POLYMORPHIC FORMS OF KRAS INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION(S)

[0001] This application claims priority to and the benefit of International Patent Application No. PCT/CN2024/082455, filed March 19, 2024, the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] The present disclosure relates generally to polymorphic forms of a KRAS inhibitor, and more specifically to polymorphic forms of a pyridopyrimidine derivative, and uses thereof.

BACKGROUND

[0003] KRAS is a molecular switch. Under normal physiological conditions, the protein is bound to guanosine diphosphate (GDP) in the "off state." In response to signaling through receptor tyrosine kinases (RTKs) such as EGFR, the GDP is exchanged to guanosine triphosphate (GTP) in a process facilitated by guanine nucleotide exchange factors (GEFs) such as SOS. The GTP-bound form of KRAS is in the "on state," and interacts with proteins such as RAF and PI3K to promote downstream signaling that leads to cell proliferation and survival. KRAS can slowly hydrolyze GTP back to GDP, thus returning to the off-state, in a process facilitated by GAPs (GTPase-activating Proteins).

[0004] KRAS mutations are found in approximately 30% of all human cancers, and are highly prevalent among three of the deadliest forms of cancer: pancreatic (95%), colorectal (45%), and lung (35%). Together, these cancers occur in more than 200,000 patients annually in the US alone. One particular mutation, a glycine to cysteine substitution at position 12 (G12C), occurs in more than 40,000 patients per year. The KRAS G12C mutation impairs hydrolysis of GTP to GDP, thus trapping KRAS in the on-state and promoting cancer cell proliferation.

[0005] The cysteine residue of G12C provides an opportunity to develop targeted covalent drugs for this mutant KRAS. Early clinical trial results for KRAS G12C inhibitors AMG 510 and MRTX849 have shown encouraging results for non-small cell lung cancer

(NSCLC), but the data are less compelling for colorectal cancer (CRC). Moreover, even in cases where patients respond to initial treatment, there are signs that the response may be limited in duration and that resistance could arise rapidly.

[0006] Most inhibitors of KRAS mutants bind preferentially to the GDP-bound form of the protein. For example, Amgen KRAS inhibitor AMG 510 and Mirati KRAS inhibitor MRTX849 react with the GDP-bound form of KRAS G12C at least 1000-fold more rapidly than with the GTP-bound form of the protein. One form of resistance that has been observed is for cancer cells to increase signaling through RTKs, thus increasing the amount of GTP-bound KRAS, which is less affected by current inhibitors. Thus, creating a molecule that could bind to and inhibit both the GDP- and GTP-bound forms of KRAS could have substantial utility.

[0007] What is needed is a compound useful in the treatment of cancer, such as cancers characterized by KRAS G12C. What is further needed is a compound useful in the treatment of cancers characterized by KRAS G12C, wherein the compounds bind to and inhibit both the inactive GDP- and activated GTP-bound forms of KRAS. What is further needed is a compound useful in the treatment of cancers characterized by KRAS G12C, wherein the compound has improved inhibition of the GTP-bound form of KRAS G12C. What is further needed is a crystalline form of such compound.

BRIEF SUMMARY

[0008] In one aspect, provided herein is a crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1).

[0009] In some embodiments, the crystalline form is a hydrate. In some embodiments, the crystalline form is a channel hydrate.

[0010] In some embodiments, the crystalline form is characterized by having (i) an XRPD pattern comprising peaks at angle 2-theta of about 6.9, about 15.0, and about 22.4 as measured at between about 50% to about 80% relative humidity at room temperature; (ii) an XRPD pattern comprising peaks at angle 2-theta of about 7.1, about 14.0, and about 22.5 as measured at about 30% relative humidity at room temperature; and/or (iii) an XRPD pattern

comprising peaks at angle 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5 as measured at less than about 20% relative humidity at room temperature.

[0011] In some embodiments, the crystalline form is characterized by having (i) an XRPD pattern substantially as shown in FIG. 1A as measured at between about 50% to about 80% relative humidity at room temperature; (ii) an XRPD pattern substantially as shown in FIG. 2A as measured at about 30% relative humidity at room temperature; and/or (iii) an XRPD pattern substantially as shown in FIG. 9A as measured at less than about 20% relative humidity at room temperature.

[0012] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form A substantially as shown in FIG. 1A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.9. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 15.0, and about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 16.4, about 17.4, about 19.3, about 20.7, about 22.4, about 24.1, about 28.2, and about 31.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 17.4, about 19.3, about 20.7, and about 22.4. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 73.5 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 76.0 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 194.9 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 1B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 1B. In some embodiments, the crystalline form is characterized by having a DVS graph substantially as shown in FIG. 1C. In some embodiments, the crystalline form comprises water. In some embodiments, the molar ratio of water:Compound 1 is about 3.5:1.

[0013] In all of the embodiments provided in this paragraph, the XRPD pattern is measured at between about 50% to about 80% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form A substantially as shown in FIG. 1A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.9. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 15.0, and about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 16.4, about 17.4, about 19.3, about 20.7, about 22.4, about 24.1, about 28.2, and about 31.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 17.4, about 19.3, about 20.7, and about 22.4. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 73.5 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 76.0 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 194.9 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 1B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 1B. In some embodiments, the crystalline form is characterized by having a DVS graph substantially as shown in FIG. 1C. In some embodiments, the crystalline form comprises water. In some embodiments, the molar ratio of water:Compound 1 is about 3.5:1.

[0014] In some embodiments, the crystalline form is characterized by having an XRPD pattern of Form E substantially as shown in FIG. 2A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.1. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.6. In some embodiments, the crystalline form is characterized by having an XRPD pattern

comprising a peak at angle 2-theta of about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 14.0, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 11.1, about 12.6, about 14.0, about 14.6, about 15.6, about 20.3, and about 22.5. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 69.7 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 190.5 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 2B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 2B.

[0015] In all of the embodiments provided in this paragraph, the XRPD pattern is measured at about 30% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern of Form E substantially as shown in FIG. 2A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.1. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.6. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 14.0, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 11.1, about 12.6, about 14.0, about 14.6, about 15.6, about 20.3, and about 22.5. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 69.7 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 190.5 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 2B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 2B.

[0016] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form C substantially as shown in FIG. 3A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Tables C-1 or C-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.9. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 14.9, and about 22.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 7.5, about 11.0, about 12.7, about 13.7, about 14.6, about 14.9, about 16.3, about 17.0, about 18.5, about 19.5, about 19.9, about 20.4, about 22.2, about 23.3, about 24.2, about 25.2, about 25.7, about 27.0, about 28.0, and about 34.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 7.5, about 12.7, about 13.7, about 14.6, about 14.9, about 16.3, about 17.0, about 18.5, about 19.5, about 19.9, about 20.4, and about 22.2. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 80.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 189.4 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 3B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 3B.

[0017] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form D substantially as shown in FIG. 4A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table D. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 13.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.6. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 23.3. In some embodiments, the crystalline form

is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, 13.3, 14.6, and 23.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 13.3, about 14.6, about 15.5, about 21.0, about 22.4, about 23.3, about 25.7, and about 27.1. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 13.3, about 14.6, about 15.5, about 21.0, about 22.4, and about 23.3. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 80.8 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 189.4 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 4B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 4B.

[0018] In some embodiments, the crystalline form is a solvate.

[0019] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form B substantially as shown in FIG. 5A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table B-1 or B-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 14.7, and about 22.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 12.5, about 12.9, about 14.1, about 14.7, about 18.0, about 18.8, about 22.3, about 23.0, and about 25.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 12.5, about 12.9, about 14.1, about 14.7, about 18.0, about 18.8, and about 22.3. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 84.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 187.1 °C. In some embodiments, the crystalline form is characterized by having a DSC

graph substantially as shown in FIG. 5B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 5B. In some embodiments, the crystalline form is an isomorphic form. In some embodiments, the crystalline form comprises DMAc, wherein the molar ratio of DMAc:Compound 1 is about 0.7:1.

[0020] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form F substantially as shown in FIG. 6. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table F. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 13.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 6.7, and about 13.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 6.7, about 12.4, about 13.4, about 15.1, about 16.8, about 18.7, about 20.1, about 21.7, about 23.2, about 25.7, about 26.9, about 27.7, about 29.9, and about 33.9. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 6.7, about 13.4, about 15.1, about 20.1, and about 21.7. In some embodiments, the crystalline form comprises DMAc or IPA, or both.

[0021] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form G substantially as shown in FIG. 7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table G. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 13.8. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.2. In some embodiments, the crystalline form

is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.0, about 13.8, about 15.4, and about 22.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.0, about 11.0, about 13.8, about 14.5, about 15.2, about 15.4, about 17.3, about 20.1, about 21.0, about 22.2, about 23.0, about 24.1, about 25.4, about 27.8, and about 30.6. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.0, about 11.0, about 13.8, about 14.5, about 15.2, about 15.4, about 17.3, about 20.1, about 21.0, and about 22.2. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 72.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 113.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 196.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 8. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 8. In some embodiments, the crystalline form comprises DMSO, wherein the molar ratio of DMSO:Compound 1 is about 0.8.

[0022] In some embodiments, the crystalline form is an anhydrate.

[0023] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form H substantially as shown in FIG. 9A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 17.7, about 20.3, about 21.8, about 22.5, and about 28.1. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 21.8, and about 22.5. In some embodiments, the crystalline

form is characterized by having a DSC graph comprising an endothermic peak at about 73.6 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 194.1 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 9B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 9B.

[0024] In all of the embodiments provided in this paragraph, the XRPD pattern is measured at less than about 20% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form H substantially as shown in FIG. 9A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 17.7, about 20.3, about 21.8, about 22.5, and about 28.1. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 21.8, and about 22.5. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 73.6 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 194.1 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 9B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 9B.

[0025] In some embodiments, the purity of the crystalline form is at least about 95%.

[0026] In one aspect, provided is a pharmaceutical composition comprising a crystalline form provided herein, and a pharmaceutically acceptable excipient.

[0027] In one aspect, provided is a method of treating cancer in a subject in need thereof. In some embodiments, the method comprises administering a therapeutically effective amount of the crystalline form or the pharmaceutical composition provided herein to the subject. In some embodiments, the cancer is a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer. In some embodiments, the cancer is glioblastoma multiforme, lower grade glioma, head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, brain lower grade glioma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma, metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, glioma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma. In some embodiments, the cancer is a non-small cell lung cancer (NSCLC). In some embodiments, the cancer is a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed as having a KRAS G12C mediated cancer. In some embodiments, the subject is human.

[0028] In one aspect, provided is a method of preparing a crystalline form provided herein. In some embodiments, the method comprises (i) contacting Compound 1 with one or more solvents to form a mixture; and (ii) crystallizing Compound 1. In some embodiments, the one or more solvents comprise ethyl acetate, tetrahydrofuran, or ethanol, or any combination thereof. In some embodiments, the one or more solvents comprise ethyl acetate, tetrahydrofuran, and ethanol. In some embodiments, the one or more solvents comprise ethyl

acetate, tetrahydrofuran, and ethanol at about 400:100:1 volume ratio. In some embodiments, the method further comprises stirring the mixture at about 60°C.

[0029] In some embodiments, the method comprises: (i) placing a sample comprising a solid form of Compound 1 in a first container; (ii) placing the first container of step (i) inside a second container containing a solvent; and (iii) allowing vapor from the solvent to interact with the sample in the first container. In some embodiments, the sample of step (i) comprises freebase Form A. In some embodiments, step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container at a room temperature and for a duration of about 7 days. In some embodiments, the solvent comprises EtOH, IPA, MIBK, EtOAc, MTBE, 2-MeTHF, acetonitrile, toluene, DMSO, or water, or any mixture thereof. In some embodiments, the solvent comprises EtOH, IPA, EtOAc, acetonitrile, or water, or any mixture thereof, and the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises MIBK or MTBE, or any mixture thereof, and the crystalline form prepared from the method comprises freebase form C. In some embodiments, the solvent comprises 2-MeTHF or toluene, or any mixture thereof, and the crystalline form prepared from the method comprises freebase form A or freebase form C, or both. In some embodiments, the solvent comprises DMSO, and the crystalline form prepared from the method comprises freebase form C. In some embodiments, the solvent comprises DMSO, and the crystalline for prepared from the method comprises freebase form G. In some embodiments, step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container for the duration of about 19 days.

[0030] In some embodiments, the method comprises: (i) dissolving Compound 1 in a first solvent in a first container; (ii) placing the first container of step (i) inside a second container containing a second solvent; (iii) sealing the second container of step (ii); (iv) allowing vapor of the second solvent to interact with Compound 1 in the first container to form precipitant; and (v) isolating the precipitant of step (iv) from the first solvent and/or the second solvent. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, step (iv) comprises allowing vapor of the second solvent to interact with Compound 1 in the first container at room temperature. In some embodiments, isolating the precipitant in step (v) comprises evaporating the first solvent and/or the second solvent at room temperature. In some embodiments, the first solvent comprises 1,4-dioxane or DMAc, or a mixture thereof, and the second solvent comprises IPA, MTBE, n-Heptane, or water, or

any mixture thereof. In some embodiments, the first solvent comprises 1,4-dioxane, the second solvent comprises MTBE, and the crystalline form prepared from the method comprises freebase Form C. In some embodiments, the first solvent comprises DMAc, the second solvent comprises IPA, and the crystalline form prepared from the method comprises freebase Form F. In some embodiments, the first solvent comprises DMAc, the second solvent comprises MTBE or water, or a mixture thereof, and the crystalline form prepared from the method comprises freebase Form B. In some embodiments, the first solvent comprises 1,4-dioxane, the second solvent comprises IPA, and the crystalline form prepared from the method comprises freebase Form A or freebase Form E, or both. In some embodiments, the first solvent comprises 1,4-dioxane, the second solvent comprises n-heptane, and the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both. In some embodiments, the first solvent comprises 1,4-dioxane, the second solvent comprises water, and the crystalline form prepared from the method comprises freebase Form A or freebase Form D, or both.

[0031] In some embodiments, the method comprises: (i) preparing a suspension of Compound 1 in a solvent; (ii) heating the suspension of step (i) to a first temperature; (iii) filtering the suspension of step (ii) to obtain filtrate; (iv) cooling the filtrate of step (iii) to a second temperature. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, the first temperature is about 50°C. In some embodiments, the second temperature is about 5°C or about -20°C. In some embodiments, the temperature of the filtrate in step (iv) is changed at a rate of about 0.1°C/min. In some embodiments, the method further comprises evaporating the solvent at room temperature. In some embodiments, the solvent comprises EtOh, MIBK, EtOAc, IPAc, 2MeTHF, acetonitrile, or toluene. In some embodiments, the solvent comprises EtOH, EtOAc, 2-MeTHF, or acetonitrile, or any mixture thereof, wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises MIBK, wherein the crystalline form prepared from the method comprises freebase Form C. In some embodiments, the solvent comprises IPAc or toluene, or a mixture thereof, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both.

[0032] In some embodiments, the method comprises: (i) preparing a suspension of Compound 1 in solvent; and (ii) stirring the suspension of step (i) at a temperature for a

duration. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, a solid forms from the suspension after step (ii), and the method further comprises centrifuging the suspension of step (ii) to isolate the solid. In some embodiments, the temperature is room temperature. In some embodiments, the duration is between about 2 days and about 6 days. In some embodiments, the solvent comprises MeOH, MTBE, EtOH, acetone, water, EtOAc, MTBE, THF, 1,4-dioxane, n-Heptane, acetonitrile, DCM, toluene, NMP, or IPA, or any mixture thereof. In some embodiments, the solvent comprises a mixture of MeOH and MTBE at a volume ratio of about 1:1; EtOH; a mixture of acetone and water at a volume ratio of about 1:1; EtOAc; MTBE; a mixture of TFH and water at a volume ratio of about 1:1; a mixture of 1,4-dioxane and n-heptane at a volume ratio of about 1:4; acetonitrile; a mixture of DCM and n-heptane at volume ratio of about 1:1; n-heptane; toluene; water; or a mixture of EtOH and water at a volume ratio of about 97:3 or about 93:7, wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises a mixture of NMP and IPA at a volume ratio of about 1:4, wherein the crystalline form prepared from the method comprises freebase Form B. In some embodiments, the temperature is between about 40°C and about 60°C, and the duration is between about 1 day and about 5 days. In some embodiments, the solvent comprises IPA, MIBK, IPAc, MTBE, 2-MeTHF, 1,4-dioxane, acetonitrile, $CHCl_3$, n-heptane, toluene, water, or DMSO, or any mixture thereof. In some embodiments, the solvent comprises IPA; MIBK; IPAc; MTBE; 2-MeTHF; a mixture of 1,4-dioxane and MTBE at a volume ratio of about 1:9; a mixture of acetonitrile and IPA at a volume ratio of about 1:4; a mixture of $CHCl_3$ and n-heptane at a volume ratio of about 1:9; n-heptane; toluene; or water, wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises a mixture of DMSO and water at a volume ratio of about 1:9, wherein the crystalline form prepared from the method comprises freebase Form C. In some embodiments, the method further comprises cooling the suspension of step (ii) to a temperature of 5°C or lower.

[0033] In some embodiments, the method comprises: (i) preparing a suspension of Compound 1 in a solvent; (ii) heating the suspension to a first temperature and cooling the suspension to a second temperature; and (iii) heating the suspension to a third temperature, and cooling the suspension to a fourth temperature. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, a solid forms from the suspension after step (iii), and the method further comprises centrifuging the suspension of step (iii) to

isolate the solid. In some embodiments, the first temperature and the third temperature are each independently in between about 40°C and about 50°C, and the second temperature and the fourth temperature are each independently in between about 0°C and about 10°C. In some embodiments, the heating and cooling of steps (ii) and (iii) are each independently conducted at a rate of between about 0.01 °C/min and about 1 °C/min. In some embodiments, the solvent comprises EtOH, acetone, IPA, EtOAc, IPAc, MTBE, 2-MeTHF, $CHCl_3$, n-heptane, toluene, water, DMAc, MTBE, or acetonitrile, or any mixture thereof. In some embodiments, the solvent comprises EtOH; a mixture of acetone and IPA at a volume ratio of about 1:40; EtOAc; IPAc; MTBE; 2-MeTHF; a mixture of $CHCl_3$ and n-heptane at a volume ratio of about 1:9; n-heptane; toluene; water; a mixture of DMAc and MTBE at a volume ratio of about 1:9; or a mixture of acetonitrile and MTBE at a volume ratio of about 1:9, wherein the crystalline form prepared from the method comprises freebase Form A.

[0034] In some embodiments, the method comprises: (i) dissolving Compound 1 in a solvent; and (ii) evaporating the solvent of step (i) at a temperature. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, the temperature of step (ii) is room temperature. In some embodiments, the solvent comprises MeOH, EtOH, acetone, EtOAc, THF, 1,4-dioxane, acetonitrile, $CHCl_3$, DCM, or n-heptane, or any mixture thereof. In some embodiments, the solvent comprises MeOH; EtOH; EtOAc; 1,4-dioxane; acetonitrile; $CHCl_3$; a mixture of MeOH and water at a volume ratio of about 9:1; or a mixture of DCM and n-heptane at a volume ratio of about 9:1, wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises a mixture of acetone and water at a volume ratio of about 9:1, wherein the crystalline form prepared from the method comprises freebase Form D. In some embodiments, the solvent comprises acetone, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both. In some embodiments, the solvent comprises THF, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form D, or both.

[0035] In some embodiments, the method comprises grinding Compound 1. In some embodiments, Compound 1 comprises freebase Form A. In some embodiments, the method further comprises contacting Compound 1 with a solvent while grinding. In some embodiments, the solvent comprises water. In some embodiments, the crystalline form prepared from the method comprises freebase Form A.

[0036] In some embodiments, the method comprises: (i) adding Compound 1 to a solvent to form a first mixture; and (ii) adding an anti-solvent to the first mixture to form a second mixture. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, the anti-solvent is added until a precipitate is produced. In some embodiments, the method further comprises cooling the second mixture to a cooling temperature. In some embodiments, the cooling temperature is between about -25°C and about 10°C. In some embodiments, the method further comprises evaporating the solvent and the antisolvent from the second mixture at an evaporation temperature. In some embodiments, the evaporation temperature is room temperature. In some embodiments, the solvent comprises acetone, THF, acetonitrile, $CHCl_3$, MeOH, 1,4-dioxane, DCM, NMP, EtOH, toluene, or DMAc, or any mixture thereof; and the anti-solvent comprises IPA, MTBE, n-heptane, or water, or any mixture thereof. In some embodiments, the solvent comprises acetone, acetonitrile, or $CHCl_3$, or any mixture thereof, and the anti-solvent comprises IPA; or the solvent comprises acetone, and the anti-solvent comprises MTBE; wherein the crystalline form prepared from the method comprises freebase Form E. In some embodiments, the solvent comprises THF, and the anti-solvent comprises IPA; or the solvent comprises 1,4-dioxane, and the anti-solvent comprises MTBE; wherein the crystalline form prepared from the method comprises freebase Form C. In some embodiments, the solvent comprises DCM, and the antisolvent comprises MTBE; or the solvent comprises EtOH, acetone, 1,4-dioxane, toluene, or DCM, or any mixture thereof, and the anti-solvent comprises n-heptane; wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises NMP, and the anti-solvent comprises MTBE; the solvent comprises NMP or DMAc, or a mixture thereof, and the anti-solvent comprises water; wherein the crystalline form prepared from the method comprises freebase Form B. In some embodiments, the solvent comprises THF, and the anti-solvent comprises n-heptane; or the solvent comprises MeOH, acetone, THF, 1,4-dioxane, or acetonitrile, or any mixture thereof, and the anti-solvent comprises water, wherein the crystalline form prepared from the method comprises freebase Form D. In some embodiments, the solvent comprises MeOH, and the anti-solvent comprises MTBE, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form E, or both.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures.

[0038] **FIGS. 1A-1L** depict XRPD data (FIG. 1A); TGA and DSC data (FIG. 1B); DVS data (FIG. 1C); ^{1}H NMR spectrum in DMSO-d_6 (FIG. 1D); ^{1}H NMR spectrum in ACN-d_3 (FIG. 1E); PLM imaging (FIG. 1F); SEM imaging (FIG. 1G); XRPD overlay before and after grinding (FIG. 1H); XRPD overlay before and after DVS (FIG. 1I); XRPD overlay of after stability test (FIG. IJ); XRPD overlay of residual solids after solubility test (FIG. 1K); and XPS result (FIG. 1L) of freebase Form A of Compound 1.

[0039] **FIG. 1M** depicts XRPD Overlay of freebase Types A, C, D, E, and H.

[0040] **FIG. 1N** depicts inter-conversion diagram of Compound 1 freebase polymorphs.

[0041] **FIGS. 2A** and **2B** depict XRPD data (FIG. 2A) and TGA and DSC data (FIG. 2B) of freebase Form E of Compound 1.

[0042] **FIGS. 3A** and **3B** depict XRPD data (FIG. 3A) and TGA and DSC data (FIG. 3B) of freebase Form C of Compound 1.

[0043] **FIGS. 4A** and **4B** depict XRPD data (FIG. 4A) and TGA and DSC data (FIG. 4B) of freebase Form D of Compound 1.

[0044] **FIGS. 5A** and **5B** depict XRPD data (FIG. 5A) and TGA and DSC data (FIG. 5B) of freebase Form B of Compound 1.

[0045] **FIG. 6** depicts XRPD data of freebase Form F of Compound 1.

[0046] **FIGS. 7** and **8** depict XRPD data (FIG. 7) and TGA and DSC data (FIG. 8) of freebase Form G of Compound 1.

[0047] **FIGS. 9A** and **9B** depict XRPD data (FIG. 9A) and TGA and DSC data (FIG. 9B) of freebase Form H of Compound 1.

[0048] **FIGS. 10A-10F** depict VT-XRPD (FIG. 10A); VH-XRPD (FIGS. 10B-10D) overlay; XRPD overlay before and after solid vapor diffusion in H_2O (FIG. 10E); TGA and

DSC curves after solid vapor diffusion in H_2O (FIG. 10F) of freebase Form A of Compound 1.

[0049] **FIGS. 11A-11G** depict overlay of XRPD patterns (FIG. 11A); over lay of XRPD patterns of re-prepared sample (FIG. 11B); the ^{1}H NMR spectrum re-prepared sample (FIG. 11C); the UPLC chromatogram re-prepared sample (FIG. 11D); XRPD overlay before and after heating (FIG. 11E); the ^{1}H NMR spectrum after heating (FIG. 11F); overlay of XRPD patterns (FIG. 11G) obtained from studies in relation to freebase Form B of Compound 1.

[0050] **FIGS. 12A-12H** depict XRPD patterns (FIGS. 12A and 12B); XRPD pattners re-prepared sample (FIG. 12C); ^{1}H NMR spectrum re-prepared sample (FIG. 12D); UPLC chromatogram re-prepared sample (FIG. 12E); XRPD overlay (FIG. 12F); VT-XRPD (FIG. 12G); XRPD overlay after stored at RT (FIG. 12H) of freebase Form C of Compound 1.

[0051] **FIGS. 13A-13I** depict XRPD data (FIG. 13A); TGA and DSC data (FIG. 13B); ^{1}H NMR spectrum (FIG. 13C); UPLC chromatogram (FIG. 13D); XRPD overlay before and after heating (FIG. 13E); XRPD overlay of wet and dry re-prepared samples (FIG. 13F); ^{1}H NMR spectrum of re-prepared sample (FIG. 13G); UPLC chromatogram of re-prepared sample (FIG. 13 H); VT-XRPD of re-prepared sample (FIG. 13I) of freebase Form D of Compound 1.

[0052] **FIGS. 14A-14D** depicts the ^{1}H NMR spectrum (FIG. 14A); UPLC chromatogram (FIG. 14B); XRPD patterns before and after storage (FIG. 14C); XRPD pattern of re-prepared sample (FIG. 14D) of freebase Form E of Compound 1.

[0053] **FIG. 15** depicts XRPD pattern of freebase Form F of Compound 1.

[0054] **FIG. 16A-16F** depict XRPD pattern (FIG. 16A); ^{1}H NMR spectrum in ACN-d_6 (FIG. 16B); UPLC chromatogram (FIG. 16C); XRPD pattern before and after heating (FIG. 16D); ^{1}H NMR spectra in ACN-d_6 after heating to 100 °C (FIG. 16E); and ^{1}H NMR spectra in ACN-d_6 after heating to 160 °C (FIG. 16F) of freebase Form G of Compound 1.

[0055] **FIGS. 17A** and **17B** depict XRPD patterns of freebase Form H of Compound 1.

[0056] **FIGS. 18A** and **18B** depict XRPD overlay of solids from competitive slurry in EtOH/H_2O system.

[0057] **FIGS. 18C** and **18D** depict XRPD overlay of solids from competitive slurry after drying.

[0058] **FIG. 18E** depicts XRPD overlay of solids from competitive slurry in EtOH/H_2O system.

[0059] **FIG. 18F** depicts XRPD overlay of solids from competitive slurry in EtOH/H_2O system with freebase Type H addition.

[0060] **FIG. 18G** depicts XRPD overlay of solid from competitive slurry in H_2O system with freebase Type H addition.

DETAILED DESCRIPTION

[0061] The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

I. Definitions

[0062] As used herein, the following definitions shall apply unless otherwise indicated. Further, if any term or symbol used herein is not defined as set forth below, it shall have its ordinary meaning in the art.

[0063] As used herein, reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X". As used herein, and unless otherwise specified, the terms "about" and "approximately," when used in connection with doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. Specifically, the terms "about" and "approximately," when used in this context, contemplate a dose, amount, or weight percent within 20%, within 15%, within 10%, within 5%, within 4%, within 3%, within 2%, within 1%, or within 0.5% of the specified dose, amount, or weight percent.

[0064] As used herein, the term "crystalline form" refers to a crystalline solid form of a chemical compound, including, but not limited to, a single-component or multiple-component crystal form, e.g., a polymorph of a compound. The term "crystal forms" and related terms herein refer to the various crystalline modifications of a given substance, including, but not limited to, anhydrates and solvates thereof. Crystal forms of a substance can be obtained by a number of methods, as known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, slurrying, recrystallization in confined spaces such as, e.g., in nanopores or capillaries, recrystallization on surfaces or templates such as, e.g., on polymers, recrystallization in the presence of additives, such as, e.g., anti-solvents, co-crystal counter-molecules, desolvation, dehydration, rapid evaporation, rapid cooling, slow cooling, vapor diffusion, sublimation, grinding and solvent-drop grinding.

[0065] As used herein, "solvate" encompasses solvates, partial solvates, and channel solvates. As such, a solvate need not contain an exact stoichiometric ratio of compound:solvent, but may include ratios of compound:solvent permitted by experimental variance. The term "solvate" is further intended to include aqueous and non-aqueous solvated forms (e.g., hydrates, ethanolates, etc.). Thus, it is understood that a solvate encompasses stoichiometric solvates, channel solvates and partial solvates. It is also understood that a hydrate encompasses stoichiometric hydrates, channel hydrates and partial hydrates.

[0066] As used herein, the term "substantially as shown in" when referring, for example, to an XRPD pattern, a DSC graph, a TGA graph, or a GVS graph, includes a pattern or graph that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art.

[0067] The term "excipient" as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the present disclosure as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent.

[0068] The terms "individual", "subject" and "patient" refer to mammals and includes humans and non-human mammals. Examples of patients include, but are not limited to, mice,

rats, hamsters, guinea pigs, pigs, rabbits, cats, dogs, goats, sheep, cows, and humans. In some embodiments, patient refers to a human.

[0069] As used herein, the term "mammal" includes, but is not limited to, humans, mice, rats, guinea pigs, monkeys, dogs, cats, horses, cows, pigs, and sheep.

[0070] "Pharmaceutically acceptable" refers to safe and non-toxic, and suitable for in vivo or for human administration.

[0071] The compounds of the present disclosure can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present disclosure also embraces isotopically-labeled variants of the present disclosure which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the present disclosure and include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^{2}H ("D"), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Certain isotopically labeled compounds of the present disclosure (*e.g.*, those labeled with ^{3}H or ^{14}C) are useful in Compound 1 and/or substrate tissue distribution assays. Tritiated (^{3}H) and carbon-14 (^{14}C) isotopes are useful for their ease of preparation and detectability. Further substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present disclosure can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0072] "Treating" or "treatment" of a disease in a patient refers to inhibiting the disease or arresting its development; or ameliorating or causing regression of the disease. As used herein, "treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. For purposes of this disclosure, beneficial or desired results include,

but are not limited to, one or more of the following: decreasing one more symptoms resulting from the disease or disorder, diminishing the extent of the disease or disorder, stabilizing the disease or disorder (e.g., preventing or delaying the worsening of the disease or disorder), delaying the occurrence or recurrence of the disease or disorder, delay or slowing the progression of the disease or disorder, ameliorating the disease or disorder state, providing a remission (whether partial or total) of the disease or disorder, decreasing the dose of one or more other medications required to treat the disease or disorder, enhancing the effect of another medication used to treat the disease or disorder, delaying the progression of the disease or disorder, increasing the quality of life, and/or prolonging survival of a patient. Also encompassed by "treatment" is a reduction of pathological consequence of the disease or disorder. The methods of the present disclosure contemplate any one or more of these aspects of treatment.

[0073] "Preventing", "prevention", or "prophylaxis" of a disease in a patient refers to preventing the disease from occurring in a patient that is predisposed or does not yet display symptoms of the disease.

[0074] The phrase "therapeutically effective amount" means an amount of a compound of the present disclosure that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

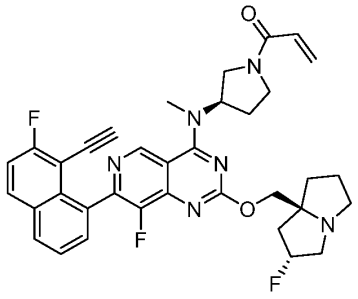
[0075] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth.

[0076] It is appreciated that certain features of the present disclosure, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (*i.e.*, compounds that can be isolated, characterized,

and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

II. Crystalline forms

[0077] In one aspect, provided herein is a crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), having the structure shown below:



(Compound 1).

Compound 1 and an exemplary method of making Compound 1 are described herein and in International Patent Application Publication No. WO 2023/081840 A1, which is incorporated herein by reference in its entirety. Throughout this application, unless the context indicates otherwise, reference to a compound such as Compound 1 includes all tautomers thereof.

[0078] The crystalline forms disclosed herein may provide the advantages of bioavailability and stability and may be suitable for use as an active agent in a pharmaceutical composition. Variations in the crystal structure of a pharmaceutical drug substance may affect the dissolution rate (which may affect bioavailability, etc.), manufacturability (e.g., ease of handling, ease of purification, ability to consistently prepare doses of known strength, etc.) and stability (e.g., thermal stability, shelf life (including resistance to degradation), etc.) of a pharmaceutical drug product. Such variations may affect the methods of preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solid oral dosage forms including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, crystalline forms may provide desired or suitable hygroscopicity, particle size control, dissolution rate, solubility, purity, physical and chemical

stability, manufacturability, yield, reproducibility, and/or process control. Thus, the crystalline forms disclosed herein may provide advantages of improving the manufacturing process of an active agent or the stability or storability of a drug product form of the active agent or having suitable bioavailability and/or stability as an active agent.

[0079] In one aspect, provided herein is a crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1).

[0080] In some embodiments, a crystalline form is interchangeably referenced as a "Form" or "Type." For example, in some embodiments, "freebase Form A" indicates the same crystalline form as "freebase Type A," and vice versa.

[0081] In some embodiments, the purity of the crystalline form is at least about 95%. In some embodiments, the purity of the crystalline form is at least about 96%. In some embodiments, the purity of the crystalline form is at least about 97%. In some embodiments, the purity of the crystalline form is at least about 98%. In some embodiments, the purity of the crystalline form is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, or 99.99%. In some embodiments, the crystalline form is substantially pure.

[0082] In some embodiments, "about" before an XRPD angle 2-theta value indicates ±0.2 of that value. For example, an angle 2-theta of about 5 can indicate 5±0.2. In some embodiments, "about" before an XRPD angle 2-theta value indicates ±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, ±2.0, or ±2.5 of that value.

[0083] In one aspect, provided is a pharmaceutical composition comprising a crystalline form provided herein, and a pharmaceutically acceptable excipient.

[0084] In some embodiments, the crystalline form is a hydrate. In some embodiments, the crystalline form is a channel hydrate. In some embodiments, the crystalline form is a solvate. In some embodiments, the crystalline form is an anhydrate. In some embodiments, a freebase crystalline form of Compound 1 is advantageously more stable than a crystalline form of a salt of Compound 1.

[0085] The X-ray source for XRPD is copper Kα. In some embodiments, the Kα1 wavelength is about 1.54 Å. In some embodiments, the Kα2 wavelength is about 1.54 Å. In some embodiments, the intensity ratio of Kα2/Kα1 is about 0.5. In some embodiments, XRPD is measured at room temperature.

Channel hydrate

[0086] In some embodiments, the crystalline form is a channel hydrate whose XRPD pattern is provided as a function of relative humidity. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 6.9, about 15.0, and about 22.4 as measured at between about 50% to about 80% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 6.9, about 15.0, and about 22.4 as measured at about 60% to about 70% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 7.1, about 14.0, and about 22.5 as measured at about 30% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5 as measured at less than about 20% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5 as measured at less than about 10% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having (i) an XRPD pattern comprising peaks at angle 2-theta of about 6.9, about 15.0, and about 22.4 as measured at about 50% to about 80% relative humidity at room temperature; (ii) an XRPD pattern comprising peaks at angle 2-theta of about 7.1, about 14.0, and about 22.5 as measured at about 30% relative humidity at room temperature; and (iii) an XRPD pattern comprising peaks at angle 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5 as measured at less than about 20% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having (i) an XRPD pattern comprising peaks at angle 2-theta of about 6.9, about 15.0, and about 22.4 as measured at about 60% to about 70% relative humidity at room temperature; (ii) an XRPD pattern comprising peaks at angle 2-theta of about 7.1, about 14.0, and about 22.5 as measured at about 30% relative humidity at room temperature; and (iii) an XRPD pattern comprising peaks at angle 2-theta of about 7.2, about

14.1, about 15.9, and about 22.5 as measured at less than about 10% relative humidity at room temperature.

[0087] In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in FIG. 1A as measured at between about 50% to about 80% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in FIG. 1A as measured at between about 60% to about 70% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in FIG. 2A as measured at about 30% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in FIG. 9A as measured at less than about 20% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in FIG. 9A as measured at less than about 10% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having (i) an XRPD pattern substantially as shown in FIG. 1A as measured at between about 50% to about 80% relative humidity at room temperature; (ii) an XRPD pattern substantially as shown in FIG. 2A as measured at about 30% relative humidity at room temperature; and (iii) an XRPD pattern substantially as shown in FIG. 9A as measured at less than about 20% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having (i) an XRPD pattern substantially as shown in FIG. 1A as measured at between about 60% to about 70% relative humidity at room temperature; (ii) an XRPD pattern substantially as shown in FIG. 2A as measured at about 30% relative humidity at room temperature; and (iii) an XRPD pattern substantially as shown in FIG. 9A as measured at less than about 10% relative humidity at room temperature.

[0088] In some embodiments, the XRPD pattern is measured at between about 50% to about 80% relative humidity at room temperature. In some embodiments, the XRPD pattern is measured at between about 60% to about 70% relative humidity at room temperature. In some embodiments, the XRPD pattern is measured at about 50%, about 60%, about 70%, or about 80% relative humidity at room temperature. In some embodiments, the XRPD pattern is measured at about 30% relative humidity at room temperature. In some embodiments, the XRPD pattern is measured at about 20% or less than about 20% relative humidity at room temperature. In some embodiments, the XRPD pattern is measured at about 10% or less than

about 10% relative humidity at room temperature. In some embodiments, the XRPD pattern is measured at between about 10% and about 20% relative humidity at room temperature. In some embodiments, the XRPD pattern is measured at less than about 20% relative humidity at room temperature. In some embodiments, the XRPD pattern is measured at less than about 10% relative humidity at room temperature.

Freebase Form A

[0089] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form A substantially as shown in FIG. 1A. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees recited in Table A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.9. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 15.0, and about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 16.4, about 17.4, about 19.3, about 20.7, about 22.4, about 24.1, about 28.2, and about 31.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 17.4, about 19.3, about 20.7, and about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, at least four, at least five, at least six, or at least seven peaks selected from angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 16.4, about 17.4, about 19.3, about 20.7, about 22.4, about 24.1, about 28.2, and about 31.0. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 73.5 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 76.0 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 194.9 °C. In

some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 1B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 1B. In some embodiments, the crystalline form is characterized by having a DVS graph substantially as shown in FIG. 1C. In some embodiments, the crystalline form comprises water. In some embodiments, the molar ratio of water:Compound 1 is about 3.5:1.

[0090] In all of the embodiments provided in this paragraph, the XRPD pattern is measured at between about 50% to about 80% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form A substantially as shown in FIG. 1A. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees recited in Table A. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.9. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 15.0, and about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 16.4, about 17.4, about 19.3, about 20.7, about 22.4, about 24.1, about 28.2, and about 31.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 17.4, about 19.3, about 20.7, and about 22.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, at least four, at least five, at least six, or at least seven peaks selected from angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 16.4, about 17.4, about 19.3, about 20.7, about 22.4, about 24.1, about 28.2, and about 31.0. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 73.5 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 76.0 °C. In some embodiments, the crystalline form is

characterized by having a DSC graph comprising an exothermic peak at about 194.9 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 1B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 1B. In some embodiments, the crystalline form is characterized by having a DVS graph substantially as shown in FIG. 1C. In some embodiments, the crystalline form comprises water. In some embodiments, the molar ratio of water:Compound 1 is about 3.5:1.

Table A. XRPD pattern of freebase Form A.

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
6.8941	6975.73	0.1023	12.82	100.00
7.4891	299.51	0.0768	11.80	4.29
12.8093	239.52	0.0768	6.91	3.43
13.7720	308.17	0.0768	6.43	4.42
13.9623	442.03	0.0768	6.34	6.34
14.9864	959.61	0.1023	5.91	13.76
16.3515	54.25	0.3070	5.42	0.78
17.3855	288.67	0.1023	5.10	4.14
19.3119	87.80	0.4093	4.60	1.26
20.6560	249.45	0.1791	4.30	3.58
22.4283	932.05	0.1279	3.96	13.36
24.1233	125.05	0.1535	3.69	1.79
28.2226	119.95	0.1535	3.16	1.72
30.9999	74.96	0.3070	2.88	1.07

Freebase Form E

[0091] In some embodiments, the crystalline form is characterized by having an XRPD pattern of Form E substantially as shown in FIG. 2A. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table E. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table E. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.1. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.6. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.5. In

some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 14.0, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 11.1, about 12.6, about 14.0, about 14.6, about 15.6, about 20.3, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, or at least four peaks selected from angles 2-theta of about 7.1, about 11.1, about 12.6, about 14.0, about 14.6, about 15.6, about 20.3, and about 22.5. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 69.7 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 190.5 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 2B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 2B.

[0092] In all of the embodiments provided in this paragraph, the XRPD pattern is measured at about 30% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern of Form E substantially as shown in FIG. 2A. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table E. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table E. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.1. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.6. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 14.0, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 11.1, about 12.6, about 14.0, about 14.6, about 15.6, about 20.3, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, or at least four peaks selected from angles 2-theta of about 7.1, about 11.1, about

12.6, about 14.0, about 14.6, about 15.6, about 20.3, and about 22.5. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 69.7 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 190.5 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 2B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 2B.

Table E. XRPD pattern of freebase Form E.

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
7.0977	1527.54	0.2047	12.45	100.00
11.0667	53.26	0.3070	8.00	3.49
12.6268	71.31	0.3070	7.01	4.67
14.0277	385.80	0.1279	6.31	25.26
14.6136	217.85	0.1279	6.06	14.26
15.5970	214.16	0.4093	5.68	14.02
20.3091	78.92	0.3070	4.37	5.17
22.5096	371.51	0.1791	3.95	24.32

Freebase Form C

[0093] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form C substantially as shown in FIG. 3A. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table C-1. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table C-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Tables C-1 or C-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.9. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 14.9, and about 22.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 7.5, about 11.0, about 12.7, about 13.7, about 14.6,

about 14.9, about 16.3, about 17.0, about 18.5, about 19.5, about 19.9, about 20.4, about 22.2, about 23.3, about 24.2, about 25.2, about 25.7, about 27.0, about 28.0, and about 34.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 7.5, about 12.7, about 13.7, about 14.6, about 14.9, about 16.3, about 17.0, about 18.5, about 19.5, about 19.9, about 20.4, and about 22.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten peaks selected from angles 2-theta of about 6.7, about 7.5, about 11.0, about 12.7, about 13.7, about 14.6, about 14.9, about 16.3, about 17.0, about 18.5, about 19.5, about 19.9, about 20.4, about 22.2, about 23.3, about 24.2, about 25.2, about 25.7, about 27.0, about 28.0, and about 34.5. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 80.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 189.4 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 3B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 3B.

Table C-1. XRPD pattern of freebase Form C.

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
6.7208	18522.11	0.1279	13.15	100.00
7.4869	860.86	0.1023	11.81	4.65
10.9857	178.10	0.2047	8.05	0.96
12.6975	332.93	0.1535	6.97	1.80
13.7075	790.95	0.1279	6.46	4.27
14.5795	553.18	0.1023	6.08	2.99
14.9381	3458.26	0.1791	5.93	18.67
16.3498	257.48	0.1023	5.42	1.39
17.0412	224.72	0.1791	5.20	1.21
18.5203	395.10	0.1023	4.79	2.13
19.4651	444.87	0.1791	4.56	2.40
19.9175	272.81	0.0768	4.46	1.47
20.3970	209.91	0.3070	4.35	1.13
22.1760	2007.82	0.1279	4.01	10.84
23.3398	287.96	0.1279	3.81	1.55
24.2257	119.31	0.2047	3.67	0.64
25.1583	184.27	0.1535	3.54	0.99
25.7368	225.00	0.1279	3.46	1.21
26.9757	156.60	0.2558	3.31	0.85
28.0375	309.67	0.1279	3.18	1.67

34.4925	40.61	0.6140	2.60	0.22

Table C-2. XRPD pattern of freebase Form C (wet).

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
6.6556	2542.45	0.1279	13.28	100.00
12.5954	53.07	0.4093	7.03	2.09
13.6583	225.35	0.2047	6.48	8.86
14.4259	147.96	0.2047	6.14	5.82
14.8514	759.84	0.2047	5.97	29.89
16.3069	74.40	0.3070	5.44	2.93
16.9985	61.55	0.3070	5.22	2.42
18.5072	75.11	0.3070	4.79	2.95
19.3852	144.45	0.1535	4.58	5.68
20.3367	72.98	0.6140	4.37	2.87
22.0751	546.85	0.1791	4.03	21.51
23.2498	82.11	0.3070	3.83	3.23
24.9805	55.56	0.3070	3.56	2.19
25.7042	68.34	0.2047	3.47	2.69
27.9518	99.02	0.2047	3.19	3.89

Freebase Form D

[0094] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form D substantially as shown in FIG. 4A. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table D. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table D. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 13.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.6. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 23.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, 13.3, 14.6, and 23.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 13.3, about 14.6, about 15.5, about 21.0, about 22.4, about 23.3, about 25.7, and about 27.1. In some embodiments, the crystalline form is characterized by

having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 13.3, about 14.6, about 15.5, about 21.0, about 22.4, and about 23.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, or at least four peaks selected from angles 2-theta of about 6.7, about 13.3, about 14.6, about 15.5, about 21.0, about 22.4, about 23.3, about 25.7, and about 27.1. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 80.8 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 189.4 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 4B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 4B.

Table D. XRPD pattern of freebase Form D.

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
6.7286	4026.52	0.1535	13.14	100.00
13.3372	374.23	0.2558	6.64	9.29
14.5660	483.20	0.1535	6.08	12.00
15.4696	375.73	0.1535	5.73	9.33
21.0196	170.37	0.2558	4.23	4.23
22.4285	165.98	0.3070	3.96	4.12
23.3339	405.42	0.1279	3.81	10.07
25.6914	67.91	0.3070	3.47	1.69
27.0841	98.93	0.4093	3.29	2.46

Freebase Form B

[0095] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form B substantially as shown in FIG. 5A. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table B-1. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table B-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table B-1 or B-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.7. In some embodiments, the crystalline form

is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 14.7, and about 22.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 12.5, about 12.9, about 14.1, about 14.7, about 18.0, about 18.8, about 22.3, about 23.0, and about 25.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 12.5, about 12.9, about 14.1, about 14.7, about 18.0, about 18.8, and about 22.3. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, at least four, or at least five peaks selected from angles 2-theta of about 6.2, about 12.5, about 12.9, about 14.1, about 14.7, about 18.0, about 18.8, about 22.3, about 23.0, and about 25.7. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 84.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 187.1 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 5B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 5B. In some embodiments, the crystalline form is an isomorphic form. In some embodiments, the crystalline form comprises DMAc, wherein the molar ratio of DMAc:Compound 1 is about 0.7:1.

Table B-1. XRPD pattern of freebase Form B.

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
6.2478	5948.07	0.1279	14.15	100.00
12.4831	194.34	0.1535	7.09	3.27
12.9168	190.72	0.1279	6.85	3.21
14.1037	178.11	0.1535	6.28	2.99
14.6517	255.12	0.1535	6.05	4.29
17.9500	73.19	0.3070	4.94	1.23
18.7671	116.06	0.2047	4.73	1.95
22.2800	385.40	0.1791	3.99	6.48
23.0146	163.78	0.1535	3.86	2.75
25.7269	129.11	0.2558	3.46	2.17

Table B-2. XRPD pattern of freebase Form B (wet).

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]

6.1956	1222.44	0.1279	14.27	100.00
12.8651	163.93	0.2047	6.88	13.41
14.6014	269.09	0.2047	6.07	22.01
22.1632	341.16	0.1535	4.01	27.91
25.3559	98.26	0.4093	3.51	8.04

Freebase Form F

[0096] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form F substantially as shown in FIG. 6. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table F. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table F. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 13.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 6.7, and about 13.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 6.7, about 12.4, about 13.4, about 15.1, about 16.8, about 18.7, about 20.1, about 21.7, about 23.2, about 25.7, about 26.9, about 27.7, about 29.9, and about 33.9. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 6.7, about 13.4, about 15.1, about 20.1, and about 21.7. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, at least four, at least five, at least six, or at least seven peaks selected from angles 2-theta of about 6.2, about 6.7, about 12.4, about 13.4, about 15.1, about 16.8, about 18.7, about 20.1, about 21.7, about 23.2, about 25.7, about 26.9, about 27.7, about 29.9, and about 33.9. In some embodiments, the crystalline form comprises DMAc or IPA, or both.

Table F. XRPD pattern of freebase Form F (wet).

Pos. [°2θ]	**Height [cts]**	**FWHM Left [°2θ]**	**d-spacing [Å]**	**Rel. Int. [%]**
6.2351	3755.76	0.0768	14.18	9.27
6.6721	40529.49	0.0768	13.25	100.00
12.4372	147.80	0.1535	7.12	0.36

13.3556	2341.48	0.1023	6.63	5.78
15.1198	421.02	0.1279	5.86	1.04
16.8118	253.52	0.1535	5.27	0.63
18.7462	215.95	0.1023	4.73	0.53
20.0977	424.97	0.1023	4.42	1.05
21.7322	607.92	0.1791	4.09	1.50
23.2310	206.14	0.1279	3.83	0.51
25.7074	81.15	0.1535	3.47	0.20
26.9217	518.16	0.1791	3.31	1.28
27.6667	128.37	0.2558	3.22	0.32
29.8989	228.38	0.1279	2.99	0.56
33.8987	22.23	0.6140	2.64	0.05
38.9280	41.94	0.3070	2.31	0.10

Freebase Form G

[0097] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form G substantially as shown in FIG. 7. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table G. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table G In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.0. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 13.8. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.4. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.0, about 13.8, about 15.4, and about 22.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.0, about 11.0, about 13.8, about 14.5, about 15.2, about 15.4, about 17.3, about 20.1, about 21.0, about 22.2, about 23.0, about 24.1, about 25.4, about 27.8, and about 30.6. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.0, about 11.0, about 13.8, about 14.5, about 15.2, about 15.4, about 17.3, about 20.1, about 21.0, and about 22.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, at least four, at least five, at least six, at least seven, or at least eight peaks selected from angles 2-theta of about 6.5, about

7.0, about 11.0, about 13.8, about 14.5, about 15.2, about 15.4, about 17.3, about 20.1, about 21.0, about 22.2, about 23.0, about 24.1, about 25.4, about 27.8, and about 30.6. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 72.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 113.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 196.3 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 8. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 8. In some embodiments, the crystalline form comprises DMSO, wherein the molar ratio of DMSO:Compound 1 is about 0.8.

Table G. XRPD pattern of freebase Form G.

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
6.5031	377.09	0.1023	13.59	11.26
6.9602	3349.94	0.1023	12.70	100.00
10.9946	108.31	0.1535	8.05	3.23
13.8302	716.74	0.1023	6.40	21.40
14.4858	278.85	0.1279	6.11	8.32
15.1918	522.60	0.1023	5.83	15.60
15.4427	746.38	0.1023	5.74	22.28
17.3262	88.18	0.2047	5.12	2.63
20.0924	165.72	0.2558	4.42	4.95
20.9969	250.56	0.1279	4.23	7.48
22.2060	806.58	0.1279	4.00	24.08
22.9617	81.83	0.3070	3.87	2.44
24.0796	133.27	0.1535	3.70	3.98
25.4390	86.25	0.6140	3.50	2.57
27.8463	144.46	0.1535	3.20	4.31
30.5869	77.40	0.3070	2.92	2.31

Freebase Form H

[0098] In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form H substantially as shown in FIG. 9A. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table H-1. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table H-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-

theta in degrees as recited in Table H-1 or H-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 17.7, about 20.3, about 21.8, about 22.5, and about 28.1. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 21.8, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, at least four, at least five, or at least six peaks selected from angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 17.7, about 20.3, about 21.8, about 22.5, and about 28.1. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 73.6 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 194.1 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 9B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 9B.

[0099] In all of the embodiments provided in this paragraph, the XRPD pattern is measured at less than about 20% relative humidity at room temperature. In some embodiments, the crystalline form is characterized by having an XRPD pattern of freebase Form H substantially as shown in FIG. 9A. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table H-1. In some embodiments, the crystalline form is characterized by having an XRPD pattern substantially as shown in Table H-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table H-1 or H-2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.5. In some embodiments, the

crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.2. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 17.7, about 20.3, about 21.8, about 22.5, and about 28.1. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 21.8, and about 22.5. In some embodiments, the crystalline form is characterized by having an XRPD pattern comprising at least two, at least three, at least four, at least five, or at least six peaks selected from angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 17.7, about 20.3, about 21.8, about 22.5, and about 28.1. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an endothermic peak at about 73.6 °C. In some embodiments, the crystalline form is characterized by having a DSC graph comprising an exothermic peak at about 194.1 °C. In some embodiments, the crystalline form is characterized by having a DSC graph substantially as shown in FIG. 9B. In some embodiments, the crystalline form is characterized by having a TGA graph substantially as shown in FIG. 9B.

Table H-1. XRPD pattern of freebase Form H.

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
6.5016	468.87	0.1023	13.60	5.14
7.2412	9128.29	0.0768	12.21	100.00
11.1967	164.95	0.1023	7.90	1.81
13.7550	404.36	0.1023	6.44	4.43
14.0811	516.92	0.1279	6.29	5.66
14.4660	395.14	0.1535	6.12	4.33
15.9210	489.32	0.1023	5.57	5.36
17.7282	77.89	0.2047	5.00	0.85
20.3193	68.89	0.3070	4.37	0.75
21.7728	131.85	0.1535	4.08	1.44
22.4966	715.59	0.1535	3.95	7.84
28.0593	79.90	0.3070	3.18	0.88

Table H-2. XRPD pattern of freebase Form H (obtained from N_2 purge of freebase Type E).

Pos. [°2θ]	Height [cts]	FWHM Left [°2θ]	d-spacing [Å]	Rel. Int. [%]
6.4205	337.37	0.0669	13.77	4.04
7.2108	8352.73	0.0669	12.26	100.00
11.1310	276.49	0.0836	7.95	3.31
12.5994	155.20	0.1338	7.03	1.86
13.7790	728.77	0.1004	6.43	8.72
14.0424	905.14	0.1004	6.31	10.84
14.4902	865.32	0.1171	6.11	10.36
15.6838	580.68	0.1171	5.65	6.95
15.9450	833.41	0.1338	5.56	9.98
16.7306	184.10	0.1004	5.30	2.20
17.6985	147.43	0.1338	5.01	1.77
18.3251	112.27	0.1004	4.84	1.34
20.2104	181.33	0.1338	4.39	2.17
20.9168	81.13	0.2007	4.25	0.97
21.7808	279.49	0.1338	4.08	3.35
22.0760	372.03	0.1004	4.03	4.45
22.3959	1224.88	0.1338	3.97	14.66
22.8784	232.02	0.1338	3.89	2.78
24.7563	93.95	0.2007	3.60	1.12
25.4050	104.03	0.2007	3.51	1.25
26.4244	57.98	0.2007	3.37	0.69
27.9318	137.41	0.1338	3.19	1.65
29.0265	50.79	0.6691	3.08	0.61
30.9127	24.52	0.8029	2.89	0.29

III. Methods of Preparing

[0100] In one aspect, provided herein is a method for preparing a crystalline form of Compound 1.

[0101] In some embodiments, "room temperature" indicates a temperature between about 15°C and about 35°C. In some embodiments, "room temperature" indicates a temperature between about 15°C and about 30°C. In some embodiments, "room temperature" indicates a temperature between about 20°C and about 30°C. In some embodiments, "room temperature" indicates a temperature at about 25°C.

[0102] In one aspect, provided is a method of preparing a crystalline form provided herein. In some embodiments, the method comprises (i) contacting Compound 1 with one or more solvents to form a mixture; and (ii) crystallizing Compound 1. In some embodiments, the one or more solvents comprise ethyl acetate, tetrahydrofuran, or ethanol, or any combination thereof. In some embodiments, the one or more solvents comprise ethyl acetate,

tetrahydrofuran, and ethanol. In some embodiments, the one or more solvents comprise ethyl acetate, tetrahydrofuran, and ethanol at about 400:100:1 volume ratio. In some embodiments, the method further comprises stirring the mixture at about 60°C.

1. Vapor-solid diffusion

[0103] In some embodiments, the method comprises: (i) placing a sample comprising a solid form of Compound 1 in a first container; (ii) placing the first container of step (i) inside a second container containing a solvent; and (iii) allowing vapor from the solvent to interact with the sample in the first container. In some embodiments, the sample of step (i) comprises freebase Form A. In some embodiments, step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container at a room temperature and for a duration of about 7 days. In some embodiments, step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container at a room temperature. In some embodiments, step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container for a duration of about 7 days. In some embodiments, step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container for a duration of about between about 3 days and about 11 days; or between about 5 days and about 9 days. In some embodiments, the solvent comprises EtOH, IPA, MIBK, EtOAc, MTBE, 2-MeTHF, acetonitrile, toluene, DMSO, or water, or any mixture thereof. In some embodiments, the solvent comprises EtOH, IPA, EtOAc, acetonitrile, or water, or any mixture thereof, and the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises MIBK or MTBE, or any mixture thereof, and the crystalline form prepared from the method comprises freebase form C. In some embodiments, the solvent comprises 2-MeTHF or toluene, or any mixture thereof, and the crystalline form prepared from the method comprises freebase form A or freebase form C, or both. In some embodiments, the solvent comprises DMSO, and the crystalline form prepared from the method comprises freebase form C. In some embodiments, the solvent comprises DMSO, and the crystalline for prepared from the method comprises freebase form G. In some embodiments, step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container for the duration of about 19 days. In some embodiments, step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container for the duration of between about 10 days and about 30 days; or between about 15 days and about 25 days.

2. Vapor-solid diffusion

[0104] In some embodiments, the method comprises: (i) dissolving Compound 1 in a first solvent in a first container; (ii) placing the first container of step (i) inside a second container containing a second solvent; (iii) sealing the second container of step (ii); (iv) allowing vapor of the second solvent to interact with Compound 1 in the first container to form precipitant; and (v) isolating the precipitant of step (iv) from the first solvent and/or the second solvent. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, step (iv) comprises allowing vapor of the second solvent to interact with Compound 1 in the first container at room temperature. In some embodiments, isolating the precipitant in step (v) comprises evaporating the first solvent and/or the second solvent at room temperature. In some embodiments, the first solvent comprises 1,4-dioxane or DMAc, or a mixture thereof, and the second solvent comprises IPA, MTBE, n-Heptane, or water, or any mixture thereof. In some embodiments, the first solvent comprises 1,4-dioxane, the second solvent comprises MTBE, and the crystalline form prepared from the method comprises freebase Form C. In some embodiments, the first solvent comprises DMAc, the second solvent comprises IPA, and the crystalline form prepared from the method comprises freebase Form F. In some embodiments, the first solvent comprises DMAc, the second solvent comprises MTBE or water, or a mixture thereof, and the crystalline form prepared from the method comprises freebase Form B. In some embodiments, the first solvent comprises 1,4-dioxane, the second solvent comprises IPA, and the crystalline form prepared from the method comprises freebase Form A or freebase Form E, or both. In some embodiments, the first solvent comprises 1,4-dioxane, the second solvent comprises n-heptane, and the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both. In some embodiments, the first solvent comprises 1,4-dioxane, the second solvent comprises water, and the crystalline form prepared from the method comprises freebase Form A or freebase Form D, or both.

3. Slow cooling

[0105] In some embodiments, the method comprises: (i) preparing a suspension of Compound 1 in a solvent; (ii) heating the suspension of step (i) to a first temperature; (iii) filtering the suspension of step (ii) to obtain filtrate; (iv) cooling the filtrate of step (iii) to a second temperature. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, the first temperature is about 50°C. In some embodiments, the

second temperature is about 5°C or about -20°C. In some embodiments, the temperature of the filtrate in step (iv) is changed at a rate of about 0.1°C/min. In some embodiments, the method further comprises evaporating the solvent at room temperature. In some embodiments, the solvent comprises EtOh, MIBK, EtOAc, IPAc, 2MeTHF, acetonitrile, or toluene. In some embodiments, the solvent comprises EtOH, EtOAc, 2-MeTHF, or acetonitrile, or any mixture thereof, wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises MIBK, wherein the crystalline form prepared from the method comprises freebase Form C. In some embodiments, the solvent comprises IPAc or toluene, or a mixture thereof, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both.

4. Slurry

[0106] In some embodiments, the method comprises: (i) preparing a suspension of Compound 1 in solvent; and (ii) stirring the suspension of step (i) at a temperature for a duration. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, a solid forms from the suspension after step (ii), and the method further comprises centrifuging the suspension of step (ii) to isolate the solid. In some embodiments, the temperature is room temperature. In some embodiments, the duration is about 4 days. In some embodiments, the duration is between about 2 days and about 6 days. In some embodiments, the duration is between about 3 days and about 5 days. In some embodiments, the solvent comprises MeOH, MTBE, EtOH, acetone, water, EtOAc, MTBE, THF, 1,4-dioxane, n-Heptane, acetonitrile, DCM, toluene, NMP, or IPA, or any mixture thereof. In some embodiments, the solvent comprises a mixture of MeOH and MTBE at a volume ratio of about 1:1; EtOH; a mixture of acetone and water at a volume ratio of about 1:1; EtOAc; MTBE; a mixture of TFH and water at a volume ratio of about 1:1; a mixture of 1,4-dioxane and n-heptane at a volume ratio of about 1:4; acetonitrile; a mixture of DCM and n-heptane at volume ratio of about 1:1; n-heptane; toluene; water; or a mixture of EtOH and water at a volume ratio of about 97:3 or about 93:7, wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises a mixture of NMP and IPA at a volume ratio of about 1:4, wherein the crystalline form prepared from the method comprises freebase Form B. In some embodiments, the temperature is about 50°C. In some embodiments, the temperature is between about 40°C and about 60°C. In

some embodiments, the duration is about 3 days. In some embodiments, the duration is between about 1 day and about 5 days. In some embodiments, the solvent comprises IPA, MIBK, IPAc, MTBE, 2-MeTHF, 1,4-dioxane, acetonitrile, $CHCl_3$, n-heptane, toluene, water, or DMSO, or any mixture thereof. In some embodiments, the solvent comprises IPA; MIBK; IPAc; MTBE; 2-MeTHF; a mixture of 1,4-dioxane and MTBE at a volume ratio of about 1:9; a mixture of acetonitrile and IPA at a volume ratio of about 1:4; a mixture of $CHCl_3$ and n-heptane at a volume ratio of about 1:9; n-heptane; toluene; or water, wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises a mixture of DMSO and water at a volume ratio of about 1:9, wherein the crystalline form prepared from the method comprises freebase Form C. In some embodiments, the method further comprises cooling the suspension of step (ii) to a temperature of 5°C or lower.

5. Temperature cycling

[0107] In some embodiments, the method comprises: (i) preparing a suspension of Compound 1 in a solvent; (ii) heating the suspension to a first temperature and cooling the suspension to a second temperature; and (iii) heating the suspension to a third temperature, and cooling the suspension to a fourth temperature. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, a solid forms from the suspension after step (iii), and the method further comprises centrifuging the suspension of step (iii) to isolate the solid. In some embodiments, the first temperature and the third temperature are each independently in between about 40°C and about 50°C, and the second temperature and the fourth temperature are each independently in between about 0°C and about 10°C. In some embodiments, the heating and cooling of steps (ii) and (iii) are each independently conducted at a rate of between about 0.01 °C/min and about 1 °C/min. In some embodiments, the solvent comprises EtOH, acetone, IPA, EtOAc, IPAc, MTBE, 2-MeTHF, $CHCl_3$, n-heptane, toluene, water, DMAc, MTBE, or acetonitrile, or any mixture thereof. In some embodiments, the solvent comprises EtOH; a mixture of acetone and IPA at a volume ratio of about 1:40; EtOAc; IPAc; MTBE; 2-MeTHF; a mixture of $CHCl_3$ and n-heptane at a volume ratio of about 1:9; n-heptane; toluene; water; a mixture of DMAc and MTBE at a volume ratio of about 1:9; or a mixture of acetonitrile and MTBE at a volume ratio of about 1:9, wherein the crystalline form prepared from the method comprises freebase Form A.

6. Slow evaporation

[0108] In some embodiments, the method comprises: (i) dissolving Compound 1 in a solvent; and (ii) evaporating the solvent of step (i) at a temperature. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, the temperature of step (ii) is room temperature. In some embodiments, the solvent comprises MeOH, EtOH, acetone, EtOAc, THF, 1,4-dioxane, acetonitrile, $CHCl_3$, DCM, or n-heptane, or any mixture thereof. In some embodiments, the solvent comprises MeOH; EtOH; EtOAc; 1,4-dioxane; acetonitrile; $CHCl_3$; a mixture of MeOH and water at a volume ratio of about 9:1; or a mixture of DCM and n-heptane at a volume ratio of about 9:1, wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises a mixture of acetone and water at a volume ratio of about 9:1, wherein the crystalline form prepared from the method comprises freebase Form D. In some embodiments, the solvent comprises acetone, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both. In some embodiments, the solvent comprises THF, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form D, or both.

7. Grinding

[0109] In some embodiments, the method comprises grinding Compound 1. In some embodiments, Compound 1 comprises freebase Form A. In some embodiments, the method further comprises contacting Compound 1 with a solvent while grinding. In some embodiments, the solvent comprises water. In some embodiments, the crystalline form prepared from the method comprises freebase Form A.

8. Anti-solvent addition

[0110] In some embodiments, the method comprises: (i) adding Compound 1 to a solvent to form a first mixture; and (ii) adding an anti-solvent to the first mixture to form a second mixture. In some embodiments, Compound 1 of step (i) comprises freebase Form A. In some embodiments, the anti-solvent is added until a precipitate is produced. In some embodiments, the method further comprises cooling the second mixture to a cooling temperature. In some embodiments, the cooling temperature is between about -25°C and about 10°C. In some embodiments, the cooling temperature is about 5°C. In some embodiments, the cooling temperature is about -20°C. In some embodiments, the method further comprises evaporating the solvent and the antisolvent from the second mixture at an evaporation temperature. In

some embodiments, the evaporation temperature is room temperature. In some embodiments, the solvent comprises acetone, THF, acetonitrile, $CHCl_3$, MeOH, 1,4-dioxane, DCM, NMP, EtOH, toluene, or DMAc, or any mixture thereof; and the anti-solvent comprises IPA, MTBE, n-heptane, or water, or any mixture thereof. In some embodiments, the solvent comprises acetone, acetonitrile, or $CHCl_3$, or any mixture thereof, and the anti-solvent comprises IPA; or the solvent comprises acetone, and the anti-solvent comprises MTBE; wherein the crystalline form prepared from the method comprises freebase Form E. In some embodiments, the solvent comprises THF, and the anti-solvent comprises IPA; or the solvent comprises 1,4-dioxane, and the anti-solvent comprises MTBE; wherein the crystalline form prepared from the method comprises freebase Form C. In some embodiments, the solvent comprises DCM, and the antisolvent comprises MTBE; or the solvent comprises EtOH, acetone, 1,4-dioxane, toluene, or DCM, or any mixture thereof, and the anti-solvent comprises n-heptane; wherein the crystalline form prepared from the method comprises freebase Form A. In some embodiments, the solvent comprises NMP, and the anti-solvent comprises MTBE; the solvent comprises NMP or DMAc, or a mixture thereof, and the anti-solvent comprises water; wherein the crystalline form prepared from the method comprises freebase Form B. In some embodiments, the solvent comprises THF, and the anti-solvent comprises n-heptane; or the solvent comprises MeOH, acetone, THF, 1,4-dioxane, or acetonitrile, or any mixture thereof, and the anti-solvent comprises water, wherein the crystalline form prepared from the method comprises freebase Form D. In some embodiments, the solvent comprises MeOH, and the anti-solvent comprises MTBE, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form E, or both.

IV. Pharmaceutical Compositions and Formulations

[0111] Any of the crystalline forms described herein may be formulated as a pharmaceutically acceptable composition.

[0112] Pharmaceutical compositions of any of the crystalline forms detailed herein are embraced by this disclosure. Thus, the present disclosure includes pharmaceutical compositions comprising a crystalline form as detailed herein, and a pharmaceutically acceptable carrier or excipient. Pharmaceutical compositions may take a form suitable for oral, buccal, parenteral, nasal, topical, or rectal administration or a form suitable for administration by inhalation.

[0113] A crystalline form as detailed herein may in one aspect be in a purified form and compositions comprising a crystalline form in purified forms are detailed herein. Compositions comprising a crystalline form, as detailed herein are provided, such as compositions of substantially pure crystalline forms. In some embodiments, a composition containing a crystalline form, as detailed herein is in substantially pure form. In one variation, "substantially pure" intends a composition that contains no more than 35% impurity. In some embodiments, the impurity denotes a compound other than the crystalline form. In some embodiments, the impurity denotes a compound other than Compound 1. In some embodiments, the impurity denotes a compound other than Compound 1 and its isomers. In one variation, a composition of substantially pure crystalline form, is provided wherein the composition contains no more than 25% impurity. In another variation, a composition of substantially pure crystalline form, is provided wherein the composition contains or no more than 20% impurity. In still another variation, a composition of substantially pure crystalline form, is provided wherein the composition contains or no more than 10% impurity. In a further variation, a composition of substantially pure crystalline form, is provided wherein the composition contains no more than 5% impurity. In another variation, a composition of substantially pure crystalline form, is provided wherein the composition contains no more than 3% impurity. In still another variation, a composition of substantially pure crystalline form, is provided wherein the composition contains no more than 1% impurity. In a further variation, a composition of substantially pure crystalline form, is provided wherein the composition contains no more than 0.5% impurity. In yet other variations, a composition of substantially pure crystalline form means that the composition contains no more than 15%, no more than 10%, no more than 5%, no more than 3%, or no more than 1% impurity, which impurity may be the crystalline form in a different stereochemical form. For instance, and without limitation, a composition of substantially pure (S) crystalline form means that the composition contains no more than 15% or no more than 10% or no more than 5% or no more than 3% or no more than 1% of the (R) form of the crystalline form.

[0114] In one variation, the crystalline forms herein are synthetic crystalline forms prepared for administration to an individual. In another variation, compositions are provided containing a crystalline form in substantially pure form. In another variation, the present disclosure embraces pharmaceutical compositions comprising a crystalline form detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a crystalline form are provided. The purified forms, pharmaceutical

compositions and methods of administering the crystalline forms are suitable for any crystalline form or form thereof detailed herein. In some embodiments, the crystalline forms and compositions as provided herein are sterile. Methods for sterilization known in the art may be suitable for any crystalline forms or form thereof and compositions thereof as detailed herein.

[0115] A crystalline form detailed herein, may be formulated for any available delivery route, including an oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal or rectal), parenteral (*e.g.*, intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A crystalline form, may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (*e.g.*, nasal spray or inhalers), gels, suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[0116] A crystalline form detailed herein can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the crystalline form or crystalline forms, with a pharmaceutically acceptable carrier. Depending on the therapeutic form of the system (*e.g.*, transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the crystalline form may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable methods of preparing pharmaceutical formulations can be found, *e.g.*, in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), which is incorporated herein by reference.

[0117] A crystalline form detailed herein, may be administered to individuals in a form of generally accepted oral compositions, such as tablets, coated tablets, and gel capsules in a hard or in soft shell, emulsions or suspensions. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[0118] Any of the crystalline forms, described herein can be formulated in a tablet in any dosage form described.

[0119] Compositions comprising a crystalline form, provided herein are also described. In one variation, the composition comprises a crystalline form, and a pharmaceutically acceptable carrier or excipient. I n another variation, a composition of substantially pure crystalline form, is provided. In some embodiments, the composition is for use as a human or veterinary medicament. In some embodiments, the composition is for use in a method described herein. In some embodiments, the composition is for use in the treatment of a disease or disorder described herein.

[0120] Compositions formulated for co-administration of a crystalline form provided herein and one or more additional pharmaceutical agents are also described. The co-administration can be simultaneous or sequential in any order. A crystalline form provided herein may be formulated for co-administration with the one or more additional pharmaceutical agents in the same dosage form (*e.g.*, single tablet or single i.v.) or separate dosage forms (*e.g.*, two separate tablets, two separate i.v., or one tablet and one i.v.). Furthermore, co-administration can be, for example, 1) concurrent delivery, through the same route of delivery (*e.g.*, tablet or i.v.), 2) sequential delivery on the same day, through the same route or different routes of delivery, or 3) delivery on different days, through the same route or different routes of delivery.

V. Methods of Use

[0121] Crystalline forms and compositions disclosed herein, such as a pharmaceutical composition comprising a crystalline form of Compound 1 and a pharmaceutically acceptable carrier or excipient, may be used in a method of administration and treatment as provided herein. The crystalline forms and compositions may also be used in *in vitro* methods, such as *in vitro* methods of administering a crystalline form or composition to cells for screening purposes and/or for conducting quality control assays.

[0122] In one aspect, provided herein is a method of inhibiting the activity of KRAS G12C. In some embodiments, the method comprises contacting the KRAS G12C with a crystalline form or composition provided herein. In some embodiments, the crystalline form or composition provided herein is in a therapeutically effective amount.

[0123] In one aspect, provided herein is a method of inhibiting the activity of KRAS G12C in a cell. In some embodiments, the method comprises administering a crystalline form or composition provided herein to the cell. In some embodiments, the method comprises contacting the cell with a crystalline form or composition provided herein. In some embodiments, the crystalline form or composition provided herein is in a therapeutically effective amount.

[0124] In one aspect, provided is a method of treating cancer in a subject in need thereof. In some embodiments, the method comprises administering a therapeutically effective amount of the crystalline form or the pharmaceutical composition provided herein to the subject.

[0125] In some embodiments, the cancer is a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer. In some embodiments, the cancer is glioblastoma multiforme, lower grade glioma, head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, brain lower grade glioma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma, metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, glioma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma. In some embodiments, the cancer is a non-small cell lung cancer (NSCLC). In some embodiments, the cancer is a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed as having a KRAS G12C mediated cancer.

[0126] In some embodiments, the subject is human.

Brain metastasis

[0127] In one aspect, provided is a method of treating or preventing central nervous system (CNS) metastasis in a subject in need thereof. In some embodiments, the method comprises administering a therapeutically effective amount of a crystalline form disclosed herein to the subject.

[0128] In some embodiments, the method is for treating CNS metastasis. In some embodiments, the method is for preventing CNS metastasis. In some embodiments, the CNS metastasis is brain metastasis. In some embodiments, the CNS metastasis is spinal metastasis.

[0129] In some embodiments, the CNS metastasis is a CNS metastasis from a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer. In some embodiments, the CNS metastasis is a CNS metastasis from head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma, metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma. In some embodiments, the CNS metastasis is a CNS metastasis from a non-small cell lung cancer (NSCLC).

[0130] In some embodiments, the CNS metastasis is a CNS metastasis from a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed as having a KRAS G12C mediated cancer.

[0131] In some embodiments, the method further comprises administering a therapeutically effective amount of an additional anticancer agent. In some embodiments, the additional anticancer agent is a chemotherapeutic agent.

[0132] In some embodiments, there is at least about a 90% reduction in the CNS metastasis. In some embodiments, there is at least about a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% reduction in the CNS metastasis. In some embodiments, there is about a 100% reduction in the CNS metastasis. In some embodiments, the CNS metastasis is completely eliminated.

[0133] In some embodiments, there is at least about a 90% reduction in the size of the CNS metastasis. In some embodiments, there is at least about a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% reduction in the size of the CNS metastasis. In some embodiments, there is about a 100% reduction in the size of the CNS metastasis.

[0134] In some embodiments, the method reduces one or more symptoms of the CNS metastasis. In some embodiments, the one or more symptoms are selected from the group consisting of headache, mental changes, seizures, and weakness or numbness on one side of the body.

[0135] In one aspect, provided is a method of increasing cerebrospinal fluid (CSF) exposure to an anticancer agent in a subject. In some embodiments, the method comprises administering a crystalline form disclosed herein to the subject.

[0136] In some embodiments, the subject is human.

Combination therapy

[0137] In one aspect, provided is a method of treating cancer in a subject in need thereof. In some embodiments, the method comprises administering a therapeutically effective amount of a crystalline form disclosed herein, and an immune checkpoint inhibitor to the

subject. In some embodiments, the method comprises administering a therapeutically effective amount of a crystalline form disclosed herein to the subject, wherein the subject receives an immune checkpoint inhibitor. In some embodiments, the method comprises administering a therapeutically effective amount of an immune checkpoint inhibitor to the subject, wherein the subject receives a crystalline form disclosed herein.

[0138] In some embodiments, the method comprises administering a therapeutically effective amount of a crystalline form disclosed herein and Pembrolizumab (Keytruda®) to the subject. In some embodiments, the method comprises administering a therapeutically effective amount of a crystalline form disclosed herein to the subject, wherein the subject receives Pembrolizumab (Keytruda®). In some embodiments, the method comprises administering a therapeutically effective amount of Pembrolizumab (Keytruda®) to the subject, wherein the subject receives a crystalline form disclosed herein.

[0139] In some embodiments, the subject receives a crystalline form disclosed herein and the immune checkpoint inhibitor concurrently or separately. In some embodiments, the subject receives a crystalline form disclosed herein and the immune checkpoint inhibitor concurrently. In some embodiments, the subject receives a crystalline form disclosed herein and the immune checkpoint inhibitor separately. In some embodiments, the subject receives a crystalline form disclosed herein and the immune checkpoint inhibitor sequentially. In some embodiments, the subject receives a crystalline form disclosed herein before the immune checkpoint inhibitor. In some embodiments, the subject receives a crystalline form disclosed herein after the immune checkpoint inhibitor.

[0140] In some embodiments, the subject receives a crystalline form disclosed herein and Pembrolizumab (Keytruda®) concurrently or separately. In some embodiments, the subject receives a crystalline form disclosed herein and Pembrolizumab (Keytruda®) concurrently. In some embodiments, the subject receives a crystalline form disclosed herein and Pembrolizumab (Keytruda®) separately. In some embodiments, the subject receives a crystalline form disclosed herein and Pembrolizumab (Keytruda®) sequentially. In some embodiments, the subject receives a crystalline form disclosed herein before Pembrolizumab (Keytruda®). In some embodiments, the subject receives a crystalline form disclosed herein after Pembrolizumab (Keytruda®).

[0141] In some embodiments, the method further comprises administering a therapeutically effective amount of one or more additional anticancer agents. In some embodiments, the one or more additional anticancer agents comprise a chemotherapeutic agent.

[0142] In one aspect, provided is a composition comprising a crystalline form disclosed herein for use in treating cancer in a subject in need thereof, wherein a crystalline form disclosed herein is administered in combination with an immune checkpoint inhibitor. In one aspect, provided is a composition comprising a crystalline form disclosed herein for use in treating cancer in a subject in need thereof, wherein a crystalline form disclosed herein is administered in combination with Pembrolizumab (Keytruda®).

[0143] In one aspect, provided is a composition comprising an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof, wherein the immune checkpoint inhibitor is administered in combination with a crystalline form disclosed herein. In one aspect, provided is a composition comprising Pembrolizumab (Keytruda®) for use in treating cancer in a subject in need thereof, wherein Pembrolizumab (Keytruda®) is administered in combination with a crystalline form disclosed herein.

[0144] In one aspect, provided is a composition comprising a crystalline form disclosed herein and an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof. In one aspect, provided is a composition comprising a crystalline form disclosed herein and Pembrolizumab (Keytruda®) for use in treating cancer in a subject in need thereof.

[0145] In one aspect, provided is a combination therapeutic comprising a crystalline form disclosed herein and an immune checkpoint inhibitor, as separate entities. In one aspect, provided is a combination therapeutic comprising a crystalline form disclosed herein and Pembrolizumab (Keytruda®), as separate entities.

[0146] In one aspect, provided is a use of the combination therapeutic in the treatment of cancer in a subject in need thereof.

[0147] In some embodiments, a crystalline form disclosed herein and the immune checkpoint inhibitor are administered concurrently or separately. In some embodiments, a crystalline form disclosed herein and the immune checkpoint inhibitor are administered

concurrently. In some embodiments, a crystalline form disclosed herein and the immune checkpoint inhibitor are administered separately. In some embodiments, a crystalline form disclosed herein and the immune checkpoint inhibitor are administered sequentially. In some embodiments, A crystalline form disclosed herein is administered before the immune checkpoint inhibitor is administered. In some embodiments, a crystalline form disclosed herein is administered after the immune checkpoint inhibitor is administered.

[0148] In some embodiments, a crystalline form disclosed herein and Pembrolizumab (Keytruda®) are administered concurrently or separately. In some embodiments, a crystalline form disclosed herein and Pembrolizumab (Keytruda®) are administered concurrently. In some embodiments, a crystalline form disclosed herein and Pembrolizumab (Keytruda®) are administered separately. In some embodiments, a crystalline form disclosed herein and Pembrolizumab (Keytruda®) are administered sequentially. In some embodiments, a crystalline form disclosed herein is administered before Pembrolizumab (Keytruda®) is administered. In some embodiments, a crystalline form disclosed herein is administered after Pembrolizumab (Keytruda®) is administered.

[0149] In some embodiments, the immune checkpoint inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor. In some embodiments, the immune checkpoint inhibitor is a PD-1 inhibitor. In some embodiments, the immune checkpoint inhibitor is a PD-L1 inhibitor. In some embodiments, the immune checkpoint inhibitor is Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), Cemiplimab (Libtayo®), Atezolizumab (Tecentriq®), Avelumab (Bavencio®), Durvalumab (ImfinziTM), or Dostarlimab (Jemperli). In some embodiments, the immune checkpoint inhibitor is Pembrolizumab (Keytruda®).

[0150] In some embodiments, a crystalline form disclosed herein is administered orally. In some embodiments, the immune checkpoint inhibitor is administered intravenously or subcutaneously.

[0151] In some embodiments, the cancer is a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer. In some embodiments, the cancer is glioblastoma multiforme, lower grade glioma, head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine

adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, brain lower grade glioma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma, metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, glioma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma. In some embodiments, the cancer is a non-small cell lung cancer (NSCLC).

[0152] In some embodiments, the cancer is a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed as having a KRAS G12C mediated cancer.

[0153] In some embodiments, the subject is human.

[0154] In some embodiments, administering a crystalline form disclosed herein and the immune checkpoint inhibitor such as Pembrolizumab (Keytruda®) to the subject shows synergistic effect. In some embodiments, the effect of administering the combination of a crystalline form disclosed herein and the immune checkpoint inhibitor such as Pembrolizumab (Keytruda®) to the subject is greater than the sum of the effects from administering a crystalline form disclosed herein alone, and the effect from administering the checkpoint inhibitor such as Pembrolizumab (Keytruda®) alone. In some embodiments, the effect comprises reducing tumor volume, inhibiting growth or proliferation of cancer cells, or increasing survival of the subject, or any combination thereof.

VI. Dosing and Method of Administration

[0155] The dose of a crystalline form described herein, administered to an individual (such as a human) may vary with the particular crystalline form, the method of administration, and the particular cancer, such as type and stage of cancer, being treated. In some embodiments, the amount of the crystalline form, is a therapeutically effective amount.

[0156] The crystalline forms provided herein, may be administered to an individual via various routes, including, *e.g.*, intravenous, intramuscular, subcutaneous, oral, and transdermal.

[0157] The effective amount of the crystalline form may in one aspect be a dose of between about 0.01 and about 100 mg/kg. Effective amounts or doses of the crystalline forms of the present disclosure may be ascertained by routine methods, such as modeling, dose escalation, or clinical trials, taking into account routine factors, *e.g.*, the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease to be treated, the subject's health status, condition, and weight.

[0158] Any of the methods provided herein may in one aspect comprise administering to an individual a pharmaceutical composition that contains an effective amount of a crystalline form provided herein, and a pharmaceutically acceptable excipient.

[0159] A crystalline form or composition provided herein may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration. Any of the dosing frequencies can employ any of the crystalline forms described herein together with any of the dosages described herein.

VII. Articles of Manufacture and Kits

[0160] The present disclosure further provides articles of manufacture comprising a crystalline form described herein, a composition described herein, or one or more unit dosages described herein in suitable packaging. In certain embodiments, the article of manufacture is for use in any of the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

[0161] The present disclosure further provides kits for carrying out the methods of the present disclosure, which comprises one or more crystalline forms described herein or a composition comprising a crystalline form described herein. The kits may employ any of the crystalline forms disclosed herein. In one variation, the kit employs a crystalline form described herein, thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of any disease or described herein, for example for the treatment of cancer.

[0162] The kits optionally further comprise a container comprising one or more additional pharmaceutical agents and which kits further comprise instructions on or in the package insert for treating the subject with an effective amount of the one or more additional pharmaceutical agents.

[0163] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any crystalline form described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

[0164] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a crystalline form as disclosed herein and/or an additional pharmaceutically active crystalline form useful for a disease detailed herein to provide effective treatment of an individual for an extended period. Kits may also include multiple unit doses of the crystalline forms and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[0165] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present disclosure. The instructions included with the kit generally include information as to the components and their administration to an individual.

ENUMERATED EMBODIMENTS

[0166] The following enumerated embodiments are representative of some aspects of the invention.

Enumerated embodiments set A

[0167] The embodiment numbers referenced in this set refer to those within set A. For example, "embodiment 1" recited in embodiment A2 refers to embodiment A1.

A1. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1).

A2. The crystalline form of embodiment 1, wherein the crystalline form is a hydrate.

A3. The crystalline form of embodiment 2, wherein the crystalline form is a channel hydrate.

A4. The crystalline form of any one of embodiments 1 to 3, characterized by having an XRPD pattern of freebase Form A substantially as shown in FIG. 1A.

A5. The crystalline form of any one of embodiments 1 to 4, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.9.

A6. The crystalline form of any one of embodiments 1 to 5, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.0.

A7. The crystalline form of any one of embodiments 1 to 6, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.4.

A8. The crystalline form of any one of embodiments 1 to 7, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 16.4, about 17.4, about 19.3, about 20.7, about 22.4, about 24.1, about 28.2, and about 31.0.

A9. The crystalline form of any one of embodiments 1 to 8, characterized by having a DSC graph comprising an endothermic peak at about 76.0 °C.

A10. The crystalline form of any one of embodiments 1 to 9, characterized by having a DSC graph comprising an exothermic peak at about 194.9 °C.

A11. The crystalline form of any one of embodiments 1 to 10, characterized by having a DSC graph substantially as shown in FIG. 1B.

A12. The crystalline form of any one of embodiments 1 to 11, characterized by having a TGA graph substantially as shown in FIG. 1B.

A13. The crystalline form of any one of embodiments 1 to 12, characterized by having a DVS graph substantially as shown in FIG. 1C.

A14. The crystalline form of any one of embodiments 1 to 13, wherein the crystalline form comprises water, wherein the molar ratio of water:Compound 1 is about 3.5:1.

A15. The crystalline form of embodiment 1 or 2, characterized by having an XRPD pattern of Form E substantially as shown in FIG. 2A.

A16. The crystalline form of any one of embodiments 1 to 3 and 15, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.1.

A17. The crystalline form of any one of embodiments 1 to 3, 15, and 16, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.0.

A18. The crystalline form of any one of embodiments 1 to 3 and 15 to 17, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.6.

A19. The crystalline form of any one of embodiments 1 to 3 and 15 to 18, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.5.

A20. The crystalline form of any one of embodiments 1 to 3 and 15 to 19, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 11.1, about 12.6, about 14.0, about 14.6, about 15.6, about 20.3, and about 22.5.

A21. The crystalline form of any one of embodiments 1 to 3 and 15 to 20, characterized by having a DSC graph comprising an endothermic peak at about 69.7 °C.

A22. The crystalline form of any one of embodiments 1 to 3 and 15 to 21, characterized by having a DSC graph comprising an exothermic peak at about 190.5 °C.

A23. The crystalline form of any one of embodiments 1 to 3 and 15 to 22, characterized by having a DSC graph substantially as shown in FIG. 2B.

A24. The crystalline form of any one of embodiments 1 to 3 and 15 to 23, characterized by having a TGA graph substantially as shown in FIG. 2B.

A25. The crystalline form of embodiment 1 or 2, characterized by having an XRPD pattern of freebase Form C substantially as shown in FIG. 3A.

A26. The crystalline form of any one of embodiments 1, 2, and 25, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.7.

A27. The crystalline form of any one of embodiments 1, 2, 25, and 26, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.9.

A28. The crystalline form of any one of embodiments 1, 2, and 25 to 27, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.2.

A29. The crystalline form of any one of embodiments 1, 2, and 25 to 28, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 7.5, about 11.0, about 12.7, about 13.7, about 14.6, about 14.9, about 16.3, about 17.0, about 18.5, about 19.5, about 19.9, about 20.4, about 22.2, about 23.3, about 24.2, about 25.2, about 25.7, about 27.0, about 28.0, and about 34.5.

A30. The crystalline form of any one of embodiments 1, 2, and 25 to 29, characterized by having a DSC graph comprising an endothermic peak at about 80.3 °C.

A31. The crystalline form of any one of embodiments 1, 2, and 25 to 30, characterized by having a DSC graph comprising an exothermic peak at about 189.4 °C.

A32. The crystalline form of any one of embodiments 1, 2, and 25 to 31, characterized by having a DSC graph substantially as shown in FIG. 3B.

A33. The crystalline form of any one of embodiments 1, 2, and 25 to 32, characterized by having a TGA graph substantially as shown in FIG. 3B.

A34. The crystalline form of embodiment 1 or 2, characterized by having an XRPD pattern of freebase Form D substantially as shown in FIG. 4A.

A35. The crystalline form of any one of embodiments 1, 2, and 34, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.7.

A36. The crystalline form of any one of embodiments 1, 2, 34, and 35, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 13.3.

A37. The crystalline form of any one of embodiments 1, 2, and 34 to 36, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.6.

A38. The crystalline form of any one of embodiments 1, 2, and 34 to 37, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 23.3.

A39. The crystalline form of any one of embodiments 1, 2, and 34 to 38, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.7, about 13.3, about 14.6, about 15.5, about 21.0, about 22.4, about 23.3, about 25.7, and about 27.1.

A40. The crystalline form of any one of embodiments 1, 2, and 34 to 39, characterized by having a DSC graph comprising an endothermic peak at about 80.8 °C.

A41. The crystalline form of any one of embodiments 1, 2, and 34 to 40, characterized by having a DSC graph comprising an exothermic peak at about 189.4 °C.

A42. The crystalline form of any one of embodiments 1, 2, and 34 to 41, characterized by having a DSC graph substantially as shown in FIG. 4B.

A43. The crystalline form of any one of embodiments 1, 2, and 34 to 42, characterized by having a TGA graph substantially as shown in FIG. 4B.

A44. The crystalline form of embodiment 1, wherein the crystalline form is a solvate.

A45. The crystalline form of embodiment 1 or 44, characterized by having an XRPD pattern of freebase Form B substantially as shown in FIG. 5A.

A46. The crystalline form of any one of embodiments 1, 44, and 45, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.2.

A47. The crystalline form of any one of embodiments 1 and 44 to 46, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 14.7.

A48. The crystalline form of any one of embodiments 1 and 44 to 47, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.3.

A49. The crystalline form of any one of embodiments 1 and 44 to 48, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 12.5,

about 12.9, about 14.1, about 14.7, about 18.0, about 18.8, about 22.3, about 23.0, and about 25.7.

A50. The crystalline form of any one of embodiments 1 and 44 to 49, characterized by having a DSC graph comprising an endothermic peak at about 84.3 °C.

A51. The crystalline form of any one of embodiments 1 and 44 to 50, characterized by having a DSC graph comprising an exothermic peak at about 187.1 °C.

A52. The crystalline form of any one of embodiments 1 and 44 to 51, characterized by having a DSC graph substantially as shown in FIG. 5B.

A53. The crystalline form of any one of embodiments 1 and 44 to 52, characterized by having a TGA graph substantially as shown in FIG. 5B.

A54. The crystalline form of any one of embodiments 1 and 44 to 53, wherein the crystalline form is an isomorphic form.

A55. The crystalline form of embodiment any one of embodiments 1 and 44 to 54, wherein the crystalline form comprises DMAc, wherein the molar ratio of DMAc:Compound 1 is about 0.7:1.

A56. The crystalline form of embodiment 1 or 44, characterized by having an XRPD pattern of freebase Form F substantially as shown in FIG. 6.

A57. The crystalline form of any one of embodiments 1, 44, and 56, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.2.

A58. The crystalline form of any one of embodiments 1, 44, 56, and 57, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.7.

A59. The crystalline form of any one of embodiments 1, 44, and 56 to 58, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 13.4.

A60. The crystalline form of any one of embodiments 1, 44, and 56 to 59, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.2, about 6.7, about 12.4, about 13.4, about 15.1, about 16.8, about 18.7, about 20.1, about 21.7, about 23.2, about 25.7, about 26.9, about 27.7, about 29.9, and about 33.9.

A61. The crystalline form of any one of embodiments 1, 44, and 56 to 60, wherein the crystalline form comprises DMAc or IPA, or both.

A62. The crystalline form of embodiment 1 or 44, characterized by having an XRPD pattern of freebase Form G substantially as shown in FIG. 7.

A63. The crystalline form of any one of embodiments 1, 44, and 62, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.0.

A64. The crystalline form of any one of embodiments 1, 44, 62, and 63, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 13.8.

A65. The crystalline form of any one of embodiments 1, 44, and 62 to 64, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 15.4.

A66. The crystalline form of any one of embodiments 1, 44, and 62 to 65, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.2.

A67. The crystalline form of any one of embodiments 1, 44, and 62 to 66, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.0, about 11.0, about 13.8, about 14.5, about 15.2, about 15.4, about 17.3, about 20.1, about 21.0, about 22.2, about 23.0, about 24.1, about 25.4, about 27.8, and about 30.6.

A68. The crystalline form of any one of embodiments 1, 44, and 62 to 67, characterized by having a DSC graph comprising an endothermic peak at about 72.3 °C.

A69. The crystalline form of any one of embodiments 1, 44, and 62 to 68, characterized by having a DSC graph comprising an endothermic peak at about 113.3 °C.

A70. The crystalline form of any one of embodiments 1, 44, and 62 to 69, characterized by having a DSC graph comprising an exothermic peak at about 196.3 °C.

A71. The crystalline form of any one of embodiments 1, 44, and 62 to 70, characterized by having a DSC graph substantially as shown in FIG. 8.

A72. The crystalline form of any one of embodiments 1, 44, and 62 to 71, characterized by having a TGA graph substantially as shown in FIG. 8.

A73. The crystalline form of any one of embodiments 1, 44, and 62 to 72, wherein the crystalline form comprises DMSO, wherein the molar ratio of DMSO:Compound 1 is about 0.8.

A74. The crystalline form of embodiment 1, wherein the crystalline form is an anhydrate.

A75. The crystalline form of embodiment 1 or 74, characterized by having an XRPD pattern of freebase Form H substantially as shown in FIG. 9A.

A76. The crystalline form of any one of embodiments 1, 74, and 75, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 6.5.

A77. The crystalline form of any one of embodiments 1 and 74 to 76, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 7.2.

A78. The crystalline form of any one of embodiments 1 and 74 to 77, characterized by having an XRPD pattern comprising a peak at angle 2-theta of about 22.5.

A79. The crystalline form of any one of embodiments 1 and 74 to 78, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2,

about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 17.7, about 20.3, about 21.8, about 22.5, and about 28.1.

A80. The crystalline form of any one of embodiments 1 and 74 to 79, characterized by having a DSC graph comprising an endothermic peak at about 73.6 °C.

A81. The crystalline form of any one of embodiments 1 and 74 to 80, characterized by having a DSC graph comprising an exothermic peak at about 194.1 °C.

A82. The crystalline form of any one of embodiments 1 and 74 to 81, characterized by having a DSC graph substantially as shown in FIG. 9B.

A83. The crystalline form of any one of embodiments 1 and 74 to 82, characterized by having a TGA graph substantially as shown in FIG. 9B.

A84. The crystalline form of any one of embodiments 1 to 83, wherein the purity of the crystalline form is at least about 95%.

A85. A pharmaceutical composition comprising a crystalline form of any one of embodiments 1 to 84, and a pharmaceutically acceptable excipient.

A86. A method of treating cancer in a subject in need thereof, the method comprising: administering a therapeutically effective amount of the crystalline form of any one of embodiments 1 to 84, or the pharmaceutical composition of embodiment 85, to the subject.

A87. The method of embodiment 86, wherein the cancer is a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer.

A88. The method of embodiment 86 or 87, wherein the cancer is glioblastoma multiforme, lower grade glioma, head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, brain lower grade glioma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and

paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma, metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, glioma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma.

A89. The method of any one of embodiments 86 to 88, wherein the cancer is a non-small cell lung cancer (NSCLC).

A90. The method of any one of embodiments 86 to 89, wherein the cancer is a KRAS G12C mediated cancer.

A91. The method of any one of embodiments 86 to 90, wherein the subject has been diagnosed as having a KRAS G12C mediated cancer.

A92. The method of any one of embodiments 86 to 91, wherein the subject is human.

A93. A method of preparing a crystalline form of any one of embodiments 1 to 84, the method comprising:

(i) contacting Compound 1 with one or more solvents to form a mixture; and

(ii) crystallizing Compound 1.

A94. The method of embodiment 93, wherein the one or more solvents comprise ethyl acetate, tetrahydrofuran, or ethanol, or any combination thereof.

A95. The method of embodiment 94, wherein the one or more solvents comprise ethyl acetate, tetrahydrofuran, and ethanol at about 400:100:1 volume ratio.

A96. The method of any one of embodiments 93 to 95, the method further comprising stirring the mixture at about 60°C.

A97. A method of preparing a crystalline form of any one of embodiments 1 to 84, wherein the method comprises:

(i) placing a sample comprising a solid form of Compound 1 in a first container;

(ii) placing the first container of step (i) inside a second container containing a solvent; and

(iii) allowing vapor from the solvent to interact with the sample in the first container.

A98. The method of embodiment 97, wherein the sample of step (i) comprises freebase Form A.

A99. The method of embodiment 97 or 98, wherein step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container at a room temperature and for a duration of about 7 days.

A100. The method of any one of embodiments 97 to 99, wherein the solvent comprises EtOH, IPA, MIBK, EtOAc, MTBE, 2-MeTHF, acetonitrile, toluene, DMSO, or water, or any mixture thereof.

A101. The method of any one of embodiments 97 to 99, wherein the solvent comprises EtOH, IPA, EtOAc, acetonitrile, or water, or any mixture thereof, and the crystalline form prepared from the method comprises freebase Form A.

A102. The method of any one of embodiments 97 to 99, wherein the solvent comprises MIBK or MTBE, or any mixture thereof, and the crystalline form prepared from the method comprises freebase form C.

A103. The method of any one of embodiments 97 to 99, wherein the solvent comprises 2-MeTHF or toluene, or any mixture thereof, and the crystalline form prepared from the method comprises freebase form A or freebase form C, or both.

A104. The method of any one of embodiments 97 to 99, wherein the solvent comprises DMSO, and the crystalline form prepared from the method comprises freebase form C.

A105. The method of any one of embodiments 97 to 99, wherein the solvent comprises DMSO, and the crystalline for prepared from the method comprises freebase form G.

A106. The method of embodiment 105, wherein step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container for the duration of about 19 days.

A107. A method of preparing a crystalline form of any one of embodiments 1 to 84, wherein the method comprises:

(i) dissolving Compound 1 in a first solvent in a first container;

(ii) placing the first container of step (i) inside a second container containing a second solvent;

(iii) sealing the second container of step (ii);

(iv) allowing vapor of the second solvent to interact with Compound 1 in the first container to form precipitant; and

(v) isolating the precipitant of step (iv) from the first solvent and/or the second solvent.

A108. The method of embodiment 107, wherein Compound 1 of step (i) comprises freebase Form A.

A109. The method of embodiment 107 or 108, wherein step (iv) comprises allowing vapor of the second solvent to interact with Compound 1 in the first container at room temperature.

A110. The method of any one of embodiments 107 to 109, wherein isolating the precipitant in step (v) comprises evaporating the first solvent and/or the second solvent at room temperature.

A111. The method of any one of embodiments 107 to 110, wherein the first solvent comprises 1,4-dioxane or DMAc, or a mixture thereof, and the second solvent comprises IPA, MTBE, n-Heptane, or water, or any mixture thereof.

A112. The method of any one of embodiments 107 to 110, wherein the first solvent comprises 1,4-dioxane, the second solvent comprises MTBE, and the crystalline form prepared from the method comprises freebase Form C.

A113. The method of any one of embodiments 107 to 110, wherein the first solvent comprises DMAc, the second solvent comprises IPA, and the crystalline form prepared from the method comprises freebase Form F.

A114. The method of any one of embodiments 107 to 110, wherein the first solvent comprises DMAc, the second solvent comprises MTBE or water, or a mixture thereof, and the crystalline form prepared from the method comprises freebase Form B.

A115. The method of any one of embodiments 107 to 110, wherein the first solvent comprises 1,4-dioxane, the second solvent comprises IPA, and the crystalline form prepared from the method comprises freebase Form A or freebase Form E, or both.

A116. The method of any one of embodiments 107 to 110, wherein the first solvent comprises 1,4-dioxane, the second solvent comprises n-heptane, and the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both.

A117. The method of any one of embodiments 107 to 110, wherein the first solvent comprises 1,4-dioxane, the second solvent comprises water, and the crystalline form prepared from the method comprises freebase Form A or freebase Form D, or both.

A118. A method of preparing a crystalline form of any one of embodiments 1 to 84, wherein the method comprises:

(i) preparing a suspension of Compound 1 in a solvent;

(ii) heating the suspension of step (i) to a first temperature;

(iii) filtering the suspension of step (ii) to obtain filtrate;

(iv) cooling the filtrate of step (iii) to a second temperature.

A119. The method of embodiment 118, wherein Compound 1 of step (i) comprises freebase Form A.

A120. The method of embodiment 118 or 119, wherein the first temperature is about 50°C.

A121. The method of any one of embodiments 118 to 120, wherein the second temperature is about 5°C or about -20°C.

A122. The method of any one of embodiments 118 to 121, wherein the temperature of the filtrate in step (iv) is changed at a rate of about 0.1°C/min.

A123. The method of any one of embodiments 118 to 122, further comprising evaporating the solvent at room temperature.

A124. The method of any one of embodiments 118 to 123, wherein the solvent comprises EtOh, MIBK, EtOAc, IPAc, 2MeTHF, acetonitrile, or toluene.

A125. The method of any one of embodiments 118 to 123, wherein the solvent comprises EtOH, EtOAc, 2-MeTHF, or acetonitrile, or any mixture thereof, wherein the crystalline form prepared from the method comprises freebase Form A.

A126. The method of any one of embodiments 118 to 123, wherein the solvent comprises MIBK, wherein the crystalline form prepared from the method comprises freebase Form C.

A127. The method of any one of embodiments 118 to 123, wherein the solvent comprises IPAc or toluene, or a mixture thereof, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both.

A128. A method of preparing a crystalline form of any one of embodiments 1 to 84, wherein the method comprises:

(i) preparing a suspension of Compound 1 in solvent; and

(ii) stirring the suspension of step (i) at a temperature for a duration.

A129. The method of embodiment 128, wherein Compound 1 of step (i) comprises freebase Form A.

A130. The method of embodiment 128 or 129, wherein a solid forms from the suspension after step (ii), and the method further comprises centrifuging the suspension of step (ii) to isolate the solid.

A131. The method of any one of embodiments 128 to 130, wherein the temperature is room temperature, and the duration is between about 2 days and about 6 days.

A132. The method of any one of embodiments 128 to 131, wherein the solvent comprises MeOH, MTBE, EtOH, acetone, water, EtOAc, MTBE, THF, 1,4-dioxane, n-Heptane, acetonitrile, DCM, toluene, NMP, or IPA, or any mixture thereof.

A133. The method of any one of embodiments 128 to 131, wherein the solvent comprises a mixture of MeOH and MTBE at a volume ratio of about 1:1; EtOH; a mixture of acetone and water at a volume ratio of about 1:1; EtOAc; MTBE; a mixture of TFH and water at a volume ratio of about 1:1; a mixture of 1,4-dioxane and n-heptane at a volume ratio of about 1:4; acetonitrile; a mixture of DCM and n-heptane at volume ratio of about 1:1; n-heptane; toluene; water; or a mixture of EtOH and water at a volume ratio of about 97:3 or about 93:7, wherein the crystalline form prepared from the method comprises freebase Form A.

A134. The method of any one of embodiments 128 to 131, wherein the solvent comprises a mixture of NMP and IPA at a volume ratio of about 1:4, wherein the crystalline form prepared from the method comprises freebase Form B.

A135. The method of any one of embodiments 128 to 130, wherein the temperature is between about 40°C and about 60°C, and the duration is between about 1 day and about 5 days.

A136. The method of any one of embodiments 128 to 130 and 135, wherein the solvent comprises IPA, MIBK, IPAc, MTBE, 2-MeTHF, 1,4-dioxane, acetonitrile, $CHCl_3$, n-heptane, toluene, water, or DMSO, or any mixture thereof.

A137. The method of any one of embodiments 128 to 130 and 135, wherein the solvent comprises IPA; MIBK; IPAc; MTBE; 2-MeTHF; a mixture of 1,4-dioxane and MTBE at a volume ratio of about 1:9; a mixture of acetonitrile and IPA at a volume ratio of about 1:4; a mixture of $CHCl_3$ and n-heptane at a volume ratio of about 1:9; n-heptane; toluene; or water, wherein the crystalline form prepared from the method comprises freebase Form A.

A138. The method of any one of embodiments 128 to 130 and 135, wherein the solvent comprises a mixture of DMSO and water at a volume ratio of about 1:9, wherein the crystalline form prepared from the method comprises freebase Form C.

A139. The method of any one of embodiments 128 to 138, wherein the method further comprises cooling the suspension of step (ii) to a temperature of 5°C or lower.

A140. A method of preparing a crystalline form of any one of embodiments 1 to 84, wherein the method comprises:

(i) preparing a suspension of Compound 1 in a solvent;

(ii) heating the suspension to a first temperature and cooling the suspension to a second temperature; and

(iii) heating the suspension to a third temperature, and cooling the suspension to a fourth temperature.

A141. The method of embodiment 140, wherein Compound 1 of step (i) comprises freebase Form A.

A142. The method of embodiment 140 or 141, wherein a solid forms from the suspension after step (iii), and the method further comprises centrifuging the suspension of step (iii) to isolate the solid.

A143. The method of any one of embodiments 140 to 142, wherein the first temperature and the third temperature are each independently in between about 40°C and about 50°C, and the second temperature and the fourth temperature are each independently in between about 0°C and about 10°C.

A144. The method of any one of embodiments 140 to 143, wherein the heating and cooling of steps (ii) and (iii) are each independently conducted at a rate of between about 0.01 °C/min and about 1 °C/min.

A145. The method of any one of embodiments 140 to 144, wherein the solvent comprises EtOH, acetone, IPA, EtOAc, IPAc, MTBE, 2-MeTHF, $CHCl_3$, n-heptane, toluene, water, DMAc, MTBE, or acetonitrile, or any mixture thereof.

A146. The method of any one of embodiments 140 to 144, wherein the solvent comprises EtOH; a mixture of acetone and IPA at a volume ratio of about 1:40; EtOAc; IPAc; MTBE; 2-MeTHF; a mixture of $CHCl_3$ and n-heptane at a volume ratio of about 1:9; n-heptane; toluene; water; a mixture of DMAc and MTBE at a volume ratio of about 1:9; or a mixture of acetonitrile and MTBE at a volume ratio of about 1:9, wherein the crystalline form prepared from the method comprises freebase Form A.

A147. A method of preparing a crystalline form of any one of embodiments 1 to 84, wherein the method comprises:

(i) dissolving Compound 1 in a solvent; and

(ii) evaporating the solvent of step (i) at a temperature.

A148. The method of embodiment 147, wherein Compound 1 of step (i) comprises freebase Form A.

A149. The method of embodiment 147 or 148, wherein the temperature of step (ii) is room temperature.

A150. The method of any one of embodiments 147 to 149, wherein the solvent comprises MeOH, EtOH, acetone, EtOAc, THF, 1,4-dioxane, acetonitrile, $CHCl_3$, DCM, or n-heptane, or any mixture thereof.

A151. The method of any one of embodiments 147 to 149, wherein the solvent comprises MeOH; EtOH; EtOAc; 1,4-dioxane; acetonitrile; $CHCl_3$; a mixture of MeOH and water at a volume ratio of about 9:1; or a mixture of DCM and n-heptane at a volume ratio of about 9:1, wherein the crystalline form prepared from the method comprises freebase Form A.

A152. The method of any one of embodiments 147 to 149, wherein the solvent comprises a mixture of acetone and water at a volume ratio of about 9:1, wherein the crystalline form prepared from the method comprises freebase Form D.

A153. The method of any one of embodiments 147 to 149, wherein the solvent comprises acetone, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both.

A154. The method of any one of embodiments 147 to 149, wherein the solvent comprises THF, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form D, or both.

A155. A method of preparing a crystalline form of any one of 1 to 84, wherein the method comprises grinding Compound 1.

A156. The method of embodiment 155, wherein Compound 1 comprises freebase Form A.

A157. The method of embodiment 155 or 156, further comprising contacting Compound 1 with a solvent while grinding.

A158. The method of embodiment 157, wherein the solvent comprises water.

A159. The method of any one of embodiments 155 to 158, wherein the crystalline form prepared from the method comprises freebase Form A.

A160. A method of preparing a crystalline form of any one of 1 to 84, wherein the method comprises:

(i) adding Compound 1 to a solvent to form a first mixture; and

(ii) adding an anti-solvent to the first mixture to form a second mixture.

A161. The method of embodiment 160, wherein Compound 1 of step (i) comprises freebase Form A.

A162. The method of embodiment 160 or 161, wherein the anti-solvent is added until a precipitate is produced.

A163. The method of any one of embodiments 160 to 162, further comprising cooling the second mixture to a cooling temperature.

A164. The method of embodiment 163, wherein the cooling temperature is between about -25°C and about 10°C.

A165. The method of any one of embodiments 160 to 164, further comprising evaporating the solvent and the antisolvent from the second mixture at an evaporation temperature.

A166. The method of embodiment 165, wherein the evaporation temperature is room temperature.

A167. The method of any one of embodiments 160 to 166, wherein the solvent comprises acetone, THF, acetonitrile, $CHCl_3$, MeOH, 1,4-dioxane, DCM, NMP, EtOH, toluene, or DMAc, or any mixture thereof; and the anti-solvent comprises IPA, MTBE, n-heptane, or water, or any mixture thereof.

A168. The method of any one of embodiments 160 to 166, wherein the solvent comprises acetone, acetonitrile, or $CHCl_3$, or any mixture thereof, and the anti-solvent comprises IPA; or the solvent comprises acetone, and the anti-solvent comprises MTBE; wherein the crystalline form prepared from the method comprises freebase Form E.

A169. The method of any one of embodiments 160 to 166, wherein the solvent comprises THF, and the anti-solvent comprises IPA; or the solvent comprises 1,4-dioxane, and the anti-solvent comprises MTBE; wherein the crystalline form prepared from the method comprises freebase Form C.

A170. The method of any one of embodiments 160 to 166, wherein the solvent comprises DCM, and the antisolvent comprises MTBE; or the solvent comprises EtOH, acetone, 1,4-dioxane, toluene, or DCM, or any mixture thereof, and the anti-solvent comprises n-heptane; wherein the crystalline form prepared from the method comprises freebase Form A.

A171. The method of any one of embodiments 160 to 166, wherein the solvent comprises NMP, and the anti-solvent comprises MTBE; the solvent comprises NMP or DMAc, or a mixture thereof, and the anti-solvent comprises water; wherein the crystalline form prepared from the method comprises freebase Form B.

A172. The method of any one of embodiments 160 to 166, wherein the solvent comprises THF, and the anti-solvent comprises n-heptane; or the solvent comprises MeOH, acetone, THF, 1,4-dioxane, or acetonitrile, or any mixture thereof, and the anti-solvent comprises water, wherein the crystalline form prepared from the method comprises freebase Form D.

A173. The method of any one of embodiments 160 to 166, wherein the solvent comprises MeOH, and the anti-solvent comprises MTBE, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form E, or both.

Enumerated embodiments set B

[0168] The embodiment numbers referenced in this set refer to those within set A. For example, "embodiment 1" recited in embodiment B2 refers to embodiment B1.

B1. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern comprising peaks at angle 2-theta of about 6.9, about 15.0, and about 22.4 as measured at between about 50% to about 80% relative humidity at room temperature; (ii) an XRPD pattern comprising peaks at angle 2-theta of about 7.1, about 14.0, and about 22.5 as measured at about 30% relative humidity at room temperature; and/or (iii) an XRPD pattern comprising peaks at angle 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5 as measured at less than about 20% relative humidity at room temperature.

B2. The crystalline form of embodiment 1, characterized by having (i) an XRPD pattern substantially as shown in FIG. 1A as measured at between about 50% to about 80% relative humidity at room temperature; (ii) an XRPD pattern substantially as shown in FIG. 2A as measured at about 30% relative humidity at room temperature; and/or (iii) an XRPD pattern substantially as shown in FIG. 9A as measured at less than about 20% relative humidity at room temperature.

B3. The crystalline form of embodiment 1 or 2, wherein the crystalline form is a channel hydrate.

B4. The crystalline form of any one of embodiments 1 to 3, characterized by having an XRPD pattern of freebase Form A substantially as shown in FIG. 1A as measured at between about 50% to about 80% relative humidity at room temperature.

B5. The crystalline form of any one of embodiments 1 to 4, characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 6.9, about 15.0, and about 22.4 as measured at between about 50% to about 80% relative humidity at room temperature.

B6. The crystalline form of any one of embodiments 1 to 4, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 17.4, about 19.3, about 20.7, and about 22.4 as measured at between about 50% to about 80% relative humidity at room temperature.

B7. The crystalline form of any one of embodiments 1 to 6, characterized by having (i) a DSC graph comprising an endothermic peak at about 76.0 °C; (ii) a DSC graph comprising an exothermic peak at about 194.9 °C; (iii) a DSC graph substantially as shown in FIG. 1B; (iv) a TGA graph substantially as shown in FIG. 1B; (v) a DVS graph substantially as shown in FIG. 1C; and/or (vi) the molar ratio of water:Compound 1 of about 3.5:1.

B8. The crystalline form of any one of embodiments 1 to 3, characterized by having an XRPD pattern of freebase Form E substantially as shown in FIG. 2A as measured at about 30% relative humidity at room temperature.

B9. The crystalline form of any one of embodiments 1 to 3 and 8, characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 7.1, about 14.0, and about 22.5 as measured at about 30% relative humidity at room temperature.

B10. The crystalline form of any one of embodiments 1 to 3, 8, and 9, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 11.1, about 12.6, about 14.0, about 14.6, about 15.6, about 20.3, and about 22.5 as measured at about 30% relative humidity at room temperature.

B11. The crystalline form of any one of embodiments 1 to 3 and 8 to 10, characterized by having (i) a DSC graph comprising an endothermic peak at about 69.7 °C; (ii) a DSC graph comprising an exothermic peak at about 190.5 °C; (iii) a DSC graph substantially as shown in FIG. 2B; and/or (iv) a TGA graph substantially as shown in FIG. 2B.

B12. The crystalline form of embodiment 1 or 2, wherein the crystalline form is an anhydrate.

B13. The crystalline form of embodiment 1, 2, or 12, characterized by having an XRPD pattern of freebase Form H substantially as shown in FIG. 9A as measured at less than about 20% relative humidity at room temperature.

B14. The crystalline form of any one of embodiments 1, 2, 12, and 13, characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5 as measured at less than about 20% relative humidity at room temperature.

B15. The crystalline form of any one of embodiments 1, 2, and 12 to 14, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 21.8, and about 22.5 as measured at less than about 20% relative humidity at room temperature.

B16. The crystalline form of any one of embodiments 1, 2, and 12 to 15, characterized by having (i) a DSC graph comprising an endothermic peak at about 73.6 °C; (ii) a DSC graph comprising an exothermic peak at about 194.1 °C; (iii) a DSC graph substantially as shown in FIG. 9B; and/or (iv) a TGA graph substantially as shown in FIG. 9B.

B17. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form C substantially as shown in FIG. 3A; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Tables C-1 or C-2; (iii) an XRPD pattern comprising peaks at angle 2-theta of about 6.7, about 14.9, and about 22.2; (iv) a DSC graph comprising an endothermic peak at about 80.3 °C; (v) a DSC graph comprising an exothermic peak at about 189.4 °C; (vi) a DSC graph substantially as shown in FIG. 3B; and/or (v) a TGA graph substantially as shown in FIG. 3B.

B18. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form D substantially as shown in FIG. 4A; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table D; (iii) an XRPD pattern comprising peaks at angle 2-theta of about 6.7, 13.3, 14.6, and 23.3; (iv) a DSC graph comprising an endothermic peak at about 80.8 °C; (v) a DSC graph comprising an exothermic peak at about 189.4 °C; (vi) a DSC graph substantially as shown in FIG. 4B; and/or (vii) a TGA graph substantially as shown in FIG. 4B.

B19. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form B substantially as shown in FIG. 5A; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table B-1 or B-2; (iii) an XRPD pattern comprising peaks at angle 2-theta of about 6.2, about 14.7, and about 22.3; (iv) a DSC graph comprising an endothermic peak at about 84.3 °C; (v) a DSC graph comprising an exothermic peak

at about 187.1 °C; (vi) a DSC graph substantially as shown in FIG. 5B; and/or (vii) a TGA graph substantially as shown in FIG. 5B.

B20. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form F substantially as shown in FIG. 6; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table F; and/or (iii) an XRPD pattern comprising peaks at angle 2-theta of about 6.2, about 6.7, and about 13.4.

B21. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form G substantially as shown in FIG. 7; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table G; (iii) an XRPD pattern comprising peaks at angle 2-theta of about 7.0, about 13.8, about 15.4, and about 22.2; (iv) a DSC graph comprising an endothermic peak at about 72.3 °C; (v) a DSC graph comprising an endothermic peak at about 113.3 °C; (vi) a DSC graph comprising an exothermic peak at about 196.3 °C; (vii) a DSC graph substantially as shown in FIG. 8; and/or (viii) a TGA graph substantially as shown in FIG. 8.

B22. The crystalline form of any one of embodiments 1 to 21, wherein the purity of the crystalline form is at least about 95%.

B23. A method of preparing a crystalline form of any one of embodiments 1 to 22, the method comprising:

(i) contacting Compound 1 with one or more solvents to form a mixture; and

(ii) crystallizing Compound 1.

B24. The method of embodiment 23, wherein the one or more solvents comprise ethyl acetate, tetrahydrofuran, or ethanol, or any combination thereof.

B25. The method of embodiment 24, wherein the one or more solvents comprise ethyl acetate, tetrahydrofuran, and ethanol at about 400:100:1 volume ratio.

B26. The method of any one of embodiments 23 to 25, the method further comprising stirring the mixture at about 60°C.

B27. A method of preparing a crystalline form of any one of embodiments 1 to 22, wherein the method comprises:

(i) placing a sample comprising a solid form of Compound 1 in a first container;
(ii) placing the first container of step (i) inside a second container containing a solvent; and
(iii) allowing vapor from the solvent to interact with the sample in the first container.

B28. The method of embodiment 27, wherein the sample of step (i) comprises freebase Form A.

B29. The method of embodiment 27 or 28, wherein step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container at a room temperature and for a duration of about 7 days.

B30. The method of any one of embodiments 27 to 29, wherein the solvent comprises EtOH, IPA, MIBK, EtOAc, MTBE, 2-MeTHF, acetonitrile, toluene, DMSO, or water, or any mixture thereof.

B31. The method of any one of embodiments 27 to 29, wherein the solvent comprises EtOH, IPA, EtOAc, acetonitrile, or water, or any mixture thereof, and the crystalline form prepared from the method comprises freebase Form A.

B32. The method of any one of embodiments 27 to 29, wherein the solvent comprises MIBK or MTBE, or any mixture thereof, and the crystalline form prepared from the method comprises freebase form C.

B33. The method of any one of embodiments 27 to 29, wherein the solvent comprises 2-MeTHF or toluene, or any mixture thereof, and the crystalline form prepared from the method comprises freebase form A or freebase form C, or both.

B34. The method of any one of embodiments 27 to 29, wherein the solvent comprises DMSO, and the crystalline form prepared from the method comprises freebase form C.

B35. The method of any one of embodiments 27 to 29, wherein the solvent comprises DMSO, and the crystalline for prepared from the method comprises freebase form G.

B36. The method of embodiment 35, wherein step (iii) comprises allowing vapor from the solvent to interact with the sample in the first container for the duration of about 19 days.

B37. A method of preparing a crystalline form of any one of embodiments 1 to 22, wherein the method comprises:
(i) dissolving Compound 1 in a first solvent in a first container;

(ii) placing the first container of step (i) inside a second container containing a second solvent;

(iii) sealing the second container of step (ii);

(iv) allowing vapor of the second solvent to interact with Compound 1 in the first container to form precipitant; and

(v) isolating the precipitant of step (iv) from the first solvent and/or the second solvent.

B38. The method of embodiment 37, wherein Compound 1 of step (i) comprises freebase Form A.

B39. The method of embodiment 37 or 38, wherein step (iv) comprises allowing vapor of the second solvent to interact with Compound 1 in the first container at room temperature.

B40. The method of any one of embodiments 37 to 39, wherein isolating the precipitant in step (v) comprises evaporating the first solvent and/or the second solvent at room temperature.

B41. The method of any one of embodiments 37 to 30, wherein the first solvent comprises 1,4-dioxane or DMAc, or a mixture thereof, and the second solvent comprises IPA, MTBE, n-Heptane, or water, or any mixture thereof.

B42. The method of any one of embodiments 37 to 40, wherein the first solvent comprises 1,4-dioxane, the second solvent comprises MTBE, and the crystalline form prepared from the method comprises freebase Form C.

B43. The method of any one of embodiments 37 to 40, wherein the first solvent comprises DMAc, the second solvent comprises IPA, and the crystalline form prepared from the method comprises freebase Form F.

B44. The method of any one of embodiments 37 to 40, wherein the first solvent comprises DMAc, the second solvent comprises MTBE or water, or a mixture thereof, and the crystalline form prepared from the method comprises freebase Form B.

B45. The method of any one of embodiments 37 to 40, wherein the first solvent comprises 1,4-dioxane, the second solvent comprises IPA, and the crystalline form prepared from the method comprises freebase Form A or freebase Form E, or both.

B46. The method of any one of embodiments 37 to 40, wherein the first solvent comprises 1,4-dioxane, the second solvent comprises n-heptane, and the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both.

B47. The method of any one of embodiments 37 to 40, wherein the first solvent comprises 1,4-dioxane, the second solvent comprises water, and the crystalline form prepared from the method comprises freebase Form A or freebase Form D, or both.

B48. A method of preparing a crystalline form of any one of embodiments 1 to 22, wherein the method comprises:

(i) preparing a suspension of Compound 1 in a solvent;

(ii) heating the suspension of step (i) to a first temperature;

(iii) filtering the suspension of step (ii) to obtain filtrate;

(iv) cooling the filtrate of step (iii) to a second temperature.

B49. The method of embodiment 48, wherein Compound 1 of step (i) comprises freebase Form A.

B50. The method of embodiment 48 or 49, wherein the first temperature is about 50°C.

B51. The method of any one of embodiments 48 to 50, wherein the second temperature is about 5°C or about -20°C.

B52. The method of any one of embodiments 48 to 51, wherein the temperature of the filtrate in step (iv) is changed at a rate of about 0.1°C/min.

B53. The method of any one of embodiments 48 to 52, further comprising evaporating the solvent at room temperature.

B54. The method of any one of embodiments 48 to 53, wherein the solvent comprises EtOh, MIBK, EtOAc, IPAc, 2MeTHF, acetonitrile, or toluene.

B55. The method of any one of embodiments 48 to 53, wherein the solvent comprises EtOH, EtOAc, 2-MeTHF, or acetonitrile, or any mixture thereof, wherein the crystalline form prepared from the method comprises freebase Form A.

B56. The method of any one of embodiments 48 to 53, wherein the solvent comprises MIBK, wherein the crystalline form prepared from the method comprises freebase Form C.

B57. The method of any one of embodiments 48 to 53, wherein the solvent comprises IPAc or toluene, or a mixture thereof, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both.

B58. A method of preparing a crystalline form of any one of embodiments 1 to 22, wherein the method comprises:

(i) preparing a suspension of Compound 1 in solvent; and

(ii) stirring the suspension of step (i) at a temperature for a duration.

B59. The method of embodiment 58, wherein Compound 1 of step (i) comprises freebase Form A.

B60. The method of embodiment 58 or 59, wherein a solid forms from the suspension after step (ii), and the method further comprises centrifuging the suspension of step (ii) to isolate the solid.

B61. The method of any one of embodiments 58 to 60, wherein the temperature is room temperature, and the duration is between about 2 days and about 6 days.

B62. The method of any one of embodiments 58 to 61, wherein the solvent comprises MeOH, MTBE, EtOH, acetone, water, EtOAc, MTBE, THF, 1,4-dioxane, n-Heptane, acetonitrile, DCM, toluene, NMP, or IPA, or any mixture thereof.

B63. The method of any one of embodiments 58 to 61, wherein the solvent comprises a mixture of MeOH and MTBE at a volume ratio of about 1:1; EtOH; a mixture of acetone and water at a volume ratio of about 1:1; EtOAc; MTBE; a mixture of TFH and water at a volume ratio of about 1:1; a mixture of 1,4-dioxane and n-heptane at a volume ratio of about 1:4; acetonitrile; a mixture of DCM and n-heptane at volume ratio of about 1:1; n-heptane; toluene; water; or a mixture of EtOH and water at a volume ratio of about 97:3 or about 93:7, wherein the crystalline form prepared from the method comprises freebase Form A.

B64. The method of any one of embodiments 58 to 61, wherein the solvent comprises a mixture of NMP and IPA at a volume ratio of about 1:4, wherein the crystalline form prepared from the method comprises freebase Form B.

B65. The method of any one of embodiments 58 to 60, wherein the temperature is between about 40°C and about 60°C, and the duration is between about 1 day and about 5 days.

B66. The method of any one of embodiments 58 to 60 and 65, wherein the solvent comprises IPA, MIBK, IPAc, MTBE, 2-MeTHF, 1,4-dioxane, acetonitrile, $CHCl_3$, n-heptane, toluene, water, or DMSO, or any mixture thereof.

B67. The method of any one of embodiments 58 to 60 and 65, wherein the solvent comprises IPA; MIBK; IPAc; MTBE; 2-MeTHF; a mixture of 1,4-dioxane and MTBE at a volume ratio of about 1:9; a mixture of acetonitrile and IPA at a volume ratio of about 1:4; a mixture of $CHCl_3$ and n-heptane at a volume ratio of about 1:9; n-heptane; toluene; or water, wherein the crystalline form prepared from the method comprises freebase Form A.

B68. The method of any one of embodiments 58 to 60 and 65, wherein the solvent comprises a mixture of DMSO and water at a volume ratio of about 1:9, wherein the crystalline form prepared from the method comprises freebase Form C.

B69. The method of any one of embodiments 58 to 68, wherein the method further comprises cooling the suspension of step (ii) to a temperature of 5°C or lower.

B70. A method of preparing a crystalline form of any one of embodiments 1 to 22, wherein the method comprises:

(i) preparing a suspension of Compound 1 in a solvent;

(ii) heating the suspension to a first temperature and cooling the suspension to a second temperature; and

(iii) heating the suspension to a third temperature, and cooling the suspension to a fourth temperature.

B71. The method of embodiment 70, wherein Compound 1 of step (i) comprises freebase Form A.

B72. The method of embodiment 70 or 71, wherein a solid forms from the suspension after step (iii), and the method further comprises centrifuging the suspension of step (iii) to isolate the solid.

B73. The method of any one of embodiments 70 to 72, wherein the first temperature and the third temperature are each independently in between about 40°C and about 50°C, and the second temperature and the fourth temperature are each independently in between about 0°C and about 10°C.

B74. The method of any one of embodiments 70 to 73, wherein the heating and cooling of steps (ii) and (iii) are each independently conducted at a rate of between about 0.01 °C/min and about 1 °C/min.

B75. The method of any one of embodiments 70 to 74, wherein the solvent comprises EtOH, acetone, IPA, EtOAc, IPAc, MTBE, 2-MeTHF, $CHCl_3$, n-heptane, toluene, water, DMAc, MTBE, or acetonitrile, or any mixture thereof.

B76. The method of any one of embodiments 70 to 74, wherein the solvent comprises EtOH; a mixture of acetone and IPA at a volume ratio of about 1:40; EtOAc; IPAc; MTBE; 2-MeTHF; a mixture of $CHCl_3$ and n-heptane at a volume ratio of about 1:9; n-heptane; toluene; water; a mixture of DMAc and MTBE at a volume ratio of about 1:9; or a mixture of acetonitrile and MTBE at a volume ratio of about 1:9, wherein the crystalline form prepared from the method comprises freebase Form A.

B77. A method of preparing a crystalline form of any one of embodiments 1 to 22, wherein the method comprises:
(i) dissolving Compound 1 in a solvent; and
(ii) evaporating the solvent of step (i) at a temperature.

B78. The method of embodiment 77, wherein Compound 1 of step (i) comprises freebase Form A.

B79. The method of embodiment 77 or 78, wherein the temperature of step (ii) is room temperature.

B80. The method of any one of embodiments 77 to 79, wherein the solvent comprises MeOH, EtOH, acetone, EtOAc, THF, 1,4-dioxane, acetonitrile, $CHCl_3$, DCM, or n-heptane, or any mixture thereof.

B81. The method of any one of embodiments 77 to 79, wherein the solvent comprises MeOH; EtOH; EtOAc; 1,4-dioxane; acetonitrile; $CHCl_3$; a mixture of MeOH and water at a volume ratio of about 9:1; or a mixture of DCM and n-heptane at a volume ratio of about 9:1, wherein the crystalline form prepared from the method comprises freebase Form A.

B82. The method of any one of embodiments 77 to 79, wherein the solvent comprises a mixture of acetone and water at a volume ratio of about 9:1, wherein the crystalline form prepared from the method comprises freebase Form D.

B83. The method of any one of embodiments 77 to 79, wherein the solvent comprises acetone, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form C, or both.

B84. The method of any one of embodiments 77 to 79, wherein the solvent comprises THF, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form D, or both.

B85. A method of preparing a crystalline form of any one of 1 to 22, wherein the method comprises grinding Compound 1.

B86. The method of embodiment 85, wherein Compound 1 comprises freebase Form A.

B87. The method of embodiment 85 or 86, further comprising contacting Compound 1 with a solvent while grinding.

B88. The method of embodiment 87, wherein the solvent comprises water.

B89. The method of any one of embodiments 85 to 88, wherein the crystalline form prepared from the method comprises freebase Form A.

B90. A method of preparing a crystalline form of any one of 1 to 22, wherein the method comprises:
(i) adding Compound 1 to a solvent to form a first mixture; and
(ii) adding an anti-solvent to the first mixture to form a second mixture.

B91. The method of embodiment 90, wherein Compound 1 of step (i) comprises freebase Form A.

B92. The method of embodiment 90 or 91, wherein the anti-solvent is added until a precipitate is produced.

B93. The method of any one of embodiments 90 to 92, further comprising cooling the second mixture to a cooling temperature.

B94. The method of embodiment 93, wherein the cooling temperature is between about -25°C and about 10°C.

B95. The method of any one of embodiments 90 to 94, further comprising evaporating the solvent and the antisolvent from the second mixture at an evaporation temperature.

B96. The method of embodiment 95, wherein the evaporation temperature is room temperature.

B97. The method of any one of embodiments 90 to 96, wherein the solvent comprises acetone, THF, acetonitrile, $CHCl_3$, MeOH, 1,4-dioxane, DCM, NMP, EtOH, toluene, or DMAc, or any mixture thereof; and the anti-solvent comprises IPA, MTBE, n-heptane, or water, or any mixture thereof.

B98. The method of any one of embodiments 90 to 96, wherein the solvent comprises acetone, acetonitrile, or $CHCl_3$, or any mixture thereof, and the anti-solvent comprises IPA; or the solvent comprises acetone, and the anti-solvent comprises MTBE; wherein the crystalline form prepared from the method comprises freebase Form E.

B99. The method of any one of embodiments 90 to 96, wherein the solvent comprises THF, and the anti-solvent comprises IPA; or the solvent comprises 1,4-dioxane, and the anti-solvent comprises MTBE; wherein the crystalline form prepared from the method comprises freebase Form C.

B100. The method of any one of embodiments 90 to 96, wherein the solvent comprises DCM, and the antisolvent comprises MTBE; or the solvent comprises EtOH, acetone, 1,4-dioxane, toluene, or DCM, or any mixture thereof, and the anti-solvent comprises n-heptane; wherein the crystalline form prepared from the method comprises freebase Form A.

B101. The method of any one of embodiments 90 to 96, wherein the solvent comprises NMP, and the anti-solvent comprises MTBE; the solvent comprises NMP or DMAc, or a mixture thereof, and the anti-solvent comprises water; wherein the crystalline form prepared from the method comprises freebase Form B.

B102. The method of any one of embodiments 90 to 96, wherein the solvent comprises THF, and the anti-solvent comprises n-heptane; or the solvent comprises MeOH, acetone, THF, 1,4-dioxane, or acetonitrile, or any mixture thereof, and the anti-solvent comprises water, wherein the crystalline form prepared from the method comprises freebase Form D.

B103. The method of any one of embodiments 90 to 96, wherein the solvent comprises MeOH, and the anti-solvent comprises MTBE, wherein the crystalline form prepared from the method comprises freebase Form A or freebase Form E, or both.

EXAMPLES

[0169] The presently disclosed subject matter will be better understood by reference to the following Examples, which are provided as exemplary of the invention, and not by way of limitation.

[0170] The following abbreviations may be used herein:

XRPD	X-Ray Powder Diffraction
DSC	Differential Scanning Calorimetry
TGA	Thermogravimetric Analysis
^{1}H NMR	Proton Nuclear Magnetic Resonance
HPLC	High Performance Liquid Chromatography
DVS	Dynamic vapor sorption
MeOH	Methanol
EtOH	Ethanol
IPA	Isopropyl alcohol
MIBK	4-Methyl-2-pentanone
EtOAc	Ethyl acetate
IPAc	Isopropyl acetate
MTBE	Methyl tert-butyl ether
THF	Tetrahydrofuran
2-MeTHF	2-Methyltetrahydrofuran
DCM	Dichloromethane
ACN	Acetonitrile
DMSO	Dimethylsulfoxide
DMAc	N,N-Dimethylacetamide
NMP	1-Methyl-2-pyrrolidone

RT	Room temperature
RH	Relative humidity

[0171] The crystalline forms were characterized by various analytical techniques, including XRPD, DSC, TGA, DVS, ^{1}H NMR, and HPLC using the procedures described below.

[0172] For XRPD, PANalytical Empyrean and X' Pert3 X-ray powder diffract meters were used. The XRPD parameters used are listed below. In some embodiments, the X-ray source for XRPD is copper Kα. In some embodiments, the Kα1 wavelength is about 1.54 Å. In some embodiments, the Kα2 wavelength is about 1.54 Å. In some embodiments, the intensity ratio of Kα2/Kα1 is about 0.5. In some embodiments, XRPD is measured at room temperature.

Parameters	**Empyrean (VT/VH-XRPD)**	**X' Pert3/Empyrean**
X-Ray wavelength	Cu, Kα; Kα1 (Å): 1.540598 Kα2 (Å): 1.544426 intensity ratio Kα2/Kα1: 0.50	Cu, Kα; Kα1 (Å): 1.540598 Kα2 (Å): 1.544426 intensity ratio Kα2/Kα1: 0.50
X-Ray tube setting	45 kV, 40 mA	45 kV, 40 mA
Divergence slit	1/8°	1/8 °
Scan mode	Continuous	Continuous
Scan range (2θ/°)	3-40	3~40
Step size (2θ/°)	0.0167	0.0263
Scan step time (s)	17.8	46.665
Test time	~10 min	About 5 mins

[0173] For TGA, TA Discovery 5500 TGA from TA Instruments was used. For DSC, TA Discovery 2500 DSC from TA Instruments was used. TGA and DSC parameters used are listed below.

Parameters	TGA	DSC
Method	Ramp	Ramp
Sample pan	Aluminum, open	Aluminum, crimped/open
Temperature	RT- Target temperature	25 ℃- Target temperature
Heating rate	10 ℃/min	10 ℃/min
Purge gas	N_2	N_2

[0174] For DVS, a Surface Measurement Systems (SMS) DVS Intrinsic Plus was used. The relative humidity at 25 ℃ was calibrated against deliquescence point of LiCl, $Mg(NO_3)_2$, and KCl. Parameters for DVS test are listed below.

Parameters	Values
Temperature	25 ℃
Sample size	10-20 mg
Gas and flow rate	N_2, 200 mL/min
dm/dt	0.002%/min
Min.dm/dt stability duration	10 min
Max. equilibrium time	180 min
RH range	40%RH-95%RH-0% RH-95% RH
RH step size	10% (90% RH-0% RH-90% RH) 5% (95% RH-90% RH and 90% RH-95% RH)

[0175] For solution NMR, Bruker 400M NMR Spectrometer was used, in DMSO-d_6 or ACN-d_3.

[0176] For HPLC/IC, Waters H-Class UPLC was used. Chromatographic conditions used are listed below.

Parameters	*Waters H-Class with PDA detector*	
Column	Waters HSS T3, 2.1×50 mm, 1.8 μm	
Mobile phase	A: 0.1% TFA in H_2O	
	B: 0.1% TFA in ACN	
	Time (min)	**%B**
	0.0	5

Parameters	*Waters H-Class with PDA detector*	
	7.0	55
	8.0	90
	9.0	90
	9.1	10
	11.0	10
Run time	11.0 min	
Flow rate	0.5 mL/min	
Injection volume	2 µL	
Detector wavelength	UV at 220 nm	
Column temperature	40 ℃	
Sampler temperature	RT	
Diluent	ACN/H_2O (1:1, v/v)	

[0177] IC parameters used are listed below.

IC	**ThermoFisher ICS-1100**
Column	Dionex IonPac™ AS18 RFIC™ 4×250mm Analytical
Mobile phase	25 mM NaOH
Injection volume	25 µL
Flow rate	1.0 mL/min
Cell temperature	35 ℃
Column temperature	35 ℃
Current	80 mA
Run time	16.0 mins

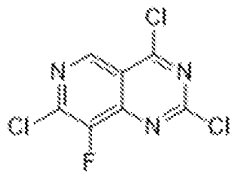
[0178] For LC-MS, Agilent 1290 with single quadrupole MS Detector was used. Chromatographic conditions used are listed below.

LC-MS	**Agilent 1290 UPLC with single quadrupole MS Detector**
Column	Waters HSS T3, 2.1×50 mm, 1.8 µm
Mobile phase	A: 0.1% FA in H_2O B: 0.1% FA in ACN

LC-MS	Agilent 1290 UPLC with single quadrupole MS Detector	
	Time (min)	%B
	0.0	10
	7.0	55
Gradient table	8.0	90
	9.0	90
	9.1	10
	11.0	10
Run time	11.0 min	
Flow rate	0.5 mL/min	
Injection volume	2 μL	
Detector wavelength	UV at 220 nm	
Column temperature	40 ℃	
Sampler temperature	RT	
Diluent	ACN/H_2O (1:1, v/v)	
MS model	Scan from 100-1000 Positive	
Capillary voltage	4000 V(Positive)	
Fragmentor voltage	70 V	
Drying gas temperature	350 ℃	
Drying gas flow	12.0 L/min	
Nebulizer pressure	45 psi	

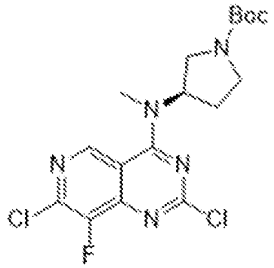
[0179] PLM data were collected with Axio Lab. A1 upright microscope. SEM images were captured on a HITACHI S-4700 FE-SEM. XPS was collected on Thermofisher ESCALAB Xi+.

Example 1: Synthesis of freebase Type A of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1)



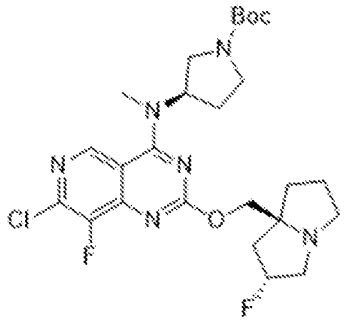
Step 1: 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine

[0180] To a solution of 7-chloro-8-fluoropyrido[4,3-d]pyrimidine-2,4-diol (100 g, 464 mmol) and phosphorus oxychloride (500 mL) in anhydrous toluene (600 mL) was added *N*,*N* diisopropylethylamine (148 g, 1.15 mol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 110 °C for 12 h. The mixture was carefully diluted with water (5 L) and extracted with ethyl acetate (3 x 2 L). The reaction mixture was concentrated *in vacuo* affording 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (117 g, crude) as a yellow oil, used in next step without any further purification. LCMS Rt = 0.725 min, m/z = 250.9 $[M + H]^+$.



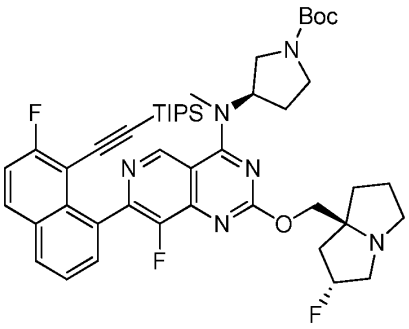
Step 2: (R)-tert-butyl 3-((2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate

[0181] To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (177 g, 701 mmol) in tetrahydrofuran (2.4 L) and *N*,*N*-diisopropylethylamine (119 g, 927 mmol) was added (R)-tert-butyl 3-(methylamino)pyrrolidine-1-carboxylate (79 g, 394 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 0.5 h. The mixture was then diluted with water (5 L) and extracted with ethyl acetate (3 x 2 L). The combined organic layers were dried over sodium sulphate and concentrated in *vacuo*. The crude residue was diluted with *tert*-butyl methyl ether (400 mL) and the resulting precipitate was filtered affording (R)-tert-butyl 3-((2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (120 g, 62.18%) as a light yellow solid. LCMS Rt = 0.798 min, m/z = 415.1 $[M + H]^+$.



Step 3: (R)-tert-butyl 3-((7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate

[0182] To a solution of ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (38.24 g, 240.22 mmol) and 4Å MS (25 g) in dioxane (1 L) was added (R)-tert-butyl 3-((2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (50 g, 120.11 mmol) and *N*,*N*-diisopropylethylamine (46.57 g, 360.34 mmol), and the resulting mixture was stirred at 100 °C for 24 h under nitrogen atmosphere. The mixture was then filtered, and the collected solid was suspended in a (2.5:1) mixture of petroleum ether: ethyl acetate (14 L). The slurry was then filtered, and the solid was resuspended in a (2.5:1) mixture of petroleum ether: ethyl acetate (14 L). The resulting precipitate was filtered and concentrated to dryness in *vacuo* affording (R)-tert-butyl 3-((7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (160 g, crude) as a white solid, used in next step without any further purification: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.87 (s, 1H), 5.39 – 5.29 (m, 1H), 5.21 (s, 1H), 4.32 – 4.25 (m, 1H), 4.24 – 4.15 (m, 1H), 3.82 (dd, J = 11.2, 8.0 Hz, 1H), 3.66 (d, J = 4.0 Hz, 1H), 3.47-3.39 (m, 2H), 3.37 (s, 3H), 3.32-3.22 (m, 2H), 3.17 (s, 1H), 3.04 – 2.93 (m, 1H), 2.34 – 2.08 (m, 5H), 2.04 – 1.78 (m, 3 H), 1.49 (s, 9H). LCMS Rt = 0.545 min, m/z = 538.2 $[M + H]^+$.

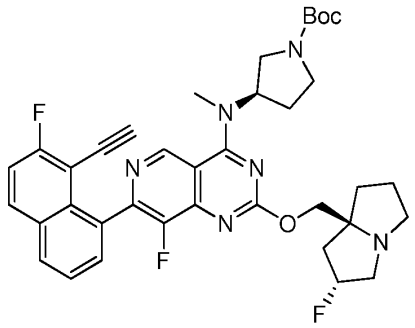


Step 4: (R)-tert-butyl 3-((8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate

[0183] A mixture of (R)-tert-butyl 3-((7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (80 g, 148.42 mmol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (70.51 g, 155.84 mmol), cataCXium® A Pd G2 (9.92 g, 14.84 mmol), potassium phosphate (94.51 g, 445.26 mmol) in dioxane (1.5 L) and water (0.3 L) was evacuated and backfilled with nitrogen three times, and then the mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. Three equivalent batches of the outlined reaction mixture were then combined, diluted with water (1 L) and extracted with ethyl acetate (3 x 500 mL). The combined organic layers were washed with brine (1 L), dried over sodium sulphate, and concentrated *in vacuo*. The crude residue was purified by column chromatography (silica gel, 100-200 mesh, 0-100% tetrahydrofuran in petroleum ether) affording (R)-tert-butyl 3-((8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (360 g, 97.52%) (3 batches) as a brown oil. LCMS Rt = 0.888 min, m/z = 829.7 $[M+H]^+$.

[0184] To a solution of (R)-tert-butyl 3-((8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (180 g, 217.11 mmol) in ethyl acetate (2 L) was added Functionalised Silica Gels (200.25 g, 2.17 mol) to remove Pd. The mixture was then stirred at 70 °C for 12 h. Two equivalent batches of this mixture were combined, filtered and the filtrate was concentrated to dryness *in vacuo* affording (R)-tert-butyl 3-((8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-

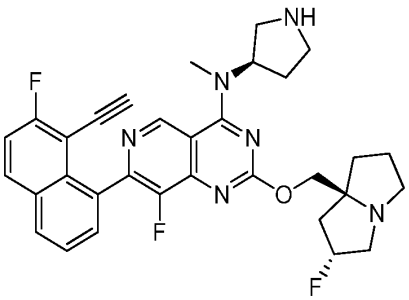
yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (320 g, crude) (2 batches) as a yellow solid, used in next step without further purification: ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.22 (d, *J* = 4.4 Hz, 1H), 8.11 – 8.06 (m, 2H), 7.66 – 7.59 (m, 2H), 7.46 (t, *J* = 9.0 Hz, 1H), 5.34 – 5.17 (m, 2H), 4.21 – 4.14 (m, 1H), 4.09 – 4.06 (m, 1H), 4.06 – 4.03 (m, 1H), 3.81 (br d, *J* = 6.6 Hz, 1H), 3.66 – 3.62 (m, 1H), 3.62 – 3.55 (m, 1H), 3.42 (s, 1H), 3.40 (s, 1H), 3.38 – 3.32 (m, 2H), 3.19 – 3.10 (m, 2H), 3.07 (s, 1H), 2.94 – 2.86 (m, 1H), 2.36 – 2.28 (m, 1H), 2.27 – 2.22 (m, 1H), 2.10 (br d, *J* = 4.5 Hz, 2H), 2.08 – 2.03 (m, 1H), 1.97 (s, 1H), 1.92 – 1.83 (m, 2H), 1.83 – 1.76 (m, 2H), 1.47 – 1.44 (m, 9H), 0.90 – 0.83 (m, 18H). LCMS Rt = 0.913 min, m/z = 829.6 [M +H]$^+$.



Step 5: (R)-tert-butyl 3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate

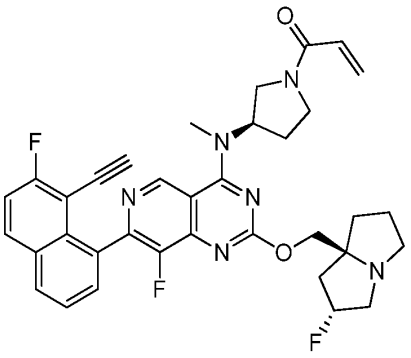
[0185] To a solution of (R)-tert-butyl 3-((8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (135 g, 162.83 mmol) in acetonitrile (1.6 L) was added cesium fluoride (148.41 g, 976.99 mmol). The resulting mixture was stirred at 25 °C for 12 h. Two equivalent batches of the reaction mixture were then combined, diluted with water (800 mL) and concentrated under reduced pressure to remove the acetonitrile. Then, the mixture was diluted with water (400 mL) and extracted with ethyl acetate (3 x 1 L). The combined organic layers were dried over sodium sulphate and concentrated in *vacuo*. The crude residue was then diluted with a (10:1) mixture of petroleum ether: ethyl acetate (1.8 L) and the resulting precipitate was filtered affording

(R)-tert-butyl 3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (180 g, 82.16%) as a yellow solid: ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.14 (d, *J* = 2.9 Hz, 1H), 8.14 – 8.08 (m, 2H), 7.68 – 7.63 (m, 2H), 7.44 (t, *J* = 9.1 Hz, 1H), 5.35 – 5.16 (m, 2H), 4.22 – 4.17 (m, 1H), 4.14 – 4.09 (m, 1H), 3.87 – 3.72 (m, 1H), 3.63 – 3.56 (m, 1H), 3.41 (d, *J* = 1.8 Hz, 3H), 3.40 – 3.30 (m, 2H), 3.25 (d, *J* = 13.4 Hz, 1H), 3.18 – 3.08 (m, 2H), 3.06 (s, 1H), 2.92 – 2.85 (m, 1H), 2.35 – 2.24 (m, 2H), 2.16 – 2.09 (m, 2H), 2.07 – 2.03 (m, 1H), 1.92 – 1.80 (m, 3H), 1.46 (s, 9H). LCMS Rt = 1.725 min, m/z = 673.2 $[M+H]^+$.



Step 6: 7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-methyl-N-((R)-pyrrolidin-3-yl)pyrido[4,3-d]pyrimidin-4-amine

[0186] A mixture of (R)-tert-butyl 3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidine-1-carboxylate (190 g, 282.43 mmol) in hydrochloric acid (4 M in dioxane, 800 mL) was stirred at 25 °C for 0.5 h. The reaction mixture was then concentrated *in vacuo* affording 7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-methyl-N-((R)-pyrrolidin-3-yl)pyrido[4,3-d]pyrimidin-4-amine (183 g crude, hydrochloride salt) as a yellow solid which was used in the next step without further purification. LCMS Rt = 0.489 min, m/z = 573.2 $[M+H]^+$.



(Compound 1)

Step 7: 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1)

[0187] To a solution of 7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-methyl-N-((R)-pyrrolidin-3-yl)pyrido[4,3-d]pyrimidin-4-amine (61 g, 94.49 mmol, hydrochloride salt) and sodium bicarbonate (63.51 g, 755.95 mmol) in tetrahydrofuran (1.5 L) and water (300 mL) was added acryloyl chloride (17.10 g, 188.99 mmol), the mixture was stirred at 0 °C for 0.5 h under nitrogen atmosphere. Three equivalent batches of this reaction mixture were combined, diluted with water (500 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic layers were dried over sodium sulphate and concentrated in *vacuo.* The crude residue was diluted with a (5:1) mixture of petroleum ether : ethyl acetate (1.2 L) and the resulting precipitate was filtered. The crude residue was then suspended in a (10:1) mixture of ethyl acetate : ethanol (550 mL) and the resulting precipitate was collected by filtration. The crude residue was finally dissolved in ethyl acetate (800 mL), tetrahydrofuran (200 mL) and ethanol (2 mL). The resulting mixture was then stirred at 60 °C, filtered and cooled down at room temperature. The resulting precipitate was filtered affording 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (83 g, 45.68%) (3 batches) as a light yellow solid: ^{1}H NMR (400 MHz, Acetonitrile-d3) δ 9.17 – 9.13 (m, 1H), 8.15 – 8.08 (m, 2H), 7.69 – 7.63 (m, 2H), 7.44 (t, *J* = 9.1 Hz, 1H), 6.59 (dt, *J* = 10.4, 15.9 Hz, 1H), 6.24 (td, *J* = 2.5, 16.8 Hz, 1H), 5.71 – 5.64 (m, 1H), 5.42 – 5.17 (m, 2H), 4.22 – 4.17 (m, 1H), 4.14 – 4.09 (m, 1H), 4.09 – 3.78 (m, 2H), 3.74 – 3.45 (m, 2H), 3.42 (s, 3H), 3.28 – 3.22 (m, 1H), 3.19 – 3.08 (m, 2H), 3.06 (s, 1H), 2.93 – 2.84 (m, 1H), 2.46 – 2.25 (m, 2H), 2.15 – 1.98 (m, 3H), 1.92 – 1.78 (m, 3H). LCMS Rt = 3.799 min, m/z = 627.3 $[M+H]^+$. LCMS (5 to

95% acetonitrile in water + 0.1% trifluoroacetic acid over 6 min); retention time 3.799 min, ESI+ found $[M+H]^+ = 627.3$. This final product is referred to as freebase Type A or freebase Type A starting material.

Example 2: Characterization of freebase Type A

[0188] Freebase Type A was characterized by XRPD, TGA, DSC, and ^{1}H NMR. The XRPD result in FIG. 1A showed freebase Type A was crystalline. The TGA/DSC curves of freebase Type A were measured and are displayed in FIG. 1B, which shows a weight loss of 2.23% up to 150 ℃, one endotherm at 73.5 ℃ (peak) and one exotherm at 194.9 ℃ (peak). ^{1}H NMR was measured and the result is displayed in FIG. 1D (DMSO-d_6) and FIG. 1E (ACN-d_3). The detailed UPLC showed the UPLC purity of freebase Type A was 97.12 area%. PLM image and SEM images of freebase Type A were taken and are listed in FIG. 1F and FIG. 1G, respectively. Grinding experiment was performed for freebase Type A. XRPD results (FIG. 1H) show no form change but decreased crystallinity after grinding manually for ~3 min.

[0189] Approximate solubility of freebase Type A was determined in 20 solvents at RT. Approximately 2 mg of sample was added into a 3-mL glass vial. Solvents in Table 2-1 were then added stepwise into the vials until the solids were dissolved visually or a total volume of 2 mL was reached. Solubility results summarized in Table 2-1 were used to guide the solvent selection in screening experiment design.

Table 2-1.

Solvent	Solubility (mg/mL)	Solvent	Solubility (mg/mL)
MeOH	21.0<S<42.0	1,4-Dioxane	S>46.0
EtOH	5.8<S<11.5	ACN	11.5<S<23.0
IPA	S<1.1	$CHCl_3$	S>40.0
Acetone	24.0<S<48.0	DCM	21.0<S<42.0
MIBK	1.1<S<2.1	n-Heptane	S<1.0
EtOAc	2.0<S<5.0	Toluene	2.0<S<5.0
IPAc	1.0<S<2.0	DMAc	S>46.0
MTBE	S<1.1	DMSO	S>52.0
THF	25.0<S<50.0	NMP	S>40.0
2-MeTHF	2.4<S<6.0	H_2O	S<1.1

[0190] In order to evaluate the hygroscopicity of freebase Type A, DVS isotherm plot was collected at 25 ℃ between 0%RH and 95%RH. XRPD characterization was performed for the samples after DVS test. The DVS plot and XRPD results are shown in FIG. 1C and FIG. 1I, respectively. The water uptake of freebase Type A was 7.775%. No form change was observed for freebase Type A after DVS test.

[0191] For solid stability evaluation, freebase Type A was placed under the conditions of 25 ℃/60%RH and 40 ℃/75%RH for 1 week and 1 month. The physical and chemical stability were evaluated by XRPD and UPLC purity, respectively. The results are summarized in **Error! Reference source not found.**. The detailed UPLC results are shown in Table 2-3. The XRPD results are shown in FIG. 1J. The results showed that no form change or obvious purity decrease was observed for freebase Type A after stability evaluation.

Table 2-2.

Starting material	Condition	Time	UPLC purity (Area%)	Form
Freebase Type A	Initial	-	97.11	-
	25 ℃/60%RH	1 week	97.43	Freebase Type A
		1 month	97.11	Freebase Type A
	40 ℃/75%RH	1 week	97.32	Freebase Type A
		1 month	97.18	Freebase Type A

Table 2-3.

# Peak	RRT	Initial	25 ℃/60%RH /1 week	25 ℃/60%RH /1 month	40 ℃/75%RH /1 week	40 ℃/75%RH /1 month
1	0.63	-	-	-	-	0.05
2	0.77	0.09	0.08	0.08	0.08	0.10
3	0.86	0.38	0.31	0.36	0.32	0.26

# Peak	RRT	Initial	25 °C/60%RH /1 week	25 °C/60%RH /1 month	40 °C/75%RH /1 week	40 °C/75%RH /1 month
4	0.88	0.54	0.45	0.55	0.44	0.44
5	0.91	0.06	0.07	0.06	0.07	0.07
6	0.93	-	-	0.05	-	0.05
7	0.95	0.55	0.48	0.57	0.58	0.66
8	0.98	0.30	0.31	0.27	0.28	0.26
9	**1.00**	**97.11**	**97.43**	**97.11**	**97.32**	**97.18**
10	1.05	0.15	0.16	0.15	0.16	0.15
11	1.07	0.45	0.41	0.44	0.40	0.43
12	1.09	0.28	0.23	0.29	0.28	0.28
13	1.11	0.07	0.07	0.07	0.07	0.07

[0192] The equilibrium solubility was tested for freebase Type A in H_2O, SGF, FaSSIF, and FeSSIF at RT.

[0193] Around 5 mg material was weighed into an HPLC vial followed by addition of 1.0 mL media. The sample was transferred to slurry at 37 ℃ at 500 rpm for 24 hrs. Then the sample was centrifuged (12000 rpm, 3 min) and filtered (0.45 μm PTFE filter). Supernatant was tested by UPLC solubility and solid was tested by XRPD. The results are summarized in **Error! Reference source not found.**. The XRPD results are shown in FIG. 1K.

Table 2-4.

Material	Media	pH	Solubility (mg/mL)	Form
Freebase Type A	H_2O	8.76	0.0042	Freebase Type A
	SGF	2.59	2.8753	Amorphous
	FaSSIF	6.55	0.0509	Freebase Type A
	FeSSIF	5.15	2.6841	Amorphous

[0194] X-ray photoelectron spectroscopy (XPS) test was performed for freebase Type A. The results were summarized in Table 2-5. FIG. 1L shows XPS results for freebase Type A.

Table 2-5

Crystalline form	Binding energy of N (eV)
Freebase Type A	401.0, 399.5, 398.5

Example 3: Polymorph screen: analysis

[0195] Using Freebase Type A as starting material, a total of 100 polymorph screening experiments were performed, including vapor-solid diffusion, vapor-solution diffusion, slow cooling, slurry (RT and 50 °C), temperature cycling, slow evaporation, grinding and anti-solvent addition (see Example 4).

[0196] Based on the XRPD results of polymorph screening and further experiments, a total of eight polymorphs were obtained (freebase Types A to H). Of the eight polymorphic forms, a total of four hydrates (freebase Types A, C, D, and E) and one anhydrate (freebase Type H) were identified; the remaining three polymorph Types were solvates (freebase Types B, F, and G). The XRPD overlay of freebase Types A, C, D, E, and H is shown in FIG. 1M. The characterization results of freebase polymorphs are summarized in **Error! Reference source not found.**1.

[0197] Competitive slurry experiments were performed for hydrates freebase Type A, C, and D, and anhydrate firebase Type H in EtOH/H_2O solvent system with various water activities at RT. Based on the XRPD results, freebase Type C was obtained in EtOH and a_w 0.2~0.8 system as wet solids, which further converted to freebase Type A after drying. Freebase Type A was obtained in H_2O. The competitive slurry results suggested Type A was the lead form of freebase. The inter-conversion relationship among the freebase polymorphs is displayed in FIG. 1N, and the conversion conditions used are summarized in Table .

Table 3-1.

Type	Weight loss (%, 150 °C)	Endotherm (°C, peak)	UPLC Purity (Area%)	Form
Freebase Type A#	11.52	76.0, 194.9*	97.12%	Hydrate
Freebase Type B	13.06	84.3, 187.1*	97.84%	Solvate
Freebase Type C	4.81	80.3, 189.4*	96.85%	Hydrate
Freebase Type D	6.49	80.8, 189.4*	98.32%	Hydrate
Freebase Type E	4.49	69.7, 190.5*	96.81%	Hydrate

Type	Weight loss (%, 150 °C)	Endotherm (°C, peak)	UPLC Purity (Area%)	Form
Freebase Type F	Converted to freebase Type B after drying			Solvate
Freebase Type G	20.15	72.3, 113.3, 196.3*	96.71%	Solvate
Freebase Type H	0.87	73.6, 194.1*	N/A	Anhydrate

#: The TGA/DSC data of freebase Type A after solid vapor diffusion in water was used, since freebase Type A was a channel hydrate with variable water content under different humidity conditions, which reached the maximum after solid vapor diffusion in water.
*: Exotherm.
-: The characterization was not performed due to the limited solid amount.
N/A: The sample was obtained from freebase Type A after storage at RT and HPLC purity was not tested.

Table 3-2.

# in FIG. 1N	Method
1	Heat to 100 °C and cool to RT (~48%RH)
2	Dry at RT (~45%RH)
3	N_2 purge for 20 min
4	Exposed to air for 30 min at RT (~46%RH), competitive slurry in H_2O at RT
5	Humidity ~30%RH in VH-XRPD
6	Humidity ~20%RH and 10%RH in VH-XRPD
7	Slurry in NMP/IPA (1:4, v/v) at RT
8	Dry under vacuum at RT (room humidity ~59%RH)
9	Heat to 150 °C and cool to RT (~41%RH)
10	Competitive slurry in H_2O at RT
11	Slurry in DMSO/H_2O (1:9, v/v) at 50 °C
12	Dry at RT (~35%RH)
13	Heat to 120 °C and cool to RT, dry at RT (~56%RH)
14	Heat to 150 °C and cool to 30 °C under N_2 purge
15	Heat to 115 °C and cool to RT (~35%RH)
16	Store at RT under ~50%RH
17	Solid-vapor diffusion in different organic solvents at RT for 7 days
18	Solid-vapor diffusion in DMSO at RT for 12 days
19	Heat to 160 °C and cool to RT (~47%RH)
20	Competitive slurry in EtOH and EtOH/H_2O systems (a_w 0.2~0.8) at RT

Freebase Type A

[0198] Variable temperature XRPD (VT-XRPD) was performed for freebase Type A. The XRPD results displayed in FIG. 10A show the sample before N_2 purge had converted to freebase Type E. After N_2 purge for 20 min, freebase Type E converted to a new form, which was named as freebase Type H. A form change was observed for freebase Type E after N_2 purge, indicating that freebase Type E is a hydrate. After freebase Type H was heated to 110 ℃ and cooled to 30 ℃ under N_2 purge, no form change was observed, which indicated Type H was an anhydrate. After freebase Type H was exposed to air for 30 min (~46%RH), it converted to freebase Type A, indicating that freebase Type A is a hydrate.

[0199] Variable humidity XRPD (VH-XRPD) was performed for freebase Type A. The XRPD results in FIGS. 10B to 10D show that at humidity 50%RH~80%RH, no form change was observed for freebase Type A. When the humidity decreased to 40%RH, peak shift was observed for freebase Type A. When the humidity decreased to 30%RH, freebase Type E was observed. When the humidity decreased to 20%RH and 10%RH, freebase Type H was observed. Based on the VH-XRPD results, the inter-conversion relationship of Type A/E/H was related to humidity at RT, with Type A being stable at ≥50%RH and Type E being stable at ~30%RH, and Type E would convert to Type H at lower humidity (≤ 20%RH).

[0200] The single crystal structure of freebase Type A was further determined, which was identified as a hemiheptahydrate (molar ratio of water:freebase was 3.5:1, and the water content was consistent with the DVS water uptake of freebase Type A at 95%RH in FIG. 1C) with channels in the crystal lattice. The channel structures suggest that water can go into and out of the lattice easily without obvious change of the lattice. Similarity of freebase Type A/E/H XRPD patterns and the conversion relationship among Type A/E/H with different humidity conditions indicate that Type A/E/H have similar crystal structures with only difference in water content.

[0201] Considering that freebase Type A is a channel hydrate and the water content is affected by the humidity condition (based on DVS result), to collect representative characterization data, solid vapor diffusion in H_2O was performed for freebase Type A at RT for 5 days. XRPD, TGA, and DSC tests were performed for the sample after solid vapor diffusion. The XRPD result in FIG. 10E confirmed the sample was freebase Type A. The

TGA/DSC results (FIG. 10F) show a weight loss of 11.52% up to 150 °C and one endotherm at 76.0 °C (peak) with one exotherm at 194.9 °C (peak).

Freebase Type B

[0202] Freebase Type B was obtained via anti-solvent addition of freebase Type A in DMAc/H_2O. After drying at RT for 18 days, the sample was not completely dried, and no form change was observed. When the sample was dried at RT under vacuum for 3 days, freebase Type C was obtained. The XRPD pattern is displayed in FIG. 11A.

[0203] Freebase Type B was re-prepared via anti-solvent addition of freebase Type A in DMAc/H_2O followed by drying at RT for 13 days. The XRPD pattern is displayed in FIG. 11B. The TGA/DSC results are displayed in FIG. 5B, which show a weight loss of 13.06% up to 150 °C, one endotherm at 84.3 °C (peak) with one exotherm at 187.1 °C (peak). ^1H NMR result (FIG. 11C) showed the molar ratio of residual DMAc/API was 0.7 (7.3 wt%). The UPLC purity of freebase Type B was 97.84 area% (FIG. 11D).

[0204] In order to investigate the DSC signal, freebase Type B was heated to 150 °C and cooled to RT for XRPD test (the room humidity was ~41%RH). The XRPD results (FIG. 11E) show freebase Type B converted to freebase Type E after heated to 150 °C. ^1H NMR results (FIG. 11F) show after heated to 150 °C, the molar ratio of residual DMAc/API was 0.2 (2.3 wt%). The results indicate that freebase Type B is a DMAc solvate.

[0205] Freebase Type B was obtained via stirring freebase Type A in NMP/IPA (1:4, v/v) at RT for 4 days. After drying at RT for 18 days, the sample was not completely dried, and no form change was observed. When the sample was dried at RT under vacuum for 3 days, freebase Type C was obtained. The XRPD pattern is displayed in FIG. 11G. Since freebase Type B is a DMAc solvate and it is also obtained in another solvent system (NMP/IPA) with peak shifts, the results indicate that freebase Form B is an isomorphic form.

Freebase Type C

[0206] Freebase Type C was obtained via stirring freebase Type A (in DMSO/H_2O (1:9, v/v) at 50 °C for 3 days. The XRPD pattern is displayed in FIG. 12A. Due to limited sample amount, TGA/DSC characterization was not performed.

[0207] Freebase Type C was obtained via anti-solvent addition of freebase Type A in 1,4-Dioxane/MTBE system. XRPD result (FIG. 12B) shows the sample converted to freebase Type E after dried at RT for 12 days.

[0208] Freebase Type C was obtained via anti-solvent addition of freebase Type A in Acetone/MTBE system followed by evaporation at RT. XRPD result is shown inFIG. 12C. The TGA/DSC results are displayed inFIG. 3B, which show a weight loss of 4.81% up to 150 °C, one endotherm at 80.3 °C (peak) with one exotherm at 189.4 °C (peak). ^{1}H NMR result (FIG. 12D) shows the molar ratio of residual Acetone/API was 0.06 (0.6 wt%), the molar ratio of residual MTBE/API was 0.1 (2.0 wt%). The UPLC purity of freebase Type C was 96.85 area% (FIG. 12E).

[0209] In order to investigate the DSC signal, freebase Type C was heated to 120 °C and cooled to RT for XRPD test (the room humidity was ~56%RH). The result in FIG. 12F shows freebase Type C converted to freebase Type A after heated to 120 °C.

[0210] VT-XRPD was performed for freebase Type C. The XRPD results displayed in FIG. 12Gshow after N_2 purge for 20 min, peak shift was observed for freebase Type C. After heated to 150 °C and cooled to 30 °C under N_2 purge, freebase Type H was obtained. The results indicate that freebase Type C is a hydrate. After exposed to air for 30 min, freebase Type H converted to freebase Type A.

[0211] After stored at RT for 2 months (room humidity was ~30%RH), freebase Type C converted to freebase Type E. The XRPD pattern is displayed in FIG. 12H.

Freebase Type D

[0212] Freebase Type D was obtained via anti-solvent addition of freebase Type A in Acetone/H_2O system. The XRPD pattern was displayed inFIG. 13A. The TGA/DSC results are displayed inFIG. 13B, which show a weight loss of 4.99% up to 150 °C, one endotherm at 90.3 °C (peak) and one exotherm at 186.5 °C (peak). ^{1}H NMR result (FIG. 13C) shows the molar ratio of residual Acetone/API was 0.015 (0.1 wt%). The UPLC purity of freebase Type D was 98.30 area% (FIG. 13D).

[0213] In order to investigate the DSC signal, freebase Type D was heated to 115 ℃ and cooled to RT for XRPD test (The room humidity was ~35%RH). The result in FIG.13Eshows freebase Type D converted to freebase Type E after heated to 115 ℃.

[0214] Freebase Type D was re-prepared via anti-solvent addition of freebase Type A in Acetone/H_2O system followed by evaporation at RT. The XRPD pattern is displayed in FIG. 13F. The TGA/DSC results are displayed in FIG. 4B, which show a weight loss of 6.49% up to 150 ℃, one endotherm at 80.8 ℃ (peak) and one exotherm at 189.4 ℃ (peak). ^{1}H NMR result (FIG. 13G) shows the molar ratio of residual Acetone/API was 0.018 (0.2 wt%). The UPLC purity of freebase Type D was 98.32 area% (FIG. 13H).

[0215] VT-XRPD was performed for freebase Type D. The XRPD results displayed in FIG. 13I show after N_2 purge for 20 min, peak shift is observed for freebase Type D. After heated to 150 ℃ and cooled to 30 ℃ under N_2 purge, freebase Type H was obtained. The results indicate that freebase Type D is a hydrate. After exposed to air for 30 min, freebase Type H converted to freebase Type A.

Freebase Type E

[0216] Freebase Type E was obtained via anti-solvent addition of freebase Type A in Acetone/MTBE system followed by slurry at 5 ℃ and -20 ℃. The sample was obtained under evaporation at RT. The XRPD pattern is displayed in FIG. 2A. The TGA/DSC results are displayed in FIG. 2B, which show a weight loss of 4.49% up to 150 ℃, one endotherm at 69.7 ℃ (peak) and one exotherm at 190.5 ℃ (peak). ^{1}H NMR result (FIG. 14A) shows the molar ratio of residual Acetone/API was 0.02 (0.2 wt%), the molar ratio of residual MTBE/API was 0.02 (0.3 wt%). The UPLC purity of freebase Type E was 96.81 area% (FIG. 14B).

[0217] After stored at RT for 11 days (The room humidity was ~50%RH), freebase Type E converted to freebase Type A. XRPD result is displayed in FIG. 14C.

[0218] Freebase Type E was attempted to be re-prepared via anti-solvent addition in Acetone/MTBE system followed by vacuum drying at 50 ℃ and RT, respectively. XRPD result listed in FIG. 14D shows an amorphous form was obtained.

[0219] VT-XRPD result of freebase Type A (FIG. 10A) showed that form change was observed for freebase Type E after N_2 purge. These results indicate that freebase Type E is a hydrate.

Freebase Type F

[0220] Freebase Type F was obtained via vapor-solution diffusion of freebase Type A in DMAc/IPA. The XRPD pattern displayed in FIG. 15 shows that after dried at RT, freebase Type B was obtained. Since freebase Type B is a solvate, the results indicate that Type F is also a solvate.

Freebase Type G

[0221] Freebase Type G was obtained via vapor-solid diffusion of freebase Type A in DMSO. The XRPD pattern displayed in FIG. 16A shows freebase Type C was obtained after vapor-solid diffusion for 7 days and a new form was obtained after vapor-solid diffusion for additional 12 days, which was named as freebase Type G. The TGA/DSC results are displayed in FIG. 8, which show a weight loss of 20.15% up to 150 °C, two endotherms at 72.3 and 113.3 °C (peak) and one exotherm at 196.3 °C (peak). ^{1}H NMR result (FIG. 16B)shows the molar ratio of residual DMSO/API was 0.8 (8.6 wt%). The UPLC purity of freebase Type G was 96.71 area% (FIG. 16C).

[0222] In order to investigate the DSC signal, freebase Type G was heated to 100 °C and 160 °C and cooled to RT for XRPD test (The room humidity was ~47%RH). The result in FIG. 16D shows freebase Type G converted to freebase Type A after heated to 100 °C and 160 °C. ^{1}H NMR result (FIG. 16E and FIG. 16F) shows after heated to 100 °C, the molar ratio of residual DMSO/API was 0.03 (0.3 wt%). After heated to 160 °C, no residual solvent was observed. This result in combination with form change after heating indicate that freebase Type G is a DMSO solvate.

Freebase Type H

[0223] Freebase Type H was obtained after N_2 purge for 20 min of freebase Type E. After exposed to air for 30 min (~46%RH), freebase Type H converted to freebase Type A. The XRPD pattern is displayed in FIG. 17A**Error! Reference source not found.**. No form

change was observed for Type H after heating under N_2 purge, indicating that Form H is an anhydrate.

[0224] Another batch of freebase Type H was obtained from freebase Type A after stored at 20%RH at RT. The XRPD pattern is shown in FIG. 17B. The TGA/DSC curves are displayed in FIG. 9B**Error! Reference source not found.**, which show a weight loss of 0.87% up to 150 ℃ and one endotherm at 73.6 ℃ (peak) with one exotherm at 194.1 ℃ (peak).

Example 4: Polymorph screen: process

[0225] A total of 100 polymorph screening experiments were performed for freebase using different crystallization or solid transformation methods.

Vapor-solid diffusion

[0226] Vapor-solid diffusion experiments were conducted using 10 different solvents. Approximately 20 mg of freebase Type A was weighed into a 3-mL vial, which was placed into a 20-mL vial with 4 mL of volatile solvent. The 20-mL vial was sealed with a cap and kept at RT for 7 days allowing solvent vapor to interact with sample. The solids were tested by XRPD. The results summarized below show that freebase Type A/C/G were obtained.

No.	Solvent	Result
1	EtOH	Freebase Type A
2	IPA	Freebase Type A
3	MIBK	Freebase Type C
4	EtOAc	Freebase Type A
5	MTBE	Freebase Type C
6	2-MeTHF	Freebase Type A+C
7	ACN	Freebase Type A
8	Toluene	Freebase Type A+C
9	DMSO	Freebase Type G*
10	H_2O	Freebase Type A

*: Freebase Type C was obtained after vapor-solid diffusion for 7 days and a new form was obtained after vapor-solid diffusion for 19 days, which was named as freebase Type G.

Vapor-solution diffusion

[0227] 7 vapor-solution diffusion experiments were conducted. Approximately 25 mg of freebase Type A was dissolved in 0.5~0.7 mL of appropriate solvent to obtain a clear solution in a 3-mL vial. This solution was then placed into a 20-mL vial with 4 mL of volatile solvent. The 20-mL vial was sealed with a cap and kept at RT allowing sufficient time for organic vapor to interact with the solution. The precipitants were isolated for XRPD analysis. The results summarized below show that freebase Type A/B/C/D/E/F were obtained.

No.	Solvent	Anti-solvent	Result
1	1,4-Dioxane	IPA	Freebase Type A+E
2		MTBE	Freebase Type C
3		n-Heptane	Freebase Type A+C
4		H_2O	Freebase Type A+D
5	DMAc	IPA	Freebase Type F*
6		MTBE	Freebase Type B
7		H_2O	Freebase Type B

*: The sample was obtained under evaporation at RT.

Slow cooling

[0228] Slow cooling experiments were conducted in 7 solvent systems. 20~30 mg of freebase Type A was suspended in 1.0~2.5 mL of solvent in a 3-mL glass vial at RT. The suspension was then heated to 50 ℃, equilibrated for about 2 hrs and filtered to a new vial. Filtrates were slowly cooled down to 5 ℃ at a rate of 0.1 ℃/min. The obtained solids were kept isothermal at 5 ℃ and then solids were tested by XRPD. Results summarized below show that freebase Type A and/or C was obtained.

No.	Solvent	Result
1	EtOH	Freebase Type A*
2	MIBK	Freebase Type C#
3	EtOAc	Freebase Type A*
4	IPAc	Freebase Type A+C
5	2-MeTHF	Freebase Type A
6	ACN	Freebase Type A

No.	Solvent	Result
7	Toluene	Freebase Type A+C

*: The sample is clear under 5 °C and solid was obtained under -20 °C.
#: The sample is clear under 5 °C and -20 °C and solid was obtained after evaporation at RT.

Slurry at RT

[0229] About 20 mg of freebase Type A was suspended in 0.5 mL of solvent in an HPLC glass vial. After the suspension was stirred magnetically (1000 rpm) for 4 days at RT, the remaining solids were centrifuged for XRPD analysis. Results summarized below show that freebase Type A or B was generated.

No.	Solvent (v/v)	Result
1	MeOH/MTBE (1:1)	Freebase Type A
2	EtOH	Freebase Type A
3	Acetone/H_2O (1:1)	Freebase Type A
4	EtOAc	Freebase Type A
5	MTBE	Freebase Type A
6	THF/H_2O (1:1)	Freebase Type A
7	1,4-Dioxane/n-Heptane (1:4)	Freebase Type A
8	ACN	Freebase Type A
9	DCM/n-Heptane (1:1)	Freebase Type A
10	n-Heptane	Freebase Type A
11	Toluene	Freebase Type A
12	NMP/IPA (1:4)	Freebase Type B
13	H_2O	Freebase Type A
14	EtOH/H_2O (97:3, a_w~0.2)	Freebase Type A
15	EtOH/H_2O (93:7, a_w~0.4)	Freebase Type A
16	EtOH/H_2O (86:14, a_w~0.6)	Freebase Type A
17	EtOH/H_2O (70:30, a_w~0.8)	Freebase Type A

Slurry at 50 °C

[0230] About 20 mg of freebase Type A was suspended in 0.5 mL of solvent in an HPLC glass vial. After the suspension was stirred (1000 rpm) for about 3 days at 50 °C, the

remaining solids were centrifuged for XRPD analysis. Results summarized below show that freebase Type A or C was generated.

No.	Solvent (v/v)	Result
1	IPA	Freebase Type A
2	MIBK	Freebase Type A
3	IPAc	Freebase Type A
4	MTBE	Freebase Type A
5	2-MeTHF	Freebase Type A
6	1,4-Dioxane/MTBE (1:9)	Freebase Type A
7	ACN/IPA (1:4)	Freebase Type A*
8	$CHCl_3$/n-Heptane (1:9)	Freebase Type A
9	n-Heptane	Freebase Type A
10	Toluene	Freebase Type A
11	H_2O	Freebase Type A
12	DMSO/H_2O (1:9)	Freebase Type C

*: The sample was clear at 50 ℃ and RT. The solid was obtained under 5 ℃.

Temperature cycling

[0231] About 20 mg of freebase Type A was suspended in 0.5 mL of solvent in an HPLC glass vial. After heating-cooling (50 ℃~5 ℃, 0.1 ℃/min) was performed for the suspension for 2 cycles, the remaining solids were centrifuged for XRPD analysis. Results summarized below show that freebase Type A was generated.

No.	Solvent (v/v)	Result
1	EtOH	Freebase Type A
2	Acetone/IPA (1:4)	Freebase Type A
3	EtOAc	Freebase Type A
4	IPAc	Freebase Type A
5	MTBE	Freebase Type A
6	2-MeTHF	Freebase Type A
7	$CHCl_3$/n-Heptane (1:9)	Freebase Type A
8	n-Heptane	Freebase Type A
9	Toluene	Freebase Type A

No.	Solvent (v/v)	Result
10	H_2O	Freebase Type A
11	DMAc/MTBE (1:9)	Freebase Type A
12	ACN/MTBE (1:9)	Freebase Type A

Slow evaporation

[0232] Slow evaporation experiments were performed under 11 conditions. ~20 mg of freebase Type A was dissolved in 1.0~2.5 mL of solvent in a 3-mL glass vial. The resulting solution was subjected to slow evaporation at RT with vials sealed and poked with 4 pinholes. The solids were isolated for XRPD analysis and the results summarized below show that freebase Type A, C, and/or D was obtained.

No.	Solvent (v/v)	Result
1	MeOH	Freebase Type A
2	EtOH	Freebase Type A
3	Acetone	Freebase Type A+C
4	EtOAc	Freebase Type A
5	THF	Freebase Type A+D
6	1,4-Dioxane	Freebase Type A
7	ACN	Freebase Type A
8	$CHCl_3$	Freebase Type A
9	MeOH/H_2O (9:1)	Freebase Type A
10	Acetone/H_2O (9:1)	Freebase Type D
11	DCM/n-Heptane (9:1)	Freebase Type A

Grinding

[0233] Grinding experiments were performed with or without solvent addition. Approximately 20 mg of freebase Type A was weighed into the mortar. 20 μL solvent was added into the mortar. The solids were grinded for 3~5 min. The solids were isolated for XRPD analysis. Results summarized below show that freebase Type A was obtained.

No.	Solvent	Result
1	NA	Freebase Type A

2	H_2O	Freebase Type A

Anti-solvent Addition

[0234] A total of 22 anti-solvent addition experiments were carried out. 15~20 mg of freebase Type A was dissolved in 0.5~1.6 mL solvent to obtain a clear solution and the solution was magnetically stirred (~1000 rpm) followed by addition of anti-solvent until precipitate appeared or the total amount of anti-solvent reached 10.0 mL. The samples without precipitate were transferred to slurry at 5 ℃ and then transferred to slurry at -20 ℃. The clear samples were transferred to RT for evaporation. The solids were isolated for XRPD analysis. Results summarized below show that freebase Type A, B, C, D, and/or E was obtained.

No.	Solvent	Anti-solvent	Result
1	Acetone	IPA	Freebase Type E*#
2	THF		Freebase Type C*
3	ACN		Freebase Type E*#
4	$CHCl_3$		Freebase Type E*#
5	MeOH	MTBE	Freebase Type A+E*
6	Acetone		Freebase Type E*#
7	1,4-Dioxane		Freebase Type C
8	DCM		Freebase Type A
9	NMP		Freebase Type B*
10	EtOH	n-Heptane	Freebase Type A
11	Acetone		Freebase Type A
12	THF		Freebase Type D
13	1,4-Dioxane		Freebase Type A
14	Toluene		Freebase Type A
15	DCM		Freebase Type A
16	MeOH	H_2O	Freebase Type D
17	Acetone		Freebase Type D
18	THF		Freebase Type D
19	1,4-Dioxane		Freebase Type D
20	ACN		Freebase Type D
21	NMP		Freebase Type B

No.	Solvent	Anti-solvent	Result
22	DMAc		Freebase Type B

*: The sample is clear under RT, 5 ℃ and -20 ℃ and solid was obtained after evaporation at RT.
#: After storage at RT for 11 days, the sample converted to freebase Type A.

Example 5: Interconversion relationship study

[0235] Four hydrate freebase Types A, C, D, and E and one anhydrate freebase Type H were obtained. In order to investigate the inter-conversion relationship between hydrates and anhydrate, competitive slurry experiments were performed.

[0236] Competitive slurry experiments were firstly performed for hydrate freebase Types A and D in EtOH/H_2O system with various water activities at RT. Approximately 15 mg of freebase Type A was weighed into each HPLC vial followed by addition of 1.0 mL solvent with various water activities. After slurry at RT for 2 hrs, the samples were filtered with 0.45 μm PTFE filter. The filtrates were transferred into the HPLC vials containing freebase Type A and freebase Type D followed by slurry at RT before XRPD test. The results are summarized in **Error! Reference source not found.**, and the XRPD results are displayed in FIGS. 18A and 18B (the wide diffraction peak near 25° (2θ) was produced by test with film). The results showed that freebase Type C was obtained in EtOH and a_w 0.2~0.8 systems at RT. Freebase Type A was obtained in H_2O. After the film was removed, XRPD results (FIG. 18C and 18D) showed freebase Type A was obtained in EtOH and a_w 0.2~0.8 systems at RT after drying. Freebase Type A was obtained in H_2O at RT after drying.

[0237] To further confirm the results, competitive slurry experiments were re-performed for hydrate freebase Types A, C, and D in EtOH/H_2O system with various water activities at RT. The results are summarized in **Error! Reference source not found.**, and the XRPD results are displayed in FIG. 18E (the wide diffraction peak near 25° (2θ) was produced by test with film). The results showed that freebase Type C was obtained in EtOH and a_w 0.2~0.8 systems at RT.

[0238] After freebase Type H was obtained, it was added into the competitive slurry experiments in **Error! Reference source not found.** and in water system followed by slurry at RT for 1 day. The XRPD overlay (FIGS. 18F and 18G) show the same results after Type H addition.

Table 5-1

No.	Starting material	Solvent (v/v)	Temp.	Time	Wet solid result	Dry solid result
1	Freebase Type A/D	EtOH	RT	5 days	Freebase Type C*	Freebase Type A
2		EtOH/H_2O (97:3, a_w~0.2)		5 days	Freebase Type C*	Freebase Type A
3		EtOH/H_2O (93:7, a_w~0.4)		5 days	Freebase Type C*	Freebase Type A
4		EtOH/H_2O (86:14, a_w~0.6)		5 days	Freebase Type C*	Freebase Type A
5		EtOH/H_2O (7:3, a_w~0.8)		5 days	Freebase Type C*	Freebase Type A
6		H_2O		9 days	Freebase Type A	Freebase Type A

*: Slight peak shift was observed.

Table 5-2

No.	Starting material	Solvent (v/v)	Temp.	Time	Wet solid result
1	Freebase Type A/C/D	EtOH	RT	2 days	Freebase Type C*
2		EtOH/H_2O (97:3, a_w~0.2)		2 days	Freebase Type C*
3		EtOH/H_2O (93:7, a_w~0.4)		2 days	Freebase Type C*
4		EtOH/H_2O (86:14, a_w~0.6)		2 days	Freebase Type C*
5		EtOH/H_2O (7:3, a_w~0.8)		2 days	Freebase Type C*

*: Slight peak shift was observed.

CLAIMS

What is claimed is:

1. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern comprising peaks at angle 2-theta of about 6.9, about 15.0, and about 22.4 as measured at between about 50% to about 80% relative humidity at room temperature; (ii) an XRPD pattern comprising peaks at angle 2-theta of about 7.1, about 14.0, and about 22.5 as measured at about 30% relative humidity at room temperature; and/or (iii) an XRPD pattern comprising peaks at angle 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5 as measured at less than about 20% relative humidity at room temperature.
2. The crystalline form of claim 1, characterized by having (i) an XRPD pattern substantially as shown in FIG. 1A as measured at between about 50% to about 80% relative humidity at room temperature; (ii) an XRPD pattern substantially as shown in FIG. 2A as measured at about 30% relative humidity at room temperature; and/or (iii) an XRPD pattern substantially as shown in FIG. 9A as measured at less than about 20% relative humidity at room temperature.
3. The crystalline form of claim 1 or 2, wherein the crystalline form is a channel hydrate.
4. The crystalline form of any one of claims 1 to 3, characterized by having an XRPD pattern of freebase Form A substantially as shown in FIG. 1A as measured at between about 50% to about 80% relative humidity at room temperature.
5. The crystalline form of any one of claims 1 to 4, characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 6.9, about 15.0, and about 22.4 as measured at between about 50% to about 80% relative humidity at room temperature.
6. The crystalline form of any one of claims 1 to 4, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.9, about 7.5, about 12.8, about 13.8, about 14.0, about 15.0, about 17.4, about 19.3, about 20.7, and about 22.4 as measured at between about 50% to about 80% relative humidity at room temperature.
7. The crystalline form of any one of claims 1 to 6, characterized by having (i) a DSC graph comprising an endothermic peak at about 76.0 °C; (ii) a DSC graph comprising an exothermic peak at about 194.9 °C; (iii) a DSC graph substantially as shown in FIG. 1B; (iv) a TGA graph substantially as shown in FIG. 1B; (v) a DVS graph

substantially as shown in FIG. 1C; and/or (vi) the molar ratio of water:Compound 1 of about 3.5:1.

8. The crystalline form of any one of claims 1 to 3, characterized by having an XRPD pattern of freebase Form E substantially as shown in FIG. 2A as measured at about 30% relative humidity at room temperature.

9. The crystalline form of any one of claims 1 to 3 and 8, characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 7.1, about 14.0, and about 22.5 as measured at about 30% relative humidity at room temperature.

10. The crystalline form of any one of claims 1 to 3, 8, and 9, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 7.1, about 11.1, about 12.6, about 14.0, about 14.6, about 15.6, about 20.3, and about 22.5 as measured at about 30% relative humidity at room temperature.

11. The crystalline form of any one of claims 1 to 3 and 8 to 10, characterized by having (i) a DSC graph comprising an endothermic peak at about 69.7 °C; (ii) a DSC graph comprising an exothermic peak at about 190.5 °C; (iii) a DSC graph substantially as shown in FIG. 2B; and/or (iv) a TGA graph substantially as shown in FIG. 2B.

12. The crystalline form of claim 1 or 2, wherein the crystalline form is an anhydrate.

13. The crystalline form of claim 1, 2, or 12, characterized by having an XRPD pattern of freebase Form H substantially as shown in FIG. 9A as measured at less than about 20% relative humidity at room temperature.

14. The crystalline form of any one of claims 1, 2, 12, and 13, characterized by having an XRPD pattern comprising peaks at angle 2-theta of about 7.2, about 14.1, about 15.9, and about 22.5 as measured at less than about 20% relative humidity at room temperature.

15. The crystalline form of any one of claims 1, 2, and 12 to 14, characterized by having an XRPD pattern comprising peaks at angles 2-theta of about 6.5, about 7.2, about 11.2, about 13.8, about 14.1, about 14.5, about 15.9, about 21.8, and about 22.5 as measured at less than about 20% relative humidity at room temperature.

16. The crystalline form of any one of claims 1, 2, and 12 to 15, characterized by having (i) a DSC graph comprising an endothermic peak at about 73.6 °C; (ii) a DSC graph comprising an exothermic peak at about 194.1 °C; (iii) a DSC graph substantially as shown in FIG. 9B; and/or (iv) a TGA graph substantially as shown in FIG. 9B.

17. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-

4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form C substantially as shown in FIG. 3A; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Tables C-1 or C-2; (iii) an XRPD pattern comprising peaks at angle 2-theta of about 6.7, about 14.9, and about 22.2; (iv) a DSC graph comprising an endothermic peak at about 80.3 °C; (v) a DSC graph comprising an exothermic peak at about 189.4 °C; (vi) a DSC graph substantially as shown in FIG. 3B; and/or (v) a TGA graph substantially as shown in FIG. 3B.

18. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form D substantially as shown in FIG. 4A; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table D; (iii) an XRPD pattern comprising peaks at angle 2-theta of about 6.7, 13.3, 14.6, and 23.3; (iv) a DSC graph comprising an endothermic peak at about 80.8 °C; (v) a DSC graph comprising an exothermic peak at about 189.4 °C; (vi) a DSC graph substantially as shown in FIG. 4B; and/or (vii) a TGA graph substantially as shown in FIG. 4B.

19. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form B substantially as shown in FIG. 5A; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table B-1 or B-2; (iii) an XRPD pattern comprising peaks at angle 2-theta of about 6.2, about 14.7, and about 22.3; (iv) a DSC graph comprising an endothermic peak at about 84.3 °C; (v) a DSC graph comprising an exothermic peak at about 187.1 °C; (vi) a DSC graph substantially as shown in FIG. 5B; and/or (vii) a TGA graph substantially as shown in FIG. 5B.

20. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form F substantially as shown in FIG. 6; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as

recited in Table F; and/or (iii) an XRPD pattern comprising peaks at angle 2-theta of about 6.2, about 6.7, and about 13.4.

21. A crystalline form of 1-((R)-3-((7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)pyrrolidin-1-yl)prop-2-en-1-one (Compound 1), characterized by having (i) an XRPD pattern of freebase Form G substantially as shown in FIG. 7; (ii) an XRPD pattern comprising one or more peaks at about angles 2-theta in degrees as recited in Table G; (iii) an XRPD pattern comprising peaks at angle 2-theta of about 7.0, about 13.8, about 15.4, and about 22.2; (iv) a DSC graph comprising an endothermic peak at about 72.3 °C; (v) a DSC graph comprising an endothermic peak at about 113.3 °C; (vi) a DSC graph comprising an exothermic peak at about 196.3 °C; (vii) a DSC graph substantially as shown in FIG. 8; and/or (viii) a TGA graph substantially as shown in FIG. 8.

22. The crystalline form of any one of claims 1 to 21, wherein the purity of the crystalline form is at least about 95%.

23. A pharmaceutical composition comprising a crystalline form of any one of claims 1 to 22, and a pharmaceutically acceptable excipient.

24. A method of treating cancer in a subject in need thereof, the method comprising: administering a therapeutically effective amount of the crystalline form of any one of claims 1 to 22, or the pharmaceutical composition of claim 23, to the subject.

25. The method of claim 24, wherein the cancer is a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer.

26. The method of claim 24 or 25, wherein the cancer is glioblastoma multiforme, lower grade glioma, head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, brain

lower grade glioma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma, metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, glioma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma.

27. The method of any one of claims 24 to 26, wherein the cancer is a non-small cell lung cancer (NSCLC).

28. The method of any one of claims 24 to 27, wherein the cancer is a KRAS G12C mediated cancer.

29. The method of any one of claims 24 to 28, wherein the subject has been diagnosed as having a KRAS G12C mediated cancer.

30. The method of any one of claims 24 to 29, wherein the subject is human.

31. A method of preparing a crystalline form of any one of claims 1 to 22, the method comprising:

(i) contacting Compound 1 with one or more solvents to form a mixture; and

(ii) crystallizing Compound 1.

32. A method of preparing a crystalline form of any one of claims 1 to 22, wherein the method comprises:

(i) placing a sample comprising a solid form of Compound 1 in a first container;

(ii) placing the first container of step (i) inside a second container containing a solvent; and

(iii) allowing vapor from the solvent to interact with the sample in the first container.

33. A method of preparing a crystalline form of any one of claims 1 to 22, wherein the method comprises:

(i) dissolving Compound 1 in a first solvent in a first container;

(ii) placing the first container of step (i) inside a second container containing a second solvent;

(iii) sealing the second container of step (ii);

(iv) allowing vapor of the second solvent to interact with Compound 1 in the first container to form precipitant; and

(v) isolating the precipitant of step (iv) from the first solvent and/or the second solvent.

34. A method of preparing a crystalline form of any one of claims 1 to 22, wherein the method comprises:

(i) preparing a suspension of Compound 1 in a solvent;

(ii) heating the suspension of step (i) to a first temperature;

(iii) filtering the suspension of step (ii) to obtain filtrate;

(iv) cooling the filtrate of step (iii) to a second temperature.

35. A method of preparing a crystalline form of any one of claims 1 to 22, wherein the method comprises:

(i) preparing a suspension of Compound 1 in solvent; and

(ii) stirring the suspension of step (i) at a temperature for a duration.

36. A method of preparing a crystalline form of any one of claims 1 to 22, wherein the method comprises:

(i) preparing a suspension of Compound 1 in a solvent;

(ii) heating the suspension to a first temperature and cooling the suspension to a second temperature; and

(iii) heating the suspension to a third temperature, and cooling the suspension to a fourth temperature.

37. A method of preparing a crystalline form of any one of claims 1 to 22, wherein the method comprises:

(i) dissolving Compound 1 in a solvent; and

(ii) evaporating the solvent of step (i) at a temperature.

38. A method of preparing a crystalline form of any one of 1 to 22, wherein the method comprises grinding Compound 1.

39. A method of preparing a crystalline form of any one of 1 to 22, wherein the method comprises:

(i) adding Compound 1 to a solvent to form a first mixture; and

(ii) adding an anti-solvent to the first mixture to form a second mixture.