SOLID FORMS AND FORMULATIONS OF (S)-4-(8-AMINO-3-(1 -(BUT-2-YNOYL)PYRROLIDIN-2-YL)IMIDAZO[1 ,5-A]PYRAZIN-1 -YL)-N-(PYRIDIN-2-YL)BENZAMIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application is an international application claiming the benefit of U.S. Provisional Application No. 62/188,468, filed on July 2, 2015, and U.S. Provisional Application No. 62/271,708, filed on December 28, 2015, the entirety of each of which is incorporated herein by reference.

FIELD OF THE INVENTION

[002] In some embodiments, the invention relates to crystalline Form I of (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide. In other embodiments, the invention relates to pharmaceutical compositions including Form I, including pharmaceutical compositions that overcome the effects of acid reducing agents, and methods for treating cancers or other disorders by administering the pharmaceutical compositions to a subject. In some embodiments, the invention relates to crystalline salts of (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide. In other embodiments, the invention relates to pharmaceutical compositions including crystalline salts of (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide, including pharmaceutical compositions that overcome the effects of acid reducing agents, and methods for treating cancers or other disorders by administering the pharmaceutical compositions to a subject.

BACKGROUND OF THE INVENTION

[003] Bruton's Tyrosine Kinase (BTK) is a Tec family non-receptor protein kinase expressed in B cells and myeloid cells. BTK is composed of the pleckstrin homology (PH), Tec homology (TH), Src homology 3 (SH3), Src homology 2 (SH2), and tyrosine kinase or Src homology 1 (TK or SH1) domains. The function of BTK in signaling pathways activated by the engagement of the B cell receptor (BCR) in mature B cells and FCER1 on mast cells is well established. Functional mutations in BTK in humans result in a primary immunodeficiency disease (X-linked agammaglobuinaemia) characterized by a defect in B cell development with a block between pro- and pre-B cell stages. The result is an almost complete absence of B lymphocytes, causing a pronounced reduction of serum immunoglobulin of all classes. These findings support a key role

for BTK in the regulation of the production of auto-antibodies in autoimmune diseases.

[004] BTK is expressed in numerous B cell lymphomas and leukemias. Other diseases with an important role for dysfunctional B cells are B cell malignancies, as described in Hendriks, *et al.*, *Nat. Rev. Cancer,* **2014,** *14,* 219-231. The reported role for BTK in the regulation of proliferation and apoptosis of B cells indicates the potential for BTK inhibitors in the treatment of B cell lymphomas. BTK inhibitors have thus been developed as potential therapies for many of these malignancies, as described in D'Cruz, *et al.*, *OncoTargets and Therapy* **2013,** *6,* 161-176. International Patent Application Publication No. WO 2013/010868 discloses BTK inhibitors including (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide for use in therapy.

[005] The present invention includes the unexpected discovery of novel crystalline solid forms of (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide, referred to herein as Formula (1), including crystalline free base Form I. Formula (1) is a BTK inhibitor that is useful, *inter alia*, in pharmaceutical compositions and methods for treatment of cancers, inflammation, immume, and autoimmune diseases. The novel solid forms of Formula (1) disclosed herein, including Form I, have surprising and useful properties.

SUMMARY OF THE INVENTION

[006] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base.

[007] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by an X-ray powder diffraction pattern comprising peaks at 6.4, 8.6, 10.5, 11.6, and 15.7 °2θ ± 0.2 °2θ.

[008] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-

yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by an X-ray powder diffraction pattern comprising peaks at 6.4, 8.6, 10.5, 11.6, and 15.7 °2θ ± 0.2 °2θ, and further comprising peaks at 10.9, 12.7, 13.4, 14.3, 14.9, and 18.2 °2θ ± 0.2 °2θ.

[009] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by an X-ray powder diffraction pattern comprising peaks at 6.4, 8.6, 10.5, 11.6, and 15.7 °2θ ± 0.2 °2θ, further comprising peaks at 10.9, 12.7, 13.4, 14.3, 14.9, and 18.2 °2θ ± 0.2 °2θ, and further comprising one or more peaks selected from the group consisting of 11.3, 15.1, 15.7, 16.1, 17.3, 19.2, 19.4, 19.8, 20.7, 21.1, 21.4, 21.6, 21.9, 22.6, 23.3, 23.6, 24.9, 25.2, 25.4, 25.7, 26.1, 26.4, 26.8, 26.9, 27.7, 28.6, 29.1, 29.4, 30.1, 30.5, 31.7, 31.9, 32.2, 32.6, 33.1, 33.4, 34.5, 35.9, 36.1, 36.8, 37.4, 38.1, 38.9, and 39.5 °2θ ± 0.2 °2θ.

[0010] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by a transmission X-ray powder diffraction pattern substantially the same as the representative X-ray powder diffraction pattern shown in FIG. 1.

[0011] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by a Raman spectrum comprising peaks at 1620, 1609, 1547, 1514 and 1495 cm^{-1} ± 2 cm^{-1}.

[0012] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by a Raman spectrum comprising peaks at 1620, 1609, 1547, 1514 and 1495 cm^{-1} ± 2 cm^{-1}, further comprising one or more peaks selected from the group consisting of 1680, 1574, 1454, 1433,

1351, 1312, 1255, 1232, 1187, 1046, 995, 706, 406, and 280 $cm^{-1} \pm 2\ cm^{-1}$.

[0013] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by a Raman spectrum substantially the same as the representative Raman spectrum shown in FIG. 2.

[0014] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by an infrared (IR) spectrum comprising peaks at 1621, 1608, 1403, 1303, and 764 $cm^{-1} \pm 4\ cm^{-1}$.

[0015] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by an infrared (IR) spectrum comprising peaks at 1621, 1608, 1403, 1303, and 764 $cm^{-1} \pm 4\ cm^{-1}$, further comprising one or more peaks selected from the group consisting of 3367, 3089, 2246, 1682, 1574, 1514, 1504, 1454, 1428, 1345, 1248, 1194, 1177, 1149, 1109, 1049, 1023, 1003, 947, 900, 858, 842, 816, 734, 729, 701, 689, 665, 623, and 612 $cm^{-1} \pm 4\ cm^{-1}$.

[0016] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by an IR spectrum substantially the same as the representative IR spectrum shown in FIG. 3.

[0017] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base is characterized by the absence of water in the crystal structure.

[0018] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base and an extragranular acidulant.

[0019] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base and an extragranular acidulant, wherein the extragranular acidulant is selected from the group consisting of fumaric acid, succinic acid, D-tartaric acid, L-tartaric acid, racemic tartaric acid, ascorbic acid, isoascorbic acid (also known as erythorbic acid and D-araboascorbic acid), alginic acid or a salt thereof, Protacid F 120 NM, Protacid AR 1112 (also known as Kelacid NF), and Carbopol 971P (carboxypolymethylene), and combinations thereof.

[0020] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base and an extragranular acidulant, wherein the extragranular acidulant is alginic acid, or a sodium or potassium salt thereof, at a concentration of between about 5% to about 33% by weight.

[0021] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base and an extragranular acidulant, wherein the extragranular acidulant is alginic acid, or a sodium or potassium salt thereof, at a concentration of between about 5% to about 33% by weight, and wherein the composition further comprises at least one pharmaceutically-acceptable excipient.

[0022] In an embodiment, the invention provides a method of treating a hyperproliferative disease comprising the step of administering a therapeutically effective amount of a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I to a mammal, wherein the hyperproliferative

disease is selected from the group consisting of chronic lymphocytic leukemia, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, B-cell lymphoproliferative disease, B cell acute lymphoblastic leukemia, Waldenström's macroglobulinemia, Burkitt's leukemia, Hodgkin's disease, multiple myeloma, acute myeloid leukemia, juvenile myelomonocytic leukemia, hairy cell leukemia, mast cell leukemia, mastocytosis, myeloproliferative disorders (MPDs), myeloproliferative neoplasms, polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), myelodysplastic syndrome, chronic myelogenous leukemia (BCR-ABL1-positive), chronic neutrophilic leukemia, chronic eosinophilic leukemia, primary central nervous system (CNS) lymphoma, primary multifocal lymphoma of peripheral nervous system (PNS), thymus cancer, brain cancer, glioblastoma, lung cancer, squamous cell cancer, skin cancer (*e.g.,* melanoma), eye cancer, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal cancers, bladder cancer, gastric cancer, stomach cancer, pancreatic cancer, breast cancer, cervical cancer, head and neck cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, bone cancer (*e.g.*, metastatic bone cancer), esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, epidermoid cancer, AIDS-related cancer (*e.g.*, lymphoma), viral-induced cervical carcinoma (human papillomavirus), nasopharyngeal carcinoma (Epstein-Barr virus), Kaposi's sarcoma, primary effusion lymphoma (Kaposi's sarcoma herpesvirus), hepatocellular carcinoma (hepatitis B and hepatitis C viruses), T-cell leukemias (Human T-cell leukemia virus-1), benign hyperplasia of the skin, restenosis, benign prostatic hypertrophy, tumor angiogenesis, chronic inflammatory disease, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcet's disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidratenitis suppurativa, Sjögren's syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, lupus, and lupus nephritis.

[0023] In an embodiment, the invention provides a method of treating a hyperproliferative disease comprising the step of administering a therapeutically effective amount of a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I to a mammal, wherein the hyperproliferative

disease is selected from the group consisting of chronic lymphocytic leukemia, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, and Waldenström's macroglobulinemia.

[0024] In an embodiment, the invention provides a method of treating a hyperproliferative disease comprising the step of administering a therapeutically effective amount of a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I and an extragranular acidulant to a mammal, wherein the hyperproliferative disease is selected from the group consisting of chronic lymphocytic leukemia, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, and Waldenström's macroglobulinemia.

[0025] In an embodiment, the invention provides a method of treating a hyperproliferative disease comprising the step of administering a therapeutically effective amount of a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I and an extragranular acidulant to a mammal, further comprising the step of administering a therapeutically effective amount of an acid-reducing agent to the mammal.

[0026] In an embodiment, the invention provides a method of treating a hyperproliferative disease comprising the step of administering a therapeutically effective amount of a composition comprising a crystalline fumarate, maleate, phosphate, L-tartrate, citrate, gentisate, oxalate, or sulfate salt of (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I to a mammal, further comprising the step of administering a therapeutically effective amount of an acid-reducing agent to the mammal.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings.

[0028] FIG. 1 illustrates a transmission PXRD pattern of Form I (sample PP502-P1) of the free base of Formula (1).

[0029] FIG. 2 illustrates a Raman spectrum of Form I of the free base of Formula (1).

[0030] FIG. 3 illustrates an infrared (IR) spectrum of Form I of the free base of Formula (1).

[0031] FIG. 4 illustrates a transmission PXRD pattern of Form II of the free base of Formula (1).

[0032] FIG. 5 illustrates a Raman spectrum of Form II of the free base of Formula (1).

[0033] FIG. 6 illustrates a transmission PXRD pattern of Form III of the free base of Formula (1).

[0034] FIG. 7 illustrates a Raman spectrum of Form III of the free base of Formula (1).

[0035] FIG. 8 illustrates a PXRD pattern of metastable Form IV of the free base of Formula (1).

[0036] FIG. 9 illustrates a PXRD pattern of metastable Form V of the free base of Formula (1).

[0037] FIG. 10 illustrates a PXRD pattern of metastable Form VI of the free base of Formula (1).

[0038] FIG. 11 illustrates a PXRD pattern of metastable Form VII of the free base of Formula (1).

[0039] FIG. 12 illustrates a PXRD pattern of metastable Form VIII of the free base of Formula (1).

[0040] FIG. 13 illustrates the PXRD pattern of amorphous Formula (1).

[0041] FIG. 14 illustrates the Raman spectrum of amorphous Formula (1).

[0042] FIG. 15 illustrates a reflection PXRD pattern of Form A of the fumarate salt of Formula (1).

[0043] FIG. 16 illustrates a reflection PXRD pattern of Form A of the maleate salt of Formula (1).

[0044] FIG. 17 illustrates a PXRD pattern of Form A of the phosphate salt of Formula (1).

[0045] FIG. 18 illustrates a PXRD pattern of Form A of the L-tartrate salt of Formula (1).

[0046] FIG. 19 illustrates a PXRD pattern of Form A of the citrate salt of Formula (1) (sample SP211-CIT-P4) crystallized from acetone-water.

[0047] FIG. 20 illustrates a PXRD pattern of Form A of the citrate salt of Formula (1) (sample SP211-CIT-P6) crystallized from 1-propanol.

[0048] FIG. 21 illustrates a PXRD pattern of a sample of Form A of the gentisate salt of Formula (1) monohydrate.

[0049] FIG. 22 illustrates a PXRD pattern of Form A of the oxalate salt of Formula (1).

[0050] FIG. 23 illustrates a PXRD pattern of a sample of Form A of a sulfate salt of Formula (1).

[0051] FIG. 24 illustrates a species distribution for Formula (1) based on calculated pH values: 2.2, 6.1 and 11.5.

[0052] FIG. 25 illustrates the pH-dependent solubility of the free base of Formula (1) (sample PP502-P1) with HCl and buffer solutions as the solvent media. The circle markers correspond to results from the first set of experiments, and the diamond markers correspond to results from the second set of experiments.

[0053] FIG. 26 illustrates the species distribution and solubility as a function of pH for Formula (1).

[0054] FIG. 27 illustrates the temperature dependent solubility of Formula (1) in acetone (squares), ethanol (dots and line), 96%-ethanol (triangles), and 1-propanol (diamonds). The vertical line shows the boiling temperature of ethanol.

[0055] FIG. 28 shows intrinsic dissolution rate results for Forms I and II of Formula (1) free base.

[0056] FIG. 29 shows exposure data in dogs for Forms I and II of Formula (1) free base.

[0057] FIG. 30 illustrates a comparison of the dissolution profiles of formulations of Formula (1) at a pH of 3.4.

[0058] FIG. 31 illustrates a comparison of the dissolution profiles of formulations of Formula (1) at a pH of 5.5.

[0059] FIG. 32 shows trends in the AUC, C_{max}, and T_{max} for conditioned dogs treated with a formulation of Formula (1) with acidulant and four salt forms of Formula (1). Liquid capsules ("liq cap") (100 mg) were administered for comparison with the solid forms. Solid capsules of 100 mg strength in the clinical formulation of Form I of Formula (1) were administered to dogs prior to or following daily treatment with omeprazole to reduce stomach acidity. The subsequent

study phases followed 4 days of dosing with omeprazole (10 mg/day); omeprazole treatment continued throughout the study. An acidulant formulation of Form I of Formula (1) ("FA-3") was compared with the F-1 maleate, F-1 phosphate, F-1 fumarate, F-1 tartrate salts, as well as control formulations (F-1 free base and F-2) and administered as 100 mg equivalent of free base in capsules. Exposures of salts and the capsules of Form I of Formula (1) formulated with acidulant or using a salt form of Formula (1) were increased relative to exposure of Form I in the presence of omeprazole.

[0060] FIG. 33 illustrates dose-normalized AUC and Cmax for Formula (1) in dogs, comparing liquid capsules ("Liq Caps") (average of n = 2), formulation F-2 (average of n = 5), formulation F-2 with omeprazole ("F-2 / Omep," showing loss of exposure for Formula (1)), and five formulations of the present invention that restore exposure in the presence of omeprazole: FA-3 (with acidulant, "FA-3 / Omep"), F-1 maleate ("Maleate / Omep"), F-1 phosphate ("Phosphate / Omep"), F-1 fumarate ("Fumarate / Omep"), and F-1 tartrate ("Tartrate / Omep").

DETAILED DESCRIPTION OF THE INVENTION

[0061] While preferred embodiments of the invention are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the invention. Various alternatives to the described embodiments of the invention may be employed in practicing the invention.

Definitions

[0062] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

[0063] The term "solid form" may refer to a crystalline solid form or phase, including a crystalline free base and a crystalline salt.

[0064] The terms "co-administration," "co-administering," "administered in combination with," and "administering in combination with" as used herein, encompass administration of two or more agents to a subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a

composition in which two or more agents are present.

[0065] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, *etc.* which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[0066] The terms "QD," "qd," or "q.d." mean *quaque die*, once a day, or once daily. The terms "BID," "bid," or "b.i.d." mean *bis in die,* twice a day, or twice daily. The terms "TID," "tid," or "t.i.d." mean *ter in die*, three times a day, or three times daily. The terms "QID," "qid," or "q.i.d." mean *quater in die*, four times a day, or four times daily.

[0067] A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0068] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions, including fumarate, maleate, phosphate, L-tartrate, citrate, gentisate, oxalate, and sulfate counter ions. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids.

[0069] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the

invention is contemplated. Supplementary active ingredients can also be incorporated into the described compositions.

[0070] The term "*in vivo*" refers to an event that takes place in a subject's body.

[0071] The term "*in vitro*" refers to an event that takes places outside of a subject's body. *In vitro* assays encompass cell-based assays in which cells alive or dead are employed and may also encompass a cell-free assay in which no intact cells are employed.

[0072] The term "extragranular" refers to substances that are outside of a granule, *e.g.*, a substance added to granules (multiparticle compacts formed by a granulation process) and physically mixed with granules, but not contained within the granules.

[0073] The term "intragranular" refers to substances that are within a granule (a multiparticle compact formed formed by a granulation process). Granules may be formed by processes such as wet granulation (*i.e.*, prepared using moisture or steam, thermal, melt, freeze, foam, and other processes) or dry granulation.

[0074] The term "acidulant" refers to a substance that increases acidity.

[0075] The terms "transmission" or "transmission mode," when used in conjunction with powder X-ray diffraction, refers to the transmission (also known as Debye-Scherrer) sampling mode. The terms "reflection" or "reflection mode," when used in conjunction with powder X-ray diffraction, refers to the reflection (also known as Bragg-Brentano) sampling mode.

[0076] Unless otherwise stated, the chemical structures depicted herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds where one or more hydrogen atoms is replaced by deuterium or tritium, or wherein one or more carbon atoms is replaced by ^{13}C- or ^{14}C-enriched carbons, are within the scope of this invention.

[0077] When ranges are used herein to describe, for example, physical or chemical properties such as molecular weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term "about" or "approximately" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for

example, between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments such as, for example, an embodiment of any composition of matter, method or process that "consist of" or "consist essentially of" the described features.

[0078] "Enantiomeric purity" as used herein refers to the relative amounts, expressed as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For example, if a compound, which may potentially have an (*R*)- or an (*S*)-isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (*R*)- or (*S*)-isomer. If that compound has one isomeric form predominant over the other, for example, 80% (*S*)-isomer and 20% (*R*)-isomer, the enantiomeric purity of the compound with respect to the (S)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or Pirkle's reagents, or derivatization of a compounds using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

[0079] In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions*, Wiley Interscience, New York, 1981; Eliel, *Stereochemistry of Carbon Compounds,* McGraw-Hill, NY, 1962; and Eliel and Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, 1994.

[0080] The terms "enantiomerically enriched" and "non-racemic," as used herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (*e.g.*, greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (*S*)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (*S*)-enantiomer relative to the (*R*)-enantiomer, such as at least 75% by weight, or such as at least 80% by weight. In some

embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially enantiomerically enriched" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, such as at least 90% by weight, or such as at least 95% by weight. The terms "enantiomerically pure" or "substantially enantiomerically pure" refers to a composition that comprises at least 98% of a single enantiomer and less than 2% of the opposite enantiomer.

[0081] "Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0082] "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (*e.g.*, in solution), a chemical equilibrium of tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. The formation of solid forms in different tautomerization states is known as "desmotropy" and such forms are known as "desmotropes."

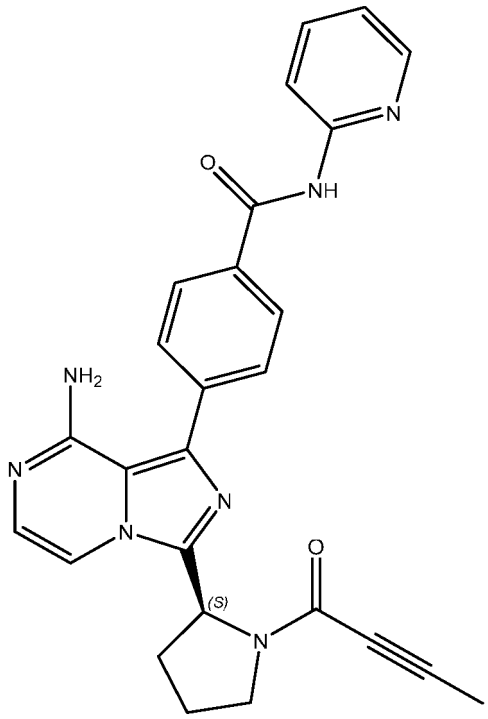
[0083] Compositions of the invention also include crystalline forms of Formula (1), including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), and conformational polymorphs, as well as mixtures thereof. "Crystalline form", "form," and "polymorph" are intended to include all crystalline forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), and conformational polymorphs, as well as mixtures thereof, unless a particular crystalline form is referred to.

[0084] "Solvate" refers to a crystalline phase of a compound in physical association with one or more molecules of a solvent. The crystalline phase of a compound in physical association with one or more molecules of water is referred to as a "hydrate."

[0085] "Amorphous form" refers to a form of a compound, or a salt or molecular complex of a compound, that lacks long range crystalline order.

Crystalline Forms

[0086] In an embodiment, the invention provides a crystalline solid form of (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide (Formula (1)). Formula (1) has the following chemical structure:



[0087] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I is characterized by at least one of: (1) an X-ray powder diffraction pattern with at least five peaks selected from the group consisting of 6.4, 8.6, 10.5, 10.9, 11.3, 11.6, 12.7, 13.4, 14.3, 14.9, 15.1, 15.7, 16.1, 17.3, 18.2, 19.2, 19.4, 19.8, 20.7, 21.1, 21.4, 21.6, 21.9, 22.6, 23.3, 23.6, 24.9, 25.2, 25.4, 25.7, 26.1, 26.4, 26.8, 26.9, 27.7, 28.6, 29.1, 29.4, 30.1, 30.5, 31.7, 31.9, 32.2, 32.6, 33.1, 33.4, 34.5, 35.9, 36.1, 36.8, 37.4, 38.1, 38.9, and 39.5, with peak positions measured in °2θ ± 0.2 °2θ; (2) a Raman spectrum with at least three peaks selected from the group consisting of 1680, 1620, 1609, 1574, 1547, 1514, 1495, 1454, 1433, 1351, 1312, 1255, 1232, 1187, 1046, 995, 706,

406, and 280, with peak positions measured in $cm^{-1} \pm 2\ cm^{-1}$; (3) an IR spectrum with at least three peaks selected from the group consisting of 3367, 3089, 2246, 1682, 1621, 1608, 1574, 1514, 1504, 1454, 1428, 1403, 1345, 1303, 1248, 1194, 1177, 1149, 1109, 1049, 1023, 1003, 947, 900, 858, 842, 816, 764, 734, 729, 701, 689, 665, 623, and 612, with peak positions measured in $cm^{-1} \pm 4\ cm^{-1}$; and (4) the absence of water in the crystal structure.

[0088] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I is characterized by an X-ray powder diffraction pattern comprising peaks at 6.4, 8.6, 10.5, 11.6, and 15.7 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I is characterized by an X-ray powder diffraction pattern comprising peaks at at 6.4, 8.6, 10.5, 11.6, and 15.7 °2θ ± 0.2 °2θ and peaks at 10.9, 12.7, 13.4, 14.3, 14.9, and 18.2 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern of FIG. 1, which may be measured using transmission mode or reflection mode. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in transmission mode. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in reflection mode.

[0089] It is known in the art that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment, sample preparation or instrument used). In particular, it is generally known that intensities in an X-ray powder diffraction pattern may vary depending on measurement conditions and sample preparation. For example, persons skilled in the art of X-ray powder diffraction will realise that the relative intensities of peaks may vary according to the orientation of the sample under test

and based on the type and settings of the instrument used. The skilled person will also realise that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer, the sample's surface planarity, and the zero calibration of the diffractometer. Hence a person skilled in the art will appreciate that the diffraction pattern data presented herein is not to be construed as absolute and any crystalline form that provides a power diffraction pattern substantially the same as those disclosed herein fall within the scope of the present disclosure. For further information, see Jenkins and Snyder, *Introduction to X-Ray Powder Diffractometry*, John Wiley & Sons, 1996.

[0090] It is also known in the art that IR and Raman spectra may be obtained which may vary depending on measurement conditions. The instrument, sampling mode (*e.g.*, attenuated total reflectance IR sampling versus transmission IR sampling), and the calibration of the instrument may affect the peak positions and intensities. A person skilled in the art will appreciate that the spectra presented herein is not to be construed as absolute and any crystalline form that provides a spectrum substantially the same as those disclosed herein fall within the scope of the present disclosure. For further information, see Colthup, *et al.*, *Introduction to Infrared and Raman Spectroscopy*, 3rd Ed., Academic Press, 1990.

[0091] Crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base Form I provides numerous surprising advantages over the amorphous (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base of the prior art, including improved chemical stability and greatly reduced hygroscopicity. With respect to other novel crystalline forms of the free base of (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide disclosed herein, Form I provides further surprising advantages including improved thermodynamic stability, faster dissolution rate, improved performance in the stomach and gastric environment (including the avoidance of, or reduced, precipitation from solution upon a change to higher pH), improved exposure in mammals, and superior processability for formulation of drug into finished products suitable for patients.

[0092] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide fumarate. In an embodiment, the invention provides a composition comprising

crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide fumarate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide fumarate Form A is characterized by at least one of: (1) an X-ray powder diffraction pattern with at least five peaks selected from the group consisting of 4.9, 5.4, 7.0, 9.8, 10.8, 11.5, 12.1, 14.1, 16.1, 16.6, 17.8, 18.5, 19.4, 20.3, 20.5, 21.9, 22.1, 22.5, 23.1, 24.0, 24.8, 26.6, 26.8, 27.3, and 28.2, with peak positions measured in °2θ ± 0.2 °2θ; and (2) the presence of water in the crystal structure with a stoichiometry relative to Formula (1) that is approximately equivalent to a sesquihydrate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide fumarate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide fumarate Form A is characterized by an X-ray powder diffraction pattern comprising peaks at 4.9, 5.4, 7.0, 10.8, and 11.5 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide fumarate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide fumarate Form A is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern of FIG. 15.

[0093] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide maleate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide maleate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide maleate Form A is characterized by at least one of: (1) an X-ray powder diffraction pattern with at least five peaks selected from the group consisting of 5.3, 9.8, 10.6, 11.6, 13.5, 13.8, 13.9, 14.3, 15.3, 15.6, 15.8, 15.9, 16.6, 17.4, 17.5, 18.7, 19.3, 19.6, 19.8, 20.0, 20.9, 21.3, 22.1, 22.3, 22.7, 23.2, 23.4, 23.7, 23.9, 24.5, 24.8, 25.2, 25.6, 26.1, 26.4, 26.7, 26.9, 27.1, 27.6, 28.8, 29.5, 30.0, 30.3, 30.9, 31.5, 31.9, 32.5, 34.0, and 35.1, with peak positions measured in °2θ ± 0.2 °2θ; and (2) the presence of water in the crystal structure with a stoichiometry relative to Formula (1) that is approximately

equivalent to a monohydrate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide maleate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide maleate Form A is characterized by an X-ray powder diffraction pattern comprising peaks at 5.3, 9.8, 10.6, 11.6, and 19.3 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide maleate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide maleate Form A is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern of FIG. 16. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in transmission mode. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in reflection mode.

[0094] In an embodiment, the invention provides a composition comprising comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide phosphate. In an embodiment, the invention provides a composition comprising comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide phosphate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide phosphate Form A is characterized by at least one of: (1) an X-ray powder diffraction pattern with at least five peaks selected from the group consisting of 4.5, 6.0, 7.2, 10.4, 12.0, 12.5, 13.1, 14.3, 15.5, 17.4, 18.0, 18.3, 18.9, 19.3, 20.2, 20.5, 20.9, 21.4, 21.9, 22.0, 22.6, 22.9, 23.1, 23.3, 24.2, 24.6, 25.0, 25.7, 26.2, 26.4, 26.9, 27.3, 27.5, 29.3, 30.0, 30.3, 30.5, 30.9, 31.2, 31.9, and 35.7, with peak positions measured in °2θ ± 0.2 °2θ; and (2) the presence of water in the crystal structure with a stoichiometry relative to Formula (1) that is approximately equivalent to a dihydrate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide phosphate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide phosphate Form A is characterized by an X-ray powder diffraction

pattern comprising peaks at 4.5, 6.0, 10.4, 12.0, and 14.3 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide phosphate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide phosphate Form A is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern of FIG. 17. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in transmission mode. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in reflection mode.

[0095] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide L-tartrate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide L-tartrate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide L-tartrate Form A is characterized by at least one of: (1) an X-ray powder diffraction pattern with at least five peaks selected from the group consisting of 4.6, 5.5, 7.2, 9.3, 10.7, 10.9, 11.8, 14.3, 14.9, 16.4, 17.0, 17.7, 19.2, 19.4, 19.5, 20.3, 21.6, 22.4, 23.3, 23.8, 24.3, 24.5, 24.7, 25.1, 25.6, 26.8, 27.2, 27.8, 28.4, 28.7, 29.0, 29.5, 30.0, 30.9, 31.6, 32.1, 32.4, 33.0, 33.5, and 33.9, with peak positions measured in °2θ ± 0.2 °2θ; and (2) the presence of water in the crystal structure with a stoichiometry relative to Formula (1) that is approximately equivalent to a sesquihydrate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide L-tartrate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide L-tartrate Form A is characterized by an X-ray powder diffraction pattern comprising peaks at 4.6, 5.5, 10.9, 11.8, and 14.9 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide L-tartrate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide L-tartrate Form A is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern

of FIG. 18. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in transmission mode. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in reflection mode.

[0096] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A is characterized by at least one of: (a) an X-ray powder diffraction pattern with at least five peaks selected from the group consisting of 6.1, 6.6, 7.2, 7.9, 8.3, 9.7, 10.8, 11.1, 12.2, 13.5, 14.1, 14.9, 15.9, 16.6, 17.5, 17.9, 18.3, 18.9, 19.5, 20.3, 21.5, 21.9, 22.7, 23.8, 24.4, 24.8, 26.1, 26.3, 27.2, 27.4, 27.9, and 29.3, with peak positions measured in °2θ ± 0.2 °2θ; (b) a Raman spectrum with at least three peaks selected from the group consisting of 3068, 2921, 2237, 1682, 1612, 1551, 1505, 1436, 1332, 1313, 1241, 1188, 993, and 712, with peak positions measured in cm^{-1} ± 2 cm^{-1}; (c) an IR spectrum with at least three peaks selected from the group consisting 3396, 2234, 1673, 1606, 1537, 1428, 1304, 1264, 1200, 1092, 1008, 893, 866, 773, 735, and 693, with peak positions measured in cm^{-1} ± 4 cm^{-1}; and (d) the presence of water in the crystal structure at a concentration between about 0% to 8% by weight. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A is characterized by at least one of: (a) an X-ray powder diffraction pattern with at least five peaks selected from the group consisting of 6.1, 6.4, 7.2, 7.9, 8.2, 9.6, 10.9, 12.0, 13.4, 13.8, 14.0, 14.9, 15.5, 15.9, 16.4, 17.3, 17.5, 18.2, 18.6, 19.3, 20.1, 20.4, 21.4, 21.6, 22.6, 23.2, 23.7, 24.3, 26.0, 27.0, 27.3, 27.8, and 29.2, with peak positions measured in °2θ ± 0.2 °2θ; (b) a Raman spectrum with at least three peaks selected from the group consisting of 3055, 2920, 2237, 1685, 1612, 1549, 1504, 1436, 1333, 1313, 1286, 1240, 1187, 993, and 712, with peak positions measured in cm^{-1} ± 2 cm^{-1}; (c) an IR spectrum with at least three peaks selected from the group consisting 3403, 2960, 2872, 2233, 1678, 1608, 1582, 1538, 1434, 1403, 1352, 1302, 1253, 1201, 1094, 1055, 1010, 967, 895, 813, 772, 750, 735, 693,

and 612, with peak positions measured in $cm^{-1} \pm 4\ cm^{-1}$; and (d) the presence of water in the crystal structure at a concentration between about 0% to about 8% by weight. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A is characterized by an X-ray powder diffraction pattern comprising peaks at 6.1, 7.2, 9.7, 11.1, and 12.2 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern of FIG. 19. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A is characterized by an X-ray powder diffraction pattern comprising peaks at 6.1, 7.2, 9.6, 10.9, and 12.0 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide citrate Form A is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern of FIG. 20. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in transmission mode. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in reflection mode.

[0097] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide gentisate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide gentisate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide gentisate Form A

is characterized by at least one of: (a) an X-ray powder diffraction pattern with at least five peaks selected from the group consisting of 4.6, 8.2, 9.0, 9.7, 11.8, 12.9, 13.8, 14.5, 15.5, 16.6, 16.8, 18.4, 19.6, 20.5, 21.1, 24.1, 24.5, 25.5, 25.8, 26.0, 26.6, 26.9, 27.4, and 29.8, with peak positions measured in °2θ ± 0.2 °2θ; (b) a Raman spectrum with at least three peaks selected from the group consisting of 3057, 2919, 2223, 1681, 1613, 1576, 1552, 1518, 1437, 1333, 1312, 1228, 1192, 1156, 990, 716, 485, and 257, with peak positions measured in cm^{-1} ± 2 cm^{-1}; (c) an IR spectrum with at least three peaks selected from the group consisting 2957, 1682, 1668, 1602, 1574, 1523, 1504, 1481, 1429, 1377, 1346, 1302, 1274, 1228, 1157, 1092, 1010, 939, 896, 865, 826, 810, 778, 748, 734, 686, 660, and 617, with peak positions measured in cm^{-1} ± 4 cm^{-1}; and (d) the presence of water in the crystal structure with a stoichiometry relative to Formula (1) that is approximately equivalent to a monohydrate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide gentisate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide gentisate Form A is characterized by an X-ray powder diffraction pattern comprising peaks at 4.6, 9.0, 12.9, 13.8, and 19.6 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide gentisate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide gentisate Form A is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern of FIG. 21. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in transmission mode. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in reflection mode.

[0098] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A is characterized by at least one of: (a) an X-ray powder diffraction pattern with peaks selected from

the group consisting of 5.5, 5.8, 7.4, 9.3, 11.0, 11.5, 12.7, 15.2, 16.5, 17.3, 18.5, 18.7, 19.1, 19.7, 20.2, 20.8, 22.0, 22.33, 23.32, 23.6, 24.8, 27.4, 28.6, 29.3, 29.6, 31.2, 33.1, and any combination thereof, with peak positions measured in °2θ ± 0.2 °2θ; (b) a Raman spectrum with peaks selected from the group consisting of 3073, 2992, 2950, 2922, 2247, 1671, 1612, 1584, 1552, 1504, 1469, 1440, 1336, 1311, 1273, 1235, 1191, 1162, 1095, 1012, 897, 718, 633, 409, 370, 263, and any combination thereof, with peak positions measured in $cm^{-1} \pm 4\ cm^{-1}$; (c) an IR spectrum with peaks selected from the group consisting 3419, 2249, 1670, 1615, 1544, 1503, 1438, 1391, 1334, 1304, 1262, 1195, 1151, 1126, 1093, 1013, 894, 877, 823, 783, 765, 738, 652, and any combination thereof, with peak positions measured in $cm^{-1} \pm 4\ cm^{-1}$; and (d) the presence of water in the crystal structure at a concentration between about 0% to about 9% by weight. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A is characterized by an X-ray powder diffraction pattern comprising peaks at 5.5, 5.8, 9.3, 11.5, and 12.7 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern of FIG. 22. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in transmission mode. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in reflection mode.

[0099] In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide sulfate. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide sulfate, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide sulfate is characterized by at least one of: (a) an X-ray powder diffraction pattern with at least five peaks selected from the group consisting of 4.6, 5.0, 8.0, 9.0, 9.8, 12.0, 12.7, 13.2, 14.6, 15.0, 15.6,

16.2, 17.5, 18.0, 19.8, 20.2, 21.9, 23.8, 24.4, 24.9, 25.7, 26.0, 27.2, 29.5, 30.4, 31.6, and 32.5, with peak positions measured in °2θ ± 0.2 °2θ; (b) a Raman spectrum with at least three peaks selected from the group consisting of 3115, 2977, 2926, 2224, 1675, 1611, 1537, 1498, 1449, 1409, 1361, 1327, 1310, 1288, 1243, 1198, 1155, 1042, 1009, 978, 948, 906, 849, 771, 713, 652, 632, 464, 370, and 254, with peak positions measured in cm^{-1} ± 4 cm^{-1}; (c) an IR spectrum with at least three peaks selected from the group consisting 3430, 3101, 3029, 2225, 1667, 1633, 1615, 1598, 1563, 1557, 1508, 1428, 1350, 1328, 1308, 1276, 1225, 1088, 1036, 1018, 925, 891, 848, 816, 783, 736, 723, 694, and 612, with peak positions measured in cm^{-1} ± 4 cm^{-1}; and (d) the presence of water in the crystal structure at a concentration between about 2.5% to about 12.5% by weight. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A is characterized by an X-ray powder diffraction pattern comprising peaks at 4.6, 9.0, 9.8, 17.5, and 18.0 °2θ ± 0.2 °2θ. In an embodiment, the invention provides a composition comprising crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A, wherein the crystalline (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide oxalate Form A is characterized by an X-ray powder diffraction pattern substantially in agreement with the X-ray powder diffraction pattern of FIG. 23. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in transmission mode. In an embodiment, the X-ray powder diffraction pattern of any of the foregoing embodiments is measured in reflection mode.

Pharmaceutical Compositions

[00100] In an embodiment, the invention provides a pharmaceutical composition comprising a crystalline form of the free base of the BTK inhibitor of Formula (1). In an embodiment, the invention provides a pharmaceutical composition comprising a crystalline solvate of the free base of Formula (1). In an embodiment, the invention provides a pharmaceutical composition comprising a crystalline hydrate of the free base of the BTK inhibitor of Formula (1). In an embodiment, the invention provides a pharmaceutical composition comprising a crystalline salt of Formula (1). In an embodiment, the invention provides a pharmaceutical composition

comprising Form I of the free base of Formula (1).

[00101] The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a solid form of the BTK inhibitor of Formula (1), as the active ingredient, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, permeation enhancers, solubilizers, or adjuvants. The pharmaceutical compositions may also contain an acidulant, as described herein, for reducing or overcoming the effects of acid reducing agents on the exposure of BTK inhibitor of Formula (1).

[00102] In some embodiments, the concentration of a solid form of the BTK inhibitor of Formula (1) provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, or 0.001% w/w, w/v, or v/v, relative to the total mass or volume of the pharmaceutical composition. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00103] In some embodiments, the concentration of a solid form of the BTK inhibitor of Formula (1) provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, or 0.001% w/w, w/v, or v/v, relative to the total mass or volume of the pharmaceutical composition. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00104] In some embodiments, the concentration of a solid form of the BTK inhibitor of Formula (1) of the invention is independently in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12% or approximately 1% to approximately 10% w/w, w/v or v/v, relative to the total mass or volume of the pharmaceutical composition. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00105] In some embodiments, the concentration of a solid form of the BTK inhibitor of Formula (1) of the invention is independently in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v, or v/v, relative to the total mass or volume of the pharmaceutical composition. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00106] In some embodiments, the amount of a solid form of the BTK inhibitor of Formula (1) of the invention is independently equal to or less than 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g or 0.0001 g. In an embodiment, the solid

form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00107] In some embodiments, the amount of a solid form of the BTK inhibitor of Formula (1) of the invention is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, or 3 g. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00108] Each of the solid forms of the BTK inhibitor of Formula (1) according to the invention is effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently range from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, from 2 to 40 mg per day, and from 5 to 25 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00109] In selected embodiments, the invention provides a pharmaceutical composition for oral administration containing a BTK inhibitor of Formula (1) and a pharmaceutical excipient suitable for oral administration. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00110] In selected embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of the BTK inhibitor of Formula (1), and (ii) a pharmaceutical excipient suitable for oral administration. In selected embodiments, the composition further contains (iii) an effective amount of another active pharmaceutical ingredient. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00111] In selected embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the

invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, sachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil emulsion. Pharmaceutical compositions of the invention also include powder for reconstitution, powders for oral consumptions, bottles (such as powder or liquid in bottle), orally dissolving films, lozenges, pastes, tubes, gums, and packs. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient(s) into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00112] The invention further encompasses anhydrous pharmaceutical compositions and dosage forms since water can facilitate the degradation of some compounds. For example, water may be added (*e.g.*, 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose

containers, blister packs, and strip packs.

[00113] Each of the solid forms of the BTK inhibitor of Formula (1) can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, glidants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[00114] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00115] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00116] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which disintegrate in the bottle. Too little may be insufficient for disintegration to occur, thus altering the rate and extent of release of the active ingredients from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds

disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

[00117] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium stearyl fumarate, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, silicified microcrystalline cellulose, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[00118] When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00119] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00120] Surfactants which can be used to form pharmaceutical compositions and dosage forms

of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[00121] An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.*, hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00122] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00123] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00124] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00125] Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00126] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate,

PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10-oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00127] Suitable lipophilic surfactants include, by way of example only: fatty alcohols, glycerol fatty acid esters, acetylated glycerol fatty acid esters, lower alcohol fatty acids esters, propylene glycol fatty acid esters, sorbitan fatty acid esters, polyethylene glycol sorbitan fatty acid esters, sterols and sterol derivatives, polyoxyethylated sterols and sterol derivatives, polyethylene glycol alkyl ethers, sugar esters, sugar ethers, lactic acid derivatives of mono- and di-glycerides, and hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols, oil-soluble vitamins/vitamin derivatives, and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00128] In an embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for compositions for non-oral use - *e.g.*, compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[00129] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, xylitol,

transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, Ɛ-caprolactam, *N*-alkylpyrrolidone, *N*-hydroxyalkylpyrrolidone, *N*-alkylpiperidone, *N*-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, .epsilon.-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, *N*-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00130] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, *N*-methylpyrrolidone, *N*-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00131] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00132] The composition can further include one or more pharmaceutically acceptable additives

and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00133] In addition, an acid or a base may be incorporated into the pharmaceutical composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, *para*-bromophenylsulfonic acid, propionic acid, *p*-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals and alkaline earth metals. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00134] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, *para*-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, and uric acid.

Dosages and Dosing Regimens

[00135] The amounts of the solid form of the BTK inhibitor of Formula (1) or Form I of the free base of Formula (1) administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, for example by dividing such larger doses into several small doses for administration throughout the day.

[00136] In selected embodiments, a solid form of the BTK inhibitor of Formula (1) is administered in a single dose. Typically, such administration will be by injection, for example by intravenous injection, in order to introduce the active pharmaceutical ingredients quickly. However, other routes may be used as appropriate. A single dose of a solid form of the BTK inhibitor of Formula (1) may also be used for treatment of an acute condition.

[00137] In selected embodiments, a solid form of the BTK inhibitor of Formula (1) is administered in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In other embodiments, a solid form of the BTK inhibitor of Formula (1) is administered about once per day to about 6 times per day. In another embodiment the administration of the solid forms of the BTK inhibitor of Formula (1) continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00138] Administration of the active pharmaceutical ingredients of the invention may continue as long as necessary. In selected embodiments, a solid form of the BTK inhibitor of Formula (1) is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the solid forms of the BTK inhibitor of Formula (1) are administered for less than 28, 14, 7, 6, 5, 4, 3, 2,

or 1 day. In selected embodiments, a solid form of the BTK inhibitor of Formula (1) is administered chronically on an ongoing basis - *e.g.*, for the treatment of chronic effects. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00139] In some embodiments, an effective dosage of a solid form of the BTK inhibitor of Formula (1) is in the range of about 1 mg to about 500 mg, about 10 mg to about 300 mg, about 20 mg to about 250 mg, about 25 mg to about 200 mg, about 10 mg to about 200 mg, about 20 mg to about 150 mg, about 30 mg to about 120 mg, about 10 mg to about 90 mg, about 20 mg to about 80 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 48 mg to about 52 mg, about 50 mg to about 150 mg, about 60 mg to about 140 mg, about 70 mg to about 130 mg, about 80 mg to about 120 mg, about 90 mg to about 110 mg, about 95 mg to about 105 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, about 195 mg to about 205 mg, or about 198 to about 202 mg. In some embodiments, an effective dosage of a solid form of the BTK inhibitor of Formula (1) is about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg. In some embodiments, an effective dosage of a solid form of the BTK inhibitor of Formula (1) is 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00140] In some embodiments, an effective dosage of a solid form of the BTK inhibitor of Formula (1) is in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2 mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.15 mg/kg to about 2.85 mg/kg, about 0.3 mg to about 2.15 mg/kg, about 0.45 mg/kg to about 1.7 mg/kg, about 0.15 mg/kg to about 1.3 mg/kg, about 0.3 mg/kg to about 1.15 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.55 mg/kg to about 0.85 mg/kg, about 0.65 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.75 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg mg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 2.15

mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg. In some embodiments, an effective dosage of a solid form of the BTK inhibitor of Formula (1) is about 0.35 mg/kg, about 0.7 mg/kg, about 1 mg/kg, about 1.4 mg/kg, about 1.8 mg/kg, about 2.1 mg/kg, about 2.5 mg/kg, about 2.85 mg/kg, about 3.2 mg/kg, or about 3.6 mg/kg. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00141] In some embodiments, a solid form of the BTK inhibitor of Formula (1) is adminstered at a dosage of 10 to 400 mg once daily (QD), including a dosage of 5 mg, 10 mg, 12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, and 500 mg once daily (QD). In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00142] In some embodiments, a solid form of the BTK inhibitor of Formula (1) is adminstered at a dosage of 10 to 400 mg BID, including a dosage of 5 mg, 10 mg, 12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, and 500 mg BID. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00143] In some embodiments, a solid form of the BTK inhibitor of Formula (1) is adminstered at a dosage of 10 to 400 mg TID, including a dosage of 5 mg, 10 mg, 12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, and 500 mg TID. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00144] An effective amount of a solid form of the BTK inhibitor of Formula (1) may be administered in either single or multiple doses by any of the accepted modes of administration of active pharmaceutical ingredients having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

Pharmaceutical Compositions for Overcoming the Effects of Acid Reducing Agents

[00145] The compositions and methods described herein can be used to overcome the effects of acid reducing agents. Acid-reducing agents can greatly limit the exposure of weakly acidic drugs (such as Formula (1) free base) in mammals. Smelick, *et al.*, *Mol. Pharmaceutics* **2013,** *10,* 4055-4062. Acid reducing agents include proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole, and ilaprazole; H_2 receptor antagonists, such as cimetidine, ranitidine, and famotidine; and antacids such as bicarbonates, carbonates, and hydroxides of aluminium, calcium, magnesium, potassium, and sodium, as well as mixtures of antacids with agents targeting mechanisms of gastric secretion. Overcoming the effects of acid reducing agents is a significant issue in the treatment of patients with cancer, inflammatory diseases, immune diseases, and autoimmune diseases, since these patients are commonly co-administered acid reducing agents for gastric irritation that often accompanies their conditions. Acid reducing agents are the most commonly prescribed medications in North America and Western Europe. Most recently approved oral cancer therapeutrics have pH-dependent solubility and thus a potential drug-drug interaction with regards to acid reducing agents. In cancer patients, it is estimated that 20-33% of all patients are using some form of acid-reducing agent. In particular cancers, such as pancreatic cancer or gastrointestinal cancers, acid reducing agent use is as high as 60-80% of patients. Smelick, *et al.*, *Mol. Pharmaceutics* **2013,** *10,* 4055-4062.

[00146] In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant selected from the group consisting of fumaric acid, tartaric acid, ascorbic acid, alginic acid, sodium alginate, potassium alginate, and Carbopol 971P (carboxypolymethylene). In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant selected from the group consisting of fumaric acid, succinic acid, D-tartaric acid, L-tartaric acid, racemic tartaric acid, ascorbic acid, isoascorbic acid (also known as erythorbic acid and D-araboascorbic acid), alginic acid, Protacid F 120 NM, Protacid AR 1112 (also known as Kelacid NF), Carbomer 941 (polyacrylic acid), and Carbopol 971P (carboxypolymethylene). In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base. In an embodiment, the acidulant is extragranular. In an embodiment, the acidulant is intragranular.

[00147] Alginic acid is a polysaccharide copolymer, β-D-mannuronic acid (M) and α-L-guluronic acid (G) linked by 1-4 glycosidic bonds. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant that is an alginic acid or salt thereof, wherein the alginic acid or salt thereof exhibits an M/G ratio selected from the group consisting of between 0.1 and 0.5, between 0.2 and 0.6, between 0.3 and 0.7, between 0.4 and 0.8, between 0.5 and 0.9, between 0.6 and 1.0, between 0.7 and 1.1, between 0.8 and 1.2, between 0.9 and 1.3, between 1.0 and 1.4, between 1.1 and 1.5, between 1.2 and 1.6, between 1.3 and 1.7, between 1.4 and 1.8, between 1.5 and 1.9, between 1.6 and 2.0, between 1.7 and 2.1, between 1.8 and 2.2, between 1.9 and 2.3, between 2.0 and 2.4, and between 2.1 and 2.5. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant that is an alginic acid or salt thereof, wherein the alginic acid or salt thereof exhibits an M/G ratio selected from the group consisting of less than 0.5, less than 1.0, less than 1.5, less than 2.0, and less than 2.5. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant that is an alginic acid or salt thereof, wherein the alginic acid or salt thereof exhibits an M/G ratio selected from the group consisting of greater than 0.5, greater than 1.0, greater than 1.5, greater than 2.0, and greater than 2.5. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant that is an alginic acid or salt thereof, wherein the alginic acid or salt thereof exhibits an M/G ratio selected from the group consisting of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, and 2.5. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base. M/G ratio, as well as the fraction of M and G groups, the fractions of MM and GG "diads," the fractions of "triads" (*e.g.*, MGG), and the fractions of larger sequences of M and G groups, may be determined by methods known to those of ordinary skill in the art, including nuclear magnetic resonance (NMR) spectroscopy (with or without digestion) and mass spectrometry. Larsen, *et al.*, *Carbohydr. Res.*, **2003,** *338,* 2325-2336.

[00148] In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant in a concentration (% mass) selected from the group consisting of between 1% and 5%, between 5% and 10%, between 10% and 15%, between 15% and 20%, between 20% and 25%, between 25% and 30%, and between 30% and 35%. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an

acidulant in a concentration (% mass) selected from the group consisting of between 1% and 5%, between 5% and 10%, between 10% and 15%, between 15% and 20%, between 20% and 25%, between 25% and 30%, and between 30% and 35%, wherein the acidulant is selected from the group consisting of fumaric acid, succinic acid, D-tartaric acid, L-tartaric acid, racemic tartaric acid, ascorbic acid, isoascorbic acid (also known as erythorbic acid and D-araboascorbic acid), alginic acid, sodium alginate, potassium alginate, Protacid F 120 NM, Protacid AR 1112 (also known as Kelacid NF), and Carbopol 971P (carboxypolymethylene). In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00149] In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant in a concentration (% mass) selected from the group consisting of less than 1%, less than 5%, less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, and less than 35%. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant in a concentration (% mass) selected from the group consisting of less than 1%, less than 5%, less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, and less than 35%, wherein the acidulant is selected from the group consisting of fumaric acid, succinic acid, D-tartaric acid, L-tartaric acid, racemic tartaric acid, ascorbic acid, isoascorbic acid (also known as erythorbic acid and D-araboascorbic acid), alginic acid, sodium alginate, potassium alginate, Protacid F 120 NM, Protacid AR 1112 (also known as Kelacid NF), and Carbopol 971P (carboxypolymethylene). In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00150] In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant in a concentration (% mass) selected from the group consisting of greater than 1%, greater than 5%, greater than 10%, greater than 15%, greater than 20%, greater than 25%, greater than 30%, and greater than 35%. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant in a concentration (% mass) selected from the group consisting of greater than 1%, greater than 5%, greater than 10%, greater than 15%, greater than 20%, greater than 25%, greater than 30%, and greater than 35%, wherein the acidulant is selected from the group consisting of fumaric acid, succinic acid, D-tartaric acid, L-tartaric acid, racemic tartaric acid, ascorbic acid, isoascorbic acid (also known as erythorbic acid and D-araboascorbic acid), alginic acid, sodium alginate, potassium alginate, Protacid F 120 NM, Protacid AR 1112 (also known as Kelacid NF), and

Carbopol 971P (carboxypolymethylene). In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00151] In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant in a concentration (% mass) selected from the group consisting of about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, and about 40%. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant in a concentration (% mass) selected from the group consisting of about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, and about 40%, wherein the acidulant is selected from the group consisting of fumaric acid, succinic acid, D-tartaric acid, L-tartaric acid, racemic tartaric acid, ascorbic acid, isoascorbic acid (also known as erythorbic acid and D-araboascorbic acid), alginic acid, sodium alginate, potassium alginate, Protacid F 120 NM, Protacid AR 1112 (also known as Kelacid NF), and Carbopol 971P (carboxypolymethylene). In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00152] In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an extragranular acidulant, wherein the extragranular acidulant is selected from the group consisting of fumaric acid, succinic acid, D-tartaric acid, L-tartaric acid, racemic tartaric acid, ascorbic acid, isoascorbic acid (also known as erythorbic acid and D-araboascorbic acid), alginic acid, sodium alginate, potassium alginate, Protacid F 120 NM, Protacid AR 1112 (also known as Kelacid NF), and Carbopol 971P (carboxypolymethylene), and combinations thereof. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an extragranular acidulant, wherein the extragranular acidulant is fumaric acid at a concentration of between about 15% to about 33% by weight. In an embodiment, a

pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an extragranular acidulant, wherein the extragranular acidulant is alginic acid or a salt thereof (such as sodium alginate or potassium alginate) at a concentration of between about 5% to about 33% by weight. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an extragranular acidulant, wherein the extragranular acidulant is L-tartaric acid at a concentration of between about 25% to about 33% by weight. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an extragranular acidulant, wherein the extragranular acidulant is ascorbic acid at a concentration of between about 20% to about 50% by weight and Carbopol 971P (carboxypolymethylene) at a concentration of between about 2.5% to about 10% by weight. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an extragranular acidulant, wherein the extragranular acidulant is fumaric acid at a concentration of between about 5% to about 15% by weight and alginic acid or a salt thereof at a concentration of about 15% to about 33% by weight. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an extragranular acidulant, wherein the extragranular acidulant is L-tartaric acid at a concentration of between about 5% to 15% by weight and alginic acid at a concentration of between about 15% to about 33% by weight.

[00153] In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant, wherein the acidulent is selected from the group consisting of fumaric acid, maleic acid, phosphoric acid, L-tartaric acid, citric acid, gentisic acid, oxalic acid, and sulfuric acid. In an embodiment, a pharmaceutical composition comprises a BTK inhibitor according to Formula (1) and an acidulant, wherein the acidulent is selected from the group consisting of fumaric acid, maleic acid, phosphoric acid, L-tartaric acid, citric acid, gentisic acid, oxalic acid, and sulfuric acid, and wherein the acidulant is a salt counterion included in a single crystalline phase with Formula (1).

[00154] In an embodiment, in addition to an acidulant, a pharmaceutical composition includes an excipient to prolong the exposure of Formula (1) to the acidic microenvironment. In an embodiment, this excipient is a polymer of natural, synthetic or semisynthetic origins. The polymer may contain acidic, anionic, or non-ionic monomers, oligomers or polymers or a mixture of acidic, anionic and non-ionic monomers or copolymers. In one version the excipient

is selected from the group consisting of hydroxypropylmethylcellulose, low substituted hydroxypropylcellulose, hydroxypropylcellulose, tocopherol polyethyleneoxide succinate (D-α-tocopherol polyethylene glycol succinate, TPGS, or vitamin E TPGS), methylcellulose, comboxymethylcellulose, sodium carboxymethylcellulose, methylacrylate, ethylacrylate, co-polymers of methyl and ethyl acrylate, hydroxypropylmethylcellulose acetate succinate, gelatin, maize starch, pea starch, modified maize starch, potato starch, modified potato starch, sodium starch glycolate, croscarmellose, crospovidone, copovidone, polyethylene glycol, polypropylene glycol, polyethylene and polypropylene glycol copolymers, polyvinylalcohol, polyvinylalcohol and polyethylene oxide copolymers. Copolymers of the foregoing polymers, where applicable, may also be used. Copolymers may be block, branched or terminal copolymers. In an embodiment, the polymer exhibits swelling, binding, or gelling properties that inhibit the disintegration, dissolution, and erosion of the pharmaceutical composition in order to prolong dissolution or to increase total dissolution. In an embodiment, the inclusion of the polymer increases dissolution rate and extent of dissolution over the use of an acidulant alone. The swelling, binding or gelling properties are pH-dependant in one embodiment, wherein the polymer swells, binds, or gels at one pH or range of pH in a different manner than at another pH. In one embodiment this may decrease dissolution at a lower pH than at a higher pH or *vice versa.* In another embodiment this leads to similar dissolution of Formula I in acidic, neutral or basic pH. This leads to similar plasma exposure independent of stomach pH.

[00155] The dissolution profile of a formulation containing one or more swelling, gelling, or binding excipients may exhibit a zero, first, or second differential rate order at one or more pH value or a mixture of different rate orders at different pH values. In an embodiment, a pharmaceutical composition will provide a constant level of drug into the gastrointestinal tract of a mammal by dissolution. Where the Formula (1) is absorbed, this leads to a sustained plasma level of drug over a period, delays the t_{max}, and reduces the c_{max} of an equivalent dose of an immediate release formulation of Formula (1). In another embodiment this leads to similar exposure in a mammal regardless of stomach pH.

Methods of Treating Solid Tumor Cancers, Hematological Malignancies, Inflammatory Diseases, Autoimmune Disorders, Immune Disorders, and Other Diseases

[00156] The pharmaceutical compositions described herein can be used in a method for treating diseases. In preferred embodiments, they are for use in treating hyperproliferative disorders.

They may also be used in treating other disorders as described herein and in the following paragraphs.

[00157] In some embodiments, the invention provides a method of treating a hyperproliferative disorder in a mammal that comprises administering to the mammal a therapeutically effective amount of a crystalline solid form of Formula (1), or a pharmaceutical composition comprising a crystalline solid form of Formula (1), including Form I of the free base of Formula (1), as described herein. In preferred embodiments, the mammal is a human. In some embodiments, the hyperproliferative disorder is cancer. In preferred embodiments, the cancer is selected from the group consisting of chronic lymphocytic leukemia, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, and Waldenström's macroglobulinemia. In preferred embodiments, the cancer is selected from the group consisting of non-Hodgkin's lymphomas (such as diffuse large B-cell lymphoma), acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, bone (*e.g.*, metastatic bone), esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (*e.g.*, lymphoma and Kaposi's sarcoma), viral-induced cancers such as cervical carcinoma (human papillomavirus), B-cell lymphoproliferative disease and nasopharyngeal carcinoma (Epstein-Barr virus), Kaposi's sarcoma and primary effusion lymphomas (Kaposi's sarcoma herpesvirus), hepatocellular carcinoma (hepatitis B and hepatitis C viruses), and T-cell leukemias (Human T-cell leukemia virus-1), B cell acute lymphoblastic leukemia, Burkitt's leukemia, juvenile myelomonocytic leukemia, hairy cell leukemia, Hodgkin's disease, multiple myeloma, mast cell leukemia, and mastocytosis. In selected embodiments, the method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate conditions (*e.g.*, benign prostatic hypertrophy (BPH)). In some embodiments, the hyperproliferative disorder is an inflammatory, immune, or autoimmune disorder. In some embodiments, the hyperproliferative disorder is selected from the group consisting of tumor angiogenesis, chronic inflammatory disease, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma and melanoma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcet's

disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidratenitis suppurativa, Sjögren's syndrome, psoriatic arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, lupus, and lupus nephritis. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base. In an embodiment, the method of any of the foregoing embodiments further includes the step of administering an acid reducing agent to the mammal. In an embodiment, the acid reducing agent is selected from the group consisting of proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole, and ilaprazole; H_2 receptor antagonists, such as cimetidine, ranitidine, and famotidine; and antacids such as bicarbonates, carbonates, and hydroxides of aluminium, calcium, magnesium, potassium, and sodium.

[00158] In some embodiments, the invention provides pharmaceutical compositions of a solid form of Formula (1) described herein for use in the treatment of cancers such as thymus cancer, brain cancer (*e.g.,* glioma), lung cancer, squamous cell cancer, skin cancer (*e.g.,* melanona), eye cancer, retinoblastoma cancer, intraocular melanoma cancer, oral cavity cancer, oropharyngeal cancer, bladder cancer, gastric cancer, stomach cancer, pancreatic cancer, bladder cancer, breast cancer, cervical cancer, head and neck cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, colon cancer, esophageal cancer, testicular cancer, gynecological cancer, ovarian cancer, thyroid cancer, CNS cancer, PNS cancer, AIDS-related cancer (*e.g.*, lymphoma and Kaposi's sarcoma), viral-induced cancer, and epidermoid cancer. In some embodiments, the invention provides pharmaceutical compositions of a solid form of Formula (1) described herein for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e.g.*, psoriasis), restenosis, or prostate (*e.g.*, benign prostatic hypertrophy (BPH)). In some embodiments, the invention provides pharmaceutical compositions of a solid form of Formula (1) described herein for use in the treatment of disorders such as myeloproliferative disorders (MPDs), myeloproliferative neoplasms, polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), myelodysplastic syndrome, chronic myelogenous leukemia (BCR-ABL1-positive), chronic neutrophilic leukemia, chronic eosinophilic leukemia, or mastocytosis. The invention also provides compositions for use in treating a disease related to vasculogenesis or angiogenesis in a mammal which can manifest as tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis,

inflammatory bowel disease, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, and hemangioma. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00159] In some embodiments, the invention provides a method of treating a solid tumor cancer with a composition including a solid form of Formula (1) described herein. In some embodiments, the invention provides a method of treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, squamous cell carcinoma including head and neck cancer. In an embodiment, the invention provides a method for treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, head and neck cancer, and colorectal cancer using a combination of a solid form of Formula (1) described herein and a second agent selected from the group consisting of bendamustine, venetoclax, gemcitabine, albumin-bound paclitaxel, rituximab, obinutuzumab, ofatumumab, pembrolizumab, nivolumab, durvalumab, avelumab, and atezolizumab. In an embodiment, the invention provides a method for treating pancreatic cancer, breast cancer, ovarian cancer, melanoma, lung cancer, head and neck cancer, and colorectal cancer using a combination of a BTK inhibitor and bendamustine, venetoclax, gemcitabine, albumin-bound paclitaxel, rituximab, obinutuzumab, ofatumumab, pembrolizumab, nivolumab, durvalumab, avelumab, and atezolizumab, wherein the BTK inhibitor is a solid form of Formula (1) described herein. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00160] In some embodiments, the invention relates to a method of treating an inflammatory, immune, or autoimmune disorder in a mammal with a composition including a solid form of Formula (1) described herein. In selected embodiments, the invention also relates to a method of treating a disease with a composition including a solid form of Formula (1) described herein, wherein the disease is selected from the group consisting of tumor angiogenesis, chronic inflammatory disease, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma and melanoma, ulcerative colitis, atopic dermatitis, pouchitis, spondylarthritis, uveitis, Behcets disease, polymyalgia rheumatica, giant-cell arteritis, sarcoidosis, Kawasaki disease, juvenile idiopathic arthritis, hidratenitis suppurativa, Sjögren's syndrome, psoriatic arthritis, juvenile rheumatoid

arthritis, ankylosing spoldylitis, Crohn's Disease, lupus, and lupus nephritis. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00161] In some embodiments, the invention relates to a method of treating a hyperproliferative disorder in a mammal with a composition including a solid form of Formula (1) described herein, wherein the hyperproliferative disorder is a B cell hematological malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, myelodysplatic syndromes, or myelofibrosis. In some embodiments, the invention relates to a method of treating a hyperproliferative disorder in a mammal with a composition including a solid form of Formula (1) described herein, wherein the hyperproliferative disorder is selected from the group consisting of chronic myelocytic leukemia, acute myeloid leukemia, DLBCL (including activated B-cell (ABC) and germinal center B-cell (GCB) subtypes), follicle center lymphoma, Hodgkin's disease, multiple myeloma, indolent non-Hodgkin's lymphoma, and mature B-cell ALL. In an embodiment, the solid form of Formula (1) in any of the foregoing embodiments is Form I of the free base.

[00162] In some embodiments, the hyperproliferative disorder is a subtype of CLL. A number of subtypes of CLL have been characterized. CLL is often classified for immunoglobulin heavy-chain variable-region (IgV_H) mutational status in leukemic cells. R. N. Damle, *et al.*, *Blood* **1999,** *94,* 1840-47; T. J. Hamblin, *et al.*, *Blood* **1999**, *94,* 1848-54. Patients with IgV_H mutations generally survive longer than patients without IgV_H mutations. ZAP70 expression (positive or negative) is also used to characterize CLL. L. Z. Rassenti, *et al.*, *N. Engl. J. Med.* **2004,** *351,* 893-901. The methylation of ZAP-70 at CpG3 is also used to characterize CLL, for example by pyrosequencing. R. Claus, *et al.*, *J. Clin. Oncol.* **2012,** *30,* 2483-91; J. A. Woyach, *et al.*, *Blood* **2014,** *123,* 1810-17. CLL is also classfied by stage of disease under the Binet or Rai criteria. J. L. Binet, *et al.*, *Cancer* **1977,** *40,* 855-64; K. R. Rai, T. Han, *Hematol. Oncol. Clin. North Am.* **1990,** *4,* 447-56. Other common mutations, such as 11q deletion, 13q deletion, and 17p deletion can be assessed using well-known techniques such as fluorescence *in situ* hybridization (FISH). In an embodiment, the invention relates to a method of treating a CLL in a human, wherein the CLL is selected from the group consisting of IgV_H mutation negative CLL, ZAP-70 positive

CLL, ZAP-70 methylated at CpG3 CLL, CD38 positive CLL, chronic lymphocytic leukemia characterized by a 17p13.1 (17p) deletion, and CLL characterized by a 11q22.3 (11q) deletion.

[00163] In some embodiments, the hyperproliferative disorder is a CLL wherein the CLL has undergone a Richter's transformation. Methods of assessing Richter's transformation, which is also known as Richter's syndrome, are described in Jain and O'Brien, *Oncology*, **2012,** *26,* 1146–52. Richter's transformation is a subtype of CLL that is observed in 5-10% of patients. It involves the development of aggressive lymphoma from CLL and has a generally poor prognosis.

[00164] In some embodiments, the hyperproliferative disorder is a CLL or SLL in a patient, wherein the patient is sensitive to lymphocytosis. In an embodiment, the invention relates to a method of treating CLL or SLL in a patient, wherein the patient exhibits lymphocytosis caused by a disorder selected from the group consisting of a viral infection, a bacterial infection, a protozoal infection, or a post-splenectomy state. In an embodiment, the viral infection in any of the foregoing embodiments is selected from the group consisting of infectious mononucleosis, hepatitis, and cytomegalovirus. In an embodiment, the bacterial infection in any of the foregoing embodiments is selected from the group consisting of pertussis, tuberculosis, and brucellosis.

EXAMPLES

Example 1. Form I of (*S*)-4-(8-Amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide (Free Base) Crystalline Anhydrate

Example 1.1. Preparation of Form I Crystalline Anhydrate

[00165] A crystallization study was performed using amorphous (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide as input. The amorphous character of this batch was confirmed by PXRD. For cooling crystallization experiments, 25 mg of amorphous Formula (1) was dissolved in 300 μL solvent, heated to 60 °C at a rate of 5 °C/hour, held for 1 hour at that temperature, and then cooled down to 5°C at the same rate. For slurry experiments, 25 mg of amorphous Formula (1) was suspended in 150 μL solvent at 20 °C for 3 days. All solids were isolated for PXRD analysis. The solvents were evaporated under vacuum (200 mbar) when a clear solution was obtained. The results are summarized in Table 1.

TABLE 1. Results of crystallization and slurry experiments for (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide.

Sample	Solvent	Type	Appearance	Appearance after evaporation	PXRD	DSC	TGA
1	methanol	Cooling crystallization	Dissolved	Solid	Amorphous	-	-
2	ethanol	Cooling crystallization	Dissolved	Gel	-	-	-
3	2-propanol	Cooling crystallization	Gel	Gel	-	-	-
4	N,N-dimethylacetamide	Cooling crystallization	Dissolved	Gel	-	-	-
5	acetone	Cooling crystallization	Dissolved	Solid	Amorphous	-	-
6	2-butanone	Cooling crystallization	Dissolved	Gel	-	-	-
7	cyclohexanone	Cooling crystallization	Dissolved	Gel	-	-	-
8	dimethyl sulfoxide	Cooling crystallization	Dissolved	Gel	-	-	-
9	chlorobenzene	Cooling crystallization	Solid	-	Amorphous	-	-
10	dichloromethane	Cooling crystallization	Dissolved	Solid	Amorphous	-	-
11	methanol - water 3:1	Cooling crystallization	Dissolved	Solid	Amorphous	-	-
12	methanol - water 1:1	Cooling crystallization	Gel	Gel	-	-	-
13	methanol - water 1:3	Cooling crystallization	Gel	Gel	-	-	-
14	ethanol - water 3:1	Cooling crystallization	Dissolved	Solid	Amorphous	-	-
15	ethanol - water 1:1	Cooling crystallization	Gel	Gel	-	-	-
16	ethanol - water 1:3	Cooling crystallization	Gel	Gel	-	-	-
17	2-propanol - water 3:1	Cooling crystallization	Dissolved	Solid	Amorphous	-	-
18	2-propanol - water 1:1	Cooling crystallization	Dissolved	Solid	Amorphous	-	-
19	2-propanol - water 1:3	Cooling crystallization	Gel	Gel	-	-	-
20	N,N-dimethylacetamide - water 3:1	Cooling crystallization	Dissolved	Gel	-	-	-
21	N,N-dimethylacetamide - water 1:1	Cooling crystallization	Dissolved	Gel	-	-	-
22	N,N-dimethylacetamide - water 1:3	Cooling crystallization	Gel	Gel	-	-	-
23	acetone - heptane 3:1	Cooling crystallization	Solid	-	Form I	-	-
24	acetone - heptane 1:1	Cooling crystallization	Solid	-	Form I	-	-
25	acetone - heptane 1:3	Cooling crystallization	Gel	Gel	-	-	-

Sample	Solvent	Type	Appearance	Appearance after evaporation	PXRD	DSC	TGA
26	2-butanone - heptane 3:1	Cooling crystallization	Gel	Gel	-	-	-
27	2-butanone - heptane 1:1	Cooling crystallization	Gel	Gel	-	-	-
28	2-butanone - heptane 1:3	Cooling crystallization	Solid	-	Amorphous	-	-
29	cyclohexanone - heptane 3:1	Cooling crystallization	Dissolved	Gel	-	-	-
30	cyclohexanone - heptane 1:1	Cooling crystallization	Gel	Gel	-	-	-
31	cyclohexanone - heptane 1:3	Cooling crystallization	Gel	Gel	-	-	-
32	dimethyl sulfoxide - water 3:1	Cooling crystallization	Gel	Gel	-	-	-
33	dimethyl sulfoxide - water 1:1	Cooling crystallization	Gel	Gel	-	-	-
34	dimethyl sulfoxide - water 1:3	Cooling crystallization	Solid	-	Amorphous	-	-
35	chlorobenzene - heptane 3:1	Cooling crystallization	Solid	-	Amorphous	-	-
36	chlorobenzene - heptane 1:1	Cooling crystallization	Solid	-	Amorphous	-	-
37	chlorobenzene - heptane 1:3	Cooling crystallization	Solid	-	Amorphous	-	-
38	dichloromethane - heptane 3:1	Cooling crystallization	Dissolved	Solid	Amorphous	-	-
39	dichloromethane - heptane 1:1	Cooling crystallization	Solid	-	Form I	207°C (-161 J/g)	-1.6% (40-140°C) -1.2% (150-240°C)
40	dichloromethane - heptane 1:3	Cooling crystallization	Gel	Gel	-	-	-
41	methyl *tert*-butyl ether	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
42	tetrahydrofuran	Slurry (20°C for 3 days)	Dissolved	Solid	Amorphous	-	-
43	diisopropyl ether	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
44	2-methyltetrahydrofuran	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
45	cyclopentyl methyl ether	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
46	methanol - water 3:1	Slurry (20°C for 3 days)	Dissolved	Solid	Amorphous	-	-
47	methanol - water 1:1	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
48	methanol - water 1:3	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
49	ethanol - water 3:1	Slurry (20°C for 3 days)	Dissolved	Solid	Amorphous	-	-
50	ethanol - water 1:1	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
51	ethanol - water 1:3	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
52	2-propanol - water 3:1	Slurry (20°C for 3 days)	Dissolved	Solid	Amorphous	-	-

Sample	Solvent	Type	Appearance	Appearance after evaporation	PXRD	DSC	TGA
53	2-propanol - water 1:1	Slurry (20°C for 3 days)	Solid	-	Form II	~105°C ~150°C ~220°C	-9.7% (40-120°C)
54	2-propanol - water 1:3	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
55	N,N-dimethylacetamide - water 3:1	Slurry (20°C for 3 days)	Dissolved	Gel	-	-	-
56	N,N-dimethylacetamide - water 1:1	Slurry (20°C for 3 days)	Dissolved	Gel	-	-	-
57	N,N-dimethylacetamide - water 1:3	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
58	acetone - heptane 3:1	Slurry (20°C for 3 days)	Solid	-	Form I	-	-
59	acetone - heptane 1:1	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
60	acetone - heptane 1:3	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
61	2-butanone - heptane 3:1	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
62	2-butanone - heptane 1:1	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
63	2-butanone - heptane 1:3	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
64	cyclohexanone - heptane 3:1	Slurry (20°C for 3 days)	Dissolved	Gel	-	-	-
65	cyclohexanone - heptane 1:1	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
66	cyclohexanone - heptane 1:3	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
67	dimethyl sulfoxide - water 3:1	Slurry (20°C for 3 days)	Solid	-	Poorly crystalline	-	-
68	dimethyl sulfoxide - water 1:1	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
69	dimethyl sulfoxide - water 1:3	Slurry (20°C for 3 days)	Solid	-	Form II	-	-
70	chlorobenzene - heptane 3:1	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
71	chlorobenzene - heptane 1:1	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
72	chlorobenzene - heptane 1:3	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-
73	dichloromethane - heptane 3:1	Slurry (20°C for 3 days)	Dissolved	Solid	Amorphous	-	-
74	dichloromethane - heptane 1:1	Slurry (20°C for 3 days)	Gel	Gel	-	-	-
75	dichloromethane - heptane 1:3	Slurry (20°C for 3 days)	Solid	-	Amorphous	-	-

[00166] The results indicate that, when solids are obtained, the amorphous form of Formula (1) is obtained from most solvents, and that Form I is difficult to crystallize but may be prepared from a very limited set of solvents, in particular certain mixtures with *n*-heptane (*e.g.*, with acetone). Form I may also be crystallized or recrystallized from ethanol at larger scales, including at 60 g scale.

[00167] Anti-solvent addition experiments were performed by stepwise addition of anti-solvent until crystallization, to a clear solution of Formula (1) in the solvent shown in Table 2. The results again highlight the difficulty in preparing crystalline Formula (1).

TABLE 2. Results of anti-solvent addition experiments for (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide.

Sample	Solvent	Type	Anti-solvent	Appearance[1]	PXRD
76	methanol	Anti-solvent	Water	FFP	Amorphous
77	ethanol	Anti-solvent	Water	FFP	Amorphous
78	2-propanol	Anti-solvent	Water	No solids	-
79	N,N-	Anti-solvent	Water	FFP	Amorphous
80	acetone	Anti-solvent	Heptane	Sticky solids	Amorphous
81	2-butanone	Anti-solvent	Heptane	Sticky solids	Amorphous
82	cyclohexanone	Anti-solvent	Heptane	FFP	Amorphous
83	dimethyl sulfoxide	Anti-solvent	Water	FFP + sticky solids	Amorphous
84	chlorobenzene	Anti-solvent	Heptane	FFP + sticky soldis	Amorphous
85	dichloromethane	Anti-solvent	Heptane	FFP	Amorphous

1. FFP refers to free flowing powder.

Example 1.2. Physical Characterization of Form I Crystalline Anhydrate

[00168] Characterization of Form I of the free base of Formula (1) produced by crystallization from acetone in the presence of methanol (referred to as sample PP502-P1 herein) was carried out using various techniques including: transmission PXRD (FIG. 1), Raman (FIG. 2) and IR spectroscopy (FIG. 3), solution-state NMR spectroscopy after dissolution of Form I, TG-FTIR, differential scanning calorimetry (DSC), semi-quantitative solubility testing, and dynamic vapor sorption (DVS; also known as gravimetric vapor sorption or GVS).

[00169] The transmission PXRD pattern of Form I was acquired using a Stoe Stadi P high-precision two circle goniometer instrument equipped with a Mythen1K Detector and a Cu-$K_{\alpha 1}$

radiation source operating at standard measurement conditions of: 40 kV tube voltage and 40 mA tube current; curved Ge monochromator; 0.02 °2θ step size; 48 seconds step time, 1.5-50.5°2θ scanning range; and detector mode including a step scan at 1°2θ detector step. Samples were prepared by placing 10 to 20 mg of material between two acetate foils in the Stoe transmission sample holder, which was rotated during measurement. The measurements using the Stoe Stadi diffractometer were taken in transmission (Debye-Scherrer) mode. This instrument can also be operated in reflection (Bragg-Brentano) mode.

[00170] FIG. 1 shows the PXRD pattern for Form I measured using transmission geometry. The following peaks were identified in the PXRD pattern of FIG. 1: 6.4, 8.7, 10.5, 11.0, 11.4, 11.6, 12.8, 13.5, 14.3, 14.9, 15.1, 15.5, 15.7, 16.1, 17.3, 18.2, 19.1, 19.2, 19.5, 19.8, 20.6, 20.8, 21.2, 21.4, 21.6, 22.0, 22.2, 22.3, 22.6, 22.8, 23.3, 23.7, 24.9, 25.2, 25.4, 25.8, 26.1, 26.5, 26.8, 27.0, 27.1, 27.7, 28.7, 29.2, 29.9, 30.5, 31.7, 32.0, 32.6, 33.1, 33.2, 33.5, 34.5, and 35.1 °2θ ± 0.2 °2θ. Form I shows distinctive peaks (relative to the other forms) at 6.4, 8.6, 10.5, 11.6, and 15.7 °2θ ± 0.2 °2θ, and shows further distinctive peaks (relative to the other forms) at 10.9, 12.7, 13.4, 14.3, 14.9, and 18.2 °2θ ± 0.2 °2θ. The PXRD pattern of FIG. 1 along with the birefringence observed the polarized optical microscopy images of Form I (sample PP502-P1), show that the anhydrate of Form I of Formula (1) is crystalline.

[00171] Reflection PXRD measurements were also performed using a second instrument, a Bruker D8 Advance powder X-ray diffractometer equipped with a LynxEye detector and operating in Bragg-Brentano reflection geometry mode. 2θ values are generally accurate to within an error of ± 0.2°. The samples were generally prepared without any special treatment other than the application of slight pressure to get a flat surface. Samples were measured uncovered unless otherwise noted. Operating conditions included a tube voltage of 40 kV and current of 40 mA. A variable divergence slit was used with a 3° window. The step size was 0.02 °2θ with a step time of 37 seconds. The sample was rotated at 0.5 rps during the measurement. When calibrated, the reflection mode PXRD pattern of Form I may be compared to the transmission mode PXRD pattern of Form I, although the person of skill in the art will appreciate that the diffraction patterns may vary, particularly with respect to peak intensities, as described herein.

[00172] The reflection PXRD pattern for Form I of Formula (1) was measured, and the

following peaks were identified in the reflection PXRD pattern: 6.36, 8.60, 10.50, 10.90, 11.32, 11.57, 12.73, 13.4, 14.27, 14.86, 15.08, 15.66, 16.09, 17.28, 18.17, 19.15, 19.39, 19.76, 20.70, 21.10, 21.36, 21.56, 21.94, 22.59, 23.3, 23.63, 24.87, 25.19, 25.37, 25.72, 26.05, 26.42, 26.77, 26.93, 27.68, 28.62, 29.11, 29.42, 30.14, 30.49, 31.69, 31.90, 32.22, 32.57, 33.05, 33.39, 34.45, 35.87, 36.09, 36.80, 37.42, 38.08, 38.86, and 39.54 °2θ ± 0.20 °2θ.

[00173] The Fourier-transform (FT) Raman spectrum of Form I was acquired using a Bruker RFS 100 FT-Raman spectrophotometer equipped with a liquid nitrogen-cooled germanium detector and a near IR Nd:YAG laser operating at 1064 nm with a power setting of 100 mW. Spectra were the result of 64 scans collected with a resolution of 2 cm^{-1} in the range between 3500 and 50 cm^{-1}. The FT-Raman spectrum of Form I is shown in FIG. 2, and exhibits peaks at 1680, 1620, 1609, 1574, 1547, 1514, 1495, 1454, 1433, 1351, 1312, 1255, 1232, 1187, 1046, 995, 706, 406, and 280 (Raman shift, $cm^{-1} \pm 2\ cm^{-1}$).

[00174] The IR spectrum of Form I (sample PP502-P1) was obtained using IR spectroscopy. The spectra were obtained by recording 32 scans using attenuated total reflectance (ATR) sampling and a Perkin Elmer BXII IR spectrometer at a resolution of 2 wavenumbers (cm^{-1}). For the spectrum shown here, the original spectra in transmission mode were converted to absorption mode using the OPUS 7.0 software from Bruker and peak tables were generated. The IR spectrum of Form I is illustrated in FIG. 3. The characteristic peaks for Form I are observed at 3367, 3089, 2246, 1682, 1621, 1608, 1574, 1514, 1504, 1454, 1428, 1403, 1345, 1303, 1248, 1194, 1177, 1149, 1109, 1049, 1023, 1003, 947, 900, 858, 842, 816, 764, 734, 729, 701, 689, 665, 623 and 612 (IR frequency, $cm^{-1} \pm 4\ cm^{-1}$).

[00175] The ^1H NMR spectrum of Form I recorded in deuterated dimethyl sulfoxide (d_6-DMSO) confirmed the molecular structure of (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide present in this crystalline anhydrate.

[00176] TGA and TG-FTIR analysis was carried out using a Netzsch Thermo-Microbalance TG 209 coupled to a Bruker FTIR spectrometer (instrument model Vector 22). The sample pans having a pinhole were tared before the sample was introduced and then and heated to 350 °C at a ramp rate of 10 °C/minute under a constant flow of a nitrogen. TG-FTIR analysis of the sample of Form I revealed a mass loss of about 0.8% upon heating to 250 °C. TG-FTIR spectroscopy showed that the observed mass loss up to 250 °C is essentially attributable to acetone solvent,

which appears to be strongly retained by Form I powders since the mass loss occurs above 200 °C. Weight loss above 250 °C is mostly attributable to decomposistion.

[00177] DSC was carried out with a Perkin Elmer DSC-7 or with a TA Instruments Q2000 instrument. Samples were prepared in a closed gold sample pan at temperature ramp rates of 10°C/minute or 20 °C/minute up to approximately 250 °C. Melting begins at about 200 °C and a peak is observed at about 214.7 °C with a heat flow of approximately 16 mW (81.9 J/g) for the melting endotherm; however, melting was concurrent with thermal decomposition and the enthalpy of fusion is thus an estimate. Nevertheless, the temperature range of the mass loss observed in the TGA analysis suggests that Form I must be molten in order to release the residual solvent. The DSC thermogram showed that after the melting event at about 214.7 °C, exothermic degradation occurs at 226.4 °C.

[00178] Form I was also tested with respect to solubilities in various water-solvent mixtures and non-aqueous solvents. Solubility studies were conducted by a stepwise dilution of a suspension of about 10 mg of Form I in 0.1 mL of analytical grade solvent. Results of the approximate solubilities are shown in Table 3. Solubility values are estimated approximations and are subject to variable experimental error.

TABLE 3. Approximate solubility measurements for Form I.

Pure Solvent	Solubility [S, mg/mL]	Solvent mixture	Solubility [S, mg/mL]
acetic acid	102 < S < 204	acetic acid:water 1:1	104 < S < 208
acetone	S ~ 2	acetic acid:ethyl acetate 1:1	92 < S < 184
acetonitrile	S < 1	acetic acid:ethyl acetate 1:9	60 < S < 90
dichloromethane, DCM	36 < S < 43	acetic acid:MEK 1:9	63 < S < 95
N,N-dimethylformamide, DMF	49 < S < 65	acetic acid:isopropanol 1:9	S ~ 4
dimethyl sulfoxide, DMSO	39 < S < 49	acetone:water 4:1	26 < S < 31
ethyl acetate	S < 1	ethanol:water 1:1	S ~ 6
ethanol	S ~ 3	ethanol:water 9:1 at 60°C	S > 60
formic acid	97 < S < 194	ethanol:water 95:5	S ~ 8
2-butanone, MEK	S < 1	MEK saturated with water	26 < S < 30
methanol	S ~ 14	methanol:MEK 1:1 at reflux	S > 90
N-methyl-2-pyrrolidone, NMP	39 < S < 49	methanol:water 9:1	S ~ 15
2-propanol	S < 1	THF:water 9:1	S > 50
tetrahydrofuran, THF	S ~ 5		
trifluoroethane	97 < S < 194		

[00179] The aqueous solubility of Form I was determined after equilibrating at 25 °C for three days. High-performance liquid chromatography (HPLC) was used to determine the concentration in filtered solution, which resulted in S ~ 68 μg/mL. PXRD of the solid residue confirmed that Form I was retained.

[00180] A gravimetric vapor sorption study was run using a standard procedure. Samples were run using a dynamic vapor sorption (DVS) analyzer. Sample sizes were approximately 10 mg. A moisture adsorption-desorption isotherm was performed as outlined below. Samples were exposed to a starting 50% RH, decreasing humidity to 0% RH, increasing humidity to 95% RH, and finally decreasing humidity back to the starting 50% RH. The DVS results, including sorption and desorption isotherm curves, show the total weight gain observed between 0% RH and 80% RH to be about 0.17%, which indicates that Form I is non-hygroscopic according to the European Pharmacopoeia (EP) classification (non-hygroscopic: < 0.2%; slightly hygroscopic: ≥ 0.2% and < 2%; hygroscopic: ≥ 2% and < 15%; very hygroscopic: ≥ 15%; deliquescent: sufficient water is absorbed to form a liquid; all values measured as weight increase at 80% RH and 25 °C). The desorption curve indicates that Form I lost moisture at a similar rate to the moisture gained during sorption, with limited hysteresis. Almost all of the adsorbed water was

removed by the end of the DVS experiment. No form change was observed by PXRD after the DVS experiment.

Example 2. Form II of (*S*)-4-(8-Amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide (Free Base) Trihydrate

Example 2.1. Preparation of Form II Crystalline Trihydrate

[00181] The crystallization study described above and reported in Table 1 also yielded Form II in a very limited set of solvents.

[00182] Form II (sample PP502-P21) of the free base of Formula (1) was also produced by dissolving Form I in an acetone-water (8:2) mixture at reflux temperature followed by cooling of the solution and removing 50% of the solvent volume under a slight nitrogen purge. The obtained samples were dried at room temperature in air and under ambient conditions (at about 45% RH). A mass loss of about 9.7% was observed after drying, corresponding to approximately 2.7 water molecules per molecule of Formula (1) (*i.e.*, a trihydrate).

Example 2.2. Physical Characterization of Form II Crystalline Trihydrate

[00183] Characterization of Form II of the free base of Formula (1) was carried out using various techniques including PXRD (FIG. 4), optical microscopy, Raman spectroscopy (FIG. 5), IR spectroscopy, TG-FTIR, DSC, DVS, and semi-quantitative solubility testing. Characterization methods used for Form II were performed as described previously for the characterization of Form I.

[00184] FIG. 4 shows the PXRD pattern for Form II of Formula (1) measured in transmission mode. The following characteristic peaks were identified in the PXRD pattern of FIG. 4: 6.6, 9.9, 11.0, 13.6, 14.0, 14.3, 18.1, 18.4, 18.9, 19.3, 20.2, 21.1, 22.0, 22.2, 22.5, 22.7, 22.9, 23.4, 23.5, 23.9, 24.2, 24.6, 25.0, 26.1, 26.6, 26.9, 27.5, 28.2, 31.0, 32.1, 32.4, 32.7, 33.4, 33.9, and 34.4 °2θ ± 0.2 °2θ. The PXRD patterns of Form I and Form II show distinct reflections for each of these forms of the free base of Formula (1). Form II shows distinctive peaks (relative to the other forms) at 5.7, 6.6, 8.2, and 9.8 °2θ ± 0.2 °2θ, and shows further distinctive peaks (relative to the other forms) at 11.0, 14.1, 14.3, 18.9, 20.1, and 24.6 °2θ ± 0.2 °2θ. An optical microscopic image of Form II showed that the Form II sample (PP502-P21) exhibits rod-shaped particles with lengths up to about 50 μm, which may adversely affect the flow and processing properties of this form, as described in Example 12.

[00185] The FT-Raman spectrum of Form II is shown in FIG. 5, and exhibits peaks (Raman shift, $cm^{-1} \pm 2\ cm^{-1}$) at 1668, 1611, 1580, 1564, 1537, 1506, 1493, 1454, 1436, 1416, 1401, 1349, 1321, 1287, 1272, 1252, 1244, 1183, 1165, 1097, 1039, 1025, 996, 950, 871, 853, 776, 730, 645, 633, 375, 352, 279, and 247.

[00186] The IR spectrum of Form II (sample PP502-P21) showed characteristic peaks at 3212, 2206, 1665, 1618, 1577, 1548, 1535, 1504, 1465, 1452, 1432, 1416, 1397, 1348, 1316, 1243, 1208, 1181, 1164, 1149, 1095, 1038, 1004, 948, 891, 869, 821, 776, 736, 716, 643, and 617 (IR frequency, $cm^{-1} \pm 4\ cm^{-1}$).

[00187] TG-FTIR preparation of Form II samples consisted of exposing two samples (PP502-P14 and PP502-P21) to 60% RH for about three days at which point both contained identical amounts of water. TG-FTIR analysis of the samples of Form II revealed a mass loss of about 10.2% upon heating to approximately 130 °C. This decrease is essentially attributable to release of water and agrees well with the theoretical water content for a trihydrate of 10.4%. Mass loss of about 0.3% upon heating thereafter to approximately 250 °C was due primarily to decomposition.

[00188] A representative DSC analysis of a Form II sample was performed. The sample was stabilized at equilibrium under approximately 62% RH before analysis using temperature ramp rates of 10 °C/minute or 20 °C/minute up to approximately 150 °C. Melting begins at about 75 °C and a peak is observed near about 109 °C with an enthalpy of fusion of about 127 J/g. The DSC thermogram shows a slight shoulder on the left side of the peak that suggests that some of the hydrate water might have been released from the sample into the residual volume of the hermetically sealed sample pan.

[00189] DVS analysis of the Form II (sample PP502-P14) was performed by exposing samples to a starting 50% RH, decreasing humidity to 0% RH, increasing humidity to 95% RH, and finally decreasing humidity back to the starting 50% RH. The DVS results, including sorption and desorption curves, show that significant water loss occurs below about 10% RH, when the trihydrate water content rapidly decreases from approximately 10% to approximately 0%. This result is consistent with the mass loss in the TGA analysis. Upon increasing the RH to 95%, water was re-adsorbed to achieve a maximum water content of about 10.4%, which corresponds to the expected water content for a trihydrate. Hysteresis was also observed between the sorption

and desorption curves. Form II thus behaves as a variable hydrate. The DVS results, including sorption and desorption isotherm curves, show the total weight gain observed between 0% RH and 80% RH to be about 10%, which indicates that Form II is hygroscopic according to the EP classification (see Example 1.2).

[00190] Finally, Form II was tested with respect to solubilities in various water-solvent mixtures and non-aqueous solvents. The aqueous solubility of Form II was determined after equilibrating at 25 °C for three days. High-performance liquid chromatography (HPLC) was used to determine the concentration of Form II in the filtered solution at approximately 14 μg/mL, which translates into a critical water activity (a_w) of about 0.59. In comparison, the aqueous solubility for Form I is about 68 μg/mL.

[00191] Critical water activity is a measure of the relative thermodynamic stability of Form I in comparison to the trihydrate Form II. Below an a_w of about 0.59, Form I is more stable at room temperature while above this value Form II is more stable. This indicates that in solvent mixtures with low water content, which are preferable for crystallization of Formula (1), Form I is the more stable form. Suspension equilibration experiments in ethanol-water mixtures, each having a different water activity, affirmed this conclusion. Water activities included in the experiments were maintained at: about 0.35 (ethanol-water ratio of 95:5, PP502-P32), about 0.53 (ethanol-water ratio of 9:1, PP502-P33) and about 0.77 (ethanol-water ratio of 7:3, PP502-P34). At an a_w of about 0.53, suspension experiments having mixtures of Form I and Form II resulted in pure Form I and at an a_w of about 0.77, the result was pure Form II.

Example 3. Form III of (*S*)-4-(8-Amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide (Free Base) Dihydrate

Example 3.1. Preparation of Form III Crystalline Dihydrate

[00192] Form III of the free base of Formula (1) was prepared from seeded crystallization experiments using Form I seeds. Saturated solutions of Formula (1) were prepared at 60 °C. The solutions were cooled and seeds of Form I were added before spontaneous crystallization occurred. The results are summarized in Table 4.

TABLE 4. Results of seeded crystallization experiments for (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide.

Sample	Solvent	Type	Appearance	PXRD	DSC	TGA
86	methanol - water 1:1	Seeding	Solid	Form III	147°C (-23.7 J/g) 215°C (141 J/g)	-4.8% (40-130°C)
87	ethanol - water 1:3	Seeding	Solid	Form III	-	-
88	2-propanol - water 1:3	Seeding	Solid	Form III	-	-
89	N,N-dimethylacetamide - water 1:2	Seeding	Solid	Poorly crystalline	-	-
90	Acetone - heptane 1:1	Seeding	Solid	Form I	-	-
91	2-butanone - heptane 1:1	Seeding	Gel	-	-	-
92	cyclohexanone - heptane 1:1	Seeding	Solid	Form I	-	-
93	dimethyl sulfoxide - water 1:3	Seeding	Solid	Poorly crystalline	-	-
94	methyl tert-butyl ether	Seeding	Solid	Amorphous	-	-
95	tetrahydrofuran - water 1:6	Seeding	Solid	Form III	-	-
96	diisopropyl ether	Seeding	Solid	Amorphous	-	-
97	2-methyltetrahydrofuran	Seeding	Solid	Poorly crystalline	-	-
98	cyclopentyl methyl ether	Seeding	Solid	Poorly crystalline	-	-
99	chlorobenzene	Seeding	Solid	Poorly crystalline	-	-
100	dichloromethane - water 1:3	Seeding	Gel	-	-	-

[00193] Form III may be prepared by crystallization of amorphous Formula (1) free base in pure water. For instance, sample PP502-P120 was the result of a slurry of amorphous Formula (1) free base (sample PP502-P107A) in water. After one day, Form III was found in the suspension, and after an extended stirring period of three days, Form III was still retained. However, because Form II may also be obtained in other experiments under similar conditions, additional procedures to prepare Form III were development.

[00194] Form III may also been prepared from amorphous Formula (1) suspended in water. To about 160 mg of amorphous Formula (1), 5.0 mL of water is added and the resulting suspension is stirred at ambient temperature. Investigation of the solid after about 24 hours of equilibration at room temperature led to crystallization of Form III.

[00195] Form III may also be prepared by direct precipitation via pH adjustment. 940 mg of Formula (1) Form I is dissolved in 4.0 mL of 1 N aqueous hydrochloric acid solution. The solution neutralized with the same amount of 1 N aqueous sodium hydroxide solution. Further dilution with 8.0 mL of water leads to a thick suspension from which the solid is separated by filtration. The glass bottle is rinsed with 16 mL of water and the wash liquid is poured onto the

glass frit filter and pulled through the filtration unit by application of vacuum. The obtained solid material is dried in an air dryer at 40 °C for about 24 hours. Powder X-ray diffraction confirms that Formula (1) Form III is obtained and thermogravimetry coupled with infrared spectroscopy shows that the sample contains about 6% water, which suggests that the material was slightly overdried. The water content found is still consistent with the result from the DVS testing as this water content is found near 40% RH.

Example 3.2. Physical Characterization of Form III Crystalline Dihydrate

[00196] Initial TGA, and DSC characterization studies of Form III of the free base of Formula (1) were performed using a Mettler Toledo TGA/DSC1 STARe System with a 34-position auto sampler. The samples were prepared using aluminium crucibles (40 µL; pierced). Typically, 5 - 10 mg of sample was loaded into a pre-weighed aluminium crucible and was kept at 30 °C for 5 minutes, after which it was heated at 10 °C/min from 30 °C to 300 °C. A nitrogen purge of 40 mL/min was maintained over the sample. As system suitability check, indium and zinc are used as references. The software used for data collection and evaluation is STARe Software v10.00 build 2480. No corrections are applied to the thermogram. Further DSC characterization of Form III was performed as described in Examples 1 and 2, using a heating rate of 20 °C/min and an open-pan configuration.

[00197] The transmission PXRD pattern of Form III is shown in FIG. 6 (sample PP502-P120). The following peaks were identified in the PXRD pattern of FIG. 6: 10.4, 12.6, 12.8, 17.9, 21.3, 21.7, 23.1, 24.2, 25.2, and 27.0 °2θ ± 0.2 °2θ. Form III shows distinctive peaks (relative to the other forms) at 7.6, 8.5, 12.6, 12.8, 14.6, 16.8, and 23.2 °2θ ± 0.2 °2θ. The weak nature of the PXRD pattern indicates that Form III is poorly crystalline. An image obtained by optical microscopy of Form III showed the presence of some crystalline material with an irregular habit.

[00198] The Raman spectrum of Form III was obtained in a similar manner as described in Example 1.2 for Form I, is shown in FIG. 7, and exhibits peaks (Raman shift, $cm^{-1} \pm 2\ cm^{-1}$) at 1668, 1609, 1562, 1535, 1494, 1450, 1350, 1324, 1306, 1264, 1245, 1190, 997, and 272.

[00199] The IR spectrum of Form III was obtained using the same method as described in Example 1.2 for Form I. The IR spectrum of Form III (sample PP502-P120) exhibits characteristic peaks at 3446, 2248, 1667, 1592, 1531, 1504, 1428, 1349, 1305, 1243, 1189, 1158, 1089, 1001, 896, 862, 829, 780, 759, 736, and 699 (IR frequency, $cm^{-1} \pm 4\ cm^{-1}$).

[00200] A DSC thermogram of Form III showed events at 147 °C (-23.7 J/g) and 215 °C (141 J/g) assigned to solvent loss and melting, respectively. Using an open pan and a 20 °C/minute heating rate, a DSC thermogram was obtained that exhibited an endotherm at 128.6 °C. By TGA, Form III was observed to lose 4.8% mass over the temperature range of 40-130 °C. Additional TGA experiments confirmed that Form III was observed to lose 6.9% mass over the temperature range of approximately 25-200 °C.

[00201] Very slight changes of the Form III PXRD pattern were found when a sample of Form III was subjected to drying under vacuum at 40 °C for about 20 hours. The changes were minute and the pattern was still characteristic to Form III. However, upon drying between 90 and 100 °C in an air dryer substantial peak shift in the PXRD pattern was observed.

[00202] Because it was known that Form III is a metastable hydrate, the DVS analysis of Form III (sample PP502-P120) was programmed to begin with increasing relative humidity instead of decreasing relative humidity. The experiment began at 50% RH, which was increased to 95% RH, decreased to 0% RH, and finally increased back to the starting 50% RH. The resulting DVS shows a maximum water content of about 8.5% at 95% RH and nearly all of the water is removed at 0% RH. The DVS results, including sorption and desorption isotherm curves, show the total weight gain observed between 0% RH and 80% RH to be about 8%, which indicates that Form III is hygroscopic according to the EP classification (see Example 1.2). Little hysteresis is observed between the sorption and desorption curves. The DVS results, combined with PXRD data taken before and after the DVS experiments, indicates that Form III is a non-stoichiometric channel hydrate, rather than a dihydrate, because the water content can vary continuously over the whole relative humidity range. Like Form II, Form III thus also behaves as a variable hydrate.

Example 4. Forms Prepared From Form II (Forms IV-VIII of the Free Base of Formula (1))

[00203] In addition to Form II, which is a trihydrate with a typical water content of about 10%, several other derivatives of Form II were also investigated. For example, when Form II is dehydrated below about 20% relative humidity (RH), another non-solvated form is obtained. This form is designated as Form IV. Characterization of Form IV was carried out using various techniques including PXRD and DSC, which were performed as described previously for the characterization of Forms I and II.

[00204] In order to evaluate the state of dehydrated Form II, a sample of the trihydrate (Form II) was placed into a 1.0 mm PXRD sample holder and kept under dry nitrogen overnight. After 24 hours, the sample holder was covered with a poly(methyl methacrylate) (PMMA) dome to keep the sample under nitrogen, and a PXRD pattern was recorded. FIG. 8 depicts the PXRD pattern for Form IV. The following peaks were identified in the PXRD pattern of FIG. 8: 7.0, 8.5, 9.6, 10.3, 11.5, 11.9, 14.3, 14.9, 16.1, 17.0, 18.2, 19.3, 20.2, 20.6, 21.1, 21.6, 22.1, 22.8, 23.1, 24.0, 25.4, 26.9, 27.6, 28.4, 28.7, 29.3, 30.4, 31.8, 32.5, 33.5, 33.9, and 34.9 °2θ ± 0.2 °2θ.

[00205] Because the DVS results of Form II indicate reversible moisture sorption-desorption behavior (see above), tests were performed to confirm that storage of the dehydrated Form II sample (*i.e.,* Form IV) at about 60% RH would again lead to the trihydrate form (Form II). Reexamination by PXRD confirms that dehydrated Form IV does revert to Form II after storage at 60% RH for three days.

[00206] DSC analysis of Form IV was performed after the sample was equilibrated under dry nitrogen for about 60 hours. The dehydrated sample was exposed to temperature ramp rates of 10 °C/minute or 20 °C/minute up to approximately 240 °C. The DSC thermogram illustrates a melting peak at approximately 159 °C with an enthalpy of fusion of about 57 J/g. Thermal decomposition begins immediately after melting.

[00207] Another dehydrated form was obtained when Form II was dried at 100 °C under vacuum for 2 hours. This form is designated as Form V. From DVS analysis of Form II (see above), it is known that Form II loses water when kept under dry nitrogen. Form V was identified while studying the behavior of Form II after exposure to elevated temperatures. Characterization of Form V was carried out using various techniques including: PXRD (FIG. 9); TG-FTIR; DSC; and Raman spectroscopy. Form V shows a distinct PXRD pattern and a new Raman spectrum, which were performed as described previously for the characterization of Forms I and II. ^{1}H NMR spectroscopy confirmed the chemical integrity of the compound.

[00208] FIG. 9 shows the PXRD pattern for Form V, and specifically, sample PP502-P44. The following peaks were identified in the PXRD pattern of FIG. 9: 4.5, 5.5, 5.9, 8.1, 10.6, 11.1, 11.9, 13.2, 17.9, 19.2, 19.9, 20.4, 21.3, 21.8, 22.6, 23.9, 24.3, 24.7, 25.0, 26.0, 26.3, 27.6, 28.6, and 30.0 °2θ ± 0.2 °2θ. Comparisons between the PXRD pattern for Form II and the PXRD pattern for Form V show overlapping peaks at 11.0, 19.3, 22.0, 22.5, 22.7, 23.9, 24.2, 24.6, 25.0,

26.1, 27.5 °2θ ± 0.2 °2θ for Form II and 11.1, 19.2, 21.8, 22.6, 23.9, 24.3, 24.7, 25.0, 26.0, 27.6 °2θ ± 0.2 °2θ for Form V with the following peaks of Form II either disappearing entirely or decreasing in intensity: 9.9, 11.0, 14.3, 18.1, 18.4, 18.9, 20.2, 22.0, 22.2, 22.5, 22.7, 22.9, 23.9, 24.6, 26.1, 26.6, 28.2, and 32.7 °2θ.

[00209] Thermoanalytical characterization of Form V was carried out using TG-FTIR and DSC analytical techniques. The TG-FTIR thermogram showed that the sample immediately loses about 5% of its water mass upon heating at a rate of 10 °C per minute to about 100 °C to 120 °C. The sample remains stable till approximately 200 °C, at which point an additional mass change of about 17% is seen due to sample decomposition upon continued heating up to approximately 340 °C to 350 °C.

[00210] DSC of a Form V sample was carried out in a sample pan sealed under ambient conditions. The DSC thermogram showed a very broad endotherm with a peak at about 125 °C. A substantial part of this endothermic signal corresponds to release of water from the sample into the void volume of the hermetically sealed sample pan since the TG-FTIR thermogram shows that the release of water commences just above ambient temperature, indicating that the water is likely to be loosely bound in the crystal structure.

[00211] The FT-Raman spectrum of Form V in the relevant fingerprint region (200 cm^{-1} to 1800 cm^{-1}) exhibits peaks (Raman shift, cm^{-1} ± 2 cm^{-1}) at 1686, 1613, 1574, 1540, 1504, 1488, 1349, 1314, 1288, 1266, 1193, 1153, 1052, 1027, 852, 775, 708, and 378. Differences in the Raman spectra of Form V and Form II are highlighted by peaks at 1686, 1574, 1488, 1314, 1266, 1193, 1153, 1052, and 708 cm^{-1} of the Form V spectra, all of which do not appear in the Form II spectrum. Furthermore, peaks appearing at 1668, 1580, 1564, 1493, 1454, 1436, 1416, 1401, 1321, 1272, 1252, 1244, 1183, 1165, 1097, 1039, 996, 950, 871, 730, 645, 633, 352, 279, and 247 cm^{-1} of the Form II spectrum are not present in the Form V spectra, indicating the presence of distinct phases.

[00212] Crystallization of Formula (1) in methanol and methanol-water mixtures (95:5) led to samples with new PXRD patterns (samples P502-P26 and PP502-P16, respectively). Form VI was the product from a crystallization experiment conducted in a methanol-water mixture (95:5) at 5 °C (sample PP502-P16). Form VI exhibits a unique PXRD pattern (FIG. 10) and Raman spectrum. Comparison of the PXRD pattern for Form VI with those of Form I and Form II

shows that neither Form I nor Form II is present in sample PP502-P16. The following characteristic peaks were identified in the PXRD pattern of Form VI: 6.5, 6.8, 8.5, 11.8, 12.6, 13.5, 13.8, 14.8, 15.0, 16.2, 16.4, 16.9, 18.5, 19.4, 19.9, 20.6, 21.6, 22.1, 22.7, 23.6, 24.5, 24.8, 25.3, 26.0, 27.2, 27.8, 28.5, 28.9, 30.2, and 34.3 °2θ ± 0.2 °2θ. Characteristic Raman peaks for Form VI are observed at 1667, 1609, 1580, 1562, 1535, 1495, 1450, 1350, 1323, 1306, 1264, 1245, 1190, 1161, 1042, 997, 838, 762, 717, 630, and 272 cm^{-1} ± 2 cm^{-1}.

[00213] Form VII was obtained from the crystallization experiment conducted in pure methanol where the obtained solid sample PP502-P26 precipitated out when stored at 4 °C. Form VII exhibits a unique PXRD pattern (FIG. 11) and Raman spectrum. Comparison of the PXRD pattern for Form VII with those of Form I and Form II shows that neither Form I nor Form II is present in sample PP502-P26. The following characteristic peaks were identified in the PXRD pattern of Form VII: 5.9, 6.5, 6.9, 7.8, 8.5, 9.6, 9.9, 10.4, 13.4, 13.9, 15.0, 16.5, 16.9, 17.7, 18.5, 19.0, 19.9, 20.8, 21.6, 22.4, 23.7, 23.9, 24.8, 25.2, 27.5, 28.3, and 30.0 °2θ ± 0.2 °2θ. Characteristic Raman peaks for Form VII are observed at 1687, 1663, 1604, 1578, 1561, 1534, 1486, 1462, 1443, 1397, 1361, 1348, 1327, 1305, 1251, 1234, 1184, 1163, 1037, 1001, 835, 774, 757, 717, 653, 606, 422, 348, and 268 cm^{-1} ± 2 cm^{-1}.

[00214] ^{1}H NMR spectroscopy shows that both Form VI and VII contain about 0.7 equivalents of methanol, and according to TG-FTIR, both forms also contain substantial amounts of water. Forms VI and VII are likely to be metastable methanol solvates or mixed solvate-hydrates (*i.e.*, methanolate-hydrate). Suspension equilibration experiments conducted at 5°C in methanol with a mixture of Forms I, VI, and VII show that pure Form I was recovered after five days, suggesting that even in pure methanol, Form I is likely to be more stable than either Form VI or Form VII.

[00215] Form VIII (sample PP502-P23) is a putative acetic acid disolvate. The PXRD pattern of Form VIII is shown in FIG. 12. The following peaks were identified in the PXRD pattern of Form VIII: 4.3, 6.2, 6.6, 8.6, 11.8, 12.0, 12.4, 15.6, 17.2, 18.0, 18.6, 19.4, 20.0, 20.9, 22.1, 22.7, 23.7, 25.1, 26.0, 26.4, and 27.5 °2θ ± 0.2 °2θ. Characteristic Raman peaks for Form VIII are observed at 1681, 1580, 1529, 1497, 1456, 1437, 1349, 1313, 1302, 1268, 1243, 1193, 1157, 1047, 1025, 1006, 951, 896, 851, 775, and 264 cm^{-1} ± 2 cm^{-1}.

[00216] An overview of the forms is presented in Table 5.

TABLE 5. Overview of crystalline forms of the free base of Formula (1).

Form	Description	Stability at Room Temperature	Comments
Form I	anhydrous, non-solvated	stable relative to Form II below a_w = 0.6	Stability at lower a_w enables isolation of Form I from organic solvents
Form II	trihydrate	stable relative to Form I above a_w = 0.6	Variable hydrate; contains up to about 10% water at variable levels
Form III	dihydrate	metastable	Higher energy variable hydrate; contains up to about 8% water at variable levels
Form IV	anhydrous, non-solvated	metastable	Form II dehydrated by low moisture
Form V	anhydrous, non-solvated	metastable	Form II dehydrated by heat
Form VI	methanol solvate	metastable	Organic solvate
Form VII	methanol solvate	metastable	Organic solvate
Form VIII	acetic acid disolvate	metastable	Organic solvate

Example 5. Preparation and Characterization of Amorphous (*S*)-4-(8-Amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide

[00217] Amorphous (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide can be prepared by various methods, including the procedure described in Example 6 of U.S. Patent Application Publication No US 2014/0155385 A1 and International Patent Application Publication No. WO 2013/010868 A1, the disclosure of which is incorporated herein by reference. Fast evaporation of the solvent from a solution in dichloromethane or in a mixture of dichloromethane with a co-solvent, *e.g.*, acetone or an alcohol, can be used to prepare the amorphous form. In addition, the amorphous form can be produced by freeze drying of an aqueous solution that contains a small amount of an acid, *e.g.*, formic acid or acetic acid, to solubilize the free base Form I.

[00218] Amorphous (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide can be prepared by adding 3.0 mL of water to 200 mg of crystalline Form I. Formic acid is then added dropwise until dissolution of the solid is complete. About 50 microliter of formic acid is typically sufficient to achieve complete dissolution of the form I. The clear solution is filtered into a 100 mL round flask through a 0.22 μm micropore polytetrafluoroethylene (PTFE) filter (for instance using a syringe) and the solution in the round flask is freeze dried. The resulting product (sample PP502-P107) is the amorphous form. Characterization of the product after freeze drying by powder X-ray diffraction reveals that the amorphous form is obtained. The resulting PXRD pattern is shown in FIG. 13. No Bragg reflections are observed, and the PXRD pattern is characterized by diffuse scattering typical of an amorphous material.

[00219] The Raman spectrum of a similarly-prepared sample of amorphous Formula (1) (sample PP502-P118) is shown in FIG. 14. The spectrum is distinct from the spectra of other crystalline forms of Formula (1). Characteristic Raman peaks are observed at 1674, 1608, 1577, 1537, 1492, 1449, 1348, 1307, 1238, 1188, and 992 cm^{-1} +/- 2 cm^{-1}.

[00220] The IR spectrum of a similarly-prepared sample of amorphous Formula (1) (sample number P502-P148) obtained with ATR sampling shows a spectrum distinct from the spectra of other crystalline forms of Formula (1). Characteristic IR peaks are observed at 1668, 1605, 1505, 1428, 1302, 1237, 1200, 1153, 1091, 997, 944, 894, 863, 776, and 735 cm^{-1} +/- 4 cm^{-1}.

[00221] Further characterization of the product after freeze drying by TG-FTIR revealed that a small amount of formic acid is present. Therefore, the obtained amorphous sample was further dried under vacuum at 80°C for about 20 hours and retested by TG-FTIR and DSC (sample PP502-P107A). TG-FTIR of the dried sample showed that only very little water and residual solvent was present. DSC of the essentially solvent-free amorphous form shows a glass transition temperature at about 130°C with a ΔC_p of about 0.3 J/(g·K). A smaller change of the heat capacity at about 120°C might be due to another fraction of amorphous material that might contain traces of solvents, thus showing a reduced glass transition temperature. Thermal degradation begins above about 160°C.

[00222] The DVS results for a similarly-prepared sample of amorphous Formula (1) (sample P502-P148), including sorption and desorption curves, was performed by exposing samples to a

starting 50% RH, decreasing humidity to 0% RH, increasing humidity to 95% RH, and finally decreasing humidity back to the starting 50% RH. The DVS results, including sorption and desorption curves, show that significant water gain occurs during sorption starting at about 20% RH. The total water gain observed between 0% RH and 80% RH is about 6% by weight, which indicates that Form II is hygroscopic according to the EP classification (see Example 1.2). Furthermore, the total mass gained up to 95% RH is approximately 13%, and the mass is irreveribily gained after sorption (with the final decrease to 50% RH only removing 5 % of the 10% moisture gained in the 50 to 95% RH range). The results illustrate the hygroscopic nature of the amorphous form, including the irreversible uptake of a large amount of water upon exposure to high RH.

Example 6. Crystalline Salts of (*S*)-4-(8-Amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide

[00223] A salt screening with (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide free base (sample PP502-P1, prepared as described above) comprised crystallization experiments with 11 different acids, including: benzoic acid, benzenesulfonic acid, citric acid, fumaric acid, hydrochloric acid, maleic acid, nicotinic acid, phosphoric acid, saccharin, succinic acid, and L-tartaric acid. Of these, crystalline samples were obtained with citric acid, fumaric acid, maleic acid, phosphoric acid, succinic acid and L-tartaric acid.

[00224] A summary of the starting materials for the salt preparations is provided in Table 6. Each prepared product was given a sample identifier as follows: SP221-XXX-Pn (XXX = salt identification code, and n = experiment/sample number).

TABLE 6. Summary of starting materials for salt preparation.

Compound	pK_a	m [g/mol]	Source / Number	Sample Designation
Free base	~5.7	465.5	Formula (1) / CML1476, Lot CS13-083 HB873-98	PP502-P1
Fumaric acid	3.0 (4.4)	116.07	Sigma # 240745	SP221-FUM-Pn
Maleic acid	1.9 (6.2)	116.1	Fluka # 63180	SP221-MLE-Pn
Phosphoric acid	2.0 (7.1)	98.0	Fluka # 79606	SP221-PO4-Pn
L-Tartaric acid	3.0 (4.4)	150.09	Fluka # 95310	SP221-LTA-Pn

[00225] Characterization of fumarate salt, maleate salt, phosphate salt and L-tartrate salt was conducted using ^{1}H NMR spectroscopy, TG-FTIR, DSC, dynamic vapor sorption, optical microscopy, high-performance liquid chromatography (HPLC) purity, laser diffraction, approximate bulk and tapped density, and aqueous solubility analytical techniques.

[00226] Once seeding crystals were obtained, the formation of crystalline salts was shown to be reproducible, with the various salts showing a good tendency towards crystallization. A summary of salt properties is detailed in Table 7.

TABLE 7. Summary of Formula (1) salt properties in comparison to free base.

Salt	Solubility (3 hours)	Melting Pt. / Thermal Stability (Decomposition Pt.)	Behavior in DVS	Solid Form Assessment
Free base	S < 1 mg/mL	215 °C, (Form I)	Form I is not hygroscopic; higher melting point	Anhydrate Form I and trihydrate Form II
Fumarate	~ 1.8 mg/mL	~ 170 °C / 170 °C	Reversible anhydrate-hydrate formation, Δm ~ 0.8% (20-80% RH)	Sesquihydrate, possibly multiple forms
Maleate	2.2 mg/mL	~ 161 °C / 170 °C	Water more strongly bound than in the fumarate, Δm ~ 0.7% (20-80% RH)	Possibly sesqui-hydrate, multiple forms
Phosphate	9.8 mg/mL	~ 157 °C / 180 °C	Reversible anhydrate-hydrate formation, Δm ~ 0.7% (20-80% RH)	At least two forms, anhydrate and hydrate
L-Tartrate	5.3 mg/mL	~ 158 °C / 165 °C	Does not completely dehydrate at 0% RH, Δm ~ 0.7% (20-80% RH)	Possibly sesqui-hydrate, possibly multiple forms

[00227] Because the solubility was measured after an equilibration time of only three hours and without adjustment of pH, the solubility of all salts is dramatically increased in comparison to the free base. Whereas the free base is a poor water soluble drug, the salts were well soluble in water.

[00228] All of the salts described above appear to form hydrates. Preliminary test experiments consisted of one to three suspension equilibration experiments for each salt. Results show that all four salts can exist in multiple solid forms including polymorphic forms.

Example 6.1. Form A of the Fumarate Salt of Formula (1)

[00229] Crystalline Form A of the fumarate salt of Formula (1) was prepared by dissolving 16.294 g of PP502-P1 free base and 4.065 g fumaric acid in 500 mL acetone. The mixture was subsequently heated to 50°C, whereby 50 mL of water was added. The water addition led to a clear solution at which time, the solution was allowed to cool to room temperature while stirring at about 300 rpm. At room temperature, the clear solution was seeded with about 20 mg of SP221-FUM-P5 and after about 48 hours, the suspension was filtered to obtain a solid which was dried in air at 40 °C for about 24 hours. Initial characterization of the obtained solid resulted in a

yield of approximately 13.6 grams (about 64%) at about 99.9% purity, as measured by high-performance liquid chromatography (HPLC).

[00230] Form A of the fumarate salt was characterized by ^{1}H NMR spectroscopy; optical microscopy, Fraunhofer laser diffraction, reflection PXRD (FIG. 15), TG-FTIR, DSC, and dynamic vapor sorption (DVS).

[00231] The chemical identity of the fumarate salt was confirmed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of the fumarate salt (sample SP221-FUM-P9) recorded in acetone solvent is consistent with a 1:1 fumarate salt. A peak near 2.1 ppm indicated a trace of acetone as residual solvent that is still present after drying.

[00232] The fumarate salt was obtained as small particles. Because the obtained salt was clumpy, the dried material was sieved through a 500 µm sieve prior to further characterization. Examination by polarized light optical microscopy was conducted by dispersing the compound in heptane and thereafter sonicating for short period of time sufficient to disperse the crystals. Optical microscopy revealed very small crystalline particles that, after sieving and dispersion, are still largely agglomerated.

[00233] Particle size distribution testing was conducted using Fraunhofer laser diffraction with values for the maximum particle size for a given percentage volume of the sample shown in Table 8 below. For example, the size dimension at x50 (42 µm) represents the maximum particle diameter below which 50% of the sample volume exists. This parameter is also known as the median particle size by volume.

TABLE 8. Particle size distribution results for the fumarate salt.

Sample	x10	x50 (median)	x90
SP221-FUM-P9a	3.6 µm	42 µm	329 µm

[00234] By monitoring these three parameters (x10, x50, x90), it is possible to determine if there are significant changes in the main particle size, as well as changes at the extremes of the distribution, possibly due to the presence of fines or oversized particles or agglomerates in the particle size distribution. The results are consisting with optical microscopy, showing a particle

size distribution function where a significant proportion of agglomerates are present.

[00235] Static light scattering techniques such as laser diffraction give a volume weighted distribution wherein the contribution of each particle in the distribution relates to the volume of that particle (equivalent to mass if the density is uniform). This is extremely useful since the distribution represents the composition of the sample in terms of its volume/mass.

[00236] PXRD, along with optical microscopy, confirmed the crystalline nature of the salt. The reflection PXRD pattern of fumarate salt sample SP221-FUM-P9 is depicted in FIG. 15 and shows the following representative peaks at: 4.9, 5.4, 7.0, 9.8, 10.8, 11.5, 12.1, 14.1, 16.1, 16.6, 17.8, 18.5, 19.4, 20.3, 20.5, 21.8, 22.1, 22.5, 23.1, 24.0, 24.8, 26.6, 26.8, 27.3, and 28.2 ± 0.2 °2θ.

[00237] Thermoanalytical characterization of Form A of the fumarate salt was carried out using TG-FTIR (sample SP221-FUM-P9) and DSC (sample SP221-FUM-P9a). TG-FTIR analysis of a representative crystalline Formula (1) fumarate sample revealed a mass loss of about 4.5%; this is essentially attributable to water loss. The amount of water attributed to the loss in mass closely matches the theoretical water content of a sesquihydrate at 4.6%. Mass loss of about 12.75% upon heating thereafter to approximately 300 °C was due primarily to decomposition. DSC of the same sample shows an endothermic peak near 162 °C that deviates from the baseline above about 120 °C and increases slowly. However, because of an exothermic degradation beginning at around 170 °C, the enthalpy of fusion cannot be evaluated reliably.

[00238] Hygroscopic behavior of the fumarate salt (sample SP221-FUM-P9a) was measured using dynamic vapor sorption. The DVS sorption and desorption results indicate that the salt loses nearly all water content at low humidity conditions while reaching a maximum saturation of approximately 6% at a RH of about 95%. The water content change between 20% and 80% RH is about 0.8%. Similar to previously described moisture adsorption-desorption isotherms, samples were exposed to a starting 50% RH, decreasing humidity to 0% RH, increasing humidity to 95% RH, and finally decreasing humidity back to the starting 50% RH.

Example 6.2. Form A of the Maleate Salt of Formula (1)

[00239] Crystalline Form A maleate salt (sample SP221-MLE-P9) was prepared by dissolving 16.296 g of PP502-P1 free base in a 350 mL of acetone and 35 mL of water mixture. The mixture was subsequently heated to 50 °C, which led to a clear solution. Thereafter, 20 mL of an

aqueous solution containing 4.043 g of maleic acid was added. Moreover, the vessel and pipette holding the aqueous maleic acid solution were washed with 1.0 mL of water and the wash solution was also included in the mixture. The solution was allowed to cool while stirring at about 300 rpm. At about 45 °C, the solution was seeded with about 20 mg of SP221-MLE-8 and further cooled to approximately 20 °C. After about 24 hours, the suspension was filtered to obtain a solid which was dried in air at 40 °C for about 20 hours. Initial characterization of the obtained solid resulted in a yield of approximately 14.1 grams (about 66%).

[00240] The maleate salt was characterized by ^{1}H NMR spectroscopy, optical microscopy, Fraunhofer laser diffraction, reflection PXRD (FIG. 16), TG-FTIR, DSC, and DVS.

[00241] The chemical identity of the maleate salt was confirmed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of the maleate salt (sample SP221-MLE-P9) recorded in acetone solvent is consistent with a 1:1 maleate salt. Similar to the ^{1}H NMR analysis of the fumarate salt of Formula (1), a minute trace (0.7%) of acetone as residual solvent is also present in the spectra.

[00242] Examination by polarized optical microscopy revealed that the maleate salt consists of small crystalline particles ranging in size from about 10 µm to about 100 µm. The prepared maleate salt was substantially larger than the particles of the fumarate salt (discussed above), the phosphate salt and the L-tartrate salt (latter two discussed below). The fine powder showed favorable flow properties and no sieving was necessary after drying.

[00243] Particle size distribution testing was conducted using Fraunhofer laser diffraction with values for the maximum particle size for a given percentage volume of the sample shown in Table 9 below.

TABLE 9. Particle size distribution results for the maleate salt.

Sample	x10	x50 (median)	x90
SP221-MLE-P9	10.7 µm	38 µm	73 µm

[00244] The particle size distribution function for the maleate salt confirmed the optical microscopy analysis in illustrating a particle size distribution ranging roughly between 10 µm and 100 µm.

[00245] Powder X-ray diffraction, along with the optical microscopy images, confirmed the

crystalline nature of the salt. The reflection PXRD pattern of maleate salt sample SP221-MLE-P9 is depicted in FIG. 16 and shows the following representative peaks at: 5.3, 9.8, 10.6, 11.6, 13.5, 13.8, 13.9, 14.3, 15.3, 15.6, 15.8, 15.9, 16.6, 17.4, 17.5, 18.7, 19.3, 19.6, 19.8, 20.0, 20.9, 21.3, 22.1, 22.3, 22.7, 23.2, 23.4, 23.7, 23.9, 24.5, 24.8, 25.2, 25.6, 26.1, 26.4, 26.7, 26.9, 27.1, 27.6, 28.8, 29.5, 30.0, 30.3, 30.9, 31.5, 31.9, 32.5, 34.0, and 35.1 °2θ ± 0.2 °2θ.

[00246] Thermoanalytical characterization of the maleate salt was carried out using TG-FTIR and DSC. TG-FTIR analysis of the representative crystalline Formula (1) maleate sample revealed a mass loss of about 5.3%; this is essentially attributable to water loss. The amount of water attributed to the loss in mass closely matches the theoretical water content of sesquihydrates at 4.6%. However, no acetone was detected. Mass loss of about 10.1% upon heating thereafter to approximately 300 °C was due primarily to decomposition. DSC of the same sample shows an endothermic peak near 174 °C, followed by decomposition.

[00247] Hygroscopic behavior of the maleate salt (sample SP221-MLE-P9) was measured using dynamic vapor sorption. The DVS sorption and desorption results indicate that the salt loses very little water at 0% RH. The sample reaches a maximum saturation of approximately 5.8 % at a RH of about 95%. The water content change between 20% and 80% RH is about 0.5%. Samples were exposed to a starting 50% RH, decreasing humidity to 0% RH, increasing humidity to 95% RH, and finally decreasing humidity back to the starting 50% RH.

Example 6.3. Form A of the Phosphate Salt of Formula (1)

[00248] Preparation of Form A of the phosphate salt of Formula (1) was accomplished as follows. First, 350 mL of acetone and 35 mL of water were added to 16.2998 grams (35 mmol) of Formula (1) free base PP502-P1. Upon heating to 50 °C, a clear solution was obtained. To this solution was slowly added 2.5 mL of 85-90% phosphoric acid (35 mmol). The solution was allowed to cool while stirring at about 300 rpm. At about 38 °C, crystallization was observed without seeding. After about 80 hours the suspension was filtered and the obtained solid was dried in air at 40 °C for about 24 hours. The yield was approximately 20.48 grams (97%). The phosphate salt was obtained as small particles. After drying the material was clumpy and very strongly agglomerated particles were observed. In order to obtain a free flowing powder for the tapped density test and particle size analysis, the dried material was sieved through a 500 μm sieve. The sample after drying was termed SP221-PO4-P5 and the sample after sieving was

termed SP221-PO4-P5a.

[00249] Initial characterization of the obtained solid resulted in a purity of about 99.9%, as measured by HPLC. Based on DVS and TG-FTIR, the phosphate salt form produced is likely to be a dihydrate having a theoretical phosphorus content of about 5.2%. The phosphorus content was examined by inductively-coupled plasma optical emission spectrometry (ICP-OES) and was determined to be approximately 4.7%, which is slightly below the required content for a 1:1 salt.

[00250] The phosphate salt was characterized by ^{1}H NMR spectroscopy, optical microscopy, Fraunhofer laser diffraction, reflection PXRD (FIG. 17), TG-FTIR, DSC, and DVS.

[00251] The chemical identity of the phosphate salt (sample SP221-PO4-P5) was confirmed by ^{1}H NMR spectroscopy as being consistent with the structure of a crystalline phosphate salt. Examination by polarized optical microscopy revealed that the phosphate salt was a crystalline material that consisted of very small particles, most of which were less than about 10 µm in diameter. The particles were clearly needle-shaped in sample SP221-PO4-P4.

[00252] Particle size distribution testing was conducted using Fraunhofer laser diffraction with values for the maximum particle size for a given percentage volume of the sample shown in Table 10 below.

TABLE 10. Particle size distribution results for the phosphate salt.

Sample	x10	x50 (median)	x90
SP221-PO4-P5	2.8 µm	29 µm	191 µm

[00253] PXRD, along with the optical microscopy analysis, confirmed the crystalline nature of the salt. The reflection PXRD pattern of a sample taken from a 20 gram batch (sample SP221-PO4-P5) of the phosphate salt is depicted in FIG. 17 and shows the following representative peaks at: 4.5, 6.0, 7.2, 10.4, 12.0, 12.5, 13.1, 14.3, 15.5, 17.4, 18.0, 18.3, 18.9, 19.3, 20.2, 20.5, 20.9, 21.4, 21.9, 22.0, 22.6, 22.9, 23.1, 23.3, 24.2, 24.6, 25.0, 25.7, 26.2, 26.4, 26.9, 27.3, 27.5, 29.3, 30.0, 30.3, 30.5, 30.9, 31.2, 31.9, and 35.7 °2θ ± 0.2 °2θ. The phosphate salt exists in at least two different crystalline forms, an anhydrous form of the crystalline structure and a hydrate form of the crystalline structure, with each form exhibiting unique PXRD patterns. The peaks of FIG. 17 correspond to the hydrate form of the crystalline phosphate salt.

[00254] Thermoanalytical characterization of the phosphate salt was carried out using TG-FTIR and DSC. TG-FTIR analysis of the crystalline Formula (1) phosphate salt (sample SP221-PO4-P1) revealed a mass loss of about 5.9%; this is essentially attributable to water loss. This result suggests that the obtained crystalline form of the phosphate is a dihydrate since the 5.9% water content of the phosphate sample is close to the expected content for a dihydrate (6.0%). Additional mass losses upon heating thereafter to approximately 250 °C were due primarily to decomposition. DSC of the same sample shows a broad endothermic peak near 138 °C. The enthalpy of fusion is estimated to about 134 J/g.

[00255] Hygroscopic behavior of the phosphate salt (sample SP221-PO4-P1) was measured using DVS. The DVS sorption and desorption results indicate that the salt loses nearly all water content at low RH conditions while reaching a reaching a maximum saturation of approximately 6.6 % at a RH of about 95%. DVS analysis suggests that the phosphate salt forms a dihydrate with a water content of about 6.0%. Samples were exposed to a starting 50% RH, decreasing humidity to 0% RH, increasing humidity to 95% RH, and finally decreasing humidity back to the starting 50% RH.

Example 6.4. Form A of the L-Tartrate Salt of Formula (1)

[00256] Crystalline Form A of Formula (1) L-tartrate salt was prepared by dissolving 16.298 g of PP502-P1 free base in a 350 mL of acetone and 35 mL of water mixture. The mixture was subsequently heated to 50 °C, which led to a clear solution. Thereafter, 20 mL of an aqueous solution containing 5.257 g of L-tartaric acid was added to the clear solution. The solution was allowed to cool to approximately 20 °C while stirring at about 300 rpm. After about 24 hours, the suspension was filtered to obtain a solid which was dried in air at 40 °C for about 20 hours. Initial characterization of the obtained solid resulted in a yield of approximately 20.1 grams (about 89%) at about a 99.78% purity, as measured by HPLC.

[00257] The L-tartrate salt was characterized by ^{1}H NMR spectroscopy, optical microscopy, Fraunhofer laser diffraction, reflection PXRD (FIG. 18), TG-FTIR, DSC, and DVS.

[00258] The chemical identity of the L-tartrate salt (sample SP221-LTA-P8) was confirmed by ^{1}H NMR spectroscopy as being consistent with the structure of a 1:1 crystalline L-tartrate salt. The L-tartrate salt was obtained as a crystalline material; examination by polarized optical microscopy revealed that the material consists of partially agglomerated fine needles varying in

length from about 2 to about 40 μm and widths on the order of a few μm.

[00259] Particle size distribution testing was conducted using Fraunhofer laser diffraction with values for the maximum particle size for a given percentage volume of the sample shown in Table 11 below.

TABLE 11. Particle size distribution results for the L-tartrate salt.

Sample	x10	x50 (median)	x90
SP221-LTA-P8a	1.7 μm	17 μm	59 μm

[00260] PXRD, along with the optical microscopy images of FIG. 18, confirmed the crystalline nature of the salt. The reflection PXRD pattern of L-tartrate salt sample SP221-LTA-P8 is depicted in FIG. 18 and shows the following representative peaks at: 4.6, 5.5, 7.2, 9.3, 10.7, 10.9, 11.8, 14.3, 14.9, 16.4, 17.0, 17.7, 19.2, 19.4, 19.5, 20.3, 21.6, 22.4, 23.3, 23.8, 24.3, 24.5, 24.7, 25.1, 25.6, 26.8, 27.2, 27.8, 28.4, 28.7, 29.0, 29.5, 30.0, 30.9, 31.6, 32.1, 32.4, 33.0, 33.5, and 33.9 °2θ ± 0.2 °2θ.

[00261] Thermoanalytical characterization of the L-tartrate salt was carried out using TG-FTIR and DSC. TG-FTIR analysis of the crystalline Formula (1) L-tartrate salt (sample SP221-LTA-P8) revealed a mass loss of about 4.8%; this is essentially attributable to water loss. This amount of water is near the theoretical amount of water for a sesquihydrate which is 4.3%. Additional mass loss of about 20% upon heating thereafter to approximately 300 °C was due primarily to decomposition. DSC of sample SP221-LTA-P8a shows an endothermic peak near 156.5 °C with an enthalpy of fusion of about 40.70 J/g.

[00262] Hygroscopic behavior of the L-tartrate salt (sample SP221-LTA-P8a) was measured using dynamic vapor sorption. The DVS sorption and desorption results indicate that the salt loses water at low humidity conditions while reaching a maximum saturation of approximately 5.4% at a RH of about 95%. Moreover, from an initial water content of about 4.8% at 50% RH (confirmed by TG-FTIR, which showed a total water content of about 4.8%), the DVS analysis suggests that about 30% of this water was removed within the timescale of the measurement. The water content change between 20% and 80% RH is about 0.7%. Moisture adsorption-desorption isotherms were prepared in a similar manner as described above.

Example 6.5. Form A of the Citrate Salt of Formula (1)

[00263] Citric acid has the molecular formula $C_6H_8O_7$ and a molecular mass of 192.12 g/mol. The pK_a values of the three carboxylic acid groups in citric acid are 2.93, 4.76 and 6.40. Crystallization of the citrate salt from acetone-water mixtures led to samples that contained significant amounts of acetone and some water, while crystallization from 1-propanol led to a sample that contained a large amount of 1-propanol, indicating that both phases may be solvates.

[00264] Sample SP221-CIT-P4 was prepared as follows: 941 mg of free base of Formula (1) (PP502-P1) and 384.5 mg citric acid was dissolved in 22 mL of acetone-water (10:1) by heating the mixture to 50 °C. Upon cooling to room temperature, a dilute suspension formed that was stirred in an open vial to let some solvent evaporate. More acetone was added, which led to a thicker suspension and which was filtered after stirring at room temperature for about one hour. About 436 mg of a white solid product was obtained after drying in air at room temperature. The product from experiment SP221-CIT-P4 was further dried in air at 40°C for 24 hours to provide sample SP221-CIT-P4A. Batches produced by the procedures used for SP221-CIT-P4 and SP221-CIT-P4A may be additionally exposed to controlled humidity in order to exchange acetone for water.

[00265] Sample SP221-CIT-P6 was prepared as follows: 466 mg of free base of Formula (1) (PP502-P1) and 96.4 mg citric acid was dissolved in 10 mL 1-propanol 10:1 by heating the mixture to 70 °C. At 50 °C the mixture was seeded with SP221-CIT-P4 and let cool to room temperature. A suspension formed from which the solid product was filtered off after stirring at room temperature for about one hour. About 660 mg of a white solid product was obtained after drying in air at room temperature. Batches produced by the procedure used for SP221-CIT-P6 may be additionally exposed to controlled humidity in order to exchange 1-propanol for water.

[00266] ^{1}H NMR spectroscopy of the product from experiment SP221-CIT-P4 revealed a ratio of Formula (1) to citric acid of about 2:1 (1.83) based on the sum of the integrals for the 10 aromatic protons of Formula (1) divided by the integral from the four protons from the methylene groups of citric acid between 2.6 and 2.9 ppm. The 1:2 citric acid:Formula(I) may be a phase containing both ionized citric acid (as in a salt) and non-ionized citric acid (as in a cocrystal). The molecular formula of a 2:1 salt or co-crystal of Formula (1) with citric acid is $2\cdot[C_{26}H_{23}N_7O_2] + C_6H_8O_7$ with a molecular weight of 1123.1 g/mol. In an initial attempt to

convert the acetone solvate into a hydrate sample, SP221-CIT-P4 was subjected to suspension equilibration in water at 25 °C for 24 hours, which resulted in conversion to Form III of the free base of Formula (1) (the dihydrate).

[00267] Reflection PXRD patterns of the citrate salt obtained from acetone-water (SP221-CIT-P4) and 1-propanol (SP221-CIT-P6) are shown in FIG. 19 and FIG. 20, respectively. A comparison of the two PXRD patterns illustrates that the PXRD patterns of the two forms show remarkable similarities, indicating a similar crystal lattice for both samples, and thus the two patterns likely represent two different solvation states of a single host structure comprising citrate and Formula (1). Both samples are therefore designated Form A. Form A of the citrate salt of Formula (1) can also include other small organic solvents and water in variable amounts. The following peaks are characteristic of Form A of the citrate salt of Formula (1), when in the approximate solvation state of sample SP221-CIT-P4a: 6.1, 6.6, 7.2, 7.9, 8.3, 9.7, 10. 8, 11.1, 12.2, 13.5, 14.1, 14.9, 15.9, 16.6, 17.5, 17.9, 18.3, 18.9, 19.5, 20.3, 21.5, 21.9, 22.7, 23.8, 24.4, 24.8, 26.1, 26.3, 27.2, 27.4, 27.9, and 29.3 °2θ ± 0.2 °2θ. The following peaks are characteristic of Form A of the citrate salt of Formula (1), when in the approximate solvation state of sample SP221-CIT-P6: 6.1, 6.4, 7.2, 7.9, 8.2, 9.6, 10.9, 12.0, 13.4, 13.8, 14.0, 14.9, 15.5, 15.9, 16.4, 17.3, 17.5, 18.2, 18.6, 19.3, 20.1, 20.4, 21.4, 21.6, 22.6, 23.2, 23.7, 24.3, 26.0, 27.0, 27.3, 27.8, and 29.2 °2θ ± 0.2 °2θ. The foregoing characteristic peaks may vary in their position with the exchange of solvent into this crystalline phase.

[00268] Raman spectroscopy of Form A of the citrate salt of Formula (1) was performed on samples SP221-CIT-P4a and SP221-CIT-P6. The Raman spectrum of a dried sample of SP221-CIT-P4, named sample SP221-CIT-P4a, was obtained. Characteristic Raman peaks for Form A of the citrate salt of Formula (1), when in the approximate solvation state of sample SP221-CIT-P4a, are observed at 3068, 2921, 2237, 1682, 1612, 1551, 1505, 1436, 1332, 1313, 1241, 1188, 993 and 712 (Raman shift, $cm^{-1} \pm 2\ cm^{-1}$). The Raman spectrum for sample SP221-CIT-P6 was also obtained. Characteristic Raman peaks for Form A of the citrate salt of Formula (1), when in the approximate solvation state of sample SP221-CIT-P6, are observed at 3055, 2920, 2237, 1685, 1612, 1549, 1504, 1436, 1333, 1313, 1286, 1240, 1187, 993 and 712 (Raman shift, $cm^{-1} \pm 2\ cm^{-1}$). The foregoing characteristic peaks may vary in their position with the exchange of solvent into this crystalline phase.

[00269] ATR-IR spectroscopy of Form A of the citrate salt of Formula (1) was performed on samples SP221-CIT-P4a and SP221-CIT-P6. The IR spectrum of sample SP221-CIT-P4a was obtained. Characteristic IR peaks for Form A of the citrate salt of Formula (1), when in the approximate solvation state of sample SP221-CIT-P4a, are observed at 3396, 2234, 1673, 1606, 1537, 1428, 1304, 1264, 1200, 1092, 1008, 893, 866, 773, 735, and 693 (IR frequency, $cm^{-1} \pm 4$ cm^{-1}). The IR spectrum of sample SP221-CIT-P6 was also obtained. Characteristic IR peaks for Form A of the citrate salt of Formula (1), when in the approximate solvation state of sample SP221-CIT-P6, are observed at 3403, 2960, 2872, 2233, 1678, 1608, 1582, 1538, 1434, 1403, 1352, 1302, 1253, 1201, 1094, 1055, 1010, 967, 895, 813, 772, 750, 735, 693, and 612 (IR frequency, $cm^{-1} \pm 4$ cm^{-1}). The foregoing characteristic peak positions may vary in their position with the exchange of solvent into this crystalline phase.

[00270] TG-FTIR analysis was carried out on three different samples of the citrate salt. The TG-FTIR thermogram of sample SP221-CIT-P4 showed that the sample contains both water and acetone and that the water is less strongly bound than the acetone. A sample of SP221-CIT-P4 was stored for three months after preparation at ambient conditions and denoted sample SP221-CIT-P3. TG-FTIR analysis of this sample revealed that most of the mass loss was due to water. This provides evidence that acetone was slowly replaced by water over time, with a water content increase to about 8%. This observation is supported by the finding that typically the mass loss occurs in two steps. In the first step water and some acetone is released and in the second step the mass loss is predominantly due to acetone. The theoretical acetone content for a Formula (1):citrate 2:1 salt acetone monosolvate would be 5% and the theoretical water content for a pentahydrate would be 8%. Therefore, in addition to an acetone solvate (or a mixed acetone solvate-hydrate), a pure hydrated state of Form A of the citrate salt of Formula (1) can be prepared. The result from TG-FTIR analysis of the 1-propanol solvate showed two distinct steps, which may indicate that a second 1-propanol solvate phase with a different stoichiometry exists.

[00271] Sample SP221-CIT-P3 of Form A of the citrate salt of Formula (1) was selected for a DSC test in a closed sample pan and was observed to exhibit a broad endotherm that obscured melting. For a second DSC experiment, the citrate sample SP221-CIT-P3 was stored under 33% relative humidity for several days of equilibration. The resulting DSC thermogram did not show any significant differences. The maximum of the endothermic signal is at 90 °C; however, the

deviation from the baseline begins even below 60°C and a pronounced shoulder is found at about 82 °C. An exotherm that begins at about 140 °C is likely the result of thermal degradation.

[00272] Dynamic vapor sorption (DVS) analysis of the citrate salt (sample SP221-CIT-P4) shows that the given salt form absorbs a substantial amount of water at high humidity conditions (up to 12% over the range of 0 to 100% RH) and that at the end of the test the water content is about 7.5% by weight. It is likely that part of the acetone that was found by TG-FTIR was exchanged by water during the DVS test.

Example 6.6. Form A and Other Forms of the Gentisate Salt of Formula (1)

[00273] Gentisic acid has the chemical name 2,5-dihydroxybenzoic acid, the molecular formula $C_7H_6O_4$, and a molecular mass of 154.12 g/mol. The pK_a of gentisic acid is 2.93. The gentisate salt was first identified in the screen described above (sample SP221-GEN-P1) and was reproduced by crystallization from an acetone-water mixture as an acetone hemisolvate (SP221-GEN-P2). Suspension equilibration of the acetone hemisolvate in acetonitrile led to a crystalline sample that did not contain residual organic solvent (sample SP221-GEN-P3). TG-FTIR showed that this sample contained about 2.6% of water. This result agreed well with the theoretical water content for a gentisate monohydrate of 2.8%.

[00274] Sample SP221-GEN-P1 was prepared as follows: 235.6 mg of Formula (1) free base (PP502-P1, 0.5 mmol) was dissolved in 4.0 mL of acetone-water (9:1) at 57 °C and 5.0 mL of a 0.1 M stock solution of gentisic acid in acetone was added. The mixture was allowed to cool to room temperature and stirred while the cap was kept open to let acetone evaporate. After a suspension with a volume of about 3 mL was obtained, the solid product was filtered off and dried in air at room temperature.

[00275] Sample SP221-GEN-P2 was prepared as follows: 470 mg of Formula (1) free base (PP502-P1, 0.5 mmol) was dissolved in 11.0 mL of a 0.1 M stock solution of gentisic acid in acetone. 2.0 mL of water was added to this solution. The solution was seeded with a small amount of SP221-GEN-P1 and stirred in an open vial to allow solvent evaporation. The solution was allowed to cool to room temperature and was stirred while the cap was left open to continue to allow acetone to evaporate. After a suspension with a volume of about 3 mL was obtained, the solid product was filtered off and dried in air at room temperature.

[00276] Sample SP221-GEN-P3 was prepared as follows: 2.0 mL of acetonitrile was added to

58 mg of sample SP221-GEN-P2, and the resulting suspension was stirred at room temperature for three days. The solids were filtered and dried in air at room temperature.

[00277] Sample SP221-GEN-P4 was prepared as follows: 466 mg of PP502-P1 (0.5 mmol) and 154 mg of gentisic acid dissolved in 10.0 mL of 2-propanol by heating to 70 °C. To facilitate dissolution, 0.2 mL of formic acid was added. The solution was allowed to cool to room temperature and was seeded with SP221-GEN-P2 at about 45 °C, and 5.0 mL of 2-propanol was added. Within about four hours a suspension was obtained from which the solid product was filtered off and dried in air at room temperature.

[00278] An additional batch (sample SP221-GEN-P5) of the gentisate salt of Formula (1) monohydrate was prepared by a similar method as was used to prepare SP221-GEN-P3. To about 400 mg of sample SP221-GEN-P4 was added 4.2 mL of acetonitrile containing 5% water. The resulting suspension was stirred at room temperature for one day. The solids were filtered off and dried product in air at room temperature. Sample SP221-GEN-P5A was prepared by keeping sample SP221-GEN-P5 at 33% relative humidity for two weeks.

[00279] A second hydrate, possibly a dihydrate, was obtained as the solid residue after a solubility test (sample SP221-GEN-P6).

[00280] ^{1}H NMR spectroscopy of the product from experiment SP221-GEN-P5 revealed a ratio of Formula (1) free base to gentisic acid of 1:1 based upon the sum of integrated signals of four aromatic protons of Formula (1) between 7.5 and 8.5 ppm and two aromatic protons of gentisic acid that appear between 6.6 and 7.0 ppm. The ^{1}H NMR spectrum also showed that the obtained material is essentially free of organic solvent.

[00281] In addition, sample SP221-GEN-P5 was analyzed for CHNO content by elemental composition analysis. The molecular formula of a 1:1 salt of Formula (1) with gentisic acid is expected to be $C_{33}H_{29}N_7O_6$ with a molecular weight of 619.6 g/mol. A monohydrate of a 1:1 salt of Formula (1) with gentisic acid would have the molecular formula of $C_{33}H_{31}N_7O_7$ and a molecular weight of 637.65 g/mol (with a water content of 2.8%). The results as presented in Table 12 are in agreement with the expected formula for a monohydrate.

TABLE 12. Results from elemental composition analysis and water content determination for sample SP221-GEN-P5.

Element	% found	$C_{33}H_{31}N_7O_7$
C	60.9	62.16
H	5.1	4.90
N	15.0	15.38
O	16.5	17.56
water	2.6*	2.82

*This value was taken from the TG-FTIR analysis of sample SP221-GEN-P3, as described below.

[00282] Optical microscopy of the gentisate salt of Formula (1) monohydrate (sample SP221-GEN-P5) showed crystalline material with predominantly needle-shaped particles with lengths of about 5 to 50 μm and widths of about 1 to 10 μm.

[00283] A reflection PXRD pattern of the gentisate salt of Formula (1) monohydrate is shown in FIG. 21 (sample SP221-GEN-P3). The PXRD pattern of sample SP221-GEN-P5 (not shown) was indistinguishable from the pattern of sample SP221-GEN-P3, indicating that both samples are representative of the same crystalline phase. This crystalline phase is designated Form A (monohydrate) of the gentisate salt of Formula (1). The following peaks are characteristic of Form A (monohydrate) of the gentisate salt of Formula (1): 4.6, 8.2, 9.0, 9.7, 11.8, 12.9, 13.8, 14.5, 15.5, 16.6, 16.8, 18.4, 19.6, 20.5, 21.1, 24.1, 24.5, 25.5, 25.8, 26.0, 26.6, 26.9, 27.4, and 29.8 °2θ ± 0.2 °2θ.

[00284] Raman spectroscopy was performed using a sample of Form A (monohydrate) of the gentisate salt of Formula (1) (sample SP221-GEN-P5). The Raman spectrum was obtained in a similar manner as described in Example 1.2 for Form I. Characteristic Raman peaks for Form A (monohydrate) of the gentisate salt of Formula (1) were observed at 3057, 2919, 2223, 1681, 1613, 1576, 1552, 1518, 1437, 1333, 1312, 1228, 1192, 1156, 990, 716, 485, and 257 (Raman shift, $cm^{-1} \pm 2\ cm^{-1}$).

[00285] IR spectroscopy was performed using a sample of Form A (monohydrate) of the gentisate salt of Formula (1) (sample SP221-GEN-P5). The IR spectrum was obtained in a similar manner as described in Example 1.2 for Form I. Characteristic IR peaks for Form A (monohydrate) of the gentisate salt of Formula (1) are observed at 2957, 1682, 1668, 1602, 1574,

1523, 1504, 1481, 1429, 1377, 1346, 1302, 1274, 1228, 1157, 1092, 1010, 939, 896, 865, 826, 810, 778, 748, 734, 686, 660, and 617 (IR frequency, $cm^{-1} \pm 4\ cm^{-1}$).

[00286] The TG-FTIR thermogram of Form A (monohydrate) of the gentisate salt of Formula (1) (sample SP221-GEN-P3) showed 2.64% mass loss by 120 °C and decomposition beginning at 220 °C. DSC of Form A (monohydrate) of the gentisate salt of Formula (1) (sample SP221-GEN-P5A) revealed two small endothermic peaks at 106 °C and 121 °C. These peaks are unlikely to correspond to melting of the salt, but can be assigned to phase transformations. The deviation from the baseline at 180 °C is tentatively attributed to the beginning of a melting process; however, thermal degradation is the dominating phenomenon above 195 °C and a distinct melting point could not be identified by DSC.

[00287] DVS analysis of Form A (monohydrate) of the gentisate salt of Formula (1) (sample SP221-GEN-P5) reveals several steps of approximately 2% water content when scanning from high to lower RH. This suggests that more than one hydrate might exist. Even though the observed hysteresis was not symmetrical, a second test of the same sample has shown that the entire DVS hydration-dehydration cycle is reversible. PXRD of the sample recovered from the DVS sample pan showed the same pattern as the solid residue of the solubility experiments. The water content of 5.2% essentially corresponds to the water content of a dihydrate. The following peaks are characteristic of the dihydrate gentisate salt of Formula (1) obtained after the DVS test: 4.6, 8.7, 11.7, 12.5, 12.8, 13.1, 14.1, 15.1, 15.6, 16.5, 16.8, 19.7, 24.1, 24.5, 25.3, 25.7, 25.9, 26.6, 26.9, and 29.4 °2θ ± 0.2 °2θ.

[00288] In total, five different PXRD patterns were obtained for the six different samples of the gentisate salt of Formula (1). The PXRD pattern of the gentisate salt acetone solvate (sample SP221-GEN-P2) was distinct. TG-FTIR analysis of this solvate (sample SP221-GEN-P2) showed 5.0% mass loss by 150 °C (corresponding to acetone and water) with decomposition beginning at 220 °C. The PXRD pattern of the gentisate salt of Formula (1) formic acid solvate (sample SP221-GEN-P2) was also distinct. TG-FTIR analysis of this solvate (sample SP221-GEN-P4) showed 8.6% mass loss by 150 °C (corresponding to formic acid and water), with decomposition beginning at 220 °C. Finally, the PXRD pattern of the gentisate salt of Formula (1) dihydrate (sample SP221-GEN-P6) was also distinct from the other phases.

Example 6.7. Form A of the Oxalate Salt of Formula (1)

[00289] Oxalic acid has the molecular formula $C_2H_2O_4$ with a molecular mass of 90.04 g/mol. The pKa values of the two acid groups are 1.27 and 4.27. The oxalate salt was first identified in the screen described above.

[00290] Sample SP221-OXA-P1 was prepared as follows: 236 mg of sample PP502-P1 and 45.4 mg of oxalic acid (Sigma Aldrich #75688) were added to 5.0 mL of acetone:water (95:5) and the mixture was heated to about 55 °C. The compound did not dissolve; the mixture was allowed to cool to room temperature and stirred overnight, after which the solid was filtered off and dried in air at room temperature.

[00291] Sample SP221-OXA-P2 was prepared as follows: 468.2 mg of sample PP502-P1 and 90.9 mg of oxalic acid (Sigma Aldrich #75688) was added to 10.0 mL of 1-propanol and heated to 70 °C. An essentially unstirable gel was obtained to which another 15.0 mL of 1-propanol and 1.0 mL of water were added. Stirring was continued at room temperature for three days before the solid was filtered off and examined by PXRD after short drying in air at room temperature.

[00292] Sample SP221-OXA-P3 was prepared as follows: 468 mg of sample PP502-P1 was dissolved in 10.0 mL of methanol at reflux, and 90 mg of oxalic acid dissolved in 2.0 mL of methanol was added. The material was cooled to room temperature, seeded with SP221-OXA-P2, and about half of the suspension was taken and stirred at room temperature then heated again to 50 °C; after which all solids dissolved. The solution was allowed to cool to room temperature again and stirred before part of the sample was filtered and solid investigated after drying in air at room temperature. This sample was designated SP221-OXA-P3A. To the other half of the suspension from was added 3.0 mL of water. All solid immediately dissolved, then the mixture was stirred under nitrogen purge at room temperature until all solvents were removed. To the dry residue was added 2.0 mL of acetonitrile, 2.0 mL of ethanol and 0.2 mL of water and stirred for two days at room temperature. A suspension was obtained from which the solid was filtered off and dried in air at room temperature. This sample was designated SP221-OXA-P3B.

[00293] Sample SP221-OXA-P4 was prepared as follows: 468 mg of sample PP502-P1 was dissolved in 10.0 mL of acetone and 1.0 mL of water at reflux, and 45 mg of oxalic acid (Sigma Aldrich #75688) dissolved in 1.0 mL of water was added. No crystallization was observed. An additional 46 mg of solid oxalic acid and 5.0 mL of acetone were added and stirring at room

temperature was continued while the vial was kept open. After overnight stirring, a thick paste was obtained. Heating the mixture to 50 °C led to complete dissolution and cooling to room temperature again led to a very thick suspension. Part of the suspension was filtered and the solid dried in air at room temperature.

[00294] Sample SP221-OXA-P5 was prepared as follows: 470 mg of sample PP502-P1 and 90 mg of oxalic acid (Sigma Aldrich #75688) were combined in 10.0 mL of tetrahydrofuran and 1.0 mL of methanol heated to reflux to achieve dissolution of the solids. Upon seeding with SP221-OXA-P2 and cooling to room temperature, a thick paste was obtained that was heated to 60°C to 65 °C and stirred for two days before the solid was filtered off and dried in air at room temperature.

[00295] Sample SP221-OXA-P7 was prepared as follows: the remaining products from experiments SP221-OXA-P4 and SP221-OXA-P5 (about 300 mg) were combined and were suspended in 5.0 mL of water. The mixture was stirred at room temperature for four days. The suspension was filtered and the solids were dried in air at room temperature for 24 hours.

[00296] ^{1}H NMR spectroscopy of the oxalate was not carried out because of the lack of non-exchangeable hydrogens in oxalic acid. The CHNO content of SP221-OXA-P1 was determined by elemental composition analysis, with the results shown in Table 13. The molecular formula of a 1:1 salt of Formula (1) with oxalic acid is predicted to be $C_{28}H_{25}N_7O_6$ with a molecular weight of 555.55 g/mol. A hydrate with a stoichiometry of 2.5 moles of water to 1 mole of Formula (1) would have the molecular formula of $C_{28}H_{30}N_7O_{8.5}$ and a molecular weight of 602.6 g/mol (with a water content of 7.5%). The results as presented for sample SP221-OXA-P7 are in fair agreement with the molecular formula for such a "2.5 hydrate." An assumed water content of about 7.5% is based on the result from TG-FTIR which revealed a mass loss of 8.3% essentially attributable to water. A trihydrate would contain 8.9% of water and therefore a trihydrate is also possible.

TABLE 13. Results from elemental composition analysis of oxalate salts and theoretical compositions.

Element	% found for SP221-OXA-P1	% found for SP221-OXA-P7	% theoretical for anhydrous form	% theoretical for monohydrate	% theoretical for 2.5 hydrate
C	57.4	53.8	60.54	58.63	55.81
H	4.9	5.3	4.54	4.74	5.35
N	16.6	15.9	17.65	17.09	16.27
O	17.4	21.1	17.28	19.53	22.57
Sum	96.3%	96.1%	100%	100%	100%

[00297] A reflection PXRD pattern of the oxalate salt of Formula (1) monohydrate is shown in FIG. 22 (sample SP221-OXA-P7). This crystalline phase is designated Form A (2.5 hydrate) of the oxalate salt of Formula (1). The following peaks are characteristic of Form A (2.5 hydrate) of the oxalate salt of Formula (1): 5.5, 5.8, 7.4, 9.3, 11.0, 11.5, 12.7, 15.2, 16.5, 17.3, 18.5, 18.7, 19.1, 19.7, 20.2, 20.8, 22.0, 22.3, 23.3, 23.6, 24.8, 27.4, 28.6, 29.3, 29.6, 31.2, and 33.1 °2θ ± 0.2 °2θ.

[00298] Raman spectroscopy was performed using a sample of Form A (2.5 hydrate) of the oxalate salt of Formula (1) (sample SP221-OXA-P7). The Raman spectrum was obtained in a similar manner as described in Example 1.2 for Form I. Characteristic Raman peaks for Form A (2.5 hydrate) of the oxalate salt of Formula (1) are observed at 3073, 2992, 2950, 2922, 2247, 1671, 1612, 1584, 1552, 1504, 1469, 1440, 1336, 1311, 1273, 1235, 1191, 1162, 1095, 1012, 897, 718, 633, 409, 370, and 263 (Raman shift, $cm^{-1} \pm 2\ cm^{-1}$).

[00299] IR spectroscopy was performed using a sample of Form A (2.5 hydrate) of the oxalate salt of Formula (1) (sample SP221-OXA-P7). The IR spectrum was obtained in a similar manner as described in Example 1.2 for Form I. Characteristic IR peaks for Form A (2.5 hydrate) of the oxalate salt of Formula (1) are observed at 3419, 2249, 1670, 1615, 1544, 1503, 1438, 1391, 1334, 1304, 1262, 1195, 1151, 1126, 1093, 1013, 894, 877, 823, 783, 765, 738, and 652 (IR frequency, $cm^{-1} \pm 4\ cm^{-1}$).

[00300] The TG-FTIR thermogram of Form A (2.5 hydrate) of the oxalate salt of Formula (1) (sample SP221-OXA-P7) was obtained. The observed mass loss, likely due to water, is between

the expected water content for a trihydrate (8.9 %) and a dihydrate (6.1 %). The water appears to be weakly bound, because the beginning of the mass loss is essentially at room temperature. Differential scanning calorimetry results for Form A (2.5 hydrate) of the oxalate salt of Formula (1) (sample SP221-OXA-P7) revealed a melting endotherm at 127 °C with an enthalpy of fusion of about 70 J/g. Thermal events observed in the DSC above 150 °C are likely due to thermal decomposition.

[00301] DVS analysis of Form A (2.5 hydrate) of the oxalate salt of Formula (1) (sample SP221-OXA-P7) reveals that the water is removed at 0% RH, and a reversible isotherm involving uptake of about 6.5% water is observed over the range of 0% to 100%. PXRD of the sample recovered from the DVS sample pan showed the same pattern as pattern before the start of the DVS test. At 50% RH, the water content is about 5.5% and at 95% RH, the water content is about 6.5%. This result suggests that Form A may form a stable dihydrate.

[00302] Two additional PXRD patterns were obtained from the other preparations of oxalate (samples SP221-OXA-P3B and SP221-OXA-P4). Based on their PXRD patterns, these samples likely represent other crystalline phases of oxalate salts of Formula (1).

Example 6.8. Form A of the Sulfate Salt of Formula (1)

[00303] A sulfate salt of Formula (1) (sample SP221-SO4-P1) was prepared as follows. To 5.0 mL of a 0.1 M stock solution of Formula (1) free base in acetone-water (sample SL20150415FB, 0.1 M) was added one equivalent of sulfuric acid in form of concentrated sulfuric acid (27.8 μL), which was heated to 50 °C and allowed to cool to room temperature. As crystallization did not occur the mixture was seeded with a few mg of crystalline phosphate salt. After overnight stirring at room temperature a yellow/white suspension was obtained from which the solid was filtered off and dried in air at room temperature.

[00304] Sample SP221-SO4-P3 was prepared by repetition of the experiment used to produce SP221-SO4-P1 using a 1:1 ratio of sulfuric acid to free base.

[00305] Sample SP221-SO4-P4 was prepared by dissolving 941 mg of PP502-P1 in 22 mL of acetone-water 10:1 at about 50 °C and adding one equivalent of concentrated sulfuric acid (112 μL). A suspension formed at 50 °C; the mixture was allowed to cool to room temperature and then stirred overnight at room temperature before solid was filtered off and dried in air. About 880 mg of slightly yellowish solid was obtained.

[00306] Sample SP221-SO4-P5 was prepared by adding 300 mg of SP221-SO4-P4 to 3.0 mL of acetonitrile and 0.3 mL of water. The suspension was stirred at room temperature for one day. The suspension was filtered, and solids were dried in air at room temperature.

[00307] Sample SP221-SO4-P6 was prepared by adding 944 mg of Formula (1) free base (sample PP502-P1) to 15.0 mL of acetone:water (9:1) and heating to reflux to achieve dissolution. Sulfuric acid (0.8 mL/1 equivalent) was then added in the form of a 2.5 M aqueous solution. The solution was seeded with SP221-SO4-P1 and allowed to cool to 35 °C while stirring was continued overnight. A suspension was obtained that was reheated to 50 °C for about three hours then allowed to cool again to room temperature and stirred for two hours before the solid was filtered off and dried in air at room temperature. A yield of about 950 mg was obtained.

[00308] ^{1}H NMR spectroscopy (spectrum not shown) of the product from experiment SP221-SO4-P4 was consistent with Formula (1). Samples SP221-SO4-P4 and SP221-SO4-P5 were analyzed by CHONS elemental composition analysis, with the results shown in Table 14. The molecular sum formula expected for a solvent-free monostoichiometric sulfate salt of Formula (1) is $C_{26}H_{25}N_7O_6S$, with a molecular weight of 563.6 g/mol. A trihydrate monostoichiometric sulfate salt of Formula (1) is expected to have a sum molecular formula of $C_{26}H_{31}N_7O_9S$ and a molecular weight of 617.6 g/mol (with a water content of 8.7%). A tetrahydrate monostoichiometric sulfate salt of Formula (1) is expected to have a molecular sum formula of $C_{26}H_{33}N_7O_{10}S$ and a molecular weight of 635.7 g/mol (with a water content of 11.3%). The best fit to the experimental values for sample SP221-SO4-P4 is to a tetrahydrate with an excess of sulfuric acid equivalent to a molar ratio of about 1.25. The best fit to the experimental values for sample SP221-SO4-P5 was found for a monosulfate tetrahydrate salt, wherein good agreement with the theoretically expected hydrogen, oxygen and sulfur content was found, with only a slight discrepancy found for carbon and nitrogen.

TABLE 14. Results from elemental composition (CHNOS analysis) analysis for samples SP221-SO4-P4 and SP221-SO4-P5 of the sulfate salt of Formula (1).

Element	SP221-SO4-P4 (% found, experimental)	SP221-SO4-P5 (% found, experimental)	$C_{26}H_{33.5}N_7O_{11}S_{1.25}$ tetrahydrate sulfate salt (theoretical)	Tetrahydrate monosulfate salt (theoretical)
C	47.4	46.8	47.30	49.13
H	4.9	4.7	5.11	5.23
N	14.9	14.4	14.85	15.42
O	not determined	25.0	26.66	25.17
S	6.2	5.0	6.07	5.04
water*	10.6	Not available	10.9	11.3

*Water content was determined by Karl Fischer titration.

[00309] Optical microscopy of sample SP221-SO4-P5 showed crystalline material with predominantly needle-shaped particles. The particles in sample SP221-SO4-P5 were considerably smaller than those for sample SP221-SO4-P6, which showed particle lengths up to about 100 µm and widths of about 5 to 10 µm.

[00310] The reflection PXRD pattern of sample SP221-SO4-P6 is shown in FIG. 23. This crystalline phase is designated Form A of the sulfate salt of Formula (1). The following peaks are characteristic of Form A of the sulfate salt of Formula (1): 4.6, 5.0, 8.0, 9.0, 9.8, 12.0, 12.7, 13.2, 14.6, 15.0, 15.6, 16.2, 17.5, 18.0, 19.8, 20.2, 21.9, 23.8, 24.4, 24.9, 25.7, 26.0, 27.2, 29.5, 30.4, 31.6, and 32.5 °2θ ± 0.2 °2θ. The PXRD patterns for three other samples (SP221-SO4-P1, SP221-SO4-P3, and SP221-SO4-P4) indicate that the same crystalline form of the sulfate salt was obtained in these other experiments as well.

[00311] Raman spectroscopy was performed using a sample of Form A of the sulfate salt cocrystal of Formula (1) (sample SP221-SO4-P4). The Raman spectrum was obtained in a similar manner as described in Example 1.2 for Form I. Characteristic Raman peaks for Form A of the sulfate salt of Formula (1) are observed at 3115, 2977, 2926, 2224, 1675, 1611, 1537, 1498, 1449, 1409, 1361, 1327, 1310, 1288, 1243, 1198, 1155, 1042, 1009, 978, 948, 906, 849, 771, 713, 652, 632, 464, 370, and 254 (Raman shift, $cm^{-1} \pm 2\ cm^{-1}$).

[00312] IR spectroscopy was performed using a sample of Form A of the sulfate salt of Formula (1) (sample SP221-SO4-P4). The IR spectrum was obtained in a similar manner as described in Example 1.2 for Form I. Characteristic IR peaks for Form A of the sulfate salt of Formula (1)

are observed at 3430, 3101, 3029, 2225, 1667, 1633, 1615, 1598, 1563, 1557, 1508, 1428, 1350, 1328, 1308, 1276, 1225, 1088, 1036, 1018, 925, 891, 848, 816, 783, 736, 723, 694, and 612 (IR frequency, $cm^{-1} \pm 4\ cm^{-1}$).

[00313] The TG-FTIR thermogram of Form A of the sulfate salt of Formula (1) (sample SP221-SO4-P4) showed an observed mass loss of 10.1%, which was due to water. The water loss begins with heating and is complete by about 110 °C using a heating rate of 10 °C per minute. DSC results for Form A of the sulfate salt of Formula (1) (sample SP221-SO4-P4) showed a melting endotherm with a peak temperature of 118 °C and an enthalpy of fusion of about 92 J/g. DSC revealed a melting endotherm at 127 °C with an enthalpy of fusion of about 70 J/g.

[00314] DVS analysis was performed for Form A of the sulfate salt of Formula (1) (sample SP221-SO4-P4). The DVS results show that the water is not completely removed at 0% RH after five hours. The initial water content of the given sulfate sample was determined by Karl Fischer titration, and the DVS isotherm varied from 2.5% to 12.5% over the range of 0% RH to 100% RH. The vapor sorption was found to be largely reversible; at the end of the test, the water content is almost the same as at the beginning of the measurement.

Example 7. Solubility as a Function of pH

Example 7.1. Free Base Solubility

[00315] The aqueous solubility of Formula (1) free base was examined as a function of pH. Experiments were conducted in aqueous HCl solution and buffer solutions at pHs of 1, 3, 5, 6.8, 7.4 and 9. It was determined that at low pH values of 1 and 3, the solid completely dissolved over the equilibration time while the pH in the system stabilized to approximately 3 in both experiments. It was found that the solubility in HCl solution having a pH of about 1 is at least 150 mg/mL. Solubility of the free base Form I (PP502-P1) at various pH values greater than 3 is presented in Table 15.

TABLE 15. Solubility data for Formula (1) free base.

Effective pH at the end of the test	Solubility (mg/mL)
5.0	0.69
6.7	0.056
7.3	0.049
8.9	0.051

[00316] Data shows that aqueous solubility of Formula (1) free base (sample PP502-P1) stabilizes at approximately 50 μg/mL at about pH 6.7. FIG. 24 displays the possible species of Formula (1) based on the calculated pK_a values ranging from 2.2 (basic) to 6.1 (basic) to 11.5 (acidic). Therefore, a doubly-positive charged molecule is highly soluble in water, whereas the singly positive and the neutral forms are poorly soluble. This highlights the challenges in successful delivery of Formula (1) through the stomach into the higher pH enviroment of the duodenum.

[00317] The equilibrium pH-solubility relationship calculated for the free base of Formula (1) is shown in FIG. 25 in comparison to experimental measurements at selected intervals. At pH 6.7 and greater, the aqueous solubility reaches a constant level of about 50 μg/mL, further illustrating the challenges with delivery of Formula (1).

[00318] The pK_a values for Formula (1) free base were determined and used to create the speciation plot shown in FIG. 26, to illustrate the species present as the Formula (1) passes through the gastrointestinal tract. The sample pK_a values were determined using an ultraviolet (UV) spectrometric technique. The sample was initially titrated in a fast-UV triple titration between pH 2 – 12 at concentrations of 31 – 19 μM, under aqueous conditions. Three pK_a values, with average values of ~3.6, ~5.8 and ~12.0, were determined. The sample was subsequently titrated in six titrations, under aqueous conditions over a total range of pH 1.5 - 12.5 at concentrations of 30 - 18 μM. Three pK_a values for Formula (1), with average values of 3.54 ± 0.01, 5.77 ± 0.01 and 12.12 ± 0.03, were determined from the spectroscopic data collected.

[00319] The logP of Formula (1) free base was determined using the potentiometric (pH-metric) technique. The sample was titrated in various ratios of octanol/water from pH 1.9 - 12.1 at concentrations of 1.1 - 0.5 mM at 25 °C in an ionic environment of 0.15 M KCl. The potentiometric data collected were used to calculate the logP of the neutral (2.03 ± 0.01) and the cationic (-0.31 ± 0.06) species.

Example 7.2. Salt Solubility

[00320] Tests were directed to determine the aqueous solubility of the maleate salt as a function of pH. Experiments were conducted in aqueous HCl solution and buffer solutions at pHs of 1, 3, 5, 6.8, 7.4 and 9. It was determined that at low pH values of 1 and 3, the solid completely dissolved over the equilibration time while the pH in the system stabilized to approximately 3 in both experiments. In parallel, aqueous solubilities of the fumarate, maleate, phosphate, and L-tartrate was determined in pure water. Solubility data for the fumarate, maleate, phosphate, and L-tartrate salts in pure water are presented in Table 16, with the phosphate salt showing the highest apparent solubility after 24 hours. The solubility data for the maleate salt as a function of pH in various aqueous media is presented in Table 17.

TABLE 16. Solubility data for selected salts in pure water at 25 °C.

Salt	Sample name	pH	Solubility (mg/mL) after 24 hours equilibration
Fumarate	SP221-FUM-P9a	4.0	2.1
Maleate	SP221-MLE-P9	4.1	2.3
Phosphate	SP221-PO4-P5	3.6	15.0
L-tartrate	SP221-LTA-P8	3.8	3.7

TABLE 17. Solubility data for the maleate salt as a function of pH in aqueous media.

Sample name	Description	pH after 24 hours	Solubility (mg/mL)
SP221-MLE-P8_pH1	0.1N HCl, Sigma # 71763	1.8	37.0
SP221-MLE-P8_pH3	citrate buffer pH 3, VWR #109434	3.2	8.0
SP221-MLE-P8_pH5	buffer pH 5, Sigma # 33544	4.8	4.3
SP221-MLE-P8_pH6.8	phosphate buffer pH 7, KH2PO4	4.8	1.2
SP221-MLE-P8_pH7.4	phosphate buffer pH 7, KH2PO4	5.0	0.8
SP221-MLE-P8_pH9	borate buffer, VWR # 109408	4.7	1.2

Example 8. Crystallization Optimization for Formula (1) Free Base Form I

[00321] Crystallization experiments were performed towards optimized production of Formula (1) free base Form I. The starting material for the crystallization experiments was recrystallized Formula (1) Form I. The study was supplemented with additional crystallizations of the free base from a sample of crude oil. The obtained products were characterized using powder X-ray diffraction (PXRD) or Raman spectroscopy to investigate crystalline form and by TG-FTIR or ^{1}H NMR or both to investigate residual solvent contents. Polarized microscopy images were recorded to determine particle size.

[00322] Acetone, ethanol, and 1-propanol are the most promising solvents for the recrystallization of Form I. Since crystalline Form I has a low solubility in many ICH class 3 solvents, the addition of potentially useful co-solvents was explored. For example, ethanol, water, and acetic acid are solvents that may be used to increase the solubility of Form I, which is important in the design of a crystallization process that maximizes volume efficiency and yield.

[00323] Solubility data was collected for several solvent systems. Temperature dependence of the Form I solubility was estimated for acetone, ethanol, ethanol-water 94:4 (v/v) and 1-propanol. Linear and non-linear cooling profiles and various temperature cycling strategies were applied in order to improve the quality of crystalline nature of Form I.

[00324] One method is based on crystallization of the maleate salt from a crude oil wherein the crystalline maleate salt is neutralized with base and the free base is extracted (presumably in amorphous form). Thereafter, the free base is crystallized from acetone and crystalline Form I (anhydrous form) is obtained. The resultant crystalline Form I consistently contains substantial amounts of residual solvent although PXRD patterns of all produced samples are identical.

[00325] For example, a sample of recrystallized Form I (sample PP502-P1) contains about 0.9% of acetone as determined by TG-FTIR. No mass loss was observable below about 200 °C; however, heating thereafter results in a release of acetone solvent along with melting of the solid form (melting point of the solid form is approximately 215°C). Prolonged drying at conventional drying temperatures does not necessarily efficiently reduce the residual solvents. However, recrystallization from other solvents (*e.g.*, ethanol) have been shown to remove residual solvent from Form I.

[00326] Crystallization of an amorphous material after conversion of a salt to the free base is fundamentally different from the process of recrystallization of a stable polymorphic form such as Form I. Form I is much less soluble than the amorphous form since it is typically recovered after the extraction and evaporation of the solvent; however, solubility can change if the free base crystallizes spontaneously after the extraction step. Thought the specific difference in solubility between the amorphous form and the stable crystalline form is not known, it ranges from a factor of 10 to 100.

[00327] In the current methodology, 100 mg/mL of stable Form I is preferably mixed into an ICH class 3 solvent or solvent mixture for the purposes of recrystallization. Solvent possibilities were narrowed by collecting detailed solubility data for the most common solvents. Formula (1) is not known to crystallize in different polymorphs, *i.e.,* no other non-solvated form was obtained from a crystallization experiment from a saturated solution.

[00328] The polymorphism study showed that Form I is stable and that this form is obtained consistently when the water activity was below the critical limit for hydrate formation. A seeded process is recommended because seeding allows a better control of the crystallization process to obtain a more reproducible form, particle size, and shape distribution. The samples in Table 18 were used in this study.

TABLE 18. Samples used in the optimization of the crystallization process for Formula (1) free

base Form I study.

Sample name	Sample No.	Sample code	Form
Formula (1), recrystallized	CS13-083 HB873-98	PP502-P1	Form I
Formula (1), crude oil	CS13-083 HB933-54-4	PP502-P61	Oil
Formula (1), (CML 1476) maleate salt	CS13-083 HB933-54-5	PP502-P67	Crystalline
Formula (1), recrystallized	CS13-083, Am-1406	PP502-P62	Form I

Example 8.1. Solubility by HPLC

[00329] The solubility of recrystallized Formula (1) Form I was tested in various water-solvent mixtures and non-aqueous solvents. Complete solubility data generated for these and other solvent systems is presented in Table 19 below.

TABLE 19. Solubility data for Form I. MEK refers to methyl ethyl ketone and THF refers to tetrahydrofuran.

Pure solvent	Solubility (S, mg/mL)	Solvent mixture	Solubility (S, mg/mL)
acetone, 25 °C	4.1	ethanol – water 96:4, 0 °C	6.7
acetone at RFT	10.0	ethanol – water 96:4, 25 °C	10.0
ethyl acetate, 25 °C	1.5	ethanol – water 96:4, 60 °C	24.7
ethanol, 5 °C	3.6	ethanol – water 9:1, 25 °C	23.7
ethanol, 25 °C	4.4		
ethanol, 50 °C	10.2		
MEK, 25 °C	3.7		
methanol, 25 °C	19.9		
1-propanol, 5 °C	3.4		
1-propanol, r.t.	4.7		
1-propanol, 25 °C	4.0		
1-propanol, 60 °C	14.4		
2-propanol, 25 °C	1.3		
THF, 25 °C	20.4		

[00330] Acetone, ethanol, 96%-ethanol and 1-propanol were considered as promising solvent

systems. Solubility in 96% ethanol is rather high at room temperature (approximately 22 °C) and cooling to low temperature would be necessary to obtain good yields. Cooling below 0 °C was not explored during the polymorphism study as crystallization at sub-zero temperatures leads to hydrate formation. Though the presence of water in high-temperature co-solvent mixtures might lead to deteriorating Formula (1) stability (indicated by a red discoloration), water still serves as a useful co-solvent at low concentration levels from about 0.5 to 4%.

Example 8.2. Multimax Solubility Tests

[00331] Metastable zone width experiments were conducted in a Mettler-Toledo Multimax crystallization process optimization system equipped with turbidity probes, in order to demonstrate control of crystallization for Form I.

[00332] Acetone, ethanol, and ethanol-water (96:4) were selected as the solvent systems. Three different concentrations were selected for acetone and ethanol; two different concentrations were selected for the ethanol-water (96:4) solvent system. Solubility data obtained from the Multimax experiments were in agreement with previously obtained data; however, values from the Multimax experiment are slightly lower than the actual value due to the kinetic nature of the Multimax experiment. The temperature dependence of the solubility of the Formula (1) free base Form I in ethanol and acetone is depicted in FIG. 27.

[00333] Ethanol and 1-propanol display similar solubility characteristics given that data points for the 1-propanol solvent appear to align well with the curve fit for the ethanol data points. Moreover, because the boiling point of 1-propanol is 97 °C as compared to a boiling point of 78 °C for ethanol, 1-propanol is considered a viable alternative to ethanol resulting in a substantial increase of the volume efficiency and yield.

[00334] Without seeding, the crystallization experiments from cooling of supersaturated solutions did not lead to crystallization in any of the examined solvents. As a consequence, the metastable zones in all tested solvents are very wide. Therefore, seeding is mandatory to control the crystallization process and is applied soon after oversaturation has been achieved.

Example 9. Comparison of Dissolution Rate and Exposure in Dogs for Free Base Form I and Free Base Form II

[00335] The intrinsic dissolution rate (IDR) was measured for Forms I and II of the free base of Formula (1). IDR was measured using a paddle over stationary disc equipped dissolution

apparatus with concentration determined using liquid chromatographic analysis against a standard. The y-intercept normalized results are shown in FIG. 28 with the slopes and regression coefficient displayed. Form I has an IDR of 6.8 mg/cm^2/min in simulated gastric fluid (SGF) (pH 1.2) and an IDR of 0.44 mg/cm^2/min in pH 2.5 HCl/NaCl buffer. Form II has an IDR of 5.4 mg/cm^2/min in SGF and an IDR of 0.35 mg/cm^2/min in pH 2.5 HCl/NaCl buffer. Form I therefore shows about a 26% increase in IDR at both conditions relative to Form II, which provides a significantly higher rate of dissolution that is advantageous.

[00336] The plasma exposure of Forms I and II of the free base of Formula (1) were compared in nine fasted beagle dogs after a single oral administration of 6 mg/kg of either form using batches with a similar particle size distribution. The experiment was performed in 5 weekly phases, with the Form II phase last. The area under the plasma drug concentration-time curve (AUC), shown in FIG. 29, reflects the exposure to drug after administration of each preparation of Formula (1) and is expressed in ng*h/L. Form II shows lower AUC than Form I in all dogs. Form II also shows lower C_{max} (maximum concentration) than Form I in all dogs. It was concluded that Form I had higher exposure in the beagle than Form II. There was a good *in vitro in vivo* correlation for the dissolution rates of Form 1 and Form II, and the performance of each form of Formula (1) when delivered by oral capsule to dogs. The superior performance of Form I in this dog study demonstrates that more favorable dosing is possible in humans relative to Form II.

Example 10. Overcoming the Effects of Acid Reducing Agents with Formulations of (*S*)-4-(8-Amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide

[00337] Acid-reducing agents, such as omeprazole, may limit the exposure of Formula (1) free base in mammals because of previously-discussed pH-solubility profile of Formula (1). This is a significant issue in the treatment of patients with cancer, inflammatory diseases, immune diseases, and autoimmune diseases, since these patients are commonly co-administered acid reducing agents for gastric irritation that often accompanies their conditions. Acid reducing agents are the most commonly prescribed medications in North America and Western Europe. Of recently approved oral cancer therapeutics, >50% have pH-dependent solubility, and therefore have a potential drug-drug interaction with regards to acid reducing agents. In cancer patients, it is estimated that 20-33% of all patients are using some form of acid-reducing agent.

In particular cancers, such as pancreatic cancer or gastrointestinal cancers, acid reducing agent use is as high as 60-80% of patients. Smelick, *et al.*, *Mol. Pharmaceutics* **2013,** *10,* 4055-4062.

[00338] The concern of potential drug-drug interactions with acid reducing agents for weakly basic drugs has led to the development of risk assessment strategies and drug-drug interaction studies designs for new drugs that exhibit pH dependent solubility and dissolution. Smelick, *et al.*, *Mol. Pharmaceutics* **2013,** *10,* 4055-4062. Acid reducing agents include proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole, and ilaprazole; H_2 receptor antagonists, such as cimetidine, ranitidine, and famotidine; and antacids such as bicarbonates, carbonates, and hydroxides of aluminium, calcium, magnesium, potassium, and sodium. Mixtures of antacids plus agents targeting mechanisms of gastric secretion may also be used as prescription or non-prescription acid-reducing agents. Any other acid reducing agent known in the art may also be used. In some cases, the effect of an acid-reducing agent is transient and depends on presence of the agent in the stomach. In other cases, the effect of an acid-reducing agent may be pronounced throughout the treatment interval, providing a constant elevation of gastric pH to levels greater than pH 4.

[00339] The terms hypochlorhydria and achlorhydria refer to conditions where gastric secretion of hydrochloric acid is lower than normal or severely reduced to nonexistent. The natural pH of the stomach is lowered by acid secretions in response to food stimulation; in certain medical conditions the ability of the gastric proton pump to secrete acid is compromised. Infections with *H. pylori* have been associated with impaired secretion of gastric acid (hypochlorhydria or achlorhydria). Other disease states, including those in which gastric parietal cells are destroyed or depleted, or the signaling to gastric parietal cells is altered, can lead to hypochlorhydria or achlorhydria. Long-term use of proton pump inhibitors or H_2 receptor antagonists may also result in these conditions. The evaluation of gastric pH over the course of a day (through meals) may be monitored in patients with *in situ* pH probes, if needed, as a diagnostic aid.

[00340] Dissolution of Form 1 of Formula (1) into aqueous media such as stomach fluid is pH dependent (*see, e.g.,* FIG. 30 and FIG. 31, discussed in more detail in Example 11). The bioavailability of Formula (1) may therefore be modified by factors that improve its dissolution. Alternate forms of Formula (1), and acidification of the formulation of Form 1 of Formula (1) were tested in dogs treated with omeprazole 10 mg/day to evaluate the extent to which an

alternate form of Formula (1) can overcome the effects of acid-reducing agents.

[00341] Dogs were treated with Formula (1) 100 mg capsules in several related studies using the same animals and a strict dosing schedule to minimize intra- and inter-animal variability. All doses were chased with 35 mL of distilled H_2O by oral gavage to standardize the dissolution volume with each dose administration. Dogs were conditioned to receive sham capsules and chase water on non-dosing days; food was also controlled to reduce the variability associated with gastric acid secretions in response to presentation and consumption of chow. The conditioning regimen was followed continuously for at least six months, and the same 12 dogs were used for all studies described below.

[00342] Study 2219-057 used 100 mg of Formula (1) in liquid capsules (hydroxyl-β-cyclodextrin/citrate, 2 doses) to set the bar for absorption without a dissolution component associated with solid form. Study 2219-059 used Formula (1) with formulation F-1 and Study 2219-061 used Formula (1) with formulation F-2 alone or following pre-treatment of the dogs with omeprazole, then proceeded to test Formula (1) salt forms in the F-1 formulation and an acidic formulation of Form I of Formula (1) designated FA-3 (see Example 11 below for the preparation of formulations). Conditioned dogs were dosed with 100 mg of Formula (1) in sequential dosing phases separated by washout periods of 4-7 days. Liquid capsules or solid capsules containing Form I of Formula (1) were administered; for comparison, a clinical formulation or hand-filled capsules with an Avicel blend were administered. After these initial study phases, dogs were treated with 10 mg/day omeprazole throughout the remainder of the study. After four days of omeprazole treatment, 100 mg of Form I of Formula (1) was administered in the clinical formulation, in a formulation containing acidulants, or in capsules containing 100 mg free base equivalent of the Formula (1) salts of maleate, phosphate, fumarate or tartrate, and plasma concentrations of Formula (1) were measured at multiple timepoints between 0 and 12 hours.

[00343] Study 2219-061 used Form I of Formula (1) recrystallized from ethanol, as described herein, and the maleate, phosphate, fumarate, and tartrate salt forms of Formula (1) desribed herein. Following collection of pharmacokinetics data after one dose administration of 100 mg capsules in the F-2 formulation, omeprazole treatment (10 mg/day) was initiated as a part of the conditioning regimen. The remaining study phases were conducted in omeprazole treated dogs.

After 4 days on omeprazole, the dogs were dosed with experimental Formula (1) drug forms or formulation on top of the continuing daily omeprazole dose. Salt forms were dosed to equal 100 mg of Formula (1) free base. The F-1 formulation was used for dosing the salt forms after correction for counterion and water content. The prototype acid formulation (FA-3) used both fumaric acid and alginic acid as an extra-granular mix with the granulated Formula (1) in formulation F-2.

[00344] FIG. 32 shows changes in the AUC, C_{max} and T_{max} by study phase, with each study or study phase presented sequentially. The initial study using liquid formulation in capsules to deliver 100 mg Formula (1) in solution was designed to show exposures following this dose (*i.e.*, not dissolution limited), and to characterize the variability in dogs when dissolution-associated variance is removed. The higher mean exposure and smaller within- and between- animal variability observed following administration of the fully dissolved Formula (1) in liquid capsules to conditioned dogs demonstrate that dissolution of Form I of Formula (1) plays a role in limiting oral absorption, indicating that optimal dissolution will enhance absorption.

[00345] The remaining variance in pharmacokinetic parameters observed following administration of liquid capsules may be due to intrinsic factors that vary between the inbred beagle dogs. This effect has also been demonstrated using 25 mg liquid capsules and Form I of Formula (1) capsules using a dose scaled version of F-1. Between-animal variability following administration of a liquid capsule or matching solid capsules containing Form 1 of Formula (1) at a fixed dose, may result from small variations in the mg/kg dosage of test article as well as other intrinsic factors such as those governing drug metabolism and elimination. Adding a weight-based normalization for the AUC's in the solid form experiments with this group of dogs will further tighten the between-animal variance at each dosing interval. Dose adjusted AUC and C_{max} values can be compared most accurately for statistical analysis of the experimental results.

[00346] After administration of the salt forms or Form I of Formula (1) in acidic formulation to overcome the omeprazole effect, T_{max} increased in most of the dogs. Although there was a trend towards a lower mean C_{max} in these study phases (FIG. 32), the pattern was not observed with every phase or for all dogs. A similar trend has been observed in dogs and humans when Form I of Formula (1) is administered with food. Notably, the mean AUC levels in dogs treated with

salt forms of Formula (1) or with the acidic formulation of Form I, were similar to AUCs observed in dogs after administration of Form I without omeprazole. There was a trend to decrease between-animal variability when these experimental dosage forms were administered, compared with the Form I capsules administered in conditioned dogs without omeprazole treatment. Therefore, exposures after oral dosing with Formula (1) in a salt form are increased in the presence of omeprazole, and variability in exposure is decreased in both omeprazole-treated dogs and conditioned dogs without omeprazole treatment. The prototype acidic formulation (FA-3) for Form I of Formula (1) has a similar effect.

[00347] The observed effect of alternate salt forms and acidulents with Formula (1) on oral absorption in omeprazole-treated dogs is novel and surprising. The pH-dependence of Formula (1) dissolution is associated with the stability of acidic and basic species in aqueous solutions, and with the free energy of dissolution during phase transition. *In vitro-in vivo* correlations demonstrated that dissolution limitations were associated with poor absorption of Form I of Formula (1) in omeprazole-treated dogs (or dogs treated with alternate gastric acid reducing agents, such as famotidine, calcium carbonate, or the other treatments listed above). In a human Phase 1, single-center, open-label, fixed-sequence, 2-period, 3-part study to evaluate the one-way interaction of calcium carbonate, omeprazole, or rifampin on Formula (1) in healthy adult subjects, treatment of subjects with acid reducing agents prior to administration of Form I of Formula (1) resulted in significant decreases in exposure. The role of pH in dissolution of Formula (1) was demonstrated *in vitro*, and the dissolution limitation on absorption was postulated *in vivo*. The addition of acidulants to the formulation, or the administration of fully dissolved Formula (1), are methods to facilitate dissolution by lowering pH in the microenvironment, or to circumvent the dissolution step for a proof-of-concept *in vivo* model. In contrast, dosing with the alternate salt forms of Formula (1), which were expected to have little impact on gastric pH, demonstrated that the solid form of Formula (1) has significant and unexpected effects on oral absorption characteristics in mammals.

[00348] FIG. 33 compares dose-normalized AUC and C_{max}, with additional averaging of repeated exposures for dogs for liquid capsules (n = 2 per dog) and F-2 (n = 5 per dog). The results again show that Formula (1) exposure can be recovered in the presence of omeprazole using the FA-3 acidulant formulation of the present invention as well as the salts of the present invention.

[00349] These studies demonstrate that good exposures can be achieved in omeprazole treated dogs via either an enabling formulation for Form I of Formula (1), or by generating a new salt form of Formula (1). The exposures obtained using formulation FA-3 with acidulant and the salts with omeprazole are surprisingly similar to exposures observed without omeprazole, and would be expected to perform well for other salts and acidulants as well as for other acid-reducing agents. The dissolution-mediated absorption observed in human subjects can be modeled in dogs. The *in vitro* dissolution assay is also a good predictor of *in vivo* absorption characteristics of different encapsulated formulations of Form I of Formula (1).

[00350] A separate PK comparability study (2219-060) has been completed to characterize exposures from the acetone-recrystallized and ethanol-recrystallized drug substance in capsules manufactured with the F-2 formulation. These data more fully characterize the between- and within-dog variability associated with absorption of Formula (1) in conditioned dogs that are not treated with omeprazole and indicate that ethanol-recrystallized drug substance is suitable for late-phase clinical development.

Example 11. Formulations of (*S*)-4-(8-Amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide

[00351] Formulations of Formula (1) solid forms (salts and free base Form I) were prepared as shown in Table 20.

TABLE 20. Description of Formulation 1 (F-1) and acidic salt formulations.

	F-1 free base (Form I)	F-1 maleate (Form A)	F-1 fumarate (Form A)	F-1 L-tartrate (Form A)	F-1 phosphate (Form A)
	w/w %	w/w %	w/w %	w/w %	w/w %
Formula (1)	10-50%	10-50%	10-50%	10-50%	10-50%
Microcrystalline Cellulose	50-90%	50-90%	50-90%	50-90%	50-90%

[00352] Additional formulations were prepared as shown in Table 21 using the following procedure. Formula (1) dry-granulate was blended with extragranular acidulants. The blends were then filled into hard gelatin capsules (in the case of FA-1, FA-2, FA-4, and FA-5) or compressed into a tablet (in the case of FA-4).

TABLE 21. Formulations of Formula (1), showing intragranular components and extragranular components.

			FORMULA (1)	SILICIFIED MICROCRYSTALLINE CELLULOSE	PARTIALLY PRE-GELATINIZED MAIZE STARCH	SODIUM STARCH GLYCOLATE	MAGNESIUM STEARATE		MAGNESIUM STEARATE	FUMARIC ACID	ALGINIC ACID	POLOXAMER 407	HYDROXYPROPYL METHYLCELLULOSE
F-2	w/w %	Intragranular	25-50%	25-33%	20-33%	0-5%	0.05-1%	Extragranular	0.05-1%	--	--	--	--
FA-1	w/w %		25-35%	15-35%	20-33%	0-5%	0.05-1%		0.05-1%	25-33%	--	--	1-5%
FA-2	w/w %		25-35%	15-35%	20-33%	0-5%	0.05-1%		0.05-1%	--	15-33%	--	--
FA-3	w/w %		25-35%	15-35%	20-33%	0-5%	0.05-1%		0.05-1%	15-33%	5-15%	--	--
FA-4	w/w %		25-35%	15-35%	20-33%	0-5%	0.05-1%		0.05-1%	15-33%	5-15%	--	--
FA-5	w/w %		25-35%	15-35%	20-33%	0-5%	0.05-1%		0.05-1%	15-33%	5-15%	0.5-5%	--

1. Polaxamer 407 refers to triblock copolymer of polypropylene glycol and polyethylene glycol (available from BASF, Inc., under the tradename PLURONIC F127).

[00353] The results of dissolution experiments using formulations representative of those in Table 21 at two different pH values are shown in FIG. 30 and FIG. 31. The dissolution system was a U.S. Pharmacopeia Type II apparatus equipped with paddles (at 50 rpm) and 900 mL vessels equilibrated at 37 °C. Samples are taken at intervals using a cannula at a set depth through an in-line filter and analyzed by reversed phase HPLC with UV spectroscopic detection. Capsules were tested in sinkers, and the tablet was tested neat.

[00354] Additional formulations may be prepared according to Table 22. Intragranular formulations may be prepared by the following procedure. Materials are pre-blended in a 250 mL V-blender for 300 revolutions. After blending, lubricant is added and blending is performed for 100 additional revolutions. The blend is roller compacted on a TF-mini roller compactor and then feed through an oscillating granulator equipped with a 20 mesh screen. Extragranular formulations may be prepared by the following procedure. When extragranular acids or

polymers are added, they are added to the preblended or neat extragranular material and then add granulated in a 250 mL V-blender and for 300 revolutions. After blending, lubricant is added and blending is performed for an additional 100 revolutions. Lubricated granules are then filled into size 1 hard gelatin capsules using a dosing disk or dosator-equipped semi-automatic or automatic encapsulator. Alternately, material may be compressed on a tablet press or mold.

TABLE 22. Formulations of Formula (1).

			FORMULA (1) (FORM I FREE BASE)	SILICIFIED MICROCRYSTALLINE CELLULOSE	PARTIALLY PRE-GELATINIZED MAIZE STARCH	SODIUM STARCH GLYCOLATE	TARTARIC ACID	MAGNESIUM STEARATE	ALGINIC ACID		MAGNESIUM STEARATE	TARTARIC ACID	ALGINIC ACID	ASCORBIC ACID	CARBOPOL 971P[1]	HYDROXYPROPYL METHYLCELLULOSE
FA-7	w/w %	Intragranular	25-50%	25-33%	20-33%	0-5%	15-33%	0.05-1%	5-15 %	Extragranular	0.05-1%	--	--	--	--	--
FA-8	w/w %		25-35%	15-35%	20-33%	0-5%	--	0.05-1%	--		0.05-1%	25-33%	5-15%	--	--	--
FA-9	w/w %		25-35%	15-35%	20-33%	0-5%	--	0.05-1%	--		0.05-1%	--	15-33%	--	--	7.5-15%
FA-10	w/w %		25-35%	15-35%	20-33%	0-5%	--	0.05-1%	--		0.05-1%	--	--	20-50%	2.5 - 10%	--

1. Carbopol 971P (Lubrizol, Inc.) is also referred to as carboxypolymethylene or "carbomers" (*e.g.*, in pharmaceutical monographs such as USP/NF or Ph. Eur.).

[00355] In addition to the formulations described in Table 21 and Table 22, other acidulants may also be used as described herein, including fumaric acid, succinic acid, D-tartaric acid, L-tartaric acid, racemic tartaric acid, ascorbic acid, isoascorbic acid (also known as erythorbic acid and D-araboascorbic acid), alginic acid, Protacid F 120 NM, Protacid AR 1112 (also known as Kelacid NF), Carbopol 971P (carboxypolymethylene), and Carbomer 941 (polyacrylic acid).

[00356] Additional non-limiting formulations are given in Table 23, and may be prepared as described above or by using methods known in the art. These formulations, and all of the foregoing formulations, may be prepared as capsules or tablets, with or without coating.

TABLE 23. Formulations of Formula (1).

			FORMULA (I) (FORM I FREE BASE)	SILICIFIED MICROCRYSTALLINE CELLULOSE	PARTIALLY PRE-GELATINIZED MAIZE STARCH	SODIUM STARCH GLYCOLATE	TARTARIC ACID	MAGNESIUM STEARATE	ALGINIC ACID	HYDROXYPROPYL METHYLCELLULOSE		MAGNESIUM STEARATE	TARTARIC ACID	SODIUM STARCH GLYCOLATE
FA-11	w/w %	Intragranular	25-50%	10-25%	10-25%	0-5%	10-30%	0.05-1%	10-30%	--	Extragranular	0.05-2%	--	0-6%
FA-12	w/w %		25-50%	10-25%	10-25%	0-5%	--	0.05-1%	--	0-20%		0.05-2%	10-35%	0-6%

Example 12. Comparison of Processability for Free Base Form I and Free Base Form II

[00357] Both Form I and Form II of Formula (1) free base were processed under similar parameters using the process and composition for formulation F-2 (as described above). Formula (1) was blended with the ingredients and then lubricated, then roller compacted with a top feeding roller compacter with a separate granulation step. The granules were then lubricated. The resultant granules from the Form I and Form II were then characterized for tapped and aerated density. The Form II granules showed a general trend towards poor flow and poor uniformity.

[00358] Flowability typically affects the ease of handling pharmaceutical product during processing. When flowability is very poor, problems occur with handling and processing during blending, granulation and filling/compression. The flowability based on interparticulate interactions can be measured using the Hausner ratio or the compressibility index by measuring the aerated and tapped density of the powders. These values are calculated and ranked as

outlined in the U.S. Pharmacoepia Monograph USP <1174> monograph. Hausner, *Int. J. Powder Metall.* **1967,** *3,* 7-13; Carr, *Chem. Eng.* **1965,** *72,* 163-168. The U.S. Pharmacoepia Monograph USP <1174> defines the following categories of flow character: Excellent (compressability index ≤ 10%, Hausner's ratio 1.00 to 1.11); Good (compressability index 11-15%, Hausner's ratio 1.12 to 1.18); Fair (compressability index 16-20%, Hausner's ratio 1.19 to 1.25); Passable (compressability index 21-25%, Hausner's ratio 1.26 to 1.34); Poor (compressability index 26-31%, Hausner's ratio 1.35 to 1.45); Very poor (compressability index 32-37%, Hausner's ratio 1.46 to 1.59); and Very, very poor (compressability index >38%, Hausner's ratio > 1.60).

[00359] The Hausner ratio and compressibility index for the Form I granules was 1.33 and 25% respectively while the Form II granules exhibited a Hausner ratio of 1.47 and compressibility index of 32%. The results thus indicates that Form I granules have a passable flow while Form II granules have poor to very poor flow.

[00360] The blends were then filled into capsules using an automated encapsulator operating on the dosing disc principle. After filling to a target weight, capsules are checked for weight uniformity with out of weight capsules being rejected. The Form I capsules have a yield of 90-100 % acceptable capsules while the Form II containing capsules had a yield of only 40-60%.

[00361] Upon measuring the content uniformity as defined by the U.S. Pharmacoepia Monograph USP <905> for a hard gelatin capsule, the Form II containing capsules have an acceptance value greater than 15, while the Form I containing capsules have an acceptance value below 15.

[00362] The results are summarized in Table 24.

TABLE 24. Results of Processability Tests for Form I and Form II of Formula (1) free base.

Lot	Bulk Density g/cc	Tap Density g/cc	Hausner ratio	Compressibility Index (%)
F-2 using Form I	0.527	0.703	1.33	25
F-2 using Form II	0.438	0.644	1.47	32

CLAIMS

1. A crystal form of (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide characterized by a reflection X-ray powder diffraction pattern comprising peaks at 6.4° ± 0.2° 2θ, 8.6° ± 0.2° 2θ, 10.5° ± 0.2° 2θ, 11.6° ± 0.2° 2θ and 15.7° ± 0.2° 2θ.

2. The crystal form of claim 1, wherein the reflection X-ray powder diffraction pattern further comprises peaks at 10.9° ± 0.2° 2θ, 12.7° ± 0.2° 2θ, 13.4° ± 0.2° 2θ, 14.3° ± 0.2° 2θ, 14.9° ± 0.2° 2θ and 18.2° ± 0.2° 2θ.

3. The crystal form of claim 2, wherein the reflection X-ray powder diffraction pattern comprises one or more peaks at 11.3° ± 0.2° 2θ, 15.1° ± 0.2° 2θ, 16.1° ± 0.2° 2θ, 17.3° ± 0.2° 2θ, 19.2° ± 0.2° 2θ, 19.4° ± 0.2° 2θ, 19.8° ± 0.2° 2θ, 20.7° ± 0.2° 2θ, 21.1° ± 0.2° 2θ, 21.4° ± 0.2° 2θ, 21.6° ± 0.2° 2θ, 21.9° ± 0.2° 2θ, 22.6° ± 0.2° 2θ, 23.3° ± 0.2° 2θ, 23.6° ± 0.2° 2θ, 24.9° ± 0.2° 2θ, 25.2° ± 0.2° 2θ, 25.4° ± 0.2° 2θ, 25.7° ± 0.2° 2θ, 26.1° ± 0.2° 2θ, 26.4° ± 0.2° 2θ, 26.8° ± 0.2° 2θ, 26.9° ± 0.2° 2θ, 27.7° ± 0.2° 2θ, 28.6° ± 0.2° 2θ, 29.1° ± 0.2° 2θ, 29.4° ± 0.2° 2θ, 30.1° ± 0.2° 2θ, 30.5° ± 0.2° 2θ, 31.7° ± 0.2° 2θ, 31.9° ± 0.2° 2θ, 32.2° ± 0.2° 2θ, 32.6° ± 0.2° 2θ, 33.1° ± 0.2° 2θ, 33.4° ± 0.2° 2θ° ± 0.2° 2θ, 34.5° ± 0.2° 2θ, 35.9° ± 0.2° 2θ, 36.1° ± 0.2° 2θ, 36.8° ± 0.2° 2θ, 37.4° ± 0.2° 2θ, 38.1° ± 0.2° 2θ, 38.9° ± 0.2° 2θ and 39.5° ± 0.2° 2θ.

4. The crystal form of claim 2, wherein the reflection X-ray powder diffraction pattern further comprises peaks at 11.3° ± 0.2° 2θ, 15.1° ± 0.2° 2θ, 16.1° ± 0.2° 2θ, 17.3° ± 0.2° 2θ, 19.2° ± 0.2° 2θ, 19.4° ± 0.2° 2θ, 19.8° ± 0.2° 2θ, 20.7° ± 0.2° 2θ, 21.1° ± 0.2° 2θ, 21.4° ± 0.2° 2θ, 21.6° ± 0.2° 2θ, 21.9° ± 0.2° 2θ, 22.6° ± 0.2° 2θ, 23.3° ± 0.2° 2θ, 23.6° ± 0.2° 2θ, 24.9° ± 0.2° 2θ, 25.2° ± 0.2° 2θ, 25.4° ± 0.2° 2θ, 25.7° ± 0.2° 2θ, 26.1° ± 0.2° 2θ, 26.4° ± 0.2° 2θ, 26.8° ± 0.2° 2θ, 26.9° ± 0.2° 2θ, 27.7° ± 0.2° 2θ, 28.6° ± 0.2° 2θ, 29.1° ± 0.2° 2θ, 29.4° ± 0.2° 2θ, 30.1° ± 0.2° 2θ, 30.5° ± 0.2° 2θ, 31.7° ± 0.2° 2θ, 31.9° ± 0.2° 2θ, 32.2° ± 0.2° 2θ, 32.6° ± 0.2° 2θ, 33.1° ± 0.2° 2θ, 33.4° ± 0.2° 2θ° ± 0.2° 2θ, 34.5° ± 0.2° 2θ, 35.9° ± 0.2° 2θ, 36.1° ± 0.2° 2θ, 36.8° ± 0.2° 2θ, 37.4° ± 0.2° 2θ, 38.1° ± 0.2° 2θ, 38.9° ± 0.2° 2θ and 39.5° ± 0.2° 2θ.

5. The crystal form of claim 2, wherein the crystal form is a crystalline anhydrate.

6. The crystal form of claim 1, 2, 3, 4 or 5, wherein the peaks are present when the reflection x-ray powder diffraction is carried out using Cu-Kα radiation.

7. The crystal form of claim 1, 2, 3, 4 or 5, wherein the peaks are present when the reflection x-ray powder diffraction is carried out using a Bruker D8 Advance powder X-ray diffractometer equipped with a LynxEye detector and operating in Bragg-Brentano reflection geometry, a tube voltage of 40 kV and current of 40 mA, a variable divergence slit with a 3° window, a step size of 0.02° 2θ, sample rotation of 0.5 rps, and a step time of 37 seconds.

8. A pharmaceutical composition comprising the crystal form of any of claims 1, 2, 3, 4 or 5 and at least one pharmaceutically acceptable excipient.

9. The pharmaceutical composition of claim 8, wherein the pharmaceutical composition further comprises an extragranular acidulant.

10. The pharmaceutical composition of claim 9, wherein the extragranular acidulant is selected from the group consisting of fumaric acid, succinic acid, D-tartaric acid, L-tartaric acid, (±)-tartaric acid, ascorbic acid, isoascorbic acid, alginic acid, a salt of alginic acid, Protacid F 120 NM, Protacid AR 1112 and Carbopol 971P, and a combination thereof.

11. The pharmaceutical composition of claim 9, wherein the extragranular acidulant is selected from the group consisting of alginic acid, a sodium salt of alginic acid and a potassium salt of alginic acid.

12. The pharmaceutical composition of claim 8 for use in the treatment of a hyperproliferative disease, wherein the hyperproliferative disease is selected from the group consisting of chronic lymphocytic leukemia, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, B-cell lymphoproliferative disease, B cell acute lymphoblastic leukemia, Waldenström's macroglobulinemia, Burkitt's leukemia, Hodgkin's disease, multiple myeloma, acute myeloid leukemia, juvenile myelomonocytic leukemia, hairy cell leukemia, mast cell leukemia, mastocytosis, myeloproliferative disorders (MPDs), myeloproliferative neoplasms, polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), myelodysplastic syndrome, chronic myelogenous leukemia (BCR-ABL1-positive), chronic neutrophilic leukemia, chronic eosinophilic leukemia, primary central nervous system (CNS) lymphoma, primary multifocal lymphoma of peripheral nervous system (PNS), thymus cancer, brain cancer, glioblastoma, lung cancer, squamous cell cancer, skin cancer (*e.g.,* melanoma), eye cancer, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal cancers, bladder cancer, gastric cancer, stomach cancer, pancreatic cancer, breast cancer, cervical cancer, head and neck cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, bone cancer (*e.g.*, metastatic bone cancer), esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, epidermoid cancer, AIDS-related cancer (*e.g.*, lymphoma), viral-induced cervical carcinoma (human papillomavirus), nasopharyngeal carcinoma (Epstein-Barr virus), Kaposi's sarcoma, primary effusion lymphoma (Kaposi's sarcoma herpesvirus), hepatocellular carcinoma (hepatitis B and hepatitis C viruses), T-cell leukemias (Human T-cell leukemia virus-1), benign hyperplasia of the skin, restenosis, benign prostatic hypertrophy, and tumor angiogenesis.

13. The pharmaceutical composition of claim 8 for use in the treatment of diffuse large B-cell lymphoma (DLBCL).

14. The pharmaceutical composition of claim 8 for use in the treatment of chronic lymphocytic leukemia (CLL).

15. The pharmaceutical composition of claim 8 for use in the treatment of small lymphocytic lymphoma (SLL).

16. The pharmaceutical composition of claim 8 for use in the treatment of mantle cell lymphoma (MCL).

17. The pharmaceutical composition of claim 8 for use in the treatment of Waldenstrom's macroglobulinemia.