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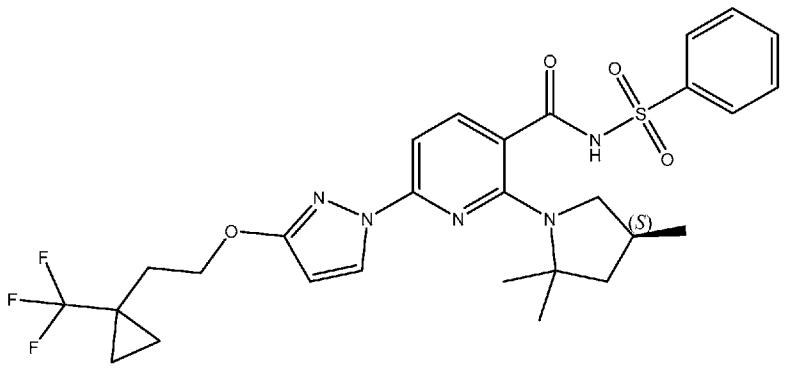

(I)

(57) **Abstract:** Crystalline Forms of Compound (I): (Formula (I)) and pharmaceutically acceptable salts thereof are disclosed. Pharmaceutical compositions comprising the same, methods of treating cystic fibrosis using the same, and methods for making the same are also disclosed.

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CRYSTALLINE FORMS AND COMPOSITIONS OF CFTR MODULATORS

[0001] This application claims priority to U.S. Provisional Application No. 62/574,677, filed October 19, 2017; U.S. Provisional Application No. 62/574,670, filed October 19, 2017; and U.S. Provisional Application No. 62/650,057, filed March 29, 2018, the entire contents of each of which are expressly incorporated herein by reference in their respective entireties.

[0002] Disclosed herein are crystalline forms of Compound **I** and pharmaceutically acceptable salts thereof, which are modulators of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), compositions comprising the same, methods of using the same, and processes for making the same.

[0003] Cystic fibrosis (CF) is a recessive genetic disease that affects approximately 70,000 children and adults worldwide. Despite progress in the treatment of CF, there is no cure.

[0004] In patients with CF, mutations in CFTR endogenously expressed in respiratory epithelia lead to reduced apical anion secretion causing an imbalance in ion and fluid transport. The resulting decrease in anion transport contributes to enhanced mucus accumulation in the lung and accompanying microbial infections that ultimately cause death in CF patients. In addition to respiratory disease, CF patients typically suffer from gastrointestinal problems and pancreatic insufficiency that, if left untreated, result in death. In addition, the majority of males with cystic fibrosis are infertile, and fertility is reduced among females with cystic fibrosis.

[0005] Sequence analysis of the CFTR gene has revealed a variety of disease-causing mutations (Cutting, G. R. et al. (1990) Nature 346:366-369; Dean, M. et al. (1990) Cell 61:863:870; and Kerem, B-S. et al. (1989) Science 245:1073-1080; Kerem, B-S et al. (1990) Proc. Natl. Acad. Sci. USA 87:8447-8451). To date, greater than 2000 mutations in the CF gene have been identified; currently, the CFTR2 database contains information on only 322 of these identified mutations, with sufficient evidence to define 281 mutations as disease causing. The most prevalent disease-causing mutation is a deletion of phenylalanine at position 508 of the CFTR amino acid sequence and is

commonly referred to as the F508del mutation. This mutation occurs in approximately 70% of the cases of cystic fibrosis and is associated with severe disease.

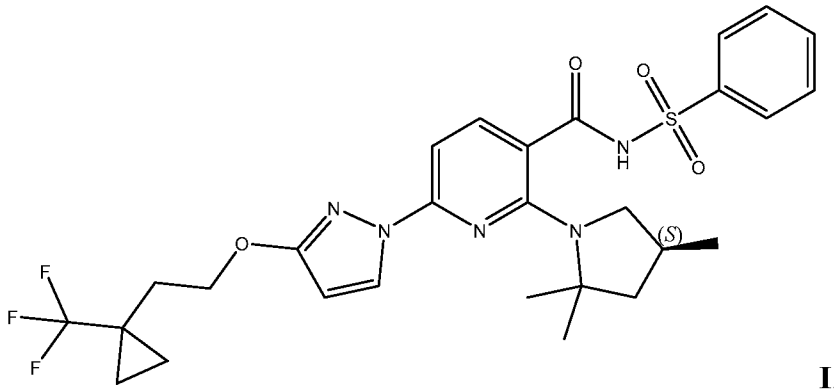
[0006] The deletion of residue 508 in CFTR prevents the nascent protein from folding correctly. This results in the inability of the mutant protein to exit the endoplasmic reticulum (ER) and traffic to the plasma membrane. As a result, the number of CFTR channels for anion transport present in the membrane is far less than observed in cells expressing wild-type CFTR, i.e., CFTR having no mutations. In addition to impaired trafficking, the mutation results in defective channel gating. Together, the reduced number of channels in the membrane and the defective gating lead to reduced anion and fluid transport across epithelia. (Quinton, P. M. (1990), FASEB J. 4: 2709-2727). The channels that are defective because of the F508del mutation are still functional, albeit less functional than wild-type CFTR channels. (Dalemans et al. (1991), Nature Lond. 354: 526-528; Pasyk and Foskett (1995), J. Cell. Biochem. 270: 12347-50). In addition to F508del, other disease-causing mutations in CFTR that result in defective trafficking, synthesis, and/or channel gating could be up- or down-regulated to alter anion secretion and modify disease progression and/or severity.

[0007] CFTR is a cAMP/ATP-mediated anion channel that is expressed in a variety of cell types, including absorptive and secretory epithelia cells, where it regulates anion flux across the membrane, as well as the activity of other ion channels and proteins. In epithelial cells, normal functioning of CFTR is critical for the maintenance of electrolyte transport throughout the body, including respiratory and digestive tissue. CFTR is composed of approximately 1480 amino acids that encode a protein which is made up of a tandem repeat of transmembrane domains, each containing six transmembrane helices and a nucleotide binding domain. The two transmembrane domains are linked by a large, polar, regulatory (R)-domain with multiple phosphorylation sites that regulate channel activity and cellular trafficking.

[0008] Chloride transport takes place by the coordinated activity of ENaC and CFTR present on the apical membrane and the Na^+-K^+-ATPase pump and Cl- channels expressed on the basolateral surface of the cell. Secondary active transport of chloride from the luminal side leads to the accumulation of intracellular chloride, which can then passively leave the cell via Cl^- channels, resulting in a vectorial transport. Arrangement

of $Na^+/2Cl^-/K^+$ co-transporter, Na^+-K^+-ATPase pump and the basolateral membrane K^+ channels on the basolateral surface and CFTR on the luminal side coordinate the secretion of chloride via CFTR on the luminal side. Because water is probably never actively transported itself, its flow across epithelia depends on tiny transepithelial osmotic gradients generated by the bulk flow of sodium and chloride.

[0009] Compound **I** and pharmaceutically acceptable salts thereof are potent CFTR modulators. Compound **I** is N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl) cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide, and has the following structure:



I.

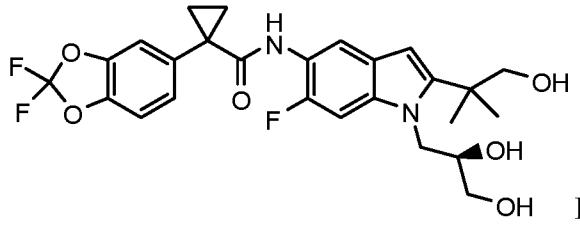
[0010] Crystalline forms are of interest in the pharmaceutical industry, where the control of the crystalline form(s) of the active ingredient may be desirable or even required. Reproducible processes for producing a compound with a particular crystalline form in high purity may be desirable for compounds intended to be used in pharmaceuticals, as different crystalline forms may possess different properties. For example, different crystalline forms may possess different chemical, physical, and/or pharmaceutical properties.

[0011] Accordingly, there is a need for novel crystalline forms of compounds useful for treatment of CFTR mediated diseases.

[0012] Disclosed herein are novel crystalline forms of Compound **I** and pharmaceutically acceptable salts thereof, compositions comprising the same, and methods of using and making the same.

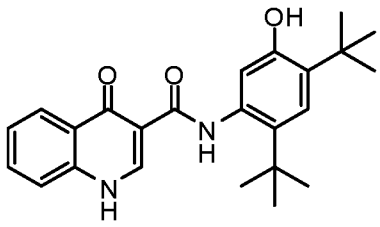
[0013] Also, disclosed are pharmaceutical compositions comprising combinations of Compound **I** and/or pharmaceutically acceptable salts thereof with (R)-1-(2,2-

difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide (Compound **II**) and/or pharmaceutically acceptable salts thereof



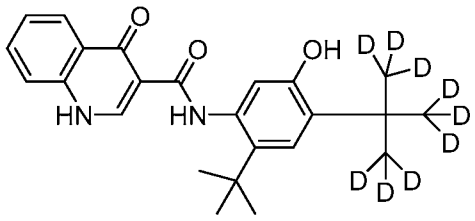
II

and/or with *N*-(5-hydroxy-2,4-di-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (Compound **III**)



III

or N-(2-(tert-butyl)-5-hydroxy-4-(2-(methyl-d3)propan-2-yl-1,1,1,3,3,3-d6)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (Compound **III-d**)



III-d.

[0014] Also disclosed are methods of using a crystalline form of Compound **I** and/or pharmaceutically acceptable salts thereof disclosed herein alone or in combination with other CFTR modulators to treat cystic fibrosis. In certain embodiments, the crystalline form of Compound **I** and/or pharmaceutically acceptable salts thereof is administered with Compound **II** and/or Compound **III** or Compound **III-d**, either in a single pharmaceutical composition or in multiple compositions to treat cystic fibrosis.

Brief Description of the Drawings

[0015] **FIG. 1A** shows a selection from an X-ray powder diffractogram of crystalline Form B of a potassium salt of Compound **I**, and **FIG. 1B** shows a full scan view of an X-ray powder diffractogram of crystalline Form B of a potassium salt of Compound **I**.

[0016] **FIG. 2** shows an X-ray powder diffractogram of crystalline Form B of a potassium salt of Compound **I** at 3% relative humidity (RH) (red) initial and 100%RH (blue).

[0017] **FIG. 3** shows a a dynamic vapor sorption (DVS)- plot of crystalline Form B of a potassium salt of Compound **I**.

[0018] **FIG. 4** shows a differential scanning calorimetry (DSC) plot of crystalline Form B of a potassium salt of Compound **I**.

[0001] **FIG. 5** shows a TGA plot of crystalline Form B of a potassium salt of Compound **I**.

[0019] **FIG. 6** shows a ball and stick plot of crystalline Form B of a potassium salt of Compound **I**.

[0020] **FIG. 7A** shows a selection from an X-ray powder diffractogram of crystalline Form C of a potassium salt/co-crystal of Compound **I**, and **FIG. 7B** shows a full scan view of an X-ray powder diffractogram of crystalline Form C of a potassium salt/co-crystal of Compound **I**.

[0021] **FIG. 8A** shows a selection from an X-ray powder diffractogram of crystalline Form A of a sodium salt of Compound **I**, and **FIG. 8B** shows a full scan view of an X-ray powder diffractogram of crystalline Form A of a sodium salt of Compound **I**.

[0022] **FIG. 9A** shows a selection from an X-ray powder diffractogram of crystalline Form D of a sodium salt of Compound **I**, and **FIG. 9B** shows a full scan view of an X-ray powder diffractogram of crystalline Form D of a sodium salt of Compound **I**.

[0023] **FIG. 10A** shows a selection from an X-ray powder diffractogram of crystalline Form M of a sodium salt of Compound **I**, and **FIG. 10B** shows a full scan view of an X-ray powder diffractogram of crystalline Form M of a sodium salt of Compound **I**.

[0024] **FIG. 11A** shows a selection from an X-ray powder diffractogram of crystalline Form H of a sodium salt of Compound **I**, and **FIG. 11B** shows a full-scan view of an X-ray powder diffractogram of crystalline Form H of a sodium salt of Compound **I**.

[0025] **FIG. 12A** shows a selection from an X-ray powder diffractogram of crystalline Form E of a sodium salt of Compound **I**, and **FIG. 12B** shows a full scan view of an X-ray powder diffractogram of crystalline Form E of a sodium salt of Compound **I**.

[0026] **FIG. 13A** shows a selection from an X-ray powder diffractogram of crystalline Form A of Compound **I**, and **FIG. 13B** shows a full scan view of an X-ray powder diffractogram of crystalline Form A of Compound **I**.

[0027] **FIG. 14** shows the X-ray powder diffractogram of a spray-dried dispersion (SDD) of 50 wt% Compound **I** in HPMCAS-HG.

[0028] **FIG. 15** is spectrum showing modulated differential scanning calorimetry (MDSC) plot of a SDD of 50 wt% Compound **I** in HPMCAS-HG.

[0029] **FIG. 16** shows the X-ray powder diffractogram spectrum of an amorphous sodium salt of Compound **I**.

[0030] **FIG. 17** is a representative list of CFTR genetic mutations.

[0031] **FIG. 18** shows tablet dissolution of Compound **I** of a Control tablet comprising a spray dried dispersion of Compound **I**, and a fixed dose combination (FDC) tablet comprising a potassium salt of Compound **I**, a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III**.

[0032] **FIG. 19** shows tablet dissolution of Compound **II** of a Control tablet comprising a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III**, and of an FDC tablet comprising a potassium salt of Compound **I**, a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III**.

[0033] **FIG. 20** shows tablet dissolution of Compound **III** of a Control tablet comprising a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III**, and of an FDC tablet comprising a potassium salt of Compound **I**, a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III**.

[0034] **FIG. 21** shows bioavailability of Compound **I** of a Control tablet comprising a spray dried dispersion of Compound **I**, and an FDC tablet comprising a potassium salt of Compound **I**, a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III** in a dog.

[0035] **FIG. 22** shows bioavailability of Compound **II** of a Control tablet comprising a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III**, and of an FDC tablet comprising a potassium salt of Compound **I**, a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III** in a dog.

[0036] **FIG. 23** shows bioavailability of Compound **III** of a Control tablet comprising a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III**, and of an FDC tablet comprising a potassium salt of Compound **I**, a spray dried dispersion of Compound **II** and a spray dried dispersion of Compound **III** in a dog.

[0037] **FIG. 24** shows tablet dissolution data of K salt of Compound **I** of FDC Tablets C1, C2, C3, C4, and C5. The tablet dissolution data were obtained using dissolution media 1, which included 0.8 wt% SDS in pH 6.8 sodium phosphate buffer.

[0038] **FIG. 25** shows tablet dissolution data for Compound **II** of FDC Tablets C1, C2, C3, C4, and C5. The tablet dissolution data were obtained using dissolution media 2, which included 0.1 wt% SDS in 0.1 N HCl.

[0039] **FIG. 26** shows tablet dissolution data for Compound **III** of FDC Tablets C1, C2, C3, C4, and C5. The tablet dissolution data were obtained using dissolution media 1, which included 0.8 wt% SDS in pH 6.8 sodium phosphate buffer.

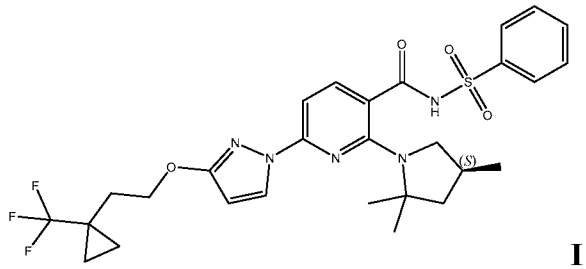
[0040] **FIG. 27** shows tablet dissolution data of the potassium salt of Compound **I** of FDC Tablets D3, D4, D5, and D6. The tablet dissolution data were obtained using dissolution media 1, which included 1.0% SDS in 50 mM sodium phosphate monobasic buffer at pH 6.8.

[0041] **FIG. 28** shows tablet dissolution data for Compound **II** of FDC Tablets D3, D4, D5, and D6. The tablet dissolution data were obtained using dissolution media 2, which included 0.07% SDS in 0.1 N HCl.

[0042] **FIG. 29** shows tablet dissolution data for Compound **III** of FDC Tablets D3, D4, D5, and D6. The tablet dissolution data were obtained using dissolution media 1, which included 1.0% SDS in 50 mM sodium phosphate monobasic buffer at pH 6.8.

Definitions

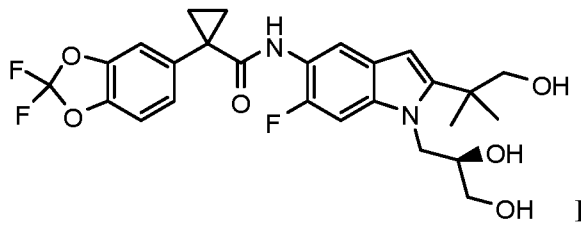
[0043] As used herein, "Compound **I**" refers to a compound having a chemical name N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide, which has the following structure:



I

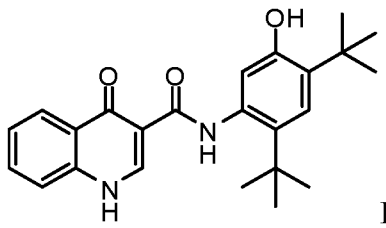
either as an isomeric mixture or enantioenriched (e.g., >90% ee, >95% ee, or >98% ee) isomers.

[0044] As used herein, "Compound **II**" refers to a compound having a chemical name (R)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropane carboxamide, which has the following structure:



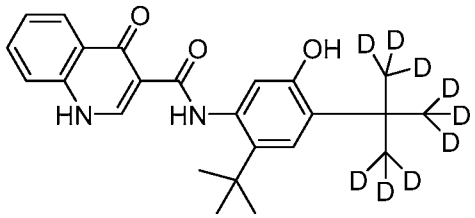
II.

[0045] As used herein, "Compound **III**" refers to a compound having a chemical name *N*-(5-hydroxy-2,4-di-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide, which has the following structure:



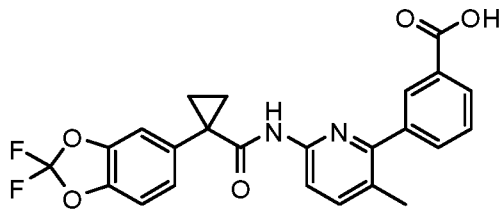
III.

[0046] As used herein, "Compound **III-d**" refers to a compound having a chemical name N-(2-(tert-butyl)-5-hydroxy-4-(2-(methyl-d3)propan-2-yl-1,1,1,3,3,3-d6)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide, which has the following structure:



III-d.

[0047] As used herein, "Compound **IV**" refers to a compound having a chemical name 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid, which has the following structure:



IV.

[0048] As used herein, the term "pharmaceutically acceptable salt" refers to a salt form of a compound of this disclosure wherein the salt is nontoxic. Pharmaceutically acceptable salts of Compound **I**, Compound **II**, Compound **III**, Compound **III-d**, and Compound **IV** of this disclosure include those derived from suitable inorganic and organic acids and bases. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, *66*, 1-19.

[0049] Suitable pharmaceutically acceptable salts are, for example, those disclosed in S. M. Berge, *et al. J. Pharmaceutical Sciences*, 1977, *66*, 1-19. For example, that article provides the following pharmaceutically acceptable salts:

Acetate	Iodide	Benzathine
Benzenesulfonate	Isethionate	Chloroprocaine
Benzoate	Lactate	Choline
Bicarbonate	Lactobionate	Diethanolamine
Bitartrate	Malate	Ethylenediamine
Bromide	Maleate	Meglumine
Calcium edetate	Mandelate	Procaine
Camsylate	Mesylate	Aluminum
Carbonate	Methylbromide	Calcium
Chloride	Methylnitrate	Lithium
Citrate	Methylsulfate	Magnesium
Dihydrochloride	Mucate	Potassium

Edetate	Napsylate	Sodium
Edisylate	Nitrate	Zinc
Estolate	Pamoate (Embonate)	
Esylate	Pantothenate	
Fumarate	Phosphate/diphosphate	
Gluceptate	Polygalacturonate	
Gluconate	Salicylate	
Glutamate	Stearate	
Glycollylarsanilate	Subacetate	
Hexylresorcinate	Succinate	
Hydrabamine	Sulfate	
Hydrobromide	Tannate	
Hydrochloride	Tartrate	
Hydroxynaphthoate	Teociate	
	Triethiodide	

[0050] Non-limiting examples of pharmaceutically acceptable salts derived from appropriate acids include: salts formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, or perchloric acid; salts formed with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid; and salts formed by using other methods used in the art, such as ion exchange. Non-limiting examples of pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}alkyl)_4$ salts. This disclosure also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Suitable non-limiting examples of alkali and alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium. Further non-limiting examples of pharmaceutically acceptable salts include ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate,

lower alkyl sulfonate and aryl sulfonate. Other suitable, non-limiting examples of pharmaceutically acceptable salts include besylate and glucosamine salts.

[0051] As used herein, the term "co-crystal" is a crystalline material composed of two or more different molecules, typically the compound and co-crystal formers (or coformers), in the same crystal lattice. Co-crystals components are in a neutral state and interact nonionically.

[0052] As used herein, the term "ambient conditions" means room temperature, open air condition and uncontrolled humidity condition.

[0053] As used herein, the terms "crystal form," "crystalline form," and "Form" interchangeably refer to a crystal structure (or polymorph) having a particular molecular packing arrangement in the crystal lattice. Crystalline forms can be identified and distinguished from each other by one or more characterization techniques including, for example, X-ray powder diffraction (XRPD), single crystal X-ray diffraction, differential scanning calorimetry (DSC), dynamic vapor sorption (DVS), and/or thermogravimetric analysis (TGA). Accordingly, as used herein, the terms "crystalline Form [X] of Compound **I**" and "crystalline Form [C] of a [pharmaceutically acceptable] salt of Compound **I**" refer to unique crystalline forms that can be identified and distinguished from each other by one or more characterization techniques including, for example, X-ray powder diffraction (XRPD), single crystal X-ray diffraction, differential scanning calorimetry (DSC), dynamic vapor sorption (DVS), and/or thermogravimetric analysis (TGA). In some embodiments, the novel crystalline forms are characterized by an X-ray powder diffractogram having one or more signals at one or more specified two-theta values (° 2θ).

[0054] As used herein, the terms "solvate" and "pseudo-polymorph" interchangeably refer to a crystal form comprising one or more molecules of a compound of the present disclosure and, incorporated into the crystal lattice, one or more molecules of a solvent or solvents in stoichiometric or nonstoichiometric amounts. When the solvent is water, the solvate is referred to as a "hydrate".

[0055] As used herein, a "variable hydrate" is a crystal form comprising nonstoichiometric water in the crystal lattice. The amount of water present in a variable hydrate varies as a function of at least the relative humidity ("RH") in the environment

of the variable hydrate. Since the positions of the signals in the X-ray powder diffractogram of a crystalline form correlate to the dimensions of its unit cell, a change in the size of the unit cell due to the presence (or absence) of water can be determined by comparison of X-ray diffractograms under different RH environments.

[0056] As used herein, the term "XRPD" refers to the analytical characterization method of X-ray powder diffraction. XRPD patterns can be recorded at ambient conditions in transmission or reflection geometry using a diffractometer.

[0057] As used herein, the terms "X-ray powder diffractogram," "X-ray powder diffraction pattern," "XRPD pattern" interchangeably refer to an experimentally obtained pattern plotting signal positions (on the abscissa) versus signal intensities (on the ordinate). For an amorphous material, an X-ray powder diffractogram may include one or more broad signals; and for a crystalline material, an X-ray powder diffractogram may include one or more signals, each identified by its angular value as measured in degrees 2θ (° 2θ), depicted on the abscissa of an X-ray powder diffractogram, which may be expressed as "a signal at … degrees two-theta," "a signal at [a] two-theta value(s)of …" and/or "a signal at at least … two-theta value(s) chosen from …." The term "X-ray powder diffractogram having a signal at … two-theta values" as used herein refers to an XRPD pattern that contains X-ray reflection positions as measured and observed in X-ray powder diffraction experiments (° 2θ).

[0058] A "signal" or "peak" as used herein refers to a point in the XRPD pattern where the intensity as measured in counts is at a local. One of ordinary skill in the art would recognize that one or more signals (or peaks) in an XRPD pattern may overlap and may, for example, not be apparent to the naked eye. Indeed, one of ordinary skill in the art would recognize that some art-recognized methods are capable of and suitable for determining whether a signal exists in a pattern, such as Rietveld refinement.

[0059] As used herein, "a signal at … degrees two-theta," "a signal at [a] two-theta value[s] of …" and/or "a signal at at least … two-theta value(s) chosen from …." refer to X-ray reflection positions as measured and observed in X-ray powder diffraction experiments (° 2θ).

[0060] The repeatability of the angular values is in the range of ±0.2° 2θ, i.e., the angular value can be at the recited angular value + 0.2 degrees two-theta, the angular

value - 0.2 degrees two-theta, or any value between those two end points (angular value +0.2 degrees two-theta and angular value -0.2 degrees two-theta).

[0061] The terms "signal intensities" and "peak intensities" interchangeably refer to relative signal intensities within a given X-ray powder diffractogram. Factors that can affect the relative signal or peak intensities include sample thickness and preferred orientation (e.g., the crystalline particles are not distributed randomly).

[0062] As used herein, an X-ray powder diffractogram is "substantially similar to that in [a particular] Figure" when at least 90%, such as at least 95%, at least 98%, or at least 99%, of the signals in the two diffractograms overlap. In determining "substantial similarity," one of ordinary skill in the art will understand that there may be variation in the intensities and/or signal positions in XRPD diffractograms even for the same crystalline form. Thus, those of ordinary skill in the art will understand that the signal maximum values in XRPD diffractograms (in degrees two-theta (°2θ) referred to herein) generally mean that value reported ±0.2 degrees 2θ of the reported value, an art-recognized variance.

[0063] As used herein, a crystalline form is "substantially pure" when it accounts for an amount by weight equal to or greater than 90% of the sum of all solid form(s) in a sample as determined by a method in accordance with the art, such as quantitative XRPD. In some embodiments, the solid form is "substantially pure" when it accounts for an amount by weight equal to or greater than 95% of the sum of all solid form(s) in a sample. In some embodiments, the solid form is "substantially pure" when it accounts for an amount by weight equal to or greater than 99% of the sum of all solid form(s) in a sample.

[0064] As used herein, the term "DSC" refers to the analytical method of Differential Scanning Calorimetry.

[0065] As used herein, the term "onset of decomposition" refers to the intersection point of the baseline before transition and the interflection tangent.

[0066] As used herein, the term "glass transition temperature" or "Tg" refers to the temperature above which a glassy amorphous solid becomes rubbery.

[0067] As used herein, the term "TGA" refers to the analytical method of Thermo Gravimetric (or thermogravimetric) Analysis.

[0068] As used herein, the term “solvent” refers to any liquid in which the product is at least partially soluble (solubility of product >1 g/l).

[0069] As used herein, the term “anti-solvent” refers to any liquid in which the product is insoluble or at maximum sparingly soluble (solubility of product <0.01 mol/l).

[0070] As used herein, the term “anti-solvent crystallization” refers to a process wherein supersaturation is achieved and, as a result thereof, crystallization is induced by addition of an antisolvent to the product solution.

[0071] As used herein, the term “amorphous” refers to a solid material having no long range order in the position of its molecules. Amorphous solids are generally supercooled liquids in which the molecules are arranged in a random manner so that there is no well-defined arrangement, e.g., molecular packing, and no long range order. For example, an amorphous material is a solid material having no sharp characteristic signal(s) in its X-ray power diffractogram (i.e., is not crystalline as determined by XRPD). Instead, one or more broad peaks (e.g., halos) appear in its diffractogram. Broad peaks are characteristic of an amorphous solid. See, e.g., US 2004/0006237 for a comparison of diffractograms of an amorphous material and crystalline material.

[0072] As used herein, the term "substantially amorphous" refers to a solid material having little or no long-range order in the position of its molecules. For example, substantially amorphous materials have less than 15% crystallinity (e.g., less than 10% crystallinity or less than 5% crystallinity). It is also noted that the term 'substantially amorphous' includes the descriptor, 'amorphous', which refers to materials having no (0%) crystallinity.

[0073] As used herein, the term "dispersion" refers to a disperse system in which one substance, the dispersed phase, is distributed, in discrete units, throughout a second substance (the continuous phase or vehicle). The size of the dispersed phase can vary considerably (e.g. colloidal particles of nanometer dimension, to multiple microns in size). In general, the dispersed phases can be solids, liquids, or gases. In the case of a solid dispersion, the dispersed and continuous phases are both solids. In pharmaceutical applications, a solid dispersion can include a crystalline drug (dispersed phase) in an amorphous polymer (continuous phase); or alternatively, an amorphous drug (dispersed

phase) in an amorphous polymer (continuous phase). In some embodiments, a solid dispersion includes the polymer constituting the dispersed phase, and the drug constitute the continuous phase. Or, a solid dispersion includes the drug constituting the dispersed phase, and the polymer constituting the continuous phase.

[0074] As used herein, "CFTR" means cystic fibrosis transmembrane conductance regulator.

[0075] As used herein, "mutations" can refer to mutations in the *CFTR* gene or the CFTR protein. A "*CFTR* gene mutation" refers to a mutation in the *CFTR* gene, and a "CFTR protein mutation" refers to a mutation in the CFTR protein. A genetic defect or mutation, or a change in the nucleotides in a gene in general results in a mutation in the CFTR protein translated from that gene, or a frame shift(s).

[0076] The term "F508del" refers to a mutant CFTR protein which is lacking the amino acid phenylalanine at position 508.

[0077] As used herein, a patient who is "homozygous" for a particular gene mutation has the same mutation on each allele.

[0078] As used herein, a patient who is "heterozygous" for a particular gene mutation has this mutation on one allele, and a different mutation on the other allele.

[0079] As used herein, the term "modulator" refers to a compound that increases the activity of a biological compound such as a protein. For example, a CFTR modulator is a compound that increases the activity of CFTR. The increase in activity resulting from a CFTR modulator includes but is not limited to compounds that correct, potentiate, stabilize and/or amplify CFTR.

[0080] As used herein, the term "CFTR corrector" refers to a compound that facilitates the processing and trafficking of CFTR to increase the amount of CFTR at the cell surface. Compound **I**, Compound **II**, Compound **IV**, and their pharmaceutically acceptable salts thereof disclosed herein are CFTR correctors.

[0081] As used herein, the term "CFTR potentiator" refers to a compound that increases the channel activity of CFTR protein located at the cell surface, resulting in enhanced ion transport. Compound **III** and Compound **III-d** disclosed herein are CFTR potentiators.

[0082] As used herein, the term “active pharmaceutical ingredient” (“API”) refers to a biologically active compound.

[0083] The terms “patient” and “subject” are used interchangeably and refer to an animal including humans.

[0084] The terms "effective dose" and "effective amount" are used interchangeably herein and refer to that amount of a compound that produces the desired effect for which it is administered (e.g., improvement in CF or a symptom of CF, or lessening the severity of CF or a symptom of CF). The exact amount of an effective dose will depend on the purpose of the treatment and will be ascertainable by one skilled in the art (see, e.g., Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

[0085] As used herein, the terms "treatment," "treating," and the like generally mean the improvement of CF or a CFTR mediated disease or its symptoms or lessening the severity of CF or a CFTR mediated disease or its symptoms in a subject. “Treatment,” as used herein, includes, but is not limited to, the following: increased growth of the subject, increased weight gain, reduction of mucus in the lungs, improved pancreatic and/or liver function, reduction of chest infections, and/or reductions in coughing or shortness of breath. Improvements in or lessening the severity of any of these symptoms can be readily assessed according to standard methods and techniques known in the art.

[0086] As used herein, the term “in combination with,” when referring to two or more compounds, agents, or additional active pharmaceutical ingredients, means the administration of two or more compounds, agents, or active pharmaceutical ingredients to the patient prior to, concurrent with, or subsequent to each other in a single composition or in multiple compositions.

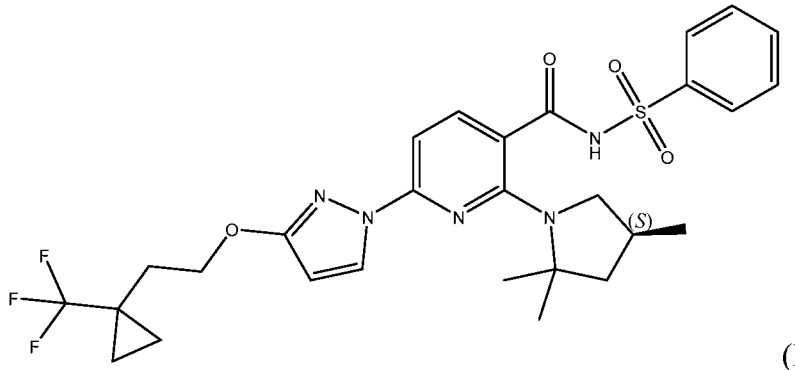
[0087] The terms “about” and “approximately”, when used in connection with doses, amounts, or weight percent of ingredients of a composition or a dosage form, include the value of a specified dose, amount, or weight percent or a range of the dose, amount, or weight percent that is recognized by one of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. In some embodiments, the term “about” modifies a specified number by + or – 10%. In some embodiments, the term “about” modifies a specified number by

+ or – 5%. In some embodiments, the term "about" modifies a specified number by + or – 2%. In some embodiments, the term "about" modifies a specified number by + or – 1%.

[0088] As used herein, the term "room temperature" or "ambient temperature" means 15 °C to 30 °C.

Crystalline Form B of a Potassium Salt of Compound I

[0089] As stated above, disclosed herein are crystalline forms of Compound **I**:



(**I**) and pharmaceutically acceptable salts thereof, either as an isomeric mixture or enantioenriched (e.g., >90% ee, >95% ee, or >98% ee) isomers.

[0090] In some embodiments, the present disclosure provides crystalline Form B of a potassium salt of Compound **I**.

[0091] FIG. 1A shows an X-ray powder diffractogram of crystalline Form B of a potassium salt of Compound **I** at ambient conditions.

[0092] FIG. 2 shows an overlay of the X-ray powder diffractogram of crystalline Form B of a potassium salt of Compound **I** at 3%RH (red) initial and at 100%RH (blue).

[0093] FIG. 3 shows the results of dynamic vapor sorption (DVS) plot of crystalline Form B of a potassium salt of Compound **I**. In some embodiments, the crystalline Form B of a potassium salt of Compound **I** is characterized by a weight change ranging from 1% to 2% or1.5% to 1.8% in a dynamic vapor sorption experiment, while varying the relative humidity from 0-95% RH at 25 °C

[0094] FIG. 4 shows a DSC trace of the crystalline Form B of a potassium salt of Compound **I**. In some embodiments, the crystalline Form B of a potassium salt of

Compound **I** is characterized by a DSC having an onset of decomposition temperature of 254 °C and/or a peak temperature of 256 °C.

[0095] FIG. 5 shows TGA results of crystalline Form B of a potassium salt of Compound **I**. In some embodiments, the crystalline Form B of a potassium salt of Compound **I** is characterized by a TGA having an onset of decomposition temperature of 322 °C.

[0096] In some embodiments, the crystalline Form B of a potassium salt of Compound **I** is a variable hydrate. In some embodiments, the crystalline Form B of a potassium salt of Compound **I** comprises 71% water (molar %). In some embodiments, the crystalline Form B of a potassium salt of Compound **I** comprises 26% water (molar %). In some embodiments, the crystalline Form B of a potassium salt of Compound **I** comprises 38% water (molar %).

[0097] In some embodiments, crystalline Form B of a potassium salt of Compound **I** is in substantially pure form. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation.

[0098] In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 5.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 8.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.6 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 10.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 13.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 15.1 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 16.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 17.2 ± 0.2 degrees

two-theta. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 19.1 ± 0.2 degrees two-theta.

[0099] In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one two-

theta value chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2.

[00100] In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 16.3 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 5.8 ± 0.2, 10.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 5.8 ± 0.2, 10.2 ± 0.2, and 19.1 ± 0.2. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 5.8 ± 0.2, 8.2 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 16.3 ± 0.2, and 19.1 ± 0.2.

[00101] In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 1A**.

[00102] In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by an orthorhombic crystal system. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized as belonging to a P212121 space group. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by having a unit cell characterized by three edges of 9.0058 ± 0.0009 Å, 11.5389 ± 0.0012Å, and 30.9399 ± 0.003 Å. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by having a unit cell characterized by three edges of 9.006 ± 0.005 Å, 11.539 ± 0.005 Å, and 30.940 ± 0.005 Å. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by having a unit cell characterized by three edges of 9.01 ± 0.09 Å, 11.54 ± 0.09 Å, and 30.9 ± 0.2 Å. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by having a unit cell characterized by three edges of 9.0± 0.2 Å, 11.5 ± 0.2 Å, and 31.0 ± 0.2 Å. In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by having a unit cell of an orthorhombic crystal system characterized by three edges of 9.0± 0.2 Å, 11.5 ± 0.2 Å, and 31.0 ± 0.2 Å.

[00103] In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by having a unit cell with the following characteristics measured at 298°K and 1.54178 Å:

Crystal System:	Orthorhombic
Space Group:	P212121
a (Å):	9.0058(3)
b (Å):	11.5389(4)
c (Å):	30.9399(10)
α (°):	90
β (°):	90
γ (°):	90
V (Å3):	3215.18(19)
Z/Z':	4/1

[00104] In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by having a unit cell characterized by three angles of 90°.

[00105] In some embodiments, crystalline Form B of a potassium salt of Compound **I** is characterized by having a unit cell with volume of 3215 $Å^3$.

[00106] In some embodiments, the present disclosure provides crystalline Form B of a potassium salt of Compound **I** prepared by a process comprising reacting Compound **I** with a potassium base.

[00107] In some embodiments, the present disclosure provides methods of preparing crystalline Form B of a potassium salt of Compound **I**, comprising reacting Compound **I** with a potassium base. In some embodiments, the potassium base is chosen from potassium hydroxide, potassium t-butoxide, potassium acetate, potassium bicarbonate, potassium carbonate, potassium methoxide, and potassium ethoxide. In some embodiments, the potassium base is chosen from potassium hydroxide. In some embodiments, the potassium base is chosen from potassium carbonate. In some embodiments, the reaction is performed at room temperature.

[00108] Crystalline Form B of a potassium salt of Compound **I**, is a crystalline channel/variable-hydrate that has been found to be thermodynamically stable during development. The potassium salt Form B of Compound I is stable across a wide

humidity range. In addition, it was found to be particularly amenable to scale up manufacturing processes.

Crystalline Form C of a Potassium Salt/Co-Crystal of Compound I

[00109] In some embodiments, the present disclosure provides crystalline form of a potassium salt or co-crystal of Compound **I**, designated as Form C.

[00110] **FIG. 7**A shows an X-ray powder diffractogram of Form C of a potassium salt/co-crystal of Compound **I** at ambient conditions.

[00111] In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is in substantially pure form. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation.

[00112] In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 3.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 7.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 7.4 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 8.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.5 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 11.4 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 11.5 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 12.4 ± 0.2 degrees two-theta. In some embodiments,

crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 16.0 ± 0.2 degrees two-theta.

[00113] In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12. 4 ± 0.2, and 16.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12. 4 ± 0.2, and 16.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12. 4 ± 0.2, and 16.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12. 4 ± 0.2, and 16.0 ± 0.2 degrees two-theta.

[00114] In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12. 4 ± 0.2, and 16.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12. 4 ± 0.2, and 16.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12. 4 ± 0.2, and 16.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12. 4 ± 0.2, and 16.0 ± 0.2

degrees two-theta. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12. 4 ± 0.2, and 16.0 ± 0.2 degrees two-theta.

[00115] In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, and 11.5 ± 0.2.

[00116] In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 3.7 ± 0.2, 7.0 ± 0.2, and 11.4 ± 0.2. In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, and 11.5 ± 0.2.

[00117] In some embodiments, crystalline Form C of a potassium salt/co-crystal of Compound **I** is characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 7A.**

[00118] In some embodiments, the present disclosure provides crystalline Form C of a potassium salt/co-crystal of Compound **I** prepared by a process comprising stirring a potassium salt of Compound **I** with a solvent system comprising at least one source of water. In some embodiments, the solvent system comprises water. In some embodiments, the solvent system comprises at least one organic solvent miscible with water. In some embodiments, the solvent system comprises acetonitrile. In some embodiments, the solvent system comprises at least one alcohol chosen from C_1-C_4 alcohols. In some embodiments, the solvent system comprises at least one alkane chosen from C_5-C_8 alcohols. In some embodiments, the solvent system comprises at least one alkane chosen from pentane, hexane and heptane. In some embodiments, the solvent system comprises water. In some embodiments, the at least one source of water is water. In some embodiments, the at least one source of water is a hydrate of a potassium salt of Compound **I**. In some embodiments, stirring occurs at a temperature ranging from 20 °C to 100 °C.

[00119] In some embodiments, the present disclosure provides methods of preparing crystalline Form C of a potassium salt/co-crystal Compound **I** comprising stirring a potassium salt of Compound **I** with a solvent system comprising at least one source of water. In some embodiments, the solvent system comprises water. In some embodiments, the solvent system comprises at least one organic solvent miscible with water. In some embodiments, the solvent system comprises acetonitrile. In some embodiments, the solvent system comprises at least one alcohol chosen from C_1-C_4 alcohols. In some embodiments, the solvent system comprises at least one alkane chosen from C_5-C_8 alcohols. In some embodiments, the solvent system comprises at least one alkane chosen from pentane, hexane and heptane. In some embodiments, the solvent system comprises water. In some embodiments, the at least one source of water is water. In some embodiments, the solvent system is a 1:10 v/v mixture of acetonitrile and water.

[00120] In some embodiments, the at least one source of water is a hydrate of a potassium salt of Compound **I**. In some embodiments, stirring occurs at a temperature ranging from 20 °C to 100 °C. In some embodiments, stirring occurs at a temperature ranging from 60 °C to 80 °C. In some embodiments, stirring occurs in 1:10 v/v acetonitrile: water at a temperature ranging from 60 °C to 90 °C. In some embodiments, stirring occurs in 1:10 v/v acetonitrile: water at a temperature ranging from 70 °C to 80 °C (e.g, at 75°C).

Crystalline Form A of a Sodium Salt of Compound I

[00121] In some embodiments, the present disclosure provides crystalline Form A of a sodium salt of Compound **I**.

[00122] **FIG. 8A** shows an X-ray powder diffractogram of crystalline Form A of a sodium salt of Compound **I** at ambient conditions.

[00123] In some embodiments, crystalline Form A of a sodium salt of Compound **I** is in substantially pure form.

[00124] In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation.

[00125] In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 4.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 4.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 6.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 8.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 8.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 11.1 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 12.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 12.6 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 14.0 ± 0.2 degrees two-theta.

[00126] In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized

by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2.

[00127] In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 12.2 ± 0.2, and 12.6 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 4.7 ± 0.2, 8.0 ± 0.2, and 12.2 ± 0.2. In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 4.7 ± 0.2, 4.9 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 12.2 ± 0.2, and 12.6 ± 0.2.

[00128] In some embodiments, crystalline Form A of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 8A**.

[00129] In some embodiments, the present disclosure provides crystalline Form A of a sodium salt of Compound **I** prepared by a process comprising reacting Compound **I** with a sodium base. In some embodiments, the sodium base is chosen from sodium hydroxide, sodium t-butoxide, sodium acetate, sodium bicarbonate, sodium carbonate, sodium methoxide, and sodium ethoxide. In some embodiments, the sodium base is sodium hydroxide. In some embodiments, the sodium base is sodium methoxide. In some embodiments, the reaction is performed at room temperature. In some embodiments, Compound **I** in acetonitrile solution is reacted with a sodium base in solvent system comprising water. In some embodiments, Compound **I** in acetonitrile solution is reacted with a sodium base in solvent system comprising water at room temperature.

[00130] In some embodiments, the present disclosure provides methods for preparing crystalline Form A of a sodium salt of Compound **I** comprising reacting Compound **I** with a sodium base. In some embodiments, the sodium base is sodium hydroxide. In some embodiments, the sodium base is sodium methoxide. In some embodiments, Compound **I** in acetonitrile solution is reacted with a sodium base in solvent system comprising water. In some embodiments, Compound **I** in acetonitrile solution is reacted with a sodium base in solvent system comprising water at room temperature. In some embodiments, the reaction is performed at room temperature.

Crystalline Form D of a Sodium Salt of Compound I

[00131] In some embodiments, the present disclosure provides crystalline Form D of a sodium salt of Compound **I**.

[00132] **FIG. 9A** shows an X-ray powder diffractogram of crystalline Form D of a sodium salt of Compound **I** at ambient conditions.

[00133] In some embodiments, crystalline Form D of a sodium salt of Compound **I** is in substantially pure form. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation.

[00134] In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 4.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is

characterized by an X-ray powder diffractogram having a signal at 5.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 7.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 8.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 11.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 12.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 14.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 16.0 ± 0.2 degrees two-theta.

[00135] In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2. In some embodiments, crystalline Form D of a

sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2.

[00136] In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 12.2 ± 0.2, and 14.0 ± 0.2. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 4.9 ± 0.2, 8.0 ± 0.2, and 12.2 ± 0.2. In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 4.9 ± 0.2, 5.7 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 12.2 ± 0.2, and 14.0 ± 0.2.

[00137] In some embodiments, crystalline Form D of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 9A**.

[00138] In some embodiments, the present disclosure provides crystalline Form D of a sodium salt of Compound **I** prepared by a process comprising heating a crystalline Form M or crystalline Form E of the sodium salt of Compound **I** at a temperature in a range from 280 °C to 300 °C under an anhydrous condition. In some embodiments, the anhydrous condition is under dry N_2 or Ar_2. In some embodiments, the anhydrous condition is under dry N_2. In some embodiments, crystalline Form M or crystalline Form E is heated to a temperature ranging from 290 °C to295 °C.

[00139] In some embodiments, the present disclosure provides methods of preparing crystalline Form D of a sodium salt Compound **I** comprising heating an ethanol solvate of the sodium salt of Compound **I** at a temperature in a range from 280 °C to 300 °C under an anhydrous condition. In some embodiments, the anhydrous condition is under dry N_2 or Ar_2. In some embodiments, the anhydrous condition is under dry N_2. In some embodiments, the heating temperature is 290 °C -295 °C. Crystalline Form D of a sodium salt of Compound **I** was obtained by heating either Form M of a sodium salt of Compound **I** or Form E of a sodium salt of Compound **I** at 290°C under dry N_2. In one example, 8 mg of crystalline Form E of a sodium salt of Compound **I** was heated in a TGA pan at a 10 °C/minute rate from room temperature to 290 °C and was then maintained at 290 °C for 2 minutes under dry N_2 (50 mL per minute).

Crystalline Form M of a Sodium Salt of Compound I

[00140] In some embodiments, the present disclosure provides crystalline Form M of a sodium salt of Compound **I**:

[00141] **FIG. 10A** shows an X-ray powder diffractogram of crystalline Form M of a sodium salt of Compound **I** at ambient conditions.

[00142] Crystalline Form M is a solvate of a sodium salt of Compound **I** comprising up to 1 mole of solvent chosen from methanol, water, and mixtures thereof. Accordingly, crystalline Form M can comprise up to 1 mole of methanol, up to 1 mole of water, or up to 1 mole of a mixture of methanol and water.

[00143] In some embodiments, crystalline Form M of a sodium salt of Compound **I** is in substantially pure form. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation.

[00144] In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 10.5 ± 0.2 degrees two-theta. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is

characterized by an X-ray powder diffractogram having a signal at 11.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 13.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 15.1 ± 0.2 degrees two-theta. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 18.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 19.5 ± 0.2 degrees two-theta. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 19.9 ± 0.2 degrees two-theta.

[00145] In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of

Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2.

[00146] In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, and 18.8 ± 0.2.

[00147] In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 9.3 ± 0.2, 11.3 ± 0.2, and 15.1 ± 0.2. In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 9.3 ± 0.2, 9.9 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, and 18.8 ± 0.2.

[00148] In some embodiments, crystalline Form M of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 10A**.

[00149] In some embodiments, the present disclosure provides crystalline Form M of a sodium salt of Compound **I** prepared by a process comprising reacting Compound **I** with a sodium base in methanol. In some embodiments, the sodium base is chosen from sodium hydroxide, sodium t-butoxide, sodium acetate, sodium bicarbonate, sodium carbonate, sodium methoxide, and sodium ethoxide. In some embodiments, the sodium base is chosen from sodium hydroxide. In some embodiments, the sodium base is

sodium methoxide. In some embodiments, Compound **I** in methanol is reacted with a sodium base, such as sodium hydroxide or sodium methoxide, to generate crystalline Form M of a sodium salt of Compound **I**. In some embodiments, the reaction is performed at room temperature.

[00150] In some embodiments, the present disclosure provides methods of preparing crystalline Form M of a sodium salt of Compound **I** comprising reacting Compound **I** with a sodium base in methanol. In some embodiments, the sodium base is chosen from sodium hydroxide, sodium t-butoxide, sodium acetate, sodium bicarbonate, sodium carbonate, sodium methoxide, and sodium ethoxide. In some embodiments, the sodium base is sodium methoxide. In some embodiments, Compound **I** in methanol is reacted with a sodium base, such as sodium hydroxide or sodium methoxide, to generate crystalline Form M of a sodium salt of Compound **I**. In some embodiments, the reaction is performed at room temperature.

Crystalline Form H of a Sodium Salt of Compound I

[00151] In some embodiments, the present disclosure provides crystalline Form H of a sodium salt of Compound **I**.

[00152] **FIG. 11A** shows an X-ray powder diffractogram of crystalline Form H of a sodium salt of Compound **I** at ambient conditions. In some embodiments, the present disclosure provides crystalline Form H of Compound **I** prepared by a process comprising de-solvating Form M of a sodium salt of Compound **I** disclosed herein.

[00153] In some embodiments, crystalline Form H of a sodium salt of Compound **I** is in substantially pure form. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is the methanol solvate, crystalline Form H of a sodium salt of Compound **I**.

[00154] In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is

characterized by an X-ray powder diffractogram having a signal at 10.5 ± 0.2 degrees two-theta. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 11.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 13.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 15.1 ± 0.2 degrees two-theta. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 18.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 19.5 ± 0.2 degrees two-theta. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 19.9 ± 0.2 degrees two-theta.

[00155] In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen

from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2.

[00156] In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, and 19.9 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, and 18.8 ± 0.2.

[00157] In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 9.3 ± 0.2, 11.3 ± 0.2, and 15.1 ± 0.2. In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 9.3 ± 0.2, 9.9 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, and 18.8 ± 0.2.

[00158] In some embodiments, crystalline Form H of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 11A**.

[00159] In some embodiments, the present disclosure provides crystalline Form H of a sodium salt of Compound **I** prepared by a process comprising de-solvating crystalline Form M or Form E of a sodium salt of Compound **I** in the presence of at least one

source of water. In some embodiments, the at least one source of water is water. In some embodiments, the at least one source of water is moisture in air.

[00160] In some embodiments, the present disclosure provides methods of preparing crystalline Form H of a sodium salt of Compound **I** comprising de-solvating crystalline Form M or Form E of a sodium salt of Compound **I** in the presence of at least one source of water. In some embodiments, the at least one source of water is water. In some embodiments, the at least one source of water is moisture in air.

Crystalline Form E of a Sodium Salt of Compound I

[00161] In some embodiments, the present disclosure provides crystalline Form E of a sodium salt of Compound **I**.

[00162] **FIG. 12A** shows an X-ray powder diffractogram of crystalline Form E of a sodium salt of Compound **I** at ambient conditions.

[00163] Crystalline Form E is a solvate of a sodium salt of Compound **I** comprising up to 1 mole of solvent chosen from ethanol, water, and mixtures thereof. Accordingly, crystalline Form E can comprise up to 1 mole of ethanol, up to 1 mole of water, or up to 1 mole of a mixture of ethanol and water.

[00164] In some embodiments, crystalline Form E of a sodium salt of Compound **I** is in substantially pure form. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation.

[00165] In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 5.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 11.4 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 14.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is

characterized by an X-ray powder diffractogram having a signal at 15.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 16.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 17.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 19.0 ± 0.2 degrees two-theta.

[00166] In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 5.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 9.9 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 10.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 11.4 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 14.0 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 15.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 16.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 17.3 ± 0.2 degrees two-theta. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at 19.0 ± 0.2 degrees two-theta.

[00167] In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2,

and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least eight two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2.

[00168] In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at

least eight two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least seven two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least six two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least five two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least four two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two two-theta values chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 5.7 ± 0.2, 9.0 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one two-theta value chosen from 5.7 ± 0.2, 9.0 ± 0.2, 10.0 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2.

[00169] In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.7 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 15.2 ± 0.2, 17.3 ± 0.2, and 19.0

± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 11.4 ± 0.2, 15.2 ± 0.2, and 19.0 ± 0.2. In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 5.7 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 15.2 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2.

[00170] In some embodiments, crystalline Form E of a sodium salt of Compound **I** is characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 12A**.

[00171] In some embodiments, the present disclosure provides crystalline Form E of a sodium salt of Compound **I** prepared by a process comprising reacting Compound **I** with a sodium base in ethanol. In some embodiments, the sodium base is chosen from sodium hydroxide, sodium t-butoxide, sodium acetate, sodium bicarbonate, sodium carbonate, sodium methoxide, and sodium ethoxide. In some embodiments, the sodium base is sodium hydroxide. In some embodiments, the sodium base is sodium methoxide. In some embodiments, Compound **I** in ethanol is reacted with a sodium base, such as sodium hydroxide or sodium methoxide, to generate crystalline Form E of a sodium salt of Compound **I**. In some embodiments, the reaction is performed at room temperature.

[00172] In some embodiments, the present disclosure provides methods of preparing crystalline Form E of a sodium salt of Compound **I** comprising reacting Compound **I** with a sodium base in ethanol. In some embodiments, the sodium base is chosen from sodium hydroxide, sodium t-butoxide, sodium acetate, sodium bicarbonate, sodium carbonate, sodium methoxide, and sodium ethoxide. In some embodiments, the sodium base is sodium hydroxide. In some embodiments, the sodium base is sodium methoxide. In some embodiments, Compound **I** in ethanol is reacted with a sodium base, such as sodium hydroxide or sodium methoxide, to generate crystalline Form E of a sodium salt of Compound **I**. In some embodiments, the reaction is performed at room temperature.

Crystalline Form A of Compound I

[00173] In some embodiments, the present disclosure provides crystalline Form A of Compound **I**.

[00174] **FIG. 13A** shows an X-ray powder diffractogram of crystalline Form A of Compound **I** at ambient conditions.

[00175] In some embodiments, the present disclosure provides crystalline Form A of Compound **I** prepared by a process comprising de-solvating a methanol or ethanol solvate of crystalline Form A of Compound **I**. In some embodiments, the present disclosure provides crystalline Form A of Compound **I** prepared by a process comprising de-solvating a methanol solvate of crystalline Form A of Compound **I**. In some embodiments, the present disclosure provides crystalline Form A of Compound **I** prepared by a process comprising de-solvating an ethanol solvate of crystalline Form A of Compound **I**.

[00176] In some embodiments, crystalline Form A of Compound **I** is in substantially pure form. In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu Kα radiation.

[00177] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram wherein one or more of the signals may shift from batch to batch. As would be recognized by one of ordinary skill in the art, this is likely due to the collapse of the solvate structure from which crystalline Form A of Compound **I** is produced.

[00178] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal ranging from 5.3 ± 0.2 to 5.5 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal ranging from 7.2 ± 0.2 to 7.5 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal ranging from 11.8 ± 0.2 to 12.2 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal ranging from 14.7 ± 0.2 to 15.0 ± 0.2 degrees two-theta. In some embodiments, crystalline

Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal ranging from 16.7 ± 0.2 to 17.1 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal ranging from 17.4 ± 0.2 to 17.7 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal ranging from 18.5 ± 0.2 to 18.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal ranging from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

[00179] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal ranging from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

[00180] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least eight of the following ranges from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

[00181] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least seven of the following ranges chosen from: from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta. In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least six of the following ranges chosen from: from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

[00182] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least five of the following ranges

chosen from: from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

[00183] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least four of the following ranges chosen from: from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

[00184] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three of the following ranges chosen from: from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

[00185] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least two of the following ranges chosen from: from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

[00186] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least one of the following ranges chosen from: from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

[00187] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.5 ± 0.2, 7.6 ± 0.2, 15.1 ± 0.2, 16.7 ± 0.2, 18.9 ± 0.2, and 19.6 ± 0.2. In some

embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at three two-theta values of 7.6 ± 0.2, 15.1 ± 0.2, and 16.7 ± 0.2. In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram having a signal at two-theta values of 5.5 ± 0.2, 7.6 ± 0.2, 15.1 ± 0.2, 16.7 ± 0.2, 18.9 ± 0.2, and 19.6 ± 0.2.

[00188] In some embodiments, crystalline Form A of Compound **I** is characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 13A**. In some embodiments, the present disclosure provides methods of preparing crystalline Form A of Compound **I** comprising de-solvating at least one solvate of Compound **I** chosen from ethanol solvates of Compound **I** and methanol solvates of Compound **I**.

Solvates

[00189] In some embodiments, the present disclosure provides at least one solvate of Compound **I** chosen from 1,4-dioxane solvates, 2-methyl tetrahydrofuran solvates, ethanol solvates, nitromethane solvates, 1-propanol solvates, tetrahydrofuran solvates, toluene solvates, pyridine solvates, chlorobenzene solvates, diethyl ether solvates, 2-propanol solvates, 2-butanol solvates, hexane solvates, heptane solvates, ethyl acetate solvates, methanol solvates, dichloromethane solvates, acetone solvates, methyl tert-butyl ether solvates, n-butanol solvates, N-methyl-2-pyrrolidone solvates, and t-butanol solvates of Compound **I**. Such solvates of Compound **I** can be prepared by stirring Compound **I** in a relevant solvent.

[00190] In some embodiments, the present disclosure provides at least one solvate of a sodium salt of Compound **I** chosen from ethanol solvates and methanol solvates of a sodium salt of Compound **I**. Such solvates of Compound **I** can be prepared by stirring a sodium salt of Compound **I** in a relevant solvent or reacting Compound **I** with a sodium base in a relevant solvent. In some embodiments, ethanol solvates of a sodium salt of Compound **I** are prepared by reacting Compound **I** with a sodium base in ethanol. In some embodiments, methanol solvates of a sodium salt of Compound **I** are prepared by reacting Compound **I** with a sodium base in methanol. Examples of suitable sodium bases are as described above for crystalline Form M and Form E of a sodium salt of Compound **I**.

[00191] In some embodiments, the present disclosure provides at least one solvate of a potassium salt of Compound **I** chosen from 1-pentanol solvates, isopropyl acetate solvates, 1-propanol solvates, acetone solvates, acetonitrile solvates, 2-methyl tetrahydrofuran solvates, ethyl acetate solvates, methanol solvates, ethanol solvates, methyl tert-butyl ether solvates, and methyl ethyl ketone solvates of a potassium salt of Compound **I**. In some embodiments, a solvate of a potassium salt of Compound **I** is chosen from 1-pentanol solvates, isopropyl acetate solvates, acetone solvates, acetonitrile solvates, 2-methyl tetrahydrofuran solvates, ethyl acetate solvates, methyl tert-butyl ether solvates, and methyl ethyl ketone solvates of a potassium salt of Compound **I**. Such solvates of Compound **I** can be prepared by stirring a potassium salt of Compound **I** in a relevant solvent or reacting Compound **I** with a potassium base in a relevant solvent. In some embodiments, ethanol solvates of a postassium salt of Compound **I** are prepared by reacting Compound **I** with a potassium base in ethanol. In some embodiments, methanol solvates of a potassium salt of Compound **I** are prepared by reacting Compound **I** with a potassium base in methanol. Examples of suitable potassium bases are as described above for crystalline Form B of a potassium salt of Compound **I**.

Isotopically Enriched Compounds

[00192] In some embodiments, the disclosure also is directed to isotope-labelled compounds of the afore-mentioned compounds, which have the same structures as disclosed herein except that one or more atoms therein have been replaced by an atom or atoms having an atomic mass or mass number which differs from the atomic mass or mass number of the atom which usually occurs naturally (isotope labelled). Examples of isotopes which are commercially available and suitable for the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, for example ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively.

[00193] The isotope-labelled compounds and salts can be used in a number of beneficial ways. They can be suitable for medicaments and/or various types of assays, such as substrate tissue distribution assays. For example, tritium (^{3}H)- and/or carbon-14 (^{14}C)-labelled compounds are particularly useful for various types of assays, such as substrate tissue distribution assays, due to relatively simple preparation and excellent detectability. For example, deuterium (^{2}H)-labelled ones are therapeutically useful with

potential therapeutic advantages over the non-^{2}H-labelled compounds. In general, deuterium (^{2}H)-labelled compounds and salts can have higher metabolic stability as compared to those that are not isotope-labelled owing to the kinetic isotope effect described below. Higher metabolic stability translates directly into an increased in vivo half-life or lower dosages, which could be desired. The isotope-labelled compounds and salts can usually be prepared by carrying out the procedures disclosed in the synthesis schemes and the related description, in the example part and in the preparation part in the present text, replacing a non-isotope-labelled reactant by a readily available isotope-labelled reactant.

[00194] In some embodiments, the isotope-labelled compounds and salts are deuterium (^{2}H)-labelled ones. In some specific embodiments, the isotope-labelled compounds and salts are deuterium (^{2}H)-labelled, wherein one or more hydrogen atoms therein have been replaced by deuterium. In chemical structures, deuterium is represented as "^{2}H" or "D."

[00195] The deuterium (^{2}H)-labelled compounds and salts can manipulate the oxidative metabolism of the compound by way of the primary kinetic isotope effect. The primary kinetic isotope effect is a change of the rate for a chemical reaction that results from exchange of isotopic nuclei, which in turn is caused by the change in ground state energies necessary for covalent bond formation after this isotopic exchange. Exchange of a heavier isotope usually results in a lowering of the ground state energy for a chemical bond and thus causes a reduction in the rate-limiting bond breakage. If the bond breakage occurs in or in the vicinity of a saddle-point region along the coordinate of a multi-product reaction, the product distribution ratios can be altered substantially. For explanation: if deuterium is bonded to a carbon atom at a non-exchangeable position, rate differences of k_M/k_D = 2-7 are typical. For a further discussion, see S. L. Harbeson and R. D. Tung, *Deuterium In Drug Discovery and Development*, Ann. Rep. Med. Chem. 2011, 46, 403-417; and T.G. Gant "Using deuterium in drug discovery: leaving the label in the drug" J. Med. Chem. 2014, 57, 3595-3611, relevant portions of which are independently incorporated herein by reference.

[00196] The concentration of the isotope(s) (e.g., deuterium) incorporated into the isotope-labelled compounds and salt of the disclosure may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio

between the isotopic abundance and the natural abundance of a specified isotope. In some embodiments, if a substituent in a compound of the disclosure is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[00197] When discovering and developing therapeutic agents, the person skilled in the art attempts to optimize pharmacokinetic parameters while retaining desirable in vitro properties. It may be reasonable to assume that many compounds with poor pharmacokinetic profiles are susceptible to oxidative metabolism.

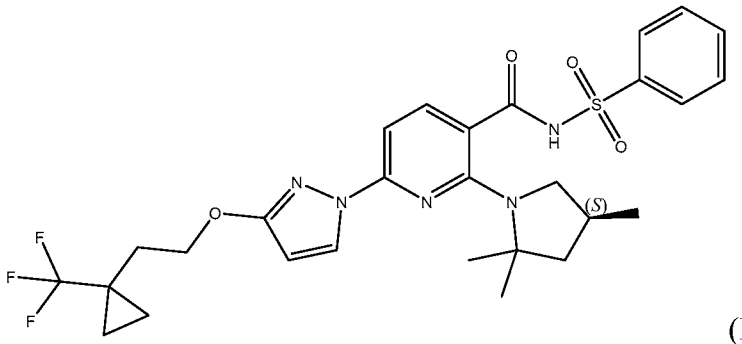
[00198] One of ordinary skill in the art would understand that deuteration of one or more metabolically labile positions on a compound or active metabolite may lead to improvement of one or more superior DMPK properties while maintaining biological activity as compared to the corresponding hydrogen analogs. The superior DMPK property or properties may have an impact on the exposure, half-life, clearance, metabolism, and/or even food requirements for optimal absorption of the drug product. Deuteration may also change the metabolism at other non-deuterated positions of the deuterated compound.

[00199] In some embodiments, the pharmaceutical compositions are a tablet. In some embodiments, the tablets are suitable for oral administration. In some embodiments, the tablets can be administered concurrently with, prior to, or subsequent to, at least one active pharmaceutical ingredients or medical procedures.

Exemplary Embodiments of Crystalline Forms of Compound I

[00200] Exemplary embodiments of crystalline forms of Compound **I** and pharmaceutically acceptable salts and solvates thereof include:

1. Crystalline Form B of a potassium salt of Compound **I**:



(I).

2. Crystalline Form B according to embodiment 1 in substantially pure form.

3. Crystalline Form B according to embodiment 1, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2.

4. Crystalline Form B according to embodiment 1, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 16.3 ± 0.2, and 19.1 ± 0.2.

5. Crystalline Form B according to embodiment 1, characterized by an X-ray powder diffractogram having a signal at three two-theta values of 5.8 ± 0.2, 10.2 ± 0.2, and 19.1 ± 0.2.

6. Crystalline Form B according to embodiment 1, characterized by an X-ray powder diffractogram having a signal at six two-theta values of 5.8 ± 0.2, 8.2 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 16.3 ± 0.2, and 19.1 ± 0.2.

7. Crystalline Form B of embodiment 1, characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 1A**.

8. Crystalline Form B of embodiment 1 having a unit cell characterized by three edges of 9.0 ± 0.2 Å, 11.5 ± 0.2 Å, and 31.0 ± 0.2 Å.

9. Crystalline Form B of a potassium salt of Compound **I** prepared by a process comprising reacting Compound **I** with a potassium base.

10. A method of preparing Crystalline Form B of a potassium salt of Compound **I**, comprising reacting Compound **I** with a potassium base.

11. The method of embodiment 1, wherein said potassium base is KOH.

12. Crystalline Form C of a potassium salt/co-crystal of Compound **I**.

13. Crystalline Form C according to embodiment 12 in substantially pure form.

14. Crystalline Form C according to embodiment 12, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12.4 ± 0.2, and 16.0 ± 0.2.

15. Crystalline Form C according to embodiment 12, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, and 11.5 ± 0.2.

16. Crystalline Form C according to embodiment 12, characterized by an X-ray powder diffractogram having a signal at three two-theta values of 3.7 ± 0.2, 7.0 ± 0.2, and 11.4 ± 0.2.

17. Crystalline Form C according to embodiment 12, characterized by an X-ray powder diffractogram having a signal at six two-theta values of 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, and 11.5 ± 0.2.

18. Crystalline Form C of embodiment 12, characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 7A**.

19. Crystalline Form C of a potassium salt/co-crystal of Compound **I** prepared by a process comprising stirring a potassium salt of Compound **I** with a solvent system comprising at least one source of water.

20. A method of preparing Crystalline Form C of a potassium salt/co-crystal of Compound **I**, comprising stirring a potassium salt of Compound **I** with a solvent system comprising at least one source of water.

21. Crystalline Form A of a sodium salt of Compound **I**.

22. Crystalline Form A according to embodiment 21 in substantially pure form.

23. Crystalline Form A according to embodiment 21, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 6.3 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 11.1 ± 0.2, 12.2 ± 0.2, 12.6 ± 0.2, and 14.0 ± 0.2.

24. Crystalline Form A according to embodiment 21, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.7 ± 0.2, 4.9 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 12.2 ± 0.2, and 12.6 ± 0.2.

25. Crystalline Form A according to embodiment 21, characterized by an X-ray powder diffractogram having a signal at three two-theta values of 4.7 ± 0.2, 8.0 ± 0.2, and 12.2 ± 0.2.

26. Crystalline Form A according to embodiment 21, characterized by an X-ray powder diffractogram having a signal at six two-theta values of 4.7 ± 0.2, 4.9 ± 0.2, 8.0 ± 0.2, 8.3 ± 0.2, 12.2 ± 0.2, and 12.6 ± 0.2.

27. Crystalline Form A of embodiment 21, characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 8A**.

28. A method of preparing crystalline Form A of a sodium salt of Compound **I** comprising reacting Compound **I** with a sodium base.

29. Crystalline Form D of a sodium salt of Compound **I**.

30. Crystalline Form D according to embodiment 29 in substantially pure form.

31. Crystalline Form D according to embodiment 29, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 7.0 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 11.3 ± 0.2, 12.2 ± 0.2, 14.0 ± 0.2, and 16.0 ± 0.2.

32. Crystalline Form D according to embodiment 29, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 4.9 ± 0.2, 5.7 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 12.2 ± 0.2, and 14.0 ± 0.2.

33. Crystalline Form D according to embodiment 29, characterized by an X-ray powder diffractogram having a signal at three two-theta values of 4.9 ± 0.2, 8.0 ± 0.2, and 12.2 ± 0.2.

34. Crystalline Form D according to embodiment 29, characterized by an X-ray powder diffractogram having a signal at six two-theta values of 4.9 ± 0.2, 5.7 ± 0.2, 8.0 ± 0.2, 9.8 ± 0.2, 12.2 ± 0.2, and 14.0 ± 0.2.

35. Crystalline Form D of embodiment 29, characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 9A**.

36. A method of preparing crystalline Form D of a sodium salt Compound **I**, comprising heating a crystalline Form M or Form E of a sodium salt of Compound **I** at a temperature in a range from 280 °C to 300 °C under anhydrous conditions.

37. Crystalline Form M of a sodium salt of Compound **I**.

38. Crystalline Form M according to embodiment 37 in substantially pure form.

39. Crystalline Form M according to embodiment 37, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.50 ± 0.2, and 19.9 ± 0.2.

40. Crystalline Form M according to embodiment 37, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, and 18.8 ± 0.2.

41. Crystalline Form M according to embodiment 37, characterized by an X-ray powder diffractogram having a signal at three two-theta values of 9.3 ± 0.2, 11.3 ± 0.2, and 15.1 ± 0.2.

42. Crystalline Form M according to embodiment 37, characterized by an X-ray powder diffractogram having a signal at six two-theta values of 9.3 ± 0.2, 9.9 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, and 18.8 ± 0.2.

43. Crystalline Form M of embodiment 37, characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 10A**.

44. A method of preparing crystalline Form M of a sodium salt of Compound **I** comprising reacting Compound **I** with a sodium base in methanol.

45. Crystalline Form A of Compound **I**.

46. Crystalline Form A according to embodiment 45 in substantially pure form.

47. Crystalline Form A according to embodiment 45, characterized by an X-ray powder diffractogram having a signal ranging from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

48. Crystalline Form A according to embodiment 45, characterized by an X-ray powder diffractogram having at least three signals chosen from signals in the following two-theta value ranges: from 5.3 ± 0.2 to 5.5 ± 0.2, from 7.2 ± 0.2 to 7.5 ± 0.2, from 11.8 ± 0.2 to 12.2 ± 0.2, from 14.7 ± 0.2 to 15.0 ± 0.2, from 16.7 ± 0.2 to 17.1 ± 0.2, from 17.4 ± 0.2 to 17.7 ± 0.2, from 18.5 ± 0.2 to 18.8 ± 0.2, and from 19.5 ± 0.2 to 19.8 ± 0.2 degrees two-theta.

49. Crystalline Form A of embodiment 45, characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 13A**.

50. A method of preparing crystalline Form A of Compound **I** comprising de-solvating at least one solvate of Compound **I** chosen from ethanol solvates of Compound **I** and methanol solvates of Compound **I**.

51. A crystalline form of Compound **I** prepared by de-solvating at least one solvate of Compound **I** chosen from ethanol solvates of Compound **I** and methanol solvates of Compound **I**.

52. Crystalline Form E of a sodium salt of Compound **I**.

53. Crystalline Form E according to embodiment 52 in substantially pure form.

54. Crystalline Form E according to embodiment 52, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.7± 0.2, 9.1 ± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2.

55. Crystalline Form E according to embodiment 52, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.7 ± 0.2, 9.1 ± 0.2, 9.9 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2.

56. Crystalline Form E according to embodiment 52, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.7 ± 0.2, 9.1 ± 0.2, 10.0 ± 0.2, 10.2 ± 0.2, 11.4 ± 0.2, 14.0 ± 0.2, 15.2 ± 0.2, 16.3 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2.

57. Crystalline Form E according to embodiment 52, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.7± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 15.2 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2.

58. Crystalline Form E according to embodiment 52, characterized by an X-ray powder diffractogram having a signal at three two-theta values of 11.4 ± 0.2, 15.2 ± 0.2, and 19.0 ± 0.2.

59. Crystalline Form E according to embodiment 52, characterized by an X-ray powder diffractogram having a signal at sixtwo-theta values of 5.7± 0.2, 9.9 ± 0.2, 11.4 ± 0.2, 15.2 ± 0.2, 17.3 ± 0.2, and 19.0 ± 0.2.

60. Crystalline Form E of embodiment 52, characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 12A**.

61. A method of preparing crystalline Form E of a sodium salt of Compound **I** comprising reacting Compound **I** with a sodium base in ethanol.

62. Crystalline Form H of a sodium salt of Compound **I**.

63. Crystalline Form H according to embodiment 62 in substantially pure form.

64. Crystalline Form H according to embodiment 62, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 10.5 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, 18.8 ± 0.2, 19.50 ± 0.2, and 19.9 ± 0.2.

65. Crystalline Form H according to embodiment 62, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 9.3 ± 0.2, 9.9 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, and 18.8 ± 0.2.

66. Crystalline Form H according to embodiment 62, characterized by an X-ray powder diffractogram having a signal at three two-theta values of 9.3 ± 0.2, 11.3 ± 0.2, and 15.1 ± 0.2.

67. Crystalline Form H according to embodiment 62, characterized by an X-ray powder diffractogram having a signal at six two-theta values of 9.3 ± 0.2, 9.9 ± 0.2, 11.3 ± 0.2, 13.9 ± 0.2, 15.1 ± 0.2, and 18.8 ± 0.2.

68. A method of preparing crystalline Form H of a sodium salt of Compound **I** comprising de-solvating crystalline Form M or Form E of a sodium salt of Compound **I** or crystalline Form E of a sodium salt of Compound **I** in the presence of one source of water.

69. A pharmaceutical formulation comprising at least one crystalline form according to any one of embodiments 1 – 68 and a pharmaceutically acceptable carrier.

70. A method of treating cystic fibrosis comprising administering to a patient in need thereof at least one crystalline form according to any one of embodiments 1 – 68 or pharmaceutical composition of embodiment 69.

71. At least one solvate of Compound **I** chosen from 1,4-dioxane solvates, 2-methyl tetrahydrofuran solvates, ethanol solvates, nitromethane solvates, 1-propanol solvates, tetrahydrofuran solvates, toluene solvates, pyridine solvates, chlorobenzene solvates, diethyl ether solvates, 2-propanol solvates, 2-butanol solvates, hexane solvates, heptane solvates, ethyl acetate solvates, methanol solvates, dichloromethane solvates, acetone solvates, methyl tert-butyl ether solvates, n-butanol solvates, N-methyl-2-pyrrolidone solvates, and t-butanol solvates of Compound **I**.

72. At least one solvate of a sodium salt Compound **I** chosen from ethanol solvates and methanol solvates of the sodium salt of Compound **I**.

73. At least one solvate of a potassium salt Compound **I** chosen from 1-pentanol solvates, isopropyl acetate solvates, 1-propanol solvates, acetone solvates, acetonitrile

solvates, 2-methyl tetrahydrofuran solvates, ethyl acetate solvates, methanol solvates, ethanol solvates, methyl tert-butyl ether solvates, and methyl ethyl ketone solvates of a potassium salt of Compound **I**.

Compositions

[00201] In some embodiments, the present disclosure provides compositions comprising at least one crystalline form of Compound **I** and pharmaceutically acceptable salts thereof disclosed herein and a pharmaceutically acceptable carrier. In some embodiments, the compositions of the invention comprise at least one crystalline form of salt/co-crystal of Compound **I** disclosed herein and a pharmaceutically acceptable carrier. In some embodiments, these compositions comprise one or more additional CFTR modulating agents.

[00202] In some embodiments, the pharmaceutical compositions disclosed herein comprise a potassium salt of Compound I (in some embodiments, potassium salt crystalline Form B), either as a mixture with other forms (crystalline and/or amorphous) or a substantially pure form. In some embodiments, the pharmaceutical compositions disclosed herein comprise substantially pure crystalline Form B of a potassium salt of Compound **I**.

[00203] In some embodiments, the pharmaceutical compositions disclosed herein comprise crystalline Form C of a potassium salt/co-crystal of Compound **I,** either as a mixture with other forms (crystalline and/or amorphous) or a substantially pure form. In some embodiments, the pharmaceutical compositions disclosed herein comprise substantially pure crystalline Form C of a potassium salt/co-crystal of Compound **I**.

[00204] In some embodiments, the pharmaceutical compositions disclosed herein comprise a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), either alone or in combination with one or more CFTR modulating agents. In some embodiments, the pharmaceutical composition comprises a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), in combination with Compound **II** and optionally one or more additional CFTR modulating agents. In some embodiments, the pharmaceutical composition comprises a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) in combination with Compound **III** and optionally one or more additional CFTR

modulating agents. In some embodiments, the pharmaceutical compositions disclosed herein comprise a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) in combination with Compound **II** and/or Compound **III** or **III-d**.

Solid Dispersions

[00205] In some embodiments, the pharmaceutical compositions disclosed herein comprise a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), either as a mixture with other forms (crystalline and/or amorphous) or a substantially pure form together with a first solid dispersion and/or a second solid dispersion. In some embodiments, the first solid dispersion is a spray dried dispersion comprising Compound **II**. In some embodiments, the second solid dispersion is selected from a spray-dried dispersion comprising Compound **III** or Compound **III-d**. In some embodiments, the first solid dispersion is a spray dried dispersion comprising Compound **II** and the second solid dispersion is a spray dried dispersion comprising Compound **III** or Compound **III-d**.

[00206] In some embodiments, each of the first and second solid dispersions, such as the first and second spray dried dispersions, independently comprises a plurality of particles having a mean particle diameter of 5 to 100 microns. In some embodiments, each of the first and second solid dispersions, such as the first and secondspray dried dispersions, independently comprises a plurality of particles having a mean particle diameter of 5 to 30 microns. In some embodiments, each of the first and second solid dispersions, such as the first and second spray dried dispersions, independently comprises a plurality of particles having a mean particle diameter of 15 microns.

[00207] In some embodiments, the first solid dispersions and the first spray dried dispersions of the disclosure independently comprises substantially amorphous Compound **II**. In some embodiments, the second solid dispersions and the second spray dried dispersions of the disclosure independently comprises substantially amorphous Compound **III** or Compound **III-d**.

[00208] In some embodiments, the solid dispersions and the spray dried dispersions of the disclosure can comprise other excipients, such as polymers and/or surfactants. Any suitable polymers and surfactants known in the art can be used in the disclosure. Certain exemplary polymers and surfactants are as described below.

[00209] Solid dispersions of any one of Compounds **II**, Compound **III** and Compound **III-d** may be prepared by any suitable method know in the art, e.g., spray drying,

lyophilizing, hot melting, or cyrogrounding/cryomilling techniques. For example, see WO2015/160787. Typically such spray drying, lyophilizing, hot melting or cyrogrounding/cryomilling techniques generates an amorphous form of API (e.g., Compound **II** or Compound **III**, or Compound **III-d**).

[00210] Spray drying is a process that converts a liquid feed to a dried particulate form. Optionally, a secondary drying process such as fluidized bed drying or vacuum drying may be used to reduce residual solvents to pharmaceutically acceptable levels. Typically, spray drying involves contacting a highly dispersed liquid suspension or solution, and a sufficient volume of hot gasto produce evaporation and drying of the liquid droplets. The preparation to be spray dried can be any solution, coarse suspension, slurry, colloidal dispersion, or paste that may be atomized using the selected spray drying apparatus. In one procedure, the preparation is sprayed into a current of warm filtered gas that evaporates the solvent and conveys the dried product to a collector (e.g. a cyclone). The spent gas is then exhausted with the solvent, or alternatively the spent air is sent to a condenser to capture and potentially recycle the solvent. Commercially available types of apparatus may be used to conduct the spray drying. For example, commercial spray dryers are manufactured by Buchi Ltd. And Niro (e.g., the PSD line of spray driers manufactured by Niro) (see, US 2004/0105820; US 2003/0144257).

[00211] Techniques and methods for spray drying may be found in Perry's Chemical Engineering Handbook, 6th Ed., R. H. Perry, D. W. Green & J. O. Maloney, eds.), McGraw-Hill book co. (1984); and Marshall "Atomization and Spray-Drying" 50, Chem. Eng. Prog. Monogr. Series 2 (1954).

[00212] Removal of the solvent may require a subsequent drying step, such as tray drying, fluid bed drying, vacuum drying, microwave drying, rotary drum drying or biconical vacuum drying.

[00213] In one embodiment, the solid dispersions and the spray dried dispersions of the disclosure are fluid bed dried.

[00214] In one process, the solvent includes a volatile solvent, for example a solvent having a boiling point of less than 100 °C. In some embodiments, the solvent includes a mixture of solvents, for example a mixture of volatile solvents or a mixture of volatile and non-volatile solvents. Where mixtures of solvents are used, the mixture can include one or more non-volatile solvents, for example, where the non-volatile solvent is present

in the mixture at less than 15%, e.g., less than 12%, less than 10%, less than 8%, less than 5%, less than 3%, or less than 2%.

[00215] In some processes, solvents are those solvents where the API(s) (e.g., Compound **II** and/or Compound **III**) has solubilities of at least 10 mg/ml, (e.g., at least 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 35 mg/ml, 40 mg/ml, 45 mg/ml, 50 mg/ml, or greater). In other processes, solvents include those solvents where the API(s) (e.g., Compound **II** and/or Compound **III**) has a solubility of at least 20 mg/ml.

[00216] Exemplary solvents that could be tested include acetone, cyclohexane, dichloromethane or methylene chloride (DCM), N,N-dimethylacetamide (DMA), N,N-dimethylformamide (DMF), 1,3-dimethyl-2-imidazolidinone (DMI), dimethyl sulfoxide (DMSO), dioxane, ethyl acetate, ethyl ether, glacial acetic acid (HAc), methyl ethyl ketone (MEK), N-methyl-2-pyrrolidinone (NMP), methyl tert-butyl ether (MTBE), tetrahydrofuran (THF), pentane, acetonitrile, methanol, ethanol, isopropyl alcohol, isopropyl acetate, and toluene. Exemplary co-solvents include DCM/methanol, acetone/DMSO, acetone/DMF, acetone/water, MEK/water, THF/water, dioxane/water. In a two solvent system, the solvents can be present in of from 0.1% to 99.9% w/w. In some preferred embodiments, water is a co-solvent with acetone where water is present from 0.1% to 15%, for example 9% to 11%, e.g., 10%. In some preferred embodiments, water is a co-solvent with MEK where water is present from 0.1% to 15%, for example 9% to 11%, e.g., 10%. In some embodiments the solvent system includes three solvents. Certain exemplary solvents include those described above, for example, MEK, DCM, water, methanol, IPA, and mixtures thereof.

[00217] The particle size and the temperature drying range may be modified to prepare an optimal solid dispersion. As would be appreciated by skilled practitioners, a small particle size would lead to improved solvent removal. Applicants have found however, that smaller particles can lead to fluffy particles that, under some circumstances do not provide optimal solid dispersions for downstream processing such as tableting.

[00218] A solid dispersion (e.g., a spray dried dispersion) dislcosed herein may optionally include a surfactant. A surfactant or surfactant mixture would generally decrease the interfacial tension between the solid dispersion and an aqueous medium. An appropriate surfactant or surfactant mixture may also enhance aqueous solubility and bioavailability of the API(s) (e.g., Compound **II** and/or Compound **III**) from a solid dispersion. The surfactants for use in connection with the disclosure include, but are not

limited to, sorbitan fatty acid esters (e.g., Spans®), polyoxyethylene sorbitan fatty acid esters (e.g., Tweens®), sodium lauryl sulfate (SLS), sodium dodecylbenzene sulfonate (SDBS) dioctyl sodium sulfosuccinate (Docusate sodium), dioxycholic acid sodium salt (DOSS), Sorbitan Monostearate, Sorbitan Tristearate, hexadecyltrimethyl ammonium bromide (HTAB), Sodium N-lauroylsarcosine, Sodium Oleate, Sodium Myristate, Sodium Stearate, Sodium Palmitate, Gelucire 44/14, ethylenediamine tetraacetic acid (EDTA), Vitamin E d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), Lecithin, MW 677-692, Glutanic acid monosodium monohydrate, Labrasol, PEG 8 caprylic/capric glycerides, Transcutol, diethylene glycol monoethyl ether, Solutol HS-15, polyethylene glycol/hydroxystearate, Taurocholic Acid, Pluronic F68, Pluronic F108, and Pluronic F127 (or any other polyoxyethylene-polyoxypropylene co-polymers (Pluronics®) or saturated polyglycolized glycerides (Gelucirs®)). Specific example of such surfactants that may be used in connection with this disclosure include, but are not limited to, Span 65, Span 25, Tween 20, Capryol 90, Pluronic F108, sodium lauryl sulfate (SLS), Vitamin E TPGS, pluronics and copolymers.

[00219] In some embodiments, SLS is used as a surfactant in the solid dispersion of Compound **III**.

[00220] In some embodiments, SLS is used as a surfactant in the solid dispersion of Compound **III-d**.

[00221] The amount of the surfactant (e.g., SLS) relative to the total weight of the solid dispersion may be between 0.1 - 15% w/w. For example, it is from 0.5% to 10%, such as from 0.5 to 5%, e.g., 0.5 to 4%, 0.5 to 3%, 0.5 to 2%, 0.5 to 1%, or 0.5%.

[00222] In certain embodiments, the amount of the surfactant relative to the total weight of the solid dispersion is at least 0.1% or at least 0.5%. In these embodiments, the surfactant would be present in an amount of no more than 15%, or no more than 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1%. In some mebodiments, the surfactant is in an amount of 0.5% by weight.

[00223] Candidate surfactants (or other components) can be tested for suitability for use in the disclosure in a manner similar to that described for testing polymers.

[00224] One aspect of the disclosure provides a method of generating a spray dried dispersion comprising (i) providing a mixture of one or more APIs and a solvent; and

(ii) forcing the mixture through a nozzle and subjecting the mixture to spray drying conditions to generate the spray dried dispersion.

[00225] Another aspect of the disclosure provides a method of generating a spray dried dispersion comprising: (i) providing a mixture comprising one or more APIs and a solvent(s); and (ii) forcing the mixture out of a nozzle under spray dry drying conditions to generate a spray dried dispersion.

[00226] Another aspect of the disclosure provides a method of generating a spray dried dispersion comprising (i) spraying a mixture through a nozzle, wherein the mixture comprises one or more APIs and a solvent; and (ii) forcing the mixture through a nozzle under spray drying conditions to generate a particle that comprises the APIs.

[00227] Another aspect of the disclosure provides a spray dried dispersion comprising one or more APIs, wherein the dispersion is substantially free of a polymer, and wherein the spray dried dispersion is generated by (i) providing a mixture that consists essentially of one or more APIs and a solvent; and (ii) forcing the mixture through a nozzle under spray drying conditions to generate the spray dried dispersion.

[00228] Another aspect of the disclosure provides a spray dried dispersion comprising one or more APIs, wherein the dispersion is generated by (i) providing a mixture that comprising one or more APIs, a polymer(s), and a solvent(s); and (ii) forcing the mixture through a nozzle under spray drying conditions to generate the spray dried dispersion.

[00229] Another aspect of the disclosure provides a spray dried dispersion comprising a particle, wherein the particle comprises one or more APIs and a polymer(s), and wherein the spray dried dispersion is generated by (i) spraying a mixture through a nozzle, wherein the mixture comprises one or more APIs and a solvent; and (ii) forcing the mixture through a nozzle under spray drying conditions to generate the spray dried dispersion.

[00230] Another aspect of the disclosure provides a spray dried dispersion comprising a particle, wherein the particle comprises one or more APIs, and the particle is substantially free of a polymer, and wherein the spray dried dispersion is generated by (i) spraying a mixture through a nozzle, wherein the mixture comprises one or more

APIs and a solvent; and (ii) forcing the mixture through a nozzle under spray drying conditions to generate the spray dried dispersion.

[00231] In some embodiments, the one or more APIs are selected from Compound **II** and Compound **III**. In some embodiments, the one or more APIs are selected from Compound **II** and Compound **III-d**.

[00232] Some embodiments further comprise further drying the spray dried dispersion. For example, the spray dried dispersion is dried under reduced pressure. In other examples, the spray dried dispersion is dried at a temperature of from 50 °C to 100 °C.

[00233] In some embodiments, the solvent comprises a polar organic solvent. Examples of polar organic solvents include methylethyl ketone, THF, DCM, methanol, or IPA, or any combination thereof, such as, for example DCM/methanol. In other examples, the solvent further comprises water. In other examples, the solvent further comprises water. For instance, the solvent could be methylethyl ketone/water, THF/water, or methylethyl ketone/water/IPA. For example, the ratio of the polar organic solvent to water is from 70:30 to 95:5 by volume. In other instances, the ratio of the polar organic solvent to water is 90:10 by volume.

[00234] Some embodiments further comprise filtering the mixture before it is forced through the nozzle. Such filtering can be accomplished using any suitable filter media having a suitable pore size.

[00235] Some embodiments further comprise applying heat to the mixture as it enters the nozzle. This heating can be accomplished using any suitable heating element.

[00236] In some embodiments, the nozzle comprises an inlet and an outlet, and the inlet is heated to a temperature that is less than the boiling point of the solvent. For example, the inlet is heated to a temperature of from 90 °C to 150 °C.

[00237] In some embodiments, the mixture is forced through the nozzle by a pressurized gas. Examples of suitable pressurized gases include those pressurized gas that are inert to the first agent, the second agent, and the solvent. In one example, the pressurized gas comprises elemental nitrogen.

[00238] In some embodiments, the pressurized gas has a positive pressure of from 90 psi to 150 psi.

[00239] Some embodiments further comprise further drying the spray dried dispersion. For example, the spray dried dispersion is dried under reduced pressure. In other examples, the spray dried dispersion is dried at a temperature of from 50 °C to 100 °C.

[00240] In some embodiments, the solvent comprises a polar organic solvent. Examples of polar organic solvents include methylethyl ketone, THF, DCM, methanol, or IPA, or any combination thereof. In other examples, the solvent further comprises water. In other examples, the solvent further comprises water. For instance, the solvent could be methylethyl ketone/water, THF/water, or methylethyl ketone/water/IPA. For example, the ratio of the polar organic solvent to water is from 70:30 to 95:5 by volume. In other instances, the ratio of the polar organic solvent to water is 90:10 by volume.

[00241] In some embodiments, a pharmaceutically acceptale composition of the disclosure comprising substantially amorphous API(s) (e.g., Compound **II** and/or Compound **III** or **III-d**) may be prepared by non-spray drying techniques, such as, for example, cyrogrounding/cryomilling techniques. A composition comprising substantially amorphous API(s) (e.g., Compound **II** and/or Compound **III** or **III-d**) may also be prepared by hot melt extrusion techniques.

[00242] In some embodiments, the solid dispersions (e.g., spray dried dispersions) of the disclosure comprise a polymer(s). Any suitable polymers known in the art can be used in the disclosure. Exemplary suitable polymers include polymers selected from cellulose-based polymers, polyoxyethylene-based polymers, polyethylene–propylene glycol copolymers, vinyl-based polymers, PEO-polyvinyl caprolactam-based polymers, and polymethacrylate-based polymers.

[00243] The cellulose-based polymers include a methylcellulose, a hydroxypropyl methylcellulose (HPMC) (hypromellose), a hypromellose phthalate (HPMC-P), a hypromellose acetate succinate, and co-polymers thereof. The polyoxyethylene-based polymers include a polyethylene–propylene glycol, a polyethylene glycol, a poloxamer, and co-polymers thereof. The vinyl-based polymers include a polyvinylpyrrolidine (PVP), and PVP/VA. The PEO-polyvinyl caprolactam-based polymers include a polyethylene glycol, polyvinyl acetate and polyvinylcaprolactame-based graft copolymer (e.g., Soluplus®). The polymethacrylate-based polymers are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several types are commercially available and may be obtained as the dry powder, aqueous dispersion, or organic solution.

Examples of such polymethacrylate-based polymers include a poly(methacrylic acid, ethyl acrylate) (1:1), a dimethylaminoethyl methacrylate-methylmethacrylate copolymer, and a Eudragit®.

[00244] In some embodiments, the cellulose-based polymer is a hypromellose acetate succinate (also known as hydroxypropyl methylcellulose acetate succinate or HMPCAS) and a hypromellose (also known as hydroxypropyl methylcellulose or HPMC), or a combination of hypromellose acetate succinate and a hypromellose. HPMCAS is available in various grades based on the content of acetyl and succinoyl groups (wt%) in the HPMCAS molecule and on particle size. For example, HPMCAS grades L, M, and H are available. HPMCAS-H is a grade that contains about 10-14 wt% of acetyl groups and about 4-8 wt% of succinoyl groups. Each HPMCAS grade is available in two particle sizes, F (fine) and G (granular). HPMC comes in various types (for example, HPMC E, F, J, and K-types). HPMC E type means that there are about 28-30% methoxy groups and about 7-12% hydroxpropoxy groups. There are various E grades ranging from low to high viscosity. For example, E3 means the viscosity is about 2.4-3.6 millipascal seconds (mPa·s) for HPMC measured at 2% in water at 20°C; E15 means the viscosity is about 12-18 mPa·s for the HPMC measured at 2% in water at 20°C; and E50 means the viscosity is about 40-60 mPa·s for the HPMC measured at 2% in water at 20°C.

[00245] In some embodiments, the cellulose-based polymer is hypromellose E15, hypromellose acetate succinate L or hypromellose acetate succinate H.

[00246] In some embodiments, the polyoxyethylene-based polymer or polyethylene–propylene glycol copolymer is a polyethylene glycol or a pluronic.

[00247] In some embodiments, the polyoxyethylene-based polymer or polyethylene–propylene glycol copolymer is polyethylene glycol 3350 or poloxamer 407.

[00248] In some embodiments, the vinyl-based polymer is a vinylpolyvinylpyrrolidine-based polymer, such as polyvinylpyrrolidine K30 or polyvinylpyrrolidine VA 64.

[00249] In some embodiments, the polymethacrylate polymer is Eudragit L100-55 or Eudragit® E PO.

[00250] In some embodiments, the polymer(s) is selected from cellulosic polymers such as HPMC and/or HPMCAS.

[00251] In one embodiment, a polymer is able to dissolve in aqueous media. The solubility of the polymers may be pH independent or pH dependent. The latter include one or more enteric polymers. The term "enteric polymer" refers to a polymer that is preferentially soluble in the less acidic environment of the intestine relative to the more acid environment of the stomach, for example, a polymer that is insoluble in acidic aqueous media but soluble when the pH is above 5-6. An appropriate polymer is chemically and biologically inert. In order to improve the physical stability of the solid dispersions, the glass transition temperature (Tg) of the polymer is as high as possible. For example, polymers have a glass transition temperature at least equal to or greater than the glass transition temperature of the API. Other polymers have a glass transition temperature that is within 10 to 15 °C of the API.

[00252] Additionally, the hygroscopicity of the polymers is as low, e.g., less than 10%. For the purpose of comparison in this application, the hygroscopicity of a polymer or composition is characterized at 60% relative humidity. In some preferred embodiments, the polymer has less than 10% water absorption, for example less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, or less than 2% water absorption. The hygroscopicity can also affect the physical stability of the solid dispersions. Generally, moisture adsorbed in the polymers can greatly reduce the Tg of the polymers as well as the resulting solid dispersions, which will further reduce the physical stability of the solid dispersions as described above.

[00253] In one embodiment, the polymer is one or more water-soluble polymer(s) or partially water-soluble polymer(s). Water-soluble or partially water-soluble polymers include but are not limited to, cellulose derivatives (e.g., hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC)) or ethylcellulose; polyvinylpyrrolidones (PVP); polyethylene glycols (PEG); polyvinyl alcohols (PVA); acrylates, such as polymethacrylate (e.g., Eudragit® E); cyclodextrins (e.g., β-cyclodextin) and copolymers and derivatives thereof, including for example PVP-VA (polyvinylpyrollidone-vinyl acetate).

[00254] In some embodiments, the polymer is hydroxypropylmethylcellulose (HPMC), such as HPMC E50, HPMC E15, or HPMC E3.

[00255] As discussed herein, the polymer can be a pH-dependent enteric polymer. Such pH-dependent enteric polymers include, but are not limited to, cellulose

derivatives (e.g., cellulose acetate phthalate (CAP)), hydroxypropyl methyl cellulose phthalates (HPMCP), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), carboxymethylcellulose (CMC) or a salt thereof (e.g., a sodium salt such as (CMC-Na)); cellulose acetate trimellitate (CAT), hydroxypropylcellulose acetate phthalate (HPCAP), hydroxypropylmethyl-cellulose acetate phthalate (HPMCAP), and methylcellulose acetate phthalate (MCAP), or polymethacrylates (e.g., Eudragit® S). In some embodiments, the polymer is hydroxypropyl methyl cellulose acetate succinate (HPMCAS). In some embodiments, the polymer is hydroxypropyl methyl cellulose acetate succinate HG grade (HPMCAS-HG).

[00256] In yet another embodiment, the polymer is a polyvinylpyrrolidone co-polymer, for example, avinylpyrrolidone/vinyl acetate co-polymer (PVP/VA).

[00257] In embodiments where Compound **II**, Compound **III** and/or Compound **III-d** forms a solid dispersion with a polymer, for example with an HPMC, HPMCAS, or PVP/VA polymer, the amount of polymer relative to the total weight of the solid dispersion ranges from 0.1% to 99% by weight. Unless otherwise specified, percentages of drug, polymer and other excipients as described within a dispersion are given in weight percentages. The amount of polymer is typically at least 20%, and preferably at least 30%, for example, at least 35%, at least 40%, at least 45%, or 0% (e.g., 49.5%). The amount is typically 99% or less, and preferably 80% or less, for example 75% or less, 70% or less, 65% or less, 60% or less, or 55% or less. In one embodiment, the polymer is in an amount of up to 50% of the total weight of the dispersion (and even more specifically, between 40% and 50%, such as 49%, 49.5%, or 50%).

[00258] In some embodiments, the API (e.g., Compound **II** or Compound **III**) and polymer are present in roughly equal amounts in weight, for example each of the polymer and the drug make up half of the percentage weight of the dispersion. For example, the polymer is present in 49.5 wt % and Compound **II**, Compound **III**, or Compound **III-d** is present in 50 wt%. In another embodiment Compound **II**, Compound **III**, or Compound **III-d** is present in an amount greater than half of the percentage weight of the dispersions. For example, the polymer is present in 20 wt% and Compound **II**, Compound **III**, or Compound **III-d** is present in 80 wt%. In other

embodiments, the polymer is present in 19.5 wt% and Compound **II**, Compound **III**, or Compound **III-d** is present in 80 wt%.

[00259] In some embodiments, the API (e.g., Compound **II** or Compound **III**) and the polymer combined represent 1% to 20% w/w total solid content of the spray drying solution prior to spray drying. In some embodiments, Compound **II**, Compound **III**, or Compound **III-d**, and the polymer combined represent 5% to 15% w/w total solid content of the spray drying solution prior to spray drying. In some embodiments, Compound **II**, Compound **III**, or Compound **III-d**, and the polymer combined represent 11% w/w total solid content of the spray drying solution prior to spray drying.

[00260] In some embodiments, the dispersion further includes other minor ingredients, such as a surfactant (e.g., SLS). In some embodiments, the surfactant is present in less than 10% of the dispersion, for example less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, 1%, or 0.5%.

[00261] In embodiments including a polymer, the polymer is present in an amount effective for stabilizing the solid dispersion. Stabilizing includes inhibiting or preventing, the crystallization of an API (e.g., Compound **II** or Compound **III**). Such stabilizing would inhibit the conversion of the API from amorphous to crystalline form. For example, the polymer would prevent at least a portion (e.g., 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or greater) of the API from converting from an amorphous to a crystalline form. Stabilization can be measured, for example, by measuring the glass transition temperature of the solid dispersion, measuring the amount of crystalline material, measuring the rate of relaxation of the amorphous material, or by measuring the solubility or bioavailability of the API.

[00262] In some embodiments, the polymers for use in the disclosure have a glass transition temperature of no less than 10-15 °C lower than the glass transition temperature of API. In some instances, the glass transition temperature of the polymer is greater than the glass transition temperature of API, and in general at least 50°C higher than the desired storage temperature of the drug product. For example, at least 100 °C, at least 105 °C, at least 105 °C, at least 110 °C, at least 120 °C, at least 130 °C, at least 140 °C, at least 150 °C, at least 160 °C, at least 160 °C, or greater.

[00263] In some embodiments, the polymers for use in the disclosure have similar or better solubility in solvents suitable for spray drying processes relative to that of an API (e.g., Compound **II** or Compound **III**). In some embodiments, the polymer will dissolve in one or more of the same solvents or solvent systems as the API.

[00264] In some embodiments, the polymers for use in the disclosure can increase the solubility of an API (e.g., Compound **II** or Compound **III**) in aqueous and physiologically relative media either relative to the solubility of the API in the absence of polymer or relative to the solubility of the API when combined with a reference polymer. For example, the polymers can increase the solubility of Compound **II**, Compound **III**, or Compound **III-d** by reducing the amount of amorphous Compound **II**, Compound **III**, or Compound **III-d** that converts to a crystalline form(s), either from a solid amorphous dispersion or from a liquid suspension.

[00265] In some embodiments, the polymers for use in the disclosure can decrease the relaxation rate of the amorphous substance.

[00266] In some embodiments, the polymers for use in the disclosure can increase the physical and/or chemical stability of an API (e.g., Compound **II** or Compound **III**).

[00267] In some embodiments, the polymers for use in the disclosure can improve the manufacturability of an API (e.g., Compound **II** or Compound **III**).

[00268] In some embodiments, the polymers for use in the disclosure can improve one or more of the handling, administration or storage properties of an API (e.g., Compound **II** or Compound **III**).

[00269] In some embodiments, the polymers for use in the disclosure have little or no unfavorable interaction with other pharmaceutical components, for example excipients.

[00270] The suitability of a candidate polymer (or other component) can be tested using the spray drying methods (or other methods) described herein to form an amorphous composition. The candidate composition can be compared in terms of stability, resistance to the formation of crystals, or other properties, and compared to a reference preparation, e.g., a preparation of neat amorphous Compound **II**, Compound **III**, or Compound **III-d**. For example, a candidate composition could be tested to determine whether it inhibits the time to onset of solvent mediated crystallization, or the percent conversion at a given time under controlled conditions, by at least 50 %, 75 %,

or 100% as well as the reference preparation, or a candidate composition could be tested to determine if it has improved bioavailability or solubility relative to crystalline Compound **II**, Compound **III**, or Compound **III-d**.

[00271] In one aspect, the disclosure provides pharmaceutical compositions comprising neat Compound **I**-potassium salt (in some embodiments, potassium salt crystalline Form B), a first solid dispersion comprising Compound **II**, and a second solid dispersion compirising Compound **III**.

[00272] In another aspect, the disclosure provides pharmaceutical compositions comprising neat Compound **I**-potassium salt (in some embodiments, potassium salt crystalline Form B), a first solid dispersion comprising Compound **II**, and a second solid dispersion compirising Compound **III-d**.

[00273] In some embodiments, the first solid dispersion comprises a cellulose polymer. For example, the first solid dispersion comprises a hydroxypropyl methylcellulose (HPMC). In some embodiments, the first solid dispersion comprises a weight ratio of HPMC to Compound **II** ranging from 1:10 to 1:1. In some instances, the ratio of HPMC to Compound **II** is from 1:3 to 1:5.

[00274] In some embodiments, the second solid dispersion comprises a cellulose polymer. For example, the second solid dispersion comprises a hydroxypropyl methylcellulose acetate succinate (HPMCAS).

[00275] In some embodiments, each of the first and second solid dispersions comprises a plurality of particles having a mean particle diameter of 5 to 100 microns. In some embodiments, the particles have a mean particle diameter of 5 to 30 microns. In some embodiments, the particules have a mean particle diameter of 15 microns.

[00276] In some embodiments, the first solid dispersion comprises from 70 wt% to 90 wt% (e.g., from 75 wt% to 85 wt%) of Compound **II**.

[00277] In some embodiments, the second solid dispersion comprises from 70 wt% to 90 wt% (e.g., from 75 wt% to 85 wt%) of Compound **III**.

[00278] In some embodiments, the second solid dispersion comprises from 70 wt% to 90 wt% (e.g., from 75 wt% to 85 wt%) of Compound **III-d**.

[00279] In some embodiments, each of the first and second solid dispersions is a spray dried dispersion.

[00280] In some embodiments, the compositions of the invention comprise 100 to 260 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), and optionally comprise one or more additional CFTR modulating agents. In some embodiments, the compositions comprise about 128 mg or about 255-256 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), and optionally comprise one or more additional CFTR modulating agents. In some embodiments, the compositions comprise about 128 mg or about 255-256 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), together with 100 mg of Compound **II** and 150 mg of Compound **III** or 200 mg of Compound **III-d**. In some embodiments the compositions comprise about 128 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), 50 mg of Compound **II,** and 75 mg of Compound **III**. In some embodiments the compositions comprise about 64 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), about 25 mg of Compound **II,** and about 35 mg to 40 mg of Compound **III**.

Exemplary Formulations

[00281] In some embodiments, the pharmaceutical compositions disclosed herein further comprise one or more pharmaceutically acceptable excipients, such as pharmaceutically acceptable vehicles, adjuvants, or carriers.

[00282] Remington: *The Science and Practice of Pharmacy*, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, the contents of each of which is incorporated by reference herein, disclose various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the disclosure, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this disclosure.

[00283] In one embodiment, the pharmaceutical compositions of the disclosure comprise one or more fillers, a disintegrant, and a lubricant.

[00284] Fillers suitable for the pharmaceutical compositions disclosed herein are compatible with the other ingredients of the pharmaceutical compositions, i.e., they do not substantially reduce the solubility, the hardness, the chemical stability, the physical stability, or the biological activity of the pharmaceutical compositions. Exemplary fillers include: celluloses, modified celluloses, (e.g. sodium carboxymethyl cellulose, ethyl cellulose hydroxymethyl cellulose, hydroxypropylcellulose), cellulose acetate, microcrystalline cellulose, calcium phosphates, dibasic calcium phosphate, starches (e.g. corn starch, potato starch), sugars (e.g., mannitol, lactose, sucrose, or the like), or any combination thereof. In one embodiment, the filler is microcrystalline cellulose.

[00285] In some embodiments, the pharmaceutical compositions comprises one or more fillers in an amount of at least 5 wt% (e.g., at least 20 wt%, at least 30 wt%, or at least 40 wt%) by weight of the pharmaceutical composition. For example, the pharmaceutical compositions comprise from 10 wt% to 60 wt% (e.g., from 20 wt% to 55 wt%, from 25 wt% to 50 wt%, or from 27 wt% to 45 wt%) of filler, by weight of the tablet. In another example, the pharmaceutical compositions comprise at least 20 wt% (e.g., at least 30 wt% or at least 40 wt%) of microcrystalline cellulose, for example MCC Avicel PH102 or Avicel PH101, by weight of the pharmaceutical composition. In yet another example, the pharmaceutical compositions comprise from 10 wt% to 60 wt% (e.g., from 20 wt% to 55 wt% or from 25 wt% to 45 wt%) of microcellulose, by weight of the pharmaceutical composition.

[00286] Disintegrants suitable for the pharmaceutical compositions disclosed herein can enhance the dispersal of the pharmaceutical compositions and are compatible with the other ingredients of the pharmaceutical compositions, i.e., they do not substantially reduce the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical compositions. Exemplary disintegrants include croscarmellose sodium, sodium starch glycolate, crospovidone or a combination thereof. In one embodiment, the disintegrant is croscarmellose sodium.

[00287] In some embodiments, the pharmaceutical compositions discosed herein comprise disintegrant in an amount of 10 wt% or less (e.g., 7 wt% or less, 6 wt% or less, or 5 wt% or less) by weight of the pharmaceutical composition. For example, the

pharmaceutical compositionscomprise from 1 wt% to 10 wt% (e.g., from 1.5 wt% to 7.5 wt% or from 2.5 wt% to 6 wt%) of disintegrant, by weight of the pharmaceutical composition. In another example, the pharmaceutical compositions comprise 10 wt% or less (e.g., 7 wt% or less, 6 wt% or less, or 5 wt% or less) of croscarmellose sodium, by weight of the pharmaceutical composition. In yet another example, the pharmaceutical compositions comprise from 1 wt% to 10 wt% (e.g., from 1.5 wt% to 7.5 wt% or from 2.5 wt% to 6 wt%) of croscarmellose sodium, by weight of the pharmaceutical composition. In some examples, the pharmaceutical compositions comprise from 0.1% to 10 wt% (e.g., from 0.5 wt% to 7.5 wt% or from 1.5 wt% to 6 wt%) of disintegrant, by weight of the pharmaceutical composition. In still other embodiments, the pharmaceutical compositions comprise from 0.5% to 10 wt% (e.g., from 1.5 wt% to 7.5 wt% or from 2.5 wt% to 6 wt%) of disintegrant, by weight of the pharmaceutical composition.

[00288] In some embodiments, the pharmaceutical compositions disclosed herein comprise a lubricant. A lubricant can prevent adhesion of a mixture compoent to a surface (e.g., a surface of a mixing bowl, a granulation roll, a compression die and/or punch). A lubricant can also reduce interparticle friction within the granulate and improve the compression and ejection of compressed pharmaceutical compositions from a granulator and/or die press. A suitable lubricant for the pharmaceutical compositions disclosed herein is compatible with the other ingredients of the pharmaceutical compositions, i.e., they do not substantially reduce the solubility, the hardness, or the biological activity of the pharmaceutical compositions. Exemplary lubricants include magnesium stearate, sodium stearyl fumarate, calcium stearate, zinc stearate, sodium stearate, stearic acid, aluminum stearate, leucine, glyceryl behenate, hydrogenated vegetable oil or any combination thereof. In embodiment, the lubricant is magnesium stearate.

[00289] In one embodiment, the pharmaceutical compositions comprise a lubricant in an amount of 5 wt% or less (e.g., 4.75 wt%, 4.0 wt% or less, or 3.00 wt% or less, or 2.0 wt% or less) by weight of the pharmaceutical composition. For example, the pharmaceutical compositions comprise from 5 wt% to 0.10 wt% (e.g., from 4.5 wt% to 0.5 wt% or from 3 wt% to 1 wt%) of lubricant, by weight of the pharmaceutical composition. In another example, the pharmaceutical compositions comprise 5 wt% or

less (e.g., 4.0 wt% or less, 3.0 wt% or less, or 2.0 wt% or less, or 1.0 wt% or less) of magnesium stearate, by weight of thepharmaceutical composition. In yet another example, the pharmaceutical compositionscomprise from 5 wt% to 0.10 wt% (e.g., from 4.5 wt% to 0.15 wt% or from 3.0 wt% to 0.50 wt%) of magnesium stearate, by weight of the pharmaceutical composition.

[00290] Any suitable spray dried dispersions of Compound **II**, Compound **III**, and Compound **III-d** can be used for the pharmaceutical compositions disclosed herein. Some examples for Compound II and its pharmaceutically acceptable salts can be found in WO 2011/119984 and WO 2014/015841, all of which are incorporated herein by reference. Some examples for Compound **III** and its pharmaceutically acceptable salts can be found in WO 2007/134279, WO 2010/019239, WO 2011/019413, WO 2012/027731, and WO 2013/130669, all of which are incorporated herein by reference. Spray dried dispersions of Compound **III-d** can be prepared as those of Compound **III** as described in WO 2007/134279, WO 2010/019239, WO 2011/019413, WO 2012/027731, and WO 2013/130669.

[00291] Pharmaceutical compositions comprising Compound **II** and Compound **III** are disclosed in PCT Publication No. WO 2015/160787, incorporated herein by reference. An exemplary embodiment is shown in the following Table 1 for administration with crystalline Form B of the potassium salt of Compound **I**.

Table 1: Exemplary Tablet Comprising 100 mg of Compound **II** and 150 mg of Compound **III**

	Ingredient	**Amount per tablet (mg)**
Intra-granular	Compound **II** SDD (spray dried dispersion) (80 wt % Compound II; 20 wt % HPMC)	125
	Compound **III** SDD (80 wt % Compound III; 19.5 wt% HPMCAS-HG; 0.5 wt% sodium lauryl sulfate)	187.5
	Microcrystalline cellulose	131.4
	Croscarmellose Sodium	29.6

	Ingredient	Amount per tablet (mg)
	Total	**473.5**
Extra-granular	Microcrystalline cellulose	112.5
	Magnesium Stearate	5.9
	Total	**118.4**
Total uncoated Tablet		**591.9**
Film coat	Opadry	17.7
Total coated Tablet		**609.6**

[00292] Pharmaceutical compositions comprising Compound **III** are disclosed in PCT Publication No. WO 2010/019239, incorporated herein by reference. An exemplary embodiment is shown in the following Table 2 for administration with crystalline Form B of the potassium salt of Compound **I** alone or in combination with Compound **II.**

Table 2: Ingredients for Exemplary Tablet of Compound **III**

Tablet Formulation	Percent Dose %Wt./Wt	Dose (mg)	Batch (g)
Compound **III** SDD (80 wt % Compound **III**; 19.5 wt% HPMCAS-HG; 0.5 wt% sodium lauryl sulfate)	34.09%	187.5	23.86
Microcrystalline cellulose	30.51%	167.8	21.36
Lactose	30.40%	167.2	21.28
Sodium croscarmellose	3.000%	16.50	2.100
SLS	0.500%	2.750	0.3500
Colloidal silicon dioxide	0.500%	2.750	0.3500
Magnesium stearate	1.000%	5.500	0.7000
Total	**100%**	**550**	**70**

[00293] Additional pharmaceutical compositions comprising Compound **III** are disclosed in PCT Publication No. WO 2013/130669, incorporated herein by reference. Exemplary mini-tablets (~2 mm diameter, ~2 mm thickness, each mini-tablet weighing 6.9 mg) was formulated to have 50 mg of Compound **III** per 26 mini-tablets and 75 mg of Compound **III** per 39 mini-tablets using the amounts of ingredients recited in Table

3, below for administration with crystalline Form B of the potassium salt of Compound **I** alone or in combination with Compound **II**.

Table 3: Ingredients for mini-tablets for 50 mg and 75 mg potency

Tablet Formulation	**Percent Dose %Wt./Wt.**	**Dose (mg) 50 mg potency**	**Dose (mg) 75 mg potency**	**Batch (g)**
Compound **III** SDD (80 wt % Compound **III**; 19.5 wt% HPMCAS-HG; 0.5 wt% sodium lauryl sulfate)	35	62.5	93.8	1753.4
Mannitol	13.5	24.1	36.2	675.2
Lactose	41	73.2	109.8	2050.2
Sucralose	2.0	3.6	5.4	100.06
Croscarmellose sodium	6.0	10.7	16.1	300.1
Colloidal silicon dioxide	1.0	1.8	2.7	50.0
Magnesium stearate	1.5	2.7	4.0	74.19
Total	**100**	**178.6**	**268**	**5003.15**

[00294] In some embodiments, the pharmaceutical compositions disclosed herein comprise one of the following formulations:

Table 4:

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	200 mg to 215 mg
solid dispersion containing 80% Compound **II**, 20% hypromellose	60 mg to 65 mg
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	90 mg to 95 mg
microcrystalline cellulose	175 mg to 215 mg
croscarmellose sodium (CCS)	15 mg to 30 mg
magnesium stearate	3 mg to 7 mg

Table 5

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	212.9 mg
solid dispersion containing 80% Compound **II**, 20% hypromellose	62.5 mg
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93.8 mg
microcrystalline cellulose	196.7 mg
croscarmellose sodium	24.7 mg
magnesium stearate	5.3 mg

Table 6

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	115 mg to 140 mg
solid dispersion containing 80% Compound **II**, 20% hypromellose	60 mg to 65 mg
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	90 mg to 95 mg
microcrystalline cellulose	120 mg to 135 mg
croscarmellose sodium	15 mg to 25 mg
magnesium stearate	2 mg to 7 mg

Table 7

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127.7 mg
solid dispersion containing 80% Compound **II**, 20% hypromellose	62.5 mg
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93.8 mg

Component	**Amount (mg) per composition**
microcrystalline cellulose	130.6 mg
croscarmellose sodium	18.1 mg
magnesium stearate	3.9 mg

[00295] In some embodiments, the pharmaceutical compositions disclosed herein comprise an intra-granular part and an extragranular part, and the intra-granular part and the extra-granular part comprise components as shown in the tables below:

Table 8

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	200 mg to 215 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	60 mg to 65 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	90 mg to 95 mg
	microcrystalline cellulose (e.g., PH101)	120 mg to 150 mg
	croscarmellose sodium (CCS)	10 mg to 20 mg
	magnesium stearate	3 mg to 7 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	55 mg to 65 mg
	croscarmellose sodium	5 mg to 10 mg

Table 9

	Component	**Amount (mg) per composition**
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	115 mg to 140 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	60 mg to 65 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose	90 mg to 95 mg

	Component	Amount (mg) per composition
	acetate succinate, and 0.5% sodium lauryl sulfate	
	microcrystalline cellulose (e.g., PH101)	80 mg to 90 mg
	croscarmellose sodium	10 mg to 15 mg
	magnesium stearate	2 mg to 7 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	40 mg to 45 mg
	croscarmellose sodium	5 mg to 10 mg

Table 10

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	115 mg to 140 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	60 mg to 65 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	90 mg to 95 mg
	microcrystalline cellulose (e.g., PH101)	80 mg to 90 mg
	croscarmellose sodium	10 mg to 15 mg
	magnesium stearate	1 mg to 3 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	40 mg to 45 mg
	croscarmellose sodium	5 mg to 10 mg
	magnesium stearate	1 mg to 3 mg

Table 11

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	115 mg to 140 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	60 mg to 65 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose	90 mg to 95 mg

	Component	Amount (mg) per composition
	acetate succinate, and 0.5% sodium lauryl sulfate	
	microcrystalline cellulose (e.g., PH101)	80 mg to 90 mg
	croscarmellose sodium	8 mg to 15 mg
	magnesium stearate	0.5 mg to 5 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	35 mg to 50 mg
	croscarmellose sodium	5 mg to 10 mg
	magnesium stearate	0.5 mg to 5 mg

Table 12

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	115 mg to 140 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	60 mg to 65 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	90 mg to 95 mg
	microcrystalline cellulose (e.g., PH101)	80 mg to 90 mg
	croscarmellose sodium	8 mg to 15 mg
	magnesium stearate	0.5 mg to 5 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	35 mg to 50 mg
	croscarmellose sodium	5 mg to 10 mg

Table 13

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	115 mg to 140 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	60 mg to 65 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose	90 mg to 95 mg

	Component	Amount (mg) per composition
	acetate succinate, and 0.5% sodium lauryl sulfate	
	microcrystalline cellulose (e.g., PH101)	80 mg to 90 mg
	croscarmellose sodium	8 mg to 15 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	35 mg to 50 mg
	croscarmellose sodium	5 mg to 10 mg
	magnesium stearate	0.5 mg to 5 mg

Table 14

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	212-213 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62-63 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93-94 mg
	microcrystalline cellulose (e.g., PH101)	137-138 mg
	croscarmellose sodium	15-16 mg
	magnesium stearate	5-6 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	59-60 mg
	croscarmellose sodium	8-9 mg

Table 15

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	212.9 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62.5 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose	93.8 mg

	Component	Amount (mg) per composition
	acetate succinate, and 0.5% sodium lauryl sulfate	
	microcrystalline cellulose (e.g., PH101)	137.1 mg
	croscarmellose sodium	15.8 mg
	magnesium stearate	5.3 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	59.6 mg
	croscarmellose sodium	8.9 mg
	Uncoated Tablet	595.9 mg
	Coating	18.4 mg

Table 16

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127-128 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62-63 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93-94 mg
	microcrystalline cellulose (e.g., PH101)	86-87 mg
	croscarmellose sodium	11-12 mg
	magnesium stearate	3-4 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	43-44 mg
	croscarmellose sodium	6-7 mg

Table 17

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127.7 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62.5 mg

	Component	Amount (mg) per composition
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93.8 mg
	microcrystalline cellulose (e.g., PH101)	86.9 mg
	croscarmellose sodium	11.6 mg
	magnesium stearate	3.9 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	43.7 mg
	croscarmellose sodium	6.5 mg
	Uncoated Tablet	436.6 mg
	Coating	13.5 mg

Table 18

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127-128 mg
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62-63 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93-94 mg
	microcrystalline cellulose (e.g., PH101)	86-87 mg
	croscarmellose sodium	11-12 mg
	magnesium stearate	1-2 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	43-44 mg
	croscarmellose sodium	6-7 mg
	magnesium stearate	1-2 mg

Table 19

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127.7 mg

	Component	Amount (mg) per composition
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62.5 mg
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93.8 mg
	microcrystalline cellulose (e.g., PH101)	86.3 mg
	croscarmellose sodium	11.5 mg
	magnesium stearate	1.9 mg
Extra-granular part	microcrystalline cellulose (e.g., PH102)	43.6 mg
	croscarmellose sodium	6.5 mg
	magnesium stearate.	1.9 mg
	Uncoated tablet	435.8 mg
	Coating	13.5mg

[00296] In some embodiments, the pharmaceutical compositions disclosed herein comprise a formulation selected from one of the following:

Table 20

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	45-80 mg
solid dispersion containing 80% Compound **II**, 20% hypromellose	20-50 mg
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	30-70 mg
microcrystalline cellulose	60-150 mg
croscarmellose sodium	5-25 mg
magnesium stearate	1-7 mg

Table 21

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15 – 45 wt%

Component	**weight % based on the total weight of composition**
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III** or Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10-40 wt%

Table 22

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15 – 45 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III** or Compound III-d, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 – 40 wt%
microcrystalline cellulose	5 – 50 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
Optionally magnesium stearate in an amount of 0.05 wt% - 2 wt%	

Table 23

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15 – 45 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III** or Compound III-d, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 40 wt%
microcrystalline cellulose	5 – 50 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
magnesium stearate	0.05 – 2 wt%

Table 24

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15 – 35 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 - 40 wt%
microcrystalline cellulose	20 – 40 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
magnesium stearate	0.05 – 2 wt%

Table 25

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	20 – 40 wt%
solid dispersion containing 80% Compound II**,** 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 25 wt%
microcrystalline cellulose	20 – 40 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
magnesium stearate	0.05 – 2 wt%

Table 26

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	30 - 40 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 - 15 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 20 wt%

Component	weight % based on the total weight of composition
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
magnesium stearate	0.05 – 2 wt%

Table 27

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	33 - 38 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	8 - 13 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	13 - 18 wt%
microcrystalline cellulose	30 – 35 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
magnesium stearate	0.05– 2 wt%

Table 28

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	25 - 35 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	10 - 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 - 25 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
magnesium stearate	0.05 – 2 wt%

Table 29

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	27 - 32 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	12 - 17 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	18 - 23 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	3 – 6 wt%
magnesium stearate	0.05– 1.5 wt%

Table 30

	Component	**Amount (mg) per composition**
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	207 - 217
	solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	182-193
	microcrystalline cellulose (e.g., PH101)	125 - 145
	croscarmellose sodium	10 - 20
	magnesium stearate	3 - 9
Extra-granular part	microcrystalline cellulose (e.g., PH102)	50 - 70
	croscarmellose sodium	5 - 15

Table 31

	Component	**Amount (mg) per composition**
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	212 - 213

	Component	Amount (mg) per composition
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62 - 63
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	187-188
	microcrystalline cellulose (e.g., PH101)	136 - 138
	croscarmellose sodium	15 - 16
	magnesium stearate	5 - 6
Extra-granular part	microcrystalline cellulose (e.g., PH102)	59 - 60
	croscarmellose sodium	8 - 9

Table 32

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	28 - 33 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	7 - 12 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	25 - 30 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
magnesium stearate	0.05 – 1.5 wt%

Table 33

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122 – 132
solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68

Component	Amount (mg) per composition
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	182 - 193
microcrystalline cellulose	110 - 145
croscarmellose sodium	13 - 25
magnesium stearate	1.5 – 8

Table 34

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127 – 128
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62 - 63
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	187 - 188
	microcrystalline cellulose (e.g., PH101)	86 - 87
	croscarmellose sodium	11 - 12
	magnesium stearate	1 – 2.5
Extra-granular part	microcrystalline cellulose (e.g., PH102)	43 - 44
	croscarmellose sodium	6 - 7
	magnesium stearate	1 – 2.5

Table 35

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127 – 128
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62 - 63
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose	187 - 188

	Component	Amount (mg) per composition
	acetate succinate, and 0.5% sodium lauryl sulfate	
	microcrystalline cellulose (e.g., PH101)	86 - 88
	croscarmellose sodium	13 - 16
	magnesium stearate	1 – 1.5
Extra-granular part	microcrystalline cellulose (e.g., PH102)	48 - 50
	croscarmellose sodium	7 - 9
	magnesium stearate	4 – 5.5

Table 36

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	62 – 65
	solid dispersion containing 80% Compound **II**, 20% hypromellose	30 - 33
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	90 - 95
	microcrystalline cellulose (e.g., PH101)	42 - 45
	croscarmellose sodium	7 - 8
	magnesium stearate	0.5 – 1
Extra-granular part	microcrystalline cellulose (e.g., PH102)	23 - 26
	croscarmellose sodium	3 - 5
	magnesium stearate	2 – 3.5

Table 37

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	58 – 68
solid dispersion containing 80% Compound **II**, 20% hypromellose	25 - 35
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	87 - 97
microcrystalline cellulose	60 – 100

Component	**Amount (mg) per composition**
croscarmellose sodium	5 - 15
magnesium stearate	1.5 – 7

Table 38

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	50 – 80
solid dispersion containing 80% Compound **II**, 20% hypromellose	20 - 40
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	70 - 120
microcrystalline cellulose	60 – 300
croscarmellose sodium	5 - 25
magnesium stearate	1 – 7

Table 39

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	20– 30 wt%
solid dispersion containing 80% Compound II, 20% hypromellose	7 - 15 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	30 – 40 wt%
microcrystalline cellulose	15 – 40 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
magnesium stearate	0.05 – 1.5 wt%

Table 40

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	22 - 27 wt%

Component	**weight % based on the total weight of composition**
solid dispersion containing 80% Compound **II**, 20% hypromellose	8 - 13 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	32 - 37 wt%
microcrystalline cellulose	20 – 30 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
magnesium stearate	0.05 – 1.5 wt%

Table 41

	Component	**Amount (mg) per composition**
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	207-217
	solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68
	solid dispersion containing 80% Compound **III**-d, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	120 -130
	microcrystalline cellulose (e.g., PH101)	125 - 150
	croscarmellose sodium	10 - 20
	magnesium stearate	3 - 8
Extra-granular part	microcrystalline cellulose (e.g., PH102)	50 - 70
	croscarmellose sodium	5 -12

Table 42

	Component	**Amount (mg) per composition**
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	212-213
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62 - 63
	solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose	124 -126

	Component	Amount (mg) per composition
	acetate succinate, and 0.5% sodium lauryl sulfate	
	microcrystalline cellulose (e.g., PH101)	137 - 138
	croscarmellose sodium	15 - 16
	magnesium stearate	5 - 6
Extra-granular part	microcrystalline cellulose (e.g., PH102)	59 - 60
	croscarmellose sodium	8 -9

Table 43

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	25– 40 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	7 - 15 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 – 35 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
magnesium stearate	0.05 – 1.5 wt%

Table 44

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	29 - 36 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	8 - 13 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 - 25 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
magnesium stearate	0.05 – 1.5 wt%

Table 45

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122 – 132
solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	124 - 126
microcrystalline cellulose	129 - 131
croscarmellose sodium	17 - 19
magnesium stearate	3 – 5

Table 46

	Component	**Amount (mg) per composition**
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122 – 132
	solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68
	solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	124 - 126
	microcrystalline cellulose (e.g., PH101)	86 - 87
	croscarmellose sodium	11 - 12
	magnesium stearate	3 - 4
Extra-granular part	microcrystalline cellulose (e.g., PH102)	43 - 44
	croscarmellose sodium	6 - 7

Table 47

	Component	**Amount (mg) per composition**
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122 – 132
	solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68

	Component	Amount (mg) per composition
	solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	124 - 126
	microcrystalline cellulose (e.g., PH101)	86 - 87
	croscarmellose sodium	11 - 12
	magnesium stearate	1.5 – 2.5
Extra-granular part	microcrystalline cellulose (e.g., PH102)	43 - 44
	croscarmellose sodium	6 - 7
	magnesium stearate	1.5 – 2.5

Table 48

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122-132
	solid dispersion containing 80% Compound **II**, 20% hypromellose	58 -68
	solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	120-130
	Microcrystalline cellulose	75-95
	Croscarmellose sodium	5-20
	Magnesium Stearate	1-6
Extra-granular part	Microcrystalline cellulose	35-50
	Croscarmellose sodium	3-10

Table 49

	Component	Amount (mg) per composition
Intra-granular part	potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127-128
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62 -63

	Component	Amount (mg) per composition
	solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	124-126
	Microcrystalline cellulose	84-85
	Croscarmellose sodium	11-12
	Magnesium Stearate	3-4
Extra-granular part	Microcrystalline cellulose	43-44
	Croscarmellose sodium	6-7

Table 50

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	250-260
solid dispersion containing 80% Compound **II**, 20% hypromellose	120-130
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	245-255
Microcrystalline cellulose	80 -110
Croscarmellose sodium	15-30
optionally magnesium stearate	0.01-10

Table 51

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	255-256
solid dispersion containing 80% Compound **II**, 20% hypromellose	124-126
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	249-251
microcrystalline cellulose	89 -98
mroscarmellose sodium	22-23
optionally magnesium stearate in an amount of 0.01 – 10 mg per composition	

Table 52

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122-132
solid dispersion containing 80% Compound **II**, 20% hypromellose	57-67
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	120-130
microcrystalline cellulose	275 -305
croscarmellose sodium	10 -25
optionally magnesium stearate in an amount of 0.05 – 10 mg per composition	

Table 53

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127-128
solid dispersion containing 80% Compound **II,** 20% hypromellose	62-63
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	124-126
Microcrystalline cellulose	289 -297
Croscarmellose sodium	18 -19
optionally magnesium stearate in an amount of 0.01 – 10 mg per composition	

Table 54

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122 - 132
solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68

Component	**Amount (mg) per composition**
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	120 - 130
microcrystalline cellulose	110 - 130
croscarmellose sodium	10 - 20
optionally magnesium stearate in an amount of 0.01 – 10 mg per composition	

Table 55

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	127 - 128
solid dispersion containing 80% Compound **II**, 20% hypromellose	62 - 63
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	124 - 126
Microcrystalline cellulose	117 - 122
Croscarmellose sodium	13 - 14
optionally magnesium stearate in an amount of 0.01 – 10 mg per composition	

Table 56

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15– 40 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 - 20 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 – 40 wt%
microcrystalline cellulose	10 – 50 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 2 wt% based on the total weight of composition	

Table 57

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	20 - 30 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	8-18 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 - 30 wt%
microcrystalline cellulose	20 – 30 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight of composition	

Table 58

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	28 – 38 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	10 -20 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	27 - 37 wt%
microcrystalline cellulose	5 – 20 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight of composition	

Table 59

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15 - 25 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5-15 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 - 25 wt%
microcrystalline cellulose	40 – 50 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight ofcomposition	

Table 60

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	22 - 32 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	10-20 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 - 30 wt%
microcrystalline cellulose	20 – 30 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight of composition	

Table 61

Component	**Amount (mg) per composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	50 – 80

Component	Amount (mg) per composition
solid dispersion containing 80% Compound **II**, 20% hypromellose	20 - 40
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	45 - 80
microcrystalline cellulose	60 - 300
croscarmellose sodium	5 - 25
optionally magnesium stearate in an amount of 0.01 – 10 mg per composition	

Table 62

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	95-160
solid dispersion containing 80% Compound **II**, 20% hypromellose	45-80
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	95-155
Microcrystalline cellulose	60 -300
Croscarmellose sodium	5 - 25
optionally magnesium stearate in an amount of 0.01 – 10 mg per composition	

Processes of Making Tablets

[00297] The tablets of the disclosure can be produced by compacting or compressing an admixture or composition, for example, powder or granules, under pressure to form a stable three-dimensional shape (e.g., a tablet). As used herein, "tablet" includes compressed pharmaceutical dosage unit forms of all shapes and sizes, whether coated or uncoated. In some embodiments, the methods of preparing the tablets disclosed herein comprise (a) mixing a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) and the first and second solid dispersions to form a first mixture; and (b) compressing a tablet mixture comprising the first mixture into a tablet. As used herein, the term “mixing” include mixing, blending and combinding. In some embodiments, the tablet mixture further comprises one or more pharmaceutically

acceptable excipients, and the methods further comprise mixing the first mixture with said one or more excipients to form the tablet mixture. Mixing the first mixture with one or more excipients can be performed in one or more steps. In one embodiment, the one or more excipients are mixed to form a second mixture; and the first and second mixtures are mixed together to form the tablet mixture prior to the compression step. In one embodiment, the one or more excipients can be mixed with the first mixture in more than one parts, for example, some excipients mixed with the first mixture first and the other excipients followed later. In some embodiments, the tablets disclosed herein an intra-granular part and an extra-grandular part as described above, and one or more excipients included in the intra-granular part are mixed to form a second mixture, and one or more excipients included in the extra-granular part are mixed to form a third mixture, and the first mixture are combined with the second mixture, and the combined first and second mixtures are combined with the third mixture to form a tablet mixture.

[00298] In some embodiments, the methods of preparing the tablets disclosed herein comprise:(a) mixing a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) and the first and second solid dispersions to form a first mixture; (b) mixing the first mixture with a microcrystalline cellulose, croscarmellose sodium and magnesium stearate to form a tablet mixture; and (c) compressing the tablet mixture into a tablet.

[00299] In some embodiments, the methods of preparing the tablets disclosed herein comprise:

(a) mixing a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) and the first and second solid dispersions described above to form a first mixture;

(b) mixing a microcrystalline cellulose, croscarmellose sodium and magnesium stearate in an intra-granular part to form a second mixture;

(c) mixing a microcrystalline cellulose and croscarmellose sodium in an extra-granular part to form a third mixture;

(d) mixing the first, second, and third mixtures to form a tablet mixture; and

(e) compressing the tablet mixture comprising the first, second and third mixtures into a tablet. It is noted that step (a) can occur prior to step (b) or step (b) can occur prior to step (a).

[00300] In some embodiments, the methods of preparing the tablets disclosed herein comprise:

(a) mixing a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) and the first and second solid dispersions to form a first mixture;

(b) mixing a microcrystalline cellulose, croscarmellose sodium and magnesium stearate in an intra-granular part to form a second mixture;

(c) mixing a microcrystalline cellulose, croscarmellose sodium, and magnesium stearate comprised in an extra-granular part to form a third mixture;

(d) mixing the first, second, and third mixtures to form a tablet mixture;

(e) compressing the tablet mixture comprising the first, second and third mixtures into a tablet.

[00301] In some embodiments, the methods disclosed herein further comprise coating the tablet.

[00302] In some embodiments, the methods disclosed herein further comprise granulating the first, second, and/or third mixtures prior to the compression the tablet mixture. Any suitable methods known in the art for granulation and compression of pharmaceutical compositions can be used. It is noted that step (a) can occur prior to step (b) or step (b) can occur prior to step (a).

Granulation and Compression

[00303] In some embodiments, solid forms, including powders comprising one or more APIs (e.g., Compound **I**, Compound **II**, and/or Compound **III** or **III-d**) and the included pharmaceutically acceptable excipients (e.g. filler, diluent, disintegrant, surfactant, glidant, binder, lubricant, or any combination thereof) can be subjected to a dry granulation process. The dry granulation process causes the powder to agglomerate into larger particles having a size suitable for further processing. Dry granulation can improve the flowability of a mixture to produce tablets that comply with the demand of mass variation or content uniformity.

[00304] In some embodiments, formulations can be produced using one or more mixing and dry granulations steps. The order and the number of the mixing by granulation. At least one of the excipients and the API(s) can be subject to dry granulation or wet high shear granulation or twin screw wet granulation before compression into tablets. Dry granulation can be carried out by a mechanical process, which transfers energy to the mixture without any use of any liquid substances (neither in the form of aqueous solutions, solutions based on organic solutes, or mixtures thereof) in contrast to wet granulation processes, also contemplated herein. Generally, the mechanical process requires compaction such as the one provided by roller compaction. An example of an alternative method for dry granulation is slugging. In some embodiments, wet granulations instead of the dry granulation can be used.

[00305] In some embodiments, roller compaction is a granulation process comprising mechanical compacting of one or more substances. In some embodiments, a pharmaceutical composition comprising an admixture of powders is pressed, that is roller compacted, between two rotating rollers to make a solid sheet that is subsequently crushed in a sieve to form a particulate matter. In this particulate matter, a close mechanical contact between the ingredients can be obtained. An example of roller compaction equipment is Minipactor® a Gerteis 3W-Polygran from Gerteis Maschinen+Processengineering AG.

[00306] In some embodiments, tablet compression according to the disclosure can occur without any use of any liquid substances (neither in the form of aqueous solutions, solutions based on organic solutes, or mixtures thereof), i.e., a dry granulation process. In a typical embodiment the resulting core or tablet has a compressive strength in the range of from 1kp to 15 kP; such as 1.5 to 12.5 kP, preferably in the range of 2 to 10 kP.

[00307] In some embodiments, the ingredients are weighed according to the formula set herein. Next, all of the intragranular ingredients are sifted and mixed well. The ingredients can be lubricated with a suitable lubricant, for example, magnesium stearate. The next step can comprise compaction/slugging of the powder admixture and sized ingredients. Next, the compacted or slugged blends are milled into granules and sifted to obtain the desired size. Next, the granules can be further lubricated with, for example, magnesium stearate. Next, the granular composition of the disclosure can be

compressed on suitable punches into various pharmaceutical formulations in accordance with the disclosure. Optionally the tablets can be coated with a film coat.

[00308] Another aspect of the disclosure provides a method for producing a pharmaceutical composition comprising an admixture of a composition comprising one or more APIs (e.g., Compound **I**, Compound **II** and/or Compound **III**); and one or more excipients selected from: one or more fillers, a diluent, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and compressing the composition into a tablet.

Coating

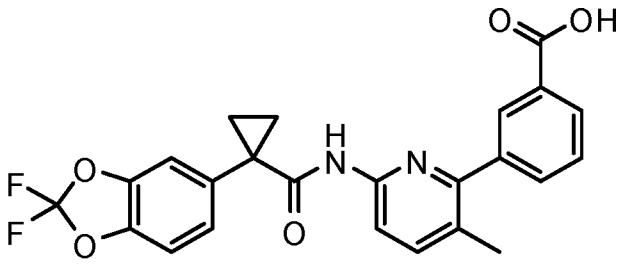
[00309] In some embodiments, the tablets disclosed herein can be coated with a film coating and optionally labeled with a logo, other image and/or text using a suitable ink. In still other embodiments, the tablets disclosed herein can be coated with a film coating, waxed, and optionally labeled with a logo, other image and/or text using a suitable ink. Suitable film coatings and inks are compatible with the other ingredients of the tablets, e.g., they do not substantially reduce the solubility, the chemical stability, the physical stability, the hardness, or the biological activity of the tablets. The suitable colorants and inks can be any color and are water based or solvent based. In one embodiment, the tablets disclosed herein are coated with a colorant and then labeled with a logo, other image, and/or text using a suitable ink.

[00310] In some embodiments, the tablets disclosed herein are coated with a film that comprises 2-6 wt% by the weight of the uncoated tablet. In some embodiments, the film comprises one or more colorants and/or pigments. In some embdodiments, the tablets disclosed herein are coated with a film that comprises one or more colorants and/or pigments and wherein the film comprises 2 – 5 wt% by the weight of the uncoated tablet. In some embodiments, the tablets disclosed herein are coated with a film that comprises one or more colorants and/or pigments and wherein the film comprises 2 – 4 wt% by the weight of the uncoated tablet. The colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink.

Methods of Treatment

[00311] One aspect of the invention provides methods of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising

administering an effective amount of at least one crystalline form of Compound **I** or pharmaceutically acceptable salt thereof disclosed herein, alone or in combination with one or more additional CFTR modulating agents to the patient. In some embodiments, the method comprises administering at least one crystalline form of Compound **I** or pharmaceutically acceptable salt thereof disclosed herein, in combination with Compound **II**, and/or Compound **III** or Compound **III-d**. In some embodiments, the combination may include 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid ("Compound **IV**"):



IV.

[00312] In some embodiments, the method comprises administering a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), alone or in combination with one or more additional CFTR modulating agents, to the patient in need thereof. In some embodiments, the method comprises administering a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) in combination Compound **II**, and optionally, one or more additional CFTR modulating agents. In some embodiments, the method comprises administering a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) in combination Compound **III**, and optionally, one or more additional CFTR modulating agents. In some embodiments, the method comprises administering a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), in combination with Compound **II**, and Compound **III** or **III-d**. In some embodiments, the combination may include Compound **IV**.

[00313] In one embodiment, the method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprises administering an effective amount of at least one crystalline form, including crystalline salt forms, of Compound **I** as disclosed herein, in combination with one or more additional CFTR

modulating agents, wherein the at least one crystalline form of Compound **I** as disclosed herein and the additional modulating agent(s) are administered together in a single composition. In some embodiment, the at least one crystalline form of Compound **I** as disclosed herein and the additional modulating agent(s) are administered as two or more separate compositions.

[00314] In some embodiments, the method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprises administering an effective amount of at least one crystalline form, including crystalline salt forms, of Compound **I** as disclosed herein, in combination with Compound **II** and/or Compound **III** or **III-d**, wherein the at least one crystalline form of Compound **I** as disclosed herein and Compound **II** and/or Compound **III** or **III-d** are administered together in a single composition. In some embodiment, the at least one crystalline form of Compound **I** as disclosed herein and Compound **II** and/or Compound **III** or **III-d** are administered as two or more separate compositions.

[00315] In some embodiments, the method comprises administering an effective amount of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) in combination with one or more additional CFTR modulating agents, wherein the potassium salt of Compound **I** and the additional modulating agent(s) are administered together in a single composition. In some embodiments, the potassium salt of Compound **I** and the additional modulating agent(s) are administered as two or more separate compositions.

[00316] In some embodiments, the method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprises administering an effective amount of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) in combination with Compound **II** and/or Compound **III** or **III-d**, wherein the potassium salt of Compound **I** and Compound **II** and/or Compound **III** or **III-d** are administered together in a single composition. In some embodiments, the potassium salt of Compound **I** and Compound **II** and/or Compound **III** or **III-d** are administered in two or more separate compositions.

[00317] In some embodiments, the patient has a F508del heterozygous or homozygous genotype. In some embodiments, the patient is homozygous or heterozygous for the CFTR genetic mutation G551D. In some embodiments, the patient

is heterozygous for the G551D genetic mutation on one allele and the other CF-causing genetic mutation on the other allele is any one of F508del, G542X, N1303K, W1282X, R117H, R553X, 1717-1G->A, 621+1G->T, 2789+5G->A, 3849+10kbC->T, R1162X, G85E, 3120+1G->A, ΔI507, 1898+1G->A, 3659delC, R347P, R560T, R334W, A455E, 2184delA, or 711+1G->T. In some embodiments, the patient is heterozygous for the G551D genetic mutation, and the other CFTR genetic mutation is F508del. In some embodiments, the patient is heterozygous for the G551D genetic mutation, and the other CFTR genetic mutation is R117H.

[00318] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation F508del. In some embodiments, the patient is homozygous for the F508del genetic mutation. In some embodiments, the patient is heterozygous for the F508del genetic mutation wherein the patient has the F508del genetic mutation on one allele and any CF-causing genetic mutation on the other allele. In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is any CF-causing mutation, including, but not limited to G551D, G542X, N1303K, W1282X, R117H, R553X, 1717-1G->A, 621+1G->T, 2789+5G->A, 3849+10kbC->T, R1162X, G85E, 3120+1G->A, ΔI507, 1898+1G->A, 3659delC, R347P, R560T, R334W, A455E, 2184delA, or 711+1G->T. In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is G551D. In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is R117H.

[00319] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R, S1251N, E193K, F1052V, G1069R, R117C, D110H, R347H, R352Q, E56K, P67L, L206W, A455E, D579G, S1235R, S945L, R1070W, F1074L, D110E, D1270N, D1152H, 1717-1G->A, 621+1G->T, 3120+1G->A, 1898+1G->A, 711+1G->T, 2622+1G->A, 405+1G->A, 406-1G->A, 4005+1G->A, 1812-1G->A, 1525-1G->A,

712-1G->T, 1248+1G->A, 1341+1G->A, 3121-1G->A, 4374+1G->T, 3850-1G->A, 2789+5G->A, 3849+10kbC->T, 3272-26A->G, 711+5G->A, 3120G->A, 1811+1.6kbA->G, 711+3A->G, 1898+3A->G, 1717-8G->A, 1342-2A->C, 405+3A->C, 1716G/A, 1811+1G->C, 1898+5G->T, 3850-3T->G, IVS14b+5G->A, 1898+1G->T, 4005+2T->C, 621+3A->G, 1949del84, 3141del9, 3195del6, 3199del6, 3905InsT, 4209TGTT->A, A1006E, A120T, A234D, A349V, A613T, C524R, D192G, D443Y, D513G, D836Y, D924N, D979V, E116K, E403D, E474K, E588V, E60K, E822K, F1016S, F1099L, F191V, F311del, F311L, F508C, F575Y, G1061R, G1249R, G126D, G149R, G194R, G194V, G27R, G314E, G458V, G463V, G480C, G622D, G628R, G628R(G->A), G91R, G970D, H1054D, H1085P, H1085R, H1375P, H139R, H199R, H609R, H939R, I1005R, I1234V, I1269N, I1366N, I175V, I502T, I506S, I506T, I601F, I618T, I807M, I980K, L102R, L1324P, L1335P, L138ins, L1480P, L15P, L165S, L320V, L346P, L453S, L571S, L967S, M1101R, M152V, M1T, M1V, M265R, M952I, M952T, P574H, P5L, P750L, P99L, Q1100P, Q1291H, Q1291R, Q237E, Q237H, Q452P, Q98R, R1066C, R1066H, R117G, R117L, R117P, R1283M, R1283S, R170H, R258G, R31L, R334L, R334Q, R347L, R352W, R516G, R553Q, R751L, R792G, R933G, S1118F, S1159F, S1159P, S13F, S549R(A->C), S549R(T->G), S589N, S737F, S912L, T1036N, T1053I, T1246I, T604I, V1153E, V1240G, V1293G, V201M, V232D, V456A, V456F, V562I, W1098C, W1098R, W1282R, W361R, W57G, W57R, Y1014C, Y1032C, Y109N, Y161D, Y161S, Y563D, Y563N, Y569C, and Y913C.In some embodiments, the patient has at least one combination mutation chosen from: G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R, S1251N, E193K, F1052V, G1069R, R117C, D110H, R347H, R352Q, E56K, P67L, L206W, A455E, D579G, S1235R, S945L, R1070W, F1074L, D110E, D1270N, D1152H, 1717-1G->A, 621+1G->T, 3120+1G->A, 1898+1G->A, 711+1G->T, 2622+1G->A, 405+1G->A, 406-1G->A, 4005+1G->A, 1812-1G->A, 1525-1G->A, 712-1G->T, 1248+1G->A, 1341+1G->A, 3121-1G->A, 4374+1G->T, 3850-1G->A, 2789+5G->A, 3849+10kbC->T, 3272-26A->G, 711+5G->A, 3120G->A, 1811+1.6kbA->G, 711+3A->G, 1898+3A->G, 1717-8G->A, 1342-2A->C, 405+3A->C, 1716G/A, 1811+1G->C, 1898+5G->T, 3850-3T->G, IVS14b+5G->A, 1898+1G->T, 4005+2T->C, and 621+3A->G.

[00320] In some embodiments, the patient has at least one combination mutation chosen from: 1949del84, 3141del9, 3195del6, 3199del6, 3905InsT, 4209TGTT->A, A1006E, A120T, A234D, A349V, A613T, C524R, D192G, D443Y, D513G, D836Y,

D924N, D979V, E116K, E403D, E474K, E588V, E60K, E822K, F1016S, F1099L, F191V, F311del, F311L, F508C, F575Y, G1061R, G1249R, G126D, G149R, G194R, G194V, G27R, G314E, G458V, G463V, G480C, G622D, G628R, G628R(G->A), G91R, G970D, H1054D, H1085P, H1085R, H1375P, H139R, H199R, H609R, H939R, I1005R, I1234V, I1269N, I1366N, I175V, I502T, I506S, I506T, I601F, I618T, I807M, I980K, L102R, L1324P, L1335P, L138ins, L1480P, L15P, L165S, L320V, L346P, L453S, L571S, L967S, M1101R, M152V, M1T, M1V, M265R, M952I, M952T, P574H, P5L, P750L, P99L, Q1100P, Q1291H, Q1291R, Q237E, Q237H, Q452P, Q98R, R1066C, R1066H, R117G, R117L, R117P, R1283M, R1283S, R170H, R258G, R31L, R334L, R334Q, R347L, R352W, R516G, R553Q, R751L, R792G, R933G, S1118F, S1159F, S1159P, S13F, S549R(A->C), S549R(T->G), S589N, S737F, S912L, T1036N, T1053I, T1246I, T604I, V1153E, V1240G, V1293G, V201M, V232D, V456A, V456F, V562I, W1098C, W1098R, W1282R, W361R, W57G, W57R, Y1014C, Y1032C, Y109N, Y161D, Y161S, Y563D, Y563N, Y569C, and Y913C.

[00321] In some embodiments, the patient has at least one combination mutation chosen from:

D443Y; G576A; R668C,

F508C;S 1251N,

G576A; R668C,

G970R; M470V,

R74W; D1270N,

R74W; V201M, and

R74W; V201M; D1270N.

[00322] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R, S1251N, E193K, F1052V and G1069R. In some embodiments, this disclosure provides a method of treating CFTR comprising administering a compound of Formula (I), (II),

(III), (IV), (V), or a pharmaceutically acceptable salt thereof to a patient possessing a human CFTR mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R and S1251N. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from E193K, F1052V and G1069R. In some embodiments, the method produces an increase in chloride transport relative to baseline chloride transport of the patient of the patient.

[00323] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from R117C, D110H, R347H, R352Q, E56K, P67L, L206W, A455E, D579G, S1235R, S945L, R1070W, F1074L, D110E, D1270N and D1152H. In some embodiments, the method produces an increase in chloride transport above the baseline chloride transport of the patient.

[00324] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 1717-1G->A, 621+1G->T, 3120+1G->A, 1898+1G->A, 711+1G->T, 2622+1G->A, 405+1G->A, 406-1G->A, 4005+1G->A, 1812-1G->A, 1525-1G->A, 712-1G->T, 1248+1G->A, 1341+1G->A, 3121-1G->A, 4374+1G->T, 3850-1G->A, 2789+5G->A, 3849+10kbC->T, 3272-26A->G, 711+5G->A, 3120G->A, 1811+1.6kbA->G, 711+3A->G, 1898+3A->G, 1717-8G->A, 1342-2A->C, 405+3A->C, 1716G/A, 1811+1G->C, 1898+5G->T, 3850-3T->G, IVS14b+5G->A, 1898+1G->T, 4005+2T->C and 621+3A->G. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 1717-1G->A, 1811+1.6kbA->G, 2789+5G->A, 3272-26A->G and 3849+10kbC->T. In some embodiments, disclosed herein is a method of

treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 2789+5G->A and 3272-26A->G.

[00325] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R, S1251N, E193K, F1052V, G1069R, R117C, D110H, R347H, R352Q, E56K, P67L, L206W, A455E, D579G, S1235R, S945L, R1070W, F1074L, D110E, D1270N, D1152H, 1717-1G->A, 621+1G->T, 3120+1G->A, 1898+1G->A, 711+1G->T, 2622+1G->A, 405+1G->A, 406-1G->A, 4005+1G->A, 1812-1G->A, 1525-1G->A, 712-1G->T, 1248+1G->A, 1341+1G->A, 3121-1G->A, 4374+1G->T, 3850-1G->A, 2789+5G->A, 3849+10kbC->T, 3272-26A->G, 711+5G->A, 3120G->A, 1811+1.6kbA->G, 711+3A->G, 1898+3A->G, 1717-8G->A, 1342-2A->C, 405+3A->C, 1716G/A, 1811+1G->C, 1898+5G->T, 3850-3T->G, IVS14b+5G->A, 1898+1G->T, 4005+2T->C and 621+3A->G, and a human CFTR mutation selected from F508del, R117H, and G551D.

[00326] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R, S1251N, E193K, F1052V and G1069R, and a human CFTR mutation selected from F508del, R117H, and G551D. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R and S1251N, and a human CFTR mutation selected from F508del, R117H, and G551D. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient

comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from E193K, F1052V and G1069R, and a human CFTR mutation selected from F508del, R117H, and G551D. In some embodiments, the method produces an increase in chloride transport relative to baseline chloride transport of the patient.

[00327] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from R117C, D110H, R347H, R352Q, E56K, P67L, L206W, A455E, D579G, S1235R, S945L, R1070W, F1074L, D110E, D1270N and D1152H, and a human CFTR mutation selected from F508del, R117H, and G551D. In some embodiments, the method produces an increase in chloride transport which is above the baseline chloride transport of the patient.

[00328] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 1717-1G->A, 621+1G->T, 3120+1G->A, 1898+1G->A, 711+1G->T, 2622+1G->A, 405+1G->A, 406-1G->A, 4005+1G->A, 1812-1G->A, 1525-1G->A, 712-1G->T, 1248+1G->A, 1341+1G->A, 3121-1G->A, 4374+1G->T, 3850-1G->A, 2789+5G->A, 3849+10kbC->T, 3272-26A->G, 711+5G->A, 3120G->A, 1811+1.6kbA->G, 711+3A->G, 1898+3A->G, 1717-8G->A, 1342-2A->C, 405+3A->C, 1716G/A, 1811+1G->C, 1898+5G->T, 3850-3T->G, IVS14b+5G->A, 1898+1G->T, 4005+2T->C and 621+3A->G, and a human CFTR mutation selected from F508del, R117H, and G551D. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 1717-1G->A, 1811+1.6kbA->G, 2789+5G->A, 3272-26A->G and 3849+10kbC->T, and a human CFTR mutation selected from F508del, R117H, and G551D. In some embodiments, disclosed herein is a method of treating, lessening the

severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 2789+5G->A and 3272-26A->G, and a human CFTR mutation selected from F508del, R117H.

[00329] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R, S1251N, E193K, F1052V, G1069R, R117C, D110H, R347H, R352Q, E56K, P67L, L206W, A455E, D579G, S1235R, S945L, R1070W, F1074L, D110E, D1270N, D1152H, 1717-1G->A, 621+1G->T, 3120+1G->A, 1898+1G->A, 711+1G->T, 2622+1G->A, 405+1G->A, 406-1G->A, 4005+1G->A, 1812-1G->A, 1525-1G->A, 712-1G->T, 1248+1G->A, 1341+1G->A, 3121-1G->A, 4374+1G->T, 3850-1G->A, 2789+5G->A, 3849+10kbC->T, 3272-26A->G, 711+5G->A, 3120G->A, 1811+1.6kbA->G, 711+3A->G, 1898+3A->G, 1717-8G->A, 1342-2A->C, 405+3A->C, 1716G/A, 1811+1G->C, 1898+5G->T, 3850-3T->G, IVS14b+5G->A, 1898+1G->T, 4005+2T->C and 621+3A->G, and a human CFTR mutation selected from F508del, R117H, and G551D.

[00330] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R, S1251N, E193K, F1052V and G1069R. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R and S1251N. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical

composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from E193K, F1052V and G1069R. In some embodiments, the method produces an increase in chloride transport relative to baseline chloride transport of the patient.

[00331] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from R117C, D110H, R347H, R352Q, E56K, P67L, L206W, A455E, D579G, S1235R, S945L, R1070W, F1074L, D110E, D1270N and D1152H. In some embodiments, the method produces an increase in chloride transport which is above the baseline chloride transport of the patient.

[00332] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 1717-1G->A, 621+1G->T, 3120+1G->A, 1898+1G->A, 711+1G->T, 2622+1G->A, 405+1G->A, 406-1G->A, 4005+1G->A, 1812-1G->A, 1525-1G->A, 712-1G->T, 1248+1G->A, 1341+1G->A, 3121-1G->A, 4374+1G->T, 3850-1G->A, 2789+5G->A, 3849+10kbC->T, 3272-26A->G, 711+5G->A, 3120G->A, 1811+1.6kbA->G, 711+3A->G, 1898+3A->G, 1717-8G->A, 1342-2A->C, 405+3A->C, 1716G/A, 1811+1G->C, 1898+5G->T, 3850-3T->G, IVS14b+5G->A, 1898+1G->T, 4005+2T->C and 621+3A->G. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 1717-1G->A, 1811+1.6kbA->G, 2789+5G->A, 3272-26A->G and 3849+10kbC->T. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 2789+5G->A and 3272-26A->G.

[00333] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R, S1251N, E193K, F1052V, G1069R, R117C, D110H, R347H, R352Q, E56K, P67L, L206W, A455E, D579G, S1235R, S945L, R1070W, F1074L, D110E, D1270N, D1152H, 1717-1G->A, 621+1G->T, 3120+1G->A, 1898+1G->A, 711+1G->T, 2622+1G->A, 405+1G->A, 406-1G->A, 4005+1G->A, 1812-1G->A, 1525-1G->A, 712-1G->T, 1248+1G->A, 1341+1G->A, 3121-1G->A, 4374+1G->T, 3850-1G->A, 2789+5G->A, 3849+10kbC->T, 3272-26A->G, 711+5G->A, 3120G->A, 1811+1.6kbA->G, 711+3A->G, 1898+3A->G, 1717-8G->A, 1342-2A->C, 405+3A->C, 1716G/A, 1811+1G->C, 1898+5G->T, 3850-3T->G, IVS14b+5G->A, 1898+1G->T, 4005+2T->C and 621+3A->G, and a human CFTR mutation selected from F508del, R117H, and G551D, and one or more human CFTR mutations selected from F508del, R117H, and G551D.

[00334] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R, S1251N, E193K, F1052V and G1069R, and one or more human CFTR mutations selected from F508del, R117H, and G551D. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from G178R, G551S, G970R, G1244E, S1255P, G1349D, S549N, S549R and S1251N, and one or more human CFTR mutations selected from F508del, R117H, and G551D. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from E193K, F1052V and

G1069R, and one or more human CFTR mutations selected from F508del, R117H, and G551D. In some embodiments, the method produces an increase in chloride transport relative to baseline chloride transport of the patient.

[00335] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from R117C, D110H, R347H, R352Q, E56K, P67L, L206W, A455E, D579G, S1235R, S945L, R1070W, F1074L, D110E, D1270N and D1152H, and one or more human CFTR mutations selected from F508del, R117H, and G551D. In some embodiments, the method produces an increase in chloride transport which is above the baseline chloride transport of the patient.

[00336] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 1717-1G->A, 621+1G->T, 3120+1G->A, 1898+1G->A, 711+1G->T, 2622+1G->A, 405+1G->A, 406-1G->A, 4005+1G->A, 1812-1G->A, 1525-1G->A, 712-1G->T, 1248+1G->A, 1341+1G->A, 3121-1G->A, 4374+1G->T, 3850-1G->A, 2789+5G->A, 3849+10kbC->T, 3272-26A->G, 711+5G->A, 3120G->A, 1811+1.6kbA->G, 711+3A->G, 1898+3A->G, 1717-8G->A, 1342-2A->C, 405+3A->C, 1716G/A, 1811+1G->C, 1898+5G->T, 3850-3T->G, IVS14b+5G->A, 1898+1G->T, 4005+2T->C and 621+3A->G, and one or more human CFTR mutations selected from F508del, R117H, and G551D. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from 1717-1G->A, 1811+1.6kbA->G, 2789+5G->A, 3272-26A->G and 3849+10kbC->T, and one or more human CFTR mutations selected from F508del, R117H, and G551D. In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR

genetic mutation selected from 2789+5G->A and 3272-26A->G, and one or more human CFTR mutations selected from F508del, R117H, and G551D.

[00337] In some embodiments, the patient is heterozygous having one CF-causing mutation on one allele and another CF-causing mutation on the other allele. In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is any CF-causing mutation, including, but not limited to F508del on one CFTR allele and a CFTR mutation on the second CFTR allele that is associated with minimal CFTR function, residual CFTR function, or a defect in CFTR channel gating activity.

[00338] In some embodiments, the CF-causing mutation is selected from Table 63. In some embodiments, the patient is heterozygous having one CF-causing mutation on one CFTR allele selected from the mutations listed in the table from **FIG. 17** and another CF-causing mutation on the other CFTR allele is selected from the CFTR mutations listed in Table 63.

Table 63. CFTR Mutations

Criteria: Truncation mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no full-length protein				
S4X	C276X	G542X	R792X	E1104X
G27X	Q290X	G550X	E822X	R1158X
Q39X	G330X	Q552X	W846X	R1162X
W57X	W401X	R553X	Y849X	S1196X
E60X	Q414X	E585X	R851X	W1204X
R75X	S434X	G673X	Q890X	L1254X
E92X	S466X	Q685X	S912X	S1255X
Q98X	S489X	R709X	Y913X	W1282X
Y122X	Q493X	K710X	W1089X	Q1313X
E193X	W496X	L732X	Y1092X	E1371X
L218X	C524X	R764X	W1098X	Q1382X
Q220X	Q525X	R785X	R1102X	Q1411X
Criteria: Splice Mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no or little mature mRNA				
185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
405+1G→A	1248+1G→A	1811+1G→C	3040G→C (G970R)	3600+2insT
405+3A→C	1249-1G→A	1811+1.6kbA→G		3850-1G→A

406-1G→A	1341+1G→A	1812-1G→A	3120G→A	4005+1G→A
621+1G→T	1525-2A→G	1898+1G→A	3120+1G→A	4374+1G→T
711+1G→T	1525-1G→A	1898+1G→C	3121-2A→G	
Criteria: Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations • %PI >50% and/or SwCl$^-$ >86 mmol/L • garbled and/or truncated protein				
182delT	1119delA	1782delA	2732insA	3876delA
306insA	1138insG	1824delA	2869insG	3878delG
365-366insT	1154insTC	2043delG	2896insAG	3905insT
394delTT	1161delC	2143delT	2942insT	4016insT
442delA	1213delT	2183AA→G [a]	2957delT	4021dupT
444delA	1259insA	2184delA	3007delG	4040delA
457TAT→G	1288insTA	2184insA	3028delA	4279insA
541delC	1471delA	2307insA	3171delC	4326delTC
574delA	1497delGG	2347delG	3659delC	
663delT	1548delG	2585delT	3737delA	
935delA	1609del CA	2594delGT	3791delC	
1078delT	1677delTA	2711delT	3821delT	
Note: [a] = Also known as 2183delAA→G.				
Criteria: Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations • %PI >50% and/or SwCl$^-$ >86 mmol/L • garbled and/or truncated protein				
CFTRdele2,3	1461ins4	2991del32		
CFTRdele22,23	1924del7	3667ins4		
124del23bp	2055del9→A	4010del4		
852del22	2105-2117del13insAGAAA	4209TGTT→AA		
991del5	2721del11			
Criteria: Class II, III, IV mutations not responsive to Compound **III** alone or in combination with Compound **II** or Compound **IV** • %PI>50% and/or SwCl >86 mmol/L and • Not responsive in vitro to Compound **III** alone or in combination with Compound **II** or Compound **IV**				
A46D[b]	V520F	Y569D[b]	N1303K	
G85E	A559T[b]	L1065P		
R347P	R560T	R1066C		
L467P[b]	R560S	L1077P[b]		
I507del	A561E	M1101K		
Note: %PI: percentage of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry who are pancreatic insufficient; SwCl$^-$: mean sweat chloride of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry [b] = Unpublished data.				

Additional CFTR Mutations			
4382delA	S341P	G178R	2789+5G→A
3600+2insT	R1066M	S549N	3849+10kbC→T
T338I	H1085R	S549R	3272-26A→G
L927P	F1052V	G551D	711+3A→G
A455E	R1070W	G551S	E56K
D579G	F1074L	G1244E	P67L
E831X	D1152H	S1251N	R74W
S945L	D1270N	S1255P	D110E
S977F	R117H	G1349D	D110H
R117C	L206W	R347H	R352Q
G178R	G551D	G1244E	S1255P
S549N	G551S	S1251N	G1349D
S549R			

[00339] Table 63 above includes certain exemplary CFTR minimal function mutations, which are detectable by an FDA-cleared genotyping assay, but does not include an exhaustive list.

[00340] In some embodiments, the patient has *F508del*/MF (F/MF) genotypes; with *F508del*/*F508del* (F/F) genotype (homozygous for F508del); and/or with *F508del*/gating (F/G) genotypes (heterozygous for F508del and a gating mutation known to be CFTR modulator-responsive (e.g., Compound **III**-responsive). In some embodiments, a patient with *F508del*/MF (F/MF) genotypes has any one of the MF mutations in Table 63.

[00341] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is any CF-causing mutation, including truncation mutations, splice mutations, small (≤3 nucleotide) insertion or deletion (ins/del) frameshift mutations; non-small (>3 nucleotide) insertion or deletion (ins/del) frameshift mutations; and Class II, III, IV mutations not responsive to Compound **III** alone or in combination with Compound **II** or Compound **IV**.

[00342] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is a truncation mutation. In some specific embodiments, the truncation mutation is a truncation mutation listed in Table 63.

[00343] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is a splice mutation. In some specific embodiments, the splice mutation is a splice mutation listed in Table 63.

[00344] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is a small (≤3 nucleotide) insertion or deletion (ins/del) frameshift mutation. In some specific embodiments, the small (≤3 nucleotide) insertion or deletion (ins/del) frameshift mutation is a small (≤3 nucleotide) insertion or deletion (ins/del) frameshift mutation listed in Table 63.

[00345] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is any CF-causing mutation expected to be and/or is responsive to, based on in vitro and/or clinical data, the combination of a crystalline form of Compound **I**, or pharmaceutically acceptable salt thereof disclosed herein, Compound **II** (or a pharmaceutically acceptable salts thereof), and/or Compound **III** or Compound **III-d** (or a pharmaceutically acceptable salt thereof).

[00346] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is any CF-causing mutation expected to be and/or is responsive, based on in vitro and/or clinical data, to the triple combination of a crystalline form of Compound **I**, or pharmaceutically acceptable salt thereof disclosed herein, Compound **II** (or pharmaceutically acceptable salt thereof) and/or Compound **III** or Compound **III-d** (or a pharmaceutically acceptable salts thereof).

[00347] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is a non-small (>3 nucleotide) insertion or deletion (ins/del) frameshift mutation. In some specific embodiments, the non-small (>3 nucleotide) insertion or deletion (ins/del) frameshift mutation is a non-small (>3 nucleotide) insertion or deletion (ins/del) frameshift mutation listed in Table 63.

[00348] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is a Class II, III, IV mutations not responsive to Compound **III** alone or in combination with Compound **II**. In some specific embodiments, the Class II, III, IV mutations not responsive to Compound **III** alone or in combination with Compound **II** is a Class II, III, IV mutations not responsive to Compound **III** alone or in combination with Compound **II** or Compound **IV** listed in Table 63.

[00349] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is any mutation listed in Table 63.

[00350] In some embodiments, the patient is heterozygous for F508del, and the other CFTR genetic mutation is any mutation listed in **FIG. 17**.

[00351] In some embodiments, the patient is homozygous for F508del.

[00352] In some embodiments, the patient is heterozygous having one CF-causing mutation on one CFTR allele selected from the mutations listed in the table from **FIG. 17** and another CF-causing mutation on the other CFTR allele is selected from the CFTR mutations listed in Table 63.

[00353] Patients with an *F508del*/gating mutation genotype are defined as patients that are heterozygous *F508del-CFTR* with a second *CFTR* allele that contains a mutation associated with a gating defect and clinically demonstrated to be responsive to Compound **III**. Examples of such mutations include: G178R, S549N, S549R, G551D, G551S, G1244E, S1251N, S1255P, and G1349D.

[00354] Patients with an *F508del*/residual function genotype are defined as patients that are heterozygous *F508del-CFTR* with a second *CFTR* allele that contains a mutation that results in reduced protein quantity or function at the cell surface which can produce partial CFTR activity. CFTR gene mutations known to result in a residual function phenotype include in some embodiments, a CFTR residual function mutation selected from 2789+5G→ A, 3849+10kbC→T, 3272-26A→ G, 711+3A→ G, E56K, P67L, R74W, D110E, D110H, R117C, L206W, R347H, R352Q, A455E, D579G, E831X, S945L, S977F, F1052V, R1070W, F1074L, D1152H, D1270N, E193K, and K1060T. In some embodiments, the CFTR residual function mutation is selected from R117H, S1235R, I1027T, R668C, G576A, M470V, L997F, R75Q, R1070Q, R31C, D614G, G1069R, R1162L, E56K, A1067T, E193K, or K1060T. In some embodiments, the CFTR residual function mutation is selected from R117H, S1235R, I1027T, R668C, G576A, M470V, L997F, R75Q, R1070Q, R31C, D614G, G1069R, R1162L, E56K, or A1067T.

[00355] In some embodiments, disclosed herein is a method of treating, lessening the severity of, or symptomatically treating cystic fibrosis in a patient comprising administering an effective amount of a pharmaceutical composition of this disclosure to the patient, such as a mammal, wherein the patient possesses a CFTR genetic mutation selected from the mutations listed in **FIG. 17**.

[00356] In some embodiments, the composition disclosed herein is useful for treating, lessening the severity of, or symptomatically treating cystic fibrosis in patients who

exhibit residual CFTR activity in the apical membrane of respiratory and non-respiratory epithelia. The presence of residual CFTR activity at the epithelial surface can be readily detected using methods known in the art, e.g., standard electrophysiological, biochemical, or histochemical techniques. Such methods identify CFTR activity using *in vivo* or *ex vivo* electrophysiological techniques, measurement of sweat or salivary Cl^- concentrations, or *ex vivo* biochemical or histochemical techniques to monitor cell surface density. Using such methods, residual CFTR activity can be readily detected for patients that are heterozygous or homozygous for a variety of different mutations, including patients heterozygous for the most common mutation, F508del, as well as other mutations such as the G551D mutation, or the R117H mutation. In some embodiments, compositions disclosed herein are useful for treating, lessening the severity of, or symptomatically treating cystic fibrosis in patients who exhibit little to no residual CFTR activity. In some embodiments, compositions disclosed herein are useful for treating, lessening the severity of, or symptomatically treating cystic fibrosis in patients who exhibit little to no residual CFTR activity in the apical membrane of respiratory epithelia.

[00357] In some embodiments, the compositions disclosed herein are useful for treating or lessening the severity of cystic fibrosis in patients who exhibit residual CFTR activity using pharmacological methods. Such methods increase the amount of CFTR present at the cell surface, thereby inducing a hitherto absent CFTR activity in a patient or augmenting the existing level of residual CFTR activity in a patient.

[00358] In some embodiments, the compositions disclosed herein are useful for treating or lessening the severity of cystic fibrosis in patients with certain genotypes exhibiting residual CFTR activity.

[00359] In some embodiments, compositions disclosed herein are useful for treating, lessening the severity of, or symptomatically treating cystic fibrosis in patients within certain clinical phenotypes, e.g., a mild to moderate clinical phenotype that typically correlates with the amount of residual CFTR activity in the apical membrane of epithelia. Such phenotypes include patients exhibiting pancreatic sufficiency.

[00360] In some embodiments, the compositions disclosed herein are useful for treating, lessening the severity of, or symptomatically treating patients diagnosed with

pancreatic sufficiency, idiopathic pancreatitis and congenital bilateral absence of the vas deferens, or mild lung disease wherein the patient exhibits residual CFTR activity.

[00361] In some embodiments, this disclosure relates to a method of augmenting or inducing anion channel activity *in vitro* or *in vivo*, comprising contacting the channel with a composition disclosed herein**.** In some embodiments, the anion channel is a chloride channel or a bicarbonate channel. In some embodiments, the anion channel is a chloride channel.

[00362] The exact amount of a pharmaceutical composition required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular agent, its mode of administration, and the like. The compounds of this disclosure may be formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of this disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term “patient”, as used herein, means an animal, such as a mammal, and even further such as a human.

[00363] In some embodiments, the disclosure also is directed to methods of treatment using isotope-labelled compounds of the afore-mentioned compounds, which have the same structures as disclosed herein except that one or more atoms therein have been replaced by an atom or atoms having an atomic mass or mass number which differs from the atomic mass or mass number of the atom which usually occurs naturally (isotope labelled). Examples of isotopes which are commercially available and suitable for the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, for example ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and

^{36}Cl, respectively. In some embodiments, the isotope-labelled compounds and salts are deuterium (^{2}H)-labelled ones. In some specific embodiments, the isotope-labelled compounds and salts are deuterium (^{2}H)-labelled, wherein one or more hydrogen atoms therein have been replaced by deuterium. In chemical structures, deuterium is represented as "^{2}H" or "D."

[00364] In some embodiments, the pharmaceutical compositions are a tablet. In some embodiments, the tablets are suitable for oral administration. In some embodiments, the tablets can be administered concurrently with, prior to, or subsequent to, at least one active pharmaceutical ingredients or medical procedures.

[00365] The compositions disclosed herein comprising a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), alone or in combination with Compound **II** and/or Compound **III** or Compound **III-d** can be administered once a day, twice a day, or three times a day. In some embodiments, one or more of the tablets are administered per dosing. In some embodiments, two tablets per dosing are administered. In some embodiments, two tablets per dosing are administered twice a day. An effective amount of the APIs (e.g., Compound **I**) is administered to the patient with or using one or more tablets disclosed herein.

[00366] In some embodiments, methods of treating, lessening the severity of, or symptomatically treating patients diagnosed with cystic fibrosis or a CFTR mediated disease comprise admininstering a crystalline form of Compound **I** as disclosed herein, in a daily dosage amount of 100 mg to 260 mg. In some embodiments, a 100 mg to 260 mg daily dose of a crystalline form of Compound **I**, or pharmaceutically acceptable salt thereof disclosed herein, is administered with 50 mg to 150 mg/day of Compound **II** and/or 50 mg to 300 mg/day of Compound **III** or **III-d**.

[00367] In some embodiments, methods of treating, lessening the severity of, or symptomatically treating patients diagnosed with cystic fibrosis or a CFTR mediated disease comprise admininstering 100 mg to 260 mg of Compound **I** potassium salt (in some embodiments, potassium salt crystalline Form B) daily. In some embodiments, the 100 mg to 260 mg daily dose of Compound **I** potassium salt is administered with 50 mg to 150 mg/day of Compound **II** and/or 50 mg to 300 mg/day of Compound **III** or **III-d** either in a single composition or in separate compositions.

[00368] In some embodiments, methods of treating, lessening the severity of, or symptomatically treating patients diagnosed with cystic fibrosis or a CFTR mediated disease comprise admininstering about 128 mg or about 255-256 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) daily. In some embodiments, the about 128 mg or about 255-256 mg daily dose of Compound **I** potassium salt is administered with 50 mg or 100 mg/day of Compound **II** and/or 75 mg, 150 mg, 200 mg, or 300 mg/day of Compound **III** or **III-d** either in a single composition or in separate compositions.

[00369] In some embodiments, about 255-256 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) is administered daily with 100 mg of Compound **II** and either 300 mg of Compound **III** or 200 mg of Compound **III-d**. In some embodiments, the methods of treating, lessening the severity of, or symptomatically treating patients diagnosed with cystic fibrosis or a CFTR mediated disease comprise admininstering about 128 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), 50 mg of Compound **II,** and 75 mg of Compound **III** and optionally administering an additional 150 mg of Compound **III** daily. For example, two compositions each comprising about 128 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), 50 mg of Compound **II,** and 75 mg of Compound **III** may be administered in the morning and one composition comprising 150 mg of Compound **III** may be administered in the evening. In some embodiments, the methods comprise administering about 128 mg of a crystalline potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B). In some embodiments, the methods comprise administering two compositions, each with about 128 mg of a crystalline potassium salt of Compound **I** in Form B.

[00370] In some embodiments, about 128 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) is administered with 50 mg of Compound **II** and 150 mg of Compound **III** daily. In some embodiments, the methods of treating, lessening the severity of, or symptomatically treating patients diagnosed with cystic fibrosis or a CFTR mediated disease comprise administering daily two pharmaceutical compositions, each comprising about 64 mg of crystalline Form B of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form

B), 25 mg of Compound **II,** and 35 mg to 40 mg of Compound **III** and optionally administering an additional 75 mg of Compound **III** daily. For example, two compositions each comprising about 64 mg of crystalline Form B of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), 25 mg of Compound **II,** and 35 mg to 40 mg of Compound **III** may be administered in the morning and 75 mg of Compound **III** may be administered in the evening.

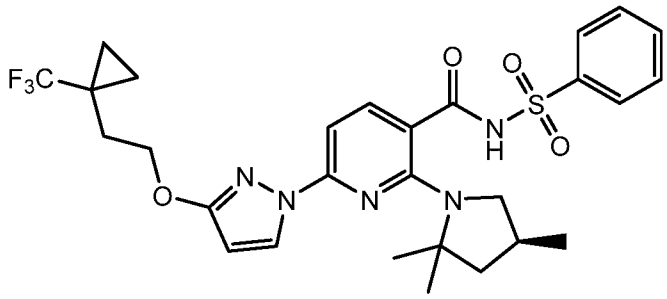
[00371] Some embodiments of the invention provide a method of treating, lessening the severity of, or symptomatically treating patients diagnosed with cystic fibrosis or a CFTR mediated disease comprising administering a fixed dose composition comprising about 128 mg of a crystalline form of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), 50 mg of Compound **II**, and 150 mg of Compound **III** twice a day, e.g., morning and evening or every 12 hours. In an alternate embodiment, the methods comprise administering a fixed dose composition comprising about 128 mg of a crystalline form of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), 50 mg of Compound **II**, and 100 mg of Compound **III-d** twice a day. In an alternate embodiment, the methods comprise administering two fixed dose compositions, each comprising about 128 mg of a crystalline form of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), 50 mg of Compound **II**, and 100 mg of Compound **III-d**, once a day. In an alternate embodiment, the methods comprise administering a fixed dose composition comprising about 255-256 mg of a crystalline form of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), 100 mg of Compound **II**, and 200 mg of Compound **III-d** once a day.

Exemplary Embodiments

[00372] Exemplary embodiments of the invention include:

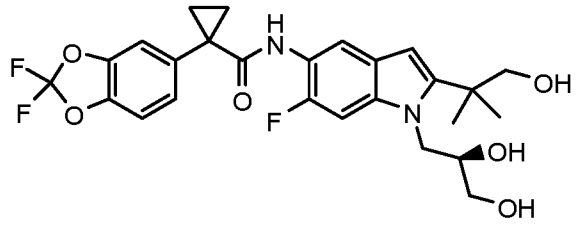
1. A pharmaceutical composition comprising

(a) 50 mg to 600 mg of a crystalline form selected from a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), a sodium salt of Compound **I** (Form A, D, E, H, or M) and crystalline Form A of Compound **I**:



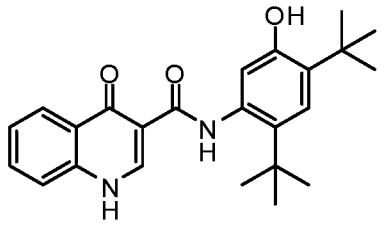
;

(b) a first solid dispersion comprising 25 mg to 125 mg of Compound **II**:

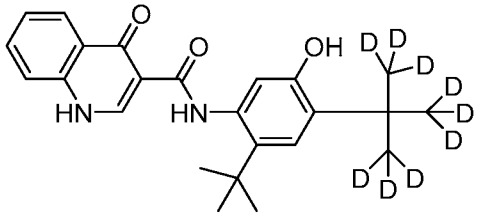


and 10 wt% to 30 wt% of a polymer relative to the total weight of the first solid dispersion; and

(c) a second solid dispersion comprising 5 mg to 300 mg of Compound **III** or Compound **III-d**:



(Compound **III**) or



(Compound **III-d**)

and 10 wt% to 30 wt% of a polymer relative to the total weight of the second solid dispersion.

2. The pharmaceutical composition of embodiment 1, wherein at least one of the first or second solid dispersions is a spray-dried dispersion.

3. The pharmaceutical composition of embodiment 1, wherein both of the first and second solid dispersions are spray-dried dispersions.

4. The pharmaceutical composition of embodiment 1, wherein said polymer for the first solid dispersion is hypromellose; and said polymer for the second solid dispersion is hypromellose acetate succinate.

5. The pharmaceutical composition of embodiment 1, wherein said polymer for the first solid dispersion is HPMC E15; and said polymer for the second solid dispersion is hypromellose acetate succinate H.

6. The pharmaceutical composition of embodiment 1, wherein said polymer for the first solid dispersion is HPMC E15; and said polymer for the second solid dispersion is hypromellose acetate succinate HG.

7. The pharmaceutical composition of any one of embodiments 1-6, comprising 50 mg to 500 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B).

8. The pharmaceutical composition of any one of embodiments 1-6, comprising 50 mg to 400 mg, 50 mg to 300 mg, 100 mg to 300 mg, 100 mg to 250 mg, 100 mg to 150 mg, or 200 mg to 250 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B).

9. The pharmaceutical composition of any one of embodiments 1-6, comprising 100 mg to 250 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B).

10. The pharmaceutical composition of any one of embodiments 1-6, comprising 100 mg to 150 mg or 150 mg to 250 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B).

11. The pharmaceutical composition of any one of embodiments 1-10, wherein the first solid dispersion comprises 25 mg to 75 mg of Compound **II**.

12. The pharmaceutical composition of any one of embodiments 1-10, wherein the first solid dispersion comprises 30 mg to 60 mg of Compound **II**.

13. The pharmaceutical composition of any one of embodiments 1-10, wherein the second solid dispersion comprises 25 mg to 50 mg, 25 mg to 75 mg, 50 mg to 100 mg, 75 mg to 125 mg, or 125 mg to 175 mg of Compound **III** or Compound **III-d**.

14. The pharmaceutical composition of any one of embodiments 1-10, wherein the second solid dispersion comprises 50 mg to 100 mg of Compound **III** or Compound **III-d**.

15. The pharmaceutical composition of any one of embodiments 1-6, comprising

100 mg to 250 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B); and wherein

the first solid dispersion comprises 25 mg to 75 mg of Compound **II**; and

the second solid dispersion comprises 50 mg to 100 mg of Compound **III** or Compound **III-d**.

16. The pharmaceutical composition of any one of embodiments 1-6, comprising

100 mg to 150 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B); and wherein

the first solid dispersion comprises 50 mg of Compound **II**; and

the second solid dispersion comprises 75 mg or 150 mg of Compound **III** or 100 mg of Compound **III-d**.

17. The pharmaceutical composition of any one of embodiments 1-6, comprising

170 mg to 250 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B); and wherein

the first solid dispersion comprises 50 mg or 100 mg of Compound **II**; and

the second solid dispersion comprises 75 mg or 150 mg of Compound **III** or 100 mg or 200 mg of Compound **III-d**.

18. The pharmaceutical composition of any one of embodiments 1-17, wherein the second solid dispersion further comprises 0.5% sodium lauryl sulfate relative to the total weight of the second solid dispersion.

19. The pharmaceutical composition of any one of embodiments 1-18, further comprising one or more pharmaceutically acceptable excipients selected from one or more fillers, a disintegrant, and a lubricant.

20. The pharmaceutical composition of embodiment 19, wherein one or more fillers are selected from microcrystalline cellulose, silicified microcrystalline cellulose, lactose, dicalcium phosphate, mannitol, copovidone, hydroxypropyl cellulose, hypromellose, methyl cellulose, ethyl cellulose, starch, Maltodextrin, agar, and guar gum.

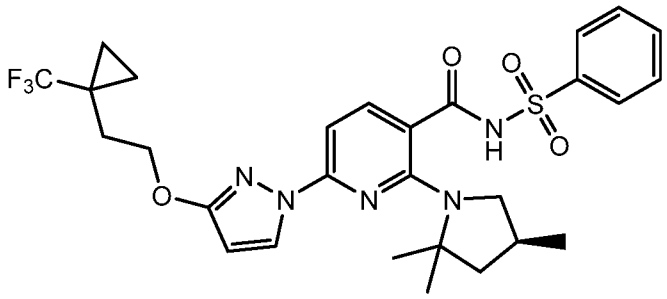
21. The pharmaceutical composition of embodiment 19, wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, corn or pre-gelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, and microcrystalline cellulose.

22. The pharmaceutical composition of embodiment 19, wherein the lubricant is selected from magnesium stearate, sodium stearyl fumarate, calcium stearate, sodium stearate, stearic acid, and talc.

23. The pharmaceutical composition of any one of embodiments 1-22, wherein the potassium salt of Compound **I** is substantially crystalline, and wherein each of Compound **II**, Compound **III** and Compound **III-d** are independently substantially amorphous.

24. A pharmaceutical composition comprising:

(a) 15 wt% to 45 wt% of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B):

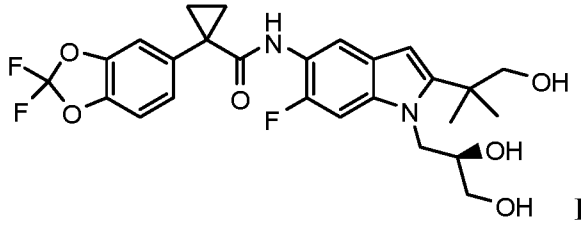


I

relative to the total weight of the pharmaceutical composition;

(b) 5 wt% to 20 wt% of a first solid dispersion relative to the total weight of the pharmaceutical composition,

wherein the first solid dispersion comprises 70 wt% to 90 wt% of Compound **II** relative to the total weight of the first solid dispersion:

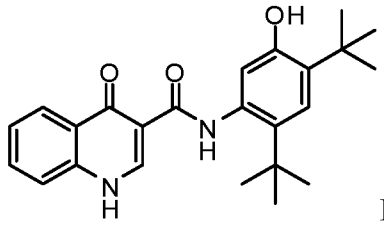


II

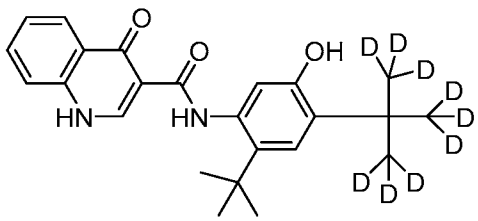
and 10 wt% to 30 wt% of a polymer relative to the total weight of the first solid dispersion; and

(c) 10 wt% to 40 wt% of a second solid dispersion relative to the total weight of the pharmaceutical composition;

wherein the second solid dispersion comprises 70 wt% to 90 wt% of Compound **III** or Compound **III-d** relative to the total weight of the second solid dispersion:



III



III-d

and 10 wt% to 30 wt% of a polymer relative to the total weight of the second solid dispersion.

25. The pharmaceutical composition of embodiment 24, wherein at least one of the first or second solid dispersions is a spray-dried dispersion.

26. The pharmaceutical composition of embodiment 24, wherein both of the first and second solid dispersions are spray-dried dispersions.

27. The pharmaceutical composition of embodiment 24, wherein said polymer for the first solid dispersion is hypromellose; and said polymer for the second solid dispersion is hypromellose acetate succinate.

28. The pharmaceutical composition of embodiment 24, wherein said polymer for the first solid dispersion is hypromellose (HPMC E15); and said polymer for the second solid dispersion is hypromellose acetate succinate H.

29. The pharmaceutical composition of embodiment 24, wherein:

the first solid dispersion comprises 70 wt% to 85 wt% of Compound **II** relative to the total weight of the first solid dispersion, and the polymer is a hydroxypropyl methylcellulose in an amount of 15 wt% to 30 wt% relative to the total weight of the first solid dispersion; and

the second solid dispersion comprises 70 wt% to 85 wt% of Compound **III** or Compound **III-d** relative to the total weight of the second solid dispersion, 0.5% sodium

lauryl sulfate relative to the total weight of the second solid dispersion, and the polymer is hypromellose acetate succinate in an amount of 14.5 wt% to 29.5 wt% relative to the total weight of the second solid dispersion.

30. The pharmaceutical composition of any one of embodiments 24-29, wherein the first solid dispersion comprises 75 wt% to 85 wt% of Compound **II** relative to the total weight of the first solid dispersion.

31. The pharmaceutical composition of any one of embodiments 24-29, wherein the first solid dispersion comprises 80 wt% of Compound **II** relative to the total weight of the first solid dispersion; and 20 wt% of a hydroxypropyl methylcellulose relative to the total weight of the first solid dispersion.

32. The pharmaceutical composition of any one of embodiments 24-31, wherein the second solid dispersion comprises 75 wt% to 85 wt% of Compound **III** or Compound **III-d** relative to the total weight of the second solid dispersion.

33. The pharmaceutical composition of any one of embodiments 24-32, wherein the second solid dispersion comprises 80 wt% of Compound **III** or Compound **III-d** relative to the total weight of the second solid dispersion; 0.5% of sodium lauryl sulfate relative to the total weight of the second solid dispersion, and 19.5 wt% of hypromellose acetate succinate relative to the total weight of the second solid dispersion.

34. The pharmaceutical composition of any one of embodiments 24-33, further comprising one or more pharmaceutically acceptable excipients selected from fillers, disintegrants, and lubricants.

35. The pharmaceutical composition of embodiment 34, wherein the filler is selected from microcrystalline cellulose, silicified microcrystalline cellulose, lactose, dicalcium phosphate, mannitol, copovidone, hydroxypropyl cellulose, hypromellose, methyl cellulose, ethyl cellulose, starch, Maltodextrin, agar, and guar gum.

36. The pharmaceutical composition of embodiment 34, wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, corn or pre-gelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, and microcrystalline cellulose.

37. The pharmaceutical composition of embodiment 34, wherein the lubricant is selected from magnesium stearate, sodium stearyl fumarate, calcium stearate, sodium stearate, stearic acid, and talc.

38. The pharmaceutical composition of any one of embodiments 24-37, the potassium salt of Compound **I** is substantially crystalline, and wherein each of Compound **II**, Compound **III** and Compound **III-d** is independently substantially amorphous.

39. A single tablet comprising:

(a) 200 mg to 215 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 90 mg to 95 mg of a second solid dispersion comprising 80 wt% of Compound **III** relative to the total weight of the second solid dispersion**,** 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion; and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion

(d) 175 mg to 215 mg of a microcrystalline cellulose;

(e) 20 mg to 30 mg of a croscarmellose sodium; and

(f) 3 mg to 7 mg of magnesium stearate.

40. The single tablet of embodiment 39, wherein the tablet comprises:

(a) 200 mg to 215 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of said first solid dispersion;

(c) 90 mg to 95 mg of said second solid dispersion;

(d) 175 mg to 215 mg of said microcrystalline cellulose;

(e) 15 mg to 30 mg of said croscarmellose sodium; and

(f) 3 mg to 7 mg of magnesium stearate.

41. The single tablet of embodiment 39, wherein the tablet comprises an intra-granular part and extra-granular part, and

(a) wherein the intra-granular part comprises:

(i) 200 mg to 215 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(ii) 60 mg to 65 mg of said first solid dispersion;

(iii) 90 mg to 95 mg of said second solid dispersion;

(iv) 120 mg to 150 mg of said microcrystalline cellulose;

(v) 10 mg to 20 mg of said croscarmellose sodium; and

(vi) 3 mg to 7 mg of magnesium stearate; and

(b) wherein the extra-granular part comprises:

(i) 55 mg to 65 mg of said microcrystalline cellulose; and

(ii) 5 mg to 10 mg of said croscarmellose sodium.

42. The single tablet of embodiment 39, wherein the tablet comprises:

(a) 210 mg to 215 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of said first solid dispersion;

(c) 90 mg to 95 mg of said second solid dispersion;

(d) 193 mg to 203 mg of said microcrystalline cellulose;

(e) 21 mg to 27 mg of said croscarmellose sodium; and

(f) 4 mg to 7 mg of magnesium stearate.

43. The single tablet of embodiment 39, wherein the tablet comprises an intra-granular part and extra-granular part, and

(a) wherein the intra-granular part comprises:

(i) 210 mg to 215 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(ii) 60 mg to 65 mg of said first solid dispersion;

(iii) 90 mg to 95 mg of said second solid dispersion;

(iv) 135 mg to 140 mg of said microcrystalline cellulose;

(v) 14 mg to 17 mg of said croscarmellose sodium; and

(vi) 4 mg to 7 mg of magnesium stearate; and

(b) wherein the extra-granular part comprises:

(i) 58 mg to 63 mg of said microcrystalline cellulose; and

(ii) 7 mg to 10 mg of said croscarmellose sodium.

44. A single tablet comprising:

(a) 115 mg to 140 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 90 mg to 95 mg of a second solid dispersion comprising 80 wt% of Compound **III** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion; and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion;

(d) 120 mg to 135 mg of a microcrystalline cellulose;

(e) 15 mg to 25 mg of a croscarmellose sodium; and

(f) 2 mg to 6 mg of magnesium stearate.

45. The single tablet of embodiment 44, wherein the tablet comprises:

(a) 115 mg to 140 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of said first solid dispersion;

(c) 90 mg to 95 mg of said second solid dispersion;

(d) 120 mg to 135 mg of said microcrystalline cellulose;

(e) 15 mg to 25 mg of said croscarmellose sodium; and

(f) 3 mg to 5 mg of magnesium stearate.

46. The single tablet of embodiment 44, wherein the tablet comprises an intra-granular part and extra-granular part, and

(a) wherein the intra-granular part comprises:

(i) 115 mg to 140 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(ii) 60 mg to 65 mg of said first solid dispersion;

(iii) 90 mg to 95 mg of said second solid dispersion;

(iv) 80 mg to 90 mg of said microcrystalline cellulose;

(v) 10 mg to 15 mg of said croscarmellose sodium; and

(vi) 3 mg to 5 mg of magnesium stearate; and

(b) wherein the extra-granular part comprises:

(i) 40 mg to 45 mg of said microcrystalline cellulose; and

(i) 5 mg to10 mg of said croscarmellose sodium.

47. The single tablet of embodiment 44, wherein the tablet comprises:

(a) 115 mg to 140 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of said first solid dispersion;

(c) 90 mg to 95 mg of said second solid dispersion;

(d) 125 mg to 140 mg of said microcrystalline cellulose;

(e) 15 mg to 25 mg of said croscarmellose sodium; and

(f) 2 mg to 6 mg of magnesium stearate.

48. The single tablet of embodiment 44, wherein the tablet comprises an intra-granular part and extra-granular part, and

(a) wherein the intra-granular part comprises:

(i) 115 mg to 140 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(ii) 60 mg to 65 mg of said first solid dispersion;

(iii) 90 mg to 95 mg of said second solid dispersion;

(iv) 85 mg to 95 mg of said microcrystalline cellulose;

(v) 10 mg to 15 mg of said croscarmellose sodium; and

(vi) 1 mg to 3 mg of magnesium stearate; and

(b) wherein the extra-granular part comprises:

(i) 40 mg to 45 mg of said microcrystalline cellulose; and

(ii) 5 mg to 10 mg of said croscarmellose sodium; and

(iii) 1 mg to 3 mg of magnesium stearate.

49. The pharmaceutical composition of any one of embodiments 1-48, wherein the pharmaceutical composition is a single tablet.

50. The pharmaceutical composition of any one of embodiments 1-49, further comprising a microcrystalline cellulose in an amount 20 wt % - 40 wt% relative to the total weight of the pharmaceutical composition.

51. The pharmaceutical composition of embodiment 50, further comprising a croscarmellose sodium in an amount 1 wt % - 10 wt% relative to the total weight of the pharmaceutical composition.

52. The pharmaceutical composition of embodiment 51, further comprising a magnesium stearate in an amount 0.5 wt % - 1.5 wt% relative to the total weight of the pharmaceutical composition.

53. A pharmaceutical composition comprising:

(a) 20 wt% to 35 wt% of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) relative to the total weight of the pharmaceutical composition ;

(b) 5 wt% to 20 wt% of a first solid dispersion relative to the total weight of the pharmaceutical composition, wherein the first solid dispersion comprises 70 wt% to 90 wt% of Compound **II** relative to the total weight of the first solid dispersion and 10 wt% to 30 wt% of a polymer relative to the total weight of the first solid dispersion; and

(c) 20 wt% to 40 wt% of a second solid dispersion relative to the total weight of the pharmaceutical composition, wherein the second solid dispersion comprises 70 wt% to 90 wt% of Compound **III** relative to the total weight of the second solid dispersion, and

10 wt% to 30 wt% of a polymer relative to the total weight of the second solid dispersion.

54. The pharmaceutical composition of embodiment 53, wherein at least one of the first or second solid dispersions is a spray-dried dispersion.

55. The pharmaceutical composition of embodiment 53, wherein both of the first and second solid dispersions are spray-dried dispersions.

56. The pharmaceutical composition of embodiment 53, wherein said polymer for the first solid dispersion is hypromellose; and said polymer for the second solid dispersion is hypromellose acetate succinate.

57. The pharmaceutical composition of embodiment 53, wherein said polymer for the first solid dispersion is hypromellose (HPMC E15); and said polymer for the second solid dispersion is hypromellose acetate succinate H.

58. The pharmaceutical composition of embodiment 53, wherein:

the first solid dispersion comprises 70 wt% to 85 wt% of Compound **II** relative to the total weight of the first solid dispersion, and the polymer is a hydroxypropyl methylcellulose in an amount of 15 wt% to 30 wt% relative to the total weight of the first solid dispersion; and

the second solid dispersion comprises 70 wt% to 85 wt% of Compound **III** relative to the total weight of the second solid dispersion, 0.5% sodium lauryl sulfate relative to the total weight of the second solid dispersion, and the polymer is hypromellose acetate succinate in an amount of 14.5 wt% to 29.5 wt% relative to the total weight of the second solid dispersion.

59. The pharmaceutical composition of any one of embodiments 53-58, wherein the first solid dispersion comprises 75 wt% to 85 wt% of Compound **II** relative to the total weight of the first solid dispersion.

60. The pharmaceutical composition of embodiment 59, wherein the first solid dispersion comprises 80 wt% of Compound **II** relative to the total weight of the first solid dispersion; and 20 wt% of a hydroxypropyl methylcellulose relative to the total weight of the first solid dispersion.

61. The pharmaceutical composition of any one of embodiments 53-60, wherein the second solid dispersion comprises 75 wt% to 85 wt% of Compound **III** relative to the total weight of the second solid dispersion.

62. The pharmaceutical composition of embodiment 61, wherein the second solid dispersion comprises 80 wt% of Compound **III** relative to the total weight of the second solid dispersion; 0.5% of sodium lauryl sulfate relative to the total weight of the second solid dispersion, and 19.5 wt% of a hypromellose acetate succinate relative to the total weight of the second solid dispersion.

63. The pharmaceutical composition of any one of embodiments 53-62, further comprising one or more pharmaceutically acceptable excipients selected from fillers, disintegrants, and lubricants.

64. The pharmaceutical composition of embodiment 63, wherein the filler is selected from microcrystalline cellulose, silicified microcrystalline cellulose, lactose, dicalcium phosphate, mannitol, copovidone, hydroxypropyl cellulose, hypromellose, methyl cellulose, ethyl cellulose, starch, Maltodextrin, agar, and guar gum.

65. The pharmaceutical composition of embodiment 64, wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, corn or pre-gelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, and microcrystalline cellulose.

66. The pharmaceutical composition of embodiment 65, wherein the lubricant is selected from magnesium stearate, sodium stearyl fumarate, calcium stearate, sodium stearate, stearic acid, and talc.

67. The pharmaceutical composition of any one of embodiments 53-66, the potassium salt of Compound **I** is substantially crystalline, and wherein each of Compound **II** and Compound **III** is independently substantially amorphous.

68. The pharmaceutical composition of any one of embodiments 1-38 and 49-52, wherein said potassium salt of Compound **I**, said Compound **II**, and said Compound **III** are present in a ratio of 8:2:3 based on the respective weight of free base Compound **I**: Compound **II**: Compound **III**.

69. The pharmaceutical composition of any one of embodiments 1-38 and 49-52, wherein said potassium salt of Compound **I**, said Compound **II**, and said Compound **III**

are present in a ratio of 24:10:15 based on the respective weight of free base Compound **I**: Compound **II**: Compound **III**.

70. The pharmaceutical composition of any one of embodiments 1-38 and 49-52, wherein said potassium salt of Compound **I**, said Compound **II**, and said Compound **III-d** are present in a ratio of 4:1:2 based on the respective weight of free base Compound **I**: Compound **II**: Compound **III-d**.

71. The pharmaceutical composition of any one of embodiments 1-38 and 49-52, wherein said potassium salt of Compound **I**, said Compound **II**, and said Compound **III-d** are present in a ratio of 12:5:10 based on the respective weight of free base Compound **I**: Compound **II**: Compound **III-d**.

72. The pharmaceutical composition of any one of embodiments 1-38 and 53-67, wherein said potassium salt of Compound **I**, said Compound **II**, and said Compound **III** are present in a ratio of 4:1:3 based on the respective weight of free base Compound **I**: Compound **II**: Compound **III**.

73. The pharmaceutical composition of any one of embodiments 1-38 and 53-67, wherein said potassium salt of Compound **I**, said Compound **II**, and said Compound **III** are present in a ratio of 12:5:15 based on the respective weight of free base Compound **I**: Compound **II**: Compound **III**.

74. The pharmaceutical composition of embodiment 24, wherein the pharmaceutical composition comprises:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	20 – 45 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10-30 wt%

75. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15 – 45 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III** or Compound III-d, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 40 wt%
microcrystalline cellulose	5 – 50 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 2 wt% based on the total weight of composition	

76. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15 – 45 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III** or Compound III-d, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 40 wt%
microcrystalline cellulose	5 – 50 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
magnesium stearate	0.05 – 2 wt%

77. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15 – 35 wt%

Component	weight % based on the total weight of composition
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 - 40 wt%
microcrystalline cellulose	20 – 40 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
magnesium stearate	0.05 – 2 wt%

78. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	20 – 40 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 25 wt%
microcrystalline cellulose	20 – 40 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
magnesium stearate	0.05 – 2 wt%

79. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	30 - 40 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 - 15 wt%

Component	weight % based on the total weight of composition
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 20 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
magnesium stearate	0.05 – 2 wt%

80. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	33 - 38 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	8 - 13 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	13 - 18 wt%
microcrystalline cellulose	30 – 35 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
magnesium stearate	0.05– 2 wt%

81. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	28 - 33 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	7 - 12 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	25 - 30 wt%

Component	weight % based on the total weight of composition
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
magnesium stearate	0.05 – 1.5 wt%

82. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	25 - 35 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	10 - 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 - 25 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
magnesium stearate	0.05 – 2 wt%

83. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	27 - 32 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	12 - 17 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	18 - 23 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	3 – 6 wt%
magnesium stearate	0.05 – 1.5 wt%

84. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	20– 30 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	7 - 15 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	30 – 40 wt%
microcrystalline cellulose	15 – 40 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
magnesium stearate	0.05 – 1.5 wt%

85. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	22 - 27 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	8 - 13 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	32 - 37 wt%
microcrystalline cellulose	20 – 30 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
magnesium stearate	0.05 – 1.5 wt%

86. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	25– 40 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	7 - 15 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 – 35 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
magnesium stearate	0.05 – 1.5 wt%

87. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	29 - 36 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	8 - 13 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 - 25 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
magnesium stearate	0.05 – 1.5 wt%

88. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and optionally magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15– 40 wt%

Component	weight % based on the total weight of composition
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 - 20 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 – 40 wt%
microcrystalline cellulose	10 – 50 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 2 wt% based on the total weight of composition	

89. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and optionally magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	20 - 30 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	8-18 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 - 30 wt%
microcrystalline cellulose	20 – 30 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight of composition	

90. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and optionally magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	28 – 38 wt%

Component	weight % based on the total weight of composition
solid dispersion containing 80% Compound **II**, 20% hypromellose	10 -20 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	27 - 37 wt%
microcrystalline cellulose	5 – 20 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight of composition	

91. The pharmaceutical composition of embodiment 24, further comprising microcrystalline cellulose, croscarmellose sodium and optionally magnesium stearate, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	15 - 25 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5-15 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 - 25 wt%
microcrystalline cellulose	40 – 50 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight of composition	

92. The pharmaceutical composition of embodiment 24, wherein the pharmaceutical composition comprises:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	22 - 32 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	10-20 wt%

Component	weight % based on the total weight of composition
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 - 30 wt%
microcrystalline cellulose	20 – 30 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight of composition	

93. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	207 - 217
solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	182-193
microcrystalline cellulose (e.g., PH101)	175 - 215
croscarmellose sodium	15 - 35
magnesium stearate	3 - 9

94. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122 – 132
solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	182 - 193
microcrystalline cellulose	110 - 145
croscarmellose sodium	13 - 25
magnesium stearate	1.5 – 8

95. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	62 – 65
solid dispersion containing 80% Compound **II**, 20% hypromellose	30 - 33
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	90 - 95
microcrystalline cellulose	65 - 71
croscarmellose sodium	10 - 13
magnesium stearate	2.5 – 4.5

96. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	58 – 68
solid dispersion containing 80% Compound **II**, 20% hypromellose	25 - 35
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	87 - 97
microcrystalline cellulose	60 – 100
croscarmellose sodium	5 - 15
magnesium stearate	1.5 – 7

97. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	207-217
solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68

Component	Amount (mg) per composition
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	120 -130
microcrystalline cellulose	175 - 220
croscarmellose sodium	15 - 32
magnesium stearate	3 - 8

98. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122 – 132
solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	124 - 126
microcrystalline cellulose (e.g., PH101)	129 - 131
croscarmellose sodium	17 - 19
magnesium stearate	3 – 5

99. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount(mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122-132
solid dispersion containing 80% Compound **II**, 20% hypromellose	58 -68
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	120-130
Microcrystalline cellulose	110-145
Croscarmellose sodium	8-30
Magnesium Stearate	1-7

100. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and optionally magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount(mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	250-260
solid dispersion containing 80% Compound **II**, 20% hypromellose	120-130
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	245-255
Microcrystalline cellulose	80 -110
Croscarmellose sodium	15-30

and optionally further comprises magnesium stearate, in an amount of 0.01 mg – 10 mg per composition.

101. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and optionally magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount(mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122-132
solid dispersion containing 80% Compound **II**, 20% hypromellose	57-67
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	120-130
Microcrystalline cellulose	275 -305
Croscarmellose sodium	10 -25

and optionally further comprises magnesium stearate, in an amount of 0.01 mg – 10 mg per composition.

102. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and optionally magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount(mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	122 - 132
solid dispersion containing 80% Compound **II**, 20% hypromellose	58 - 68
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	120 - 130
Microcrystalline cellulose	100 - 135
Croscarmellose sodium	10 - 20

and optionally further comprises magnesium stearate, in an amount of 0.01 mg – 10 mg per composition.

103. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	45-80 mg
solid dispersion containing 80% Compound **II**, 20% hypromellose	20-50 mg
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	30-70 mg
microcrystalline cellulose	60-300 mg
croscarmellose sodium	5-25 mg
magnesium stearate	1-7 mg

104. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and optionally magnesium stearate, wherein the pharmaceutical composition comprises:

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	50 – 80
solid dispersion containing 80% Compound **II**, 20% hypromellose	20 - 40
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	70 - 120
microcrystalline cellulose	60 – 300

Component	Amount (mg) per composition
croscarmellose sodium	5 - 25
magnesium stearate	1– 7

105. The pharmaceutical composition of embodiment 1, further comprising microcrystalline cellulose, croscarmellose sodium and magnesium stearate, wherein the pharmaceutical composition comprises:

(a)

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	50 – 80
solid dispersion containing 80% Compound **II**, 20% hypromellose	20 - 40
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	45 - 80
microcrystalline cellulose	60 - 300
croscarmellose sodium	5 - 25

and optionally further comprises magnesium stearate, in an amount of 0.01 mg – 10 mg per composition; or

(b)

Component	Amount (mg) per composition
potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B)	95-160
solid dispersion containing 80% Compound **II**, 20% hypromellose	45-80
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	95-155
Microcrystalline cellulose	60 -300
Croscarmellose sodium	5 - 25

and optionally further comprises magnesium stearate, in an amount of 0.01 mg – 10 mg per composition.

106. A single tablet comprising:

(a) 50 mg to 140 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 25 mg to 65 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 75 mg to 200 mg of a second solid dispersion comprising 80 wt% of Compound **III** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion, and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion

(d) 60 mg to 150 mg of a microcrystalline cellulose;

(e) 5 mg to 25 mg of a croscarmellose sodium; and

(f) 1 mg to 6 mg of magnesium stearate.

107. The single tablet of embodiment 106, wherein the single tablet comprises:

(a) 115 mg to 140 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of said first solid dispersion;

(c) 170 mg to 200 mg of said second solid dispersion;

(d) 60 mg to 140 mg of said microcrystalline cellulose;

(e) 10 mg to 30 mg of said croscarmellose sodium; and

(f) 3 mg to 8 mg of said magnesium stearate.

108. The single tablet of embodiment 106, wherein the tablet comprises:

(a) 115 mg to 140 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of said first solid dispersion;

(c) 180 mg to 190 mg of said second solid dispersion;

(d) 120 mg to 135 mg of said microcrystalline cellulose;

(e) 15 mg to 25 mg of said croscarmellose sodium; and

(f) 3 mg to 5 mg of magnesium stearate .

109. The single tablet of embodiment 106, wherein the tablet comprises:

(a) 115 mg to 140 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of said first solid dispersion;

(c) 180 mg to 190 mg of said second solid dispersion;

(d) 130 mg to 140 mg of said microcrystalline cellulose;

(e) 20 mg to 30 mg of said croscarmellose sodium; and

(f) 5 mg to 8 mg of magnesium stearate.

110. The single tablet of embodiment 106, wherein the single tablet comprises:

(a) 60 mg to 65 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 28 mg to 33 mg of said first solid dispersion;

(c) 90 mg to 95 mg of said second solid dispersion;

(d) 50 mg to 100 mg of said microcrystalline cellulose;

(e) 5 mg to 15 mg of said croscarmellose sodium; and

(f) 1 mg to 5 mg of said magnesium stearate.

111. A single tablet comprising:

(a) 100 mg to 250 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 30 mg to 65 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 75 mg to 200 mg of a second solid dispersion comprising 80 wt% of Compound **III** relative to the total weight of the second solid dispersion 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion, and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion.

(d) 85 mg to 215 mg of a microcrystalline cellulose;

(e) 10 mg to 30 mg of a croscarmellose sodium; and

(f) 1 mg to 7 mg of magnesium stearate.

112. The single tablet of embodiment 111, wherein the tablet comprises:

(a) 103 mg to 108 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 30 mg to 35 mg of said first solid dispersion;

(c) 90 mg to 95 mg of said second solid dispersion;

(d) 85 mg to 215 mg of said microcrystalline cellulose;

(e) 10 mg to 30 mg of said croscarmellose sodium; and

(f) 1 mg to 7 mg of magnesium stearate.

113. A single tablet comprising:

(a) 100 mg to 215 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 30 mg to 65 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 50 mg to 300 mg of a second solid dispersion comprising 80 wt% of Compound **III-d** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion, and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion;

(d) 85 mg to 215 mg of a microcrystalline cellulose;

(e) 10 mg to 30 mg of a croscarmellose sodium; and

(f) 1 mg to 7 mg of magnesium stearate.

114. The single tablet of embodiment 113, wherein the tablet comprises:

(a) 200 mg to 215 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of said first solid dispersion;

(c) 100 mg to 150 mg of said second solid dispersion;

(d) 85 mg to 215 mg of said microcrystalline cellulose;

(e) 10 mg to 30 mg of said croscarmellose sodium; and

(f) 1 mg to 7 mg of magnesium stearate.

115. The single tablet of embodiment 113, wherein the tablet comprises:

(a) 100 mg to 110 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 30 mg to 35 mg of said first solid dispersion;

(c) 50 mg to 75 mg of said second solid dispersion;

(d) 85 mg to 215 mg of said microcrystalline cellulose;

(e) 10 mg to 30 mg of said croscarmellose sodium; and

(f) 1 mg to 7 mg of magnesium stearate.

116. A single tablet comprising:

(a) 55 mg to 300 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 30 mg to 130 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion, and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 50 mg to 300 mg of a second solid dispersion comprising 80 wt% of Compound **III-d** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion; and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion

(d) 60 mg to 300 mg of a microcrystalline cellulose;

(e) 7 mg to 25 mg of a croscarmellose sodium; and

(f) optionally 0.05 mg to 6 mg of magnesium stearate.

117. The single tablet of embodiment 116, wherein the tablet comprises:

(a) 245 mg to 260 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 120 mg to 130 mg of said first solid dispersion;

(c) 230 mg to 275 mg of said second solid dispersion;

(d) 60 mg to 135 mg of said microcrystalline cellulose;

(e) 7 mg to 25 mg of said croscarmellose sodium; and

(f) optionally 0.05 mg to 6 mg of magnesium stearate.

118. The single tablet of embodiment 116, wherein the tablet comprises:

(a) 115 mg to 140 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);

(b) 60 mg to 65 mg of said first solid dispersion;

(c) 100 mg to 150 mg of said second solid dispersion;

(d) 60 mg to 135 mg of said microcrystalline cellulose;

(e) 7 mg to 25 mg of said croscarmellose sodium; and

(f) optionally 0.05 mg to 6 mg of magnesium stearate .

119. The single tablet of embodiment 116, wherein the tablet comprises:

(a) 60 mg to 70 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);
(b) 25 mg to 35 mg of said first solid dispersion;
(c) 55 mg to 65 mg of said second solid dispersion;
(d) 60 mg to 135 mg of said microcrystalline cellulose;
(e) 7 mg to 25 mg of said croscarmellose sodium; and
(f) optionally 0.05 mg to 6 mg of magnesium stearate.

120. The single tablet of embodiment 116, wherein the tablet comprises:

(a) 125 mg to 130 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);
(b) 60 mg to 65 mg of said first solid dispersion;
(c) 122 mg to 127 mg of said second solid dispersion;
(d) 275 mg to 325 mg of said microcrystalline cellulose;
(e) 10 mg to 25 mg of said croscarmellose sodium; and
(f) optionally 0.05 mg to 6 mg of magnesium stearate.

121. The single tablet of embodiment 116, wherein the tablet comprises:

(a) 125 mg to 130 mg of said potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B);
(b) 60 mg to 65 mg of said first solid dispersion;
(c) 122 mg to 127 mg of said second solid dispersion;
(d) 110 mg to 125 mg of said microcrystalline cellulose;
(e) 10 mg to 25 mg of said croscarmellose sodium; and
(f) optionally 0.05 mg to 6 mg of magnesium stearate.

122. A method of treating cystic fibrosis in a patient comprising orally administering to the patient one or more of the pharmaceutical composition of any one of embodiments 1-38 and 49-105 or the single tablet of any one of embodiments 39-48 and 106-121.

123. The method of embodiment 122, wherein one or more of the pharmaceutical compositions or single tablets are administered once daily.

124. The method of embodiment 122, wherein one or more of the pharmaceutical compositions or single tablets are administered twice daily.

125. The method of embodiment 122, wherein two pharmaceutical compositions or tablets are administered concurrently per dosing.

126. The method according to any one of embodiments 122- 125, wherein said patient has cystic fibrosis is chosen from patients with F508del/minimal function genotypes, patients with F508del/F508del genotypes, patients with F508del/gating genotypes, and patients with F508del/residual function genotypes.

127. The method of embodiment 126, wherein the patient with a F508del/minimal function genotype has a minimal function mutation selected from:

Mutation				
S4X	C276X	G542X	R792X	E1104X
G27X	Q290X	G550X	E822X	R1158X
Q39X	G330X	Q552X	W846X	R1162X
W57X	W401X	R553X	Y849X	S1196X
E60X	Q414X	E585X	R851X	W1204X
R75X	S434X	G673X	Q890X	L1254X
E92X	S466X	Q685X	S912X	S1255X
Q98X	S489X	R709X	Y913X	W1282X
Y122X	Q493X	K710X	W1089X	Q1313X
E193X	W496X	L732X	Y1092X	E1371X
L218X	C524X	R764X	W1098X	Q1382X
Q220X	Q525X	R785X	R1102X	Q1411X
185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
405+1G→A	1248+1G→A	1811+1G→C	3040G→C	3600+2insT
405+3A→C	1249-1G→A	1811+1.6kbA→G	(G970R)	3850-1G→A
406-1G→A	1341+1G→A	1812-1G→A	3120G→A	4005+1G→A
621+1G→T	1525-2A→G	1898+1G→A	3120+1G→A	4374+1G→T
711+1G→T	1525-1G→A	1898+1G→C	3121-2A→G	
182delT	1119delA	1782delA	2732insA	3876delA
306insA	1138insG	1824delA	2869insG	3878delG
365-366insT	1154insTC	2043delG	2896insAG	3905insT
394delTT	1161delC	2143delT	2942insT	4016insT
442delA	1213delT	2183AA→G	2957delT	4021dupT
444delA	1259insA	2184delA	3007delG	4040delA
457TAT→G	1288insTA	2184insA	3028delA	4279insA
541delC	1471delA	2307insA	3171delC	4326delTC

Mutation			
574delA	1497delGG	2347delG	3659delC
663delT	1548delG	2585delT	3737delA
935delA	1609del CA	2594delGT	3791delC
1078delT	1677delTA	2711delT	3821delT
CFTRdele2,3	1461ins4		2991del32
CFTRdele22,23	1924del7		3667ins4
124del23bp	2055del9→A		4010del4
852del22	2105-2117del13insAGAAA		4209TGTT→AA
991del5	2721del11		
A46D	V520F	Y569D	N1303K
G85E	A559T	L1065P	
R347P	R560T	R1066C	
L467P	R560S	L1077P	
I507del	A561E	M1101K	

128. The method of embodiment 127, wherein the patient with a F508del/gating genotype has a gating mutation selected from G178R, S549N, S549R, G551D, G551S, G1244E, S1251N, S1255P, and G1349D.

129. The method of embodiment 127, wherein the patient with a F508del/ residual function genotype has a residual function mutation selected from 2789+5G→ A, 3849+10kbC→T, 3272-26A→ G, 711+3A→ G, E56K, P67L, R74W, D110E, D110H, R117C, L206W, R347H, R352Q, A455E, D579G, E831X, S945L, S977F, F1052V, R1070W, F1074L, D1152H, D1270N, E193K, K1060T, R117H, S1235R, I1027T, R668C, G576A, M470V, L997F, R75Q, R1070Q, R31C, D614G, G1069R, R1162L, E56K, A1067T, E193K, and K1060T.

130. A method of preparing a pharmaceutical composition of embodiment 1, 24 or 49, wherein the pharmaceutical composition is a tablet and the method comprises:

(a) mixing the potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) and the first and second solid dispersions to form a first mixture; and

(b) compressing a tablet mixture comprising the first mixture into a tablet.

131. The method of embodiment 130, wherein the tablet mixture further comprises one or more pharmaceutically acceptable excipients, and the method further comprising mixing the first mixture with said one or more excipients to form the tablet mixture.

132. The method of embodiment 130 or 131, further comprising coating the tablet.

133. A method of preparing a single tablet of any one of embodiments 39-48 and 106-121, comprising

(a) mixing the potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) and the first and second solid dispersions to form a first mixture;

(b) mixing the first mixture with said microcrystalline cellulose, croscarmellose sodium and magnesium stearate to form a tablet mixture; and

(c) compressing the tablet mixture into a tablet.

134. The method of embodiment 133, further comprising coating the tablet.

135. A method of preparing a single tablet of embodiment 39, 42, 74, 77, or 80, comprising

(a) mixing the potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) and the first and second solid dispersions to form a first mixture;

(b) mixing a first portion of said microcrystalline cellulose, a first portion of said croscarmellose sodium and a first portion of said magnesium stearate comprised in the intra-granular part to form a second mixture;

(c) mixing a second portion of said microcrystalline cellulose and a second portion of said croscarmellose sodium to form a third mixture;

(d) mixing the first, second, and third mixtures to form a tablet mixture; and

(e) compressing the tablet mixture comprising the first, second and third mixtures into a tablet.

136. The method of embodiment 135, further comprising coating the tablet.

137. A method of preparing a single tablet of any one of embodiments 1, 39-48 and 106-123, comprising

(a) mixing the potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) and the first and second solid dispersions to form a first mixture;

(b) mixing a first portion of said microcrystalline cellulose, a first portion of said croscarmellose sodium and magnesium stearate to form a second mixture;

(c) mixing a second portion of said microcrystalline cellulose and a second portion of said croscarmellose sodium comprised to form a third mixture;

(d) mixing the first, second, and third mixtures to form a tablet mixture; and

(e) compressing the tablet mixture comprising the first, second and third mixtures into a tablet.

138. The method of embodiment 137, further comprising coating the tablet.

139. A method of preparing a single tablet of any one of embodiments 39-48 and 106-123, comprising

(a) mixing the potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B) and the first and second solid dispersions to form a first mixture;

(b) mixing a first portion of said microcrystalline cellulose, a first portion of said croscarmellose sodium and a first portion of said magnesium stearate to form a second mixture;

(c) mixing said a second portion of said microcrystalline cellulose, a second portion of said croscarmellose sodium, and a second portion of said magnesium stearate to form a third mixture;

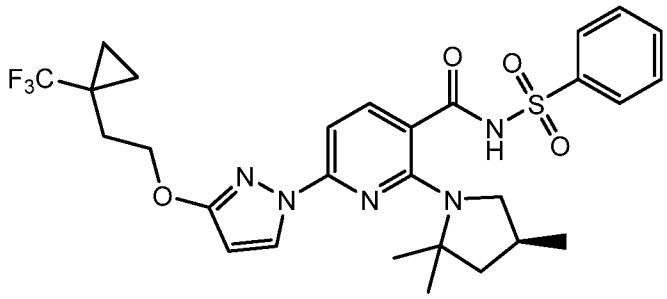
(d) mixing the first, second, and third mixtures to form a tablet mixture; and

(e) compressing the tablet mixture comprising the first, second and third mixtures into a tablet.

140. The method of embodiment 139, further comprising coating the tablet.

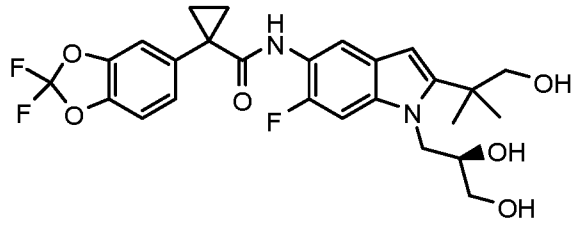
141. A pharmaceutical composition comprising

(a) 50 mg to 600 mg of a crystalline form selected from a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B), a sodium salt of Compound **I** (Form A, D, E, H, or M) and crystalline Form A of Compound **I**:



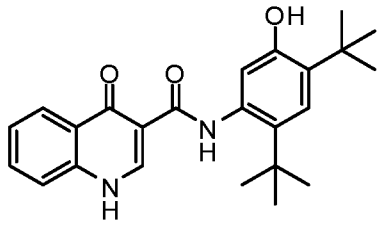
;

(b) a first solid dispersion comprising 15 mg to 75 mg of Compound **II**:

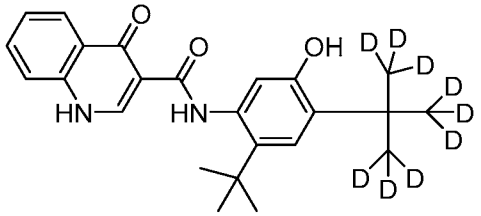


and 10 wt% to 30 wt% of a polymer relative to the total weight of the first solid dispersion; and

(c) a second solid dispersion comprising 5 mg to 300 mg of Compound **III** or Compound **III-d**:



(Compound **III**) or



(Compound **III-d**)

and 10 wt% to 30 wt% of a polymer relative to the total weight of the second solid dispersion.

142. The pharmaceutical composition of embodiment 141, wherein at least one of the first or second solid dispersions is a spray-dried dispersion.

143. The pharmaceutical composition of embodiment 141, wherein both of the first and second solid dispersions are spray-dried dispersions.

144. The pharmaceutical composition of embodiment 141, wherein said polymer for the first solid dispersion is hypromellose; and said polymer for the second solid dispersion is hypromellose acetate succinate.

145. The pharmaceutical composition of embodiment 141, wherein said polymer for the first solid dispersion is HPMC E15; and said polymer for the second solid dispersion is hypromellose acetate succinate H.

146. The pharmaceutical composition of embodiment 141, wherein said polymer for the first solid dispersion is HPMC E15; and said polymer for the second solid dispersion is hypromellose acetate succinate HG.

147. The pharmaceutical composition of any one of embodiments 141-146, comprising 50 mg to 500 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B).

148. The pharmaceutical composition of any one of embodiments 141-146, comprising 50 mg to 400 mg, 50 mg to 300 mg, 100 mg to 300 mg, 100 mg to 250 mg, 100 mg to 150 mg, or 200 mg to 250 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B).

149. The pharmaceutical composition of any one of embodiments 141-146, comprising 100 mg to 250 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B).

150. The pharmaceutical composition of any one of embodiments 141-146, comprising 100 mg to 150 mg or 150 mg to 250 mg of a potassium salt of Compound **I** (in some embodiments, potassium salt crystalline Form B).

151. The pharmaceutical composition of any one of embodiments 141-150, wherein the first solid dispersion comprises 20 mg to 60 mg of Compound **II**.

152. The pharmaceutical composition of any one of embodiments 141-150, wherein the second solid dispersion comprises 25 mg to 75 mg of Compound **III** or Compound **III-d**.

153. The pharmaceutical composition of any one of embodiments 1-10, wherein the second solid dispersion comprises 150 mg to 250 mg of Compound **III** or Compound **III-d**.

154. The pharmaceutical composition of any one of embodiments 1-6, comprising 50 mg to 400 mg, 50 mg to 300 mg, 100 mg to 300 mg, 100 mg to 250 mg, 100 mg to 150

mg, or 200 mg to 250 mg of a sodium salt of Compound **I** (in some embodiments, sodium salt crystalline Form H).

155. The pharmaceutical composition of any one of embodiments 1-6, comprising

100 mg to 250 mg of a sodium salt of Compound **I** (in some embodiments, sodium salt crystalline Form H); and wherein

the first solid dispersion comprises 25 mg to 75 mg of Compound **II**; and

the second solid dispersion comprises 50 mg to 100 mg of Compound **III** or Compound **III-d**.

156. The pharmaceutical composition of any one of embodiments 1-6, comprising

about 125 mg of a sodium salt of Compound **I** (in some embodiments, sodium salt crystalline Form H); and wherein

the first solid dispersion comprises about 50 mg of Compound **II**; and

the second solid dispersion comprises about 75 mg of Compound **III** or Compound **III-d**.

157. The pharmaceutical composition of embodiment 141, comprising

50 mg to 125 mg of a sodium salt of Compound **I** (in some embodiments, sodium salt crystalline Form H); and wherein

the first solid dispersion comprises 15 mg to 40 mg of Compound **II**; and

the second solid dispersion comprises 25 mg to 50 mg of Compound **III** or Compound **III-d**.

158. The pharmaceutical composition of embodiment 141, comprising

about 62 mg of a sodium salt of Compound **I** (in some embodiments, sodium salt crystalline Form H); and wherein

the first solid dispersion comprises about 25 mg of Compound **II**; and

the second solid dispersion comprises about 37-38 mg of Compound **III** or Compound **III-d**.

159. A pharmaceutical composition comprising:

(a) 20 wt% to 35 wt% of a sodium salt of Compound **I** (in some embodiments, sodium salt crystalline Form H) relative to the total weight of the pharmaceutical composition;

(b) 5 wt% to 20 wt% of a first solid dispersion relative to the total weight of the pharmaceutical composition, wherein the first solid dispersion comprises 70 wt% to 90 wt% of Compound **II** relative to the total weight of the first solid dispersion and 10 wt% to 30 wt% of a polymer relative to the total weight of the first solid dispersion; and

(c) 20 wt% to 40 wt% of a second solid dispersion relative to the total weight of the pharmaceutical composition, wherein the second solid dispersion comprises 70 wt% to 90 wt% of Compound **III** or Compound **III-d** relative to the total weight of the second solid dispersion and 10 wt% to 30 wt% of a polymer relative to the total weight of the second solid dispersion.

160. A pharmaceutical composition comprising:

(a) 10 wt% to 18 wt% of a sodium salt of Compound **I** (in some embodiments, sodium salt crystalline Form H) relative to the total weight of the pharmaceutical composition;

(b) 2 wt% to 10 wt% of a first solid dispersion relative to the total weight of the pharmaceutical composition, wherein the first solid dispersion comprises 70 wt% to 90 wt% of Compound **II** relative to the total weight of the first solid dispersion and 10 wt% to 30 wt% of a polymer relative to the total weight of the first solid dispersion; and

(c) 10 wt% to 20 wt% of a second solid dispersion relative to the total weight of the pharmaceutical composition, wherein the second solid dispersion comprises 70 wt% to 90 wt% of Compound **III** or Compound **III-d** relative to the total weight of the second solid dispersion and 10 wt% to 30 wt% of a polymer relative to the total weight of the second solid dispersion.

161. A method of treating cystic fibrosis in a patient comprising orally administering to the patient one or more of the pharmaceutical compositions of any one of embodiments 154-160.

162. The method of embodiment 161, wherein one or more of the pharmaceutical compositions are administered once daily.

163. The method of embodiment 161, wherein one or more of the pharmaceutical compositions are administered twice daily.

164. The method of embodiment 161, wherein two pharmaceutical compositions are administered concurrently per dosing.

General Experimental Procedures

[00373] Reagents and starting materials were obtained by commercial sources unless otherwise stated and were used without purification. Proton and carbon NMR spectra were acquired on either of a Bruker Biospin DRX 400 MHz FTNMR spectrometer operating at a ^{1}H and ^{13}C resonant frequency of 400 and 100 MHz respectively, or on a 300 MHz NMR spectrometer. One dimensional proton and carbon spectra were acquired using a broadband observe (BBFO) probe with 20 Hz sample rotation at 0.1834 and 0.9083 Hz/Pt digital resolution respectively. All proton and carbon spectra were acquired with temperature control at 30°C using standard, previously published pulse sequences and routine processing parameters.

[00374] Solid state ^{13}C and ^{19}F NMR data was obtained using Bruker-Biospin 400 MHz wide-bore spectrometer equipped with Bruker-Biospin 4mm HFX probe was used. Samples were packed into 4mm rotors and spun under Magic Angle Spinning (MAS) condition with typical spinning speed of 12.5 kHz. The proton relaxation time was estimated from ^{1}H MAS T_1 saturation recovery relaxation experiment and used to set up proper recycle delay of the ^{13}C cross-polarization (CP) MAS experiment. The fluorine relaxation time was estimated from ^{19}F MAS T_1 saturation recovery relaxation experiment and used to set up proper recycle delay of the ^{19}F MAS experiment. The CP contact time of CPMAS experiments was set to 2 ms. A CP proton pulse with linear ramp (from 50% to 100%) was employed. All spectra were externally referenced by adjusting the magnetic field to set carbon resonance of adamantane to 29.5ppm. TPPM15 proton decoupling sequence was used with the field strength of approximately 100 kHz for both ^{13}C and ^{19}F acquisitions.

[00375] Final purity of compounds was determined by reversed phase UPLC using an Acquity UPLC BEH C_{18} column (50 × 2.1 mm, 1.7 μm particle) made by Waters (pn: 186002350), and a dual gradient run from 1-99% mobile phase B over 3.0 minutes. Mobile phase A = H_2O (0.05 % CF_3CO_2H). Mobile phase B = CH_3CN (0.035 % CF_3CO_2H). Flow rate = 1.2 mL/min, injection volume = 1.5 μL, and column temperature = 60 °C. Final purity was calculated by averaging the area under the curve (AUC) of two UV traces (220 nm, 254 nm). Low-resolution mass spectra were reported

as $[M+H]^+$ species obtained using a single quadrupole mass spectrometer equipped with an electrospray ionization (ESI) source capable of achieving a mass accuracy of 0.1 Da and a minimum resolution of 1000 (no units on resolution) across the detection range. Optical purity of methyl (2S)-2,4-dimethyl-4-nitro-pentanoate was determined using chiral gas chromatography (GC) analysis on an Agilent 7890A/MSD 5975C instrument, using a Restek Rt-βDEXcst (30m x 0.25mm x 0.25um_df) column, with a 2.0 mL/min flow rate (H_2 carrier gas), at an injection temperature of 220°C and an oven temperature of 120°C, 15 minutes.

Powder X-ray Diffraction

[00376] The powder x-ray diffraction measurements were performed using PANalytical's X-pert Pro diffractometer at room temperature with copper radiation (1.54060 Å). The incident beam optic was comprised of a variable divergence slit to ensure a constant illuminated length on the sample and on the diffracted beam side; a fast linear solid state detector was used with an active length of 2.12 degrees 2 theta measured in a scanning mode. The powder sample was packed on the indented area of a zero background silicon holder and spinning was performed to achieve better statistics. A symmetrical scan was measured from 4 – 40 degrees 2 theta with a step size of 0.017 degrees and a scan step time of 15.5s.

Modulated Differential Scanning Calorimetry (MDSC)

[00377] MDSC was used to determine the glass transition temperature of the amorphous material. MDSC was performed using TA Discovery DSC differential scanning calorimeter (TA Instruments, New Castle, DE). The instrument was calibrated with indium. Samples of approximately 1-3 mg were weighed into hermetic pans that were crimped using lids with one hole. The MDSC sample was scanned from from -20°C to 200°C at a heating rate of 2°C/min with +/- 1°C of modulation within 1 minute. Data was collected and analyzed by TA Instruments Trios Software (TA Instruments, New Castle, DE).

Single-Crystal Analysis

[00378] X-ray diffraction data were acquired at 100K or 298K on a Bruker diffractometer equipped with Mo K_α radiation (λ = 0.71073 Å) or Cu K_α radiation (λ =

1.5478) and an CCD detector. The structure was solved and refined using SHELX program (Sheldrick, G.M., Acta Cryst., (2008) A64, 112-122).

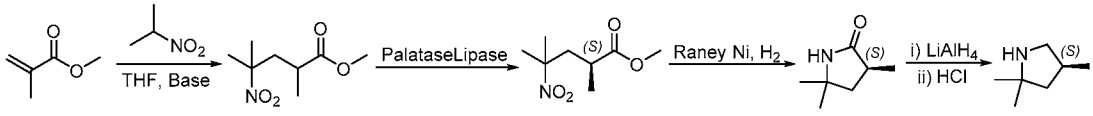
Thermogravimetric Analysis (TGA)

[00379] TGA was used to investigate the presence of residual solvents in the lots characterized, and identify the temperature at which decomposition of the sample occurs. TGA data were collected on a TA Discovery Thermogravimetric Analyzer or equivalent instrumentation. A sample with weight of approximately 1-5 mg was scanned from 25 °C to 350 °C at a heating rate of 10 °C/min. Data were collected and analyzed by Trios software (TA Instruments, New Castle, DE) or collected by Thermal Advantage Q SeriesTM software and analyzed by Universal Analysis software (TA Instruments, New Castle, DE). Differential Scanning Calorimetry (DSC).

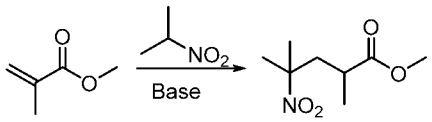
[00380] DSC data were acquired using a TA Instruments Q2000 or equivalent instrumentation. A sample with a weight between 1 and 10 mg was weighed into an aluminum pan. This pan was placed in the sample position in the calorimeter cell. An empty pan was placed in the reference position. The calorimeter cell was closed and a flow of nitrogen was passed through the cell. The heating program was set to heat the sample at a heating rate of 10° C./min to a temperature of 200-350° C. When the run was completed, the data were analyzed using the DSC analysis program in the system software. The observed endo- and exotherms were integrated between baseline temperature points that were above and below the temperature range over which the endotherm was observed. The data reported were the onset of decomposition temperature, peak temperature and enthalpy.

Example 1: Synthesis of N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide (Compound I)

Part A: Synthesis of (4S)-2,2,4-trimethylpyrrolidine hydrochloride

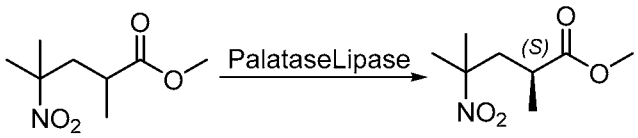


Step 1: Synthesis of methyl-2,4-dimethyl-4-nitro-pentanoate



[00381] Tetrahydrofuran (THF, 4.5 L) was added to a 20 L glass reactor and stirred under N_2 at room temperature. 2-Nitropropane (1.5 kg, 16.83 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.282 kg, 8.42 mol) were then charged to the reactor, and the jacket temperature was increased to 50 °C. Once the reactor contents were close to 50 °C, methyl methacrylate (1.854 kg, 18.52 mol) was added slowly over 100 minutes. The reaction temperature was maintained at or close to 50 °C for 21 hours. The reaction mixture was concentrated *in vacuo* then transferred back to the reactor and diluted with methyl *tert*-butyl ether (MTBE) (14 L). 2 M HCl (7.5 L) was added, and this mixture was stirred for 5 minutes then allowed to settle. Two clear layers were visible – a lower yellow aqueous phase and an upper green organic phase. The aqueous layer was removed, and the organic layer was stirred again with 2 M HCl (3 L). After separation, the HCl washes were recombined and stirred with MTBE (3 L) for 5 minutes. The aqueous layer was removed, and all of the organic layers were combined in the reactor and stirred with water (3 L) for 5 minutes. After separation, the organic layers were concentrated *in vacuo* to afford a cloudy green oil. This was dried with $MgSO_4$ and filtered to afford methyl-2,4-dimethyl-4-nitro-pentanoate as a clear green oil (3.16 kg, 99% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.68 (s, 3H), 2.56 – 2.35 (m, 2H), 2.11 – 2.00 (m, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.19 (d, J = 6.8 Hz, 3H).

Step 2: Synthesis of methyl (2S)-2,4-dimethyl-4-nitro-pentanoate

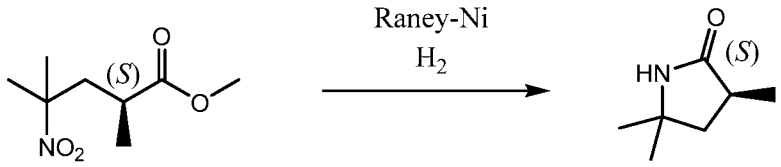


[00382] A reactor was charged with purified water (2090 L; 10 vol) and then potassium phosphate monobasic (27 kg, 198.4 moles; 13 g/L for water charge). The pH of the reactor contents was adjusted to pH 6.5 (± 0.2) with 20% (w/v) potassium carbonate solution. The reactor was charged with racemic methyl-2,4-dimethyl-4-nitro-pentanoate (209 kg; 1104.6 moles), and Palatase 20000L lipase (13 L, 15.8 kg; 0.06 vol).

[00383] The reaction mixture was adjusted to 32 ± 2 °C and stirred for 15-21 hours, and pH 6.5 was maintained using a pH stat with the automatic addition of 20% potassium carbonate solution. When the racemic starting material was converted to >98% ee of the S-enantiomer, as determined by chiral GC, external heating was

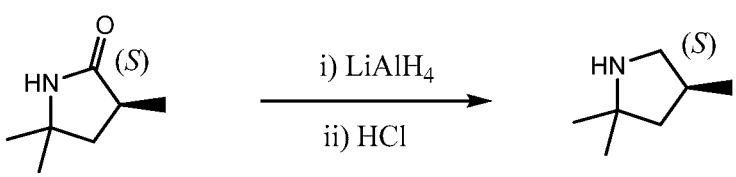
switched off. The reactor was then charged with MTBE (35 L; 5 vol), and the aqueous layer was extracted with MTBE (3 times, 400-1000L). The combined organic extracts were washed with aqueous Na_2CO_3 (4 times, 522 L, 18 % w/w 2.5 vol), water (523 L; 2.5 vol), and 10% aqueous NaCl (314 L, 1.5 vol). The organic layer was concentrated *in vacuo* to afford methyl (2*S*)-2,4-dimethyl-4-nitro-pentanoate as a mobile yellow oil (>98% ee, 94.4 kg; 45 % yield).

Step 3: Synthesis of (3S)-3,5,5-trimethylpyrrolidin-2-one



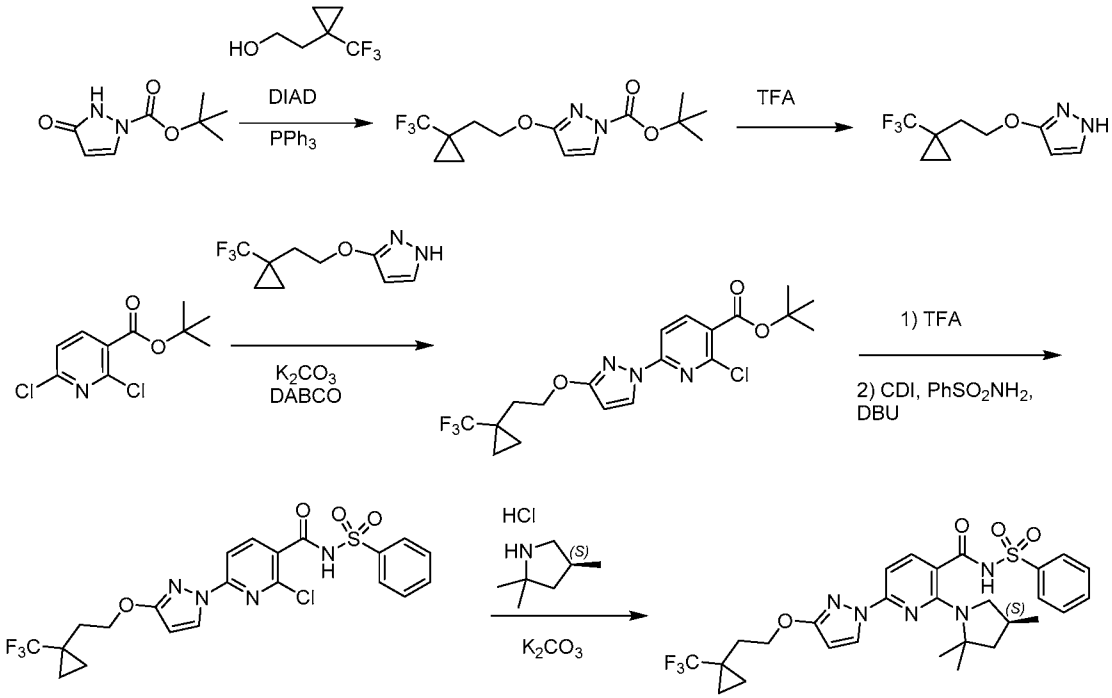
[00384] A 20 L reactor was purged with N_2. The vessel was charged sequentially with DI water-rinsed, damp Raney® Ni (2800 grade, 250 g), methyl (2S)-2,4-dimethyl-4-nitro-pentanoate (1741g, 9.2 mol), and ethanol (13.9 L, 8 vol). The reaction was stirred at 900 rpm, and the reactor was flushed with H_2 and maintained at ~2.5 bar. The reaction mixture was then warmed to 60 °C for 5 hours. The reaction mixture was cooled and filtered to remove Raney nickel, and the solid cake was rinsed with ethanol (3.5 L, 2 vol). The ethanolic solution of the product was combined with a second equal sized batch and concentrated *in vacuo* to reduce to a minimum volume of ethanol (~1.5 volumes). Heptane (2.5 L) was added, and the suspension was concentrated again to ~1.5 volumes. This was repeated 3 times; the resulting suspension was cooled to 0-5 °C, filtered under suction, and washed with heptane (2.5 L). The product was dried under vacuum for 20 minutes then transferred to drying trays and dried in a vacuum oven at 40 °C overnight to afford (3S)-3,5,5-trimethylpyrrolidin-2-one as a white crystalline solid (2.042 kg, 16.1 mol, 87 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.39 (s, 1H), 2.62 (ddq, J = 9.9, 8.6, 7.1 Hz, 1H), 2.17 (dd, J = 12.4, 8.6 Hz, 1H), 1.56 (dd, J = 12.5, 9.9 Hz, 1H), 1.31 (s, 3H), 1.25 (s, 3H), 1.20 (d, J = 7.1 Hz, 3H).

Step 4: Synthesis of (4S)-2,2,4-trimethylpyrrolidine hydrochloride



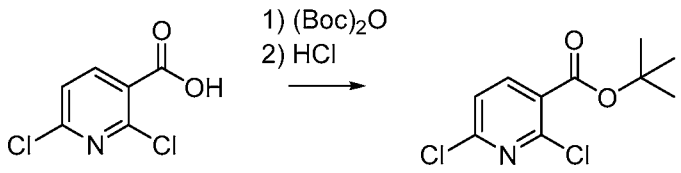
[00385] A glass lined 120 L reactor was charged with lithium aluminium hydride pellets (2.5 kg, 66 mol) and dry THF (60 L) and warmed to 30 °C. The resulting suspension was charged with *(S)*-3,5,5-trimethylpyrrolidin-2-one (7.0 kg, 54 mol) in THF (25 L) over 2 hours while maintaining the reaction temperature at 30 to 40 °C. After complete addition, the reaction temperature was increased to 60 - 63 °C and maintained overnight. The reaction mixture was cooled to 22 °C, then cautiously quenched with the addition of ethyl acetate (EtOAc) (1.0 L, 10 moles), followed by a mixture of THF (3.4 L) and water (2.5 kg, 2.0 eq), and then a mixture of water (1.75 kg) with 50 % aqueous sodium hydroxide (750 g, 2 equiv water with 1.4 equiv sodium hydroxide relative to aluminum), followed by 7.5 L water. After the addition was complete, the reaction mixture was cooled to room temperature, and the solid was removed by filtration and washed with THF (3 x 25 L). The filtrate and washings were combined and treated with 5.0 L (58 moles) of aqueous 37% HCl (1.05 equiv.) while maintaining the temperature below 30°C. The resultant solution was concentrated by vacuum distillation to a slurry. Isopropanol (8 L) was added and the solution was concentrated to near dryness by vacuum distillation. Isopropanol (4 L) was added, and the product was slurried by warming to about 50 °C. MTBE (6 L) was added, and the slurry was cooled to 2-5 °C. The product was collected by filtration and rinsed with 12 L MTBE and dried in a vacuum oven (55 °C/300 torr/N_2 bleed) to afford *(4S)*-2,2,4-trimethylpyrrolidine•HCl as a white, crystalline solid (6.21 kg, 75% yield). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.34 (br d, 2H), 3.33 (dd, *J* = 11.4, 8.4 Hz, 1H), 2.75 (dd, *J* = 11.4, 8.6 Hz, 1H), 2.50 – 2.39 (m, 1H), 1.97 (dd, *J* = 12.7, 7.7 Hz, 1H), 1.42 (s, 3H), 1.38 (dd, *J* = 12.8, 10.1 Hz, 1H), 1.31 (s, 3H), 1.05 (d, *J* = 6.6 Hz, 3H).

Part B: Synthesis of N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide



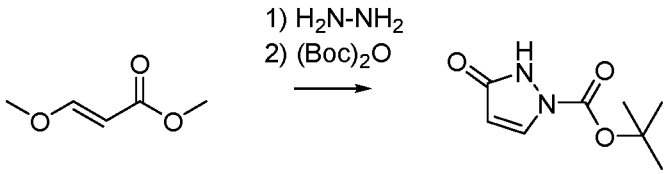
Synthesis of starting materials:

Synthesis of *tert*-Butyl 2,6-dichloropyridine-3-carboxylate



[00386] A solution of 2,6-dichloropyridine-3-carboxylic acid (10 g, 52.08 mmol) in THF (210 mL) was treated successively with di-*tert*-butyl dicarbonate (17 g, 77.89 mmol) and 4-(dimethylamino)pyridine (3.2 g, 26.19 mmol) and stirred overnight at room temperature. At this point, HCl 1N (400 mL) was added, and the mixture was stirred vigorously for about 10 minutes. The product was extracted with ethyl acetate (2x300mL), and the combined organic layers were washed with water (300 mL) and brine (150 mL) and dried over sodium sulfate and concentrated under reduced pressure to give 12.94 g (96% yield) of *tert*-butyl 2,6-dichloropyridine-3-carboxylate as a colorless oil. ESI-MS *m/z* calc. 247.02, found 248.1 $(M+1)^+$; Retention time: 2.27 minutes. ^{1}H NMR (300 MHz, $CDCl_3$) ppm 1.60 (s, 9H), 7.30 (d, *J*=7.9 Hz, 1H), 8.05 (d, *J*=8.2 Hz, 1H).

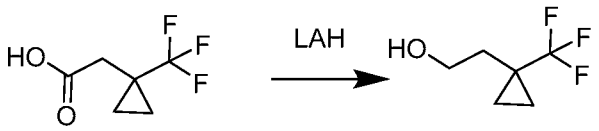
Synthesis of *tert*-Butyl 3-oxo-2,3-dihydro-1H-pyrazole-1-carboxylate



[00387] A 50L reactor was started, and the jacket was set to 20 °C, with stirring at 150 rpm, reflux condenser (10 °C) and nitrogen purge. MeOH (2.860 L) and methyl (E)-3-methoxyprop-2-enoate (2.643 kg, 22.76 mol) were added, and the reactor was capped. The reaction was heated to an internal temperature of 40 °C, and the system was set to hold jacket temperature at 40 °C. Hydrazine hydrate (1300 g of 55 %w/w, 22.31 mol) was added portion wise via addition funnel over 30 min. The reaction was heated to 60 °C for 1 h. The reaction mixture was cooled to 20 °C and triethyamine (2.483 kg, 3.420 L, 24.54 mol) was added portion-wise, maintaining reaction temperature <30 °C. A solution of Boc anhydride (di-tert-butyl dicarbonate) (4.967 kg, 5.228 L, 22.76 mol) in MeOH (2.860 L) was added portion-wise maintaining temperature <45 °C. The reaction mixture was stirred at 20 °C for 16 h. The reaction solution was partially concentrated to remove MeOH, resulting in a clear, light amber oil. The resulting oil was transferred to the 50L reactor, stirred and water (7.150 L) and heptane (7.150 L) were added. The additions caused a small amount of the product to precipitate. The aqueous layer was drained into a clean container, and the interface and heptane layer were filtered to separate the solid (product). The aqueous layer was transferred back to the reactor, and the collected solid was placed back into the reactor and mixed with the aqueous layer. A dropping funnel was added to the reactor and loaded with acetic acid (1.474 kg, 1.396 L, 24.54 mol) and added dropwise. The jacket was set to 0 °C to absorb the quench exotherm. After the addition was complete (pH=5), the reaction mixture was stirred for 1 h. The solid was collected by filtration and washed with water (7.150 L) and washed a second time with water (3.575 L). The crystalline solid was transferred into a 20L rotovap bulb, and heptane (7.150 L) was added. The mixture was slurried at 45 °C for 30 mins, and 1-2 volumes of solvent were distilled off. The slurry in the rotovap flask was filtered, and the solids were washed with heptane (3.575 L). The solid was further dried *in vacuo* (50 °C, 15 mbar) to give *tert*-butyl 5-oxo-1H-pyrazole-2-carboxylate (2921 g, 71%) as a coarse, crystalline solid. ^{1}H NMR

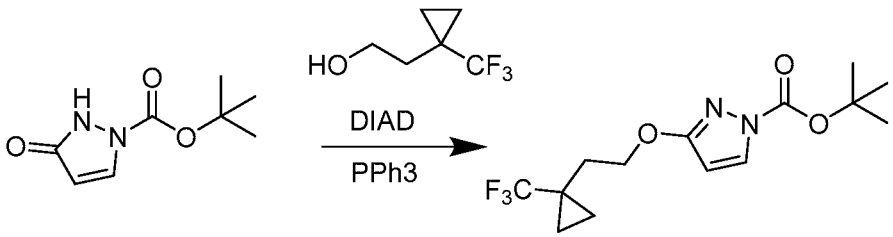
(400 MHz, DMSO-d6) δ 10.95 (s, 1H), 7.98 (d, *J* = 2.9 Hz, 1H), 5.90 (d, *J* = 2.9 Hz, 1H), 1.54 (s, 9H).

Synthesis of 2-[1-(trifluoromethyl)cyclopropyl]ethanol



[00388] To a solution of lithium aluminum hydride (293 mg, 7.732 mmol) in THF (10.00 mL) in an ice-bath, 2-[1-(trifluoromethyl)cyclopropyl]acetic acid (1.002 g, 5.948 mmol) in THF (3.0 mL) was added dropwise over a period of 30 minutes keeping the reaction temperature below 20 ° C. The mixture was allowed to gradually warm to ambient temperature and was stirred for 18 h. The mixture was cooled with an ice-bath and sequentially quenched with water (294 mg, 295 µL, 16.36 mmol), NaOH (297 µL of 6 M, 1.784 mmol), and then water (884.0 µL, 49.07 mmol) to afford a granular solid in the mixture. The solid was filtered off using celite, and the precipitate was washed with ether. The filtrate was further dried with $MgSO_4$ and filtered and concentrated in vacuo to afford the product with residual THF and ether. The mixture was taken directly into the next step without further purification.

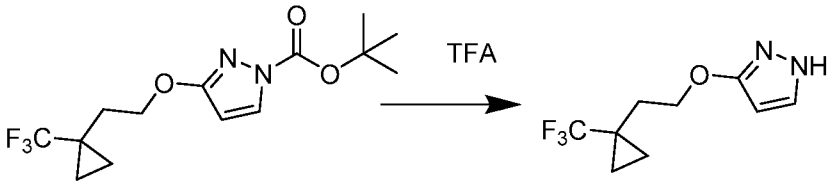
Step 1: *tert*-Butyl 3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazole-1-carboxylate



[00389] *tert*-Butyl 5-oxo-1H-pyrazole-2-carboxylate (1.043 g, 5.660 mmol), 2-[1-(trifluoromethyl)cyclopropyl]ethanol (916 mg, 5.943 mmol), and triphenyl phosphine (1.637 g, 6.243 mmol) were combined in THF (10.48 mL) and the reaction was cooled in an ice-bath. Diisopropyl azodicarboxylate (1.288 g, 1.254 mL, 6.368 mmol) was added dropwise to the reaction mixture, and the reaction was allowed to warm to room temperature for 16 hours. The mixture was evaporated, and the resulting material was partitioned between ethyl acetate (30 mL) and 1N sodium hydroxide (30 mL). The organic layer was separated, washed with brine (30 mL), dried over sodium sulfate, and

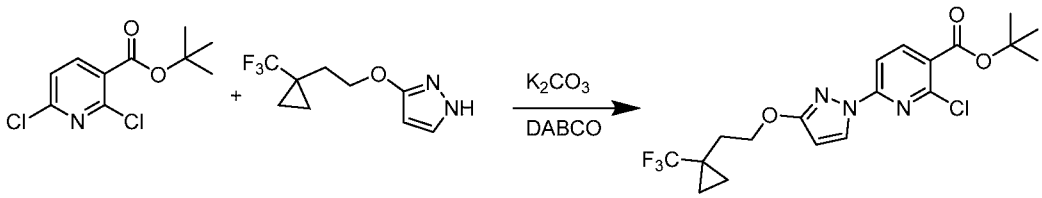
concentrated. The crude material was purified by silica gel chromatography eluting with a gradient of ethyl acetate in hexanes (0- 30%) to give *tert*-butyl 3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazole-1-carboxylate (1.03 g, 57%). ESI-MS *m/z* calc. 320.13, found 321.1 $(M+1)^+$; Retention time: 0.72 minutes.

Step 2: 3-[2-[1-(Trifluoromethyl)cyclopropyl]ethoxy]-1H-pyrazole



[00390] *tert*-Butyl-3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazole-1-carboxylate (1.03 g, 3.216 mmol) was dissolved in dichloromethane (10.30 mL) with trifluoroacetic acid (2.478 mL, 32.16 mmol), and the reaction was stirred at room temperature for 2 hours. The reaction was evaporated, and the resulting oil was partitioned between ethyl acetate (10 mL) and a saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated to give 3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]-1H-pyrazole (612 mg, 86%). ESI-MS *m/z* calc. 220.08, found 221.0 $(M+1)^+$; Retention time: 0.5 minutes. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.86 (s, 1H), 7.50 (t, J = 2.1 Hz, 1H), 5.63 (t, J = 2.3 Hz, 1H), 4.14 (t, J = 7.1 Hz, 2H), 2.01 (t, J = 7.1 Hz, 2H), 0.96 - 0.88 (m, 2H), 0.88 - 0.81 (m, 2H).

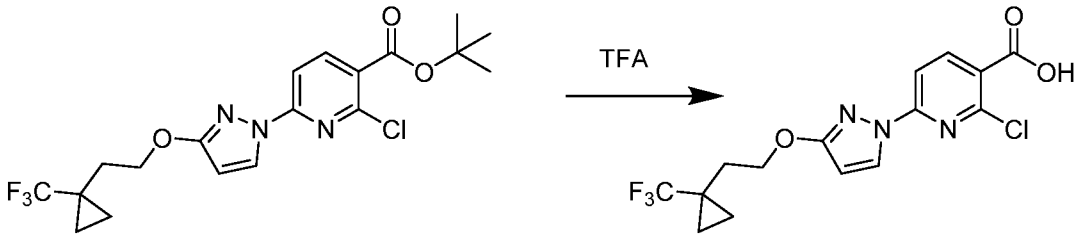
Step 3: *tert*-Butyl 2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl] ethoxy]pyrazol-1-yl]pyridine-3-carboxylate



[00391] *tert*-Butyl 2,6-dichloropyridine-3-carboxylate (687 mg, 2.770 mmol), 3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]-1H-pyrazole (610 mg, 2.770 mmol), and freshly ground potassium carbonate (459 mg, 3.324 mmol) were combined in anhydrous DMSO (13.75 mL). 1,4-diazabicyclo[2.2.2]octane (DABCO (1,4-diazabicyclo[2.2.2]octane), 62 mg, 0.5540 mmol) was added, and the mixture was

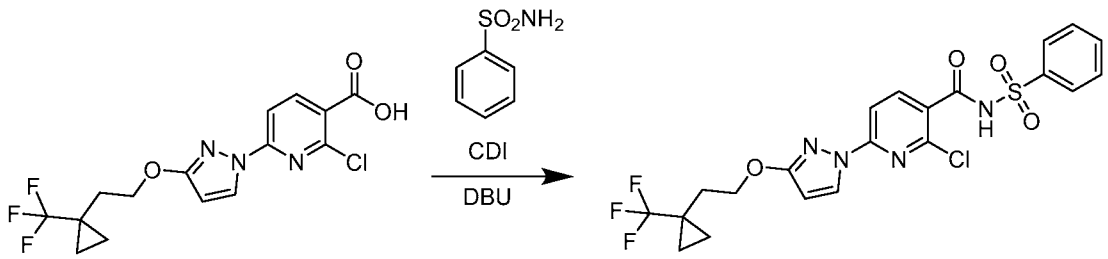
stirred at room temperature under nitrogen for 16 hours. The reaction mixture was diluted with water (20 mL) and stirred for 15 minutes. The resulting solid was collected and washed with water. The solid was dissolved in dichloromethane and dried over magnesium sulfate. The mixture was filtered and concentrated to give *tert*-butyl 2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]pyridine-3-carboxylate (1.01 g, 84%). ESI-MS *m/z* calc. 431.12, found 432.1 $(M+1)^+$; Retention time: 0.88 minutes.

Step 4: 2-Chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]pyridine-3-carboxylic acid



[00392] *tert*-Butyl 2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]pyridine-3-carboxylate (1.01 g, 2.339 mmol) and trifluoroacetic acid (1.8 mL, 23.39 mmol) were combined in dichloromethane (10 mL) and heated at 40 °C for 3 h. The reaction was concentrated. Hexanes were added, and the mixture was concentrated again to give 2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]pyridine-3-carboxylic acid (873 mg, 99%) ESI-MS *m/z* calc. 375.06, found 376.1 $(M+1)^+$; Retention time: 0.69 minutes.

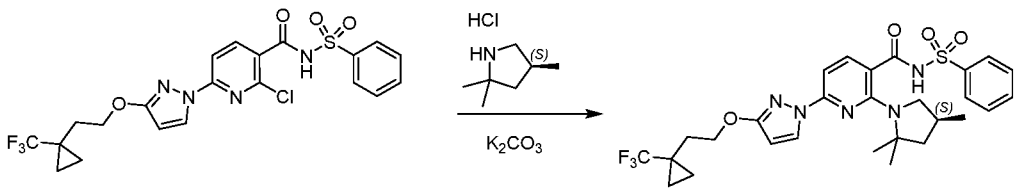
Step 5: N-(Benzenesulfonyl)-2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl] ethoxy]pyrazol-1-yl]pyridine-3-carboxamide



[00393] A solution of 2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl] ethoxy]pyrazol-1-yl]pyridine-3-carboxylic acid (0.15 g, 0.3992 mmol) and carbonyl diimidazole (77 mg, 0.4790 mmol) in THF (2.0 mL) was stirred for one hour, and

benzenesulfonamide (81 mg, 0.5190 mmol) and DBU (72 µL, 0.4790 mmol) were added. The reaction was stirred for 16 hours, acidified with 1 M aqueous citric acid, and extracted with ethyl acetate. The combined extracts were dried over sodium sulfate and evaporated. The residue was purified by silica gel chromatography eluting with a gradient of methanol in dichloromethane (0-5%) to give N-(benzenesulfonyl)-2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]pyridine-3-carboxamide (160 mg, 78%). ESI-MS *m/z* calc. 514.07, found 515.1 $(M+1)^+$; Retention time: 0.74 minutes.

Step 6: N-(Benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl)cyclopropyl] ethoxy]pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide



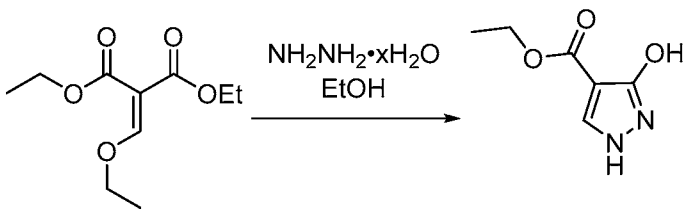
[00394] A mixture of N-(benzenesulfonyl)-2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl] ethoxy]pyrazol-1-yl]pyridine-3-carboxamide (160 mg, 0.3107 mmol), (4S)-2,2,4-trimethylpyrrolidine hydrochloride salt (139 mg, 0.9321 mmol), and potassium carbonate (258 mg, 1.864 mmol) in DMSO (1.5 mL) was stirred at 130 °C for 17 hours. The reaction mixture was acidified with 1 M aqueous citric acid and extracted with ethyl acetate. The combined extracts were dried over sodium sulfate and evaporated to yield a crude product that was purified by reverse-phase HPLC utilizing a gradient of 10-99% acetonitrile in 5 mM aqueous HCl to yield N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide (87 mg, 47%). ESI-MS *m/z* calc. 591.21, found 592.3 $(M+1)^+$; Retention time: 2.21 minutes. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 8.19 (d, *J* = 2.8 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.70 – 7.62 (m, 2H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.10 (d, *J* = 2.8 Hz, 1H), 4.31 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 10.5 Hz, 1H), 2.28 (dd, *J* = 10.2, 7.0 Hz, 1H), 2.17 – 2.01 (m, 3H), 1.82 (dd, *J* = 11.9, 5.5 Hz, 1H), 1.52 (d, *J* = 9.4 Hz, 6H), 1.36 (t, *J* = 12.1 Hz, 1H), 1.01 – 0.92 (m, 2H), 0.92 – 0.85 (m, 2H), 0.65 (d, J = 6.3 Hz, 3H). pKa: 4.95±0.06.

Synthesis of sodium salt of N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl) cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide (sodium salt of Compound I)

[00395] N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide (1000 mg, 1.679 mmol) was dissolved in ethanol (19.87 ml) under warming, filtered clear through a syringe filter (0.2 µm), washed with warm ethanol (10 ml) and the warm solution was treated with 1M NaOH (1.679 ml, 1.679 mmol). The solution was evaporated at 30-35 °C, co-evaporated 3 times with ethanol (~20 ml), to give a solid, which was dried overnight under vacuum in a drying cabinet at 45 °C with a nitrogen bleed to give 951 mg of a cream colored solid. The solid was further dried under vacuum in a drying cabinet at 45 °C with a nitrogen bleed over the weekend. 930 mg (89%) of the sodium salt of N-(benzenesulfonyl)-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide was obtained as an off-white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 2.7 Hz, 1H), 7.81 (dd, J = 6.7, 3.1 Hz, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.39 (dd, J = 4.9, 2.0 Hz, 3H), 6.74 (d, J = 7.9 Hz, 1H), 6.01 (d, J = 2.6 Hz, 1H), 4.29 (t, J = 7.0 Hz, 2H), 2.93 - 2.78 (m, 2H), 2.07 (t, J = 7.1 Hz, 3H), 1.78 (dd, J = 11.8, 5.6 Hz, 1H), 1.52 (d, J = 13.6 Hz, 6H), 1.33 (t, J = 12.0 Hz, 1H), 1.00 - 0.92 (m, 2H), 0.89 (q, J = 5.3, 4.6 Hz, 2H), 0.71 (d, J = 6.3 Hz, 3H). EST-MS m/z calc. 591.2127, found 592.0 $(M+1)^+$; Retention time: 3.28 minutes. XRPD (see **FIG. 16**).

Alternate synthesis of 2-Chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy] pyrazol-1-yl]pyridine-3-carboxylic acid

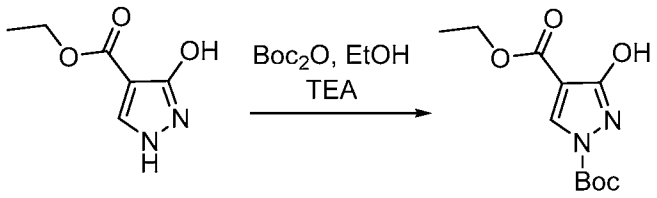
Step 1: ethyl 3-hydroxy-1H-pyrazole-4-carboxylate



[00396] A mixture of EtOH (20.00 L, 10 vol) and diethyl 2-(ethoxymethylene) propanedioate (2000 g, 9.249 mol, 1.0 equiv) was added under nitrogen purge a to a 50 L reactor equipped with a reflux condenser (10 °C) and the jacket set to 40 °C. The

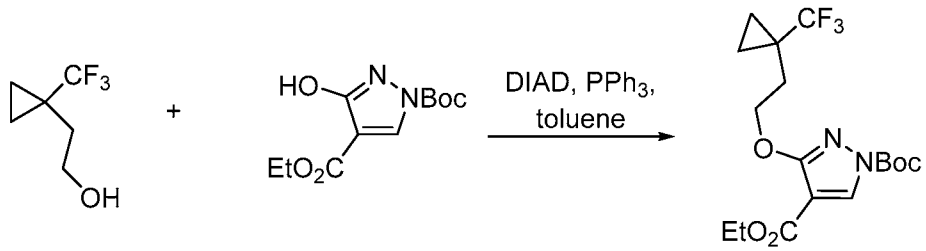
mixture was stirred, and then hydrazine hydrate (538.9 g of 55 %w/w, 523.7 mL of 55 %w/w, 9.249 mol, 1.00 equiv) was added in portions via an addition funnel. Once the addition was complete, the reaction was heated to 75 °C for 22 h to afford a solution of ethyl 3-hydroxy-1H-pyrazole-4-carboxylate that was used directly in the next step.

Step 2: 1-(tert-butyl) 4-ethyl 3-hydroxy-1H-pyrazole-1,4-dicarboxylate



[00397] The solution of ethyl 3-hydroxy-1H-pyrazole-4-carboxylate was cooled from 75 °C to 40 °C, then triethylamine (TEA) (46.80 g, 64.46 mL, 462.5 mmol, 0.05 eq.) was added. A solution of Boc anhydride (2.119 kg, 9.711 mol1.05 equiv) in EtOH (2.000 L, 1 equiv) was added to the reactor over 35 min. The mixture was stirred for 4 hours to complete the reaction; then water (10.00 L, 5.0 vol) was added over 15 mins. The resulting mixture was cooled to 20 °C to complete crystallization of the product. The crystals were allowed to age for 1 hour, then the mixture was filtered. The solid was washed with a mixture of EtOH (4.000 L, 2.0 vol) and water (2.000 L, 1.0 vol). The solid was then dried in vacuo to afford 1-(tert-butyl)-4-ethyl-3-hydroxy-1H-pyrazole-1,4-dicarboxylate (1530 g, 65%) as colorless, fine needle, crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.40 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.56 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H).

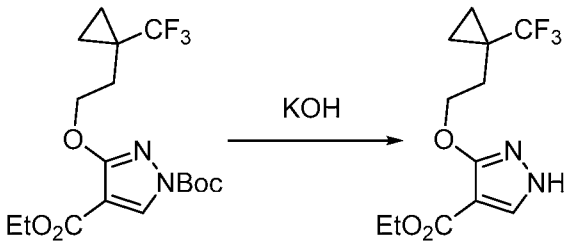
Step 3: 1-(tert-butyl) 4-ethyl 3-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)-1H-pyrazole-1,4-dicarboxylate



[00398] A 5L reactor was started with the jacket set to 40 °C, stirring at 450 rpm, reflux condenser at room temperature and nitrogen purge. The vessel was charged with toluene (1.0L, 10.0 vol), 2-[1-(trifluoromethyl)cyclopropyl]ethanol (100.0g, 648.8

mmol, 1.0 equiv), and 1-(tert-butyl) 4-ethyl 3-hydroxy-1H-pyrazole-1,4-dicarboxylate (166.3 g, 648.8 mmol), and the mixture was stirred. The reaction mixture was charged with triphenyl phosphine (195.7 g, 746.1 mmol, 1.15 equiv), then the reactor was set to maintain an internal temperature of 40 °C. Diisopropyl azoldicarboxylate (150.9 g, 746.1 mmol, 1.15 equiv) was added into an addition funnel and was added to the reaction while maintaining the reaction temperature between 40 and 50 °C (addition was exothermic, exotherm addition controlled), and stirred for a total of 2.5 hours. Once the reaction was deemed complete by HPLC, heptane was added (400 mL, 4 vol), the solution was cooled to 20 °C over 60 minutes, and the bulk of triphenylphosphine oxide-DIAD complex (TPPO-DIAD) crystallized out. Once at room temp, the mixture was filtered, and the solid was washed with heptane (400 mL, 4.0 vol) and pulled dry. The filtrate was used in the next step as a solution in toluene-heptane without further purification.

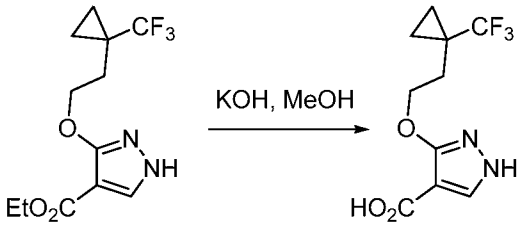
Step 4: ethyl 3-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)-1H-pyrazole-4-carboxylate



[00399] A 500mL reactor was started with the jacket set to 40 °C, stirring at 450 rpm, reflux condenser at room temp, and nitrogen purge. The vessel was charged with a toluene solution consisting of approximately 160 mmol, 65.0 g of 1-(tert-butyl) 4-ethyl 3-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)-1H-pyrazole-1,4-dicarboxylate in 3 vol of toluene (prepared by concentrating a 25% portion of filtrate from previous reaction down to 4 volumes in a rotovap). The reaction was set to maintain an internal temperature at 40 °C and KOH (33.1 g, 1.5 eq. of aqueous 45 % KOH solution) was added in one portion, resulting in a mild exothermic addition, while CO_2 was generated upon removal of the protecting group. The reaction proceeded for 1.5 hr, monitored by HPLC, with the product partially crystallizing during the reaction. Heptane (160 mL, 2.5 vol) was added to the reaction mixture and the reaction was cooled to room temperature over 30 minutes. The resulting mixture was filtered, and the solid was

washed with heptane (80.00 mL, 1.25 vol), pulled dry, then dried *in vacuo* (55 °C, vacuum). 52.3 g of ethyl 3-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)-1H-pyrazole-4-carboxylate was obtained as a crude, colorless solid that was used without further purification.

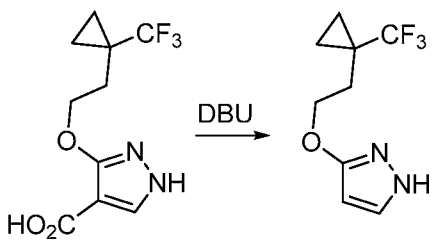
Step 5: 3-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)-1H-pyrazole-4-carboxylic acid



[00400] A 500mL reactor was started with the jacket set to 40 °C, stirring at 450 rpm, reflux condenser at room temp, and nitrogen purge. The vessel was charged with methanol (150.0 mL, 3.0 vol), a solution of ethyl 3-(2-(1-(trifluoromethyl)cyclopropyl) ethoxy)-1H-pyrazole-4-carboxylate (50.0 g, 171.1 mmol, 1.0 equiv), and the reaction was stirred to suspend the solids. The reactor was set to maintain internal temperature at 40 °C. To the mixture was added KOH (96 g of aqueous 45 % KOH, 1.71 mol, 10.0 equiv) in portions maintaining the internal temperature <50 °C. Once addition was complete, the reaction was set to maintain temperature at 50 °C, and the reaction proceeded for 23 hours, monitored by HPLC. Once complete the reaction was cooled to 10 °C then partially concentrated on a rotary evaporator to remove most of the MeOH. The resulting solution was diluted with water (250 mL, 5.0 vol) and 2-Me-THF (150 mL, 3.0 vol), and transferred to the reactor, stirred at room temp, then stopped, and layers were allowed to separate. The layers were tested, with remaining TPPO-DIAD complex in the organic layer and product in the aqueous layer. The aqueous layer was washed again with 2-Me-THF (100 mL, 2.0 vol), the layers separated, and the aqueous layer returned to the reactor vessel. The stirrer was started and set to 450 rpm, and the reactor jacket was set to 0 °C. The pH was adjusted to pH acidic by addition of 6M aqueous HCl (427mL, 15 equiv) portion wise, maintaining the internal temperature between 10 and 30 °C. The product began to crystallize close to pH neutral and was accompanied with strong off-gassing, and so the acid was added slowly, and then further added to reach pH 1 once the off-gassing had ended. To the resulting suspension was added 2-Me-THF (400 mL, 8.0 vol), and the product was allowed to dissolve into

the organic layer. Stirring was stopped, the layers were separated, and the aqueous layer was returned to the reactor, stirred and re-extracted with 2-Me-THF (100 mL, 2.0 vol). The organic layers were combined in the reactor and stirred at room temperature, washed with brine (100mL, 2 vols), dried over Na_2SO_4, filtered through celite, and the solid was washed with 2-Me-THF (50 mL, 1.0 vol). The filtrate was transferred to a clean rotovap flask, stirred, warmed to 50 °C and heptane (200 mL, 4.0 vol) added, and then partially concentrated with the addition of heptane (300 mL, 6.0 vol) and then seeded with 50mg of 3-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)-1H-pyrazole-4-carboxylic acid), and the product crystallized during solvent removal. The distillation was stopped when the bulk of the 2-Me-THF had distilled off. The bath heater was turned off, the vacuum removed, and the mixture was allowed to stir and cool to room temperature. The mixture was filtered (slow speed) and the solid was washed with heptane (100 mL, 2.0 vol), and the solid was collected and dried *in vacuo* (50 °C, rotovap). 22.47 g of 3-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)-1H-pyrazole-4-carboxylic acid was obtained as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 2H), 8.01 (s, 1H), 4.26 (t, J = 7.0 Hz, 2H), 2.05 (t, J = 7.0 Hz, 2H), 0.92 (m, 4H).

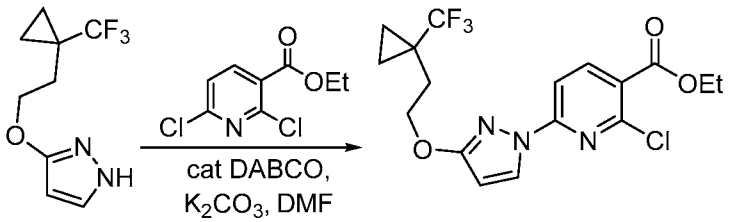
Step 6: 3-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)-1H-pyrazole



[00401] A mixture of toluene (490.0 mL), 3-(2-(1-(trifluoromethyl)cyclopropyl) ethoxy)-1H-pyrazole-4-carboxylic acid (70.0 g, 264.9 mmol), and DMSO (70.00 mL) was placed in a reactor and heated to 100 °C with stirring. DBU (approximately 20.16 g, 19.80 mL, 132.4 mmol) was added to the reactor over 15 min. The mixture was stirred for 20 h to complete the reaction and then cooled to 20 °C. The mixture was washed with water (350.0 mL), then 0.5N aq HCl (280.0 mL), then water (2 x 140.0 mL), and lastly with brine (210.0 mL). The organic layer was dried with Na_2SO_4, and then activated charcoal (5 g, Darco 100 mesh) was added to the stirred slurry. The dried mixture was filtered through celite, and the solid was washed with toluene (140.0 mL)

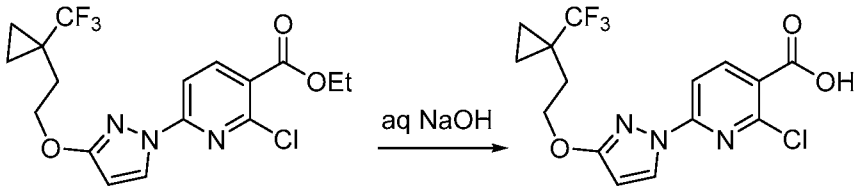
and then pulled dry. The filtrate was concentrated in a rotovap (50 °C, vac) to afford 3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]-1H-pyrazole (30.89 g, 53%) as an amber oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 7.50 (d, J = 2.4 Hz, 1H), 5.63 (d, J = 2.4 Hz, 1H), 4.23 – 4.06 (m, 2H), 2.01 (t, J = 7.1 Hz, 2H), 1.00 – 0.77 (m, 4H).

Step 7: ethyl 2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy] pyrazol-1-yl]pyridine-3-carboxylate



[00402] A mixture of DMF (180.0 mL), ethyl 2,6-dichloropyridine-3-carboxylate (approximately 29.97 g, 136.2 mmol), 3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]-1H-pyrazole (30.0 g, 136.2 mmol), and K_2CO_3, (325 mesh, approximately 24.48 g, 177.1 mmol) was added to a stirred reactor at 20 °C. DABCO (approximately 2.292 g, 20.43 mmol) was then added to the reactor, and the mixture was stirred at 20 °C for 1 hour, and then the temperature was increased to 30 °C, and the mixture stirred for 24 hours to complete the reaction. The mixture was cooled to 20 °C; then water (360 mL) was added slowly. The mixture was then drained from the reactor and the solid was isolated by filtration. The solid was then washed with water (2 x 150 mL), and then the solid was dried under vacuum at 55 °C to afford ethyl 2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]pyridine-3-carboxylate (51.37 g, 93%) as a fine, beige colored solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (d, J = 2.9 Hz, 1H), 8.41 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 6.21 (d, J = 2.9 Hz, 1H), 4.34 (m, 4H), 2.09 (t, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.00 – 0.84 (m, 4H).

Step 8: 2-Chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]pyridine-3-carboxylic acid



[00403] A solution of ethyl 2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl] ethoxy]pyrazol-1-yl]pyridine-3-carboxylate (50.0 g, 123.8 mmol) in THF (300.0 mL) was prepared in a reactor at 20 °C. EtOH (150.0 mL) was added, followed by aqueous NaOH (approximately 59.44 g of 10 %w/w, 148.6 mmol). The mixture was stirred for 1 hour to complete the reaction; then aq 1N HCl (750.0 mL) was slowly added. The resulting suspension was stirred for 30 min at 10 °C, and then the solid was isolated by filtration. The solid was washed with water (150 mL then 2 x 100 mL) and then pulled dry by vacuum. The solid was then further dried under vacuum with heating to afford 2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl]ethoxy]pyrazol-1-yl]pyridine-3-carboxylic acid (42.29 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.63 (s, 1H), 8.48 – 8.35 (m, 2H), 7.73 (d, J = 8.4 Hz, 1H), 6.20 (d, J = 2.9 Hz, 1H), 4.35 (t, J = 7.1 Hz, 2H), 2.09 (t, J = 7.1 Hz, 2H), 1.01 – 0.82 (m, 4H).

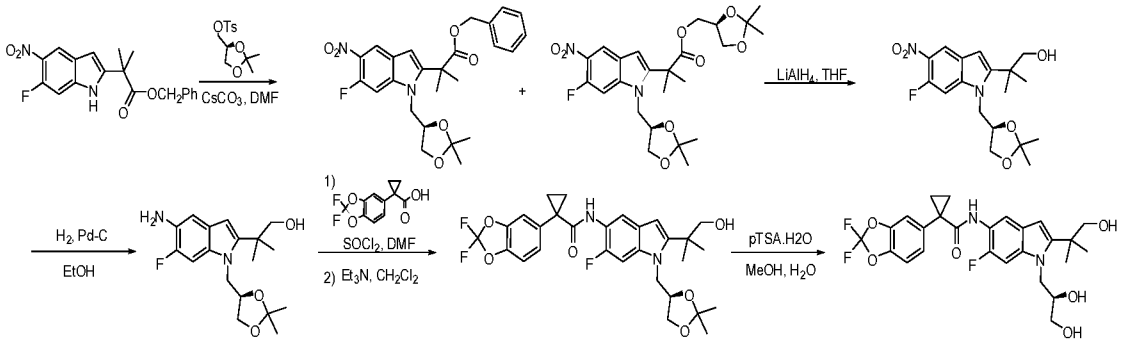
Example 2: Preparation of a Spray Dried Dispersion (SDD) of Compound I

[00404] A spray dried dispersion of Compound **I** (free form) was prepared using Buchi Mini Spray Dryer B290. HPMCAS-HG (6.0 grams) was dissolved in 200 mL of MeOH/DCM (1/1), and Compound **I** (6.0 grams) was added and stirred for 30 minutes forming a clear solution. The resulting solution was spray dried under the following conditions resulting in a 50 wt% Compound **I**/50 wt% HPMCAS- HG spray dried dispersion (Yield: 80%, Solid load: 6%). **FIG. 14** shows the XRPD spectrum of a SDD of 50% Compound **I** in HPMCAS-HG. **FIG. 15** is spectrum showing modulated differential scanning calorimetry (MDSC) spectrum of a spray dried dispersion (SDD) of 50% Compound **I** in HPMCAS-HG.

Table 64. SDD of Compound I

	Conditions
Inlet Temperature (°C)	77
Outlet Temperature (°C)	39
Nitrogen Pressure (PSI)	95
Aspirator (%)	100
Pump (%)	30
Rotameter (mm)	60
Filter Pressure (mBar)	-50
Condenser Temperature (°C)	-10

Example 3: Synthesis of Compound II: (R)-1-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide



Step 1: (R)-Benzyl 2-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-5-nitro-1H-indol-2-yl)-2-methylpropanoate and ((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 2-(1-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-5-nitro-1H-indol-2-yl)-2-methylpropanoate

[00405] Cesium carbonate (8.23 g, 25.3 mmol) was added to a mixture of benzyl 2-(6-fluoro-5-nitro-1H-indol-2-yl)-2-methylpropanoate (3.0 g, 8.4 mmol) and (S)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (7.23 g, 25.3 mmol) in DMF (N,N-dimethylformamide) (17 mL). The reaction was stirred at 80 °C for 46 hours under a nitrogen atmosphere. The mixture was then partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product, a viscous brown oil which contains both of the products shown above, was taken directly to the next step without further purification. (R)-Benzyl 2-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-5-nitro-1H-indol-2-yl)-2-methylpropanoate, ESI-MS *m/z* calc. 470.2, found 471.5 $(M+1)^+$. Retention time 2.20 minutes. ((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 2-(1-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-5-nitro-1H-indol-2-yl)-2-methylpropanoate, ESI-MS *m/z* calc. 494.5, found 495.7 $(M+1)^+$. Retention time 2.01 minutes.

Step 2: (R)-2-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-5-nitro-1H-indol-2-yl)-2-methylpropan-1-ol

[00406] The crude reaction mixture obtained in step (A) was dissolved in THF (tetrahydrofuran) (42 mL) and cooled in an ice-water bath. $LiAlH_4$ (16.8 mL of 1 M solution, 16.8 mmol) was added drop-wise. After the addition was complete, the

mixture was stirred for an additional 5 minutes. The reaction was quenched by adding water (1 mL), 15% NaOH solution (1 mL) and then water (3 mL). The mixture was filtered over Celite, and the solids were washed with THF and ethyl acetate. The filtrate was concentrated and purified by column chromatography (30-60% ethyl acetate-hexanes) to obtain (R)-2-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-5-nitro-1H-indol-2-yl)-2-methylpropan-1-ol as a brown oil (2.68g, 87 % over 2 steps). ESI-MS *m/z* calc. 366.4, found 367.3 $(M+1)^+$. Retention time 1.68 minutes. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.34 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 13.4 Hz, 1H), 6.57 (s, 1H), 4.94 (t, J = 5.4 Hz, 1H), 4.64 - 4.60 (m, 1H), 4.52 - 4.42(m, 2H), 4.16 - 4.14 (m, 1H), 3.76 - 3.74 (m, 1H), 3.63 - 3.53 (m, 2H), 1.42 (s, 3H), 1.38 - 1.36 (m, 6H) and 1.19 (s, 3H) ppm. (DMSO is dimethylsulfoxide).

Step 3: (R)-2-(5-amino-1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-1H-indol-2-yl)-2-methylpropan-1-ol

[00407] (R)-2-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-5-nitro-1H-indol-2-yl)-2-methylpropan-1-ol (2.5 g, 6.82 mmol) was dissolved in ethanol (70 mL) and the reaction was flushed with N_2. Then Pd-C (250 mg, 5% wt) was added. The reaction was flushed with nitrogen again and then stirred under H_2 (atm). After 2.5 hours only partial conversion to the product was observed by LCMS. The reaction was filtered through Celite and concentrated. The residue was re-subjected to the conditions above. After 2 hours LCMS indicated complete conversion to product. The reaction mixture was filtered through Celite. The filtrate was concentrated to yield the product (1.82 g, 79 %). ESI-MS *m/z* calc. 336.2, found 337.5 $(M+1)^+$. Retention time 0.86 minutes. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.17 (d, J = 12.6 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 6.03 (s, 1H), 4.79 - 4.76 (m, 1H), 4.46 (s, 2H), 4.37 - 4.31 (m, 3H),4.06 (dd, J = 6.1, 8.3 Hz, 1H), 3.70 - 3.67 (m, 1H), 3.55 - 3.52 (m, 2H), 1.41 (s, 3H), 1.32 (s, 6H) and 1.21 (s, 3H) ppm.

Step 4: (R)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide

[00408] DMF (3 drops) was added to a stirring mixture of 1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxylic acid (1.87 g, 7.7 mmol) and thionyl chloride (1.30 mL, 17.9 mmol). After 1 hour a clear solution had formed. The

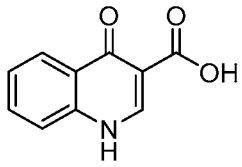
solution was concentrated under vacuum and then toluene (3 mL) was added and the mixture was concentrated again. The toluene step was repeated once more and the residue was placed on high vacuum for 10 minutes. The acid chloride was then dissolved in dichloromethane (10 mL) and added to a mixture of (R)-2-(5-amino-1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-1H-indol-2-yl)-2-methylpropan-1-ol (1.8 g, 5.4 mmol) and triethylamine (2.24 mL, 16.1 mmol) in dichloromethane (45 mL). The reaction was stirred at room temperature for 1 hour. The reaction was washed with 1N HCl solution, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated to yield the product (3g, 100%). ESI-MS *m/z* calc. 560.6, found 561.7 $(M+1)^+$. Retention time 2.05 minutes. ^1H NMR (400 MHz, DMSO-*d6*) δ 8.31 (s, 1H), 7.53 (s, 1H), 7.42 - 7.40 (m, 2H), 7.34 - 7.30 (m, 3H), 6.24 (s, 1H), 4.51 - 4.48 (m, 1H), 4.39 - 4.34 (m,2H), 4.08 (dd, J = 6.0, 8.3 Hz, 1H), 3.69 (t, J = 7.6 Hz, 1H), 3.58 - 3.51 (m, 2H), 1.48 - 1.45 (m, 2H), 1.39 (s, 3H), 1.34 - 1.33 (m, 6H), 1.18 (s, 3H) and 1.14 - 1.12 (m, 2H) ppm

Step 5: (R)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide

[00409] (R)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide (3.0 g, 5.4 mmol) was dissolved in methanol (52 mL). Water (5.2 mL) was added followed by p-TsOH.H_2O (p-toluenesulfonic acid hydrate) (204 mg, 1.1 mmol). The reaction was heated at 80 °C for 45 minutes. The solution was concentrated and then partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The ethyl acetate layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (50-100 % ethyl acetate - hexanes) to yield the product. (1.3 g, 47 %, ee >98% by SFC). ESI-MS *m/z* calc. 520.5, found 521.7 $(M+1)^+$. Retention time 1.69 minutes. ^1H NMR (400 MHz, DMSO-*d6*) δ 8.31 (s, 1H), 7.53 (s, 1H), 7.42 - 7.38 (m, 2H), 7.33 - 7.30 (m, 2H), 6.22 (s, 1H), 5.01 (d, J = 5.2 Hz, 1H), 4.90 (t, J = 5.5 Hz, 1H), 4.75 (t, J = 5.8 Hz, 1H), 4.40 (dd, J = 2.6, 15.1 Hz, 1H), 4.10 (dd, J = 8.7, 15.1 Hz, 1H), 3.90 (s, 1H), 3.65 - 3.54 (m, 2H), 3.48 - 3.33 (m, 2H), 1.48 - 1.45 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H) and 1.14 - 1.11 (m, 2H) ppm.

Example 4: Synthesis of Compound III: N-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

Part A: Synthesis of 4-oxo-1,4-dihydroquinoline-3-carboxylic acid



Step 1: 2-Phenylaminomethylene-malonic acid diethyl ester

[00410] A mixture of aniline (25.6 g, 0.275 mol) and diethyl 2-(ethoxymethylene)malonate (62.4 g, 0.288 mol) was heated at 140-150 °C for 2 h. The mixture was cooled to room temperature and dried under reduced pressure to afford 2-phenylaminomethylene-malonic acid diethyl ester as a solid, which was used in the next step without further purification. ^{1}H NMR (DMSO-d_6) δ 11.00 (d, 1H), 8.54 (d, J = 13.6 Hz, 1H), 7.36-7.39 (m, 2H), 7.13-7.17 (m, 3H), 4.17-4.33 (m, 4H), 1.18-1.40 (m, 6H).

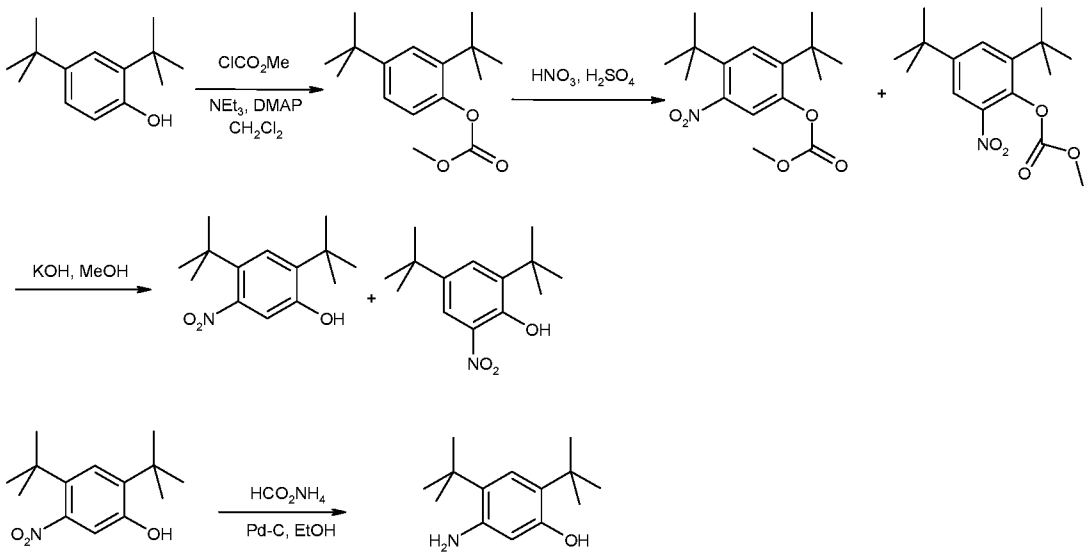
Step 2: 4-Hydroxyquinoline-3-carboxylic acid ethyl ester

[00411] A 1 L three-necked flask fitted with a mechanical stirrer was charged with 2-phenylaminomethylene-malonic acid diethyl ester (26.3 g, 0.100 mol), polyphosphoric acid (270 g) and phosphoryl chloride (750 g). The mixture was heated to 70 °C and stirred for 4 h. The mixture was cooled to room temperature and filtered. The residue was treated with aqueous Na_2CO_3 solution, filtered, washed with water and dried. 4-Hydroxyquinoline-3-carboxylic acid ethyl ester was obtained as a pale brown solid (15.2 g, 70%). The crude product was used in next step without further purification.

Step 3: 4-Oxo-1,4-dihydroquinoline-3-carboxylic acid

[00412] 4-Hydroxyquinoline-3-carboxylic acid ethyl ester (15 g, 69 mmol) was suspended in sodium hydroxide solution (2N, 150 mL) and stirred for 2 h at reflux. After cooling, the mixture was filtered, and the filtrate was acidified to pH 4 with 2N HCl. The resulting precipitate was collected via filtration, washed with water and dried under vacuum to give 4-oxo-1,4-dihydroquinoline-3-carboxylic acid as a pale white solid (10.5 g, 92 %). ^{1}H NMR (DMSO-d_6) δ 15.34 (s, 1 H), 13.42 (s, 1 H), 8.89 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.88 (m, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.60 (m, 1H).

Part B: Synthesis of N-(2,4-di-*tert*-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide



Step 1: Carbonic acid 2,4-di-*tert*-butyl-phenyl ester methyl ester

[00413] Methyl chloroformate (58 mL, 750 mmol) was added dropwise to a solution of 2,4-di-*tert*-butyl-phenol (103.2 g, 500 mmol), Et_3N (139 mL, 1000 mmol) and DMAP (3.05 g, 25 mmol) in dichloromethane (400 mL) cooled in an ice-water bath to 0 °C. The mixture was allowed to warm to room temperature while stirring overnight, then filtered through silica gel (approx. 1L) using 10% ethyl acetate – hexanes (~ 4 L) as the eluent. The combined filtrates were concentrated to yield carbonic acid 2,4-di-*tert*-butyl-phenyl ester methyl ester as a yellow oil (132 g, quant.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (d, J = 2.4 Hz, 1H), 7.29 (dd, J = 8.5, 2.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 1.30 (s, 9H), 1.29 (s, 9H).

Step 2: Carbonic acid 2,4-di-*tert*-butyl-5-nitro-phenyl ester methyl ester and Carbonic acid 2,4-di-*tert*-butyl-6-nitro-phenyl ester methyl ester

[00414] To a stirring mixture of carbonic acid 2,4-di-*tert*-butyl-phenyl ester methyl ester (4.76 g, 180 mmol) in conc. sulfuric acid (2 mL), cooled in an ice-water bath, was added a cooled mixture of sulfuric acid (2 mL) and nitric acid (2 mL). The addition was done slowly so that the reaction temperature did not exceed 50 °C. The reaction was

allowed to stir for 2 h while warming to room temperature. The reaction mixture was then added to ice-water and extracted into diethyl ether. The ether layer was dried ($MgSO_4$), concentrated and purified by column chromatography (0 – 10% ethyl acetate – hexanes) to yield a mixture of carbonic acid 2,4-di-*tert*-butyl-5-nitro-phenyl ester methyl ester and carbonic acid 2,4-di-*tert*-butyl-6-nitro-phenyl ester methyl ester as a pale yellow solid (4.28 g), which was used directly in the next step.

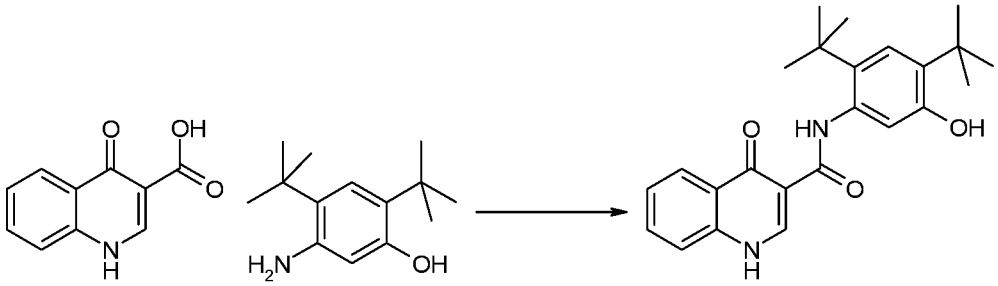
Step 3: 2,4-Di-*tert*-butyl-5-nitro-phenol and 2,4-Di-*tert*-butyl-6-nitro-phenol

[00415] The mixture of carbonic acid 2,4-di-*tert*-butyl-5-nitro-phenyl ester methyl ester and carbonic acid 2,4-di-*tert*-butyl-6-nitro-phenyl ester methyl ester (4.2 g, 14.0 mmol) was dissolved in MeOH (65 mL) before KOH (2.0 g, 36 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was then made acidic (pH 2-3) by adding conc. HCl and partitioned between water and diethyl ether. The ether layer was dried ($MgSO_4$), concentrated and purified by column chromatography (0 – 5 % ethyl acetate – hexanes) to provide 2,4-di-*tert*-butyl-5-nitro-phenol (1.31 g, 29% over 2 steps) and 2,4-di-*tert*-butyl-6-nitro-phenol. 2,4-Di-*tert*-butyl-5-nitro-phenol**:** ^1H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H, OH), 7.34 (s, 1H), 6.83 (s, 1H), 1.36 (s, 9H), 1.30 (s, 9H). 2,4-Di-*tert*-butyl-6-nitro-phenol: ^1H NMR (400 MHz, $CDCl_3$) δ 11.48 (s, 1H), 7.98 (d, J = 2.5 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 1.47 (s, 9H), 1.34 (s, 9H).

Step 4: 5-Amino-2,4-di-*tert*-butyl-phenol

[00416] To a refluxing solution of 2,4-di-*tert*-butyl-5-nitro-phenol (1.86 g, 7.40 mmol) and ammonium formate (1.86 g) in ethanol (75 mL) was added Pd-5% wt. on activated carbon (900 mg). The reaction mixture was stirred at reflux for 2 h, cooled to room temperature and filtered through Celite. The Celite was washed with methanol and the combined filtrates were concentrated to yield 5-amino-2,4-di-*tert*-butyl-phenol as a grey solid (1.66 g, quant.). ^1H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H, OH), 6.84 (s, 1H), 6.08 (s, 1H), 4.39 (s, 2H, NH_2), 1.27 (m, 18H); HPLC ret. time 2.72 min, 10-99 % CH_3CN, 5 min run; ESI-MS 222.4 m/z $[M+H]^+$.

Step 5: N-(5-hydroxy-2,4-di-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide



[00417] To a suspension of 4-oxo-1,4-dihydroquinolin-3-carboxylic acid (35.5 g, 188 mmol) and HBTU (85.7 g, 226 mmol) in DMF (280 mL) was added Et_3N (63.0 mL, 451 mmol) at ambient temperature. The mixture became homogeneous and was allowed to stir for 10 min before 5-amino-2,4-di-*tert*-butyl-phenol (50.0 g, 226 mmol) was added in small portions. The mixture was allowed to stir overnight at ambient temperature. The mixture became heterogeneous over the course of the reaction. After all of the acid was consumed (LC-MS analysis, MH+ 190, 1.71 min), the solvent was removed *in vacuo*. EtOH (ethyl alcohol) was added to the orange solid material to produce a slurry. The mixture was stirred on a rotovap (bath temperature 65 °C) for 15 min without placing the system under vacuum. The mixture was filtered and the captured solid was washed with hexanes to provide a white solid that was the EtOH crystalate. Et_2O (diethyl ether) was added to the solid obtained above until a slurry was formed. The mixture was stirred on a rotovapor (bath temperature 25 °C) for 15 min without placing the system under vacuum. The mixture was filtered and the solid captured. This procedure was performed a total of five times. The solid obtained after the fifth precipitation was placed under vacuum overnight to provide N-(5-hydroxy-2,4-di-*tert*-butyl-phenyl)-4-oxo-1H-quinoline-3-carboxamide (38 g, 52%). HPLC ret. time 3.45 min, 10-99% CH_3CN, 5 min run; ^1H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 11.83 (s, 1H), 9.20 (s, 1H), 8.87 (s, 1H), 8.33 (dd, J = 8.2, 1.0 Hz, 1H), 7.83-7.79 (m, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.54-7.50 (m, 1H), 7.17 (s, 1H), 7.10 (s, 1H), 1.38 (s, 9H), 1.37 (s, 9H); ESI-MS m/z calc'd 392.21; found 393.3 $[M+H]^+$.

Example 5: Preparation of Solid Forms of Sodium Salt of Compound I

A. Preparation of crystalline Form A of a sodium salt of Compound I

[00418] Crystalline Form A of Compound **I** (free form) (1184 mg, 2 mmole) was dissolved in acetonitrile (ACN) at 100 mg/mL and reacted with 320 µL of 25% aqueous sodium hydroxide (2 mmol) in water at room temperature. After 5 minutes, the mixture was seeded with crystalline Form A of a sodium salt of Compound **I** and slurried at room temperature overnight. The resulting suspension was filtered under vacuum. The resulting solid has purity of 99.92% as determined by HPLC.

[00419] A seed for the preparation of crystalline Form A of a sodium salt of Compound **I** could be obtained by stirring approximately 60 mg of amorphous sodium salt of Compond (I) in 1 mL of acetonitrile at room temperature for 2 weeks.

[00420] The XRPD data of crystalline Form A of a sodium salt of Compound **I** are summarized below in Table 65. X-ray powder diffractogram of crystalline Form A of a sodium salt of Compound **I** is shown in **FIG. 8A**.

Table 65. XRPD signals for crystalline Form A of a sodium salt of Compound I

Pos. [°2Th.]	D spacings
4.65	18.97
4.88	18.11
6.30	14.03
7.95	11.11
8.32	10.62
11.08	7.98
12.19	7.26
12.61	7.02
13.96	6.34

[00421] The C^{13} and F^{19} soild state nmr data of crystalline Form A of a sodium salt of Compound **I** are summarized below in Tables 66 and 67 below.

Table 66. C^{13} soild state nmr data of crystalline Form A of a sodium salt of Compound I

Peak #	Chem Shift [ppm]	Intensity [rel]
1	177.2	12.8
2	176.1	23.4
3	163.8	59.0
4	153.2	28.5
5	148.4	41.7
6	145.0	25.5
7	144.0	45.4
8	141.1	30.2
9	132.3	43.8
10	130.8	21.8
11	128.9	100.0
12	128.0	74.8
13	127.3	50.7
14	115.8	21.3
15	97.8	14.7
16	95.9	43.6
17	94.1	24.8
18	93.0	23.6
19	65.5	44.4
20	63.5	51.9
21	63.1	55.1
22	59.9	30.2
23	58.4	40.4
24	52.8	51.9
25	32.7	28.2
26	30.6	53.8
27	30.0	65.9
28	26.7	59.9
29	26.1	66.1
30	25.5	51.0
31	24.4	20.2
32	19.9	47.6
33	17.0	40.7
34	16.5	60.1
35	11.7	13.4
36	9.8	24.1
37	8.1	38.6
38	7.3	27.9

Table 67. F^{19} soild state nmr data of crystalline Form A of a sodium salt of Compound I

	Form A of a sodium salt of Compound I ^{19}F Chem. Shifts	
Peak #	Chem. Shift [ppm]	Intensity [rel]
1	-68.6	10.9
2	-70.3	12.5

B. Preparation of crystalline Form M of a sodium salt of Compound I (Variable Methanol-hydrate solvates of a sodium salt of Compound I)

[00422] Crystalline Form A of Compound **I** (free acid neutral form) (592.05 mg, 1 mmole) was dissolved in either MeOH at 33 mg/mL and reacted with 233 μL of 25% NaOMe in MeOH (1 mmole). The resulting solution was stirred at RT and become suspension. The suspension was stirred at RT for overnight. The resulting solid was collected by filtration under vacuum. The purity was 99.57% as determined by HPLC.

[00423] According to GC (gas chromatography) and KF (Karl Fisher) data, the resulting product contained 2.0 wt% of MeOH (theoreatical monomethanol would be 4.94 wt% of methanol) and 1.7 wt% of water, based on the weight of the product, were detected, indicating that the final form was solvates of a mixture of methanol and water. It was observed that the methanol in the product was labile and could leave the crystalline Form M and replaced with water without changes to the form according to the XRPD data. It is noted that Form M is isostructural to Form Hby their X-ray powder diffractograms.

[00424] The XRPD data of crystalline Form M of a sodium salt of Compound **I** are summarized below in Table 68. X-ray powder diffractogram of crystalline Form M of a sodium salt of Compound **I** is shown in **FIG. 10A**.

Table 68. XRPD signals of crystalline Form M of a sodium salt of Compound I

Pos. [°2Th.]	D spacings
9.26	9.55
9.94	8.89
10.46	8.45
11.26	7.85
13.94	6.35

Pos. [°2Th.]	D spacings
15.13	5.85
18.83	4.71
19.51	4.55
19.93	4.45

[00425] A single crystal structure of crystalline Form M of a sodium salt of Compound **I** that includes 1:1:1 in molar ratio of Na: Compound **I**: MeOH was obtained and the result is shown in Table 69. The single crystal was obtained by dissolving crystalline Form M of a sodium salt of Compound **I** in methanol folowed by slow evaporation at room temperature overnight.

Table 69. Single crystal structure of Form M of Na salt of Compound I (1:1:1 Na: Compound I: MeOH in molar ratio)

Empirical formula	C29 H35 F3 N5 Na O5 S	
Molecular formula	C29 H35 F3 N5 Na O5 S	
Formula weight	645.67	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 9.7434(2) Å	α= 90°.
	b = 10.7467(2) Å	β= 95.5790(10)°.
	c = 15.2452(3) Å	γ = 90°.
Volume	1588.75(5) $Å^3$	
Z	2	
Density (calculated)	1.350 Mg/m^3	

C. Preparation of crystalline Form E of a sodium salt of Compound I (Variable Ethanol-hydratesolvates of a sodium salt of Compound I)

[00426] 592.20 mg of Crystalline Form A of Compound **I** (free form) (1 mmole) was suspended in ethanol at 100 mg/mL and reacted 1:1 stoichiometry with NaOH in water. The resulting solution was stirred at room temperature and became suspension. The suspension was stirred overnight. The resulting solid was collected by filtration under vacuum.

[00427] It was observed that the ethanol in the product was labile and could leave the crystalline Form E and replaced with water without changes to the crystalline Form E according to the XRPD data. Desolvating Form E at 60 °C or 70 °C under vacuum resulted in Form H with variable amounts of water that is isostructural to Form M by their X-ray powder diffractograms.

[00428] The XRPD data of crystalline Form E of a sodium salt of Compound **I** are summarized below in Table 70. X-ray powder diffractogram of crystalline Form M of a sodium salt of Compound **I** is shown in **FIG. 12A**.

Table 70. XRPD signals for crystalline Form E of a sodium salt of Compound I

Pos. [°2Th.]	D spacings
11.36	7.79
15.23	5.81
18.96	4.68
5.67	15.56
17.30	5.12
9.94	8.90
9.05	9.77
14.01	6.32
16.33	5.42

[00429] A single crystal structure of Form E of Na salt of Compound **I** that includes 1:1:1 in molar ratio of Na: Compound **I**: EtOH was obtained and the result is shown in Table 71. The single crystal was obtained by dissolving crystalline Form E of a sodium salt of Compound **I** in ethanol and allowed for slow evaporation at room temperature overtime.

Table 71. Single crystal structure of Form E of Na salt of Compound I (1:1:1 in morlar ration of Na: Compound I: EtOH)

Empirical formula	C30 H37 F3 N5 Na O5 S	
Molecular formula	C30 H37 F3 N5 Na O5 S	
Formula weight	659.69	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 9.8500(6) Å	α= 90°.
	b = 10.6432(7) Å	β= 96.671(2)°.
	c = 15.3937(9) Å	γ = 90°.
Volume	1602.88(17) $Å^3$	
Z	2	
Density (calculated)	1.367 Mg/m^3	

D. Preparation of crystalline Form D of a sodium salt of Compound I

[00430] Crystalline Form D of a sodium salt of Compound **I** was obtained by heating either Form M of a sodium salt of Compound **I** or Form E of a sodium salt of Compound **I** at 290°C under dry N_2. In one example, 8 mg of crystalline Form E of a sodium salt of Compound **I** was heated in a TGA pan at a 10 °C/minute rate from room temperature to 290 °C and was then maintained at 290 °C for 2 minutes under dry N_2 (50 mL per minute).

[00431] The XRPD data of crystalline Form D of a sodium salt of Compound **I** are summarized below in Table 72. X-ray powder diffractogram of crystalline Form M of a sodium salt of Compound **I** is shown in **FIG. 9A**.

Table 72. XRPD signals for crystalline Form D of a sodium salt of Compound I

Pos. [°2Th.]	D spacings
4.89	18.04
5.68	15.54
6.95	12.71
8.03	11.00
9.76	9.05
11.32	7.81
12.23	7.23
14.01	6.32

Pos. [°2Th.]	D spacings
16.01	5.53

E. Preparation of crystalline Form H of a sodium salt of Compound I

[00432] Crystalline Form H of a sodium salt of Compound **I** was obtained by desolvating (e.g., heating at ~70 °C to ~92 °C under vacuum) either Form M of a sodium salt of Compound **I** or Form E of a sodium salt of Compound **I**.

[00433] In one example, 7 mg of crystalline Form M of a sodium salt of Compound **I** was heated in a TGA pan at a 10 °C/minute rate from room temperature to 92 °C and was then maintained at 92 °C for 2 minutes.

[00434] In another example, crystalline Form E of a sodium salt of Compound **I** was heated in a vacuum oven at 70°C for 2 days to obtain crystalline Form H of a sodium salt of Compound **I**. Crystalline Form H of a sodium salt of Compound **I** was obtained and determined to contain 0.2 wt % EtOH by GC, 2.9 wt % water, based on the weight of the product, by Karl Fisher.

[00435] Crystalline Form H was iso-structural to crystalline Form M by their X-ray powder diffractograms. X-ray powder diffractogram of crystalline Form H of a sodium salt of Compound **I**, is shown in **FIG. 11A**.

Example 6: Preparation of Solid Forms of Potassium Salt of Compound I

A. Preparation of Crystalline Form B of a potassium salt of Compound I

[00436] Crystalline Form B of a potassium salt of Compound **I**, is a crystalline channel hydrate/variable-hydrate that has been found to be thermodynamically stable during development. Crystalline Form B of a potassium salt of Compound **I** demonstrated superior stability compared to neat amorphous or crystalline Form A Compound I. The potassium salt Form B of Compound I is stable across a wide humidity range. In addition, it was found to be particularly amenable to scale up manufacturing processes, providing substantially higher yields than seen with scale up of certain other crystalline forms, e.g., the sodium salt of Compound **I**.

Method 6A:

[00437] 100mg of Compound **I** (free form) was dissolved in 1mL of acetonitrile. 10.0mL of 0.1N KOH solution in water was stirred at room temperature, to which the Compound **I** acetonitrile solution was added slowly. Precipitate was observed during addition of acetonitrile solution, and solids formed on the stir bar. The mixure was stirred for several hours, during which time the clump broke up into smaller agglomerates. After stirring overnight (approximately 18 hours), solids were isolated by filtration, analyzed by XRPD, and determined to be crystalline Form B of a potassium salt of **Compound I**.

Method 6B:

[00438] 25g of Compound **I** (free form) was charged with 100 mL ethanol and 100 mL of water. The slurry was stirred to assure free flowing solids. Into the mixture was charged 1.6 eq of KOH. Water (40 mL) was added to the resulting solution to make a 60 vol% water solution. The resulting solution was heated to 40°C then cooled to 20°C and stirred for 1 hour. The solution cooled to 20°C was seeded with 40 mg of crystalline Form B of a potassium salt of Compound **I** seed. Water (160 mL) was then charged over a 5-hour period of time. The resulting slurry was allowed to stir 12 hours. The resulting solids were collected by vacuum filtration and allowed to air dry for 2 hrs. The air-dried wet cake was transferred to a vacuum at 45°C with a slight N_2 bleed for 18 hrs to yield 25.89g of crystalline Form B of a potassium salt of Compound **I** (97% isolated yield).

[00439] An X-ray powder diffractogram, DVS, and DSC plots of crystalline Form B of a potassium salt of Compound **I** are shown in **FIG. 1A**, **FIG. 3**, and **FIG. 4**, respectively. The XRPD data of crystalline Form B of a potassium salt of Compound **I** are summarized below in Table 73.

Table 73. XRPD signals for crystalline Form B of a potassium salt of Compound I

Pos. [°2Th.]	D spacings
5.76	15.32
8.20	10.77
9.58	9.22
10.25	8.62
13.80	6.41

Pos. [°2Th.]	D spacings
15.11	5.86
16.27	5.44
17.18	5.16
19.1	4.64

[00440] A single crystal strucrue of Form B of a potassium salt of Compound **I** was obtained and the result is shown in Table 74.

Table 74. Single crystal structure of Form B of a potassium salt of Compound I (1:1 in molar ratio of potassium: Compound I)

Empirical Formula:	C28H31.76N5O4.38F3SK
Formula Weight:	636.63
Temperature (K):	298(2)
Wavelength (Å):	1.54178
Crystal System:	Orthorhombic
Space Group:	P212121
a (Å):	9.0058(3)
b (Å):	11.5389(4)
c (Å):	30.9399(10)
α (°):	90
β (°):	90
γ (°):	90
V (Å3):	3215.18(19)
Z/Z':	4/1

[00441] C^{13} and F^{19} solid state nmr data of crystalline Form B of a potassium salt of Compound **I** are summarized in Tables 75 and 76.

Table 75. C^{13} nmr peaks of crystalline Form B of a potassium salt of Compound I

Peak #	Chem Shift [ppm]	Intensity [rel]
1	178.0	32.8
2	165.0	50.7
3	151.9	20.7
4	147.7	35.1
5	143.2	39.7
6	141.5	27.8
7	132.7	31.5
8	129.9	7.8

Peak #	Chem Shift [ppm]	Intensity [rel]
9	127.8	49.2
10	127.1	9.6
11	121.3	37.6
12	96.1	44.9
13	89.0	47.0
14	68.5	47.0
15	63.6	66.0
16	56.8	41.5
17	51.3	48.8
18	30.3	100.0
19	26.4	81.7
20	24.7	72.4
21	20.5	31.2
22	15.9	79.8
23	10.3	31.5
24	8.1	27.8

Table 76. F^{19} nmr peaks of crystalline Form B of a potassium salt of Compound I

Peak #	Chem. Shift [ppm]	Intensity [rel]
1	-69.1	12.5

B. Hydration of Form B of a potassium salt of Compound I

[00442] As shown in **FIG. 2** and **FIG. 5**, crystalline Form B of a potassium salt of Compound **I** can be hydrated with water without substantial changes to its crystalline form Form B. **FIG. 2** shows XRPD patterns of crystalline Form B of a potassium salt of Compound **I** at 3% relative humidity (RH) (red) initial and 100%RH (blue). **FIG. 5** shows a TGA plot of crystalline Form B of a potassium salt of Compound **I**.

C. Preparation of Crystalline Form C of a potassium salt of Compound I

[00443] A solution of Form B of Compound **I** potassium salt in 1:10(v/v) acetonitrile (MeCN):water was kept at 75 °C, and then the solvents were evaporated slowly at 75 °C. Crystals were formed over approximately 24 h.

[00444] The XRPD data of crystalline Form C of a potassium salt of Compound **I** are summarized below in Table 77. An X-ray powder diffractogram of crystalline Form C of a potassium salt of Compound **I** is shown in **FIG. 7A**.

Table 77. XRPD signals for crystalline Form C of a potassium salt of Compound I

Pos. [°2Th.]	D spacings
3.66	24.14
6.96	12.68
7.41	11.92
8.70	10.16
9.49	9.31
11.40	7.75
11.52	7.68
12.43	7.11
16.04	5.52

Example 7: Preparation of Crystalline Form A of Compound I

[00445] Crystalline Form A of Compound **I** was generally prepared by de-solvating the ethanol solvates of Compound **I** under vacuum. In one particular example, it was prepared as described below:

[00446] N-(benzenesulfonyl)-2-chloro-6-[3-[2-[1-(trifluoromethyl)cyclopropyl] ethoxy]pyrazol-1-yl]pyridine-3-carboxamide (15.5 g, 30.10 mmol) and K_2CO_3 (20.80 g, 150.5 mmol) were stirred in NMP (77.50 mL) and 1,2-diethoxyethane (15.50 mL) and carefully treated with (4S)-2,2,4-trimethylpyrrolidine (Hydrochloric Acid (1)) (9.911 g, 66.22 mmol). The cream suspension was cycled 3 times under vacuum/nitrogen and heated at an external temperature of 135 °C (oil bath) for 20 hours. The suspension was carefully added to a stirred solution of acetic acid (27.11 g, 25.67 mL, 451.5 mmol) in water (465.0 mL) keeping the temperature at 15-20 °C by ice cooling. The resulting suspension was stirred at room temperature for 1h, filtered and washed with water. The filtered solid was crystalized from ethanol (hot solution was filtered clear) and the formed needles were filtered, washed with a little dry ice cold ethanol and dried under vacuum in a drying cabinet at 45 °C with a nitrogen bleed over the weekend to give Form A of Compound **I** as colorless needles. ^{1}H and ^{19}Fnmr (in DMSO): no EtOH was detected.

[00447] In the XRPD data of crystalline Form A of Compound **I**, there were some peak shifts from batch to batch due to inherent disorder during the desolvation process. The XRPD data were asummarized below in Table 78. An exemplary X-ray powder diffractogram of crystalline Form A of Compound **I** is shown in **FIG. 13A**.

Table 78. Ranges of XRPD signals for crystalline Form A of Compound I

Pos. [°2Th.]
5.37-5.45
7.24-7.49
11.87-12.19
14.76-15.03
16.71-17.08
17.48-17.68
18.56-18.80
19.51-19.82
22.02-22.47

[00448] C^{13} and F^{19} solid state nmr data of Form A of Compound I are summarized below in Tables 79 and 80.

Table 79. C^{13} nmr peaks of crystalline Form A of Compound I

Peak #	Form A of Compound I ^{13}C Chem Shift [ppm]	Intensity [rel]
1	165.4	26.1
2	164.9	40.2
3	154.1	22.0
4	151.8	30.3
5	141.3	23.2
6	138.8	12.6
7	136.8	36.2
8	130.8	100.0
9	128.6	46.0
10	127.3	59.0
11	109.4	26.4
12	98.1	50.2
13	97.4	42.2
14	65.5	88.3
15	60.4	28.6
16	51.0	38.1
17	29.9	58.2
18	28.2	17.2
19	26.1	51.7

Peak #	Form A of Compound I ^{13}C Chem Shift [ppm]	Intensity [rel]
20	25.5	46.0
21	20.1	26.5
22	16.4	53.1
23	6.8	43.3

Table 80. F^{19} nmr peaks of crystalline Form A of Compound I

Peak #	Chem Shift [ppm]	Intensity
1	-72.3	12.5

Example 8: Preparation of Solvates of Compound I

A. Methanol Solvate of Compound I

[00449] 1 mL of methanol (MeOH) was added to 60 mg of Compound **I** (free acid neutral form), and the resulting mixture was stirred at room temperature for 2 weeks. The resulting crystalline solids were methanol solvates of Compound **I**.

[00450] The XRPD data of methanol solvate of Compound **I** are summarized below in Table 81.

Table 81. XRPD signals for methanol solvate of Compound I

Pos. [°2Th.]	D spacings
5.23	16.88
8.31	10.63
10.27	8.61
11.54	7.66
11.78	7.51
14.36	6.16
15.66	5.65
19.11	4.64
22.20	4.00

[00451] A single crystal structure of methanol solvate of Compound **I** was obtained and the result is shown in Table 82.

Table 82.

Empirical formula	C30 H40 F3 N5 O6 S	
Molecular formula	C28 H32 F3 N5 O4 S, 2(C H4 O)	
Formula weight	655.73	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 11.7199(18) Å	α= 90°.
	b = 8.3852(12) Å	β= 102.973(5)°.
	c = 17.332(3) Å	γ = 90°.
Volume	1659.8(4) $Å^3$	
Z	2	
Density (calculated)	1.312 Mg/m^3	

B. Ethanol Solvate of Compound I

[00452] 1 mL ethanol (EtOH) was added to 100 mg of Compound **I** (neat free acid neutral form). The mixture was stirred at 60 °C for 30 minutes, and a solution was formed. The solution was cooled to room temperature, and crystalline solids of ethanol solvate of Compound **I** were precipitated.

[00453] The XRPD data of ethanol solvate of Compound **I** are summarized below in Table 83.

Table 83. XRPD signals for ethanol solvate of Compound I

Pos. [°2Th.]	D spacings
4.61	19.16
7.75	11.40
9.18	9.63
10.16	8.70
13.58	6.52
13.77	6.43
17.81	4.98
18.41	4.82
23.1	3.85

[00454] A single crystal structure of ethanol solvate of Compound **I** was obtained and the result is shown in Table 84.

Table 84. Single crystal structure of ethanol solvate of Compound I

Empirical formula	C30 H38 F3 N5 O5 S	
Molecular formula	C28 H32 F3 N5 O4 S, C2 H6 O	
Formula weight	637.71	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 11.9559(16) Å	α= 90°.
	b = 7.5294(9) Å	β= 107.124(4)°.
	c = 19.662(2) Å	γ = 90°.
Volume	1691.5(4) $Å^3$	
Z	2	
Density (calculated)	1.252 Mg/m^3	

C. IPA (Iso-Propyl Alcohol) Solvate of Compound I

[00455] 1 mL isopropanol (2-PrOH) was added to 100 mg of Compound **I** (neat free acid neutral form). The mixture was stirred at 60 °C for 30 minutes, and a solution was formed. The solution was cooled to room temperature, and crystalline solids precipitated.

[00456] The XRPD data of isopropanol solvate of Compound **I** are summarized below in Table 85.

Table 85. XRPD signals for isopropanol solvate of Compound I

Pos. [°2Th.]	D spacings
4.64	19.03
7.82	11.30
9.30	9.50
10.12	8.73
10.27	8.61
12.62	7.01
13.72	6.45
15.62	5.67
18.08	4.90

[00457] A single crystal structure of isopropanol solvate of Compound **I** was obtained and the result is shown in Table 86.

Table 86. Single crystal structure of isopropanol solvate of Compound I

Empirical formula	C31 H40 F3 N5 O5 S	
Molecular formula	C28 H32 F3 N5 O4 S, C3 H8 O	
Formula weight	651.74	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 11.894(2) Å	α= 90°.
	b = 7.5356(16) Å	β= 106.569(6)°.
	c = 19.837(4) Å	γ = 90°.
Volume	1704.2(6) $Å^3$	
Z	2	
Density (calculated)	1.270 Mg/m^3	

D. n-Butanol Solvate of Compound I

[00458] 1 mL of n-butanol added to 199 mg of Compound **I** (neat free acid neutral form). The resulting slurry was stirred at room temperature for 10 days. Solids isolated were crystalline and shown to be a n-butanol solvate of Compound **I**.

[00459] The XRPD data of n-butanol solvate of Compound **I** are summarized below in Table 87.

Table 87. XRPD signals for n-butanol solvate of Compound I

Pos. [°2Th.]	D spacings
4.59	19.20
7.68	11.50
9.16	9.65
10.01	8.83
13.55	6.53
14.64	6.04
15.34	5.77
18.34	4.83
19.23	4.61

E. EtOAc (Ethyl Acetate) Solvate of Compound I

[00460] 1 mL of ethyl acetate added to 60 mg of Compound **I** (neat free acid neutral form). A solution was formed. 5 mL of heptane added in 0.5 mL increments to the

resulting solution. The resulting solution was then evaporated slowly. ethyl acetate solvates of Compound **I** were isolated.

[00461] The XRPD data of ethyl acetate solvate of Compound **I** are summarized below in Table 88.

Table 88. XRPD signals for ethyl acetate solvate of Compound I

Pos. [°2Th.]	D spacings
4.82	18.33
7.89	11.20
9.60	9.20
9.82	9.00
13.55	6.53
14.45	6.13
15.84	5.59
19.02	4.66
24.22	3.67

[00462] A single crystal strucrue of EtOAc solvate of Compound **I** was obtained and the result is shown in Table 89.

Table 89. Single crystal structure of EtOAc solvate of Compound I

Empirical formula	C32 H40 F3 N5 O6 S	
Molecular formula	C28 H32 F3 N5 O4 S, C4 H8 O2	
Formula weight	679.75	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 11.9825(4) Å	α= 90°.
	b = 8.0104(2) Å	β= 102.7770(10)°.
	c = 18.4808(6) Å	γ = 90°.
Volume	1729.95(9) $Å^3$	
Z	2	
Density (calculated)	1.305 Mg/m^3	

Example 9. Preparation of a Potassium Salt of Compound I Tablet Formulations

[00463] Single tablets of fixed dose combination (FDC) of a potassium salt of Compound **I** in combination with a SDD of Compound **II** and a SDD of Compound **III** as shown in the Tables 90, 91, and 92 below were prepared.

A. Preparation of a Potassium Salt of Compound I FDC Tablet Formulations A1 and A2

Table 90. FDC Tablet A1

	Component	mg/tablet	g/batch
Intra-granular part	potassium salt of Compound **I**	212.9 mg	550.0 g
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62.5 mg	161.5 g
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93.8 mg	242.2 g
	microcrystalline cellulose (e.g., PH101)	137.1 mg	354.2 g
	croscarmellose sodium	15.8 mg	40.8 g
	magnesium stearate	5.3 mg	13.7 g
Extra-granular part	microcrystalline cellulose (e.g., PH102)	59.6 mg	153.9 g[1]
	croscarmellose sodium	8.9 mg	23.1 g[1]
	Uncoated Tablet	595.9 mg	n/a
	Coating (20A100017)	18.4 mg	47.6[2]

[1] Weights adjusted based on granulation yield.
[2] Coating weight adjusted based on weight of tablet charged to coater. Actual coating was 2.75% of coated tablet.

Table 91. FDC Tablet A2

	Component	mg/tablet	g/batch
Intra-granular part	potassium salt of Compound **I**	212.9 mg	550.0 g
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62.5 mg	161.5 g
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93.8 mg	242.2 g
	microcrystalline cellulose (e.g., PH101)	137.1 mg	354.2 g
	croscarmellose sodium	15.8 mg	40.8 g
	magnesium stearate	5.3 mg	13.7 g
Extra-granular part	microcrystalline cellulose (e.g., PH102)	59.6 mg	153.9 g[1]
	croscarmellose sodium	8.9 mg	23.1 g[1]
	Uncoated Tablet	595.9 mg	n/a

[1] Weights adjusted based on granulation yield.

Dry Granulation

[00464] Prior to granulation, the potassium salt of Compound **I**, the solid dispersion comprising 80 wt% substantially amorphous Compound **II** and 20 wt% HPMC (see PCT Publication No. WO 2015/160787, the entire contents are incorporated herein by reference), the solid dispersion comprising 80 wt% substantially amorphous Compound **III**, 19.5 wt% HPMCAS and 0.5 wt% sodium lauryl sulfate (see WO 2015/160787), and intragranular excipients were screened prior to or after weighing and then blended in a bin blender. The blend was granulated using a Gerteis roller compactor using combined smooth/smooth rolls and an integrated 1.0 mm mesh milling screen with pocketed rotor and paddle agitator. The roller compactor was operated with a roll gap of 2 mm, roll pressure of 4.7 kNcm, roll speed of 2 rpm, granulation speed of 80/80 (CW/CCW) rpm, and oscillation of 360/330 (CW/CCW)degrees..

Compression

[00465] For the FDC tablet A1 of Table 90, prior to compression, extragranular excipients were screened prior to or after weighing and then blended in a bin blender with the roller compacted granules. The blend was compressed into a tablet using a non-

instrumented Riva Piccola rotary tablet press. The press was assembled with tooling of a desired shape and size. The tablet target weight was 595.9mg. The hardness was 15.7kp.

[00466] For the FDC tablet A2 of Table 91, the final uncoated tablet was compressed on the MTS. Using tooling of a desired shape and size, tablets were compressed to a target weight 301 mg and hardness of 10.2kp.

Coating

[00467] For the FDC tablet A2 of Table 91, no coating was done. For the FDC tablet A1, the core tablets were film coated using a Thomas tablet film coater. The film coat suspension was prepared according to manufacturer instructions by adding the coating material to purified water and mixing with overhead mixer. The required amount of film coating suspension was sprayed onto the tablets to achieve the weight gain of 2.6% of the core tablet weight.

B. Preparation of a Potassium Salt of Compound I FDC Tablet Formulations B1

Table 92. FDC Tablet B1

	Component	mg/tablet	g/batch
Intra-granular part	potassium salt of Compound **I**	127.7 mg	151.8 g
	solid dispersion containing 80% Compound **II**, 20% hypromellose	62.5 mg	75.3 g
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	93.8 mg	111.4 g
	microcrystalline cellulose (e.g., PH101)	86.3 mg	102.6 g
	croscarmellose sodium	11.5 mg	13.7 g
	magnesium stearate	1.9 mg	2.3 g
Extra-granular part	microcrystalline cellulose (e.g., PH102)	43.6 mg	51.8 g[1]
	croscarmellose sodium	6.5 mg	7.8 g[1]
	magnesium stearate	1.9 mg	
	Uncoated Tablet	435.8 mg	n/a
	Coating (20A100017)	13.5 mg	15.5[2]

[1] Weights adjusted based on granulation yield.
[2] Coating weight adjusted based on weight of tablet charged to coater.

Dry Granulation:

[00468] Prior to granulation, the potassium salt of Compound **I**, the solid dispersion comprising 80 wt% substantially amorphous Compound **II** and 20 wt% HPMC (see PCT Publication No. WO 2015/160787, the entire contents are incorporated herein by reference), the solid dispersion comprising 80 wt% substantially amorphous Compound **III**, 19.5 wt% HPMCAS and 0.5 wt% sodium lauryl sulfate (see WO 2015/160787), and intragranular excipients were screened prior to or after weighing and then blended in a bin blender. The blend was granulated using a Gerteis roller compactor using combined smooth/smooth rolls and an integrated 1.0 mm mesh milling screen with pocketed rotor and paddle agitator. The roller compactor was operated with a roll gap of 2 mm, roll pressure of 4.7 kNcm, roll speed of 2 rpm, granulation speed of 80/80 (CW/CCW) rpm, and oscillation of 360/330 (CW/CCW) degrees..

Compression:

[00469] Prior to compression, extragranular excipients were screened prior to or after weighing and then blended in a bin blender with the roller compacted granules. The blend was compressed into a tablet using a non-instrumented Riva Piccola rotary tablet press. The press was assembled with tooling of a desired shape and size. The tablet target weight was 435.8 mg. The hardness was 12kp.

Coating:

[00470] Some of the core tables during this manufacture were retained as uncoated tablets. The remainder of these core tablets were film coated using a Thomas tablet film coater. The film coat suspension was prepared according to manufacturer instructions by adding the coating material to purified water and mixing with overhead mixer. The required amount of film coating suspension was sprayed onto the tablets to achieve the weight gain of 3% of the core tablet weight.

Example 10: Dissolution Properties

[00471] For the purposes of the dissolution (Example 10) and bioavailability (Example 11) studies, FDC tablets A2 ("Compound **I** K salt FDC Tablet") that comprise a potassium salt of Compound **I** (crystalline Form B); a SDD comprising 80 wt% substantially amorphous Compound **II** and 20 wt% HPMC; and a SDD comprising 80

wt% substantially amorphous Compound **III**, 19.5 wt% HPMCAS and 0.5 wt% sodium lauryl sulfate (see Example 9A above) were used.

[00472] As control tablets in Examples 10 and 11, Control tablets 1 comprising a SDD of 50 wt% Compound **I** and 50 wt% HPMCAS- HG (see, for example, Example 2 above); and Control tablet 2 comprising a SDD of 80 wt% substantially amorphous Compound **II** and 20 wt% HPMC; and a SDD comprising 80 wt% substantially amorphous Compound **III**, 19.5 wt% HPMCAS and 0.5 wt% sodium lauryl sulfate were used.

A. Preparation of Control Tablets 1

[00473] Control tablets 1 were prepared as specified below in Table 93.

Table 93. Control Tablet 1

	Component	mg/tablet	g/batch
Intra-granular part	Solid dispersion containing 50 wt% Compound **I**, 50 wt% hypromellose acetate succinate	200.0 mg	250 g
	microcrystalline cellulose (e.g., PH101)	540.0 mg	675 g
	croscarmellose sodium	24.0 mg	30 g
	sodium stearyl fumarate	16.0 mg	20 g
Extra-granular part	croscarmellose sodium	12.0 mg	15 g[1]
	sodium stearyl fumarate	8.0 mg	10 g[1]
	Uncoated Tablet	800.0 mg	n/a

[1] Weights adjusted based on granulation yield.

Dry Granulation:

[00474] Prior to granulation, solid dispersion containing 50 wt% Compound **I**, 50 wt% hypromellose acetate succinate (see Example 6) and intragranular excipients were screened prior to or after weighing and then blended in a bin blender. The blend was granulated with a Gerteis roller compactor using combined smooth/knurled rolls and an integrated 1.0 mm mesh milling screen with pocketed rotor and paddle agitator. The roller compactor was operated with a roll gap of 2 mm, roll pressure of 5.2 kNcm, roll speed of 2 rpm, granulation speed of 80/80 (CW/CCW) rpm, and oscillation of 360/330 (CW/CCW)degrees.

Compression:

[00475] Prior to compression, extragranular excipients were screened prior to or after weighing and then blended in a bin blender with the roller compacted granules. The blend was compressed into a tablet using the MTS. Using tooling of a desired shape and size, tablets were compressed to a target weight 800.0 mg and hardness of 14.8kp.

B. Preparation of Control Tablets 2

[00476] Control tablets 2 were prepared as specified below in Table 94.

Table 94. Control Tablet 2

	Components	mg/tablet	g/batch
Intra-granular part	solid dispersion containing 80% Compound **II**, 20% hypromellose	31.3 mg	1.25 g
	solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	46.9 mg	1.88 g
	microcrystalline cellulose (e.g., PH101)	32.8 mg	1.31 g
	croscarmellose sodium	7.4 mg	0.3 g
Extra-granular part	microcrystalline cellulose (e.g., PH102)	28.1 mg	1.1 g
	magnesium stearate	1.5 mg	0.06 g
	Uncoated Tablet	148.0 mg	n/a

Granules prepared at large scale. Batch size scaled down to match amount of granules used in the extragranular blend.

Dry Granulation:

[00477] Prior to granulation, the solid dispersion comprising 80 wt% substantially amorphous Compound **II** and 20 wt% HPMC (see PCT Publication No. WO 2015/160787, the entire contents are incorporated herein by reference), the solid dispersion comprising 80 wt% substantially amorphous Compound **III**, 19.5 wt% HPMCAS and 0.5 wt% sodium lauryl sulfate (see WO 2015/160787) and intragranular excipients were screened prior to or after weighing and then blended in a bin blender. The blend was granulated using a Gerteis roller compactor using combined smooth/knurled rolls and an integrated 1.0 mm mesh milling screen with pocketed rotor and paddle agitator. The roller compactor was operated with a roll gap of 2 mm, roll

pressure of 5.2 kNcm, roll speed of 2 rpm, granulation speed of 80/80 (CW/CCW) rpm, and oscillation of 360/330 (CW/CCW)degrees.

Compression:

[00478] Prior to compression, extragranular excipients were screened prior to or after weighing and then blended in a turbula blender with the roller compacted granules. The blend was compressed into a tablet using the MTS. Using tooling of a desired shape and size, tablets were compressed to a target weight 148.0 mg and hardness of 9.3kp.

Dissoultion Results

[00479] **FIG. 18** shows comparison of tablet dissoluton of Compound **I** of Control tablet 1 and FDC tablets A2. **FIG. 19** shows comparison of tablet dissolution of Compound **II** of Control tablet 2 and FDC tablets A2. **FIG. 20** shows comparison of tablet dissolution of Compound **III** of Control tablet 2 and FDC tablets A2.

[00480] For the data shown in **FIGs**. **18**, **19**, and **20**, dissoluton method was two stage; first stage media was 250ml PH 5.5 simulated fed gastric fluid, second stage, 30 minutes after start, first stage media was diluted with 650mls of PH 7.2 simulated fed intestinal fluid with a mixture final PH of 6.7. As shown in **FIGs**. **18**, **19**, and **20**, the FDC tablets demonstrated higher concentrations of Compound **I**, Compound **II** and Compound **III** at earlier timepoints than the respective Control tablets.

C. Preparation of Stability Control Tablets 1

[00481] Stability Control Tablets 1 were prepared as specified below in Table 95.

Table 95. Stability Control Tablet 1

	Component	mg/tablet	g/batch
Intra-granular part	Solid dispersion containing 50 wt% Compound **I**, 50 wt% hypromellose acetate succinate	50.0 mg	10 g
	microcrystalline cellulose (e.g., PH101)	135.0 mg	27 g
	croscarmellose sodium	6.0 mg	1.2 g
	sodium stearyl fumarate	4.0 mg	0.8 g
Extra-granular part	croscarmellose sodium	3.0 mg	0.58 g[1]
	sodium stearyl fumarate	2.0 mg	0.38 g[1]
	Uncoated Tablet	200.0 mg	n/a

[1] Weights adjusted based on granulation yield.

Dry Granulation:

[00482] Prior to granulation, solid dispersion containing 50 wt% Compound **I**, 50 wt% hypromellose acetate succinate (see Example 6) and intragranular excipients were screened prior to or after weighing and then blended in a turbula blender. The blend was granulated by slugging and then milling slugs through 1.0mm screen.

Compression:

[00483] Prior to compression, extragranular excipients were screened prior to or after weighing and then blended in a Turbula blender with the roller compacted granules. The blend was compressed into a tablet using the Huxley Bertram compaction simulator. Using tooling of a desired shape and size, tablets were compressed to a target weight 200.0 mg.

Example 11: In vivo Bioavailability

[00484] In this bioavailability study, FDC tablets A2 that comprise a potassium salt of Compound **I** (crystalline Form B); an SDD comprising 80 wt% substantially amorphous Compound **II** and 20 wt% HPMC; and an SDD comprising 80 wt% substantially amorphous Compound **III**, 19.5 wt% HPMCAS and 0.5 wt% sodium lauryl sulfate (see Example 9A above) were used. As control tablets, Control tablets 1 comprising a SDD of 50 wt% Compound **I** and 50 wt% HPMCAS- HG (see Example 10 above) and Control tablet 2 comprising a SDD of 80 wt% substantially amorphous Compound **II** and 20 wt% HPMC; and a SDD comprising 80 wt% substantially amorphous Compound **III**, 19.5 wt% HPMCAS and 0.5 wt% sodium lauryl sulfate (see Example 10 above) were used.

[00485] **FIG. 21** shows bioavailability of Compound **I** of Control tablet 1 and FDC tablet A2. **FIG. 22** shows bioavailability of Compound **II** of Control tablet 2 and FDC tablet A2. **FIG. 23** shows comparison of tablet dissolution of Compound **III** of Control tablet 2 and FDC tablet A2.

[00486] For the data shown in **FIG. 21**, **FIG. 22**and **FIG. 23**, the PK study design was a full crossover, two dose period with 5 dogs per dose group per period. Both the Control and FDC tablets demonstrated statistically equivalent Compound **I** bioavailability in dogs. The FDC tablets demonstrated statictically superior

bioavailability in dog when compared to the Control tablets, for both Compound **II** and Compound **III**.

Example 12: Stability of Compound I SDD and Compound I K salt Drug Substance

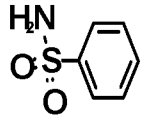
[00487] Crystalline Form B of a potassium salt of Compound **I** ("Compound **I** Potassium Salt") drug substance (DS) was shown to have greater chemical stability than the spray dried dispersion (SDD) of Compound **I** [Compound **I** SDD with HPMCAS, 500 mg/g drug load] ("Compound **I** SDD") (see Example 2) after 6 months at 25°C/60%RH (relative humidity) and 40°C/75%RH in open dish conditions. The degradation products (impurity 1 and impurity 2) in the Compound **I** Potassium Salt DS were below the ICH Q3A Reporting Threshold (<0.05% area), whereas the degradation products for the Compound **I** SDD were > 1.0% area (total impurities). High Performance Liquid Chromatography (HPLC) was used to analyze the purity profile of the samples.

Table 96. Summary of Organic Impurity Results for Compound I SDD (see Example 1 above) and Compound I Potassium Salt Drug Substance (DS) in Open Dish Conditions.

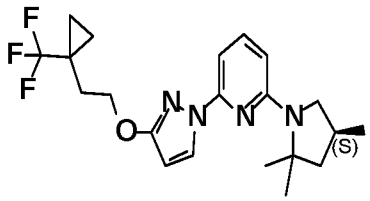
		Total Impurities (% area)	Impurity 1 (% area)	Impurity 2 (% area)
Initial	Compound **I** SDD	1.15	0.22	0.63
	Compound **I** Potassium Salt DS	< RT	< RT	< RT
25°C / 60% RH, 6 Months	Compound **I** SDD	1.49	0.33	0.75
	Compound **I** Potassium Salt DS	< RT	< RT	< RT
40°C / 75% RH, 6 Months	Compound **I** SDD	3.49	1.30	1.74
	Compound **I** Potassium Salt DS	< RT	< RT	< RT

RT = ICH Q3A Reporting Threshold (< 0.05 % area)

[00488] Impurities 1 and 2 are degradation products of Compound **I**:



(Impurity 1); and



(Impurity 2)

[00489] The FDC tablets A2 containing a potassium salt of Compound **I** (crystalline Form B) in combination with the Compound **II** SDD and Compound **III** SDD (see Table 91 and Example 9 above) ("Compound **I** K salt FDC Tablet" in Table 97 below) showed to have greater chemical stability than Stability Control Tablet 1 ("Compound **I** Mono Tablet" in Table 97 below) (see Example 9 above), comprised of Compound **I** SDD [Compound **I** SDD with HPMCAS, 500 mg/g drug load] at accelerated conditions in open dish. High Performance Liquid Chromatography (HPLC) was used to analyze the purity profile of the samples.

Table 97. Summary of Degradation Product Results for Compound I Mono Tablets[1] and Compound I K Salt Fixed Dose Combination (FDC)[2] Tablets (Open Dish Conditions)

		Total Impurities (% area)	Impurity 1 (% area)	Impurity 2 (% area)
50°C / 75% RH, 14 days	Compound **I** Mono Tablet	1.13	0.20	0.47
	Compound **I** K salt FDC Tablet	0.04	< RT	0.01
60°C / 40% RH, 14 days	Compound **I** Mono Tablet	3.14	0.58	1.42
	Compound **I** K salt FDC Tablet	0.06	< RT	0.01
70°C / 5% RH, 14 days	Compound **I** Mono Tablet	11.06	2.06	5.50
	Compound **I** K salt FDC Tablet	0.08	< RT	0.01
70°C / 75% RH, 3 days	Compound **I** Mono Tablet	4.82	0.87	2.26

		Total Impurities (% area)	Impurity 1 (% area)	Impurity 2 (% area)
	Compound **I** K salt FDC Tablet	0.35	< RT	0.02

RT = ICH Q3A Reporting Threshold (< 0.05 % area)
[1] Compound **I** Mono Tablets are comprised of 50 mg/g Spray Dried Dispersion of Compound **I**
[2] Compound **I** K salt FDC Tablets contain Compound **I** Potassium Salt, Compound **II** SDD (80% Compound **II**, 20% HPMC-E15), and Compound **III** SDD (80% Compound **III**, 19.5% HPMCAS-H, 0.5% SLS).

Example 13: Stability Study of Compounds in Formulations

A. Preparation of Stability Control Tablets 1

[00490] Stability Control Tablets 1 were prepared as specified below in Table 98.

Table 98. Stability Control Tablet 1

	Component	**mg/tablet**	**g/batch**
Intra-granular part	Solid dispersion containing 50wt% Compound **I**, 50wt% hypromellose acetate succinate	50.0 mg	10 g
	microcrystalline cellulose (e.g., PH101)	135.0 mg	27 g
	croscarmellose sodium	6.0 mg	1.2 g
	sodium stearyl fumarate	4.0 mg	0.8 g
Extra-granular part	croscarmellose sodium	3.0 mg	0.58 g[1]
	sodium stearyl fumarate	2.0 mg	0.38 g[1]
	Uncoated Tablet	200.0 mg	n/a

[1] Weights adjusted based on granulation yield.

Dry Granulation:

[00491] Prior to granulation, solid dispersion containing 50wt% Compound **I**, 50wt% hypromellose acetate succinate (see Example 2) and intragranular excipients were screened prior to or after weighing and then blended in a turbula blender. The blend was granulated by slugging and then milling slugs through 1.0mm screen.

Compression:

[00492] Prior to compression, extragranular excipients were screened prior to or after weighing and then blended in a Turbula blender with the roller compacted granules. The blend was compressed into a tablet using the Huxley Bertram compaction simulator.

Using tooling of a desired shape and size, tablets were compressed to a target weight 200.0 mg.

B. Stability Results

[00493] The FDC tablets A2 containing a potassium salt of Compound **I** (crystalline Form B) in combination with the Compound **II** SDD and Compound **III** SDD (see Example 9A above) ("Compound **I** K salt FDC Tablet" in Table 99 below) showed to have greater chemical stability than the Stability Control Tablet 1 ("Compound **I** Mono Tablet" in Table 99 below) (see above Stability Control Tablet 1) comprised of Compound **I** SDD [Compound **I** SDD with HPMCAS, 500 mg/g drug load] at accelerated conditions in open dish. High Performance Liquid Chromatography (HPLC) was used to analyze the purity profile of the samples.

Table 99. Summary of Degradation Product Results for Compound I Mono Tablets[1] and Compound I K Salt Fixed Dose Combination (FDC)[2] Tablets (Open Dish Conditions)

		Total Impurities (% area)	Impurity 1 (% area)	Impurity 2 (% area)
50°C / 75% RH, 14 days	Compound **I** Mono Tablet	1.13	0.20	0.47
	Compound **I** K salt FDC Tablet	0.04	< RT	0.01
60°C / 40% RH, 14 days	Compound **I** Mono Tablet	3.14	0.58	1.42
	Compound **I** K salt FDC Tablet	0.06	< RT	0.01
70°C / 5% RH, 14 days	Compound **I** Mono Tablet	11.06	2.06	5.50
	Compound **I** K salt FDC Tablet	0.08	< RT	0.01
70°C / 75% RH, 3 days	Compound **I** Mono Tablet	4.82	0.87	2.26
	Compound **I** K salt FDC Tablet	0.35	< RT	0.02

RT = ICH Q3A Reporting Threshold (< 0.05 % area)

[1] Compound **I** Mono Tablets are comprised of 50 mg/g Spray Dried Dispersion of Compound **I**

[2] Compound **I** K salt FDC Tablets contain Compound **I** Potassium Salt, Compound **II** SDD (80% Compound **II**, 20% HPMC-E15), and Compound **III** SDD (80% Compound **III**, 19.5% HPMCAS-H, 0.5% SLS).

Example 14. Preparation of Additional Fixed Dose Combination Tablet Formulations of a Potassium Salt of Compound I

[00494] The FDC Tablets C1-C5 were made in a similar manner as described in Example 9 above. **FIGs. 24**, **25** and **26** show tablet dissolution data of K salt of Compound **I**, Compound **II**, and Compound **III**, respectively, of FDC Tablets C1, C2, C3, C4, and C5. The tablet dissolution data were obtained using dissolution media 1 for the K salt of Compound **I** and Compound **III**, and dissolution media 2 for Compound **II**. The dissolution media 1 included 0.8 wt% SDS in pH 6.8 sodium phosphate buffer. The dissolution media 2 included 0.1 wt% SDS in 0.1 N HCl. The dissolution testing of the tablets was performed using USP Apparatus II at 65 rpm for both media. Samples were collected and analyzed using reverse phase HPLC.

Table 100. FDC Tablet C1

	Component	Amount per Tablet (mg)	% IG	%EG	% Tablet (% w/w)
Core Tablet					
Intra-granular (IG)	Compound **I** Potassium Salt	127.73	33.28	29.46	28.6
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	16.29	14.41	13.99
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	93.75	24.43	21.62	20.99
	Croscarmellose sodium	11.51	3.00	2.65	2.58
	Microcrystalline cellulose	84.43	22.00	19.47	18.9
	Magnesium Stearate	3.84	1.00	0.89	0.86
Extra-granular (EG)	Microcrystalline cellulose	43.36	--	10.00	9.71
	Croscarmellose sodium	6.5	--	1.50	1.46
Total (core tablet)		**433.62**	100.00	100.00	**97.09**
Film Coat	film coat	13.01	--	--	2.91
Total (final tablet)		**446.63**			**100**

Table 101. FDC Tablet C2

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
Core Tablet					
Intra-granular	Compound **I** Potassium Salt	127.73	33.28	29.46	28.6
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	16.29	14.41	13.99
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	93.75	24.43	21.62	20.99
	Croscarmellose sodium	11.51	3.00	2.65	2.58
	Microcrystalline cellulose	88.27	23.00	20.36	19.76
	Magnesium Stearate	0	0.00	0.00	0
Extra-granular	Microcrystalline cellulose	39.52	--	9.11	8.85
	Croscarmellose sodium	6.5	--	1.50	1.46
	Magnesium Stearate	3.84	--	0.89	0.86
Total (core tablet)		**433.62**	**100**	**100.00**	**97.09**
Film Coat	film coat	13.01	--	--	2.91
Total (final tablet)		**446.63**			**100**

Table 102. FDC Tablet C3

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
Core Tablet					
Intra-granular	Compound **I** Potassium Salt	127.73	33.28	29.46	28.6
	solid dispersion containing 80 wt%	62.5	16.29	14.41	13.99

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
	Compound **II**, 20 wt% hypromellose				
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	93.75	24.43	21.62	20.99
	Croscarmellose sodium	11.51	3.00	2.65	2.58
	Microcrystalline cellulose	87.31	22.75	20.14	19.55
	Magnesium Stearate	0.96	0.25	0.22	0.21
Extra-granular	Microcrystalline cellulose	40.48	--	9.34	9.06
	Croscarmellose sodium	6.5	--	1.50	1.46
	Magnesium Stearate	2.88	--	0.66	0.64
Total (core tablet)		**433.62**	**100**	**100.00**	**97.09**
Film Coat	film coat	13.01	--		2.91
Total (final tablet)		**446.63**			**100**

Table 103: **FDC Tablet C4**

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
Core Tablet					
Intra-granular	Compound **I** Potassium Salt	127.73	33.28	29.46	28.60
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	16.29	14.41	13.99
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	93.75	24.43	21.62	20.99

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
	Croscarmellose sodium	11.51	3.00	2.65	2.58
	Microcrystalline cellulose	87.31	22.75	20.14	19.55
	Magnesium Stearate	0.96	0.25	0.22	0.21
Extra-granular	Microcrystalline cellulose	39.03	--	9.00	8.74
	Croscarmellose sodium	6.5	--	1.50	1.46
	Magnesium Stearate	4.33	--	1.00	0.97
Total (core tablet)		**433.62**	**100**	**100.00**	**97.09**
Film Coat	film coat	13.01	--	--	2.91
Total (final tablet)		**446.63**			**100**

Table 104. FDC Tablet C5

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
Core Tablet					
Intra-granular	Compound **I** Potassium Salt	127.73	33.28	29.46	28.60
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	16.29	14.41	13.99
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	93.75	24.43	21.62	20.99
	Croscarmellose sodium	11.51	3.00	2.65	2.58
	Microcrystalline cellulose	87.31	22.75	20.14	19.55
	Magnesium Stearate	0.96	0.25	0.22	0.21
Extra-granular	Microcrystalline cellulose	39.41	--	9.09	8.82
	Croscarmellose sodium	6.5	--	1.50	1.46
	Magnesium Stearate	3.95	--	0.91	0.89

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
Total (core tablet)		**433.62**	**100**	**100.00**	**97.09**
Film Coat	film coat	13.01	--	--	2.91
Total (final tablet)		**446.63**			**100**

[00495] FDC Tablet C5-1 can be made in a similar manner as described in Example 9 above. In some embodiments, "Compound **I** Potassium Salt" in Table 105 below refers to Compound **I** potassium salt crystalline Form B.

Table 105. FDC Tablet C5-1

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
Core Tablet					
Intra-granular	Compound **I** Potassium Salt	63.87	33.28	29.46	28.60
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	31.25	16.29	14.41	13.99
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	46.88	24.43	21.62	20.99
	Croscarmellose sodium	5.76	3.00	2.65	2.58
	Microcrystalline cellulose	43.66	22.75	20.14	19.55
	Magnesium Stearate	0.48	0.25	0.22	0.21
Extra-granular	Microcrystalline cellulose	19.70	--	9.09	8.82
	Croscarmellose sodium	3.25	--	1.50	1.46
	Magnesium Stearate	1.98	--	0.91	0.89
Total (core tablet)		216.81	100.00	100.00	97.09
Film Coat	film coat	6.51	--	--	2.91
Total (final tablet)		**223.32**			**100**

Example 15. Preparation of Additional Fixed Dose Combination Tablet Formulations of a Potassium Salt of Compound I

[00496] The tablets D1-D2 can be made in a similar manner as described in Example 9 above. In some embodiments, "Compound **I** Potassium Salt" in Tables 106 and 107 below refers to Compound **I** potassium salt crystalline Form B.

Table 106. FDC Tablet D1

	Component	Amount per Tab (mg)	% IG	%EG	Tablet Content (%w/w)
Core Tablet					
Intra-granular	Compound **I** Potassium Salt	127.73	26.57	23.51	22.83
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	13.00	11.51	11.17
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	187.5	39.00	34.52	33.51
	Croscarmellose sodium	14.5	3.02	2.67	2.59
	Microcrystalline cellulose	87.31	18.16	16.07	15.60
	Magnesium Stearate	1.2	0.25	0.22	0.21
Extra-granular	Microcrystalline cellulose	49.38	--	9.09	8.83
	Croscarmellose sodium	8.15	--	1.50	1.46
	Magnesium Stearate	4.94	--	0.91	0.88
Total (core tablet)		**543.21**	**100**	**100.00**	**97.09**
Film Coat	film coat	16.3	--	--	2.91
Total (final tablet)		**559.51**			**100**

Table 107. FDC Tablet D2

	Component	Amount per Tab (mg)	% IG	%EG	Tablet Content (% w/w)
Core Tablet					
Intra-granular	Compound **I** Potassium Salt	63.865	26.57	23.51	22.83
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	31.25	13.00	11.51	11.17
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	93.75	39.00	34.52	33.51
	Croscarmellose sodium	7.25	3.02	2.67	2.59
	Microcrystalline cellulose	43.655	18.16	16.07	15.60
	Magnesium Stearate	0.6	0.25	0.22	0.21
Extra-granular	Microcrystalline cellulose	24.69	--	9.09	8.83
	Croscarmellose sodium	4.075	--	1.50	1.46
	Magnesium Stearate	2.47	--	0.91	0.88
Total (core ablet)		**271.605**	**100**	**100.00**	**97.09**
Film Coat	film coat	8.15	--	--	2.91
Total (final tablet)		**279.755**			**100**

[00497] FDC Tablets D3, D4, and D5, shown in Tables 108-111 below, were prepared in a similar manner as described in Example 9 above. Tablet D6, shown in Table 108 below, was prepared in a similar manner as described in Example 9, but using direct compression and not including an intermediate granulation of ingredients.

[00498] Dissolution data for FDC Tablets D3, D4, D5, and D6 are shown in **FIGs. 27**, **28** and **29**. The dissolution media 1 included 1.0% SDS in 50 mM sodium phosphate monobasic buffer, pH 6.8. The dissolution media 2 included 0.07% SDS in 0.1 N HCl. The dissolution testing of the tablets was performed using USP Apparatus II (paddle apparatus) at 65 rpm for both media. Samples were collected and analyzed using reverse

phase HPLC. USP Apparatus II (paddle apparatus) is described in the United States Pharmacopeia (USP) in General Chapter Dissolution <711>.

Table 108. FDC Tablet D3

	Component	Amount per Tablet (mg)	% IG	%EG
Core Tablet				
Intra-granular (IG)	Compound **I** Potassium Salt	127.73	26.75	23.40
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.50	13.09	11.45
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	187.50	39.26	34.36
	Croscarmellose sodium	11.52	2.41	2.11
	Microcrystalline cellulose	87.33	18.29	16.00
	Magnesium Stearate	0.96	0.20	0.18
Extra-granular (EG)	Microcrystalline cellulose	54.58	--	10.00
	Croscarmellose sodium	8.19	--	1.50
	Magnesium Stearate	5.46	--	1.00
Total (core tablet)		**545.75**	**100**	**100**

Table 109. FDC Tablet D4

	Component	Amount per Tablet (mg)	% IG	%EG
Core Tablet				
Intra-granular (IG)	Compound **I** Potassium Salt	127.73	25.03	22.14
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	12.25	10.84

	Component	Amount per Tablet (mg)	% IG	%EG
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	187.5	36.74	32.51
	Croscarmellose sodium	15.30	3.00	2.65
	Microcrystalline cellulose	116.10	22.75	20.13
	Magnesium Stearate	1.26	0.25	0.22
Extra-granular (EG)	Microcrystalline cellulose	52.50	--	9.10
	Croscarmellose sodium	8.65	--	1.50
	Magnesium Stearate	5.25	--	0.91
Total (core tablet)		**576.79**	**100**	**100.00**

Table 110. FDC Tablet D5

	Component	Amount per Tablet (mg)	% IG	%EG
Core Tablet				
Intra-granular (IG)	Compound **I** Potassium Salt	127.73	24.26	21.23
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.50	11.87	10.39
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	187.50	35.62	31.16
	Croscarmellose sodium	17.16	3.26	2.85
	Microcrystalline cellulose	130.13	24.72	21.63
	Magnesium Stearate	1.43	0.27	0.24

	Component	Amount per Tablet (mg)	% IG	%EG
Extra-granular (EG)	Microcrystalline cellulose	60.17	--	10.00
	Croscarmellose sodium	9.02	--	1.50
	Magnesium Stearate	6.02	--	1.00
Total (core tablet)		**601.66**	**100**	**100**

Table 111. FDC Tablet D6

	Component	Amount per Tablet (mg)	Tablet Content (% w/w)
Core Tablet			
	Compound **I** Potassium Salt	127.73	21.98
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.50	10.76
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	187.50	32.27
	Croscarmellose sodium	17.43	3.00
	Microcrystalline cellulose	180.15	31.00
	Magnesium Stearate	5.81	1.00
Total (core tablet)		**581.12**	**581.12**

[00499] FDC Tablets D3, D4, D5, and D6 can be film coated between about 2-4% w/w of the final tablet content, as shown in Tables 112-115 below. In some embodiments, "Compound **I** Potassium Salt" in Tables 112-115 below refers to Compound **I** potassium salt crystalline Form B.

Table 112. FDC Tablet D3, film coated

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
Core Tablet					
Intra-granular (IG)	Compound **I** Potassium Salt	127.73	26.75	23.40	22.72
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.50	13.09	11.45	11.12
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	187.50	39.26	34.36	33.36
	Croscarmellose sodium	11.52	2.41	2.11	2.05
	Microcrystalline cellulose	87.33	18.29	16.00	15.54
	Magnesium Stearate	0.96	0.20	0.18	0.17
Extra-granular (EG)	Microcrystalline cellulose	54.58	--	10.00	9.71
	Croscarmellose sodium	8.19	--	1.50	1.46
	Magnesium Stearate	5.46	--	1.00	0.97
Total (core tablet)		**545.75**	**100**	**100**	**97.09**
Film Coat	film coat	16.37	--	--	2.91
Total (final tablet)		**562.12**			**100**

Table 113. FDC Tablet D4, film coated

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
Core Tablet					
Intra-granular (IG)	Compound **I** Potassium Salt	127.73	25.03	22.14	21.50
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	12.25	10.84	10.52

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	187.5	36.74	32.51	31.56
	Croscarmellose sodium	15.30	3.00	2.65	2.58
	Microcrystalline cellulose	116.10	22.75	20.13	19.54
	Magnesium Stearate	1.26	0.25	0.22	0.21
Extra-granular (EG)	Microcrystalline cellulose	52.50	--	9.10	8.84
	Croscarmellose sodium	8.65	--	1.50	1.46
	Magnesium Stearate	5.25	--	0.91	0.88
Total (core tablet)		**576.79**	**100**	**100.00**	**97.09**
Film Coat	film coat	17.30	--	--	2.91
Total (final tablet)		**594.09**			**100**

Table 114. FDC Tablet D5, film coated

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
Core Tablet					
Intra-granular (IG)	Compound **I** Potassium Salt	127.73	24.26	21.23	20.61
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.50	11.87	10.39	10.09
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	187.50	35.62	31.16	30.26
	Croscarmellose sodium	17.16	3.26	2.85	2.77

	Component	Amount per Tablet (mg)	% IG	%EG	Tablet Content (% w/w)
	Microcrystalline cellulose	130.13	24.72	21.63	21.00
	Magnesium Stearate	1.43	0.27	0.24	0.23
Extra-granular (EG)	Microcrystalline cellulose	60.17	--	10.00	9.71
	Croscarmellose sodium	9.02	--	1.50	1.46
	Magnesium Stearate	6.02	--	1.00	0.97
Total (core tablet)		**601.66**	**100**	**100**	**97.09**
Film Coat	film coat	18.05	--	--	2.91
Total (final tablet)		**619.71**			**100**

Table 115. FDC Tablet D6, film coated

	Component	Amount per Tablet (mg)	% Core Tablet	Tablet Content (% w/w)
Core Tablet				
Intra-granular (IG)	Compound **I** Potassium Salt	127.73	21.98	21.34
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.50	10.76	10.44
	solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	187.50	32.27	31.33
	Croscarmellose sodium	17.43	3.00	2.91
	Microcrystalline cellulose	180.15	31.00	30.10
	Magnesium Stearate	5.81	1.00	0.97
Total (core tablet)		**581.12**	**100.00**	**97.09**
Film Coat	film coat	17.42		2.91
Total (final tablet)		**598.54**		**100**

Example 16. Preparation of Additional Fixed Dose Combination Tablet Formulations of a Potassium Salt of Compound I in Combination with Compound II and Compound III-d

[00500] The FDC Tablet E1 was prepared in a similar manner as described in Example 9 above. **FIGs. 24, 25,** and **26** show tablet dissolution data of K salt of Compound **I**, Compound **II**, and Compound **III-d**, respectively, of FDC Tablet E1. The tablet dissolution data were obtained using dissolution media 1 for the K salt of Compound **I** and Compound **III-d**, and dissolution media 2 for Compound **II**. The dissolution media 1 included 0.8 wt% SDS in pH 6.8 sodium phosphate buffer. The dissolution media 2 included 0.1 wt% SDS in 0.1 N HCl. The dissolution testing of the tablets was performed using USP Apparatus II at 65 rpm for both media. Samples were collected and analyzed using reverse phase HPLC.

[00501] The tablets E2-E4 can be prepared in a similar manner as described in Example 9 above, but using direct compression and may not include intermediate granulation of ingredients. The solid dispersion containing 80 wt% Compound **III-d**, 19.5 wt% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate can be made in the same manner as that for the solid dispersion containing 80 wt% Compound **III**, 19.5 wt% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate.

Table 116. FDC Tablet E1

IG / EG	Component	Tablet Qty (mg)	% IG	% EG	% Coated tablet
IG	Compound **I** Potassium Salt	127.73	30.78	27.48%	26.68%
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	15.06	13.44%	13.05%
	solid dispersion containing 80 wt% Compound **III-d**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	125	30.12	26.89%	26.11%
	Microcrystalline cellulose	84.43	20.34	18.16%	17.63%
	Croscarmellose sodium	11.51	2.77	2.48%	2.40%
	Magnesium Stearate	3.84	0.93	0.83%	0.80%
EG	Microcrystalline cellulose	43.36		9.33%	9.06%
	Croscarmellose sodium	6.5		1.40%	1.36%

IG / EG	Component	Tablet Qty (mg)	% IG	% EG	% Coated tablet
	Magnesium Stearate				0.00%
Coating	film coat	13.95			2.91%
Total		**478.82**	**100.00**	**100.00%**	**100.00%**

Table 117. FDC Tablet E2

	Component	Tablet Qty (mg)	% Core tablet	% Coated tablet
	Compound **I** K salt	255.46	34.06%	33.07%
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	125	16.67%	16.18%
	solid dispersion containing 80 wt% Compound **III-d**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	250	33.33%	32.36%
	Microcrystalline cellulose	89.54-97.04	11.94-12.94%	11.59-12.56%
	Croscarmellose sodium	22.5	3.00%	2.91%
	Magnesium Stearate	0-7.5	0-1%	0-0.97%
Total Core		**750**	**100.00%**	97.09%
	film coating	22.5		2.91%
Total coated		**772.5**		**100.00%**

Table 118. FDC Tablet E3

	Component	Tablet Qty (mg)	% Core tablet	% Coated tablet
	Compound **I** K salt	127.73	20.26%	19.67%
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	9.91%	9.62%
	solid dispersion containing 80 wt% Compound **III-d**, 19.5 wt% hypromellose acetate	125	19.83%	19.25%

	Component	Tablet Qty (mg)	% Core tablet	% Coated tablet
	succinate, and 0.5 wt% sodium lauryl sulfate			
	Microcrystalline cellulose	290.01-296.32	46-47%	44.66-45.63%
	Croscarmellose sodium	18.91	3.00%	2.91%
	Magnesium Stearate	0-6.31	0-1%	0-0.97%
Total Core		**630.46**	**100.00%**	**97.09%**
	film coating	18.91		2.91%
Total coated		**649.37**		**100.00%**

Table 119. FDC Tablet E4

	Component	Tablet Qty (mg)	% Core tablet	% Coated tablet
	Compound **I** K salt	127.73	28.36%	27.54%
	solid dispersion containing 80 wt% Compound **II**, 20 wt% hypromellose	62.5	13.88%	13.47%
	solid dispersion containing 80 wt% Compound **III-d**, 19.5 wt% hypromellose acetate succinate, and 0.5 wt% sodium lauryl sulfate	125	27.76%	26.95%
	Microcrystalline cellulose	117.09-121.59	26-27%	25.24-26.21%
	Croscarmellose sodium	13.51	3.00%	2.91%
	Magnesium Stearate	0-4.5	0-1%	0-0.97%
Total Core		**450.33**	**100.00%**	**97.09%**
	film coating	13.51		2.91%
Total coated		**463.84**		**100.00%**

Example 17: ASSAYS & DATA

17A. Assays for Detecting and Measuring F508del-CFTR modulator Properties of Compounds

Membrane potential optical methods for assaying properties of F508del-CFTR modulators

[00502] The assay utilizes fluorescent voltage sensing dyes to measure changes in membrane potential using a fluorescent plate reader (e.g., FLIPR III, Molecular Devices, Inc.) as a readout for increase in functional F508del in NIH 3T3 cells. The driving force for the response is the creation of a chloride ion gradient in conjunction with channel activation and concurrent with compound treatment by a single liquid addition step after the cells have previously been loaded with a voltage sensing dye.

17A-A1. Identification of F508del-CFTR modulators

[00503] To identify modulators of F508del, a fluorescence based HTS assay format was developed. This HTS assay utilizes fluorescent voltage sensing dyes to measure changes in membrane potential on the FLIPR III as a measurement for increase in gating (conductance) of F508del NIH 3T3 cells. The driving force for the response is the creation of a chloride ion gradient in conjunction with channel activation and concurrent with compound treatment by a single liquid addition step after the cells have previously been loaded with a voltage sensing dye. Data for Compounds **I** that were obtained using the assay described here are summarized in Table 120 below. For example, using this method, Compound **I** had an EC_{50} of less than 3 μM and a % Efficacy of ≥ 100% relative to Compound **II**.

Solutions

[00504] Bath Solution #1: (in mM) NaCl 160, KCl 4.5, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7.4 with NaOH, Glucose 10.

[00505] Chloride-free bath solution: Chloride salts in Bath Solution #1 (above) are substituted with gluconate salts.

Cell Culture

[00506] NIH3T3 mouse fibroblasts stably expressing F508del are used for optical measurements of membrane potential. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM

glutamine, 10 % fetal bovine serum, 1 X NEAA, β-ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For all optical assays, the cells were seeded at 12,000 cells/well in 384-well matrigel-coated plates and cultured for 18-24 hrs at 37 °C for the potentiator assay. For the correction assays, the cells are cultured at 37 °C with and without compounds for 18 – 24 hours.

Electrophysiological Assays for assaying F508del modulation properties of compounds.

Ussing Chamber Assay

[00507] Ussing chamber experiments were performed on polarized airway epithelial cells expressing F508del to further characterize the F508del modulators identified in the optical assays. Non-CF and CF airway epithelia were isolated from bronchial tissue, cultured as previously described (Galietta, L.J.V., Lantero, S., Gazzolo, A., Sacco, O., Romano, L., Rossi, G.A., & Zegarra-Moran, O. (1998) *In Vitro Cell. Dev. Biol.* **34**, 478-481), and plated onto Costar® Snapwell™ filters that were precoated with NIH3T3-conditioned media. After four days the apical media was removed and the cells were grown at an air liquid interface for >14 days prior to use. This resulted in a monolayer of fully differentiated columnar cells that were ciliated, features that are characteristic of airway epithelia. Non-CF HBE were isolated from non-smokers that did not have any known lung disease. CF-HBE were isolated from patients homozygous for *F508del* or compound heterozygous for *F508del* with a different disease causing mutation on the other allele.

[00508] HBE grown on Costar® Snapwell™ cell culture inserts were mounted in an Ussing chamber (Physiologic Instruments, Inc., San Diego, CA), and the transepithelial resistance and short-circuit current in the presence of a basolateral to apical Cl^- gradient (I_{SC}) were measured using a voltage-clamp system (Department of Bioengineering, University of Iowa, IA). Briefly, HBE were examined under voltage-clamp recording conditions (V_{hold} = 0 mV) at 37 °C. The basolateral solution contained (in mM) 145 NaCl, 0.83 K_2HPO_4, 3.3 KH_2PO_4, 1.2 $MgCl_2$, 1.2 $CaCl_2$, 10 Glucose, 10 HEPES (pH adjusted to 7.35 with NaOH) and the apical solution contained (in mM) 145 NaGluconate, 1.2 $MgCl_2$, 1.2 $CaCl_2$, 10 glucose, 10 HEPES (pH adjusted to 7.35 with NaOH).

17A-A2. Identification of F508del-CFTR modulators

[00509] Typical protocol utilized a basolateral to apical membrane Cl^- concentration gradient. To set up this gradient, normal ringers was used on the basolateral membrane, whereas apical NaCl was replaced by equimolar sodium gluconate (titrated to pH 7.4 with NaOH) to give a large Cl^- concentration gradient across the epithelium. Modulators were added either to the basolateral side 18 – 24 prior to assay or to the apical side during the assay. Forskolin (10 μM) was added to the apical side during the assay to stimulate CFTR-mediated Cl^- transport.

Patch-clamp Recordings

[00510] Total Cl^- current in F508del-NIH3T3 cells was monitored using the perforated-patch recording configuration as previously described (Rae, J., Cooper, K., Gates, P., & Watsky, M. (1991) *J. Neurosci. Methods* **37**, 15-26). Voltage-clamp recordings were performed at 22 °C using an Axopatch 200B patch-clamp amplifier (Axon Instruments Inc., Foster City, CA). The pipette solution contained (in mM) 150 *N*-methyl-D-glucamine (NMDG)-Cl, 2 $MgCl_2$, 2 $CaCl_2$, 10 EGTA, 10 HEPES, and 240 μg/mL amphotericin-B (pH adjusted to 7.35 with HCl). The extracellular medium contained (in mM) 150 NMDG-Cl, 2 $MgCl_2$, 2 $CaCl_2$, 10 HEPES (pH adjusted to 7.35 with HCl). Pulse generation, data acquisition, and analysis were performed using a PC equipped with a Digidata 1320 A/D interface in conjunction with Clampex 8 (Axon Instruments Inc.). To activate F508del, 10 μM forskolin and 20 μM genistein were added to the bath and the current-voltage relation was monitored every 30 sec.

17A-A3. Identification of F508del-CFTR modulators

[00511] The ability of F508del-CFTR modulators to increase the macroscopic F508del Cl^- current ($I_{F508del}$) in NIH3T3 cells stably expressing F508del was also investigated using perforated-patch-recording techniques. Modulators identified from the optical assays evoked a dose-dependent increase in $I\Delta_{F508}$ with similar potency and efficacy observed in the optical assays.

Cell Culture

[00512] NIH3T3 mouse fibroblasts stably expressing F508del are used for whole-cell recordings. The cells are maintained at 37 °C in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM glutamine, 10 % fetal

bovine serum, 1 X NEAA, β-ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For whole-cell recordings, 2,500 - 5,000 cells were seeded on poly-L-lysine-coated glass coverslips and cultured for 18 - 24 hrs in the presence or absence of modulators 37 °C.

Single-channel recordings

[00513] Gating activity of F508del-CFTR expressed in NIH3T3 cells following modulator treatment was observed using excised inside-out membrane patch recordings as previously described (Dalemans, W., Barbry, P., Champigny, G., Jallat, S., Dott, K., Dreyer, D., Crystal, R.G., Pavirani, A., Lecocq, J-P., Lazdunski, M. (1991) *Nature* 354, 526 – 528) using an Axopatch 200B patch-clamp amplifier (Axon Instruments Inc.). The pipette contained (in mM): 150 NMDG, 150 aspartic acid, 5 $CaCl_2$, 2 $MgCl_2$, and 10 HEPES (pH adjusted to 7.35 with Tris base). The bath contained (in mM): 150 NMDG-Cl, 2 $MgCl_2$, 5 EGTA, 10 TES, and 14 Tris base (pH adjusted to 7.35 with HCl). After excision, both wt- and F508del were activated by adding 1 mM Mg-ATP, 75 nM of the catalytic subunit of cAMP-dependent protein kinase (PKA; Promega Corp. Madison, WI), and 10 mM NaF to inhibit protein phosphatases, which prevented current rundown. The pipette potential was maintained at 80 mV. Channel activity was analyzed from membrane patches containing ≤ 2 active channels. The maximum number of simultaneous openings determined the number of active channels during the course of an experiment. To determine the single-channel current amplitude, the data recorded from 120 sec of F508del activity was filtered "off-line" at 100 Hz and then used to construct all-point amplitude histograms that were fitted with multigaussian functions using Bio-Patch Analysis software (Bio-Logic Comp. France). The total microscopic current and open probability (P_o) were determined from 120 sec of channel activity. The P_o was determined using the Bio-Patch software or from the relationship $P_o = I/i(N)$, where I = mean current, i = single-channel current amplitude, and N = number of active channels in patch.

Cell Culture

[00514] NIH3T3 mouse fibroblasts stably expressing F508del are used for excised-membrane patch-clamp recordings. The cells are maintained at 37 ºC in 5% CO_2 and 90 % humidity in Dulbecco's modified Eagle's medium supplemented with 2 mM

glutamine, 10 % fetal bovine serum, 1 X NEAA, β-ME, 1 X pen/strep, and 25 mM HEPES in 175 cm^2 culture flasks. For single channel recordings, 2,500 - 5,000 cells were seeded on poly-L-lysine-coated glass coverslips and cultured for 18 - 24 hrs in the presence or absence of modulators at 37 °C.

17B. Chromatographic determination of Human Serum Albumin (HSA) Assay

[00515] Chromatographic determination of Human Serum Albumin (HSA) values was performed on a UPLC-MS system using a ChiralPak® HSA column (p/n: 58469AST) from Sigma Aldrich. Mobile phase A consisted of 50 mM ammonium acetate buffer in water adjusted to pH=7.4, and mobile phase B was 2-propanol. The column compartment was kept at constant temperature of 30°C. Determination of retention time on the HSA column was performed by injecting 3 mL of 0.5 mM of compound (in DMSO) using a linear gradient from 0% - 30% B in 2.5 minutes, followed by a hold at 30 %B for 2 minutes, and the final equilibration step from 30% - 0% B in 1.5 minutes, for a total run time of 6 minutes. Flow rate was kept constant throughout the gradient and set to 1.8 mL/min. Compound retention time on the HSA column was converted to %HSA values according to a previously published protocol (Valko, et. al, 2003) correlating column retention times to standard plasma protein binding (PPB) values obtained from dialysis experiments.

[00516] Valko, K., Nunhuck, S., Bevan, C., Abraham, M. H., Reynolds, D. P. Fast Gradient HPLC Method to Determine Compounds Binding to Human Serum Albumin. Relationships with Octanol/Water and Immobilized Artificial Membrane Lipophilicity. *J. of Pharm. Sci.* **2003,** 92, 2236-2248.

17C. Experimental Protocol for Rat IV and PO PK studies

[00517] The tested compound was administered to male Sprague-Dawley rats as a single nominal intravenous dose of 3.0 mg/kg as a solution in 10% NMP, 10% solutol, 15% EtOH, 35% PEG400 and 30% D5W. The tested compound was also administered to male Sprague-Dawley rats at single nominal oral dose of 3 mg/kg as a solution in 5% NMP, 30% PEG400, 10% TPGS, 5% PVP-K30 at 5 mL/kg dose volume. Analyses of plasma and dose preparations were performed using LC/MS/MS.

[00518] Plasma concentration-time profiles of the tested compound in Sprague-Dawley rats at scheduled (nominal) sampling times were analyzed by noncompartmental pharmacokinetic methods using PK function within Watson LIMS

software, Version 7.4.2 (Thermo Scientific Inc, Waltham, MA). AUC values were calculated using the linear trapezoidal rule.

17D. Experimental Protocol for PXR assay

[00519] The propensity for PXR mediated CYP3A4 induction is assessed using the DPX-2 cell line *in vitro*. This cell line, which has been licensed from Puracyp Inc. was derived from HepG2 cells and has been stably transfected with genes encoding human PXR as well as a modified luciferase reporter linked to the CYP3A4 promoter region and related distal and proximal enhancers.

[00520] The assay is run in 384 well format and each test article is administered in 11 doses ranging from 0.1 to 60 μM. On day 1, DPX-2 cells which have previously been expanded in-house and cryopreserved are thawed and seeded in tissue culture plates. The following day, media is changed and cells are cultured in media containing test article, vehicle control or the positive control compound, the clinically validated CYP3A4 inducer rifampicin. Cells are cultured in the presence of test article for 48 hours and then cell viability is assessed using fluorescence based assay (Cell Titer-Fluor, Promega) with an EnVision Plate Reader (PerkinElmer). Subsequently, CYP3A4 transactivation, which is proportional to luciferase activity, is measured by reading luminescense using the Promega One-Glo reagent system using the same plate reader.

[00521] Data processing within the Genedata software package allows reporting of max fold induction compared to vehicle control, an EC_{50} value for CYP3A4 inducers and an 11 point-dose response curve. Wells with cell viability less than 70% are not used for the analysis and plates where the rifampicin positive control response falls outside of the expected range, either in potency or max fold induction, are not reported.

17E. CFTR Data of Compound I

[00522] Compound **I** is useful as a modulator of CFTR activity. The Table 120 below illustrates the EC50 of Compound **I** using procedures described above (assay described above in Example 11A-A1). In Table 120 below, the following meanings apply. EC50: "+++" means < 0.1 μM; "++" means between 0.1 μM and 1 μM; "+" means greater than 1 μM.

Table 120. CFTR Activity

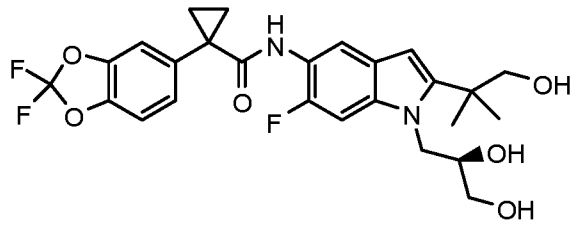
Comp. No.	CFTRdF508 EC50 (μM)
I	+++

Example 18: Chloride Transport Experiments

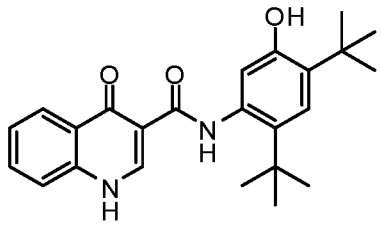
[00523] In one Ussing Chamber experiment with F508del/F508del-HBE cells, Compound **I** enhanced chloride transport. The effect of Compound **I** on chloride transport was additive to the effect of Compound **II**. In addition, F508del-CFTR delivered to the cell surface by either Compound **I** alone or in combination with Compound **II** was potentiated by Compound **III**. The triple combination of Compound **I** / Compound **II** / Compound **III** provided a superior (approximately 3-fold) increase in chloride transport compared to the 3 dual regimens under most conditions tested.

Example 19: F508del-CFTR Processing and Trafficking In Vitro Experiments

[00524] In vitro, Compound **I** improved the processing and trafficking of F508del-CFTR, thereby increasing the quantity of functional F508del-CFTR protein at the cell surface. The CFTR protein delivered to the cell surface by Compound **I** alone or in combination with Compound **II** (Compound **I** / Compound **II**) was potentiated by Compound **III**. In human bronchial epithelial (HBE) cells studied in vitro, the triple combination of Compound **I**, Compound **II**, and Compound **III** (Compound I / Compound **II** / Compound **III**) increased CFTR chloride transport more than any of the dual combinations (Compound **I** / Compound **II**, Compound **I** / Compound **III**, and Compound **II** / Compound **III**) or individual components (Compound **I**, Compound **II**, and Compound **III**) under most conditions studied.



(Compound **II**); and



(Compound **III**).

[00525] Processing and trafficking of F508del-CFTR was directly monitored by the appearance of a 170 to 180 kDa band. Such monitoring established that Compound **I** is a CFTR corrector, as it facilitates the processing and trafficking of F508del-CFTR to increase the amount of functional F508del-CFTR at the cell surface.

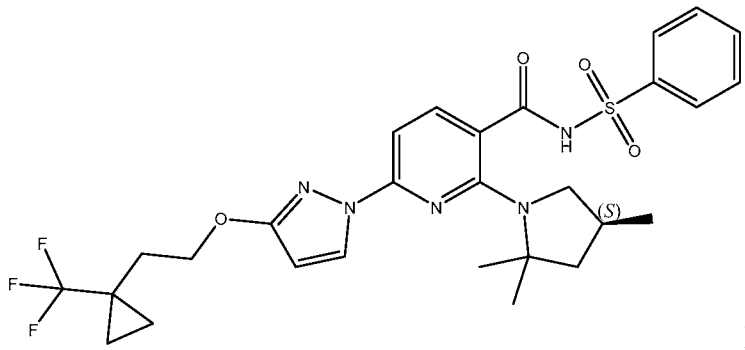
[00526] Incubation of F508del/F508del-HBE cells for 16 to 24 hours with 1 μM Compound **I** alone or in combination with 3 μM Compound **II** resulted in an increase in steady-state levels, reaching 6.5-fold and 18.7-fold of untreated levels, respectively.

Other Embodiments

[00527] The foregoing discussion discloses and describes merely exemplary embodiments of this disclosure. One skilled in the art will readily recognize from such discussion and from the accompanying drawings and claims, that various changes, modifications and variations can be made therein without departing from the spirit and scope of this disclosure as defined in the following claims.

CLAIMS

1. Crystalline Form B of a potassium salt of Compound **I**:



I.

2. Crystalline Form B according to claim 1 in substantially pure form.

3. Crystalline Form B according to claim 1, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 9.6 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 15.1 ± 0.2, 16.3 ± 0.2, 17.2 ± 0.2, and 19.1 ± 0.2.

4. Crystalline Form B according to claim 1, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 5.8 ± 0.2, 8.2 ± 0.2, 10.2 ± 0.2, 13.8 ± 0.2, 16.3 ± 0.2, and 19.1 ± 0.2.

5. Crystalline Form B according to claim 1, characterized by an X-ray powder diffractogram having a signal at three two-theta values of 5.8 ± 0.2, 10.2 ± 0.2, and 19.1 ± 0.2.

6. Crystalline Form B of claim 1, characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 1A**.

7. Crystalline Form B of claim 1 having a unit cell characterized by three edges of 9.0 ± 0.2 Å, 11.5 ± 0.2 Å, and 31.0 ± 0.2 Å.

8. Crystalline Form B of a potassium salt of Compound **I** prepared by a process comprising reacting Compound **I** with a potassium base.

9. A method of preparing Crystalline Form B of a potassium salt of Compound **I**, comprising reacting Compound **I** with a potassium base.

10. The method of claim 9, wherein said potassium base is KOH.

11. Crystalline Form C of a potassium salt/co-crystal of Compound **I.**

12. Crystalline Form C according to claim 12 in substantially pure form.

13. Crystalline Form C according to claim 12, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 8.7 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, 11.5 ± 0.2, 12.4 ± 0.2, and 16.0 ± 0.2.

14. Crystalline Form C according to claim 12, characterized by an X-ray powder diffractogram having a signal at at least three two-theta values chosen from 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, and 11.5 ± 0.2.

15. Crystalline Form C according to claim 12, characterized by an X-ray powder diffractogram having a signal at three two-theta values of 3.7 ± 0.2, 7.0 ± 0.2, and 11.4 ± 0.2.

16. Crystalline Form C according to claim 12, characterized by an X-ray powder diffractogram having a signal at six two-theta values of 3.7 ± 0.2, 7.0 ± 0.2, 7.4 ± 0.2, 9.5 ± 0.2, 11.4 ± 0.2, and 11.5 ± 0.2.

17. Crystalline Form C of claim 12, characterized by an X-ray powder diffractogram substantially similar to that in **FIG. 7A**.

18. Crystalline Form C of a potassium salt of Compound **I** prepared by a process comprising stirring a potassium salt of Compound **I** with a solvent system comprising at least one source of water.

19. A method of preparing Crystalline Form C of the potassium salt of Compound **I**, comprising stirring a potassium salt of Compound **I** with a solvent system comprising at least one source of water.

20. Crystalline Form A of a sodium salt of Compound **I** in substantially pure form.

21. A method of preparing crystalline Form A of a sodium salt of Compound **I,** comprising reacting Compound **I** with a sodium base.

22. Crystalline Form D of a sodium salt of Compound **I** in substantially pure form.

23. A method of preparing crystalline Form D of a sodium salt Compound **I**, comprising heating a crystalline Form M or Form E of a sodium salt of Compound **I** at a temperature in a range from 280 °C to 300 °C under a anhydrous condition.

24. Crystalline Form M of a sodium salt of Compound **I** in substantially pure form.

25. A method of preparing crystalline Form M of a sodium salt of Compound **I**, comprising reacting Compound **I** with a sodium base in methanol.

26. Crystalline Form A of Compound **I**.

27. Crystalline Form A according to claim 26 in substantially pure form.

28. A method of preparing crystalline Form A of Compound I, comprising de-solvating at least one solvate of Compound **I** chosen from ethanol solvates of Compound **I** and methanol solvates of Compound **I**.

29. Crystalline Form E of a sodium salt of Compound **I** in substantially pure form.

30. A method of preparing crystalline Form E of a sodium salt of Compound **I**, comprising reacting Compound **I** with a sodium base in ethanol.

31. Crystalline Form H of a sodium salt of Compound **I** in substantially pure form.

32. A method of preparing crystalline Form H of a sodium salt of Compound **I** comprising de-solvating crystalline Form M or Form E of a sodium salt of Compound **I** or crystalline Form E of a sodium salt of Compound **I** in the presence of one source of water.

33. A pharmaceutical composition comprising at least one crystalline form according to any one of claims 1-8, 11-18, 20, 22, 24, 26, 27, 29 and 31 and a pharmaceutically acceptable carrier.

34. A method of treating cystic fibrosis comprising administering to a patient in need thereof at least one crystalline form according to any one of claims 1-8, 11-18, 20, 22, 24, 26, 27, 29 and 31 or the pharmaceutical composition of claim 33.

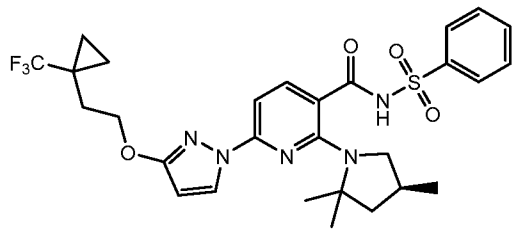
35. At least one solvate of Compound **I** chosen from 1,4-dioxane solvates, 2-methyl tetrahydrofuran solvates, ethanol solvates, nitromethane solvates, 1-propanol solvates, tetrahydrofuran solvates, toluene solvates, pyridine solvates, chlorobenzene solvates, diethyl ether solvates, 2-propanol solvates, 2-butanol solvates, hexane solvates, heptane solvates, ethyl acetate solvates, methanol solvates, dichloromethane solvates, acetone solvates, methyl tert-butyl ether solvates, n-butanol solvates, N-methyl-2-pyrrolidone solvates, and t-butanol solvates of Compound **I**.

36. At least one solvate of a sodium salt Compound **I** chosen from ethanol solvates and methanol solvates of the sodium salt of Compound **I**.

37. At least one solvate of a potassium salt Compound **I** chosen from 1-pentanol solvates, isopropyl acetate solvates, 1-propanol solvates, acetone solvates, acetonitrile solvates, 2-methyl tetrahydrofuran solvates, ethyl acetate solvates, methanol solvates, ethanol solvates, methyl tert-butyl ether solvates, and methyl ethyl ketone solvates of a potassium salt of Compound **I**.

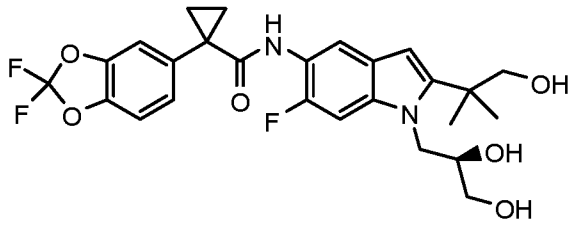
38. A pharmaceutical composition comprising

(a) 50 mg to 600 mg of a potassium salt of Compound **I** (crystalline Form B):



I

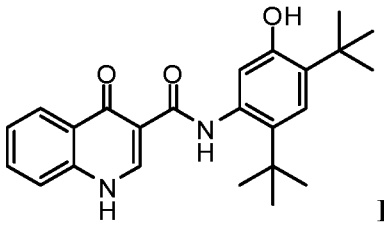
a first solid dispersion comprising 25 mg to 125 mg of Compound **II**:



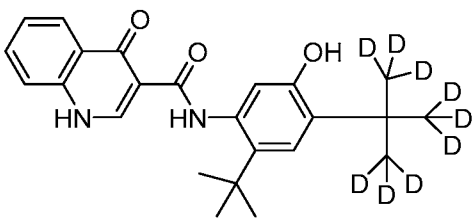
II

and 10 wt% to 30 wt% of a polymer relative to the total weight of the first solid dispersion; and

(c) a second solid dispersion comprising 5 mg to 300 mg of Compound **III** or Compound **III-d**:



III or



III-d

and 10 wt% to 30 wt% of a polymer relative to the total weight of the second solid dispersion.

39. A pharmaceutical composition comprising:

(a) 15 wt% to 45 wt% of a potassium salt of Compound **I** (Form B) relative to the total weight of the pharmaceutical composition;

(b) 5 wt% to 20 wt% of a first solid dispersion relative to the total weight of the pharmaceutical composition,

wherein the first solid dispersion comprises 70 wt% to 90 wt% of Compound **II** relative to the total weight of the first solid dispersion and 10 wt% to 30 wt% of a polymer relative to the total weight of the first solid dispersion; and

(c) 10 wt% to 40 wt% of a second solid dispersion relative to the total weight of the pharmaceutical composition, wherein the second solid dispersion comprises 70 wt% to 90 wt% of Compound **III** or Compound **III-d** relative to the total weight of the second solid dispersion, and 10 wt% to 30 wt% of a polymer relative to the total weight of the second solid dispersion.

40. A pharmaceutical composition comprising:

(a) 20 wt% to 35 wt% of a potassium salt of Compound **I** (Form B) relative to the total weight of the pharmaceutical composition;

(b) 5 wt% to 20 wt% of a first solid dispersion relative to the total weight of the pharmaceutical composition, wherein the first solid dispersion comprises 70 wt% to 90 wt% of Compound **II** relative to the total weight of the first solid dispersion, and 10 wt% to 30 wt% of a polymer relative to the total weight of the first solid dispersion; and

(c) 20 wt% to 40 wt% of a second solid dispersion relative to the total weight of the pharmaceutical composition, wherein the second solid dispersion comprises 70 wt% to 90 wt% of Compound **III** relative to the total weight of the second solid dispersion, and 10 wt% to 30 wt% of a polymer relative to the total weight of the second solid dispersion.

41. The pharmaceutical composition of any one of claims 38 - 40, wherein at least one of the first or second solid dispersions is a spray-dried dispersion.

42. The pharmaceutical composition of any one of claims 38 - 40, wherein both of the first and second solid dispersions are spray-dried dispersions.

43. The pharmaceutical composition of any one of claims 38 - 40, wherein said polymer for the first solid dispersion is hypromellose; and said polymer for the second solid dispersion is hypromellose acetate succinate.

44. The pharmaceutical composition of any one of claims 38 - 40, wherein said polymer for the first solid dispersion is HPMC E15; and said polymer for the second solid dispersion is hypromellose acetate succinate H.

45. The pharmaceutical composition of any one of claims 38 - 40, wherein said polymer for the first solid dispersion is HPMC E15; and said polymer for the second solid dispersion is hypromellose acetate succinate HG.

46. The pharmaceutical composition of any one of claims 38 - 45, comprising 50 mg to 500 mg, 50 mg to 400 mg, 50 mg to 300 mg, 100 mg to 300 mg, 100 mg to 250 mg, 100 mg to 150 mg, or 200 mg to 250 mg of a potassium salt of Compound **I** (Form B).

47. The pharmaceutical composition of any one of claims 38 - 45, comprising 100 mg to 250 mg of a potassium salt of Compound **I** (Form B).

48. The pharmaceutical composition of any one of claims 38 - 45, comprising 100 mg to 150 mg or 150 mg to 250 mg of a potassium salt of Compound **I** (Form B).

49. The pharmaceutical composition of any one of claims 38 - 48, wherein the first solid dispersion comprises 25 mg to 100 mg, 25 mg to 75 mg, or 30 mg to 60 mg of Compound **II**.

50. The pharmaceutical composition of any one of claims 38 - 49, wherein the first solid dispersion comprises 25 mg to 75 mg of Compound **II**.

51. The pharmaceutical composition of any one of claims 38 - 50, wherein the second solid dispersion comprises 25 mg to 50 mg, 25 mg to 75 mg, 50 mg to 100 mg, 75 mg to 125 mg, or 125 mg to 175 mg of Compound **III** or Compound **III-d**.

52. The pharmaceutical composition of any one of claims 38 - 50, wherein the second solid dispersion comprises 50 mg to 100 mg of Compound **III** or Compound **III-d**.

53. The pharmaceutical composition of any one of claims 38 - 45, comprising 100 mg to 250 mg of a potassium salt of Compound **I** (Form B); and wherein the first solid dispersion comprises 25 mg to 75 mg of Compound **II**; and the second solid dispersion comprises 50 mg to 100 mg of Compound **III** or Compound **III-d**.

54. The pharmaceutical composition of any one of claims 38 - 45, comprising 100 mg to 150 mg of a potassium salt of Compound **I** (Form B); and wherein the first solid dispersion comprises 50 mg of Compound **II**; and the second solid dispersion comprises 75 mg or 150 mg of Compound **III** or 100 mg of Compound **III-d**.

55. The pharmaceutical composition of any one of claims 38 - 54, wherein the potassium salt of Compound **I** is substantially crystalline, and wherein each of Compound **II**, Compound **III** and Compound **III-d** are independently substantially amorphous.

56. A pharmaceutical composition comprising:

(a) 115 mg to 140 mg of a potassium salt of Compound **I** (Form B);

(b) 60 mg to 65 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion, and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 90 mg to 95 mg of a second solid dispersion comprising 80 wt% of Compound **III** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion, and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion;

(d) 120 mg to 135 mg of a microcrystalline cellulose;

(e) 15 mg to 25 mg of a croscarmellose sodium; and

(f) 2 mg to 6 mg of magnesium stearate.

57. The pharmaceutical composition of any one of claims 38-55, wherein said potassium salt of Compound **I**, said Compound **II**, and said Compound **III** are present in a ratio of 8:2:3 based on the respective weight of free base Compound **I**: Compound **II**: Compound **III**.

58. A pharmaceutical composition comprising:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (Form B)	20 – 45 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10-30 wt%

59. A pharmaceutical composition comprising:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (Form B)	15 – 45 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III** or Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 40 wt%
microcrystalline cellulose	5 – 50 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 2 wt% based on the total weight of composition	

60. A pharmaceutical composition comprising:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (Form B)	15 – 45 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III** or Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 40 wt%

microcrystalline cellulose	5 – 50 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
magnesium stearate	0.05 – 2 wt%

61. A pharmaceutical composition comprising:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (Form B)	15 – 35 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 - 40 wt%
microcrystalline cellulose	20 – 40 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
magnesium stearate	0.05 – 2 wt%

62. A pharmaceutical composition comprising:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (Form B)	20 – 40 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 – 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	10 - 25 wt%
microcrystalline cellulose	20 – 40 wt%
croscarmellose sodium (CCS)	1 – 10 wt%
magnesium stearate	0.05 – 2 wt%

63. A pharmaceutical composition comprising:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (Form B)	25 - 35 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	10 - 20 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 - 25 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 7 wt%

magnesium stearate	0.05 – 2 wt%

64. A pharmaceutical composition comprising:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (Form B)	27 - 32 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	12 - 17 wt%
solid dispersion containing 80% Compound **III**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	18 - 23 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	3 – 6 wt%
magnesium stearate	0.05 – 1.5 wt%

65. A pharmaceutical composition comprising:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (Form B)	25– 40 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	7 - 15 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	15 – 35 wt%
microcrystalline cellulose	25 – 35 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
magnesium stearate	0.05 – 1.5 wt%

66. A pharmaceutical composition comprising:

Component	**weight % based on the total weight of composition**
potassium salt of Compound **I** (Form B)	15– 40 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	5 - 20 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 – 40 wt%
microcrystalline cellulose	10 – 50 wt%
croscarmellose sodium (CCS)	2 – 7 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 2 wt% based on the total weight of composition	

67. A pharmaceutical composition comprising:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (Form B)	20 - 30 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	8-18 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 - 30 wt%
microcrystalline cellulose	20 – 30 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight of composition	

68. A pharmaceutical composition comprising:

Component	weight % based on the total weight of composition
potassium salt of Compound **I** (Form B)	22 - 32 wt%
solid dispersion containing 80% Compound **II**, 20% hypromellose	10-20 wt%
solid dispersion containing 80% Compound **III-d**, 19.5% hypromellose acetate succinate, and 0.5% sodium lauryl sulfate	20 - 30 wt%
microcrystalline cellulose	20 – 30 wt%
croscarmellose sodium (CCS)	2 – 5 wt%
optionally magnesium stearate in an amount of 0.01 wt% – 1.5 wt% based on the total weight of composition	

69. A single tablet comprising:

(a) 50 mg to 140 mg of a potassium salt of Compound **I** (Form B);

(b) 25 mg to 65 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion, and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 75 mg to 200 mg of a second solid dispersion comprising 80 wt% of Compound **III** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion; and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion

(d) 60 mg to 150 mg of a microcrystalline cellulose;

(e) 5 mg to 25 mg of a croscarmellose sodium; and

(f) 1 mg to 6 mg of magnesium stearate.

70. A single tablet comprising:

(a) 100 mg to 250 mg of a potassium salt of Compound **I** (Form B);

(b) 30 mg to 65 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion, and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 75 mg to 200 mg of a second solid dispersion comprising 80 wt% of Compound **III** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion; and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion.

(d) 85 mg to 215 mg of a microcrystalline cellulose;

(e) 10 mg to 30 mg of a croscarmellose sodium; and

(f) 1 mg to 7 mg of magnesium stearate.

71. A single tablet comprising:

(a) 100 mg to 215 mg of a potassium salt of Compound **I** (Form B);

(b) 30 mg to 65 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion, and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 50 mg to 300 mg of a second solid dispersion comprising 80 wt% of Compound **III-d** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion; and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion;

(d) 85 mg to 215 mg of a microcrystalline cellulose;

(e) 10 mg to 30 mg of a croscarmellose sodium; and

(f) 1 mg to 7 mg of magnesium stearate.

72. A single tablet comprising:

(a) 55 mg to 300 mg of a potassium salt of Compound **I** (Form B);

(b) 30 mg to 130 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion, and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) 50 mg to 300 mg of a second solid dispersion comprising 80 wt% of Compound **III-d** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl sulfate relative to the total weight of the second solid dispersion; and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion

(d) 60 mg to 300 mg of a microcrystalline cellulose;

(e) 7 mg to 25 mg of a croscarmellose sodium; and

(f) optionally 0.05 mg to 6 mg of magnesium stearate.

73. A method of treating cystic fibrosis in a patient comprising orally administering to the patient one or more of the pharmaceutical compositions of any one of claims 38 – 68 or the single tablets of any one of claims 69 – 72.

74. The method of claim 73, wherein one or more of the pharmaceutical compositions or single tablets are administered once daily.

75. The method of claim 73, wherein one or more of the pharmaceutical compositions or single tablets are administered twice daily.

76. The method according to any one of claims 73 - 75, wherein said patient has cystic fibrosis is chosen from patients with F508del/minimal function genotypes, patients with F508del/F508del genotypes, patients with F508del/gating genotypes, and patients with F508del/residual function genotypes.

77. A pharmaceutical composition comprising:

(a) about 128 mg of a potassium salt of Compound **I** (Form B);

(b) about 63 mg of a first solid dispersion comprising 80 wt% Compound **II** relative to the total weight of the first solid dispersion, and 20 wt% of a hypromellose relative to the total weight of the first solid dispersion; and

(c) about 94 mg of a second solid dispersion comprising 80 wt% of Compound **III** relative to the total weight of the second solid dispersion, 0.5 wt% of sodium lauryl

sulfate relative to the total weight of the second solid dispersion; and 19.5 wt% of a hypromellose acetate succinate to the total weight of the second solid dispersion.

78. The pharmaceutical composition of any one of claims 38 - 68, wherein the pharmaceutical composition is a single tablet.

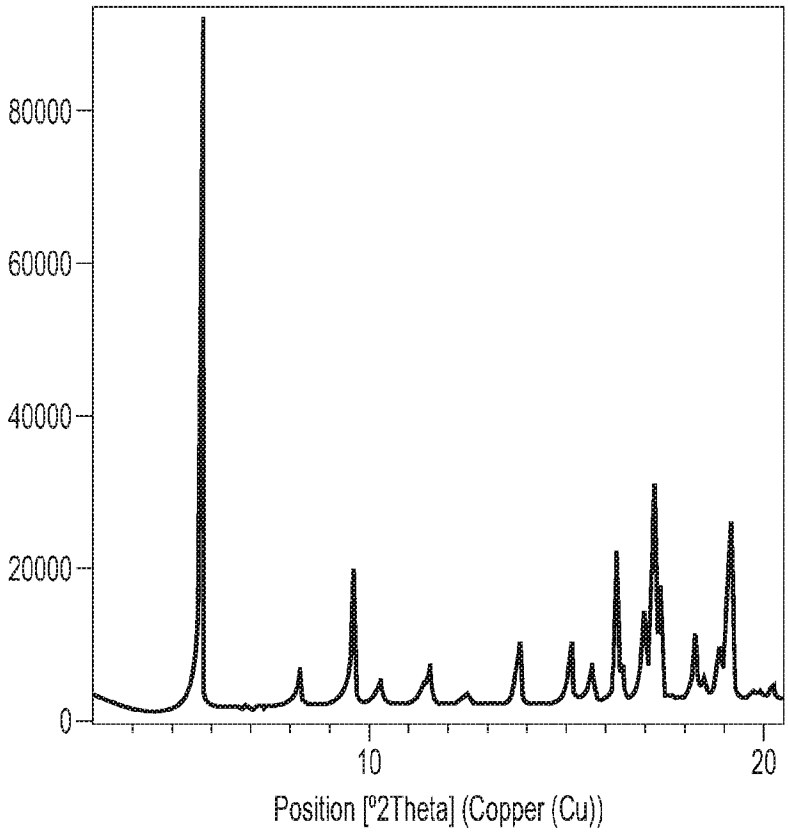

80000
60000
40000
20000
0
10
20
Position [°2Theta] (Copper (Cu))

FIG. 1A

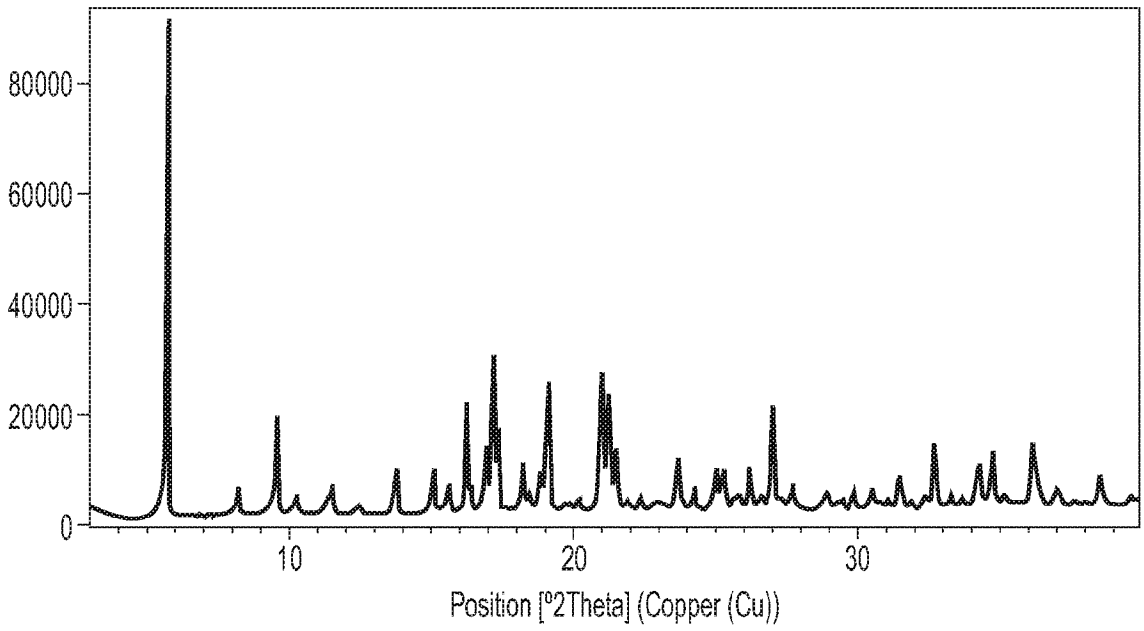

80000
60000
40000
20000
0
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 1B

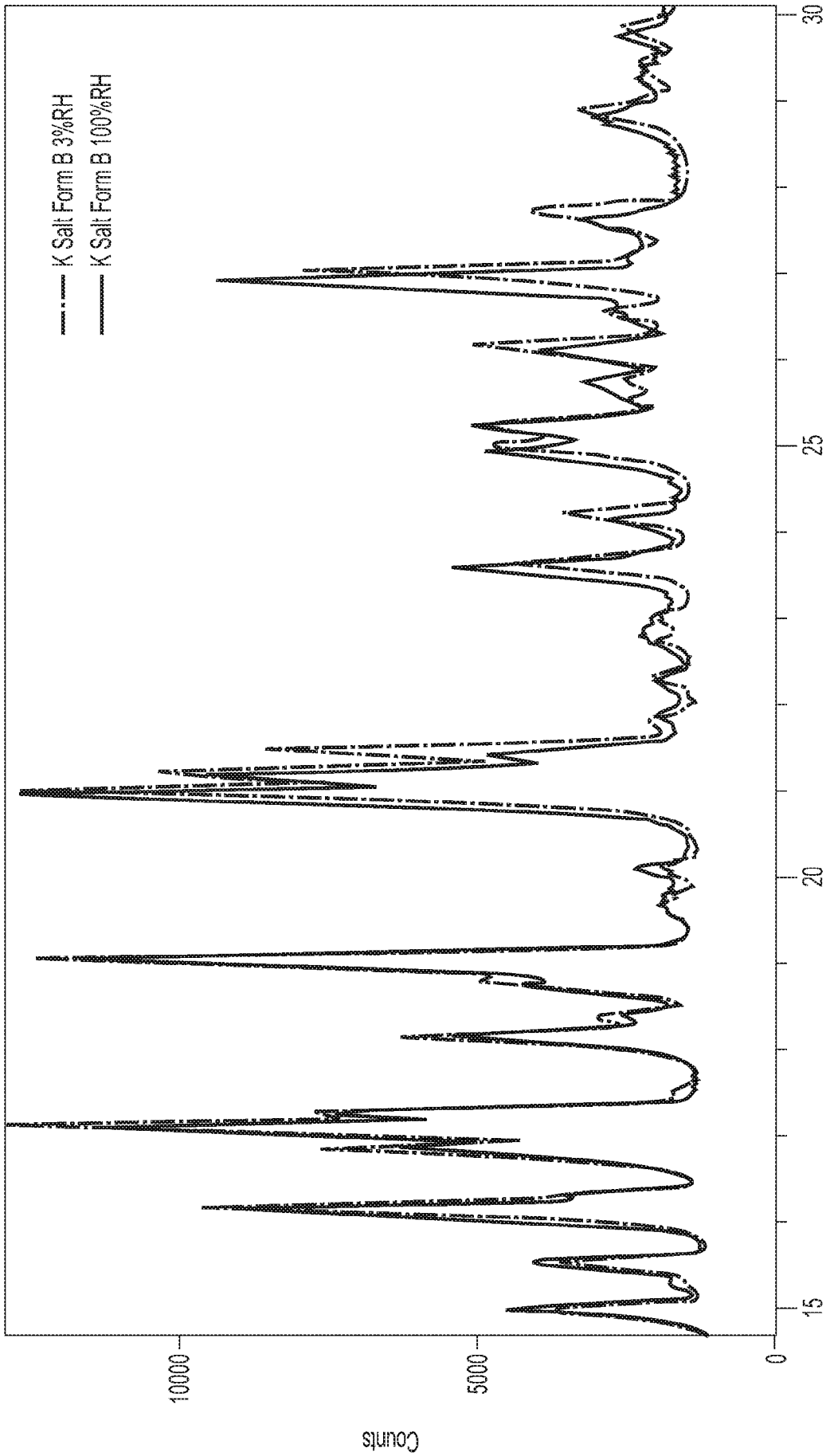

K Salt Form B 3%RH
K Salt Form B 100%RH
Counts
10000
5000
0
15
20
25
30
Position [°2Theta] (Copper (Cu))

FIG. 2

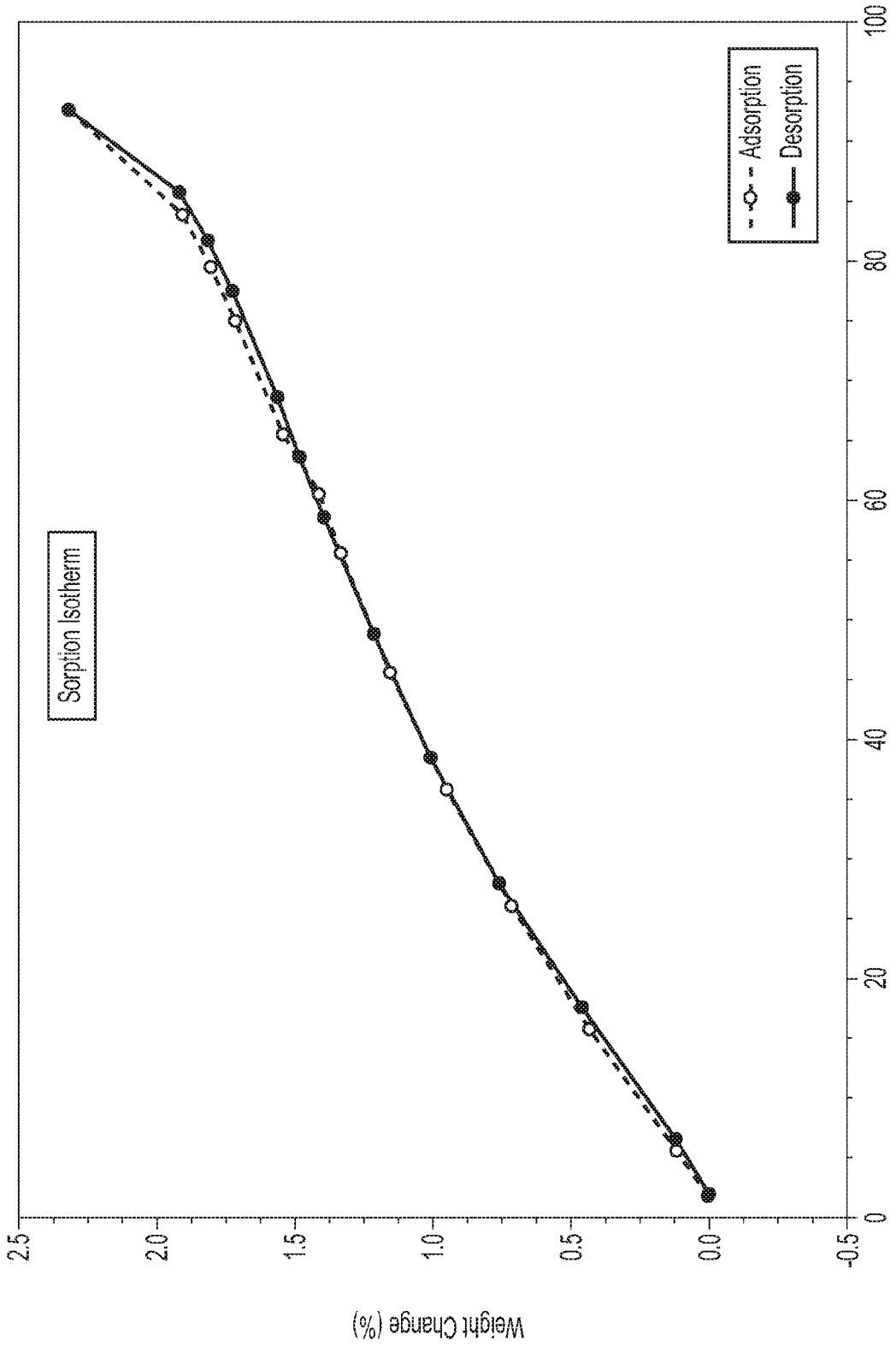

Sorption Isotherm
Adsorption
Desorption
Weight Change (%)
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
0
20
40
60
80
100
Sample Sensor RH (%)

FIG. 3

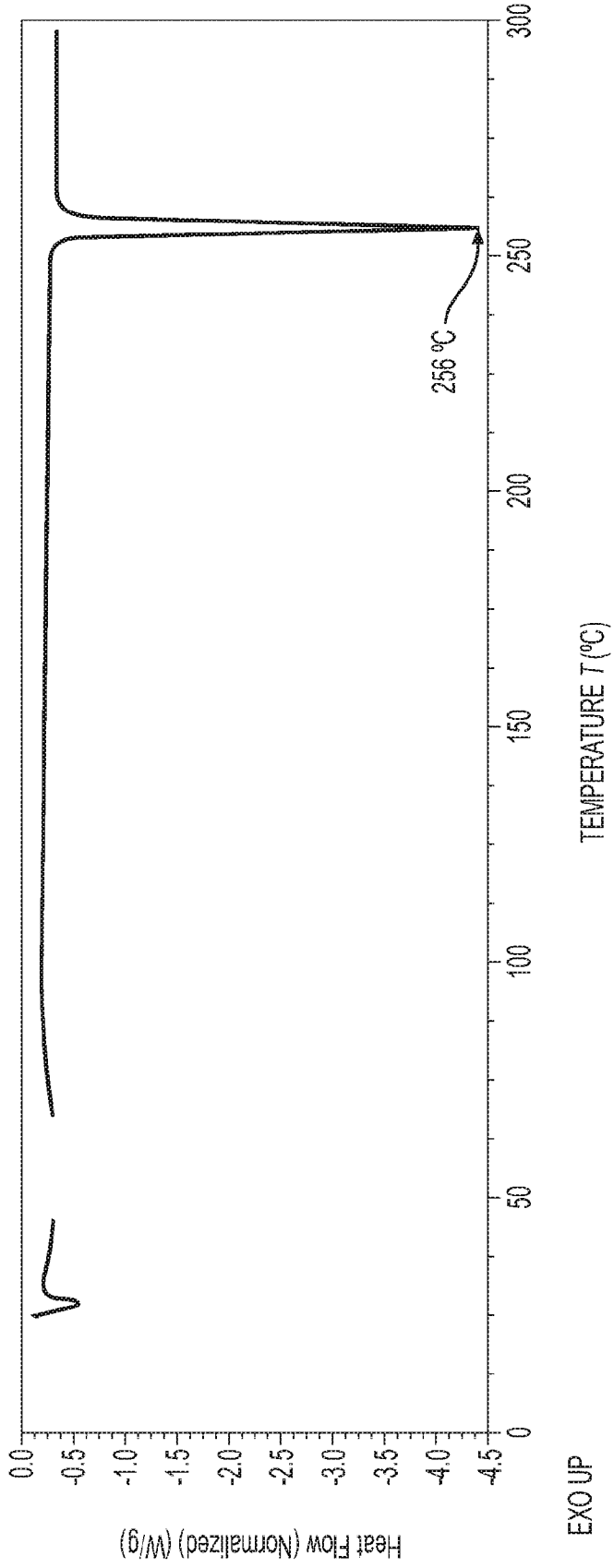

256 °C
TEMPERATURE T (°C)
Heat Flow (Normalized) (W/g)
EXO UP
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
0
50
100
150
200
250
300

FIG. 4

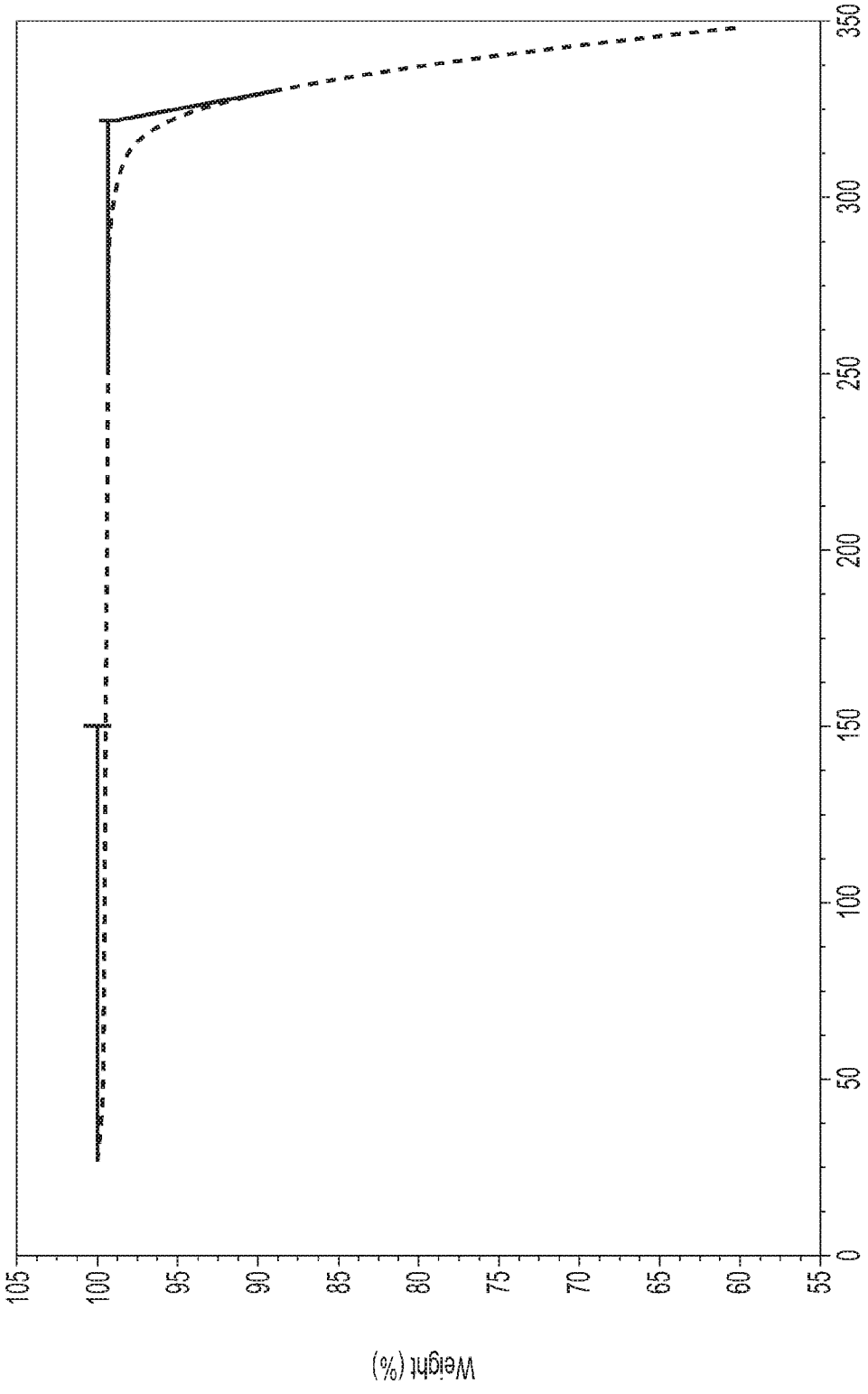

105
100
95
90
85
80
75
70
65
60
55
Weight (%)
0
50
100
150
200
250
300
350
TEMPERATURE T (°C)

FIG. 5

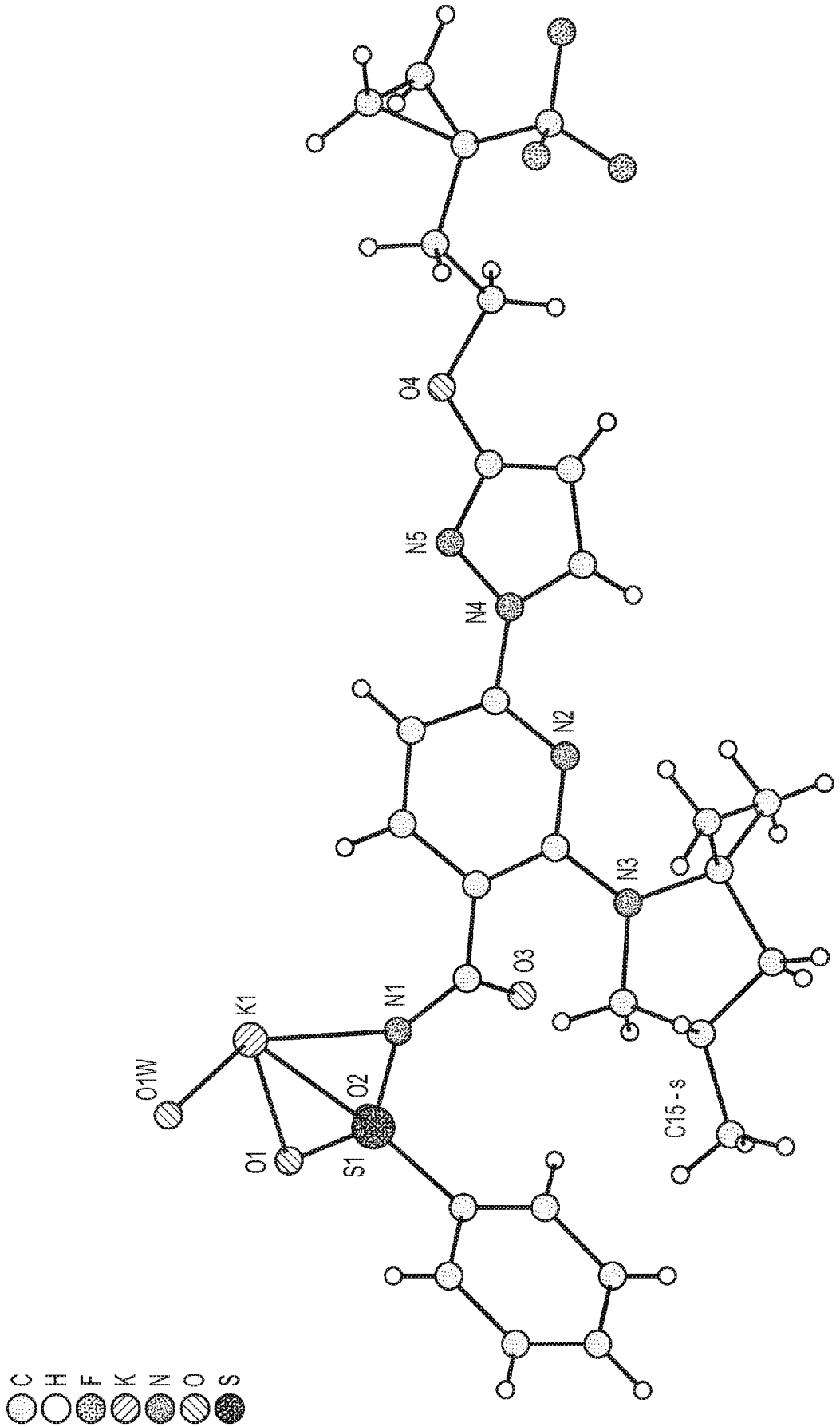


FIG. 6

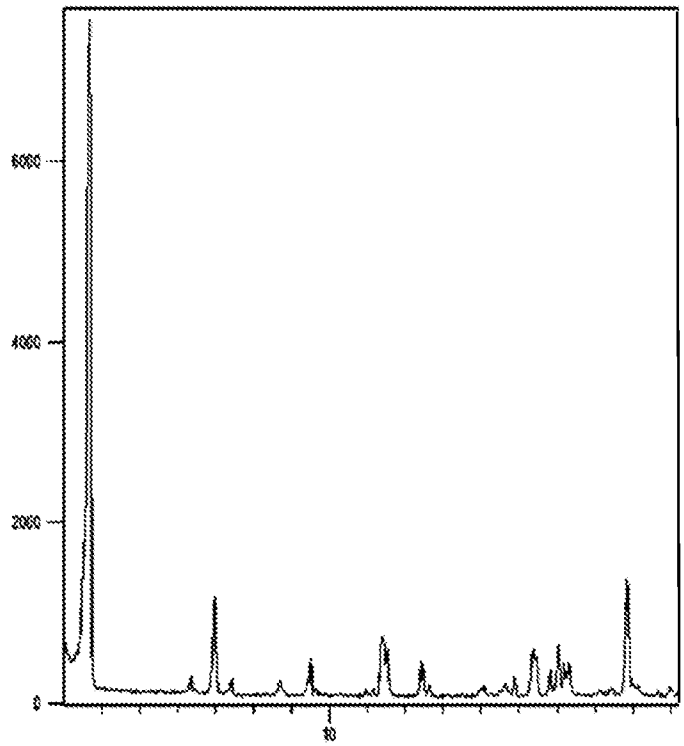


FIG. 7A

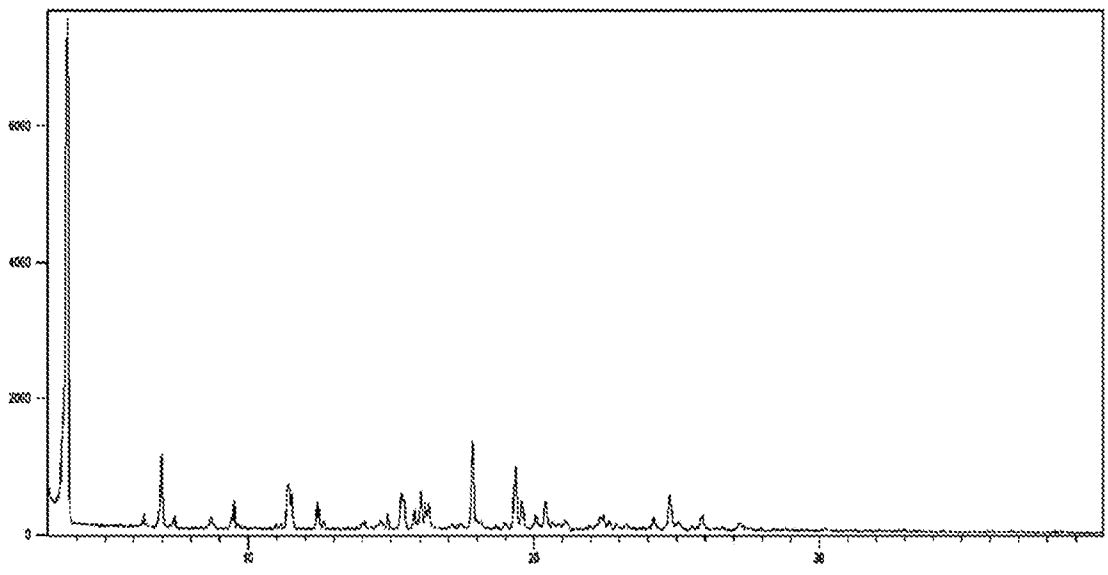


FIG. 7B

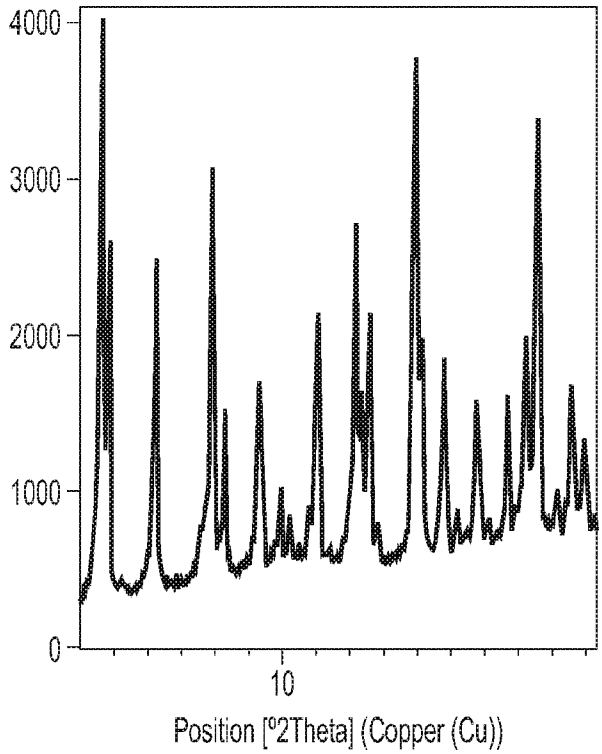

4000
3000
2000
1000
0
10
Position [°2Theta] (Copper (Cu))

FIG. 8A

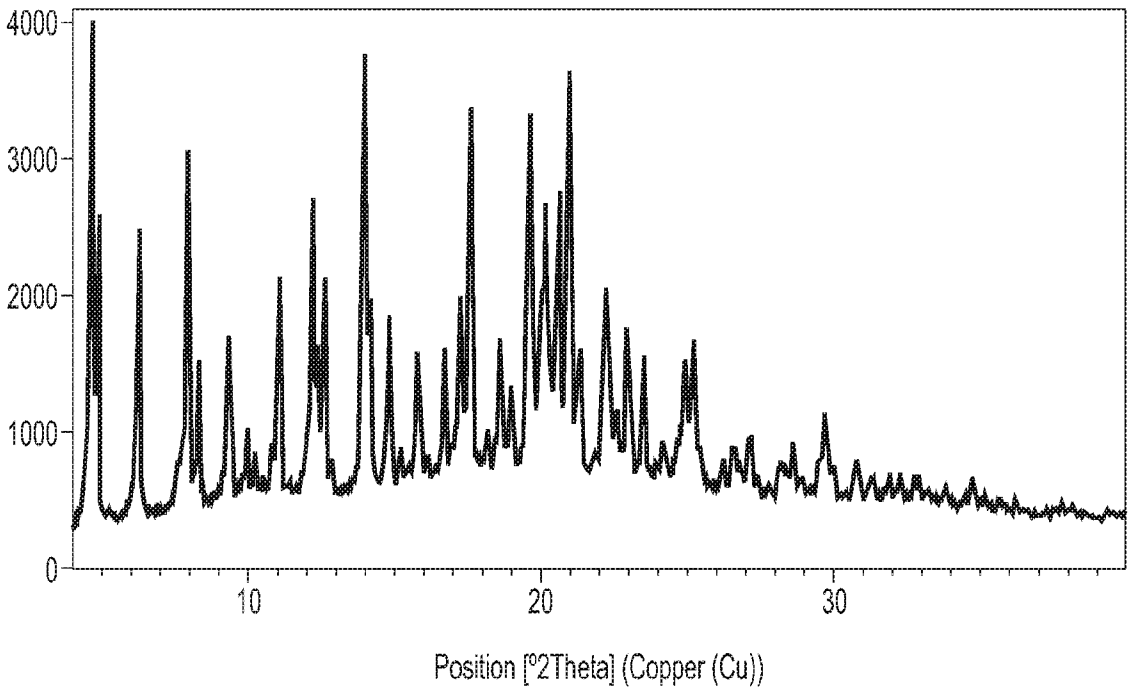

4000
3000
2000
1000
0
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 8B

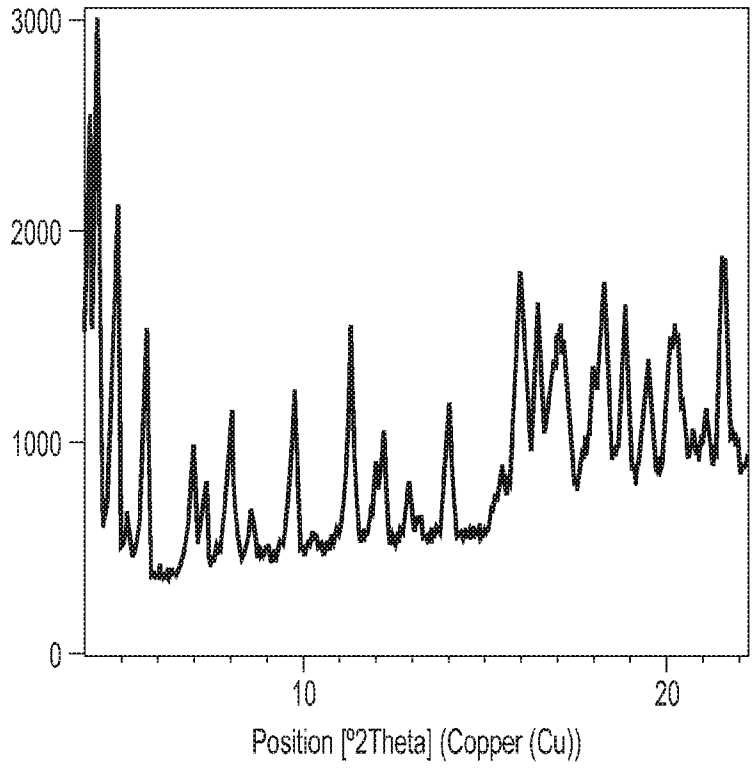

3000
2000
1000
0
10
20
Position [°2Theta] (Copper (Cu))

FIG. 9A

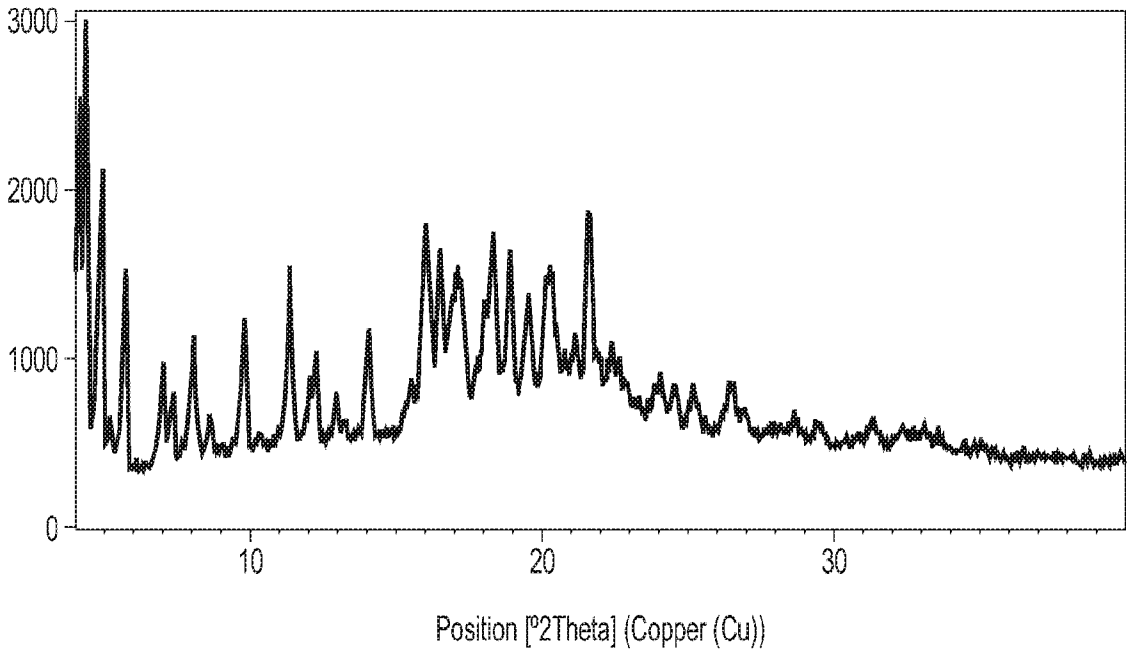

3000
2000
1000
0
10
20
30
Position [°2Theta] (Copper (Cu))

FIG. 9B

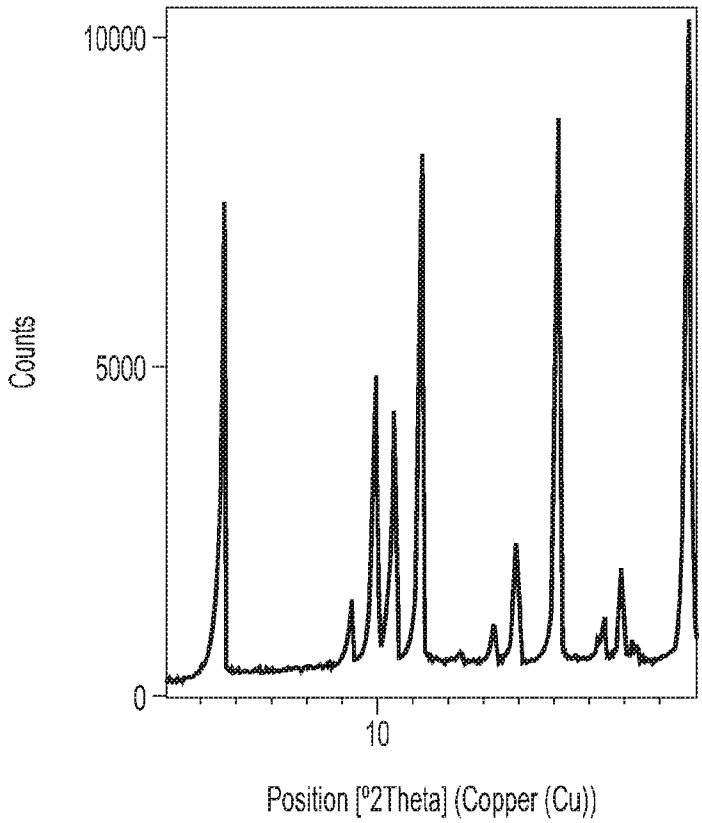


FIG. 10A

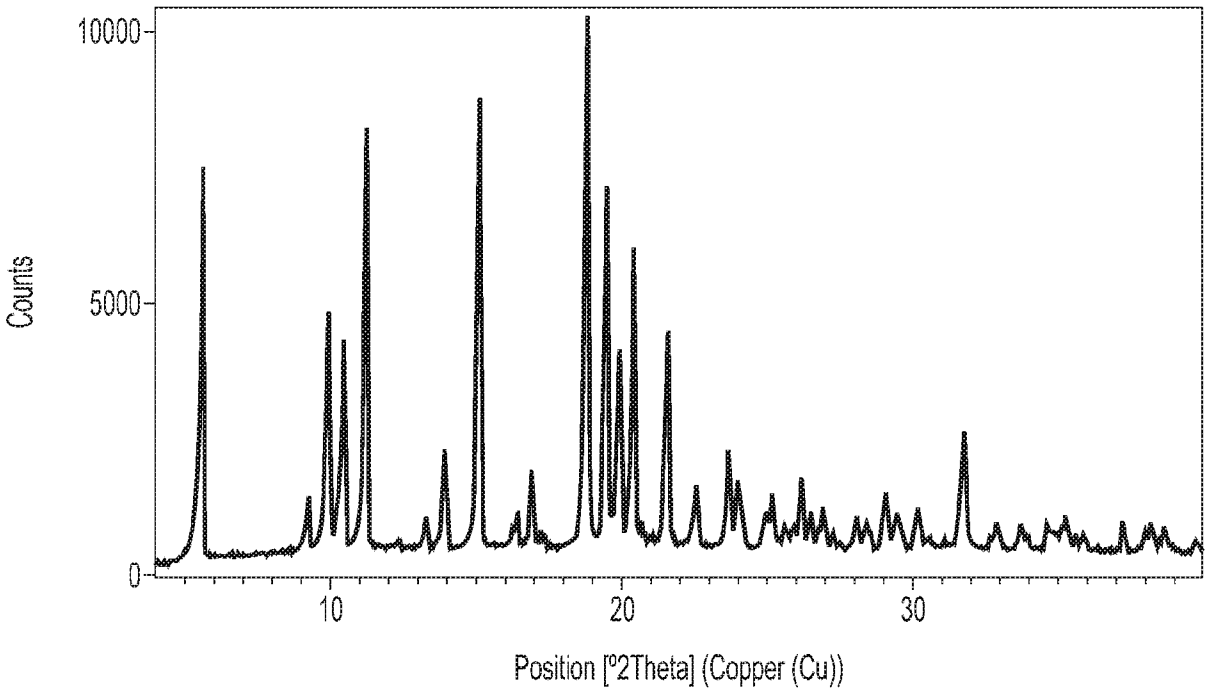


FIG. 10B

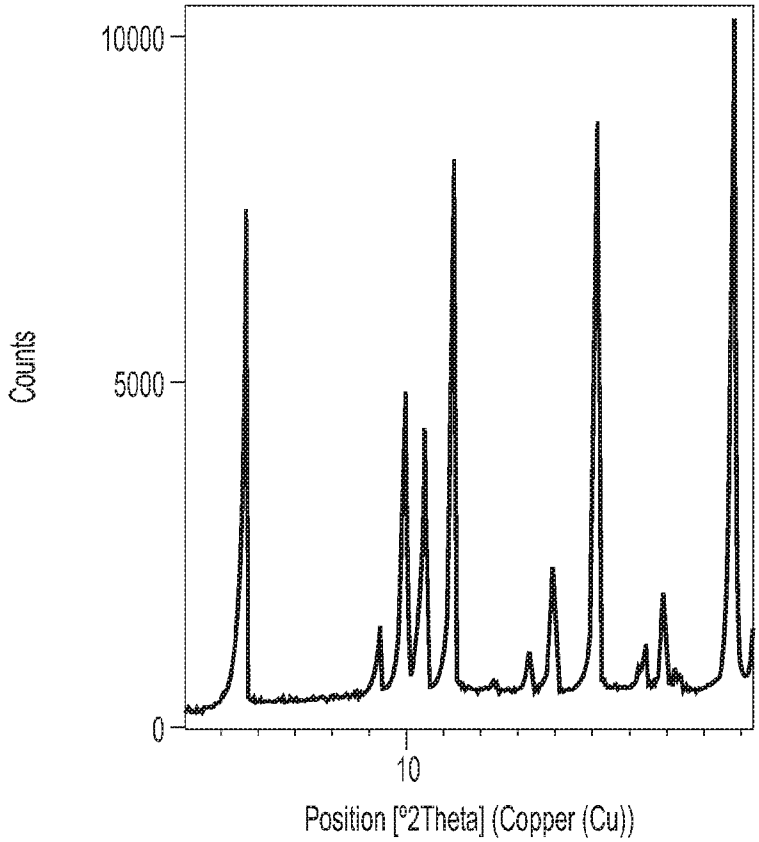


FIG. 11A

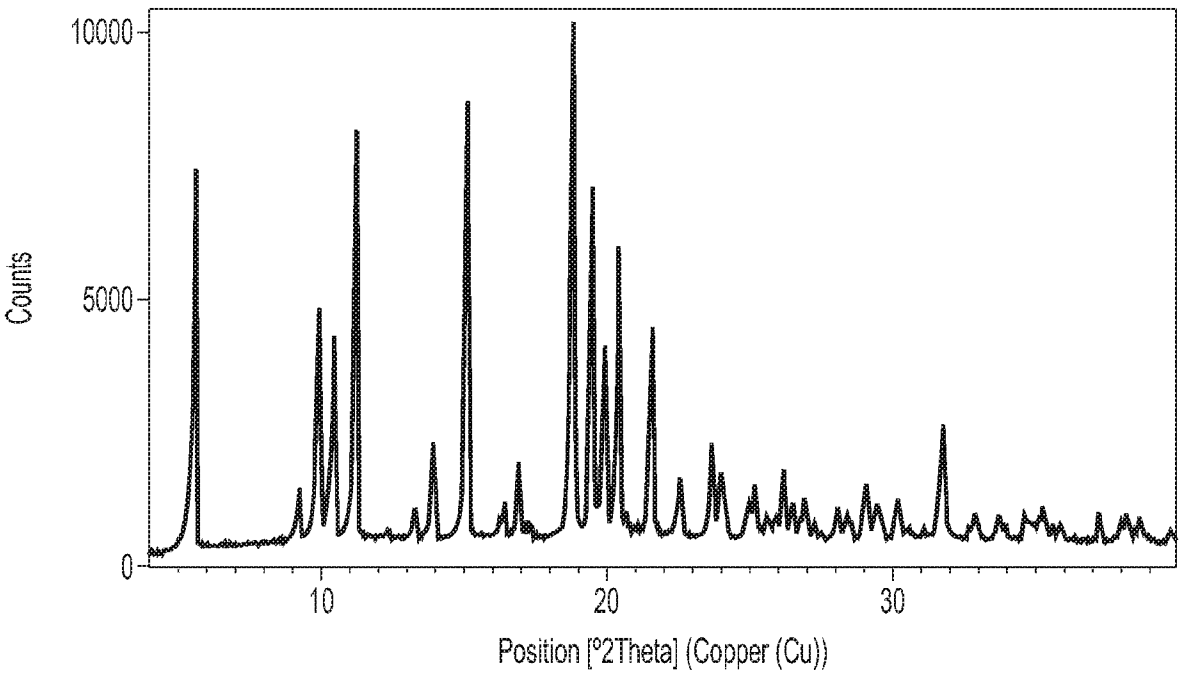


FIG. 11B

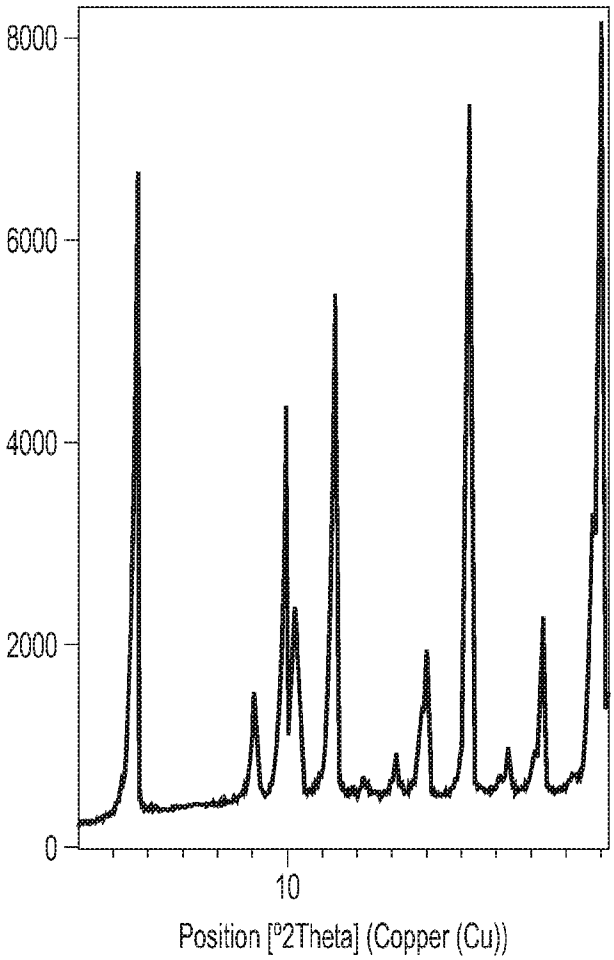


FIG. 12A

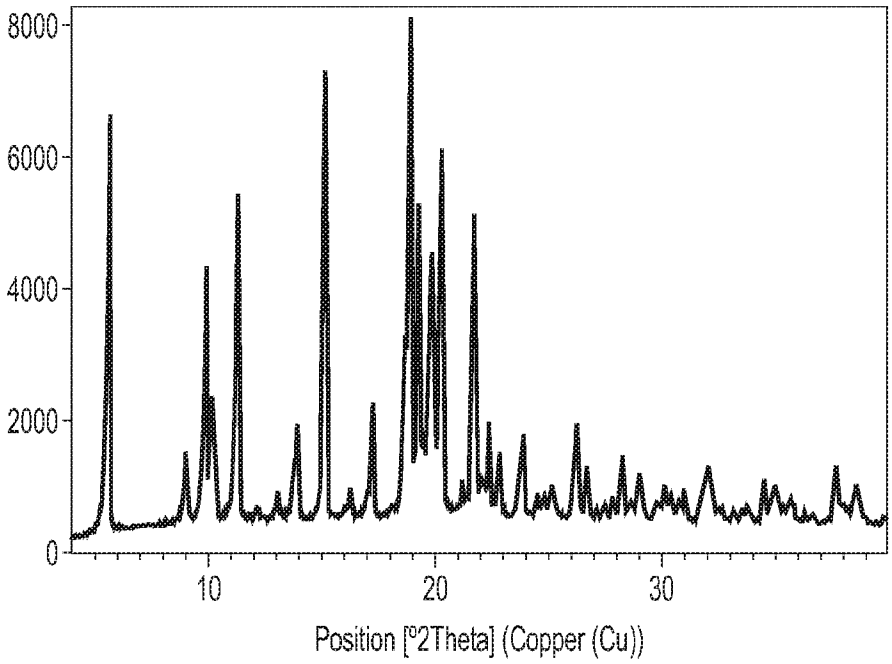


FIG. 12B

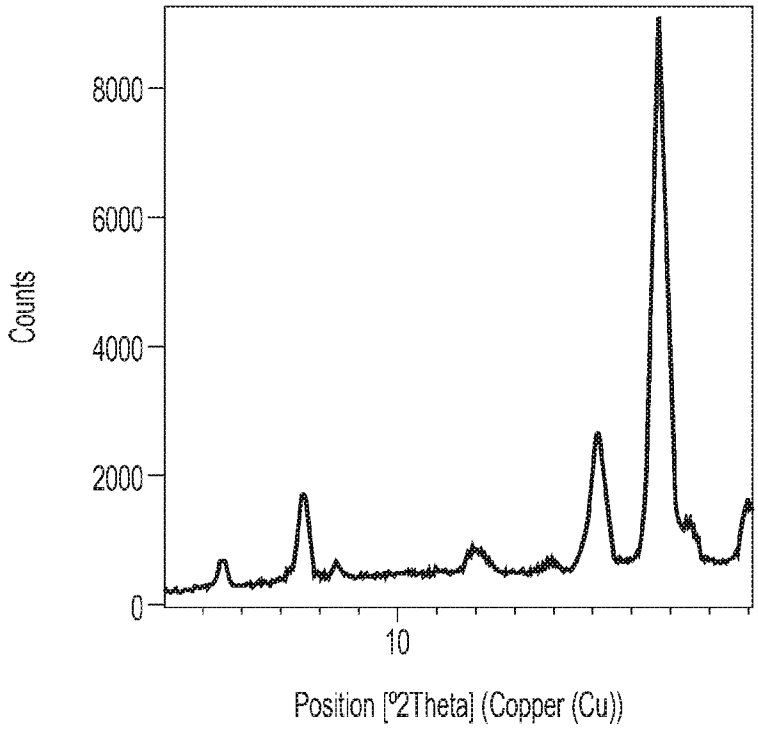


FIG. 13A

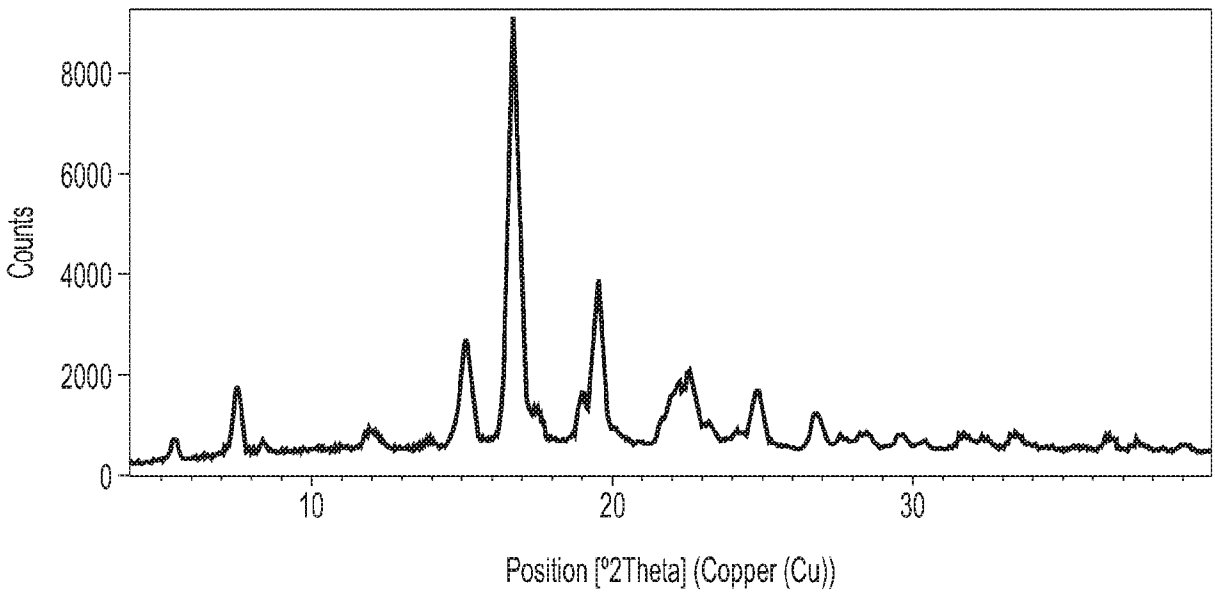


FIG. 13B

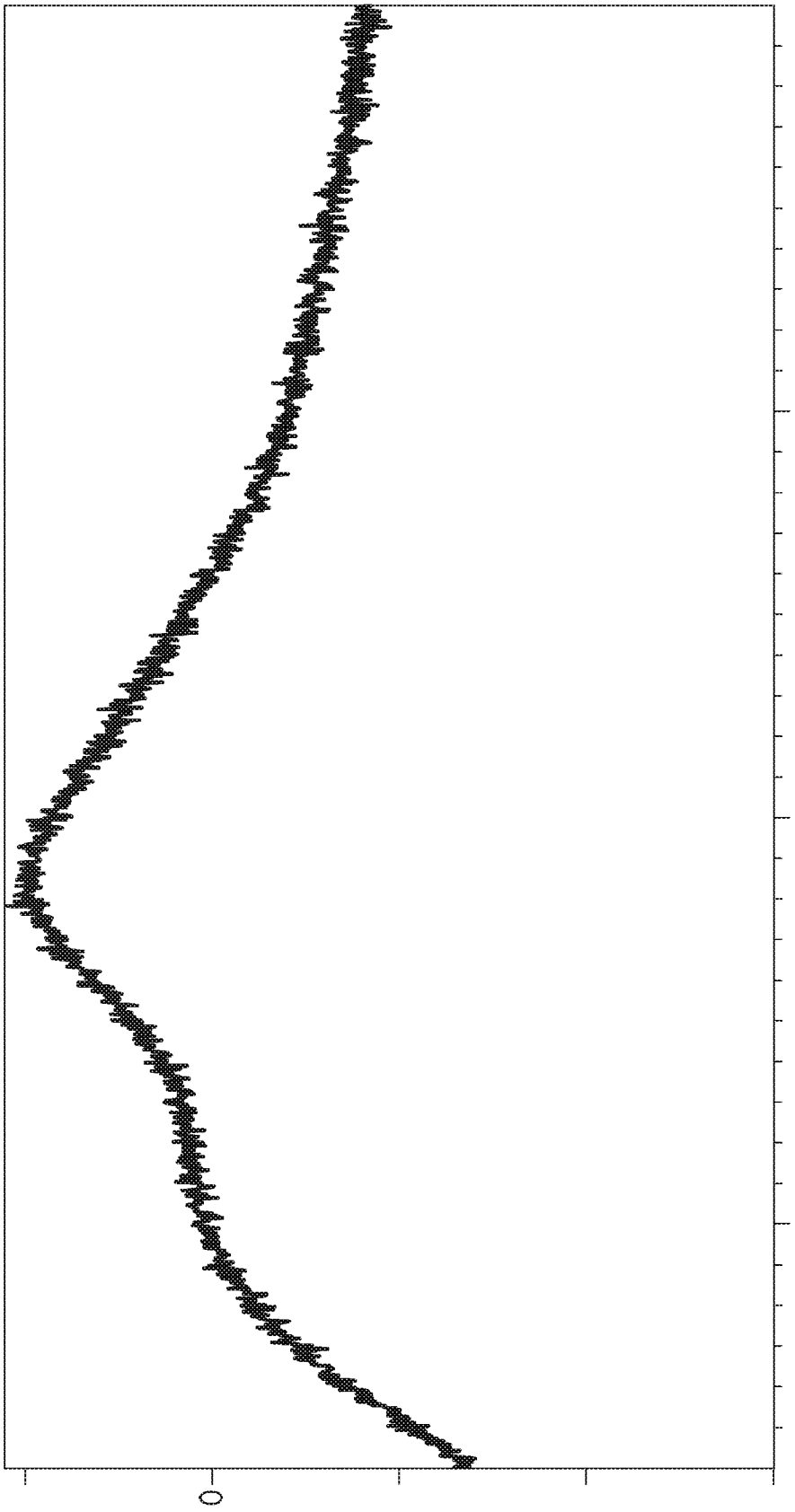


FIG. 14

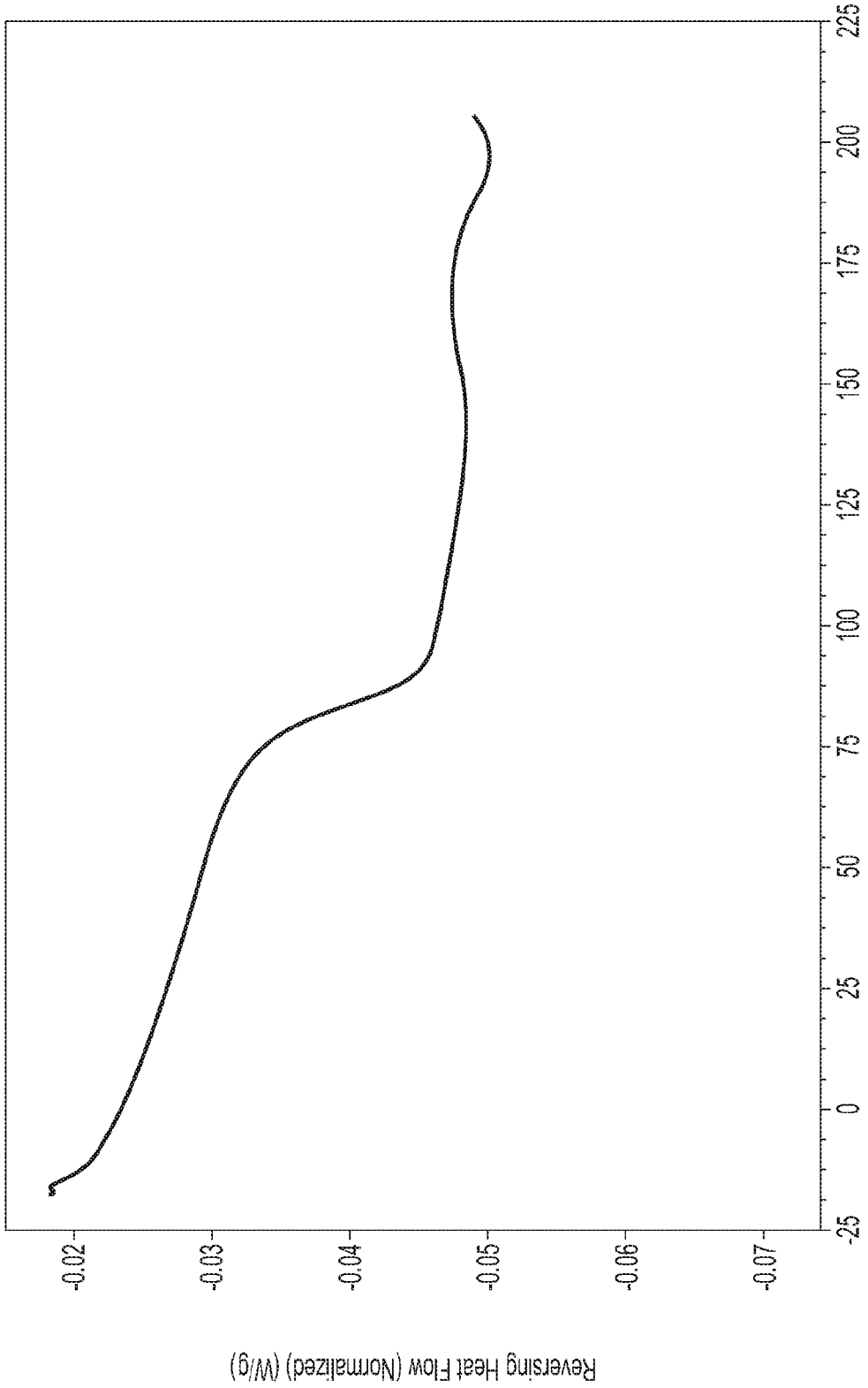

Reversing Heat Flow (Normalized) (W/g)
-0.02
-0.03
-0.04
-0.05
-0.06
-0.07
-25
0
25
50
75
100
125
150
175
200
225
Temperature (°C)

FIG. 15

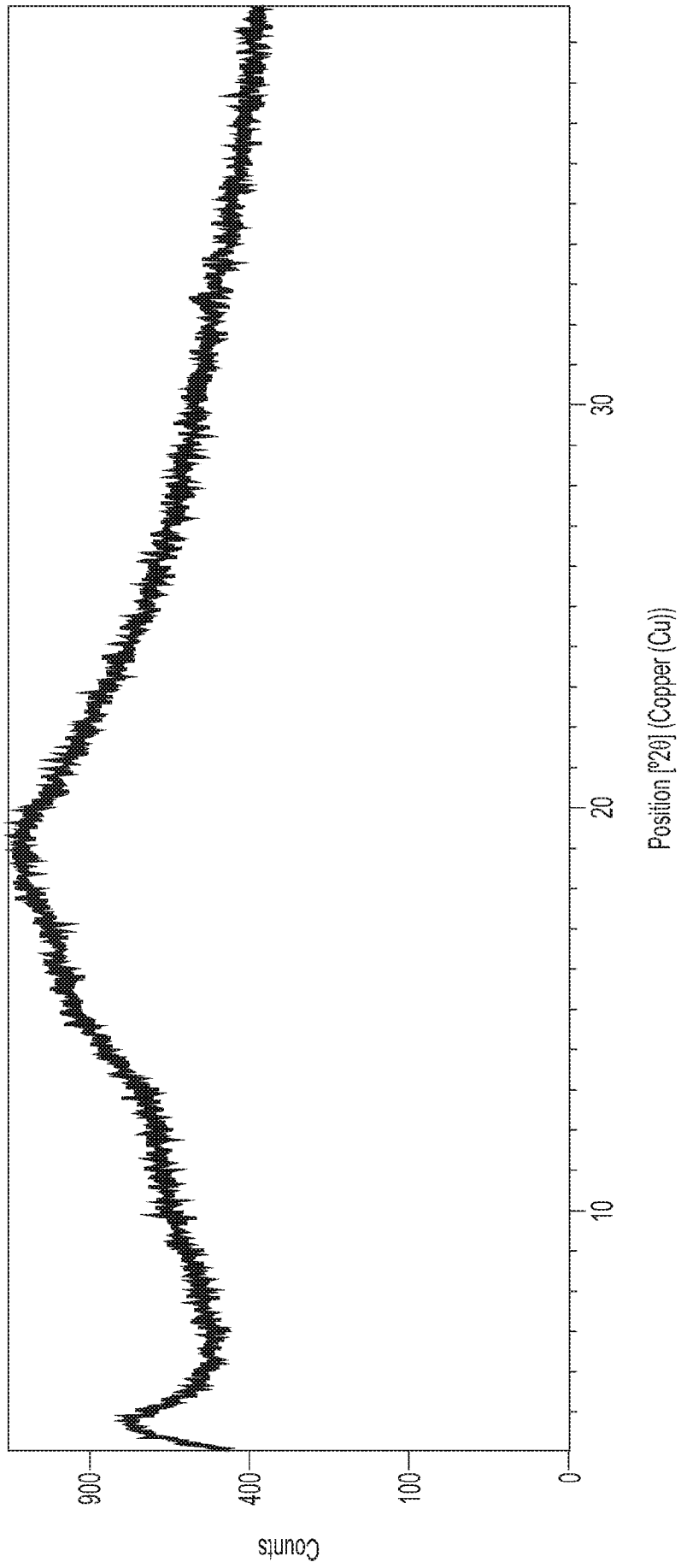


FIG. 16

FIG. 17

Mutation cDNA Name	Mutation Protein Name	Mutation Legacy Name
c1A>G		M1V
c.54-5940_273+10250del21kb	pSer18ArgfsX16	CFTRdele2,3
c.91C>T	p.Arg31Cys	R31C
c.115C>T	p.Gin39X	Q39X
c.137C>A	p.Ala46Asp	A460
c.165-1G>A	No protein name	297-1G->A
c.166G>A	p.Glu56Lys	E56K
c.174_175insA	p.Arg59LysfsX10	306insA
c.178G>T	p.Glu60X	E60X
c.200C>T	p.Pro67leu	P67L
c.220C>T	p.Arg74Trp	R74W
c.223C>T	p.Arg75X	R75X
c.224G>A	p.Arg75Gln	R75Q
c.254G>A	p.Gly85Glu	G85E
c.262_263delTT	p.Leu88llefsX22	394delTT
c.273+1G>A	No protein name	405+lG->A
c.274-1G>A	No protein name	406-lG->A
c.274G>A	p.Glu92Lys	E92K
c.274G>T	p.Glu92X	E92X
c.292C>T	p.Gln98X	Q98X
c.313delA	p.llel05SerfsX2	444delA
c.325_327delTATinsG	p.Tyrl09GlyfsX4	457TAT->G
c.328G>C	p.Asp110His	D110H
c.349C>T	p.Arg117Cys	R117C
c.350G>A	p.Arg117His	R117H
c.366T>A	p.Tyr122X	Y122X
c.442delA	p.llel48LeufsX5	574delA
c.443T>C	p.lle148Thr	I148T
c.489+1G>T	No protein name	621+1G->T
c.531delT	p.llel77MetfsX12	663delT

Mutation cDNA Name	Mutation Protein Name	Mutation Legacy Name
c.532G>A	p.Glyl78Glu	G178R
c.543_546delTAGT	p.Leu183PhefsX5	675del4
c.579+1G>T	No protein name	711+1G->T
c.579+3A>G	No protein name	711+3A->G
c.579+5G>A	No protein name	711+5G->A
c.580-1G>T	No protein name	712-1G->T
C.59SOT	p.Hisl99Tyr	H199Y
C.613CM	p.Pro205Ser	P205S
c.617T>G	p.Leu20GTrp	L206W
C.6580T	p.Gln220X	Q220X
c.580T>G	p.Leu227Arg	L227R
c.720_741delAGGG AGAATGATGATGAA GTAC	p.Gly241GlufsX13	852del22
c.828C>A	p.Cys276X	C276X
c.948delT	p.Phe316LeufsXl 2	1078delT
c.988G>T	p.Gly330X	G330X
c.1000C>T	p.Arg334Trp	R334W
c.1007T>A	p.lle336Lys	I336K
c.1013C>T	p.Thr338Ele	T338I
c.1021T>C	p.Ser341Pro	S341P
c.1022_1023insTC	p.Phe342HisfsX2 8	1154insTC
c.1040G>A	p.Arg347His	R347H
c.1040G>C	p.Arg347Pro	R347P
c.1055G>A	p.Arg352Gln	R352Q
c.[1075C>A; 10799C> A]	p.[Gln359Lys;Thr 360Lys]	Q359K/T360K
c.1081delT	p.Trp361GlyfsX8	1213delT
c.1116+1G>A	No protein name	1248+1G->A
c.1127_1128insA	p.Gln378AlafsX4	1259insA
c.1153_1154insAT	p.Asn386llefsX3	1288insTA
c.1202G>A or c.1203G>A	p.Trp401X	W401X
c.1209+1G>A	No protein name	1341+1G->A

Mutation cDNA Name	Mutation Protein Name	Mutation Legacy Name
c.1210-12[5]	No protein name	5T
c.1210-12(7]	No protein name	7T
c.1240C>T	p.Gln414X	Q414X
c.1329_1330insAGAT	p.Ile444ArgfsX3	1461ins4
c.1340delA	p.Lys447ArgfsX2	1471delA
c.1364C>A	p.Ala455Glu	A455E
c.1393-1G>A	No protein name	1525-1G->A
c.1397C>A or c.1397C>G	p.Ser466X	S466X
c.1400T>C	p.Leu467Pro	L467P
c.1408A>G	p.Met470Val	M470V
c.1418delG	p.Gly473GlufsX54	1548delG
c.1466C>A	p.Ser489X	S489X
c.1475C>T	p.Ser492Phe	S492F
c.1477C>T	p.Gln493X	Q493X
c.1519_1521delATC	' p.Ile507del	I507del
c.1521_1523delCTT	p.Phe508del	F508del
c.1545_1546delTA	p.Tyr515X	1677delTA
c.1558G>T	p.Val520Phe	V520F
c.1573C>T	p.Gln525X	Q525X
c.1585-8G>A	No protein name	1717-8G->A
c.1585-1G>A	No protein name	1717-1G->A
c.1624G>T	p.Gly542X	G542X
c.1645A>C or c.1G47T>G	p.Ser549Arg	S549R
c.1646G>A	p.Ser549Asn	S549N
c.1650delA	p.Gly551ValfsX8	1782delA
c.1651G>A	p.Gly551Ser	G551S
c.1652G>A	p.Gly551Asp	G551D
c.1654C>T	p.Gln552X	Q552X
c.1657C>T	p.Arg553X	R553X
c.1673T>C	p.Leu558Ser	L558S
c.1675G>A	p.Ala559Thr	A559T

Mutation cDNA Name	Mutation Protein Name	Mutation Legacy Name
c.1679G>A	p.Arg560Lys	R560K
c.1679G>C	p.Arg560Thr	R560T
c.1679+1G>C	No protein name	1811+1G->C
c.1679+1.6kbA>G	No protein name	1811+1.6kbA->G
c.1680-1G>A	No protein name	1812-1G->A
c.1682C>A	p.Ala561Glu	A561E
c.1692delA	p.Asp565MetfsX7	1824delA
c.1705T>G	p.Tyr569Asp	Y569D
c.1727G>C	p.Gly576Ala	G576A
c.1736A>G	p.Asp579Gly	D579G
c.1753G>T	p.Glu585X	E585X
c.1766+1G>A	No protein name	1898+1G->A
c.1766+1G>C	No protein name	1898+1G->C
c.1766+3A>G	No protein name	1898+3A->G
c.1841A>G	p.Asp614Gly	D614G
c.1923_1931del9ins	pSer641ArgfsX5	2055del9->A
c.1973_1985dell3insAGAAA	p.Arg658 LysfsX4	2105-2117dell3insAGAAA
c.1986_1989delAACT	p.Thr663ArgfsX8	2118del4
c.2002C>T	p.Arg668Cys	R668C
c.2012delT	p.Leu671X	2143delT
c.2051_2052delAAinsG	p.Lys684SerfsX38	2183AA->G+
c.2051_2052delAAinsG	p.Lys684SerfsX38	2183delAA->G#
c.2052_2053insA	p.Gln685Th rfsX4	2184insA
c.2052delA	p.Lys684AsnfsX38	2184delA
c.21250T	p.Arg709X	R709X
c.2128A>T	p.Lys710X	K710X
c.2175_2176insA	p.Glu726ArgfsX4	2307insA
c.2195T>G	p.Leu732X	L732X
c.2215delG	p.Va!739TyrfsX16	2347delG

Mutation cDNA Name	Mutation Protein Name	Mutation Legacy Name
c.2260G>A	p.Val754Met	V754M
c.2290C>T	p.Arg764X	R764X
c.2353C>T	p.Arg785X	R785X
c.2374C>T	p.Arg792X	R792X
c.2424_2425insAT	p.Ser809IlefsX13	2556insAT
c.2453delT	p.Leu818TrpfsX3	2585delT
c.2462_2463deIGT	p.Ser821ArgfsX4	No legacy name
c.2464G>T	p.Glu822X	E822X
c.2490+1G>A	No protein name	2622+lG->A
c.2491G>T	p.Glu831X	E831X
c.2537G>A or c.2538G>A	p.Trp846X	W846X
c.25470A	p.Tyr849X	Y849X
c.2551C>T	p.ArgSSIX	R851X
c.2583delT	p.Phe861LeufsX3	2711delT
c.2657+2_2657+3insA	No protein name	2789+2insA
c.2657+5G>A	No protein name	2789+5G->A
c.2658-lG>C	No protein name	2790-lG->C
c.2668C>T	p.Gln890X	Q890X
c.2735C>A	p.Ser912X	S912X
c.2737_2738insG		2869insG
c.2739T>A	p.Tyr913X	Y913X
c.2764_2765insAG	p.Val922GlufsX2	2896insAG
c.2780T>C	p.Leu927Pro	L927P
c.2834C>T	p.Ser945Leu	S945L
c.2875delG	p.Ala959HisfsX9	3007delG
c.2908G>C	p.Gly970Arg	G970R
c.2930C>T	p.Ser977Phe	S977F
c.2988G>A	No protein name	3120G->A
c.2988+1G>A	No protein name	3120+1G->A
c.2989-977_3367+248del	No protein name	3121-977_3499+248del2515
c.2989-1G>A	No protein name	3121-1G->A
c.2991G>C	p.Leu997Phe	L997F

Mutation cDNA Name	Mutation Protein Name	Mutation Legacy Name
c.3002_3003delTG	p.Vall001AspfsX45	3132delTG
c.3080T>C	p.Ilel027Thr	I1027T
c.3140-26A>G	No protein name	3272-26A->G
c.3154T>G	p.Phel052Val	F1052V
c.3160C>G	p.Hisl054Asp	H1054D
c.3181G>C	p.Glyl061Arg	G1061R
c.3194T>C	p.Leul065Pro	L1065P
c.3196C>T	p.Argl066Cys	R1066C
c.3197G>A	p.Arg!066His	R1066H
c.3205G>A	p.Glyl069Arg	G1069R
c.3208C>T	p.Argl070Trp	R1070W
c.3209G>A	p.Argl070Gln	R1070Q
c.3222T>A	p.Phel074Leu	F1074L
c.3230T>C	p.Leul077Pro	L1077P
c.3266G>A	p.Trpl089X	W1089X
c.3276C>A or c.3276C>G	p.Tyrl092X	Y1092X
c.3302T>A	p.MetllOlLys	M1101K
c.3310G>T	p.Glull04X	E1104X
c.3454G>C	p.Aspll52His	D1152H
c.3472C>T	p.Argll58X	R1158X
c.3484C>T	p.Argll62X	R1162X
c.3485G>T	p.Argll62Leu	R1162L
c.3528delC	p.Lysll77SerfsXl5	3659delC
c.3535_3536insTCAA	p.Thrll79llefsXl7	3667ins4
c.3587C>G	p.Serll96X	S1196X
c.3605delA	p.Aspl202AlafsX9	3737delA
c.3611G>A or c.3612G>A	p.Trpl204X	W1204X
c.3659delC	p.Thrl220LysfsX8	3791delC
c.3691delT	p.Serl231ProfsX4	3821delT
c.3700A>G	p.Ilel234Val	11234V

Mutation cDNA Name	Mutation Protein Name	Mutation Legacy Name
c.3705T>G	p.Serl235Arg	S1235R
c.3717+12191C>T	No protein name	3849+lOkbC->T
c.371S-1G>A	No protein name	3850-lG->A
c.3731G>A	p.Glyl244Glu	G1244E
c.3744delA	p. Lys1250ArgfsX9	3876delA
c.3752G>A	p.Ser1251Asn	S1251N
c.3763T>C	p.Ser1255Pro	S1255P
c.37640A	p.Ser1255X	S1255X
c.3773_3774insT	p.Leu1258PhefsX7	3905insT
c.3808G>A	p.Aspl270Asn	D1270N
c.3346G>A	p.Trpl2S2X	W1282X
c.3873+lG>A	No protein name	4005+lG->A
c.3883delA	p.lle1295PhefsX33	4015delA
c.3884_3885insT	p.Serl297PhefsX5	4016insT
c.3909C>G	p.Asnl303Lys	N1303K
c.3937C>T	p.Glnl313X	Q1313X
c.3964-78_4242+577del	NULL	CFTRdele22,23
c.4046G>A	p.Glyl349Asp	G1349D
c.4077_4080delTGTTinsAA	No protein name	4209TGTT->AA
c.4111G>T	p.Glul371X	E1371X
c.4196_4197delTC	p.Cysl400X	4326delTC
c.4234C>T	p.Glnl412X	Q1412X
c.4242+lG>T	No protein name	4374+lG->T
c.4251delA	p.Glul418ArgfsX14	4382delA
c.4296_4297insGA	p.Serl435GlyfsXl4	4428insGA

FIG. 18

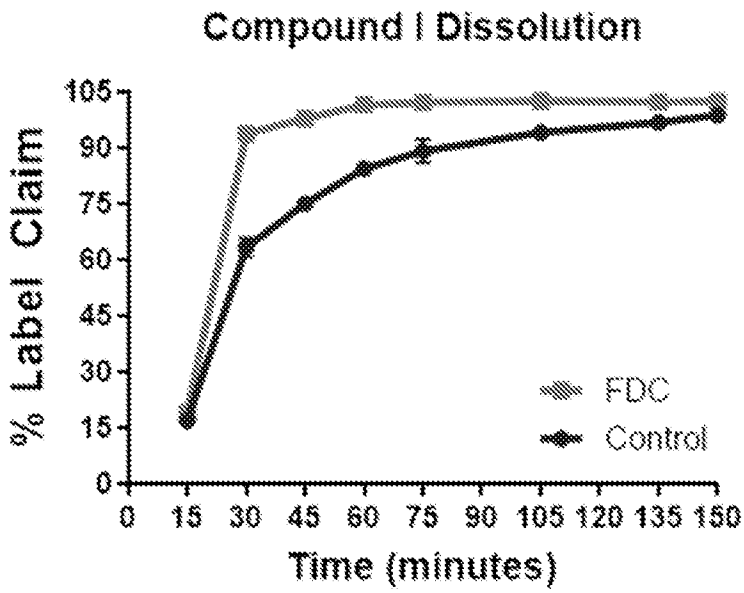

Compound I Dissolution
% Label Claim
105
90
75
60
45
30
15
0
0 15 30 45 60 75 90 105 120 135 150
Time (minutes)
FDC
Control

FIG. 19

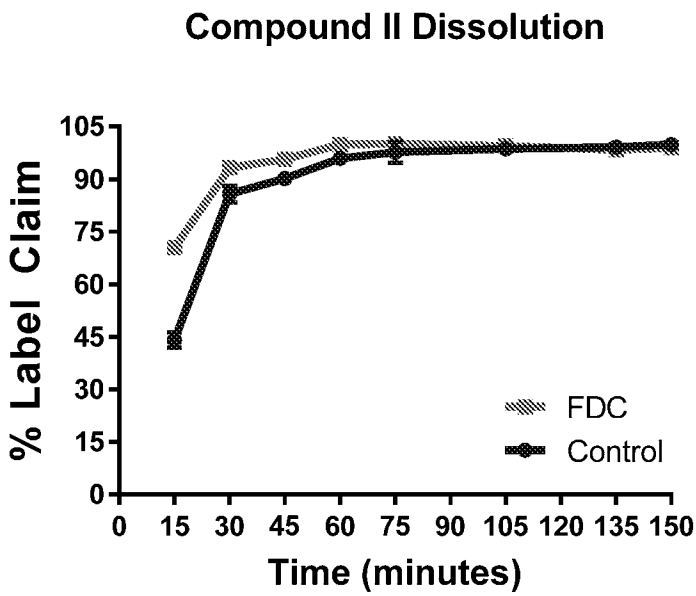

Compound II Dissolution
% Label Claim
105
90
75
60
45
30
15
0
0 15 30 45 60 75 90 105 120 135 150
Time (minutes)
FDC
Control

FIG. 20

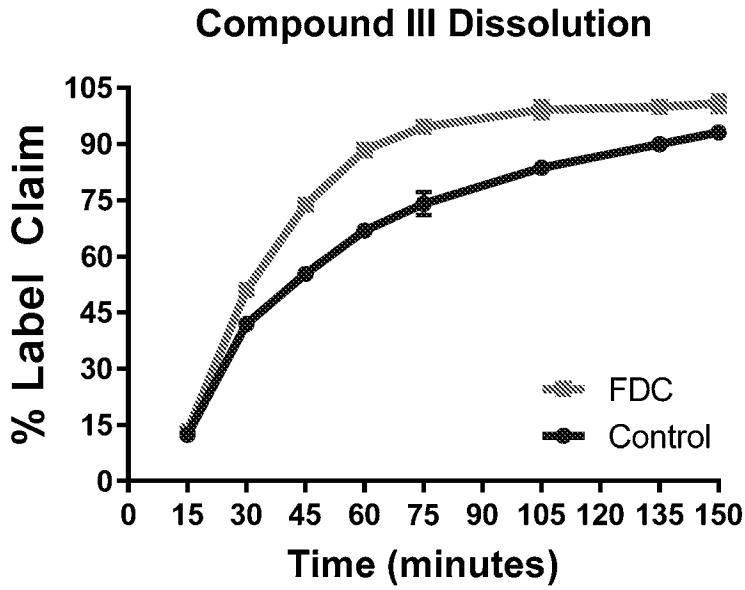

Compound III Dissolution
% Label Claim
105
90
75
60
45
30
15
0
0 15 30 45 60 75 90 105 120 135 150
Time (minutes)
FDC
Control

FIG. 21

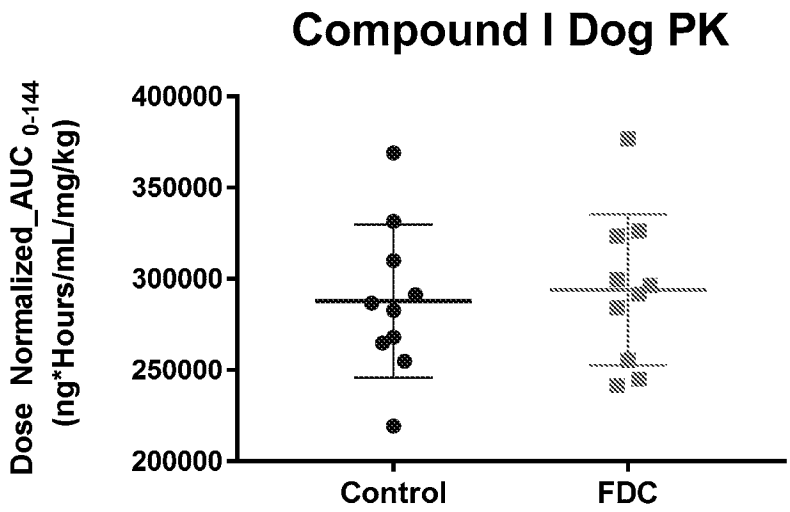

Compound I Dog PK
Dose Normalized_AUC 0-144
(ng*Hours/mL/mg/kg)
400000
350000
300000
250000
200000
Control
FDC

FIG. 22

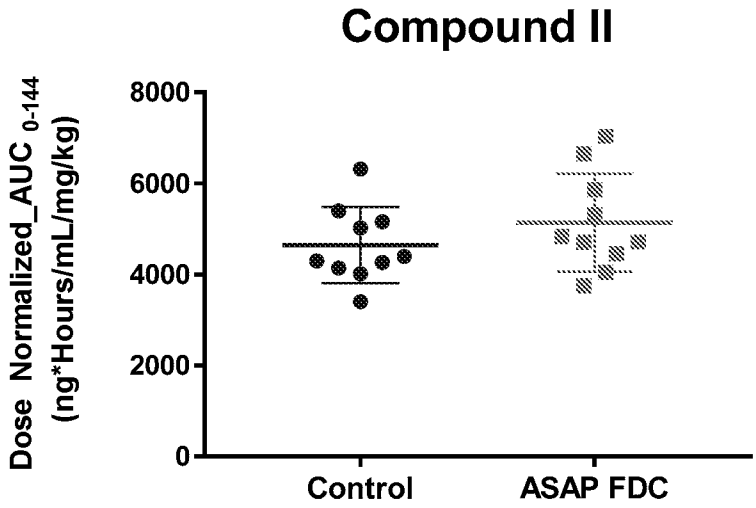

Compound II
Dose Normalized_AUC 0-144
(ng*Hours/mL/mg/kg)
8000
6000
4000
2000
0
Control
ASAP FDC

FIG. 23

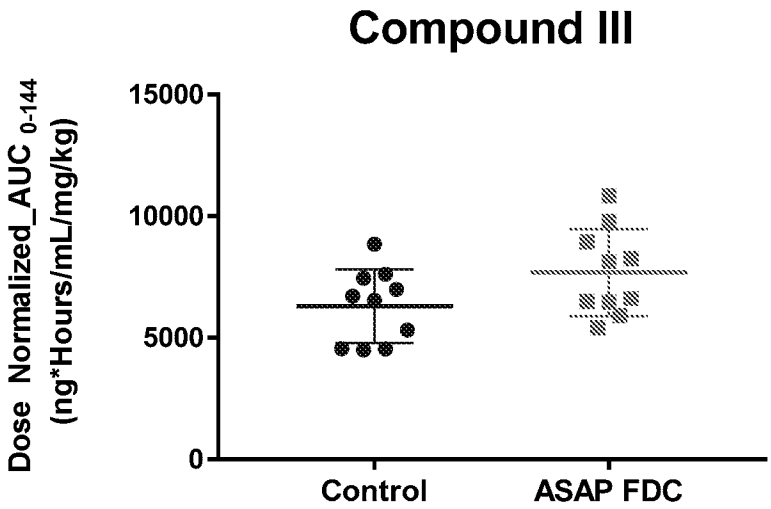

Compound III
Dose Normalized_AUC 0-144
(ng*Hours/mL/mg/kg)
15000
10000
5000
0
Control
ASAP FDC

FIG. 24

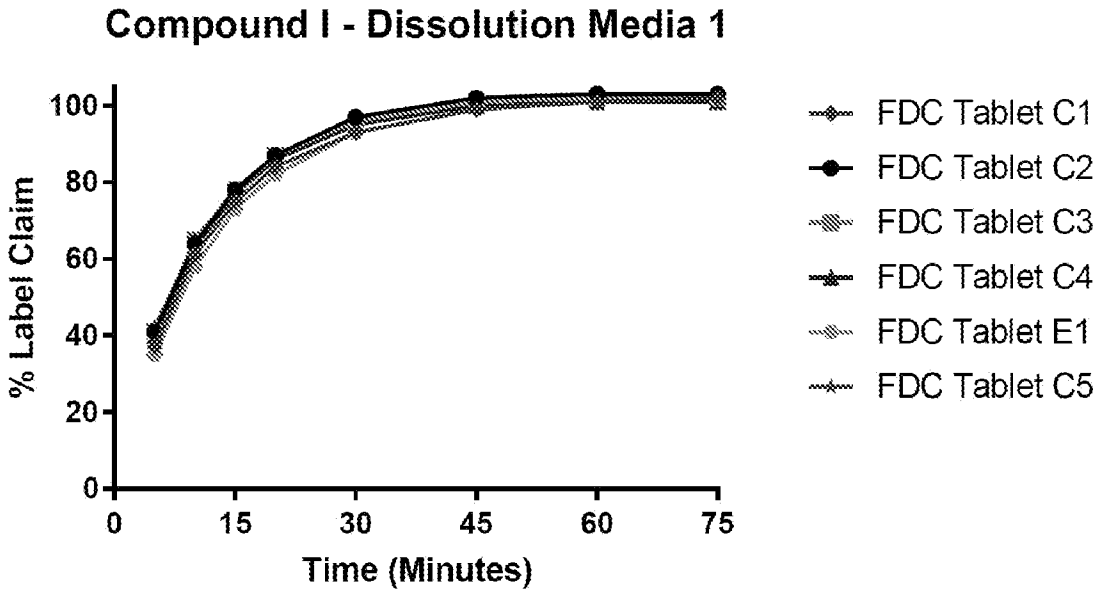

Compound I - Dissolution Media 1
% Label Claim
100
80
60
40
20
0
0
15
30
45
60
75
Time (Minutes)
FDC Tablet C1
FDC Tablet C2
FDC Tablet C3
FDC Tablet C4
FDC Tablet E1
FDC Tablet C5

FIG. 25

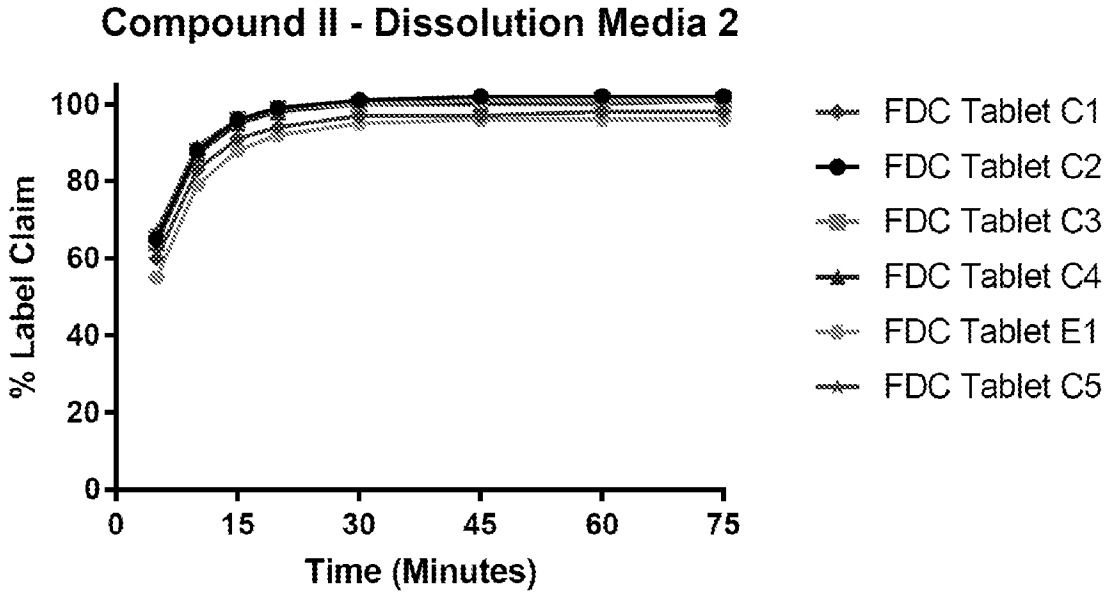

Compound II - Dissolution Media 2
% Label Claim
100
80
60
40
20
0
0
15
30
45
60
75
Time (Minutes)
FDC Tablet C1
FDC Tablet C2
FDC Tablet C3
FDC Tablet C4
FDC Tablet E1
FDC Tablet C5

FIG. 26

Compound (III) (Tablets C1 to C5); Compound (III-d) (Tablet E1)

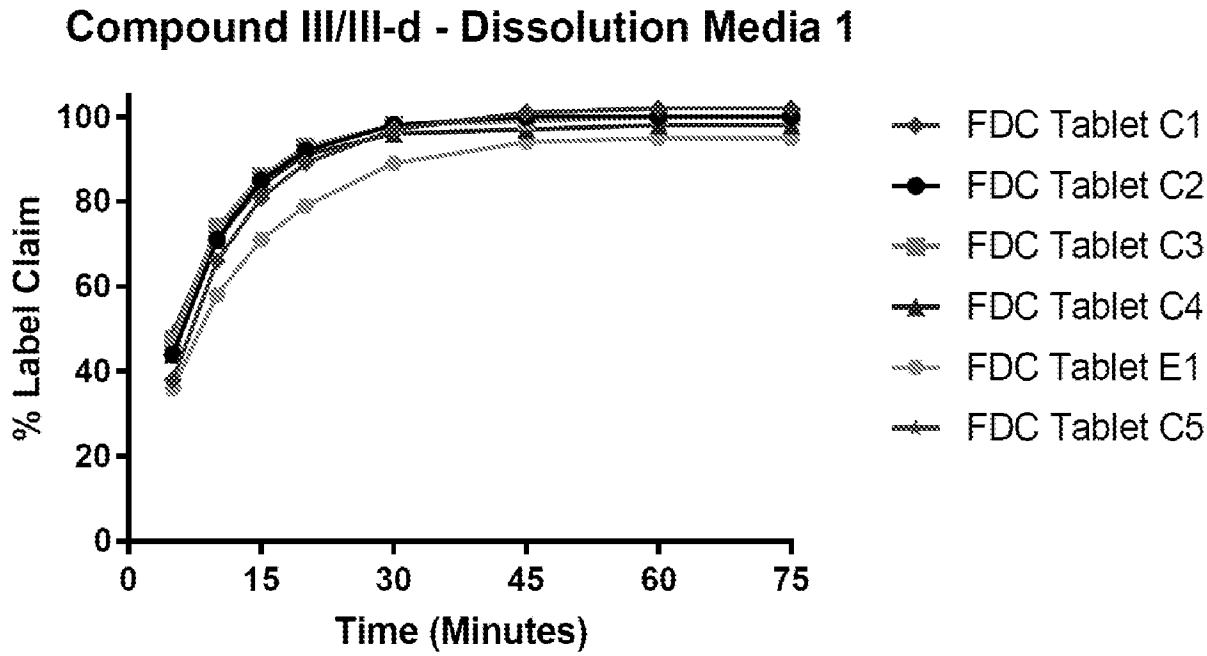


FIG. 27

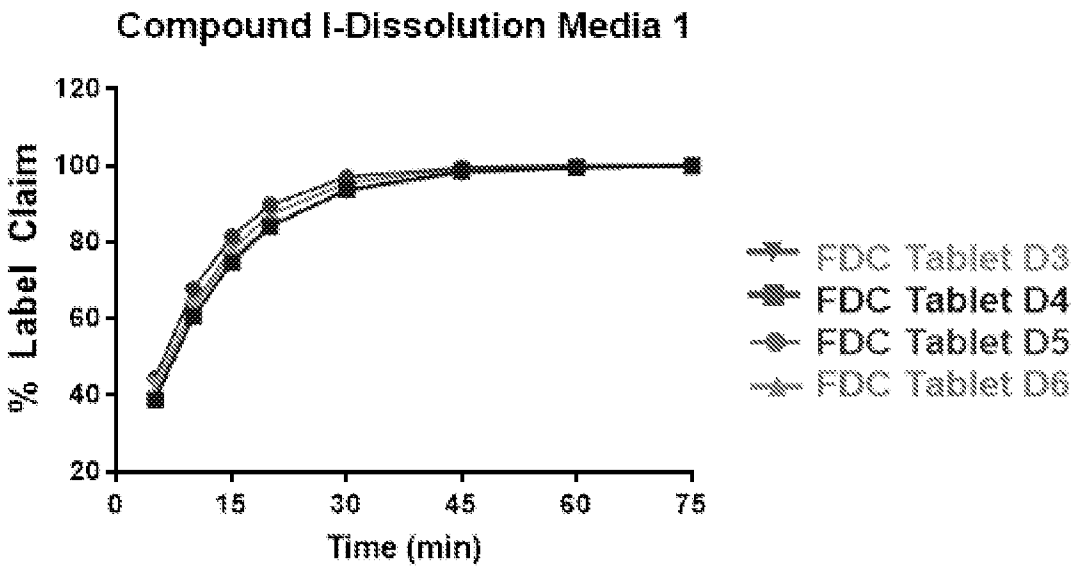

Compound I-Dissolution Media 1
% Label Claim
120
100
80
60
40
20
0
15
30
45
60
75
Time (min)
FDC Tablet D3
FDC Tablet D4
FDC Tablet D5
FDC Tablet D6

FIG. 28

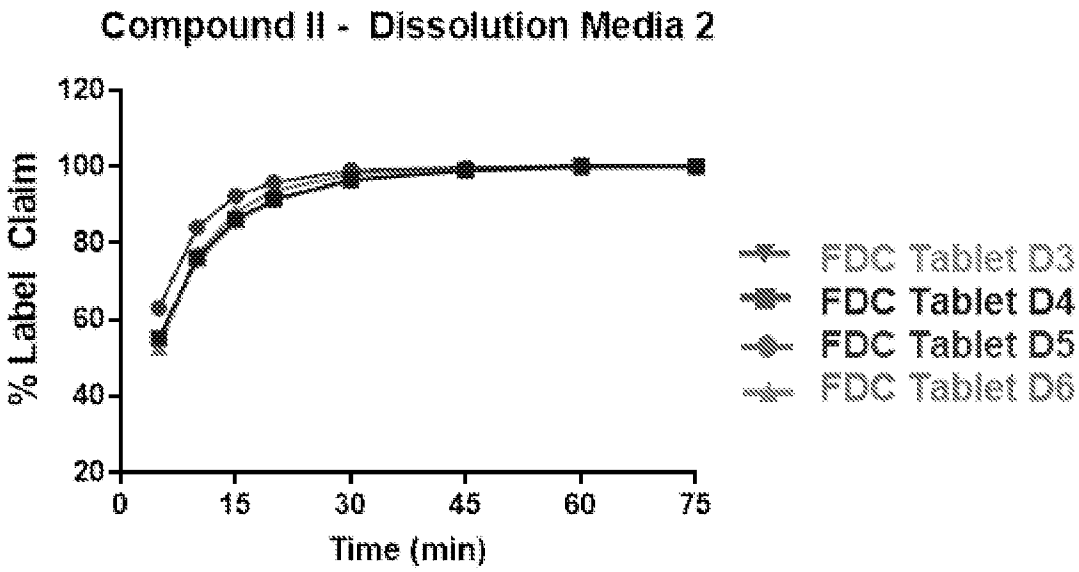
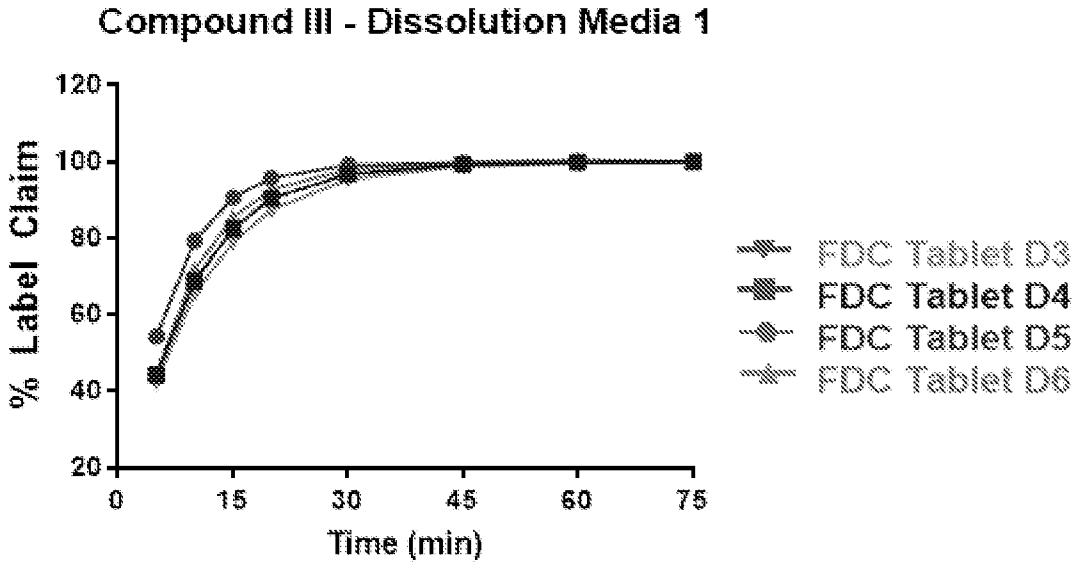

Compound II - Dissolution Media 2
% Label Claim
120
100
80
60
40
20
0
15
30
45
60
75
Time (min)
FDC Tablet D3
FDC Tablet D4
FDC Tablet D5
FDC Tablet D6

FIG. 29


Compound III - Dissolution Media 1
% Label Claim
120
100
80
60
40
20
0
15
30
45
60
75
Time (min)
FDC Tablet D3
FDC Tablet D4
FDC Tablet D5
FDC Tablet D6

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/056772

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61P11/00 A61K31/4439
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/095858 A1 (MILLER MARK THOMAS [US] ET AL) 7 April 2016 (2016-04-07) paragraph [0002]; claim 1; compounds 1114, 1912	1-78
X,P	US 2018/093969 A1 (ALCACIO TIMOTHY [US] ET AL) 5 April 2018 (2018-04-05) paragraph [0444] - paragraph [0445]; claims 1, 36; compound 1	1-78

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2019	29/01/2019

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/056772

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		BR 112017007167 A2	10-04-2018
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		EP 3203840 A1	16-08-2017
		JP 2017530167 A	12-10-2017
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		SG 11201702817S A	30-05-2017
		US 2016095858 A1	07-04-2016
		US 2018185364 A1	05-07-2018
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		US 2018093969 A1	05-04-2018
		UY 37428 A	31-05-2018
		WO 2018064632 A1	05-04-2018