Squibb Co), WO20161266460 (BristolMyers Squibb Co), WO2017087678 (BristolMyers Squibb Co), WO2016149351 (BristolMyers Squibb Co), WO2015033299 (Aurigene Discovery Technologies Ltd), WO2015179615 (Eisai Co Ltd; Eisai Research Institute), WO2017066227 (BristolMyers Squibb Co), WO2016142886 (Aurigene Discovery Technologies Ltd), WO2016142852 (Aurigene Discovery Technologies Ltd), WO2016142835 (Aurigene Discovery Technologies Ltd; Individual), WO2016142833 (Aurigene Discovery Technologies Ltd), WO2018085750 (BristolMyers Squibb Co), WO2015033303 (Aurigene Discovery

Technologies Ltd), WO2017205464 (Incyte Corp), WO2016019232 (3M Co; Individual; Texas A&M University System), WO2015160641 (BristolMyers Squibb Co), WO2017079669 (Incyte Corp), WO2015033301 (Aurigene Discovery Technologies Ltd), WO2015034820 (BristolMyers Squibb Co), WO2018073754 (Aurigene Discovery Technologies Ltd), WO2016077518 (BristolMyers Squibb Co), WO2016057624 (BristolMyers Squibb Co), WO2018044783 (Incyte Corp), WO2016100608 (BristolMyers Squibb Co), WO2016100285 (BristolMyers Squibb Co), WO2016039749 (BristolMyers Squibb Co), WO2015019284 (Cambridge Enterprise Ltd), WO2016142894 (Aurigene Discovery Technologies Ltd), WO2015134605 (BristolMyers Squibb Co), WO2018051255 (Aurigene Discovery Technologies Ltd), WO2018051254 (Aurigene Discovery Technologies Ltd), WO2017222976 (Incyte Corp), WO2017070089 (Incyte Corp), WO2018044963 (BristolMyers Squibb Co), WO2013144704 (Aurigene Discovery Technologies Ltd), WO2018013789 (Incyte Corp), WO2017176608 (BristolMyers Squibb Co), WO2018009505 (BristolMyers Squibb Co), WO2011161699 (Aurigene Discovery Technologies Ltd), WO2015119944 (Incyte Corp; Merck Sharp & Dohme Corp), WO2017192961 (Incyte Corp), WO2017106634 (Incyte Corp), WO2013132317 (Aurigene Discovery Technologies Ltd), WO2012168944 (Aurigene Discovery Technologies Ltd), WO2015036927 (Aurigene Discovery Technologies Ltd), WO2015044900 (Aurigene Discovery Technologies Ltd), WO2018026971 (Arising International).

Recombinant Thymosin Alpha-1

[0175] Examples of recombinant thymosin alpha-1 include NL-004 and PEGylated thymosin alpha-1.

Bruton's Tyrosine Kinase (BTK) Inhibitors

[0176] Examples of BTK inhibitors include ABBV-105, acalabrutinib (ACP-196), ARQ-531, BMS-986142, dasatinib, ibrutinib, GDC-0853, PRN-1008, SNS-062, ONO-4059, BGB-3111, ML-319, MSC-2364447, RDX-022, X-022, AC-058, RG-7845, spebrutinib, TAS-5315, TP-0158, TP-4207, HM-71224, KBP-7536, M-2951, TAK-020, AC-0025, and the compounds disclosed in US20140330015 (Ono Pharmaceutical), US20130079327 (Ono Pharmaceutical), and US20130217880 (Ono Pharmaceutical).

KDM Inhibitors

[0177] Examples of KDM5 inhibitors include the compounds disclosed in WO2016057924 (Genentech/Constellation Pharmaceuticals), US20140275092 (Genentech/Constellation Pharmaceuticals), US20140371195 (Epitherapeutics), US20140371214 (Epitherapeutics), US20160102096 (Epitherapeutics), US20140194469 (Quantice), US20140171432,

US20140213591 (Quantice), US20160039808 (Quantice), US20140275084 (Quantice), and WO2014164708 (Quantice).

[0178] Examples of KDM1 inhibitors include the compounds disclosed in US9186337B2 (Oryzon Genomics), GSK-2879552, and RG-6016.

STING agonists

[0179] Examples of STING agonists include SB-11285, AdVCA0848, STINGVAX, and the compounds disclosed in WO 2018065360 ("Biolog Life Science Institute Forschungslabor und Biochemica-Vertrieb GmbH, Germany), WO 2018009466 (Aduro Biotech), WO 2017186711 (InvivoGen), WO 2017161349 (Immune Sensor), WO 2017106740 (Aduro Biotech), US 20170158724 (GlaxoSmithKline), WO 2017075477 (Aduro Biotech), US 20170044206 (Merck), WO 2014179760 (University of California), WO2018098203 (Janssen), WO2018118665 (Merck), WO2018118664 (Merck), WO2018100558 (Takeda), WO2018067423 (Merck), and WO2018060323 (Boehringer).

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

[0180] Examples of NNRTI include the compounds disclosed in WO2018118826 (Merck), WO2018080903 (Merck), WO2018119013 (Merck), WO2017100108 (Idenix), WO2017027434 (Merck), WO2017007701 (Merck), and WO2008005555 (Gilead).

HBV Replication Inhibitors

[0181] Examples of hepatitis B virus replication inhibitors include isothiafludine, IQP-HBV, RM-5038, and Xingantie.

Arginase inhibitors

[0182] Examples of Arginase inhibitors include CB-1158, C-201, and resminostat.

Gene Therapy and Cell Therapy

[0183] Gene therapy and cell therapy includes the genetic modification to silence a gene; genetic approaches to directly kill the infected cells; the infusion of immune cells designed to replace most of the patient's own immune system to enhance the immune response to infected cells, or activate the patient's own immune system to kill infected cells, or find and kill the infected cells; and genetic approaches to modify cellular activity to further alter endogenous immune responsiveness against the infection.

Gene Editors

[0184] Examples of genome editing systems include a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system, a homing endonucleases system, and a meganuclease system; *e.g.*, cccDNA elimination via targeted cleavage, and altering one or more of the hepatitis B virus (HBV) viral genes. Altering (*e.g.*, knocking out and/or knocking down) the *PreC*, *C*, *X*, *PreS1*, *PreS2*, *S*, *P* or *SP* gene refers to (1) reducing or eliminating *PreC*, *C*, *X*, *PreS1*, *PreS2*, *S*, *P* or *SP* gene expression, (2) interfering with Precore, Core, X protein, Long surface protein, middle surface protein, S protein (also known as HBs antigen and HBsAg), polymerase protein, and/or Hepatitis B spliced protein function (HBe, HBc, HBx, PreS1, PreS2, S, Pol, and/or HBSP or (3) reducing or eliminating the intracellular, serum and/or intraparenchymal levels of HBe, HBc, HBx, LHBs, MHBs, SHBs, Pol, and/or HBSP proteins. Knockdown of one or more of the *PreC*, *C*, *X*, *PreS1*, *PreS2*, *S*, *P* and/or *SP* gene(s) is performed by targeting the gene(s) within HBV cccDNA and/or integrated HBV DNA.

CAR-T cell therapy

[0185] CAR T cell therapy includes a population of immune effector cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an HBV antigen-binding domain. The immune effector cell is a T cell or an NK cell. In some embodiments, the T cell is a CD4⁺ T cell, a CD8⁺ T cell, or a combination thereof. Cells can be autologous or allogeneic.

TCR-T cell therapy

[0186] TCR T cell therapy includes T cells expressing HBV-specific T cell receptors. TCR-T cells are engineered to target HBV derived peptides presented on the surface of virus-infected cells. In some embodiments, the T-cells express HBV surface antigen (HBsAg)-specific TCR. Examples of TCR-T therapy directed to treatment of HBB include LTCCR-H2-1.

[0187] In another specific embodiment, a compound disclosed herein is combined with an HBV DNA polymerase inhibitor, one or two additional therapeutic agents selected from the group consisting of immunomodulators, TLR modulators, HBsAg inhibitors, HBsAg secretion or assembly inhibitors, HBV therapeutic vaccines, HBV antibodies including HBV antibodies targeting the surface antigens of the hepatitis B virus and bispecific antibodies and “antibody-like” therapeutic proteins (such as DARTs®, DUOBODIES®, BITES®, XmAbs®, TandAbs®, Fab derivatives, or TCR-like antibodies), cyclophilin inhibitors, stimulators of retinoic acid-inducible gene 1, stimulators of RIG-I like receptors, PD-1 inhibitors, PD-L1 inhibitors, Arginase inhibitors, PI3K inhibitors, IDO inhibitors, and stimulators of NOD2, and one or two

additional therapeutic agents selected from the group consisting of HBV viral entry inhibitors, NTCP inhibitors, HBx inhibitors, cccDNA inhibitors, HBV antibodies targeting the surface antigens of the hepatitis B virus, siRNA, miRNA gene therapy agents, sshRNAs, KDM5 inhibitors, and nucleoprotein modulators (HBV core or capsid protein modulators).

[0188] In another specific embodiment, a compound disclosed herein is combined with an HBV DNA polymerase inhibitor and at least a second additional therapeutic agent selected from the group consisting of: immunomodulators, TLR modulators, HBsAg inhibitors, HBV therapeutic vaccines, HBV antibodies including HBV antibodies targeting the surface antigens of the hepatitis B virus and bispecific antibodies and “antibody-like” therapeutic proteins (such as DARTs[®], DUOBODIES[®], BITES[®], XmAbs[®], TandAbs[®], Fab derivatives, or TCR-like antibodies), cyclophilin inhibitors, stimulators of retinoic acid-inducible gene 1, stimulators of RIG-I like receptors, PD-1 inhibitors, PD-L1 inhibitors, Arginase inhibitors, PI3K inhibitors, IDO inhibitors, and stimulators of NOD2.

[0189] In another specific embodiment, a compound disclosed herein is combined with an HBV DNA polymerase inhibitor and at least a second additional therapeutic agent selected from the group consisting of: HBV viral entry inhibitors, NTCP inhibitors, HBx inhibitors, cccDNA inhibitors, HBV antibodies targeting the surface antigens of the hepatitis B virus, siRNA, miRNA gene therapy agents, sshRNAs, KDM5 inhibitors, and nucleoprotein modulators (HBV core or capsid protein inhibitors).

[0190] In a particular embodiment, a compound disclosed herein is combined with a compound such as one disclosed in U.S. Publication No. 2010/0143301 (Gilead Sciences), U.S. Publication No. 2011/0098248 (Gilead Sciences), U.S. Publication No. 2009/0047249 (Gilead Sciences), U.S. Patent No. 8722054 (Gilead Sciences), U.S. Publication No. 2014/0045849 (Janssen), U.S. Publication No. 2014/0073642 (Janssen), WO2014/056953 (Janssen), WO2014/076221 (Janssen), WO2014/128189 (Janssen), U.S. Publication No. 2014/0350031 (Janssen), WO2014/023813 (Janssen), U.S. Publication No. 2008/0234251 (Array Biopharma), U.S. Publication No. 2008/0306050 (Array Biopharma), U.S. Publication No. 2010/0029585 (Ventirx Pharma), U.S. Publication No. 2011/0092485 (Ventirx Pharma), US2011/0118235 (Ventirx Pharma), U.S. Publication No. 2012/0082658 (Ventirx Pharma), U.S. Publication No. 2012/0219615 (Ventirx Pharma), U.S. Publication No. 2014/0066432 (Ventirx Pharma), U.S. Publication No. 2014/0088085 (Ventirx Pharma), U.S. Publication No. 2014/0275167 (Novira Therapeutics), U.S. Publication No. 2013/0251673 (Novira Therapeutics), U.S. Patent No. 8513184 (Gilead Sciences), U.S. Publication No. 2014/0030221 (Gilead Sciences), U.S. Publication No. 2013/0344030 (Gilead Sciences), U.S. Publication No. 2013/0344029 (Gilead

Sciences), US20140275167 (Novira Therapeutics), US20130251673 (Novira Therapeutics), U.S. Publication No. 2014/0343032 (Roche), WO2014037480 (Roche), U.S. Publication No. 2013/0267517 (Roche), WO2014131847 (Janssen), WO2014033176 (Janssen), WO2014033170 (Janssen), WO2014033167 (Janssen), WO2015/059212 (Janssen), WO2015118057 (Janssen), WO2015011281 (Janssen), WO2014184365 (Janssen), WO2014184350 (Janssen), WO2014161888 (Janssen), WO2013096744 (Novira), US20150225355 (Novira), US20140178337 (Novira), US20150315159 (Novira), US20150197533 (Novira), US20150274652 (Novira), US20150259324 (Novira), US20150132258 (Novira), US9181288 (Novira), WO2014184350 (Janssen), WO2013144129 (Roche), US20100015178 (Incyte), US2016137652 (Flexus Biosciences, Inc.), WO2014073738 (Flexus Biosciences, Inc.), WO2015188085 (Flexus Biosciences, Inc.), U.S. Publication No. 2014/0330015 (Ono Pharmaceutical), U.S. Publication No. 2013/0079327 (Ono Pharmaceutical), U.S. Publication No. 2013/0217880 (Ono pharmaceutical), WO2016057924 (Genentech/Constellation Pharmaceuticals), US20140275092 (Genentech/Constellation Pharmaceuticals), US20140371195 (Epitherapeutics) and US20140371214 (Epitherapeutics), US20160102096 (Epitherapeutics), US20140194469 (Quantice), US20140171432, US20140213591 (Quantice), US20160039808 (Quantice), US20140275084 (Quantice), WO2014164708 (Quantice), US9186337B2 (Oryzon Genomics), and other drugs for treating HBV, and combinations thereof.

[0191] In certain embodiments, a compound as disclosed herein (*e.g.*, any compound of Formula I) may be combined with one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents in any dosage amount of the compound of Formula I (*e.g.*, from 10 mg to 1000 mg of compound).

[0192] In certain embodiments, a compound disclosed herein is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide. In certain embodiments, a compound disclosed herein is combined with 5-10; 5-15; 5-20; 5-25; 25-30; 20-30; 15-30; or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide. In certain embodiments, a compound disclosed herein is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide. In certain embodiments, a compound disclosed herein is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide. A compound as disclosed herein (*e.g.*, a compound of Formula I) may be combined with the agents provided herein in any dosage amount of the compound (*e.g.*, from 50

mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0193] In certain embodiments, a compound disclosed herein is combined with 100-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil. In certain embodiments, a compound disclosed herein is combined with 100-150; 100-200, 100-250; 100-300; 100-350; 150-200; 150-250; 150-300; 150-350; 150-400; 200-250; 200-300; 200-350; 200-400; 250-350; 250-400; 350-400 or 300-400 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil. In certain embodiments, a compound disclosed herein is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil. In certain embodiments, a compound disclosed herein, *e.g.*, a compound of Formula I, is combined with 250 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil. In certain embodiments, a compound disclosed herein is combined with 150 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil. A compound as disclosed herein (*e.g.*, a compound of Formula I) may be combined with the agents provided herein in any dosage amount of the compound (*e.g.*, from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

VII. PREPARATION OF THE SOLID FORMS

A. Synthesis of a Compound of Formula I

[0194] One method of synthesizing (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid (Formula I) has been previously described as Example 73 in co-pending United States patent application no. 15/885,390, and related co-pending PCT patent application no. PCT/US18/16243, filed January 31, 2018, entitled "COMPOUNDS FOR THE TREATMENT OF HEPATITIS B VIRUS INFECTION." These references are hereby incorporated herein by reference in their entirety, and specifically with respect to the synthesis of (R)-11-(Methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid.

B. Methods of Making Solid Forms of Formula I

[0195] In one aspect, provided is a method of producing a composition comprising one or more solid forms of Formula I, *e.g.*, a crystalline Form of Formula I, wherein the method comprises combining a compound of Formula I with a suitable solvent or a mixture of suitable solvents to produce a composition comprising one or more solid forms of the compound of

Formula I. In another aspect, provided is another method of producing a composition comprising one or more solid forms of Formula I, wherein the method comprises combining Formula I with a suitable solvent or a mixture of suitable solvents.

[0196] The choice of a particular solvent or combination of solvents or method of combining solvents affects the formation favoring one solid form of Formula I over another. Solvents suitable for crystal formation may include, for example, water, methanol, ethanol, tetrahydrofuran, acetone, and any mixtures thereof.

[0197] The presence of impurities affects the formation favoring one solid form of Formula I over another. In some embodiments, the form is prepared by a process comprising Formula I having impurities. In another embodiment, the form is prepared by a process comprising substantially pure Formula I.

[0198] In another aspect, provided is also one or more crystalline forms of Formula I produced according to any of the methods described herein.

[0199] It should be understood that the methods for preparing the solid forms described herein (including any one or more of crystalline Forms I or II and/or the amorphous form) may yield quantity and quality differences compared to the methods for preparing Formula I produced on laboratory scale.

Formula I Form I

[0200] In some embodiments, provided is a method of producing a composition comprising crystalline Form I, wherein the method comprises combining Formula I with a solvent to produce a composition comprising crystalline Formula I Form I, wherein the solvent is water.

[0201] In some embodiments, provided is a method of preparing crystalline Formula I Form I, comprising contacting Formula I and water, wherein Formula I remains substantially insoluble in water, under conditions suitable to prepare crystalline Form I.

[0202] Provided is crystalline Formula I Form I produced by combining Formula I with a solvent, wherein the solvent is water.

[0203] In some embodiments, provided is a method of producing a composition comprising crystalline Formula I Form I, wherein the method comprises combining Formula I with a solvent to produce a composition comprising crystalline Formula I Form I, wherein the solvent comprises ethanol and water.

[0204] In some embodiments, provided is a method of preparing crystalline Formula I Form I, comprising contacting Formula I and a solvent mixture comprising ethanol and aqueous base to

form a Formula I mixture, and adding the Formula I mixture to an aqueous acid, under conditions suitable to prepare Form I of Formula I.

[0205] In some embodiments, provided is a method of preparing crystalline Formula I Form I, comprising contacting Formula I and a solvent mixture comprising ethanol and aqueous base to form a Formula I mixture, and adding an aqueous acid to the Formula I mixture, under conditions suitable to prepare Form I of Formula I.

[0206] In some embodiments, the water comprises an aqueous base, such as sodium hydroxide, potassium hydroxide, or lithium hydroxide, or mixtures thereof, *e.g.*, sodium hydroxide. The aqueous base can be of any concentration ranging from about 0.1 N to about 10 N, such as about 0.1, 0.2, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or about 10 N. In some embodiments, the aqueous base is 1 N sodium hydroxide. In some embodiments, the aqueous base is lithium hydroxide.

[0207] In some embodiments, the amount of aqueous base is sufficient to produce a molar amount of the carboxylate salt of the compound of Formula I. In some embodiments, the amount of aqueous base is from about 1.01 to about 3 molar equivalents compared with the amount of the compound of Formula I in the solvent mixture, *e.g.*, about 1.01, 1.05, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.8, 2, 2.2, 2.5, 2.6, 2.8 or about 3 molar equivalents. In some embodiments, the amount of aqueous base is about 2.6 molar equivalents compared with the amount of the compound of Formula I in the solvent mixture. In some embodiments, the amount of aqueous base is about 1.3 molar equivalents compared with the amount of the compound of Formula I in the solvent mixture.

[0208] The ethanol and aqueous base can be present in the solvent mixture in any suitable ratio. Representative ratios of the ethanol and aqueous base include from about 3:1 to about 1:5 (V/V), or from about 2:1 to about 1:4 (V/V), or from about 1.5:1 to about 1:3 (V/V), or from about 1.5:1 to about 1:2 (V/V), or from about 1:1 to about 1:2 (V/V). Representative ratios of the ethanol and aqueous base include about 3:1 (V/V), as well as 2.5:1, 2.2:1, 2:1, 1.8:1, 1.6:1, 1.5:1, 1.3:1, 1.2:1, 1.1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.5, or 1:2 (V/V). In some embodiments, the solvent mixture includes ethanol and aqueous base in a ratio of from about 1.5:1 to about 1:2 (V/V). In some embodiments, the solvent mixture includes ethanol and aqueous base in a ratio of from about 1:1 to about 1:2 (V/V). In some embodiments, the solvent mixture includes ethanol and aqueous base in a ratio of at least 1:1 (V/V). In some embodiments, the solvent mixture includes ethanol and aqueous base in a ratio of about 4:3 (V/V).

[0209] The method of making crystalline Formula I Form I can be performed at any suitable temperature. Representative temperatures for preparation of crystalline Formula I Form I include about 5 °C, or 10, 15, 20, 25, 30, 35, 40, 45, or about 50 °C. Representative temperatures ranges include 5 °C to 50 °C, or 5 °C to 40 °C, 10 °C to 40 °C, 20 °C to 40 °C, 20 °C to 30 °C, or 15 °C to 30 °C. In some embodiments, the contacting step is performed at a temperature of from about 15 °C to about 40 °C. In some embodiments, the contacting step is performed at a temperature of from about 20 °C to about 30 °C. In some embodiments, the contacting step is performed at a temperature of about 20 °C.

[0210] In some embodiments, the method further comprises adding the Formula I mixture to an aqueous acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, or methanesulfonic acid, or mixtures thereof, *e.g.*, hydrochloric acid. The aqueous acid can be of any concentration ranging from about 0.1 N to about 10 N, such as about 0.1, 0.2, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or about 10 N. In some embodiments, the aqueous acid is 1 N hydrochloric acid.

[0211] In some embodiments, the amount of aqueous acid is sufficient to acidify the solvent or solvent mixture comprising the compound of Formula I. In some embodiments, the amount of aqueous acid is from about 1.01 to about 3 molar equivalents compared with the amount of aqueous base in the solvent mixture, *e.g.*, about 1.01, 1.05, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.8, 2, 2.2, 2.5, 2.8 or about 3 molar equivalents. In some embodiments, the amount of aqueous acid is from about 1.2 molar equivalents compared with the amount of aqueous base in the solvent mixture.

[0212] In some embodiments, the method further comprises adding seed crystals of Formula I Form I to the aqueous acid before adding the Formula I mixture.

[0213] Provided is crystalline Formula I Form I produced by combining Formula I with a solvent mixture, wherein the solvent mixture comprises ethanol and water, *e.g.*, ethanol and an aqueous base.

[0214] In some embodiments, the crystalline Formula I Form I is prepared substantially free of Form II and/or the amorphous form.

Formula I Form II

[0215] In some embodiments, provided is a method of producing a composition comprising crystalline Formula I Form II, wherein the method comprises combining Formula I with a solvent to produce a composition comprising crystalline Formula I Form II, wherein the solvent comprises methanol.

[0216] In some embodiments, provided is a method of preparing crystalline Formula I Form I, comprising contacting Formula I and methanol, wherein Formula I remains substantially insoluble in methanol, under conditions suitable to prepare crystalline Form II.

[0217] Provided is crystalline Formula I Form II produced by combining Formula I with a solvent, wherein the solvent comprises methanol.

[0218] In some embodiments, the crystalline Formula I Form II is prepared substantially free of Form I and/or the amorphous form.

Amorphous Formula I

[0219] In some embodiments, provided is a method of producing a composition comprising amorphous Formula I, wherein the method comprises combining Formula I with a solvent to produce a composition comprising amorphous Formula I, wherein the solvent comprises acetonitrile and water.

[0220] In some embodiments, provided is a method of preparing an amorphous form of Formula I, comprising contacting Formula I and a solvent mixture comprising acetonitrile and water, and lyophilizing under conditions suitable to prepare the amorphous form of Formula I.

[0221] Provided is amorphous solid Formula I produced by combining Formula I with a solvent mixture, wherein the solvent mixture comprises acetonitrile and water.

[0222] In some embodiments, the amorphous form of Formula I is prepared substantially free of Form I and/or Form II.

VIII. USES IN MANUFACTURING OF DRUG PRODUCT

[0223] Provided are also a use of the solid forms described herein in the manufacture of a drug product. The one or more of the compounds of Formula I described herein may be used as an intermediate in the manufacturing process to produce the drug product.

[0224] In some embodiments, a compound of Formula I is used in the manufacture of an active pharmaceutical ingredient. In some embodiments, Formula I Form I is used in the manufacture of an active pharmaceutical ingredient. In some embodiments, Formula I Form II is used in the manufacture of an active pharmaceutical ingredient. In some embodiments, amorphous Formula I is used in the manufacture of an active pharmaceutical ingredient. In some embodiments, a mixture of forms of Formula I is used in the manufacture of an active pharmaceutical ingredient.

IX. ARTICLES OF MANUFACTURE AND KITS

[0225] Compositions comprising one or more of the compounds of Formula I described herein and formulated in one or more pharmaceutically acceptable excipients or other ingredients can be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Accordingly, there also is contemplated an article of manufacture, such as a container comprising a dosage form of one or more of the compounds of Formula I described herein and a label containing instructions for use of the compound(s).

[0226] In some embodiments, the article of manufacture is a container comprising a dosage form of one or more of the compounds of Formula I described herein, and one or more pharmaceutically acceptable excipients or other ingredients. In some embodiments of the articles of manufacture described herein, the dosage form is a solution.

[0227] Kits also are contemplated. For example, a kit can comprise a dosage form of a pharmaceutical composition and a package insert containing instructions for use of the composition in treatment of a medical condition. In another embodiment a kit may comprise multiple individual dosage forms, each comprising a therapeutically effective amount of a compound as described herein, and instructions for their administration to a human in need thereof. Each of the individual dosage forms may comprise a therapeutically effective amount of a compound as described herein in combination with at least one pharmaceutically effective excipient. The individual dosage forms may be in the form of, as examples, a solution, a tablet, a pill, a capsule, a sachet, a sublingual medicament, a lyophilized powder, a spray-dried powder, or a liquid composition for oral, parenteral, or topical administration. In some embodiments, the instructions for use in the kit may be for treating a hepatitis B virus infection in a human. The instructions may be directed to any of the viral infections and methods described herein. The instructions may be for prophylaxis or the treatment of an existing viral infection.

[0228] In some embodiments, the solid forms described herein may potentially exhibit improved properties. For example, in some embodiments, a solid form described herein may potentially exhibit improved stability. Such improved stability could have a potentially beneficial impact on the manufacture of the compound of Formula I, such as for example offering the ability to store process intermediate for extended periods of time. Improved stability could also potentially benefit a composition or pharmaceutical composition of the compound of Formula I. In some embodiments, the solid form described herein may also potentially result in improved yield of the compound of Formula I, or potentially result in an improvement of the quality of the compound of Formula I. In some embodiments, the solid form and solvate forms

described herein may also exhibit improved pharmacokinetic properties and/or potentially improved bioavailability.

[0229] In one embodiment, kits comprising a compound disclosed herein in combination with one or more (*e.g.*, one, two, three, four, one or two, or one to three, or one to four) additional therapeutic agents are provided.

X. EXAMPLES

Definitions

XRPD	X-ray Powder Diffraction
DSC	Differential Scanning Calorimetry
TGA	Thermogravimetric Analysis
TGA-MS	Thermogravimetric Analysis – Mass Spectrometry
DVS	Dynamic Vapor Sorption
dpm	degrees per minute
SCXC	Single Crystal X-ray Crystallography

Example 1. Crystallization of Form I Formula I from Water and Ethanol

[0230] About 3 g of Formula I and lithium hydroxide monohydrate (0.44 g) were stirred in water (10 mL) and ethanol (30 mL) at ambient temperature for 20 minutes and then cooled in an ice-water bath. To the mixture was added 5 ml of water, adjusted to pH 4 using 1 N HCl. The resulting solids were filtered by vacuum filtration and then washed with water. The isolated Formula I Form I was dried at room temperature and under vacuum overnight.

Example 2. Crystallization of Form I Formula I Seed Crystals in Water

[0231] To a 250 mL glass jar equipped with two stir bars was charged about 10.9 grams of Formula I Form I and about 50 mL of water. The glass jar was capped and the contents were agitated at room temperature (about 20 °C) for about 15 hours. The resulting suspension was filtered and the solid Formula I Form I was washed with about 20 mL of water. The isolated Formula I Form I was dried at room temperature and pressure and then dried at about 50 °C under vacuum.

Example 3. Preparation of Crystalline Form I Formula I

[0232] *Procedure 1:* To a flask was charged with about 7 grams of Formula I, about 28 mL of ethanol, and about 21 mL of 1 N NaOH. Separately, to a 100-mL reactor was charged about 38.5 mL water, about 24.5 mL of 1 N HCl, and about 70 mg 1 wt% of Formula I Form I seeds. The contents of the 100-mL reactor were then adjusted to about 20 °C. The resulting ethanol/NaOH solution in the flask was transferred to the contents of the 100-mL reactor over the course of about 4 hours, and the resulting solids were filtered. Formula I Form I was washed 3 times with about 35 mL of water. The crystalline Formula I Form I solids were dried at room temperature and pressure and then at about 20 °C under vacuum.

[0233] *Procedure 2:* To a 50 mL flask was charged about 17 grams of Formula I, about 69 mL of ethanol, and about 52 mL of 1 N NaOH. The resulting solution was charged over about 1 hour at about 20 °C to a reactor equipped with overhead agitation containing about 95 mL of water, about 60 mL 1 N HCl, and about 183 mg of Formula I Form I seeds. The resulting suspension was filtered, and the solids were washed 3 times with about 86 mL of water. The isolated Formula I Form I was dried at room temperature and pressure and then dried at about 20 °C under vacuum.

[0234] *Procedure 3:* To a glass bottle equipped with a magnetic stir bar was charged with about 360 grams of Formula I Form I, about 1440 mL of ethanol, and about 1080 mL of 1 N NaOH. The contents of the bottle were agitated for about 20 minutes, and the resulting solution was polish filtered. To a glass lined reactor equipped with overhead agitation was charged with about 1980 mL of water, about 1260 mL of 1 N HCl, and about 3.6 grams of Formula I Form I seeds. The contents of the reactor were then adjusted to about 30 °C. The polish filtered ethanol/NaOH solution was transferred to the contents of the reactor over the course of about 2 hours, and then the temperature was adjusted to about 20 °C over the course of about 1.5 hours. The resulting suspension was filtered, and the Formula I Form I was washed 3 times with about 1800 mL of water. The isolated Formula I Form I was dried at room temperature and pressure and then dried at about 50 °C under vacuum.

[0235] *Procedure 4:* To a solution of about 38 g Formula I in about 156 mL ethanol and about 120 mL of 1 N aqueous NaOH was added about 124.4 mL 1 N HCl, resulting in a reaction mixture with a pH of about 3. About 40 mg of Formula I Form I seeds were added, and the reaction contents were cooled to about 45 °C. The reactor contents were heated to about 50 °C and about 1 mL of 1 N HCl was added to the reactor. About 40 mg of additional Formula I Form I seeds were added, at which point the reactor contents were cooled to about 45 °C. About 78 mL water was added via syringe pump over 2 h. The reactor contents were aged for about 60

min at 45 °C, then cooled to 20 °C at a rate of about 5 °C/h. The reactor contents were agitated at about 20 °C overnight. The resulting slurry was filtered, washed with about 117 mL of 25% ethanol/water, and about three times with about 195 mL water. The isolated Formula I Form I was dried at room temperature and pressure and then dried at about 50 °C under vacuum.

Example 4. Preparation of Crystalline Form II of Formula I

[0236] Approximately 0.6 grams of crude amorphous solid Formula I were stirred in about 40 mL of methanol at room temperature. After about three days the solids were filtered. The isolated Formula I Form II was washed with about 5 mL of methanol and dried at room temperature on the vacuum filter under vacuum suction.

Example 5. Preparation of an Amorphous Form of Formula I

[0237] About 50 mg of Formula I Form I was dissolved in about 4 mL of acetonitrile/water (1:1 volume/volume). The solution was frozen at about -78 °C and lyophilized to provide amorphous solid Formula I.

Example 6. Characterization of the Solid Forms

[0238] The crystalline forms of the present invention were characterized by various analytical techniques, including X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and dynamic vapor sorption (DVS) using the procedures described below.

[0239] *X-ray powder diffraction:* XRPD analysis was conducted on a diffractometer (PANalytical XPERT-PRO, PANalytical B. V., Almelo, Netherlands) using copper radiation (Cu K α , $\lambda = 1.541874$ Å). Samples were spread evenly on a zero background sample plate. The generator was operated at a voltage of 45 kV and amperage of 40 mA. Slits were Soller 0.02 rad, antiscatter 1.0°, and divergence of 7 mm. Scans were performed from 2 to 40° 2 θ with a 0.0167 step size. Data analysis was performed using X'Pert Data Viewer V1.2d (PANalytical B.V., Almelo, Netherlands).

[0240] Alternately, X-ray powder diffraction analysis was conducted on a diffractometer (Rigaku MiniFlex, Rigaku Corporation, Tokyo, Japan) using copper radiation (Cu K α , $\lambda = 1.541874$ Å). Samples were spread evenly on a zero background sample plate. The generator was operated at a voltage of 40 kV and amperage of 15 mA. Scans were performed from 2 to 40° 2 θ with a 0.050 degree step size and a speed of 2-8 degrees/minute. Data analysis was also performed using X'Pert Data Viewer V1.2d (PANalytical B.V., Almelo, Netherlands).

[0241] The XRPD pattern for Formula I Form I is represented in FIG. 1.

[0242] The XRPD pattern for Formula I Form II is represented in FIG. 5.

[0243] The XRPD pattern for amorphous Formula I is represented in FIG. 9.

[0244] *Differential Scanning Calorimetry*: DSC was run by loading 1-5 mg of material into a crimped Tzero standard aluminum pan and heating the sample at 10 °C/min from 20 to 300 °C or above. The sample and reference pans were under a 50 mL/min nitrogen purge. Data analysis was completed using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE).

[0245] The DSC for Formula I Form I is represented in FIG. 2, which shows a sharp endothermic event with an onset temperature of about 131 °C with an associated enthalpy of about 54 J/g. The exemplary DSC of Form I is characterized by a sharp peak with an onset at about 131 °C.

[0246] The DSC for Formula I Form II is represented in FIG. 6, which shows an endothermic event with an onset temperature of about 174 °C with an associated enthalpy of about 120 J/g. The exemplary DSC of Form II is characterized by a sharp peak with an onset at about 174 °C.

[0247] The DSC for amorphous Formula I is represented in FIG. 10, which shows a shift in the baseline beginning at about 48 °C and ending at about 60 °C, consistent with a glass transition.

[0248] *Thermogravimetric analysis*: TGA was used to evaluate sample weight loss as a function of temperature by loading 1-10 mg of material onto an aluminum weigh pan (TA Instruments, New Castle, DE) and heated the sample to 300 °C or above at a rate of 10 °C/min. The sample and reference pans were under a 60 mL/min and 40 mL/min nitrogen purge, respectively. Data analysis was completed using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE).

[0249] The TGA for Formula I Form I is represented in FIG. 3, which shows a mass loss of 0.43 wt% by 150 °C.

[0250] The TGA for Formula I Form II is represented in FIG. 7, which shows a mass loss of 6.4 wt% by 200 °C.

[0251] The TGA for amorphous Formula I is represented in FIG. 11, which shows a gradual loss of mass starting at about 25 °C, with a total mass loss of about 5.8 wt% by 150 °C.

[0252] *Dynamic vapor sorption*: Hygroscopicity was studied using DVS (TA Q5000 SA, TA Instruments, New Castle, DE or DVS Intrinsic, Surface Measurement Systems, London, UK). A sample (2-20 mg) was placed in an aluminum DVS pan and loaded on the sample side of the twin pan balance. The water sorption and desorption were studied as a function of relative

humidity (RH) at 25°C. In 10% RH increments, the relative humidity was increased from 5% RH to 95% RH and then decreased back to 5%. Each relative humidity increment had an equilibration time of 180 minutes, unless weight change % was less than 0.002% in 30 minutes. Data analysis was performed using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE) for TA DVS runs and Microsoft Excel for SMS DVS runs.

[0253] The DVS for Formula I Form I is represented in FIG. 4, which shows 1.1 wt% water uptake at 95% RH at 25 °C, with minimal hysteresis.

[0254] The DVS for Formula I Form II is represented in FIG. 8, which shows 0.3 wt% water uptake at 90% RH at 25 °C, with minimal hysteresis.

[0255] *Single crystal X-ray crystallography:* A colorless block having approximate dimensions of $0.32 \times 0.18 \times 0.1$ mm³, was mounted on a polymer loop in random orientation. Preliminary examination and data collection were performed on a Rigaku SuperNova diffractometer, equipped with a copper anode microfocus sealed X-ray tube (Cu $K\alpha$ $\lambda = 1.54184$ Å) and a Dectris Pilatus3 R 200K hybrid pixel array detector. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement using the setting angles of 10435 reflections in the range $3.9890^\circ < \theta < 75.9050^\circ$. The space group was determined by the program CRYSLISPRO [9] to be *P*1 (international tables no. 1). The data were collected to a maximum diffraction angle (2θ) of 156.576° at room temperature.

[0256] The single crystal X-ray crystallography data for Formula I Form I is summarized in Table 2 below. The SCXC data shows Form I is non-solvated and has the (*R*) absolute stereochemistry.

Table 2: Single Crystal Data for Formula I Form I

Empirical Formula		C ₂₄ H ₃₀ N ₂ O ₆	
Form and Identification		Form I	
Solvents in Structure		None	
Acquisition Temperature		299.08(10)	
Wavelength (Å)		1.54184	
Space Group		P 1	
Z value		2	
Density (g/cm ³)		1.287	
Unit Cell Dimensions			
Distance (Å)		Angle (°)	
a	9.9330 (3)	α	77.799 (2)
b	10.5884 (2)	β	87.547 (3)
c	11.2740 (4)	γ	80.283 (2)

[0257] *Solubility:* To a vial equipped with a magnetic stir bar was charged about 100 mg of solid Formula I. To the same vial was charged an amount of solvent until a mobile slurry was obtained. The vial mixture was allowed to agitate for about 4 h to about 24 h at room temperature. The vial mixture was filtered, the resulting mother liquor was assayed using ultra-pressure liquid chromatography.

[0258] Solubility data of Formula I Form I is summarized in Table 3.

Table 3: Solubility of Form I of Formula I in various media

Solvent	Solubility (mg/g)
Ethanol	86
50% water/EtOH	34
62% water/EtOH	22
67% water/EtOH	3
Water, pH 7	< 1

Solvent	Solubility (mg/g)
Methyl tert-butyl ether	7
Ethyl acetate	127
isopropanol	39

[0259] *Stability:* An accelerated stability study was staged at 40 °C and 75% relative humidity or 80 °C and 75% relative humidity to access the stability of the solid form and determine levels of degradants under the experimental conditions over time. Purity level of Formula I was determined by UPLC.

[0260] After 3 months, the DSC and XRPD patterns of the Formula I Form I subjected to 40 °C and 75% relative humidity remained consistent with Form I.

[0261] After 1 month, the TGA, DSC, and XRPD patterns of the Formula I Form I subjected to 80 °C and 75% relative humidity remained consistent with Form I. Degradation products accounted for <0.1% of the absorbances observed by UPLC. The stability of Formula I Form I is summarized in Table 4.

Table 4: Stability of Formula I Form I at 80 °C and 75% relative humidity

Time Point	% Formula I	% Impurity 1	% Impurity 2
Day 0	98.7	N.D.	N.D.
1 week	98.3	0.03	N.D.
1 month	98.4	0.05	0.03

N.D. = not detected

[0262] Although the foregoing invention has been described in some detail by way of illustration and Example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

1. A crystalline form of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid, or a solvate or hydrate thereof.
2. The crystalline form of claim 1, which is non-solvated.
3. The crystalline form of claim 1 or 2, which is Form I.
4. The crystalline form of any one of claims 1 to 3, characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , and $16.0^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.
5. The crystalline form of any one of claims 1 to 4, wherein the X-ray powder diffraction (XRPD) pattern has further peaks at 11.4° , 12.1° , 12.9° , and $13.6^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.
6. The crystalline form of any one of claims 1 to 5, wherein the X-ray powder diffraction (XRPD) pattern has further peaks at 26.8° , 24.3° , and $15.0^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.
7. The crystalline form of any one of claims 1 to 6, characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , 16.0° , 11.4° , 12.1° , 12.9° , 13.6° , 26.8° , 24.3° , and $15.0^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.
8. The crystalline form of any one of claims 1 to 7, characterized by a unit cell as determined by single crystal X-ray crystallography of the following dimensions: $a = 9.9330(3) \text{ \AA}$; $b = 10.5884(2) \text{ \AA}$; $c = 11.2740(4) \text{ \AA}$; $\alpha = 77.799(2)^{\circ}$; $\beta = 87.547(3)^{\circ}$; and $\gamma = 80.283(2)^{\circ}$.
9. The crystalline form of any one of claims 1 to 8, characterized by a Differential Scanning Calorimetry (DSC) thermogram peak with an onset at about 131°C .
10. The crystalline form of any one of claims 1 to 9, characterized by one or more of the following:
 - an X-ray powder diffraction (XRPD) pattern having peaks at 8.0° , 8.7° , 16.0° , 11.4° , 12.1° , 12.9° , 13.6° , 26.8° , 24.3° , and $15.0^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$;
 - a Differential Scanning Calorimetry (DSC) thermogram peak with an onset at about 131°C ; and

a unit cell as determined by single crystal X-ray crystallography of the following

dimensions: $a = 9.9330(3) \text{ \AA}$; $b = 10.5884(2) \text{ \AA}$; $c = 11.2740(4) \text{ \AA}$; $\alpha = 77.799(2)^\circ$; $\beta = 87.547(3)^\circ$; and $\gamma = 80.283(2)^\circ$.

11. The crystalline form of any one of claims 1 to 10, characterized by an X-ray powder diffraction (XRPD) pattern substantially as set forth in FIG. 1.
12. The crystalline form of any one of claims 1 to 11, characterized by a differential scanning calorimetry (DSC) pattern substantially as set forth in FIG. 2.
13. The crystalline form of any one of claims 1 to 12, characterized by a thermogravimetric analysis (TGA) pattern substantially as set forth in FIG. 3.
14. The crystalline form of any one of claims 1 to 13, characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in FIG. 4.
15. The crystalline form of claim 1, which is solvated.
16. The crystalline form of claim 15, which is a methanol solvate.
17. The crystalline form of claim 15 or 16, which is Form II.
18. The crystalline form of any one of claims 15 to 17, characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , and $8.8^\circ 2\theta \pm 0.2^\circ 2\theta$.
19. The crystalline form of any one of claims 15 to 18, wherein the X-ray powder diffraction (XRPD) pattern has further peaks at 16.3° , 26.5° , and $19.2^\circ 2\theta \pm 0.2^\circ 2\theta$.
20. The crystalline form of any one of claims 15 to 19, wherein the X-ray powder diffraction (XRPD) pattern has further peaks at 12.9° , 14.8° , and $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$.
21. The crystalline form of any one of claims 15 to 20, characterized by an X-ray powder diffraction (XRPD) pattern having peaks at 8.1° , 9.4° , 8.8° , 16.3° , 26.5° , 19.2° , 12.9° , 14.8° , and $15.4^\circ 2\theta \pm 0.2^\circ 2\theta$.
22. The crystalline form of any one of claims 15 to 21, characterized by a Differential Scanning Calorimetry (DSC) thermogram peak with an onset at about 174°C .
23. The crystalline form of any one of claims 15 to 22, characterized by one or more of the following:

an X-ray powder diffraction (XRPD) pattern having peaks at 8.1°, 9.4°, 8.8°, 16.3°, 26.5°, 19.2°, 12.9°, 14.8°, and 15.4° $2\theta \pm 0.2^\circ 2\theta$; and

a Differential Scanning Calorimetry (DSC) thermogram peak with an onset at about 174 °C.

24. The crystalline form of any one of claims 17-23, characterized by an X-ray powder diffraction (XRPD) pattern substantially as set forth in FIG. 5.

25. The crystalline form of any one of claims 17-24, characterized by a differential scanning calorimetry (DSC) pattern substantially as set forth in FIG. 6.

26. The crystalline form of any one of claims 17-25, characterized by a thermogravimetric analysis (TGA) pattern substantially as set forth in FIG. 7.

27. The crystalline form of any one of claims 17-26, characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in FIG. 8.

28. An amorphous solid form of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid, or a solvate or hydrate thereof.

29. The amorphous solid form of claim 28, characterized by a Differential Scanning Calorimetry (DSC) thermogram having a glass transition starting at about 48 °C.

30. The amorphous solid form of claim 28 or 29, characterized by an X-ray powder diffraction (XRPD) pattern substantially as set forth in FIG. 9.

31. The amorphous solid form of any one of claims 28-30, characterized by a differential scanning calorimetry (DSC) pattern substantially as set forth in FIG. 10.

32. The amorphous solid form of any one of claims 28-31, characterized by a thermogravimetric analysis (TGA) pattern substantially as set forth in FIG. 11

33. A pharmaceutical composition comprising a therapeutically effective amount of the form of any one of claims 1-32, and a pharmaceutically acceptable excipient.

34. The pharmaceutical composition of claim 33, further comprising one or more additional therapeutic agents.

35. The pharmaceutical composition of claim 34, wherein the one or more additional therapeutic agents are selected from the group consisting of HBV DNA polymerase inhibitors, toll-like receptor 7 modulators, toll-like receptor 8 modulators, toll-like receptor 7 and 8 modulators, toll-like receptor 3 modulators, interferon alpha ligands, HBsAg inhibitors, compounds targeting HBcAg, cyclophilin inhibitors, HBV therapeutic vaccines, HBV prophylactic vaccines, HBV viral entry inhibitors, NTCP inhibitors, antisense oligonucleotide targeting viral mRNA, short interfering RNAs (siRNA), HBeAg inhibitors, HBx inhibitors, cccDNA inhibitors, HBV antibodies including HBV antibodies targeting the surface antigens of the hepatitis B virus, thymosin agonists, cytokines, nucleoprotein inhibitors (HBV core or capsid protein inhibitors), stimulators of retinoic acid-inducible gene 1, stimulators of NOD2, recombinant thymosin alpha-1 and hepatitis B virus replication inhibitors, hepatitis B surface antigen (HBsAg) secretion or assembly inhibitors, IDO inhibitors, KDM5 inhibitors, and combinations thereof.

36. The pharmaceutical composition of claim 34 or 35, wherein the one or more additional therapeutic agents are selected from the group consisting of adefovir (Hepsera®), tenofovir disoproxil fumarate + emtricitabine (Truvada®), tenofovir disoproxil fumarate (Viread®), entecavir (Baraclude®), lamivudine (Epivir-HBV®), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, telbivudine (Tyzeka®), Clevudine®, emtricitabine (Emtriva®), peginterferon alfa-2b (PEG-Intron®), Multiferon®, interferon alpha 1b (Hapgen®), interferon alpha-2b (Intron A®), pegylated interferon alpha-2a (Pegasys®), interferon alfa-n1 (Humoferon®), ribavirin, interferon beta-1a (Avonex®), Bioferon, Ingaron, Inmutag (Inferon), Algeron, Roferon-A, Oligotide, Zutectra, Shaferon, interferon alfa-2b (Axxo), Alfaferone, interferon alfa-2b (BioGeneric Pharma), Feron, interferon-alpha 2 (CJ), Bevac, Laferonum, Vipeg, Blaferon-B, Blaferon-A, Intermax Alpha, Realdiron, Lanstion, Pegaferon, PDferon-B, interferon alfa-2b (IFN, Laboratorios Bioprofarma), alfainterferona 2b, Kalferon, Pegnano, Feronure, PegiHep, interferon alfa 2b (Zydus-Cadila), Optipeg A, Realfa 2B, Reliferon, interferon alfa-2b (Amega), interferon alfa-2b (Virchow), peginterferon alfa-2b (Amega), Reaferon-EC, Proquiferon, Uniferon, Urifron, interferon alfa-2b (Changchun Institute of Biological Products), Anterferon, Shanferon, MOR-22, interleukin-2 (IL-2), recombinant human interleukin-2, Layfferon, Ka Shu Ning, Shang Sheng Lei Tai, Intefen, Sinogen, Fukangtai, Alloferon, and celmoleukin, and combinations thereof.

37. The pharmaceutical composition of any one of claims 34-36, wherein the one or more additional therapeutic agents are selected from the group consisting of entecavir, adefovir, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, telbivudine and lamivudine.

38. A method of inhibiting the production and/or secretion of HBsAg in an individual infected with hepatitis B virus comprising administering to the individual a therapeutically effective amount of the form of any one of claims 1-32.

39. A method of treating or preventing a hepatitis B virus infection comprising administering to an individual in need thereof a therapeutically effective amount of the form of any one of claims 1-32.

40. The method of claim 39 wherein the individual is chronically infected with hepatitis B virus.

41. The method of any one of claims 38-40, further comprising administering one or more additional therapeutic agents.

42. The method of claim 41, wherein the one or more additional therapeutic agents are selected from the group consisting of HBV DNA polymerase inhibitors, toll-like receptor 7 modulators, toll-like receptor 8 modulators, Toll-like receptor 7 and 8 modulators, Toll-like receptor 3 modulators, interferon alpha ligands, HBsAg inhibitors, compounds targeting HBcAg, cyclophilin inhibitors, HBV therapeutic vaccines, HBV prophylactic vaccines, HBV viral entry inhibitors, NTCP inhibitors, antisense oligonucleotide targeting viral mRNA, short interfering RNAs (siRNA), HBeAg inhibitors, HBx inhibitors, cccDNA inhibitors, HBV antibodies including HBV antibodies targeting the surface antigens of the hepatitis B virus, thymosin agonists, cytokines, nucleoprotein inhibitors (HBV core or capsid protein inhibitors), stimulators of retinoic acid-inducible gene 1, stimulators of NOD2, recombinant thymosin alpha-1 and hepatitis B virus replication inhibitors, hepatitis B surface antigen (HBsAg) secretion or assembly inhibitors, IDO inhibitors, KDM5 inhibitors, and combinations thereof.

43. The method of claim 41 or 42, wherein the one or more additional therapeutic agents are selected from the group consisting of adefovir (Hepsera®), tenofovir disoproxil fumarate + emtricitabine (Truvada®), tenofovir disoproxil fumarate (Viread®), entecavir (Baraclude®), lamivudine (Epivir-HBV®), tenofovir alafenamide, tenofovir, tenofovir

disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, telbivudine (Tyzeka®), Clevudine®, emtricitabine (Emtriva®), peginterferon alfa-2b (PEG-Intron®), Multiferon®, interferon alpha 1b (Hapgen®), interferon alpha-2b (Intron A®), pegylated interferon alpha-2a (Pegasys®), interferon alfa-n1 (Humoferon®), ribavirin, interferon beta-1a (Avonex®), Bioferon, Ingaron, Inmutag (Inferon), Algeron, Roferon-A, Oligotide, Zutectra, Shaferon, interferon alfa-2b (Axxo), Alfaferone, interferon alfa-2b, Feron, interferon-alpha 2 (CJ), Bevac, Laferonum, Vipeg, Blaufferon-B, Blaufferon-A, Intermax Alpha, Realdiron, Lanstion, Pegaferon, PDferon-B, alfainterferona 2b, Kalferon, Pegnano, Feronsure, PegiHep, Optipeg A, Realfa 2B, Reliferon, peginterferon alfa-2b, Reaferon-EC, Proquiferon, Uniferon, Urifron, interferon alfa-2b, Anterferon, Shanferon, MOR-22, interleukin-2 (IL-2), recombinant human interleukin-2 (Shenzhen Neptunus), Layfferon, Ka Shu Ning, Shang Sheng Lei Tai, Intefen, Sinogen, Fukangtai, Alloferon and celmoleukin.

44. The method of any one of claims 41 to 43, wherein the one or more additional therapeutic agents are selected from entecavir, adefovir, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, telbivudine and lamivudine.

45. A form of any one of claims 1-32 for use in a method of treating a hepatitis B infection.

46. Use of a form of any one of claims 1-32 for treating a hepatitis B infection.

47. Use of a form of any one of claims 1-32 in the manufacture of a medicament for treating a hepatitis B infection.

48. An article of manufacture comprising a unit dosage of the form of any one of claims 1-32.

49. A method of preparing crystalline Form I of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid (Formula I), comprising contacting Formula I and water, wherein Formula I remains substantially insoluble in water, under conditions suitable to prepare crystalline Form I.

50. A method of preparing crystalline Form I of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid (Formula I), comprising:

contacting Formula I and a solvent mixture comprising ethanol and aqueous base to form a Formula I mixture, and

adding the Formula I mixture to an aqueous acid, under conditions suitable to prepare Form I of Formula I.

51. The method of claim 50, wherein the aqueous base comprises sodium hydroxide.

52. The method of claim 50 or 51, wherein the aqueous acid comprises hydrochloric acid.

53. The method of any one of claims 50-52, further comprising adding seed crystals of Form I of Formula I to the aqueous acid before adding the Formula I mixture.

54. The method of any one of claims 49-53, further comprising isolating the Form I of Formula I.

55. A method of preparing crystalline Form II of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid (Formula I), comprising contacting Formula I and methanol, wherein Formula I remains substantially insoluble in methanol, under conditions suitable to prepare crystalline Form II.

56. A method of preparing an amorphous form of (R)-11-(methoxymethyl)-12-(3-methoxypropoxy)-3,3-dimethyl-8-oxo-2,3,8,13b-tetrahydro-1H-pyrido[2,1-a]pyrrolo[1,2-c]phthalazine-7-carboxylic acid (Formula I), comprising:

contacting Formula I and a solvent mixture comprising acetonitrile and water, and

lyophilizing under conditions suitable to prepare the amorphous form of Formula I.

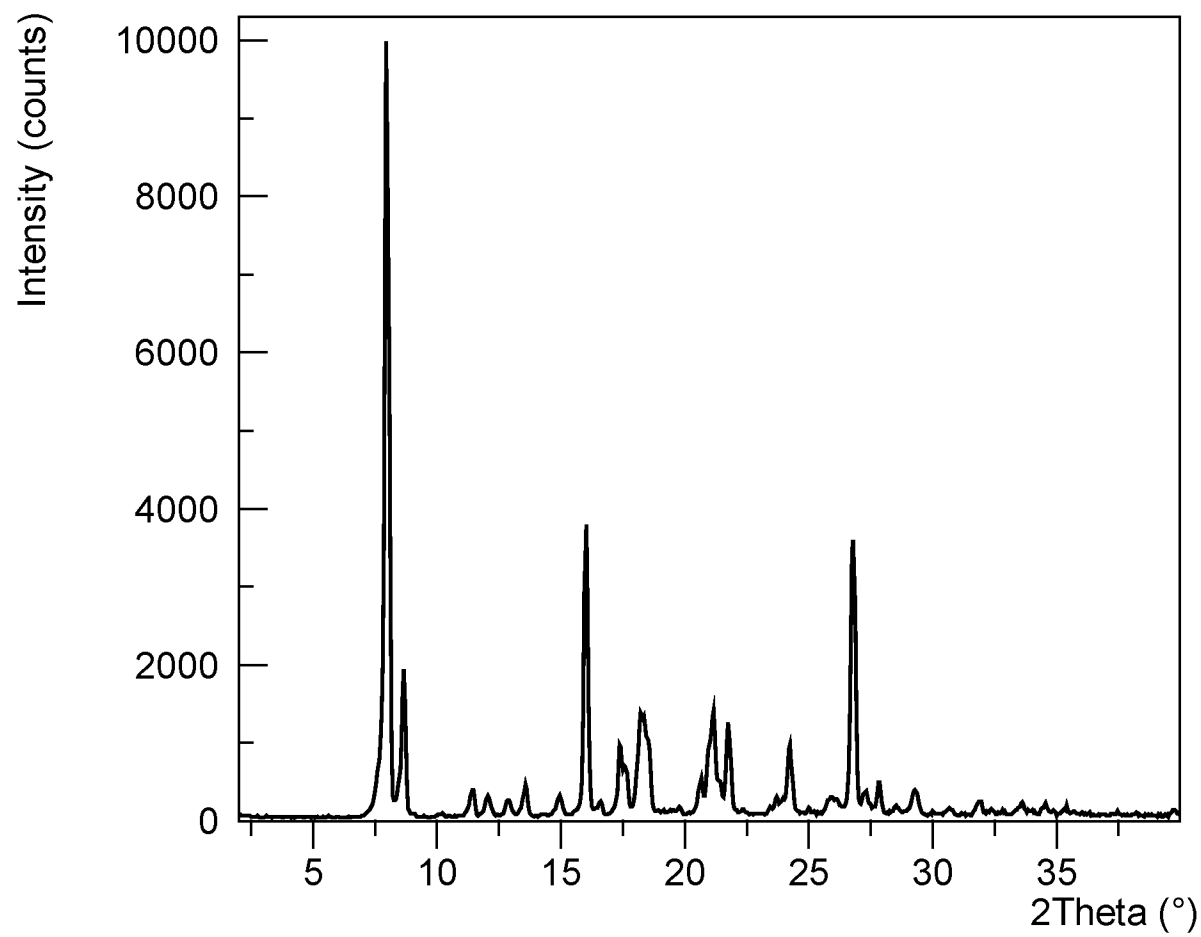


FIG. 1

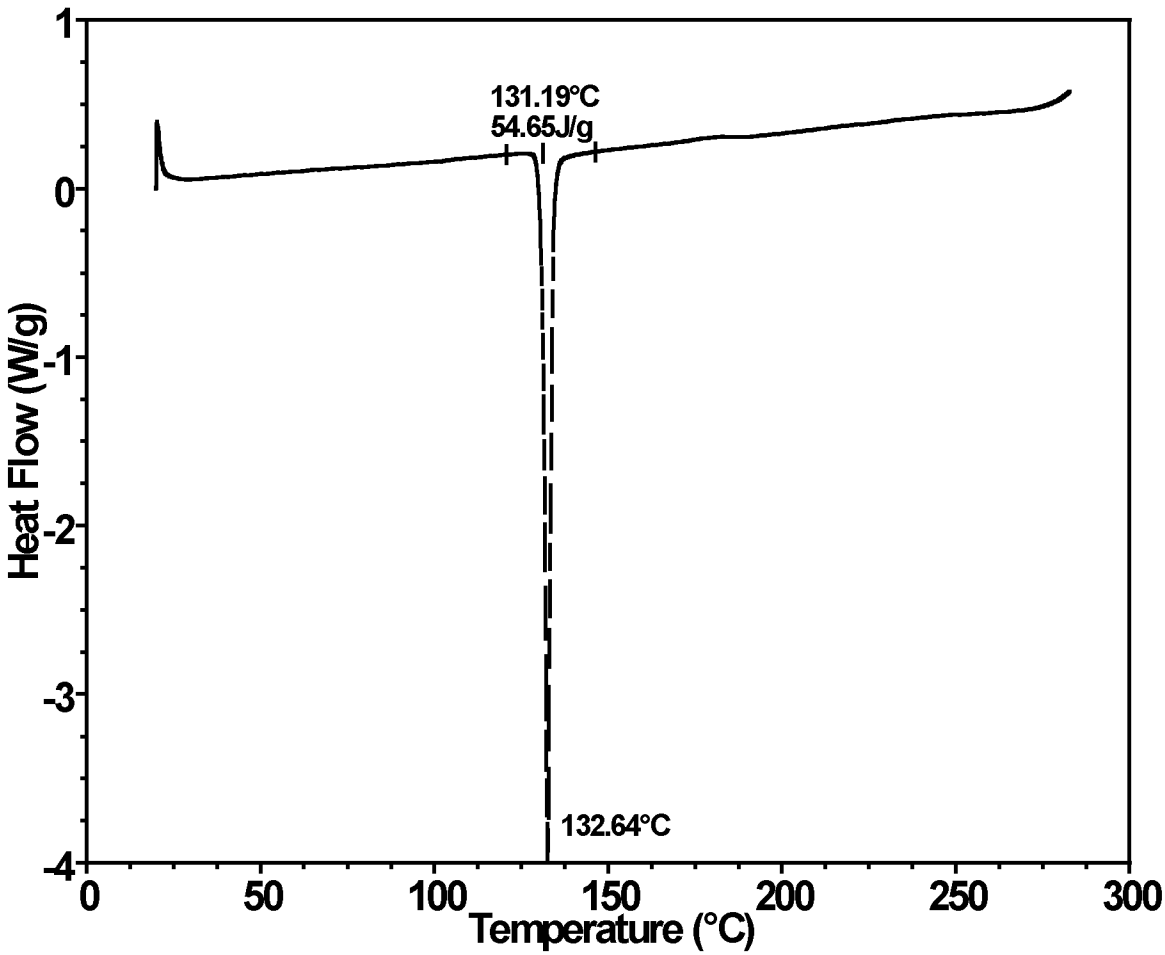


FIG. 2

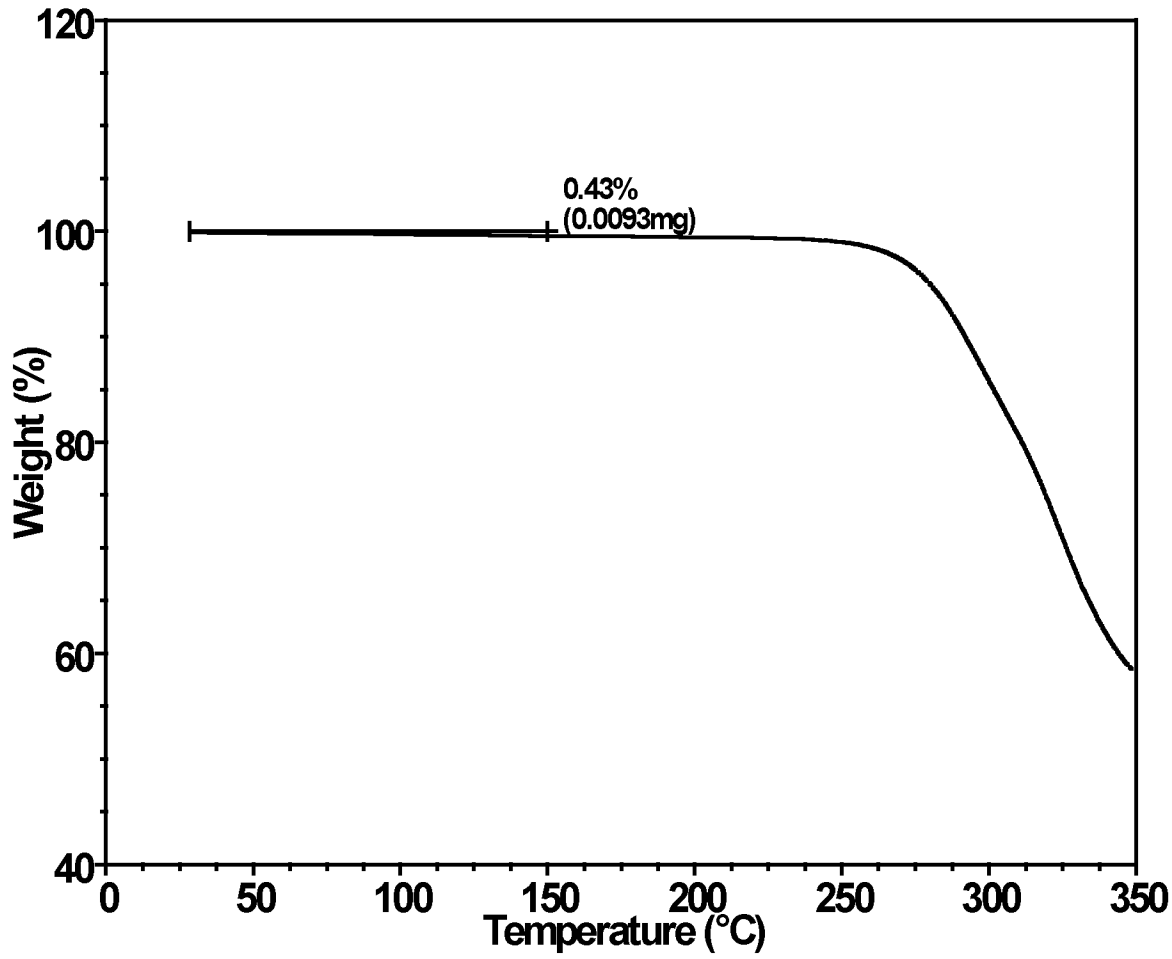


FIG. 3

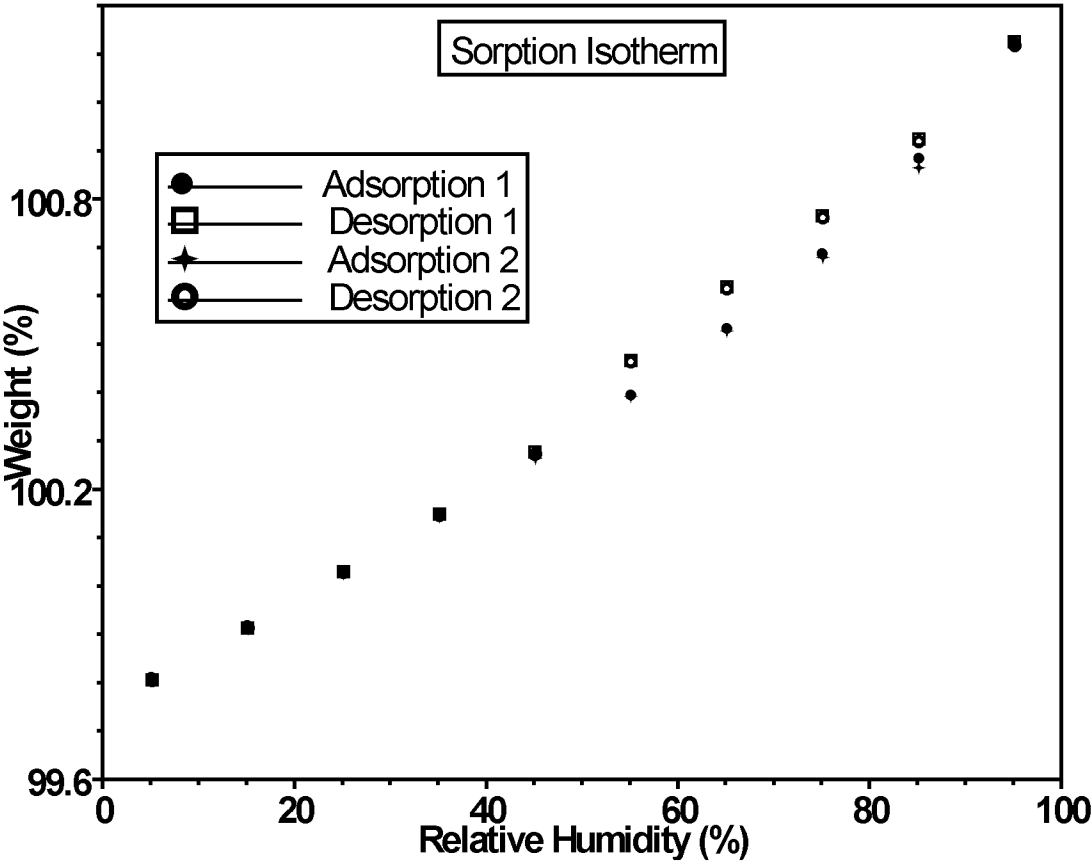


FIG. 4

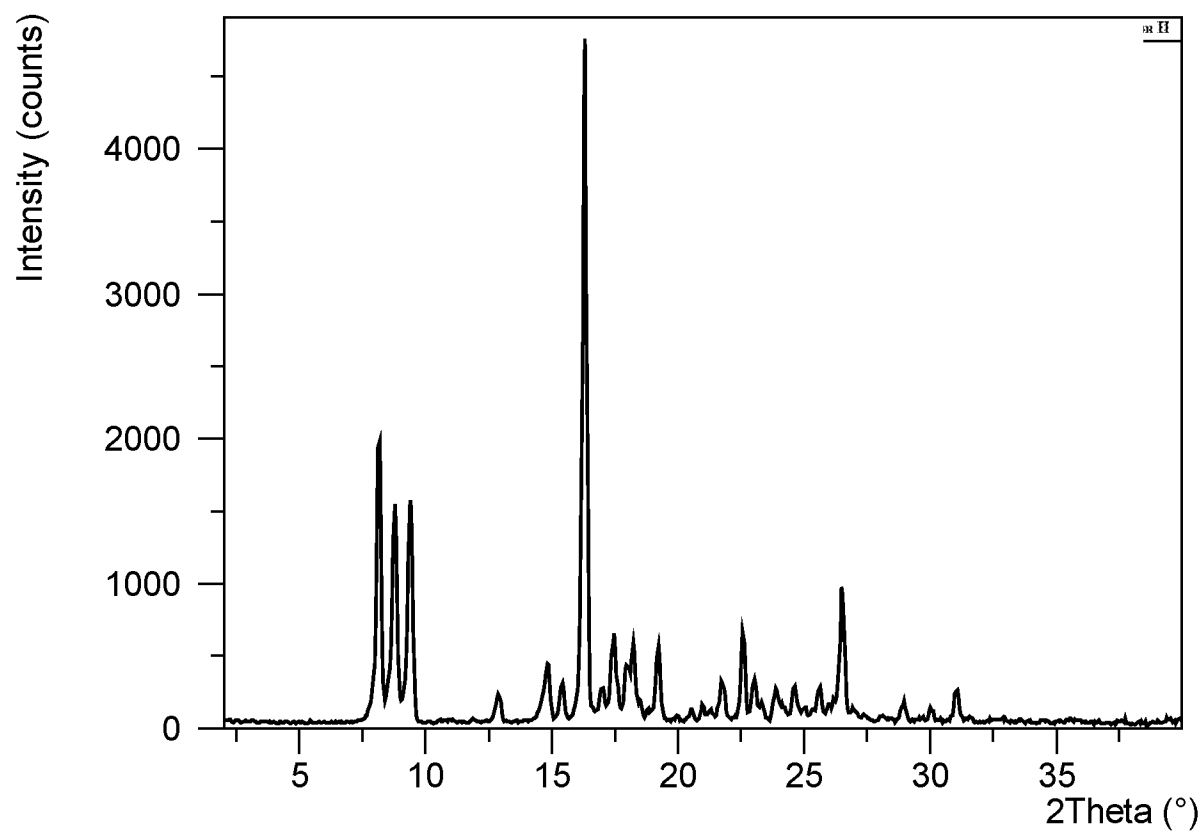


FIG. 5

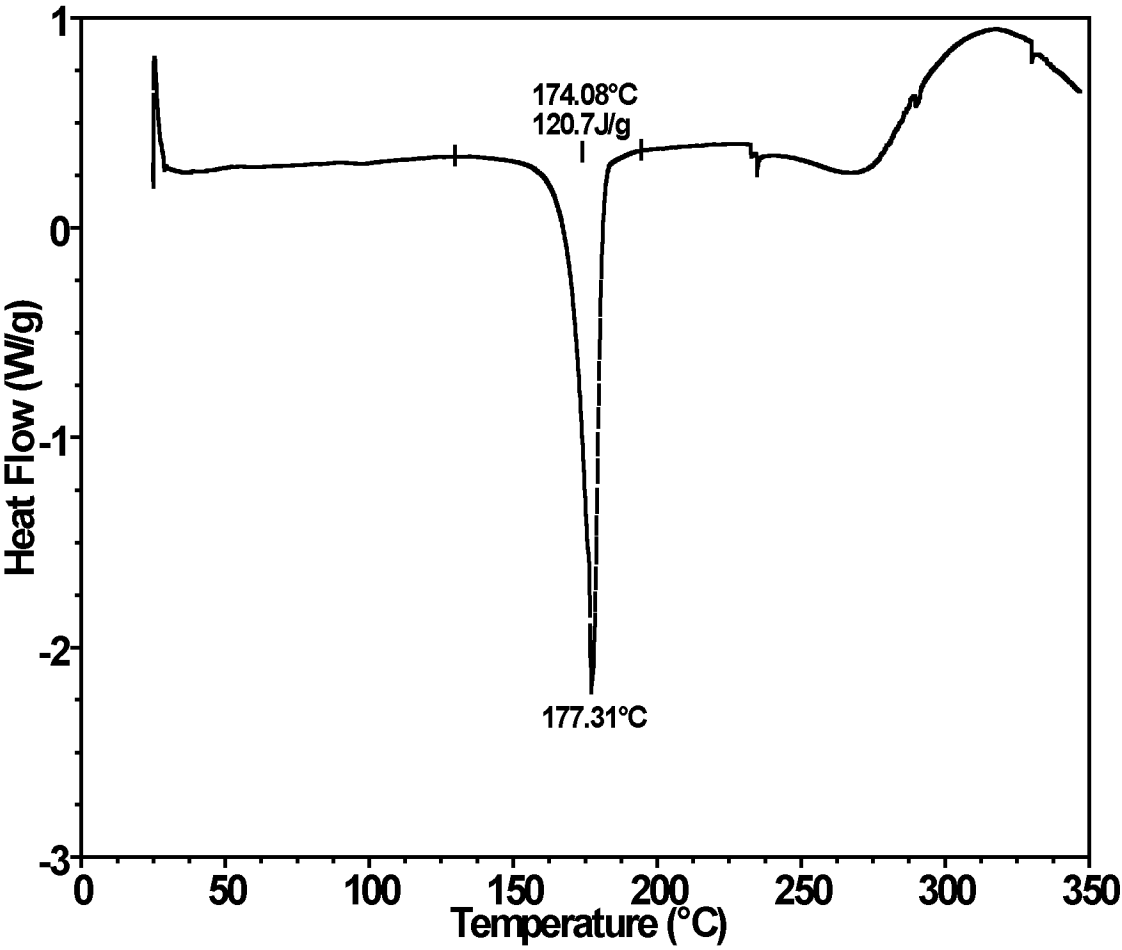


FIG. 6

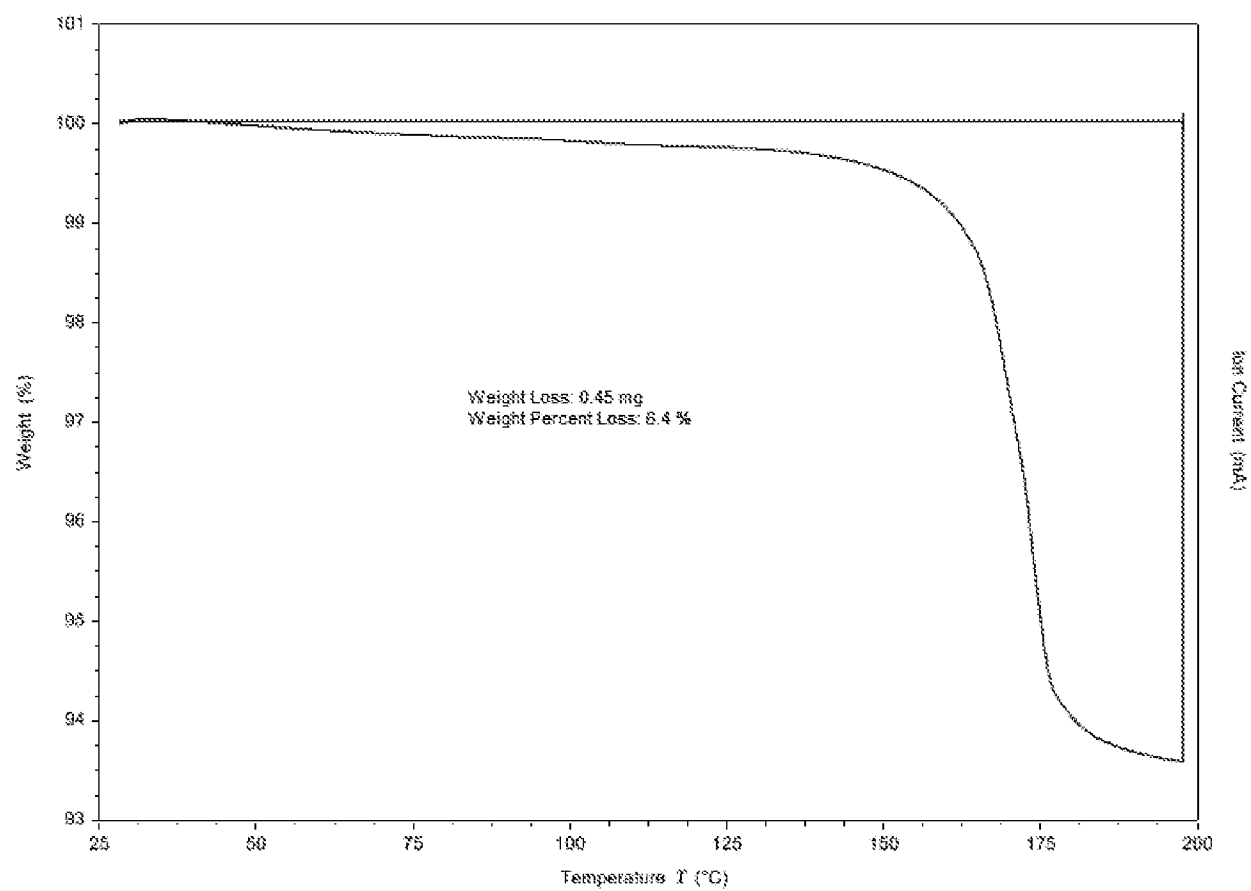


FIG. 7

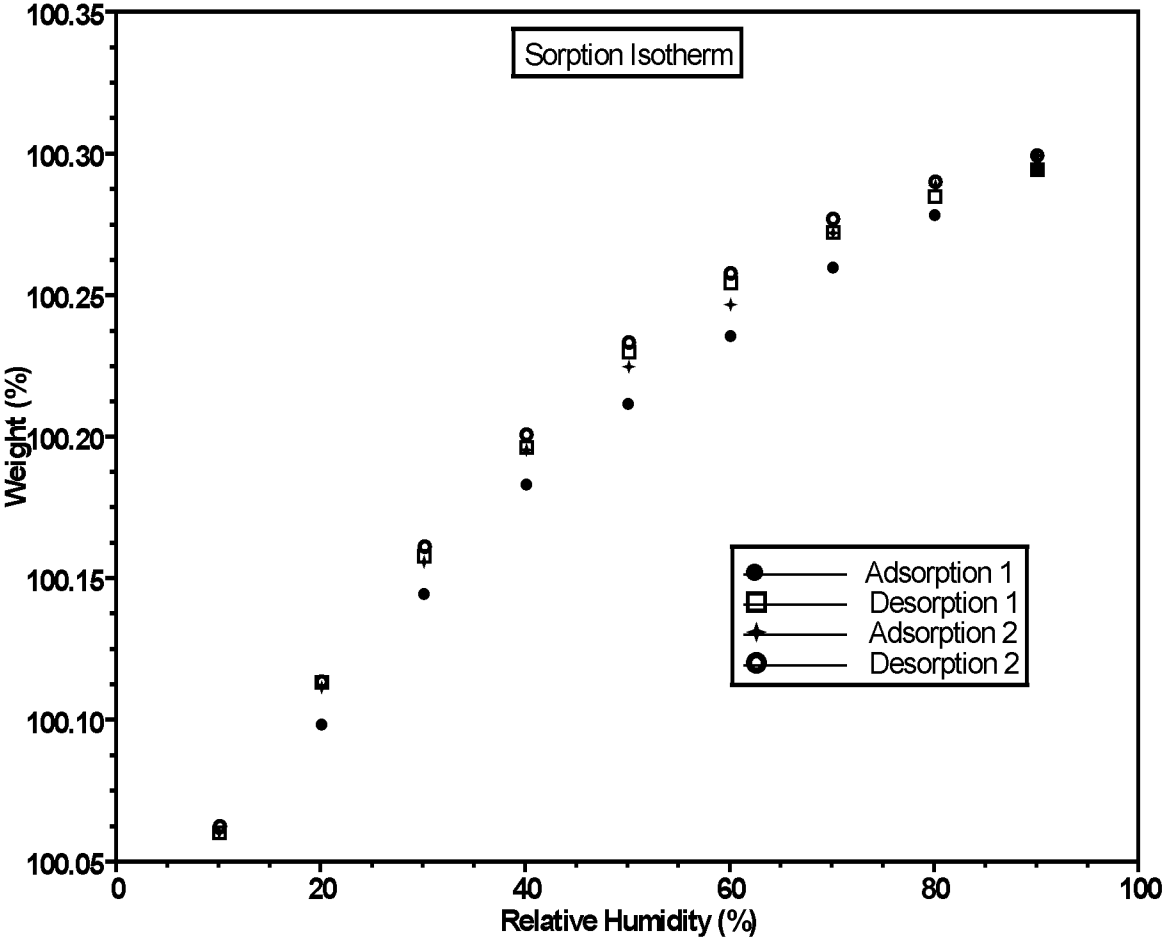


FIG. 8

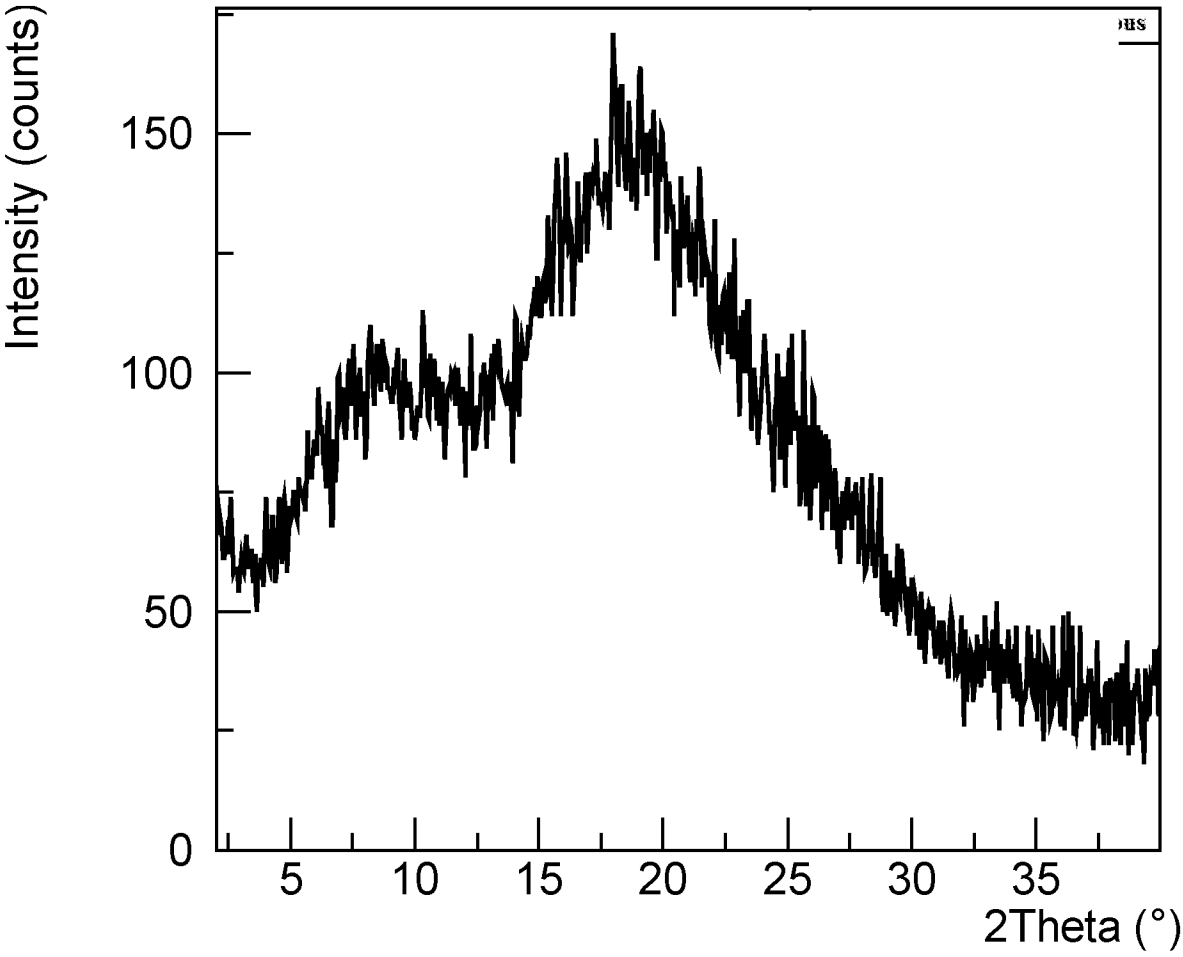


FIG. 9

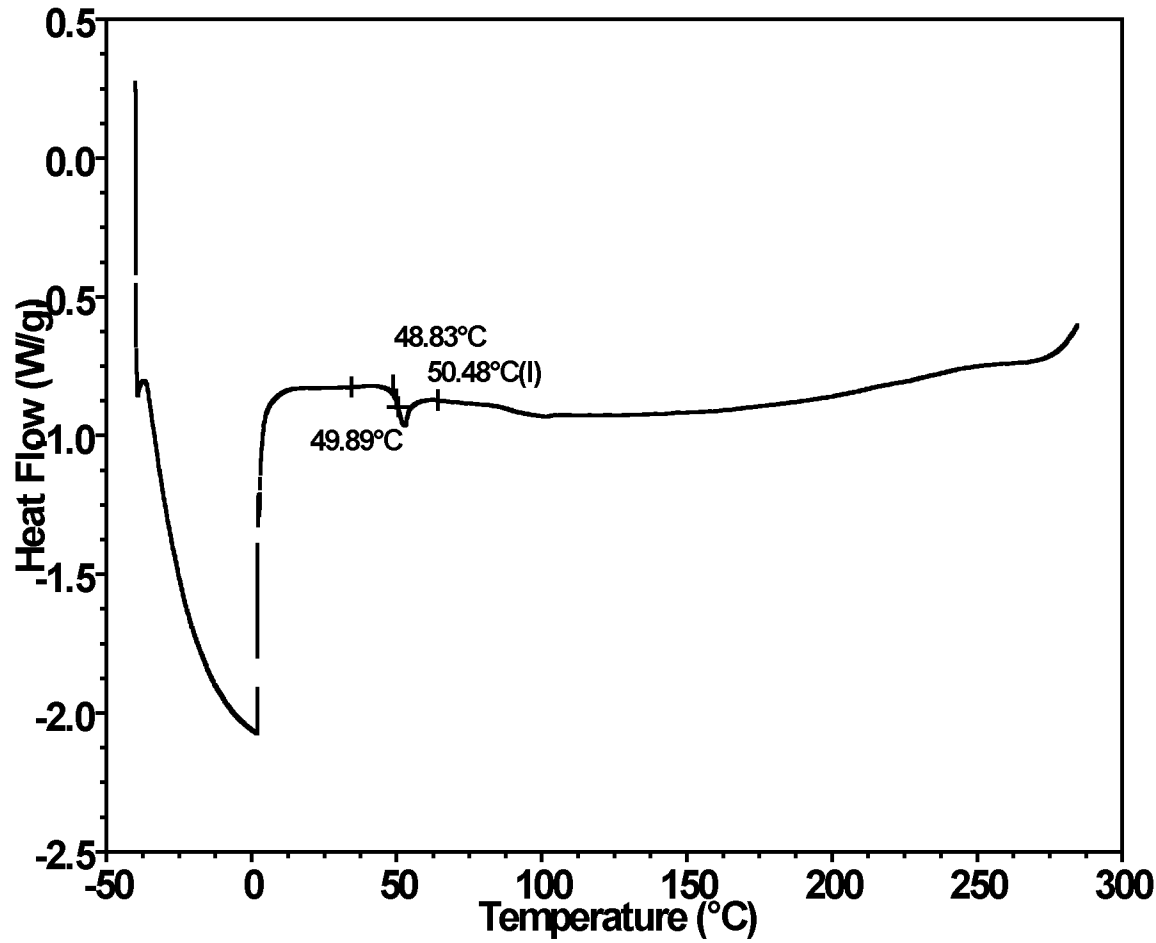


FIG. 10

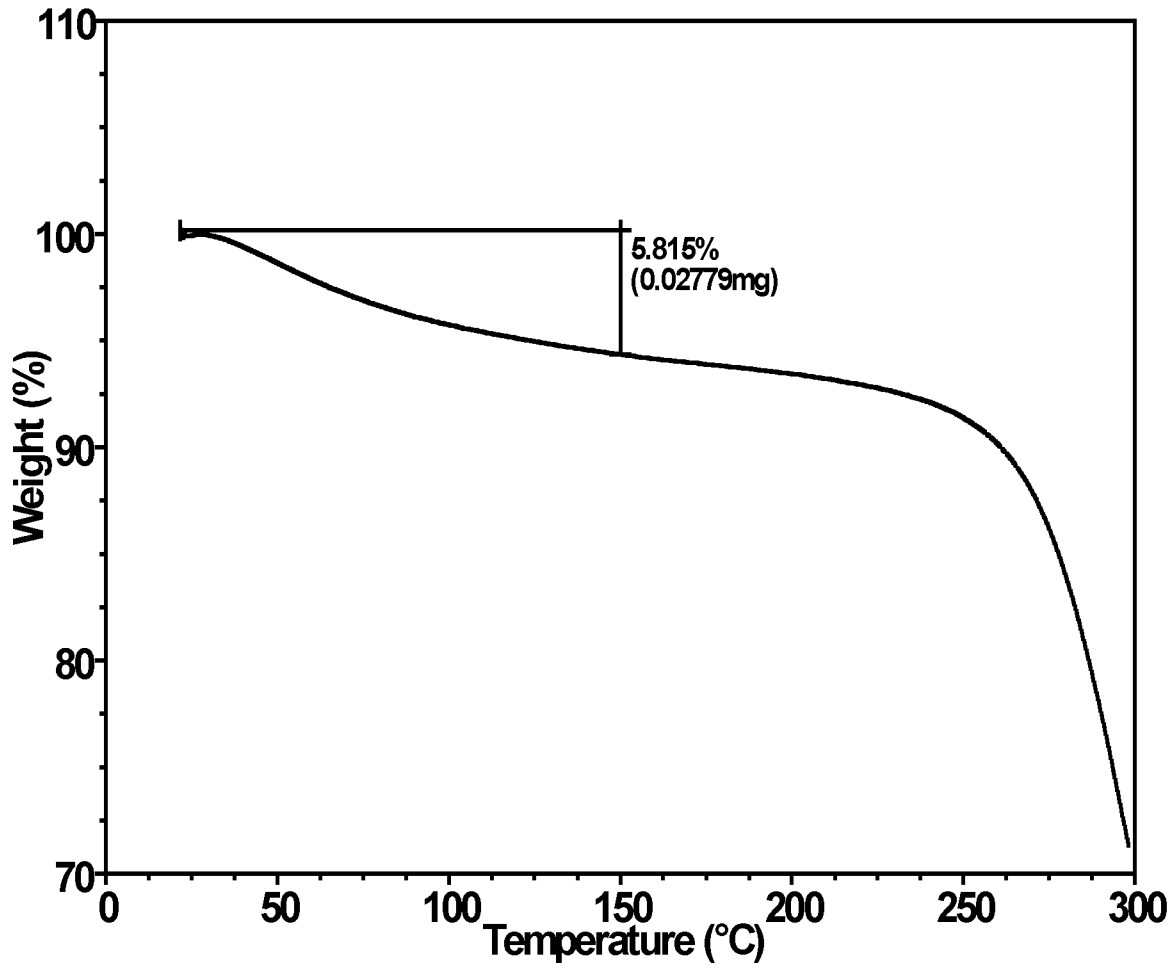


FIG. 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/043042

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/14 A61P31/12 A61K31/501
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)
A61P C07D

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017/205115 A1 (GILEAD SCIENCES INC [US]) 30 November 2017 (2017-11-30) page 1, line 4 - line 18; claim 1; examples 1-19 -----	1-56
A	WO 2017/017042 A1 (F HOFFMANN-LA ROCHE AG [CH]; HOFFMANN-LA ROCHE INC [US]) 2 February 2017 (2017-02-02) page 1, line 1 - line 3; claim 1 -----	1-56
X,P	WO 2018/144605 A1 (GILEAD SCIENCES INC [US]) 9 August 2018 (2018-08-09) page 1, line 10 - line 11; claim 1; figures 1,2; example 73 -----	1-56



Further documents are listed in the continuation of Box C.



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" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 September 2019

Date of mailing of the international search report

01/10/2019

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Authorized officer

Seelmann, Ingo

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/043042

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