From a cost and operational standpoint, use of column chromatography for large scale manufacture of drug substance is unsuitable. Therefore, there is a need to identify a scalable process that can produce Compound 1 that meets regulatory and other purity requirements and is cost effective on large scale, including commercial scale.

The polymorphic behavior of small molecule drugs can be critical in pharmacology since the same small molecule can have different physical properties as a result of the arrangement of molecules in the crystal lattice. These different properties can affect pharmaceutical parameters such as storage stability, compressibility, density, hygroscopy, dissolution rates, and bioavailability. It is known that one polymorph can convert into another polymorph, and in some cases this happens spontaneously. Accordingly, there is a need to find a thermodynamically stable polymorph of a small molecule drug. The present disclosure fulfills these and related needs.

Summary

The present disclosure may provide for a process for the synthesis of Compound 1 that is suitable for large scale synthesis of Compound 1 in a cost -effective manner. The process is based, in part, on the discovery by Applicant that Compound 1 can form amine solvates with certain organic amines. Formation of such amine solvates by Compound 1 enables removal of certain impurities generated in the synthesis of Compound 1, to provide Compound 1 in high purity without the need for column chromatography.

There is provided a crystalline form of Compound 1, designated as Form A polymorph, having an X-ray powder diffraction pattern comprising peaks at angular positions 15.8 and 18.6, wherein the angular positions may vary by + 0.2° 2θ as measured by X-ray powder diffraction at ambient temperature using (Cu Kα) an X-ray wavelength of 1.5418 Å. In an example, the X-ray powder diffraction is determined at about 23 °C to about 25 °C.

There is also provided an amine solvate of Compound 1, wherein the amine is: (i) NHR^1R^2 where (1) R^1 is hydrogen and R^2 is C_2-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; (2) R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl and R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; or (3) R^1 and R^2 together with the nitrogen atom to which they are attached form cyclylamine; or

(ii) R^3R^4N-$(CH_2)_n$-NR^5R^6 where n is an integer selected from 1 to 6 and R^3, R^4, R^5, and R^6 are independently H, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl.

In one aspect, provided is an amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, wherein the amine is:

(i) NHR^1R^2 where (1) R^1 is hydrogen and R^2 is C_2-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; (2) R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl and R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; or (3) R^1 and R^2 together with the nitrogen atom to which they are attached form cyclylamine; or

(ii) R^3R^4N-$(CH_2)_n$-NR^5R^6 where n is an integer selected from 1 to 6 and R^3, R^4, R^5, and R^6 are independently H, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl.

There is also provided a crystalline form of a diethylamine solvate of Compound 1, designated as Form B polymorph, having an X-ray powder diffraction pattern comprising peaks at angular positions 13.8 and 21.3, wherein the angular positions may vary by + 0.2° 2θ as measured by X-ray powder diffraction at ambient temperature using (Cu Kα) an X-ray wavelength of 1.5406 Å. In an example, the X-ray powder diffraction is determined at about 23°C to about 25 °C.

There is also provided a process of preparing an amine solvate of Compound 1, wherein the amine is:

(i) NHR^1R^2 where (1) R^1 is hydrogen and R^2 is C_2-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; (2) R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl and R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; or (3) R^1 and R^2 together with the nitrogen atom to which they are attached form cyclylamine; or

(ii) R^3R^4N-$(CH_2)_n$-NR^5R^6 where n is an integer selected from 1 to 6 and R^3, R^4, R^5, and R^6 are independently H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl, comprising:

(a1) contacting Compound 1 with the amine NHR^1R^2 or R^3R^4-N-$(CH_2)_n$-R^5R^6 where R^1, R^2, R^3, R^4, R^5, and R^6, and n are as defined in (i) and (ii), respectively, in the presence or absence of one or more suitable organic solvents;

(b1) optionally adding (i) one or more anti-solvents and/or (ii) a solid crystalline seed of Compound 1, or a solid crystalline seed of the amine solvate of Compound 1, or a combination thereof, to the mixture of Step (a1) to precipitate the amine solvate of Compound 1;

(c1) isolating the solid of Step (b1) to obtain a solid amine solvate of Compound 1; and

(d1) optionally converting the amine solvate of Compound 1 from any one of Steps (a1) to (c1) to Compound 1.

In another aspect, provided is a process of preparing an amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile)-benzonitrile, wherein the amine is:

(i) NHR^1R^2 where (1) R^1 is hydrogen and R^2 is C_2-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; (2) R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl and R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; or (3) R^1 and R^2 together with the nitrogen atom to which they are attached form cyclylamine; or

(ii) R^3R^4N-$(CH_2)_n$-NR^5R^6 where n is an integer selected from 1 to 6 and R^3, R^4, R^5, and R^6 are independently H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl, comprising:

(a1) contacting 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile with the amine NHR^1R^2 or R^3R^4-N-$(CH_2)_n$-R^5R^6 in the presence or absence of one or more suitable organic solvents;

(b1) optionally adding (i) one or more anti-solvent and/or (ii) a solid crystalline seed of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, or a solid crystalline seed of the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, or a combination thereof, to the mixture of Step (a1) to precipitate the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

(c1) isolating the solid of Step (b1) to obtain a solid amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile; and

(d1) optionally converting the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile from any one of Steps (a1) to (c1) to 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile.

Provided is the process as defined herein, further comprising preparing the Compound 1 of Step (a1), comprising:

(a) treating 3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile with a deoxyfluorinating agent, with or without a base, in a suitable organic solvent and optionally in the presence of triethylamine trihydrofluoride ($Et_3N \cdot 3HF$); and

(b) purifying the mixture from Step (a) to obtain Compound 1.

There is also provided a process of preparing crystalline Form B polymorph of a diethylamine solvate of Compound 1 as described in Embodiments C1 to C9 (disclosed herein below), comprising:

(a2) contacting 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile (Compound 1) with diethylamine, in the presence or absence of one or more suitable organic solvents;

(b2) optionally adding (i) one or more anti-solvents and/or (ii) a crystalline seed of Compound 1, or a solid crystalline seed of the amine solvate of Compound 1, or a combination thereof, to the mixture of Step (a2) to precipitate crystalline Form B polymorph of the diethylamine solvate of Compound 1; and

(c2) isolating the crystalline Form B polymorph of the diethylamine solvate of Compound 1; and

(d2) optionally converting the crystalline Form B polymorph of the diethylamine solvate of Compound 1 from Step (c2) to Compound 1.

There is also provided a process of preparing crystalline Form A polymorph of Compound 1 (as defined in Embodiment A1 to A11 herein below), from diethylamine solvate of Compound 1, comprising:

(a3) removing diethylamine from the diethylamine solvate of Compound 1; and

(b3) optionally recrystallizing crystalline Form A polymorph of Compound 1 obtained from Step (a3).

In another aspect, provided is a process of preparing a crystalline form of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, designated as Form A polymorph, having an X-ray powder diffraction pattern comprising peaks at angular positions 15.8 and 18.6, wherein the angular positions may vary by + 0.2^{o} 2θ as measured by X-ray powder diffraction at ambient temperature using (Cu Kα) an X-ray wavelength of 1.5418 Å, from diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, comprising:

(a3) removing of the diethylamine from the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile; and

(b3) optionally recrystallizing the crystalline Form A polymorph of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile obtained from Step (a3).

There is also provided a process of making crystalline Form A polymorph of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile (Compound 1), comprising:

(a4) contacting a solution of Compound 1 in one or more suitable organic solvents with one or more anti-solvents;

(b4) optionally adding a solid crystalline seed of Compound 1; and

(c4) isolating the crystalline Form A polymorph of Compound 1 from the mixture.

There is also provided a process for making Compound 1 from 3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile comprising:

(a5) treating 3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile with perfluorobutanesulfonyl

fluoride (PBSF) and $Et_3N \cdot 3HF$ in the presence of an organic base, in one or more suitable organic solvents;

(b5) purifying the mixture from Step (a5) to obtain Compound 1;

(c5) optionally converting Compound 1 from Step (b5) to an amine solvate as defined herein or any examples thereof disclosed herein below; and

(d5) optionally converting the amine solvate of Compound 1 obtained from Step (c5) to crystalline Form A polymorph of Compound 1 as disclosed herein or any examples thereof disclosed herein below.

In another aspect, provided is a process for preparing 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile comprising:

(a5) treating 3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile with a perfluorobutanesulfonyl fluoride and $Et_3N \cdot 3HF$ in the presence of an organic base, in a suitable organic solvent; and

(b5) purifying the mixture from Step (a5) to obtain 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile.

There is also provided a solid composition comprising a diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile and 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, wherein the % weight ratio of the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile ("DEA solvate of Compound 1") to 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile (Compound 1) in the composition is about 1 part DEA solvate to 9 or fewer parts Compound 1. In an example, provided is a solid composition comprising a diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile and 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, wherein the % weight ratio of the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile to 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile in the composition is from about 1:9 to about 1:0.001.

In another aspect, provided is a solid composition comprising a diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile and 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, wherein the % weight ratio of the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)-benzonitrile to 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile in the composition is from:

(i) about 1:9 to about 1:0.001; or

(ii) about 1:0.25 to about 1:0.001; or

(iii) about 1:0.05 to about 1:0.001.

There is also provided a method of treating a disease treatable by inhibition of HIF-2α in a patient, preferably the patient is in need of such treatment, which method comprises administering to the patient, preferably a patient in need of such treatment, a therapeutically effective amount of crystalline Form A polymorph of Compound 1 as defined herein or any one of examples thereof disclosed herein in a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

In one example, the disease is cancer, such as renal cancer, clear cell renal cell carcinoma, liver cancer, hepatocellular carcinoma (HCC), pancreatic cancer, pancreatic neuroendocrine tumor, gastric cancer, ovarian cancer, non-small cell lung

cancer, colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), biliary tract cancer (BTC), glioblastoma (*see* PNAS 2017, 114, E6137-E6146), neuroblastoma, pheochromocytomas and paragangliomas (*see* European Journal of Cancer 2017, 86, 1-4), somatostatinomas, hemangioblastomas, gastrointestinal stromal tumors (GIST), pituitary tumors, leiomyomas, leiomyosarcomas, polycythaemia, retinal tumors, cancers with one or more EPAS1/HIF2A mutations such as uterine cancer, pheochromocytoma/paraganglioma, melanoma, stomach cancer, lung adenocarcinoma, esophagus cancer, lung squamous cancer, ovarian cancer, cervical cancer, head & neck cancer, liver cancer, colorectal cancer, breast cancer, renal cell carcinoma, diffuse large B-cell lymphoma, glioblastoma, thymoma, prostate cancer, pancreatic cancer, sarcoma, and low-grade gliomas, and cancers with one or more ELOC/TCEB1 mutations such as prostate cancer, uterine cancer, liver cancer, breast cancer, pancreatic cancer, ovarian cancer, lung adenocarcinoma, head and neck cancer, stomach cancer, sarcoma cancer, colorectal cancer, lung squamous cancer, esophagus cancer, diffuse large B-cell lymphoma, melanoma, renal cell carcinoma, cervical cancer, pheochromocytoma/paraganglioma, adenoid cystic carcinoma, acute myeloid leukemia, glioblastoma, and low-grade gliomas.

In another example, non-cancer diseases that could benefit from Hif-2α inhibition include VHL (von Hippel-Lindau) disease (*see* Oncotarget, 2015, 6, 23036-23037), PAH (pulmonary artery hypertension) (*see* Mol. Cell. Biol. 2016, 36, 1584-1594), esophagitis, reflux esophagitis (*see* Current Opinion in Pharmacology 2017, 37: 93-99), hepatic steatosis (*see* Nature Medicine 2017, 23, 1298-1308), NASH, inflammatory disease such as inflammatory bowel disease (*see* Nature Reviews gastroenterology & Hepatology 2017, 14, 596), autoimmune disease such as Graft-versus-Host-Disease (*see* Blood, 2015, 126, 1865), and iron overload.

There is also provided a pharmaceutical composition comprising crystalline Form A polymorph of Compound 1 as defined herein or any one of examples thereof disclosed herein; and a pharmaceutically acceptable excipient.

There is also provided a pharmaceutical composition prepared with crystalline Form A polymorph of Compound 1 as defined herein or any one of the examples thereof disclosed herein; and a pharmaceutically acceptable excipient.

There is also provided a method of inhibiting HIF2α which method comprises contacting HIF2α with crystalline Form A polymorph of Compound 1 as defined herein or any one of examples thereof disclosed herein; or contacting HIF2α with a pharmaceutical composition comprising crystalline Form A polymorph of

Compound 1 as defined herein or any one of examples thereof disclosed herein, and a pharmaceutically acceptable excipient.

There is also provided a crystalline Form A polymorph of Compound 1 as defined herein or any one of examples thereof disclosed herein for use in the treatment of a disease mediated by HIF-2a. In an example, the disease are those disclosed herein including those disclosed above.

In any of the aforementioned involving the treatment of cancer, provided are further examples comprising administering crystalline Form A polymorph of Compound 1 as defined herein or any one of the examples thereof, in combination with at least one additional anticancer agent such as an EGFR inhibitor gefitinib, erlotinib, afatinib, icotinib, neratnib, rociletinib, cetuximab, panitumumab, zalutumumab, nimotuzumab, or matuzumab. In another example, the crystalline Form A polymorph of Compound 1 as defined herein or any one of the examples thereof, is administered in combination with a HER2/neu inhibitor including lapatinib, trastuzumab, and pertuzumab. In another example, the crystalline Form A polymorph of Compound 1 as defined herein or any one of the examples thereof, is administered in combination with a PI3k/mTOR inhibitor including idelalisib, buparlisib, BYL719, and LY3023414. In another example, the crystalline Form A polymorph of Compound 1 as defined herein or any one of examples thereof, is administered in combination with a VEGF inhibitor such as bevacizumab, and/or a multi-tyrosine kinase inhibitors such as sorafenib, sunitinib, pazopanib, and cabozantinib. In another example, the crystalline Form A polymorph of Compound 1 as defined herein or any one of the examples thereof, is administered in combination with an immunotherapeutic agents such as PD-1 and PD-L1 inhibitors, CTLA4 inhibitors, IDO inhibitors, TDO inhibitors, A2A agonists, A2B agonists, STING agonists, RIG-1 agonists, Tyro/Axl/Mer inhibitors, glutaminase inhibitors, arginase inhibitors, CD73 inhibitors, CD39 inhibitors, TGF-β inhibitors, IL-2, interferon, PI3K-γ inhibitors, CSF-1R inhibitors, GITR agonists, OX40 agonists, TIM-3 antagonists, LAG-3 antagonists, CAR-T therapies, and therapeutic vaccines. When combination therapy is used, the agents can be administered simultaneously or sequentially.

What is Claimed:

1. An amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, wherein the amine is:

(i) NHR^1R^2 where (1) R^1 is hydrogen and R^2 is C_2-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; (2) R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl and R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; or (3) R^1 and R^2 together with the nitrogen atom to which they are attached form cyclylamine; or

(ii) R^3R^4N-$(CH_2)_n$-NR^5R^6 where n is an integer selected from 1 to 6 and R^3, R^4, R^5, and R^6 are independently H, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl.

2. The amine solvate of claim 1, wherein R^1 is C_1-C_6 alkyl and R^2 is C_1-C_6 alkyl.

3. The amine solvate of claim 1 or 2, wherein the amine is diethylamine.

4. The amine solvate of claim 3, wherein the stoichiometric ratio of the diethylamine to 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]-inden-7-yl)oxy)benzonitrile in the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)-benzonitrile is about 1:1 or is 1:1.

5. The amine solvate of any one of claims 1 to 4, wherein the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]-inden-7-yl)oxy)benzonitrile is a solid.

6. The amine solvate of claim 5, wherein the amine solvate is a diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile and has a crystalline form designated as Form B polymorph, having an X-ray powder diffraction pattern comprising peaks at angular positions 13.8 and 21.3, wherein the angular positions may vary by + 0.2° 2θ as measured by X-ray powder diffraction at ambient temperature using (Cu Kα) an X-ray wavelength of 1.5406 Å.

7. The amine solvate of claim 6, wherein the Form B X-ray powder diffraction pattern further comprises:

(i) a peak at angular position 8.4, wherein the angular position may vary by ± 0.2° 2θ; or

(ii) peaks at angular positions 8.4 and 23.5, wherein the angular positions may vary by ± 0.2° 2θ; or

(iii) peaks at angular positions 8.4, 23.5, and 11.7, wherein the angular positions may vary by ± 0.2° 2θ; or

(iv) peaks at angular positions 8.4, 23.5, 11.7, and 9.5, wherein the angular positions may vary by + 0.2° 2θ.

8. The amine solvate of claim 6, having an X-ray powder diffraction pattern substantially identical as shown in Fig 1.

9. A process of preparing an amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile)-benzonitrile, wherein the amine is:

(i) NHR^1R^2 where (1) R^1 is hydrogen and R^2 is C_2-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; (2) R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl and R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl-C_{1-6} alkyl; or (3) R^1 and R^2 together with the nitrogen atom to which they are attached form cyclylamine; or

(ii) R^3R^4N-$(CH_2)_n$-NR^5R^6 where n is an integer selected from 1 to 6 and R^3, R^4, R^5, and R^6 are independently H, C_1-C_6 alkyl or C_3-C_7 cycloalkyl, comprising:

(a1) contacting 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile with the amine NHR^1R^2 or R^3R^4-N-$(CH_2)_n$-R^5R^6 in the presence or absence of one or more suitable organic solvents;

(b1) optionally adding (i) one or more anti-solvent and/or (ii) a solid crystalline seed of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, or a solid crystalline seed of the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, or a combination thereof, to the mixture of Step (a1) to precipitate the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile;

(c1) isolating the solid of Step (b1) to obtain a solid amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile; and

(d1) optionally converting the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile from any one of Steps (a1) to (c1) to 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile.

10. The process of claim 13, wherein the amine is added to a mixture of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile in one or more suitable organic solvents in Step (a1).

11. The process of claim 9 or 10, wherein the amine is diethylamine.

12. The process of any one of claims 9 to 11, wherein:

(i) one or more anti-solvents are added to the mixture of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile of Step (a1); or

(ii) one or more anti-solvents and a solid crystalline seed of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile and/or a solid crystalline seed of the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile are added to the solution of Step (a1);

to obtain a solid amine solid of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile.

13. The process of claim 12, wherein the one or more anti-solvents are independently selected from alkanes and water.

14. The process of claim 12 or 13, wherein the anti-solvent is n-heptane.

15. The process of any one of claims 9 to 14, wherein the one or more suitable organic solvents of Step (a1) are polar organic solvents independently selected from the group consisting of alcohols, ethers, toluene, ketones, esters, halogenated alkanes, nitromethane, N-methylpyrrolidinone, acetonitrile, dimethylformamide, and dimethylacetamide.

16. The process of any one of claims 9 to 14, wherein the one or more suitable organic solvents of Step (a1) are independently selected from the group consisting of methanol, n-propanol, isopropanol, n-butanol, 1,2-propanediol, methylene dichloride, chloroform, 1,2-dichloroethane, diethyl ether, diisopropyl ether, methyl *tert*-butyl ether (MTBE), methyl *tert*-amyl ether, methyl acetate (MeOAc), ethyl acetate (EtOAc), n-propylacetate, isopropylacetate (IPAc), butyl acetate, n-methyl pyrrolidinone (NMP), dimethyl formamide (DMF), dimethylacetamide (DMAc), tetrahydrofuran (THF), 2-methyl THF (2-MeTHF), dimethoxyethane (DME), toluene, acetone, methyl ethyl ketone (MEK), nitromethane, acetonitrile (ACN), and 1,4-dioxane.

17. The process of any one of claims 9 to 16, wherein the suitable organic solvent of Step (a1) is MTBE.

18. The process of any one of claims 11 to 17, wherein the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile is a crystalline solid.

19. The process of claim 18, wherein the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile is crystalline Form B polymorph having an X-ray powder diffraction pattern of any one of claims 6 to 8.

20. The process of any one of claims 9 to 19, wherein the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile is converted to 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile.

21. The process of any one of claims 9 to 20, further comprises preparing the 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile of Step (a1), comprising:

(a) treating 3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile with a deoxyfluorinating agent with or without a base, in a suitable organic solvent and optionally in the presence of triethylamine trihydrofluoride ($Et_3N.3HF$);

(b) purifying the mixture from Step (a) to obtain 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile.

22. The process of claim 21, wherein the deoxyfluorinating agent is pyridine-2-sulfonyl fluoride, perfluoro-1-butanesulfonyl fluoride, bis(2-methoxyethylamino)-sulfur trifluoride, or (diethylamino)sulfur trifluoride and the organic base is (*tert*-butylimino)tris-(pyrrolidino)phosphorane or 2-tert-butyl-1,1,3,3-tetramethyl-guanidine or 1,8-diazabicyclo-[5.4.0]undec-7-ene, or 7-methyl-1,5,7-triaza-bicyclo-[4.4.0]dec-1-ene.

23. A process of preparing a crystalline form of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, designated as Form A polymorph, having an X-ray powder diffraction pattern comprising peaks at angular positions 15.8 and 18.6, wherein the angular positions may vary by + 0.2^o 2θ as measured by X-ray powder diffraction at ambient temperature using (Cu Kα) an X-ray wavelength of 1.5418 Å, from diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, comprising:

(a3) removing of the diethylamine from the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile; and

(b3) optionally recrystallizing the crystalline Form A polymorph of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile obtained from Step (a3).

24. The process of claim 23, wherein the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile is crystalline Form B polymorph of any one of claims 6 to 8.

25. The process of claim 23 or 24, wherein the diethylamine is removed from the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile by heating the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile.

26. The process of claim 23 or 24, wherein the diethylamine is removed from the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile by partitioning the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile between one or more suitable organic solvent and an aqueous acidic solution and isolating and concentrating the one or more suitable organic solvents.

27. The process of claim 26, wherein the acid is hydrochloric acid.

28. The process of claim 26 or 27, wherein the suitable organic solvent is MTBE.

29. The process of any one of claims 23 to 28, wherein the Form A X-ray powder diffraction pattern further comprises:

(i) a peak at angular position 20.1, wherein the angular position may vary by ± 0.2° 2θ; or

(ii) peaks at angular positions 12.9 and 20.1, wherein the angular positions may vary by ± 0.2° 2θ; or

(iii) peaks at angular positions 11.4, 12.9, and 20.1, wherein the angular positions may vary by ± 0.2° 2θ; or

(iv) peaks at angular positions 10.1, 11.4, 12.9, and 20.1, wherein the angular positions may vary by + 0.2° 2θ.

30. The process of any one of claims 23 to 29, wherein the angular positions of the X-ray diffraction peaks denoted therein may vary by + 0.1^{o} 2θ.

31. The process of any one of claims 23 to 30, wherein the crystalline Form A polymorph of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile is recrystallized from one or more suitable organic solvents.

32. The process of claim 31, wherein the suitable organic solvent is isopropyl acetate.

33. The process of claim 32, wherein one or more anti-solvents and/or solid crystalline seed of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile are added.

34. The process of claim 33, wherein the one or more anti-solvents are independently selected from the group consisting of water, n-heptane, n-hexane, isooctane, pentane, cyclohexane, and cyclopentane.

35. A solid composition comprising a diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile and 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile, wherein the % weight ratio of the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)-benzonitrile to 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile in the composition is from:

(i) about 1:9 to about 1:0.001; or

(ii) about 1:0.25 to about 1:0.001; or

(iii) about 1:0.05 to about 1:0.001.

36. The solid composition of claim 35, wherein the diethylamine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile is a crystalline form B polymorph of any one of claims 6 to 8.

37. A process for preparing 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile comprising:

(a5) treating 3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile with a perfluorobutanesulfonyl fluoride and $Et_3N{\cdot}3HF$ in the presence of an organic base, in a suitable organic solvent; and

(b5) purifying the mixture from Step (a5) to obtain 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile.

38. The process of claim 37, wherein the organic base in Step (a5) is (*tert*-butylimino)tris-(pyrrolidino)phosphorane (BTPP) or 2-tert-butyl-1,1,3,3-tetramethyl-guanidine (BTMG).

39. The process of claim 37 or 38, wherein the one or more suitable organic solvents in Step (a5) are selected from ethers, esters, haloalkanes, ketones, acetates, toluene, and xylene.

40. The process of any one of claims 37 to 39, wherein the one or more suitable organic solvents in Step (a5) are selected from tetrahydrofuran, 2-methyl-tetrahydrofuran, ethyl acetate, IPAc, MTBE, methylene chloride, and toluene.

41. The process of any one of claims 37 to 40, wherein the reaction of Step (a5) is carried out from about - 20 ^{o}C to about room temperature.

42. The process of any one of claims 37 to 41, wherein the molar ratio of BTPP or BTMG:Et_3N. 3HF in Step (a5) is from about 6:1 to about 1:1 and the molar ratio of PBSF: Et_3N. 3HF in Step (a5) is from about 8:1 to about 1.7:1.

43. The process of any one of claims 37 to 42, wherein 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile is converted to an amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile according to any one of claims 1-5.

44. The process of claim 43, wherein the amine solvate of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile is converted to 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile.