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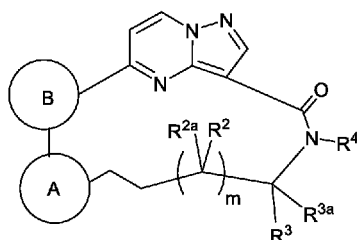
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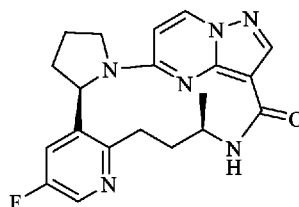
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(54) **Title:** PROCESS FOR THE PREPARATION OF PYRAZOLO[1,5-a]PYRIMIDINES AND SALTS THEREOF



Formula C,



Formula I

(57) **Abstract:** In some embodiments, provided herein are processes for preparing a compound of Formula C or a salt thereof, as disclosed herein. In some embodiments, provided herein is a compound of Formula I or a pharmaceutically acceptable salt, solvate or hydrate thereof. In some embodiments, provided herein is a solid form of the compound, such as a crystalline form of the compound crystalline Form I.





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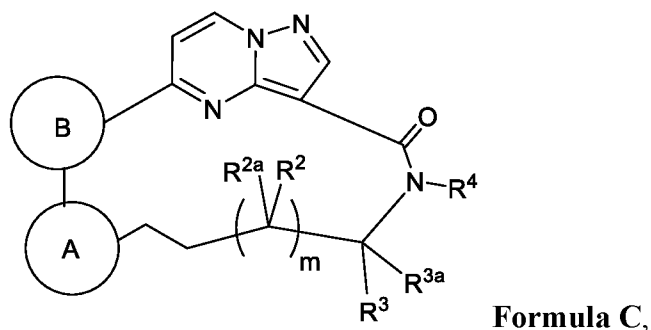
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PROCESS FOR THE PREPARATION OF PYRAZOLO[1,5-a]PYRIMIDINES AND SALTS THEREOF

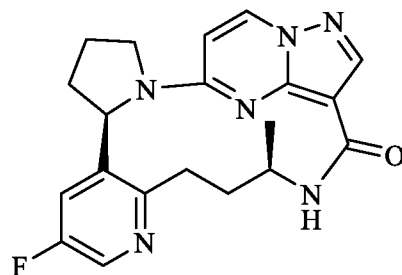
FIELD OF THE INVENTION

Provided herein are processes and intermediates useful for the preparation of a compound of Formula C:



or a salt thereof.

Provided also herein is (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one:



Formula I

or a pharmaceutically acceptable salt, solvate or hydrate thereof. The compound of Formula I is also referred to herein as “Compound 1”.

Provided also herein are crystalline forms of (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one, salt forms thereof, and crystalline forms of these salts, including methods of preparation thereof. (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one and its forms are useful in the treatment of the

Trk-associated disorders such as cancer, pain, inflammation, neurodegenerative diseases and certain infectious diseases.

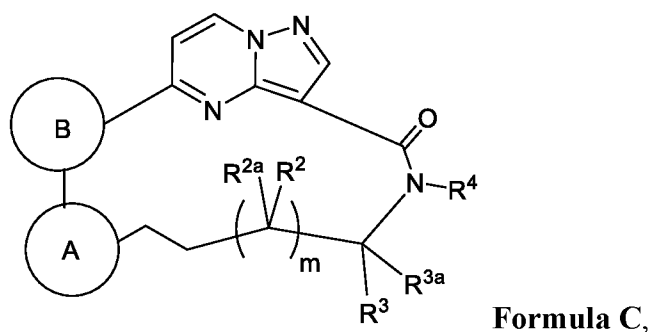
BACKGROUND

Trk's are high affinity receptor tyrosine kinases activated by a group of soluble growth factors called neurotrophins (NT). The Trk receptor family has three members: TrkA, TrkB and TrkC. Among the neurotrophins are (i) nerve growth factor (NGF) which activates TrkA, (ii) brain-derived neurotrophic factor (BDNF) and neurotrophin-4/5 which activate TrkB and (iii) neurotrophin-3 which activates TrkC. Inhibitors of the Trk/neurotrophin pathway have been demonstrated to be effective in numerous pre-clinical animal models of pain. Overexpression, activation, amplification and/or mutation of Trk kinases are associated with many cancers including neuroblastoma, ovarian and colorectal cancer, melanoma, head and neck cancer, gastric carcinoma, lung carcinoma, breast cancer, glioblastoma, medulloblastoma, secretory breast cancer, salivary gland cancer, papillary thyroid carcinoma, and adult myeloid leukemia. The neurotrophin/Trk pathway has been implicated in inflammatory diseases including asthma, interstitial cystitis, inflammatory bowel diseases including ulcerative colitis and Crohn's disease, and inflammatory skin diseases such as atopic dermatitis, eczema and psoriasis. The neurotrophin/Trk pathway has also been implicated in the etiology of neurodegenerative diseases including multiple sclerosis, Parkinson's disease and Alzheimer's Disease. The TrkA receptor is also involved the disease process in the parasitic infection of *Trypanosoma cruzi* (Chagas disease) in human hosts. As such, inhibition of Trk kinases will be useful to provide therapeutic benefit to patients suffering from the aforementioned conditions.

New forms of macrocyclic pyrazolo[1,5-a]pyrimidines can be useful in the preparation of pharmaceutical formulations and dosage forms. Furthermore, a need exists for alternative synthetic procedures for the preparation of such pyrazolo[1,5-a]pyrimidines. Such alternative synthetic procedures are provided herein.

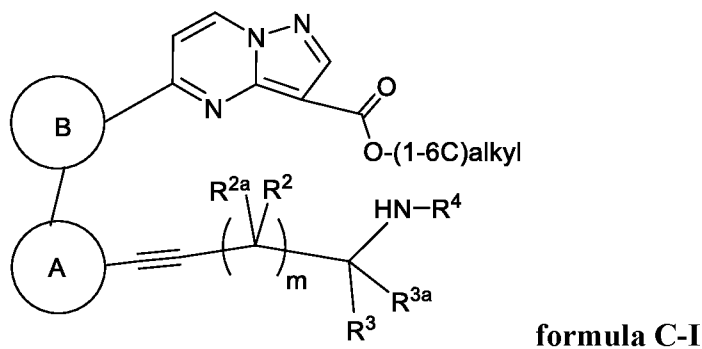
SUMMARY

Provided herein in some embodiments is a process for preparing a compound of Formula C:

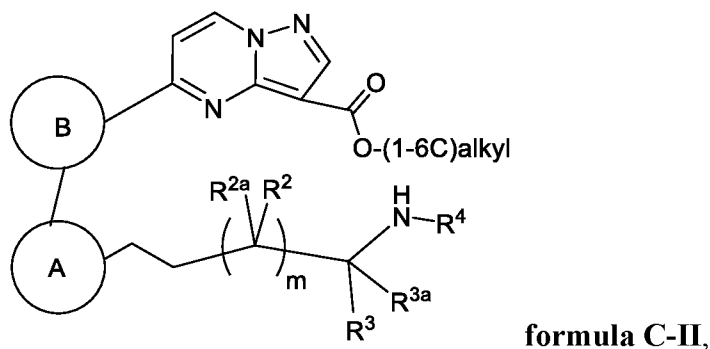


5 or a salt thereof. In some embodiments, the process comprises:

a) treating a compound of formula **C-I**

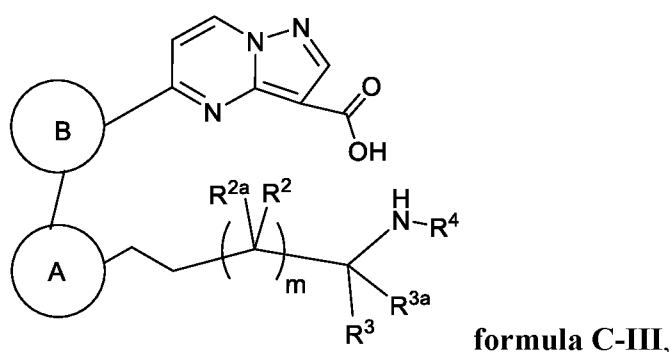


or a salt thereof, with a hydrogenation system to form a compound of formula **C-II**



10 or a salt thereof;

b) treating the compound of formula **C-II** or a salt thereof with a first strong base to form a compound of formula **C-III**

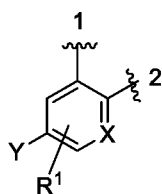


or a salt thereof; and

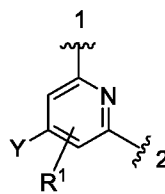
- c) cyclizing the compound of formula **C-III** or a salt thereof with a coupling agent to form the compound of **Formula C** or a salt thereof;

5 wherein:

ring A is selected from rings A-1 and A-3 having the structures:



A-1



A-3

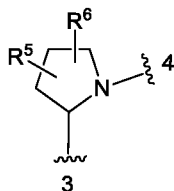
10 wherein the wavy line labeled 1 indicates the point of attachment of ring A to ring B and the wavy line labeled 2 indicates the point of attachment of ring A to the carbon atom of the ethylene linker in formulae **C**, **C-II** or **C-III**, or to the carbon atom of the alkyne linker in formula **C-I**;

X is N or CH;

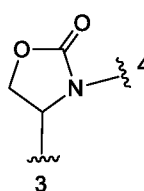
Y is H or F;

R¹ is H, (1-6C)alkyl, (1-3C)alkoxy or halogen;

15 ring B is selected from rings B-1 and B-2 having the structures:



B-1



B-2

wherein the wavy line labeled 3 indicates the point of attachment to ring A and the wavy line labeled 4 indicates the point of attachment to the pyrazolo[1,5-a]pyrimidine ring;

R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH, provided that R^2 and R^{2a} are not both OH;

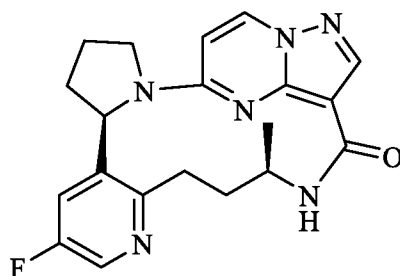
5 m is 0, 1 or 2;

R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

R^4 is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl); and

R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

10 Provided herein in some embodiments is a process for preparing a compound of Formula I

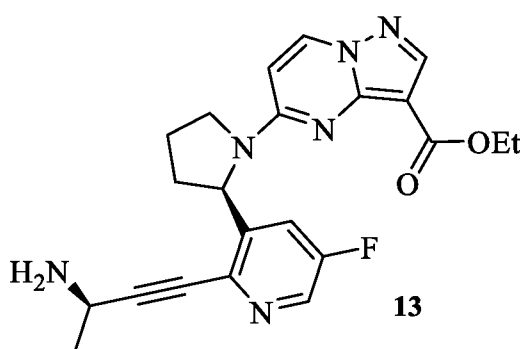


Formula I

or a salt thereof, comprising:

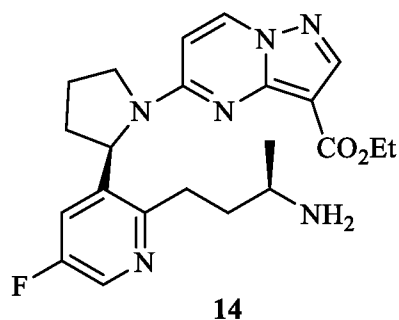
a) treating a compound of formula 13

15



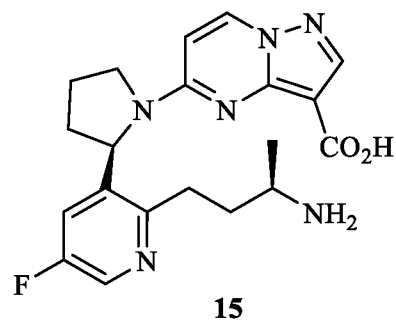
13

or a salt thereof with a hydrogenation system to form a compound of formula 14



or a salt thereof;

b) treating the compound of formula **14** or a salt thereof with a first strong base to form a compound of formula **15**

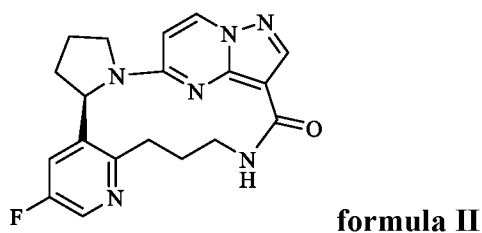


5

or a salt thereof; and

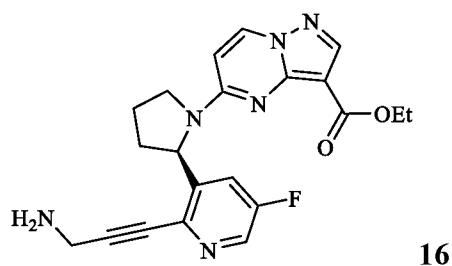
c) cyclizing the compound of formula **15** or a salt thereof with a coupling agent to form the compound of Formula **I** or a salt thereof.

Provided herein in some embodiments is a process for preparing a compound of
10 Formula **II**:

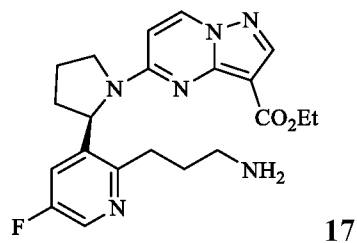


or a salt thereof, comprising:

a) treating a compound of formula **16**

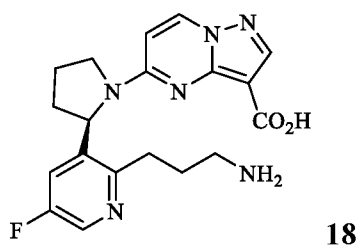


or a salt thereof with a hydrogenation system to form a compound of formula **17**



or a salt thereof;

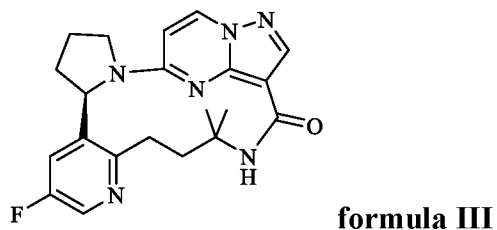
- 5 b) treating the compound of formula **17** or a salt thereof with a first strong base to form a compound of formula **18**



or a salt thereof; and

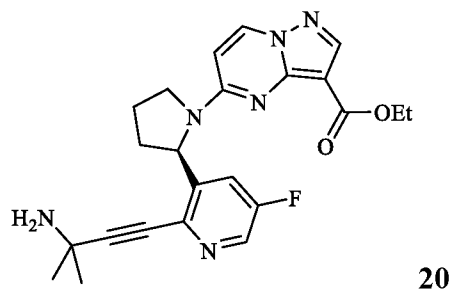
- 10 c) cyclizing the compound of formula **18** or a salt thereof with a coupling agent to form the compound of Formula **III** or a salt thereof.

Provided herein in some embodiments is a process for preparing a compound of Formula **III**:

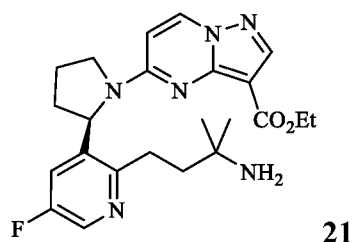


- 15 or a salt thereof, comprising:

a) treating a compound of formula **20**

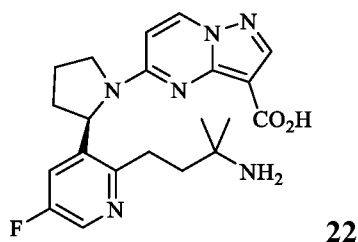


or a salt thereof with a hydrogenation system to form a compound of formula **21**



5 or a salt thereof;

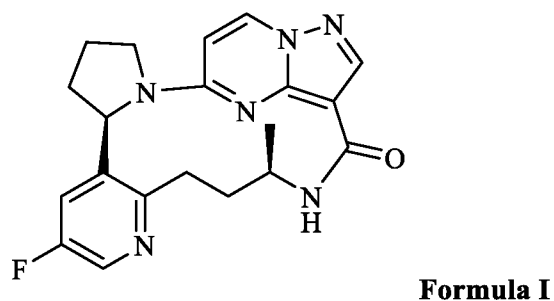
b) treating the compound of formula **21** or a salt thereof with a first strong base to form a compound of formula **22**



or a salt thereof; and

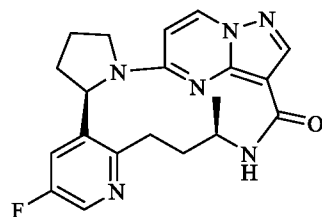
10 c) cyclizing the compound of formula **22** or a salt thereof with a coupling agent to form the compound of Formula **I** or a salt thereof.

Provided herein in some embodiments is a compound of Formula I



or a pharmaceutically acceptable salt, solvate or hydrate thereof.

The present disclosure in one embodiment is directed to a solid form of (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one having the following structural formula:



(Compound 1).

5 The present disclosure is further directed to a crystalline form of Compound 1, such as a crystalline form of Compound 1 having Form I. In some embodiments, Form I has the XRPD peaks, in terms of 2-theta (2θ), at about 9.1, about 20.2 and about 24.9. In some embodiments, Form I has the XRPD peaks, in terms of 2-theta, at about 9.1, about 11.2, about 20.2 and about 24.9. In some embodiments, Form I has the XRPD peaks, in terms of 2-theta, at about 9.1, about 11.2, about 13.4, about 14.8, about 20.2, and about 29.4. In some embodiments, Form I has the XRPD peaks, in terms of 2-theta, at about 9.1, about 11.2, about 13.4, about 14.8, about 18.3, about 18.6, about 20.2, about 23.6, about 24.9, and about 29.4. As used herein, the term “about” in conjunction with XRPD peaks refers to a variation of ±0.2. Thus, for example, a 2-theta value of “about 9.1”
10 means a 2-theta value of 9.1 ±0.2.
15

The present disclosure is further directed to salts of Compound 1.

The present disclosure is further directed to crystalline forms of benzenesulfonic acid salt, citric acid salt, methanesulfonic acid salt, 1,2-ethane disulfonic acid salt, p-toluene sulfonic acid salt, oxalic acid salt, fumaric acid salt, L-malic acid salt, and succinic acid salt of Compound 1.
20

In one aspect, the present disclosure is directed to a crystalline form of Compound 1 besylate. In some embodiments, the crystalline Compound 1 besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 13.4, and about 21.2. In some embodiments, the crystalline Compound 1 besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 12.0, about 13.4, and about 21.2. In some embodiments, the crystalline Compound 1 besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 12.0, about 13.4, about 19.0, about 19.4, and about 21.2. In some embodiments, the crystalline Compound 1
25

besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 12.0, about 13.4, about 19.0, about 19.4, about 19.9, about 20.1, about 21.2, about 25.5, and about 32.7.

In another aspect, the present disclosure is directed to a crystalline form of Compound 1 citrate, such as crystalline Compound 1 citrate Form A. In some
5 embodiments, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 20.7, about 21.6, and about 24.8. In some embodiments, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 8.9, 20.7, about 21.6, and about 24.8. In some
embodiments, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 8.9, about 11.1, about 14.4, about 15.4, about 20.7, about 21.6, and about 24.8. In some
10 embodiments, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 8.9, about 11.1, about 13.9, about 14.4, about 15.4, about 19.2, about 20.7, about 21.6, about 24.8, and about 25.6.

The present disclosure is further directed to the hydrochloric acid salt, sulfuric acid salt, naphthalene-2-sulphonic acid salt, 2-hydroxy ethanesulfonic acid salt, L-
15 aspartic acid salt, maleic acid salt, phosphoric acid salt, ethanesulfonic acid salt, L-glutamic acid salt, L-tartaric acid salt, D-glucuronic acid salt, hippuric acid salt, D-gluconic acid salt, DL-lactic acid salt, L-ascorbic acid salt, benzoic acid salt, benzenesulfonic acid salt, citric acid salt, methanesulfonic acid salt, 1,2-ethane disulfonic acid salt, p-toluene sulfonic acid salt, oxalic acid salt, fumaric acid salt, L-malic acid salt,
20 and succinic acid salt of Compound 1.

The present disclosure is further directed to a hydrate or a solvate of Compound 1, or any one of the salts of Compound 1 described herein. In some aspects, the hydrate or the solvate is crystalline.

The present disclosure is further directed to processes for preparing any one of the
25 crystalline forms, solid forms, solvates, hydrates, or salts described herein.

The present disclosure is further directed to pharmaceutical compositions comprising any one of the crystalline forms, solid forms, solvates, hydrates, or salts described herein, and at least one pharmaceutically acceptable carrier.

The present disclosure is further directed to therapeutic methods of using any one
30 of the crystalline forms, solid forms, solvates, hydrates, or salts described herein.

Unless otherwise defined, all technical and scientific terms used herein have the

same meaning as commonly understood by one of ordinary skill in the art to which the present application belongs. Materials are described herein for use in the present application; other, suitable materials known in the art can also be used. The materials and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the present application will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 is a XRPD diffractogram of Compound 1 (Form I).

FIG. 2 is a TG/DTA thermogram of Compound 1 (Form I).

FIG. 3 is a DSC thermogram of Compound 1 (Form I).

FIG. 4 is a GVS isotherm plot of Compound 1 (Form I).

FIG. 5 is a GVS kinetic plot of Compound 1 (Form I).

FIG. 6 is a DVS isotherm plot of Compound 1 (Form I).

FIG. 7 is a DVS change in mass plot of Compound 1 (Form I).

FIG. 8 is an IR spectrum Compound 1 (Form I).

FIG. 9 is a ^1H NMR spectrum of Compound 1 (Form I).

FIG. 10 is an image showing a 3-D view of Compound 1 (Form I) with atom labels.

FIG. 11 is an image showing a ORTEP view of Compound 1 (Form I) with atom labels.

FIG. 12 is an image showing a 3-D view of Compound 1, acetonitrile solvate with atom labels.

FIG. 13 is an image showing a ORTEP view of Compound 1, acetonitrile solvate with atom labels.

FIG. 14 is a XRPD diffractogram of Compound 1 edisylate.

FIG. 15 is a XRPD diffractogram of Compound 1 tosylate.

FIG. 16 is a XRPD diffractogram of Compound 1 mesylate.

FIG. 17 is a XRPD diffractogram of Compound 1 besylate (pattern 1).

FIG. 18 is a XRPD diffractogram of Compound 1 besylate (pattern 2).

- FIG. 19 is a XRPD diffractogram of Compound 1 oxalate.
- FIG. 20 is a XRPD diffractogram of Compound 1 fumarate.
- FIG. 21 is a XRPD diffractogram of Compound 1 citrate (Form A).
- FIG. 22 is a XRPD diffractogram of Compound 1 L-malate.
- 5 FIG. 23 is a XRPD diffractogram of Compound 1 succinate.
- FIG. 24 is a TG/DTA thermogram of Compound 1 tosylate.
- FIG. 25 is a TG/DTA thermogram of Compound 1 mesylate.
- FIG. 26 is a TG/DTA thermogram of Compound 1 oxalate.
- FIG. 27 is a TG/DTA thermogram of Compound 1 fumarate.
- 10 FIG. 28 is a TG/DTA thermogram of Compound 1 L-malate.
- FIG. 29 is a TG/DTA thermogram of Compound 1 succinate.
- FIG. 30 is a XRPD diffractogram of Compound 1 mesylate acetone solvate.
- FIG. 31 is a TG/DTA thermogram of Compound 1 mesylate acetone solvate.
- FIG. 32 is a DSC thermogram of Compound 1 mesylate.
- 15 FIG. 33 is a GVS isotherm of Compound 1 mesylate acetone solvate.
- FIG. 34 is a GVS kinetic plot of Compound 1 mesylate acetone solvate.
- FIG. 35 is an IR spectrum of Compound 1 mesylate acetone solvate.
- FIG. 36 is a ^1H NMR spectrum of Compound 1 mesylate acetone solvate.
- FIG. 37 is a TG/DTA thermogram of Compound 1 besylate.
- 20 FIG. 38 is a DSC thermogram of Compound 1 besylate.
- FIG. 39 is a DVS isotherm of Compound 1 besylate.
- FIG. 40 is a DVS kinetic plot of Compound 1 besylate.
- FIG. 41 is an IR spectrum of Compound 1 besylate.
- FIG. 42 is ^1H NMR spectrum of Compound 1 besylate.
- 25 FIG. 43 is a TG/DTA thermogram of Compound 1 citrate (Form A).
- FIG. 44 is a DSC thermogram of Compound 1 citrate (Form A).
- FIG. 45 is a DVS isotherm of Compound 1 citrate (Form A).
- FIG. 46 is a DVS kinetic plot of Compound 1 citrate (Form A).
- FIG. 47 is an IR spectrum of Compound 1 citrate (Form A).
- 30 FIG. 48 is a ^1H -NMR spectrum of Compound 1 citrate (Form A).
- FIG. 49 is a XRPD diffractogram of a Compound 1 citrate (Form B).

FIG. 50 is a sequence listing for an exemplary wildtype TrkA polypeptide (SEQ ID NO: 1).

FIG. 51 is a sequence listing for an exemplary wildtype TrkB polypeptide (SEQ ID NO: 2).

5 FIG. 52 is a sequence listing for an exemplary wildtype TrkC polypeptide (SEQ ID NO: 3).

DETAILED DESCRIPTION

Definitions

10 Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the invention(s) belong. All patents, patent applications, published applications and publications, databases, websites and other published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their
15 entirety. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such
20 information.

As used herein, the term “alkyl” refers to a hydrocarbon chain that can be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C₁₋₆ indicates that the group can have from 1 to 6 (inclusive) carbon atoms in it. As used herein, recitations such as “C₁₋₆ alkyl”, “(1-6C)alkyl” or “(1-6C alkyl)” are used
25 interchangeably herein to indicate a straight or branched chain alkyl group having from one to six carbon atoms. Examples of such alkyl groups include methyl, ethyl, *iso*-propyl, *tert*-butyl, and *n*-hexyl.

As used herein, “hydrogenation system” refers to a compound or complex capable of catalyzing a hydrogenation reaction, *i.e.*, the reaction of the hydrogen with a hydrogen
30 reactive group, such as a benzyl group or a carbon-carbon double/triple bond. The hydrogenation system includes hydrogen gas at atmospheric or higher pressure and a

catalyst. Catalysts useful for hydrogenation include, but are not limited to, metals, such as palladium, platinum, and rhodium and their oxides or hydroxides, preferably supported on a material such as carbon or alumina.

“Coupling agent,” as used herein, refers to a reagent that forms amide or ester bonds, such as by coupling acids and amines or alcohols, respectively. Suitable coupling agents are well known to a person of skill in the art and are commercially available. Coupling agents include, but are not limited to, dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDCI), or carbonyl diimidazole (CDI). In some embodiments, one or more than one coupling agent can be used at the same time. A coupling agent may be used in conjunction with a catalyst.

As used herein, “strong base” refers to a basic chemical compound that is able to deprotonate weak acids in an acid-base reaction. A strong base is also able to hydrolyze an ester compound in a hydrolysis reaction to produce the corresponding carboxylic acid compound. Examples of strong bases include, but are not limited to, hydroxides, alkoxides, and ammonia. Common examples of strong bases are the hydroxides of alkali metals and alkaline earth metals, *e.g.*, NaOH. Certain strong bases are even able to deprotonate very weakly acidic C—H groups in the absence of water. Strong bases include, but are not limited to, sodium hydroxide, potassium hydroxide, barium hydroxide, cesium hydroxide, strontium hydroxide, lithium hydroxide and rubidium hydroxide. In certain embodiments, NaOH is used as the strong base.

As used herein, the term “weak base” refers to inorganic and organic bases that are only partially ionized in aqueous solution. Weak bases typically have a pKa of between about 6 and about 11. A large number of such weak bases are known and are exemplified by those listed in the *Handbook of Biochemistry and Molecular Biology*, Vol. 1, 3rd ed., G. D. Fassman, CRC Press, 1976, pp. 305-347. The weak base may be soluble or insoluble in water. Suitable weak bases include, but are not limited to, alkali metal carbonates and bicarbonates, such as lithium carbonate, sodium carbonate, potassium carbonate, and sodium bicarbonate; ammonia; primary amines; secondary amines; and tertiary amines, such as the trialkylamines, *e.g.*, triethylamine,

tripropylamine and tributylamine, benzyldiethylamine, pyridine, quinoline, N-methylmorpholine, and the like.

“Non-nucleophilic base,” as used herein, refers to a base that will not act as a nucleophile, *i.e.*, a base that will not donate an electron pair to an electrophile to form a chemical bond in relation to a reaction. Typically, non-nucleophilic bases are bulky and sterically hindered, such that protons can attach to the basic center, but alkylation and complexation are prevented. Examples of non-nucleophilic bases include, but are not limited to, amines and nitrogen heterocycles, such as triethylamine and pyridine, lithium compounds, and phsophazenes.

The terms “hydrogen” and “H” are used interchangeably herein.

The terms “halogen” or “halo” refer to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

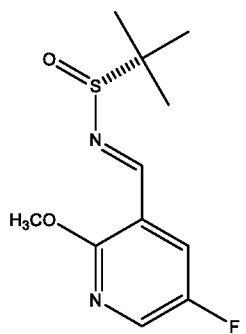
As used herein, the term “alkylamine” refers to an amine that contains one or more alkyl groups. An alkylamine can be a primary amine, a secondary amine or a tertiary amine. For example, a secondary alkylamine is an amine that contains two alkyl groups. An example includes diisopropylethylamine.

As used herein, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise.

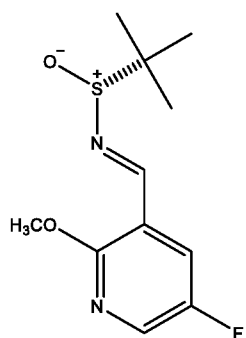
As used herein, ranges and amounts can be expressed as “about” a particular value or range. About also includes the exact amount. Hence, “about 5 grams” means “about 5 grams” and also “5 grams.” It also is understood that ranges expressed herein include whole numbers within the ranges and fractions thereof. For example, a range of between 5 grams and 20 grams includes whole number values such as 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20 grams, and fractions within the range including, but not limited to, 5.25, 6.5, 8.75 and 11.95 grams.

As used herein, “optional” or “optionally” means that the subsequently described event or circumstance does or does not occur and that the description includes instances where said event or circumstance occurs and instances where it does not. For example, a reaction mixture that “optionally includes a catalyst” means that the reaction mixture contains a catalyst or it does not contain a catalyst.

The compounds disclosed herein include compounds having a sulfoxide group, as shown, by way of example, in the structure of compound 2, below:



The sulfur-oxygen bond can also be rendered pictorially as being in ionic form. Thus, for example, compound 2 can also be rendered as shown in the structure below:



It is intended throughout this disclosure that the recitation of a given structure for a compound having a sulfoxide group encompasses all representations of the compound, whether the sulfur-oxygen bond is rendered as being an ionic bond, a covalent bond, a dative bond, or in any form that can be envisioned by the skilled artisan.

The term "compound," as used herein, is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified. Compounds herein identified by name or structure without specifying the particular configuration of a stereocenter are meant to encompass all the possible configurations at the stereocenter. For example, if a particular stereocenter in a compound of the invention could be R or S, but the name or structure of the compound does not designate which it is, then the stereocenter can be either R or S. The compounds described herein can be asymmetric (e.g., having one or more stereocenters). Compounds of the present application that contain an asymmetrically substituted carbon atom can be isolated in optically active or racemic forms. Methods on

how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. In some embodiments, an asymmetrically substituted carbon atom has the (*R*)-configuration according to Cahn-Ingold-Prelog nomenclature. In some embodiments, an asymmetrically substituted carbon atom has the (*S*)-configuration according to Cahn-Ingold-Prelog nomenclature.

“Protecting group”, as used herein, refers to any convenient functional group that allows to obtain chemoselectivity in a subsequent chemical reaction. Protecting groups are described, for example, in Greene & Wuts, eds., “Protecting Groups in Organic Synthesis”, 2nd ed. New York; John Wiley & Sons, Inc., 1991. For a particular compound and/or a particular chemical reaction, a person skilled in the art knows how to select and implement appropriate protecting groups and synthetic methods. Examples of amine protecting groups include acyl and alkoxycarbonyl groups, such as t-butoxycarbonyl (BOC), and [2-(trimethylsilyl)ethoxy]methyl (SEM). Examples of carboxyl protecting groups include (1-6C)alkyl groups, such as methyl, ethyl and t-butyl. Examples of alcohol protecting groups include benzyl, trityl, silyl ethers, and the like.

“Leaving group”, as used herein, refers to a molecule or a molecular fragment (e.g., an anion) that is displaced in a chemical reaction as stable species taking with it the bonding electrons. Examples of leaving groups include arylsulfonyloxy group or an alkylsulfonyloxy group, such as a mesylate or a tosylate group. Common anionic leaving groups also include halides such as Cl⁻, Br⁻, and I⁻.

A salt can form from a compound in any manner familiar to the skilled artisan. Accordingly, the recitation “to form a compound or salt thereof” includes embodiments where a compound is formed and the salt is subsequently formed from the compound in a manner familiar to the skilled artisan.

As used herein, the phrase “solid form” refers to Compound 1 or a salt of Compound 1 in either an amorphous state or a crystalline state (“crystalline form” or “crystalline solid”), whereby a compound in a crystalline state may optionally include solvent or water within the crystalline lattice, for example, to form a solvated or hydrated crystalline form.

The term “hydrated,” as used herein, is meant to refer to a crystalline form that

includes water molecules in the crystalline lattice.

Different crystalline forms of compounds can be characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), differential thermal analysis (DTA), and/or thermogravimetric analysis (TGA). An X-ray powder diffraction (XRPD) pattern of reflections (peaks) is typically considered a fingerprint of a particular crystalline form. It is well known that the relative intensities of the XRPD peaks can widely vary depending on the sample preparation technique, crystal size distribution, various filters used, the sample mounting procedure, and the particular instrument employed. In some instances, new peaks may be observed or existing peaks may disappear depending on the type of instrument or the settings (for example, whether a Ni filter is used or not).

As used herein, the term “peak” refers to a reflection having a relative height/intensity of at least about 5% of the maximum peak height/intensity in the XRPD. Peak assignments, such as those reported herein, can vary by plus or minus 0.2° (2-theta), and the term “substantially” or “about” as used in the context of XRPD herein is meant to refer to the above-mentioned variations. Thus, for example, a 2-theta value of “about 9.1” means a 2-theta value of 9.1 ± 0.2 .

As described herein, temperature readings in connection with DSC, TGA, or other thermal experiments can vary by ± 4 °C depending on the instrument, particular settings, sample preparation, etc. Accordingly, a crystalline form reported herein having a DSC thermogram “substantially” as shown in any of the Figures is understood to accommodate such variation. An endothermic or exothermic event at “about” a certain temperature is also understood to accommodate this variation.

As used herein, the term “melting point” refers to an endothermic event or endothermic event observed in, e.g., a DSC thermogram. An endothermic event is a process or reaction in which a sample absorbs energy from its surroundings in the form of e.g., heat as in a DSC experiment. An exothermic event is a process or reaction in which a sample releases energy. The process of heat absorption and release can be detected by DSC. In some embodiments, the term “melting point” is used to describe the major endothermic event on a DSC thermogram.

The term “room temperature” or “ambient temperature” as used herein, is

understood in the art, and refers generally to a temperature, e.g., a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

In some embodiments, the compounds, salts, and forms described herein are substantially isolated. By “substantially isolated” is meant that the compound, salt, or form is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, e.g., a composition enriched in the compound, salt or form. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound, salt or form.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

As used herein, terms “treat” or “treatment” refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment.

In one embodiment, the term “preventing” as used herein means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein (e.g., multiple types of pain including inflammatory pain, neuropathic

pain, and pain associated with cancer, surgery, and bone fracture), or a symptom thereof.

The terms “effective amount” and “therapeutically effective amount” refer to an amount of compound that, when administered to a mammal in need of such treatment, is sufficient to (i) treat or prevent a particular disease, condition, or disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) prevent or delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein. The amount of a Compound 1, or salt thereof, that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

The terms “individual” or “patient,” used interchangeably, refer to any animal, including mammals, and most preferably humans. As used herein, the term “mammal” refers to a warm-blooded animal that has or is at risk of developing a disease described herein and includes, but is not limited to, guinea pigs, dogs, cats, rats, mice, hamsters, primates, and humans.

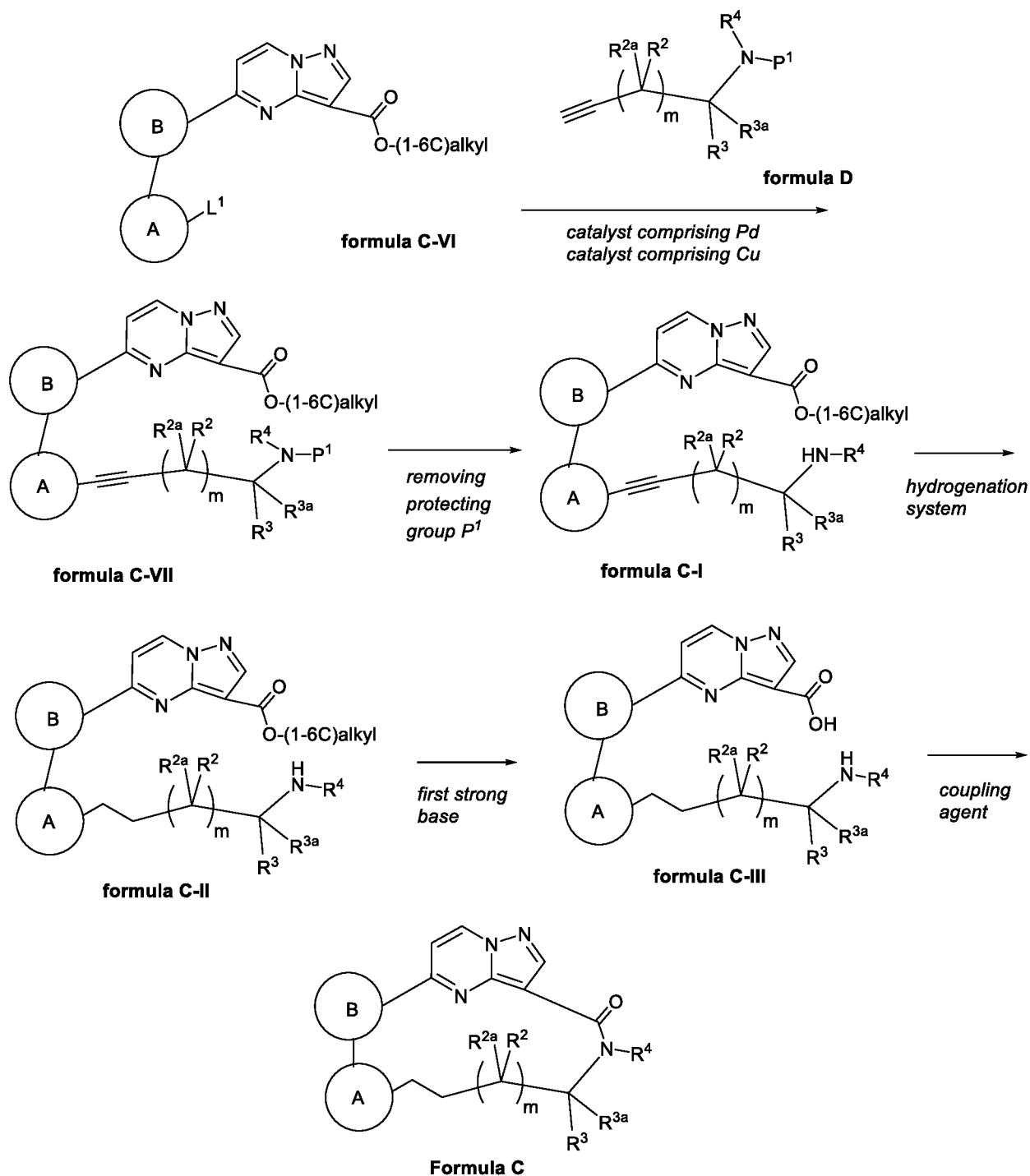
It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination.

All combinations of the embodiments pertaining to the aspects described herein are specifically embraced by the present invention just as if each and every combination was individually explicitly recited, to the extent that such combinations embrace possible aspects. In addition, all sub-combinations of the embodiments contained within the aspects described herein, as well as all sub-combinations of the embodiments contained within all other aspects described herein, are also specifically embraced by the present invention just as if each and every sub-combination of all embodiments are explicitly recited herein.

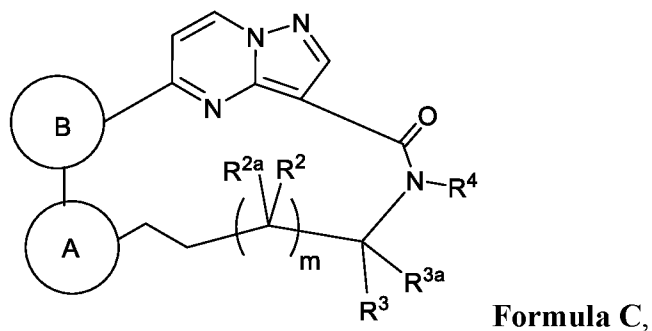
Examples of embodiments

The present application provides, *inter alia*, a process for preparing a compound of Formula C, or a salt thereof, as set out, for example, in Scheme 1:

Scheme 1

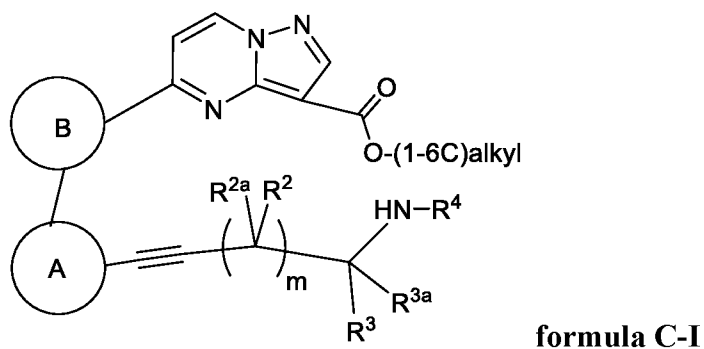


In some embodiments, provided herein is a process for preparing a compound of Formula C

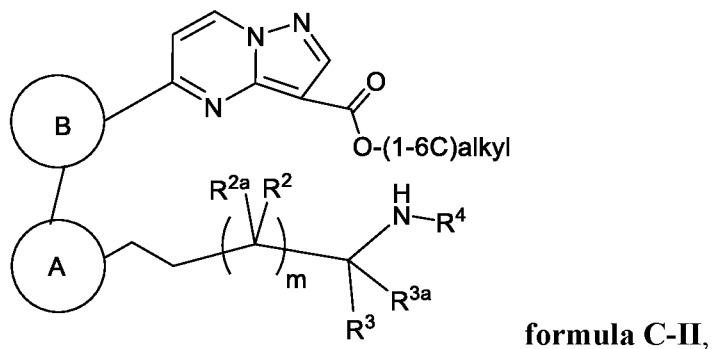


or a salt thereof, comprising:

- 5 a) treating a compound of formula C-I

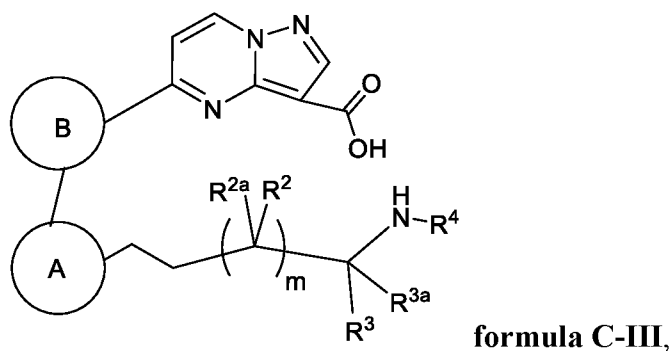


or a salt thereof, with a hydrogenation system to form a compound of formula C-II



or a salt thereof;

- 10 b) treating the compound of formula C-II or a salt thereof with a first strong base to form a compound of formula C-III

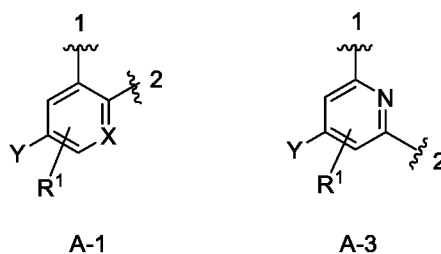


or a salt thereof; and

- c) cyclizing the compound of formula **C-III** or a salt thereof with a coupling agent to form the compound of **Formula C** or a salt thereof;

5 wherein:

ring A is selected from rings A-1 and A-3 having the structures:



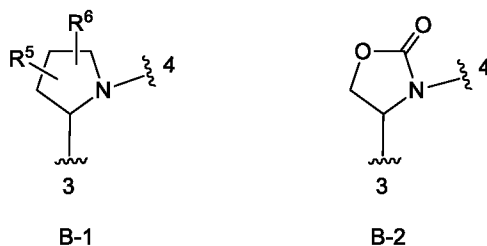
10 wherein the wavy line labeled 1 indicates the point of attachment of ring A to ring B and the wavy line labeled 2 indicates the point of attachment of ring A to the carbon atom of the ethylene linker in formulae **C**, **C-II** or **C-III**, or to the carbon atom of the alkyne linker in formula **C-I**;

X is N or CH;

Y is H or F;

R¹ is H, (1-3C)alkyl, (1-3C)alkoxy or halogen;

15 ring B is selected from rings B-1 and B-2 having the structures:



wherein the wavy line labeled 3 indicates the point of attachment to ring A and the wavy line labeled 4 indicates the point of attachment to the pyrazolo[1,5-a]pyrimidine ring;

R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH, provided that R^2 and R^{2a} are not both OH;

m is 0, 1 or 2;

R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

R^4 is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl); and

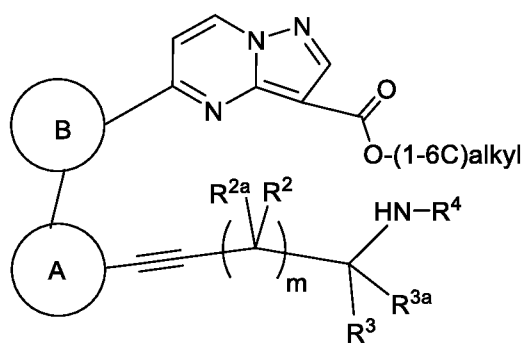
R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

In some embodiments, provided herein is a process for preparing a compound of Formula C, or a salt thereof, comprising cyclizing the compound of formula C-III, or a salt thereof, with a coupling agent to form the compound of Formula C, or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula C-III, or a salt thereof, comprising treating the compound of formula C-II, or a salt thereof, with a first strong base to form a compound of formula C-III, or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula C-II, or a salt thereof, comprising treating a compound of formula C-I, or a salt thereof, with a hydrogenation system to form a compound of formula C-II, or a salt thereof.

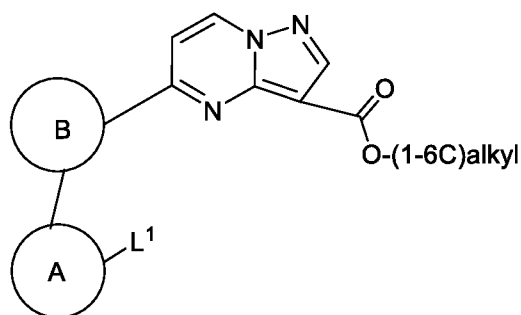
In some embodiments, the process for preparing a compound of formula C, or a salt thereof, further comprises preparing the compound of formula C-I



formula C-I,

or a salt thereof, by a process comprising:

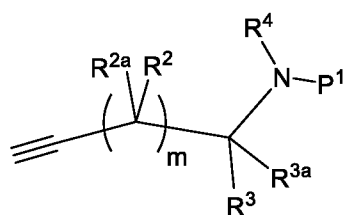
a) coupling the compound of formula C-VI



formula C-VI,

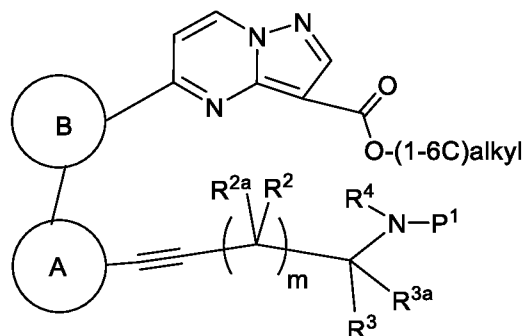
or a salt thereof;

with a compound of formula D



formula D,

- 5 or a salt thereof, in the presence of a catalyst comprising palladium and a catalyst comprising copper to form the compound of formula C-VII



formula C-VII,

or a salt thereof; and

- 10 b) deprotecting the compound of formula C-VII to obtain the compound of formula C-I or a salt thereof;

wherein:

P¹ is an amino-protecting group; and

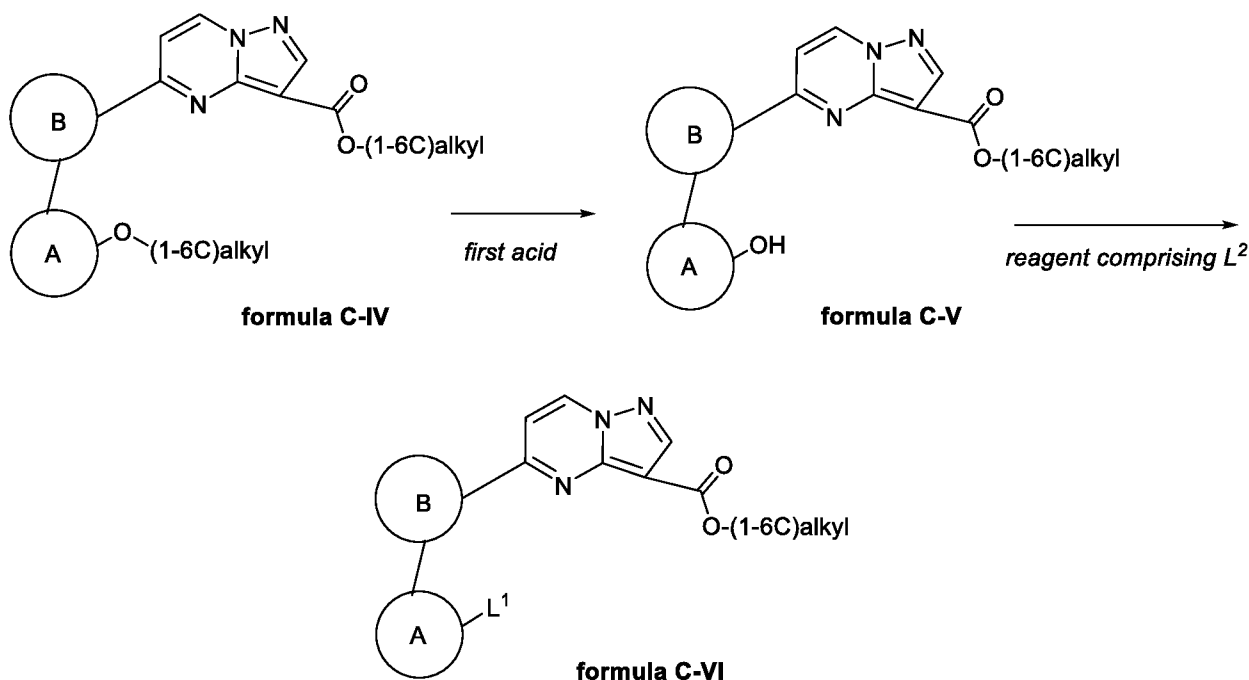
L¹ is a leaving group.

- 15 In some embodiments, provided herein is a process for preparing a compound of formula C-I, or a salt thereof, comprising deprotecting the compound of formula C-VII, or a salt thereof, to form a compound of formula C-I, or a salt thereof.

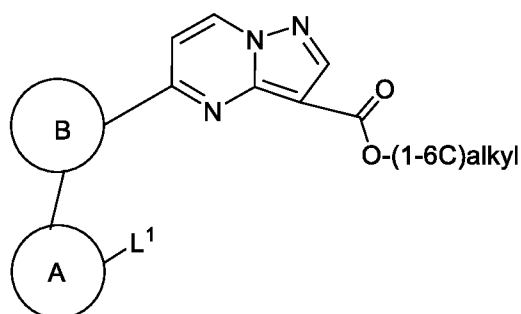
In some embodiments, provided herein is a process for preparing a compound of formula **C-VII**, or a salt thereof, comprising coupling a compound of formula **C-VI**, or a salt thereof, with a compound of formula **D** or a salt thereof, in the presence of a catalyst comprising palladium and a catalyst comprising copper to form the compound of formula **C-VII**, or a salt thereof.

In some embodiments, the compound of formula **C-VI**, or salt thereof, may be prepared as set out in Scheme 1a:

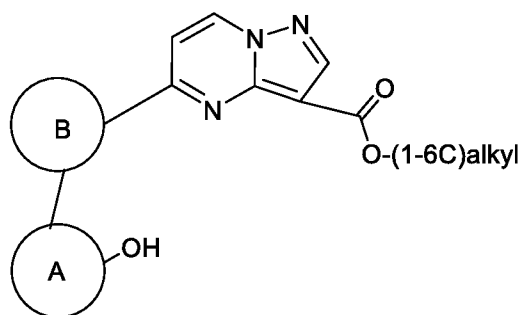
Scheme 1a



In some embodiments, provided herein is a process for preparing a compound of formula **C-VI**

formula **C-VI**,

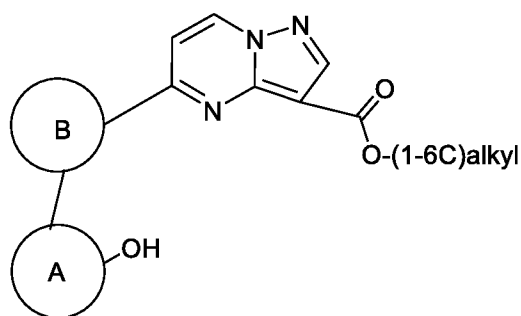
or a salt thereof, comprising treating the compound of formula **C-V**

**formula C-V,**

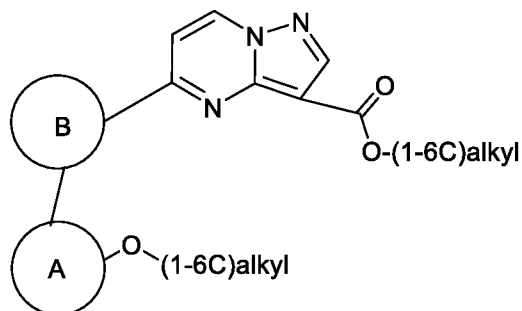
or a salt thereof, with a reagent comprising a group L^2 to form a compound of formula **C-VI**, wherein L^2 is a group that, when bonded to an oxygen atom, forms a leaving group L^1 .

- 5 For example, when the leaving group L^1 is trifluoromethanesulfonate (triflate), the group L^2 is trifluoromethanesulfonyl (triflyl); when the leaving group L^1 is tosylate, the group L^2 is tosyl; when the leaving group L^1 is mesylate, the group L^2 is mesyl; or when the leaving group L^1 is nosylate, the group L^2 is nosyl. In some more particular embodiments, the reagent comprising a group L^2 has a formula $L^2\text{-Hal}$, wherein Hal is a
- 10 halogen (e.g., Cl, Br or I). In some more particular embodiments, the reagent comprising a group L^2 has a formula $L^2\text{-O-}L^2$. In some embodiments, the reagent comprising a group L^2 is a reagent comprising a $\text{-S(O}_2\text{)LG}$ moiety, wherein LG is a leaving group such as a halogen or a $\text{OS(O}_2\text{)-alkyl}$ or $\text{OS(O}_2\text{)-aryl}$ group. In some embodiments, the reagent comprising a group L^2 is a sulfonic anhydride, such as trifluoromethanesulfonic
- 15 anhydride, trifluoromethanesulfonyl chloride, tosyl chloride, mesyl chloride or nosyl chloride. In some embodiments, the reagent comprising a group L^2 is a sulfonimide, such as N-Phenyl-bis(trifluoromethanesulfonimide).

In some embodiments, provided herein is a process for preparing a compound of formula **C-V**

**formula C-V,**

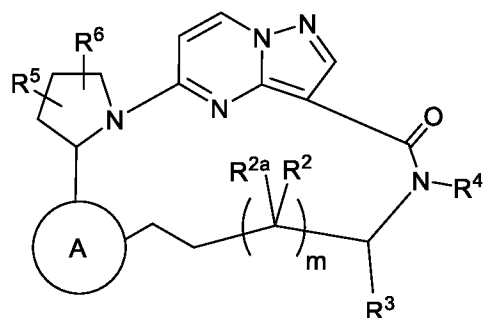
or a salt thereof, comprising treating a compound of formula **C-IV**



formula C-IV,

or a salt thereof, with a first acid to form a compound of formula **C-V**.

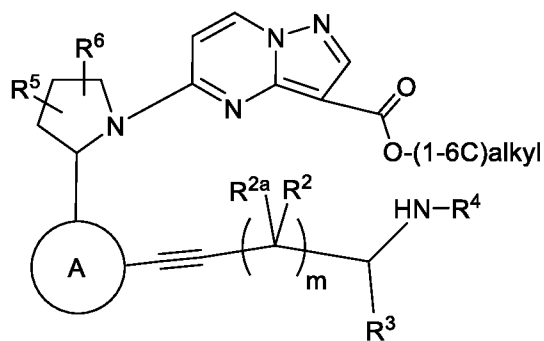
In some embodiments, the compound of Formula **C** has formula **Ca**:



formula Ca,

or a salt thereof;

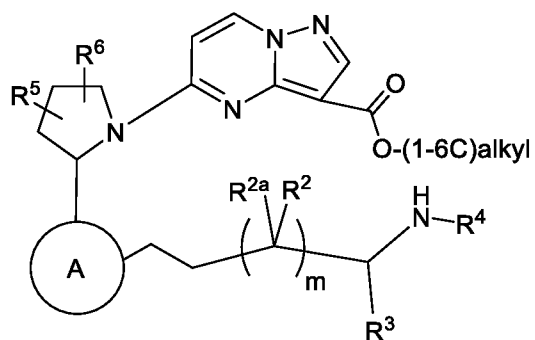
the compound of formula **C-I** has formula **C-Ia**



formula C-Ia,

or a salt thereof;

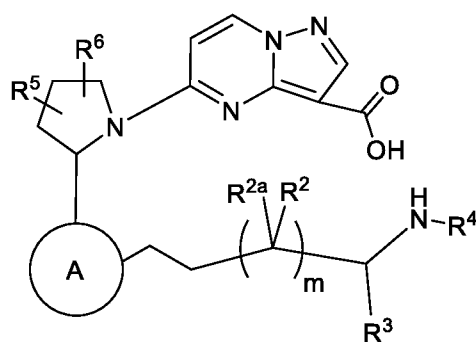
the compound of formula **C-II** has formula **C-IIa**



formula C-IIa,

or a salt thereof; and

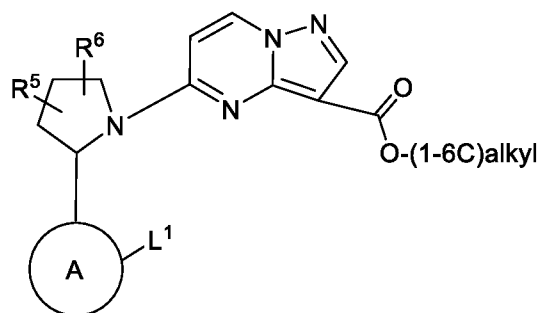
the compound of formula C-III has formula C-IIIa:



formula C-IIIa,

5 or a salt thereof.

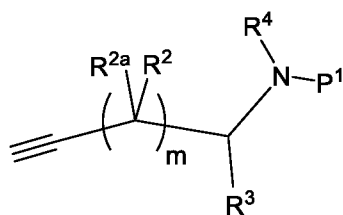
In some embodiments, the compound of formula C-VI has formula C-VIa



formula C-VIa,

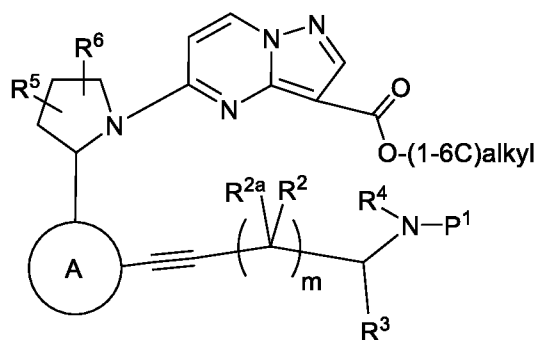
or a salt thereof;

the compound of formula D has formula D-1



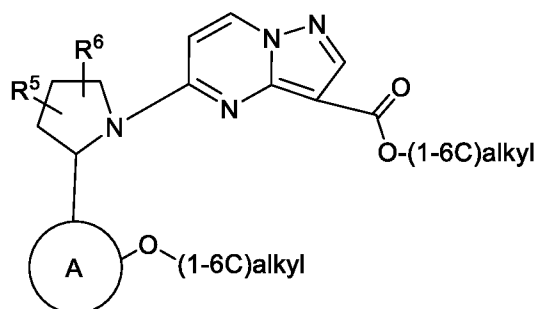
formula D-1

the compound of formula C-VII has formula C-VIIa

**formula C-VIIa,**

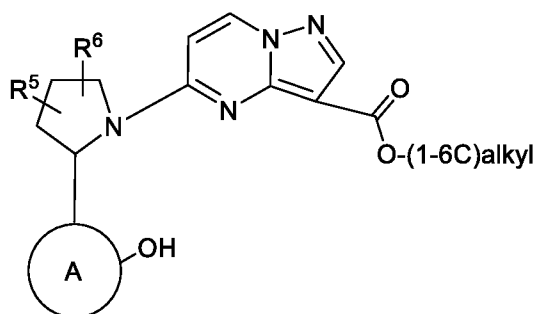
or a salt thereof.

In some embodiments, the compound of formula **C-IV** has formula **C-IVa**

**formula C-IVa,**

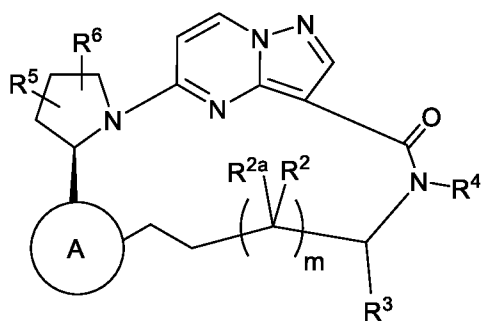
5 or a salt thereof; and

the compound of formula **C-V** has formula **C-Va**

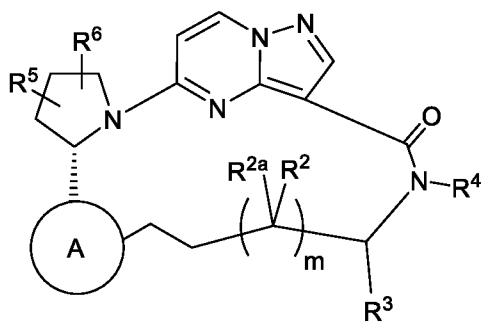
**formula C-Va,**

or a salt thereof;

In some embodiments, the compound of formula **C** has formula **Cb**

**formula Cb,**

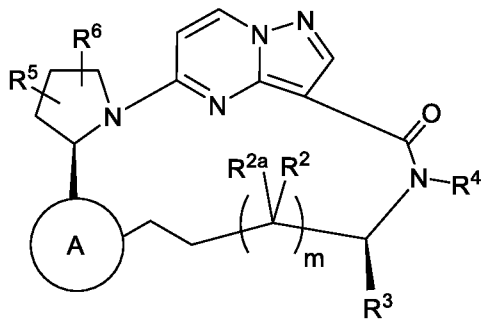
In some embodiments, the compound of formula **C** has formula **Cc**

**formula Cc,**

or a salt thereof.

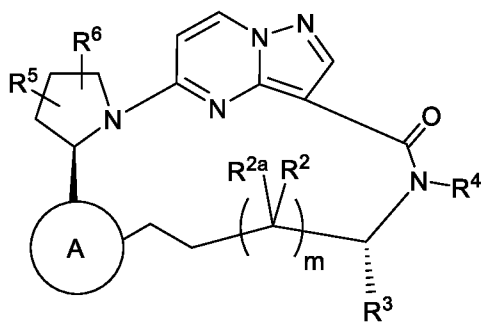
5

In some embodiments, the compound of formula **C** has formula **Cd**

**formula Cd,**

or a salt thereof.

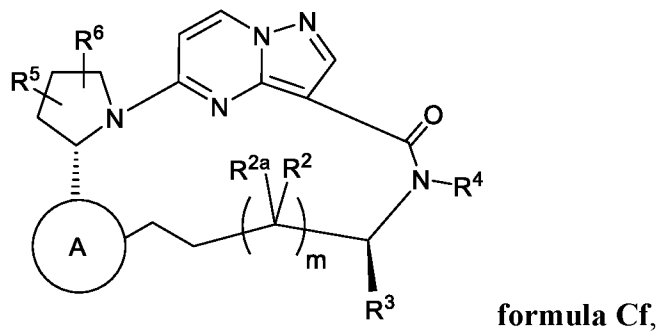
In some embodiments, the compound of formula **C** has formula **Ce**

**formula Ce,**

10

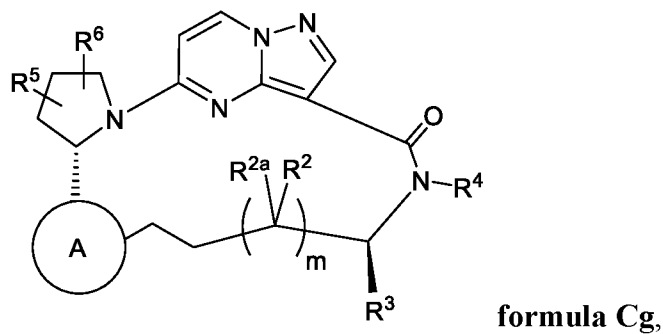
or a salt thereof.

In some embodiments, the compound of formula **C** has formula **Cf**



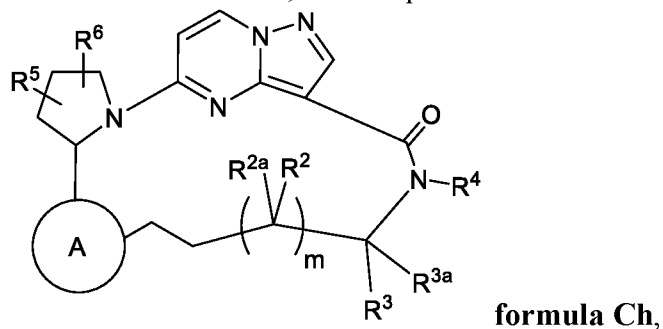
or a salt thereof.

In some embodiments, the compound of formula **C** has formula **Cg**



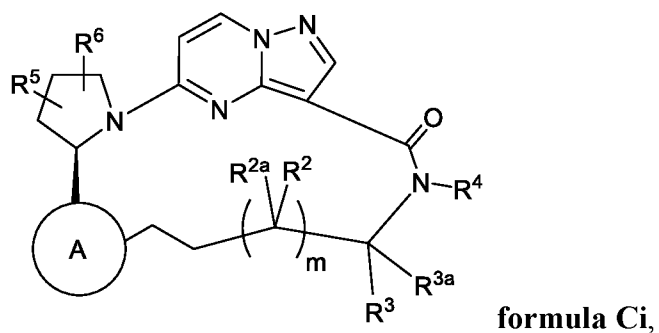
or a salt thereof.

In some embodiments, the compound of formula **C** has formula **Ch**



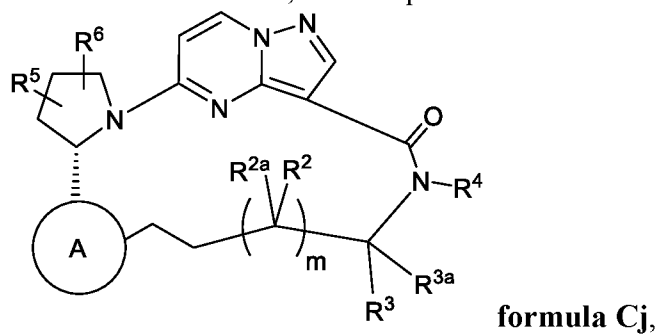
or a salt thereof.

In some embodiments, the compound of formula **C** has formula **Ci**



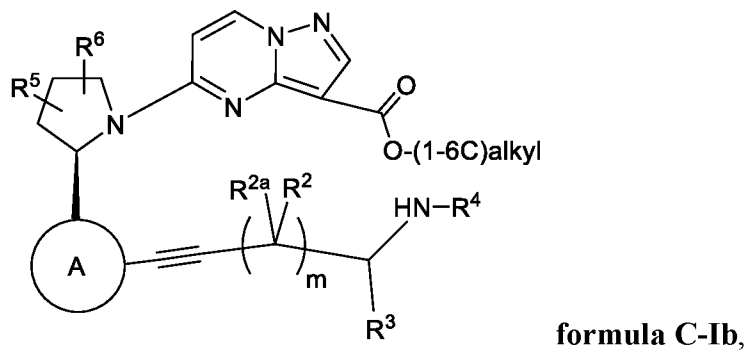
or a salt thereof.

In some embodiments, the compound of formula C has formula Cj



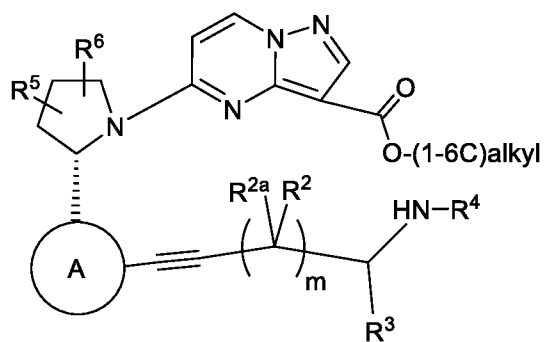
5 or a salt thereof.

In some embodiments, the compound of formula C-I has formula C-Ib



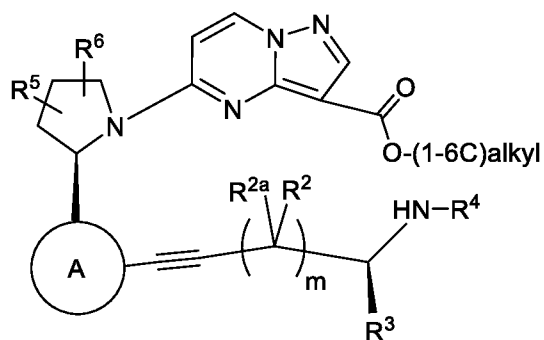
or a salt thereof.

In some embodiments, the compound of formula C-I has formula C-Ic

**formula C-Ic,**

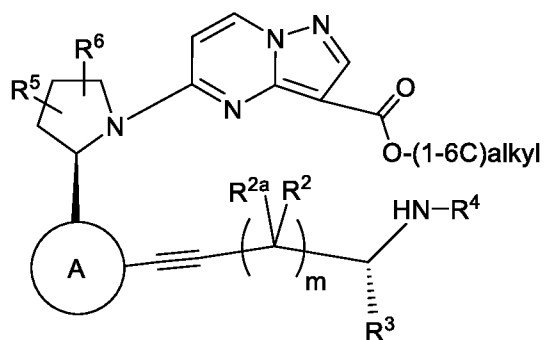
or a salt thereof.

In some embodiments, the compound of formula **C-I** has formula **C-Id**

**formula C-Id,**

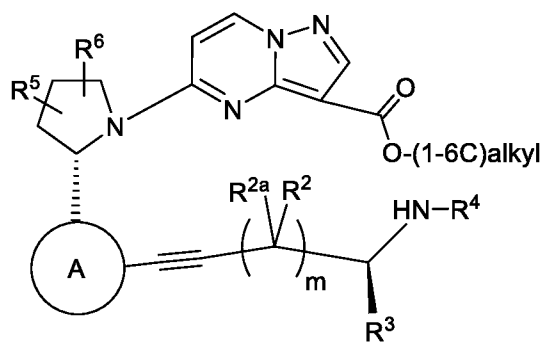
5 or a salt thereof.

In some embodiments, the compound of formula **C-I** has formula **C-Ie**

**formula C-Ie,**

or a salt thereof.

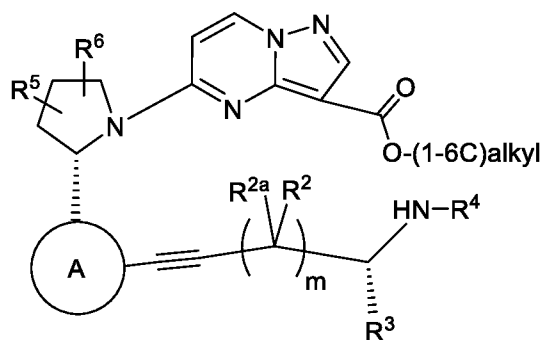
In some embodiments, the compound of formula **C-I** has formula **C-If**



formula C-Ig,

or a salt thereof.

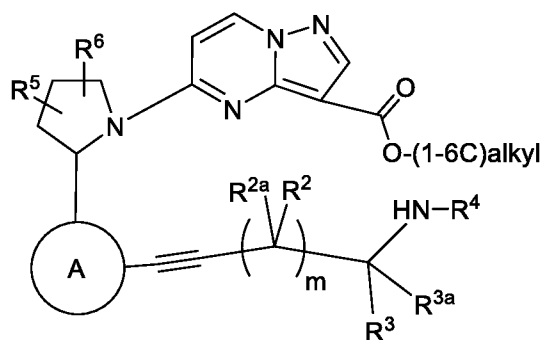
In some embodiments, the compound of formula C-I has formula C-Ig



formula C-Ih,

5 or a salt thereof.

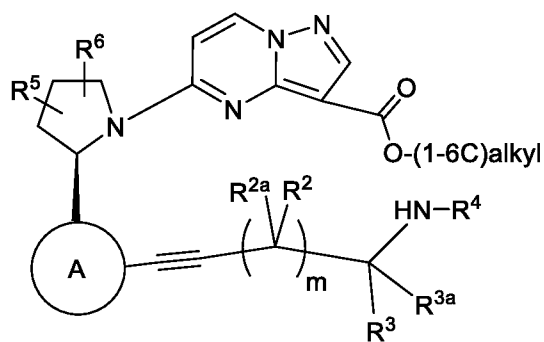
In some embodiments, the compound of formula C-I has formula C-Ih



formula C-Ii,

or a salt thereof.

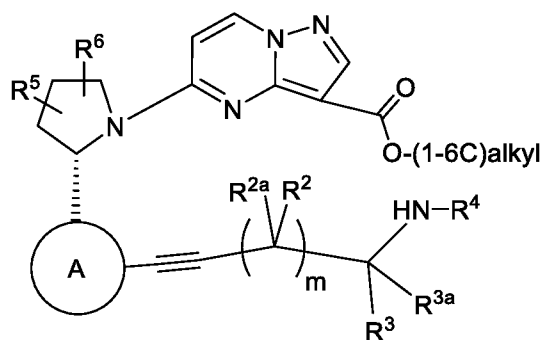
In some embodiments, the compound of formula C-I has formula C-Ii



formula C-Ii,

or a salt thereof.

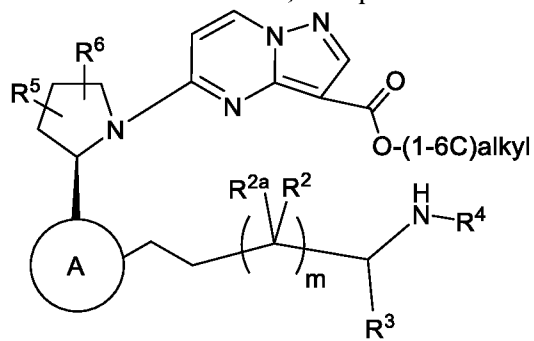
In some embodiments, the compound of formula C-I has formula C-Ij



formula C-Ij,

5 or a salt thereof.

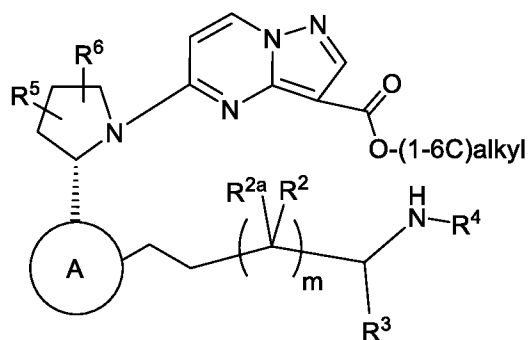
In some embodiments, compound of formula C-II has formula C-IIb



formula C-IIb,

or a salt thereof.

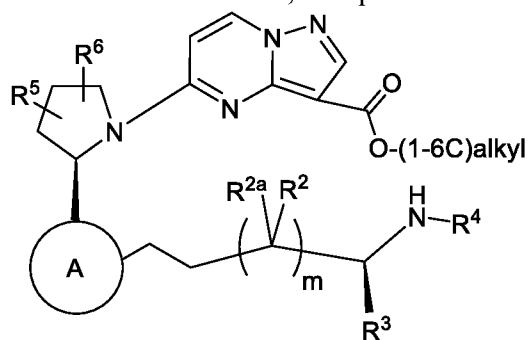
In some embodiments, compound of formula C-II has formula C-IIc



formula C-IIc,

or a salt thereof.

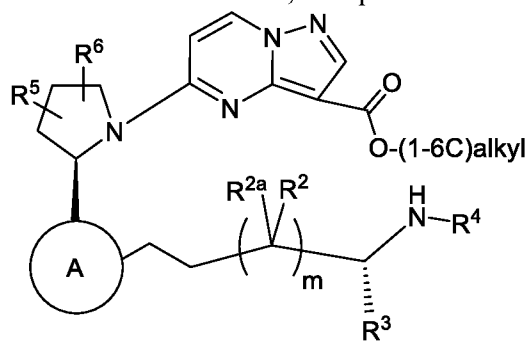
In some embodiments, compound of formula C-II has formula C-IIId



formula C-IIId,

5 or a salt thereof.

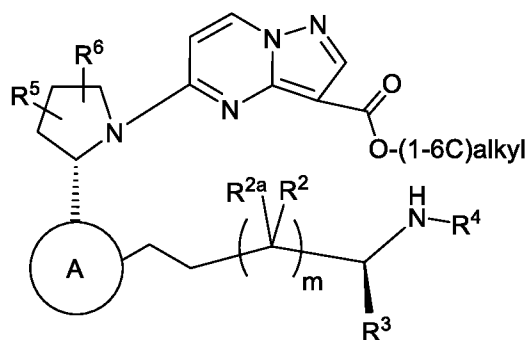
In some embodiments, compound of formula C-II has formula C-IIe



formula C-IIe,

or a salt thereof.

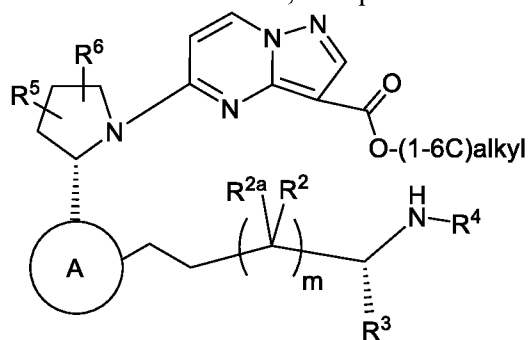
In some embodiments, compound of formula C-II has formula C-IIIf



formula C-IIe,

or a salt thereof.

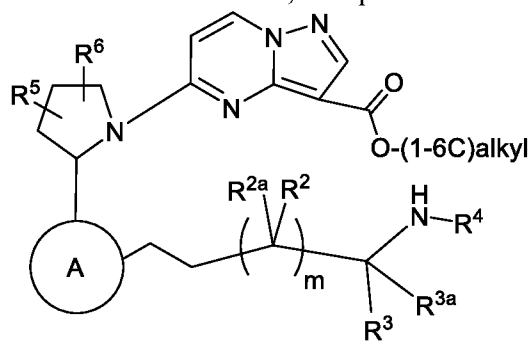
In some embodiments, compound of formula C-II has formula C-IIg



formula C-IIg,

5 or a salt thereof.

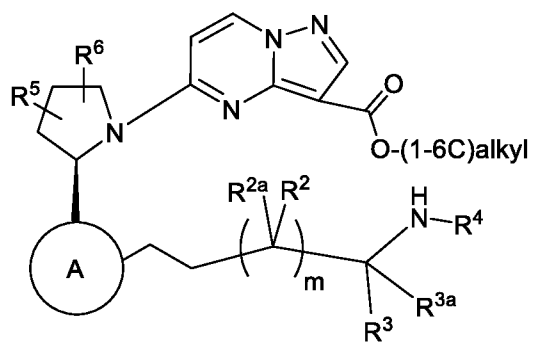
In some embodiments, compound of formula C-II has formula C-IIh



formula C-IIh,

or a salt thereof.

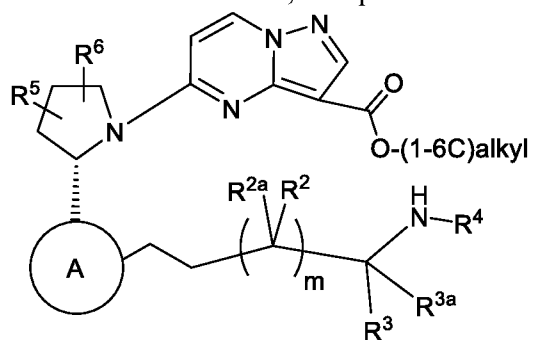
In some embodiments, compound of formula C-II has formula C-IIi



formula C-IIIi,

or a salt thereof.

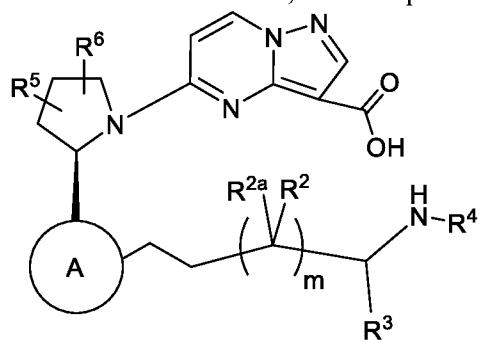
In some embodiments, compound of formula C-II has formula C-IIj



formula C-IIj,

5 or a salt thereof.

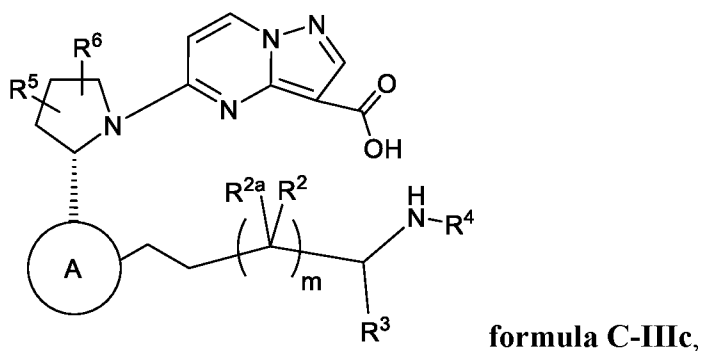
In some embodiments, the compound of formula C-III has formula C-IIIb:



formula C-IIIb,

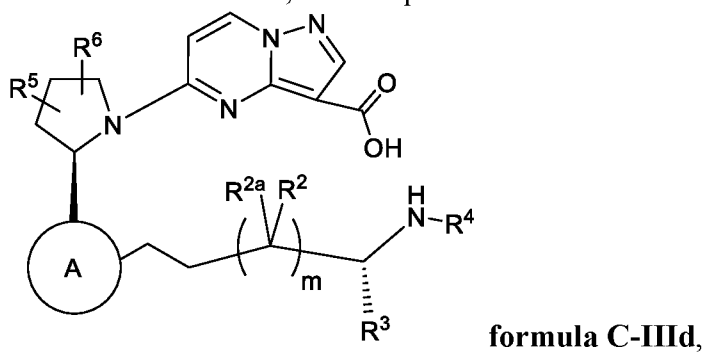
or a salt thereof.

In some embodiments, the compound of formula C-III has formula C-IIIc:



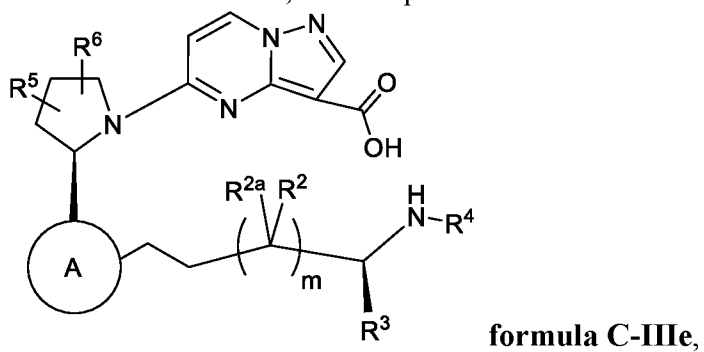
or a salt thereof.

In some embodiments, the compound of formula **C-III** has formula **C-IIIId**:



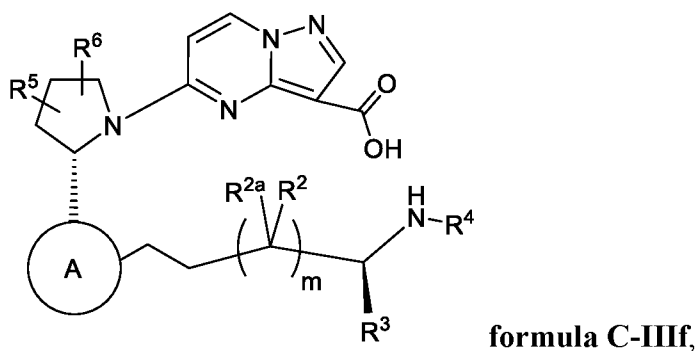
5 or a salt thereof.

In some embodiments, the compound of formula **C-III** has formula **C-IIIf**:



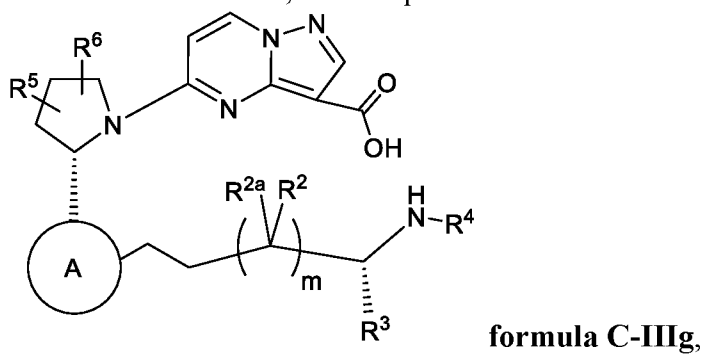
or a salt thereof.

In some embodiments, the compound of formula **C-III** has formula **C-IIIf**:



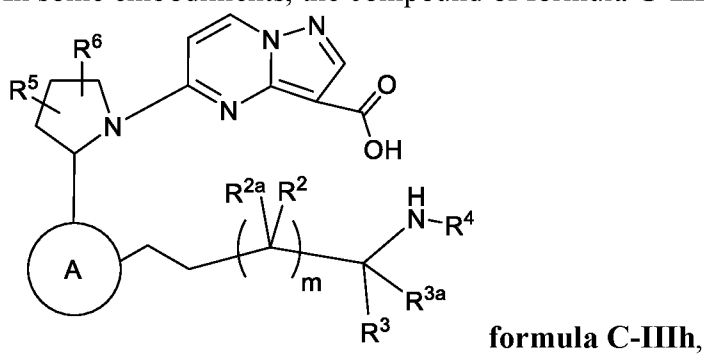
or a salt thereof.

In some embodiments, the compound of formula **C-III** has formula **C-IIIg**:



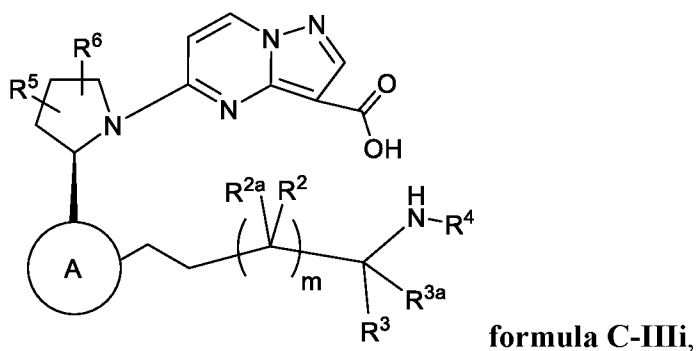
5 or a salt thereof.

In some embodiments, the compound of formula **C-III** has formula **C-IIIh**:



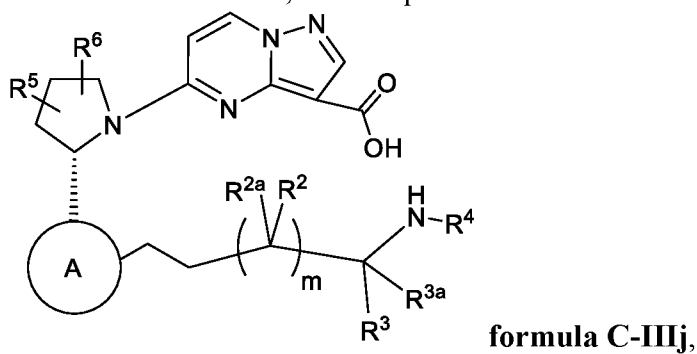
or a salt thereof.

In some embodiments, the compound of formula **C-III** has formula **C-IIIi**:



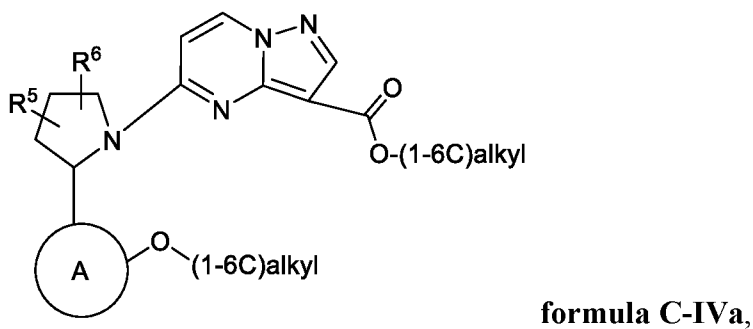
or a salt thereof.

In some embodiments, the compound of formula **C-III** has formula **C-IIIj**:



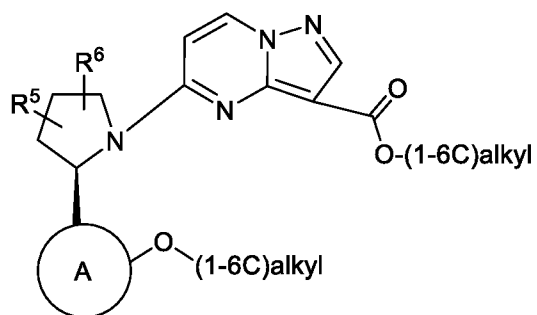
5 or a salt thereof.

In some embodiments, the compound of formula **C-IV** has formula **C-IVa**



or a salt thereof.

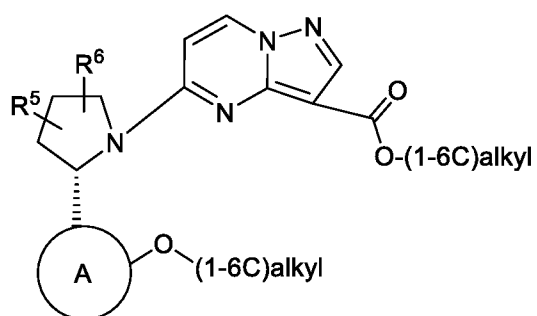
In some embodiments, the compound of formula **C-IV** has formula **C-IVb**



formula C-IVb,

or a salt thereof.

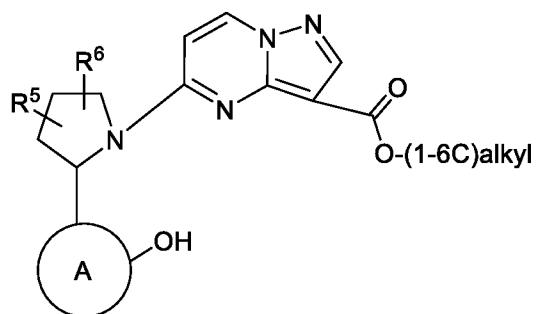
In some embodiments, the compound of formula C-IV has formula C-IVc



formula C-IVc,

5 or a salt thereof.

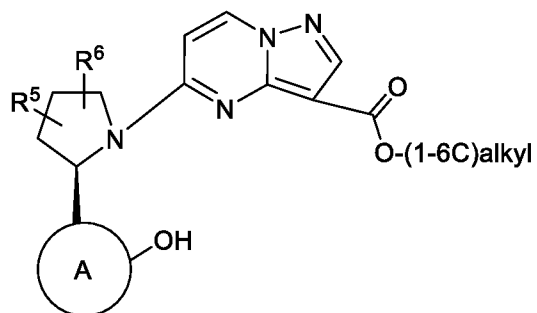
In some embodiments, the compound of formula C-V has formula C-Va



formula C-Va,

or a salt thereof.

In some embodiments, the compound of formula C-V has formula C-Vb

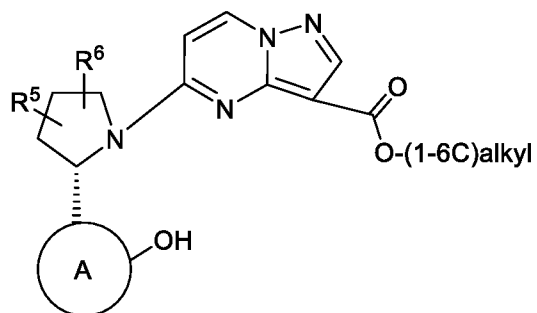


formula C-Vb,

10

or a salt thereof.

In some embodiments, the compound of formula **C-V** has formula **C-Vc**

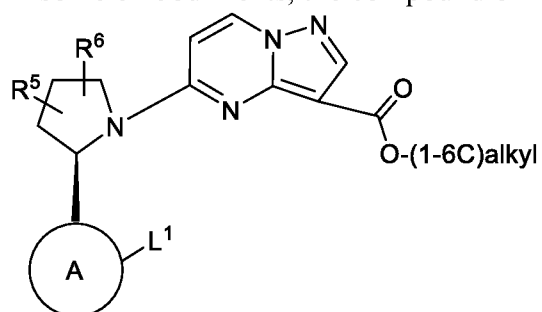


formula C-Vc,

or a salt thereof.

5

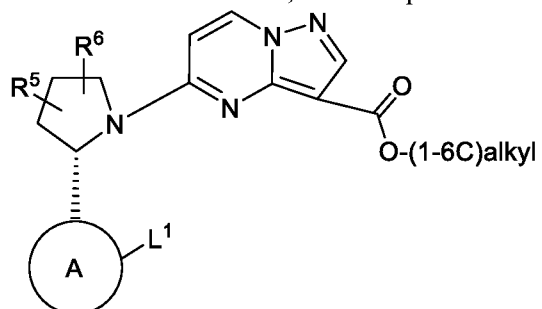
In some embodiments, the compound of formula **C-VI** has formula **C-VIb**



formula C-VIb,

or a salt thereof.

In some embodiments, the compound of formula **C-VI** has formula **C-VIc**

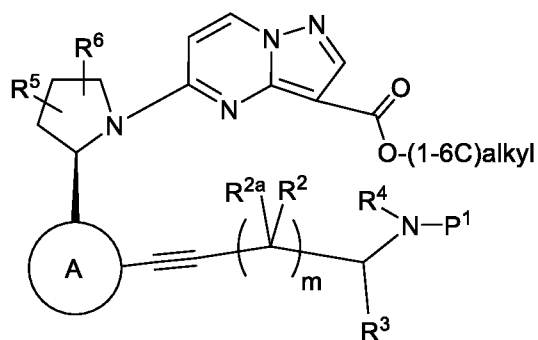


formula C-VIc,

10

or a salt thereof.

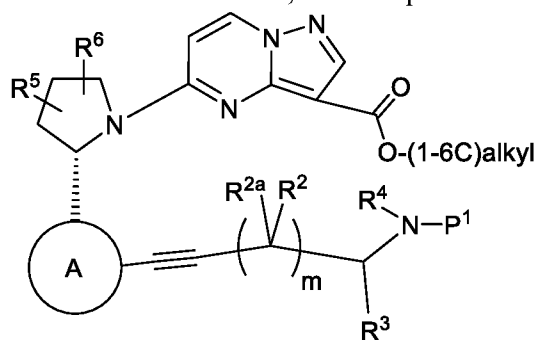
In some embodiments, the compound of formula **C-VII** has formula **C-VIIb**



formula C-VIIIb,

or a salt thereof

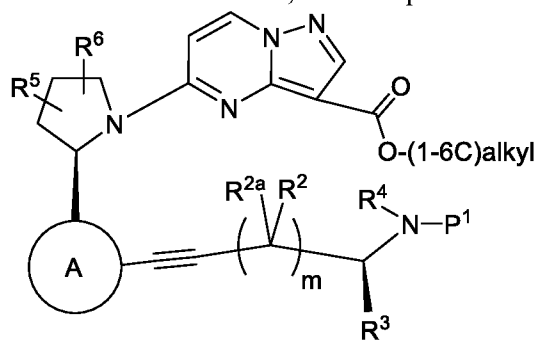
In some embodiments, the compound of formula C-VII has formula C-VIIIc



formula C-VIIIc,

5 or a salt thereof.

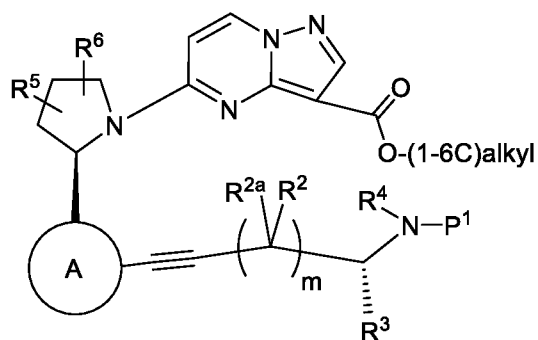
In some embodiments, the compound of formula C-VII has formula C-VIIId



formula C-VIIId,

or a salt thereof.

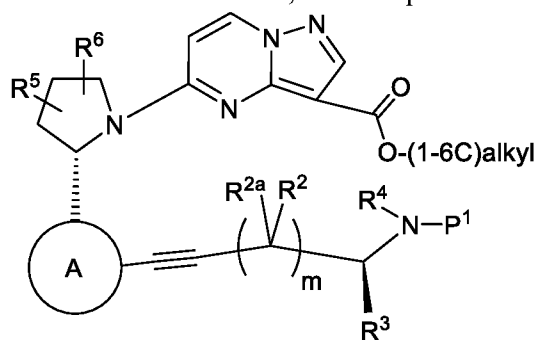
In some embodiments, the compound of formula C-VII has formula C-VIIIe



formula C-VIIe,

or a salt thereof.

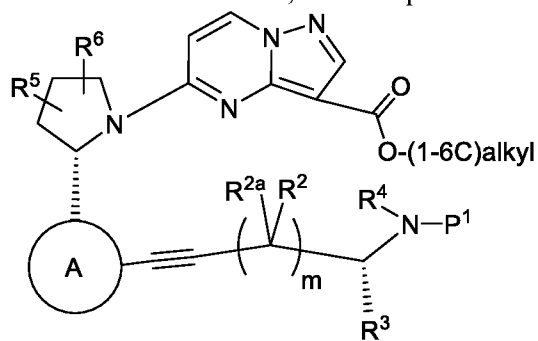
In some embodiments, the compound of formula C-VII has formula C-VIIIf



formula C-VIIIf,

5 or a salt thereof.

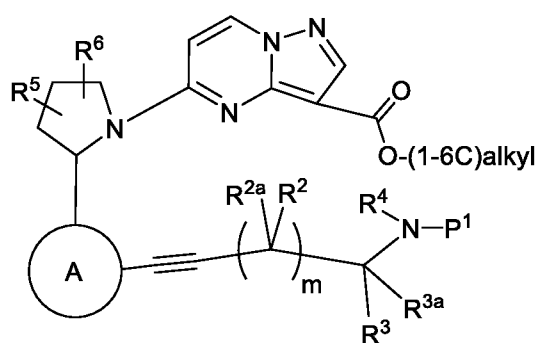
In some embodiments, the compound of formula C-VII has formula C-VIIg



formula C-VIIg,

or a salt thereof.

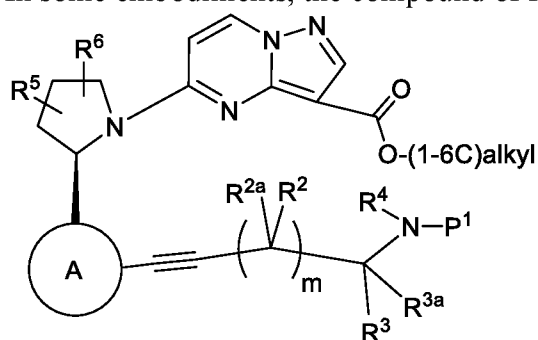
In some embodiments, the compound of formula C-VII has formula C-VIIh



formula C-VIIIh,

or a salt thereof.

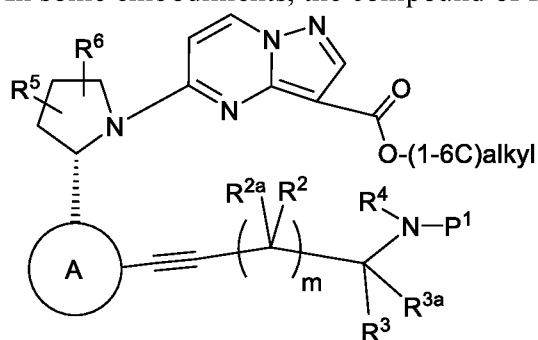
In some embodiments, the compound of formula C-VII has formula C-VIIIi



formula C-VIIIi,

5 or a salt thereof.

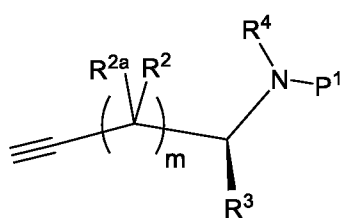
In some embodiments, the compound of formula C-VII has formula C-VIIIj



formula C-VIIIj,

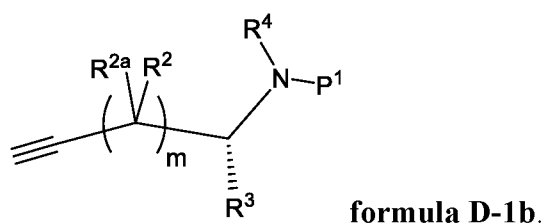
or a salt thereof.

In some embodiments, the compound of formula D-1 has formula D-1a

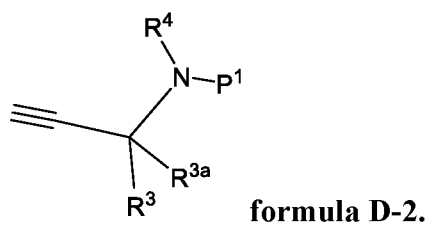


formula D-1a.

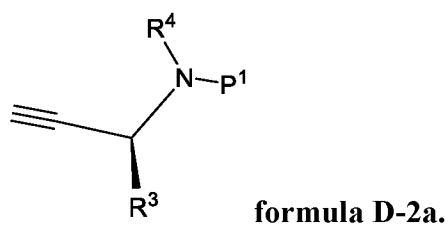
In some embodiments, the compound of formula D-1 has formula D-1b



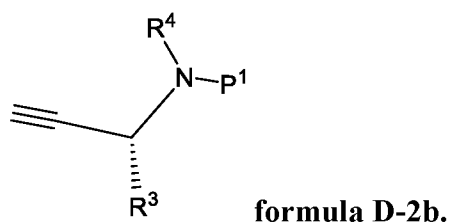
In some embodiments, the compound of formula **D** has formula **D-2**



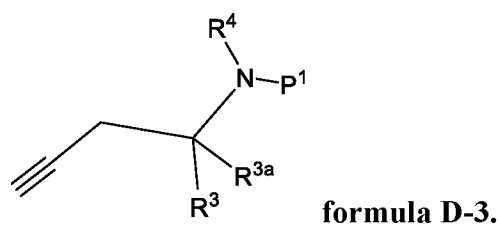
In some embodiments, the compound of formula **D-2** has formula **D-2a**



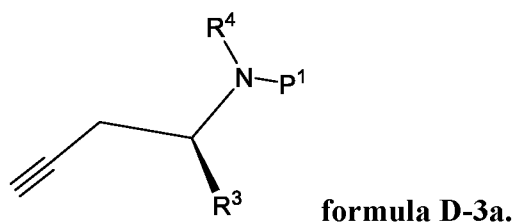
In some embodiments, the compound of formula **D-2** has formula **D-2b**



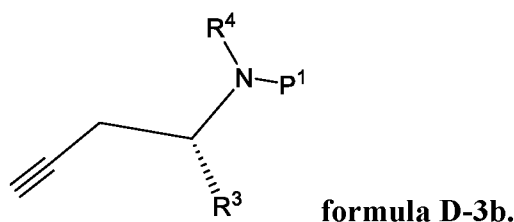
In some embodiments, the compound of formula **D** has formula **D-3**



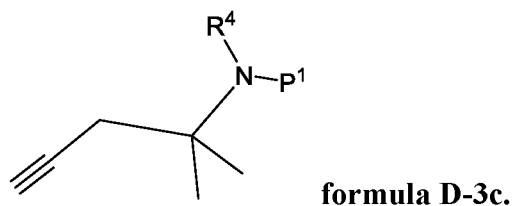
In some embodiments, the compound of formula **D-3** has formula **D-3a**



In some embodiments, the compound of formula **D-3** has formula **D-3b**

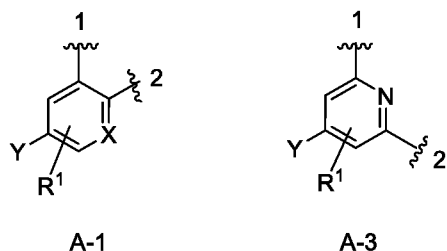


In some embodiments, the compound of formula **D-3** has formula **D-3c**



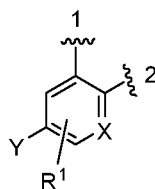
5

In any one of the formulae disclosed herein, ring A is selected from rings A-1 and A-3 having the structures:



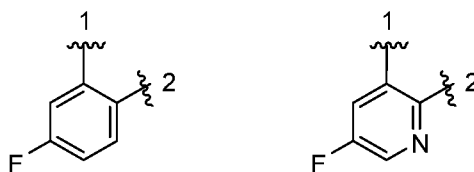
10 wherein in the ring of formulae A-1 or A-3 the wavy line labeled 1 indicates the point of attachment of ring A to ring B (e.g., the pyrrolidine ring), and the wavy line labeled 2 indicates the point of attachment of ring A to either i) the aliphatic chain connecting ring A to the NR⁴ nitrogen, ii) OH, iii) O-(1-6C) alkyl, iv) L¹, or v) OL².

In some embodiments, ring A is ring A-1 having the structure

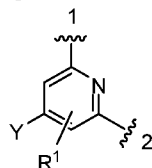


A-1

In some embodiments, X is CH. In other embodiments, X is N. In particular embodiments, ring A when represented by structure A-1 include the structures:



In some embodiments, ring A is ring A-3 having the structure



A-3

In any one of the embodiments of ring A, Y is H. In some embodiments, Y is halogen. For example, Y is Cl, F or Br. In some embodiments, Y is F. In any one of the embodiments of ring A, R¹ is H. In some embodiments, R¹ is (1-3C)alkyl or (1-3C)alkoxy. In one embodiment, R¹ is (1-3C)alkoxy. A particular example is methoxy. In one embodiment, R¹ is (1-3C)alkyl. A particular example is methyl. In some embodiments, R¹ is halogen. In one embodiment, R¹ is F.

In some embodiments of any one of the formulae disclosed herein, R⁴ is H. In some embodiments, R⁴ is (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl). In one embodiment, R⁴ is (1-6C)alkyl. Examples include methyl, ethyl, propyl, isopropyl, butyl, and isobutyl. In one embodiment, R⁴ is fluoro(1-6C)alkyl. Examples include fluoromethyl and 2-fluoroethyl. In one embodiment, R⁴ is difluoro(1-6C)alkyl. Example include difluoromethyl and 2,2-difluoroethyl. In one embodiment, R⁴ is trifluoro(1-6C)alkyl. Examples include trifluoromethyl and 2,2,2-trifluoroethyl. In one embodiment, R⁴ is hydroxy(1-6C alkyl). Examples include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl and 3-hydroxypropyl. In one embodiment, R⁴ is dihydroxy(2-6C alkyl).

An example includes 2,3-dihydroxypropyl. In one embodiment, R^4 is H or (1-6C)alkyl. In one embodiment, R^4 is H or methyl.

In some embodiments of any one of the formulae disclosed herein, R^2 and R^{2a} are independently H, F, methyl or OH, provided that R^2 and R^{2a} are not both OH. In some
5 embodiments, R^2 and R^{2a} are each hydrogen. In some embodiments, R^2 and R^{2a} are each fluoro. In some embodiments, R^2 is hydrogen and R^{2a} is fluoro. In some embodiments, R^2 is hydrogen and R^{2a} is OH. In some embodiments, R^2 is H and R^{2a} is (1-6C)alkyl. In some embodiments, R^2 is H and R^{2a} is methyl. In some embodiments, R^2 and R^{2a} are both (1-6 C) alkyl. In some embodiments, R^2 and R^{2a} are both methyl.

10 In some embodiments of any one of the formulae disclosed herein, R^3 and R^{3a} are independently H, (1-3C)alkyl or hydroxy(1-3 C)alkyl. In one embodiment, R^{3a} is H. In one embodiment, R^3 is H. In some embodiments, R^{3a} is H and R^3 is H. In one embodiment, R^{3a} is (1-3C)alkyl. Examples include methyl, ethyl, propyl and isopropyl. In one embodiment, R^3 is (1-3C)alkyl. Examples include methyl, ethyl, propyl and
15 isopropyl. In some embodiments, R^{3a} is H, and R^3 is (1-3 C)alkyl or hydroxy(1-3 C)alkyl. In one embodiment, R^{3a} is (1-3C)alkyl and R^3 is H. In one embodiment, R^{3a} is methyl and R^3 is H. In one embodiment, R^3 is hydroxy(1-3C)alkyl. Examples include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, and 3-hydroxypropyl. In one embodiment, R^3 is hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, or 3-
20 hydroxypropyl and R^{3a} is H. In some embodiments, R^{3a} is H and R^3 is (1-3 C)alkyl. In some embodiments, R^{3a} is H and R^3 is methyl. In one embodiment, R^{3a} is (1-3C)alkyl and R^3 is H. In one embodiment, R^{3a} is methyl and R^3 is H. In some embodiments, R^{3a} and R^3 are both (1-3 C)alkyl. In some embodiments, R^3 and R^{3a} are both methyl.

25 In some embodiments, R^3 and R^{3a} are different, and the configuration of the carbon atom to which R^3 and R^{3a} are attached is (*S*). In other embodiments, R^3 and R^{3a} are different, and the configuration of the carbon atom to which R^3 and R^{3a} are attached is (*R*). In some aspects of these embodiments, when R^{3a} is hydrogen, R^3 is other than hydrogen and the configuration of the carbon atom to which R^3 is attached is (*S*). In other aspects of these embodiments, when R^{3a} is hydrogen, R^3 is other than hydrogen and the
30 configuration of the carbon atom to which R^3 is attached is (*R*).

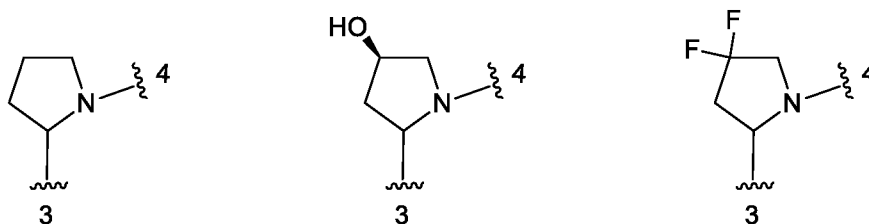
In some embodiments of any one of the formulae disclosed herein, R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl. In one embodiment, R^5 and R^6 are independently H, F, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl. In one embodiment, R^5 is H and R^6 is H, F, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl. In some

5 embodiments, R^5 and R^6 are independently H, F, OH, methyl, ethyl, HOCH₂- or HOCH₂CH₂-. In one embodiment, R^5 and R^6 are independently H, F, OH, (1-3C)alkyl or hydroxy(1-3C)alkyl. In one embodiment, R^5 is hydrogen and R^6 is H, F, OH, (1-3C)alkyl or hydroxy(1-3C)alkyl. In one embodiment, R^5 and R^6 are independently H, F, OH, methyl, ethyl, HOCH₂- or HOCH₂CH₂-. In one embodiment, R^5 is hydrogen and R^6 is H,

10 F, OH, methyl, ethyl, HOCH₂- or HOCH₂CH₂-. In one embodiment, R^5 and R^6 are independently H, F, or methyl. In one embodiment, R^5 is H and R^6 is H, F, or methyl. In one embodiment, R^5 is H and R^6 is F. In one embodiment, R^5 is H and R^6 is methyl. In one embodiment, R^5 and R^6 are both H. In one embodiment, R^5 and R^6 are both F. In one embodiment, R^5 and R^6 are both methyl. In some embodiments, R^5 is hydrogen. In some

15 embodiments, R^6 is hydrogen.

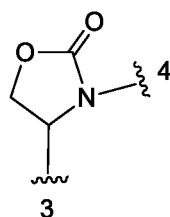
In some embodiments of formulae **C**, **C-I**, **C-II**, **C-III**, **C-IV**, **C-V**, **C-VI** and **C-VII**, ring B when represented by ring B-1 includes the structures:



wherein the wavy line labeled 3 indicates the point of attachment to ring A and the wavy

20 line labeled 4 indicates the point of attachment to the pyrazolo[1,5-a]pyrimidine ring.

In some embodiments of formulae **C**, **C-I**, **C-II**, **C-III**, **C-IV**, **C-V**, **C-VI** and **C-VII**, ring B is ring B-2 having the formula:



B-2

In some embodiments of any one of the formulae disclosed herein, m is 0, 1 or 2. In one embodiment, m is 0. In one embodiment, m is 1. In one embodiment, m is 2.

In some embodiments, one or more of C-VII, C-I, C-II and C-III are isolated after forming and prior to the respective following step in the process. In some embodiments, one or more of C-VII, C-I, C-II and C-III are not isolated after forming and prior to the respective following step in the process. In some embodiments, C-VII is not isolated after forming and prior to the following step in the process. In some embodiments, C-I is not isolated after forming and prior to the following step in the process. In some embodiments, C-II is not isolated after forming and prior to the following step in the process. In some embodiments, C-III is not isolated after forming after forming and prior to the following step in the process. In some embodiments, C-III is isolated after forming and prior to the following step in the process.

In some embodiments of any one of the formulae disclosed herein, L¹ is a leaving group selected from triflate, tosylate, mesylate, nosylate and a halogen. In some aspects of these embodiments, halogen is Cl, Br or I. In some embodiments, L¹ is a leaving group selected from triflate, tosylate, mesylate, and a halogen. In some embodiments, L¹ is triflate or mesylate. In one embodiment, L¹ is triflate. In some embodiments, L¹ is Cl or Br. In one embodiment, L¹ is Cl.

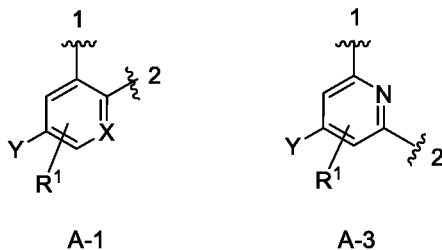
In some embodiments of any one of the formulae disclosed herein, P¹ is an amino-protecting group selected from methoxymethyl, methylthiomethyl, p-methoxybenzyloxymethyl, p-nitrobenzyloxymethyl, t-butoxymethyl, 2-methoxyethoxymethyl, 1-ethoxyethyl, allyl, p-methoxybenzyloxycarbonyl (Moz), p-nitrobenzyloxycarbonyl (PNZ), trimethylsilyl, diethylisopropylsilyl, triphenylsilyl, formyl, chloroacetyl, methanesulfonyl, tosyl, benzyloxysulfonyl, methoxymethylcarbonyl, benzyloxycarbonyl, carboxybenzyl (Cbz), t-butyloxycarbonyl (BOC), 9-fluorenylmethylcarbonyl, N-phenylcarbamoyl, and 4,4'-dimethoxytrityl.

In some embodiments, P¹ is an amino-protecting group selected from p-methoxybenzyloxymethyl, p-methoxybenzyloxycarbonyl, trimethylsilyl, diethylisopropylsilyl, triphenylsilyl, methanesulfonyl, tosyl, benzyloxycarbonyl, t-butyloxycarbonyl (BOC), 9-fluorenylmethylcarbonyl and 4,4'-dimethoxytrityl.

In some embodiments, P^1 is an amino-protecting group selected from *p*-methoxybenzyloxycarbonyl, trimethylsilyl, benzyloxycarbonyl and *t*-butyloxycarbonyl (BOC).

In one embodiment, P^1 is *t*-butyloxycarbonyl (BOC).

- 5 In some embodiments, in any one of the formulae disclosed herein, ring A is selected from rings A-1 and A-3 having the structures:



- 10 wherein in the ring of formulae A-1 or A-3 the wavy line labeled 1 indicates the point of attachment of ring A to ring B (e.g., the pyrrolidine ring), and the wavy line labeled 2 indicates the point of attachment of ring A to either i) the aliphatic chain connecting ring A to the NR^4 nitrogen, ii) OH, iii) O-(1-6C) alkyl, iv) L^1 , or v) OL^2 ;

X is N or CH;

Y is H or F;

R^1 is H, (1-6C)alkyl, (1-3C)alkoxy or halogen;

- 15 m is 0, 1 or 2;

R^2 and R^{2a} are independently H, F, or OH, provided that R^2 and R^{2a} are not both OH;

R^3 is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

R^{3a} (when present) is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

- 20 R^4 is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

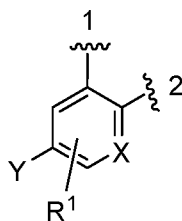
R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl;

L^1 (when present) is a leaving group selected from triflate, tosylate, mesylate, and a halogen; and

- 25 P^1 (when present) is an amino-protecting group selected from methoxybenzyloxymethyl, *p*-methoxybenzyloxycarbonyl, trimethylsilyl,

diethylisopropylsilyl, triphenylsilyl, methanesulfonyl, tosyl, benzyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 9-fluorenylmethylcarbonyl and 4,4'-dimethoxytrityl.

In some embodiments, in any one of the formulae disclosed herein, ring A is ring A-1 represented by the structure



A-1

wherein in the ring of formulae A-1 the wavy line labeled 1 indicates the point of attachment of ring A to ring B (e.g., the pyrrolidine ring), and the wavy line labeled 2 indicates the point of attachment of ring A to either i) the aliphatic chain connecting ring A to the NR⁴ nitrogen, ii) OH, iii) O-(1-6C) alkyl, iv) L¹, or v) OL²;

X is N or CH;

Y is H or F;

R¹ is H, (1-6C)alkyl, (1-3C)alkoxy or halogen;

m is 0, 1 or 2;

R² and R^{2a} are independently H, F, or OH, provided that R² and R^{2a} are not both

OH;

R³ is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

R^{3a} (when present) is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

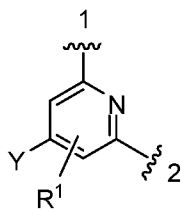
R⁴ is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

R⁵ and R⁶ are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl;

L¹ (when present) is a leaving group selected from triflate, tosylate, mesylate, and a halogen; and

P¹ (when present) is an amino-protecting group selected from methoxybenzyloxymethyl, *p*-methoxybenzyloxycarbonyl, trimethylsilyl, diethylisopropylsilyl, triphenylsilyl, methanesulfonyl, tosyl, benzyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 9-fluorenylmethylcarbonyl and 4,4'-dimethoxytrityl.

In some embodiments, in any one of the formulae disclosed herein, ring A is ring A-3 represented by the structure



A-3

wherein in the ring of formulae A-3 the wavy line labeled 1 indicates the point of attachment of ring A to ring B (e.g., the pyrrolidine ring), and the wavy line labeled 2 indicates the point of attachment of ring A to either i) the aliphatic chain connecting ring A to the NR⁴ nitrogen, ii) OH, iii) O-(1-6C) alkyl, iv) L¹, or v) OL²;

Y is H or F;

R¹ is H, (1-6C)alkyl, (1-3C)alkoxy or halogen;

R² and R^{2a} are independently H, F, or OH, provided that R² and R^{2a} are not both OH;

R³ is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

R^{3a} (when present) is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

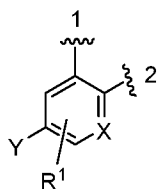
R⁴ is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

R⁵ and R⁶ are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl;

L¹ (when present) is a leaving group selected from triflate, tosylate, mesylate, and a halogen; and

P¹ (when present) is an amino-protecting group selected from methoxybenzyloxymethyl, *p*-methoxybenzyloxycarbonyl, trimethylsilyl, diethylisopropylsilyl, triphenylsilyl, methanesulfonyl, tosyl, benzyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 9-fluorenylmethylcarbonyl and 4,4'-dimethoxytrityl.

In some embodiments, in any one of the formulae disclosed herein, ring A is ring A-1 having the structure



A-1 ;

X is N;

Y is H or F;

R¹ is H or (1-6C)alkyl;

5 R⁴ is H or (1-6C)alkyl;

m is 0;

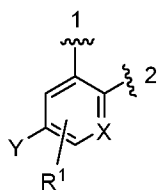
R^{3a} (when present) is H and R³ is H;

R⁵ and R⁶ are each independently H or (1-6C)alkyl;

L¹ (when present) is a triflate leaving group; and

10 P¹ (when present) is a *t*-butyloxycarbonyl (BOC) amino-protecting group.

In some embodiments, in any one of the formulae disclosed herein, ring A is ring A-1 having the structure



A-1 ;

X is CH or N;

15 Y is H or F;

R¹ is H or (1-6C)alkyl;

R⁴ is H or (1-6C)alkyl;

m is 0;

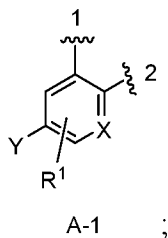
R^{3a} (when present) is H and R³ is (1-3 C)alkyl;

20 R⁵ and R⁶ are each independently H or (1-6C)alkyl;

L¹ (when present) is a triflate leaving group; and

P¹ (when present) is a *t*-butyloxycarbonyl (BOC) amino-protecting group.

In some embodiments, in any one of the formulae disclosed herein, ring A is ring A-1 having the structure



X is CH or N;

5 Y is H or F;

R^1 is H or (1-6C)alkyl;

R^4 is H or (1-6C)alkyl;

m is 0;

R^{3a} is present, and R^{3a} and R^3 are each (1-3 C)alkyl;

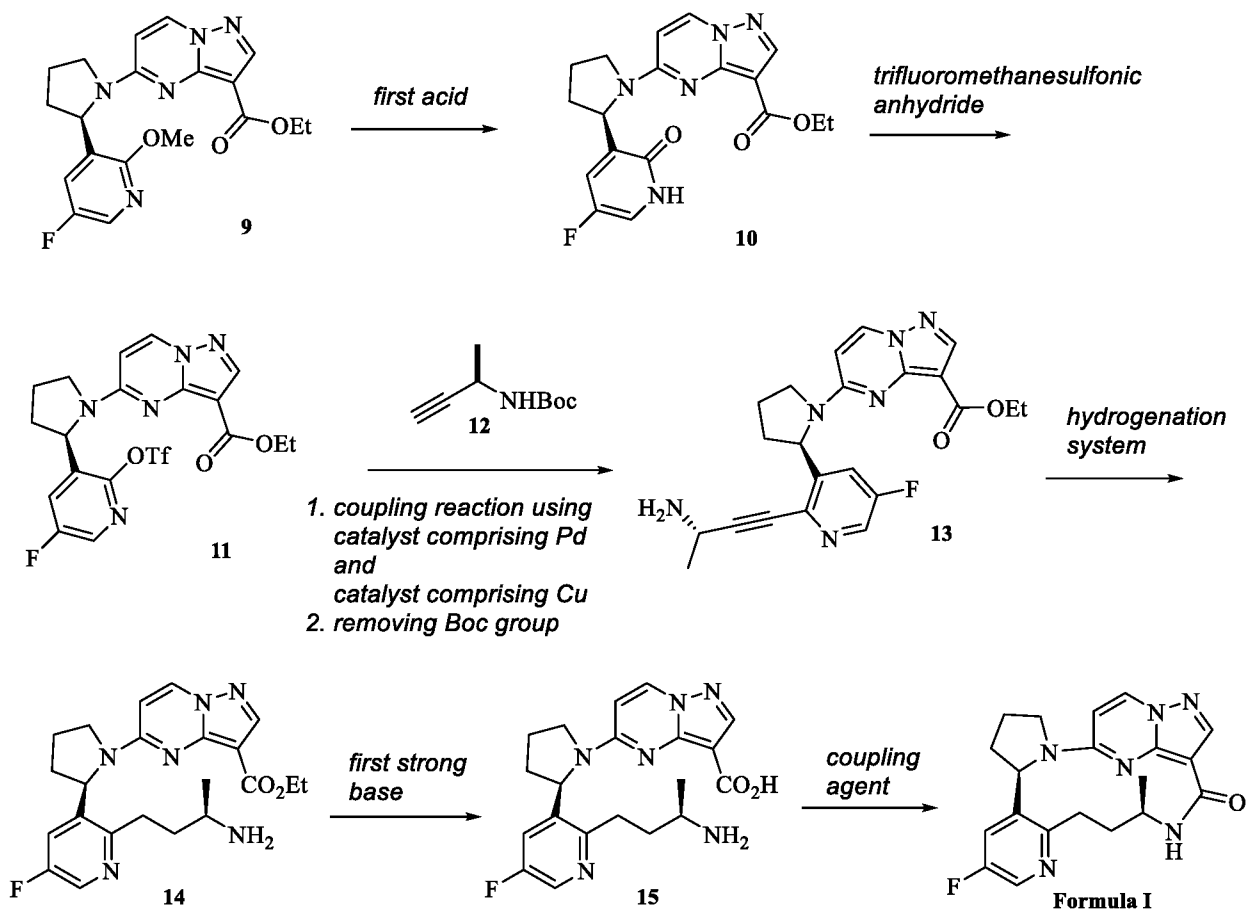
10 R^5 and R^6 are each independently H or (1-6C)alkyl;

L^1 (when present) is a triflate leaving group; and

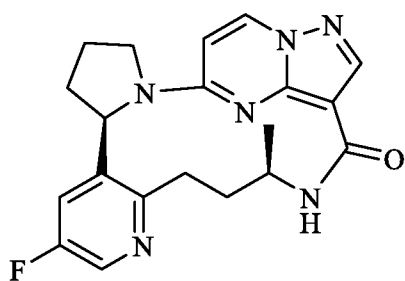
P^1 (when present) is a *t*-butyloxycarbonyl (BOC) amino-protecting group.

The present application also provides, *inter alia*, a process for preparing a compound of Formula I, or a salt thereof, as set out, for example, in Scheme 2:

Scheme 2



In some embodiments, provided herein is a process for preparing a compound of Formula I

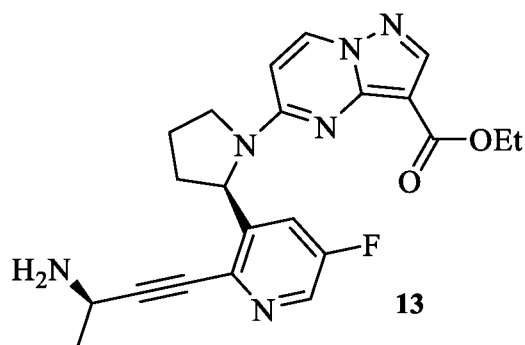


Formula I

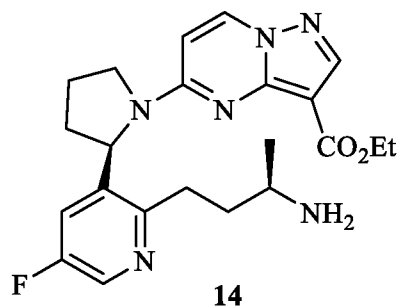
5

or a salt thereof, comprising:

a) treating a compound of formula 13

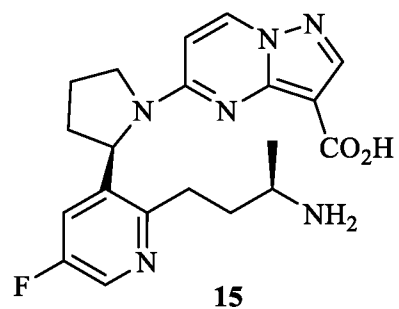


or a salt thereof with a hydrogenation system to form a compound of formula **14**



or a salt thereof;

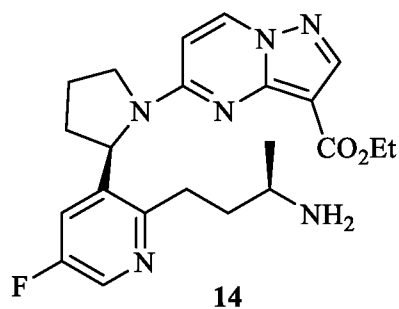
- 5 b) treating the compound of formula **14** or a salt thereof with a first strong base to form a compound of formula **15**



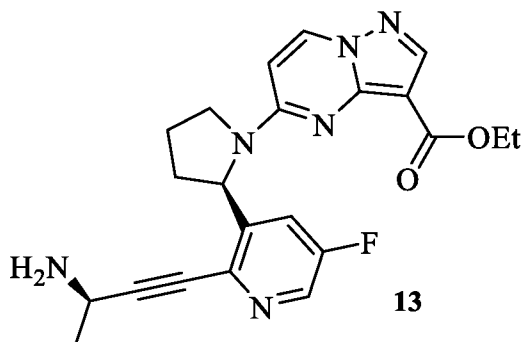
or a salt thereof; and

- 10 c) cyclizing the compound of formula **15** or a salt thereof with a coupling agent to form the compound of Formula **I** or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **14**

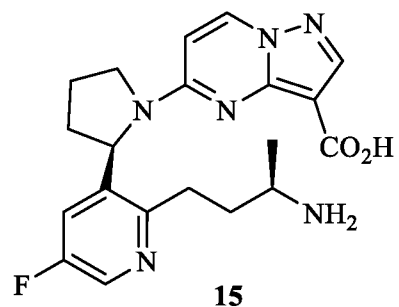


or a salt thereof, comprising treating a compound of formula **13**



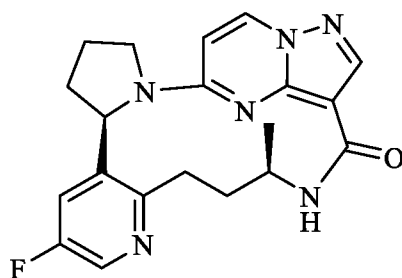
or a salt thereof, with a hydrogenation system to form the compound of formula **14** or a salt thereof.

In some embodiments, the process further comprises treating the compound of formula **14** or a salt thereof with a first strong base to form a compound of formula **15**



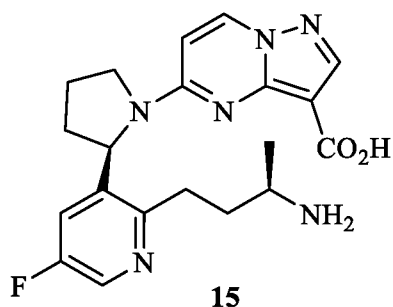
or a salt thereof.

In some embodiments, the process further comprises cyclizing the compound of formula **15** or a salt thereof with a coupling agent to form a compound of Formula **I**

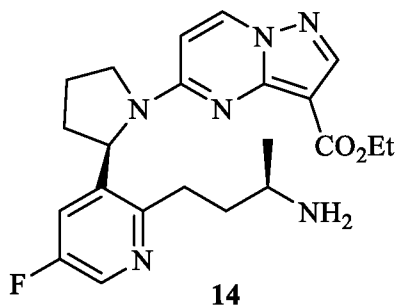
**Formula I**

or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **15**

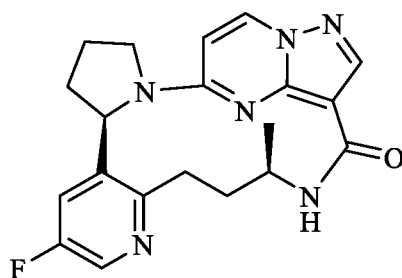
**15**

or a salt thereof, comprising treating a compound of formula **14**

**14**

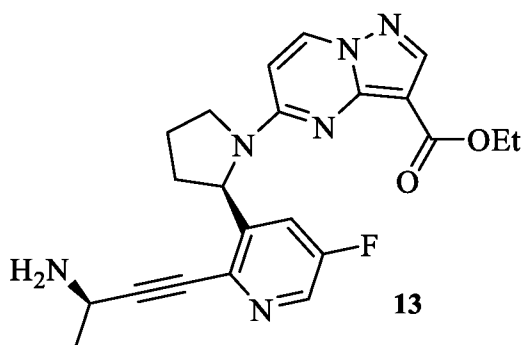
or a salt thereof, with a first strong base to form the compound of formula **15**.

In some embodiments, the process further comprises cyclizing the compound of formula **15** or a salt thereof with a coupling agent to form a compound of Formula **I**

**Formula I**

or a salt thereof.

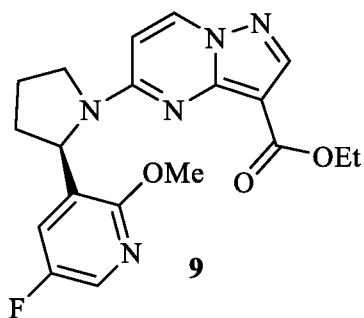
In some embodiments, the process for preparing the compound of Formula I further comprises preparing the compound of formula **13**

**13**

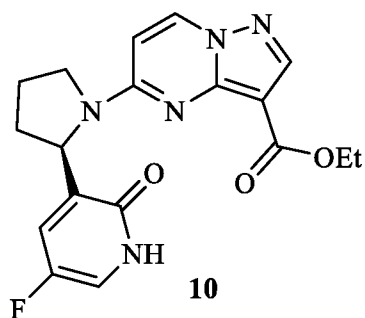
5

or a salt thereof, by a process comprising:

a) treating a compound of formula **9**

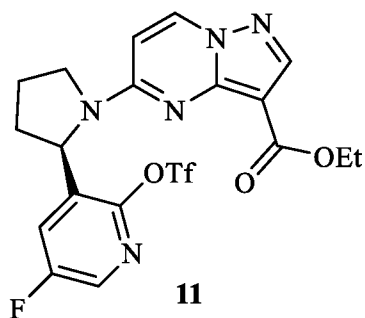
**9**

10 or a salt thereof with a first acid to form a compound of formula **10**



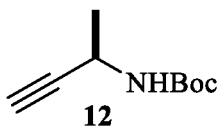
or a salt thereof;

b) treating the compound of formula **10** or a salt thereof with a reagent comprising a -S(O₂)LG moiety, such as a sulfonic anhydride, such as trifluoromethanesulfonic anhydride to form a compound of formula **11**



or a salt thereof; and

c) coupling the compound of formula **11** or a salt thereof with a compound of formula **12**

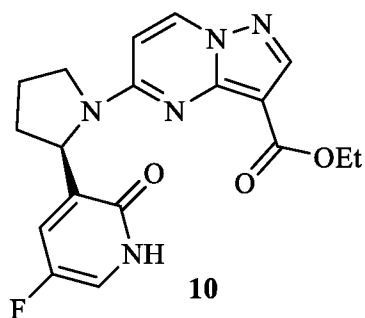


in the presence of a catalyst comprising palladium and a catalyst comprising copper; and

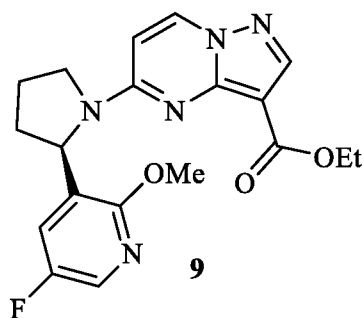
d) deprotecting the product of the coupling of compound **11** and compound **12** to form the compound of formula **13** or a salt thereof.

In some embodiments step b) is replaced by a step comprising treating the compound of formula **10** or a salt thereof with a sulfonimide, such as N-Phenyl-bis(trifluoromethanesulfonimide), to form a compound of formula **11** or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **10**

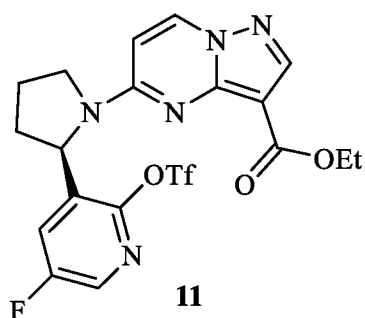


or a salt thereof, comprising treating a compound of formula **9**



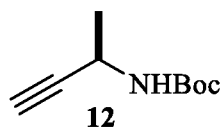
or a salt thereof with a first acid to form the compound of formula **10** or a salt thereof.

- 5 In some embodiments, the process further comprises treating the compound of formula **10** or a salt thereof with a reagent comprising a $-S(O_2)LG$ moiety, such as a sulfonic anhydride, such as trifluoromethanesulfonic anhydride to form a compound of formula **11**

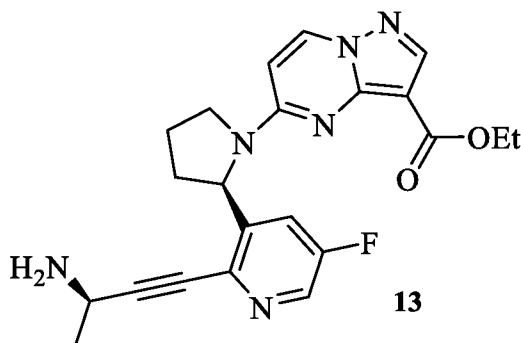


- 10 or a salt thereof. In some embodiments, the process further comprises treating the compound of formula **10** or a salt thereof with a sulfonimide, such as N-Phenyl-bis(trifluoromethanesulfonimide), to form a compound of formula **11** or a salt thereof.

In some embodiments, the process further comprises coupling the compound of formula **11** or a salt thereof with a compound of formula **12**



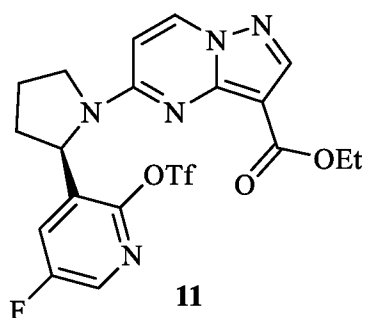
in the presence of a catalyst comprising palladium and a catalyst comprising copper;
deprotecting the product of the coupling of compound **11** and compound **12** to form the
compound of formula **13**



5

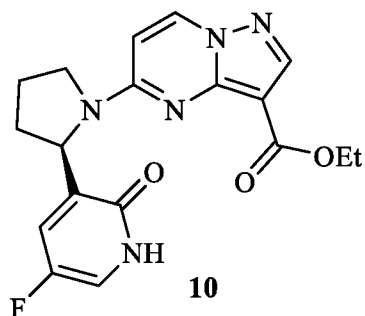
or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of
formula **11**



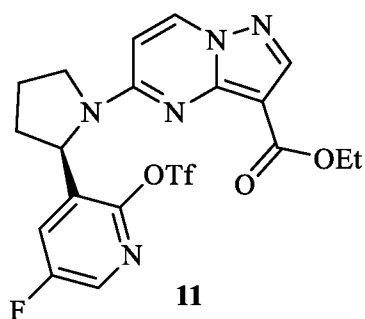
10

or a salt thereof, comprising treating a compound of formula **10**

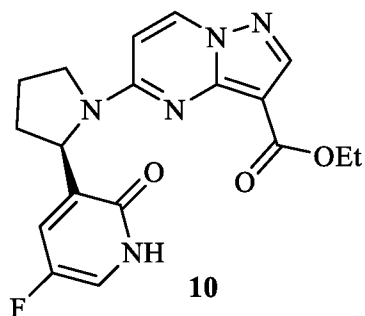


or a salt thereof with a reagent comprising a $-S(O_2)LG$ moiety, such as a sulfonic anhydride, such as trifluoromethanesulfonic anhydride to form the compound of formula **11** or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **11**

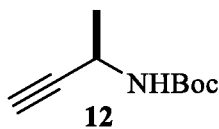


or a salt thereof, comprising treating a compound of formula **10**

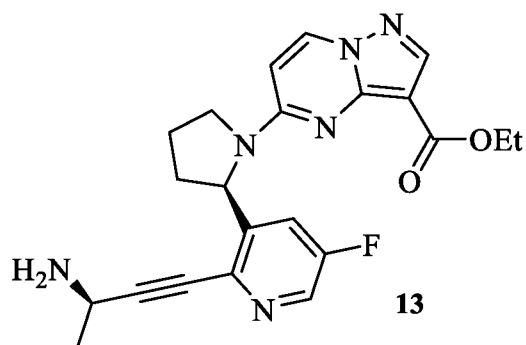


or a salt thereof with a sulfonimide, such as N-Phenyl-bis(trifluoromethanesulfonimide), to form a compound of formula **11** or a salt thereof.

In some embodiments, the process further comprises coupling the compound of formula **11** or a salt thereof with a compound of formula **12**

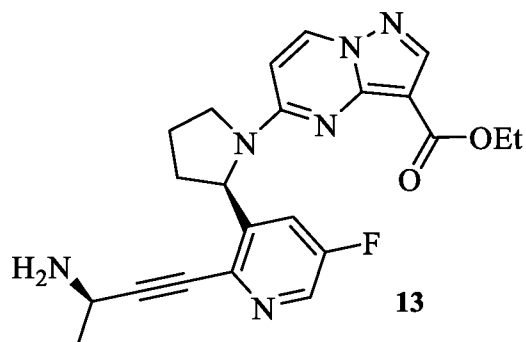


in the presence of a catalyst comprising palladium and a catalyst comprising copper; deprotecting the product of the coupling of compound **11** and compound **12** to form the compound of formula **13**

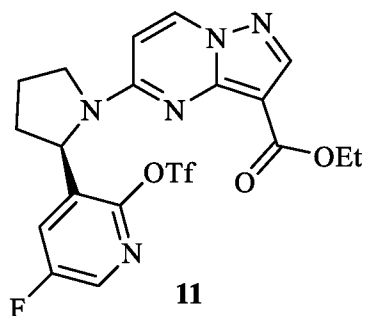


or a salt thereof.

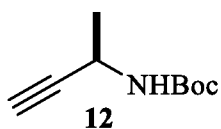
In some embodiments, provided herein is a process for preparing a compound of
 5 formula 13



or a salt thereof, comprising coupling a compound of formula 11



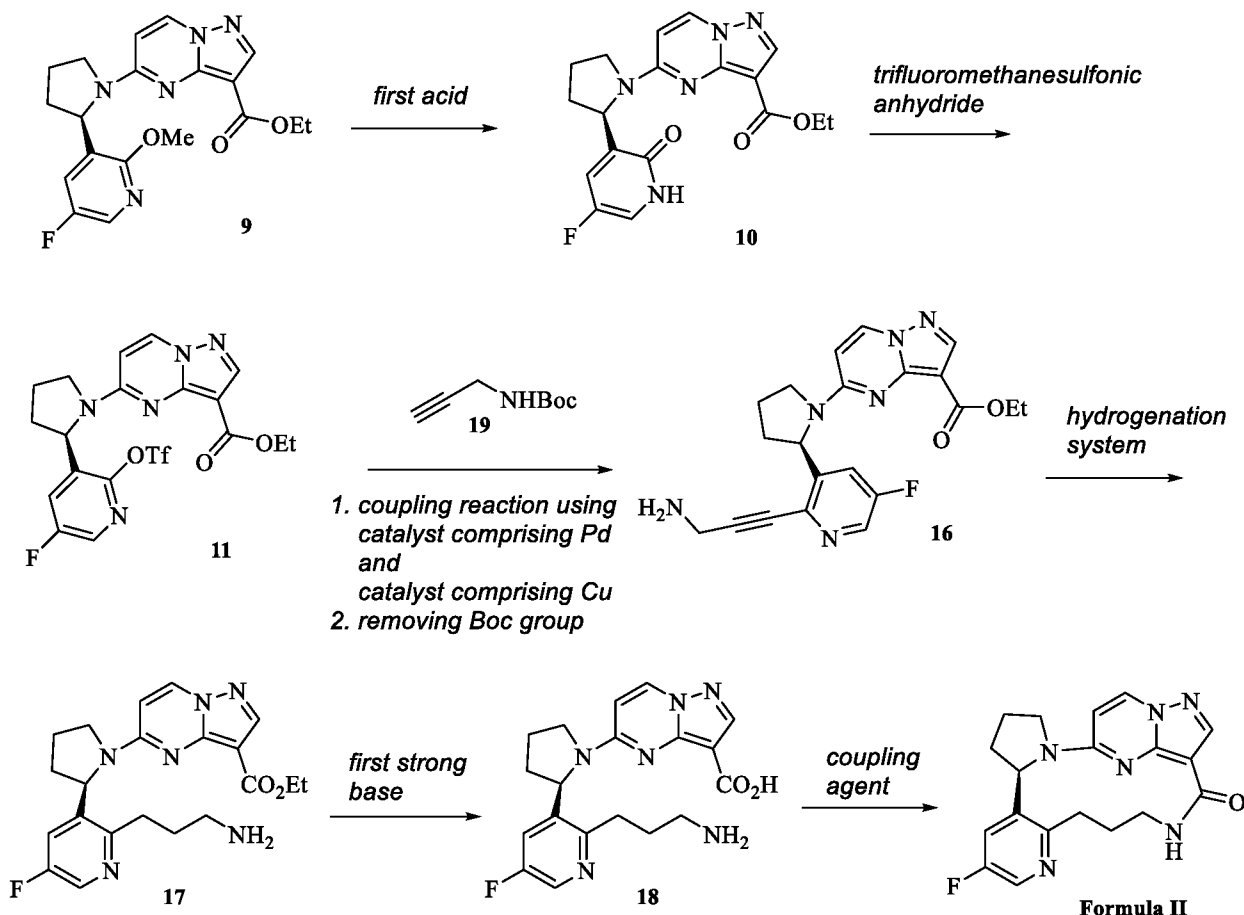
10 or a salt thereof with a compound of formula 12



in the presence of a catalyst comprising palladium and a catalyst comprising copper; and deprotecting the product of the coupling of compound **11** and compound **12** to form the compound of formula **13** or a salt thereof.

The present application also provides, *inter alia*, a process for preparing a compound of Formula **II**, or a salt thereof, as set out, for example, in Scheme 3:

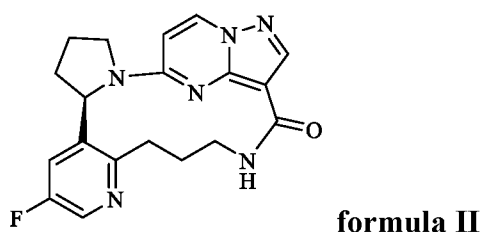
Scheme 3



In some embodiments, one or more of 10, 11, 16, 17 and 18 are isolated after forming and prior to the respective following step in the process. In some embodiments, one or more of 10, 11, 16, 17 and 18 are not isolated after forming and prior to the respective following step in the process. In some embodiments, 10 is not isolated after forming and prior to the following step in the process. In some embodiments, 11 is not isolated after forming and prior to the following step in the process. In some embodiments, 16 is not isolated after forming and prior to the following step in the process. In some embodiments, 17 is not isolated after forming and prior to the following

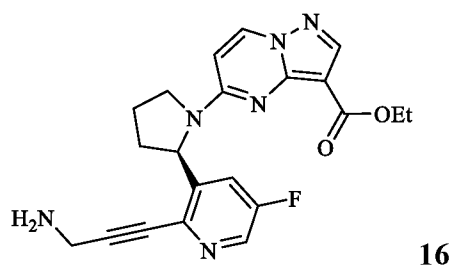
step in the process. In some embodiments, 18 is not isolated after forming after forming and prior to the following step in the process. In some embodiments, 18 is isolated after forming after forming and prior to the following step in the process.

In some embodiments, provided herein is a process for preparing a compound of
 5 Formula II

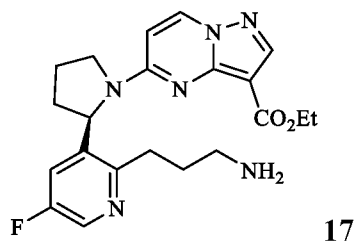


or a salt thereof, comprising:

a) treating a compound of formula 16

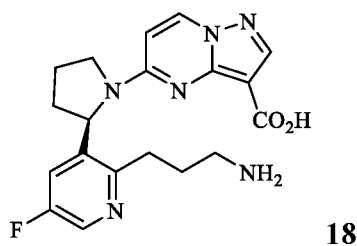


10 or a salt thereof with a hydrogenation system to form a compound of formula 17



or a salt thereof;

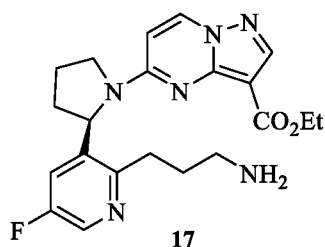
b) treating the compound of formula 17 or a salt thereof with a first strong base to form a compound of formula 18



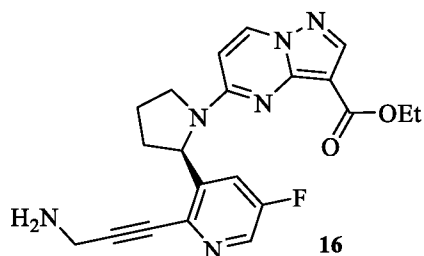
or a salt thereof; and

c) cyclizing the compound of formula **18** or a salt thereof with a coupling agent to form the compound of Formula **II** or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **17**

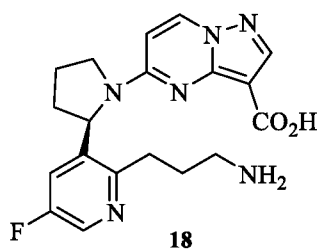


or a salt thereof, comprising treating a compound of formula **16**



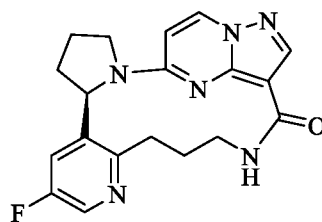
or a salt thereof, with a hydrogenation system to form the compound of formula **17** or a salt thereof.

In some embodiments, the process further comprises treating the compound of formula **17** or a salt thereof with a first strong base to form a compound of formula **18**



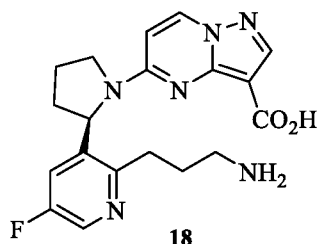
or a salt thereof.

In some embodiments, the process further comprises cyclizing the compound of formula **18** or a salt thereof with a coupling agent to form a compound of Formula **II**

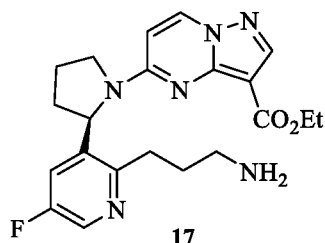
**Formula II**

or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **18**

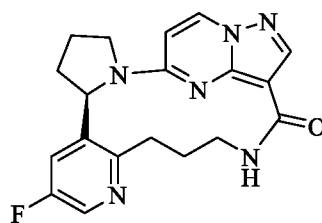
**18**

or a salt thereof, comprising treating a compound of formula **17**

**17**

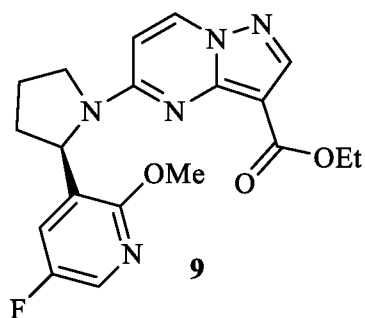
or a salt thereof, with a first strong base to form the compound of formula **18**.

In some embodiments, the process further comprises cyclizing the compound of formula **18** or a salt thereof with a coupling agent to form a compound of Formula **II**

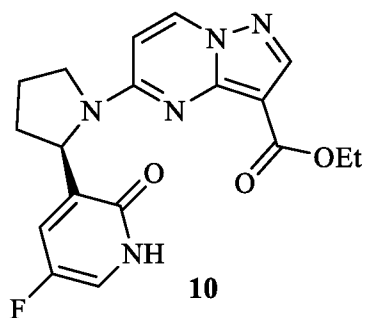
**Formula II**

In some embodiments, the process for preparing the compound of Formula **II** further comprises preparing the compound of formula **16** or a salt thereof by a process comprising:

- a) treating a compound of formula **9**

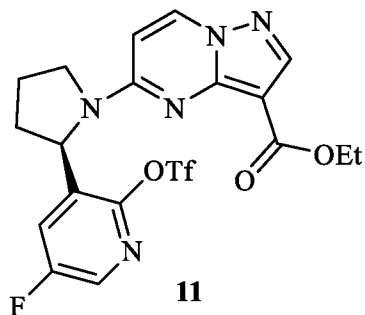


or a salt thereof with a first acid to form a compound of formula **10**



or a salt thereof;

- 5 b) treating the compound of formula **10** or a salt thereof with a reagent comprising a $-S(O_2)LG$ moiety, such as a sulfonic anhydride, such as trifluoromethanesulfonic anhydride to form a compound of formula **11**



or a salt thereof;

- 10 c) coupling the compound of formula **11** with a compound of formula **19**

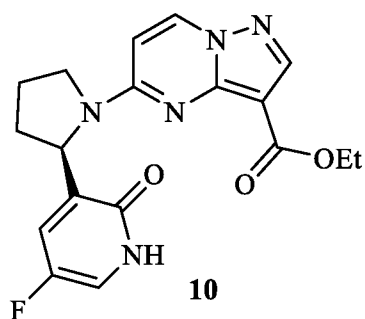


in the presence of a catalyst comprising palladium and a catalyst comprising copper; and

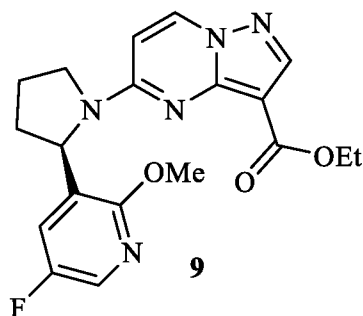
- d) deprotecting the product of the coupling of compound **11** and compound **19** to form the compound of formula **16** or a salt thereof.

In some embodiments step b) is replaced by a step comprising treating the compound of formula **10** or a salt thereof with a sulfonimide, such as N-Phenyl-bis(trifluoromethanesulfonimide), to form a compound of formula **11** or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **10**

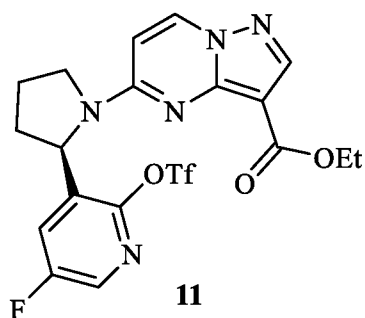


or a salt thereof, comprising treating a compound of formula **9**



or a salt thereof with a first acid to form the compound of formula **10** or a salt thereof.

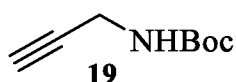
In some embodiments, the process further comprises treating the compound of formula **10** or a salt thereof with a reagent comprising a -S(O₂)LG moiety, such as a sulfonic anhydride, such as trifluoromethanesulfonic anhydride to form a compound of formula **11**



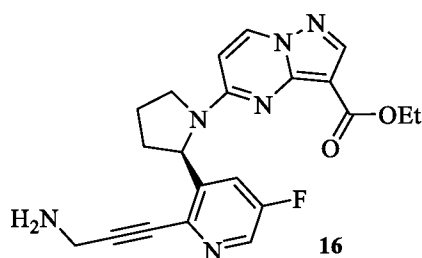
or a salt thereof.

In some embodiments, the process further comprises treating the compound of formula **10** or a salt thereof with a sulfonimide, such as N-Phenyl-bis(trifluoromethanesulfonimide), to form a compound of formula **11** or a salt thereof.

In some embodiments, the process further comprises coupling the compound of formula **11** or a salt thereof with a compound of formula **19**

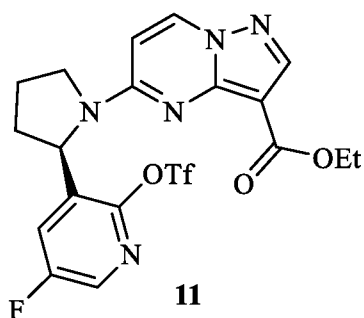


in the presence of a catalyst comprising palladium and a catalyst comprising copper; and deprotecting the product of the coupling of compound **11** and compound **19** to form a compound of formula **16**

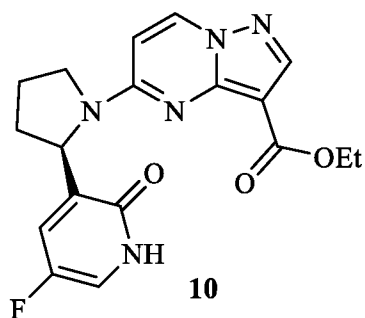


or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **11**

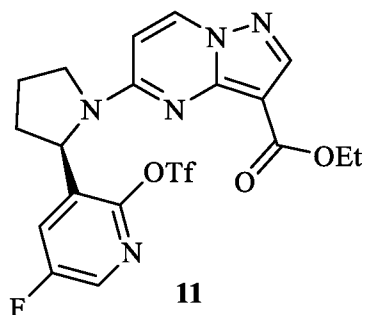


or a salt thereof, comprising treating a compound of formula **10**

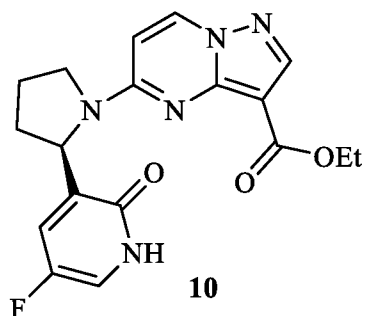


or a salt thereof with a reagent comprising a $-S(O_2)LG$ moiety, such as a sulfonic anhydride, such as trifluoromethanesulfonic anhydride to form the compound of formula **11** or a salt thereof.

5 In some embodiments, provided herein is a process for preparing a compound of formula **11**

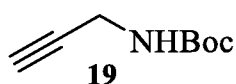


or a salt thereof, comprising treating a compound of formula **10**

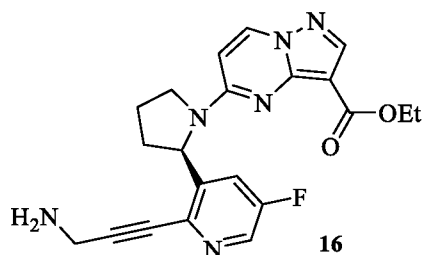


10 or a salt thereof with sulfonimide, such as N-Phenyl-bis(trifluoromethanesulfonimide), to form a compound of formula **11** or a salt thereof.

In some embodiments, the process further comprises coupling the compound of formula **11** or a salt thereof with a compound of formula **19**

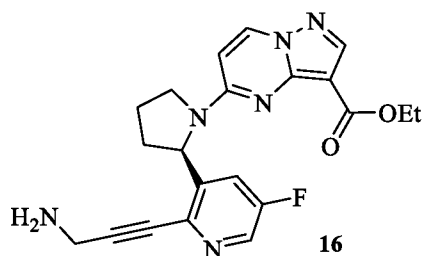


in the presence of a catalyst comprising palladium and a catalyst comprising copper; and deprotecting the product of the coupling of compound **11** and compound **19** to form a compound of formula **16**

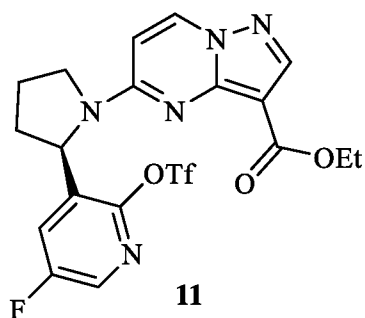


5 or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **16**

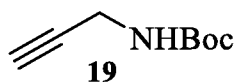


or a salt thereof, comprising coupling a compound of formula **11**



10

or a salt thereof with a compound of formula **19**

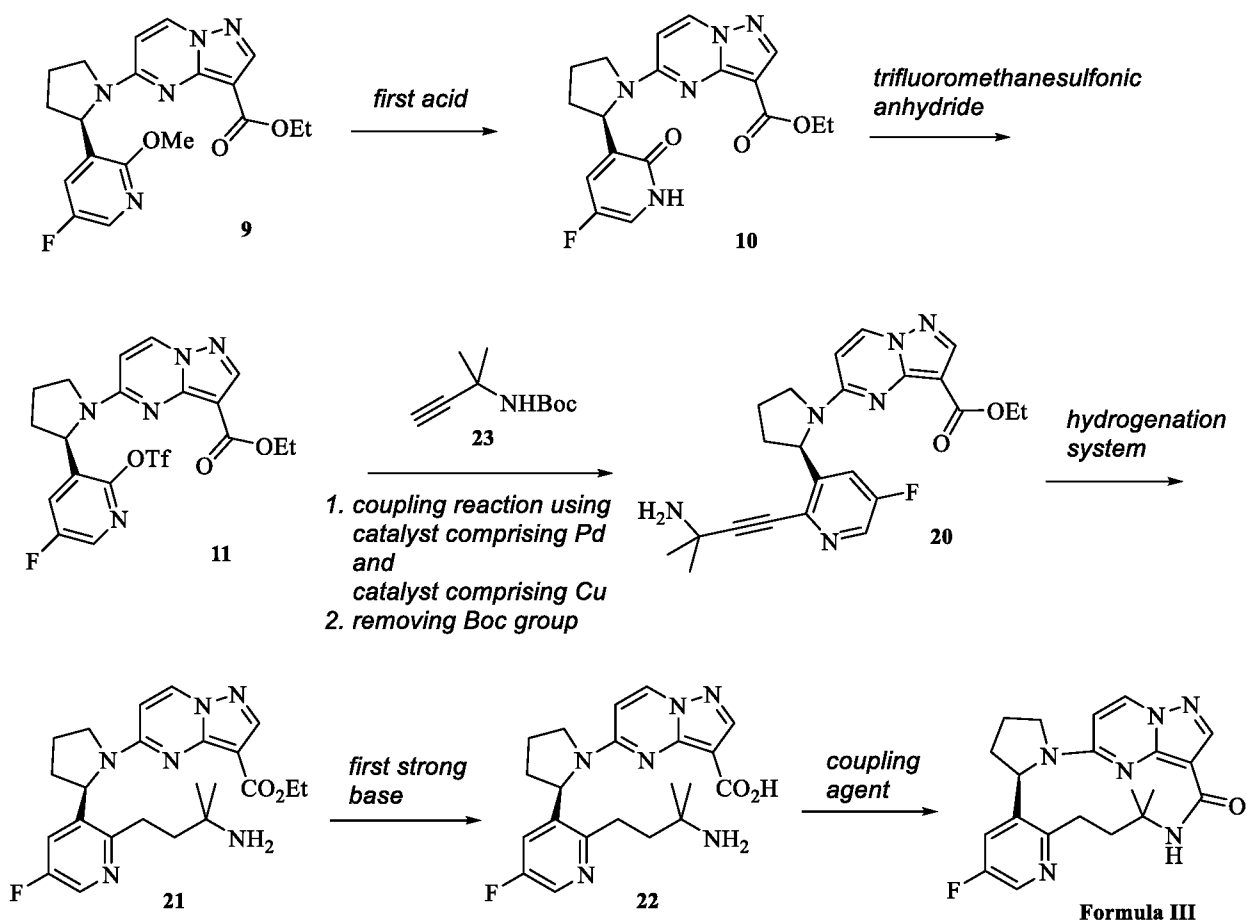


in the presence of a catalyst comprising palladium and a catalyst comprising copper; and deprotecting the product of the coupling of compound **11** and compound **19** to form the compound of formula **16** or a salt thereof.

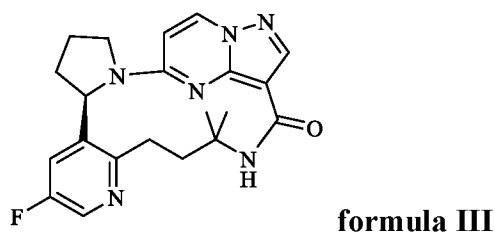
15

The present application also provides, *inter alia*, a process for preparing a compound of Formula **III**, or a salt thereof, as set out, for example, in Scheme 4:

Scheme 4

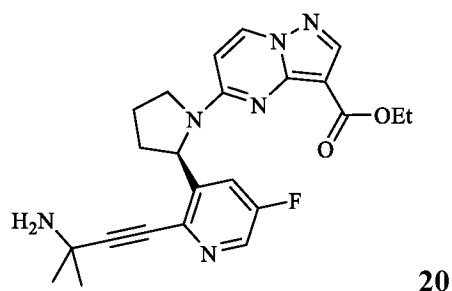


5 In some embodiments, provided herein is a process for preparing a compound of formula **III**

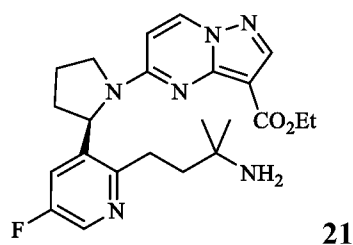


or a salt thereof, comprising:

a) treating a compound of formula **20**

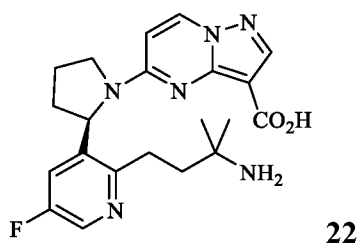


or a salt thereof with a hydrogenation system to form a compound of formula **21**



or a salt thereof;

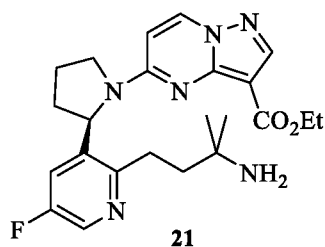
- 5 b) treating the compound of formula **21** or a salt thereof with a first strong base to form a compound of formula **22**



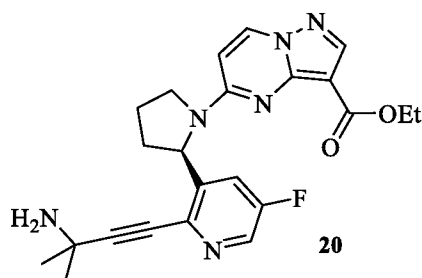
or a salt thereof; and

- 10 c) cyclizing the compound of formula **22** or a salt thereof with a coupling agent to form the compound of Formula **III** or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **22**

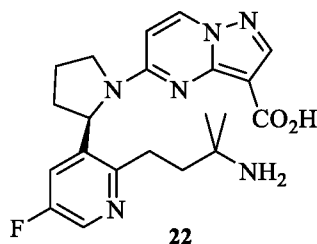


or a salt thereof, comprising treating a compound of formula **20**



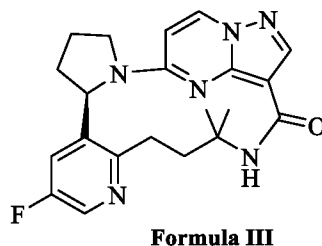
or a salt thereof, with a hydrogenation system to form the compound of formula **21** or a salt thereof.

In some embodiments, the process further comprises treating the compound of formula **21** or a salt thereof with a first strong base to form a compound of formula **22**



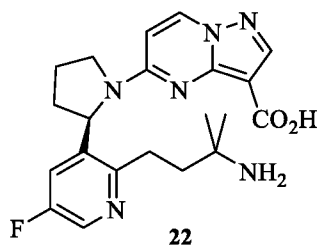
or a salt thereof.

In some embodiments, the process further comprises cyclizing the compound of formula **22** or a salt thereof with a coupling agent to form a compound of Formula **III**

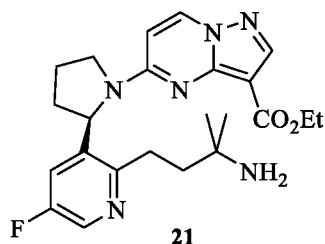


or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **22**

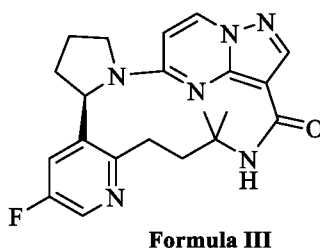


or a salt thereof, comprising treating a compound of formula **21**



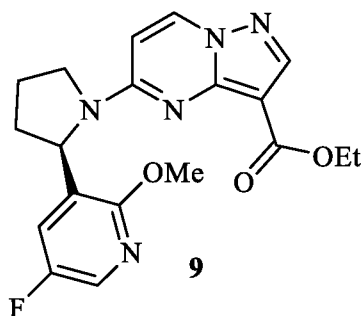
or a salt thereof, with a first strong base to form the compound of formula **22**.

In some embodiments, the process further comprises cyclizing the compound of
 5 formula **22** or a salt thereof with a coupling agent to form a compound of Formula **III**

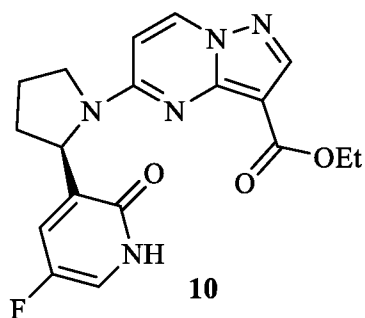


In some embodiments, the process for preparing the compound of Formula **III**
 further comprises preparing the compound of formula **20** or a salt thereof by a process
 comprising:

10 a) treating a compound of formula **9**

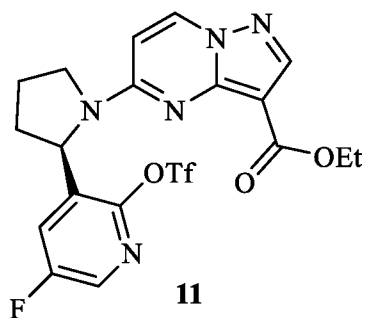


or a salt thereof with a first acid to form a compound of formula **10**



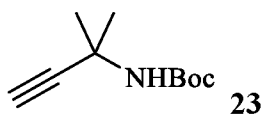
or a salt thereof;

b) treating the compound of formula **10** or a salt thereof with a reagent comprising a $-S(O_2)LG$ moiety, such as a sulfonic anhydride, such as trifluoromethanesulfonic anhydride to form a compound of formula **11**



or a salt thereof;

c) coupling the compound of formula **11** with a compound of formula **23**

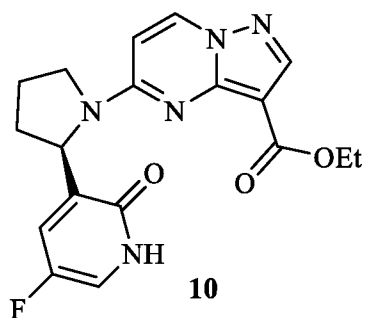


in the presence of a catalyst comprising palladium and a catalyst comprising copper; and

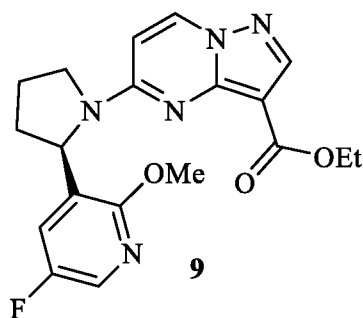
d) deprotecting the product of the coupling of compound **11** and compound **23** to form the compound of formula **20** or a salt thereof.

In some embodiments step b) is replaced by a step comprising treating the compound of formula **10** or a salt thereof with a sulfonimide, such as N-Phenyl-bis(trifluoromethanesulfonimide), to form a compound of formula **11** or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **10**

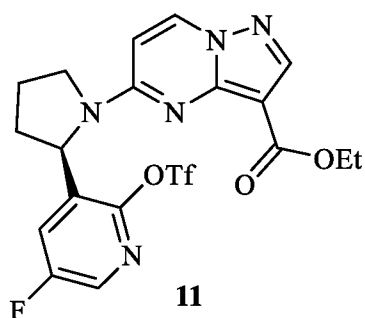


or a salt thereof, comprising treating a compound of formula **9**



or a salt thereof with a first acid to form the compound of formula **10** or a salt thereof.

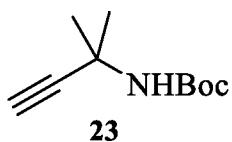
5 In some embodiments, the process further comprises treating the compound of formula **10** or a salt thereof with a reagent comprising a $-S(O_2)LG$ moiety, such as a sulfonic anhydride, such as trifluoromethanesulfonic anhydride to form a compound of formula **11**



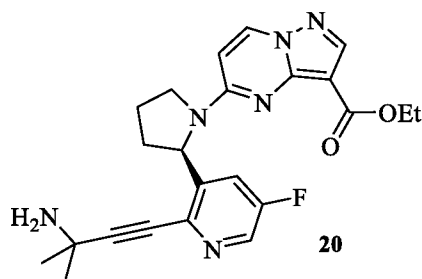
10 or a salt thereof.

 In some embodiments, the process further comprises treating the compound of formula **10** or a salt thereof with a sulfonimide, such as N-Phenyl-bis(trifluoromethanesulfonimide), to form a compound of formula **11** or a salt thereof.

15 In some embodiments, the process further comprises coupling the compound of formula **11** or a salt thereof with a compound of formula **23**



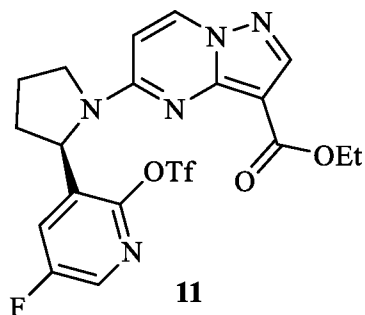
in the presence of a catalyst comprising palladium and a catalyst comprising copper; and deprotecting the product of the coupling of compound **11** and compound **23** to form a compound of formula **20**



5

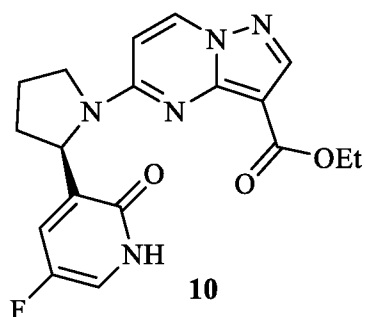
or a salt thereof.

In some embodiments, provided herein is a process for preparing a compound of formula **11**



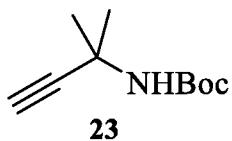
10

or a salt thereof, comprising treating a compound of formula **10**

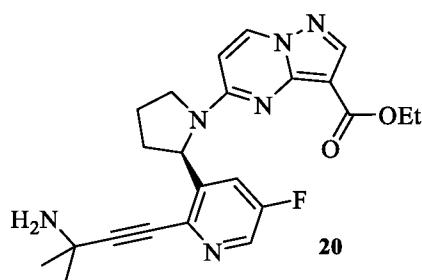


or a salt thereof with a reagent comprising a -S(O₂)LG moiety, such as a sulfonic anhydride, such as trifluoromethanesulfonic anhydride to form the compound of formula **11** or a salt thereof.

In some embodiments, the process further comprises coupling the compound of formula **11** or a salt thereof with a compound of formula **23**

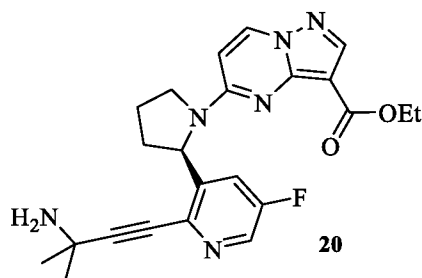


in the presence of a catalyst comprising palladium and a catalyst comprising copper; and
 5 deprotecting the product of the coupling of compound **11** and compound **23** to form a compound of formula **20**

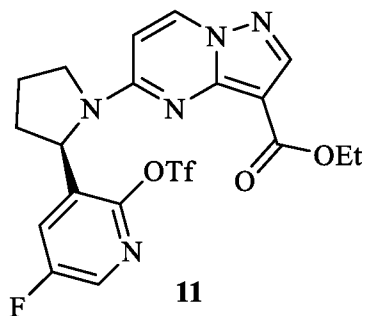


or a salt thereof.

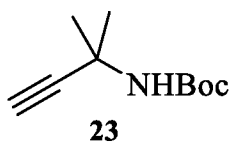
In some embodiments, provided herein is a process for preparing a compound of
 10 formula **20**



or a salt thereof, comprising coupling a compound of formula **11**



or a salt thereof with a compound of formula **23**



in the presence of a catalyst comprising palladium and a catalyst comprising copper; and deprotecting the product of the coupling of compound **11** and compound **23** to form the compound of formula **20** or a salt thereof.

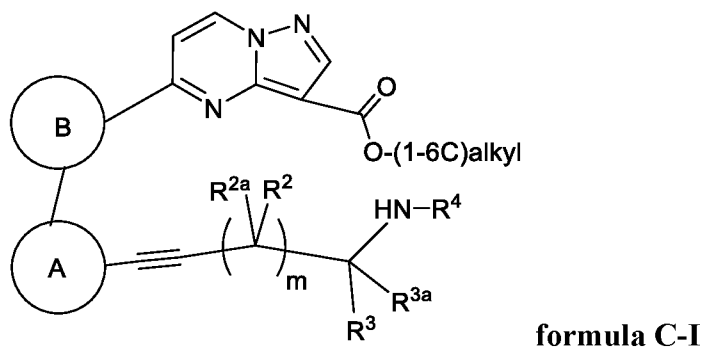
5 In some embodiments, provided herein is a process for the preparation of the compound of formula **C**, wherein the process does not comprise a chromatographic purification step following the formation of the compound of formula **C**.

10 In some embodiments, provided herein is a process for the preparation of the compound of Formula **I**, wherein the process does not comprise a chromatographic purification step following the formation of the compound of Formula **I**.

 In some embodiments, provided herein is a process for the preparation of the compound of Formula **II**, wherein the process does not comprise a chromatographic purification step following the formation of the compound of Formula **II**.

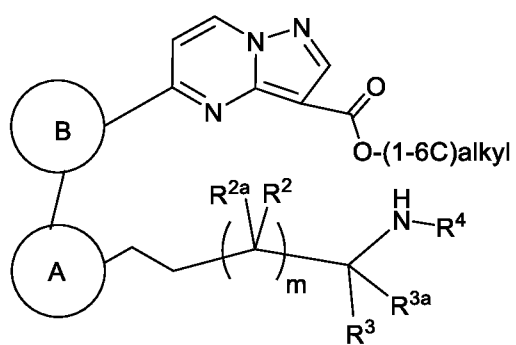
15 In some embodiments, provided herein is a process for the preparation of the compound of Formula **III**, wherein the process does not comprise a chromatographic purification step following the formation of the compound of Formula **III**.

 In some embodiments, provided herein is a compound of formula **C-I**



or a salt thereof.

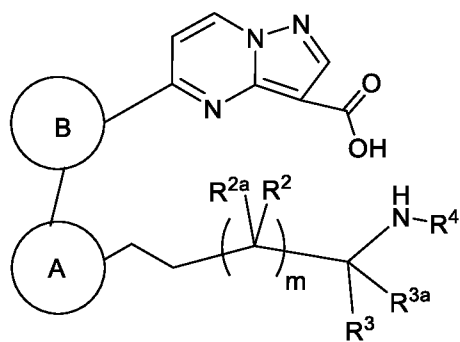
20 In some embodiments, provided herein is a compound of formula **C-II**



formula C-II,

or a salt thereof.

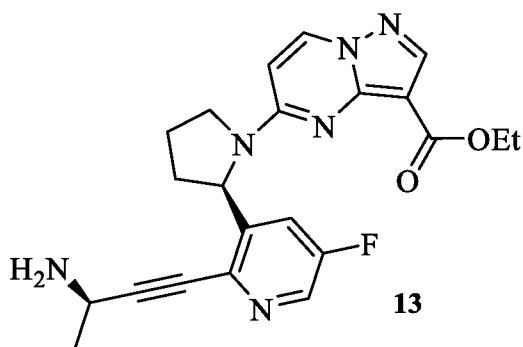
In some embodiments, provided herein is a compound of formula **C-III**



formula C-III,

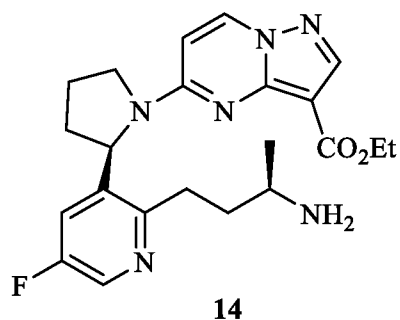
5 or a salt thereof.

In some embodiments, provided herein is a compound of formula **13**

**13**

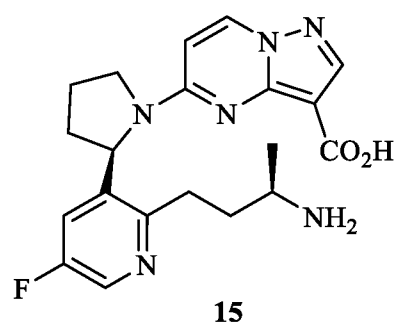
or a salt thereof.

10 In some embodiments, provided herein is a compound of formula **14**



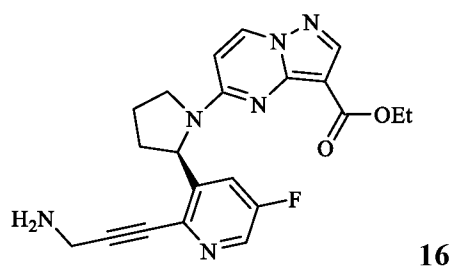
or a salt thereof.

In some embodiments, provided herein is a compound of formula **15**



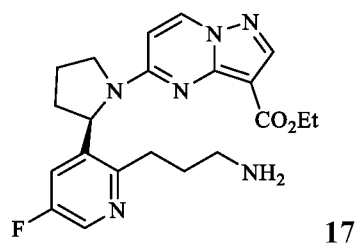
5 or a salt thereof.

In some embodiments, provided herein is a compound of formula **16**



or a salt thereof.

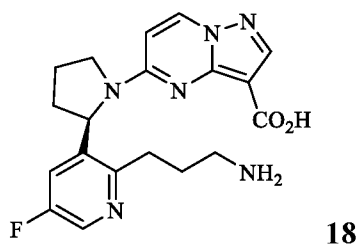
In some embodiments, provided herein is a compound of formula **17**



10

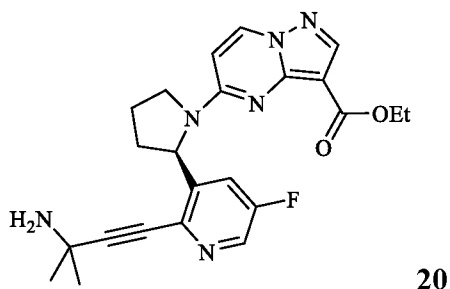
or a salt thereof.

In some embodiments, provided herein is a compound of formula **18**



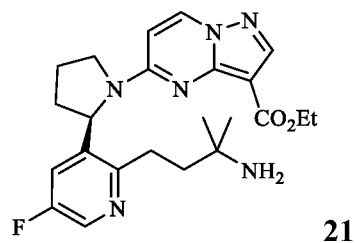
or a salt thereof.

In some embodiments, provided herein is a compound of formula **20**



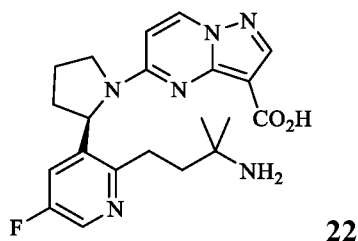
5 or a salt thereof.

In some embodiments, provided herein is a compound of formula **21**



or a salt thereof.

In some embodiments, provided herein is a compound of formula **22**

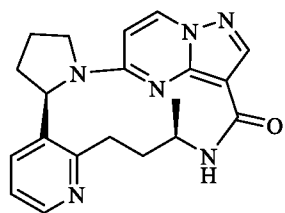


10

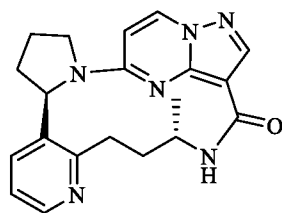
or a salt thereof.

In some embodiments, the following compounds are prepared in a manner analogous to the ones disclosed above for compounds of Formulae **I—III** using suitable starting materials:

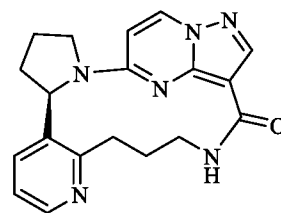
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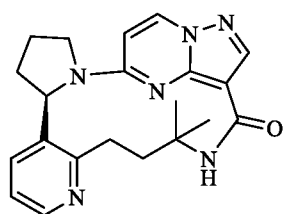
Formula IV



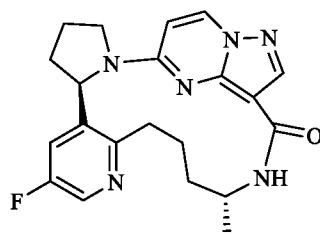
Formula V



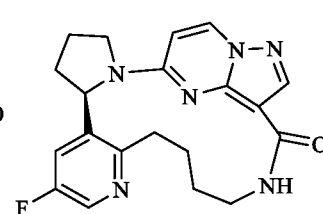
Formula VI



Formula VII

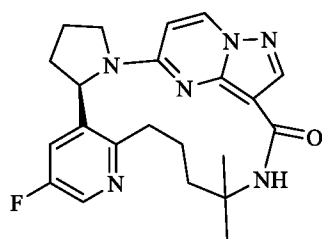


Formula VIII

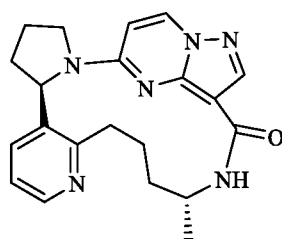


Formula IX;

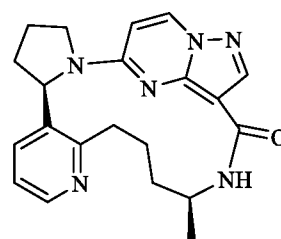
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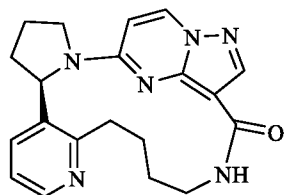
Formula X



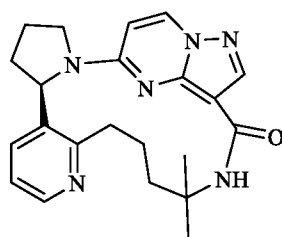
Formula XI



Formula XII



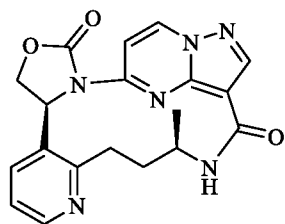
Formula XIII



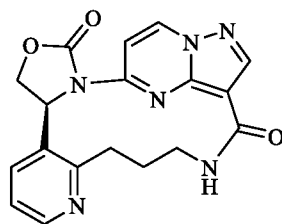
Formula XIV

10

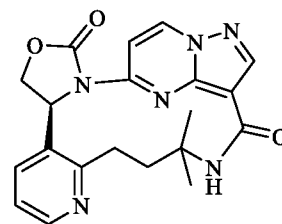
In some embodiments, the following compounds of formulae **XVa-XVp** are prepared in a manner analogous to the ones disclosed above for compounds of Formulae **I—III** using suitable starting materials:



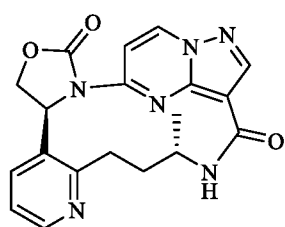
Formula XVa;



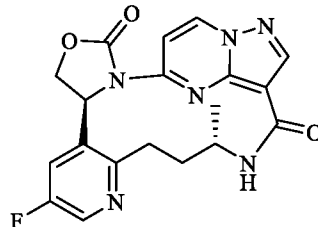
Formula XVb



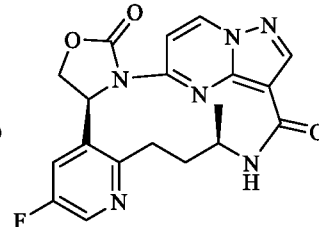
Formula XVc



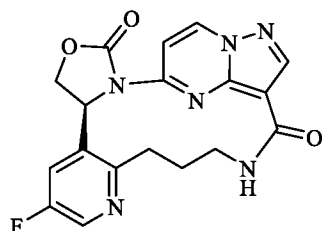
Formula XVd



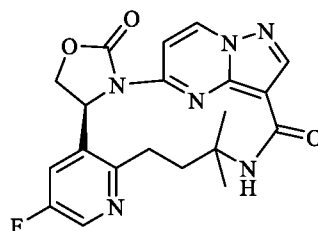
Formula XVe



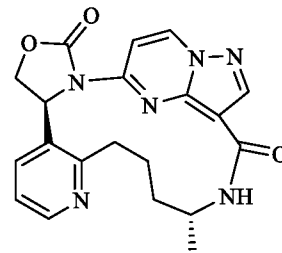
Formula XVf



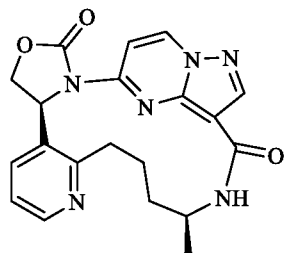
Formula XVg



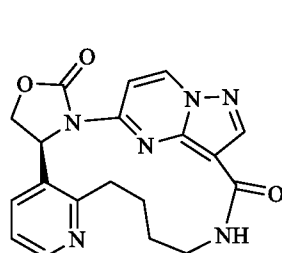
Formula XVh



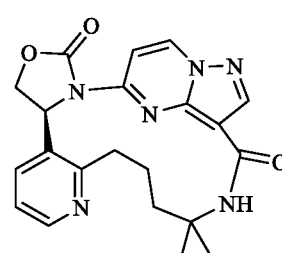
Formula XVI



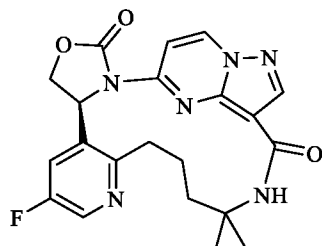
Formula XVj



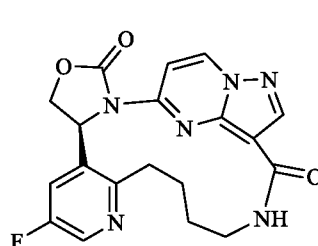
Formula XVk



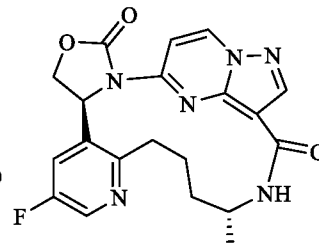
Formula XVI



Formula XVm



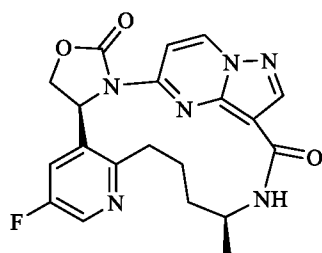
Formula XVn



Formula XV o

5

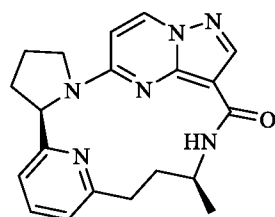
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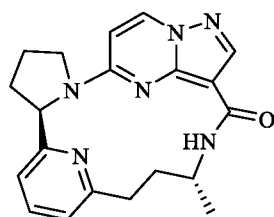
Formula XVp.

In some embodiments, the following compounds of formulae **XVIa-XVIp** are prepared in a manner analogous to the ones disclosed above for compounds of Formulae

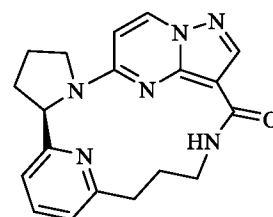
5 **I—III** using suitable starting materials:



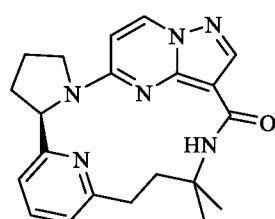
Formula XVIa



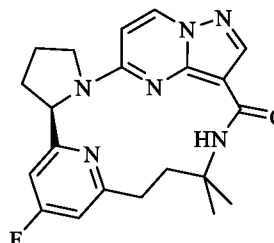
Formula XVIb



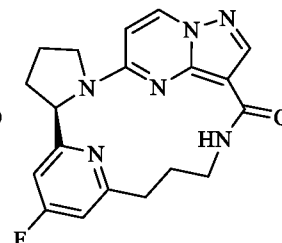
Formula XVIc



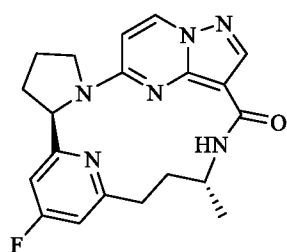
Formula XVIId



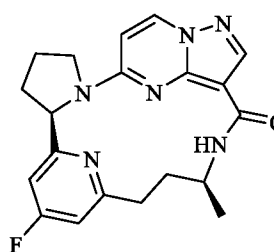
Formula XVIe



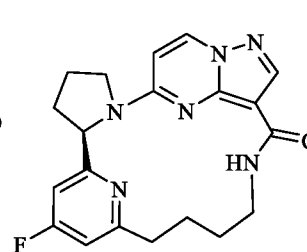
Formula XVIIf



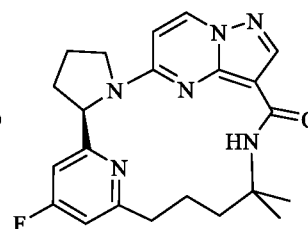
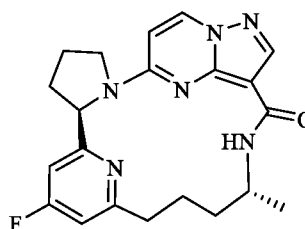
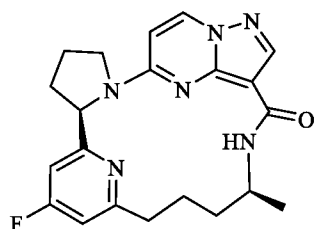
Formula XVIg



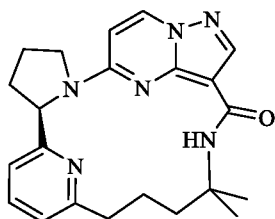
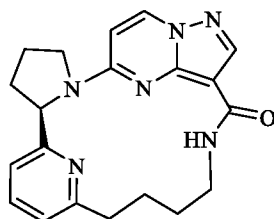
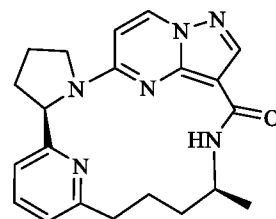
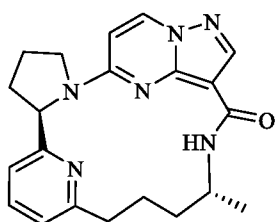
Formula XVIh



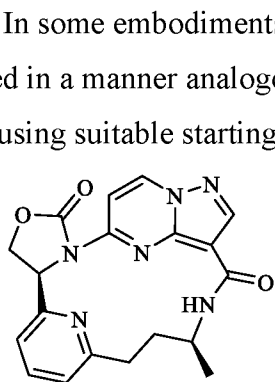
Formula XVIi



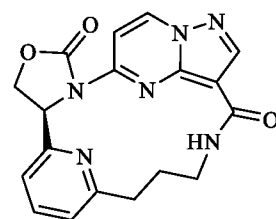
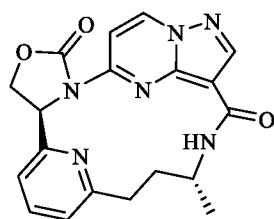
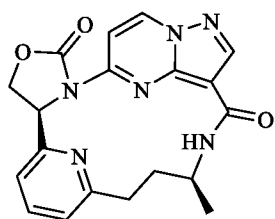
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Formula **XVIj**Formula **XVIk**Formula **XVII**Formula **XVIIm**Formula **XVIN**Formula **XVlo**

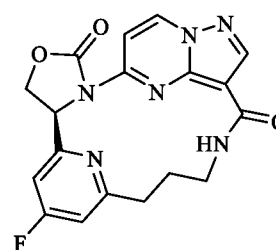
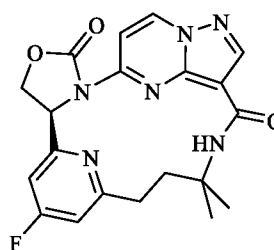
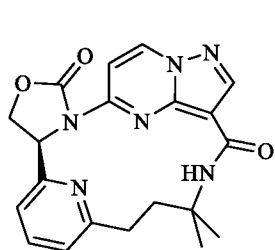
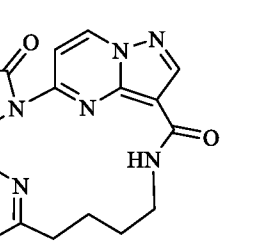
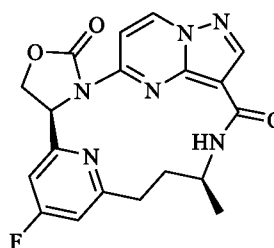
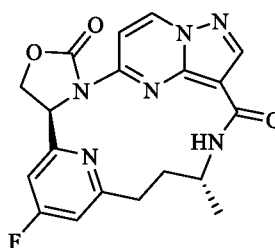
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Formula **XVIp**.

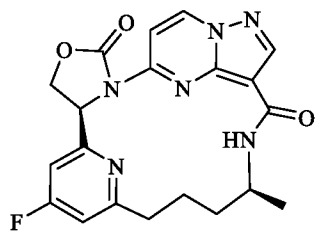
In some embodiments, the following compounds of formulae **XVIIa-XVIIp** are prepared in a manner analogous to the ones disclosed above for compounds of Formulae **I—III** using suitable starting materials:



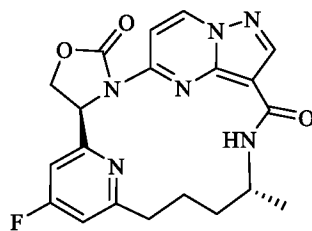
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Formula **XVIIa**Formula **XVIIb**Formula **XVIIc**Formula **XVIIId**Formula **XVIIe**Formula **XVIIIf**

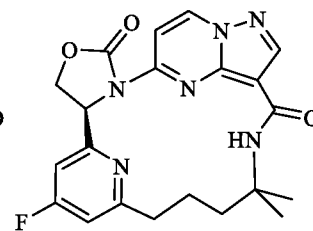
Formula XVIIg



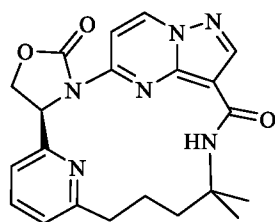
Formula XVIIh



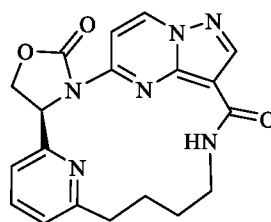
Formula XVIIi



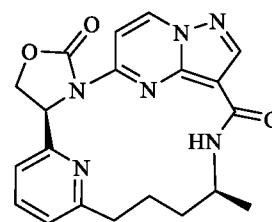
Formula XVIIj



Formula XVIIk

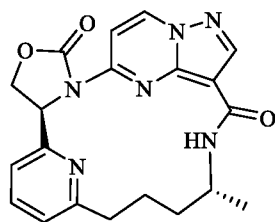


Formula XVIIl



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Formula XVIIm



Formula XVIIn



Formula XVIIo



Formula XVIIp.

Parameters of processes for preparation of any one of formulae disclosed herein

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In some embodiments of any one the processes provided herein, the hydrogenation system comprises hydrogen (H₂) and a catalyst that comprises a metal. In some embodiments, the catalyst comprises a metal selected from gold, ruthenium, sodium, indium, nickel, palladium, and platinum. In some embodiments, the catalyst is selected from gold, ruthenium, sodium sulfide, indium, nickel, palladium, and platinum.

15

In some embodiments, the catalyst comprises a metal selected from nickel, palladium, and platinum. In some embodiments, the metal is palladium. In some embodiments, the catalyst is palladium on carbon (Pd/C). In some embodiments, the hydrogenation system comprises hydrogen (H₂) and palladium on carbon (Pd/C).

In some embodiments of any one of the processes provided herein, the first strong base is selected from sodium hydroxide, lithium hydroxide, potassium hydroxide and calcium hydroxide. In some embodiments, the first strong base is sodium hydroxide.

In some embodiments of any one of the processes provided herein, the cyclizing
 5 is performed with a coupling agent that comprises one or more of a carbodiimide, an additive, a phosphonium reagent, an aminium/uranium-imonium reagent, and miscellaneous reagents. In some embodiments, the carbodiimide is selected from dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDCI). In some embodiments, the
 10 carbodiimide is dicyclohexylcarbodiimide (DCC). In some embodiments, the carbodiimide is diisopropylcarbodiimide (DIC). In some embodiments, the carbodiimide is N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDCI). In some embodiments, the additive is selected from 1-hydroxybenzotriazole (HOBt), hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOOBt), N-hydroxysuccinimide (HOSu), 1-hydroxy-7-aza-1H-benzotriazole (HOAt), 4-(N,N-dimethylamino)pyridine (DMAP), and ethyl-2-cyano-2-(hydroxyimino)acetate. In some embodiments, the phosphonium reagent is selected from benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyBOP), bromo-tripyrrolidino-phosphonium hexafluorophosphate (PYBrOP), 7-aza-benzotriazol-1-yloxy-tripyrrolidino-phosphonium hexafluorophosphate (PyAOP), ethyl
 20 cyano(hydroxyimino)acetate-O₂-tri-(1-pyrrolidinyl)-phosphonium hexafluorophosphate (PyOxim), and 3-(diethoxy-phosphoryloxy)-1,2,3-benzo[d]triazin-4(3H)-one (DEPBT). In some embodiments, the aminium/uranium-imonium reagent is selected from 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium tetrafluoroborate (TBTU), 2-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate (HBTU), 2-(6-chloro-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate (HCTU), N-[(5-chloro-1H-benzotriazol-1-yl)-dimethylamino-morpholino]-uronium hexafluorophosphate N-oxide (HDMC), 2-(7-aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethylaminium hexafluorophosphate (HATU), 1-[1-(cyano-2-ethoxy-2-oxoethylideneaminoxy)-dimethylamino-morpholino]-uronium hexafluorophosphate (COMU), 2-(1-oxy-pyridin-2-yl)-1,1,3,3-tetramethylisothiuronium tetrafluoroborate
 30

(TOTT), and tetramethylfluoroformamidinium hexafluorophosphate (TFFH). In some embodiments, the miscellaneous reagent is selected from N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoiline (EEDQ), 2-propanephosphonic acid anhydride (T3P), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium (DMTMM) salts, bis-trichloromethylcarbonate (BTC; phosgene), and 1,1'-carbonyldiimidazole (CTI). In some
5 embodiments, the coupling agent comprises EDCI and DMAP.

In some embodiments of any one of the processes provided herein, the first acid is selected from sulfuric acid and hydrochloric acid. In some embodiments, the first acid is hydrochloric acid (HCl).

10 In some embodiments of any one of the processes provided herein, treatment of a compound with a first acid is conducted in the presence of a solvent. In some embodiments, the solvent is a non-protic solvent. In some embodiments, the solvent is dioxane. In some embodiments, the solvent is a protic solvent. In some embodiments, the solvent is an aliphatic alcohol.

15 In some embodiments, the deprotecting, or removing the protecting group P^1 is conducted using any convenient synthetic method known in the art. The chemistry of protecting groups is described, for example, in in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", 2nd ed. New York; John Wiley & Sons, Inc., 1991. For example, when the protecting group P^1 is a t-butoxycarbonyl (BOC), the deprotecting is
20 carried out using an acid such as trifluoroacetic acid or hydrochloric acid. In some embodiments, the deprotecting is conducted at room temperature.

In some embodiments, the catalyst comprising palladium is a zerovalent palladium complex selected from $Pd(PPh_3)_2Cl_2$, $Pd(dppe)Cl$, $Pd(dppp)Cl_2$, and $Pd(dppf)Cl_2$. In some embodiments, the catalyst comprising palladium is $Pd(PPh_3)_2Cl_2$.

25 In some embodiments, the catalyst comprising copper is a halide salt of copper(I) selected from copper iodide, copper bromide, and copper chloride. In some embodiments, the catalyst comprising copper is copper iodide (CuI).

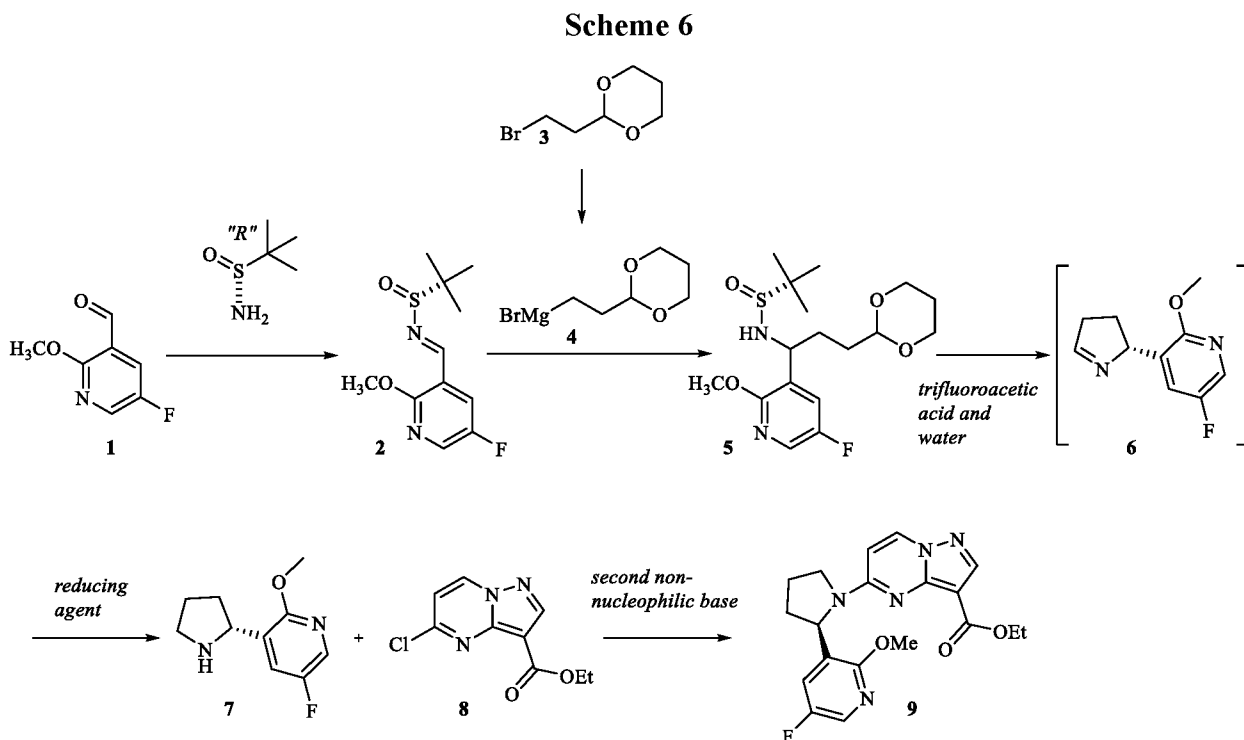
In some embodiments, the catalyst comprising palladium is $Pd(PPh_3)_2Cl_2$ and the catalyst comprising copper is CuI.

In some embodiments, in any one of the processes provided herein the coupling is performed in the presence of a base. In some embodiments, the base is an alkylamine. In some embodiments, the alkylamine is diisopropylamine (DIA).

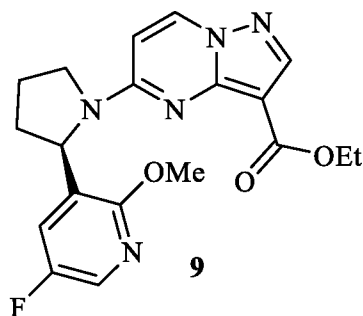
In some embodiments, in any one of the processes provided herein the coupling is followed by treating with a second acid. In some embodiments, the second acid is selected from hydrochloric acid, trifluoroacetic acid and sulfuric acid. In some embodiments, the second acid is sulfuric acid (H₂SO₄).

Compound **12** (CAS 118080-82-3), Compound **19** (*tert*-butyl prop-2-ynylcarbamate, or N-Boc-propargylamine, CAS Registry No. 92136-39-5), and compound **23** (*tert*-butyl 2-methylbut-3-yn-2-ylcarbamate, N-boc-2-amino-2-methylbut-3-yne, CAS Registry No. 113486-06-9) are commercially available from numerous commercial suppliers. Similarly to **12**, **19** and **23**, suitably substituted alkynes that may be used in the preparation of any of formulae **IV-XVIII** above are commercially available and/or readily prepared using routine procedures.

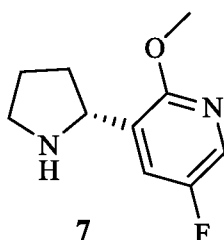
The present application also provides a method of preparing a compound **9** as set out, for example, in Scheme 6



In some embodiments, the process for preparing the compound of any one of Formulae **I**, **II** or **III** further comprises preparing the compound of formula **9**

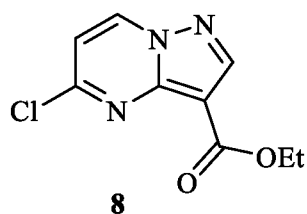


or a salt thereof, by a process comprising reacting a compound of formula **7**



5

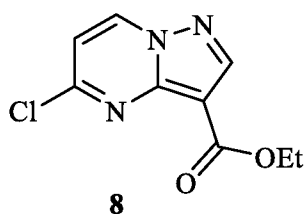
or a salt thereof, with a compound of formula **8**



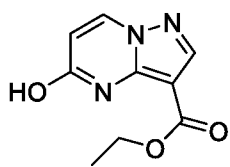
or a salt thereof, in the presence of a second non-nucleophilic base, to form a compound of formula **9**.

10

In some embodiments, the process for preparing the compound of any one of Formulae **I**, **II** or **III** further comprises preparing the compound of formula **8**

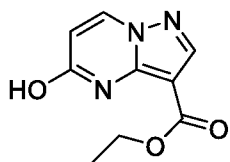


or a salt thereof, by a process comprising reacting

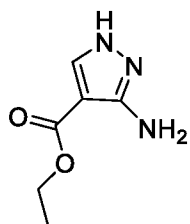


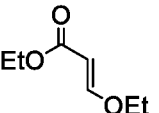
or a salt thereof with POCl_3 in an organic solvent to form a compound of formula **8**. In some embodiments, the organic solvent is acetonitrile.

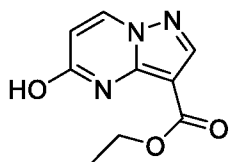
In some embodiments, the process for preparing the compound of any one of Formulae **I**, **II** or **III** further comprises preparing



5 or a salt thereof, by a process comprising reacting



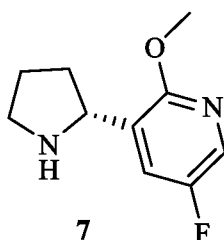
with  in the presence of a phosphate salt to form



. In some embodiments, the phosphate salt is potassium phosphate.

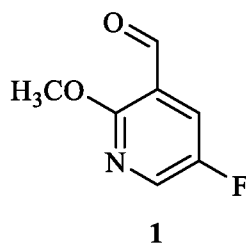
10 In some embodiments, the second non-nucleophilic base is selected from triethylamine and diisopropylethylamine. In some embodiments, the second non-nucleophilic base is triethylamine.

In some embodiments, the process for preparing the compound of any one of Formulae **I**, **II** or **III** further comprises preparing the compound of formula **7**

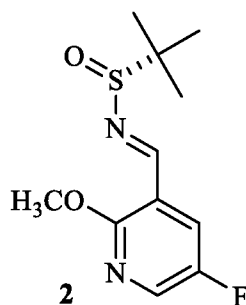


15 or a salt thereof, by a process comprising:

a) treating a compound of formula **1**

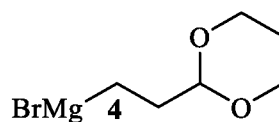


or a salt thereof, with (*R*)-2-methylpropane-2-sulfinamide to form a compound of formula **2**



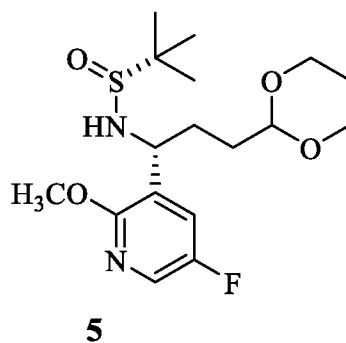
5 or a salt thereof;

b) reacting the compound of formula **2** or a salt thereof with a compound of formula **4**



to form a compound of formula **5**

10



or a salt thereof;

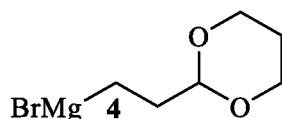
c) treating the compound of formula **5** with a first mixture comprising an acid such as trifluoroacetic acid and water to form a second mixture; and

d) treating the second mixture with a reducing agent, to form the compound of formula 7 or a salt thereof.

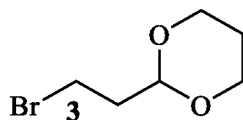
In some embodiments, the compound of formula 1 or a salt thereof, is treated with (*R*)-2-methylpropane-2-sulfinamide in the presence of an activating agent. In some
 5 embodiments, the activating agent is selected from cesium carbonate, CuSO₄, Ti(OEt)₄, other Ti(IV) compounds, sodium carbonate and lithium carbonate. In some embodiments, the activating agent is selected from cesium carbonate, CuSO₄, Ti(OEt)₄, and other Ti(IV) compounds. In some embodiments, the activating agent is cesium carbonate.

10 In some embodiments, the reducing agent is a silane. In some embodiments, the reducing agent is triethylsilane.

In some embodiments, the compound of formula 4



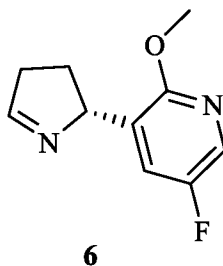
is prepared by a process comprising treating a compound of formula 3



15 with magnesium.

In some embodiments, the first mixture comprising an acid such as trifluoroacetic acid and water comprises 4:1 trifluoroacetic acid:water.

In some embodiments, the second mixture comprises a compound of formula 6



20 In some embodiments, the process comprises isolating the compound of formula 6 from the second mixture.

In some embodiments, the compound of formula 7 or a salt thereof is prepared by a process comprising:

a) treating a compound of formula **1** or a salt thereof with (*R*)-2-methylpropane-2-sulfinamide to form a compound of formula **2** or a salt thereof;

b) reacting the compound of formula **2** or a salt thereof with a compound of formula **4** to form a compound of formula **5** or a salt thereof;

5 c) treating the compound of formula **5** with a first mixture comprising an acid such as trifluoroacetic acid and water to form a compound of formula **6**;

d) isolating the compound of formula **6**; and

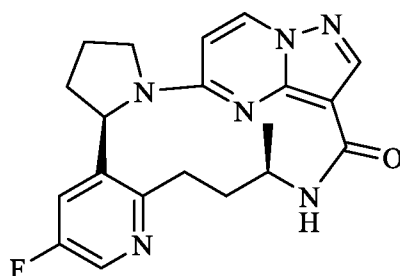
e) treating the compound of formula **6** with triethylsilane, to form the compound of formula **7** or a salt thereof.

10 In some embodiments, the compound of formula **1** or a salt thereof, is treated with (*R*)-2-methylpropane-2-sulfinamide in the presence of an activating agent. In some embodiments, the activating agent is selected from cesium carbonate, CuSO₄, Ti(OEt)₄, other Ti(IV) compounds, sodium carbonate and lithium carbonate. In some embodiments, the activating agent is selected from cesium carbonate, CuSO₄, Ti(OEt)₄, and other
15 Ti(IV) compounds. In some embodiments, the activating agent is cesium carbonate.

In some embodiments, the compound of formula **4** is prepared by a process comprising treating a compound of formula **3** with magnesium.

In some embodiments, the first mixture comprising an acid such as trifluoroacetic acid and water comprises 4:1 trifluoroacetic acid:water.

20 Provided herein in some embodiments is a compound of Formula I



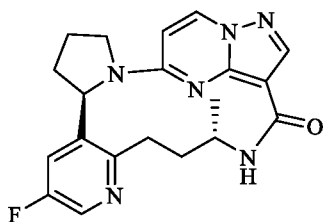
Formula I

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

25 Provided herein in some embodiments is a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a pharmaceutically acceptable carrier.

Provided herein in some embodiments is a method of treating a disease in which one or more Trk kinases (e.g., TrkA, TrkB, and/or TrkC) is activated, e.g., by a soluble growth factor such as a neurotrophin (NT), such as a disease disclosed herein, comprising administering to a subject an effective amount of the compound of Formula I or a pharmaceutically acceptable salt, solvate or hydrate thereof.

In some embodiments of the compound of Formula I, a pharmaceutical composition comprising the compound of Formula I, or a method of treating a disease comprising administering to a subject an effective amount of the compound of Formula I, the compound of Formula I is present in a diastereomeric excess (d.e.) of at least 80% relative to the diastereomeric compound of formula I':



formula I'.

In some embodiments, the compound of Formula I is present in a d.e. of at least 90% relative to the compound of formula I'. In some embodiments, the compound of Formula I is present in a d.e. of at least 92% relative to the compound of formula I'. In some embodiments, the compound of Formula I is present in a d.e. of at least 94% relative to the compound of formula I'. In some embodiments, the compound of Formula I is present in a d.e. of at least 96% relative to the compound of formula I'. In some embodiments, the compound of Formula I is present in a d.e. of at least 98% relative to the compound of formula I'.

In some embodiments, the compound of Formula I is prepared from a mixture of the compound of Formula I and the compound of formula I' by separating the two compounds. In some embodiments, the two compounds are separated by chromatography.

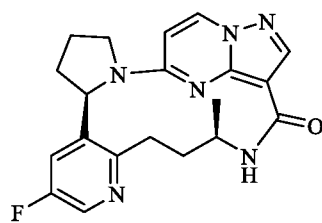
Table 54 provides exemplary properties of the compound of Formula I and of formula I':

Table 54

Compound	formula I'	Formula I
Aqueous solubility, pH 6.5 buffer (μg/mL)	43	111
Human Microsome Clearance (% ER)	92	79
Rat Microsome Clearance (% ER)	77	51
Human Hepatocyte Clearance (% ER)	74	48
Rat Hepatocyte Clearance (% ER)	83	64
MDRI efflux ratio	5	14
hERG IC ₅₀ (μM)	9	27

Referring to the Table 54, the solubility measurement protocol is disclosed in Example 33 hereinbelow. The Microsome and hepatocyte clearance measurement protocol is disclosed in Example 34 hereinbelow. The MDR1 efflux protocol is disclosed in Example 35 hereinbelow. The hERG IC₅₀ values were measured using the ChanTest Fast Patch assay, available from Charles River Laboratories International, Inc. (<http://www.criver.com/products-services/drug-discovery/capabilities/ion-channel/selectivity-profiling>).

In one general aspect, the present disclosure is directed to forms of (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosal(24),7,9,11,18(25),19,22-heptaen-17-one (Compound 1), the structure of which is shown below:



(Compound 1).

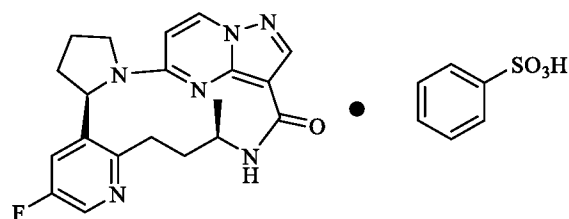
Compound 1 is an inhibitor of Trk kinase useful in the treatment of diseases in which one or more Trk kinases (e.g., TrkA, TrkB, and/or TrkC) is activated, e.g., by a soluble growth factor such as a neurotrophin (NT). Compound 1 may be referred to herein as “Compound 1 free base”. In some embodiments, Compound 1 provided herein

is a solid form. In some embodiments, the solid form is crystalline (e.g., Form I).

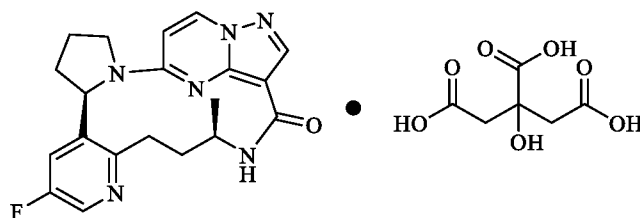
In another general aspect, the present disclosure is directed to salts of Compound 1.

In some embodiments, the salt of the present disclosure is a benzenesulfonic acid salt of Compound 1, which is referred to herein as “Compound 1 besylate”. In some

5 embodiments, Compound 1 besylate has the following structure:

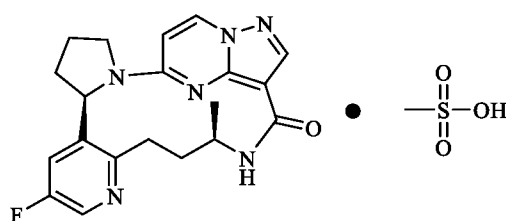


In some embodiments, the salt of the present disclosure is a citric acid salt of Compound 1, which is referred to herein as “Compound 1 citrate”. In some embodiments, the Compound 1 citrate has the following structure:



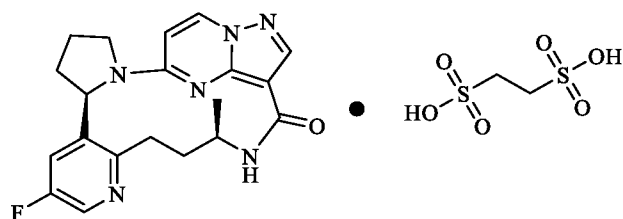
10

In some embodiments, the salt of the present disclosure is a methanesulfonic acid salt of Compound 1, which is referred to herein as “Compound 1 mesylate”. In some embodiments, the Compound 1 mesylate has the following structure:

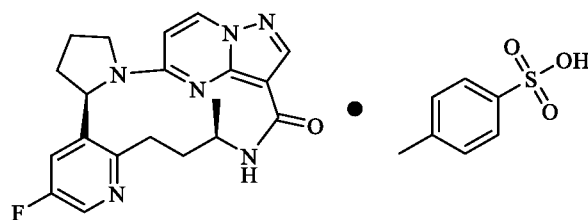


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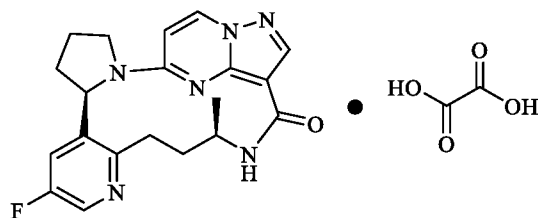
In some embodiments, the salt of the present disclosure is a 1,2-ethane disulfonic acid salt of Compound 1, which is referred to herein as “Compound 1 edisylate”. In some embodiments, the Compound 1 edisylate has the following structure:



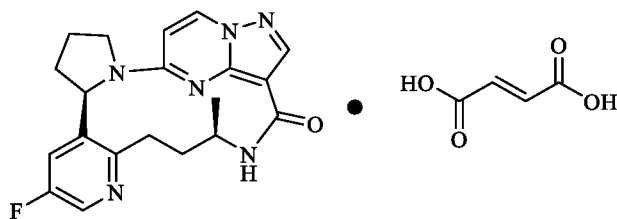
In some embodiments, the salt of the present disclosure is a *p*-toluene sulfonic acid salt of Compound 1, which is referred to herein as “Compound 1 tosylate”. In some embodiments, the Compound 1 tosylate has the following structure:



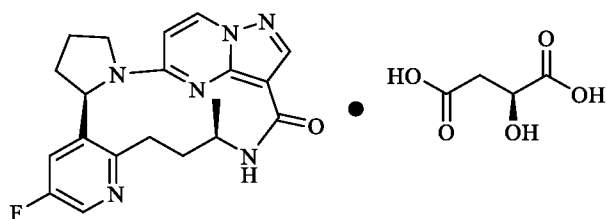
In some embodiments, the salt of the present disclosure is an oxalic acid salt of Compound 1, which is referred to herein as “Compound 1 oxalate”. In some embodiments, the Compound 1 oxalate has the following structure:



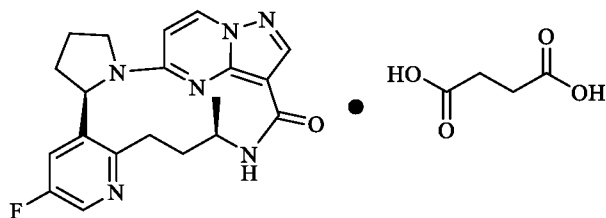
In some embodiments, the salt of the present disclosure is a fumaric acid salt of Compound 1, which is referred to herein as “Compound 1 fumarate”. In some embodiments, the Compound 1 fumarate has the following structure:



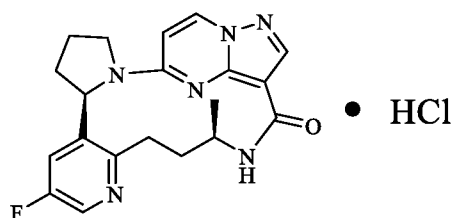
In some embodiments, the salt of the present disclosure is a L-malic acid salt of Compound 1, which is referred to herein as “Compound 1 L-malate”. In some embodiments, the Compound 1 L-malate has the following structure:



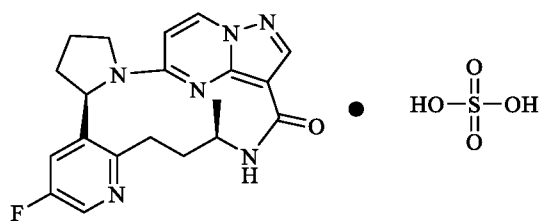
In some embodiments, the salt of the present disclosure is a succinic acid salt of Compound 1, which is referred to herein as “Compound 1 succinate”. In some embodiments, the Compound 1 succinate has the following structure:



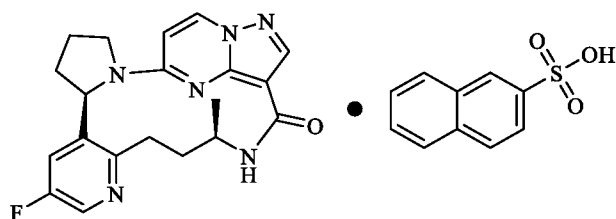
In some embodiments, the salt of the present disclosure is a hydrochloric acid salt of Compound 1, which is referred to herein as “Compound 1 hydrochloride”. In some embodiments, the Compound 1 hydrochloride has the following structure:



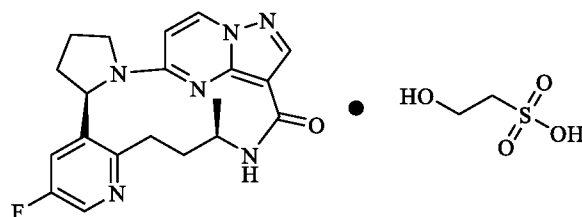
In some embodiments, the salt of the present disclosure is a sulfuric acid salt of Compound 1, which is referred to herein as “Compound 1 sulfate”. In some embodiments, the Compound 1 sulfate has the following structure:



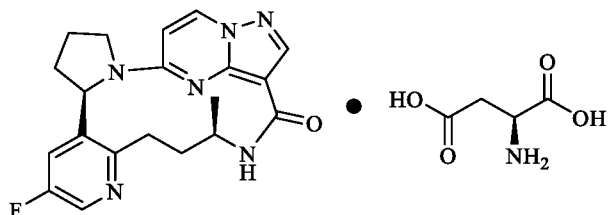
In some embodiments, the salt of the present disclosure is a naphthalene-2-sulphonic acid salt of Compound 1, which is referred to herein as “Compound 1 2-naphthalenesulfonate”. In some embodiments, the Compound 1 2-naphthalenesulfonate has the following structure:



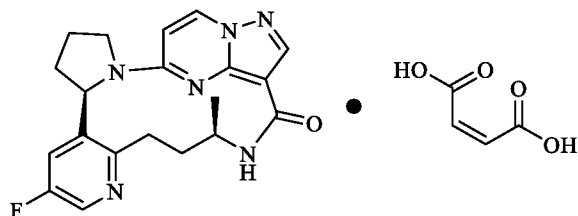
In some embodiments, the salt of the present disclosure is a 2-hydroxyethanesulfonic acid salt of Compound 1, which is referred to herein as “Compound 1 isethionate”. In some embodiments, the Compound 1 isethionate has the following structure:



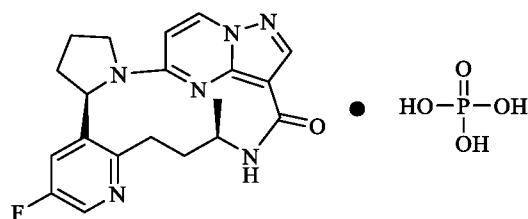
In some embodiments, the salt of the present disclosure is a L-aspartic salt of Compound 1, which is referred to herein as “Compound 1 L-aspartate”. In some embodiments, the Compound 1 L-aspartate has the following structure:



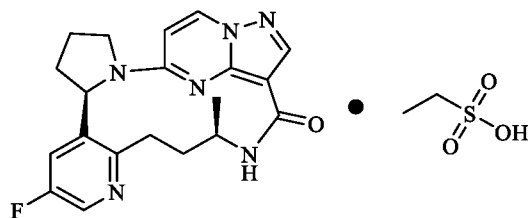
In some embodiments, the salt of the present disclosure is a maleic acid salt of Compound 1, which is referred to herein as “Compound 1 maleate”. In some embodiments, the Compound 1 maleate has the following structure:



In some embodiments, the salt of the present disclosure is a phosphoric acid salt of Compound 1, which is referred to herein as “Compound 1 phosphate”. In some embodiments, the Compound 1 phosphate has the following structure:

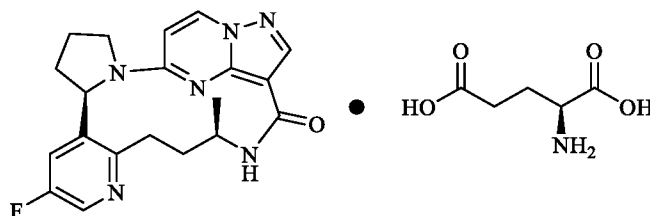


In some embodiments, the salt of the present disclosure is a ethanesulfonic acid salt of Compound 1, which is referred to herein as “Compound 1 esylate”. In some embodiments, the Compound 1 esylate has the following structure:



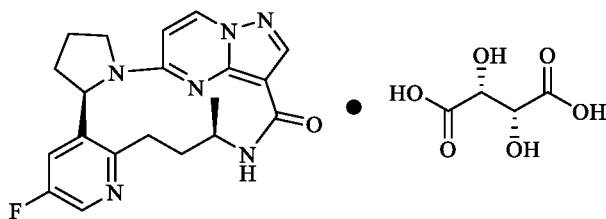
5

In some embodiments, the salt of the present disclosure is a L-glutamic acid salt of Compound 1, which is referred to herein as “Compound 1 L-glutamate”. In some embodiments, the Compound 1 L-glutamate has the following structure:



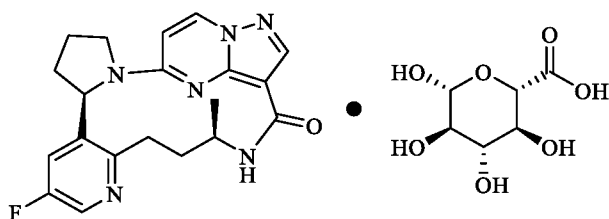
10

In some embodiments, the salt of the present disclosure is a L-tartaric acid salt of Compound 1, which is referred to herein as “Compound 1 L-tartrate”. In some embodiments, the Compound 1 L-tartrate has the following structure:

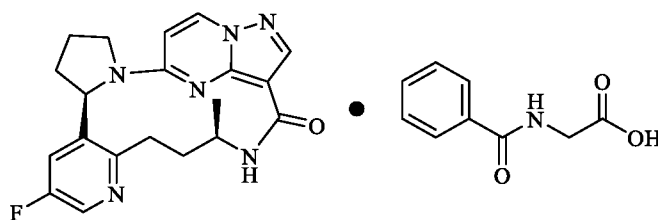


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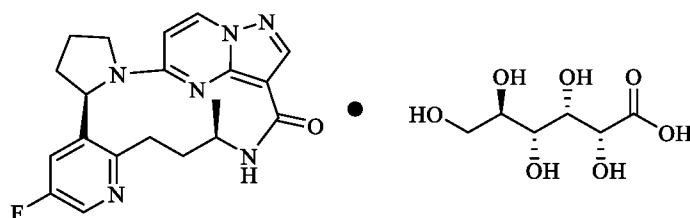
In some embodiments, the salt of the present disclosure is a D-glucuronic acid salt of Compound 1, which is referred to herein as “Compound 1 D-glucuronate”. In some embodiments, the Compound 1 D-glucuronate has the following structure:



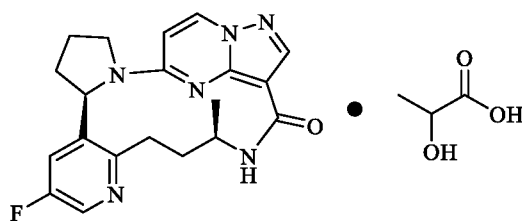
In some embodiments, the salt of the present disclosure is a hippuric acid salt of Compound 1, which is referred to herein as “Compound 1 hippurate”. In some embodiments, the Compound 1 hippurate has the following structure:



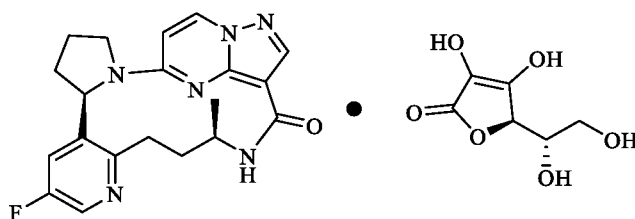
In some embodiments, the salt of the present disclosure is a D-gluconic acid salt of Compound 1, which is referred to herein as “Compound 1 D-gluconate”. In some embodiments, the Compound 1 D-gluconate has the following structure:



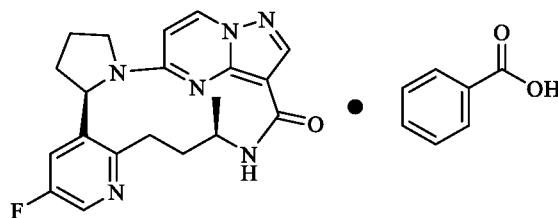
In some embodiments, the salt of the present disclosure is a DL-lactic acid salt of Compound 1, which is referred to herein as “Compound 1 lactate”. In some embodiments, the Compound 1 lactate has the following structure:



In some embodiments, the salt of the present disclosure is a L-ascorbic acid salt of Compound 1, which is referred to herein as “Compound 1 L-ascorbate”. In some embodiments, the Compound 1 L-ascorbate has the following structure:



In some embodiments, the salt of the present disclosure is a benzoic acid salt of Compound 1, which is referred to herein as “Compound 1 benzoate”. In some embodiments, the Compound 1 benzoate has the following structure:



The salts of the present application can be isolated as one or more solid forms. The solid forms, crystalline forms, solvated forms, hydrated forms of the Compound 1 and the salts of Compound 1 are described below, along with the methods of making the same and using the same for therapeutic purposes.

Compound 1 free base

In some embodiments, Compound 1 is in the form of the crystalline free base. In some embodiments, Compound 1 is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 99% crystalline.

In some embodiments, Form I is substantially free of other forms of Compound 1. In some embodiments, Form I contains less than 10%, such as less than 5%, such as less than 3%, such as less than 1% of other forms of Compound 1. In some embodiments, Form I is substantially free of the amorphous form of Compound 1. In some embodiments, Form I contains less than 10%, such as less than 5%, such as less than 3%, such as less than 1%, of the amorphous form of Compound 1.

In some embodiments, Form I is substantially free of other stereoisomers of Compound 1. In some embodiments, Form I contains less than 10%, such as less than 5%, such as less than 3%, such as less than 1% of other stereoisomers of Compound 1. In some embodiments, Form I has an XRPD pattern substantially as depicted in Figure 1. In

some embodiments, Form I has a XRPD peak, in terms of 2-theta, at about 20.2 degrees. In some embodiments, Form I has XRPD peaks, in terms of 2-theta, at about 9.1, about 20.2 and about 24.9. In some embodiments, Form I has XRPD peaks, in terms of 2-theta, at about 9.1, about 11.2, about 20.2 and about 24.9. In some embodiments, Form I has XRPD peaks, in terms of 2-theta, at about 9.1, about 11.2, about 13.4, about 14.8, about 20.2, and about 29.4. In some embodiments, Form I has XRPD peaks, in terms of 2-theta, at about 9.1, about 11.2, about 13.4, about 14.8, about 18.3, about 18.6, about 20.2, about 23.6, about 24.9, and about 29.4.

In some embodiments, Form I has at least one, at least two or at least three XRPD peaks, in terms of 2-theta, selected from about 9.1, about 11.2, about 13.4, about 20.2, and about 24.9 degrees. In some embodiments, Form I has at least one, at least two or at least three XRPD peaks, in terms of 2-theta, selected from about 9.1, about 11.2, about 13.4, about 14.8, about 16.8, about 18.3, about 18.6, about 20.2, about 21.4, about 22.7, about 23.6, about 24.9, and about 29.4. In some embodiments, Form I has at least one, at least two or at least three XRPD peaks, in terms of 2-theta, selected from about 9.1, about 11.2, about 13.4, about 14.8, about 18.3, about 18.6, about 20.2, about 23.6, about 24.9, and about 29.4. In some embodiments, Form I has at least one, at least two or at least three XRPD peaks, in terms of 2-theta, selected from about 9.1, about 11.2, about 13.4, about 14.8, about 20.2, and about 29.4.

In some embodiments, Form I has a DTA thermogram substantially as depicted in Figure 2. In some embodiments, Form I has a DTA thermogram characterized by an endothermic event at about 317 °C. In some embodiments, Form I has a DSC thermogram substantially as depicted in Figure 3. In some embodiments, Form I has a DSC thermogram characterized by an endothermic event at about 317 °C. In some aspects of the aforementioned embodiments, the endothermic event is a melting point. In some embodiments, Form I has a DSC thermogram characterized by an endothermic event at about 124 °C (e.g., at the second heating cycle). In some aspects of these embodiments, the endothermic event at about 124 °C is a glass transition temperature. Form I of Compound 1 is substantially anhydrous (Form I is not hydrated) and is substantially free of organic solvents (Form I is not solvated).

In some embodiments, Form I has hygroscopicity characterized by a mass uptake

of about 0.3% at 90% RH as determined by GVS analysis. In other embodiments, Form I has hygroscopicity characterized by a mass uptake of about 0.7% at 90% RH as determined by DVS analysis. In some embodiments, Form I is substantially pure (e.g., the purity of the compound is at least about 90 wt.%, about 95 wt.%, about 98 wt.%, or about 99 wt.%). Purity values indicate the percentage of the amount of sample that is Form I. Purity values can be determined, for example, by HPLC/UV methods. In some embodiments, Form I is substantially free of impurities, such as organic impurities (e.g., process intermediates), inorganic impurities, and/or residual solvents.

In some embodiments, the crystalline form of Compound 1 exhibits the following single crystal X-ray crystallographic parameters at 120K:

Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	6.91792(3)
b/Å	13.74742(3)
c/Å	19.22580(5)
α /°	90.00
β /°	90.00
γ /°	90.00
Volume / Å ³	1828.442(10)
Z, Z'	4
ρ_{calc} g/cm ³	1.382

In some embodiments, the crystalline form of Compound 1 is substantially as shown in Figures 10 and 11.

In some embodiments, Compound 1 forms a solvate with acetonitrile solvent. In some embodiments, the acetonitrile solvate of Compound 1 is crystalline. In some embodiments, the crystalline form of acetonitrile solvate of Compound 1 exhibits the following single crystal X-ray crystallographic parameters at 120K:

Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	6.03307(4)
b/Å	16.10794(9)
c/Å	23.72624(13)
α /°	90.00
β /°	90.00
γ /°	90.00
Volume / Å ³	2305.73(2)
Z , Z'	4
ρ calc g/cm ³	1.332

In some embodiments, the crystalline form of acetonitrile solvate is substantially as shown in Figures 12 and 13. In some embodiments, the crystalline form of acetonitrile solvate readily desolvates at room temperature to yield the crystalline Form I of

5 Compound 1.

In some embodiments, the present disclosure provides crystalline Form I of Compound 1 prepared as disclosed herein. In one example, the disclosure provides the Form I of Compound 1 prepared by precipitating the solid crystalline form of Compound 1 from a saturated solution of Compound 1 in 1-propanol at about 2 °C.

10

Compound 1 benzenesulfonic acid salt

In some embodiments, provided herein is Compound 1 besylate. In some embodiments, Compound 1 besylate is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 99% crystalline solid. In some embodiments, crystalline Compound 1 besylate is substantially free of other forms of Compound 1 besylate. In some embodiments, crystalline Compound 1 besylate contains less than 10%, such as less than 5%, such as less than 3% of other forms of Compound 1 besylate. In some embodiments, the crystalline Compound 1 besylate is substantially free of the amorphous form of Compound 1 besylate. In some embodiments, the crystalline Compound 1

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besylate contains less than 10%, less than 5%, or less than 3% of the amorphous form of Compound 1 besylate.

In some embodiments, the molar ratio of Compound 1 to the benzenesulfonic acid in the besylate is about 1:1. In some embodiments, Compound 1 besylate is a monobesylate.

In some embodiments, the crystalline Compound 1 besylate has an XRPD pattern substantially as depicted in Figure 17. In other embodiments, the crystalline Compound 1 besylate has an XRPD pattern substantially as depicted in Figure 18.

In some embodiments, the crystalline Compound 1 besylate has a XRPD peak, in terms of 2-theta, at about 8.1 degrees. In some embodiments, the crystalline Compound 1 besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 13.4, and about 21.2. In some embodiments, the crystalline Compound 1 besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 12.0, about 13.4, about 19.0, about 19.4, and about 21.2. In some embodiments, the crystalline Compound 1 besylate has XRPD peaks, in terms of 2-theta, at about 8.1, about 12.0, about 13.4, about 19.0, about 19.4, about 19.9, about 20.1, about 21.2, about 25.5, and about 32.7.

In some embodiments, the crystalline Compound 1 besylate has a XRPD peak, in terms of 2-theta, at about 8.1, about 13.4, or about 21.2. In some embodiments, the crystalline Compound 1 besylate has at least one, at least two, or at least three XRPD peaks, in terms of 2-theta, selected from about 8.1, about 9.2, about 12.0, about 13.4, about 19.0, about 19.4, about 19.9, about 20.1, about 21.2, about 25.5, about 27.0, about 32.0, and about 32.7. In some embodiments, the crystalline Compound 1 besylate has at least one, at least two, or at least three XRPD peaks, in terms of 2-theta, selected from about 8.1, about 12.0, about 13.4, about 19.0, about 19.4, and about 21.2. In some embodiments, the crystalline Compound 1 besylate has at least one, at least two, or at least three XRPD peaks, in terms of 2-theta, selected from about 8.1, about 12.0, about 13.4, about 19.0, about 19.4, about 19.9, about 20.1, about 21.2, about 25.5, and about 32.7.

In some embodiments, the crystalline Compound 1 besylate has a DTA thermogram substantially as depicted in Figure 37. In some embodiments, the crystalline Compound 1 besylate has a DTA thermogram characterized by an endothermic event at

about 248 °C. In some aspects of these embodiments, the endothermal event is a melting point. In some embodiments, the crystalline Compound 1 besylate has a DSC thermogram substantially as depicted in Figure 38. In some embodiments, the crystalline Compound 1 besylate has a DSC thermogram characterized by an endothermal event at about 249 °C.

In some embodiments, the crystalline Compound 1 besylate has hygroscopicity characterized by a mass uptake of about 0.7% at 90% RH as determined by DVS analysis. The crystalline Compound 1 besylate is substantially anhydrous (the crystalline form of the besylate is not hydrated) and is substantially free of organic solvents (the crystalline form of the besylate is not solvated).

In some embodiments, the crystalline Compound 1 besylate is substantially pure (e.g., free of organic, inorganic or other impurities). In some embodiments, the purity of the crystalline Compound 1 besylate is 90 wt.% or more, 95 wt.% or more, or 99 wt.% or more. In some embodiments, the crystalline Compound 1 besylate is substantially free of other crystalline forms of Compound 1 besylate.

In some embodiments, the benzenesulfonic acid salt of Compound 1 may form a hydrate. In some aspects of these embodiments, the hydrate is crystalline.

In some embodiments, the present disclosure provides a crystalline Compound 1 besylate prepared as disclosed herein. In one example, the application provides the crystalline Compound 1 besylate prepared by precipitating the solid crystalline form of Compound 1 besylate from a mixture of Compound 1 besylate with THF (e.g., a solution of Compound 1 besylate in THF). In another example, the application provides the crystalline Compound 1 besylate prepared by precipitating the crystalline form of Compound 1 besylate from a mixture of Compound 1 besylate with ethanol (e.g., a solution of Compound 1 besylate in ethanol).

Compound 1 citric acid salt

In some embodiments, provided herein is Compound 1 citrate. In some embodiments, Compound 1 citrate is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 99% crystalline solid. In some embodiments, crystalline Compound 1 citrate is substantially free of other forms of Compound 1 citrate. In some

embodiments, crystalline Compound 1 citrate contains less than 10%, such as less than 5%, such as less than 3% of other forms of Compound 1 citrate. In some embodiments, the crystalline form of Compound 1 citrate is substantially free of the amorphous form of Compound 1 citrate. In some embodiments, the crystalline form of Compound 1 citrate
5 contains less than 10%, less than 5%, or less than 3% of the amorphous form of compound 1 citrate.

In some embodiments, the molar ratio of Compound 1 to the citric acid in the citrate is about 1:1. In some embodiments, Compound 1 citrate is a monocitrate.

In some embodiments, crystalline Compound 1 citrate has Form A, which is described
10 below in the Examples. In some embodiments, the Compound 1 citrate Form A has an XRPD pattern substantially as depicted in Figure 21.

In some embodiments, the Compound 1 citrate Form A has a XRPD peak, in terms of 2-theta, at about 20.7 degrees. In some embodiments, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 20.7, about 21.6, and about 24.8. In
15 some embodiments, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 8.9, about 11.1, about 14.4, about 15.4, about 20.7, about 21.6, and about 24.8. In some embodiments, Compound 1 citrate Form A has XRPD peaks, in terms of 2-theta, at about 8.9, about 11.1, about 13.9, about 14.4, about 15.4, about 19.2, about 20.7, about 21.6, about 24.8, and about 25.6.

In some embodiments, Compound 1 citrate Form A has at least one, at least two, or at least three XRPD peaks, in terms of 2-theta, selected from about 6.5, about 8.9, about 9.2, about 11.1, about 13.9, about 14.4, about 15.4, about 15.9, about 18.0, about 19.2, about 19.6, about 20.7, about 21.6, about 22.7, about 23.3, about 23.7, about 24.2, about 24.8, about 25.6, about 26.3, about 26.5, about 26.8, about 27.9, about 28.9, about
20 29.1, about 30.2, about 32.5, and about 33.7. In some embodiments, Compound 1 citrate Form A has at least one, at least two, or at least three XRPD peaks, in terms of 2-theta, selected from about 6.5, about 8.9, about 9.2, about 11.1, about 13.9, about 14.4, about 15.4, about 15.9, about 18.0, about 19.2, about 19.6, about 20.7, about 21.6, about 23.3, about 23.7, about 24.2, about 24.8, about 25.6, about 26.5, and about 27.9. In some
25 30 embodiments, Compound 1 citrate Form A has at least one, at least two, or at least three XRPD peaks, in terms of 2-theta, selected from about 8.9, about 11.1, about 14.4, about

15.4, about 19.2, about 20.7, about 21.6, about 24.8, and about 25.6.

In some embodiments, Compound 1 citrate Form A has at least one, at least two, or at least three XRPD peaks, in terms of 2-theta, selected from about 6.5, about 8.9, about 9.2, about 11.1, about 13.9, about 14.4, about 15.4, about 15.9, about 18.0, about 19.2, about 19.6, about 20.7, about 21.6, about 22.3, about 22.7, about 23.3, about 23.7, about 24.2, about 24.8, about 25.6, about 26.3, about 26.5, about 26.8, about 27.9, about 28.9, about 29.1, about 30.2, about 30.6, about 31.8, about 32.5, about 33.1, about 33.7, about 34.3, and about 34.5.

In some embodiments, Compound 1 citrate Form A has a DTA thermogram substantially as depicted in Figure 43. In some embodiments, Compound 1 citrate Form A has a DTA thermogram characterized by an endothermic event at about 194 °C. In some embodiments, Compound 1 citrate Form A has a DTA thermogram characterized by an endothermic event at about 318 °C. In some embodiments, Compound 1 citrate Form A has a DTA thermogram characterized by an endothermic event at about 194 °C and an endothermic event at about 318 °C. In some embodiments, Compound 1 citrate Form A has a DSC thermogram substantially as depicted in Figure 44. In some embodiments, Compound 1 citrate Form A has a DSC thermogram characterized by an endothermic event at about 205 °C. In some embodiments, Compound 1 citrate Form A has a DSC thermogram characterized by an endothermic event at about 194 °C and an endothermic event at about 205 °C. In some aspects of these embodiments, the endothermic events are overlapping.

In some embodiments, Compound 1 citrate Form A has hygroscopicity characterized by a mass uptake of around 1.8 % at 90 % RH as determined by DVS analysis. Compound 1 citrate Form A is substantially anhydrous (Form A is not hydrated) and is substantially free of organic solvents (Form A is not solvated).

In some embodiments, Compound 1 citrate Form A is substantially pure (e.g., free of organic, inorganic or other impurities). In some embodiments, the purity of Compound 1 citrate Form A is 90 wt.% or more, 95 wt.% or more, or 99 wt.% or more. In some embodiments, Compound 1 citrate Form A is substantially free of other crystalline forms of Compound 1 citrate. For example, Compound 1 citrate Form A is substantially free of Compound 1 citrate Form B.

In some embodiments, the citric acid salt of Compound 1 may form a hydrate. In some aspects of these embodiments, the hydrate is crystalline.

In some embodiments, the crystalline Compound 1 citrate has Form B, which has an XRPD pattern substantially as depicted in Figure 49.

5 In some embodiments, the present disclosure provides a crystalline form of Compound 1 citrate prepared as disclosed herein. In one example, the present application provides Compound 1 citrate Form A prepared by precipitating Form A from a mixture of Compound 1 citrate with acetone (e.g., a solution of Compound 1 in acetone).

10 Compound 1 methanesulfonic acid salt

In some embodiments, provided herein is Compound 1 mesylate. In some embodiments, the Compound 1 mesylate is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 99% crystalline solid. In some embodiments, the crystalline form of Compound 1 mesylate is substantially free of the amorphous form of
15 Compound 1 mesylate. In some embodiments, the crystalline form of Compound 1 mesylate contains less than 10%, less than 5%, or less than 3% of the amorphous form of compound 1 mesylate.

In some embodiments, the molar ratio of the Compound 1 to the methanesulfonic acid in the mesylate is about 1:1. In some embodiments, the Compound 1 mesylate is a
20 monomesylate.

In some embodiments, the crystalline form of Compound 1 mesylate has an XRPD pattern substantially as depicted in Figure 16. In some embodiments, the crystalline solid of the Compound 1 mesylate has a DTA thermogram substantially as depicted in Figure 25. In some embodiments, the crystalline solid of the Compound 1
25 mesylate has a DTA thermogram characterized by an endothermic event at about 232 °C (e.g., a melting point of the mesylate). In some embodiments, the crystalline Compound 1 mesylate has a DSC thermogram substantially as depicted in Figure 32. In some embodiments, the crystalline Compound 1 mesylate has a DSC thermogram characterized by an endothermic event at about 233 °C. The crystalline form of the mesylate is
30 substantially anhydrous (the crystalline form is not hydrated) and is substantially free of organic solvents (the crystalline form is not solvated). In some embodiments, the

crystalline form of the mesylate is substantially pure (e.g., purity is 90 wt.% or more, 95 wt.% or more, or 99 wt.% or more). In some embodiments, the crystalline form of Compound 1 mesylate is substantially free of other crystalline forms of Compound 1 mesylate.

5 Compound 1 mesylate can be prepared as an acetone solvate. In some embodiments, the acetone solvate of the mesylate is a solid form (e.g., an amorphous solid, a crystalline solid, or a mixture thereof). In some embodiments, the acetone solvate of the mesylate is crystalline. In some embodiments, the crystalline form of the acetone solvate of the mesylate salt of Compound 1 is has an XRPD pattern substantially as depicted in Figure 30. In some embodiments, the crystalline acetone solvate has a DTA thermogram substantially as depicted in Figure 31. In some embodiments, the crystalline acetone solvate has a DTA thermogram characterized by an endothermic event at about 125 °C and an endothermic event at about 232 °C (melting point). The endothermic event at about 125 °C is likely associated with the desolvation of the material. In some
10 embodiments, the crystalline acetone solvate has a DSC thermogram characterized by an endothermic event at about 233 °C at the first heating cycle, a solidification event at about 181 °C at the first cooling cycle, and an endothermic event at about 229 °C at the second heating cycle. In some embodiments, the acetone solvate readily desolvates upon heating to produce crystalline form of the Compound 1 mesylate.

15 In some embodiments, the present disclosure provides a crystalline form of Compound 1 mesylate prepared as disclosed herein. In one example, the application provides the crystalline form of Compound 1 mesylate prepared by precipitating the solid crystalline form of Compound 1 mesylate from a mixture of Compound 1 mesylate in 2-propanol (e.g., a solution of Compound 1 in isopropanol).

Other salts

20 In some embodiments provided herein is a salt of Compound 1 which is Compound 1 edisylate, Compound 1 tosylate, Compound 1 oxalate, Compound 1 fumarate, Compound 1 L-malate or Compound 1 succinate. In some embodiments, each
25 of Compound 1 edisylate, Compound 1 tosylate, Compound 1 oxalate, Compound 1 fumarate, Compound 1 L-malate and or Compound 1 succinate can be prepared as a solid

form, e.g., as an amorphous solid, as a crystalline solid, or as a mixture thereof. In some aspects of these embodiments, any of the aforementioned salts of Compound 1 is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 99% crystalline solid. In other aspects of these embodiments, the crystalline salt of Compound 1 is
5 substantially free of the amorphous form of the salt. For example, Compound 1 salt contains less than 10%, less than 5%, or less than 3% of the amorphous form of the salt.

In some embodiments, the present disclosure provides crystalline forms of Compound 1 edisylate, Compound 1 tosylate, Compound 1 oxalate, Compound 1 fumarate, Compound 1 L-malate or Compound 1 succinate prepared as disclosed herein.

10 In some embodiments, the crystalline Compound 1 edisylate has an XRPD pattern substantially as depicted in Figure 14.

In some embodiments, the crystalline Compound 1 edisylate has XRPD peaks, in terms of 2-theta, at about 20.0, about 20.6, and about 23.3. In some embodiments, the crystalline Compound 1 edisylate has XRPD peaks, in terms of 2-theta, at about 18.1,
15 about 18.3, about 20.0, about 20.6, about 23.3, and about 25.3. In some embodiments, the crystalline Compound 1 edisylate has XRPD peaks, in terms of 2-theta, at about 11.6, about 15.5, about 17.0, about 18.1, about 18.3, about 20.0, about 20.6, about 23.3, about 24.9, and about 25.3.

In some embodiments, the crystalline Compound 1 tosylate has an XRPD pattern
20 substantially as depicted in Figure 15.

In some embodiments, the crystalline Compound 1 tosylate has XRPD peaks, in terms of 2-theta, at about 6.6, about 16.9, and about 21.2. In some embodiments, the crystalline Compound 1 tosylate has XRPD peaks, in terms of 2-theta, at about 6.6, about 8.2, about 15.0, about 16.9, about 21.2, and about 21.6. In some embodiments, the
25 crystalline Compound 1 tosylate has XRPD peaks, in terms of 2-theta, at about 6.6, about 8.2, about 11.8, about 15.0, about 16.9, about 21.2, about 21.6, about 21.9, about 24.2 and about 24.9.

In some embodiments, the crystalline Compound 1 tosylate has a DTA thermogram substantially as depicted in Figure 24. In some embodiments, the crystalline
30 Compound 1 tosylate has a DTA thermogram characterized by an endothermal event at about 90 °C.

In some embodiments, the crystalline Compound 1 oxalate has an XRPD pattern substantially as depicted in Figure 19.

In some embodiments, the crystalline Compound 1 oxalate has XRPD peaks, in terms of 2-theta, at about 20.2, about 20.5, and about 24.9. In some embodiments, the crystalline Compound 1 oxalate has XRPD peaks, in terms of 2-theta, at about 11.2, about 18.6, about 20.2, about 20.5, about 23.5, and about 24.9. In some embodiments, the crystalline Compound 1 oxalate has XRPD peaks, in terms of 2-theta, at about 11.2, about 18.6, about 20.0, about 20.2, about 20.5, about 21.1, about 22.9, about 23.5, about 24.9, and about 27.0.

In some embodiments, the crystalline Compound 1 oxalate has a DTA thermogram substantially as depicted in Figure 26. In some embodiments, the crystalline Compound 1 oxalate has a DTA thermogram characterized by an endothermal event at about 317 °C (a melting point).

In some embodiments, the crystalline Compound 1 fumarate has an XRPD pattern substantially as depicted in Figure 20.

In some embodiments, the crystalline Compound 1 fumarate has XRPD peaks, in terms of 2-theta, at about 9.3, about 21.6, and about 27.1. In some embodiments, the crystalline Compound 1 fumarate has XRPD peaks, in terms of 2-theta, at about 9.3, about 14.8, about 21.6, about 22.2, about 27.1, and about 27.9. In some embodiments, the crystalline Compound 1 fumarate has XRPD peaks, in terms of 2-theta, at about 6.4, about 9.3, about 14.8, about 19.4, about 19.8, about 20.4, about 21.6, about 22.2, about 27.1, and about 27.9.

In some embodiments, the crystalline Compound 1 fumarate has a DTA thermogram substantially as depicted in Figure 27. In some embodiments, the crystalline Compound 1 fumarate has a DTA thermogram characterized by an endothermal event at about 166 °C. In some embodiments, the crystalline Compound 1 fumarate has a DTA thermogram characterized by an endothermal event at about 191 °C. In some embodiments, the crystalline Compound 1 fumarate has a DTA thermogram characterized by an endothermal event at about 201 °C. In some embodiments, the crystalline Compound 1 fumarate has a DTA thermogram characterized by an endothermal event at about 312 °C. In some embodiments, the crystalline Compound 1 fumarate has a DTA

thermogram characterized by an endothermal event at about 166 °C, an endothermal event at about 191 °C, an endothermal event at about 201 °C, and an endothermal event at about 312 °C.

In some embodiments, the crystalline Compound 1 L-malate has an XRPD pattern substantially as depicted in Figure 22.

In some embodiments, the crystalline Compound 1 malate has XRPD peaks, in terms of 2-theta, at about 19.3, about 21.6, and about 24.9. In some embodiments, the crystalline Compound 1 malate has XRPD peaks, in terms of 2-theta, at about 10.7, about 13.4, about 18.8, about 19.3, about 21.6, and about 24.9. In some embodiments, the crystalline Compound 1 malate has XRPD peaks, in terms of 2-theta, at about 6.7, about 10.7, about 13.4, about 18.8, about 19.3, about 19.9, about 21.1, about 21.6, about 23.9, and about 24.9.

In some embodiments, the crystalline Compound 1 L-malate has a DTA thermogram substantially as depicted in Figure 28. In some embodiments, the crystalline Compound 1 L-malate has a DTA thermogram characterized by an endothermal event at about 162 °C. In some embodiments, the crystalline Compound 1 L-malate has a DTA thermogram characterized by an endothermal event at about 313 °C. In some embodiments, the crystalline Compound 1 L-malate has a DTA thermogram characterized by an endothermal event at about 162 °C and an endothermal event at about 313 °C.

In some embodiments, the crystalline form of Compound 1 succinate has pattern 1. In some embodiments, the crystalline Compound 1 succinate has an XRPD pattern substantially as depicted in Figure 23.

In some embodiments, the crystalline Compound 1 succinate has XRPD peaks, in terms of 2-theta, at about 9.1, about 21.5, and about 26.8. In some embodiments, the crystalline Compound 1 succinate has XRPD peaks, in terms of 2-theta, at about 9.1, about 11.2, about 19.4, about 21.5, about 26.0, and about 26.8. In some embodiments, the crystalline Compound 1 succinate has XRPD peaks, in terms of 2-theta, at about 6.4, about 9.1, about 11.2, about 14.5, about 15.8, about 19.4, about 20.5, about 21.5, about 26.0, about 26.8.

In some embodiments, the crystalline Compound 1 succinate has a DTA thermogram substantially as depicted in Figure 29. In some embodiments, the crystalline

Compound 1 oxalate has a DTA thermogram characterized by an endothermal event at about 151 °C. In some embodiments, the crystalline Compound 1 oxalate has a DTA thermogram characterized by an endothermal event at about 315 °C. In some
5 embodiments, the crystalline Compound 1 oxalate has a DTA thermogram characterized
by an endothermal event at about 151 °C and an endothermal event at about 315 °C.
Compound 1 hydrochloride, Compound 1 sulfate, Compound 1 2-naphthalenesulfonate,
Compound 1 isethionate, Compound 1 L-aspartate, Compound 1 maleate, Compound 1
phosphate, Compound 1 esylate, Compound 1 glutamate, Compound 1 L-tartrate,
Compound 1 D-glucuronate, Compound 1 hippurate, Compound 1 D-gluconate,
10 Compound 1 lactate, Compound 1 L-ascorbate, Compound 1 benzoate are provided
herein and each of these salts can be prepared by treating Compound 1 with the
corresponding acid.

Synthetic Preparations

Compound 1 and its forms

15 In some embodiments, Compound 1 (free base) may be prepared as described as
disclosed herein. The crystalline form of Compound 1 (e.g., Form I as described herein)
may be prepared by the method comprising precipitating the crystalline form from a
mixture comprising Compound 1 (free base). In some embodiments, the mixture further
20 comprises a solvent. In some embodiments, the method comprises obtaining a mixture of
Compound 1 with a solvent. In some embodiments, the mixture is a solution of
Compound 1 in a solvent. In some embodiments, the solution is saturated. The solvent
may be selected from acetone, acetonitrile, 2-butanone, cyclopropylmethyl ether, 1,2-
dimethoxyethane, 1,4-dioxane, ethanol, ethyl acetate, 2-ethoxy ethanol, isobutyl acetate,
25 isopropyl acetate, methanol, MIBK, 2-propanol, 1-propanol and THF.

 In some embodiments, the precipitating is carried out at a temperature above 0 °C
(e.g., 5 °C, 10 °C, 20 °C, or 30 °C). In some embodiments, the precipitating is carried out
below room temperature. In some aspects of these embodiments, the precipitating is
carried out below 10 °C. In some embodiments, the precipitating is carried out at about 2
30 °C. In some aspects of these embodiments, the solution comprises 2-propanol (e.g.,
Compound 1 is precipitated from the solution in 2-propanol).

In some embodiments, the precipitating is carried out at a temperature below 0 °C (e.g., -5 °C, -10 °C, -20 °C, or -30 °C). In some aspects of these embodiments, the precipitating is carried out at about -18 °C. In other aspects of these embodiments, the solution comprises a solvent selected from 1-butanol, ethanol, 2-propanol and 1-propanol. For example, the Form I of Compound 1 may be precipitated by cooling a saturated solution of Compound 1 in, e.g., 1-butanol, and further collecting the resultant solid.

In some embodiments, the precipitating is carried out for a time period from about 24 hours to about 72 hours (e.g., cooled solution of Compound 1 may be stored at the specified temperature for 24-72 hours).

In some embodiments, the precipitating comprises adding an anti-solvent to the solution of Compound 1. In some aspects of these embodiments, the anti-solvent is miscible with the solvent in which Compound 1 is dissolved. For example, the anti-solvent may be selected from heptane and t-butylmethyl ether (herein also referred to as TBME). In some embodiments, the precipitating is carried out at or above room temperature. In some aspects of these embodiments, the solvent may be acetone, acetonitrile, 2-butanone, 1,2-dimethoxyethane, 1,4-dioxane and ethanol. For instance, a MTBE may be added to the solution of Compound 1 in acetone at room temperature, followed by collection of the precipitated Form I. In other aspects of these embodiments, the precipitating is carried out below room temperature (e.g., at 0 °C, 5 °C, or 10 °C). In one example, the precipitating is carried out at about 2 °C. In some aspects of these embodiments, the solvent may be selected from acetone, acetonitrile, 1-butanol, 2-butanone, 1,2-dimethoxyethane, 1,4-dioxane, ethanol, ethyl acetate, MIBK, 1-propanol and THF. For instance, a heptane may be added to the solution of Compound 1 in ethyl acetate at about 2 °C, followed by collection of the precipitated Form I.

In some embodiments, the precipitating may be carried out by evaporating the solvent. In some aspects of these embodiments, the evaporating may be carried out at about room temperature. In other aspects of these embodiments, the solvent is selected from acetone, acetonitrile, 2-butanone, cyclopropylmethyl ether, 1,2-dimethoxyethane, 1,4-dioxane, ethanol, ethyl acetate, 2-ethoxy ethanol, isobutyl acetate, isopropyl acetate, methanol, MIBK, 2-propanol, 1-propanol and THF.

Compound 1 salts and crystalline forms

Generally, the salts of the Compound 1 can be prepared by combining (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one (Compound 1 free base) with an acid. That is, any one of the salts of Compound 1 described herein may be prepared by combining the Compound 1 with a benzenesulfonic acid, a citric acid, a methanesulfonic acid, a 1,2-ethane disulfonic acid, a p-toluene sulfonic acid, an oxalic acid, a fumaric acid, a L-malic acid, a hydrochloric acid, a sulfuric acid, a naphthalene-2-sulfonic acid, a 2-hydroxyethanesulfonic acid, a L-aspartic acid, a maleic acid, a phosphoric acid, a ethanesulfonic acid, a L-glutamic acid, a L-tartaric acid, a D-glucuronic acid, a hippuric acid, a D-gluconic acid, a DL-lactic acid, a L-ascorbic acid, or a benzoic acid. In some embodiments, the combining may be carried out in the presence of a solvent, such as, for example, acetone, ethanol, methanol, 2-propanol, TBME or THF. In some embodiments, Compound 1 is combined with a solvent to obtain the first solution, an acid is separately combined with a solvent to obtain the second solution, and the salt of Compound 1 is obtained by combining the first solution with the second solution. In some embodiments, the combining is carried out with the acid in molar excess with respect to the Compound 1 free base. In some aspects of these embodiments, the molar ratio of the acid to the Compound 1 is from about 1:1 to about 1.1:1 (e.g., about 1.05:1). In some embodiments, the combining is carried out from about room temperature to about 40 °C (e.g., the combining is carried out by cycling the temperature between ambient and 40 °C in 4 hour cycles). In some embodiments, the combining is carried out for a time period from 24 hours to 72 hours.

Generally, any one of the crystalline forms of the salts of Compound 1 may be obtained by precipitating the crystalline form from a mixture of the salt with a solvent (e.g., precipitating the crystalline compound from a mixture, such as precipitating the crystalline compound from a solution). In some embodiments, the precipitating is carried out by temperature cycling the reaction mixture from about room temperature to about 40 °C (e.g., 4 hour cycles between room temperature and 40 °C). In some embodiments, the precipitating is carried out by evaporating the solvent from the mixture (e.g., by

evaporating the solvent from the solution of Compound 1). In some embodiments, the precipitating is carried out by adding an anti-solvent (e.g., heptane or MTBE) to the solution of Compound 1 in a solvent.

In some embodiments, crystalline Compound 1 besylate may be obtained by precipitating the crystalline form from a mixture of Compound 1 besylate with a solvent selected from THF and *t*-BME. In some aspects of these embodiments, the mixture is a solution of Compound 1 besylate in THF or *t*-BME.

In some embodiments, crystalline Compound 1 besylate may be prepared by precipitating the crystalline form from a mixture of Compound 1 besylate with ethanol. In some aspects of these embodiments, the mixture is a solution of Compound 1 besylate in ethanol.

In some embodiments, crystalline Compound 1 citrate Form A may be prepared by precipitating Form A from a mixture of Compound 1 citrate with a solvent selected from acetone and *t*-BME. In some aspects of these embodiments, the mixture is a solution of Compound 1 citrate in acetone or *t*-BME.

In some embodiments, crystalline form of Compound 1 mesylate may be prepared by precipitating the crystalline form from a mixture of Compound 1 mesylate with a solvent selected from acetone, methanol and 2- propanol. In some aspects of these embodiments, the mixture is a solution of Compound 1 mesylate in acetone, methanol or 2- propanol.

In some embodiments, crystalline form of Compound 1 edisylate may be prepared by precipitating the crystalline form from a mixture of Compound 1 edisylate with 2- propanol. In some aspects of these embodiments, the mixture is a solution of Compound 1 edisylate in 2- propanol.

In some embodiments, crystalline form of Compound 1 tosylate may be prepared by precipitating the crystalline form from a mixture of Compound 1 tosylate with a solvent selected from acetone and THF. In some aspects of these embodiments, the mixture is a solution of Compound 1 tosylate in acetone or THF.

In some embodiments, crystalline form of Compound 1 oxalate may be prepared by precipitating the crystalline form from a mixture of Compound 1 oxalate with a solvent selected from ethanol and methanol. In some aspects of these embodiments, the

mixture is a solution of Compound 1 oxalate in ethanol or methanol.

In some embodiments, a crystalline form of Compound 1 fumarate may be prepared by precipitating the crystalline form from a mixture of Compound 1 fumarate with acetone. In some aspects of these embodiments, the mixture is a solution of

Compound 1 fumarate in ethanol or methanol.

In some embodiments, crystalline form of Compound 1 L-malate may be prepared by precipitating the crystalline form from a mixture of Compound 1 L-malate with TBME. In some aspects of these embodiments, the mixture is a solution of Compound 1 L-malate in TBME.

In some embodiments, crystalline form of Compound 1 succinate may be prepared by precipitating the crystalline form from a mixture of Compound 1 succinate with acetone. In some aspects of these embodiments, the mixture is a solution of Compound 1 succinate in acetone.

Methods of use

Certain compounds which are inhibitors of TrkA and/or TrkB may be useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, and pain associated with cancer, surgery, and bone fracture.

In one embodiment, Compound 1 or its solid forms, crystalline forms, solvates or hydrates, or the salts of Compound 1 or their solid forms, crystalline forms, solvates and hydrates as described herein, are useful for treating pain, including chronic and acute pain, in a mammal.

Acute pain, as defined by the International Association for the Study of Pain, results from disease, inflammation, or injury to tissues. This type of pain generally comes on suddenly, for example, after trauma or surgery, and may be accompanied by anxiety or stress. The cause can usually be diagnosed and treated, and the pain is confined to a given period of time and severity. In some rare instances, it can become chronic.

Chronic pain, as defined by the International Association for the Study of Pain, is widely believed to represent disease itself. It can be made much worse by environmental and psychological factors. Chronic pain persists over a longer period than acute pain and is resistant to most medical treatments, generally over 3 months or more. It can and often

does cause severe problems for patients.

Compound 1 or its solid forms, crystalline forms, solvates or hydrates, or the salts of Compound 1 or their solid forms, crystalline forms, solvates and hydrates as described herein, are also useful for treating cancer in a mammal. Particular examples include
5 neuroblastoma, ovarian, pancreatic, colorectal and prostate cancer.

Compound 1 or its solid forms, crystalline forms, solvates or hydrates, or the salts of Compound 1 or their solid forms, crystalline forms, solvates and hydrates as described herein, are also useful for treating inflammation in a mammal.

Compound 1 or its solid forms, crystalline forms, solvates or hydrates, or the salts
10 of Compound 1 or their solid forms, crystalline forms, solvates and hydrates as described herein, are also useful for treating certain infectious diseases in a mammal, such as Trypanosoma cruzi infection.

Compound 1 or its solid forms, crystalline forms, solvates or hydrates, or the salts of Compound 1 or their solid forms, crystalline forms, solvates and hydrates as described
15 herein, may also be used to treat neurodegenerative diseases in a mammal. Examples of neurodegenerative disease include demyelination and dysmyelination. Additional examples of neurodegenerative diseases include multiple sclerosis, Parkinson's disease and Alzheimer's disease.

In addition, Compound 1 or its solid forms, crystalline forms, solvates or
20 hydrates, or the salts of Compound 1 or their solid forms, crystalline forms, solvates and hydrates as described herein, may also be used to treat interstitial cystitis (IC), painful bladder syndrome (PBS), urinary incontinence, asthma, anorexia, atopic dermatitis, and psoriasis in a subject (e.g., a mammal such as a human).

Accordingly, another embodiment of the present application provides a method of
25 treating or preventing pain in a subject (e.g., mammal), comprising administering to said mammal Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, in an amount effective to treat or prevent said pain. In one embodiment, the pain is chronic pain. In one embodiment, the
30 pain is acute pain. In one embodiment, the pain is inflammatory pain. In one embodiment, the pain is neuropathic pain. In one embodiment, the pain is pain associated

with cancer. In one embodiment, the pain is pain associated with surgery. In one embodiment, the pain is pain associated with bone fracture. In one embodiment, the method comprises a method of treating said pain in a mammal. In one embodiment, the method comprises a method of preventing said pain in a mammal.

5 Another embodiment of the present disclosure provides a method of treating or preventing inflammation in a subject (e.g., mammal), comprising administering to said mammal Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, in an amount effective to treat or
10 prevent the inflammation. In one embodiment, the method comprises treating the inflammation in a subject. In one embodiment, the method comprises preventing the inflammation in a subject.

Another embodiment of the present application provides a method of treating or preventing a neurodegenerative disease in a mammal, comprising administering to said
15 mammal Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, in an amount effective to treat or prevent said neurodegenerative disease. In one embodiment, the neurodegenerative disease is demyelination. In one embodiment, the neurodegenerative disease is
20 dysmyelination. In one embodiment, the neurodegenerative disease is multiple sclerosis. In one embodiment, the neurodegenerative disease is Parkinson's disease. In one embodiment, the neurodegenerative disease is Alzheimer's disease.

Another embodiment of the present disclosure provides a method of treating or preventing an infectious disease in a subject, comprising administering to the subject
25 Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, in an amount effective to treat or prevent said infectious disease. In one embodiment, the infectious disease is Trypanosoma cruzi infection. In one embodiment, the method comprises treating the neurodegenerative
30 disease in a subject. In one embodiment, the method comprises preventing the neurodegenerative disease in a subject.

Another embodiment of the present disclosure provides a method of treating or preventing cancer in a mammal, comprising administering to said mammal Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, in an amount effective to treat or prevent the cancer. In one embodiment, the cancer is neuroblastoma. In one embodiment, the cancer is ovarian cancer. In one embodiment, the cancer is pancreatic cancer. In one embodiment, the cancer is colorectal cancer. In one embodiment, the cancer is prostate cancer. In one embodiment, the method comprises treating the cancer in a subject. In one embodiment, the method comprises preventing the cancer in a subject.

Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, may be administered alone as a sole therapy or can be administered in addition with one or more other substances and/or treatments that work by the same or a different mechanism of action. Examples include anti-inflammatory compounds, steroids (e.g., dexamethasone, cortisone and fluticasone), analgesics such as NSAIDs (e.g., aspirin, ibuprofen, indomethacin, and ketoprofen), and opioids (such as morphine), and chemotherapeutic agents. These agents may be administered with Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

In the field of medical oncology, it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to compositions of the present disclosure may be, for example, surgery, radiotherapy, chemotherapy, signal transduction inhibitors and/or immunotherapy (e.g., monoclonal antibodies).

Accordingly, Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form

thereof, or solvate or hydrate thereof, as described herein, may be administered in combination with one or more agents selected from mitotic inhibitors, alkylating agents, anti-metabolites, antisense DNA or RNA, intercalating antibiotics, growth factor inhibitors, signal transduction inhibitors, cell cycle inhibitors, enzyme inhibitors, retinoid receptor modulators, proteasome inhibitors, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, cytostatic agents anti-androgens, targeted antibodies, HMG-CoA reductase inhibitors, and prenyl-protein transferase inhibitors. These agents may be administered with one or more Compound 1, its solid form, crystalline form, solvate or hydrate, or a salt of Compound 1, or solid form, crystalline form, solvate or hydrate of the salt as described herein, as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

The term “TRK-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a TRK gene, a TRK protein, or expression or activity, or level of any of the same. Exemplary TRK-associated cancers are provided herein.

The phrase “dysregulation of a TRK gene, a TRK kinase, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a TRK gene translocation that results in the expression of a fusion protein, a deletion in a TRK gene that results in the expression of a TRK protein that includes a deletion of at least one amino acid as compared to the wild-type TRK protein, a mutation in a TRK gene that results in the expression of a TRK protein with one or more point mutations, or an alternative spliced version of a TRK mRNA that results in a TRK protein having a deletion of at least one amino acid in the TRK protein as compared to the wild-type TRK protein) or a TRK gene amplification that results in overexpression of a TRK protein or an autocrine activity resulting from the overexpression of a TRK gene in a cell that results in a pathogenic increase in the activity of a kinase domain of a TRK protein (e.g., a constitutively active kinase domain of a TRK protein) in a cell. As another example, a dysregulation of a TRK gene, a TRK protein, or expression or activity, or level of any of the same, can be a mutation in a TRK gene that encodes a TRK protein that is constitutively active or has increased activity as compared to a protein encoded by a TRK gene that does not include the

mutation. For example, a dysregulation of a TRK gene, a TRK protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of TRK that includes a functional kinase domain, and a second portion of a partner protein that is not TRK. In some examples, dysregulation of a TRK gene, a TRK protein, or expression or activity or level of any of the same can be a result of a gene translocation of one TRK gene with another non- TRK gene. Non-limiting examples of fusion proteins are described in Tables 1-3. Additional examples of TRK kinase protein mutations (e.g., point mutations) are TRK inhibitor resistance mutations.

The term "wildtype" or "wild-type" when referring to a TRK nucleic acid or protein describes a nucleic acid (e.g., a TRK gene or a TRK mRNA) or protein (e.g., a TRK protein) that is found in a subject that does not have a TRK-associated disease, e.g., a TRK-associated cancer (and optionally also does not have an increased risk of developing a TRK-associated disease and/or is not suspected of having a TRK-associated disease), or is found in a cell or tissue from a subject that does not have a TRK-associated disease, e.g., a TRK-associated cancer (and optionally also does not have an increased risk of developing a TRK-associated disease and/or is not suspected of having a TRK-associated disease).

In some embodiments, the dysregulation of a TRK gene, a TRK kinase protein, or expression or activity or level of any of the same, includes one or more chromosome translocations or inversions resulting in a TRK gene fusion. In some embodiments, the dysregulation of a TRK gene, a TRK kinase protein, or expression or activity or level of any of the same, is a result of genetic translocations in which the expressed protein is a fusion protein containing residues from a non-TRK partner protein, and includes a minimum of a functional TRK kinase domain. See, for example, Tables 1-3.

Table 1. Exemplary TrkA Fusion Proteins and Cancers

Fusion Protein	Non-TrkA Fusion Partner	Non-limiting Exemplary Trk- and Synonyms of Associated Cancer(s)
TP53-TrkA ^{1,11}	Tumor Protein P53	Spitzoid Melanoma, Spitz tumors
LMNA-TrkA ^{1, 12}	Lamin A/C	Spitzoid Melanoma, Spitz tumors, Undifferentiated Sarcoma, Adult Soft Tissue Sarcoma (e.g., Soft

Fusion Protein	Non-TrkA Fusion Partner	Non-limiting Exemplary Trk- and Synonyms of Associated Cancer(s)
		Tissue Sarcoma Metastatic to Lung), Soft Tissue Fibrosarcoma, Spindle Cell Sarcoma ^G , Congenital Infantile Fibrosarcoma ^H , Pediatric haemangiopericytoma-like sarcoma ^I , Colorectal Cancer ^K , Pediatric soft tissue tumor ^M
CD74-TrkA ²	MHC class II invariant chain	Non-Small Cell Lung Cancer (NSCLC) Lung adenocarcinoma
TFG-TrkA (TRK-T3) ³	TRK-Fused Gene	Papillary Thyroid Carcinoma (PTC), Soft Tissue Solitary Fibrous Tumor
TPM3-TrkA ³	Tropomyosin 3	Lung Cancer, Papillary Thyroid Carcinoma (PTC), Acute Myeloid Leukemia (AML), Sarcoma, Pediatric Gliomas, Colorectal Cancer (CRC), Soft Tissue Schwannoma, Spitzoid melanocytic tumors ^J
NFASC-TrkA ⁴	Neurofascin	Glioblastoma multiforme (GBM); Glioblastoma
BCAN-TrkA ⁴	Brevican	Glioblastoma multiforme (GBM)
MPRIP-TrkA ^{5, E}	Myosin Phosphatase Rho Interacting Protein or Rho Interacting Protein 3	Non-small cell lung cancer (NSCLC), Lung adenocarcinoma
TPR-TrkA (TRK-T1 or TRK-T2) ³	Translocated Promoter Region, Nuclear Basket Protein	Papillary Thyroid Carcinoma (PTC), Colorectal Cancer (CRC) ^A , Non-small cell lung cancer (NSCLC)
RFWD2-TrkA ⁶	Ring Finger and WD Repeat Domain 2	Large Cell Neuroendocrine Cancer (LCNEC); NSCLC
IRF2BP2-TrkA ⁷	Interferon Regulatory Factor 2 Binding Protein 2	Thyroid Cancer; Thyroid Gland Carcinoma
SQSTM1-TrkA ⁷	Sequestosome 1	Thyroid Cancer (e.g., Papillary Thyroid Cancer), Thyroid Gland Carcinoma, Soft Tissue Fibrosarcoma, Non-small-cell lung cancer ^L

Fusion Protein	Non-TrkA Fusion Partner	Non-limiting Exemplary Trk- and Synonyms of Associated Cancer(s)
SSBP2-TrkA ⁷	Single-Stranded DNA Binding Protein 2	Thyroid Cancer (e.g., Papillary Thyroid Cancer); Thyroid Gland Carcinoma
RABGAP1L-TrkA ⁸	RAB GTPase Activating Protein 1-Like	Intrahepatic Cholangiocarcinoma (ICC)
C18ORF8-TrkA ⁹	Chromosome 18 Open Reading Frame 8	Non-Small Cell Lung Cancer (NSCLC)
RNF213-TrkA ⁹	Ring Finger Protein 213	Non-Small Cell Lung Cancer (NSCLC)
TBC1D22A-TrkA ⁹	TBC1 Domain Family, Member 22A	Non-Small Cell Lung Cancer (NSCLC)
C20ORF112-TrkA ⁹	Chromosome 20 Open Reading Frame 112	Non-Small Cell Lung Cancer (NSCLC)
DNER-TrkA ⁹	Delta/Notch-Like EGF Repeat Containing	Non-Small Cell Lung Cancer (NSCLC)
ARHGEF2-TrkA ¹³	Rho Guanine Nucleotide Exchange Factor 2	Glioblastoma
CHTOP-TrkA ¹³	Chromatin Target of PRMT1	Glioblastoma
PPL-TrkA ¹³	Periplakin	Thyroid Carcinoma
PLEKHA6-TrkA	Pleckstrin Homology Domain-Containing Family A Member 6	
PEAR1-TrkA	Platelet Endothelial Aggregation Receptor 1	
MRPL24-TrkA	39S Ribosomal Protein L24, Mitochondrial	
MDM4-TrkA	Human Homolg of Mouse Double Minute 4	
LRRC71-TrkA	Leucine Rich Repeat Containing 71	
GRIPAP1-TrkA	GRIP1 Associated Protein 1	
EPS15-TrkA	Epidermal Growth Factor Receptor Substrate 15	
DYNC2H1-TrkA ^B	Dynein, Cytoplasmic 2, Heavy Chain 1	Sarcoma
CEL-TrkA	Carboxyl Ester Lipase	Pancreatic adenocarcinoma sample ^D
EPHB2-TrkA ^B	EPH Receptor B2	Lower Grade Glioma
TGF-TrkA ^C	Transforming Growth Factor	Papillary Thyroid Cancer
NELL1-TrkA ^F	Cytoplasmic Protein That Contains Epidermal Growth Factor (Egf)-Like Repeats	Non-Small Cell Lung Cancer (NSCLC)

Fusion Protein	Non-TrkA Fusion Partner	Non-limiting Exemplary Trk- and Synonyms of Associated Cancer(s)
EPL4-TrkA ^F	EPH-Related Receptor Tyrosine Kinase Ligand 4/ Ephrin-A4 Protein	Non-Small Cell Lung Cancer (NSCLC)
CTNND2-TrkA ^F	Catenin (Cadherin-Associated Protein), Delta 2	Non-Small Cell Lung Cancer (NSCLC)
TCEANC2-TrkA ^F	Transcription Elongation Factor A (SII) N-Terminal And Central Domain	Non-Small Cell Lung Cancer (NSCLC)
SCYL3-TrkA ^N	SCY1 Like Pseudokinase 3	Colorectal Cancer

^A Créancier et al., *Cancer Lett.* 365(1):107-111, 2015.J

^B U.S. Patent Application Publication No. 2015/0315657.

^C U.S. Patent Application Publication No. 2015/0283132.

5 ^D Egren et al., *Cancer Res.* 75(15 Supplement): 4793, 2015.

^E U.S. Patent Application Publication No. 2015/0073036.

^F P.C.T. Patent Application Publication No. WO2015184443A1.

^G Haller et al., *The Journal of pathology* 238.5 (2016): 700-710.

^H Wong et al., *J Natl Cancer Inst* 2016;108: djv307.

10 ^I Haller et al., *J. Pathol.* 238(5): 700-10.

^J Wu et al., *Mod Pathol.* 2016 Apr;29(4):359-69.

^K Konicek et al., *Cancer research*, Vol. 76, No. 14, Supp. Supplement. Abstract Number: 2647; 107th Annual Meeting of the American Association for Cancer Research, AACR 2016. New Orleans,LA; 16-20 Apr 2016.

15 ^L Drilon et al., *Cancer research*, Vol. 76, No. 14, Supp. Supplement. Abstract Number: CT007; 107th Annual Meeting of the American Association for Cancer Research, AACR 2016. New Orleans,LA; 16-20 Apr 2016.

^M Kohsaka et al., *Hum. Pathol.*, Aug 26. pii: S0046-8177(17)30299-X. doi: 10.1016/j.humpath.2017.08.017, 2017.

20 ^N Milione et al., *Oncotarget*, Jul 24;8(33):55353-55360. doi: 10.18632/oncotarget.19512, 2017.

Table 2. Exemplary TrkB Fusion Proteins and Cancers

Fusion Protein	Non-TrkB Fusion Partner	Non-limiting Exemplary Trk- and Synonyms of Associated Cancer(s)
NACC2-TrkB ¹⁰	NACC Family Member 2, BEN and BTB (POZ) Domain Containing	Pilocytic Astrocytoma
QKI-TrkB ¹⁰	QKI, KH Domain Containing, RNA Binding	Pilocytic Astrocytoma
AFAP1-TrkB ⁷	Actin Filament Associated Protein 1	Lower-grade Glioma, <i>In vitro</i> (murine Ba/F3 cells) ^B , Pilocytic astrocytoma with anaplasia (PAA) ^E
PAN3-TrkB ⁷	PAN3 Poly(A) Specific Ribonuclease Subunit	Head and Neck Squamous Cell Carcinoma
SQSTM1-TrkB ⁷	Sequestosome 1	Lower-Grade Glioma
TRIM24-TrkB ⁷	Tripartite Motif Containing 24	Lung adenocarcinoma
VCL-TrkB ¹¹	Vinculin	Pediatric gliomas
AGBL4-TrkB ¹¹	ATP/GTP Binding Protein-Like 4	Pediatric gliomas
DAB2IP-TrkB	Disabled Homolog 2-Interacting Protein	
NTRK2-TERT ^A	Telomerase Reverse Transcriptase	Thyroid Cancer
TEL-TrkB ^C (ETV6)	ETS Variant 6	<i>In vitro</i> (murine Ba/F3 cells)
QKI-TrkB ^D	Protein Quaking	Astrocytoma
NOS1AP-TrkB ^F		Anaplastic Astrocytoma
GKAP1-TrkB ^F		Glioblastoma
KCTD8-TrkB ^F		Glioblastoma
TBC1D2-TrkB ^F		Glioblastoma
SOSTM1-TrkB ^F		Glioblastoma
VCAN-TrkB ^F		Grade II Astrocytoma
SLMAP-TrkB ^G		Ganglioma

^A PCT Patent Application Publication No. WO 2015/183836A1

^B Drilon et al., *Ann Oncol.* 2016 May;27(5):920-6.

5 ^C Yuzugullu et al., *Cell Discov.* 2: 16030, 2016.

^D Ni et al., *Neuro Oncol.* 2017 Jan;19(1):22-30.

^E Lin et al., *Neuro-Oncol*, Vol. 18, Supp. Supplement 3, pp. iii58, Abstract Number: HG-48; 17th International Symposium on Pediatric Neuro-Oncology, ISPNO 2016. Liverpool, UK, 12 Jun 2016- 15 Jun 2016.

^F Subramaniam et al., *J. Clin. Onc.*, Vol. 35, No. 15, Supp. 1, 2017 Annual Meeting of the American Society of Clinical Oncology, ASCO. Chicago, IL, United States, 2017.

^G Ellison et al., *Neuropathology and Applied Neurobiology*, Vol. 42, Supp. 1, pp. 18. Abstract Number: O13, 117th Meeting of the British Neuropathological Society, Royal College of Physicians. London, United Kingdom, 2017.

Table 3. Exemplary TrkC Fusion Proteins and Cancers

Fusion Protein	Non-TrkB Fusion Partner	Non-limiting Exemplary Trk- and Synonyms of Associated Cancer(s)
ETV6-TrkC ¹¹ (TEL; or chromosomal translocation t(12;15) (p13;q25)) ^J	ETS Variant 6	Salivary Gland Cancer, Secretory Breast Carcinoma, Acute Myeloid Leukemia, Fibrosarcoma, Nephroma, Melanoma, Colorectal Cancer (CRC), Breast Cancer, Pediatric Gliomas, Thyroid Cancer (e.g., Papillary Thyroid Cancer), Infantile Fibrosarcoma, Soft Tissue Hemangioma, Gastrointestinal Stromal Tumor (GIST) (e.g., c-kit-negative GIST), Mammary Carcinoma (e.g., Mammary Analogue Secretory Carcinoma, Secretory Breast Carcinoma (SBSC)) ^K , Congenital Fibrosarcoma, Acute Myelogenous Leukemia, Polymorphous low-grade adenocarcinoma ^D , ALK-negative inflammatory myofibroblastic tumors (IMT) ^E , Infantile Fibrosarcoma (IFS) ^{F, M} , Acinic cell carcinoma (AcCC) ^G , Cellular mesoblastic nephroma ^H , Promyelocytic leukemia ^I , Burkitt Lymphoma ^I , B-cell lymphoma ^I , multiple myeloma ^I , medulloblastoma ^I ,

Fusion Protein	Non-TrkB Fusion Partner	Non-limiting Exemplary Trk- and Synonyms of Associated Cancer(s)
		neuroblastoma ^I , ovarian cancer ^I , intestinal cancer ^I , acute lymphoblastic leukemia ^K , Sinonasal Low-grade Non-intestinal-type Adenocarcinoma ^N
BTBD1-TrkC ¹¹	BTB (POZ) Domain Containing 1	Pediatric Gliomas
LYN-TrkC ⁷	V-Yes-1 Yamaguchi Sarcoma Viral Related Oncogene Homolog (also known as Lck/Yes-Related Novel Protein Tyrosine Kinase)	Head and Neck Squamous Cell Carcinoma
RBPMS-TrkC ⁷	RNA Binding Protein with Multiple Splicing	Thyroid Cancer (e.g., Papillary Thyroid Cancer)
EML4-TrkC ^A	Echinoderm Microtubule-Associated Protein-Like 4	Fibrosarcoma (e.g., Pediatric Fibrosarcoma ^L), Glioblastoma ^P , Colon Cancer ^R
HOMER2-TrkC	Homer Protein Homolog 2	Soft Tissue Sarcoma
TFG-TrkC	TRK-Fused Gene	Soft Tissue Solitary Fibrous Tumor
FAT1-TrkC	FAT Atypical Cadherin 1	Cervical Squamous Cell Carcinoma ^B
MYO5A-TrkC	Myosin VA	Spitz tumor ^C
MYH9-TrkC	Myosin Heavy Chain 9	Spitz tumor ^C
KANK1-TrkC ^N	KANK1	Renal Metanephric Adenoma (MA)
SQSTM1-TrkC ^O	Sequestosome 1	Papillary Thyroid Carcinoma

^A Tannenbaum et al., *Cold Spring Harb. Mol. Case Stud.* 1: a000471, 2015.

^B U.S. Patent Application Publication No. 2015/0315657.

^C Yeh et al., *J Pathol.* 240(3): 282-90, 2016

^D Montalli et al., *J Oral Pathol Med.* doi: 10.1111/jop.12491, 2016

5 ^E Alassiri et al., *Am J Surg Pathol.*, Aug;40(8):1051-61, 2016.

^F Nagasubramanian et al., *Pediatr Blood Cancer.*, Aug;63(8):1468-70, 2016.

^G Chintakuntlawar et al., *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016 May;121(5):542-549.e1.

^H U.S. Patent No. US9511050B2.

10 ^I U.S Patent No. US9447135B2.

^J Skalova et al., *Modern Pathology* 30, S27-S43, 2017.

^K Hycza et al., Vol. 469, Supp. Supplement 1, pp. S17. Abstract Number: OFP-1997-7; 31st International Congress of the International Academy of Pathology and the 28th Congress of the European Society of Pathology, Cologne, Germany. 25-29 September 2016.

^L Sims et al., *Journal of Immunotherapy of Cancer*, Vol. 4, Supp. Supplement 1; Abstract Number: P280; 31st Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer, SITC 2016. National Harbor, MD; 9-13 November 2016.

^K Roberts et al., *Blood*, Vol. 128, No. 22. Abstract Number: 278, 58th Annual Meeting of the American Society of Hematology, ASH 2016. San Diego, CA, United States. 03 Dec 2016-06 Dec 2016.

^M Pavlick et al., *Pediatr Blood Cancer*, doi: 10.1002/pbc.26433, 2017.

^M Andreasen et al., *Am J Surg Pathol.*, Nov;41(11):1552-1560, 2017.

^N Catic et al., *Cancer Genet.*, Aug;214-215:9-15, doi: 10.1016/j.cancergen.2017.03.001, 2017.

^O Lu et al., *Oncotarget.*, Jul 11;8(28):45784-45792. doi: 10.18632/oncotarget.17412, 2017.

^P Schram et al., *Cancer Research*, Vol. 77, No. 13, Supp. Supplement 1. Abstract Number: LB-302, American Association for Cancer Research Annual Meeting, Washington, DC, United States, 2017.

^R Coebergh et al., *Cancer Research*, Vol. 77, No. 13, Supp. Supplement 1. Abstract Number: 490, American Association for Cancer Research Annual Meeting, Washington, DC, United States, 2017.

In some embodiments, the dysregulation of a TRK gene, a TRK kinase, or expression or activity or level of any of the same, includes at least one point mutation in a TRK gene that results in the production of a TRK kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type TRK kinase.

In some embodiments, a TRK-associated cancer has been identified as having one or more TRK inhibitor resistance mutations (that result in an increased resistance to a TRK

inhibitor.

In one embodiment, Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, is useful for treating diseases and disorders which can be treated with a TRK inhibitor. Non-limiting examples of cancer (e.g., a Trk-associated cancer) include adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, leukemia lymphocytic, liver cholangiocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, lymphoma, non-

Hodgkin's lymphoma, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epithelioid cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

Additional examples of cancers (e.g., Trk inhibitor-resistant cancer) include: adrenocortical carcinoma, anal cancer, appendix cancer, atypical teratoid/rhabdoid tumor (e.g., central nervous system atypical teratoid/rhabdoid tumor), B-cell cancer, bile duct cancer, bladder cancer, bone cancer (e.g., osteosarcoma and malignant fibrous histiocytoma), brain cancer (e.g., brain and spinal cord tumor, brain stem glioma, central nervous system embryonal tumors, central nervous system germ cell tumors, craniopharyngioma, and ependymoma), breast cancer, bronchogenic carcinoma, bronchus cancer, cancer of hematological tissues, cancer of the oral cavity or pharynx, carcinoid

tumor, cervical cancer, childhood cancers, chordoma, chronic lymphocytic leukemia, chronic myeloproliferative neoplasms, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, ductal carcinoma in situ, embryonal tumor, endometrial cancer, esophageal cancer, esthesioneuroblastoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer (e.g., retinoblastoma), fallopian tube cancer, fibrosarcoma, fibrous histiocytoma of bone, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, germ cell tumor, gestational trophoblastic disease, glioblastoma multiforme, glioma (e.g., lower-grade glioma), head and neck cancer, heart cancer, histiocytosis, hypopharyngeal cancer, inflammatory myofibroblastic tumors, intrahepatic cholangiocarcinoma, islet cell tumor, kidney cancer (e.g., renal cell cancer), Langerhans cell histiocytosis, large cell neuroendocrine cancer, laryngeal cancer, leukemia (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, chronic myelogenous leukemia, and hairy cell leukemia), lip cancer, liver cancer, lung cancer, Burkitt lymphoma, Hodgkin's lymphoma, and primary central nervous system lymphoma), medulloblastoma, mesothelioma, mouth cancer, multiple myeloma, myelodysplastic syndromes, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neoplasm (e.g., a melanocystic neoplasm), nephroma, neuroblastoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, paraganglioma, parathyroid cancer, pediatric glioma, penile cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pituitary tumor, plasma cell neoplasm, primary peritoneal cancer, prostate cancer, rectum carcinoma, salivary gland cancer, sarcoma (e.g., Ewing sarcoma, rhabdomyosarcoma, uterine sarcoma, and undifferentiated sarcoma), secretory breast carcinoma, Sezary syndrome, skin cancer, small bowel cancer, small cell lung cancer, small intestine cancer, Spitz nevi, Spitz tumors, spitzoid melanoma, stomach cancer, squamous cell carcinoma, squamous neck cancer, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid carcinoma, urethral cancer, uterine cancer, urinary bladder cancer, vaginal cancer, vulvar cancer, and Wilms tumor.

In some embodiments, the cancer is a pediatric cancer. In some embodiments, the pediatric cancer is a mesenchymal cancer. For example, the mesenchymal cancer can be selected from the group consisting of: pediatric nephroma, congenital fibrosarcoma

(CFS), pediatric high-grade glioma (HGG), mesenchymal cancers (infant fibrosarcoma (IF), congenital mesoblastic nephroma, congenital infantile fibrosarcoma (CIFS); pilocytic astrocytoma, brain tumors, pediatric acute leukemia, Ph-like acute lymphoblastic leukemia, cellular congenital mesoblastic nephroma (CMN); infantile fibrosarcoma, pediatric high-grade glioma (HGG), diffuse intrinsic pontine gliomas (DIPGs), non-brainstem HGGs (NBS-HGGs), anaplastic large cell lymphoma (ALCL), non-Hodgkin's lymphoma (NHL), pediatric papillary thyroid carcinoma, soft tissue sarcoma, spitzoid melanoma, pediatric hemangiopericytoma-like sarcoma, spindle cell sarcoma, NOS with myo/haemangiopericytic growth pattern, lung cancer, advanced pediatric solid tumors, neuroectodermal-derived tumors, pediatric colorectal cancer, adrenal neuroblastoma, and central nervous system tumors.

In some embodiments, the pediatric cancer is a fibrosarcoma such as infantile fibrosarcoma.

In some embodiments, the pediatric cancer is a glioma. For example, the pediatric cancer is selected from the group consisting of: pediatric high-grade glioma (HGG), diffuse intrinsic pontine gliomas (DIPGs), and on-brainstem HGGs (NBS-HGGs).

Provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein) that include identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more of the amino acid positions shown in Tables 4, 5, 6 or 7, and administering to the identified subject Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein.

Also provided herein are methods of treating a subject that include administering a therapeutically effective amount of Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, to a subject having a clinical record that indicates that the subject has a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 4, 5, 6 or 7).

Also provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 4, 5, 6 or 7); and administering to the identified subject Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein.

Also provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 4, 5, 6 or 7); and administering to the identified subject Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, and another anticancer agent (e.g., any one or more of the anticancer agents described herein) or anticancer therapy (e.g., any one or more of the anticancer therapies provided herein).

Also provided herein are methods of treating a subject that include administering a therapeutically effective amount of Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, to a subject having a clinical record that indicates that the subject has a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 4, 5, 6 or 7).

Also provided herein are methods of treating a subject that include administering a therapeutically effective amount of Compound 1 or a solid form thereof, crystalline form thereof, or solvate or hydrate thereof, or a salt of Compound 1 or solid form thereof, crystalline form thereof, or solvate or hydrate thereof, as described herein, and another

anticancer agent (e.g., any one or more of the anticancer agents described herein) or anticancer therapies (e.g., any one or more of the anticancer therapies described herein), to a subject having a clinical record that indicates that the subject has a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 4, 5, 6 or 7).

In some embodiments, the dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same, includes one or more deletions, insertions, or point mutation(s) in a Trk protein. In some embodiments, the dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same, includes a deletion of one or more residues from the TrkA protein, resulting in constitutive activity of the Trk kinase domain. In some embodiments, the dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same, includes at least one point mutation in a NTRK1 gene that results in the production of a TrkA protein that has one or more amino acid substitutions as compared to the wildtype TrkA protein (see, for example, the point mutations listed in Tables 4 and 5). An exemplary wildtype TrkA polypeptide is SEQ ID NO: 1, an exemplary wildtype TrkB polypeptide is SEQ ID NO: 2, and an exemplary TrkC polypeptide is SEQ ID NO: 3.

Table 4. Activating TrkA Point Mutations

Mutation		Pediatric Cancer	Reference
C6773T, C7232T, C7301T	TrkA	neuroblastoma	Scaruffi et al., <i>Int. J. Oncol.</i> 14:935-938, 1999

Table 5. Activating TrkA Point Mutations^A

Point Mutation	Rationale	Exemplary Isoform in which Mutation is Present (if known)
R6W ^I		
R33W ^B		NP_001007793.1 ^F
A336E	Near NGF Binding Site	Reference TrkA sequence
A337T	Near NGF Binding Site	Reference TrkA sequence

Point Mutation	Rationale	Exemplary Isoform in which Mutation is Present (if known)
R324Q or R324W	Near NGF Binding Site	Unknown
V420M	Close to Membrane	Reference TrkA sequence
R444Q or R444W	Close to Membrane	Reference TrkA sequence
G517R or G517V	P-Loop	Reference TrkA sequence
K538A	Activating	Reference TrkA sequence
V573M ^E		Reference TrkA sequence
R583H ^I		
F589L ^E		Reference TrkA sequence
G595R or G667C ^D	Catalytic Domain	Reference TrkA sequence
F598L ^E		Unknown
R649W or R649L	Arginine may stabilize auto-inhibited conformation.	Reference TrkA sequence
R682S	Activation Loop	Reference TrkA sequence
V683G	Activation Loop	Reference TrkA sequence
I699V ^H		
Q627X ^C , Q597X ^C , Q633X ^C		NP_001012331.1 ^G , NP_001007793.1 ^F , and Reference TrkA sequence, respectively
R702C	Exposed, may form face-to-face disulfide linked dimer	Reference TrkA sequence
R744H ^I		

^A Reference TrkA sequence is UniProtKB/Swiss-Prot: P04629.4, and can be found at URL:

[www.ncbi.nlm.nih.gov/protein/94730402?report=genbank&log\\$=protalign&blast_rank=0&RID=0](http://www.ncbi.nlm.nih.gov/protein/94730402?report=genbank&log$=protalign&blast_rank=0&RID=0) (SEQ ID NO: 1)

5 ^B Zhang et al., *Blood* 124(21):1682, 2014. Mutation found in T-cell prolymphocytic leukemia.

^C Park et al., *Proc. Natl. Acad. Sci. U.S.A.* 112(40):12492-12497, 2015. Mutation found in colorectal cancer.

^D Russo et al., *Cancer Discov.* Jan;6(1):36-44, 2016.

10 ^E PCT Application No. WO2016196141A1.

^F

[www.ncbi.nlm.nih.gov/protein/56118210?report=genbank&log\\$=protalign&blast_rank=3&RID=0](http://www.ncbi.nlm.nih.gov/protein/56118210?report=genbank&log$=protalign&blast_rank=3&RID=0)

^G www.ncbi.nlm.nih.gov/protein/59889558

^H Deihimi et al., *Oncotarget*. Jun 20;8(25):39945-39962. doi:

10.18632/oncotarget.18098, 2017.¹ Iniguez-Ariza et al., *Journal of Clinical Oncology*,
(20 Jun 2017) Vol. 35, No. 15, Supp. 1, 2017 Annual Meeting of the American Society of
5 Clinical Oncology, ASCO, 2017.

In some embodiments, the dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same, includes a splice variation in a TrkA mRNA which results in an expressed protein that is an alternatively spliced variant of TrkA
10 having at least one residue deleted (as compared to a wild-type TrkA protein) resulting in constitutive activity of the TrkA kinase domain. In some embodiments, an alternatively spliced form of TrkA with constitutive activity has deletions of exons 8, 9, and 11 resulting in an expressed protein missing residues 192-284 and 393-398 relative to TrkA Isoform 2, has a deletion of exon 10 in TrkA, or has a deletion in a NTRK1 gene that
15 encodes a TrkA protein with a 75 amino acid deletion in the transmembrane domain (Reuther et al., *Mol. Cell Biol.* 20:8655-8666, 2000).

In some embodiments, the dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same, includes at least one point mutation in a NTRK1 gene that results in the production of a TrkB protein that has one or more amino
20 acid substitutions as compared to the wildtype TrkB protein (see, for example, the point mutations listed in Table 6).

Table 6. Activating TrkB Point Mutations^A

Point Mutation	Rationale	Exemplary Isoform in which Mutation is Present (if known)
A13T ^C		Reference TrkB sequence
E142K ^C		Reference TrkB sequence
R136H ^C		Reference TrkB sequence
S167Y ^F		
V619M ^B		Unknown
F633L ^B		NP_006171.2 ^D (Corresponding to position 617 of Reference TrkB sequence)
G639R ^B		NP_006171.2 ^D (Corresponding to position 623 of Reference TrkB sequence)
G709C or G709A or G709S ^B		NP_006171.2 ^D (Corresponding to position 693 of Reference TrkB sequence)
P716S ^E		

^A Reference TrkB sequence is UniProtKB/Swiss-Prot: Q16620.1, and can be found at URL:

[www.ncbi.nlm.nih.gov/protein/2497560?report=genbank&log\\$=proalign&blast_rank=0](http://www.ncbi.nlm.nih.gov/protein/2497560?report=genbank&log$=proalign&blast_rank=0&RID=0)
&RID=0 (SEQ ID NO: 2)

^B PCT Application No. WO2016196141A1.

^C Bonanno et al., *Journal of Thoracic Oncology*, Vol. 11, No. 4, Suppl. Suppl. 1, pp S67. Abstract Number: 28P; 6th European Lung Cancer Conference, ELCC 2016, Geneva, Switzerland.

^D www.ncbi.nlm.nih.gov/protein/NP_006171.2

^E Deihimi et al., *Oncotarget*. Jun 20;8(25):39945-39962. doi: 10.18632/oncotarget.18098, 2017.

^F Iniguez-Ariza et al., *Journal of Clinical Oncology*, (20 Jun 2017) Vol. 35, No. 15, Suppl. 1, 2017 Annual Meeting of the American Society of Clinical Oncology, ASCO, 2017.

In some embodiments, the dysregulation of a NTRK gene, a Trk protein, or expression or activity, or level of the same, includes at least one point mutation in a NTRK1 gene that results in the production of a TrkC protein that has one or more amino acid substitutions

as compared to the wildtype TrkC protein (see, for example, the point mutations listed in Table 7.

Table 7. Activating TrkC Point Mutations^A

Point Mutation	Rationale	Exemplary Isoform in which Mutation is Present (if known)
V603M ^C		NP_001007157.1 ^D
F617L ^C		Reference TrkC sequence
G623R ^{B,C}	Steric Hinderance	Reference TrkC sequence
G696C or G696A or G696S ^C		Reference TrkC sequence
R745L ^E		
I749M ^F		

^A Reference TrkC sequence is UniProtKB/Swiss-Prot: Q16288.2, and can be found at URL:

[www.ncbi.nlm.nih.gov/protein/134035335?report=genbank&log\\$=protalign&blast_rank=0&RID=0](http://www.ncbi.nlm.nih.gov/protein/134035335?report=genbank&log$=protalign&blast_rank=0&RID=0) (SEQ ID NO: 3)

^B Drilon et al., *Ann Oncol.* 2016 May;27(5):920-6. doi: 10.1093/annonc/mdw042. Epub 2016 Feb 15.

^C PCT Application No. WO2016196141A1.

^D www.ncbi.nlm.nih.gov/protein/NP_001007157

^E Deihimi et al., *Oncotarget.* Jun 20;8(25):39945-39962. doi: 10.18632/oncotarget.18098, 2017.

^F Iniguez-Ariza et al., *Journal of Clinical Oncology*, (20 Jun 2017) Vol. 35, No. 15, Supp. 1, 2017 Annual Meeting of the American Society of Clinical Oncology, ASCO, 2017.

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³ Greco et al., *Mol. Cell. Endocrinol.* 28:321, 2010.

⁴ Kim et al., *PloS ONE* 9(3): e91940, 2014.

⁵ Vaishnavi et al., *Nature Med.* 19:1469-1472, 2013.

⁶ Fernandez-Cuesta et al., "Cross-entity mutation analysis of lung neuroendocrine

tumors sheds light into their molecular origin and identifies new therapeutic targets,”

AACR Annual Meeting 2014, Abstract, April 2014.

⁷ Stransky et al., *Nature Comm.* 5:4846, 2014.

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5 ⁹ Doebele et al., *J. Clin. Oncol.* 32:5s, 2014.

¹⁰ Jones et al., *Nature Genetics* 45:927-932, 2013.

¹¹ Wu et al., *Nature Genetics* 46:444-450, 2014.

¹² WO 2013/059740

¹³ Zheng et al., “Anchored multiplex PCR for targeted next-generation sequencing,”

10 *Nature Med.*, published online on November 10, 2014.

¹⁴ Caria et al., *Cancer Genet. Cytogenet.* 203:21-29, 2010.

¹⁵ Frattini et al., *Nature Genet.* 45:1141-1149, 2013.

¹⁶ Martin-Zanca et al., *Nature* 319:743, 1986.

¹⁷ Meyer et al., *Leukemia* 21: 2171–2180, 2007.

15 ¹⁸ Reuther et al., *Mol. Cell. Biol.* 20:8655-8666, 2000.

¹⁹ Marchetti et al., *Human Mutation* 29(5):609-616, 2008.

²⁰ Tacconelli et al., *Cancer Cell* 6:347, 2004.

²¹ Walch et al., *Clin. Exp. Metastasis* 17: 307–314, 1999.

²² Papatsoris et al., *Expert Opin. Invest. Drugs* 16(3):303-309, 2007.

20 ²³ Van Noesel et al., *Gene* 325: 1-15, 2004.

²⁴ Zhang et al., *Oncology Reports* 14: 161-171, 2005.

²⁵ Truzzi et al., *J. Invest. Dermatol.* 128(8):2031, 2008.

²⁶ Kolokythas et al., *J. Oral Maxillofacial Surgery* 68(6):1290-1295, 2010.

²⁷ Ni et al., *Asian Pacific Journal of Cancer Prevention* 13:1511, 2012.

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In some embodiments, a TRK-associated cancer has been identified as having one or more TRK inhibitor resistance mutations (that result in an increased resistance to a TRK inhibitor. Non-limiting examples of TRK inhibitor resistance mutations are listed in Tables 8-10.

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Table 8. Exemplary TrkA Resistance Mutations

Amino acid position 517 (e.g., G517R)
Amino acid position 542 (e.g., A542V)
Amino acid position 564 (e.g., L564S ^{H2})
Amino acid position 568 (e.g., Q568x)
Amino acid position 573 (e.g., V573M)
Amino acid position 589 (e.g., F589L, F589C)
Amino acid position 595 (e.g., G595S, G595R ¹ , G595L ²)
Amino acid position 599 (e.g., D596V)
Amino acid position 600 (e.g., F600L)
Amino acid position 602 (e.g., R602x)
Amino acid position 646 (e.g., F646V, F646I ²)
Amino acid position 656 (e.g., C656Y, C656F)
Amino acid position 657 (e.g., L657V)
Amino acid position 667 (e.g., G667C ¹ , G667S)
Amino acid position 676 (e.g., Y676S)
Amino acid position 679 (e.g., D679G ²)

¹ Russo et al., Acquired Resistance to the TRK Inhibitor Entrectinib in Colorectal Cancer, *Cancer Discov.*, Jan;6(1):36-44, 2016.

5 ² Fuse et al., Mechanisms of Resistance to NTRK Inhibitors and Therapeutic Strategies in NTRK1-Rearranged Cancers, *Mol. Cancer Ther.*, Jan;6(1):36-44, 2016.

Table 9. Exemplary TrkB Resistance Mutations

Amino acid position 545 (e.g., G545R)
Amino acid position 570 (e.g., A570V)
Amino acid position 596 (e.g., Q596E, Q596P)
Amino acid position 601 (e.g., V601G)
Amino acid position 617 (e.g., F617L, F617C, F617I)
Amino acid position 623 (e.g., G623S, G623R)
Amino acid position 624 (e.g., D624V)
Amino acid position 628 (e.g., F628x)
Amino acid position 630 (e.g., R630K)
Amino acid position 639 (e.g., G639R) ¹
Amino acid position 672 (e.g., F672x)
Amino acid position 682 (e.g., C682Y, C682F)
Amino acid position 683 (e.g., L683V)
Amino acid position 693 (e.g., G693S)
Amino acid position 702 (e.g., Y702x)

¹ PCT Application No. WO2017155018A1.

Table 10. Exemplary TrkC Resistance Mutations

Amino acid position 545 (e.g., G545R)
Amino acid position 570 (e.g., A570V)
Amino acid position 596 (e.g., Q596x)
Amino acid position 601 (e.g., V601)
Amino acid position 617 (e.g., F617x, F617L)
Amino acid position 623 (e.g., G623R ¹)
Amino acid position 624 (e.g., D624V)
Amino acid position 628 (e.g., F628x)
Amino acid position 630 (e.g., R630x)
Amino acid position 675 (e.g., F675x)
Amino acid position 685 (e.g., C685Y, C684F)
Amino acid position 686 (e.g., L686V)
Amino acid position 696 (e.g., G696x, G696A)
Amino acid position 705 (e.g., Y705x)

- 5 ¹ Drilon et al., What hides behind the MASC: clinical response and acquired resistance to entrectinib after ETV6-NTRK3 identification in a mammary analogue secretory carcinoma (MASC), Ann Oncol. 2016 May;27(5):920-6. doi: 10.1093/annonc/mdw042. Epub 2016 Feb 15.

10

The letter “x” when used to describe a mutation of an amino acid at a specific amino acid position means (i) a substitution of the amino acid present at the same amino acid position in the corresponding wildtype protein with a different naturally-occurring amino acid, or (ii) a deletion of the amino acid present at the same amino acid position in the corresponding wildtype protein.

15

Pharmaceutical compositions, formulations, routes of administration

In some embodiments, provided herein is a process for preparing a pharmaceutical composition comprising mixing (i) a compound of any one of formulae described herein or salt thereof prepared according to any of the processes described herein, and (ii) a pharmaceutically acceptable carrier. Pharmaceutical compositions

20

containing the compound of any one of formulae described herein or a salt thereof as the active ingredient can be prepared by intimately mixing the compound of any one of formulae described herein or a salt thereof with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending upon the desired route of administration (*e.g.*, oral, parenteral). Thus, for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents, and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like. Solid oral preparations can also be coated with substances such as sugars or be enteric-coated so as to modulate major site of absorption. For parenteral administration, the carrier will usually consist of sterile water, and other ingredients can be added to increase solubility or preservation. Injectable suspensions or solutions can also be prepared utilizing aqueous carriers along with appropriate additives.

The pharmaceutical compositions herein contain, per unit dosage unit, *e.g.*, tablet, capsule, suspension, solution, sachet for reconstitution, powder, injection, I.V., suppository, sublingual/buccal film, teaspoonful, and the like, of from about 0.1-1000 mg or any range therein, and may be given at a dosage of from about 0.01-300 mg/kg/day, or any range therein, preferably from about 0.5-50 mg/kg/day, or any range therein. In some embodiments, the pharmaceutical compositions provided herein contain, per unit dosage unit, about 25 mg to about 500 mg of a compound provided herein (for example, about 25 mg to about 400 mg, about 25 mg to about 300 mg, about 25 mg to about 250 mg, about 25 mg to about 200 mg, about 25 mg to about 150 mg, about 25 mg to about 100 mg, about 25 mg to about 75 mg, about 25 mg to a about 50 mg, about 50 mg to about 500 mg, about 100 mg to about 500 mg, about 150 mg to about 500 mg, about 200 mg to about 500 mg, about 250 mg to about 500 mg, about 300 mg to about 500 mg, about 400 mg to about 500 mg, about 50 to about 200 mg, about 100 to about 250 mg, about 50 to about 150 mg). In some embodiments, the pharmaceutical compositions provided herein contain, per unit dosage unit, about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, or about 500 mg of

Compound 1 or any one of crystalline forms, solid forms, solvates, hydrates or salts described herein. The dosages, however, can be varied depending upon the requirement of the patient, the severity of the condition being treated, and/or (if applicable) the crystalline form, solid form, solvate, hydrate or salt being employed. In some
5 embodiments, the dosages are administered once daily (QD) or twice daily (BID). Preferably, these compositions are in unit dosage forms, such as sterile solutions or suspensions for oral administration.

To prepare the pharmaceutical compositions provided herein, the compound of any one of formulae described herein or a salt thereof as the active ingredient is
10 intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration (*e.g.*, oral or parenteral). Any one of crystalline forms, solid forms, solvates, hydrates or salts described herein can be administered by any convenient route, *e.g.*, into the gastrointestinal tract (*e.g.*, rectally
15 or orally), the nose, lungs, musculature or vasculature, or transdermally or dermally. Any one of crystalline forms, solid forms, solvates, hydrates or salts described herein can be administered in any convenient administrative form, *e.g.*, tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions can contain components that are conventional in
20 pharmaceutical preparations, *e.g.*, diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. If parenteral administration is desired, the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the present disclosure.

In preparing the compositions in oral dosage form, any of the usual
25 pharmaceutical media can be employed. Thus, for liquid oral preparations, such as, for example, suspensions, elixirs, and solutions, suitable carriers and additives include water, glycols, glycerols, oils, cyclodextrins, alcohols, *e.g.*, ethanol, flavoring agents, preservatives, coloring agents, and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives
30 include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like. Suitable binders include, without limitation, starch, gelatin, natural

sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

5 Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets can be sugar coated or enteric coated by standard techniques. For parenteral formulations, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for
10 preservation, can be included. In some embodiments, the carrier is 0.8% saline or a 5% dextrose. Injectable suspensions can also be prepared, in which case appropriate liquid carriers, suspending agents, and the like can be employed. The pharmaceutical compositions herein can contain, per dosage unit, *e.g.*, tablet, capsule, powder, injection, teaspoonful, and the like, an amount of the active ingredient necessary to deliver an
15 effective dose as described above.

 In some embodiments, the dosages are administered once daily (QD) or twice daily (BID). Alternatively, the composition can be presented in a form suitable for once-weekly or once-monthly administration. For preparing solid compositions such as tablets, any one of crystalline forms, solid forms, solvates, hydrates or salts described herein is
20 mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid composition containing any one of crystalline forms, solid forms, solvates, hydrates or salts described herein. When referring to these preformulation compositions as
25 homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 1000 mg, or any amount or range thereof, of the active ingredient provided
30 herein. The tablets or pills of the composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the

tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compositions provided herein can be incorporated for administration orally or by injection include aqueous solutions, cyclodextrins, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils, such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums, such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone, and gelatin. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Any one of crystalline forms, solid forms, solvates, hydrates or salts described herein can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in *The Handbook of Pharmaceutical Excipients*, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

Methods of formulating pharmaceutical compositions have been described in numerous publications, such as *Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded*, Volumes 1-3, edited by Lieberman *et al.*; *Pharmaceutical Dosage Forms: Parenteral Medications*, Volumes 1-2, edited by Avis *et al.*; and

Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1-2, edited by Lieberman *et al.*; published by Marcel Dekker, Inc.

Compounds provided herein can be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever treatment of cancer, pain, inflammation, neurodegenerative disease or Trypanosoma cruzi infection is required.

The daily dosage of the compound of any one of formulae described herein or a salt thereof can be varied over a wide range from 1.0 to 10,000 mg per adult human per day, or higher, or any range therein. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 or 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.1 mg/kg to about 1000 mg/kg of body weight per day, or any range therein. Preferably, the range is from about 0.5 to about 500 mg/kg of body weight per day, or any range therein. More preferably, from about 1.0 to about 250 mg/kg of body weight per day, or any range therein. More preferably, from about 0.1 to about 100 mg/kg of body weight per day, or any range therein. In an example, the range can be from about 0.1 to about 50.0 mg/kg of body weight per day, or any amount or range therein. In another example, the range can be from about 0.1 to about 15.0 mg/kg of body weight per day, or any range therein. In yet another example, the range can be from about 0.5 to about 7.5 mg/kg of body weight per day, or any amount to range therein. The compound of any one of formulae described herein or a salt thereof can be administered on a regimen of 1 to 4 times per day or in a single daily dose.

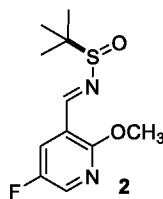
Optimal dosages to be administered can be readily determined by those skilled in the art, and can vary with the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet, and time of administration, can result in the need to adjust dosages.

EXAMPLES

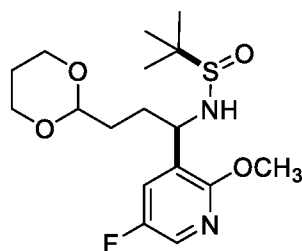
Materials and methods for the preparation of compounds, crystalline forms, solid forms, solvates, hydrates, and salts thereof.

5 Example A.

1) Preparation of Compound 1 (the compound of Formula I)



(*R,E*)-*N*-((5-fluoro-2-methoxypyridin-3-yl)methylene)-2-methylpropane-2-sulfonamide (2): A flask (equipped with a nitrogen inlet, overhead stirring, and thermocouple) was charged with DCM (3 L, 10 vol). The mixture was agitated, and the mixture was deoxygenated with subsurface nitrogen for 1 h. Next 5-fluoro-2-methoxynicotinaldehyde (**1**) (300 g, 1934 mmol) and (*R*)-2-methylpropane-2-sulfonamide (246 g, 2031 mmol) were charged. The Cs₂CO₃ (441 g, 1354 mmol) was charged in portions, with agitation, over several minutes. The reaction was agitated overnight at ambient temperature under nitrogen. The reaction was sampled and analyzed by HPLC for reaction completion. A 15 wt% solution of the citric acid (in water) was prepared (using 1.5 eq of citric acid based on the Cs₂CO₃ input). This solution was charged into the reactor with the reaction mixture, using an addition funnel. The charge was done in portions. The biphasic mixture was transferred to a separatory funnel, and the lower DCM layer was removed. The upper aqueous layer was removed and discarded. The DCM layer was transferred back into the separatory funnel, and washed with saturated brine (2 L). Again, the lower DCM layer was removed, and the upper aqueous layer was discarded. The DCM layer was concentrated under vacuum (rotovap) to give the desired product.



5

(S)-N-((S)-3-(1,3-dioxan-2-yl)-1-(5-fluoro-2-methoxypyridin-3-yl)propyl)-2-

5 **methylpropane-2-sulfinamide (5):** A flask (equipped with a nitrogen inlet, overhead stirring, reflux condenser, thermocouple, and addition funnel) was charged with Mg turnings (565 g, 23.2 moles) followed by THF (24 L, 8 vol) under nitrogen. This mixture was agitated and warmed to ~30 °C. When the internal temperature was 29.9 °C, DIBAL (31.2 mL, 0.004 eq.) was added. A separate flask was charged with 2-(2-bromoethyl)-1,3-

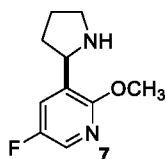
10 dioxane (4531 g, 23.2 moles) and THF (15.9 L, 5.3 vol). The mixture was agitated at ambient temperature to dissolve. The reaction flask with the Mg/Dibal-H mixture was slowly charged with the 2-(2-bromoethyl)-1,3-dioxane (**3**) /THF solution via an addition funnel. The charge was made in portions over ~5 h. The bromide solution was added so that the internal temperature did not rise above 50 °C. The reaction mixture was then held

15 for 45 minutes. After the 45-minute hold, the active Grignard mixture was cooled to -30 to -40 °C (dry ice/acetonitrile). A separate flask was charged with the (*R,E*)-N-((5-fluoro-2-methoxypyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (3000 g, 11.6 moles), followed by THF (5.1 L, 1.7 vol). Using an addition funnel, the starting material solution was portion-wise transferred at ambient temperature into the Grignard mixture over ~2 h

20 and the internal temp was kept at -37.3 to -28.9 °C. The reaction mixture was agitated at low temperature and analyzed by HPLC for reaction completion. To quench the reaction, a 15 wt% solution of citric acid (~11 vol) was charged into a round bottom flask and cooled with an ice bath to ~10 °C. The reaction mixture was transferred into the citric acid solution in portions. When the transfer was complete, the mixture was allowed to stir for ~15

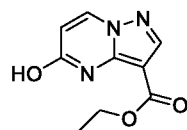
25 minutes. MTBE (9 L, 3 vol) was charged into the mixture and then the entire mixture was transferred to a separatory funnel. The reaction flask was rinsed with MTBE (3 L, 1 vol) and transferred to the separatory funnel. The biphasic mixture was agitated for 5 minutes

and then the phases were allowed to settle. The layers were separated, and the bottom aqueous layer was back extracted with additional MTBE (16 L, ~5 vol). After mixing and settling, the layers were separated. The MTBE layers were combined and washed with sat. brine (15 L, 5 vol). After mixing and settling, the aqueous layer was discarded. The MTBE layer was concentrated under vacuum. MTBE (6 L, 2 vol) was charged, and the product was dissolved with agitation at ambient temperature. To the MTBE solution, heptane (30 L, 10 vol) was charged over ~1 h. The slurry was allowed to agitate at ambient temperature overnight, and then filtered through polypropylene filter cloth. The cake was rinsed with heptane (9 L, 3 vol), and the wet solid **5** was dried in trays under vacuum at ~50 °C to constant weight.

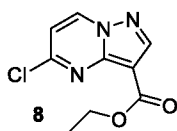


(R)-5-fluoro-2-methoxy-3-(pyrrolidin-2-yl) pyridine (7): A flask (equipped with mechanical stirring, N₂ inlet, condenser and J-Kem) was charged with **5** (1993 g, 5322 mmol) 2,2,2-trifluoroacetic acid (7971 mL) and water (1918 mL). The reaction was sampled to monitor completion of the deprotection by HPLC. After the reaction was judged to be complete, the reaction was charged with triethylsilane (2550 mL, 16.0 moles) via addition funnel over ~1 h. The reaction mixture was stirred at ambient temperature overnight and the solvent was removed under vacuum with heating to 45 - 50 °C. The resulting product was added to a 100 L separatory funnel and was diluted with MTBE (15 L) and water (15 L). The layers were agitated and the separated layers were dropped into tared carboys (Aq 1 and MTBE 1). The MTBE layer was added back to the separatory funnel and was back extracted with 6000 mL 1 M HCl. After mixing, the separated layers were dropped into tared carboys (Aq2 and MTBE 2). The aqueous layers were combined in the separatory funnel. To the aqueous layer was added DCM (16 L). To the mixture was added 50wt% NaOH (~900 mL) to reach pH ≥ 12. After mixing, the organic layer was dropped into a tared flask (DCM 1). The aqueous layer was extracted with DCM (16 L) and the organic layer was dropped into a tared flask. The aqueous layer was extracted a third time with DCM (8 L). The organic layer was dropped into a tared flask (DCM 3).

The combined organic layers were transferred to the separatory funnel and washed with sat. brine (9 L). The layers were separated and the organic layers were dropped and then the solvent was removed under vacuum to isolated the product.

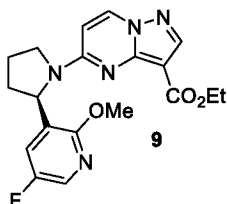


5 **Ethyl 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carboxylate:** To a reactor was charged K_3PO_4 (4104 g granular, 19.3 moles), ethyl 3-amino-1H-pyrazole-4-carboxylate (2000 g, 12.9 moles), and DMF (18.8 kg) and the mixture was agitated. After 20 min, (*E*)-ethyl 3-ethoxyacrylate, (2230 g, 15.5 moles) was added and the mixture was heated to 110-115 °C internal temperature (IT). After the reaction was judged to be complete based on
10 consumption of starting material, heating was ceased. The mixture was allowed to stir and cool overnight. Aqueous hydrochloric acid (3 M, 13 L) was added over ~ 2 h. DI water (6 L) was added and the mixture was allowed to stir overnight. The mixture was filtered through polypropylene filter cloth (PPFC) and the residue was washed with water (3 x 5 vol, 3 x 10 L). The solid was placed in trays and oven dried under vacuum at 55 °C for 3
15 days and then 45 °C for 4 days to constant weight of (2553 g 95.6%).

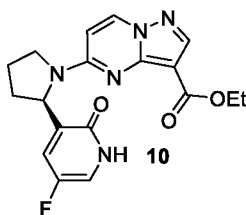


Ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (8): To a flask, under nitrogen, outfitted with mechanical stirring, J-Kem temperature probe, and condenser was added ethyl 5-hydroxypyrazolo[1,5-a]pyrimidine-3-carboxylate (2319 g, 11.2 moles),
20 acetonitrile (9200 mL), and phosphoryl trichloride (1230 mL, 13.4 mmol). The reaction mixture was heated to ~74 °C (IT) until it was judged complete by HPLC. The reaction was cooled to ~30 °C. While cooling, a separate flask was outfitted with mechanical stirring and a J-Kem temperature probe. Water (37 L) was added to this and the water was cooled to below 15 °C. The reaction mixture was added portion-wise producing a mixture
25 . The chlorination reactor was rinsed with 4:1 water/MeCN (2 L) and the rinse was added to the mixture. To the mixture was added MeCN (1 L) The transfer line was rinsed with 4:1 water/MeCN (2 L), and the rinse was added to the mixture. The mixture was cooled

back to below 20 °C and a solution of tribasic phosphate (2312 g, 10.9 mol) in water (4.0 L) was added portion-wise at a rate to keep the IT below 25 °C. The slurry was stirred at ambient temperature overnight. The slurry was filtered (PPFC) and rinsed with 4:1 water/MeCN (6 L). The cake was rinsed a second time with water (7.0 L). The solid was placed in trays and dried in a vacuum oven at 50 °C for 36 - 72 h to give **8**.

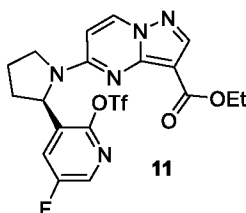


Ethyl (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (9): Combined triethylamine (1187 mL, 8518 mmol), (R)-5-fluoro-2-methoxy-3-(pyrrolidin-2-yl) pyridine (**7**) (889 g, 4259 mmol) in EtOH (200 proof, 5 mL/g, 4.4 L) and then ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (**8**) (1001 g, 4259 mmol) were added. The reaction was stirred overnight at ambient temp (19 h). The next day, water (10 mL/g, 8.9 L) was added and after stirring at room temperature for 2 h it was filtered through polypropylene filter cloth (PPFC), 23°C and washed with 2:1 water:EtOH (2 x 1.8 L) then heptane (1.8 L). The product was placed in trays and dried under vacuum (with N₂ bleed) at 55°C to give **9**.



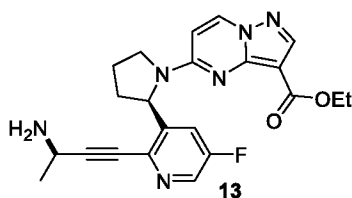
Ethyl (R)-5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (10): A solution of 4 M HCl in dioxane (1.0 L) was added to a flask containing (R)-ethyl 5-(2-(5-fluoro-2-methoxypyridin-3-yl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (**9**) (2500 g, 6486.9 mmol). The mixture was heated to 60 °C with an outlet at the top of the condenser (not under nitrogen). Once complete by HPLC, it was put under nitrogen and allowed to cool to room temperature with stirring overnight. The next day 20% K₃PO₄ (aq) (19 L, 7.5 mL/g - made by diluting

3800 g of K_3PO_4 to 19 kg total with water), was added. Once the temp was $<35^\circ C$, EtOAc (12.5 L, 5 mL/g) was added and stirring continued for another 30 min. The mixture was pumped into a separatory vessel, and the aqueous layer dropped. The organic layer was concentrated under vacuum (rotovap) and the product was dried on vacuum pump at ambient temp to give **10**.



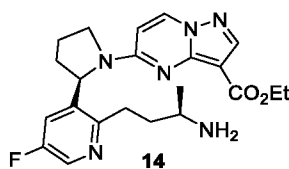
ethyl (R)-5-(2-(5-fluoro-2-(((trifluoromethyl) sulfonyl)oxy)pyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (11): To a DCM solution of **10** was added triethylamine (1467 mL, 105.2 mol) and the mixture cooled to $<5^\circ C$. Trifluoromethanesulfonic anhydride (1930 g, 684.0 mol) was added in portions maintaining temp $<15^\circ C$. After 1 h reaction time sat. $NaHCO_3$ (5 mL/g, 11 L) was added. The mixture was stirred for 1 h and was then transferred to a separatory vessel with DCM and the layers were separated. The organic layer was washed with $NaHCO_3$ (11 L). The organic layer was concentrated to minimum volume and solvent-swapped to MeOH (target MeOH volume about 10 L). The MeOH solution was added to a flask containing 1:1 MeOH:water (20 L), the suspension was stirred at room temperature for 2 h, filtered, and washed with 1:2 water:MeOH (2 x 2 mL/g). The solid was oven dried under vacuum at $55^\circ C$ until constant weight, to give **11**.

N-Phenyl-bis(trifluoromethanesulfonimide) may be used instead of Trifluoromethanesulfonic anhydride to provide **11**.

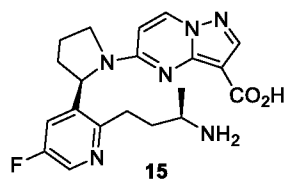


ethyl 5-((R)-2-(2-((R)-3-aminobut-1-yn-1-yl)-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (13): Toluene (16 L) was deoxygenated by N_2 bubbling for ~2 h. To a separate flask equipped with a heat source and reflux condenser

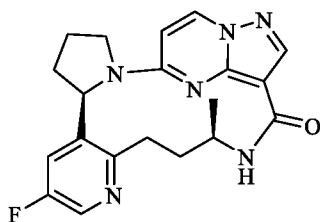
were charged (R)-ethyl 5-(2-(5-fluoro-2-(((trifluoromethyl)sulfonyl)oxy)pyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate **11** (1440 g, 2860 mmol), copper(I) iodide (105 g, 551.3 mmol), Pd catalyst (398 g, 567.0 mmol), and the deoxygenated toluene. Diisopropylamine (810 ml, 5779 mmol) was added and the mixture
5 was heated to 60°C. After ~ 1 h, the reaction temp was 60°C and commercially available (R)-tert-butyl but-3-yn-2-ylcarbamate (**12**) (728 g, 4302 mmol) was added in three portions.. After ~1 h, the mixture was cooled with an ice/water bath and then water (14 L) was added. When the reaction temp reaches ~35°C, it was filtered (PPFC) and washed with water (2 x 3.5 L). The filtrate was transferred to a separatory vessel and the aqueous layer
10 was washed with toluene (2 x 3.5 L). The aqueous layer was transferred to a separate flask and added DCM (14 L) was added. The mixture was cooled to <15°C, then sat. NH₄OH (2.4 L) was added. The solution was transferred to a separatory vessel and then washed with DCM (7 L). The DCM layers were allowed to stand at ambient temperature overnight and then they were combined and washed with brine (7 L). The organic layer was then
15 concentrated, MeOH (5 L) was added and the mixture was concentrated to give **13**.



Ethyl 5-((R)-2-(2-((R)-3-aminobutyl)-5-fluoropyridin-3-yl) pyrrolidin-1-yl) pyrazolo[1,5-a] pyrimidine-3-carboxylate (14): Palladium on carbon (235 g, 104 mmol, 4.7wt%), a 1285 g methanolic solution of ethyl 5-((R)-2-(2-((R)-3-aminobut-1-yn-1-yl)-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (**13**) (472 g, 1117 mmol) and MeOH (2.5 L~ 4 L total volume) were charged into a 8 L Parr reactor. The mixture was stirred at 50 psi H₂ until it was judged complete. The hydrogen atmosphere was replaced with nitrogen and the reaction mixture was allowed to stand overnight. The next day it was filtered through GF/F filter paper. The solution was
20 concentrated to give **14**.
25

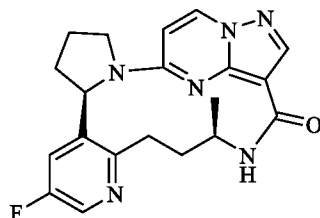


5-((*R*)-2-(2-((*R*)-3-aminobutyl)-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (15): A methanol solution of **14** (861 g, 2019 mmol) was combined with IPA (4 L) and then concentrated to 2.2 kg under vacuum. The concentrate was transferred to a reactor (with reflux condenser) with further dilution in IPA (10 L). The mixture was heated to 75°C (IT). Sodium hydroxide (184 mL, 2631 mmol) was added and the reaction continues until it was judged complete by HPLC. The heat was removed and the mixture was allowed to cool to ambient temp overnight. Concentrated hydrochloric acid (214 mL, 2632 mmol) was added. The mixture was concentrated under vacuum with external heating to 45°C to ~5 mL/g. Heptane (12 L) was added and the suspension was allowed to cool to ambient temp and then stirred for ~1 h. The suspension was filtered (PPFC) and washed with 3:1 heptane:IPA (2 x 1600 mL). The wet cake was placed in trays and dried under vacuum at 55°C to constant weight to give **15**.



(13*E*,14*E*,22*R*,6*R*)-35-fluoro-6-methyl-7-aza-1(5,3)-pyrazolo[1,5-a]pyrimidina-3(3,2)-pyridina-2(1,2)-pyrrolidinacyclooctaphan-8-one (Compound 1): To a flask containing EDCI (157 g, 819 mmol) and DMAP (133 g, 1091 mmol) in DCM (50 mL/g, 125 mL) was added 5-((*R*)-2-(2-((*R*)-3-aminobutyl)-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (**15**) (302 g, 546 mmol) in 8 portions (37.8 g each). The portions were added ~60 min apart. The reaction mixture was stirred overnight at ambient temperature. The mixture was transferred to a separatory funnel with minimal DCM and washed with sat. NaHCO₃ (2 x 3 L), and 0.25 M citric acid (2 x 3 L, pH 5.5). The combined aqueous layers were washed with DCM (3 L, 10 mL/g) and then concentrated under vacuum (rotovap). The concentrate was dissolved in 3% MeOH in DCM and loaded onto a flash column (3 kg, SiO₂) and eluted with 3% MeOH in DCM (40 L total). The fractions

containing the product were concentrated to give **Compound 1**. Combined lots of solid **Compound 1** were triturated in IPAc (2.5 L, ca. 5 mL/g) at room temperature for 2 h. The mixture was heated to 40-45 °C for 10 minutes, then triturated at room temperature. The suspension was filtered and washed with IPAc (2 x 250 mL, ca. 2 x 0.5 mL/g) to give, after
5 oven drying at 55 °C, **Compound 1**.

**Compound 1**

(13E,14E,22R,6R)-35-fluoro-6-methyl-7-aza-1(5,3)-pyrazolo[1,5-a]pyrimidina-3(3,2)-pyridina-2(1,2)-pyrrolidinacyclooctaphan-8-one(Compound 1) (alternative

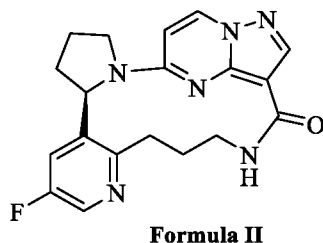
preparation): To a flask containing EDCI (1091 g, 5.7 mol, 1.7 eq) and DMAP (941 g, 7.71 mol, 2.3 eq) in DCM (38 L) were added the amino-acid **15** [5-((R)-2-(2-((R)-3-aminobutyl)-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid] (1900 g, 3.35 mol) in 6 portions (added at least one hour apart), and the reaction was stirred at room temperature overnight. Once the reaction was complete it was transferred
10 to a separatory funnel and washed with sat'd NaHCO₃ solution (2 x 19 L). The DCM layer was then washed with 0.25 M citric acid (38 L). The combined, citric acid aqueous layers were back-extracted with DCM (19 L), and the organic phases were added back to the 100 L round-bottomed flask. Charcoal (2.01 kg) and silica gel (2.01 kg) were added, and the suspension stirred at room temperature overnight. The next day, the suspension was
15 filtered, and the charcoal cake was washed with DCM (3 x 19 L). The DCM filtrates were filtered a second time. The pale yellow solution was concentrated to minimum volume. Isopropyl acetate (28.5 L) was added and concentrated to 10 to 20 L. The suspension was heated overnight at 75 °C, and the mixture was allowed to cool to room temperature. The solids were collected by filtration and washed with isopropyl acetate (2 x 1.9 L). The crude
20 product was transferred to trays and dried in a vacuum oven 55 °C until constant mass was achieved.

To a flask was charged [(1³E,1⁴E,2²R,6R)-3⁵-fluoro-6-methyl-7-aza-1(5,3)-pyrazolo[1,5-a]pyrimidina-3(3,2)-pyridina-2(1,2)-pyrrolidinacyclooctaphan-8-one] followed by 2-butanone (6.3 L). The slurry was agitated at 75 °C for 2 days and then the product was collected by filtration, and the product cake was washed with 2-butanone (2 x 950 mL g). The product was transferred to trays and dried in a vacuum oven at 55 °C until constant mass was achieved to provide **Compound 1**.

The average purity of Compound 1 was 98.8% as determined by HPLC-UV. The structure of Compound 1 was confirmed using ¹H NMR.

2) Preparation of the compound of Formula II

Compound of Formula II is prepared using methods and procedures similar to those used to prepare the compound of Formula I using *tert*-butyl prop-2-ynylcarbamate (compound 19) instead of *tert*-butyl (*R*)-but-3-yn-2-ylcarbamate (compound 12).



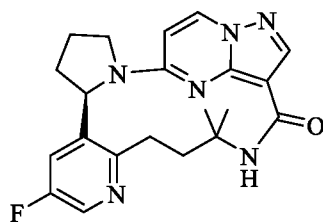
Formula II

(6R)-9-fluoro-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one (Formula II).

MS (apci) m/z = 367.3 (M+H).

3) Preparation of the compound of Formula III

Compound of Formula III is prepared using methods and procedures similar to those used to prepare the compound of Formula I, using *tert*-butyl 2-methylbut-3-yn-2-ylcarbamate (compound 23) instead of *tert*-butyl (*R*)-but-3-yn-2-ylcarbamate (compound 12).



Formula III

(6R)-9-fluoro-15,15-dimethyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one (Formula III)

5 MS (apci) m/z = 395.1 (M+H).

Preparation of crystalline forms and salts of Compound 1

General methods for preparation and characterization of Compound 1 salts

10 Approximately 20 mg Compound 1 was weighed into 2 mL vials. Acid counterions were weighed into separate vials and stock solutions prepared for the liquid counterions (1.05 eq.). Table 11 shows acid weights and volumes.

Table 11

Acid No.	Acid	pKa			Neat Addition Amounts	
		1	2	3	By Weight (mg)	By Volume (μL)
1	Hydrochloric acid 37 wt.% (12M)	-6.10			5.45	4.6
2	Sulfuric acid	-3.00	1.92		5.71	3.1
3	1-2-Ethane disulfonic acid	-2.10	-1.50		12.94	
4	p-Toluene sulfonic acid	-1.34			10.84	
5	Methane sulfonic acid	-1.20			5.31	3.6
6	Naphthalene-2-sulfonic acid	0.17			14.14	
7	Benzene sulfonic acid	0.70			8.92	
8	Oxalic acid	1.27	4.27		5.08	

Acid No.	Acid	pKa			Neat Addition Amounts	
		1	2	3	By Weight (mg)	By Volume (μL)
9	2-Hydroxy ethanesulfonic acid	1.66			8.19	
10	L-Aspartic acid	1.88	3.65		7.36	
11	Maleic acid	1.92	6.23		6.48	
12	Phosphoric acid	1.96	7.12	12.32	5.42	
13	Ethane sulfonic acid	-2.05			6.41	4.7
14	L-Glutamic acid	2.19	4.25		8.13	
15	L-Tartaric acid	3.02	4.36		8.34	
16	Fumaric acid	3.03	4.38		6.48	
17	Citric acid	3.13	4.76	6.40	10.67	
18	D- Glucuronic acid	3.18			10.73	
19	L-Malic acid	3.46	5.10		7.49	
20	Hippuric acid	3.55			10.1	
21	D-Gluconic acid (50% in water)	3.76			21.68	17.6
22	DL-Lactic acid (85% aq. solution)	3.86			5.86	4.8
23	L-Ascorbic acid	4.17	11.57		9.73	
24	Benzoic acid	4.19			6.82	
25	Succinic acid	4.21	5.64		6.59	

Preparation of samples of salts of these acids and the Compound 1 in selective solvents (acetone, ethanol, methanol, 2-propanol, TBME and THF) is described in the Examples. In the Examples 8-32, solids observed post-temperature cycling were collected and analyzed by XRPD. Samples in which solid was not observed had anti-solvent additions made to saturated solutions and the resultant solids were analyzed by XRPD.

Anti-Solvent Additions

Approximately 1 mL of anti-solvent (heptane or TBME depending on miscibility) was added dropwise to saturated salt solutions of Compound 1 free base. Any resulting solid was analyzed by XRPD.

Salt Stability Studies

Recovered salts were placed in an oven at 40 °C / 75 % RH for 1 week, and the resultant materials were analyzed by XRPD to determine any changes to form or crystallinity.

Thermodynamic Solubility

Thermodynamic solubility studies were carried out as follows: 10 mg of prepared salts were suspended in pH 1, 4.5, 6.8 and un-buffered water (300 µL). The pH of the slurries was measured and adjusted accordingly using either 0.2M HCl solution or 0.2M sodium hydroxide solution. The slurries were agitated for 24 hours at ambient temperature using an incubator shaker. The resulting slurries were filtered, any solids recovered were analyzed by XRPD and filtrate pH measured and submitted for UPLC analysis. pH 1.0 Buffer: 67 mL 0.1M hydrochloric acid solution was added to 12.5 mL 0.2M potassium chloride solution and diluted to 100 mL using de-ionized water and adjusted accordingly. pH 4.5 Buffer: 7.0 mL 0.2M sodium hydroxide solution was added to 25 mL 0.2 potassium hydrogen phthalate solution and diluted to 100 mL using de-ionized water and adjusted accordingly. pH 6.8 Buffer: 11.2 mL 0.2M sodium hydroxide solution was added to 25mL 0.2M potassium phosphate mono-basic and diluted to 100 mL using de-ionized water and adjusted accordingly.

Salt Disproportionation Studies

Salt disproportionation studies were carried out as follows: 20 mg of prepared salts were weighed into a vial and 0.5 mL of deionized water was added. The samples were then agitated for 24 h at ambient temperature. The pH of the samples was taken pre- and post-agitation. Any solids recovered were submitted for XRPD analysis to determine any changes to form.

Hydration Screen

Hydration screen was carried out as follows: 10 mg of prepared salts were suspended in several acetone/water mixtures of various water activities (low: $a_w = 0.281$, medium: $a_w = 0.776$ and high: $a_w = 0.919$) and agitated at ambient temperatures for 24

hr. Any recovered solids were submitted for XRPD analysis to determine any changes to form.

Analytical methods

5 *X-ray Powder Diffraction (XRPD)*

XRPD analysis was carried out on a Panalytical X'pert pro, scanning the samples between 3 and 35° 2 θ . The material was gently ground and loaded onto a multi-well plate with Kapton or mylar polymer film to support the sample. The multi well plate was then loaded into a Panalytical diffractometer running in transmission mode, using Cu K
10 radiation, and analyzed. The experimental conditions are shown in Table 12.

Table 12

Raw Data Origin:	XRD measurement
Scan Axis:	Gonio
Start Position [$^{\circ}2\theta$]:	3.0066
End Position [$^{\circ}2\theta$]:	34.9866
Step Size [$^{\circ}2\theta$]:	0.0130
Scan Step Time [s]:	18.8700
Scan Type:	Continuous
PSD Mode:	Scanning
PSD Length [$^{\circ}2\theta$]:	3.35
Offset [$^{\circ}2\theta$]:	0.0000
Divergence Slit Type:	Fixed
Divergence Slit Size [$^{\circ}$]:	1.0000
Measurement Temperature	25.00
Anode Material:	Cu
K-Alpha1 [$\text{\AA}$]:	1.54060
K-Alpha2 [$\text{\AA}$]:	1.54443
K-Beta [$\text{\AA}$]:	1.39225
K-A2 / K-A1 Ratio:	0.50000
Generator Settings:	40 mA, 40 kV

Raw Data Origin:	XRD measurement
Goniometer Radius [mm]:	240.00
Dist. Focus-Diverg. Slit [mm]:	91.00
Incident Beam Monochromator:	No
Spinning:	No

Single Crystal X-ray Analysis (SXRD)

SXRD analysis was conducted on a Agilent Technologies (Dual Source) SuperNova diffractometer using monochromated Cu K α ($\lambda = 1.54184 \text{ \AA}$) radiation. The diffractometer was fitted with an Oxford Cryosystems low temperature device to enable data collection to be performed at 120(1) K and the crystal encased in a protective layer of Paratone oil. The data collected were corrected for absorption effects based on Gaussian integration over a multifaceted crystal model, implemented as a part of the CrysAlisPro software package (Agilent Technologies, 2014).

The structure was solved by direct methods (SHELXS97) (Sheldrick, G. M. *Acta Cryst. Sect. A* **2008**, 64, 112.) and developed by full least squares refinement on F2 (SHELXL97) interfaced via the OLEX2 software package. Images were produced using OLEX2 (Dolomanov, O. V. et al. *J Appl. Cryst.* **2009**, 42, 339-341).

Polarized Light Microscopy (PLM)

The presence of crystallinity (birefringence) was determined using an Olympus BX50 polarizing microscope, equipped with a Motic camera and image capture software (Motic Images Plus 2.0). All images were recorded using the 20x objective, unless otherwise stated.

Thermogravimetric Analysis (TGA)/ Differential thermal analysis (DTA)

Approximately, 5 mg of material was weighed into an open aluminum pan and loaded into a simultaneous thermogravimetric/differential thermal analyzer (TG/DTA) and held at room temperature. The sample was then heated at a rate of 10 °C/min from 20 °C to 400 °C during which time the change in sample weight was recorded along with any differential thermal events (DTA). Nitrogen was used as the purge gas, at a flow rate

of 300 cm³/min.

Differential Scanning Calorimetry (DSC)

Approximately, 5 mg of material was weighed into an aluminum DSC pan and sealed non-hermetically with a pierced aluminum lid. The sample pan was then loaded into a Seiko DSC6200 (equipped with a cooler) cooled and held at 20 °C. Once a stable heat-flow response was obtained, the sample and reference were heated to 350 °C at scan rate of 10 °C/min and the resulting heat flow response monitored.

Infrared Spectroscopy (IR)

Infrared spectroscopy was carried out on a Bruker ALPHA P spectrometer. Sufficient material was placed onto the center of the plate of the spectrometer and the spectra were obtained using parameters indicated in Table 13:

Table 13

Resolution:	4 cm ⁻¹
Background Scan Time:	16 scans
Sample Scan Time:	16 scans
Data Collection:	4000 to 400 cm ⁻¹
Result Spectrum:	Transmittance

Nuclear Magnetic Resonance (NMR)

NMR experiments were performed on a Bruker AVIIIHD spectrometer equipped with a DCH cryoprobe operating at 500.12 MHz for ¹H channel. Experiments were performed in deuterated DMSO and each sample was prepared to about 10 mM concentration.

Dynamic Vapor Sorption (DVS)

Approximately, 10 mg of sample was placed into a mesh vapor sorption balance pan and loaded into a DVS-1 dynamic vapor sorption balance by Surface Measurement Systems. The sample was subjected to a ramping profile from 40 – 90% relative humidity (RH) at 10% increments, maintaining the sample at each step until a stable weight had been achieved (99.5% step completion). After completion of the sorption cycle, the sample was dried using the same

procedure to 0% RH and then a second sorption cycle back to 40% RH. The weight change during the sorption/desorption cycles were plotted, allowing for the hygroscopic nature of the sample to be determined. XRPD analysis was then carried out on any solid retained.

5 *Gravimetric Vapor Sorption (GVS)*

Approximately 10-20 mg of sample was placed into a mesh vapor sorption balance pan and loaded into an IGASorp Moisture Sorption Analyzer balance by Hiden Analytical. The sample was subjected to a ramping profile from 40 – 90% relative humidity (RH) at 10% increments, maintaining the sample at each step until a stable weight had been achieved (98% step completion). After completion of the sorption cycle, the sample was dried using the same procedure to 0 % RH, and finally taken back to the starting point of 40% RH. The weight change during the sorption/desorption cycles were plotted, allowing for the hygroscopic nature of the sample to be determined.

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

HPLC experiments were performed on Agilent 1100 HPLC instrument with diode array detector (DAD) using parameters indicated in Table 14:

Table 14

Column:	ACE3 C181-PFP 50 x 4.6 x 3 μ m
Column Temperature:	45.0 $^{\circ}$ C
Autosampler Temperature:	Ambient
UV wavelength:	265 nm
Injection Volume:	2.00 μ L
Flow Rate:	2 mL/min
Mobile Phase A:	95.0% (0.1% TFA/DI-H ₂ O)
Mobile Phase B:	5.0% (0.1% TFA/MeCN)

Gradient program is shown in Table 15:

Table 15

Time (minutes)	Solvent B [%]
0.00	5.0
2.50	60.0
3.20	80.0
3.21	5.0
5.50	5.0

Example 1 – Solubility of Compound 1 free base

A solid Compound 1 was obtained as follows. A 53 mL of solution containing about 330 mg of Compound 1 in warm 1,4-dioxane was divided between 33, 2 mL glass vials (1.5 mL in each). The solutions were frozen and freeze-dried by lyophilization overnight. The resulting material was then analyzed by XRPD to confirm mostly amorphous material.

Approximately 10 mg of amorphous Compound 1 was produced in 32×2 mL glass vials from freeze drying and 100 μ L of the appropriate solvent system was added to the appropriate vial. Between each addition, the mixture was checked for dissolution and if no dissolution was apparent, the mixture was heated to about 40 °C and checked again. This procedure was continued until dissolution was observed or until 2 mL had been added (to the compound concentration of < 5 mg/mL). The results of the solubility measurements are shown in Table 16.

Table 16

Solvent	Approx. Solubility mg/mL
Acetone	11.1
Acetonitrile	12.5
Anisole	11.1
1-Butanol	17
2-Butanone	11.1
TBME	< 5

Solvent	Approx. Solubility mg/mL
Cyclohexane	< 5
Cyclopentylmethyl ether	< 5
Dichloromethane	> 100
Diisopropyl ether	< 5
N,N-Dimethylacetamide	> 100
1,2-Dimethoxyethane	8.3
Diglyme (bis(2-methoxyethyl ether)	8.3
1,4-Dioxane	8.3
Dimethylformamide	> 100
Dimethylsulfoxide	50
Ethanol	20
Ethyl acetate	< 5
2-Ethoxy ethanol	50
Heptane	< 5
Isobutyl acetate	< 5
Isopropyl acetate	< 5
Methanol	50
Methylisobutyl ketone	6.25
2-Methyl THF	< 5
N-Methylpyrrolidone	> 100
2-Propanol	14.3
1-Propanol	> 100
Tetrahydrofuran	20
Toluene	< 5
TBME:Heptane (60:40 v/v)	<5
Water	< 5

Compound 1 showed low solubility in non-polar solvents such as toluene and 1,4-dioxane, medium solubility in polar aprotic solvents such as acetone, ethyl acetate and

acetonitrile and high solubility in polar solvents such as DMSO, DMF and protic solvents such as methanol. In the remainder of cases and where “<” is present, solid was still present after the maximum volume of 2 mL was added. XRPD analysis of the recovered solids from the solvent solubility study returned the same crystalline form of free base in all cases (Form I), however, showing varying degrees of crystallinity and peak intensity (preferred orientation may have an effect on crystallinity of a sample). Insufficient solids were recovered from anisole, 1-butanol, diglyme, 2-ethoxy ethanol, MIBK and N-methylpyrrolidone.

Example 2 – Preparation of crystalline Compound 1 (Form I)

Solid Compound 1 was obtained as follows. A 212 mL of solution containing about 1.04 g of Compound 1 in warm 1,4-dioxane was divided between 26, 20 mL glass vials (approximately 8 mL in each). The solutions were frozen and freeze-dried by lyophilization overnight. The resulting material was then analyzed by XRPD to confirm mostly amorphous material.

The 25 vials each containing approximately 40 mg of amorphous freeze-dried Compound 1 were used. A solvent was added to each vial and Compound 1 was suspended in the solvent. The following 25 solvents were used: acetone, acetonitrile, anisole, 1-butanol, 2-butanone, TBME, cyclohexane, cyclopentylmethyl ether, 1,2-dimethoxyethane, 1,4-dioxane, ethanol, ethyl acetate, 2-ethoxy ethanol, heptane, isobutyl acetate, isopropyl acetate, methanol, methylisobutyl ketone, 2-methyl THF, 2-propanol, 1-propanol, tetrahydrofuran (THF), toluene, TBME:heptane (60:40 v/v), and water. The crystallization conditions consisted of maturation cycles, evaporation, cooling and anti-solvent addition techniques.

Temperature cycling

Each of the 25 vials was temperature cycled between ambient temperature and 40 °C in 4 hour cycles over 72 h. The resulting solids were isolated by centrifugation and analyzed by XRPD and PLM. Solids recovered from temperature cycling and analyzed by XRPD appeared to be the same as the input material (Form I) with varying degrees in crystallinity. No residual solid material was recovered from anisole, 1-butanol, 2-butanone, 2-ethoxy ethanol, 2-methyl THF, 1-propanol and THF.

A filtered saturated solution of Compound 1 in a specified solvent was divided into five vials and used to prepare crystalline forms of the compound according to the procedures described below:

Crash Cool (2 °C)

- 5 Saturated solutions of Compound 1 were stored at 2 °C for 24-72h. At this time any material recovered was analyzed by XRPD. The crash cooling experiments at 2 °C recovered insufficient solids from all solvents for XRPD analysis except from 2-propanol which returned Compound 1 (Form I).

Crash Cool (-18 °C)

- 10 Saturated solutions of Compound 1 were stored at -18 °C for 24-72h. At this time any material recovered was analyzed by XRPD. The crash cooling experiments at -18 °C recovered insufficient solids from all solvents for XRPD analysis except 1-butanol, ethanol, 2-propanol and 1-propanol. From the solids that were analyzed by XRPD analysis, all returned Compound 1 (Form I) with varying degrees of crystallinity.

15 *Anti-Solvent Addition at Ambient Temperature*

- Approximately 1 mL of anti-solvent (heptane or TBME depending on miscibility) was added dropwise to saturated solutions of Compound 1 free base. Any resulting solid was analyzed by XRPD. The anti-solvent addition at ambient temperature experiments recovered insufficient solids from all solvents for XRPD analysis except acetone,
20 acetonitrile, 2-butanone, 1,2-dimethoxyethane, 1,4-dioxane and ethanol. From the solids that were analyzed by XRPD analysis, all returned Compound 1 (Form I) with varying degrees of crystallinity.

Anti-Solvent Addition at 2 °C

- 25 Approximately 1 mL of anti-solvent (heptane or TBME depending on miscibility) was added dropwise to saturated solutions of Compound 1 free base. Any resulting solid was analyzed by XRPD. The anti-solvent addition at 2 °C experiments recovered insufficient solids from all solvents for XRPD analysis except acetone, acetonitrile, 1-butanol, 2-butanone, 1,2-dimethoxyethane, 1,4-dioxane, ethanol, ethyl acetate, MIBK, 1-propanol and THF. From the solids that were analyzed by XRPD, all returned Compound
30 1 (Form I) with varying degrees of crystallinity.

Evaporation

Saturated solutions of Compound 1 were transferred to 2 mL vials, these vials were then uncapped and allowed to evaporate at ambient temperature to recover material. Any material recovered was analyzed by XRPD. The evaporation experiments recovered
5 insufficient solids from all solvents for XRPD analysis except acetone, acetonitrile, 2-butanone, cyclopropylmethyl ether, 1,2-dimethoxyethane, 1,4-dioxane, ethanol, ethyl acetate, 2-ethoxy ethanol, isobutyl acetate, isopropyl acetate, methanol, MIBK, 2-propanol, 1-propanol and THF. From the solids that were analyzed by XRPD, all returned Compound 1 (Form I) with varying degrees of crystallinity.

10

Example 3 – Characterization of crystalline Compound 1 (Form I)*X-Ray Powder Diffraction (XRPD)*

Form I of crystalline (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-
15 17-one (Compound 1 free base) was characterized by XRPD. The XRPD pattern is shown in Figure 1 and XRPD data is provided in Table 17.

Table 17

2-Theta (°)	Height	H%
7.9	692	4.0
9.1	10133	58.1
11.2	6232	35.7
12.8	695	4.0
13.4	4471	25.6
14.8	2667	15.3
15.2	479	2.8
15.5	144	0.8
16.8	929	5.3
18.3	2049	11.8
18.6	2818	16.2
19.5	792	4.5
20.2	17437	100.0
21.4	1327	7.6
22.7	1668	9.6
23.2	210	1.2
23.6	1908	10.9
24.9	6322	36.3
25.8	783	4.5
26.1	447	2.6
26.5	537	3.1
27.0	1478	8.5
27.7	220	1.3
28.4	259	1.5
28.8	228	1.3
29.4	1795	10.3
30.0	142	0.8
30.3	358	2.1

2-Theta (°)	Height	H%
31.2	197	1.1
32.1	359	2.1
32.3	357	2.1
33.3	248	1.4
34.4	70	0.4

As shown in Figure 1, according to the XRPD analysis, the material is crystalline. PLM analysis showed birefringence with irregular morphology.

Thermogravimetric/differential thermal analysis (TG/DTA)

5 Form I of crystalline (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one (Compound 1 free base) was characterized by TGA and DTA. TGA showed a weight loss of approximately 1.1% from outset up to 200 °C, while DTA showed an endothermic “melting” event at onset about 315 °C (peak at 317 °C). The TG/DTA thermogram is shown in Figure 2.

Differential Scanning Calorimetry (DSC)

15 Form I of crystalline (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one (Compound 1 free base) was characterized by DSC. DSC analysis in the first heat showed a sharp endothermic event at onset 315 °C (peak at 317 °C) which is consistent with TG/DTA. No thermal events were seen in the cooling cycle. The second heating cycle showed a small endothermic event at onset around 118 °C (peak at 124°C) which is highly likely to be a glass transition (*T_g*). The DSC thermograms are shown in Figure 3

20 In sum, Compound 1 exists as one crystalline form (Form I) with favorable thermal properties with a melting point of 315 °C and low hygroscopicity with a mass uptake of 0.3 % at 90 % RH and no changes to form or crystallinity after exposure to GVS humidity conditions.

Example 4 – Recrystallization of Compound 1 and characterization of the recrystallized material

Compound 1 was recrystallized from 1-propanol as follows. 500 mg of Compound 1 was weighed into a 20 mL vial. To this vial, 20 mL of 1-propanol was added gradually over 3 hours. The sample was placed in a 95 °C heated block to aid dissolution. The sample was slow to dissolve but a clear solution was achieved. The sample was cooled to 10 °C at 5 °C/min. Once the cooling cycle had reached 10 °C the sample remained at 10 °C for a further 24 hours to recover material. The solids were then recovered and dried using a vacuum oven at ambient temperature.

XRPD analysis of the recrystallized solid showed no changes in crystalline form, and PLM analysis showed the material to be birefringent with irregular morphology. TGA showed a weight loss of approximately 0.7% from the outset up to 250 °C, whilst DTA showed an endothermal ‘melting’ event at onset approximately at 314 °C (peak at about 318 °C).

Purity of recrystallized solid is 99.2% as determined by HPLC-UV. ¹H-NMR analysis shows that the spectrum is consistent with the structure and shows little if any obvious residual process solvents. ¹H NMR spectrum is shown in Figure 9.

Differential Scanning Calorimetry (DSC)

DSC analysis in the first heating cycle showed a sharp endothermal event at onset approximately 316 °C (peak at 317 °C). This endothermal event is consistent with TG/DTA. In the first cooling cycle of the DSC analysis, a slow broad recrystallization is observed with a peak at about 284 °C. shows the thermogram of the first cooling cycle. DSC analysis in the second heating cycle showed a series of exothermic events which could be potential recrystallizations which were followed by a sharp endothermal event at onset about 313 °C (peak at about 316 °C). shows the thermogram of the second heating cycle of the recrystallized Compound 1 free base.

Infra-Red analysis (IR)

Recrystallized Form I of crystalline Compound 1 was characterized by IR. Figure 8 shows IR spectrum and the peaks are listed in Table 18.

Table 18

Wave Number	Abs. Intensity	Rel. Intensity	Width
3344.4	0.8	0.1	27.8
3066.3	0.9	0.0	31.6
3019.9	0.9	0.0	15.3
2962.0	0.8	0.0	18.7
2929.8	0.8	0.0	25.5
2870.4	0.8	0.1	143.0
1649.6	0.6	0.1	2538.9
1625.8	0.5	0.4	43.1
1599.0	0.8	0.0	61.5
1566.9	0.6	0.3	17.6
1537.4	0.6	0.2	13.5
1492.1	0.5	0.2	2106.0
1450.6	0.4	0.5	63.7
1365.4	0.6	0.1	1743.6
1346.7	0.6	0.2	44.5
1281.8	0.7	0.1	8.5
1257.5	0.7	0.1	8.0
1234.4	0.6	0.2	40.6
1219.2	0.6	0.0	5.5
1167.6	0.7	0.1	35.4
1156.0	0.7	0.0	5.6
1114.8	0.8	0.0	9.4
1093.2	0.8	0.0	9.7
1070.8	0.7	0.1	10.7
992.3	0.8	0.0	318.0
964.0	0.7	0.1	13.0
945.2	0.8	0.0	132.0
923.0	0.8	0.1	6.9

Wave Number	Abs. Intensity	Rel. Intensity	Width
903.6	0.7	0.1	7.3
890.8	0.7	0.2	35.4
859.2	0.8	0.0	175.9
796.2	0.6	0.2	11.5
777.7	0.6	0.0	0.1
770.5	0.6	0.3	19.5
740.5	0.8	0.0	147.4
719.7	0.8	0.0	694.4
709.6	0.7	0.1	25.8
686.7	0.8	0.0	170.0
633.0	0.8	0.1	7.9
616.0	0.7	0.1	11.2
552.4	0.6	0.2	43.9
509.5	0.7	0.0	9.3
468.8	0.8	0.1	13.6
442.2	0.7	0.1	16.7
432.1	0.8	0.0	91.7
405.0	0.7	0.1	10.1

In sum, Compound 1 recrystallized from 1-propanol exhibited the same properties as the compound prior to recrystallization, with an increased purity of >99%. As shown in Example 5, the material showed no change to form or purity after exposure to stability stress conditions and no change to form after an aqueous solubility assessment.

Example 5 - Stability of Compound 1 (Form I)

Compound 1 (Form I) was subjected to various different environmental conditions to assess stability.

Vapor sorption - before recrystallization

Gravimetric vapor sorption (GVS) showed that Compound 1 exhibits slight

hygroscopicity with a mass uptake of approximately 0.3% at 90% RH. Figure 4 shows GVS isotherm plot and Figure 5 shows GVS kinetic plot. Post-XRPD analysis showed no changes in crystalline form upon exposure to GVS conditions.

Vapor sorption - recrystallized solid

Dynamic vapor sorption (DVS) analysis of the recrystallized compound shows the material to exhibit slight hygroscopicity with a mass uptake of about 0.7 % at 90 % RH. Figure 6 shows DVS analysis of the recrystallized compound. Figure 7 shows DVS kinetic plot of the recrystallized solid. Post-DVS XRPD analysis shows no change in crystalline form upon exposure to DVS humidity conditions.

Humidity, temperature, ambient light – recrystallized solid

1-week stability tests on recrystallized solid showed no change to form after exposure to 40 °C/75 % RH, 80 °C and under ambient light. UPLC analysis showed no change in purity of the samples after exposure to stability stress conditions (average purity 99.2 for relative humidity and ambient light tests, and 99.3% for 80 °C test).

Example 6 - Single Crystal X-ray Analysis of Compound 1 (Form I)

Crystals of Compound 1 (Form I) were prepared as follows. Compound 1 (2 mg) was dissolved in methanol (500 µL) in a 1.75 clear glass vial then capped with a pierced lid. The solution was left to stand at ambient for several days without agitation to allow for large rod-like crystals to grow that were suitable for interrogation by single crystal X-ray diffraction.

The highest residual Fourier peak was found to be $0.16 e \cdot \text{\AA}^{-3}$ approx $0.72 \text{ \AA}$ from C(4), and the deepest Fourier hole was found to be $-0.22 e \cdot \text{\AA}^{-3}$ approx $0.75 \text{ \AA}$ from C(10).

Crystal Data for $\text{C}_{20}\text{H}_{21}\text{FN}_6\text{O}$ ($M=380.43 \text{ g/mol}$): orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 6.91792(3) \text{ \AA}$, $b = 13.74742(3) \text{ \AA}$, $c = 19.22580(5) \text{ \AA}$, $V = 1828.442(10) \text{ \AA}^3$, $Z = 4$, $T = 207(120) \text{ K}$, $\mu(\text{CuK}\alpha) = 0.799 \text{ mm}^{-1}$, $D_{\text{calc}} = 1.382 \text{ g/cm}^3$, 169333 reflections measured ($7.9^\circ \leq 2\theta \leq 152.76^\circ$), 3833 unique ($R_{\text{int}} = 0.0639$, $R_{\text{sigma}} = 0.0180$) which were used in all calculations. The final R^1 was 0.0338 ($>2\sigma(I)$) and wR_2 was 0.0908 (all data). Crystallographic parameters and refinement indicators of Compound 1 (Form I) are shown in Table 19.

Table 19

Empirical formula	C ₂₀ H ₂₁ FN ₆ O
Formula weight	380.43
Temperature / K	120(1)
Crystal system	Orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	6.91792(3)
b/Å	13.74742(3)
c/Å	19.22580(5)
α /°	90.00
β /°	90.00
γ /°	90.00
Volume / Å ³	1828.442(10)
Z, Z'	4
ρ _{calc} g/cm ³	1.382
μ /mm ⁻¹	0.799
F(000)	800.0
Crystal size/mm ³	0.47 × 0.117 × 0.105
Radiation	CuK α (λ = 1.54178)
2 Θ range for data collection/°	7.9 to 152.76
Index ranges	-8 ≤ h ≤ 7, -17 ≤ k ≤ 17, -24 ≤ l ≤ 24
Reflections collected	169333
Independent reflections	3833 [R_{int} = 0.0639, R_{sigma} = 0.0180]
Data / restraints / parameters	3833/0/258
S	1.060
Final R indexes [$F^2 > 2\sigma(F^2)$]	R_1 = 0.0338, wR_2 = 0.0907
Final R indexes [all data]	R_1 = 0.0340, wR_2 = 0.0908
$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ / e Å ⁻³	0.16/-0.22
Flack parameter	-0.01(15)

Figure 10 shows 3-D view of Compound 1 (Form I) with atom labels. Figure 11 shows ORTEP view of Compound 1 (Form I) with atom labels. All non-hydrogen atoms are shown with thermal ellipsoids set at the 50 % probability level.

5 **Example 7 - Single Crystal X-ray Analysis of Compound 1, acetonitrile solvate**

Crystals of Compound 1, acetonitrile solvate were prepared as follows.

Compound 1 (2 mg) was dissolved in acetonitrile (500 μ l) in a 1.75 clear glass vial then capped with a pierced lid. This solution was left to stand at ambient for several days without agitation to allow for large rod-like crystals to grow that were suitable for
10 interrogation by single crystal X-ray diffraction.

The highest residual Fourier peak was found to be $0.19 \text{ e} \cdot \text{\AA}^{-3}$ approx $0.67 \text{ \AA}$ from C(11), and the deepest Fourier hole was found to be $-0.21 \text{ e} \cdot \text{\AA}^{-3}$ approx $0.81 \text{ \AA}$ from N(4).

Crystal Data for $\text{C}_{24}\text{H}_{27}\text{FN}_8\text{O}$ ($M=462.54 \text{ g/mol}$): orthorhombic, space group $\text{P2}_1\text{2}_1\text{2}_1$ (no. 19), $a = 6.03307(4) \text{ \AA}$, $b = 16.10794(9) \text{ \AA}$, $c = 23.72624(13) \text{ \AA}$, $V = 2305.73(2) \text{ \AA}^3$, $Z = 4$, $T = 294.01(10) \text{ K}$, $\mu(\text{CuK}\alpha) = 0.757 \text{ mm}^{-1}$, $D_{\text{calc}} = 1.332 \text{ g/cm}^3$, 110019 reflections measured ($6.64^\circ \leq 2\theta \leq 152.4^\circ$), 4840 unique ($R_{\text{int}} = 0.0983$, $R_{\text{sigma}} = 0.0211$) which were used in all calculations. The final R^1 was 0.0339 ($>2\sigma(I)$) and wR_2 was 0.0891 (all data). Crystallographic parameters and refinement indicators of Compound 1 (Form I) are shown in Table 20.

Table 20

Empirical formula	$\text{C}_{24}\text{H}_{27}\text{FN}_8\text{O}$
Formula weight	462.54
Temperature / K	120(1)
Crystal system	orthorhombic
Space group	$\text{P2}_1\text{2}_1\text{2}_1$
$a/\text{\AA}$	6.03307(4)
$b/\text{\AA}$	16.10794(9)
$c/\text{\AA}$	23.72624(13)
$\alpha/^\circ$	90.00
$\beta/^\circ$	90.00

$\gamma/^\circ$	90.00
Volume / $\text{\AA}^3$	2305.73(2)
Z, Z'	4
$\rho_{\text{calc}} \text{ g/cm}^3$	1.332
μ/mm^{-1}	0.757
F(000)	976.0
Crystal size/ mm^3	$0.564 \times 0.082 \times 0.033$
Radiation	$\text{CuK}\alpha$ ($\lambda = 1.54184$)
2Θ range for data collection/ $^\circ$	6.64 to 152.4
Index ranges	$7 \leq h \leq 6, -20 \leq k \leq 20, -29 \leq l \leq 29$
Reflections collected	110019
Independent reflections	4840 [$R_{\text{int}} = 0.0983, R_{\text{sigma}} = 0.0211$]
Data / restraints / parameters	4840/0/310
S	1.096
Final R indexes [$F^2 > 2\sigma(F^2)$]	$R_1 = 0.0339, wR_2 = 0.0887$
Final R indexes [all data]	$R_1 = 0.0345, wR_2 = 0.0891$
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}} / \text{e \AA}^{-3}$	0.19/-0.21
Flack parameter	-0.02(14)

Figure 12 shows 3-D view of Compound 1 bis-acetonitrile solvate with atom labels. Figure 13 shows ORTEP view of Compound 1 bis-acetonitrile solvate asymmetric unit with atom labels. All non-hydrogen atoms are shown with thermal ellipsoids set at the 50 % probability level.

Example 8 – Preparation and characterization of Compound 1 benzenesulfonic acid salt

250 μL of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μL of the appropriate solvent was added to the vial containing benzenesulfonic acid (8.92 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then

temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Scale-up preparation from ethanol

About 300 mg of Compound 1 was weighed into a vial and 133 mg of benzenesulfonic acid was weighed into a separate vial. To both vials, 3.75 mL of ethanol was added and the two mixtures combined. The resulting slurry was then temperature cycled for 24 hours (ambient to 40 °C in 4 hours cycles) (1.05 eq. of acid to free base). The resulting slurry was then allowed to evaporate at ambient temperatures to remove excess ethanol.

Observations from the treatment of Compound 1 with benzenesulfonic acid are shown in Table 21 below:

Table 21

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Solid	Clear Solution	Gum	Slurry	Slurry	Solid

To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours. XRPD analysis of benzenesulfonic acid experiments recovered 5 crystalline hits, free base (Form I) recovered from acetone and 2-propanol, pattern 1 was recovered from THF and *t*-BME (Figure 17) and pattern 2 recovered from ethanol (Figure 18).

Insufficient solids were recovered from ethanol to determine form.

XRPD data for Compound 1 besylate is provided in Table 22.

Table 22

2-Theta (°)	Height	H%
8.1	15179	100.0
9.2	864	5.7
10.0	85	0.6
11.7	591	3.9

2-Theta (°)	Height	H%
12.0	1879	12.4
12.4	394	2.6
13.4	3923	25.9
15.1	548	3.6

2-Theta (°)	Height	H%
16.0	196	1.3
16.7	156	1.0
18.4	302	2.0
19.0	2184	14.4
19.4	1644	10.8
19.9	1220	8.0
20.1	959	6.3
20.6	226	1.5
21.2	3809	25.1
21.7	587	3.9
21.9	362	2.4
22.5	749	4.9
23.3	165	1.1
23.7	114	0.8
24.1	80	0.5
25.5	1263	8.3
25.8	545	3.6

2-Theta (°)	Height	H%
26.0	183	1.2
26.4	159	1.1
26.7	420	2.8
27.0	768	5.1
27.8	126	0.8
28.1	66	0.4
28.5	153	1.0
28.9	39	0.3
29.3	478	3.2
30.3	127	0.8
30.8	50	0.3
32.0	806	5.3
32.7	1080	7.1
33.2	155	1.0
33.4	177	1.2
33.8	153	1.0
34.7	260	1.7

TG/DT Analysis

TGA of besylate pattern 1 from tBME showed a total weight loss of approximately 13 % from the outset to about 150 °C. DTA showed an endothermic event at onset about 241 °C (peak at about 247 °C). TGA of besylate pattern 1 from ethanol showed a total weight loss of approximately 0.4 % from the outset to about 250 °C. DTA showed an endothermic event at onset about 244 °C (peak at about 248 °C).

Result of stability studies

XRPD analysis of post-stability besylate pattern 1 recovered from THF showed an increase to crystallinity but no changes to form after exposure to stability conditions. XRPD analysis of post-stability besylate pattern 1 recovered from TBME showed preferred orientation but no changes to form after exposure to stability conditions. XRPD

analysis of post-stability besylate pattern 1 recovered from ethanol showed a decrease in crystallinity after exposure to stability conditions.

Secondary Salt Scale Up

XRPD analysis of besylate scale up showed successful formation of besylate pattern 2 from ethanol seen in the salt screen, a large amount of preferred orientation is seen in the sample.

TGA (Figure 37) showed a weight loss of approximately 0.7 % from the outset up to around 250 °C whilst DTA showed an endothermal “melting” event at onset around 244 °C (peak at around 248 °C).

DSC analysis (Figure 38) in the first heating cycle showed a sharp endothermal event at onset around 246 °C (peak at 249 °C). This endothermal event is consistent with TG/DTA and no thermal events were seen in the cooling or second heating cycle. Compound 1 besylate exhibits low hygroscopicity when exposed by DVS conditions with a mass uptake of about 0.7 % at 90 % RH (Figures 39 and 40). Post-DVS XRPD analysis shows no changes in crystalline form after exposure, a large amount of preferred orientation is seen in the sample. The hysteresis observed is most likely caused by a small amount of amorphous content which appears to crystallize at 90 % RH.

An IR spectrum of Compound 1 besylate was taken for reference which can be found in Figure 41 with peak lists in Table 23.

Table 23

Wave number	Wave number	Wave number	Wave number
3271	1544	1248	994
3033	1496	1222	968
2974	1464	1197	933
2864	1456	1157	923
2069	1446	1119	902
1657	1371	1077	846
1634	1343	1032	828
1573	1279	1018	791

Wave number	Wave number	Wave number	Wave number
772	692	549	445
757	640	526	415
734	628	503	
723	609	476	
708	561	459	

¹H-NMR spectrum shown in Figure 42 shows 0.88 eq. benzenesulfonic acid, and 0.028 eq. EtOH. UPLC analysis of Compound 1 besylate gave an average purity of 99.4 %.

1 week stability tests at 80 °C and under ambient light showed no change to form after exposure and no change to purity. However, by XRPD analysis, the sample held at 40 °C / 75 % RH appears to be a mixture of besylate salt and something else.

Thermodynamic solubility studies of Compound 1 besylate show the salt is highly soluble in pH 1, moderately soluble in 4.5 and unbuffered water. The sample shows low solubility in pH 6.8. pH and concentration values can be found in Table 24.

Table 24

Sample ID	Concentration (mg/mL)
pH 1	30.8
pH 4.5	12.7
pH 6.8	1.9
Un-buffered Water	17.9

XRPD analysis showed insufficient solids were recovered from pH 1, an unknown form was recovered from pH 4.5 and poorly crystalline free base was recovered from pH 6.8 and unbuffered water. Salt disproportionation studies of Compound 1 besylate showed the recovered material to be poorly crystalline free base by XRPD analysis.

Hydration studies of Compound 1 besylate found insufficient solids were

recovered from medium water activity and poorly crystalline besylate salt recovered from low and high water activities, by the poor crystallinity of the recovered material and a peak at around 21 degrees indicate the potential of a hydrate formation.

5 **Example 9 - Preparation and characterization of Compound 1 citric acid salt**

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing citric acid (10.67 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then
10 temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Scale-up preparation from acetone

About 300 mg of compound 1 was weighed into a vial and 160 mg of citric acid was weighed into a separate vial. To both vials, 3.75 mL of acetone was added and the two mixtures combined. The resulting slurry was then temperature cycled for 24 hours
15 (ambient to 40 °C in 4 hours cycles). The resulting slurry was then allowed to evaporate at ambient temperature to remove excess acetone (1.05 eq. of acid to free base). Observations from the treatment of Compound 1 with citric acid are shown in Table 25 below:

Table 25

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

20 XRPD analysis of citric acid experiments recovered 6 crystalline hits, free base (Form I) recovered from ethanol, methanol, 2-propanol, and THF and Form I recovered from acetone and TBME (Figure 21).

XRPD data for Form I is provided in Table 26.

Table 26

2-Theta (°)	Height	H%
6.5	1116	17.6
8.9	4365	68.8
9.2	1294	20.4
11.1	2946	46.5
13.9	1576	24.9
14.4	2604	41.1
15.4	2495	39.3
15.9	1182	18.6
18.0	755	11.9
19.2	2335	36.8
19.6	1370	21.6
20.7	6342	100.0
21.6	4090	64.5
22.3	274	4.3
22.7	348	5.5
23.3	1387	21.9
23.7	962	15.2

2-Theta (°)	Height	H%
24.2	737	11.6
24.8	4022	63.4
25.6	2421	38.2
26.3	533	8.4
26.5	788	12.4
26.8	581	9.2
27.9	927	14.6
28.9	378	6.0
29.1	350	5.5
30.2	533	8.4
30.6	180	2.9
31.8	205	3.2
32.5	365	5.8
33.1	137	2.2
33.7	347	5.5
34.3	151	2.4
34.5	138	2.2

5 *TG/DT Analysis*

TGA of citrate Form A showed a total weight loss of approximately 1 % from the outset up to about 175 °C. DTA showed several endothermal events; first event at onset about 187 °C (peak at about 194 °C) and the second event at onset about 316 °C (peak at about 318 °C).

10 *Result of stability studies*

XRPD analysis of post-stability citrate Form A recovered from acetone showed a decrease to crystallinity but no change to form after exposure to stability conditions.

XRPD analysis of post-stability citrate Form A recovered from TBME showed a decrease

to crystallinity but no change to form after exposure to stability conditions.

Secondary Salt Scale Up

XRPD analysis of the scaled up citrate salt shows successful formation of citrate Form A from acetone seen in the salt screen.

TGA (Figure 43) showed a total weight loss of approximately 3 % from the outset up to 175 °C. DTA showed several endothermal events, the first event at onset around 188 °C (peak at around 194 °C) and the second event at onset around 316 °C (peak at around 318 °C).

DSC analysis in the first heating cycle (Figure 44) showed a potential overlap of two endothermal events (peaks at 194 and 205 °C). No thermal events were seen in the cooling or second heating cycle.

Compound 1 citrate exhibits low hygroscopicity by DVS analysis (Figure 45) with a mass uptake of around 1.8 % at 90 % RH. Post-DVS XRPD analysis of the material showed no changes in crystalline form upon exposure to DVS conditions.

An IR spectrum of Compound 1 citrate was taken for reference which can be found in Figure 47 with peak lists in Table 27.

Table 27

Wave Number	Wave Number	Wave Number	Wave Number
3430	1497	987	578
3066	1456	929	550
2967	1373	899	532
2518	1338	790	497
2033	1281	771	478
1929	1178	747	459
1718	1141	687	446
1626	1109	667	425
1568	1074	623	

¹H-NMR spectrum shown in Figure 48 shows 0.97 eq. citric acid and 0.24 eq.

acetone. UPLC analysis of Compound 1 citrate gave an average purity of 99.4 %.
1 week stability tests at 40 °C/75 % RH, 80 °C and under ambient light showed no
change to form after exposure and no change to purity. Thermodynamic solubility studies
of Compound 1 citrate show the salt is highly soluble in un-buffered water and has high
5 solubility at pH 1 with a lower solubility at 4.5 and 6.8. pH and concentration values can
be found in Table 28.

Table 28

Sample ID	Concentration (mg/mL)
pH 1	18.6
pH 4.5	0.3
pH 6.8	0.9
Un-Buffered Water	21.0

XRPD analysis showed poorly crystalline solids were recovered from pH 1,
10 Compound 1 citrate was recovered from pH 4.5 and un-buffered water and poorly
crystalline free base was recovered from pH 6.8. Salt disproportionation studies of
Compound 1 citrate showed the recovered material to be poorly crystalline citrate salt by
XRPD analysis.

Hydration studies of Compound 1 citrate found poorly crystalline citrate salt
15 recovered from high and low water activities and unknown form, referred to here as Form
B, recovered from medium water activity. XRPD diffractogram of the Compound I citrate
Form B is shown in Figure 49.

Example 10 - Preparation and characterization of Compound 1 methanesulfonic 20 acid salt

A stock solution of methanesulfonic acid was prepared in water (36 µL of
methane sulfuric acid in 964 µL H₂O). 400 µL of the appropriate solvent was added to the
vial containing the weighed compound 1, 100 µL of the methanesulfonic acid stock
solution was then added to the solvent/compound 1 slurry (1.05 eq. of acid to free base).
25 The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles
over 24 hrs.

Scale-up preparation from acetone

About 300 mg of Compound 1 was weighed into a vial and a stock solution of methanesulfonic acid was prepared in water (538 μ L of acid in 10 mL of water). To the weighed compound 1, 6 mL of acetone was added which was then followed by 1.5 mL of the acid stock solution, this slurry was then temperature cycled for 24 hours (ambient to 40 °C in 4 hour cycles) (1.05 eq. of acid to free base). The resulting clear solution was allowed to evaporate to recover solids; to which a crystal/oil mixture was recovered. To this mixture, acetone was added and the vial sonicated to produce solids. These solids were then filtered and dried for 72 hours under vacuum at ambient temperature.

Observations from the treatment of Compound 1 with methanesulfonic acid are shown in a Table 29 below:

Table 29

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Clear Solution	Slurry	Clear Solution	Slurry	Clear Solution

To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours. XRPD analysis of methanesulfonic acid experiments recovered 4 crystalline hits, free base (Form I) recovered from THF and pattern 1 from acetone, methanol and 2-propanol (Figure 16). Insufficient solids were recovered from ethanol and TBME.

TG/DT Analysis

TGA of crystalline mesylate (Figure 25) showed a total weight loss of approximately 3 % from the outset up to about 200 °C. DTA showed an endothermal event at onset about 229 °C (peak at about 232 °C).

Result of stability studies

XRPD analysis of post-stability crystalline mesylate recovered from acetone showed no changes to crystallinity or form after exposure to stability conditions. XRPD analysis of post-stability crystalline mesylate recovered from methanol showed a

decrease in crystallinity but no changes to form after exposure to stability conditions. XRPD analysis of post-stability crystalline mesylate recovered from isopropanol showed a slight increase in crystallinity but no changes to form after exposure to stability conditions.

5 *Secondary Salt Scale Up*

XRPD analysis of the scaled up mesylate from acetone (shown in Figure 30) showed a different form than seen previously.

10 TGA showed a series of weight losses with a total of around 9 % up to 228 °C (Figure 31). The weight loss seen at around 120 °C indicates the material to be an acetone solvate. DTA (Figure 31) showed a small endothermic event at onset around 120 °C (peak at around 125 °C). This event is likely associated with the 6.74 % weight loss, which would equate to about 0.59 equivalents of acetone. A larger endothermic “melting” event at onset about 228 °C (peak at about 232 °C). This event is consistent with the earlier collected mesylate TG/DTA.

15 DSC Analysis in the first heating cycle (Figure 32) showed a sharp endothermic event at onset around 230 °C (peak at 233 °C). This endothermic event shown is consistent with TG/DTA. At this point, the material had already believed to have been desolvated otherwise there should have been an endothermic event relating to the weight loss.

20 A broad recrystallization event can be seen in the first cooling cycle with an onset of around 193 °C (peak at around 181 °C) and in the second heating cycle showed an endothermic event at onset around 223 °C (peak at 229 °C).

25 Compound 1 mesylate salt exhibits high hygroscopicity by upon exposure to GVS humidity conditions (Figures 33 and 34); mass uptake of about 32 % at 90 % RH. Post-GVS XRPD analysis of the mesylate salt shows the material to desolvate and become the mesylate form seen in the salt screen. At 30 % RH the material deliquesced and upon drying crystallized to the same form seen in the primary salt screen.

An IR spectrum of Compound 1 mesylate salt was taken for reference which can be found in Figure 35 and peak listings in Table 30.

30

Table 30

Wave Number	Wave Number
3344	923
3068	904
3020	891
2963	859
2930	796
2870	770
1805	740
1649	720
1626	708
1600	687
1566	633
1538	616
1492	552
1451	528
1367	509
1347	469
1282	442
1235	405
1167	
1153	
1115	
1071	
1020	
991	
964	
944	

¹H NMR Spectrum shown in Figure 36 shows about 1 eq. of sulfonic acid. It is not possible to accurately quantify any residual acetone from this data due to spectral overlap but the levels, if there are any, are considered low.

5 UPLC analysis of Compound 1 mesylate gave an average purity of 99.4 %.

1 Week stability tests at 40 °C/75 % RH, 80 °C and under ambient light showed change to form after exposure by XRPD. However, changes to the mesylate form seen previously in the salt screen and no change to purity.

Thermodynamic solubility studies of Compound 1 mesylate show the salt is moderately
10 soluble in pH 1, 4.5 and unbuffered water. The sample shows low solubility in pH 6.8. pH and concentration values can be found in Table 31.

Table 31

Sample ID	Concentration (mg/mL)
pH 1	14.3
pH 4.5	9.3
pH 6.8	1.5
Unbuffered Water	9.6

XRPD analysis showed insufficient solids were recovered from pH 1, mesylate salt was
15 recovered from pH 4.5 and free base was recovered from pH 6.8 and un-buffered water. Salt disproportionation studies of Compound 1 mesylate showed no change to form by XRPD analysis but crystallinity reduced. Hydration studies of Compound 1 mesylate showed mesylate salt recovered from medium water activities, a mixture of free base and salt recovered from low water activities and free base recovered from high water activities.

20

Example 11 - Preparation and characterization of Compound 1 1,2-ethane disulfonic acid salt

250 µL of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 µL of the appropriate solvent was added to the vial containing 1,2-ethane disulfonic acid (12.94 mg). The solutions/slurries were then added to the solvent/API
25 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with 1,2-ethane disulfonic acid are shown in Table 32 below:

Table 32

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Yellow solution/ dark solids	Clear solution	Slurry	Slurry	Slurry	Slurry

To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours. XRPD analysis of 1,2-ethane disulfonic acid experiments recovered 4 crystalline hits, free base (Form I) recovered from acetone, THF and TBME and pattern 1 from 2-propanol (Figure 14). Insufficient solids were recovered from ethanol and methanol.

Result of stability studies

XRPD analysis of post-stability edisylate recovered from isopropanol showed the material to become amorphous after exposure to stability conditions.

Example 12 - Preparation and characterization of Compound 1 *p*-toluene sulfonic acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing *p*-toluene sulfonic acid (10.84 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of compound 1 with *p*-toluene sulfonic acid are shown in Table 33 below:

Table 33

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Solid	Clear Solution	Slurry	Slurry	Slurry	Solid

To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours.

- 5 XRPD analysis of *p*-toluene sulfonic acid experiments recovered 4 crystalline hits, free base (Form I) recovered from 2-propanol and TBME and pattern 1 from acetone and THF (Figure 15). Insufficient solids were recovered from ethanol and methanol.

TG/DT Analysis

- 10 TGA of *p*-toluene sulfonate (Figure 24) showed a total weight loss of approximately 14 % from the outset up to about 250 °C. DTA showed an endothermal event at onset about 84 °C (peak at about 90 °C).

Result of stability studies

XRPD analysis of post-stability *p*-toluene sulfonate recovered from acetone showed the material to become amorphous after exposure to stability conditions.

15

Example 13 - Preparation and characterization of Compound 1 oxalic acid salt

- 250 µL of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 µL of the appropriate solvent was added to the vial containing oxalic acid (5.08 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.
- 20

Observations from the treatment of Compound 1 with oxalic acid are shown in Table 34 below:

Table 34

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Solid	Slurry	Slurry	Slurry

XRPD analysis of oxalic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from acetone (which was mostly amorphous), 2-propanol, THF and TBME and pattern 1 recovered from ethanol and methanol (Figure 19).

TG/DT Analysis

TGA of oxalate (Figure 26) showed a total weight loss of approximately 17 % from the outset up to about 300 °C. DTA showed a small endothermal event at onset about 314 °C (peak at about 317 °C).

Result of stability studies

XRPD analysis of post-stability oxalate recovered from ethanol showed a change in crystallinity and form after exposure to stability conditions. XRPD analysis of post-stability oxalate recovered from methanol showed no change to crystallinity however, changes to form were seen after exposure to stability conditions.

Example 14 - Preparation and characterization of Compound 1 fumaric acid salt

250 µL of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 µL of the appropriate solvent was added to the vial containing fumaric acid (6.48 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with fumaric acid are shown in Table 35 below

Table 35

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

XRPD analysis of fumaric acid experiments recovered 6 crystalline hits, free base (Form I) recovered from ethanol, methanol, 2-propanol, THF and TBME and pattern 1 recovered from acetone (Figure 20).

TG/DT Analysis

TGA of crystalline fumarate (Figure 27) showed a total weight loss of approximately 22 % from the outset up to about 250 °C. DTA showed several endothermal events; first event at onset about 164 °C (peak at about 166 °C), second event at onset about 189 °C (peak at about 191 °C), third event at onset of about 198 °C (peak at about 201 °C) and forth event at onset about 310 °C (peak at about 312 °C).

Result of stability studies

XRPD analysis of post-stability crystalline fumarate recovered from acetone showed a slight decrease to crystallinity however, no change to form after exposure to stability conditions.

Example 15 - Preparation and characterization of Compound 1 L-malic acid salt

250 µL of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 µL of the appropriate solvent was added to the vial containing L-malic acid (7.49 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with L-malic acid are shown in Table 36 below:

Table 36

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Solid

XRPD analysis of L-malic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from acetone (with a large amount of preferred orientation), ethanol, methanol, 2-propanol, and THF and pattern 1 recovered from TBME (Figure 22).

TG/DT Analysis

TGA of crystalline L-malate (Figure 28) showed a total weight loss of approximately 26 % from

the outset up to about 250 °C. DTA showed several endothermal events; first event at onset about 158 °C (peak at about 162 °C) and the second event at onset about 310 °C (peak at about 313 °C).

Result of stability studies

- 5 XRPD analysis of post-stability crystalline L-malate prepared from TBME showed no change to crystallinity and form after exposure to stability conditions.

Example 16 - Preparation and characterization of Compound 1 succinic acid salt

- 250 µL of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 µL of the appropriate solvent was added to the vial containing succinic acid (6.59 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

- Observations from the treatment of Compound 1 with succinic acid are shown in Table 37 below:

Table 37

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

- XRPD analysis of succinic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from ethanol, methanol, 2-propanol, THF and TBME and pattern 1 recovered from acetone (Figure 23).

TG/DT Analysis

- TGA of succinate Figure 29) showed a total weight loss of approximately 22 % from the outset about 210 °C. DTA showed several endothermal events; first event at onset about 147 °C (peak at about 151 °C) and the second event at onset about 315 °C (peak at about 315 °C).

Result of stability studies

XRPD analysis of post-stability crystalline succinate recovered from acetone showed a decrease in crystallinity but no change to form after exposure to stability conditions.

Example 17 - Preparation and characterization of Compound 1 hydrochloric acid salt

A stock solution of HCl was prepared in water (46 μL of HCl in 954 μL H_2O). 400 μL of the appropriate solvent was added to the vial containing the weighed compound 1, 100 μL of the HCl stock solution was then added to the solvent/compound 1 slurry (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 $^{\circ}\text{C}$ in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with HCl are shown in Table 38 below:

Table 38

Solvent	Acetone	Ethanol	Methanol	2-Propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Clear Solution	Clear Solution	Clear Solution	Clear Solution	Slurry

To the samples which were recovered as clear solutions, 2-3 mg of compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours. Further solids were recovered from ethanol, methanol, 2-propanol, TBME and THF through anti-solvent additions described in Materials and methods section. XRPD analysis of HCl experiments recovered 6 crystalline hits. Freebase (Form I) was recovered from all solvent systems analyzed.

Example 18 - Preparation and characterization of Compound 1 sulfuric acid salt

A stock solution of sulfuric acid was prepared in water (31 μL of sulfuric acid in 969 μL H_2O). 400 μL of the appropriate solvent was added to the vial containing the weighed compound 1, 100 μL of the sulfuric acid stock solution was then added to the solvent/compound 1 slurry (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 $^{\circ}\text{C}$ in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with sulfuric acid are shown in Table 39 below:

Table 39

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Clear solution	Clear solution	Clear solution	Clear solution	Clear solution	Clear solution

To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours.

- 5 Further solids were recovered from ethanol, methanol, 2-propanol, TBME and THF through anti-solvent additions described. XRPD analysis of sulfuric acid experiments recovered 6 amorphous hits from all solvent systems analyzed.

Example 19 - Preparation and characterization of Compound 1 naphthalene-2-sulfonic acid salt

- 10 250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing naphthalene-2-sulfonic acid (14.14 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature
- 15 cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with naphthalene-2-sulfonic acid are shown in Table 40 below.

Table 40

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Clear Solution	Clear Solution	Clear Solution	Clear Solution	Slurry	Solid

- 20 To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours. XRPD analysis of naphthalene-2-sulfonic acid experiments recovered 3 crystalline hits, free

base (Form I) recovered from ethanol, THF and TBME. Insufficient solids were recovered from acetone, methanol and 2-propanol.

Example 20 - Preparation and characterization of Compound 1 2-hydroxy ethanesulfonic acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing 2-hydroxy ethanesulfonic acid (8.19 mg). The solutions/slurries were then added to the solvent/compound 1 solution. The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with 2-hydroxy-ethanesulfonic acid are shown in Table 41 below:

Table 41

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Solid	Slurry	Slurry	Slurry

XRPD analysis of 2-hydroxy ethanesulfonic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

Example 21 - Preparation and characterization of Compound 1 L-aspartic acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing L-aspartic acid (7.36 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with L-aspartic acid are shown in Table 42 below:

Table 42

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

5 XRPD analysis of L-aspartic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

Example 22 - Preparation and characterization of Compound 1 maleic acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing maleic acid (6.48 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with maleic acid are shown in Table 43 below:

Table 43

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Solid	Slurry	Gum	Slurry	Slurry	Slurry

15 XRPD analysis of maleic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

Example 23 - Preparation and characterization of Compound 1 phosphoric acid salt

20 250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing phosphoric acid (5.42 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with phosphoric acid are shown in Table 44 below:

Table 44

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Solid	Clear Solution	Clear Solution	Slurry	Slurry	Slurry

5 To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours. XRPD analysis of phosphoric acid experiments recovered 3 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

10 **Example 24 - Preparation and characterization of Compound 1 ethanesulfonic acid salt**

A stock solution of ethane sulfonic acid was prepared in water (47 μ L of sulfuric acid in 953 μ L H₂O). 400 μ L of the appropriate solvent was added to the vial containing the weighed compound 1, 100 μ L of the ethane sulfonic acid stock solution was then added to the solvent/compound 1 slurry (1.05 eq. of acid to free base). The samples were then temperature
15 cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with ethanesulfonic acid are shown Table 45 below:

Table 45

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Clear Solution	Clear Solution	Clear Solution	Clear Solution	Clear Solution	Slurry

20 To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours. XRPD analysis of ethanesulfonic acid experiments recovered 4 crystalline hits, free base (Form

I) recovered from acetone, THF and TBME. Insufficient solids were recovered from methanol, ethanol and 2-propanol.

Example 25 - Preparation and characterization of Compound 1 L-glutamic acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing L-glutamic acid (8.13 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with L-glutamic acid are shown in Table 46 below:

Table 46

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

XRPD analysis of L-glutamic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

Example 26 - Preparation and characterization of Compound 1 L-tartaric acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing L-tartaric acid (8.34 mg). The solutions/slurries were then added to the solvent/compound 1 solution. The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with L-tartaric acid are shown in Table 47 below:

Table 47

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

5 XRPD analysis of L-tartaric acid experiments recovered 6 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

Example 27 - Preparation and characterization of Compound 1 D-glucuronic acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing D-glucuronic acid (10.73 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with D-glucuronic acid are shown in Table 48 below:

Table 48

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

15 XRPD analysis of D-glucuronic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

Example 28 - Preparation and characterization of Compound 1 hippuric acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing hippuric acid (10.1 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with hippuric acid are shown in Table 49 below:

Table 49

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

- 5 XRPD analysis of hippuric acid experiments recovered 6 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

Example 29 - Preparation and characterization of Compound 1 D-gluconic acid salt

- 10 A stock solution of D-gluconic acid was prepared in water (176 μ L of D-gluconic acid in 824 μ L H₂O). 400 μ L of the appropriate solvent was added to the vial containing the weighed compound 1, 100 μ L of the D-gluconic stock solution was then added to the solvent/compound 1 slurry (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

- 15 Observations from the treatment of Compound 1 with D-gluconic acid are shown in Table 50 below:

Table 50

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Clear Solution	Clear Solution	Clear Solution	Clear Solution	Clear Solution	Slurry

- 20 To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours. XRPD analysis of D-gluconic acid experiments recovered 1 crystalline hit, free base (Form I) recovered from TBME and insufficient solids recovered from acetone, ethanol, methanol, 2-propanol and THF.

Example 30 - Preparation and characterization of Compound 1 DL-lactic acid salt

A stock solution of DL-lactic acid was prepared in water (48 μ L of DL-lactic acid in 952 μ L H₂O). 400 μ L of the appropriate solvent was added to the vial containing the weighed compound 1, 100 μ L of the DL-lactic acid stock solution was then added to the solvent/compound 1 slurry (1.05 eq. of acid to free base). The samples were then temperature

5 cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with DL-lactic acid are shown in Table 51 below:

Table 51

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Clear Solution	Clear Solution	Clear Solution	Clear Solution	Gum	Slurry

To the samples which were recovered as clear solutions, 2-3 mg of Compound 1 was added to produce a mobile slurry and the sample temperature cycled for a further 2-3 hours. XRPD analysis of DL-lactic acid experiments recovered 5 crystalline hits, free base (Form I) recovered from acetone, ethanol, methanol, THF and TBME. Insufficient

10 solids recovered from 2-propanol.

Example 31 - Preparation and characterization of Compound 1 L-ascorbic acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of Compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing L-ascorbic acid (9.73 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

20

Observations from the treatment of Compound 1 with L-ascorbic acid are shown in Table 52 below:

Table 52

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

5 XRPD analysis of L-ascorbic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

Example 32 - Preparation and characterization of Compound 1 benzoic acid salt

250 μ L of the appropriate solvent was added to the vials containing 20 mg of compound 1. In a separate vial, 250 μ L of the appropriate solvent was added to the vial containing benzoic acid (6.82 mg). The solutions/slurries were then added to the solvent/compound 1 solution (1.05 eq. of acid to free base). The samples were then temperature cycled between ambient and 40 °C in 4 hour cycles over 24 hrs.

Observations from the treatment of Compound 1 with benzoic acid are shown in Table 53 below:

Table 53

Solvent	Acetone	Ethanol	Methanol	2-propanol	TBME	THF
Time-point						
Pre-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry
Post-Cycling	Slurry	Slurry	Slurry	Slurry	Slurry	Slurry

15 XRPD analysis of benzoic acid experiments recovered 6 crystalline hits, free base (Form I) recovered from all solvent systems analyzed.

Example 33. Solubility measurements

20 General method to measure the thermodynamic aqueous solubility of a crystalline, organic solid.

Preparation of Reagents:

1. Aqueous Phosphate Buffer Solution (PBS): pH 7.4, 30 mM

1 Liter of 0.05 M (50 mM) Phosphate Buffer (25 °C) at pH 7.4 was prepared as follows:
11.2 mL of 1 M potassium phosphate (monobasic) was mixed with 38.8 mL of 1 M potassium phosphate (dibasic) and diluted to one liter with water.

To make a 0.03 M (30 mM) Phosphate Buffer (25 °C) at pH 7.4, the above recipe was
5 adjusted as follows: 6.72 mL of 1 M potassium phosphate (monobasic) were mixed with 23.28 mL of 1 M potassium phosphate (dibasic) and diluted to one liter with water. The pH was adjusted with HCl or NaOH. Alternatively, 0.9144 g (6.72×10^{-3} mol) of potassium phosphate monobasic were mixed with 4.0908 g (23.28×10^{-3} mol) of potassium phosphate dibasic and diluted to 1 L with water to get a 30 mM solution of Phosphate Buffer (25 °C).

10 2. Aqueous phosphate buffer, 30 mM, adjusted to pH 6.5

3. Aqueous 0.1 N HCl with 0.2 % NaCl, adjusted to pH 1.2

4. If necessary, phosphate buffers of other pHs or other strengths could be made by adjusting the recipe above.

5. Suitable organic solvents (ACN, methanol, etc.) were used for preparation of stock
15 and standards.

Instrumentation used:

1. Balance

2. Agitator for mixing

20 3. Pipets

4. Filters or centrifuge

5. HPLC w/ UV and MS detection (Waters Acquity UPLC with PDA and ZQ MS)

Standards:

25 1. ~0.5 mg of compound were dissolved in 2.5% DMSO/MeOH (or other organic) to a final concentration of 250 µg/mL stock

2. 50 µL of stock were accurately pipetted into 96 Shallow well plate containing 200 µL methanol for high standard concentration of 50 µg/mL.

3. 50 µL of 50 µg/mL high standard were accurately pipetted into adjacent well
30 containing 200 µL methanol for medium standard concentration of 10 µg/mL.

4. 50 µL of 10 µg/mL medium standard were accurately pipetted into adjacent well containing 200 µL methanol for low standard concentration of 2 µg/mL.

Sample preparation:

1. ≥ 0.5 mg of compound were accurately weighed into a 4-mL vial for each pH to be tested.
2. The appropriate amount of desired buffer was added to the appropriate vials to get a resulting
5 concentration of 1.02 mg/mL.
3. Vials were capped and shaken at 350 rpm for 24 hours at room temperature.
4. $\sim 450 \mu\text{L}$ of sample solutions were pipetted from 4-mL vials into 96 DWP.
5. The plate was centrifuged at 3500rpm for 10 minutes at 20°C and $250 \mu\text{L}$ of supernatant were transferred to catch plate.
- 10 6. $125 \mu\text{L}$ of supernatant were pipetted into 96 shallow well plate containing $125 \mu\text{L}$ of methanol and mixed to get a 2x dilution of the sample.
7. $50 \mu\text{L}$ of 2x dilution were pipetted into 96 shallow well plate containing $200 \mu\text{L}$ of methanol and mixed to obtain a 10x dilution of sample.
8. $50 \mu\text{L}$ of 10x dilution were pipetted into 96 shallow well plate containing $200 \mu\text{L}$ of methanol
15 and mixed to obtain a 50x dilution of sample.

Analysis:

Data Collection:

1. Each standard (2, 10, $50 \mu\text{g/mL}$) and sample (2x, 10x, 50x dilution) was injected in
20 triplicate using a $3 \mu\text{L}$ injection volume on the UPLC, starting with the lowest concentrations and going to the highest. A standard, linear, rapid gradient method and 220 nm and 254 nm UV detection were used with the appropriate mobile phase and column.
 2. The UV peak areas of the analyte were integrated and recorded for each chromatogram. If MS data was available, the mass of the parent peak was confirmed for each
25 sample.
 3. The responses for the standards were fitted using a $y=mx$ linear model (through zero).
 4. The model was used to quantify the amount of compound in the aqueous solutions.
- The values of the lowest dilution sample that fit within the standard curve was reported.

- 30 Note: Adjustments could be made to the above instructions if appropriate for a given compound.

Example 34: In vitro metabolic stability of the Compound of Formula I (Compound 1) and the Compound for formula I'.

Abbreviation	Description
°C	Degrees centigrade
CL _h	Predicted hepatic clearance
CL _{int}	Predicted intrinsic clearance
DMEM	Dulbecco's modified Eagle's medium
DMPKCP	Drug Metabolism, Pharmacokinetics and Clinical Pharmacology
DMSO	Dimethyl sulfoxide
ESI ⁺	Electrospray ionization positive mode
ELN	Electronic Laboratory Notebook
ER	Extraction ratio
f _u	Unbound fraction of compound
g	Gravity
HCl	Hydrochloride
HPLC	High performance liquid chromatography
IPA	Isopropyl alcohol
IS	Internal standard
K ₂ HPO ₄	Potassium phosphate, dibasic
KH ₂ PO ₄	Potassium phosphate, monobasic
k _m	Rate of loss of test compound
KPB	Potassium phosphate buffer
MgCl ₂	Magnesium chloride
NADP ⁺	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate reduced
NaOH	Sodium hydroxide
NRS	NADPH-regenerating solution
LC-MS/MS	Liquid chromatography with tandem mass spectrometric detection
<i>m/z</i>	Mass to charge ratio
μL	Microliter
μM	Micromolar
mM	Millimolar
MRM	Multiple reaction monitoring
n	Number considered for assessment
PAR	Peak area ratio
% REM	Percent remaining

Abbreviation	Description
rpm	Revolutions per minute
$t_{1/2}$	Half-life

In vitro metabolic stabilities were studied at a concentration of 1 μ M in the presence of liver microsomes and isolated hepatocytes.

5

Materials

The following reagents were required for experimentation: acetonitrile (HPLC grade, Burdick & Jackson, Madison, WI), potassium phosphate (KH₂PO₄ and K₂HPO₄, anhydrous, Sigma-Aldrich, Co., St. Louis, MO), magnesium chloride (MgCl₂, Sigma-Aldrich), water (HPLC grade, JT Baker, Phillipsburg, NJ), isopropanol (IPA, reagent grade, EMD Chemicals, Gibbstown, NJ), formic acid (reagent grade, Sigma-Aldrich), and dimethyl sulfoxide (DMSO; reagent grade, EM Science, Gibbstown, NJ). Labetalol (Sigma-Aldrich) was used as an internal standard (IS) for analytical purposes. Human liver microsomes were purchased from Corning Life Sciences (Tewksbury MA), lot BD38289 (150-donor mixed gender pool, human). Liver microsomes from Sprague Dawley rat were purchased from XenoTech, LLC (Lenexa, KS). Lot numbers were XT1110042 and XT1310214. Cryopreserved human hepatocytes were either purchased from Invitrogen/CellzDirect (Pittsboro, NC) and lot number HUP50 or purchased from In Vitro ADMET Laboratories, LLC (Malden, MS) and lot number PHS9001 was used (10-donor mixed gender pool, human). Rat cryopreserved hepatocytes were purchased from Bioreclamation/In Vitro Technologies (Baltimore, MD) and were from pooled male donors unless otherwise noted. Lots OGN, PZG and MSO were used for this study. All other reagents, control compounds, and solvents were of the highest analytical grade supplied by Sigma (St. Louis, MO).

Methods

Liver Microsomal Incubations

A 100 mM potassium phosphate assay buffer solution (KPB) was prepared as follows.

5 Both KH₂PO₄ and K₂HPO₄ were dissolved separately in reagent grade water resulting in final concentrations 100 mM. A 75:25 mixture v/v of K₂HPO₄:KH₂PO₄ was prepared and the pH of the solution was adjusted to 7.4 using diluted HCl or diluted NaOH solutions. A stock solution of test compound was prepared at 10 mM (active compound) in DMSO. The stock solution was diluted immediately before use to 2.5 μ M using the KPB solution to create
10 the working standard. All test compounds were completely soluble in DMSO by visual inspection at room temperature. The NADPH-regenerating solution (NRS) was prepared on the day of analysis by diluting one volume of 17 mg/mL NADP⁺ with one volume of 78 mg/mL glucose-6-phosphate (both prepared in KPB, pH 7.4) and 7.9 volumes of 20 mM MgCl₂. The final concentrations of NADP⁺ and glucose-6-phosphate were 1.7 mg/mL and
15 7.8 mg/mL, respectively. Immediately prior to use, the NRS was activated by the addition of 10 μ L of glucose-6-phosphate dehydrogenase (150 Units/mL in KPB, pH 7.4) per mL of NRS stock solution. Liver microsomes were diluted to 2.5 mg protein/mL using KPB.

For the compound of formula I or the compound of formula I' or each positive control (i.e., dextromethorphan, diazepam, diltiazem, phenacetin, tolbutamide, and verapamil), 20 μ L
20 of 2.5 μ M working standard solution of test compound and 20 μ L of microsomes (2.5 mg protein/mL) were added to each well of a 96-well polypropylene plate (Costar, VWR, West Chester, PA) in duplicate. The plates were placed in an incubator at 37 °C for 5 minutes before adding the start solution. A 10- μ L aliquot of the NRS solution was added to each original well to initiate metabolism. The concentration of the test compound at the beginning of the
25 incubation was 1 μ M. One incubation plate was prepared for each time point (i.e., 0 and 20 minutes). Incubations were conducted at 37 °C and 100% relative humidity. At each time point, the appropriate incubation plate was removed from the incubator and a solution containing internal standard (150 μ L, 0.25 μ M labetalol in 60% acetonitrile) was added to each well. The plate was immediately spun in a centrifuge at 2,095 x g for 7 minutes at room
30 temperature using an Allegra benchtop centrifuge (Beckman Coulter, Fullerton, CA). A 200- μ L aliquot of the supernatant was transferred from each well to a 96-well shallow plate (Costar). The plates were sealed using disposable plate mats.

Hepatocyte Incubations

A stock solution of the test compound was prepared at 10 mM (active compound) in DMSO. The in vitro stability of the test compound (1 μ M) was assessed in the presence of hepatocytes as follows. Cryopreserved hepatocytes were thawed, isolated from shipping media and diluted to a density of 1×10^6 viable cells/mL, according to the supplier's guidelines, using Dulbecco's Modified Eagle Medium, 1X, high glucose (DMEM, Invitrogen, Carlsbad, CA). Viability was determined by trypan blue exclusion using a hemocytometer (3500 Hausser, VWR, West Chester, PA). The 10 mM stock solution of test compound was diluted to 2 μ M using supplemented DMEM to create the working standard. A 20- μ L aliquot of test compound or control (i.e., antipyrine, diazepam, diltiazem, lorazepam, propranolol, verapamil, and 7-ethyl-10-hydroxycamptothecin (SN-38)) was added to each test well of a 96-well polypropylene plate (Costar, VWR, West Chester, PA) immediately followed by the addition of 20 μ L of the hepatocyte suspension. One incubation plate was prepared for each time point (i.e., 0, 60 and 120 minutes) with samples being prepared in duplicate. Incubations were conducted at 37 °C and 100% relative humidity. At each time point, the appropriate incubation plate was removed from the incubator and a solution containing IS (200 μ L,

0.2 μ M labetalol in 60% acetonitrile) was added to each well. The plate was mixed at 600 rpm for 2 minute on a plate shaker (IKA MTS 2/4 Digital Microtiter Shaker, VWR) and immediately spun in a centrifuge at $2,095 \times g$ for 10 minutes at room temperature using an Allegra benchtop centrifuge (Beckman Coulter, Fullerton, CA). A 200- μ L aliquot of the supernatant was transferred from each well to a 96-well shallow plate (Costar). The plates were sealed using disposable plate mats.

Analytical Quantitation

The LC-MS/MS system was comprised of an HTS-PAL autosampler (Leap Technologies, Carrboro, NC), an HP1200 HPLC (Agilent, Palo Alto, CA), and an API4000 triple quadrupole mass spectrometer (PE Sciex, a division of Applied Biosystems, Foster City, CA). Chromatographic separation of the analyte and internal standard was achieved at room temperature using a C18 column (Kinetex®, 30 x 3.0 mm, 2.6 μ m particle size, Phenomenex, Torrance, CA) in conjunction with gradient conditions using mobile phases A (aqueous 0.1% formic acid with 1% isopropyl alcohol) and B (0.1% formic acid in acetonitrile). The total run

time, including re-equilibration, for a single injection was 2 minutes. Mass spectrometric detection of the analytes was accomplished using the ESI+ ionization mode. Ion current was optimized during infusion of a stock solution of test compound. Analyte responses were measured by multiple reaction monitoring (MRM) of transitions unique to each compound.

5 Data were acquired and peak areas were calculated for test compounds and the internal standard using Analyst 1.6.1 software (Sciex). For the liver microsomal and hepatocyte stability assessments, peak area tables were exported to BioAssay Enterprise (CambridgeSoft, Cambridge, MA), where the average analyte-to-internal standard peak area ratios were used to calculate percent remaining (%REM), half-life ($t_{1/2}$), predicted hepatic clearance (CL_h)
10 and predicted hepatic extraction ratio (ER).

Calculations

All calculations were performed using BioAssay Enterprise. The mean peak area ratios were calculated by averaging the peak area ratios ($n = 2$) of test compound and the internal
15 standard for each sample. Percent remaining was calculated by determining the ratio of the peak area ratio at each time point to the peak area ratio of the time-zero samples. The rate of loss of test compound (k_m) was determined by linear regression of $-\ln(f(t))$ versus time. The regression used the form “ $y=mx$ ”, therefore the model forced an intercept of 100% remaining and assumed that the metabolism followed first order kinetics. The $t_{1/2}$ was determined
20 dividing $\ln(2)$ by k_m . The predicted intrinsic clearance (CL_{int}) was calculated by scaling the in vitro half-life for stability of test compound using physical and physiological scaling factors listed in Table 5.1 and employed in the following equation:

$$CL_{int} = \frac{\ln 2}{t_{1/2}} \left(\frac{D \cdot W}{C} \right)$$

where D is the number of hepatocytes per mass of liver for a particular species. W is the average mass of liver present per weight of animal, and C is the number of hepatocytes present during the incubations per unit volume. The CL_h was calculated using the following equation:

$$CL_h = \frac{CL_{int} \cdot Q}{CL_{int} + Q}$$

where Q is the species-dependent hepatic blood flow. No adjustment was made for the unbound fraction of the test compound (fu). The ER was determined by calculating the ratio of the CL_h to Q:

$$ER = \frac{CL_h}{Q}$$

In Vitro Stability in Liver Microsomes

Test compounds were incubated with liver microsomes from Sprague Dawley rats and humans. Control compounds (i.e., dextromethorphan, diazepam, diltiazem, phenacetin, tolbutamide, and verapamil) performed within expected limits with respect to the fraction remaining after incubation in each liver microsomal system. The percentage of the compound of formula I and of the compound of formula I' remaining after 20 minutes, calculated $t_{1/2}$ values, the predicted clearance values, and the predicted hepatic ERs were determined.

In Vitro Stability in Hepatocytes

Test compounds were incubated with hepatocytes from Sprague Dawley rats and humans. Control compounds (i.e., antipyrine, diazepam, diltiazem, lorazepam, propranolol, verapamil, and 7-ethyl-10-hydroxycamptothecin) performed within expected limits with respect to the fraction remaining after incubation in each hepatocyte system. The percentage of the compound of formula I and of the compound of formula I' remaining after 2 hours, calculated $t_{1/2}$ values, the predicted clearance values, and the predicted hepatic extraction ratios as determined in hepatocyte incubations for each species were determined.

Example 35

MDR1 LLC-PK1 Cell culture and experimental conditions

Both LLC-PK1 and MDR1 transfected LLC-PK1 cells were cultured and plated according to manufacturer's recommendations with the exception that the passage media contained only 2% fetal bovine serum so as to extend passage time out to seven days.

Both positive and negative controls were used to assess functionality of P-gp efflux in the assay. Stock solutions for assay controls and the test article were prepared in DMSO for a final test concentrations of 10 μ M. Final organic concentration in the assay was 1%. All dosing solutions contained 10 μ M lucifer yellow to monitor LLC-PK1 cell monolayer integrity.

For the apical to basolateral determination (A to B), 75 μ L of the test article in transport buffer were added to the apical side of the individual transwells and 250 μ L of basolateral media, without compound or lucifer yellow, were added to each well. For the basolateral to apical determination (B to A), 250 μ L of test article in transport buffer were added to each well and 75 μ L transport buffer, without compound or lucifer yellow, were added to each transwell. All tests were

performed in triplicate, and each compound was tested for both apical to basolateral and basolateral to apical transport. The plates were incubated for 2 hours on a Lab-Line Instruments Titer Orbital Shaker (VWR, West Chester, PA) at 50 rpm and 37 °C with 5% CO₂. All culture plates were removed from the incubator and 50 µL of media were removed from the apical and basolateral portion of each well and added to 150 µL of 1 µM labetalol in 2:1 acetonitrile (ACN): H₂O, v/v. The plates were read using a Molecular Devices (Sunnyvale, CA) Gemini Fluorometer to evaluate the lucifer yellow concentrations at excitation/emission wavelengths of 425/535 nm. These values were accepted when found to be below 5% for apical to basolateral and basolateral to apical flux across the MDR1 transfected LLC-PK1 cell monolayers. The plates were sealed and the contents of each well analyzed by LC-MS/MS. The compound concentrations were determined from the ratio of the peak areas of the compound to the internal standard (labetalol) in comparison to the dosing solution.

LC-MS analysis

The LC-MS/MS system was comprised of an HTS-PAL autosampler (Leap Technologies, Carrboro, NC), an HP1200 HPLC (Agilent, Palo Alto, CA), and a MDS Sciex 4000 Q Trap system (Applied Biosystems, Foster City, CA). Chromatographic separation of the analyte and internal standard was achieved at room temperature using a C18 column (Kinetics[®], 30 x 3 mm, 2.6 µm particle size, Phenomenex, Torrance, CA) in conjunction with gradient conditions using mobile phases A (water containing 1% isopropyl alcohol and 0.1% formic acid) and B (0.1% formic acid in ACN). The total run time, including re-equilibration time, for a single injection was 1.2 minutes. Mass spectrometric detection of the analytes was accomplished using the ion spray positive mode. Analyte responses were measured by multiple reaction monitoring (MRM) of transitions unique to each compound (the protonated precursor ion and selected product ions for each test article and *m/z* 329 to *m/z* 162 for labetalol, the internal standard).

Determination of Apparent Permeability (P_{app})

Permeability (P_{app}) was calculated in BioAssay v. 9.0 (Cambridge Soft, Cambridge, MA) using the following equation:

$$P_{app} \left(\times 10^{-6} \text{ cm} / \text{s} \right) = \frac{(C_d \bullet V \bullet (1 \times 10^6))}{(t \bullet 0.12 \text{ cm}^2 \bullet C)}$$

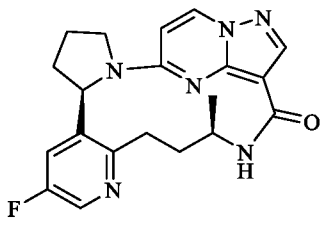
where C_d , V , t and C_0 are the detected concentration (μM), the volume on the dosing side (mL), the incubation time (s) and the initial dosing concentration (μM), respectively. The calculations for P_{app} were made for each replicate and then averaged.

OTHER EMBODIMENTS

It is to be understood that while the present application has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the present application, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

Definitions of the specific aspects of the invention as claimed herein follow.

According to a first aspect of the invention, there is provided a crystalline form of (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one having the following structure:



wherein the crystalline form is characterized by XRPD peaks, in terms of 2-theta, at 9.1, 20.2, and 24.9.

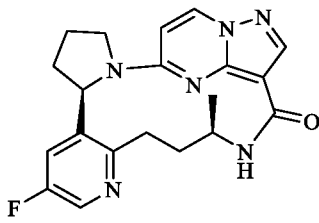
According to a second aspect of the invention, there is provided a process for making a pharmaceutical composition comprising mixing a salt or crystalline form according to the first aspect and a pharmaceutically acceptable carrier.

According to a third aspect of the invention, there is provided a method of treating a cancer mediated by a Trk kinase in a subject in need thereof, comprising administering the crystalline form according to the first aspect to the subject.

According to a fourth aspect of the invention, there is provided a use of a crystalline form according to the first aspect in the manufacture of a medicament for treating a cancer mediated by a Trk kinase in a subject in need thereof.

WE CLAIM:

1. A crystalline form of (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one having the following structure:



- wherein the crystalline form is characterized by XRPD peaks, in terms of 2-theta, at 9.1, 20.2, and 24.9.
2. The crystalline form of claim 1, having one or more additional XRPD peaks, at 11.2, 13.4, 14.8, 18.3, 18.6, 23.6, and 29.4.
 3. The crystalline form of claim 1 or claim 2, having hygroscopicity characterized by a mass uptake of about 0.3% at 90% relative humidity as determined by dynamic vapor sorption analysis.
 4. The crystalline form of any of claims 1-3, which is substantially free of an amorphous form of (6*R*,15*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one.
 5. The crystalline form of any of claims 1-4, wherein the crystalline form is characterized by a DTA thermogram characterized by an endothermal event at about 317 °C.
 6. The crystalline form of any of claims 1-5, wherein the crystalline form is characterized by a DSC thermogram characterized by an endothermal event at about 317 °C.
 7. The crystalline form of any of claims 1-6, wherein the crystalline form is characterized by a hygroscopicity characterized by a mass uptake of about 0.7% at 90% relative humidity as determined by dynamic vapor sorption analysis.

8. A process for making a pharmaceutical composition comprising mixing a salt or crystalline form according to any of claims 1-7 and a pharmaceutically acceptable carrier.
9. A method of treating a cancer mediated by a Trk kinase in a subject in need thereof, comprising administering the crystalline form according to any of claims 1-7 to the subject.
10. The method according to claim 9, wherein the cancer is selected from the group consisting of adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, leukemia lymphocytic, liver cholangiocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung

small cell undifferentiated carcinoma, lung squamous cell carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, lymphoma, non-Hodgkin's lymphoma, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epithelioid cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

11. Use of a crystalline form according to any of claims 1-7 in the manufacture of a medicament for treating a cancer mediated by a Trk kinase in a subject in need thereof.

12. The use according to claim 11, wherein the cancer is selected from the group consisting of adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, leukemia lymphocytic, liver cholangiocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, lymphoma, non-Hodgkin's lymphoma, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma,

placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epithelioid cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

FIG.1

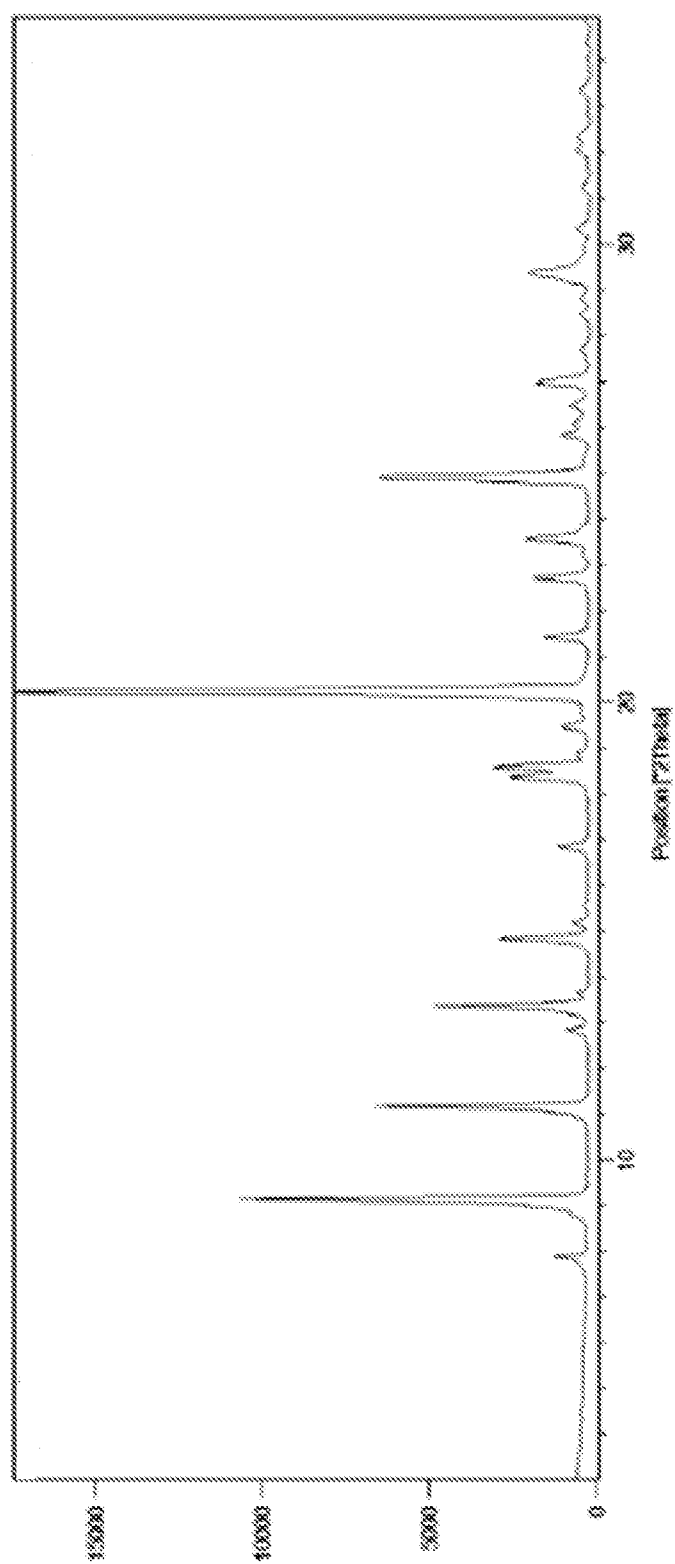


FIG. 2

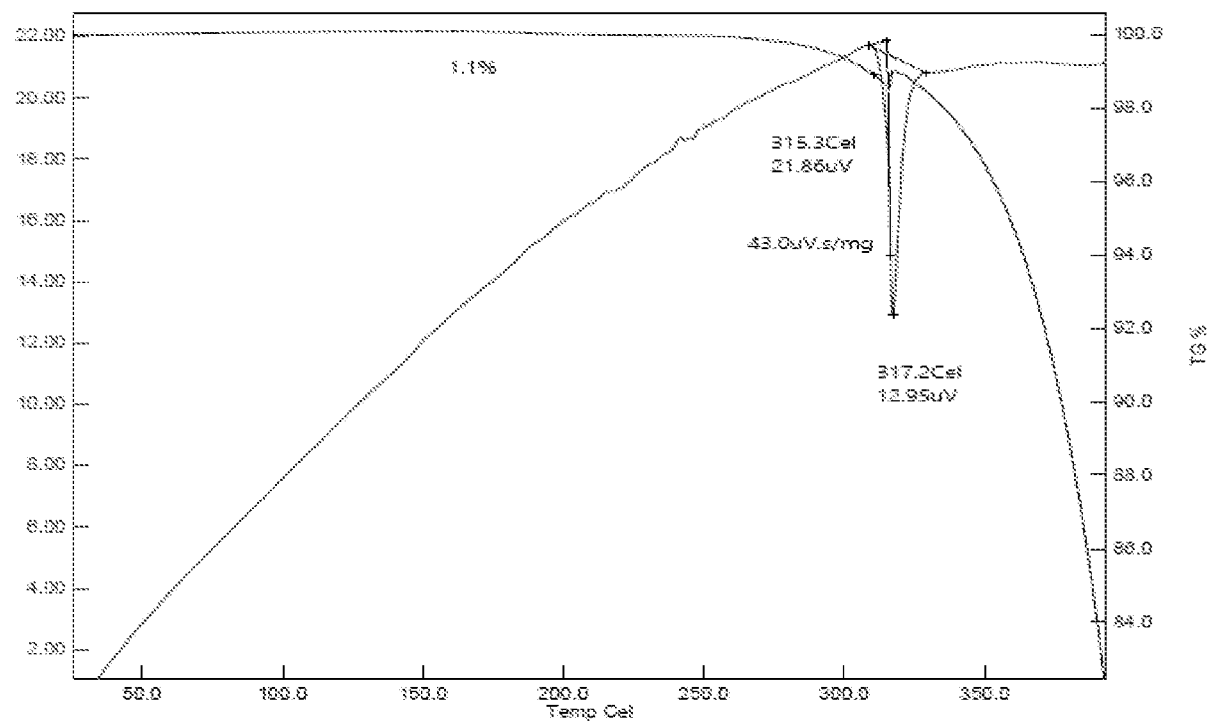


FIG. 3

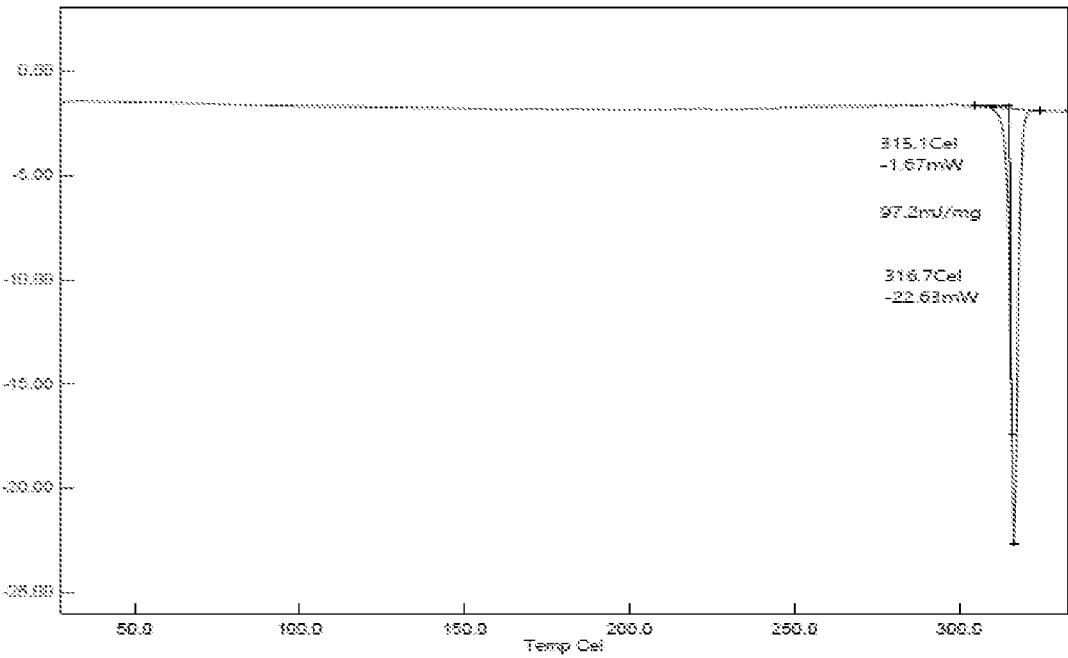


FIG. 4

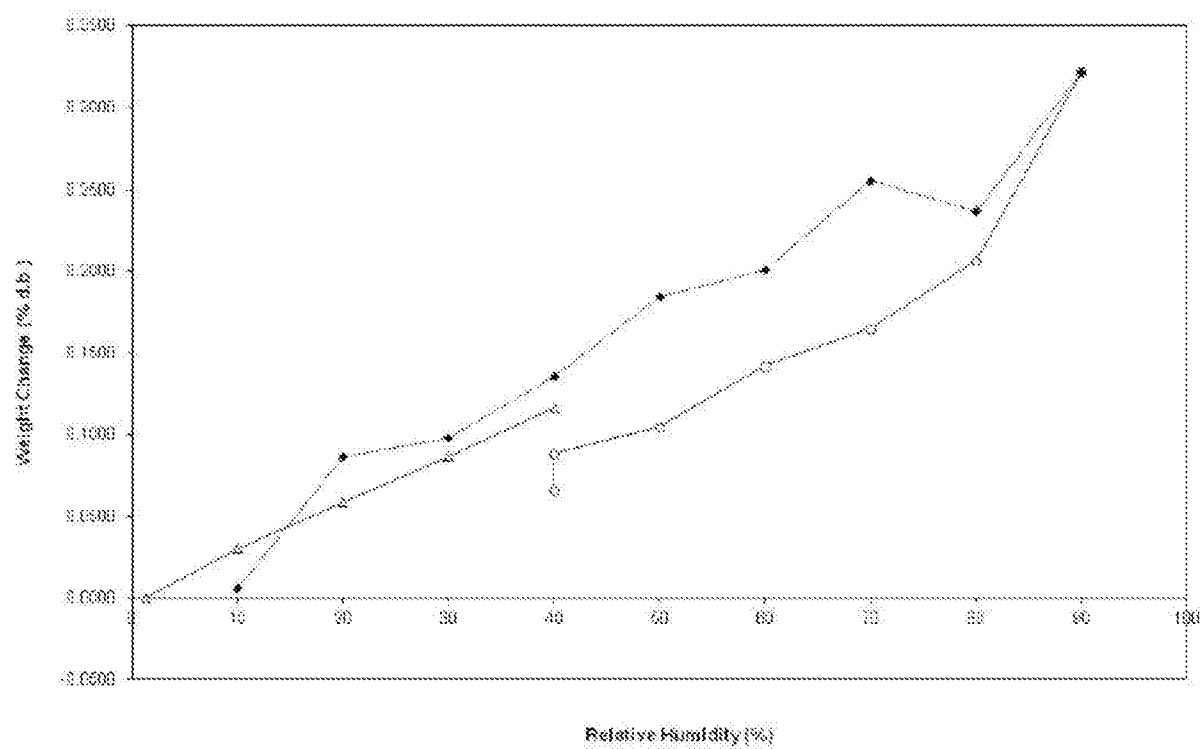


FIG. 5

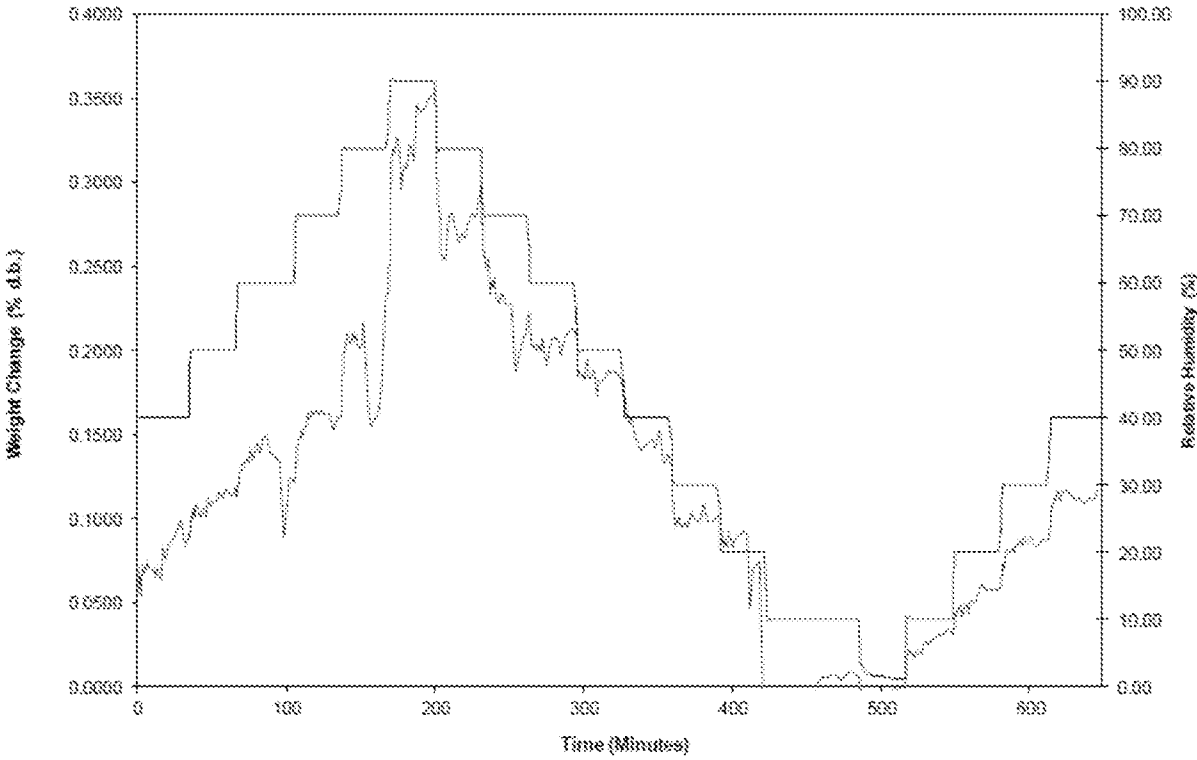


FIG. 6

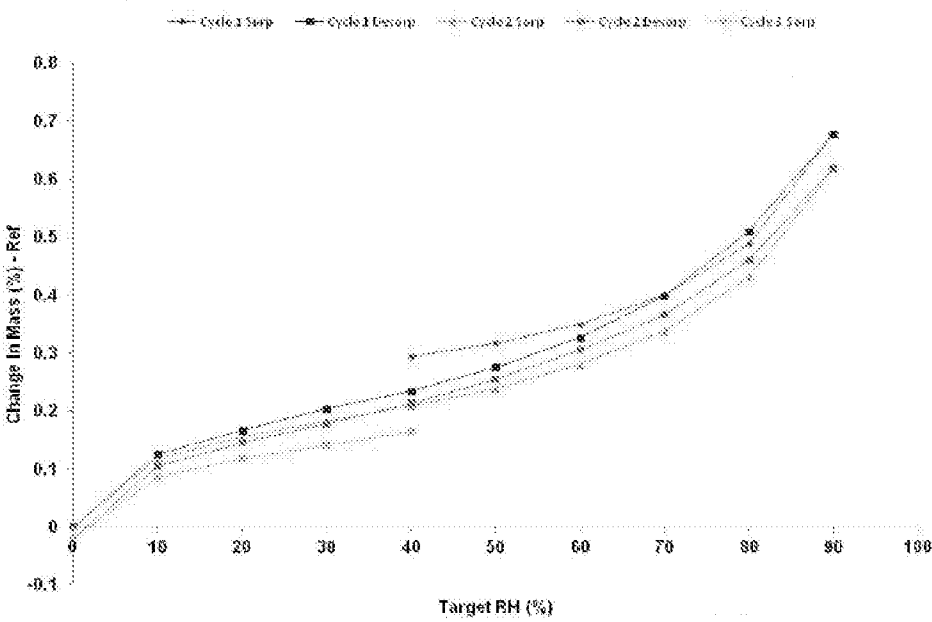


FIG. 7

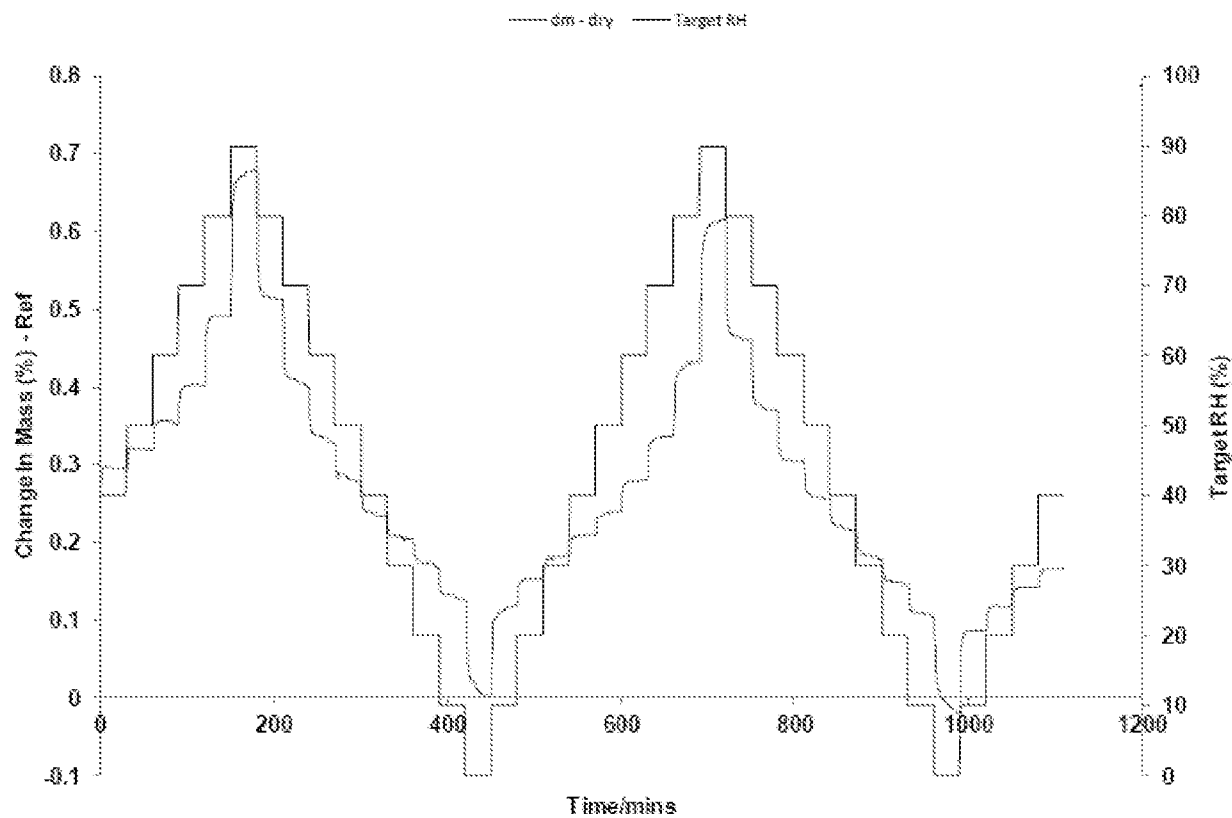


FIG. 8

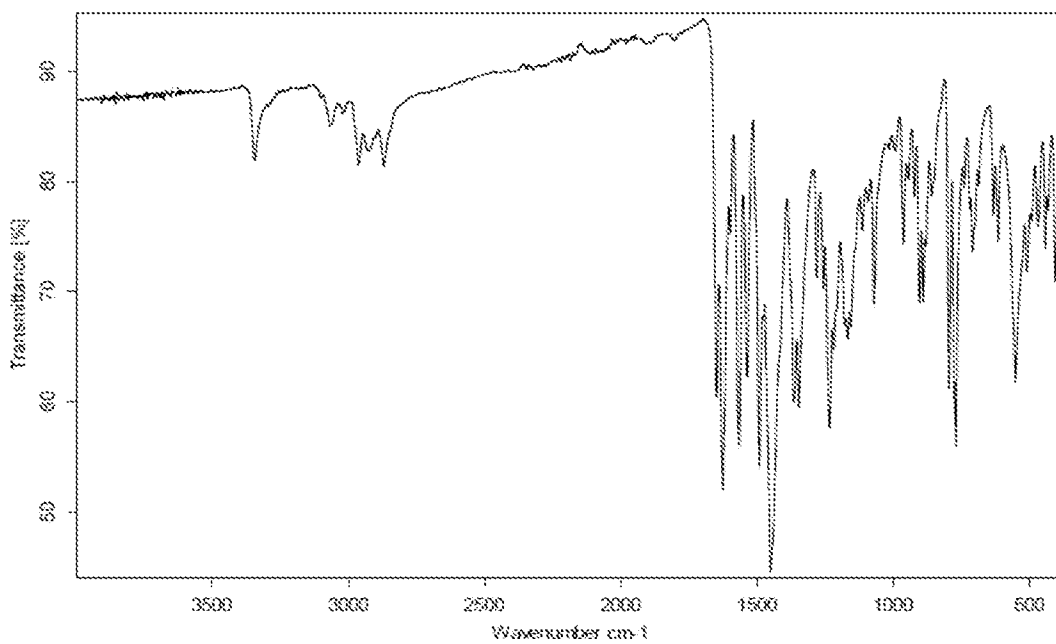


FIG. 9

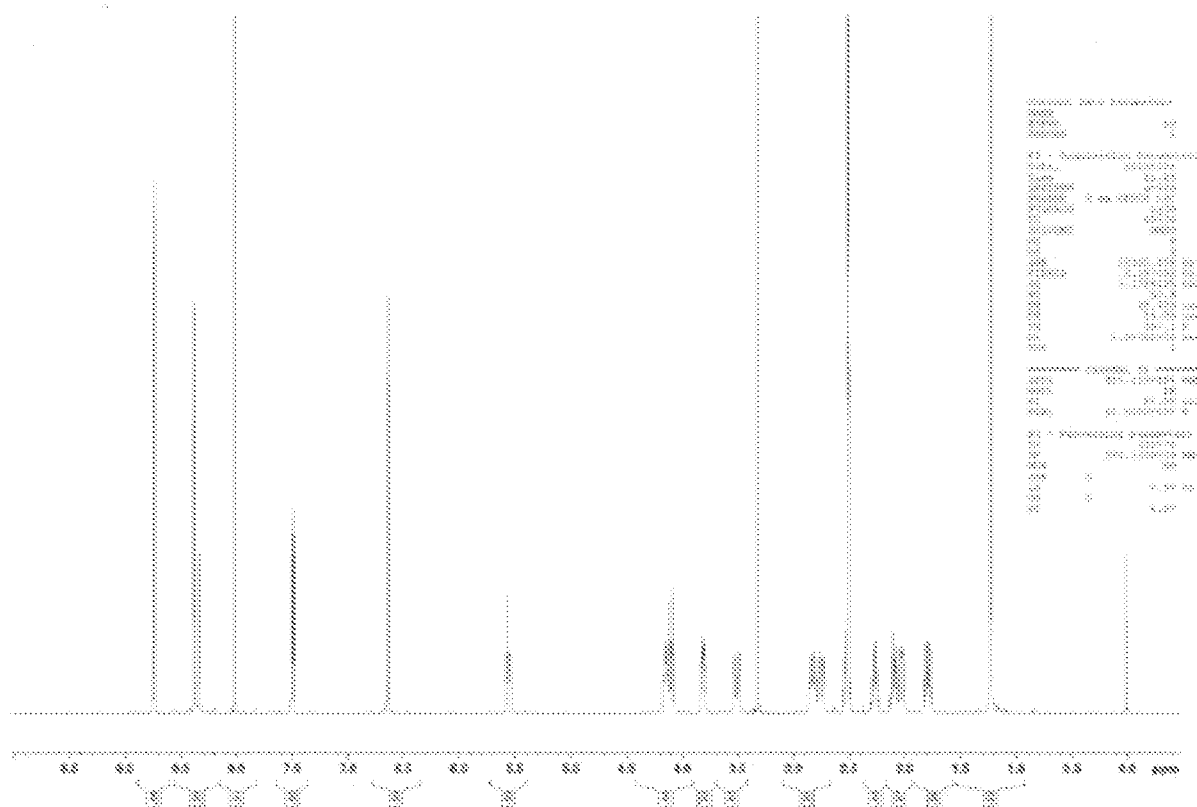


FIG. 10

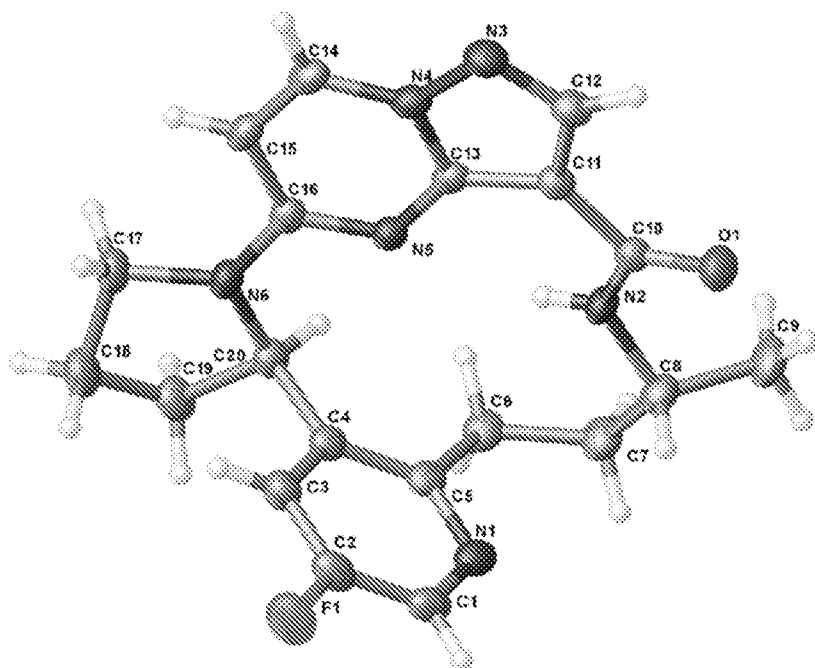


FIG. 11

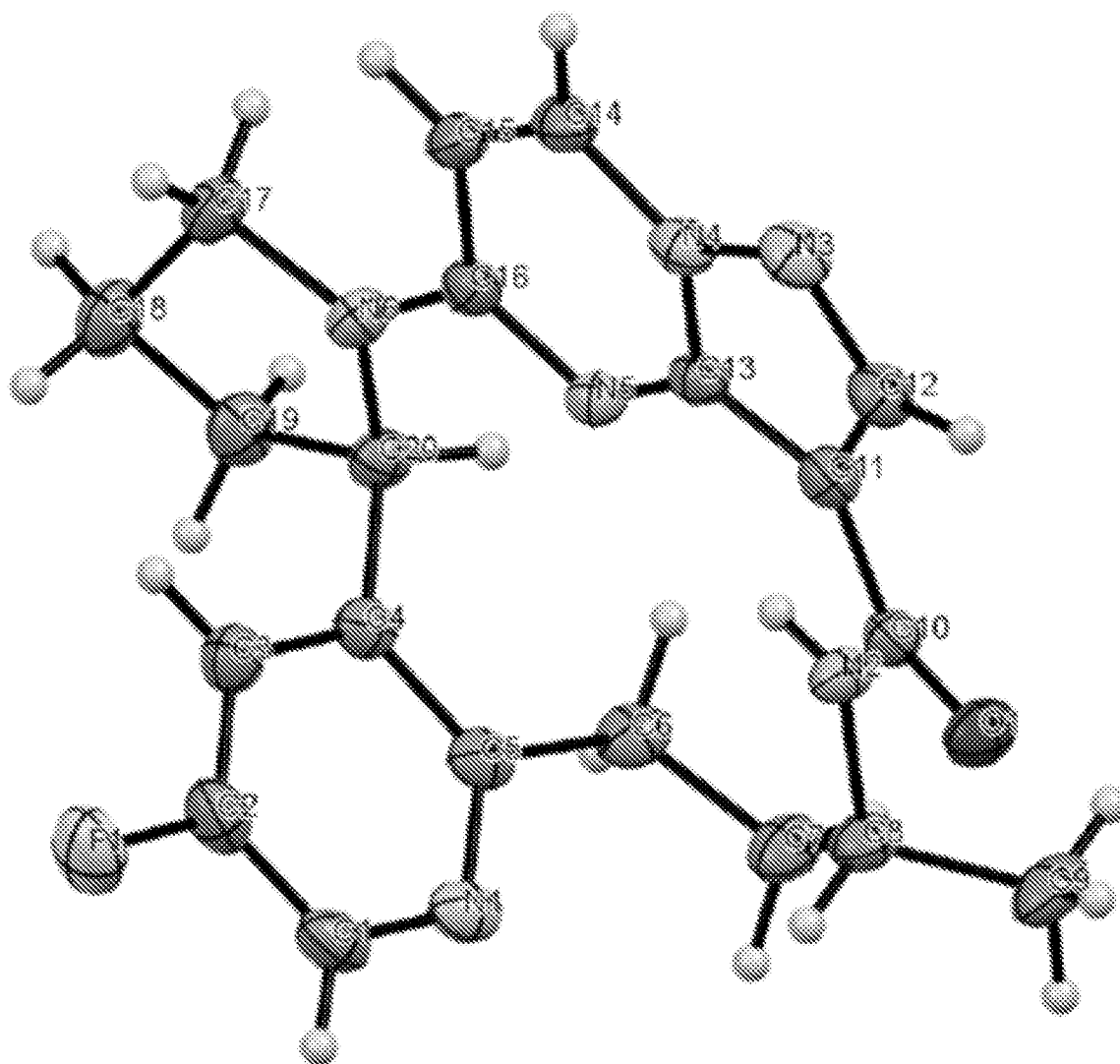


FIG. 12

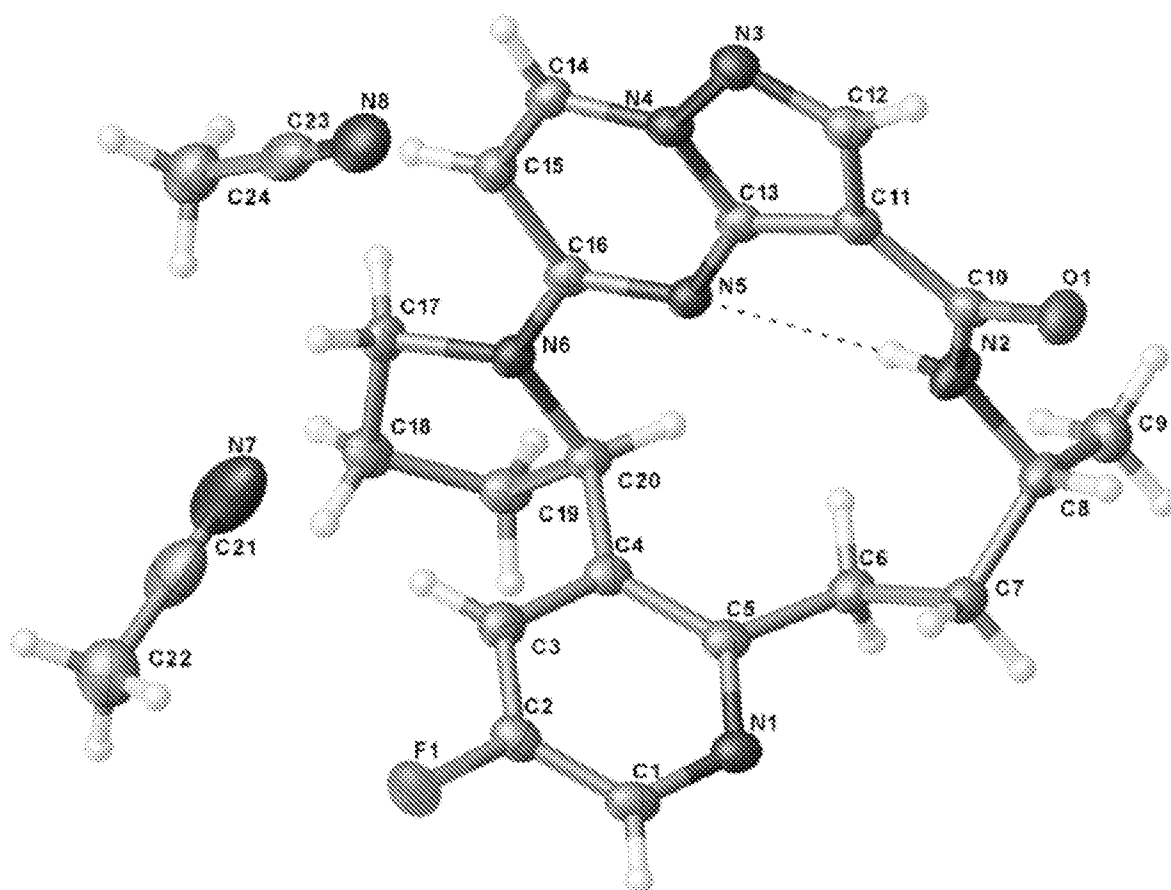


FIG. 13

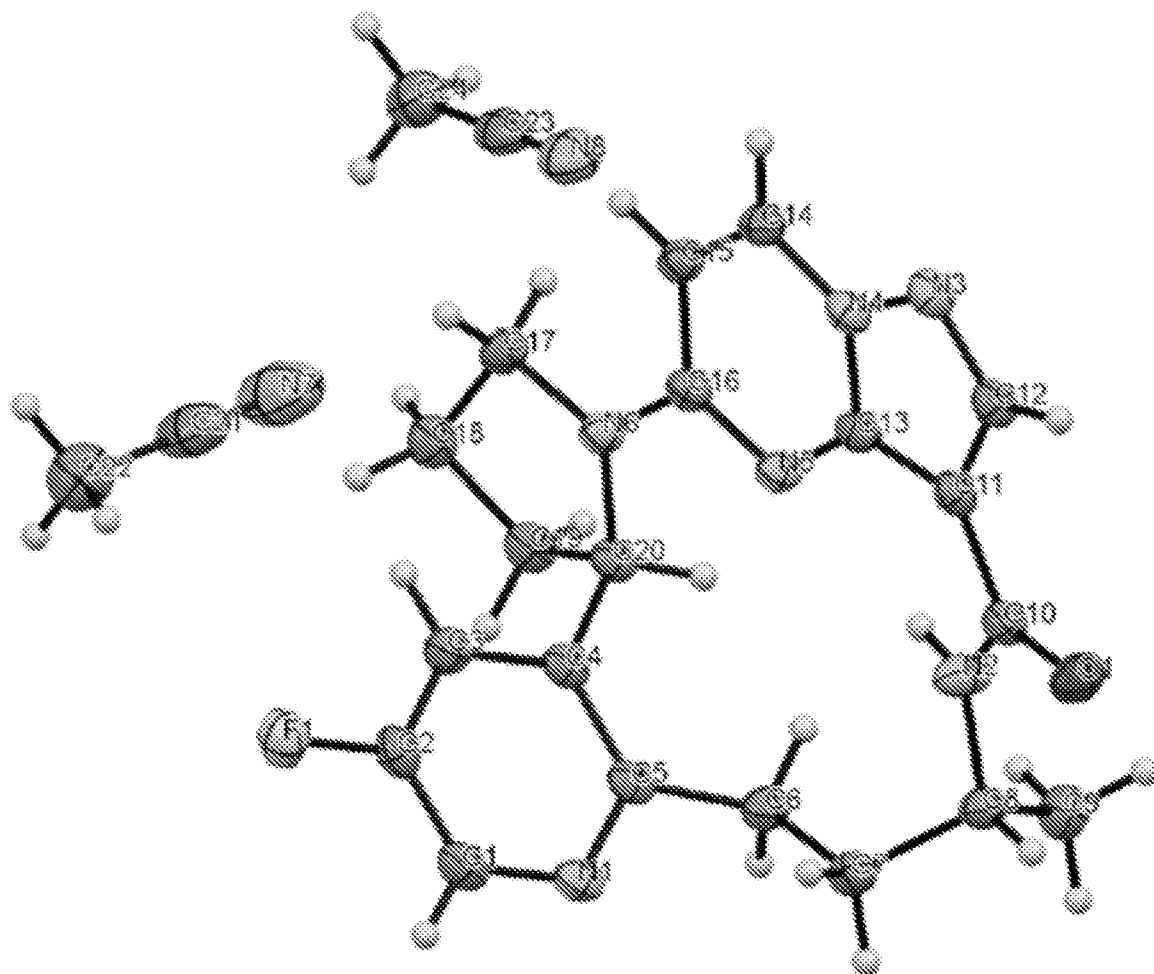


FIG. 14

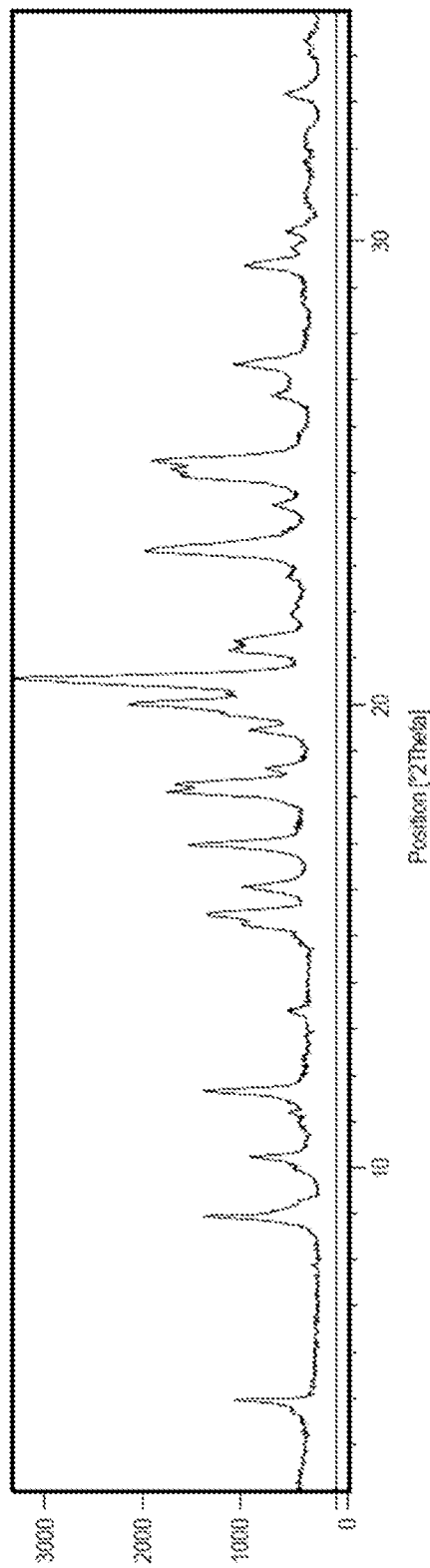


FIG. 15

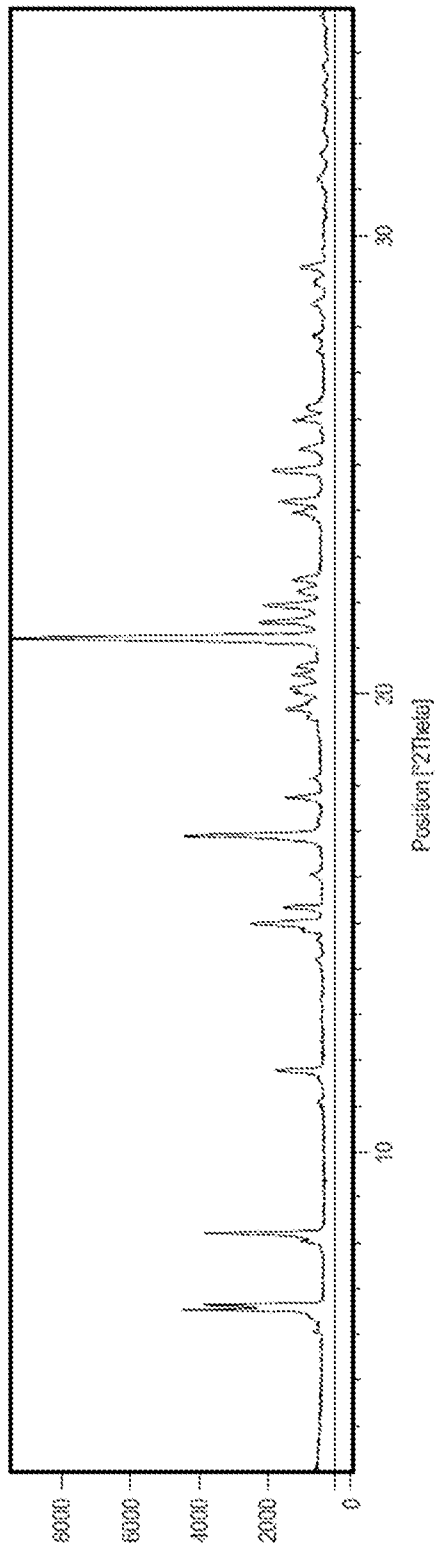


FIG. 16

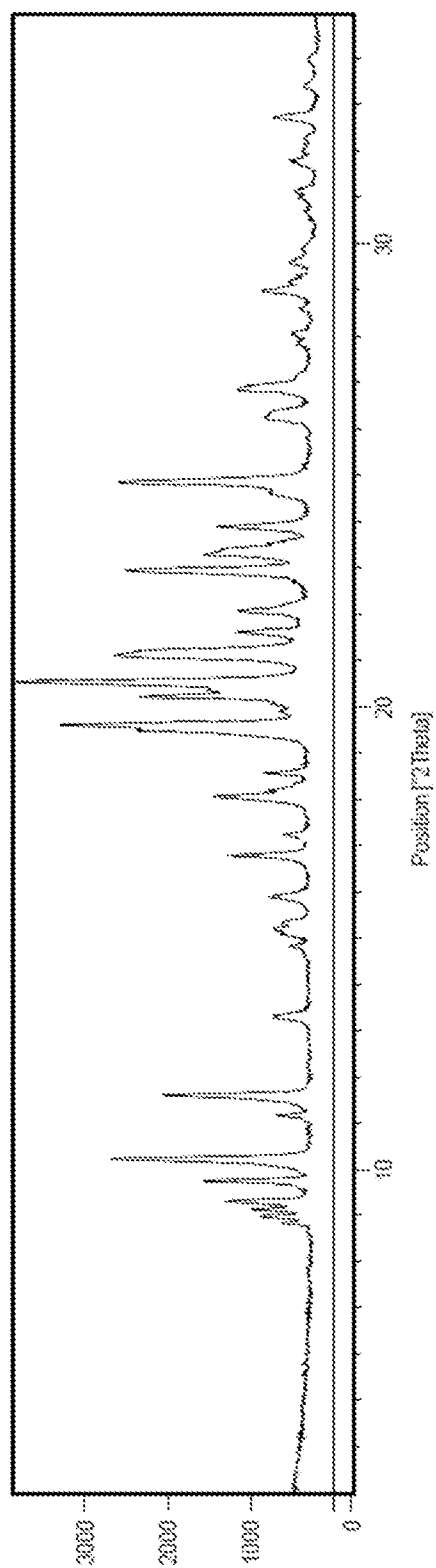


FIG. 17

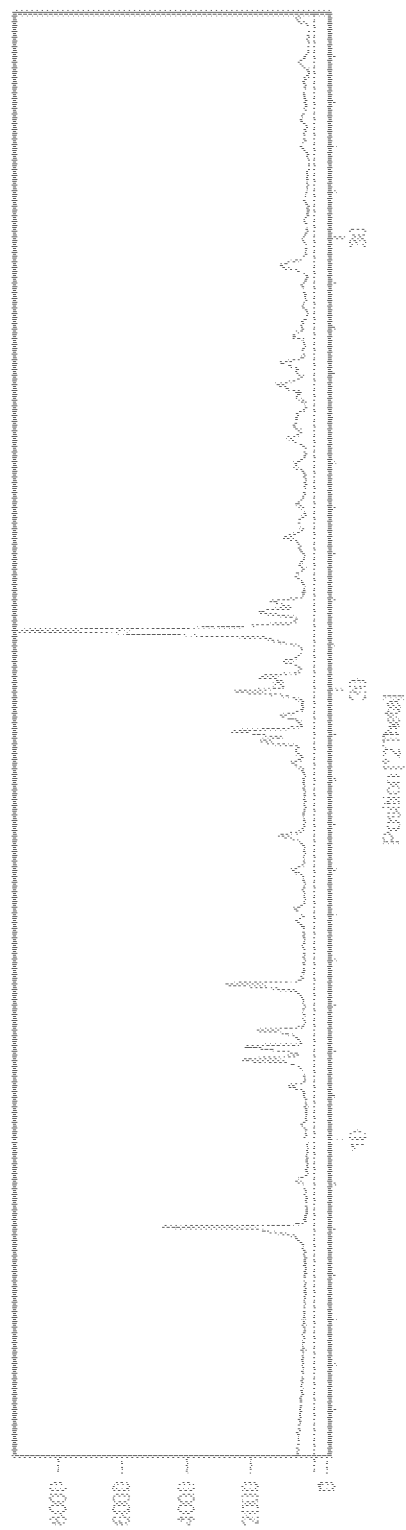


FIG. 18

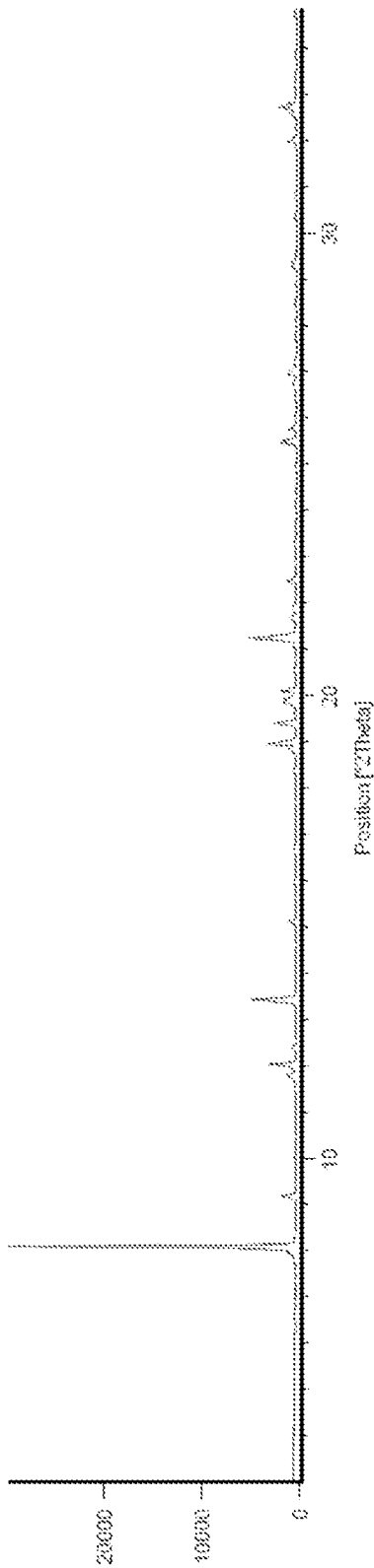


FIG. 19

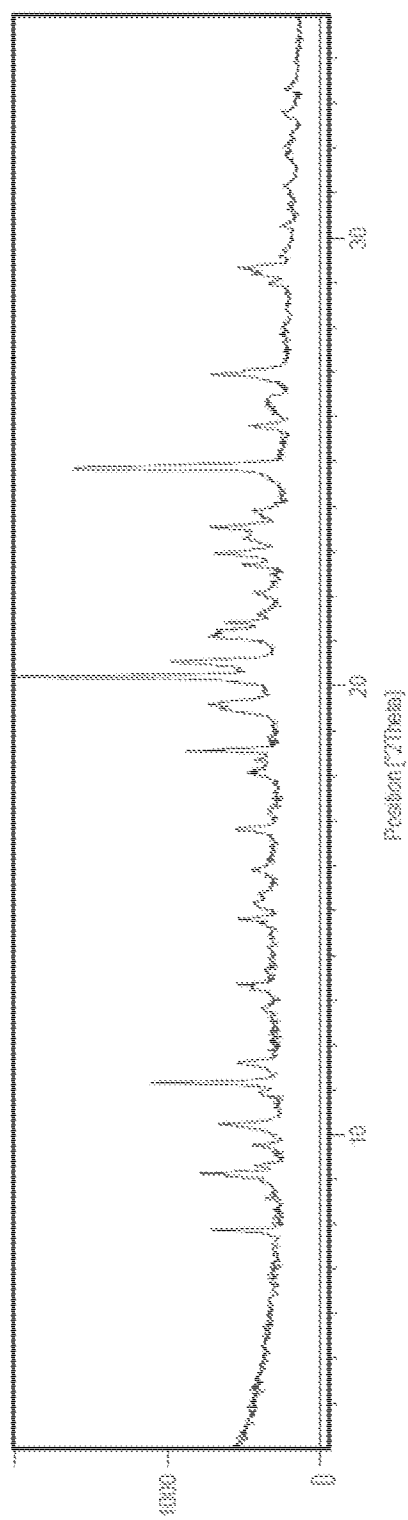


FIG. 20

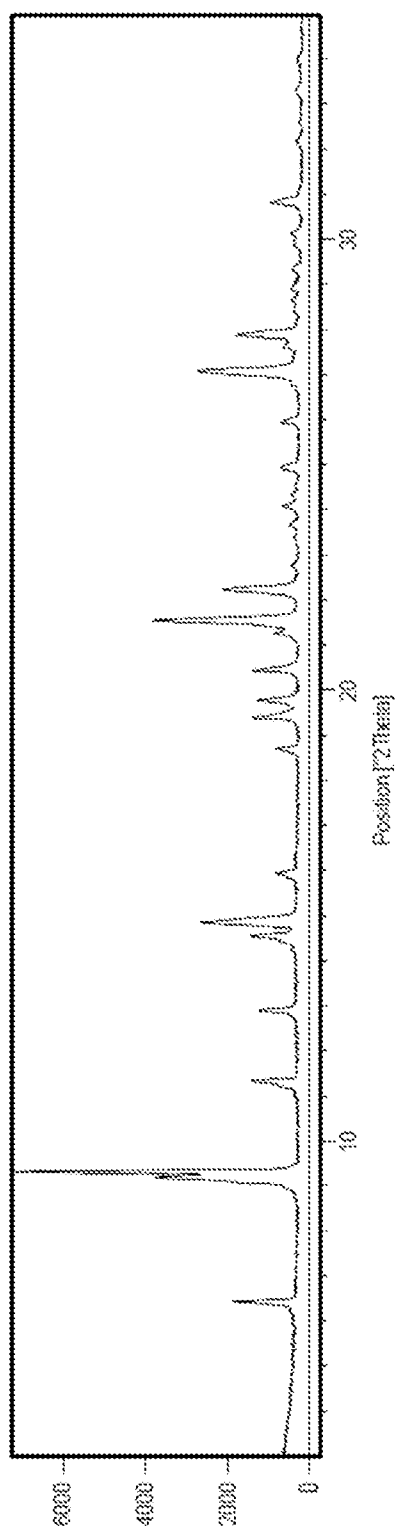


FIG. 21

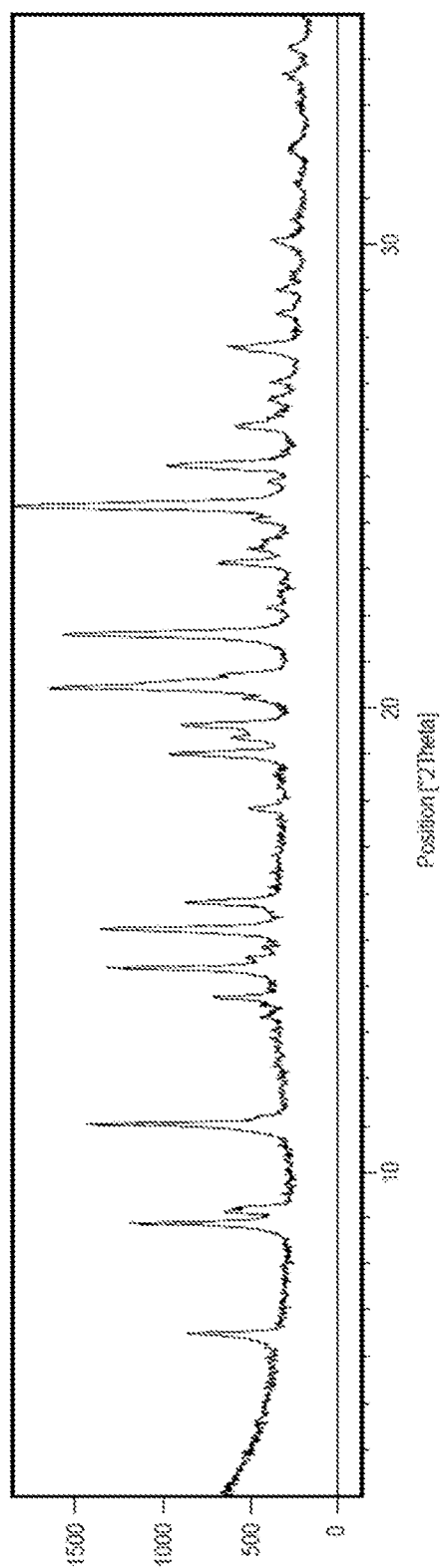


FIG. 22

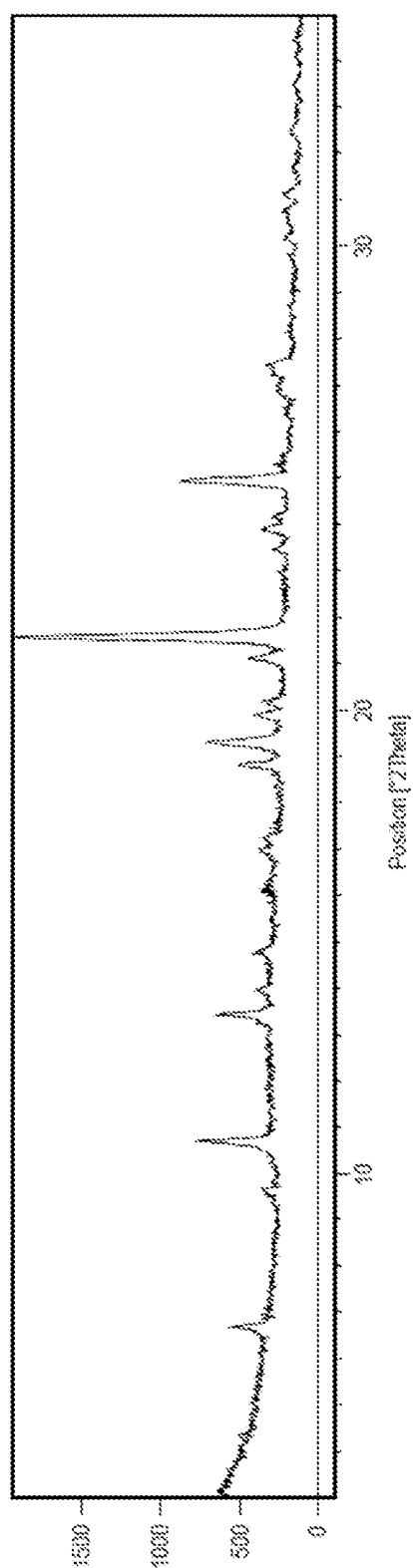


FIG. 23

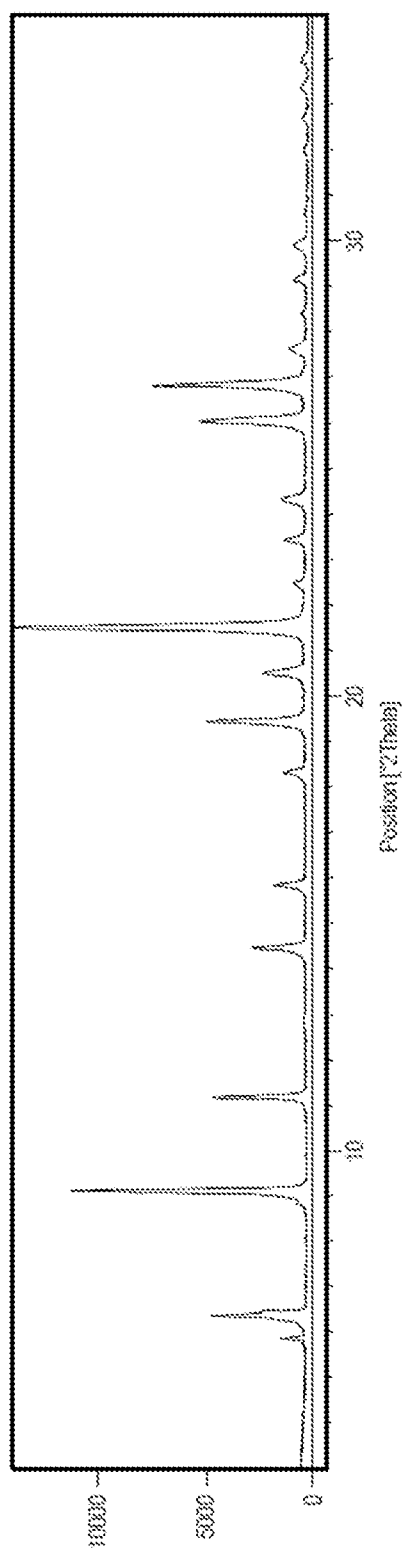


FIG. 24

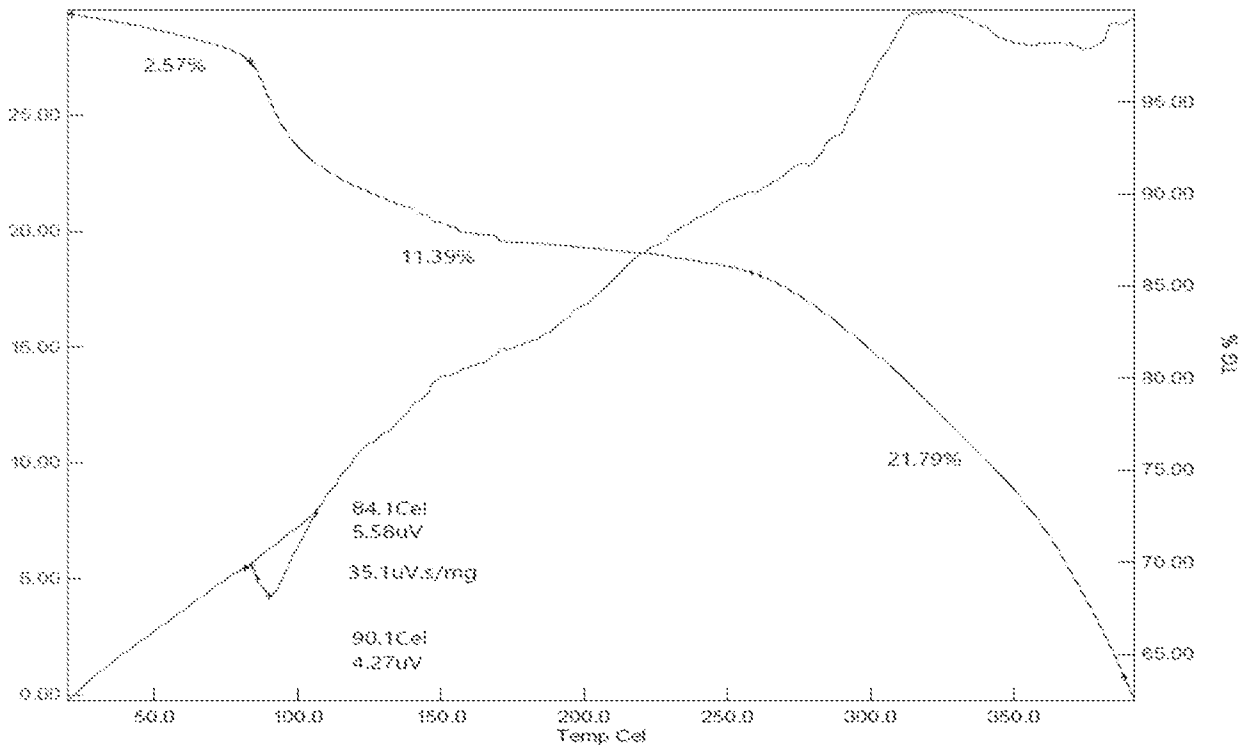


FIG. 25

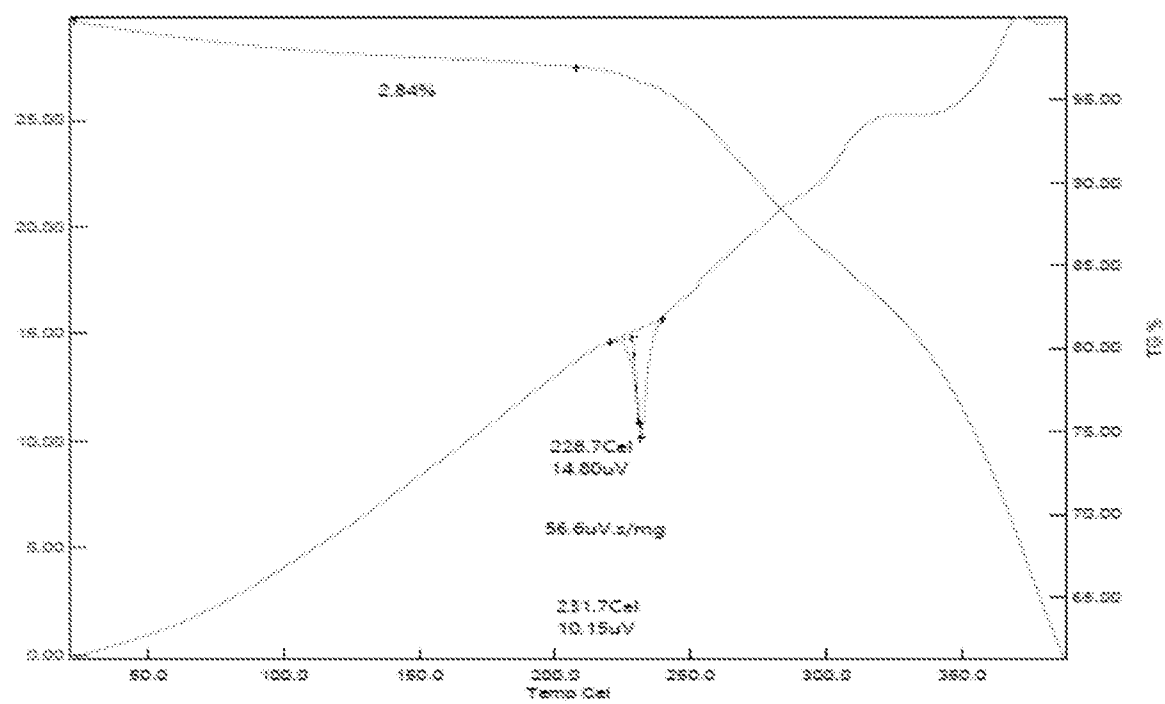


FIG. 26

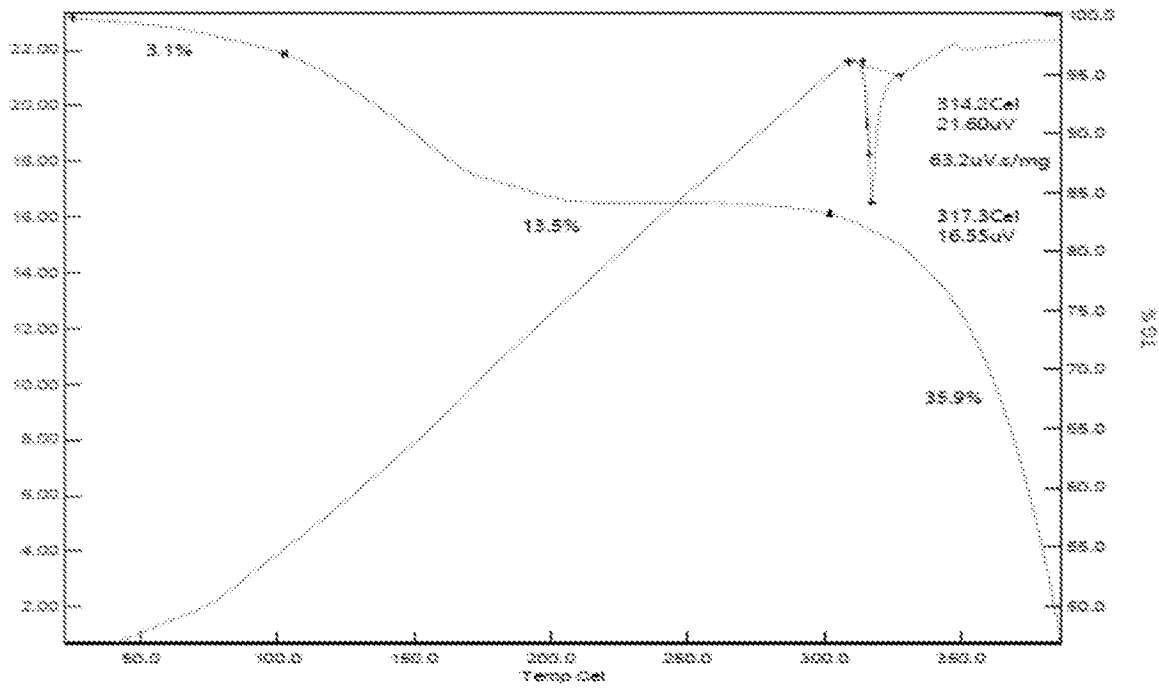


FIG. 27

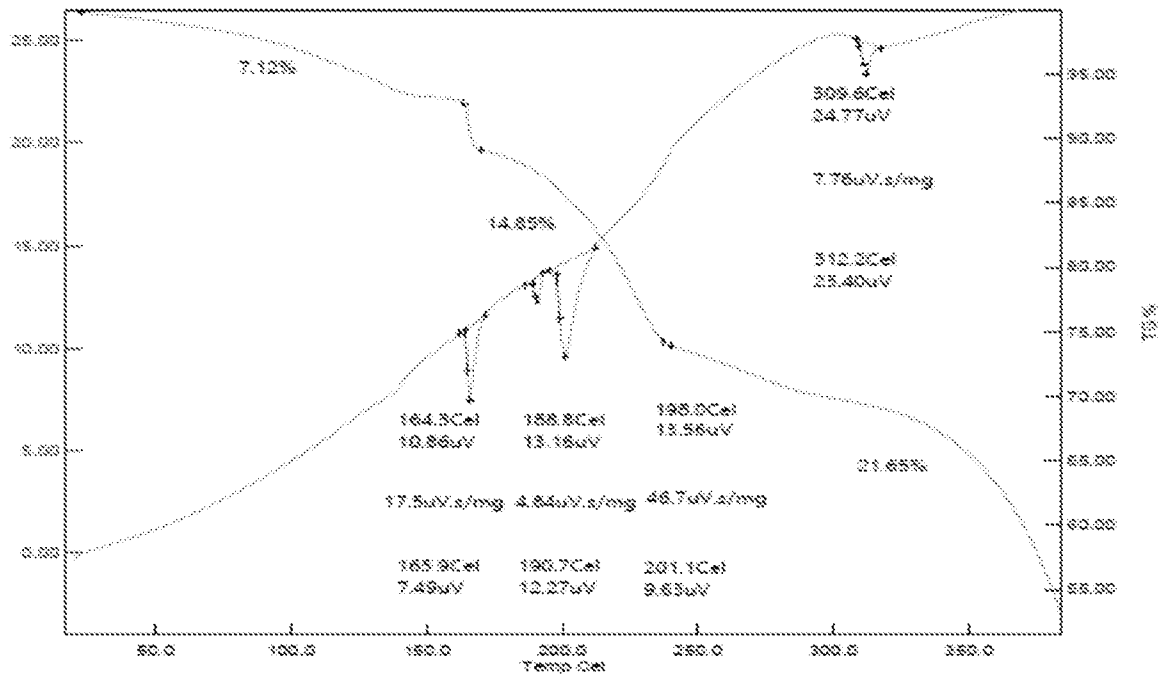


FIG. 28

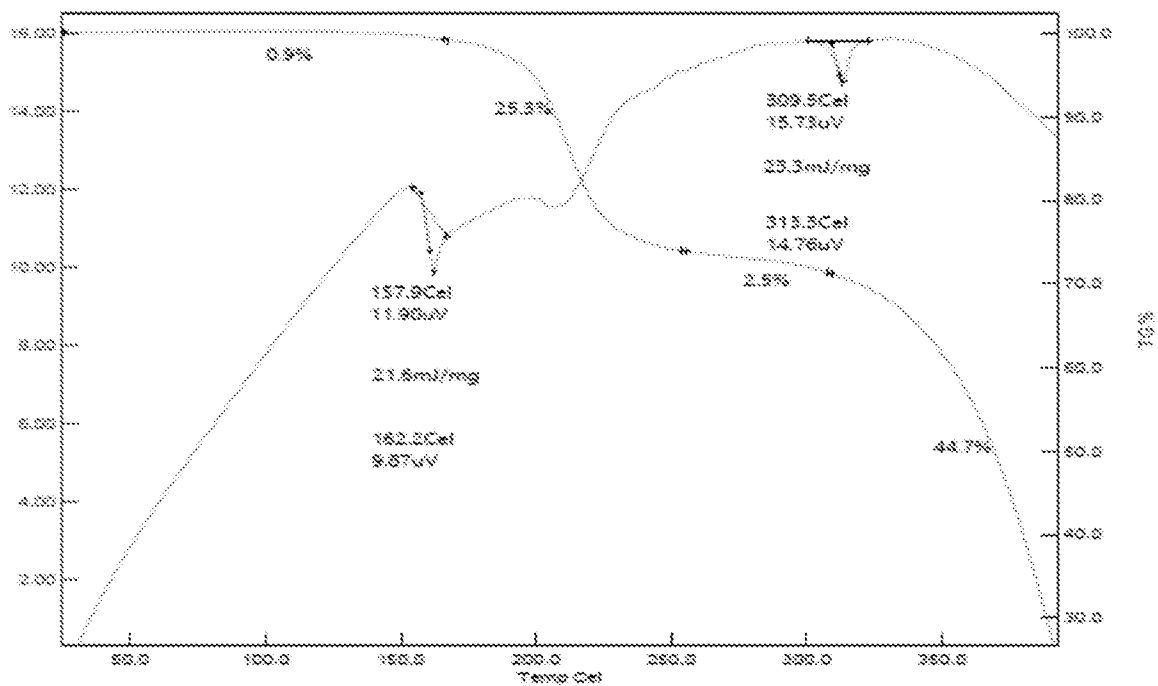


FIG. 29

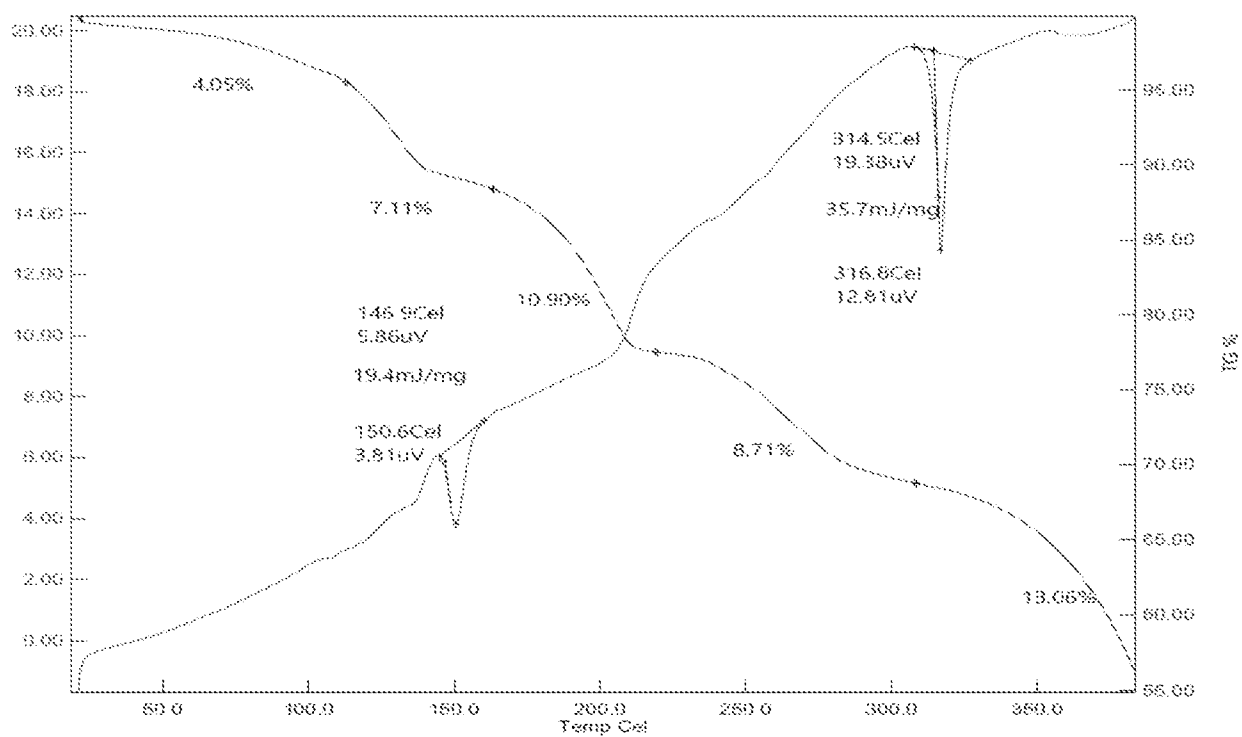


FIG. 30

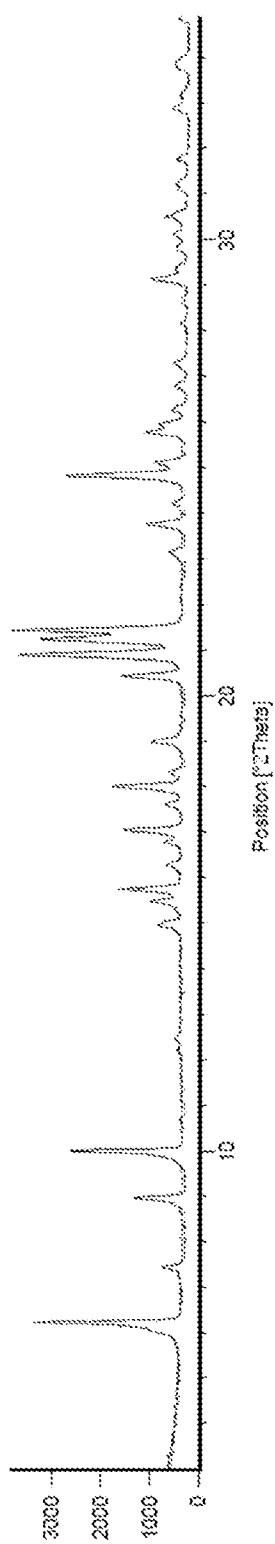


FIG. 31

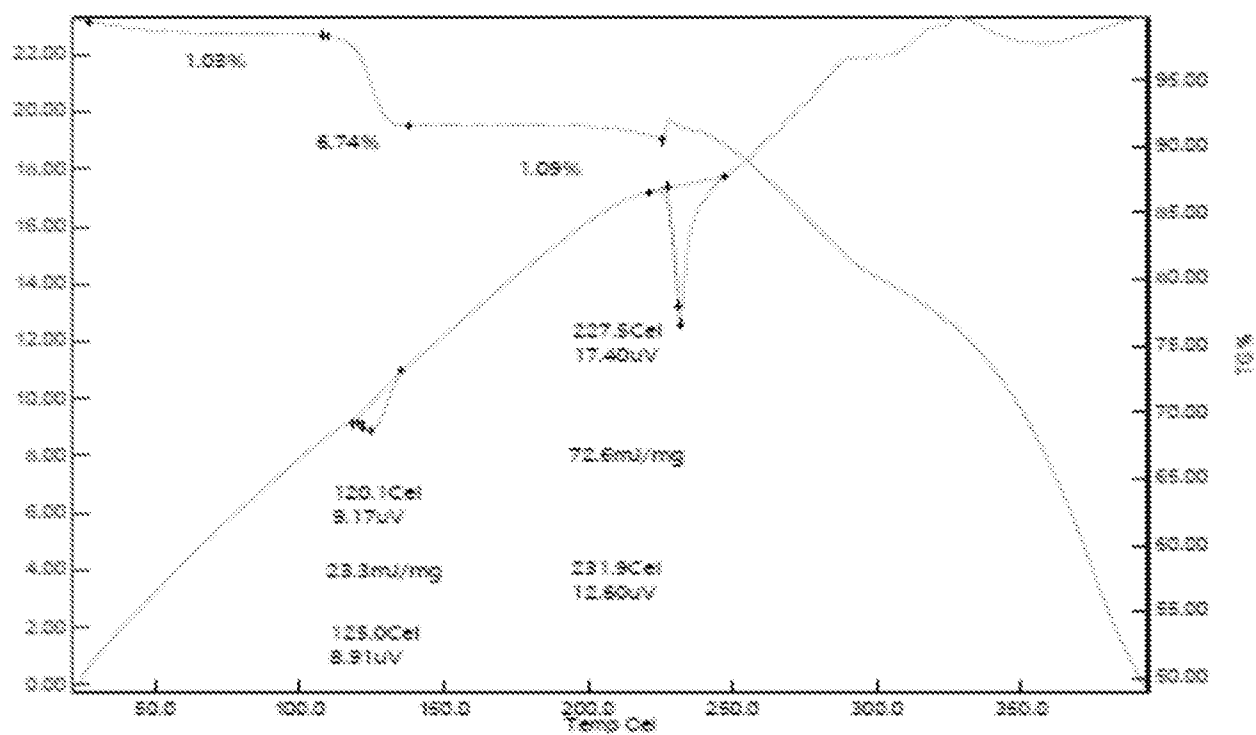


FIG. 32

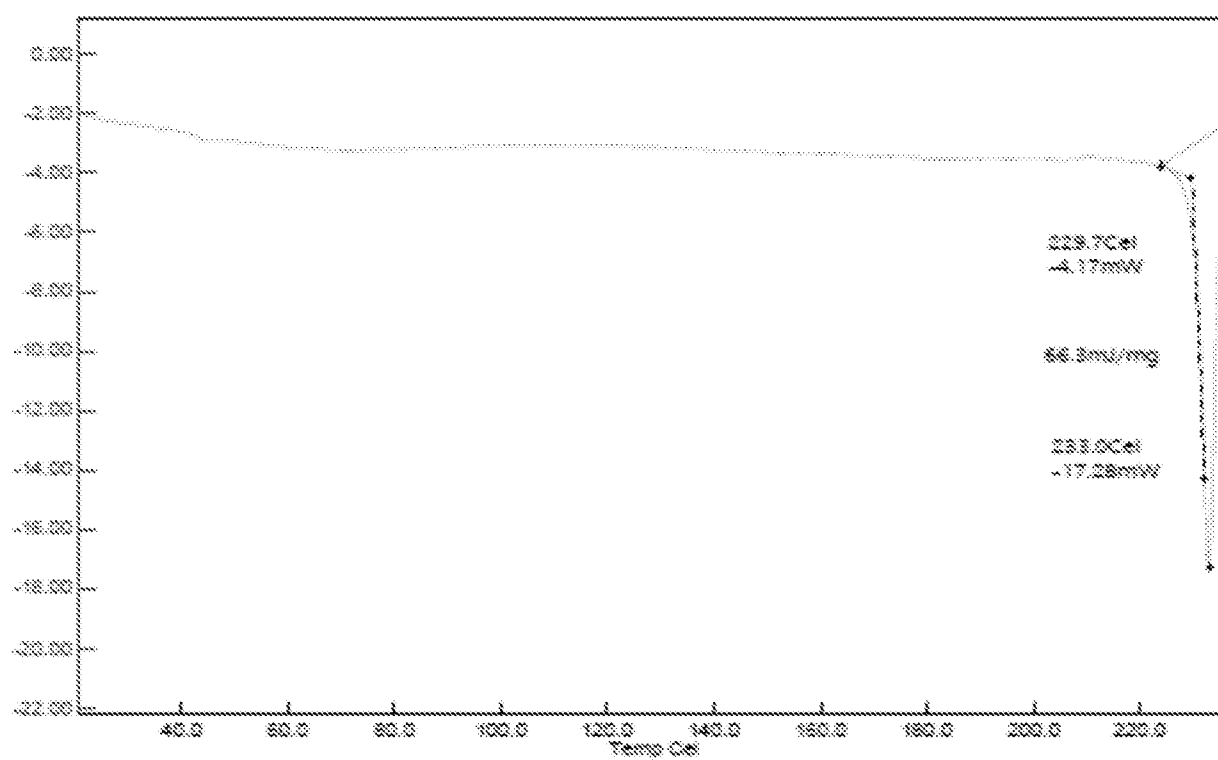


FIG. 33

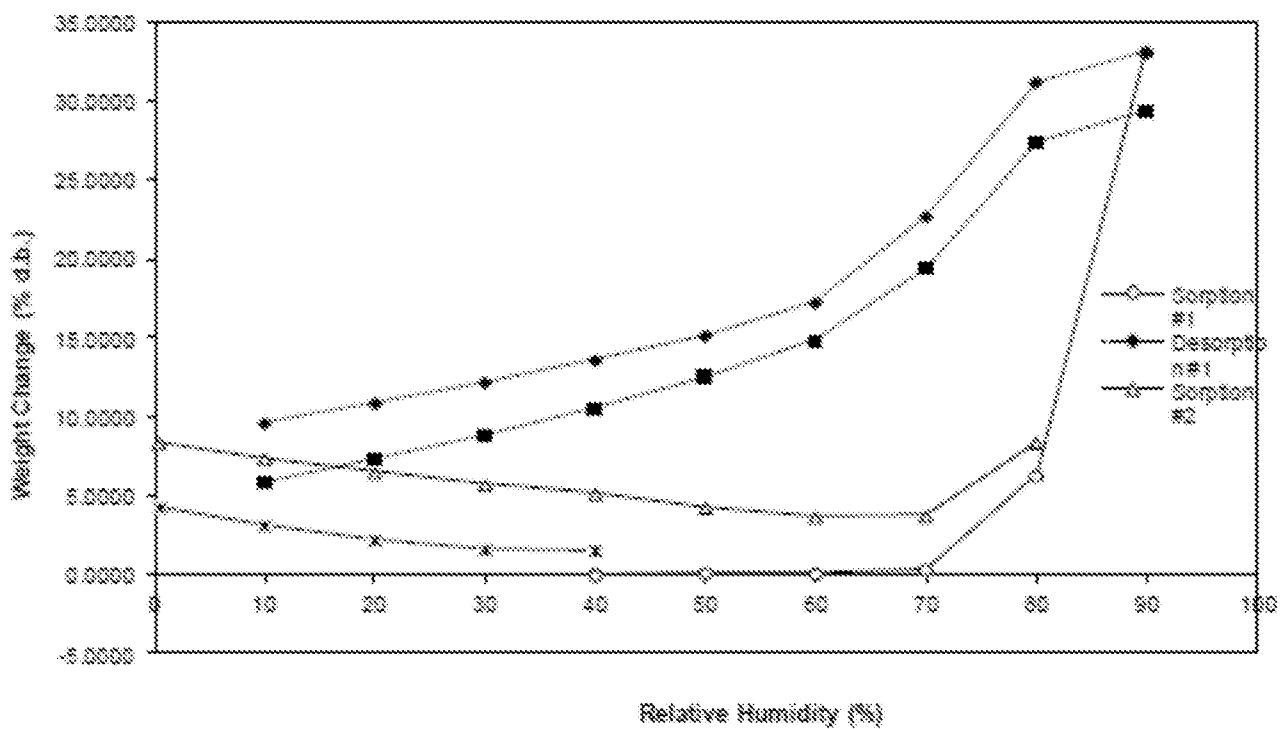


FIG. 34

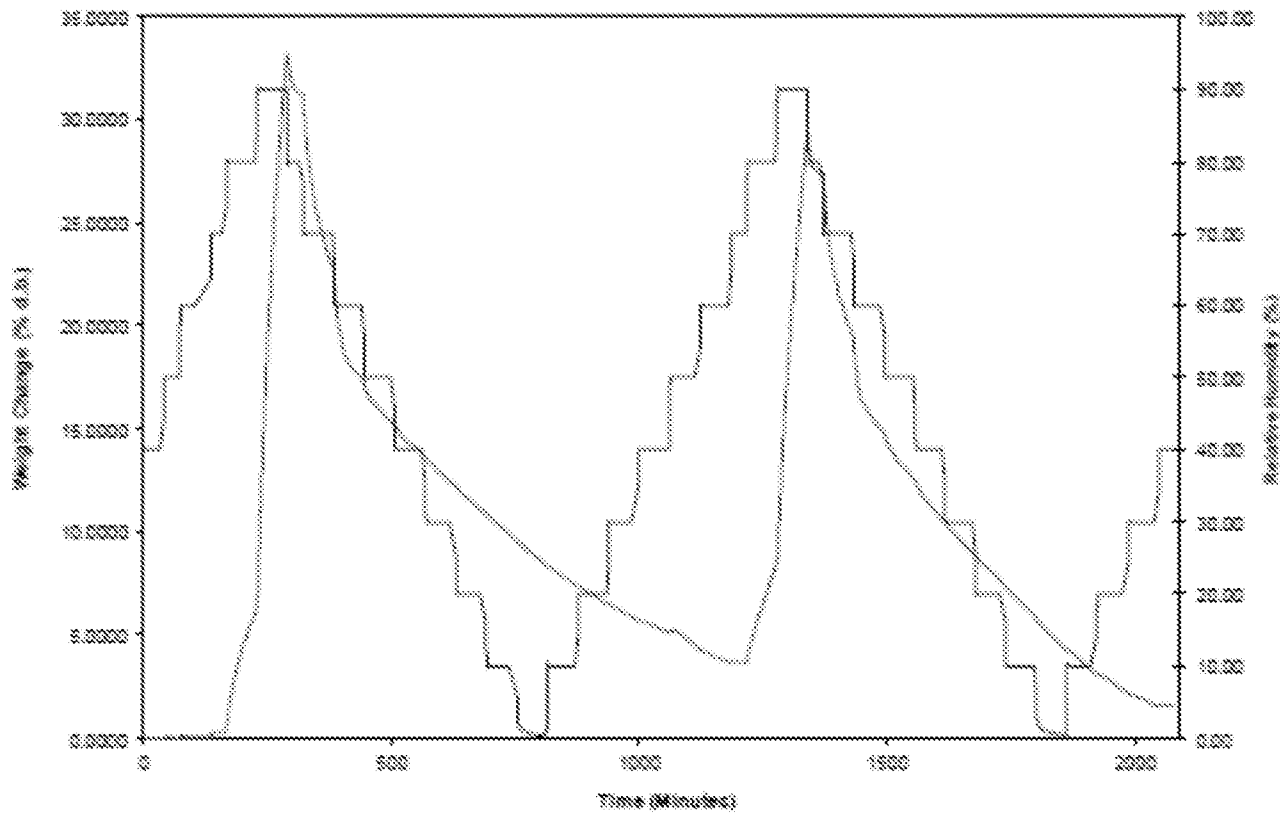


FIG. 35

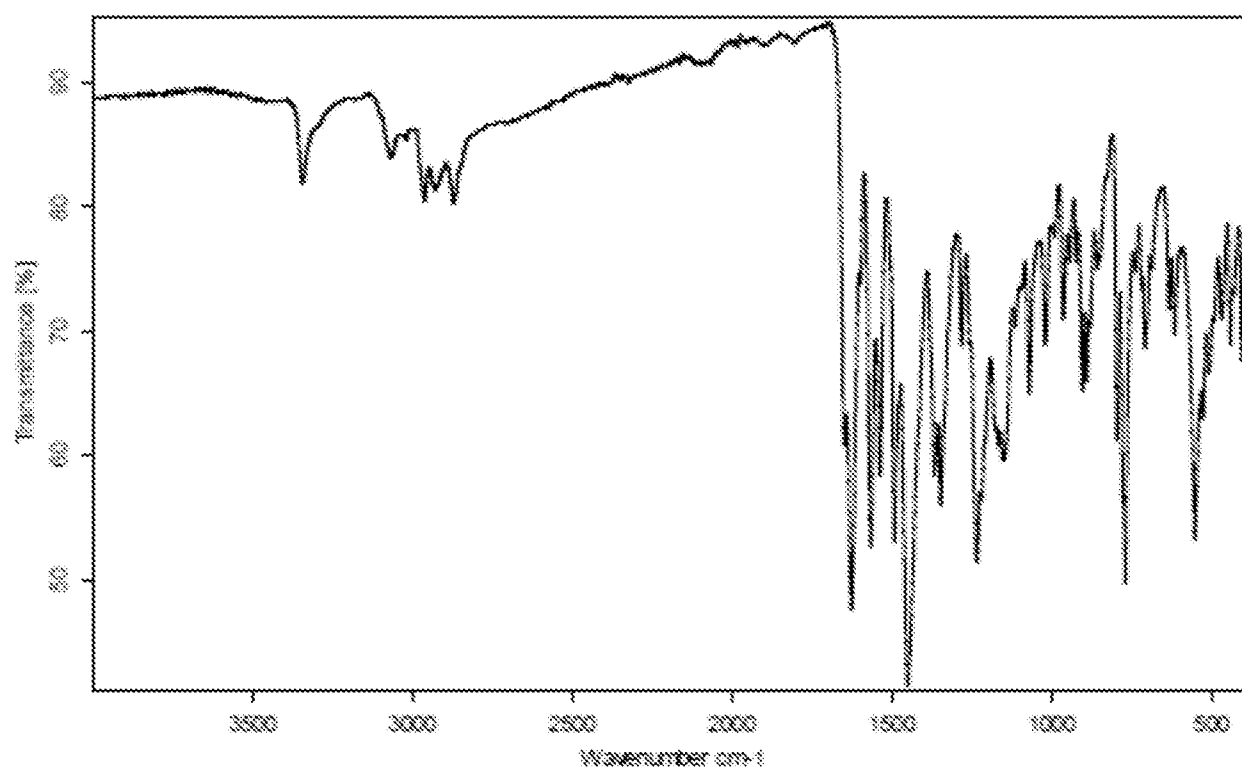


FIG. 37

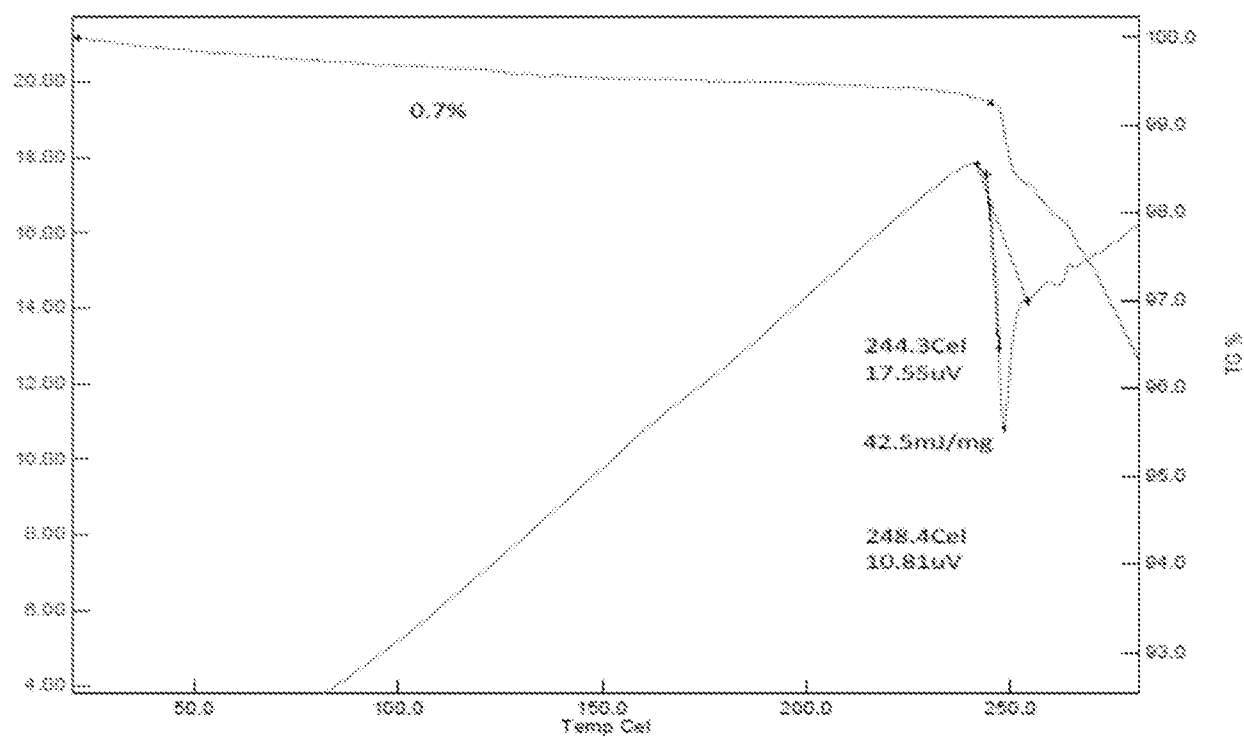


FIG. 38

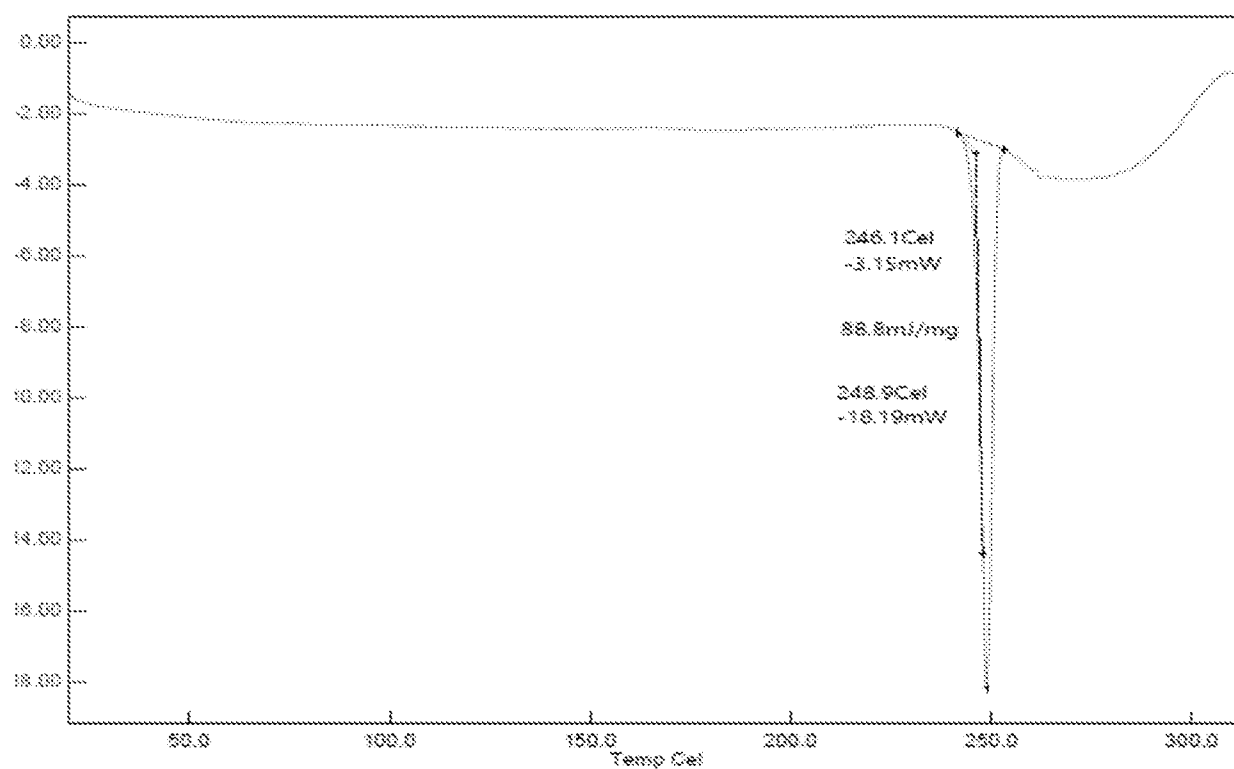


FIG. 39

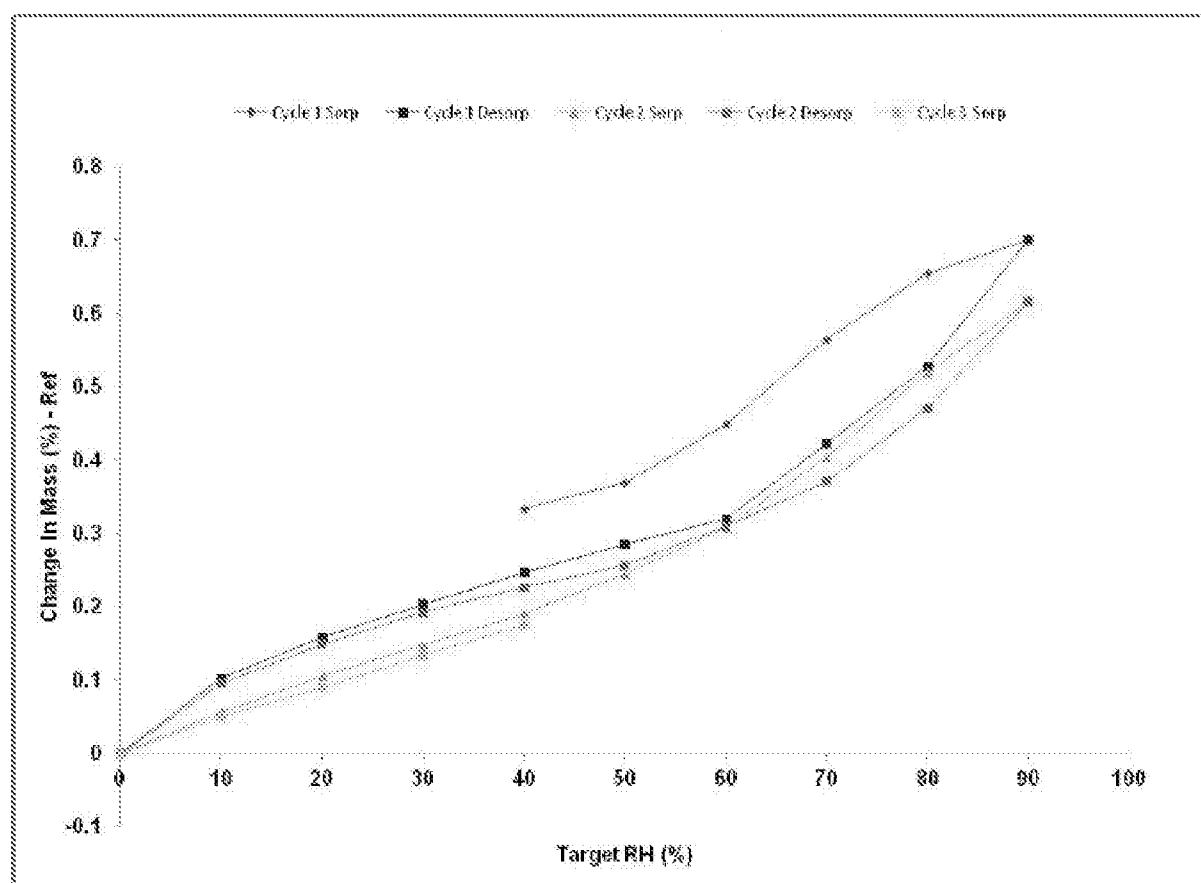


FIG. 40

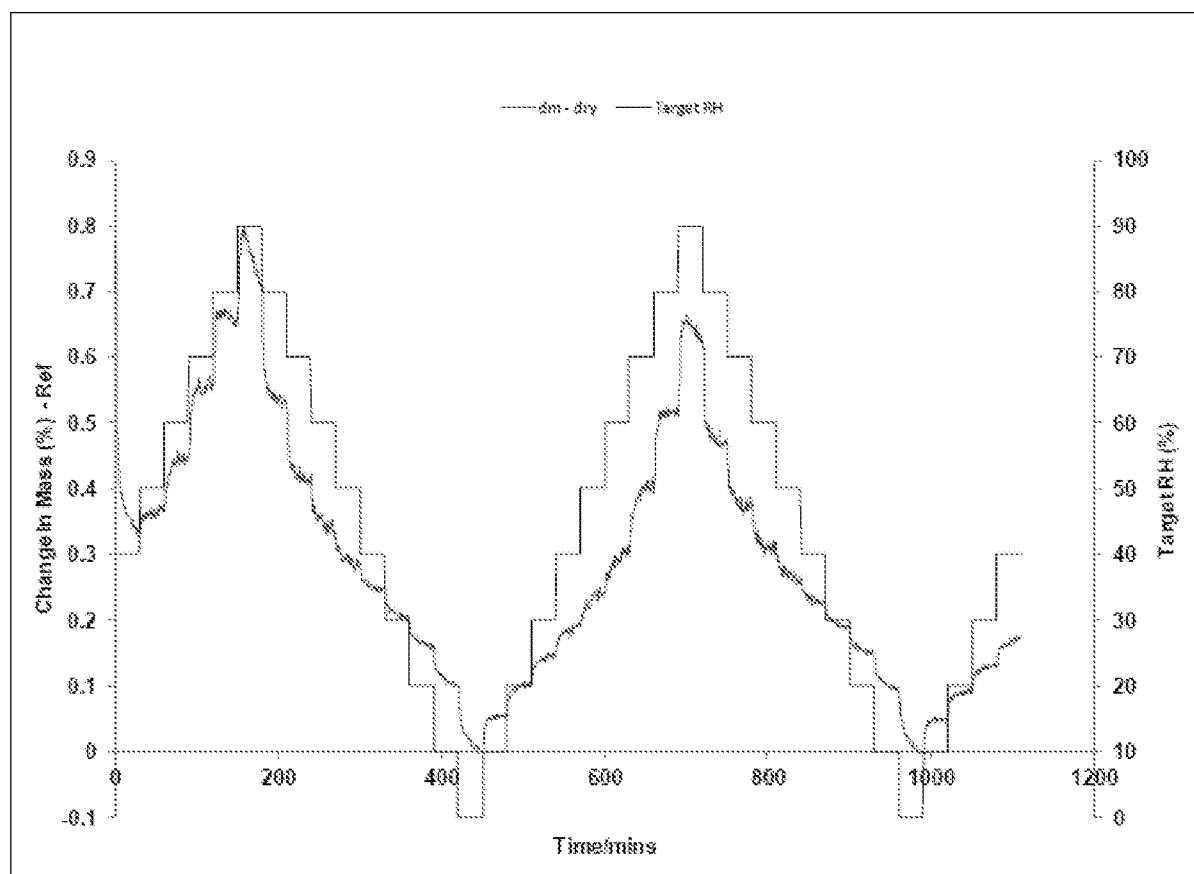


FIG. 41

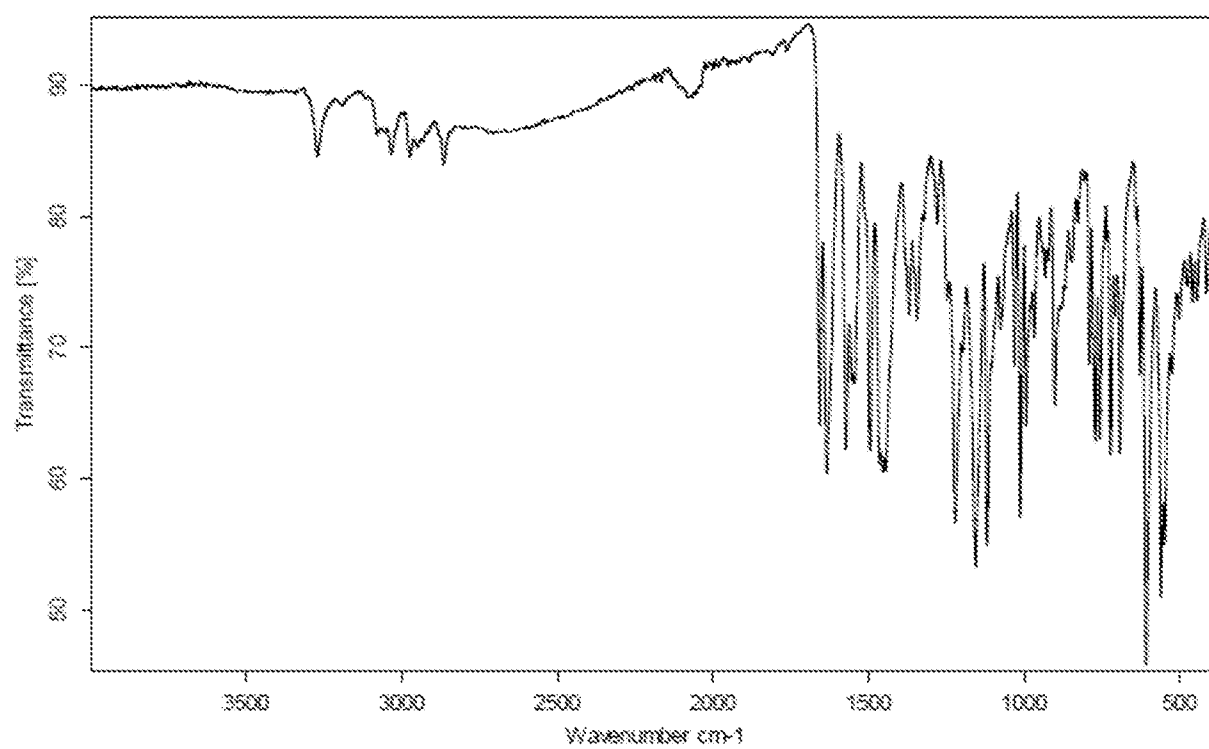


FIG. 42

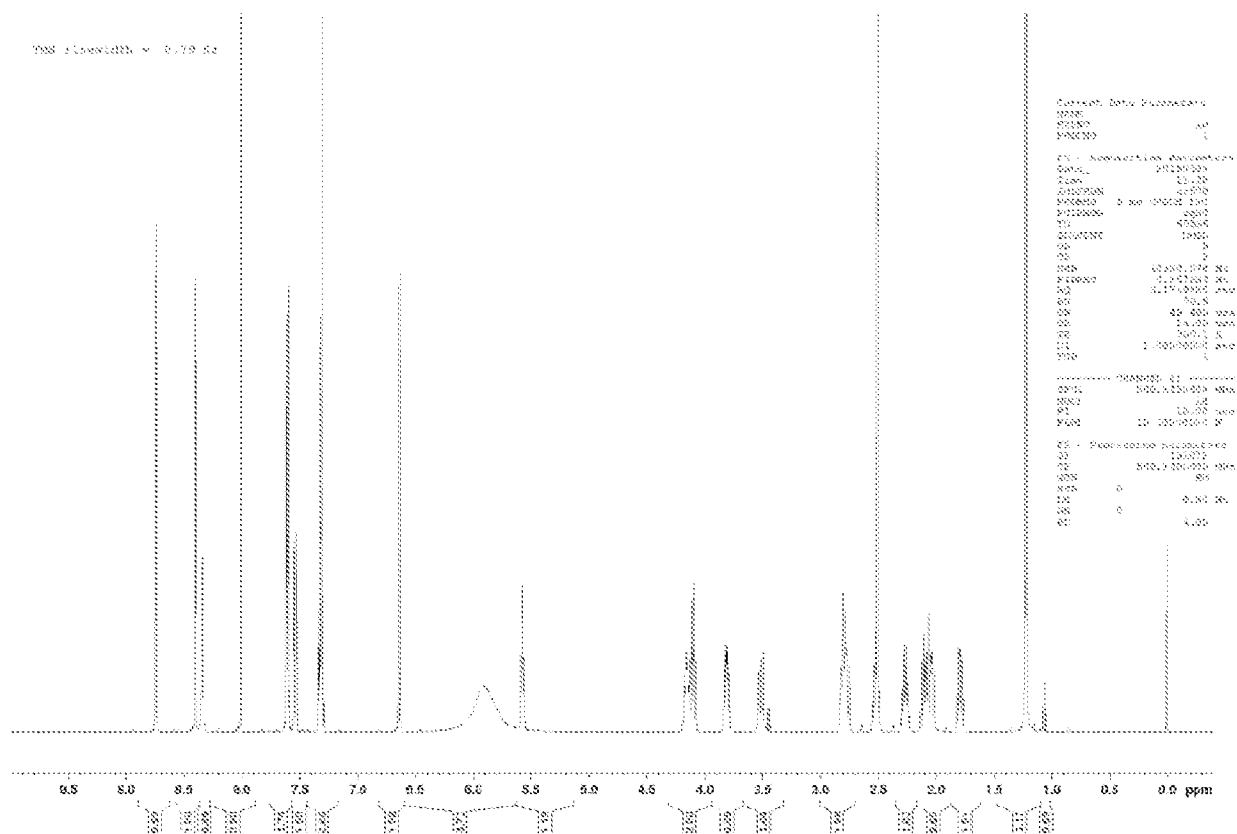


FIG. 43

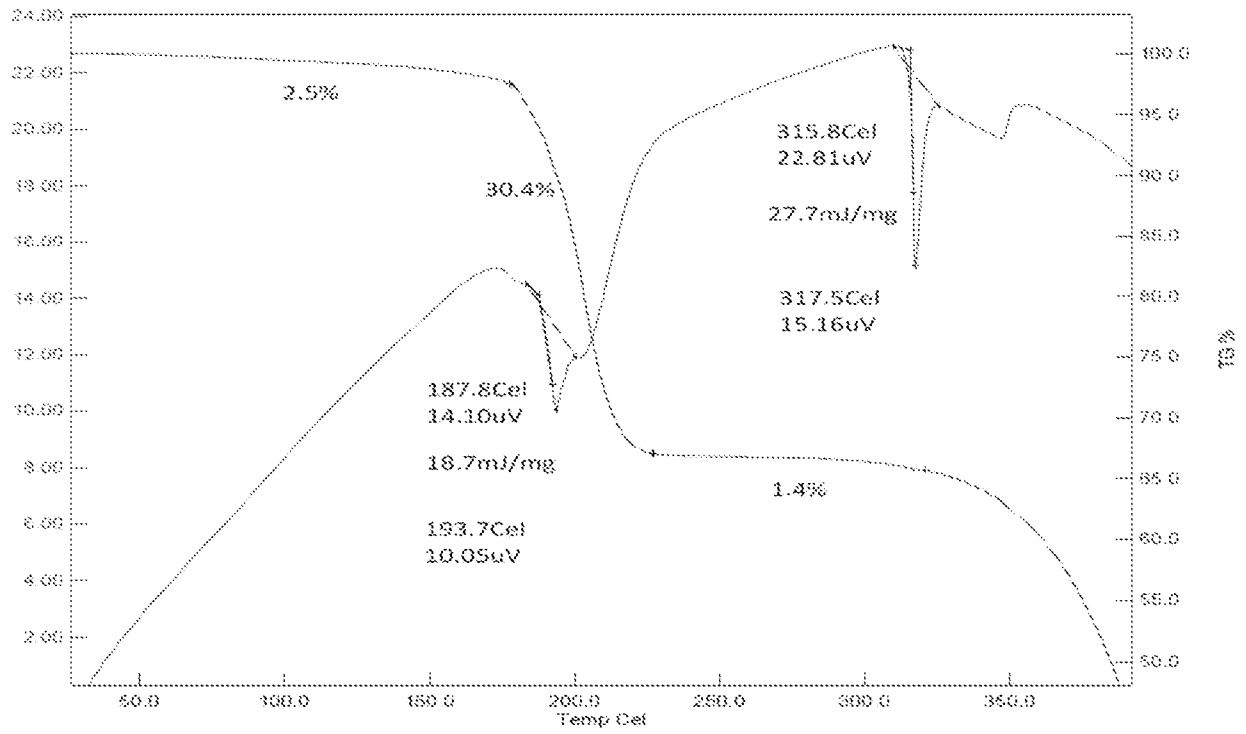


FIG. 44

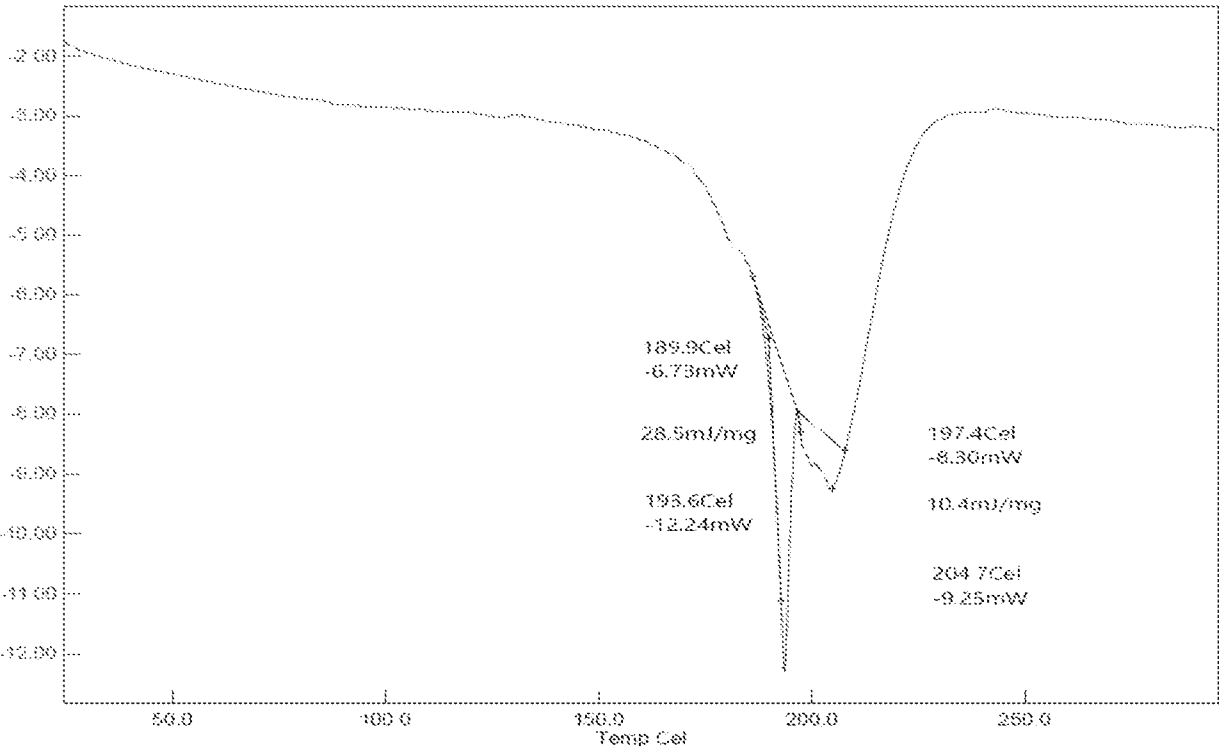


FIG. 45

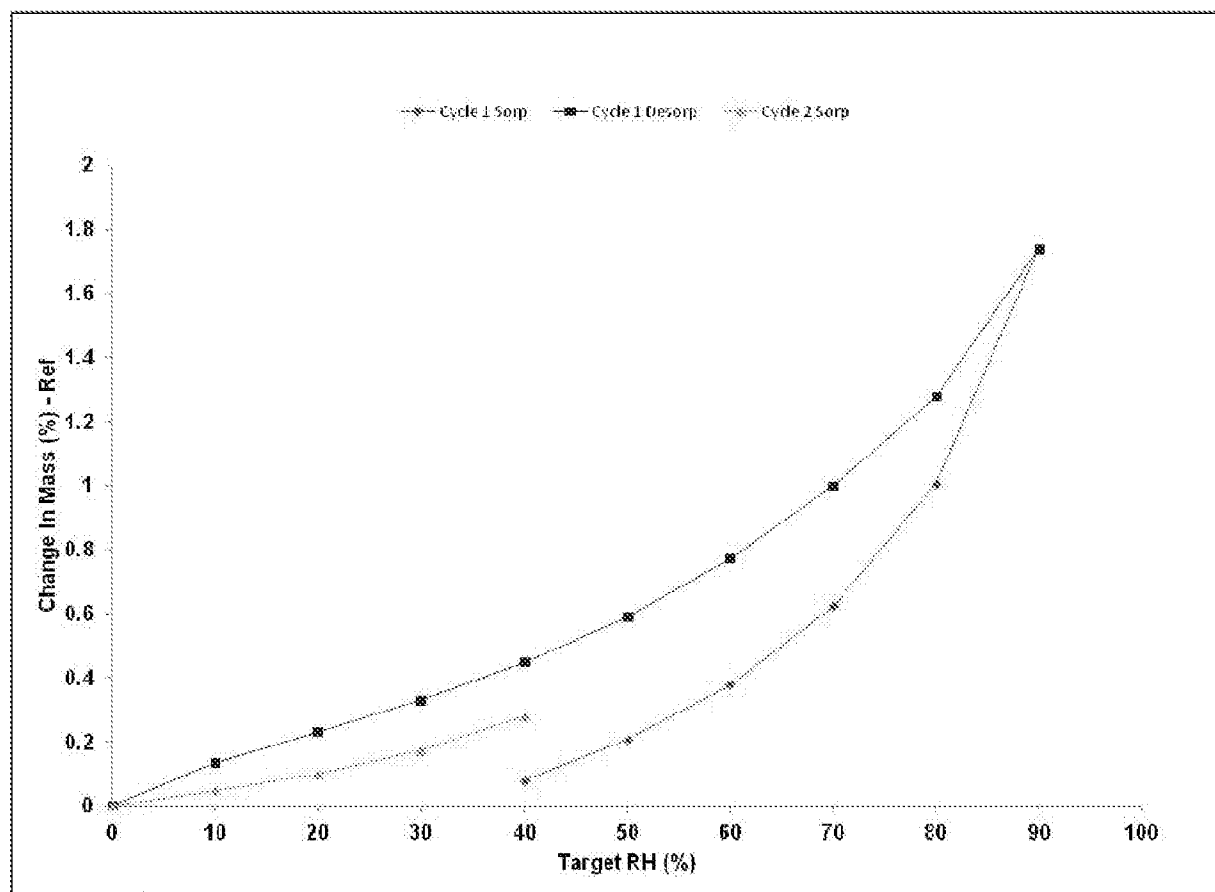


FIG. 46

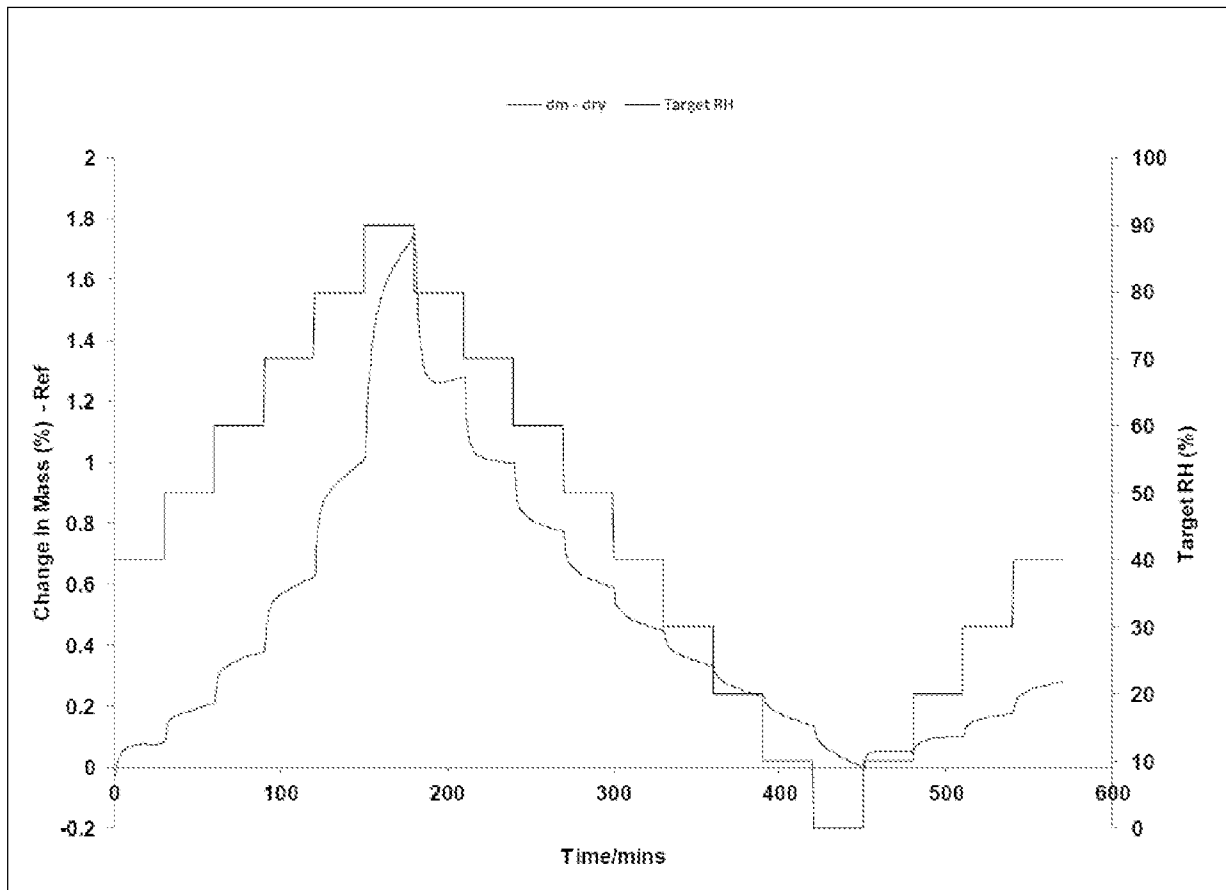


FIG. 47

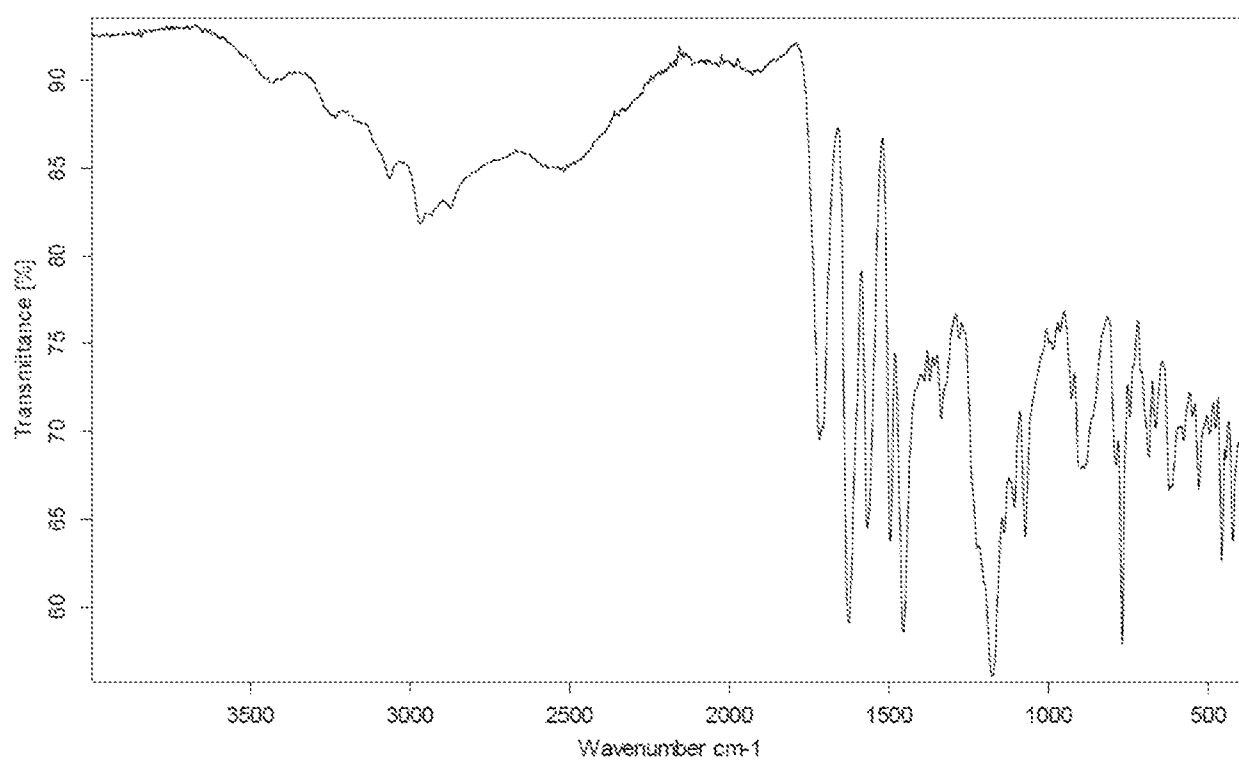


FIG. 48

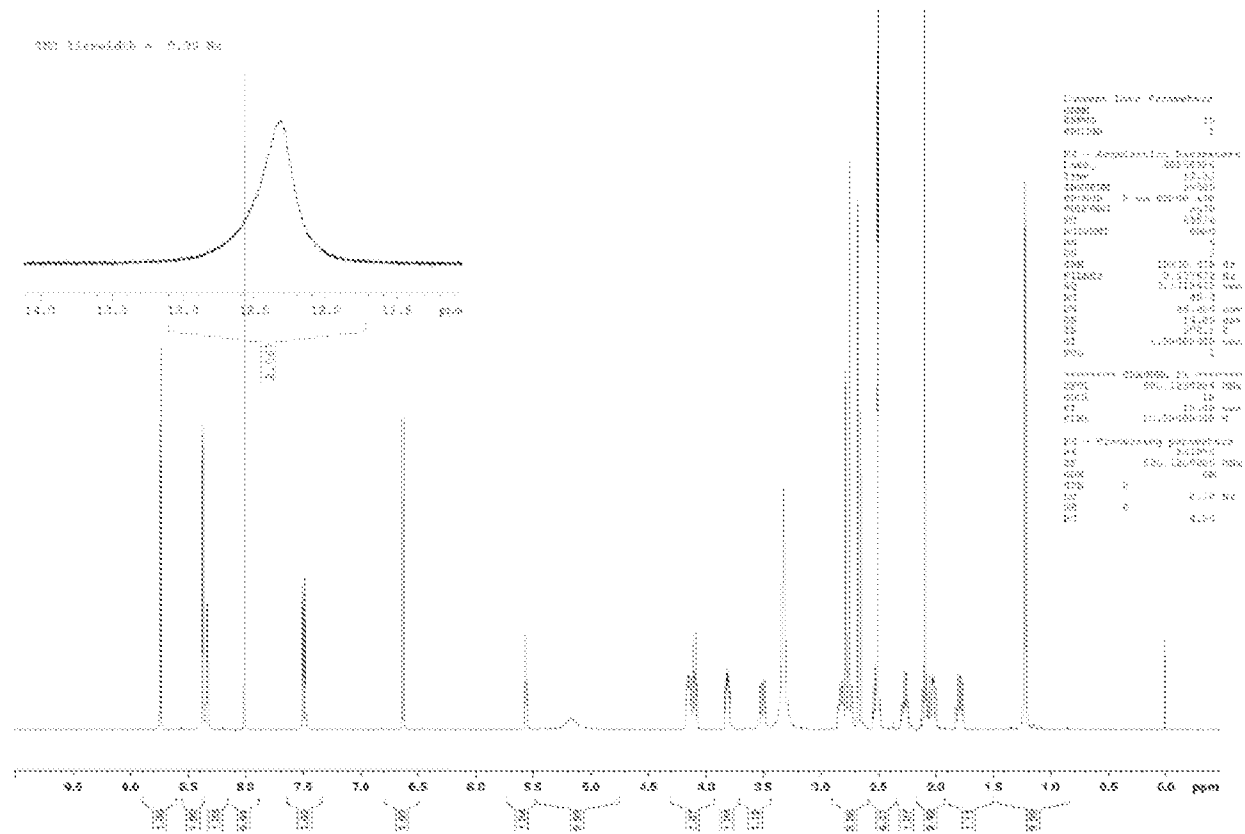


FIG. 49

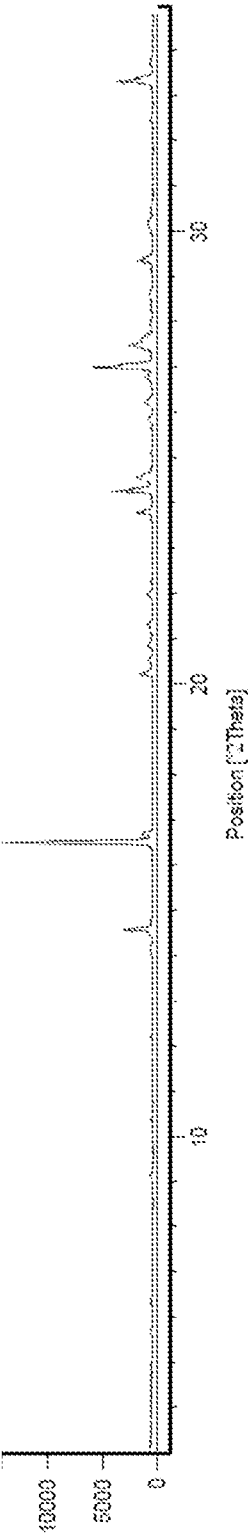


FIG. 50

Met Leu Arg Gly Gly Arg Arg Gly Gln Leu Gly Trp His Ser Trp Ala
Ala Gly Pro Gly Ser Leu Leu Ala Trp Leu Ile Leu Ala Ser Ala Gly
Ala Ala Pro Cys Pro Asp Ala Cys Cys Pro His Gly Ser Ser Gly Leu
Arg Cys Thr Arg Asp Gly Ala Leu Asp Ser Leu His His Leu Pro Gly
Ala Glu Asn Leu Thr Glu Leu Tyr Ile Glu Asn Gln Gln His Leu Gln
His Leu Glu Leu Arg Asp Leu Arg Gly Leu Gly Glu Leu Arg Asn Leu
Thr Ile Val Lys Ser Gly Leu Arg Phe Val Ala Pro Asp Ala Phe His
Phe Thr Pro Arg Leu Ser Arg Leu Asn Leu Ser Phe Asn Ala Leu Glu
Ser Leu Ser Trp Lys Thr Val Gln Gly Leu Ser Leu Gln Glu Leu Val
Leu Ser Gly Asn Pro Leu His Cys Ser Cys Ala Leu Arg Trp Leu Gln
Arg Trp Glu Glu Glu Gly Leu Gly Gly Val Pro Glu Gln Lys Leu Gln
Cys His Gly Gln Gly Pro Leu Ala His Met Pro Asn Ala Ser Cys Gly
Val Pro Thr Leu Lys Val Gln Val Pro Asn Ala Ser Val Asp Val Gly
Asp Asp Val Leu Leu Arg Cys Gln Val Glu Gly Arg Gly Leu Glu Gln
Ala Gly Trp Ile Leu Thr Glu Leu Glu Gln Ser Ala Thr Val Met Lys
Ser Gly Gly Leu Pro Ser Leu Gly Leu Thr Leu Ala Asn Val Thr Ser
Asp Leu Asn Arg Lys Asn Val Thr Cys Trp Ala Glu Asn Asp Val Gly
Arg Ala Glu Val Ser Val Gln Val Asn Val Ser Phe Pro Ala Ser Val
Gln Leu His Thr Ala Val Glu Met His His Trp Cys Ile Pro Phe Ser
Val Asp Gly Gln Pro Ala Pro Ser Leu Arg Trp Leu Phe Asn Gly Ser
Val Leu Asn Glu Thr Ser Phe Ile Phe Thr Glu Phe Leu Glu Pro Ala
Ala Asn Glu Thr Val Arg His Gly Cys Leu Arg Leu Asn Gln Pro Thr
His Val Asn Asn Gly Asn Tyr Thr Leu Leu Ala Ala Asn Pro Phe Gly
Gln Ala Ser Ala Ser Ile Met Ala Ala Phe Met Asp Asn Pro Phe Glu
Phe Asn Pro Glu Asp Pro Ile Pro Val Ser Phe Ser Pro Val Asp Thr

FIG. 50 (cont'd)

Asn Ser Thr Ser Gly Asp Pro Val Glu Lys Lys Asp Glu Thr Pro Phe
Gly Val Ser Val Ala Val Gly Leu Ala Val Phe Ala Cys Leu Phe Leu
Ser Thr Leu Leu Leu Val Leu Asn Lys Cys Gly Arg Arg Asn Lys Phe
Gly Ile Asn Arg Pro Ala Val Leu Ala Pro Glu Asp Gly Leu Ala Met
Ser Leu His Phe Met Thr Leu Gly Gly Ser Ser Leu Ser Pro Thr Glu
Gly Lys Gly Ser Gly Leu Gln Gly His Ile Ile Glu Asn Pro Gln Tyr
Phe Ser Asp Ala Cys Val His His Ile Lys Arg Arg Asp Ile Val Leu
Lys Trp Glu Leu Gly Glu Gly Ala Phe Gly Lys Val Phe Leu Ala Glu
Cys His Asn Leu Leu Pro Glu Gln Asp Lys Met Leu Val Ala Val Lys
Ala Leu Lys Glu Ala Ser Glu Ser Ala Arg Gln Asp Phe Gln Arg Glu
Ala Glu Leu Leu Thr Met Leu Gln His Gln His Ile Val Arg Phe Phe
Gly Val Cys Thr Glu Gly Arg Pro Leu Leu Met Val Phe Glu Tyr Met
Arg His Gly Asp Leu Asn Arg Phe Leu Arg Ser His Gly Pro Asp Ala
Lys Leu Leu Ala Gly Gly Glu Asp Val Ala Pro Gly Pro Leu Gly Leu
Gly Gln Leu Leu Ala Val Ala Ser Gln Val Ala Ala Gly Met Val Tyr
Leu Ala Gly Leu His Phe Val His Arg Asp Leu Ala Thr Arg Asn Cys
Leu Val Gly Gln Gly Leu Val Val Lys Ile Gly Asp Phe Gly Met Ser
Arg Asp Ile Tyr Ser Thr Asp Tyr Tyr Arg Val Gly Gly Arg Thr Met
Leu Pro Ile Arg Trp Met Pro Pro Glu Ser Ile Leu Tyr Arg Lys Phe
Thr Thr Glu Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp Glu Ile
Phe Thr Tyr Gly Lys Gln Pro Trp Tyr Gln Leu Ser Asn Thr Glu Ala
Ile Asp Cys Ile Thr Gln Gly Arg Glu Leu Glu Arg Pro Arg Ala Cys
Pro Pro Glu Val Tyr Ala Ile Met Arg Gly Cys Trp Gln Arg Glu Pro
Gln Gln Arg His Ser Ile Lys Asp Val His Ala Arg Leu Gln Ala Leu
Ala Gln Ala Pro Pro Val Tyr Leu Asp Val Leu Gly

FIG. 51

Met Ser Ser Trp Ile Arg Trp His Gly Pro Ala Met Ala Arg Leu Trp
Gly Phe Cys Trp Leu Val Val Gly Phe Trp Arg Ala Ala Phe Ala Cys
Pro Thr Ser Cys Lys Cys Ser Ala Ser Arg Ile Trp Cys Ser Asp Pro
Ser Pro Gly Ile Val Ala Phe Pro Arg Leu Glu Pro Asn Ser Val Asp
Pro Glu Asn Ile Thr Glu Ile Phe Ile Ala Asn Gln Lys Arg Leu Glu
Ile Ile Asn Glu Asp Asp Val Glu Ala Tyr Val Gly Leu Arg Asn Leu
Thr Ile Val Asp Ser Gly Leu Lys Phe Val Ala His Lys Ala Phe Leu
Lys Asn Ser Asn Leu Gln His Ile Asn Phe Thr Arg Asn Lys Leu Thr
Ser Leu Ser Arg Lys His Phe Arg His Leu Asp Leu Ser Glu Leu Ile
Leu Val Gly Asn Pro Phe Thr Cys Ser Cys Asp Ile Met Trp Ile Lys
Thr Leu Gln Glu Ala Lys Ser Ser Pro Asp Thr Gln Asp Leu Tyr Cys
Leu Asn Glu Ser Ser Lys Asn Ile Pro Leu Ala Asn Leu Gln Ile Pro
Asn Cys Gly Leu Pro Ser Ala Asn Leu Ala Ala Pro Asn Leu Thr Val
Glu Glu Gly Lys Ser Ile Thr Leu Ser Cys Ser Val Ala Gly Asp Pro
Val Pro Asn Met Tyr Trp Asp Val Gly Asn Leu Val Ser Lys His Met
Asn Glu Thr Ser His Thr Gln Gly Ser Leu Arg Ile Thr Asn Ile Ser
Ser Asp Asp Ser Gly Lys Gln Ile Ser Cys Val Ala Glu Asn Leu Val
Gly Glu Asp Gln Asp Ser Val Asn Leu Thr Val His Phe Ala Pro Thr
Ile Thr Phe Leu Glu Ser Pro Thr Ser Asp His His Trp Cys Ile Pro
Phe Thr Val Lys Gly Asn Pro Lys Pro Ala Leu Gln Trp Phe Tyr Asn
Gly Ala Ile Leu Asn Glu Ser Lys Tyr Ile Cys Thr Lys Ile His Val
Thr Asn His Thr Glu Tyr His Gly Cys Leu Gln Leu Asp Asn Pro Thr
His Met Asn Asn Gly Asp Tyr Thr Leu Ile Ala Lys Asn Glu Tyr Gly
Lys Asp Glu Lys Gln Ile Ser Ala His Phe Met Gly Trp Pro Gly Ile
Asp Asp Gly Ala Asn Pro Asn Tyr Pro Asp Val Ile Tyr Glu Asp Tyr
Gly Thr Ala Ala Asn Asp Ile Gly Asp Thr Thr Asn Arg Ser Asn Glu
Ile Pro Ser Thr Asp Val Thr Asp Lys Thr Gly Arg Glu His Leu Ser
Val Tyr Ala Val Val Val Ile Ala Ser Val Val Gly Phe Cys Leu Leu

FIG. 51 (con'td)

Val Met Leu Phe Leu Leu Lys Leu Ala Arg His Ser Lys Phe Gly Met
Lys Gly Pro Ala Ser Val Ile Ser Asn Asp Asp Asp Ser Ala Ser Pro
Leu His His Ile Ser Asn Gly Ser Asn Thr Pro Ser Ser Ser Glu Gly
Gly Pro Asp Ala Val Ile Ile Gly Met Thr Lys Ile Pro Val Ile Glu
Asn Pro Gln Tyr Phe Gly Ile Thr Asn Ser Gln Leu Lys Pro Asp Thr
Phe Val Gln His Ile Lys Arg His Asn Ile Val Leu Lys Arg Glu Leu
Gly Glu Gly Ala Phe Gly Lys Val Phe Leu Ala Glu Cys Tyr Asn Leu
Cys Pro Glu Gln Asp Lys Ile Leu Val Ala Val Lys Thr Leu Lys Asp
Ala Ser Asp Asn Ala Arg Lys Asp Phe His Arg Glu Ala Glu Leu Leu
Thr Asn Leu Gln His Glu His Ile Val Lys Phe Tyr Gly Val Cys Val
Glu Gly Asp Pro Leu Ile Met Val Phe Glu Tyr Met Lys His Gly Asp
Leu Asn Lys Phe Leu Arg Ala His Gly Pro Asp Ala Val Leu Met Ala
Glu Gly Asn Pro Pro Thr Glu Leu Thr Gln Ser Gln Met Leu His Ile
Ala Gln Gln Ile Ala Ala Gly Met Val Tyr Leu Ala Ser Gln His Phe
Val His Arg Asp Leu Ala Thr Arg Asn Cys Leu Val Gly Glu Asn Leu
Leu Val Lys Ile Gly Asp Phe Gly Met Ser Arg Asp Val Tyr Ser Thr
Asp Tyr Tyr Arg Val Gly Gly His Thr Met Leu Pro Ile Arg Trp Met
Pro Pro Glu Ser Ile Met Tyr Arg Lys Phe Thr Thr Glu Ser Asp Val
Trp Ser Leu Gly Val Val Leu Trp Glu Ile Phe Thr Tyr Gly Lys Gln
Pro Trp Tyr Gln Leu Ser Asn Asn Glu Val Ile Glu Cys Ile Thr Gln
Gly Arg Val Leu Gln Arg Pro Arg Thr Cys Pro Gln Glu Val Tyr Glu
Leu Met Leu Gly Cys Trp Gln Arg Glu Pro His Met Arg Lys Asn Ile
Lys Gly Ile His Thr Leu Leu Gln Asn Leu Ala Lys Ala Ser Pro Val
Tyr Leu Asp Ile Leu Gly

FIG. 52

Met Asp Val Ser Leu Cys Pro Ala Lys Cys Ser Phe Trp Arg Ile Phe
Leu Leu Gly Ser Val Trp Leu Asp Tyr Val Gly Ser Val Leu Ala Cys
Pro Ala Asn Cys Val Cys Ser Lys Thr Glu Ile Asn Cys Arg Arg Pro
Asp Asp Gly Asn Leu Phe Pro Leu Leu Glu Gly Gln Asp Ser Gly Asn
Ser Asn Gly Asn Ala Ser Ile Asn Ile Thr Asp Ile Ser Arg Asn Ile
Thr Ser Ile His Ile Glu Asn Trp Arg Ser Leu His Thr Leu Asn Ala
Val Asp Met Glu Leu Tyr Thr Gly Leu Gln Lys Leu Thr Ile Lys Asn
Ser Gly Leu Arg Ser Ile Gln Pro Arg Ala Phe Ala Lys Asn Pro His
Leu Arg Tyr Ile Asn Leu Ser Ser Asn Arg Leu Thr Thr Leu Ser Trp
Gln Leu Phe Gln Thr Leu Ser Leu Arg Glu Leu Gln Leu Glu Gln Asn
Phe Phe Asn Cys Ser Cys Asp Ile Arg Trp Met Gln Leu Trp Gln Glu
Gln Gly Glu Ala Lys Leu Asn Ser Gln Asn Leu Tyr Cys Ile Asn Ala
Asp Gly Ser Gln Leu Pro Leu Phe Arg Met Asn Ile Ser Gln Cys Asp
Leu Pro Glu Ile Ser Val Ser His Val Asn Leu Thr Val Arg Glu Gly
Asp Asn Ala Val Ile Thr Cys Asn Gly Ser Gly Ser Pro Leu Pro Asp
Val Asp Trp Ile Val Thr Gly Leu Gln Ser Ile Asn Thr His Gln Thr
Asn Leu Asn Trp Thr Asn Val His Ala Ile Asn Leu Thr Leu Val Asn
Val Thr Ser Glu Asp Asn Gly Phe Thr Leu Thr Cys Ile Ala Glu Asn
Val Val Gly Met Ser Asn Ala Ser Val Ala Leu Thr Val Tyr Tyr Pro
Pro Arg Val Val Ser Leu Glu Glu Pro Glu Leu Arg Leu Glu His Cys
Ile Glu Phe Val Val Arg Gly Asn Pro Pro Pro Thr Leu His Trp Leu
His Asn Gly Gln Pro Leu Arg Glu Ser Lys Ile Ile His Val Glu Tyr
Tyr Gln Glu Gly Glu Ile Ser Glu Gly Cys Leu Leu Phe Asn Lys Pro
Thr His Tyr Asn Asn Gly Asn Tyr Thr Leu Ile Ala Lys Asn Pro Leu
Gly Thr Ala Asn Gln Thr Ile Asn Gly His Phe Leu Lys Glu Pro Phe
Pro Glu Ser Thr Asp Asn Phe Ile Leu Phe Asp Glu Val Ser Pro Thr
Pro Pro Ile Thr Val Thr His Lys Pro Glu Glu Asp Thr Phe Gly Val

FIG. 52 (cont'd)

Ser Ile Ala Val Gly Leu Ala Ala Phe Ala Cys Val Leu Leu Val Val
Leu Phe Val Met Ile Asn Lys Tyr Gly Arg Arg Ser Lys Phe Gly Met
Lys Gly Pro Val Ala Val Ile Ser Gly Glu Glu Asp Ser Ala Ser Pro
Leu His His Ile Asn His Gly Ile Thr Thr Pro Ser Ser Leu Asp Ala
Gly Pro Asp Thr Val Val Ile Gly Met Thr Arg Ile Pro Val Ile Glu
Asn Pro Gln Tyr Phe Arg Gln Gly His Asn Cys His Lys Pro Asp Thr
Tyr Val Gln His Ile Lys Arg Arg Asp Ile Val Leu Lys Arg Glu Leu
Gly Glu Gly Ala Phe Gly Lys Val Phe Leu Ala Glu Cys Tyr Asn Leu
Ser Pro Thr Lys Asp Lys Met Leu Val Ala Val Lys Ala Leu Lys Asp
Pro Thr Leu Ala Ala Arg Lys Asp Phe Gln Arg Glu Ala Glu Leu Leu
Thr Asn Leu Gln His Glu His Ile Val Lys Phe Tyr Gly Val Cys Gly
Asp Gly Asp Pro Leu Ile Met Val Phe Glu Tyr Met Lys His Gly Asp
Leu Asn Lys Phe Leu Arg Ala His Gly Pro Asp Ala Met Ile Leu Val
Asp Gly Gln Pro Arg Gln Ala Lys Gly Glu Leu Gly Leu Ser Gln Met
Leu His Ile Ala Ser Gln Ile Ala Ser Gly Met Val Tyr Leu Ala Ser
Gln His Phe Val His Arg Asp Leu Ala Thr Arg Asn Cys Leu Val Gly
Ala Asn Leu Leu Val Lys Ile Gly Asp Phe Gly Met Ser Arg Asp Val
Tyr Ser Thr Asp Tyr Tyr Arg Leu Phe Asn Pro Ser Gly Asn Asp Phe
Cys Ile Trp Cys Glu Val Gly Gly His Thr Met Leu Pro Ile Arg Trp
Met Pro Pro Glu Ser Ile Met Tyr Arg Lys Phe Thr Thr Glu Ser Asp
Val Trp Ser Phe Gly Val Ile Leu Trp Glu Ile Phe Thr Tyr Gly Lys
Gln Pro Trp Phe Gln Leu Ser Asn Thr Glu Val Ile Glu Cys Ile Thr
Gln Gly Arg Val Leu Glu Arg Pro Arg Val Cys Pro Lys Glu Val Tyr
Asp Val Met Leu Gly Cys Trp Gln Arg Glu Pro Gln Gln Arg Leu Asn
Ile Lys Glu Ile Tyr Lys Ile Leu His Ala Leu Gly Lys Ala Thr Pro
Ile Tyr Leu Asp Ile Leu Gly

SEQ.txt
SEQUENCE LISTING

<110> Array BioPharma, Inc.

<120> PROCESS FOR THE PREPARATION OF PYRAZOLO[1,5-a]PYRIMIDINES AND
SALTS THEREOF

<130> 40449-0075W01

<150> PCT/US2016/058951
<151> 2016-10-26

<150> 62/524,801
<151> 2017-06-26

<160> 3

<170> PatentIn version 3.5

<210> 1
<211> 796
<212> PRT
<213> Homo sapiens

<400> 1

Met Leu Arg Gly Gly Arg Arg Gly Gln Leu Gly Trp His Ser Trp Ala
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Ala Gly Pro Gly Ser Leu Leu Ala Trp Leu Ile Leu Ala Ser Ala Gly
20 25 30

Ala Ala Pro Cys Pro Asp Ala Cys Cys Pro His Gly Ser Ser Gly Leu
35 40 45

Arg Cys Thr Arg Asp Gly Ala Leu Asp Ser Leu His His Leu Pro Gly
50 55 60

Ala Glu Asn Leu Thr Glu Leu Tyr Ile Glu Asn Gln Gln His Leu Gln
65 70 75 80

His Leu Glu Leu Arg Asp Leu Arg Gly Leu Gly Glu Leu Arg Asn Leu
85 90 95

Thr Ile Val Lys Ser Gly Leu Arg Phe Val Ala Pro Asp Ala Phe His
100 105 110

SEQ.txt

Phe Thr Pro Arg Leu Ser Arg Leu Asn Leu Ser Phe Asn Ala Leu Glu
115 120 125

Ser Leu Ser Trp Lys Thr Val Gln Gly Leu Ser Leu Gln Glu Leu Val
130 135 140

Leu Ser Gly Asn Pro Leu His Cys Ser Cys Ala Leu Arg Trp Leu Gln
145 150 155 160

Arg Trp Glu Glu Glu Gly Leu Gly Gly Val Pro Glu Gln Lys Leu Gln
165 170 175

Cys His Gly Gln Gly Pro Leu Ala His Met Pro Asn Ala Ser Cys Gly
180 185 190

Val Pro Thr Leu Lys Val Gln Val Pro Asn Ala Ser Val Asp Val Gly
195 200 205

Asp Asp Val Leu Leu Arg Cys Gln Val Glu Gly Arg Gly Leu Glu Gln
210 215 220

Ala Gly Trp Ile Leu Thr Glu Leu Glu Gln Ser Ala Thr Val Met Lys
225 230 235 240

Ser Gly Gly Leu Pro Ser Leu Gly Leu Thr Leu Ala Asn Val Thr Ser
245 250 255

Asp Leu Asn Arg Lys Asn Val Thr Cys Trp Ala Glu Asn Asp Val Gly
260 265 270

Arg Ala Glu Val Ser Val Gln Val Asn Val Ser Phe Pro Ala Ser Val
275 280 285

Gln Leu His Thr Ala Val Glu Met His His Trp Cys Ile Pro Phe Ser
290 295 300

Val Asp Gly Gln Pro Ala Pro Ser Leu Arg Trp Leu Phe Asn Gly Ser
305 310 315 320

SEQ.txt

Val Leu Asn Glu Thr Ser Phe Ile Phe Thr Glu Phe Leu Glu Pro Ala
325 330 335

Ala Asn Glu Thr Val Arg His Gly Cys Leu Arg Leu Asn Gln Pro Thr
340 345 350

His Val Asn Asn Gly Asn Tyr Thr Leu Leu Ala Ala Asn Pro Phe Gly
355 360 365

Gln Ala Ser Ala Ser Ile Met Ala Ala Phe Met Asp Asn Pro Phe Glu
370 375 380

Phe Asn Pro Glu Asp Pro Ile Pro Val Ser Phe Ser Pro Val Asp Thr
385 390 395 400

Asn Ser Thr Ser Gly Asp Pro Val Glu Lys Lys Asp Glu Thr Pro Phe
405 410 415

Gly Val Ser Val Ala Val Gly Leu Ala Val Phe Ala Cys Leu Phe Leu
420 425 430

Ser Thr Leu Leu Leu Val Leu Asn Lys Cys Gly Arg Arg Asn Lys Phe
435 440 445

Gly Ile Asn Arg Pro Ala Val Leu Ala Pro Glu Asp Gly Leu Ala Met
450 455 460

Ser Leu His Phe Met Thr Leu Gly Gly Ser Ser Leu Ser Pro Thr Glu
465 470 475 480

Gly Lys Gly Ser Gly Leu Gln Gly His Ile Ile Glu Asn Pro Gln Tyr
485 490 495

Phe Ser Asp Ala Cys Val His His Ile Lys Arg Arg Asp Ile Val Leu
500 505 510

Lys Trp Glu Leu Gly Glu Gly Ala Phe Gly Lys Val Phe Leu Ala Glu
515 520 525

SEQ.txt

Cys His Asn Leu Leu Pro Glu Gln Asp Lys Met Leu Val Ala Val Lys
530 535 540

Ala Leu Lys Glu Ala Ser Glu Ser Ala Arg Gln Asp Phe Gln Arg Glu
545 550 555 560

Ala Glu Leu Leu Thr Met Leu Gln His Gln His Ile Val Arg Phe Phe
565 570 575

Gly Val Cys Thr Glu Gly Arg Pro Leu Leu Met Val Phe Glu Tyr Met
580 585 590

Arg His Gly Asp Leu Asn Arg Phe Leu Arg Ser His Gly Pro Asp Ala
595 600 605

Lys Leu Leu Ala Gly Gly Glu Asp Val Ala Pro Gly Pro Leu Gly Leu
610 615 620

Gly Gln Leu Leu Ala Val Ala Ser Gln Val Ala Ala Gly Met Val Tyr
625 630 635 640

Leu Ala Gly Leu His Phe Val His Arg Asp Leu Ala Thr Arg Asn Cys
645 650 655

Leu Val Gly Gln Gly Leu Val Val Lys Ile Gly Asp Phe Gly Met Ser
660 665 670

Arg Asp Ile Tyr Ser Thr Asp Tyr Tyr Arg Val Gly Gly Arg Thr Met
675 680 685

Leu Pro Ile Arg Trp Met Pro Pro Glu Ser Ile Leu Tyr Arg Lys Phe
690 695 700

Thr Thr Glu Ser Asp Val Trp Ser Phe Gly Val Val Leu Trp Glu Ile
705 710 715 720

Phe Thr Tyr Gly Lys Gln Pro Trp Tyr Gln Leu Ser Asn Thr Glu Ala
725 730 735

SEQ.txt

Ile Asp Cys Ile Thr Gln Gly Arg Glu Leu Glu Arg Pro Arg Ala Cys
740 745 750

Pro Pro Glu Val Tyr Ala Ile Met Arg Gly Cys Trp Gln Arg Glu Pro
755 760 765

Gln Gln Arg His Ser Ile Lys Asp Val His Ala Arg Leu Gln Ala Leu
770 775 780

Ala Gln Ala Pro Pro Val Tyr Leu Asp Val Leu Gly
785 790 795

<210> 2
<211> 822
<212> PRT
<213> Homo sapiens

<400> 2

Met Ser Ser Trp Ile Arg Trp His Gly Pro Ala Met Ala Arg Leu Trp
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Gly Phe Cys Trp Leu Val Val Gly Phe Trp Arg Ala Ala Phe Ala Cys
20 25 30

Pro Thr Ser Cys Lys Cys Ser Ala Ser Arg Ile Trp Cys Ser Asp Pro
35 40 45

Ser Pro Gly Ile Val Ala Phe Pro Arg Leu Glu Pro Asn Ser Val Asp
50 55 60

Pro Glu Asn Ile Thr Glu Ile Phe Ile Ala Asn Gln Lys Arg Leu Glu
65 70 75 80

Ile Ile Asn Glu Asp Asp Val Glu Ala Tyr Val Gly Leu Arg Asn Leu
85 90 95

Thr Ile Val Asp Ser Gly Leu Lys Phe Val Ala His Lys Ala Phe Leu
100 105 110

SEQ.txt

Lys Asn Ser Asn Leu Gln His Ile Asn Phe Thr Arg Asn Lys Leu Thr
115 120 125

Ser Leu Ser Arg Lys His Phe Arg His Leu Asp Leu Ser Glu Leu Ile
130 135 140

Leu Val Gly Asn Pro Phe Thr Cys Ser Cys Asp Ile Met Trp Ile Lys
145 150 155 160

Thr Leu Gln Glu Ala Lys Ser Ser Pro Asp Thr Gln Asp Leu Tyr Cys
165 170 175

Leu Asn Glu Ser Ser Lys Asn Ile Pro Leu Ala Asn Leu Gln Ile Pro
180 185 190

Asn Cys Gly Leu Pro Ser Ala Asn Leu Ala Ala Pro Asn Leu Thr Val
195 200 205

Glu Glu Gly Lys Ser Ile Thr Leu Ser Cys Ser Val Ala Gly Asp Pro
210 215 220

Val Pro Asn Met Tyr Trp Asp Val Gly Asn Leu Val Ser Lys His Met
225 230 235 240

Asn Glu Thr Ser His Thr Gln Gly Ser Leu Arg Ile Thr Asn Ile Ser
245 250 255

Ser Asp Asp Ser Gly Lys Gln Ile Ser Cys Val Ala Glu Asn Leu Val
260 265 270

Gly Glu Asp Gln Asp Ser Val Asn Leu Thr Val His Phe Ala Pro Thr
275 280 285

Ile Thr Phe Leu Glu Ser Pro Thr Ser Asp His His Trp Cys Ile Pro
290 295 300

Phe Thr Val Lys Gly Asn Pro Lys Pro Ala Leu Gln Trp Phe Tyr Asn
305 310 315 320

SEQ.txt

Gly Ala Ile Leu Asn Glu Ser Lys Tyr Ile Cys Thr Lys Ile His Val
325 330 335

Thr Asn His Thr Glu Tyr His Gly Cys Leu Gln Leu Asp Asn Pro Thr
340 345 350

His Met Asn Asn Gly Asp Tyr Thr Leu Ile Ala Lys Asn Glu Tyr Gly
355 360 365

Lys Asp Glu Lys Gln Ile Ser Ala His Phe Met Gly Trp Pro Gly Ile
370 375 380

Asp Asp Gly Ala Asn Pro Asn Tyr Pro Asp Val Ile Tyr Glu Asp Tyr
385 390 395 400

Gly Thr Ala Ala Asn Asp Ile Gly Asp Thr Thr Asn Arg Ser Asn Glu
405 410 415

Ile Pro Ser Thr Asp Val Thr Asp Lys Thr Gly Arg Glu His Leu Ser
420 425 430

Val Tyr Ala Val Val Val Ile Ala Ser Val Val Gly Phe Cys Leu Leu
435 440 445

Val Met Leu Phe Leu Leu Lys Leu Ala Arg His Ser Lys Phe Gly Met
450 455 460

Lys Gly Pro Ala Ser Val Ile Ser Asn Asp Asp Asp Ser Ala Ser Pro
465 470 475 480

Leu His His Ile Ser Asn Gly Ser Asn Thr Pro Ser Ser Ser Glu Gly
485 490 495

Gly Pro Asp Ala Val Ile Ile Gly Met Thr Lys Ile Pro Val Ile Glu
500 505 510

Asn Pro Gln Tyr Phe Gly Ile Thr Asn Ser Gln Leu Lys Pro Asp Thr
515 520 525

SEQ.txt

Phe Val Gln His Ile Lys Arg His Asn Ile Val Leu Lys Arg Glu Leu
530 535 540

Gly Glu Gly Ala Phe Gly Lys Val Phe Leu Ala Glu Cys Tyr Asn Leu
545 550 555 560

Cys Pro Glu Gln Asp Lys Ile Leu Val Ala Val Lys Thr Leu Lys Asp
565 570 575

Ala Ser Asp Asn Ala Arg Lys Asp Phe His Arg Glu Ala Glu Leu Leu
580 585 590

Thr Asn Leu Gln His Glu His Ile Val Lys Phe Tyr Gly Val Cys Val
595 600 605

Glu Gly Asp Pro Leu Ile Met Val Phe Glu Tyr Met Lys His Gly Asp
610 615 620

Leu Asn Lys Phe Leu Arg Ala His Gly Pro Asp Ala Val Leu Met Ala
625 630 635 640

Glu Gly Asn Pro Pro Thr Glu Leu Thr Gln Ser Gln Met Leu His Ile
645 650 655

Ala Gln Gln Ile Ala Ala Gly Met Val Tyr Leu Ala Ser Gln His Phe
660 665 670

Val His Arg Asp Leu Ala Thr Arg Asn Cys Leu Val Gly Glu Asn Leu
675 680 685

Leu Val Lys Ile Gly Asp Phe Gly Met Ser Arg Asp Val Tyr Ser Thr
690 695 700

Asp Tyr Tyr Arg Val Gly Gly His Thr Met Leu Pro Ile Arg Trp Met
705 710 715 720

Pro Pro Glu Ser Ile Met Tyr Arg Lys Phe Thr Thr Glu Ser Asp Val
725 730 735

SEQ.txt

Trp Ser Leu Gly Val Val Leu Trp Glu Ile Phe Thr Tyr Gly Lys Gln
740 745 750

Pro Trp Tyr Gln Leu Ser Asn Asn Glu Val Ile Glu Cys Ile Thr Gln
755 760 765

Gly Arg Val Leu Gln Arg Pro Arg Thr Cys Pro Gln Glu Val Tyr Glu
770 775 780

Leu Met Leu Gly Cys Trp Gln Arg Glu Pro His Met Arg Lys Asn Ile
785 790 795 800

Lys Gly Ile His Thr Leu Leu Gln Asn Leu Ala Lys Ala Ser Pro Val
805 810 815

Tyr Leu Asp Ile Leu Gly
820

<210> 3
<211> 839
<212> PRT
<213> Homo sapiens

<400> 3

Met Asp Val Ser Leu Cys Pro Ala Lys Cys Ser Phe Trp Arg Ile Phe
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Leu Leu Gly Ser Val Trp Leu Asp Tyr Val Gly Ser Val Leu Ala Cys
20 25 30

Pro Ala Asn Cys Val Cys Ser Lys Thr Glu Ile Asn Cys Arg Arg Pro
35 40 45

Asp Asp Gly Asn Leu Phe Pro Leu Leu Glu Gly Gln Asp Ser Gly Asn
50 55 60

Ser Asn Gly Asn Ala Ser Ile Asn Ile Thr Asp Ile Ser Arg Asn Ile
65 70 75 80

SEQ.txt

Thr Ser Ile His Ile Glu Asn Trp Arg Ser Leu His Thr Leu Asn Ala
85 90 95

Val Asp Met Glu Leu Tyr Thr Gly Leu Gln Lys Leu Thr Ile Lys Asn
100 105 110

Ser Gly Leu Arg Ser Ile Gln Pro Arg Ala Phe Ala Lys Asn Pro His
115 120 125

Leu Arg Tyr Ile Asn Leu Ser Ser Asn Arg Leu Thr Thr Leu Ser Trp
130 135 140

Gln Leu Phe Gln Thr Leu Ser Leu Arg Glu Leu Gln Leu Glu Gln Asn
145 150 155 160

Phe Phe Asn Cys Ser Cys Asp Ile Arg Trp Met Gln Leu Trp Gln Glu
165 170 175

Gln Gly Glu Ala Lys Leu Asn Ser Gln Asn Leu Tyr Cys Ile Asn Ala
180 185 190

Asp Gly Ser Gln Leu Pro Leu Phe Arg Met Asn Ile Ser Gln Cys Asp
195 200 205

Leu Pro Glu Ile Ser Val Ser His Val Asn Leu Thr Val Arg Glu Gly
210 215 220

Asp Asn Ala Val Ile Thr Cys Asn Gly Ser Gly Ser Pro Leu Pro Asp
225 230 235 240

Val Asp Trp Ile Val Thr Gly Leu Gln Ser Ile Asn Thr His Gln Thr
245 250 255

Asn Leu Asn Trp Thr Asn Val His Ala Ile Asn Leu Thr Leu Val Asn
260 265 270

Val Thr Ser Glu Asp Asn Gly Phe Thr Leu Thr Cys Ile Ala Glu Asn
275 280 285

SEQ.txt

Val Val Gly Met Ser Asn Ala Ser Val Ala Leu Thr Val Tyr Tyr Pro
290 295 300

Pro Arg Val Val Ser Leu Glu Glu Pro Glu Leu Arg Leu Glu His Cys
305 310 315 320

Ile Glu Phe Val Val Arg Gly Asn Pro Pro Pro Thr Leu His Trp Leu
325 330 335

His Asn Gly Gln Pro Leu Arg Glu Ser Lys Ile Ile His Val Glu Tyr
340 345 350

Tyr Gln Glu Gly Glu Ile Ser Glu Gly Cys Leu Leu Phe Asn Lys Pro
355 360 365

Thr His Tyr Asn Asn Gly Asn Tyr Thr Leu Ile Ala Lys Asn Pro Leu
370 375 380

Gly Thr Ala Asn Gln Thr Ile Asn Gly His Phe Leu Lys Glu Pro Phe
385 390 395 400

Pro Glu Ser Thr Asp Asn Phe Ile Leu Phe Asp Glu Val Ser Pro Thr
405 410 415

Pro Pro Ile Thr Val Thr His Lys Pro Glu Glu Asp Thr Phe Gly Val
420 425 430

Ser Ile Ala Val Gly Leu Ala Ala Phe Ala Cys Val Leu Leu Val Val
435 440 445

Leu Phe Val Met Ile Asn Lys Tyr Gly Arg Arg Ser Lys Phe Gly Met
450 455 460

Lys Gly Pro Val Ala Val Ile Ser Gly Glu Glu Asp Ser Ala Ser Pro
465 470 475 480

Leu His His Ile Asn His Gly Ile Thr Thr Pro Ser Ser Leu Asp Ala
485 490 495

SEQ.txt

Gly Pro Asp Thr Val Val Ile Gly Met Thr Arg Ile Pro Val Ile Glu
500 505 510

Asn Pro Gln Tyr Phe Arg Gln Gly His Asn Cys His Lys Pro Asp Thr
515 520 525

Tyr Val Gln His Ile Lys Arg Arg Asp Ile Val Leu Lys Arg Glu Leu
530 535 540

Gly Glu Gly Ala Phe Gly Lys Val Phe Leu Ala Glu Cys Tyr Asn Leu
545 550 555 560

Ser Pro Thr Lys Asp Lys Met Leu Val Ala Val Lys Ala Leu Lys Asp
565 570 575

Pro Thr Leu Ala Ala Arg Lys Asp Phe Gln Arg Glu Ala Glu Leu Leu
580 585 590

Thr Asn Leu Gln His Glu His Ile Val Lys Phe Tyr Gly Val Cys Gly
595 600 605

Asp Gly Asp Pro Leu Ile Met Val Phe Glu Tyr Met Lys His Gly Asp
610 615 620

Leu Asn Lys Phe Leu Arg Ala His Gly Pro Asp Ala Met Ile Leu Val
625 630 635 640

Asp Gly Gln Pro Arg Gln Ala Lys Gly Glu Leu Gly Leu Ser Gln Met
645 650 655

Leu His Ile Ala Ser Gln Ile Ala Ser Gly Met Val Tyr Leu Ala Ser
660 665 670

Gln His Phe Val His Arg Asp Leu Ala Thr Arg Asn Cys Leu Val Gly
675 680 685

Ala Asn Leu Leu Val Lys Ile Gly Asp Phe Gly Met Ser Arg Asp Val
690 695 700

SEQ.txt

Tyr Ser Thr Asp Tyr Tyr Arg Leu Phe Asn Pro Ser Gly Asn Asp Phe
705 710 715 720

Cys Ile Trp Cys Glu Val Gly Gly His Thr Met Leu Pro Ile Arg Trp
725 730 735

Met Pro Pro Glu Ser Ile Met Tyr Arg Lys Phe Thr Thr Glu Ser Asp
740 745 750

Val Trp Ser Phe Gly Val Ile Leu Trp Glu Ile Phe Thr Tyr Gly Lys
755 760 765

Gln Pro Trp Phe Gln Leu Ser Asn Thr Glu Val Ile Glu Cys Ile Thr
770 775 780

Gln Gly Arg Val Leu Glu Arg Pro Arg Val Cys Pro Lys Glu Val Tyr
785 790 795 800

Asp Val Met Leu Gly Cys Trp Gln Arg Glu Pro Gln Gln Arg Leu Asn
805 810 815

Ile Lys Glu Ile Tyr Lys Ile Leu His Ala Leu Gly Lys Ala Thr Pro
820 825 830

Ile Tyr Leu Asp Ile Leu Gly
835