

properties (including chemical stability, thermal stability, solubility, hygroscopicity, and/or particle size), compound manufacturability (including yield, impurity rejection during crystallization, filtration properties, drying properties, and milling properties), and formulation feasibility (including stability with respect to pressure or compression forces during tableting) present a number of challenges that are discussed in greater detail below. Accordingly, there is a current need for one or more solid state forms of Compound 1 that have an acceptable balance of these properties and can be used in the preparation of pharmaceutically acceptable solid dosage forms.

[0005] Additionally, currently known processes for the preparation of Compound 1 involve the use of particularly hazardous reagents, such as trimethylsilyldiazomethane or diazomethane, and do not produce a crystalline product. There is thus also a need for a process for preparing Compound 1, and pharmaceutically acceptable salts thereof, that avoids the use of particularly hazardous reagents, and can produce a crystalline product and crystalline intermediates.

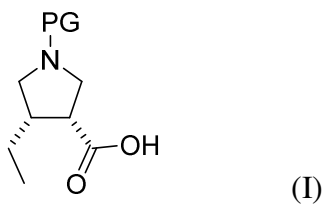
[0006] Additionally, sustained peak plasma concentrations can theoretically be achieved by means of sustained release matrix systems. However, when such systems are made of hydrophilic polymers, such as HPMC, they seldom provide pH independent drug release of pH-dependent soluble drugs, and they are normally incapable of attaining zero-order release except for practically insoluble drugs. Unexpectedly, it has been discovered that when tartaric acid is used as a pH- modifier in such a system, it allows Compound 1 to be released at a steady rate regardless of the pH of the environment.

[0007] In an unexpected finding, it was discovered that as a tablet containing the hydrophilic polymer matrix system erodes, Compound 1 reacts with the HPMC, creating a thicker gel layer which slows the release of Compound 1 from the tablet. The resulting gel layer provided an environment suitable for Compound 1 to dissolve.

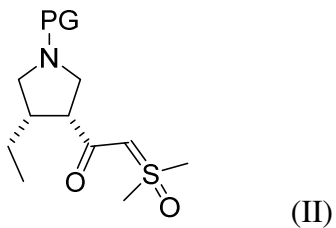
SUMMARY

[0008] In one example, the present disclosure relates to a process for preparing Compound 1, or a pharmaceutically acceptable salt thereof. The process comprises:

- a) reacting a compound of formula (I)

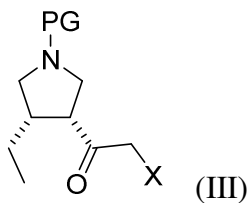


or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride to form a compound of formula (II)



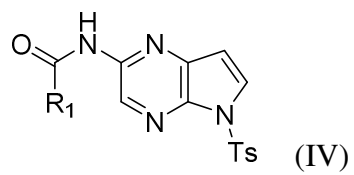
wherein PG is a protecting group;

b) contacting the compound of formula (II) with LiX and a sulfonic acid to form a compound of formula (III)

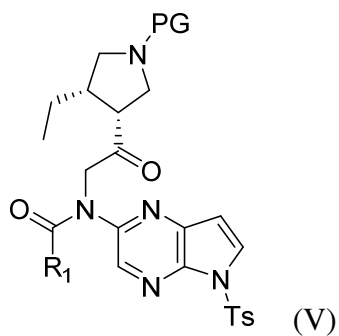


wherein X is Br or Cl;

c) reacting the compound of formula (III) with a compound of formula (IV)

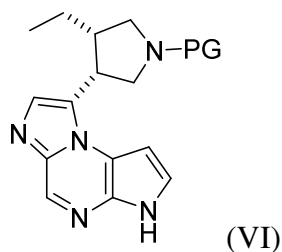


to produce a compound of formula (V)

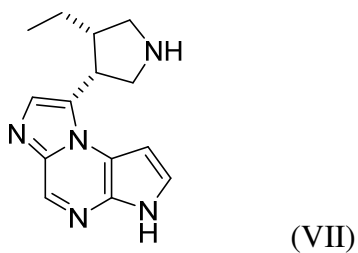


wherein R₁ is selected from the group consisting of alkyl, aryl, and –OR₂; R₂ is alkyl; and Ts is tosyl;

d) contacting the compound of formula (V) with a perfluoro acid anhydride and an organic base to form a compound of formula (VI)



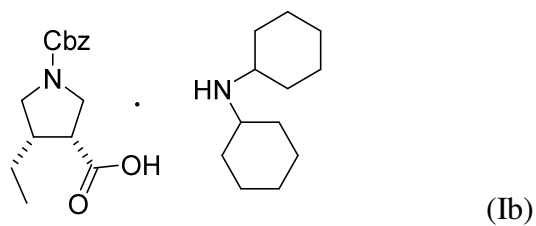
e) deprotecting the compound of formula (VI) and forming a pharmaceutically acceptable salt of the compound of formula (VII):



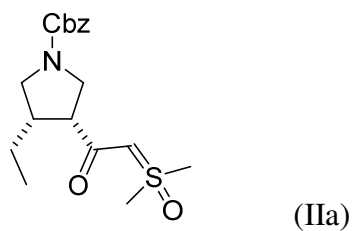
f) reacting the pharmaceutically acceptable salt of the compound of formula (VII) with 2,2,2-trifluoroethylamine to produce Compound 1.

[0009] In another example, the present disclosure relates to a process for preparing Compound 1, or a pharmaceutically acceptable salt thereof. The process comprises:

a) reacting a compound of formula (Ib)

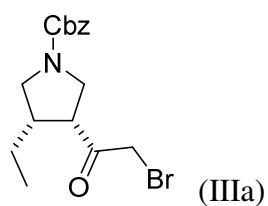


with trimethylsulfoxonium chloride in the presence of carbonyldiimidazole and a strong base to form a compound of formula (IIa)

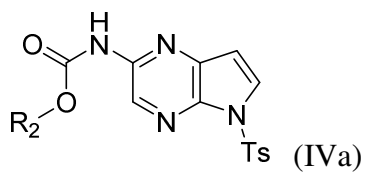


wherein Cbz is carboxybenzyl;

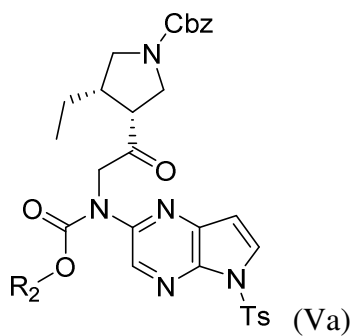
b) contacting the compound of formula (IIa) with lithium bromide and a sulfonic acid to form a compound of formula (IIIa)



c) reacting the compound of formula (IIIa) with a compound of formula (IVa)

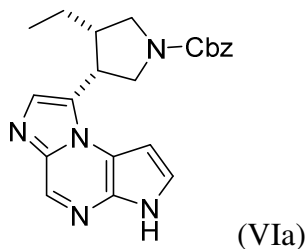


in the presence of lithium *tert*-butoxide to produce a compound of formula (Va)

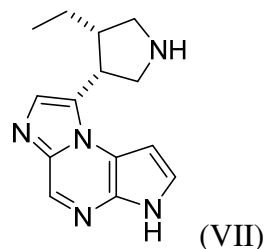


wherein R_2 is methyl or ethyl; and Ts is tosyl;

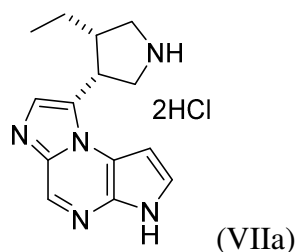
d) contacting the compound of formula (Va) with a perfluoro acid anhydride and an organic base to form a compound of formula (VIa)



e) deprotecting the compound of formula (VIa) to form a compound of formula (VII)



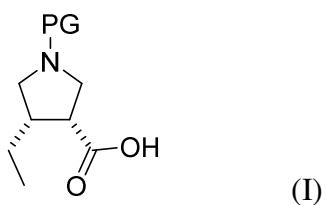
f) contacting the compound of formula (VII) with hydrochloric acid to form a compound of formula (VIIa)



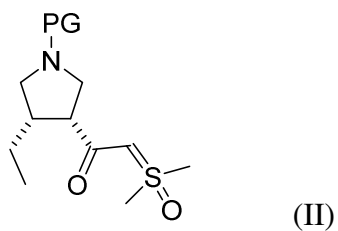
g) reacting the compound of formula (VIIa) with 2,2,2-trifluoroethylamine in the presence of carbonyldiimidazole to produce Compound 1.

[0010] In another example, the present disclosure relates to a process for preparing Compound 1. The process comprises:

a) reacting a compound of formula (I)

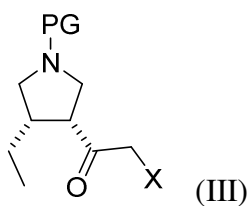


or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride to form a compound of formula (II)



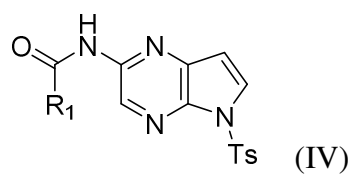
wherein PG is a protecting group;

b) contacting the compound of formula (II) with LiX and a sulfonic acid to form a compound of formula (III)

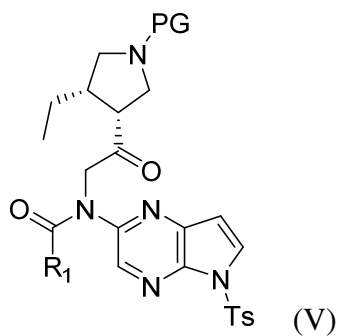


wherein X is Br or Cl;

c) reacting the compound of formula (III) with a compound of formula (IV)

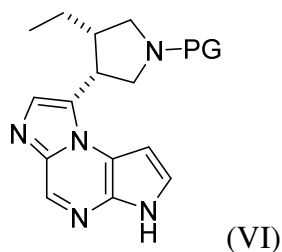


to produce a compound of formula (V)

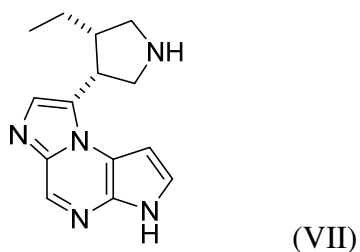


wherein R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$; R_2 is alkyl; and Ts is tosyl;

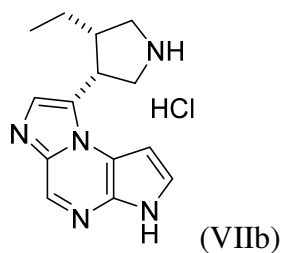
d) contacting the compound of formula (V) with a perfluoro acid anhydride and an organic base to produce a compound of formula (VI)



e) deprotecting the compound of formula (VI) to form a compound of formula (VII)



and contacting the compound of formula (VII) with hydrochloric acid to form the compound of formula (VIIb)



f) contacting the compound of formula (VIIb) with a base to form the compound of formula (VII);

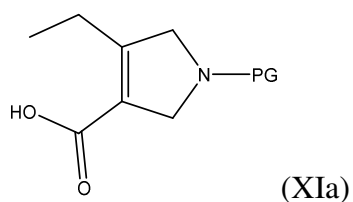
g) reacting the compound of formula (VII) with 2,2,2-trifluoroethylamine to produce Compound 1;

h) contacting Compound 1 with L-tartaric acid to produce a tartrate salt of Compound 1;
and

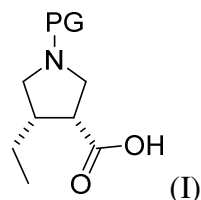
i) contacting the tartrate salt with sodium carbonate and sodium bicarbonate to produce Compound 1.

[0011] In another example, the present disclosure relates to a process for preparing Compound 1, or a pharmaceutically acceptable salt thereof. The process comprises:

a) converting a compound of formula (XIa):

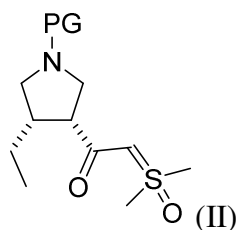


to a compound of formula (I):

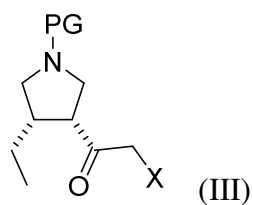


wherein PG is a protecting group;

b) reacting the compound of formula (I) with trimethylsulfoxonium chloride to form a compound of formula (II)

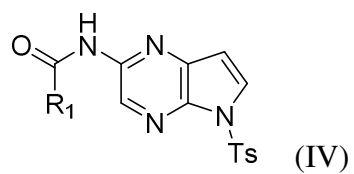


c) contacting the compound of formula (II) with an anhydrous source of HBr or HCl to form a compound of formula (III)

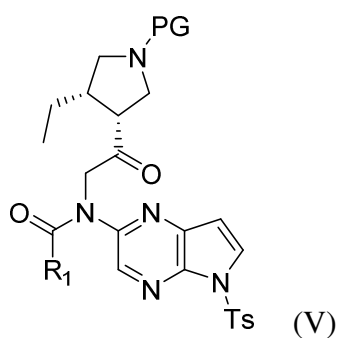


wherein X is Br or Cl;

d) reacting the compound of formula (III) with a compound of formula (IV)

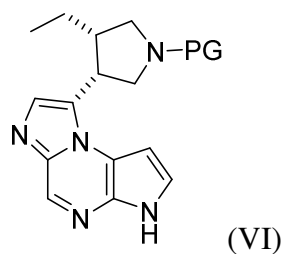


to produce a compound of formula (V)

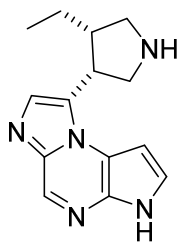


wherein R₁ is selected from the group consisting of alkyl, aryl, and –OR₂; R₂ is alkyl; and Ts is tosyl;

e) contacting the compound of formula (V) with a perfluoro acid anhydride and an organic base to form a compound of formula (VI)



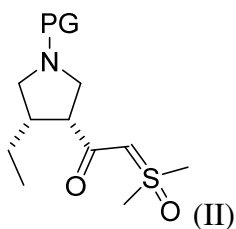
f) deprotecting the compound of formula (VI) and forming a pharmaceutically acceptable salt of the compound of formula (VII):



(VII); and

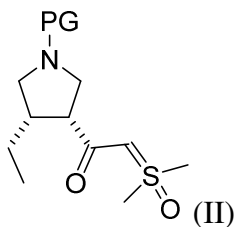
g) reacting the pharmaceutically acceptable salt of the compound of formula (VII) with 2,2,2-trifluoroethylamine to produce Compound 1.

[0012] In another example, the present disclosure relates to a compound of formula (II):

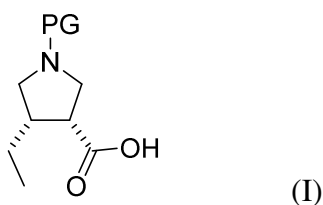


wherein PG is a protecting group.

[0013] In another example, the disclosure relates to a process for preparing a compound of formula (II):

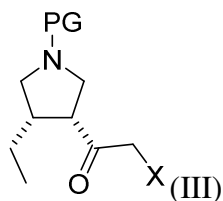


wherein PG is a protecting group, the process comprising reacting a compound of formula (I)

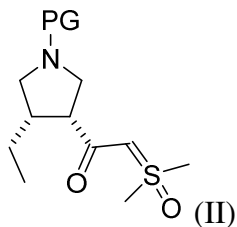


or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride to form the compound of formula (II).

[0014] In another example, the present disclosure is directed to a process for the preparation of a compound of formula (III):

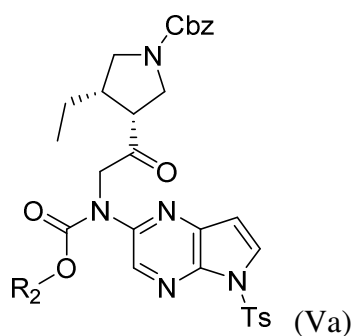


the process comprising contacting a compound of formula (II)



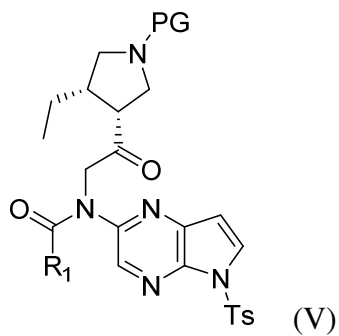
with LiX and a sulfonic acid to form the compound of formula (III); wherein PG is a protecting group; and X is Br or Cl.

[0015] In another example, the present disclosure relates to a compound of formula (Va)



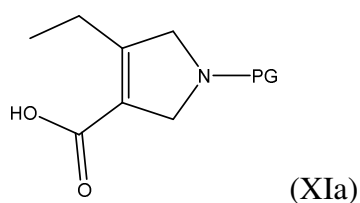
wherein R₂ is methyl or ethyl; and Ts is tosyl.

[0016] In another example, the present disclosure relates to a process for preparing a compound of formula (V)

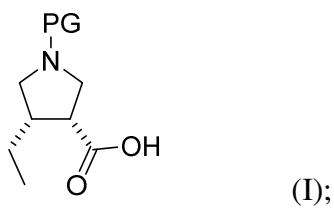


the process comprising:

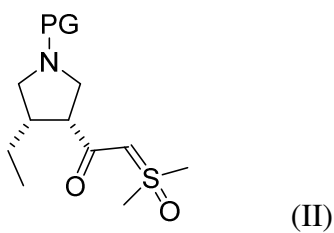
- a) converting a compound of formula (XIa):



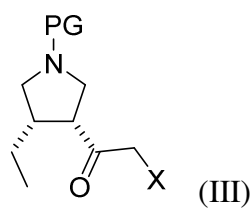
to a compound of formula (I)



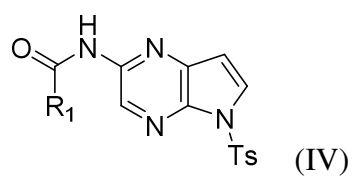
- b) reacting the compound of formula (I) with trimethylsulfoxonium chloride to form a compound of formula (II)



- c) contacting the compound of formula (II) with an anhydrous source of HBr or HCl to form a compound of formula (III)



- d) reacting the compound of formula (III) with a compound of formula (IV)



to produce the compound of formula (V);

wherein:

PG is a protecting group;

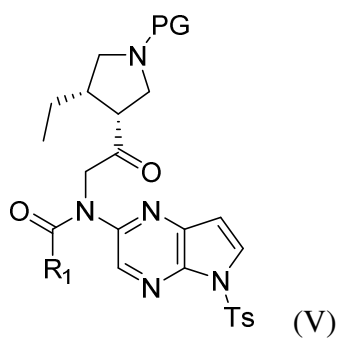
X is Br or Cl;

R₁ is selected from the group consisting of alkyl, aryl, and –OR₂;

R₂ is alkyl; and

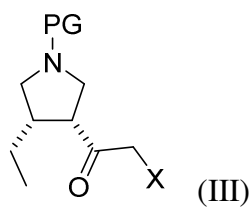
Ts is tosyl.

[0017] In another example, the disclosure is directed to a process for preparing a crystalline compound of formula (V)

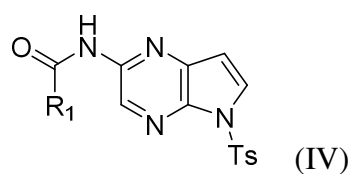


the process comprising:

- a) reacting a compound of formula (III)



with a compound of formula (IV):



to produce the compound of formula (V);

wherein:

PG is a protecting group;

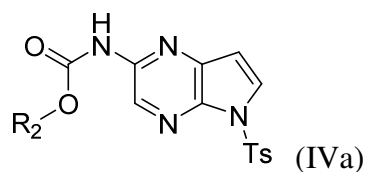
X is Br or Cl;

R₁ is -OR₂;

R₂ is methyl or ethyl; and

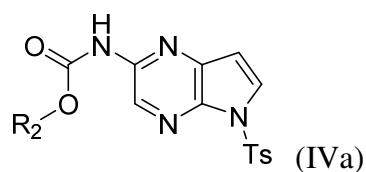
Ts is tosyl.

[0018] In another example, the present disclosure relates to a compound of formula (IVa):



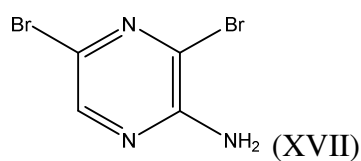
wherein R₂ is methyl or ethyl, and Ts is tosyl.

[0019] In another example, the present disclosure relates to a process for preparing a compound of formula (IVa):

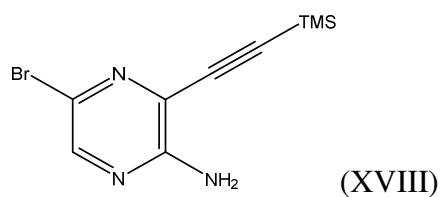


wherein R₂ is methyl or ethyl, and Ts is tosyl, the process comprising:

a) reacting a compound of formula (XVII)

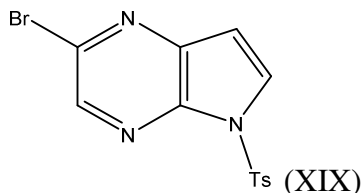


with trimethylsilylacetylene in the presence of a catalyst to form a compound of formula (XVIII):



wherein TMS is trimethylsilyl;

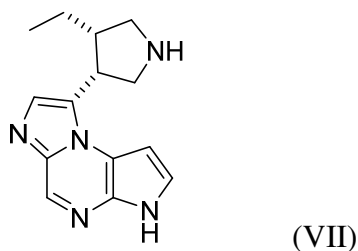
b) contacting the compound of formula (XVIII) with p-toluenesulfonyl chloride in the presence of a base to form a compound of formula (XIX)



wherein Ts is tosyl; and

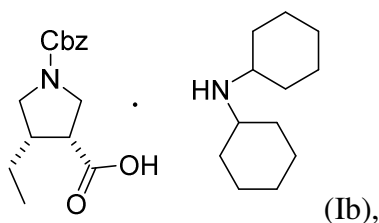
c) reacting the compound of formula (XIX) with a carbamate in the presence of a catalyst and a ligand to form the compound of formula (IVa), wherein the carbamate is selected from the group consisting of methyl carbamate and ethyl carbamate.

[0020] In another example, the present disclosure relates to a compound of formula (VII):



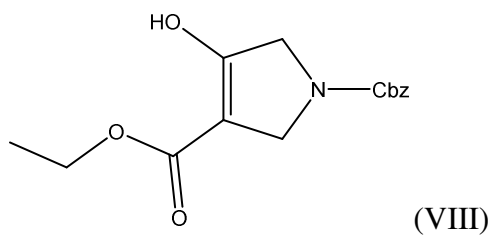
or a pharmaceutically acceptable salt thereof.

[0021] In another example, the present disclosure relates to a process for preparing a compound of formula (Ib)

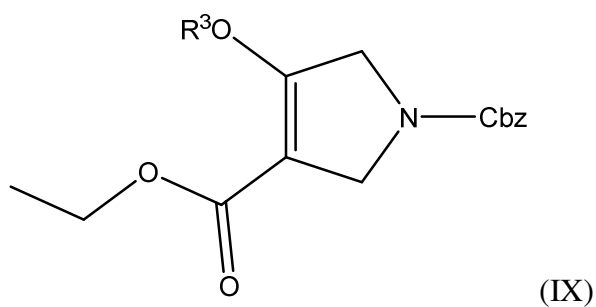


wherein Cbz is carboxybenzyl, the process comprising:

(i) reacting carboxybenzyl-glycine ethyl ester with ethyl acrylate to form a compound of formula (VIII):

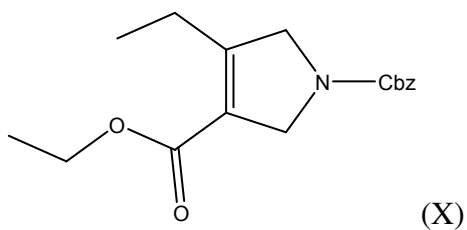


(ii) protecting the compound of formula (VIII) to form a compound of formula (IX):

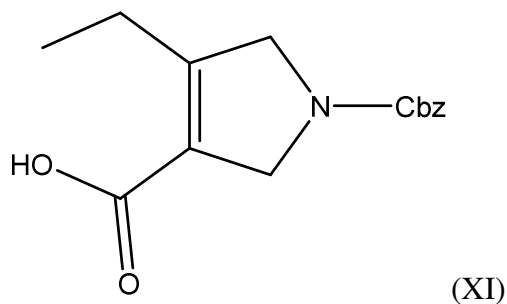


wherein R^3 is selected from the group consisting of CF_3SO_2- ; CH_3SO_2- ; and tosyl;

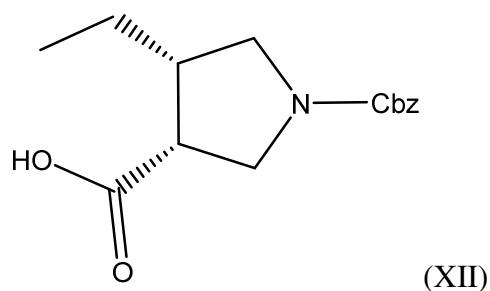
(iii) contacting the compound of formula (IX) with one of ethyl boronic acid, ethyl magnesium bromide, or ethyl zinc chloride in the presence of a catalyst to form a compound of formula (X):



(iv) hydrolyzing the compound of formula (X) to produce the compound of formula (XI):



(v) converting the compound of formula (XI) to the compound of formula (XII):



(vi) contacting the compound of formula (XII) with dicyclohexylamine to form the compound of formula (Ib).

[0022] In another example, the present disclosure relates to the dicyclohexylamine salt of (3R,4S)-1-((benzyloxy)carbonyl)-4-ethylpyrrolidine-3-carboxylate.

[0023] In one example, the present disclosure relates to pharmaceutically acceptable solid state forms of Compound 1.

[0024] In another example, the present disclosure relates to Amorphous Freebase of Compound 1.

[0025] In another example, the present disclosure relates to crystalline Compound 1.

[0026] In another example, the present disclosure relates to crystalline hydrates of Compound 1.

[0027] In another example, the present disclosure relates to crystalline tartrates of Compound 1.

[0028] In another example, the present disclosure relates to the Freebase Hydrate Form C of Compound 1.

[0029] In another example, the present disclosure relates to the Freebase Hydrate Form B of Compound 1.

[0030] In another example, the present disclosure relates to crystalline anhydrides of Compound 1.

[0031] In another example, the present disclosure relates to the Freebase Anhydrate Form D of Compound 1.

[0032] In another example, the present disclosure relates to pharmaceutical compositions comprising one or more solid state forms of Compound 1, and a pharmaceutically acceptable carrier.

[0033] In another example, the present disclosure is directed to a pharmaceutical composition comprising one or more solid state forms of Compound 1, from about 10 w/w% to about 35 w/w% of an organic acid selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, and combinations thereof, and a pharmaceutically acceptable carrier. In one example, the solid state form is Tartrate Hydrate. In one example, the solid state form is Freebase Hydrate Form C.

[0034] In another example, the present disclosure relates to pharmaceutical compositions comprising one or more solid state forms of Compound 1, and, optionally, one or more additional therapeutic agents.

[0035] In another example, the present disclosure relates to methods of treating a JAK-associated condition (such as rheumatoid arthritis) in a human subject suffering from or susceptible to such a condition comprising administering to the subject a therapeutically effective amount of a solid state form of Compound 1. In another example, the disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a solid state form of Compound 1 as described in the present disclosure, for use in treatment of a JAK-associated condition (such as rheumatoid arthritis) in a subject, particularly in a human subject suffering from or susceptible to the condition.

[0036] In another example, the present disclosure relates to methods of treating rheumatoid arthritis, wherein the term “rheumatoid arthritis” includes juvenile rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis disease, Sjogren’s syndrome, psoriatic arthritis.

[0037] In another example, the present disclosure relates to methods of treating inflammatory bowel disease, wherein the term “inflammatory bowel disease” includes Crohn’s disease, pediatric Crohn’s disease and ulcerative colitis.

[0038] In another example, the present disclosure relates to a method of treating a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn’s disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis and systemic

lupus erythematosus in a human subject suffering from or susceptible to such a condition, the method comprising administering to the subject a therapeutically effective amount a solid state form of Compound 1. In another example, the disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a solid state form of Compound 1 as described in the present disclosure, for use in treatment of a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus in a subject, particularly in a human subject suffering from or susceptible to the condition.

[0039] In another example, the present disclosure relates to methods of treating a JAK-associated condition (such as rheumatoid arthritis) in a human subject suffering from or susceptible to such a condition comprising administering to the subject a solid state form of Compound 1, in combination with one or more additional therapeutic agents (*e.g.*, a therapeutic agent for treating rheumatoid arthritis that is not a JAK inhibitor). In another example, the disclosure relates to a pharmaceutical composition comprising a solid state form of Compound 1, as described in the present disclosure, in combination with one or more additional therapeutic agents (*e.g.*, a therapeutic agent for treating rheumatoid arthritis that is not a JAK inhibitor), for use in treatment of a JAK-associated condition (such as rheumatoid arthritis) in a subject, particularly in a human subject suffering from or susceptible to the condition.

[0040] In another example, the present disclosure relates to a method of treating moderate to severely active rheumatoid arthritis, the method comprising administering a therapeutically effective amount of Compound 1 in one or more forms as disclosed herein to a subject suffering from or susceptible to the condition. In a particular example, such a method may comprise administering 7.5 mg once daily or 15 mg once daily, or 30 mg once daily, or 45 mg once daily of the Compound 1, in one or more forms as disclosed herein, to the subject. In this or another particular example, the subject may be administered the Compound 1 in Freebase Form C. In this or yet another particular example, the subject may have an inadequate response to methotrexate. In this or yet another particular example, the subject may have an inadequate response to biologics medicines approved for rheumatoid arthritis. In this or yet another particular example, the subject may have not previously been administered biologics medicines approved for rheumatoid arthritis.

[0041] In another example, the present disclosure relates to a method of treating an adult subject having moderate to severely active rheumatoid arthritis, the method comprising

administering to the subject: a) about 7.5 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent; or b) about 15 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg of Compound 1 freebase equivalent; or c) about 30 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent; or d) about 45 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent. In one example, the present disclosure is directed to a pharmaceutical composition for use in treating an adult subject having moderate to severely active rheumatoid arthritis, the use comprising administering the pharmaceutical composition to the subject, wherein the pharmaceutical composition comprises a) about 7.5 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent; or b) about 15 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg of Compound 1 freebase equivalent; or c) about 30 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent; or d) about 45 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent.

[0042] In another example, the present disclosure relates to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, the method comprising administering to the subject: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg per day of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg per day of Compound

1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg per day of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg per day of Compound 1 freebase equivalent; such that the structural damage in the adult subject is inhibited or lessened. In one example, the disclosure relates to a pharmaceutical composition for use in treating structural damage associated with rheumatoid arthritis in an adult subject, the use comprising administering the pharmaceutical composition to the subject, wherein the pharmaceutical composition comprises: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg per day of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg per day of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg per day of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg per day of Compound 1 freebase equivalent; such that the structural damage in the adult subject is inhibited or lessened.

[0043] In another example, the disclosure is directed to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, the method comprising administering to the subject: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg per day of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg per day of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg per day of Compound 1 freebase equivalent; or d) about 45 mg per day

of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg per day of Compound 1 freebase equivalent; wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In one example, the disclosure is directed to a pharmaceutical composition for use in treating moderate to severely active rheumatoid arthritis in an adult subject, the use comprising administering the pharmaceutical composition to the subject, wherein the pharmaceutical composition comprises: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg per day of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg per day of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg per day of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg per day of Compound 1 freebase equivalent; wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating.

[0044] In another example, the disclosure is directed to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an

amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent. In one example, the disclosure is directed to a pharmaceutical composition for use in reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the use comprising administering the pharmaceutical composition to the subject, wherein the pharmaceutical composition comprises: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent.

[0045] In another example, the present disclosure relates to kits comprising one or more pharmaceutical compositions comprising a solid state form of Compound 1. The kit optionally can comprise another pharmaceutical composition comprising one or more additional therapeutic agents and/or instructions, for example, instructions for using the kit.

[0046] In another example, the present disclosure relates to methods for the preparation of a solid state form of Compound 1.

[0047] In another example, the present disclosure relates to solid state forms of Compound 1 prepared in accordance with such methods.

[0048] In another example, the present disclosure relates to a method of treating an adult subject having moderate to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg of Compound 1 freebase, or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg of Compound 1 freebase equivalent. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C. In this or yet another particular example, the subject may have an inadequate response or tolerance to one or

more disease-modifying antirheumatic drugs (DMARDS), such as methotrexate. In this or yet another particular example, the subject may have not previously been administered DMARDS. In this or yet another particular example, the subject may further be administered one or more DMARD.

[0049] In another example, the present disclosure relates to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of Compound 1 freebase equivalent, such that the structural damage in the adult subject is inhibited or lessened. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0050] In another example, the present disclosure relates to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of Compound 1 freebase equivalent, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0051] In another example, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0052] In another example, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 15 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver

to the subject about 15 mg of Compound 1 freebase equivalent. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0053] In another example, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 30 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0054] In another exampleexample, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 45 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0055] In another example, the present disclosure relates to a pharmaceutical composition comprising a crystalline hydrate of Compound 1 and a pharmaceutically acceptable carrier, wherein the composition comprises the crystalline hydrate in an amount sufficient to deliver about 7.5 mg of Compound 1 freebase equivalent. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0056] In another example, the present disclosure relates to a pharmaceutical composition comprising a crystalline hydrate of Compound 1 and a pharmaceutically acceptable carrier, wherein the composition comprises the crystalline hydrate in an amount sufficient to deliver about 15 mg of Compound 1 freebase equivalent. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0057] In another example, the present disclosure relates to a pharmaceutical composition comprising a crystalline hydrate of Compound 1 and a pharmaceutically acceptable carrier, wherein the composition comprises the crystalline hydrate in an amount sufficient to

deliver about 30 mg of Compound 1 freebase equivalent. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0058] In another example, the present disclosure relates to a pharmaceutical composition comprising a crystalline hydrate of Compound 1 and a pharmaceutically acceptable carrier, wherein the composition comprises the crystalline hydrate in an amount sufficient to deliver about 45 mg of Compound 1 freebase equivalent. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0059] In another example, the present disclosure relates to a method of treating an adult subject having moderate to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg of a crystalline hydrate of Compound 1. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0060] In another example, the present disclosure relates to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of a crystalline hydrate of Compound 1, such that the structural damage in the adult subject is inhibited or lessened. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0061] In another example, the present disclosure relates to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of a crystalline hydrate of Compound 1, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0062] In another example, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of a crystalline hydrate of Compound 1. In this or another particular example, the hydrate may be a hemihydrate. In this or another example, the hemihydrate may be Freebase Hydrate Form C.

[0063] In another example, the present disclosure is directed to an extended release formulation for oral administration comprising Compound 1 or a pharmaceutically acceptable salt thereof, a hydrophilic polymer, and a pH modifier, wherein the hydrophilic polymer, in contact with water, forms a gel layer that provides an environment suitable for Compound 1 and the pH modifier to dissolve.

[0064] In another example, the present disclosure is directed to a process for preparing a pharmaceutical composition, the process comprising: (a) combining Compound 1 or a pharmaceutically acceptable salt thereof, or a solid state form of Compound 1, and at least a portion of one additional composition component to form a dry granulation mixture; (b) contacting the dry granulation mixture with a granulation fluid to form a wet granulation mixture; (c) drying the wet granulation mixture to form a granulated material; (d) milling the granulated material to form a milled granulated material; (e) combining the milled granulation material with any remaining composition components; and (f) compressing the composition to form the pharmaceutical composition.

[0064a] In one aspect, the present disclosure relates to a crystalline hemihydrate of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[0064b] In another aspect, the present disclosure relates to a composition comprising a solid state form, wherein the solid state form is Freebase Hydrate Form C of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[0064c] In another aspect, the present disclosure relates to a pharmaceutical composition comprising Freebase Hydrate Form C of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide and a pharmaceutically acceptable carrier.

[0064d] In another aspect, the present disclosure relates to a composition comprising a solid state form, wherein the solid state form is the crystalline hemihydrate as described herein.

[0064e] In another aspect, the present disclosure relates to a pharmaceutical composition comprising the crystalline hemihydrate as described herein and a pharmaceutically acceptable carrier.

[0064f] In another aspect, the present disclosure relates to a process for preparing the pharmaceutical composition as described herein, the process comprising combining the Freebase Hydrate Form C of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide and the pharmaceutically acceptable carrier.

[0064g] In another aspect, the present disclosure relates to a process for preparing the pharmaceutical composition as described herein, comprising combining the crystalline hemihydrate and the pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

[0065] Figure 1A schematically illustrates one method of preparing the Amorphous Freebase.

[0066] Figure 1B schematically illustrates one method of preparing the Freebase Hydrate Form C.

[0067] Figure 1C schematically illustrates one method of preparing the Tartrate Hydrate.

[0068] Figures 2A and 2B are powder X-ray diffraction patterns corresponding to the Amorphous Freebase (via precipitation) and the Amorphous Freebase (via dehydration), respectively.

[0069] Figure 3A is a powder X-ray diffraction pattern corresponding to the Freebase Solvate Form A (Isopropyl Acetate/Water Solvate).

[0070] Figure 3B is a powder X-ray diffraction pattern corresponding to the Freebase Hydrate Form B.

[0071] Figure 3C is a powder X-ray diffraction pattern corresponding to the Freebase Hydrate Form C.

We Claim:

1. A crystalline hemihydrate of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.
2. The crystalline hemihydrate of claim 1, having an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2 , 15.1 ± 0.2 , and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic K α 1 radiation.
3. The crystalline hemihydrate of claim 1, having an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2 , 15.1 ± 0.2 , 17.0 ± 0.2 , and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic K α 1 radiation.
4. The crystalline hemihydrate of claim 1, having an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2 , 15.1 ± 0.2 , 20.9 ± 0.2 , and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic K α 1 radiation.
5. The crystalline hemihydrate of claim 1, having an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2 , 15.1 ± 0.2 , 15.5 ± 0.2 , 17.0 ± 0.2 , 20.9 ± 0.2 , and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic K α 1 radiation.
6. The crystalline hemihydrate of claim 1, wherein the crystalline hemihydrate is Freebase Hydrate Form C of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.
7. The crystalline hemihydrate of claim 1, having an X-ray powder diffraction pattern substantially as shown in Figure 3C.
8. The crystalline hemihydrate of claim 1, having a thermogravimetric analysis profile substantially as shown in Figure 4E.

9. The crystalline hemihydrate of claim 1, having a differential scanning calorimetry profile substantially as shown in Figure 5C.
10. The crystalline hemihydrate of claim 1, having a differential scanning calorimetry profile comprising an endotherm between about 120°C and about 170°C when heated at a rate of 10°C/minute.
11. The crystalline hemihydrate of claim 1, having a moisture sorption isotherm profile substantially as shown in Figure 6B.
12. The crystalline hemihydrate of claim 1, having an orthorhombic lattice type that has a $P2_12_12_1$ space group, a unit cell a value of about 12.7Å, a unit cell b value of about 13.1Å, and a unit cell c value of about 22.6Å.
13. A composition comprising a solid state form, wherein the solid state form is Freebase Hydrate Form C of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.
14. The composition of claim 13, comprising at least about 75% by weight of the Freebase Hydrate Form C of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.
15. The composition of claim 13, comprising at least about 95% by weight of the Freebase Hydrate Form C of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.
16. A pharmaceutical composition comprising Freebase Hydrate Form C of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, wherein the pharmaceutical composition comprises the Freebase Hydrate Form C in an amount sufficient to deliver about 7.5 mg of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.
18. The pharmaceutical composition of claim 16, wherein the pharmaceutical composition comprises the Freebase Hydrate Form C in an amount sufficient to deliver about 15 mg of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.
19. The pharmaceutical composition of claim 16, wherein the pharmaceutical composition comprises the Freebase Hydrate Form C in an amount sufficient to deliver about 30 mg of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.
20. The pharmaceutical composition of claim 16, wherein the pharmaceutical composition comprises the Freebase Hydrate Form C in an amount sufficient to deliver about 45 mg of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.
21. A composition comprising a solid state form, wherein the solid state form is the crystalline hemihydrate of claim 2.
22. The composition of claim 21, comprising at least about 75% by weight of the crystalline hemihydrate.
23. The composition of claim 21, comprising at least about 95% by weight of the crystalline hemihydrate.
24. A pharmaceutical composition comprising the crystalline hemihydrate of claim 2 and a pharmaceutically acceptable carrier.

25. The pharmaceutical composition of claim 24, wherein the pharmaceutical composition comprises the crystalline hemihydrate in an amount sufficient to deliver about 7.5 mg of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

26. The pharmaceutical composition of claim 24, wherein the pharmaceutical composition comprises the crystalline hemihydrate in an amount sufficient to deliver about 15 mg of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

27. The pharmaceutical composition of claim 24, wherein the pharmaceutical composition comprises the crystalline hemihydrate in an amount sufficient to deliver about 30 mg of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

28. The pharmaceutical composition of claim 24, wherein the pharmaceutical composition comprises the crystalline hemihydrate in an amount sufficient to deliver about 45 mg of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

29. A process for preparing the pharmaceutical composition according to claim 16, the process comprising combining the Freebase Hydrate Form C of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide and the pharmaceutically acceptable carrier.

30. A process for preparing the pharmaceutical composition of claim 24, comprising combining the crystalline hemihydrate and the pharmaceutically acceptable carrier.