

SYNTHESIS OF A HIPPO-YAP PATHWAY MODULATOR AND A POLYMORPH THEREOF

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 63/492,440, filed on March 27, 2023, which is herein incorporated by reference in its entirety.

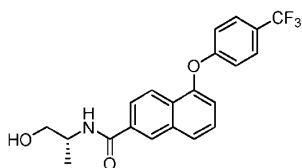
BACKGROUND OF THE DISCLOSURE

[0002] YAP and TAZ are transcriptional co-activators of the Hippo pathway network and regulate cell proliferation, migration, and apoptosis. Inhibition of the Hippo pathway promotes YAP/TAZ translocation to the nucleus, wherein YAP/TAZ interact with transcriptional enhancer associate domain (TEAD) transcription factors and coactivate the expression of target genes and promote cell proliferation. Hyperactivation of YAP and TAZ and/or mutations in one or more members of the Hippo pathway network have been implicated in numerous cancers. Described herein are inhibitors associated with one or more members of the Hippo pathway network, such as inhibitors of YAP/TAZ or inhibitors that modulate the interaction between YAP/TAZ and TEAD.

SUMMARY OF THE DISCLOSURE

[0003] Described herein is the preparation of a Hippo-YAP pathway modulator and chemical intermediates used in the synthetic process. Described herein are processes for the synthesis of a Hippo-YAP pathway modulator, wherein the Hippo-YAP pathway modulator is (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)).

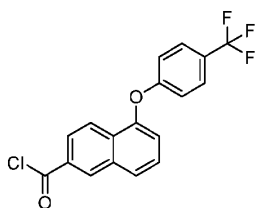
[0004] In one aspect described herein is a process of synthesizing (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)):



Compound (I)

comprising:

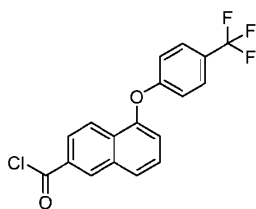
contacting Compound D



(Compound D) with (*R*)-2-aminopropan-1-ol in the presence of a solvent.

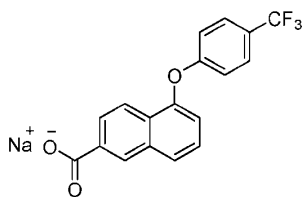
In some embodiments, the solvent is 2-methyl-THF.

[0005] In some embodiments is a process of synthesizing (*R*)-*N*-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)), wherein Compound D:



(Compound D) is prepared by a process comprising:

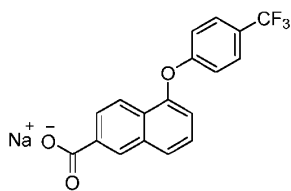
contacting Compound C



(Compound C) with a chlorinating agent in the presence of a solvent.

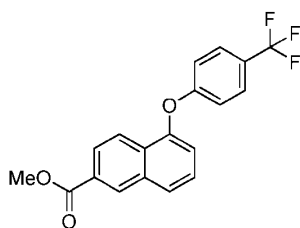
In some embodiments, the chlorinating agent is thionyl chloride. In some embodiments, the solvent is 2-methyl-THF.

[0006] In some embodiments is a process of synthesizing (*R*)-*N*-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)), wherein Compound C:



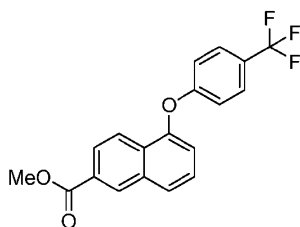
(Compound C) is prepared by a process comprising:

contacting Compound B

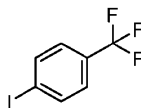
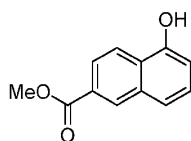


(Compound B) with a base in the presence of a solvent. In some embodiments, the base is an inorganic base. In some embodiments, the base is selected from NaOH, KOH, and CsOH. In some embodiments, the base is NaOH. In some embodiments, the solvent is a mixture of 2-methyl-THF and water.

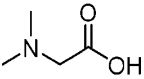
[0007] In some embodiments is a process of synthesizing (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)), wherein Compound B:



(Compound B) is prepared by a process comprising:



contacting (Compound A1) with (Compound A2) in the presence of a catalyst, a base, and a solvent. In some embodiments, the catalyst is CuI and *N,N*-dimethylglycine. In some embodiments, the base is an organic base. In some embodiments, the organic base is selected from piperidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, *N,N*-diisopropylethylamine, and triethylamine. In some embodiments, the base is an inorganic base. In some embodiments, the inorganic base is selected from NaOH, KOH, CsOH, Cs₂CO₃, K₂CO₃, Na₂CO₃, or NaHCO₃. In some embodiments, the inorganic base is K₂CO₃. In some embodiments,

Compound A1 and Compound A2 further contact . In some embodiments, the solvent is selected from ethyl acetate, dichloromethane, tetrahydrofuran, diethyl ether, dimethylformamide, dimethylsulfoxide, methanol, ethanol, acetone, acetonitrile, 1,4-dioxane, hexane, and methyl *tert*-butyl ether. In some embodiments, the solvent is 1,4-dioxane.

[0008] In another aspect, described herein is a crystalline form of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, or a solvate thereof.

[0009] In one embodiment is a crystalline form of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, wherein the crystalline form of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide is Form 1 having at least one of the following properties:

- (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 2**;
- (b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.1° 2-Theta, 16.2° 2-Theta, 18.6° 2-Theta, 18.8° 2-Theta, 19.4° 2-Theta, 20.0° 2-Theta, 23.9° 2-Theta, 24.2° 2-Theta, and 28.4° 2-Theta;
- (c) a DSC thermogram substantially similar to the one set forth in **Fig. 3**;
- (d) a DSC thermogram with an endotherm having an onset at about 140 °C;
- (e) a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Fig. 4**; or
- (f) combinations thereof.

[0010] In some embodiments is a crystalline form of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 2**.

[0011] In some embodiments is a crystalline form of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.1° 2-Theta, 16.2° 2-Theta, 18.6° 2-Theta, 18.8° 2-Theta, 19.4° 2-Theta, 20.0° 2-Theta, 23.9° 2-Theta, 24.2° 2-Theta, and 28.4° 2-Theta.

[0012] In some embodiments is crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, Form 1, wherein the crystalline form has a DSC thermogram substantially similar to the one set forth in **Fig. 3**.

[0013] In some embodiments is crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, Form 1, wherein the crystalline form has a DSC thermogram with an endotherm having an onset at about 140°C.

[0014] In some embodiments is crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, Form 1, wherein the crystalline form has a thermogravimetric analysis (TGA) substantially similar to the one set forth in **Fig. 4**.

[0015] In some embodiments is crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, Form 1, wherein the crystalline form is characterized as having properties: (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 2**; (b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.1° 2-Theta, 16.2° 2-Theta, 18.6° 2-Theta, 18.8° 2-Theta, 19.4° 2-Theta, 20.0° 2-Theta, 23.9° 2-Theta, 24.2° 2-Theta, and 28.4° 2-Theta; (c) a DSC thermogram substantially similar to the one set forth in **Fig. 3**;

(d) a DSC thermogram with an endotherm having an onset at about 140°C; and (e) a thermogravimetric analysis (TGA) substantially similar to the one set forth in **Fig. 4**.

[0016] In some embodiments is crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, Form 1, wherein the crystalline form is obtained from ethanol.

[0017] In some embodiments is a pharmaceutical composition comprising crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, Form 1, and a pharmaceutically acceptable excipient.

[0018] In some embodiments is a method of treating cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, Form 1. In some embodiments is a method of treating cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, Form 1, wherein the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

[0019] In some embodiments is a method of treating polycystic kidney disease or liver fibrosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, Form 1.

INCORPORATION BY REFERENCE

[0020] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0022] **FIG. 1** illustrates a schematic representation of the Hippo signaling network. Hippo pathway components shaded in dark gray indicate components that inhibit YAP/TAZ activity. Hippo pathway components shaded in light gray indicate components that promote YAP/TAZ activity. Pointed and blunt arrowheads indicate activating and inhibitory interactions, respectively. Abbreviations: α -CAT (α -Catenin), AJUB (Ajuba), AMOT (Angiomotin), β -TRCP (β -transducing repeat containing protein), CK1 (Casein Kinase 1), CRB (Crumbs), E-CAD (E-cadherin), EX (Expanded), GPCR (G-protein coupled receptor), HIPK (Homeodomain interacting protein kinase), KIBRA (Kidney brain), LATS (Large tumor suppressor), LGL (Lethal giant larvae), MASK (Multiple ankyrin single KH), MER (Merlin), MOB (Mps one binder), MST (Mammalian sterile 20 like), PALS (Protein Associated with Lin-7), PATJ (Pals1-associated tight junction protein), PP2A (Protein phosphatase 2A), PTPN14 (Protein tyrosine phosphatase non-receptor type 14), RASSF (Ras associated factor), SAV (Salvador), SCRIB (Scribble), SIK (Salt inducible kinase), TAO (Thousand and one amino acid protein), TAZ (transcriptional coactivator with PDZ-binding motif), TEAD (TEA domain protein), VGL4 (Vestigial-like 4), WBP2 (WW domain binding protein 2), YAP (Yes associated protein), ZO (Zonula occludens), ZYX (Zyxin).

[0023] **FIG. 2** illustrates an X-ray powder diffraction (XRPD) pattern of crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)), Form 1.

[0024] **FIG. 3** illustrates a differential scanning calorimetry (DSC) thermogram of crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)), Form 1.

[0025] **FIG. 4** illustrates a thermogravimetric analysis (TGA) thermogram of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)), Form 1.

[0026] **FIG. 5** illustrates a dynamic vapor sorption (DVS) analysis of crystalline (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)), Form 1.

DETAILED DESCRIPTION OF THE DISCLOSURE

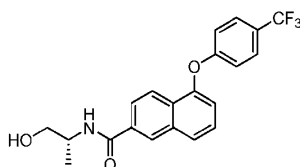
The Hippo Signaling Network

[0027] The Hippo signaling network (also known as the Salvador/Warts/Hippo (SWH) pathway) is a master regulator of cell proliferation, death, and differentiation. In some embodiments, the main function of the Hippo signaling pathway is to regulate negatively the transcriptional co-activators Yes-associated protein (YAP) and its paralogue, the transcriptional co-activator with PDZ-binding motif (TAZ; also known as WWTR1) (**FIG. 1**). The Hippo kinase cascade phosphorylates and inhibits YAP/TAZ by promoting its cytoplasmic retention and degradation, thereby inhibiting the growth promoting function regulated under the YAP/TAZ

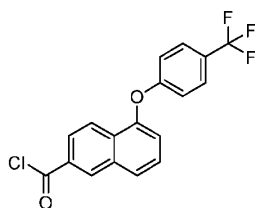
control. In an un-phosphorylated/de-phosphorylated state, YAP, also known as YAP1 or YAP65, together with TAZ, are transported into the nucleus where they interact with TEAD family of transcription factors to upregulate genes that promote proliferation and migration and inhibit apoptosis. In some instances, unregulated upregulation of these genes involved in proliferation, migration, and anti-apoptosis leads to development of cancer. In some instances, overexpression of YAP/TAZ is associated with cancer. Compound (I) disclosed herein is an inhibitor of one or more of the proteins encompassed by, or related to, the Hippo pathway shown in **Fig. 1**.

Compounds

[0028] In some embodiments, the Hippo-YAP pathway modulator described herein is (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)), or a co-crystal thereof. Compound (I) has the structure:



[0029] In some embodiments, an intermediate in the synthesis of Compound (I) is



Further Forms of Compounds

Isomers

[0030] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (*E*), and zusammen (*Z*) isomers as well as the corresponding mixtures thereof. In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some

embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, disclosed herein are dissociable complexes (e.g., crystalline diastereomeric salts). In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that does not result in racemization.

Labeled compounds

[0031] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. In some embodiments, examples of isotopes that are incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, and the metabolites, pharmaceutically acceptable salts, esters, prodrugs, solvates, hydrates, or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this disclosure. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, i.e., ^2H , produces certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof is prepared by any suitable method.

Pharmaceutically acceptable salts

[0032] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[0033] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds of the disclosure, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

Solvates

[0034] In some embodiments, the compounds described herein exist as solvates. The disclosure provides for methods of treating diseases by administering such solvates. The disclosure further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[0035] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In some embodiments, solvates of the compounds described herein are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran, or methanol. In some embodiments, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Preparation of Compound (I)

[0036] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd.

(Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

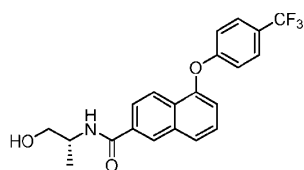
[0037] Methods known to one of ordinary skill in the art are identified through various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R. V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in

8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[0038] In some instances, specific and analogous reactants are identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., is contacted for more details). Chemicals that are known but not commercially available in catalogs are prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

[0039] In some embodiments, the compounds disclosed herein are prepared as described in the Examples section.

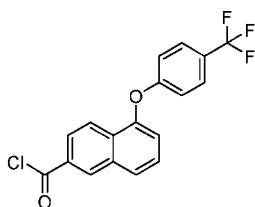
[0040] In some embodiments described herein is a process of synthesizing (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)):



Compound (I)

comprising:

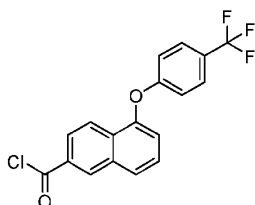
contacting Compound D



(Compound D) with (R)-2-aminopropan-1-ol in the presence of a solvent.

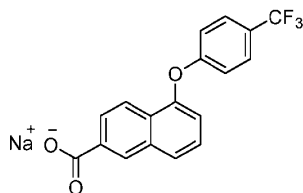
In some embodiments, the solvent is 2-methyl-THF.

[0041] In some embodiments is a process of synthesizing (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)) wherein Compound D:



(Compound D) is prepared by a process comprising:

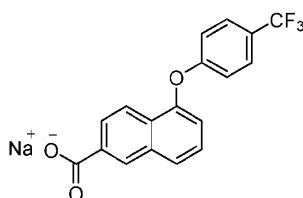
contacting Compound C



(Compound C) with a chlorinating agent in the presence of a solvent.

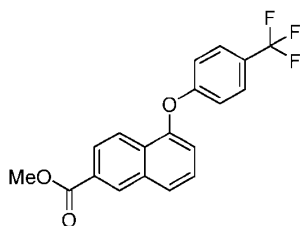
In some embodiments, the chlorinating agent is thionyl chloride. In some embodiments, the solvent is 2-methyl-THF.

[0042] In some embodiments is a process of synthesizing (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)) wherein Compound C:



(Compound C) is prepared by a process comprising:

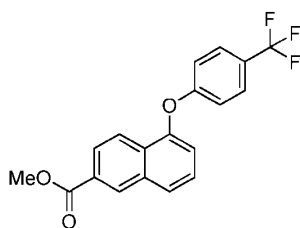
contacting Compound B



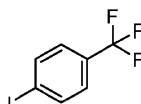
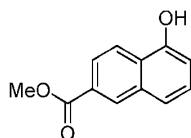
(Compound B) with a base in the presence of a solvent. In some

embodiments, the base is an inorganic base. In some embodiments, the base is selected from NaOH, KOH, and CsOH. In some embodiments, the base is NaOH. In some embodiments, the base is KOH. In some embodiments, the base is CsOH. In some embodiments, the base is Cs₂CO₃. In some embodiments, the base is K₂CO₃. In some embodiments, the base is Na₂CO₃. In some embodiments, the base is NaHCO₃. In some embodiments, the solvent is a mixture of 2-methyl-THF and water.

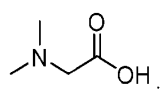
[0043] In some embodiments is a process of synthesizing (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)) wherein Compound B:



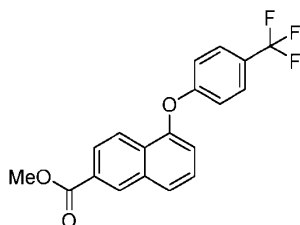
(Compound B) is prepared by a process comprising:



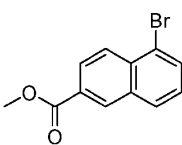
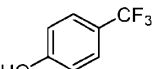
contacting (Compound A1) with (Compound A2) in the presence of a catalyst, a base, and a solvent. In some embodiments, the catalyst is CuI. In some embodiments, the catalyst is *N,N*-dimethylglycine. In some embodiments, the catalyst is CuI and *N,N*-dimethylglycine. In some embodiments, the base is an organic base. In some embodiments, the organic base is selected from piperidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, *N,N*-diisopropylethylamine, and triethylamine. In some embodiments, the organic base is piperidine. In some embodiments, the organic base is 1,8-diazabicyclo[5.4.0]undec-7-ene. In some embodiments, the organic base is *N,N*-diisopropylethylamine. In some embodiments, the organic base is triethylamine. In some embodiments, the base is an inorganic base. In some embodiments, the inorganic base is selected from NaOH, KOH, CsOH, Cs₂CO₃, K₂CO₃, Na₂CO₃, or NaHCO₃. In some embodiments, the inorganic base is K₂CO₃. In some embodiments, the base is NaOH. In some embodiments, the base is KOH. In some embodiments, the base is CsOH. In some embodiments, the base is Cs₂CO₃. In some embodiments, the base is K₂CO₃. In some embodiments, the base is Na₂CO₃. In some embodiments, the base is NaHCO₃. In some

embodiments, Compound A1 and Compound A2 further contact . In some embodiments, the solvent is selected from ethyl acetate, dichloromethane, tetrahydrofuran, diethyl ether, dimethylformamide, dimethylsulfoxide, methanol, ethanol, acetone, acetonitrile, 1,4-dioxane, hexane, and methyl *tert*-butyl ether. In some embodiments, the solvent is 1,4-dioxane. In some embodiments, the solvent is ethyl acetate. In some embodiments, the solvent is dichloromethane. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is diethyl ether. In some embodiments, the solvent is dimethylformamide. In some embodiments, the solvent is dimethylsulfoxide. In some embodiments, the solvent is methanol. In some embodiments, the solvent is ethanol. In some embodiments, the solvent is acetone. In some embodiments, the solvent is acetonitrile. In some embodiments, the solvent is hexane. In some embodiments, the solvent is methyl *tert*-butyl ether.

[0044] In some embodiments is a process of synthesizing (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)) wherein Compound B:

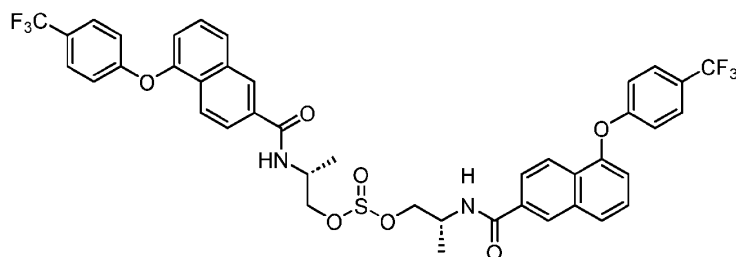


(Compound B) is prepared by a process comprising:

contacting  (Compound A3) with  (Compound A4) in the presence of a catalyst, a phosphine ligand, base, and a solvent. In some embodiments, the catalyst is allylpalladium(II) chloride dimer. In some embodiments, the phosphine ligand is RockPhos. In some embodiments, the base is an inorganic base. In some embodiments, the base is Cs₂CO₃. In some embodiments, the solvent is selected from ethyl acetate, dichloromethane, tetrahydrofuran, diethyl ether, dimethylformamide, dimethylsulfoxide, methanol, ethanol, acetone, acetonitrile, 1,4-dioxane, hexane, and methyl *tert*-butyl ether.

[0045] In some embodiments of the processes for synthesizing (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I)) described herein, Compound (I) is synthesized substantially pure. In certain embodiments, the substantially pure Compound (I) is substantially free of impurities. In certain embodiments, the purity of the substantially pure Compound (I) is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

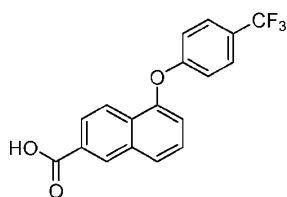
[0046] In some embodiments, an impurity in the synthetic processes described herein is bis((R)-2-(5-(4-(trifluoromethyl)phenoxy)-2-naphthamido)propyl) sulfite having the structure:



. In certain embodiments, the substantially pure Compound (I) is substantially free of bis((R)-2-(5-(4-(trifluoromethyl)phenoxy)-2-naphthamido)propyl) sulfite. In certain embodiments, the

substantially pure Compound (I) contains less than 0.5% of bis((R)-2-(5-(4-(trifluoromethyl)phenoxy)-2-naphthamido)propyl) sulfite. In certain embodiments, the substantially pure Compound (I) contains less than 0.4% of bis((R)-2-(5-(4-(trifluoromethyl)phenoxy)-2-naphthamido)propyl) sulfite. In certain embodiments, the substantially pure Compound (I) contains less than 0.3% of bis((R)-2-(5-(4-(trifluoromethyl)phenoxy)-2-naphthamido)propyl) sulfite. In certain embodiments, the substantially pure Compound (I) contains less than 0.2% of bis((R)-2-(5-(4-(trifluoromethyl)phenoxy)-2-naphthamido)propyl) sulfite. In certain embodiments, the substantially pure Compound (I) contains less than 0.15% of bis((R)-2-(5-(4-(trifluoromethyl)phenoxy)-2-naphthamido)propyl) sulfite. In certain embodiments, the substantially pure Compound (I) contains less than 0.1% of bis((R)-2-(5-(4-(trifluoromethyl)phenoxy)-2-naphthamido)propyl) sulfite. In certain embodiments, the substantially pure Compound (I) contains less than 0.05% of bis((R)-2-(5-(4-(trifluoromethyl)phenoxy)-2-naphthamido)propyl) sulfite.

[0047] In some embodiments, an impurity in the synthetic processes described herein is 5-(4-(trifluoromethyl)phenoxy)-2-naphthoic acid (protonated Compound C) having the structure:



. In certain embodiments, the substantially pure Compound (I) is substantially free of 5-(4-(trifluoromethyl)phenoxy)-2-naphthoic acid. In certain embodiments, the substantially pure Compound (I) contains less than 0.5% of 5-(4-(trifluoromethyl)phenoxy)-2-naphthoic acid. In certain embodiments, the substantially pure Compound (I) contains less than 0.4% of 5-(4-(trifluoromethyl)phenoxy)-2-naphthoic acid. In certain embodiments, the substantially pure Compound (I) contains less than 0.3% of 5-(4-(trifluoromethyl)phenoxy)-2-naphthoic acid. In certain embodiments, the substantially pure Compound (I) contains less than 0.2% of 5-(4-(trifluoromethyl)phenoxy)-2-naphthoic acid. In certain embodiments, the substantially pure Compound (I) contains less than 0.15% of 5-(4-(trifluoromethyl)phenoxy)-2-naphthoic acid. In certain embodiments, the substantially pure Compound (I) contains less than 0.1% of 5-(4-(trifluoromethyl)phenoxy)-2-naphthoic acid. In certain embodiments, the substantially pure Compound (I) contains less than 0.05% of 5-(4-(trifluoromethyl)phenoxy)-2-naphthoic acid.

Crystalline Forms

[0048] The identification and selection of a solid form of a pharmaceutical compound are complex, given that a change in solid form may affect a variety of physical and chemical properties, which may provide benefits or drawbacks in processing, formulation, stability, bioavailability, storage, and handling (*e.g.*, shipping), among other important pharmaceutical characteristics. Useful pharmaceutical solids include crystalline solids and amorphous solids, depending on the product and its mode of administration. Amorphous solids are characterized by a lack of long-range structural order, whereas crystalline solids are characterized by structural periodicity. The desired class of pharmaceutical solid depends upon the specific application; amorphous solids are sometimes selected on the basis of, *e.g.*, an enhanced dissolution profile, while crystalline solids may be desirable for properties such as, *e.g.*, physical or chemical stability.

[0049] Whether crystalline or amorphous, solid forms of a pharmaceutical compound include single-component and multiple-component solids. Single-component solids consist essentially of the pharmaceutical compound or active ingredient in the absence of other compounds. Variety among single-component crystalline materials may potentially arise from the phenomenon of polymorphism, wherein multiple three-dimensional arrangements exist for a particular pharmaceutical compound.

[0050] Notably, it is not possible to predict *a priori* if crystalline forms of a compound even exist, let alone how to successfully prepare them (*see, e.g.*, Braga and Grepioni, 2005, "Making crystals from crystals: a green route to crystal engineering and polymorphism," *Chem. Commun.*:3635-3645 (with respect to crystal engineering, if instructions are not very precise and/or if other external factors affect the process, the result can be unpredictable); Jones *et al.*, 2006, Pharmaceutical Cocrystals: An Emerging Approach to Physical Property Enhancement," *MRS Bulletin* 31:875-879 (At present it is not generally possible to computationally predict the number of observable polymorphs of even the simplest molecules); Price, 2004, "The computational prediction of pharmaceutical crystal structures and polymorphism," *Advanced Drug Delivery Reviews* 56:301-319 ("Price"); and Bernstein, 2004, "Crystal Structure Prediction and Polymorphism," *ACA Transactions* 39:14-23 (a great deal still needs to be learned and done before one can state with any degree of confidence the ability to predict a crystal structure, much less polymorphic forms)).

[0051] The variety of possible solid forms creates potential diversity in physical and chemical properties for a given pharmaceutical compound. The discovery and selection of solid forms are of great importance in the development of an effective, stable, and marketable pharmaceutical product.

Crystalline Compound (I), Form 1

[0052] In some embodiments, Compound (I) is crystalline. In some embodiments, Compound (I) is crystalline and anhydrous. In some embodiments, Compound (I) is crystalline and a hydrate. In some embodiments, Compound (I) is crystalline and a monohydrate. In some embodiments, crystalline Compound (I) is Form 1 characterized as having at least one of the following properties:

- (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 2**;
- (b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.1° 2-Theta, 16.2° 2-Theta, 18.6° 2-Theta, 18.8° 2-Theta, 19.4° 2-Theta, 20.0° 2-Theta, 23.9° 2-Theta, 24.2° 2-Theta, and 28.4° 2-Theta;
- (c) a DSC thermogram substantially similar to the one set forth in **Fig. 3**;
- (d) a DSC thermogram with an endotherm having an onset at about 140 °C;
- (e) a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Fig. 4**; or
- (f) combinations thereof.

[0053] In some embodiments, crystalline Compound (I), Form 1, is characterized as having at least two of the properties selected from (a) to (f). In some embodiments, crystalline Compound (I), Form 1, is characterized as having at least three of the properties selected from (a) to (f). In some embodiments, crystalline Compound (I), Form 1, is characterized as having at least four of the properties selected from (a) to (f). In some embodiments, crystalline Compound (I), Form 1, is characterized as having at least five of the properties selected from (a) to (f).

[0054] In some embodiments, crystalline Compound (I), Form 1, has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 2**. In some embodiments, crystalline Compound (I), Form 1, has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.1° 2-Theta, 16.2° 2-Theta, 18.6° 2-Theta, 18.8° 2-Theta, 19.4° 2-Theta, 20.0° 2-Theta, 23.9° 2-Theta, 24.2° 2-Theta, and 28.4° 2-Theta. In some embodiments, crystalline Compound (I), Form 1, has a DSC thermogram substantially similar to the one set forth in **Fig. 3**. In some embodiments, crystalline Compound (I), Form 1, has a DSC thermogram with an endotherm having an onset at about 140 °C. In some embodiments, crystalline Compound (I), Form 1, has a thermogravimetric analysis (TGA) thermogram substantially similar to the one set forth in **Fig. 4**. In some embodiments, crystalline Compound (I), Form 1, is anhydrous. In some embodiments, crystalline Compound (I), Form 1, is obtained from ethanol. In some embodiments, crystalline Compound (I), Form 1, is obtained from a solvent system as shown in **Tables 2, 3, 4, 5, 6, or 7** described herein. In some embodiments, crystalline Compound (I), Form 1, is solvated. In some embodiments, crystalline Compound (I), Form 1, is unsolvated.

Preparation of Crystalline Compound (I), Form 1

[0055] In some embodiments, crystalline Compound (I), Form 1, is prepared as outlined in the Examples. It is noted that solvents, temperatures and other reaction conditions presented herein may vary.

[0056] In another embodiment, crystalline Compound (I), Form 1, is substantially pure. In certain embodiments, the substantially pure crystalline Compound (I), Form 1, is substantially free of other solid forms, e.g., amorphous solid. In certain embodiments, the purity of the substantially pure crystalline Compound (I), Form 1, is no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 98.5%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

Suitable Solvents

[0057] Therapeutic agents that are administrable to mammals, such as humans, must be prepared by following regulatory guidelines. Such government regulated guidelines are referred to as Good Manufacturing Practice (GMP). GMP guidelines outline acceptable contamination levels of active therapeutic agents, such as, for example, the amount of residual solvent in the final product. In some embodiments, solvents disclosed herein are those that are suitable for use in GMP facilities and consistent with industrial safety concerns. Categories of solvents are defined in, for example, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Impurities: Guidelines for Residual Solvents Q3C(R6)," (October 2016).

[0058] Solvents are categorized into three classes. Class 1 solvents are toxic and are to be avoided. Class 2 solvents are solvents to be limited in use during the manufacture of the therapeutic agent. Class 3 solvents are solvents with low toxic potential and of lower risk to human health. Data for Class 3 solvents indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

[0059] Class 1 solvents, which are to be avoided, include: benzene; carbon tetrachloride; 1,2-dichloroethane; 1,1-dichloroethene; and 1,1,1-trichloroethane.

[0060] Examples of Class 2 solvents are: acetonitrile, chlorobenzene, chloroform, cumene, cyclohexane, 1,2-dichloroethene, dichloromethane, 1,2-dimethoxyethane, N,N-dimethylacetamide, N,N-dimethylformamide, 1,4-dioxane, 2-ethoxyethanol, ethylene glycol, formamide, hexane, methanol, 2-methoxyethanol, methylbutyl ketone, methylcyclohexane, methylisobutylketone, N-methylpyrrolidone, nitromethane, pyridine, sulfolane, tetrahydrofuran, tetralin, toluene, 1,1,2-trichloroethene and xylene.

[0061] Class 3 solvents, which possess low toxicity, include: acetic acid, acetone, anisole, 1-butanol, 2-butanol, butyl acetate, *tert*-butyl methyl ether (MTBE), dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methylethyl ketone, 2-methyl-1-propanol, pentane, 1-pentanol, 1-propanol, 2-propanol, propyl acetate, and triethylamine.

[0062] Residual solvents in active pharmaceutical ingredients (APIs) originate from the manufacture of APIs. In some cases, the solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of APIs may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent is a critical parameter in the synthetic process.

[0063] In some embodiments, compositions comprising Compound (I), Form 1, comprise an organic solvent(s). In some embodiments, compositions comprising Compound (I), Form 1, comprise a residual amount of an organic solvent(s). In some embodiments, compositions comprising Compound (I), Form 1, comprise a residual amount of a Class 3 solvent. In some embodiments, the organic solvent is a Class 3 solvent. In some embodiments, the Class 3 solvent is selected from the group consisting of acetic acid, acetone, anisole, 1-butanol, 2-butanol, butyl acetate, *tert*-butyl methyl ether (MTBE), dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methylethyl ketone, 2-methyl-1-propanol, pentane, 1-pentanol, 1-propanol, 2-propanol, propyl acetate, and triethylamine. In some embodiments, the Class 3 solvent is selected from the group consisting of acetone, ethyl acetate, isopropyl acetate, *tert*-butyl methyl ether, heptane, isopropanol, and ethanol.

[0064] In some embodiments, compositions comprising Compound (I), Form 1, comprise a residual amount of a Class 2 solvent. In some embodiments, the organic solvent is a Class 2 solvent. In some embodiments, the Class 2 solvent is selected from the group consisting of acetonitrile, chlorobenzene, chloroform, cumene, cyclohexane, 1,2-dichloroethene, dichloromethane, 1,2-dimethoxyethane, N,N-dimethylacetamide, N,N-dimethylformamide, 1,4-dioxane, 2-ethoxyethanol, ethylene glycol, formamide, hexane, methanol, 2-methoxyethanol, methylbutyl ketone, methylcyclohexane, methylisobutylketone, N-methylpyrrolidone, nitromethane, pyridine, sulfolane, tetrahydrofuran, tetralin, toluene, 1,1,2-trichloroethene and xylene. In some embodiments, the Class 2 solvent is selected from the group consisting of acetonitrile, tetrahydrofuran, and toluene. In some embodiments, the Class 2 solvent is acetonitrile.

[0065] In some embodiments, compositions comprising Compound (I), Form 1, comprise a residual amount of a solvent for which no adequate toxicological data were found. In some

embodiments, the organic solvent is a solvent for which no adequate toxicological data were found. In some embodiments, the solvent is selected from the group consisting of 2-butanone and 2-methyltetrahydrofuran.

Pharmaceutical Compositions

[0066] In certain embodiments, crystalline Compound (I), Form 1 as described herein is administered as a pure chemical. In other embodiments, the crystalline Compound (I), Form 1 described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)), the disclosure of which is hereby incorporated herein by reference in its entirety.

Methods

[0067] In some embodiments, crystalline Compound (I), Form 1 disclosed herein is useful for treating cancer. In some embodiments, provided herein is a method for treating a cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of crystalline Compound (I), Form 1. In some embodiments, provided herein is a compound for use in treating a cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of crystalline Compound (I), Form 1. In some embodiments, provided herein is use of crystalline Compound (I), Form 1 disclosed herein in the manufacture of a medicament for treating cancer.

[0068] In some embodiments, the cancer is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes-associated protein transcription coactivator (TAZ/YAP). In some embodiments, the cancer is mediated by modulation of the interaction of YAP/TAZ with TEAD. In some embodiments, the cancer is characterized by a mutant $G\alpha$ -protein. In some embodiments, the mutant $G\alpha$ -protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant $G\alpha$ -protein is G12. In some embodiments, the mutant $G\alpha$ -protein is G13. In some embodiments, the mutant $G\alpha$ -protein is Gq. In some embodiments, the mutant $G\alpha$ -protein is G11. In some embodiments, the mutant $G\alpha$ -protein is Gi. In some embodiments, the mutant $G\alpha$ -protein is Go. In some embodiments, the mutant $G\alpha$ -protein is Gs.

[0069] In some embodiments, the cancer is a solid tumor. In some instances, the cancer is a hematologic malignancy. In some instances, the solid tumor is a sarcoma or carcinoma. In some instances, the solid tumor is a sarcoma. In some instances, the solid tumor is a carcinoma.

[0070] In some instances, the cancer is selected from uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the cancer is uveal melanoma. In some cases, the cancer is mesothelioma. In some cases, the cancer is esophageal cancer. In some cases, the cancer is liver cancer. In some cases, the cancer is primary liver cancer.

[0071] In some instances, the cancer is a hematologic malignancy. In some embodiments, a hematologic malignancy is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, a T-cell malignancy, or a B-cell malignancy. In some instances, a hematologic malignancy is a T-cell malignancy.

[0072] In some instances, a hematologic malignancy is a B-cell malignancy.

[0073] In some instances, the cancer is a relapsed or refractory cancer.

[0074] In some embodiments, crystalline Compound (I), Form 1 is useful for treating polycystic kidney disease. In some embodiments, crystalline Compound (I), Form 1 is useful for treating liver fibrosis. In some embodiments, crystalline Compound (I), Form 1 is useful for treating a congenital disease.

Definitions

[0075] Unless defined otherwise, all terms of art, notations and other technical and scientific terms or terminology used herein are intended to have the same meaning as is commonly understood by one of ordinary skill in the art to which the claimed subject matter pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art.

[0076] Throughout this application, various embodiments may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosure. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a

range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6, etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[0077] As used in the specification and claims, the singular forms “a”, “an” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a sample” includes a plurality of samples, including mixtures thereof.

[0078] In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting.

[0079] As used herein, in some embodiments, ranges and amounts are expressed as “about” a particular value or range. About also includes the exact amount. Hence “about 5 μ L” means “about 5 μ L” and also “5 μ L.” Generally, the term “about” includes an amount that is expected to be within experimental error.

[0080] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0081] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

EXAMPLES

[0082] The following illustrative examples are representative of embodiments of the stimulation, systems, and methods described herein and are not meant to be limiting in any way.

List of abbreviations

[0083] As used above, and throughout the disclosure, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

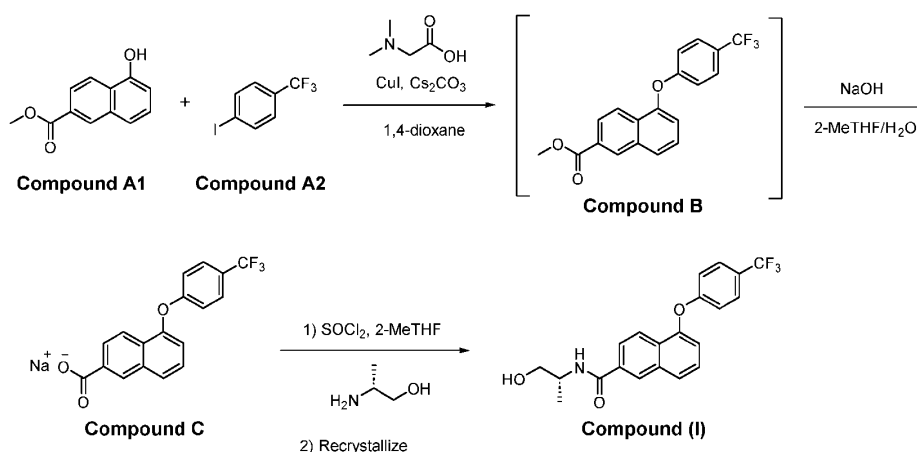
°C	degree Celsius
g	gram(s)
kg	kilogram(s)
μ L	microliter(s)
h, hr, hrs	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
T3P	2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinate-2,4,6-trioxide
HPLC	high performance liquid chromatography

GC	gas chromatography
KF	Karl Fischer titration
XRPD	X-Ray Powder Diffraction
RSMs	regulatory starting materials
Me	methyl
THF	tetrahydrofuran
DMF	<i>N,N</i> -dimethylformamide
MeOH	methanol

I. Chemical Synthesis

[0084] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. In some embodiments, in case of a discrepancy between a reaction scheme and a written procedure, the written procedure should be followed.

Example 1. Synthesis of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound I)



Step 1: Preparation of methyl 5-(4-(trifluoromethyl)phenoxy)-2-naphthoate

[0085] Methyl 5-hydroxy-2-naphthoate (**Compound A1**) (2.8 kg, 1.0 equivalent (eq.)) and 1-iodo-4-(trifluoromethyl)benzene (**Compound A2**) (4.5 kg, 1.2 eq.) were combined in 1,4-dioxane (29 kg) with *N,N*-dimethylglycine (0.45 kg, 0.3 eq.), cesium carbonate (6.9 kg, 1.5 eq.) and cuprous iodide (1.54 kg, 0.6 eq.). This mixture was heated to 95-105 °C for about 15 hours. The mixture was cooled and 1,3,5-triazine-2,4,6(1H,3H,5H)-trithione sodium salt (2.2 kg, 0.65 eq.) was added. The mixture was diluted with 2-methyl-THF (ca. 70 kg) and filtered through diatomaceous earth. This solution was held for the next step.

[0086] Step 1 was repeated using 4.4 kg of methyl 5-hydroxy-2-naphthoate and 7.1 kg of 1-iodo-4-(trifluoromethyl)benzene, and the resulting 2-methyl-THF solution of methyl 5-(4-

(trifluoromethyl)phenoxy)-2-naphthoate was combined with the solution prepared above, and the combined solution was taken into the ester saponification step as described below.

Step 2: Preparation of sodium 5-(4-(trifluoromethyl)phenoxy)-2-naphthoate

[0087] The combined 2-methyl-THF solution of methyl 5-(4-(trifluoromethyl)phenoxy)-2-naphthoate was washed with aqueous sodium chloride solution and aqueous ammonia hydroxide, and then the 2-methyl-THF solution was concentrated under vacuum. To the concentrate was added a solution of sodium hydroxide (4.4 kg) and water (71 kg), and after the addition, the mixture was stirred at 60 to 70 °C for 10 hours. The solution was concentrated under vacuum and n-heptane (25 kg) was added. The solution was seeded, and additional n-heptane (27 kg) was added. The mixture was cooled to 0 to 5 °C, filtered, and dried under vacuum to provide 8.0 kg (69% yield over two steps) of **Compound C**.

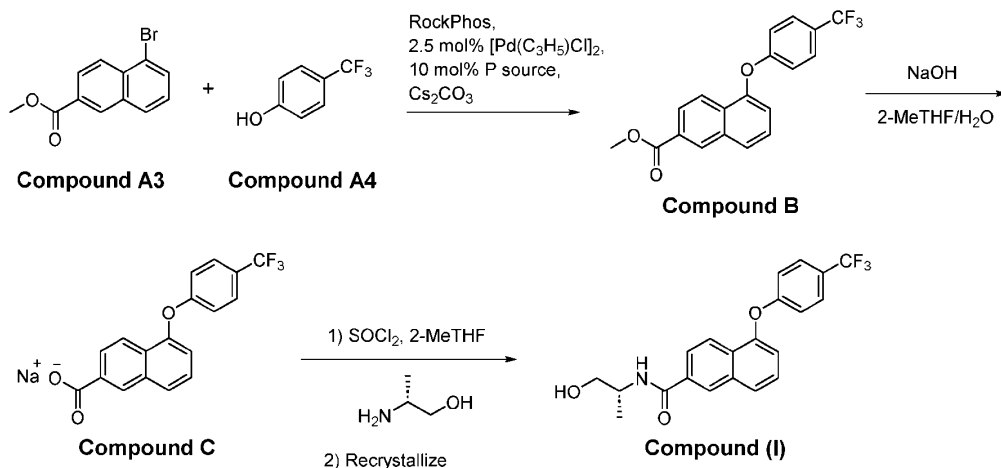
Step 3: Preparation of Compound (I)

[0088] **Compound C** (8.0 kg, 1.0 eq.) was combined with 2-methyl-THF (48 kg), thionyl chloride (7.2 kg, 2.7 eq.), and DMF (0.07 kg, 0.05 eq.). The reaction mixture was stirred at 20 to 30 °C for 5 to 10 hours. The mixture was concentrated under vacuum. The residue was dissolved in 2-methyl-THF (46 kg) and concentrated again to remove residual thionyl chloride. Additional 2-methyl-THF (38 kg) was then added to the residue followed by (*R*)-2-aminopropan-1-ol. The reaction mixture was stirred at 20 to 30 °C for 2 to 6 hours. The solution was stirred with warm aqueous sodium hydroxide solution for 5 to 10 hours. The mixture was cooled to 20 to 30 °C, the layers were separated, and the 2-ME-THF layer was washed with brine. n-Heptane was added to the organic layer, and the crude product was filtered. The product was recrystallized from DMF/water. After two recrystallizations, an additional crystallization from 2-methyl-THF/n-heptane was implemented. The solid was collected by filtration and dried under vacuum to give 6.65 kg (76% yield) of **Compound (I)**.

Recrystallization of Compound (I) to achieve desired crystal Form 1

[0089] **Compound (I)** (6.5 kg) was combined with ethanol, and the mixture was warmed to 55 to 60 °C and stirred until a clear solution was obtained. The solution was filtered through a polishing filter, and to the filtrate was added warm water (44 kg) over a few hours. The mixture was then again warmed to 70 to 80 °C for about 30 minutes and then cooled, to 55 to 60 °C, seeded and dried under vacuum to afford 6.31 kg (95% yield) of **Compound (I)**. XRPD analysis confirmed that the product was crystalline **Compound (I), Form 1**.

Example 1A: Alternative synthesis of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide (Compound (I))



II. Characterization of Polymorphs

Example 2: X-ray Powder Diffraction (XRPD)

[0090] X-ray powder diffraction studies were performed using a Bruker D8 Advance.

[0091] Parameters for Bruker D8 Advance:

Tube(s)	Cu/K-Alpha1 ($\lambda=1.5418 \text{ \AA}$)	Detector OpticsMount 1	Slit_open_1 18 [mm]
Voltage (KV)	40	SollerMount (deg)	Deflection 0
Current (MA)	40	SlitMount	No slit 10.5 [mm]
Primary Beam Path	Radius 280	Twin Secondary	Motorized Slit
TubeMount	Tube	Sample Stage	1
Twin Primary	Motorized Slit	Autochanger	AirScatter
SlitMount	No slit 10.5 [mm]	Scan type	Coupled TwoTheta/Theta
SollerMount (deg)	Axial Soller 2.5	Scan Mode	Continuous PSD fast
Secondary Beam Path	Radius 280	Rotation	15r/min
LYNXEYE-XE-T	LYNXEYE-XE-T(1D mode)	2 Theta (deg)	2-39.9978

Detector OpticsMount	Soller 25 2.5	Increment	0.020428946300
Total time(s)	240.6s	Time/step(s)	0.12s

[0092] XRPD analysis of Compound (I) Form 1 (**Fig. 2**) showed Form 1 to be crystalline with characteristic peaks at 8.1° 2-Theta, 16.2° 2-Theta, 18.6° 2-Theta, 18.8° 2-Theta, 19.4° 2-Theta, 20.0° 2-Theta, 23.9° 2-Theta, 24.2° 2-Theta, and 28.4° 2-Theta.

Example 3: Differential Scanning Calorimetry (DSC)

[0093] DSC studies were performed using a TA Discovery Q2000. The sample (~1 mg) was tested using a hermetic aluminum pan with pinhole. The sample was heated at the heating rate of 10 °C/min from 30 °C up to 300 °C.

[0094] DSC analysis of Compound (I) Form 1 (**Fig. 3**) showed an endotherm having an onset at about 140 °C.

Example 4: Thermogravimetric Analysis

[0095] Thermogravimetric analysis of solid was performed using TA Discovery TGA 5500. The sample (3-5 mg) was placed in an open aluminum pan. The sample was heated at the heating rate of 10 °C/min from room temperature to 300 °C under 25 mL/mL of N₂.

[0096] TGA of Compound (I) Form 1 (**Fig. 4**) showed a weight loss of ~0.15% from 35 °C to 130.5 °C.

Example 5: Dynamic Vapor Sorption (DVS)

[0097] DVS studies were performed using a DVS Intrinsic (SMS, UK). 10 mg of the sample was transferred into the DVS instrument and the weight change with respect to atmospheric humidity at 25 °C was recorded. The sample was analyzed with the following setting parameters:

- Equilibrium: dm/dt: 0.01%/min. (for min: 10 min and max: 180 min).
- Drying: 0%RH for 120 min
- RH (%) measurement step: 10%
- RH (%) measurement step scope: 40% - 0% - 95% - 0% - 40%

[0098] The DVS analysis of Compound (I) Form 1 (**Fig. 5**) showed Form 1 was non-hygroscopic (0.13% weight change from 0-80% RH).

III. Polymorph Screen

Example 6: Solubility Study

[0099] About 2 mg of Compound (I) was weighed into 2-mL glass vials, and then different selected solvents were added in the vials stepwise until all the solid was dissolved. The experiment

was conducted by manual dilution combined with visual observation at 25 °C and 50 °C. The total volume of solvent added was recorded. The results are shown in **Table 1**.

Table 1

Solvent	Solubility (mg/mL)		Solvent	Solubility (mg/mL)	
	25 °C	50 °C		25 °C	50 °C
MeOH	S>200	S>200	Toluene	3.3<S<5	12.5<S<25
EtOH	S>200	S>200	Heptane	S<2	S<2
IPA	100<S<200	S>200	1,4-Dioxane	S>200	S>200
ACN	50<S<100	100<S<200	H ₂ O	S<2	S<2
Acetone	S>200	S>200	EtOH/H ₂ O (v/v=1/1)	3.33<S<5	10<S<20
MEK	S>200	S>200	IPA/H ₂ O (v/v=1/1)	10<S<20	20<S<50
MTBE	10<S<20	20<S<33.3	ACN/H ₂ O (v/v=1/1)	10<S<20	20<S<50
EtOAc	100<S<200	100<S<200	THF/H ₂ O (v/v=1/1)	20<S<50	5<S<10
THF	S>200	S>200	DMF/H ₂ O(v/v=1/1)	S<2	6.67<S<10
DMF	S>400	S>400	DMSO/H ₂ O (v/v=1/1)	S<2	S<2
DMSO	S>400	S>400	1,4-Dioxane/H ₂ O (v/v=1/1)	5<S<10	50<S<100
DCM	50<S<100	100<S<200	Acetone/H ₂ O (v/v=1/1)	5<S<10	10<S<20

Example 7: Slurry Method at 25 °C

[0100] About 50 mg of Compound (I) was weighed into 2-mL vials, and then 1 mL of different solvents (MTBE, Toluene, Heptane, H₂O, EtOH/H₂O (1/1), DMF/H₂O (1/1), DMSO/H₂O (1/1), 1,4-Dioxane/H₂O (1/1), Acetone/H₂O (1/1), IPA/H₂O (1/1), ACN/H₂O (1/1) and THF/H₂O (1/1)) were added respectively with target concentration of ~50 mg/mL. The suspensions were stirred at 25 °C (700 rpm) for 2 weeks. After 1 and 2 week's slurry,

appropriate suspensions were taken out and residual solids after centrifugation (8000 rpm, 10 min) were characterized by XRPD. The results are shown in **Table 2**.

Table 2

Solvents	XRPD results at 25 °C	
	1 week	2 weeks
Acetone/H ₂ O (1/1)	Form 1	Form 1
ACN/H ₂ O (1/1)	Form 1	Form 1
1,4-dioxane/H ₂ O (1/1)	Form 1	Form 1
DMF/H ₂ O (1/1)	Form 1	Form 1
DMSO/H ₂ O (1/1)	almost amorphous	Form 1
EtOH/H ₂ O (1/1)	Form 1	Form 1
IPA/H ₂ O (1/1)	Form 1	Form 1
THF/H ₂ O (1/1)	Form 1	Form 1
H ₂ O	Form 1	Form 1
Heptane	Form 1	Form 1
MTBE	Form 1	Form 1
Toluene	Form 1	Form 1

Example 8: Slurry Method at 50 °C

[0101] About 50 mg of Compound (I) was weighed into 2-mL vials, and then 1 mL of different solvents (MTBE, Toluene, Heptane, H₂O, EtOH/H₂O (1/1), DMF/H₂O (1/1), DMSO/H₂O (1/1), Acetone/H₂O (1/1), IPA/H₂O (1/1), ACN/H₂O (1/1) and THF/H₂O (1/1)) were added respectively with target concentration of ~50 mg/mL. The suspensions were stirred at 50 °C (700 rpm) for 2 weeks. After 1 and 2 week's slurry, appropriate suspensions were taken

out and residual solids after centrifugation (8000 rpm, 10 min) were characterized by XRPD. The results are shown in **Table 3**.

Table 3

Solvents	XRPD results at 50 °C	
	1 week	2 weeks
Acetone/H ₂ O (1/1)	Form 1	Form 1
ACN/H ₂ O (1/1)	Form 1	Form 1
DMF/H ₂ O (1/1)	Form 1	Form 1
DMSO/H ₂ O (1/1)	Form 1	Form 1
EtOH/H ₂ O (1/1)	Form 1	Form 1
IPA/H ₂ O (1/1)	Form 1	Form 1
THF/H ₂ O (1/1)	Form 1	Form 1
H ₂ O	Form 1	Form 1
Heptane	Form 1	Form 1
MTBE	Form 1	Form 1
Toluene	Form 1	Form 1

Example 9: Evaporation Method

[0102] About 50 mg of Compound (I) was weighed into 2-mL vials, and then 0.3 mL of different solvents (Acetone, DCM, EtOAc, EtOH, IPA, MeOH and THF) were added respectively with target concentration of ~166.7 mg/mL. Solvents were evaporated at 25 °C to form crystals. The formed crystals were characterized by XRPD. Results are shown in **Table 4**.

Table 4

Solvents	XRPD
Acetone	Form 1

DCM	Form 1
EtOAc	Form 1
EtOH	Form 1
IPA	Form 1
MeOH	Form 1
THF	Form 1

Example 10: Solvent Thermal Heating-Cooling Method

[0103] Fast cooling method: Compound (I) was dissolved with in various solvents at 60 °C to prepare saturated solutions, and then the solutions were cooled down in the ice-bath and kept at 0 °C to precipitate out solid quickly. The residual solids after centrifugation (8000 rpm, 10 min) were characterized by XRPD. Results are shown in **Table 5**.

Table 5

Solvents	XRPD
ACN	Form 1
MTBE	Form 1
Toluene	Form 1
1,4-dioxane/H ₂ O (1/1)	Form 1
IPA/H ₂ O (1/1)	Form 1
ACN/H ₂ O (1/1)	Form 1

[0104] Slow cooling method: Compound (I) was dissolved in various solvents at 60 °C to prepare saturated solutions, and then the solutions were cooled down in temperature programmed cooling circulator (0.1 °C/min) to precipitate out solid at 5 °C. The residual solids after centrifugation (8000 rpm, 10 min) were characterized by XRPD. Results are shown in **Table 6**.

Table 6

Solvents	XRPD
ACN	Form 1
MTBE	Form 1
Toluene	Form 1
1,4-dioxane/H ₂ O (1/1)	Form 1
IPA/H ₂ O (1/1)	Form 1
ACN/H ₂ O (1/1)	Form 1

Example 11: Anti-Solvent Precipitation Method

[0105] About 20 mg of Compound (I) was dissolved in various solvents at 25 °C to prepare saturated solutions, and then certain amount of anti-solvent was added to precipitate out crystals. The residual solids after centrifugation (8000 rpm, 10 min) were characterized by XRPD. Results are shown in **Table 7**.

Table 7

Solvents	Anti-Solvents	Solvent/Anti-Solvent	XRPD
EtOH	H ₂ O	2:7	Form 1
	Heptane	2:13	Form 1
Acetone	H ₂ O	2:7	Form 1
	Heptane	2:7	Form 1
EtOAc	Heptane	2:7	Form 1
	Toluene	2:7	Form 1

IV. Biological Evaluation

Example 12: YAP Reporter Assay

[0106] HEK293T cells stably transfected with 8XTBD luciferase reporter and pRLTK in 384-well plates were treated with the test compounds, starting from 3 μ M (final concentration in assay plate), 1:3 dilution, and 10 points in quadruplicates. Post 24-hr incubation with compounds at 37 °C and 5% CO₂, cells were lysed and 8XTBD-driven firefly luciferase and control TK-driven renilla luciferase activities were measured using Promega Dual-Luciferase Reporter Assay System.

[0107] Reagents: The reagents used for this study are: DMEM: Invitrogen# 11960077, Dual-Glo Luciferase Assay System: Promega-E2980, Puromycin Dihydrochloride: Invitrogen-A1113803, 384-well plate: PerkinElmer-6007480, L-GLUTAMINE: Invitrogen-25030164, Hygromycin B: Invitrogen-10687010, and Penicillin-Streptomycin: Merk-TMS-AB2-C

[0108] Media: The media used for this assay were: Culture Medium: DMEM+ 1 μ g/mL puromycin + 200 μ g/mL hygromycin (with 10% FBS + 1 mM L-glutamine); and Assay Medium: DMEM (with 10% FBS + 1mM L-glutamine + 1x P/S).

[0109] Cell Plating: The appropriate media was warmed at 37 °C by water bath: Culture Medium, Assay Medium, 1* D-PBS, 0.05% trypsin-EDTA. The cells were trypsinized after removing all media, then washed with 1* sterile D-PBS and then with 2 ml 0.05% trypsin-EDTA. The cells were then incubated at RT for one minute. Then 10 ml/75 cm² flask Assay Medium was added to each flask. Using a 10 ml pipette, the cells were then gently resuspended in the media, until the clumps completely disappeared. The cells were then transferred into 50 ml centrifuge tubes and were centrifuged at 800 rpm for 5 mins. The medium was removed, and the cells were resuspended with Assay Medium. An aliquot of cells was used to count the cell density (cells/ml). The cell suspension was then diluted with Assay Medium to a concentration of 6x10⁴ cells/ml. 50 μ l cells suspension was then plated to 384-well plate (PerkinElmer-6007480), 3x10³ cells/well and the cells were incubated in an incubator at 37 °C, 5% CO₂.

[0110] Compound Treatment: In the afternoon (incubation of the plate with 3-4 hrs), the test compounds were added by Echo, starting from 3 μ M (final concentration in the assay plate), 1:3 dilution, 10 points, quadruplicates. The plate was placed at 37 °C, 5% CO₂ incubator for 24 hrs.

[0111] Detection: The Dual-Glo Luciferase Reagent was prepared by transferring the contents of one bottle of Dual-Glo Luciferase Buffer to one bottle of Dual-Glo Luciferase Substrate to create the Dual-Glo Luciferase Reagent. Mixing was performed by inversion until the substrate was thoroughly dissolved. After mixing, the reagent was aliquoted into 15 ml tubes. In the afternoon (24 hrs post compound treatment), the DMEM+ medium in the 384 well plates were aspirated by Microplate Washer.

[0112] Measuring firefly luciferase activity: 20 μ L Dual-Glo Luciferase Reagent was added to the 384-well plates. The plates were protected from light to prevent interference with the assay. The plates were shaken for 1min followed centrifuging plates at 1000 rpm for 30 seconds. After waiting at least 10 minutes, the firefly luminescence was measured by Envision.

[0113] Measuring renilla luciferase activity: 20 μ L Stop-Glo Reagent was added to the 384-well plates. The plates were shaken for 1min and then centrifuged at 1000 rpm for 30 seconds. After waiting at least 10 minutes, the renilla luminescence was measured by Envision.

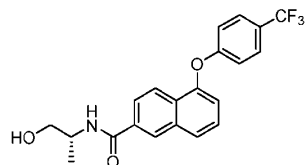
[0114] IC_{50} for firefly luciferase activity for Compound (I) is $\leq 0.1 \mu$ M.

[0115] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

What is claimed is:

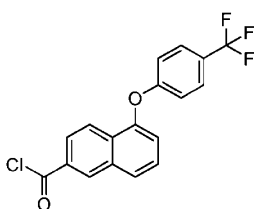
1. A process of synthesizing Compound (I):



Compound (I)

comprising:

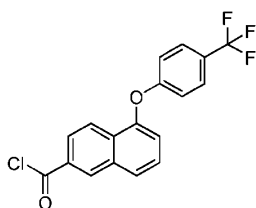
contacting Compound D



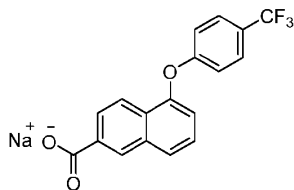
(Compound D)

with (*R*)-2-aminopropan-1-ol in the presence of a solvent.

2. The process of claim 1, wherein the solvent is 2-methyl-THF.
3. The process of claim 1 or 2, wherein Compound D:



(Compound D) is prepared by a process comprising:

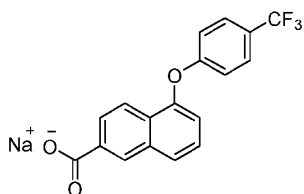


contacting Compound C

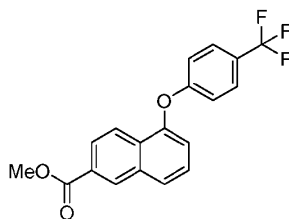
(Compound C)

with a chlorinating agent in the presence of a solvent.

4. The process of claim 3, wherein the chlorinating agent is thionyl chloride.
5. The process of claim 3 or 4, wherein the solvent is 2-methyl-THF.
6. The process of any one of claims 1-5, wherein Compound C:



(Compound C) is prepared by a process comprising:



contacting Compound B

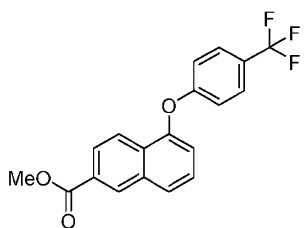
(Compound B)

with a base in the presence of a solvent.

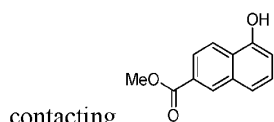
7. The process of claim 6, wherein the base is an inorganic base.
8. The process of claim 6, wherein the base is selected from NaOH, KOH, and CsOH.
9. The process of claim 8, wherein the base is NaOH.
10. The process of any one of claims 6-9, wherein the solvent is a mixture of 2-methyl-

THF and water.

11. The process of any one of claims 1-10, wherein Compound B:

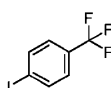


(Compound B) is prepared by a process comprising:



contacting

(Compound A1) with

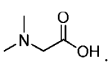


(Compound A2) in the

presence of a catalyst, a base, and a solvent.

12. The process of claim 11, wherein the catalyst is CuI and *N,N*-dimethylglycine.
13. The process of claim 11 or 12, wherein the base is an organic base.
14. The process of claim 13, wherein the organic base is selected from piperidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, *N,N*-diisopropylethylamine, and triethylamine.
15. The process of claim 11 or 12, wherein the base is an inorganic base.
16. The process of claim 15, wherein the inorganic base is selected from NaOH, KOH, CsOH, Cs_2CO_3 , K_2CO_3 , Na_2CO_3 , or $NaHCO_3$.

17. The process of claim 16, wherein the inorganic base is K_2CO_3 .
18. The process of any one of claims 11-17, wherein Compound A1 and Compound A2

further contact .

19. The process of any one of claims 11-18, wherein the solvent is selected from ethyl acetate, dichloromethane, tetrahydrofuran, diethyl ether, dimethylformamide, dimethylsulfoxide, methanol, ethanol, acetone, acetonitrile, 1,4-dioxane, hexane, and methyl *tert*-butyl ether.
20. The process of claim 19, wherein the solvent is 1,4-dioxane.
21. A crystalline form of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide, wherein the crystalline form is Form I having at least one of the following properties:
 - (a) an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 2**;
 - (b) an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.1° 2-Theta, 16.2° 2-Theta, 18.6° 2-Theta, 18.8° 2-Theta, 19.4° 2-Theta, 20.0° 2-Theta, 23.9° 2-Theta, 24.2° 2-Theta, and 28.4° 2-Theta;
 - (c) a DSC thermogram substantially similar to the one set forth in **Fig. 3**;
 - (d) a DSC thermogram with an endotherm having an onset at about 140 °C;
 - (e) a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Fig. 4**; or
 - (f) combinations thereof.
22. The crystalline form of claim 21, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern substantially the same as shown in **Fig. 2**.
23. The crystalline form of claim 21, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern with characteristic peaks at 8.1° 2-Theta, 16.2° 2-Theta, 18.6° 2-Theta, 18.8° 2-Theta, 19.4° 2-Theta, 20.0° 2-Theta, 23.9° 2-Theta, 24.2° 2-Theta, and 28.4° 2-Theta.
24. The crystalline form of claim 21, wherein the crystalline form has a DSC thermogram substantially similar to the one set forth in **Fig. 3**.
25. The crystalline form of claim 21, wherein the crystalline form has a DSC thermogram with an endotherm having an onset at about 140 °C.
26. The crystalline form of claim 21, wherein the crystalline form has a thermo-gravimetric analysis (TGA) substantially similar to the one set forth in **Fig. 4**.
27. The crystalline form of claim 21, wherein the crystalline form is characterized as having properties (a), (b), (c), (d), and (e).
28. The crystalline form of any one of claims 21-27, wherein the crystalline form is obtained from recrystallization of (R)-N-(1-hydroxypropan-2-yl)-5-(4-(trifluoromethyl)phenoxy)-2-naphthamide in ethanol.

29. A pharmaceutical composition comprising a crystalline form of any one of claims 21-28, and a pharmaceutically acceptable excipient.

30. A method of treating cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a crystalline form of any one of claims 21-28.

31. The method of claim 30, wherein the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

32. A method of treating polycystic kidney disease or liver fibrosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a crystalline form of any one of claims 21-28.