

Processes of Preparing PI3K Inhibitors

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/532,695, filed on August 15, 2023, which is incorporated by reference herein in its entirety.

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TECHNICAL FIELD

This disclosure provides processes of preparing compounds of Formula (I), such as (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1), and salts and/or solvates thereof, that inhibit phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3K α).

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BACKGROUND

Phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3K α), encoded by the *PIK3CA* gene is a part of the PI3K/AKT/TOR signaling network and is altered in several human cancers. Several investigators have demonstrated the role of PI3K/AKT signaling in physiological and pathophysiological functions that drive tumor progression such as metabolism, cell growth, proliferation, angiogenesis and metastasis. (See, Fruman, D.A. *The PI3K Pathway in Human Disease*. Cell 2017, 170, 605–635 and Janku, F. et al., *Targeting the PI3K pathway in cancer: Are we making headway?* Nat. Rev. Clin. Oncol. 2018, 15, 273–291.) Suppression (e.g., pharmacological or genetic) of PI3K/AKT/TOR signaling may cause cancer cell death and regression of tumor growth.

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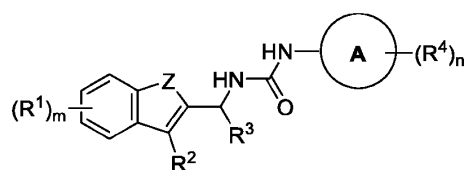
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Certain compounds of Formula (I) are described in WO 2022/265993, which is incorporated by reference herein in its entirety. There exists a need for alternative synthetic procedures for the preparation of compounds of Formula (I). Such alternative synthetic procedures are disclosed herein.

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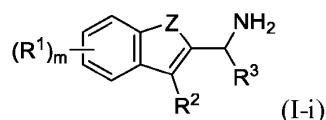
SUMMARY

Some embodiments provide a process of preparing a compound of Formula (I):



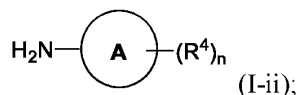
(I), or a salt and/or solvate thereof;

comprising contacting a compound of Formula (I-i):



with

- 5 (i) a carbonyl equivalent; and
(ii) a compound of Formula (I-ii)



to form the compound of Formula (I), wherein:

Z is O or NR^x;

10 R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

15 R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

20 each R⁴ is independently selected from the group consisting of:

- (i) halogen,
(ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or -NR^AR^B,
(iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,
25 (iv) C1-C6 haloalkyl,

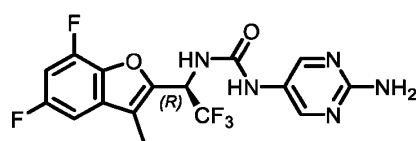
- (v) hydroxyl,
 (vi) cyano,
 (vii) -CO₂H,
 (viii) -NR^AR^B,
 5 (ix) =NR^{A2},
 (x) -C(=O)NR^CR^D,
 (xi) -SO₂(NR^ER^F),
 (xii) -SO₂(C1-C6 alkyl),
 (xiii) -S(=O)(=NH)(C1-C6 alkyl),
 10 (xiv) -C(=O)(C1-C6 alkyl),
 (xv) -CO₂(C1-C6 alkyl),
 (xvi) 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl,
 (xvii) 3-9 membered heterocyclyl optionally substituted with 1 or 2 independently selected
 R^G, and
 15 (xviii) 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected
 R^G;
 n is 0, 1, or 2;
 each R^A, R^{A1}, R^B, R^{B1}, R^C, R^{C1}, R^D, R^{D1}, R^E, and R^F is independently
 (i) hydrogen,
 20 (ii) hydroxyl,
 (iii) 4-6 membered heterocyclyl,
 (iv) C1-C6 haloalkyl,
 (v) -C(=O)(C1-C6 alkyl),
 (vi) -C(=O)O(C1-C6 alkyl),
 25 (vii) -SO₂(C1-C6 alkyl),
 (viii) 3-6 membered cycloalkyl optionally substituted with hydroxyl, or
 (ix) C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from
 hydroxyl, -C(=O)NR^{B2}R^{C2}, 5-6 membered heteroaryl, 3-6 membered cycloalkyl, -SO₂(C1-C6
 alkyl), -CO₂H, and -SO₂(NH₂); or
 30 R^C and R^D, together with the nitrogen atom to which they are attached form a 4-10
 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from

hydroxyl, halogen, $-C(=O)NR^{B1}R^{C1}$, $-SO_2(C1-C6 \text{ alkyl})$, $-CO_2H$, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, and C1-C6 haloalkoxy;

each R^{A2} , R^{B2} , and R^{C2} is independently hydrogen or C1-C6 alkyl; and

each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $=NR^{A2}$, $-C(=O)NR^{C1}R^{D1}$, $-CO_2(C1-C6 \text{ alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, C1-C6 haloalkoxy, $-SO_2(C1-C6 \text{ alkyl})$, and $-CO_2H$.

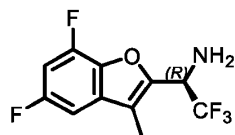
Some embodiments provide a process of preparing Compound 1, having the structure:



(1), or a salt and/or solvate thereof;

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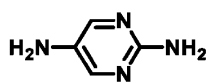
comprising contacting



with

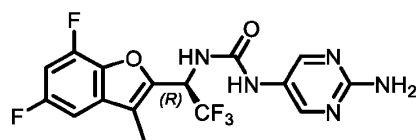
(i) a carbonyl equivalent; and

(ii) pyrimidine-2,5-diamine having the structure



to form Compound 1.

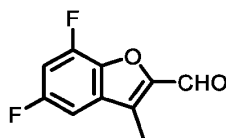
Some embodiments provide a process of preparing Compound 1, having the structure:



(1), or a salt and/or solvate thereof;

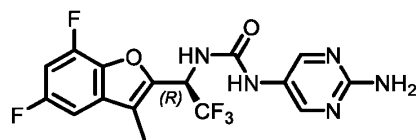
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comprising reacting

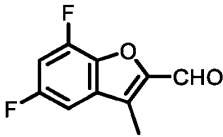
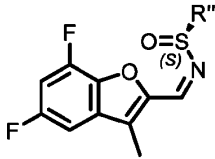


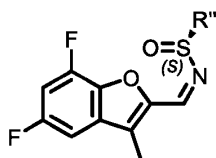
to form Compound 1.

Some embodiments provide a process of preparing Compound 1, having the structure:

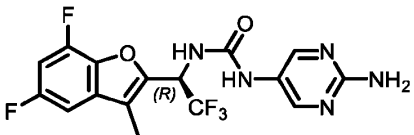


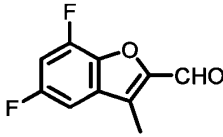
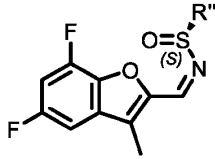
(1), or a salt and/or solvate thereof;

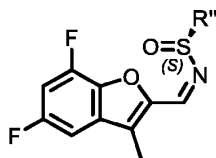
comprising contacting  with $\text{H}_2\text{N}-\text{S}^{(S)}(\text{O})-\text{R}''$ to form ,
wherein R'' is C1-C6 alkyl; and

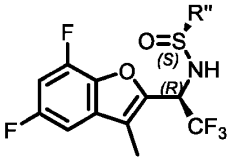
reacting  to form Compound 1.

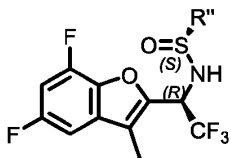
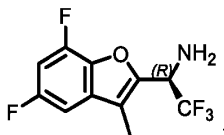
Some embodiments provide a process of preparing Compound 1, having the structure:

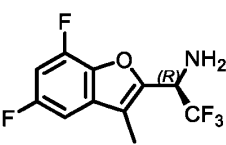
 (1), or a salt and/or solvate thereof;
comprising:

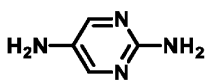
(a) contacting  with $\text{H}_2\text{N}-\text{S}^{(S)}(\text{O})-\text{R}''$ to form , wherein R'' is C1-C6 alkyl;

(b) contacting  with a trifluoromethylating reagent to form

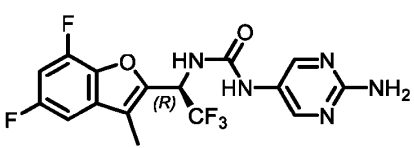
;

(c) contacting  with HCl to form ; and

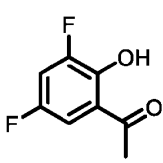
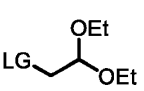
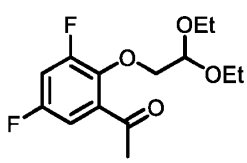
(d) contacting  with (i) a carbonyl equivalent; and (ii) pyrimidine-2,5-

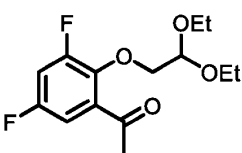
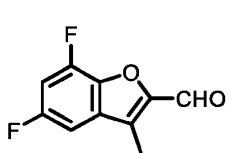
diamine having the structure  ;
to form Compound 1.

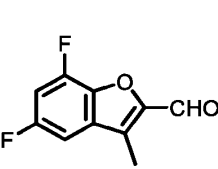
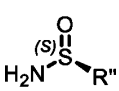
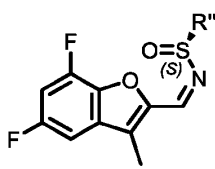
Some embodiments provide a process of preparing Compound 1, having the structure:

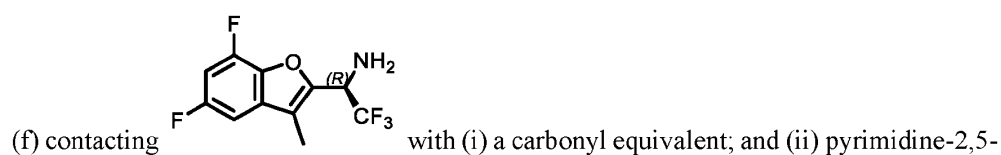
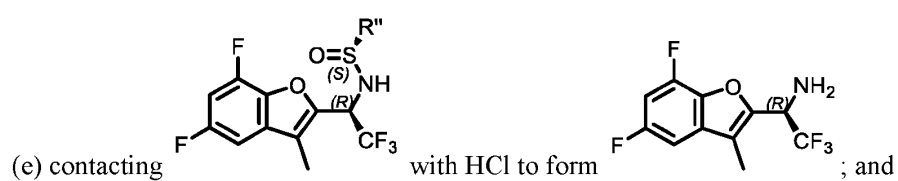
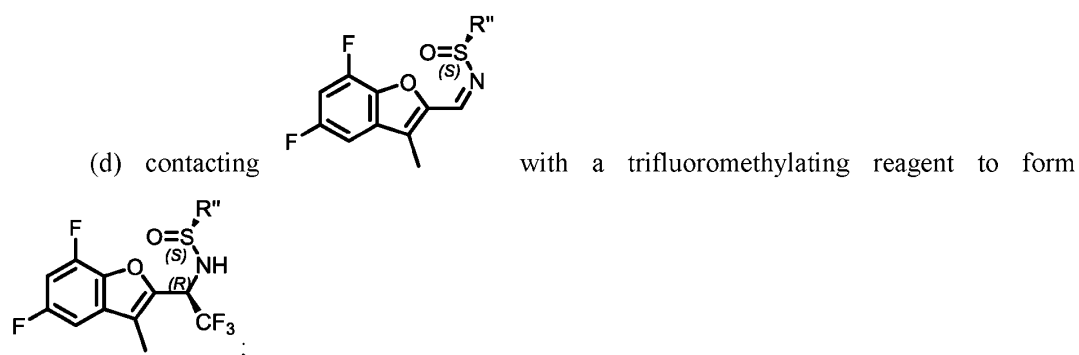
5  (1), or a salt and/or solvate thereof;

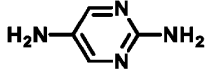
comprising:

(a) contacting  with  to form  , wherein LG is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;

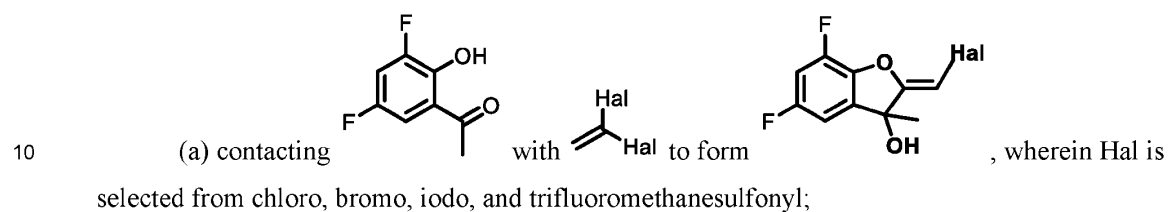
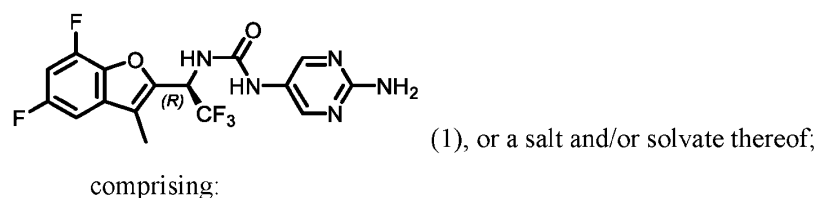
(b) contacting  with an acid to form  ;

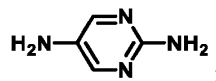
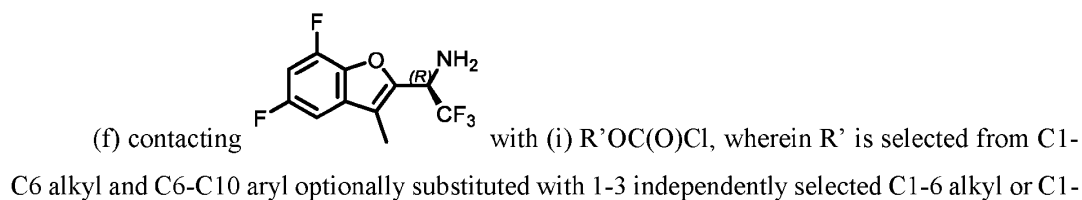
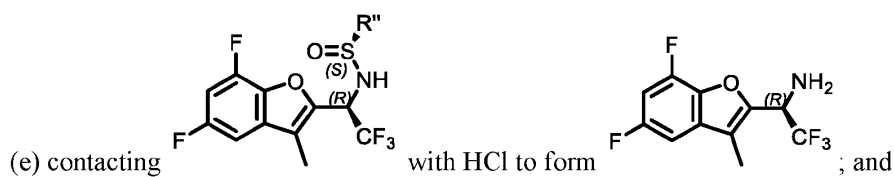
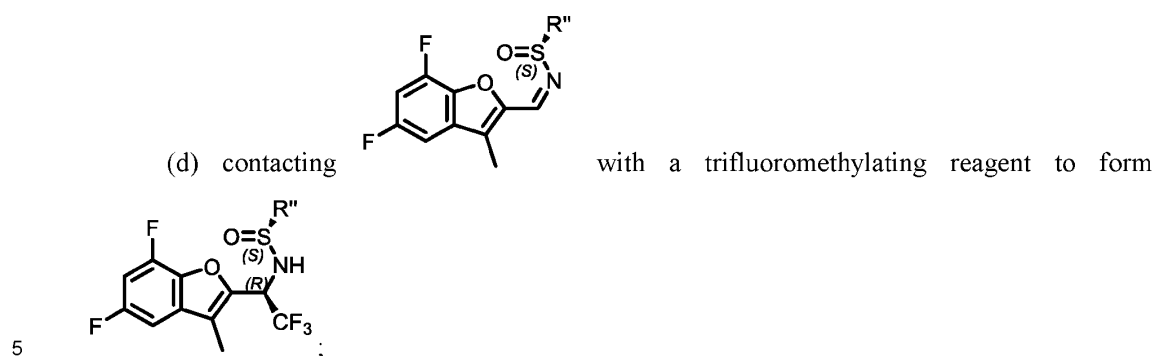
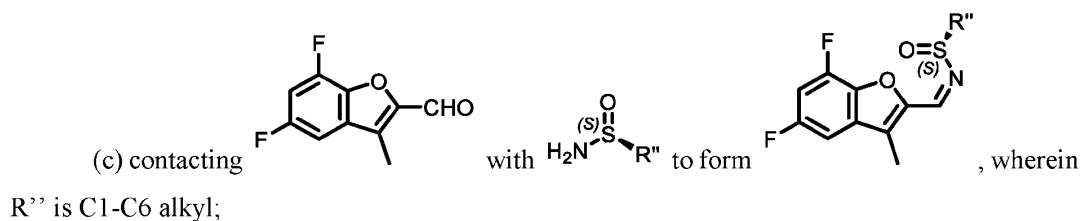
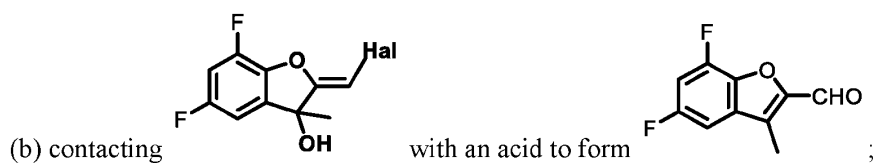
10 (c) contacting  with  to form  , wherein R'' is C1-C6 alkyl;



5 diamine having the structure ; to form Compound 1.

Some embodiments provide a process of preparing Compound 1, having the structure:





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to form Compound 1.

Other embodiments include those described in the Detailed Description and/or in the claims.

Additional Definitions

To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation, for example, within experimental variability and/or statistical experimental error, and thus the number or numerical range may vary up to $\pm 10\%$ of the stated number or numerical range.

“API” refers to an active pharmaceutical ingredient.

The term “pharmaceutically acceptable excipient” means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each component is “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid,

methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt is not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described herein form with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

The term “pharmaceutically acceptable solvate” refers to a solvate of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. A solvate is a crystalline solid that contains molecules of solvent inside its crystal lattice. Solvate forms of a compound can, in some instances, favorably alter the properties of the compound, such as solubility, stability, dissolution rate, and mechanical behavior. An exemplary solvate is a hydrate, which is a water solvate. When the average number of water molecules present in each repeating unit (i.e., unit cell) of the crystal lattice of a hydrate is known, the hydrate is affixed with a prefix denoting the average number of water molecules in each unit cell. For example, a monohydrate contains an average of one water molecule per unit cell, a dihydrate contains an average of two water molecules per unit cell, and a hemihydrate contains an average of half of a water molecule per unit cell. For more information, see, e.g., K.R. Morris, *Polymorphism in Pharmaceutical Solids* **1999**, pages 125-181; Jeffrey, G.A. *Acc. Chem. Res.* **1969**, 344-352; *Rev. Pure Appl. Chem.*, **1963**, 50-90; *Encyclopedia of Pharm. Tech.*, **1993**, 7, pages 393-441, each of which is incorporated herein in its entirety.

As used herein, the term “carbonyl equivalent” refers to a reagent that, when contacted with an amino group, reacts to form, e.g., a substrate of nucleophilic acyl substitution that can further react with a nucleophile such as an amine to form a urea. In some embodiments, the carbonyl equivalent is $R'OC(O)Cl$, wherein R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl, nitro, or C1-6 alkoxy. In some embodiments, the carbonyl equivalent is selected from the group consisting of: phenyl chloroformate, phosgene, trichloromethyl chloroformate (i.e., diphosgene), bis(trichloromethyl) carbonate (i.e., triphosgene), 4-nitrophenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester. In some embodiments, the carbonyl equivalent is phenyl chloroformate.

As used herein, the term “isocyanate-forming reagent” refers to a reagent that, when contacted with an amino group, reacts to form an isocyanate. The isocyanate can further react with an amine to form a urea. In some embodiments, the isocyanate-forming reagent is selected from the group consisting of: phosgene (toluene solution), trichloromethyl chloroformate (diphosgene), bis(trichloromethyl) carbonate (triphosgene), 4-nitrophenyl chloroformate, phenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester.

The term “halo” refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

The term “oxo” refers to a divalent doubly bonded oxygen atom (i.e., “=O”). As used herein, oxo groups are attached to carbon atoms to form carbonyls.

The term “hydroxyl” refers to an -OH radical.

The term “cyano” refers to a -CN radical.

The term “alkyl” refers to a saturated acyclic hydrocarbon radical that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_{1-10} indicates that the group may have from 1 to 10 (inclusive) carbon atoms in it. Alkyl groups can either be unsubstituted or substituted with one or more substituents. Non-limiting examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl. The term “saturated” as used in this context means only single bonds present between constituent carbon atoms and other available valences occupied by hydrogen and/or other substituents as defined herein.

The term "haloalkyl" refers to an alkyl, in which one or more hydrogen atoms is/are replaced with an independently selected halo.

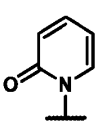
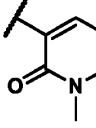
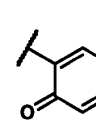
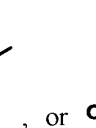
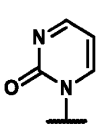
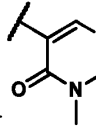
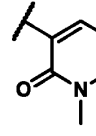
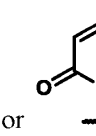
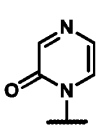
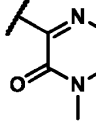
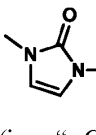
The term "alkoxy" refers to an -O-alkyl radical (e.g., -OCH₃).

The term "aryl" refers to a 6-20 carbon mono-, bi-, tri- or polycyclic group wherein at least one ring in the system is aromatic (e.g., 6-carbon monocyclic, 10-carbon bicyclic, or 14-carbon tricyclic aromatic ring system); and wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of aryl groups include phenyl, naphthyl, tetrahydronaphthyl, and the like.

The term "cycloalkyl" as used herein refers to cyclic saturated hydrocarbon groups having, e.g., 3 to 20 ring carbons, preferably 3 to 16 ring carbons, and more preferably 3 to 12 ring carbons or 3-10 ring carbons or 3-6 ring carbons, wherein the cycloalkyl group may be optionally substituted. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl may include multiple fused and/or bridged rings. Non-limiting examples of fused/bridged cycloalkyl includes: bicyclo[1.1.0]butane, bicyclo[2.1.0]pentane, bicyclo[1.1.1]pentane, bicyclo[3.1.0]hexane, bicyclo[2.1.1]hexane, bicyclo[3.2.0]heptane, bicyclo[4.1.0]heptane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[4.2.0]octane, bicyclo[3.2.1]octane, bicyclo[2.2.2]octane, and the like. Cycloalkyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic cycloalkyls include spiro[2.2]pentane, spiro[2.5]octane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[4.4]nonane, spiro[2.6]nonane, spiro[4.5]decane, spiro[3.6]decane, spiro[5.5]undecane, and the like. The term "saturated" as used in this context means only single bonds present between constituent carbon atoms.

The term "heteroaryl", as used herein, means a mono-, bi-, tri- or polycyclic group having 5 to 20 ring atoms, alternatively 5, 6, 9, 10, or 14 ring atoms; wherein at least one ring in the system contains one or more heteroatoms independently selected from the group consisting of N, O, and S and at least one ring in the system is aromatic (but does not have to be a ring which contains a heteroatom, e.g. tetrahydroisoquinoliny, e.g., tetrahydroquinoliny). Heteroaryl groups can either be unsubstituted or substituted with one or more substituents. Examples of heteroaryl include thienyl, pyridinyl, furyl, oxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranlyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl,

thiazolyl, benzothienyl, benzoxadiazolyl, benzofuranyl, benzimidazolyl, benzotriazolyl, cinnolinyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, purinyl, thienopyridinyl, pyrido[2,3-*d*]pyrimidinyl, pyrrolo[2,3-*b*]pyridinyl, quinazolinyl, quinolinyl, thieno[2,3-*c*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, pyrazolo[3,4-*c*]pyridinyl, pyrazolo[4,3-*c*]pyridine, pyrazolo[4,3-*b*]pyridinyl, tetrazolyl, chromane, 2,3-dihydrobenzo[*b*][1,4]dioxine, benzo[*d*][1,3]dioxole, 2,3-dihydrobenzofuran, tetrahydroquinoline, 2,3-dihydrobenzo[*b*][1,4]oxathiine, isoindoline, and others. In some embodiments, the heteroaryl is selected from thienyl, pyridinyl, furyl, pyrazolyl, imidazolyl, isoindolinyl, pyranyl, pyrazinyl, and pyrimidinyl. For purposes of clarification, heteroaryl also includes aromatic lactams, aromatic cyclic ureas, or vinylogous analogs thereof, in which each ring nitrogen adjacent to a carbonyl is tertiary (i.e., all three valences are occupied by non-hydrogen substituents), such as one or more

of pyridone (e.g., , , , or ) , pyrimidone (e.g., , or ) , pyridazinone (e.g., , or ) , pyrazinone (e.g., ) , or ) , and imidazolone (e.g., ) , wherein each ring nitrogen adjacent to a carbonyl is tertiary (i.e., the oxo group (i.e., “=O”) herein is a constituent part of the heteroaryl ring).

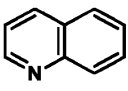
The term "heterocyclyl" refers to a mono-, bi-, tri-, or polycyclic saturated or partially unsaturated ring system with 3-16 ring atoms (e.g., 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system) having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic or polycyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein one or more ring atoms may be substituted by 1-3 oxo (forming, e.g., a lactam) and one or more N or S atoms may be substituted by 1-2 oxido (forming, e.g., an N-oxide, an S-oxide, or an S,S-dioxide), valence permitting; and wherein 0, 1, 2 or 3 atoms

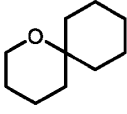
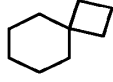
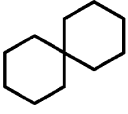
of each ring may be substituted by a substituent. Examples of heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, tetrahydropyridyl, dihydropyrazinyl, dihydropyridyl, dihydropyrrolyl, dihydrofuranyl, dihydrothiophenyl, and the like. Heterocyclyl may include multiple fused and bridged rings. Non-limiting examples of fused/bridged heterocyclyl includes: 2-azabicyclo[1.1.0]butane, 2-azabicyclo[2.1.0]pentane, 2-azabicyclo[1.1.1]pentane, 3-azabicyclo[3.1.0]hexane, 5-azabicyclo[2.1.1]hexane, 3-azabicyclo[3.2.0]heptane, octahydrocyclopenta[c]pyrrole, 3-azabicyclo[4.1.0]heptane, 7-azabicyclo[2.2.1]heptane, 6-azabicyclo[3.1.1]heptane, 7-azabicyclo[4.2.0]octane, 2-azabicyclo[2.2.2]octane, 3-azabicyclo[3.2.1]octane, 2-oxabicyclo[1.1.0]butane, 2-oxabicyclo[2.1.0]pentane, 2-oxabicyclo[1.1.1]pentane, 3-oxabicyclo[3.1.0]hexane, 5-oxabicyclo[2.1.1]hexane, 3-oxabicyclo[3.2.0]heptane, 3-oxabicyclo[4.1.0]heptane, 7-oxabicyclo[2.2.1]heptane, 6-oxabicyclo[3.1.1]heptane, 7-oxabicyclo[4.2.0]octane, 2-oxabicyclo[2.2.2]octane, 3-oxabicyclo[3.2.1]octane, and the like. Heterocyclyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic heterocyclyls include 2-azaspiro[2.2]pentane, 4-azaspiro[2.5]octane, 1-azaspiro[3.5]nonane, 2-azaspiro[3.5]nonane, 7-azaspiro[3.5]nonane, 2-azaspiro[4.4]nonane, 6-azaspiro[2.6]nonane, 1,7-diazaspiro[4.5]decane, 7-azaspiro[4.5]decane, 2,5-diazaspiro[3.6]decane, 3-azaspiro[5.5]undecane, 2-oxaspiro[2.2]pentane, 4-oxaspiro[2.5]octane, 1-oxaspiro[3.5]nonane, 2-oxaspiro[3.5]nonane, 7-oxaspiro[3.5]nonane, 2-oxaspiro[4.4]nonane, 6-oxaspiro[2.6]nonane, 1,7-dioxaspiro[4.5]decane, 2,5-dioxaspiro[3.6]decane, 1-oxaspiro[5.5]undecane, 3-oxaspiro[5.5]undecane, 3-oxa-9-azaspiro[5.5]undecane and the like.

As used herein, examples of aromatic rings include: benzene, pyridine, pyrimidine, pyrazine, pyridazine, pyridone, pyrrole, pyrazole, oxazole, thioazole, isoxazole, isothiazole, and the like.

As used herein, when a ring is described as being “partially unsaturated”, it means said ring has one or more additional degrees of unsaturation (in addition to the degree of unsaturation attributed to the ring itself; e.g., one or more double or triple bonds between constituent ring atoms), provided that the ring is not aromatic. Examples of such rings include: cyclopentene, cyclohexene, cycloheptene, dihydropyridine, tetrahydropyridine, dihydropyrrole, dihydrofuran, dihydrothiophene, and the like.

For the avoidance of doubt, and unless otherwise specified, for rings and cyclic groups (e.g., aryl, heteroaryl, heterocyclyl, cycloalkyl, and the like described herein) containing a sufficient number of ring atoms to form bicyclic or higher order ring systems (e.g., tricyclic, polycyclic ring systems), it is understood that such rings and cyclic groups encompass those having fused rings, including those in which the points of fusion are located (i) on adjacent ring atoms

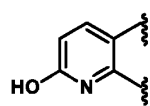
(e.g., [x.x.0] ring systems, in which 0 represents a zero atom bridge (e.g., )); (ii) a

single ring atom (spiro-fused ring systems) (e.g., , , or ), or (iii)

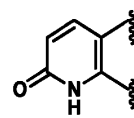
a contiguous array of ring atoms (bridged ring systems having all bridge lengths > 0) (e.g., , or ).

In addition, atoms making up the compounds of the present embodiments are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C .

In addition, the compounds generically or specifically disclosed herein are intended to include all tautomeric forms. Thus, by way of example, a compound containing the moiety:



encompasses the tautomeric form containing the moiety:



Similarly, a pyridinyl or pyrimidinyl moiety that is described to be optionally substituted with hydroxyl encompasses pyridone or pyrimidone tautomeric forms.

The compounds provided herein may encompass various stereochemical forms. The compounds also encompass enantiomers (e.g., R and S isomers), diastereomers, as well as mixtures of enantiomers (e.g., R and S isomers) including racemic mixtures and mixtures of diastereomers, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry (e.g., a “flat”

structure) and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound. Likewise, unless otherwise indicated, when a disclosed compound is named or depicted by a structure that specifies the stereochemistry (e.g., a structure with “wedge” and/or “dashed” bonds) and has one or more chiral centers, it is understood to represent the indicated stereoisomer of the compound.

The details of one or more embodiments of this disclosure are set forth in the accompanying drawings and the description below. Other features and advantages of the present disclosure will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 depicts a XRPD diffractogram of Compound 1, Form 1 hemi hydrate.

FIG. 2 depicts a TG/DSC thermogram of Form 1.

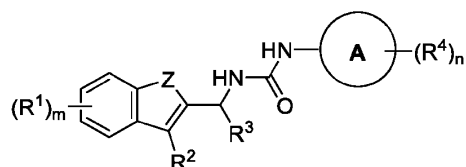
FIG. 3 depicts a DSC thermogram (first heat cycle) of Form 1.

FIG. 4 depicts a DSC thermogram (first cool cycle) of Form 1.

DETAILED DESCRIPTION

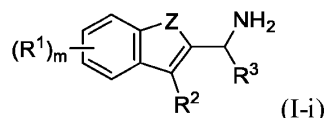
This disclosure provides processes of preparing compounds of Formula (I), such as (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1), and salts and/or solvates thereof, that inhibit phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3K α).

Some embodiments provide a process of preparing a compound of Formula (I):



(I), or a salt and/or solvate thereof;

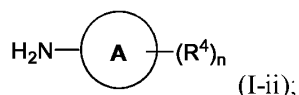
comprising contacting a compound of Formula (I-i):



(I-i)

with

- (i) a carbonyl equivalent or an isocyanate-forming reagent; and
 (ii) a compound of Formula (I-ii)



to form the compound of Formula (I), wherein:

5

Z is O or NR^x;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

10

R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

15

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

each R⁴ is independently selected from the group consisting of:

(i) halogen,

(ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or -NR^AR^B,

20

(iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,

(iv) C1-C6 haloalkyl,

(v) hydroxyl,

(vi) cyano,

(vii) -CO₂H,

25

(viii) -NR^AR^B,

(ix) =NR^{A2},

(x) -C(=O)NR^CR^D,

(xi) -SO₂(NR^ER^F),

(xii) -SO₂(C1-C6 alkyl),

30

(xiii) -S(=O)(=NH)(C1-C6 alkyl),

- (xiv) -C(=O)(C1-C6 alkyl),
- (xv) -CO₂(C1-C6 alkyl),
- (xvi) 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl,
- (xvii) 3-9 membered heterocyclyl optionally substituted with 1 or 2 independently selected

5 R^G, and

- (xviii) 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected R^G,

n is 0, 1, or 2;

each R^A, R^{A1}, R^B, R^{B1}, R^C, R^{C1}, R^D, R^{D1}, R^E, and R^F is independently

10 (i) hydrogen,

(ii) hydroxyl,

(iii) 4-6 membered heterocyclyl,

(iv) C1-C6 haloalkyl,

(v) -C(=O)(C1-C6 alkyl),

15 (vi) -C(=O)O(C1-C6 alkyl),

(vii) -SO₂(C1-C6 alkyl),

(viii) 3-6 membered cycloalkyl optionally substituted with hydroxyl, or

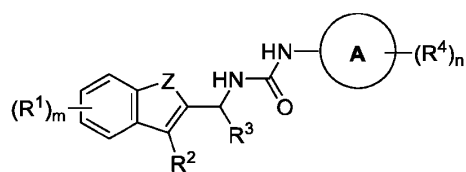
(ix) C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, -C(=O)NR^{B2}R^{C2}, 5-6 membered heteroaryl, 3-6 membered cycloalkyl, -SO₂(C1-C6 alkyl), -CO₂H, and -SO₂(NH₂); or

20 R^C and R^D, together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from hydroxyl, halogen, -C(=O)NR^{B1}R^{C1}, -SO₂(C1-C6 alkyl), -CO₂H, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, and C1-C6 haloalkoxy;

25 each R^{A2}, R^{B2}, and R^{C2} is independently hydrogen or C1-C6 alkyl; and

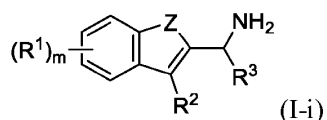
each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, -NR^{A1}R^{B1}, =NR^{A2}, -C(=O)NR^{C1}R^{D1}, -CO₂(C1-C6 alkyl), C1-C6 haloalkyl, C3-C6 cycloalkyl, C1-C6 haloalkoxy, -SO₂(C1-C6 alkyl), and -CO₂H.

30 Some embodiments provide a process of preparing a compound of Formula (I):



(I), or a salt and/or solvate thereof;

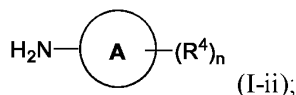
comprising contacting a compound of Formula (I-i):



(I-i)

with

- 5 (i) a carbonyl equivalent; and
(ii) a compound of Formula (I-ii)



(I-ii);

to form the compound of Formula (I), wherein:

Z is O or NR^x;

10 R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

15 R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

20 each R⁴ is independently selected from the group consisting of:

- (i) halogen,
(ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or -NR^AR^B,
(iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,
25 (iv) C1-C6 haloalkyl,

- (v) hydroxyl,
 (vi) cyano,
 (vii) -CO₂H,
 (viii) -NR^AR^B,
 5 (ix) =NR^{A2},
 (x) -C(=O)NR^CR^D,
 (xi) -SO₂(NR^ER^F),
 (xii) -SO₂(C1-C6 alkyl),
 (xiii) -S(=O)(=NH)(C1-C6 alkyl),
 10 (xiv) -C(=O)(C1-C6 alkyl),
 (xv) -CO₂(C1-C6 alkyl),
 (xvi) 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl,
 (xvii) 3-9 membered heterocyclyl optionally substituted with 1 or 2 independently selected
 R^G, and
 15 (xviii) 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected
 R^G,
 n is 0, 1, or 2;
 each R^A, R^{A1}, R^B, R^{B1}, R^C, R^{C1}, R^D, R^{D1}, R^E, and R^F is independently
 (i) hydrogen,
 20 (ii) hydroxyl,
 (iii) 4-6 membered heterocyclyl,
 (iv) C1-C6 haloalkyl,
 (v) -C(=O)(C1-C6 alkyl),
 (vi) -C(=O)O(C1-C6 alkyl),
 25 (vii) -SO₂(C1-C6 alkyl),
 (viii) 3-6 membered cycloalkyl optionally substituted with hydroxyl, or
 (ix) C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from
 hydroxyl, -C(=O)NR^{B2}R^{C2}, 5-6 membered heteroaryl, 3-6 membered cycloalkyl, -SO₂(C1-C6
 alkyl), -CO₂H, and -SO₂(NH₂); or
 30 R^C and R^D, together with the nitrogen atom to which they are attached form a 4-10
 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from

hydroxyl, halogen, $-\text{C}(=\text{O})\text{NR}^{\text{B}1}\text{R}^{\text{C}1}$, $-\text{SO}_2(\text{C}1\text{-C}6 \text{ alkyl})$, $-\text{CO}_2\text{H}$, $\text{C}1\text{-C}6 \text{ alkyl}$ optionally substituted with hydroxyl, $\text{C}1\text{-C}6 \text{ alkoxy}$, and $\text{C}1\text{-C}6 \text{ haloalkoxy}$;

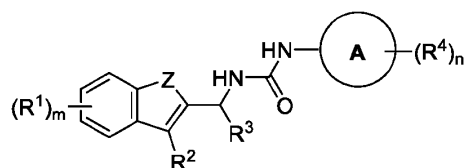
each $\text{R}^{\text{A}2}$, $\text{R}^{\text{B}2}$, and $\text{R}^{\text{C}2}$ is independently hydrogen or $\text{C}1\text{-C}6 \text{ alkyl}$; and

each R^{G} is independently selected from the group consisting of: fluoro, cyano, hydroxyl, $\text{C}1\text{-C}6 \text{ alkyl}$ optionally substituted with hydroxyl, $\text{C}1\text{-C}6 \text{ alkoxy}$, $-\text{NR}^{\text{A}1}\text{R}^{\text{B}1}$, $=\text{NR}^{\text{A}2}$, $-\text{C}(=\text{O})\text{NR}^{\text{C}1}\text{R}^{\text{D}1}$, $-\text{CO}_2(\text{C}1\text{-C}6 \text{ alkyl})$, $\text{C}1\text{-C}6 \text{ haloalkyl}$, $\text{C}3\text{-C}6 \text{ cycloalkyl}$, $\text{C}1\text{-C}6 \text{ haloalkoxy}$, $-\text{SO}_2(\text{C}1\text{-C}6 \text{ alkyl})$, and $-\text{CO}_2\text{H}$.

In some embodiments, the carbonyl equivalent or isocyanate-forming reagent is a carbonyl equivalent. In some embodiments, the carbonyl equivalent is $\text{R}'\text{OC}(\text{O})\text{Cl}$, wherein R' is selected from $\text{C}1\text{-C}6 \text{ alkyl}$ and $\text{C}6\text{-C}10 \text{ aryl}$ optionally substituted with 1-3 independently selected $\text{C}1\text{-C}6 \text{ alkyl}$, nitro, or $\text{C}1\text{-C}6 \text{ alkoxy}$. In some embodiments, the carbonyl equivalent is selected from the group consisting of: phenyl chloroformate, phosgene, trichloromethyl chloroformate (i.e., diphosgene), bis(trichloromethyl) carbonate (i.e., triphosgene), 4-nitrophenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester. In some embodiments, the carbonyl equivalent is phenyl chloroformate.

In some embodiments, the carbonyl equivalent or isocyanate-forming reagent is an or isocyanate-forming reagent. In some embodiments, the isocyanate-forming reagent is selected from the group consisting of: phosgene (toluene solution), trichloromethyl chloroformate (diphosgene), bis(trichloromethyl) carbonate (triphosgene), 4-nitrophenyl chloroformate, phenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester.

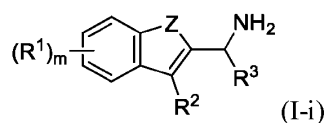
Some embodiments provide a compound of Formula (I):



(I), or a salt and/or solvate thereof

prepared by a process comprising:

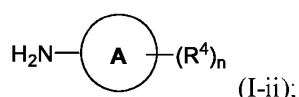
contacting a compound of Formula (I-i):



with

(i) a carbonyl equivalent or an isocyanate-forming reagent; and

(ii) a compound of Formula (I-ii)



to form the compound of Formula (I), wherein:

Z is O or NR^x;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

each R⁴ is independently selected from the group consisting of:

- (i) halogen,
- (ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or -NR^AR^B,
- (iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,
- (iv) C1-C6 haloalkyl,
- (v) hydroxyl,
- (vi) cyano,
- (vii) -CO₂H,
- (viii) -NR^AR^B,
- (ix) =NR^{A2},

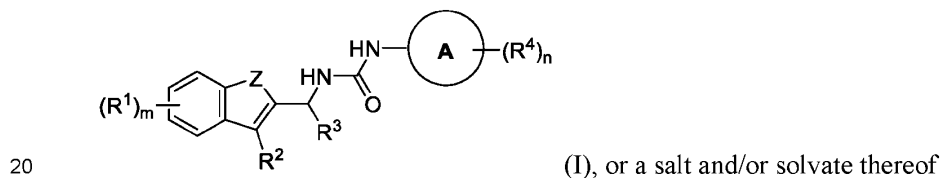
- (x) $-C(=O)NR^C R^D$,
 (xi) $-SO_2(NR^E R^F)$,
 (xii) $-SO_2(C1-C6 \text{ alkyl})$,
 (xiii) $-S(=O)(=NH)(C1-C6 \text{ alkyl})$,
 5 (xiv) $-C(=O)(C1-C6 \text{ alkyl})$,
 (xv) $-CO_2(C1-C6 \text{ alkyl})$,
 (xvi) 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl,
 (xvii) 3-9 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G , and
 10 (xviii) 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected R^G ;
 n is 0, 1, or 2;
 each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently
 (i) hydrogen,
 15 (ii) hydroxyl,
 (iii) 4-6 membered heterocyclyl,
 (iv) C1-C6 haloalkyl,
 (v) $-C(=O)(C1-C6 \text{ alkyl})$,
 (vi) $-C(=O)O(C1-C6 \text{ alkyl})$,
 20 (vii) $-SO_2(C1-C6 \text{ alkyl})$,
 (viii) 3-6 membered cycloalkyl optionally substituted with hydroxyl, or
 (ix) C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-C(=O)NR^{B2}R^{C2}$, 5-6 membered heteroaryl, 3-6 membered cycloalkyl, $-SO_2(C1-C6 \text{ alkyl})$, $-CO_2H$, and $-SO_2(NH_2)$; or
 25 R^C and R^D , together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from hydroxyl, halogen, $-C(=O)NR^{B1}R^{C1}$, $-SO_2(C1-C6 \text{ alkyl})$, $-CO_2H$, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, and C1-C6 haloalkoxy;
 each R^{A2} , R^{B2} , and R^{C2} is independently hydrogen or C1-C6 alkyl; and
 30 each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $=NR^{A2}$, -

$C(=O)NR^{C1}R^{D1}$, $-CO_2(C1-C6 \text{ alkyl})$, $C1-C6 \text{ haloalkyl}$, $C3-C6 \text{ cycloalkyl}$, $C1-C6 \text{ haloalkoxy}$, $-SO_2(C1-C6 \text{ alkyl})$, and $-CO_2H$.

In some embodiments, the carbonyl equivalent or isocyanate-forming reagent is a carbonyl equivalent. In some embodiments, the carbonyl equivalent is $R'OC(O)Cl$, wherein R' is selected from $C1-C6 \text{ alkyl}$ and $C6-C10 \text{ aryl}$ optionally substituted with 1-3 independently selected $C1-6 \text{ alkyl}$, nitro, or $C1-6 \text{ alkoxy}$. In some embodiments, the carbonyl equivalent is selected from the group consisting of: phenyl chloroformate, phosgene, trichloromethyl chloroformate (i.e., diphosgene), bis(trichloromethyl) carbonate (i.e., triphosgene), 4-nitrophenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester. In some embodiments, the carbonyl equivalent is phenyl chloroformate.

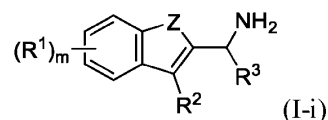
In some embodiments, the carbonyl equivalent or isocyanate-forming reagent is an or isocyanate-forming reagent. In some embodiments, the isocyanate-forming reagent is selected from the group consisting of: phosgene (toluene solution), trichloromethyl chloroformate (diphosgene), bis(trichloromethyl) carbonate (triphosgene), 4-nitrophenyl chloroformate, phenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester.

Some embodiments provide a compound of Formula (I):



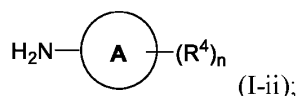
prepared by a process comprising:

contacting a compound of Formula (I-i):



with

- 25 (i) a carbonyl equivalent; and
(ii) a compound of Formula (I-ii)



to form the compound of Formula (I), wherein:

Z is O or NR^x;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

5 each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

10 R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

each R⁴ is independently selected from the group consisting of:

15 (i) halogen,

(ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or -NR^AR^B,

(iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,

(iv) C1-C6 haloalkyl,

20 (v) hydroxyl,

(vi) cyano,

(vii) -CO₂H,

(viii) -NR^AR^B,

(ix) =NR^{A2},

25 (x) -C(=O)NR^CR^D,

(xi) -SO₂(NR^ER^F),

(xii) -SO₂(C1-C6 alkyl),

(xiii) -S(=O)(=NH)(C1-C6 alkyl),

(xiv) -C(=O)(C1-C6 alkyl),

30 (xv) -CO₂(C1-C6 alkyl),

(xvi) 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl,
 (xvii) 3-9 membered heterocyclyl optionally substituted with 1 or 2 independently selected
 R^G , and

(xviii) 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected
 R^G ;

n is 0, 1, or 2;

each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently

(i) hydrogen,

(ii) hydroxyl,

(iii) 4-6 membered heterocyclyl,

(iv) C1-C6 haloalkyl,

(v) $-C(=O)(C1-C6 \text{ alkyl})$,

(vi) $-C(=O)O(C1-C6 \text{ alkyl})$,

(vii) $-SO_2(C1-C6 \text{ alkyl})$,

(viii) 3-6 membered cycloalkyl optionally substituted with hydroxyl, or

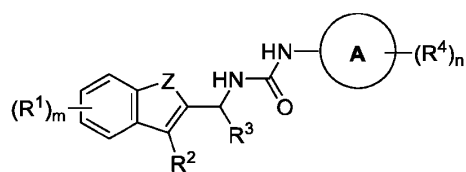
(ix) C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-C(=O)NR^{B2}R^{C2}$, 5-6 membered heteroaryl, 3-6 membered cycloalkyl, $-SO_2(C1-C6 \text{ alkyl})$, $-CO_2H$, and $-SO_2(NH_2)$; or

R^C and R^D , together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from hydroxyl, halogen, $-C(=O)NR^{B1}R^{C1}$, $-SO_2(C1-C6 \text{ alkyl})$, $-CO_2H$, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, and C1-C6 haloalkoxy;

each R^{A2} , R^{B2} , and R^{C2} is independently hydrogen or C1-C6 alkyl; and

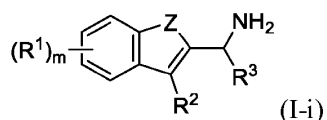
each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $=NR^{A2}$, $-C(=O)NR^{C1}R^{D1}$, $-CO_2(C1-C6 \text{ alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, C1-C6 haloalkoxy, $-SO_2(C1-C6 \text{ alkyl})$, and $-CO_2H$.

Some embodiments provide a process of preparing a compound of Formula (I):



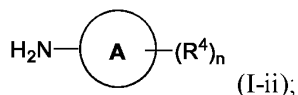
(I), or a salt and/or solvate thereof

comprising contacting a compound of Formula (I-i):



with

- 5 (i) a carbonyl equivalent; and
(ii) a compound of Formula (I-ii)



to form the compound of Formula (I), wherein:

Z is O or NR^x;

10 R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

15 R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

20 each R⁴ is independently selected from the group consisting of:

- (i) halogen,
(ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or -NR^AR^B,
(iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,
25 (iv) C1-C6 haloalkyl,

- (v) hydroxyl,
 (vi) cyano,
 (vii) -CO₂H,
 (viii) -NR^AR^B,
 5 (ix) =NR^{A2},
 (x) -C(=O)NR^CR^D,
 (xi) -SO₂(NR^ER^F),
 (xii) -SO₂(C1-C6 alkyl),
 (xiii) -S(=O)(=NH)(C1-C6 alkyl),
 10 (xiv) -C(=O)(C1-C6 alkyl),
 (xv) -CO₂(C1-C6 alkyl),
 (xvi) 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl,
 (xvii) 3-9 membered heterocyclyl optionally substituted with 1 or 2 independently selected
 R^G, and
 15 (xviii) 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected
 R^G,
 n is 0, 1, or 2;
 each R^A, R^{A1}, R^B, R^{B1}, R^C, R^{C1}, R^D, R^{D1}, R^E, and R^F is independently
 (i) hydrogen,
 20 (ii) hydroxyl,
 (iii) 4-6 membered heterocyclyl,
 (iv) C1-C6 haloalkyl,
 (v) -C(=O)(C1-C6 alkyl),
 (vi) -C(=O)O(C1-C6 alkyl),
 25 (vii) -SO₂(C1-C6 alkyl),
 (viii) 3-6 membered cycloalkyl optionally substituted with hydroxyl, or
 (ix) C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from
 hydroxyl, -C(=O)NR^{B2}R^{C2}, 5-6 membered heteroaryl, 3-6 membered cycloalkyl, -SO₂(C1-C6
 alkyl), -CO₂H, and -SO₂(NH₂); or
 30 R^C and R^D, together with the nitrogen atom to which they are attached form a 4-10
 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from

hydroxyl, halogen, $-C(=O)NR^{B1}R^{C1}$, $-SO_2(C1-C6 \text{ alkyl})$, $-CO_2H$, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, and C1-C6 haloalkoxy;

each R^{A2} , R^{B2} , and R^{C2} is independently hydrogen or C1-C6 alkyl; and

each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $=NR^{A2}$, $-C(=O)NR^{C1}R^{D1}$, $-CO_2(C1-C6 \text{ alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, C1-C6 haloalkoxy, $-SO_2(C1-C6 \text{ alkyl})$, and $-CO_2H$.

In some embodiments, contacting the compound of Formula (I-i) with the carbonyl equivalent and the compound of Formula (I-ii) to form the compound of Formula (I) comprises adding the carbonyl equivalent to the compound of Formula (I-i) and a base to form mixture 1, then adding the compound of Formula (I-ii) to mixture 1 to form mixture 2.

In some embodiments, the molar ratio of the carbonyl equivalent to the compound of Formula (I-i) is about 1.0 to about 4.0 (e.g., about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3). In some embodiments, the molar ratio of the carbonyl equivalent to the compound of Formula (I-i) is about 1.05. In some embodiments, the molar ratio of the carbonyl equivalent to the compound of Formula (I-i) is about 1.3.

In some embodiments, the molar ratio of the base to the compound of Formula (I-i) is about 1.0 to about 5.0 (e.g., about 2.0 to about 5.0, about 2.0 to about 4.0, about 2.5 to about 3.5, about 3.0, or about 3.5). In some embodiments, the molar ratio of the sodium bicarbonate to the compound of Formula (I-i) is about 3.0. In some embodiments, the molar ratio of the sodium bicarbonate to the compound of Formula (I-i) is about 3.5.

In some embodiments, adding the carbonyl equivalent to the compound of Formula (I-i) and a base to form mixture 1 is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.

In some embodiments, adding the carbonyl equivalent to the compound of Formula (I-i) and the base to form mixture 1 is performed under an inert atmosphere. In some embodiments,

the adding is performed under nitrogen. In some embodiments, the adding is performed under argon.

In some embodiments, adding the carbonyl equivalent to the compound of Formula (I-i) and the base is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 2 °C, or about 0 °C). In some embodiments, adding the carbonyl equivalent to the compound of Formula (I-i) is performed at about 0 °C to about 5 °C. In some embodiments, adding the carbonyl equivalent to the compound of Formula (I-i) is performed at about 0 °C to about 2 °C. In some embodiments, adding the carbonyl equivalent to the compound of Formula (I-i) is performed at about 0 °C.

In some embodiments, after adding the carbonyl equivalent to the compound of Formula (I-i) and the base, mixture 1 is agitated for about 1 hour to about 7 days (e.g., about 1 hour to about 2 days, about 5 hours to about 1 day, about 10 hours to about 18 hours, about 10 hours to about 14 hours, about 14 hours to about 18 hours, about 12 hours to about 16 hours, about 14 hours to about 16 hours, or about 16 hours).

In some embodiments, adding the compound of Formula (I-ii) to mixture 1 to form mixture 2 comprises adding a second base to mixture 1 and the compound of Formula (I-ii) to mixture 1. In some embodiments, adding the compound of Formula (I-ii) to mixture 1 to form mixture 2 comprises adding a second base to mixture 1 then the compound of Formula (I-ii) to mixture 1. In some embodiments, adding the compound of Formula (I-ii) to mixture 1 to form mixture 2 comprises adding the compound of Formula (I-ii) to mixture 1 then the second base to mixture 1. In some embodiments, the second base is selected from N,N-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene (DBU), and 1,5-diazabicyclo(4.3.0)non-5-ene (DBN). In some embodiments, the second base is triethylamine. In some embodiments, the second base is N,N-diisopropylethylamine.

In some embodiments, adding a second base to mixture 1 and the compound of Formula (I-ii) to mixture 1 is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 2 °C, or about 0 °C). In some embodiments, adding a second base to mixture 1 and the compound of Formula (I-ii) to mixture 1 is performed at about 0 °C to about 5 °C. In some embodiments, adding a second base to mixture 1 and the compound of Formula (I-ii) to mixture 1 is performed at about 0 °C to about 2 °C. In some embodiments, adding a second base to mixture 1 and the compound of Formula (I-ii) to mixture 1 is performed at about 0 °C.

In some embodiments, after forming mixture 2, mixture 2 is warmed to about 20 °C to about 90 °C (e.g., about 20 °C to about 60 °C, about 20 °C to about 50 °C, about 20 °C to about 40 °C, about 25 °C to about 35 °C, or about 30 °C) over about 15 minutes to about 5 hours (e.g., about 1 hour to about 3 hours, or about 2 hours); then agitated at about 20 °C to about 90 °C (e.g., about 20 °C to about 60 °C, about 20 °C to about 50 °C, about 20 °C to about 40 °C, about 25 °C to about 35 °C, or about 30 °C) for about 1 hour to about 7 days (e.g., about 1 hour to about 2 days, about 5 hours to about 1 day, about 10 hours to about 18 hours, about 10 hours to about 14 hours, about 14 hours to about 18 hours, about 12 hours to about 16 hours, about 14 hours to about 16 hours, or about 16 hours) to form the compound of Formula (I).

In some embodiments, warming then agitating mixture 2 to form the compound of Formula (I) comprises adding an aqueous base and a workup solvent after the warming and agitating. In some embodiments, the aqueous base is aqueous sodium bicarbonate. In some embodiments, the aqueous base is 5% w/w aqueous sodium bicarbonate. In some embodiments, the workup solvent is isopropyl acetate or isopropyl alcohol. In some embodiments, the solvent is isopropyl acetate.

In some embodiments, method comprises recrystallizing the compound of Formula (I) from a solvent. In some embodiments, the process comprises recrystallizing the compound of Formula (I) from a solvent after adding the aqueous base and the workup solvent. In some embodiments, the solvent is a mixture of isopropyl acetate and heptane. In some embodiments, the ratio of isopropyl acetate to heptane is about 6:1 to about 1:10 (e.g., about 6:1 to about 4:2, about 1:7 to about 3:7, about 4:6 to about 6:4, about 4:2 to about 3:1, about 2:7, about 1:1, or about 5:2). In some embodiments, after recrystallizing the compound of Formula (I), the compound of Formula (I) is rinsed with a mixture of isopropyl acetate and heptane, then water, then a mixture of isopropyl acetate and heptane. In some embodiments, after rinsing the compound of Formula (I), the compound of Formula (I) is dried. In some embodiments, drying the compound of Formula (I) comprises drying the compound of Formula (I) at a pressure lesser than atmospheric pressure. In some embodiments, drying the compound of Formula (I) comprises drying the compound of Formula (I) at ambient temperature.

In some embodiments, contacting the compound of Formula (I-i) with the carbonyl equivalent and the compound of Formula (I-ii) to form the compound of Formula (I) comprises adding the compound of Formula (I-i) to the carbonyl equivalent and a base to form mixture 1', then adding the compound of Formula (I-ii) to mixture 1' to form mixture 2'. In some

embodiments, the compound of Formula (I-i) is in the form of a salt. In some embodiments, the compound of Formula (I-i) is in the form of a salt, and contacting the compound of Formula (I-i) with the carbonyl equivalent and the compound of Formula (I-ii) to form the compound of Formula (I) comprises adding the compound of Formula (I-i) to the carbonyl equivalent and a base to form mixture 1', then adding the compound of Formula (I-ii) to mixture 1' to form mixture 2'.

In some embodiments, the compound of Formula (I-i) salt is a hydrochloride salt.

In some embodiments, adding the compound of Formula (I-i) to the carbonyl equivalent and a base to form mixture 1' is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.

In some embodiments, adding the compound of Formula (I-i) to the carbonyl equivalent and a base to form mixture 1' is performed under an inert atmosphere. In some embodiments, the contacting is performed under nitrogen. In some embodiments, the contacting is performed under argon.

In some embodiments, the molar ratio of the carbonyl equivalent to the compound of Formula (I-i) is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3, about 2.0). In some embodiments, the molar ratio of the carbonyl equivalent to the compound of Formula (I-i) is about 1.05. In some embodiments, the molar ratio of the carbonyl equivalent to the compound of Formula (I-i) is about 1.3. In some embodiments, the molar ratio of the carbonyl equivalent to the compound of Formula (I-i) is about 2.0.

In some embodiments, the molar ratio of the base to the compound of Formula (I-i) is about 1.0 to about 5.0 (e.g., about 2.0 to about 5.0, about 2.0 to about 4.0, about 2.5 to about 3.5, about 3.0, or about 3.5). In some embodiments, the molar ratio of the sodium bicarbonate to the compound of Formula (I-i) is about 3.0. In some embodiments, the molar ratio of the sodium bicarbonate to the compound of Formula (I-i) is about 3.5.

In some embodiments, adding the compound of Formula (I-i) to the carbonyl equivalent and a base to form mixture 1' is performed in a solvent. In some embodiments, the solvent

comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.

In some embodiments, adding the compound of Formula (I-i) to the carbonyl equivalent and a base to form mixture 1' is performed under an inert atmosphere. In some embodiments, the adding is performed under nitrogen. In some embodiments, the adding is performed under argon.

In some embodiments, adding the compound of Formula (I-i) to the carbonyl equivalent and a base is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C). In some embodiments, adding the carbonyl equivalent to the compound of Formula (I-i) is performed at about 5 °C or lower.

In some embodiments, adding the compound of Formula (I-ii) to mixture 1' to form mixture 2' comprises adding a third base to mixture 1' and the compound of Formula (I-ii) to mixture 1'. In some embodiments, adding the compound of Formula (I-ii) to mixture 1' to form mixture 2' comprises adding a third base to mixture 1' then the compound of Formula (I-ii) to mixture 1'. In some embodiments, adding the compound of Formula (I-ii) to mixture 1' to form mixture 2' comprises adding aqueous sodium chloride to mixture 1', a third base to mixture 1', and the compound of Formula (I-ii) to mixture 1'. In some embodiments, adding the compound of Formula (I-ii) to mixture 1' to form mixture 2' comprises adding aqueous sodium chloride to mixture 1', a third base to mixture 1', then the compound of Formula (I-ii) to mixture 1'. In some embodiments, the third base is selected from N,N-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene (DBU), and 1,5-diazabicyclo(4.3.0)non-5-ene (DBN). In some embodiments, the third base is triethylamine. In some embodiments, the third base is N,N-diisopropylethylamine.

In some embodiments, the molar ratio of the compound of Formula (I-ii) to the compound of Formula (I-i) is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.15, about 1.2, about 1.3, about 2.0, or about 3.0). In some embodiments, the molar ratio of the compound of Formula (I-ii) to the compound of Formula (I-i) is about 1.15.

In some embodiments, the molar ratio of the third base to the compound of Formula (I-i) is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.15, about 1.2, about 1.3, about 2.0, or about 3.0). In some embodiments, the molar ratio of the
5 third base to the compound of Formula (I-i) is about 2.0.

In some embodiments, adding aqueous sodium chloride to mixture 1', the third base to mixture 1', and the compound of Formula (I-ii) is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C). In some embodiments, adding aqueous sodium chloride to mixture 1', the third base to mixture 1', and the compound of Formula (I-ii) is
10 performed at about 0 °C to about 5 °C.

In some embodiments, after forming mixture 2', mixture 2' is agitated at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C) for about 1 hour to about 7 days (e.g., about 1 hour to about 4 days, about 5 hours to about 4 day, about 12 hours to about 3 days, about 1 day to about 3 days, about 24 hours to about 36 hours, about 30 hours to
15 about 40 hours, about 10 hours to about 18 hours, about 10 hours to about 14 hours, about 14 hours to about 18 hours, about 12 hours to about 16 hours, about 14 hours to about 16 hours, or about 16 hours) to form the compound of Formula (I).

In some embodiments, the process comprises adding water and an extraction solvent to mixture 2' after agitating mixture 2' to form mixture 3'. In some embodiments, the extraction
20 solvent is ethyl acetate or isopropyl acetate. In some embodiments, the extraction solvent is isopropyl acetate. In some embodiments, the process comprises agitating and/or shaking mixture 3'. In some embodiments, the process comprises separating an organic liquid from mixture 3'. In some embodiments, the process comprises adding an aqueous base to the organic liquid to form mixture 4'. In some embodiments, the aqueous base is aqueous sodium bicarbonate. In some
25 embodiments, the aqueous sodium bicarbonate is 5% w/w aqueous sodium bicarbonate. In some embodiments, the process comprises separating the organic liquid from mixture 4'. In some embodiments, the process comprises reducing the volume of the organic liquid at a pressure lesser than atmospheric pressure. In some embodiments, the process comprises adding an anti-solvent to the organic liquid to form a slurry. In some embodiments, the anti-solvent is hexanes or heptane.
30 In some embodiments, the anti-solvent is heptane. In some embodiments, the process comprises filtering the slurry to provide a solid. In some embodiments, the process comprises dissolving the

solid in isopropanol and adding water to the dissolved solid to form a slurry. In some embodiments, the slurry is cooled. In some embodiments, the slurry is filtered. In some embodiments, the slurry is dried at a pressure lesser than atmospheric pressure to provide the compound of Formula (I).

5 In some embodiments, the compound of Formula (I) is precipitated from tetrahydrofuran and heptane. In some embodiments, the compound of Formula (I) is precipitated from isopropanol and water. In some embodiments, the compound of Formula (I) is precipitated from tetrahydrofuran and heptane, then precipitated from isopropanol and water. In some embodiments, after precipitating the compound of Formula (I), the compound of Formula (I) is dried. In some
10 embodiments, drying the compound of Formula (I) comprises drying the compound of Formula (I) at a pressure lesser than atmospheric pressure. In some embodiments, drying the compound of Formula (I) comprises drying the compound of Formula (I) at about 25 °C to about 70 °C (e.g., about 20 °C to about 25 °C, about 30 °C to about 60 °C, about 40 °C to about 50 °C, or about 45 °C). In some embodiments, drying the compound of Formula (I) comprises drying the compound
15 of Formula (I) at about 45 °C. In some embodiments, drying the compound of Formula (I) comprises drying the compound of Formula (I) at a pressure lesser than atmospheric pressure at about 20 °C to about 25 °C.

In some embodiments, the carbonyl equivalent is selected from the group consisting of: phenyl chloroformate, phosgene, trichloromethyl chloroformate (i.e., diphosgene),
20 bis(trichloromethyl) carbonate (i.e., triphosgene), 4-nitrophenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester.

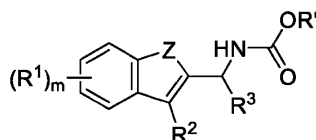
In some embodiments, the carbonyl equivalent is phenyl chloroformate.

25 In some embodiments, the carbonyl equivalent is R'OC(O)Cl, wherein R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl, nitro, or C1-6 alkoxy. In some embodiments, R' is phenyl. In some embodiments, R' is para-nitrophenyl.

In some embodiments, contacting the compound of Formula (I-i) with R'OC(O)Cl and the
30 compound of Formula (I-ii) to form the compound of Formula (I) comprises:

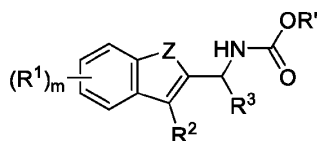
combining R'OC(O)Cl with a base;

adding the compound of Formula (I-i) to the mixture of $R'OC(O)Cl$ and the base to form



a compound of Formula (I-i-a)

In some embodiments, contacting the compound of Formula (I-i) with $R'OC(O)Cl$ and the compound of Formula (I-ii) to form the compound of Formula (I) comprises adding the compound of Formula (I-i) to a mixture of $R'OC(O)Cl$ and a base to form a compound of Formula (I-i-a)



In some embodiments, the compound of Formula (I-i) is added as a solution or slurry in a solvent. In some embodiments, the compound of Formula (I-i) is added as a solution in a solvent.

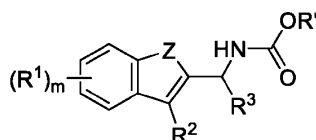
In some embodiments, the mixture of $R'OC(O)Cl$ and the base is a solution or slurry in a solvent. In some embodiments, the mixture of $R'OC(O)Cl$ and the base is a solution in a solvent.

In some embodiments, the compound of Formula (I-i) is in the form of a salt. In some embodiments, the salt is a hydrochloride salt.

In some embodiments, contacting the compound of Formula (I-i) with $R'OC(O)Cl$ and the compound of Formula (I-ii) to form the compound of Formula (I) comprises:

combining $R'OC(O)Cl$ with a base;

adding the compound of Formula (I-i) to the mixture of $R'OC(O)Cl$ and the base to form



a compound of Formula (I-i-a)

wherein the compound of Formula (I-i) is in the form of a salt.

In some embodiments, combining $R'OC(O)Cl$ with a base comprises combining the base with a solvent, then adding the $R'OC(O)Cl$. In some embodiments, combining the base with a solvent, then adding the $R'OC(O)Cl$ comprises adding the $R'OC(O)Cl$ to the base and solvent at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C), then adding the $R'OC(O)Cl$.

In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some
5 embodiments, the solvent is a combination of tetrahydrofuran and water. In some embodiments, when the base is combined with the solvent then R'OC(O)Cl added, (i) water is added to the base to form an aqueous base, (ii) tetrahydrofuran is added to the aqueous base, then (iii) R'OC(O)Cl is added to the tetrahydrofuran and aqueous base.

In some embodiments, adding the compound of Formula (I-i) to the mixture of R'OC(O)Cl
10 and the base is performed at about -10 °C to about 20 °C (e.g., about -5 °C to about 5 °C, about 0 °C to about 10 °C, about 0 °C to about 5 °C, about 0 °C to about 2 °C, or about 0 °C). In some embodiments, adding the compound of Formula (I-i) to the mixture of R'OC(O)Cl and the base is performed at about -5 °C to about 5 °C. In some embodiments, adding the compound of Formula (I-i) to the mixture of R'OC(O)Cl and the base is performed at about 0 °C to about 5 °C. In some
15 embodiments, adding the compound of Formula (I-i) to the mixture of R'OC(O)Cl and the base is performed at lesser than 5 °C. In some embodiments, the compound of Formula (I-i) is added to the mixture of R'OC(O)Cl and the base as a solution in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-
20 dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.

In some embodiments, the compound of Formula (I-i) is added to the mixture of R'OC(O)Cl and the base over a time period of about 15 minutes to about 48 hours (e.g., about 15
25 minutes to about 2 hours, about 18 hours to about 30 hours, about 18 hours to about 24 hours, about 15 minutes to about 24 hours, about 1 hour to about 7 hours, about 1 hour to about 5 hours, about 2 hours to about 4 hours, about 3 hours to about 7 hours, about 24 hours, about 21 hours, about 18 hours, about 16 hours, about 12 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, or about 1 hour).

In some embodiments, adding the compound of Formula (I-i) to the mixture of R'OC(O)Cl
30 and the base forms mixture 3. In some embodiments, mixture 3 is agitated for about 15 minutes

to about 48 hours (e.g., about 15 minutes to about 2 hours, about 18 hours to about 30 hours, about 18 hours to about 24 hours, about 15 minutes to about 24 hours, about 1 hour to about 7 hours, about 1 hour to about 5 hours, about 2 hours to about 4 hours, about 3 hours to about 7 hours, about 24 hours, about 21 hours, about 18 hours, about 16 hours, about 12 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, or about 1 hour). In some embodiments, mixture 3 is agitated at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C).

In some embodiments, agitating mixture 3 forms a biphasic mixture comprising an organic phase and an aqueous phase. In some embodiments, the organic phase is separated from the aqueous phase. In some embodiments, the organic phase is washed with an aqueous base. In some embodiments, the aqueous base is aqueous sodium bicarbonate. In some embodiments, the organic phase is concentrated at a pressure lesser than atmospheric pressure. In some embodiments, after concentrating the organic phase, an anti-solvent is added to the concentrated organic phase to form mixture 4. In some embodiments, the anti-solvent is hexane or heptane. In some embodiments, the anti-solvent is heptane.

In some embodiments, after adding the anti-solvent, mixture 4 is agitated at about 20 °C to about 80 °C (e.g., about 30 °C to about 70 °C, about 30 °C to about 60 °C, about 40 °C to about 50 °C, about 20 °C to about 50 °C, about 40 °C to about 80 °C, about 20 °C to about 80 °C, about 20 °C to about 80 °C, about 40 °C, or about 50 °C). In some embodiments, after adding the anti-solvent, mixture 4 is agitated at about 40 °C to about 50 °C. In some embodiments, the agitating is performed for about 1 minute to about 24 hours (e.g., about 1 minute to about 60 minutes, about 10 minutes, to about 50 minutes, about 15 minutes to about 45 minutes, about 20 minutes to about 40 minutes, about 25 minutes to about 35 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 1 minute to about 2 hours, or about 15 minutes to about 4 hours). In some embodiments, the agitating is performed for about 30 minutes.

In some embodiments, after adding the anti-solvent, mixture 4 is stood and/or agitated for about 10 minutes to about 48 hours (e.g. about 6 hours to about 24 hours, about 12 hours to about 24 hours, about 16 hours to about 20 hours, about 18 hours to about 30 hours, about 24 hours to about 48 hours, or about 18 hours). In some embodiments, the standing and/or agitating is performed at about -20 °C to about 15 °C (e.g., about -15 °C to about 5 °C, about -10 °C to about 0 °C, about -10 °C, about -5 °C, or about 0 °C).

In some embodiments, after adding the anti-solvent, mixture 4 is concentrated at a pressure lesser than atmospheric pressure. In some embodiments, after concentrating mixture 4, a slurry is formed. In some embodiments, the slurry is filtered to provide the compound of (I-i-a). In some embodiments, the compound of (I-i-a) is rinsed with hexane or heptane (e.g., heptane). In some
5 embodiments, after rinsing the compound of Formula (I-i-a), the compound of Formula (I-i-a) is dried. In some embodiments, drying the compound of Formula (I-i-a) comprises drying the compound of Formula (I-i-a) at a pressure lesser than atmospheric pressure. In some embodiments, drying the compound of Formula (I-i-a) comprises drying the compound of Formula (I-i-a) at about 25 °C to about 70 °C (e.g., about 30 °C to about 60 °C, about 40 °C to about 50 °C,
10 about 40 °C to about 45 °C, about 45 °C to about 50 °C, or about 45 °C). In some embodiments, drying the compound of Formula (I-i-a) comprises drying the compound of Formula (I-i-a) at about 45 °C. In some embodiments, drying the compound of Formula (I-i-a) comprises drying the compound of Formula (I-i-a) at about 40 °C to about 45 °C. In some embodiments, drying the compound of Formula (I-i-a) comprises drying the compound of Formula (I-i-a) at about 45 °C to
15 about 50 °C. In some embodiments, drying the compound of Formula (I-i-a) comprises drying the compound of Formula (I-i-a) under an inert atmosphere (e.g., under nitrogen).

In some embodiments, the molar ratio of the R'OC(O)Cl to the compound of Formula (I-i) is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1,
20 about 1.2, about 1.3, about 2.0, or about 3.0). In some embodiments, the molar ratio of the R'OC(O)Cl to the compound of Formula (I-i) is about 1.05. In some embodiments, the molar ratio of the R'OC(O)Cl to the compound of Formula (I-i) is about 1.3. In some embodiments, the molar ratio of the R'OC(O)Cl to the compound of Formula (I-i) is about 2.0. In some embodiments, the molar ratio of the R'OC(O)Cl to the compound of Formula (I-i) is about 3.0.

In some embodiments, the molar ratio of the base to the compound of Formula (I-i) is about 1.0 to about 5.0 (e.g., about 1.0 to about 3.0, about 2.0 to about 5.0, about 2.0 to about 4.0, about 2.5 to about 3.5, about 2.0, about 2.2, about 3.0, or about 3.5). In some embodiments, the molar ratio of the sodium bicarbonate to the compound of Formula (I-i) is about 2.0. In some
25 embodiments, the molar ratio of the sodium bicarbonate to the compound of Formula (I-i) is about 2.2. In some embodiments, the molar ratio of the sodium bicarbonate to the compound of Formula
30

(I-i) is about 3.0. In some embodiments, the molar ratio of the sodium bicarbonate to the compound of Formula (I-i) is about 3.5.

In some embodiments, the base is selected from sodium bicarbonate, potassium carbonate, potassium phosphate, sodium carbonate, potassium bicarbonate, N,N-diisopropylethylamine, triethylamine, trimethylamine, and citric acid. In some embodiments, the base is sodium bicarbonate.

In some embodiments, contacting the compound of Formula (I-i) with $R'OC(O)Cl$ and the compound of Formula (I-ii) to form the compound of Formula (I) comprises:

contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I).

In some embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) is performed in the presence of a third base. In some embodiments, the third base is selected from N,N-diisopropylethylamine (DIPEA), triethylamine (TEA), 1,8-diazabicycloundec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), sodium bicarbonate, potassium carbonate, and potassium phosphate. In some embodiments, the third base is triethylamine. In some embodiments, the third base is N,N-diisopropylethylamine.

In some embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) comprises adding the compound of Formula (I-i-a) to the compound of Formula (I-ii). In some embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) comprises adding the compound of Formula (I-i-a) to the compound of Formula (I-ii) in the absence of a base.

In some embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) comprises adding the compound of Formula (I-ii) to the compound of Formula (I-i-a). In some embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) comprises adding the compound of Formula (I-ii) to the compound of Formula (I-i-a); then adding a solvent to the mixture of the compound of Formula (I-ii) and the compound of Formula (I-i-a). In some embodiments, the solvent is N,N-dimethylacetamide.

In some embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) comprises adding the compound of Formula (I-ii) to the compound of Formula (I-i-a) in the absence of a base.

5 In some embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) is performed in N,N-dimethylacetamide. In some embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) is performed under an inert atmosphere. In some
10 embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) is performed under nitrogen. In some embodiments, contacting the compound of Formula (I-i-a) with the compound of Formula (I-ii) to form the compound of Formula (I) is performed under argon. In some embodiments, the N-N-dimethylacetamide comprises less than 2% water by volume (e.g., less than 1.5% water by volume, less than 1% water
15 by volume, less than 0.5% water by volume, less than 0.3% water by volume, less than 0.2% water by volume, less than 0.1% water by volume, less than 0.05% water by volume, or less than 0.02% water by volume). In some embodiments, the N-N-dimethylacetamide comprises less than 0.3% water by volume.

In some embodiments, after adding the compound of Formula (I-i-a) to the compound of Formula (I-ii) or after adding the compound of Formula (I-ii) to the compound of Formula (I-i-a), mixture 5 is formed. In some embodiments, mixture 5 is agitated. In some embodiments, mixture
20 5 is agitated for about 1 minute to about 48 hours (e.g., 1 minute to about 24 hours, 1 minute to about 12 hours, 1 minute to about 6 hours, 1 minute to about 3 hours, about 30 minutes to about 1.5 hours, about 8 hours to about 24 hours, about 12 hours to about 13 hours, about 3 hours, or about 1 hour). In some embodiments, mixture 5 is agitated for about 12 hours to about 13 hours. In some embodiments, mixture 5 is agitated for about 3 hours. In some embodiments, mixture 5 is
25 agitated for about 1 hour. In some embodiments, mixture 5 is agitated at about 10 °C to about 90 °C (e.g., about 10 °C to about 90 °C, about 20 °C to about 80 °C, about 30 °C to about 70 °C, about 30 °C to about 60 °C, about 35 °C to about 60 °C, about 40 °C to about 55 °C, about 45 °C to about 50 °C, about 45 °C, about 50 °C, or about °C).

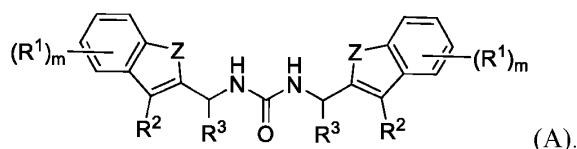
In some embodiments, after agitating mixture 5, the process comprises adding water to mixture 5 to form mixture 5'. In some embodiments, the process comprises agitating mixture 5'. In some embodiments, the process comprises agitating mixture 5' for about 1 minute to about 48

hours (e.g., 1 minute to about 24 hours, 1 minute to about 12 hours, 1 minute to about 6 hours, 1 minute to about 3 hours, about 30 minutes to about 1.5 hours, about 1 hour to about 5 hours, about 2 hours to about 4 hours, about 8 hours to about 24 hours, about 12 hours to about 13 hours, about 3 hours, or about 1 hour). In some embodiments, the process comprises agitating mixture 5' for about 12 hours to about 13 hours. In some embodiments, the process comprises agitating mixture 5' for about 3 hours. In some embodiments, the process comprises agitating mixture 5' for about 1 hour.

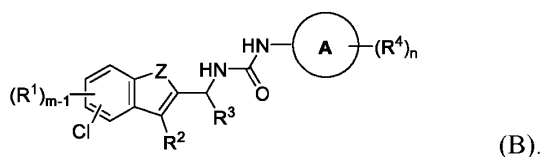
In some embodiments, after agitating mixture 5', a slurry is formed. In some embodiments, the slurry is filtered to provide the compound of Formula (I). In some embodiments, the compound of Formula (I) is washed with water. In some embodiments, the compound of Formula (I) is dried at a pressure lesser than atmospheric pressure.

In some embodiments, the compound of Formula (I) is recrystallized from a solvent. In some embodiments, the solvent is a mixture of isopropyl alcohol and water. In some embodiments, the solvent is a mixture of isopropyl acetate and heptane. In some embodiments, the ratio of isopropyl alcohol to water is about 1:3 to about 1:1 (e.g., about 1:2). In some embodiments, the ratio of isopropyl acetate to heptane is about 6:1 to about 4:2 (e.g., about 5:2). In some embodiments, after recrystallizing the compound of Formula (I), the compound of Formula (I) is rinsed with a mixture of isopropyl acetate and heptane, then water, then a mixture of isopropyl acetate and heptane. In some embodiments, after rinsing the compound of Formula (I), the compound of Formula (I) is dried. In some embodiments, drying the compound of Formula (I) comprises drying the compound of Formula (I) at a pressure lesser than atmospheric pressure. In some embodiments, drying the compound of Formula (I) comprises drying the compound of Formula (I) at ambient temperature.

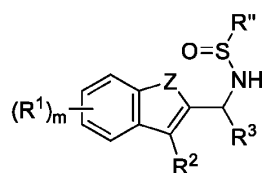
In some embodiments, the compound of Formula (I) has a purity of at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 98%, at least 99%, about 98%, about 98.5%, about 99%, about 99.5%). In some embodiments, less than 10% (e.g., less than 7%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, less than 0.1%, less than 0.6%, about 1%, about 1.3%, about 0.05%, or no detectable amount) of a compound of Formula (A) is present as an impurity with the compound of Formula (I).



In some embodiments, less than 10% (e.g., less than 7%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, less than 0.1%, less than 0.6%, about 1%, about 1.3%, about 0.05%, or no detectable amount) of a compound of Formula (B) is present as an impurity with the compound of Formula (I).



In some embodiments, the process comprises preparing the compound of Formula (I-i) by



contacting (I-iii) with an acid to form the compound of Formula (I-i); wherein R'' is C1-C6 alkyl; wherein R³ is C1-C6 haloalkyl.

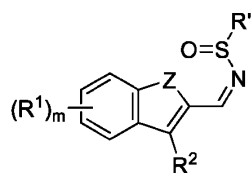
In some embodiments, R'' is isopropyl.

In some embodiments, the acid is hydrogen chloride. In some embodiments, the acid is a solution of hydrogen chloride in ethyl acetate, diethyl ether, or 1,4-dioxane. In some embodiments, the acid is a solution of hydrogen chloride in ethyl acetate. In some embodiments, the acid is a 1 molar solution of hydrogen chloride in ethyl acetate.

In some embodiments, the contacting comprises adding the compound of Formula (I-iii) to the acid. In some embodiments, the contacting comprises adding the acid to the compound of Formula (I-iii). In some embodiments, the adding is performed at about 0 °C to about 30 °C (e.g., about 0 °C to about 25 °C, about 0 °C to about 20 °C, about 0 °C to about 10 °C, or about 5 °C to about 15 °C). In some embodiments, the agitating is performed at about 0 °C to about 10 °C. In some embodiments, the agitating is performed at about 5 °C to about 15 °C. In some embodiments, the contacting comprises agitating the compound of Formula (I-iii) with the acid for about 5 minutes to about 24 hours (e.g., about 5 minutes to about 10 hours, about 5 minutes to about 5 hours, about 5 minutes to about 3 hours, about 30 minutes to about 1.5 hours, about 3 hours or about 1 hour) to

form mixture 6. In some embodiments, the contacting comprises agitating the compound of Formula (I-iii) with the acid for about 3 hours to form mixture 6. In some embodiments, the contacting comprises agitating the compound of Formula (I-iii) with the acid for about 1 hour to form mixture 6. In some embodiments, the contacting comprises agitating the compound of Formula (I-iii) with the acid for at least 1 hour to form mixture 6. In some embodiments, the agitating is performed at about 0 °C to about 30 °C (e.g., about 0 °C to about 25 °C, about 0 °C to about 20 °C, about 0 °C to 10 °C, or about 5 °C to about 15 °C). In some embodiments, the agitating is performed at about 5 °C to about 15 °C. In some embodiments, the contacting comprises adding heptane or hexanes (e.g., heptane) to mixture 6. In some embodiments, after adding the heptane or hexanes (e.g., heptane) to mixture 6, the mixture is cooled to about -20 °C to about 0 °C (e.g., about -15 °C to about -5 °C, or about -10 °C (e.g., about -15 °C to about -5 °C)) over about 5 minutes to about 48 hours (e.g., about 5 minutes to about 24 hours, about 3 hours to about 9 hours, about 24 hours, or about 6 hours (e.g., about 6 hours)) then agitated or permitted to stand (e.g., agitated) for about 10 hours to about 2 days (e.g., about 12 hours to about 24 hours, about 14 hours to about 22 hours, about 18 hours to about 30 hours, about 22 hours to about 26 hours, about 24 hours, or about 18 hours (e.g., about 24 hours)) to form a solid. In some embodiments, the solid is filtered to provide the compound of Formula (I-iii).

In some embodiments, the process comprises preparing the compound of Formula (I-iii)



by contacting a compound of Formula (I-iv) with a trihaloalkylating reagent to form the compound of Formula (I-iii); wherein R'' is C1-C6 alkyl. In some embodiments, contacting the compound of Formula (I-iv) with the trihaloalkylating reagent comprises contacting the compound of Formula (I-iv) with the trihaloalkylating reagent and a phase transfer reagent. In some embodiments, contacting the compound of Formula (I-iv) with the trihaloalkylating reagent and the phase transfer reagent forms mixture 7.

In some embodiments, the C=N double bond in the compound of Formula (I-iv) has E geometry. In some embodiments, the C=N double bond in the compound of Formula (I-iv) has Z geometry.

In some embodiments, the molar ratio of the trihaloalkylating reagent to the compound of Formula (I-iv) is about 1.0 to about 6.0 (e.g., about 1.0 to about 5.0, about 1.0 to about 4.0, about 2.0 to about 4.0, about 1.0 to about 5.0, about 2.5 to about 3.5, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3, about 2.0, about 2.5, about 3.0, or about 3.5). In some embodiments, the molar ratio of the trihaloalkylating reagent to the compound of Formula (I-iv) is about 3.0.

In some embodiments, the molar ratio of the phase transfer reagent to the compound of Formula (I-iv) is about 0.8 to about 6.0 (e.g., about 1.0 to about 5.0, about 1.0 to about 4.0, about 2.0 to about 4.0, about 1.0 to about 5.0, about 2.5 to about 3.5, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 0.8, about 0.9, about 0.95, about 1.0, about 1.05, about 1.1, about 1.2, about 1.3, about 2.0, about 2.5, about 3.0, or about 3.5). In some embodiments, the molar ratio of the phase transfer reagent to the compound of Formula (I-iv) is about 1.0.

In some embodiments, contacting the compound of Formula (I-iv) with the trihaloalkylating reagent and the phase transfer reagent comprises adding the phase transfer reagent to the compound of Formula (I-iv), then adding the trihaloalkylating reagent to the mixture of the compound of Formula (I-iv) and the phase transfer reagent.

In some embodiments, the phase transfer reagent is added to the compound of Formula (I-iv) at about 5 °C to about 40 °C (e.g., about 10 °C to about 35 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C). In some embodiments, the phase transfer reagent is added to the compound of Formula (I-iv) at about 15 °C to about 20 °C.

In some embodiments, after adding the phase transfer reagent to the compound of Formula (I-iv), the mixture of the compound of Formula (I-iv) and the phase transfer reagent is cooled to about -40 °C to about 0 °C (e.g., -30 °C to about -5 °C, -25 °C to about -10 °C, -20 °C to about -15 °C). In some embodiments, after adding the phase transfer reagent to the compound of Formula (I-iv), the mixture of the compound of Formula (I-iv) and the phase transfer reagent is cooled to about -20 °C to about -15 °C.

In some embodiments, after cooling the mixture of the compound of Formula (I-iv) and the phase transfer reagent, the mixture of the compound of Formula (I-iv) and the phase transfer reagent is agitated for about 5 minutes to about 3 hours (e.g., about 5 minutes to about 2 hours, about 30 minutes to about 1.5 hours, or about 1 hour). In some embodiments, after cooling the

mixture of the compound of Formula (I-iv) and the phase transfer reagent, the mixture of the compound of Formula (I-iv) and the phase transfer reagent is agitated for about 1 hour.

In some embodiments, adding the trihaloalkylating reagent to the mixture of the compound of Formula (I-iv) and the phase transfer reagent is performed at about -40 °C to about 0 °C (e.g., -30 °C to about -5 °C, -25 °C to about -10 °C, -20 °C to about -15 °C). In some embodiments, adding the trihaloalkylating reagent to the mixture of the compound of Formula (I-iv) and the phase transfer reagent is performed at about -20 °C to about -15 °C.

In some embodiments, the trihaloalkylating reagent is added to the mixture of the compound of Formula (I-iv) and the phase transfer reagent dropwise.

In some embodiments, contacting the compound of Formula (I-iv) with the trihaloalkylating reagent and the phase transfer reagent comprises adding the trihaloalkylating reagent to the compound of Formula (I-iv), then adding the phase transfer reagent to the mixture of the compound of Formula (I-iv) and the trihaloalkylating reagent.

In some embodiments, contacting the compound of Formula (I-iv) with the trihaloalkylating reagent and the phase transfer reagent is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, benzene, toluene, xylene, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent comprises toluene, xylene, or benzene. In some embodiments, the solvent comprises toluene. In some embodiments, the solvent is toluene.

In some embodiments, the process comprises adding the trihaloalkylating reagent to the compound of Formula (I-iv) at about -78 °C to about 25 °C (e.g., about -78 °C to about 0 °C, about -78 °C to about -5 °C, about -50 °C to about 10 °C, about -40 °C to about 0 °C, about -30 °C to about 0 °C, about -20 °C to about -10 °C, about -20 °C, or about -10 °C). In some embodiments, the trihaloalkylating reagent is added to the compound of Formula (I-iv) at about -20 °C to about -10 °C.

In some embodiments, the process comprises adding the trihaloalkylating reagent to the compound of Formula (I-iv) over about 1 minute to about 24 hours (e.g., about 1 minute to about 12 hours, about 12 hours to about 24 hours, about 6 hours to about 12 hours, about 1 minute to about 12 hours, about 1 minute to about 9 hours, about 1 minute to about 6 hours, about 1 minute

to about 4 hours, about 1 minute to about 3 hours, about 1 minute to about 2 hours, about 30 minutes to about 1.5 hours, about 45 minutes to about 1.25 hours, or about 1 hour. In some embodiments, the process comprises adding the trihaloalkylating reagent to the compound of Formula (I-iv) over about 1 hour.

5 In some embodiments, the process comprises agitating the compound of Formula (I-iv), the trihaloalkylating reagent, and the phase transfer reagent after adding the phase transfer reagent. In some embodiments, the process comprises agitating the compound of Formula (I-iv), the trihaloalkylating reagent, and the phase transfer reagent at about -78 °C to about 25 °C (e.g., about -78 °C to about 0 °C, about -78 °C to about -5 °C, about -50 °C to about 10 °C, about -40 °C to
10 about 0 °C, about -30 °C to about 0 °C, about -20 °C to about -10 °C, about -20 °C, or about -10 °C). In some embodiments, the phase transfer reagent is added to the compound of Formula (I-iv) at about -20 °C to about -10 °C.

In some embodiments, adding the phase transfer reagent to the mixture of the compound of Formula (I-iv) and the trihaloalkylating reagent comprises adding the phase transfer reagent to
15 the mixture of the compound of Formula (I-iv) and the trihaloalkylating reagent in several portions. In some embodiments, the several portions are 7 to 13 portions. In some embodiments, the several portions are 9 to 11 portions. In some embodiments, the several portions are 10 portions. In some embodiments, the 10 portions are 10 portions that are substantially the same in weight.

In some embodiments, the process comprises adding water or an aqueous acid to mixture
20 7. In some embodiments, the process comprises adding an aqueous acid to mixture 7 to form mixture 8. In some embodiments, the aqueous acid is aqueous ammonium chloride (e.g., 10% aqueous ammonium chloride by weight). In some embodiments, adding the water or aqueous acid to mixture 7 is performed at about -10 °C to about 25 °C (e.g., about -5 °C to about 5 °C).

In some embodiments, the process comprises adding a solvent to mixture 8 to form mixture
25 9. In some embodiments, mixture 9 is biphasic. In some embodiments, mixture 9 comprises an organic phase and an aqueous phase. In some embodiments, the organic phase is separated from mixture 9 and concentrated under at a pressure lesser than atmospheric pressure. In some embodiments, the solvent is dichloromethane, chloroform, ethyl acetate, or diethyl ether. In some embodiments, the solvent is ethyl acetate. In some embodiments, concentrating the organic phase
30 at a pressure lesser than atmospheric pressure provides a residue. In some embodiments, the residue is purified using silica gel to provide the compound of Formula (I-iv).

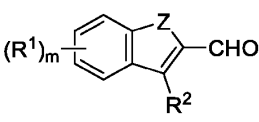
In some embodiments, the process comprises adding water and/or aqueous base to mixture 8 to form mixture 9'. In some embodiments, mixture 9' comprises an organic phase and an aqueous phase. In some embodiments, the process comprises separating the organic phase from mixture 9'. In some embodiments, the process comprises distilling the organic phase to provide a distillate. In some embodiments, the process comprises passing the distillate through carbon (e.g., activated carbon). In some embodiments, the process comprises reducing the volume of the distillate under a pressure lesser than atmospheric pressure to form a concentrate after passing the distillate through carbon. In some embodiments, the process comprises adding water to the concentrate, then reducing the volume of the mixture of water and concentrate to form mixture 9''. In some embodiments, the process comprises adding an anti-solvent to mixture 9'', then reducing the volume of mixture 9'' to form mixture 9'''. In some embodiments, the anti-solvent is heptane. In some embodiments, the process comprises adding a portion (e.g., a previously prepared portion) of the compound of Formula (I-iii) to mixture 9''' to form a precipitate. In some embodiments, the precipitate is filtered and dried to form the compound of Formula (I-iii).

In some embodiments, the trihaloalkylating reagent is selected from TMSCF_3 , [(Trifluoromethyl)thio]benzene, potassium trimethoxy(trifluoromethyl)borate, $\text{Et}_3\text{GeNa}/\text{C}_6\text{H}_5\text{SCF}_3$, N,N-dimethyl-(1-phenyl-2,2,2-trifluoroethoxytrimethylsilyl)-amine, S-(trifluoromethyl)dibenzothiophenium tetrafluoroborate, (SP-4-1)-tetrakis(trifluoromethyl)cuprate(1-), (SP-4-1)-tetrakis(trifluoromethyl)argentate(1-), [(1,1,2,2,2-pentafluoroethyl)sulfonyl]benzene, 5-(trifluoromethyl)-thianthrenium, 1,1,1-trifluoromethanesulfonate (1:1). In some embodiments, the trifluoroalkylating reagent is a trifluoromethylating reagent. In some embodiments, the trifluoromethylating reagent is TMSCF_3 .

In some embodiments, the phase transfer reagent is selected from tetrabutylammonium acetate, tetrabutylphosphonium bromide, triethylbenzylammonium chloride, decyltrimethylammonium bromide, tetraethylammonium trifluoromethanesulfonate, benzyldecyldimethylammonium chloride, benzyltrimethyltetradecylammonium chloride, benzoylcholine bromide, benzyltrimethylphenylammonium chloride, benzyltributylammonium bromide, 1,1'-(butane-1,4-diyl)bis[4-aza-1-azoniabicyclo[2.2.2]octane] dibromide, ethylhexadecyldimethylammonium bromide, decamethonium bromide, tetrapropylammonium iodide, tetrahexylammonium iodide, tetra(decyl)ammonium bromide, tetraamylammonium

chloride, and dimethyldipalmitylammonium bromide. In some embodiments, the phase transfer reagent is tetrabutylammonium acetate.

In some embodiments, the process comprises preparing the compound of Formula (I-iv)

by contacting a compound of Formula (I-v)  with $\text{H}_2\text{N}-\text{S}(=\text{O})-\text{R}''$; wherein R''

is C1-C6 alkyl. In some embodiments, Z is O. In some embodiments, contacting the compound

of Formula (I-v) with $\text{H}_2\text{N}-\text{S}(=\text{O})-\text{R}''$ comprises contacting the compound of Formula (I-v) with

$\text{H}_2\text{N}-\text{S}(=\text{O})-\text{R}''$ and a condensing base. In some embodiments, the condensing base is selected from sodium bicarbonate, potassium carbonate, potassium phosphate, sodium carbonate, potassium bicarbonate, N,N-diisopropylethylamine, triethylamine, and citric acid. In some embodiments, the condensing base is potassium carbonate.

In some embodiments, the contacting is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is ethyl acetate. In some embodiments, the solvent is tetrahydrofuran.

In some embodiments, the molar ratio of the condensing base to the compound of Formula (I-v) is about 0.8 to about 6.0 (e.g., about 1.0 to about 5.0, about 1.0 to about 4.0, about 2.0 to about 4.0, about 1.0 to about 5.0, about 2.5 to about 3.5, about 1.0 to about 2.0, about 1.3 to about 1.7, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 0.8, about 0.9, about 0.95, about 1.0, about 1.05, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 2.0, about 2.5, about 3.0, or about 3.5). In some embodiments, the molar ratio of the condensing base to the compound of Formula (I-v) is about 1.5.

In some embodiments, the molar ratio of the condensing base to the compound of Formula (I-v) is about 0.8 to about 6.0 (e.g., about 1.0 to about 5.0, about 1.0 to about 4.0, about 2.0 to about 4.0, about 1.0 to about 5.0, about 2.5 to about 3.5, about 1.0 to about 2.0, about 1.3 to about 1.7, about 1.0 to about 1.5, about 1.0 to about 1.4, about 0.8 to about 1.2, about 0.9 to about 1.1,

about 1.0 to about 1.1, about 1.2 to about 1.4, about 0.95 to about 1.05, about 1.0 to about 1.04, about 0.8, about 0.9, about 0.95, about 1.0, about 1.02, about 1.05, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 2.0, about 2.5, about 3.0, or about 3.5). In some embodiments, the molar ratio of the condensing base to the compound of Formula (I-v) is about 1.02.

In some embodiments, contacting the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the condensing base is performed at about 25 °C to about 80 °C (e.g., about 25 °C to about 70 °C, about 25 °C to about 60 °C, about 35 °C to about 50 °C, about 35 °C to about 45 °C, about 35 °C, about 40 °C, or about 45 °C). In some embodiments, contacting the compound of Formula (I-v) with

$\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the condensing base is performed at about 35 °C to about 45 °C.

In some embodiments, contacting the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the condensing base is performed at about 25 °C to about 80 °C (e.g., about 25 °C to about 70 °C, about 25 °C to about 60 °C, about 35 °C to about 50 °C, about 35 °C to about 45 °C, about 35 °C, about 40 °C, or about 45 °C).

In some embodiments, contacting the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the condensing base comprises agitating the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the condensing base. In some embodiments, agitating the compound of Formula (I-v) with

$\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the condensing base comprises agitating the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the condensing base for about 1 hour to about 48 hours (e.g., about 2 hours to about 36 hours, about 2 hours to about 24 hours, about 2 hours to about 12 hours, about 6 hours to about 24 hours, about 9 hours to about 19 hours, about 11 hours to about 17 hours, about 13 hours to about 15 hours, about 13.5 hours to about 14.5 hours, or about 14 hours). In some embodiments,

agitating the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the condensing base comprises
 agitating the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the condensing base for about 14
 hours.

5 In some embodiments, contacting the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and a
 condensing base comprises adding the $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ to the compound of Formula (I-v), then adding
 the condensing base to the mixture of $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the compound of Formula (I-v).

In some embodiments, adding the $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ to the compound of Formula (I-v) is
 performed at about 5 °C to about 40 °C (e.g., about 10 °C to about 35 °C, about 15 °C to about 25
 10 °C, about 15 °C to about 20 °C). In some embodiments adding the $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ to the compound
 of Formula (I-v) is performed at about 15 °C to about 20 °C.

In some embodiments, adding the condensing base to the mixture of $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the
 compound of Formula (I-v) is performed at about 5 °C to about 40 °C (e.g., about 10 °C to about
 35 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C). In some embodiments adding the
 15 condensing base to the mixture of $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the compound of Formula (I-v) is performed at
 about 15 °C to about 20 °C.

In some embodiments, contacting the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and a
 condensing base provides mixture 10. In some embodiments, mixture 10 is agitated for about 15
 minutes to about 48 hours (e.g., about 15 minutes to about 24 hours, about 15 minutes to about 16

hours, about 15 minutes to about 10 hours, about 2 hours to about 8 hours, about 3 hours to about 7 hours, about 4 hours to about 6 hours, or about 5 hours). In some embodiments, mixture 10 is agitated for about 15 minutes to about 5 hours. In some embodiments, agitating mixture 10 is performed at about 25 °C to about 110 °C (e.g., 40 °C to about 80 °C, 50 °C to about 70 °C, 55 °C to about 65 °C, or about 60 °C). In some embodiments, agitating mixture 10 is performed at about 60 °C.

In some embodiments, after agitating mixture 10, mixture 10 is cooled to about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, or about 20 °C). In some embodiments, after agitating mixture 10, mixture 10 is cooled to about 20 °C. In some embodiments, after agitating mixture 10, mixture 10 is cooled to about 15 °C to about 25 °C.

In some embodiments, cooling mixture 10 comprises forming a slurry. In some embodiments, the process comprises filtering the slurry to provide a solution. In some embodiments, the process comprises reducing the volume of the solution under a pressure lesser than atmospheric pressure. In some embodiments, the process comprises (i) adding a solvent to the solution; (ii) reducing the volume of the solution under a pressure lesser than atmospheric pressure; optionally (iii) adding a solvent to the solution; and optionally (iv) reducing the volume of the solution under a pressure lesser than atmospheric pressure to form a concentrate. In some embodiments, the solvent is methanol, ethanol, or isopropanol. In some embodiments, the solvent is ethanol. In some embodiments, steps (iii) and (iv) are required. In some embodiments, the process comprises cooling the concentrate to about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, or about 20 °C). In some embodiments, the process comprises cooling the concentrate to about 15 °C to about 25 °C. In some embodiments, the process comprises adding water to the concentrate after cooling the concentrate to form mixture 10'. In some embodiments, the process comprises agitating mixture 10' for about 1 hour to about 48 hours (e.g., about 2 hours to about 36 hours, about 2 hours to about 24 hours, about 2 hours to about 12 hours, about 6 hours to about 24 hours, about 9 hours to about 19 hours, about 11 hours to about 17 hours, about 13 hours to about 15 hours, about 13.5 hours to about 14.5 hours, or about 14 hours). In some embodiments, the process comprises agitating mixture 10' for about 14 hours. In some embodiments, after agitating mixture 10', a slurry is formed. In some embodiments, the slurry is filtered to provide the compound of Formula (I-v).

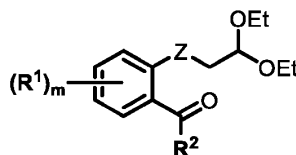
In some embodiments, the process comprises concentrating mixture 10 at a pressure lesser than atmospheric pressure to provide the compound of Formula (I-iv) after cooling mixture 10.

In some embodiments, the process comprises

In some embodiments, contacting the compound of Formula (I-v) with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and a

condensing base comprises adding the $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ to the compound of Formula (I-v), then adding
the condensing base to the mixture of $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ and the compound of Formula (I-v).

In some embodiments, the process comprises preparing the compound of Formula (I-v) by



contacting a compound of Formula (I-vi) with an acid. In some embodiments, Z is O.

In some embodiments, the acid is a protic acid. In some embodiments, the acid is a Lewis acid. In some embodiments, the acid is selected from acetic acid, hydrogen chloride, sulfuric acid, phosphoric acid, nitric acid, aluminum chloride, zinc chloride, trimethylaluminum, iron (III) bromide, and boron trifluoride (e.g., boron trifluoride dietherate).

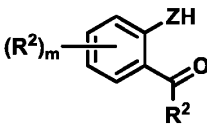
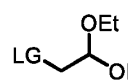
In some embodiments, the acid is acetic acid.

In some embodiments, contacting the compound of Formula (I-vi) with an acid comprises adding the compound of Formula (I-vi) to the acid. In some embodiments, contacting the compound of Formula (I-vi) with an acid comprises contacting the compound of Formula (I-vi) with the acid in a solvent. In some embodiments, the solvent is acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is N,N-dimethylformamide. In some embodiments, adding the compound of Formula (I-vi) to the acid forms mixture 11. In some embodiments, after adding the compound of Formula (I-vi) to the acid, mixture 11 is heated at about 80 °C to about 160 °C (e.g., about 90 °C to about 150 °C, about 100 °C to about 140 °C, about 110 °C to about 130 °C, about 115 °C to about 125 °C, or about 120 °C). In some

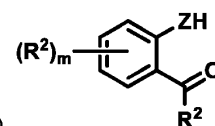
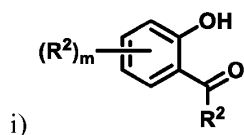
embodiments, after adding the compound of Formula (I-vi) to the acid, mixture 11 is heated at about 120 °C. In some embodiments, after adding the compound of Formula (I-vi) to the acid, mixture 11 is agitated for about 15 minutes to about 2 days (e.g., about 30 minutes to about 24 hours, about 2 hours to about 16 hours, about 4 hours to about 12 hours, about 6 hours to about 10 hours, about 7 hours to about 9 hours, or about 8 hours). In some embodiments, after adding the compound of Formula (I-vi) to the acid, mixture 11 is agitated for about 8 hours.

In some embodiments, after agitating mixture 11, water is added to mixture 11. In some embodiments, after adding water to mixture 11, a solvent is added to mixture 11 to form mixture 12. In some embodiments, mixture 12 is biphasic. In some embodiments, mixture 12 comprises an organic phase and an aqueous phase. In some embodiments, the organic phase is isolated and washed with an aqueous base. In some embodiments, the aqueous base is aqueous potassium carbonate (e.g., 15% aqueous potassium carbonate by weight). In some embodiments, after washing the organic phase with the aqueous base, the organic phase is agitated with water and Na₂S₂O₄. In some embodiments, the organic phase is agitated with water and Na₂S₂O₄ for about 5 minutes to about 2 days (e.g., about 1 hour to about 24 hours, about 4 hours to about 18 hours, about 6 hours to about 10 hours, or about 8 hours). In some embodiments, the organic phase is agitated with water and Na₂S₂O₄ for about 8 hours. In some embodiments, agitating the organic phase with water and Na₂S₂O₄ forms a solid. In some embodiments, the solid is separated from the solvent and water. In some embodiments, the solid is combined with ethyl acetate to form a solution, and the pH of the solution is adjusted to about 8 to about 11 (e.g., about 9 to about 10, about 9, or about 10) and then agitated for about 5 minutes to about 1 day (e.g., about 1 hour to about 10 hours, about 3 hours to about 7 hours, about 4 hours to about 6 hours, or about 5 hours) to form a biphasic mixture. In some embodiments, the biphasic mixture comprises an organic phase and an aqueous phase. In some embodiments, the organic phase concentrated under at a pressure lesser than atmospheric pressure to provide the compound of Formula (I-v).

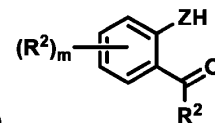
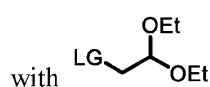
In some embodiments, the process comprises preparing the compound of Formula (I-vi)

by contacting a compound of Formula (I-vii)  with ; wherein LG is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl.

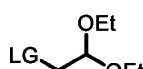
In some embodiments, the compound of Formula (I-vii) is a compound of Formula (I-vii-

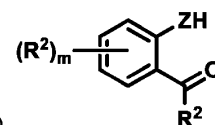


In some embodiments, contacting the compound of Formula (I-vii)

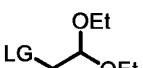


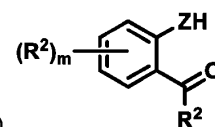
comprises contacting the compound of Formula (I-vii)

5 with  and a base. In some embodiments, the base is selected from sodium bicarbonate, potassium carbonate, potassium phosphate, sodium carbonate, potassium bicarbonate, N,N-diisopropylethylamine, triethylamine, and citric acid. In some embodiments, the base is potassium carbonate.



In some embodiments, contacting the compound of Formula (I-vii)

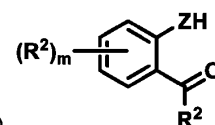
10 with  and a base is performed in a solvent. In some embodiments, the solvent is acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is N,N-dimethylformamide.



In some embodiments, contacting the compound of Formula (I-vii)

with and a base comprises contacting the compound of Formula (I-vii) with

a base, and sodium iodide.



In some embodiments, contacting the compound of Formula (I-vii)

5 with a base, and sodium iodide is performed at about 80 °C to about 160 °C (e.g., about 90 °C to about 150 °C, about 100 °C to about 140 °C, about 110 °C to about 130 °C, about 115 °C to about 125 °C, or about 120 °C). In some embodiments, contacting the compound of

Formula (I-vii) with a base, and sodium iodide is performed at about 120 °C.

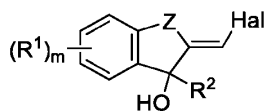
10 In some embodiments, adding the compound of Formula (I-vii) to a base, and sodium iodide forms mixture 13. In some embodiments, mixture 13 is agitated for about 15 minutes to about 2 days (e.g., about 30 minutes to about 24 hours, about 2 hours to about 16 hours, about 2 hours to about 8 hours, about 3 hours to about 7 hours, about 4 hours to about 6 hours, or about 5 hours). In some embodiments, mixture 13 is agitated for about 5 hours.

15 In some embodiments, the process comprises preparing the compound of Formula (I-v) by

contacting a compound of Formula (I-viii) with an acid; wherein Hal is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl. In some embodiments, Hal is

chloro. In some embodiments, the acid is sulfuric acid, hydrogen chloride, nitric acid, phosphoric acid, or hydrogen bromide. In some embodiments, the acid is sulfuric acid.

In some embodiments, contacting the compound of Formula (I-viii)



with the acid is performed in a solvent. In some embodiments, the solvent comprises methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether.

In some embodiments, contacting the compound of Formula (I-viii) with the acid is performed at about 10 °C to about 60 °C (e.g., about 15 °C to about 55 °C, about 15 °C to about 35 °C, about 20 °C to about 30 °C, about 23 °C to about 27 °C, or about 25 °C). In some embodiments, contacting the compound of Formula (I-viii) with the acid is performed at about 25 °C.

In some embodiments, the process comprises preparing the compound of Formula (I-viii)

by contacting a compound of Formula (I-ix) with with . In some embodiments, Z is O. In some embodiments, R² is C1-C6 alkyl. In some embodiments, R² is methyl.

In some embodiments, contacting the compound of Formula (I-ix) with comprises

contacting the compound of Formula (I-ix) with and a base. In some embodiments, the base is potassium tert-butoxide. In some embodiments, the contacting is performed in a solvent.

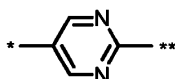
In some embodiments, the solvent comprises methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide,

water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some
 5 embodiments, the solvent is methyl tert-butyl ether.

In some embodiments, contacting the compound of Formula (I-ix) with  and a base is performed at about 10 °C to about 60 °C (e.g., about 15 °C to about 55 °C, about 15 °C to about 35 °C, about 20 °C to about 30 °C, about 23 °C to about 27 °C, or about 25 °C). In some

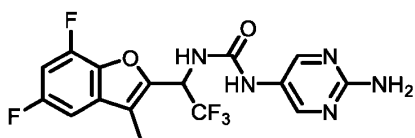
embodiments, contacting the compound of Formula (I-ix) with  and a base is performed
 10 at about 25 °C.

In some embodiments, Z is O; m is 2; each R¹ is fluoro; R² is methyl; R² is trifluoromethyl;

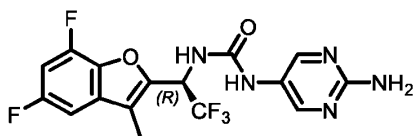
Ring A is , wherein * denotes the point of attachment to the urea and ** denotes the point of attachment to R⁴; n is 1; and R⁴ is -NH₂.

In some embodiments, the carbon substituted with R³ has the (R) configuration.

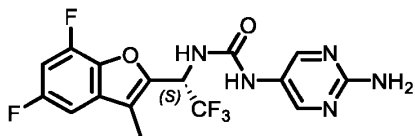
15 In some embodiments, the compound of Formula (I) is



In some embodiments, the compound of Formula (I) is

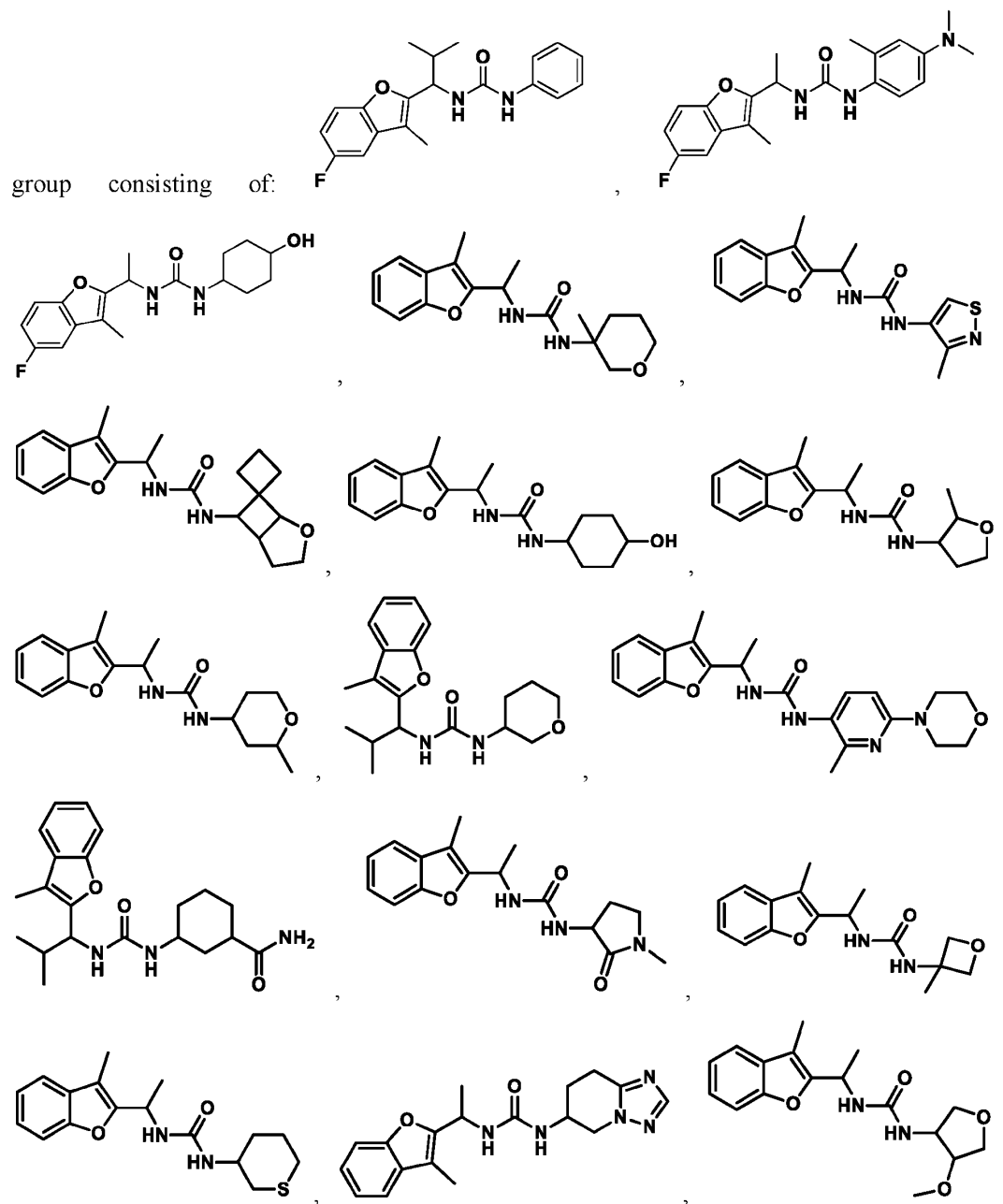


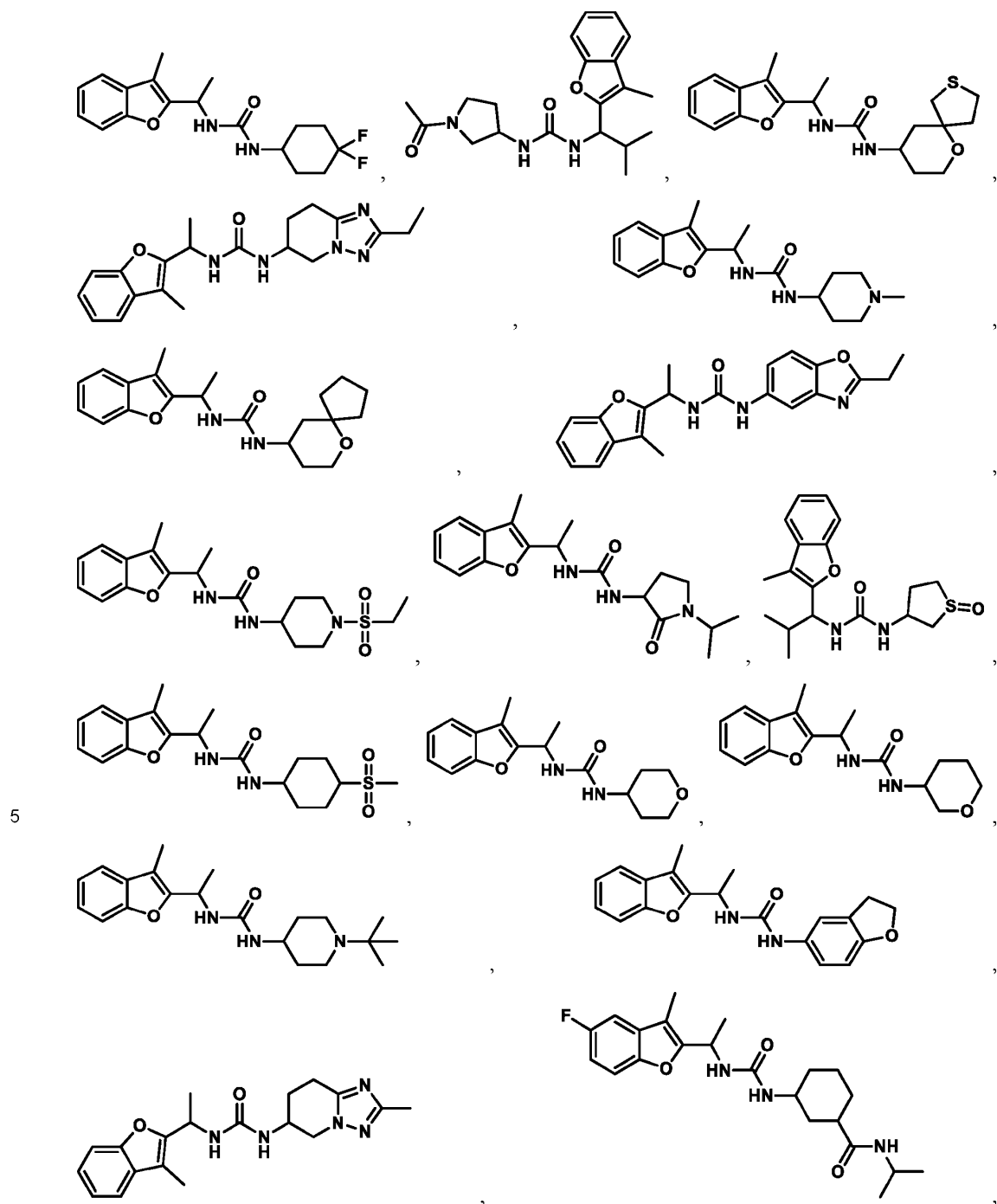
In some embodiments, the compound of Formula (I) is



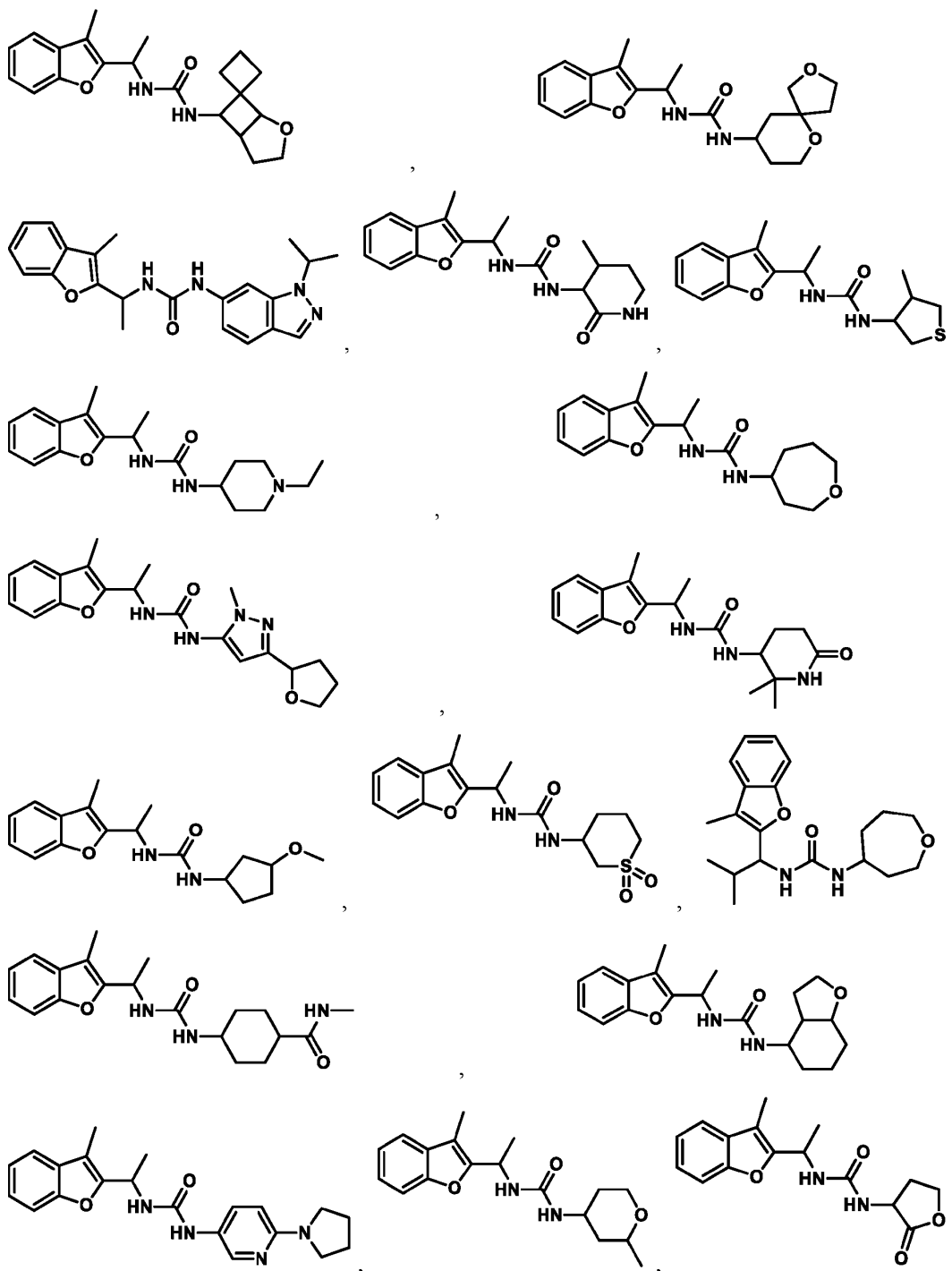
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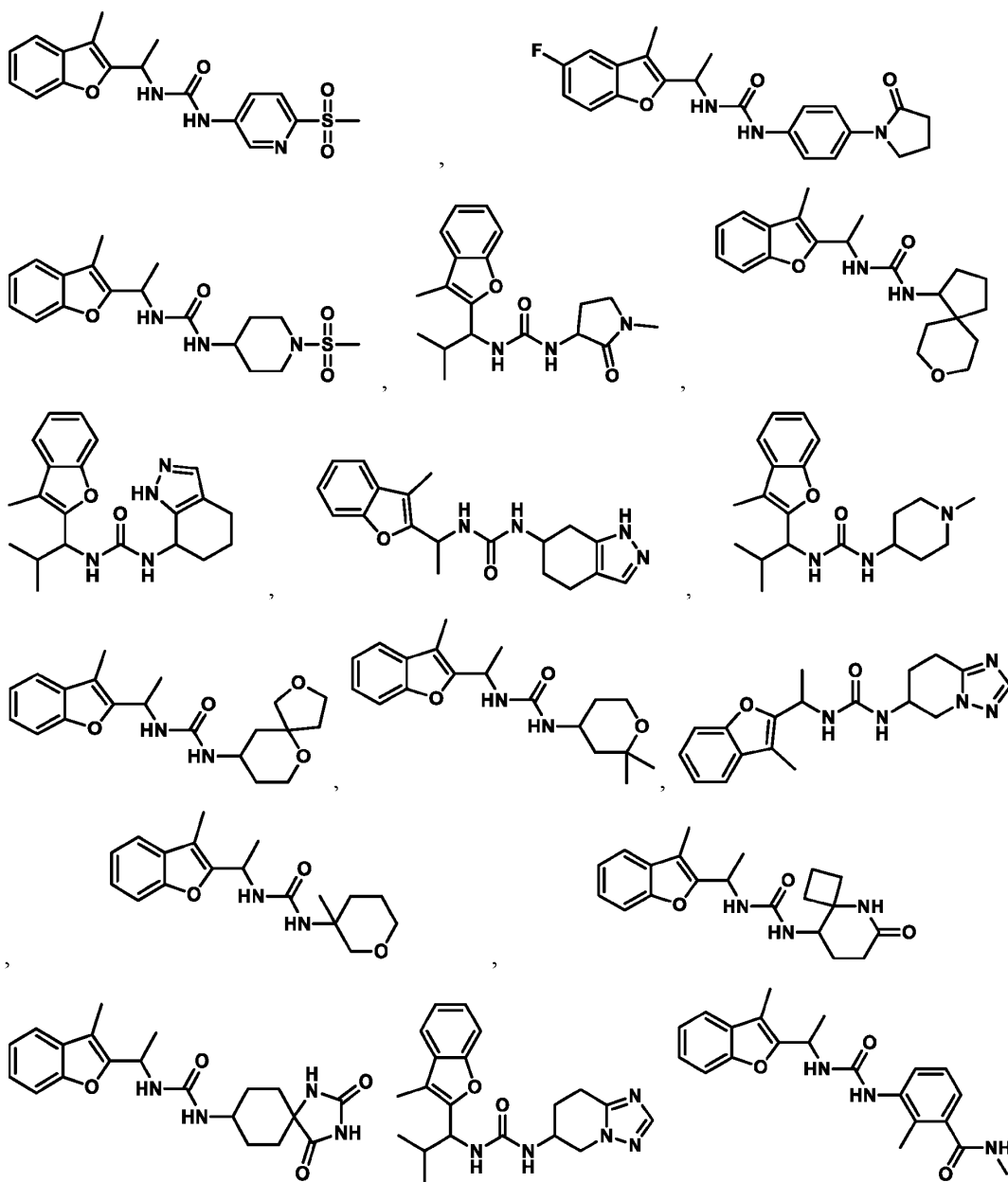
In some embodiments, the compound of Formula (I) is not a compound selected from the

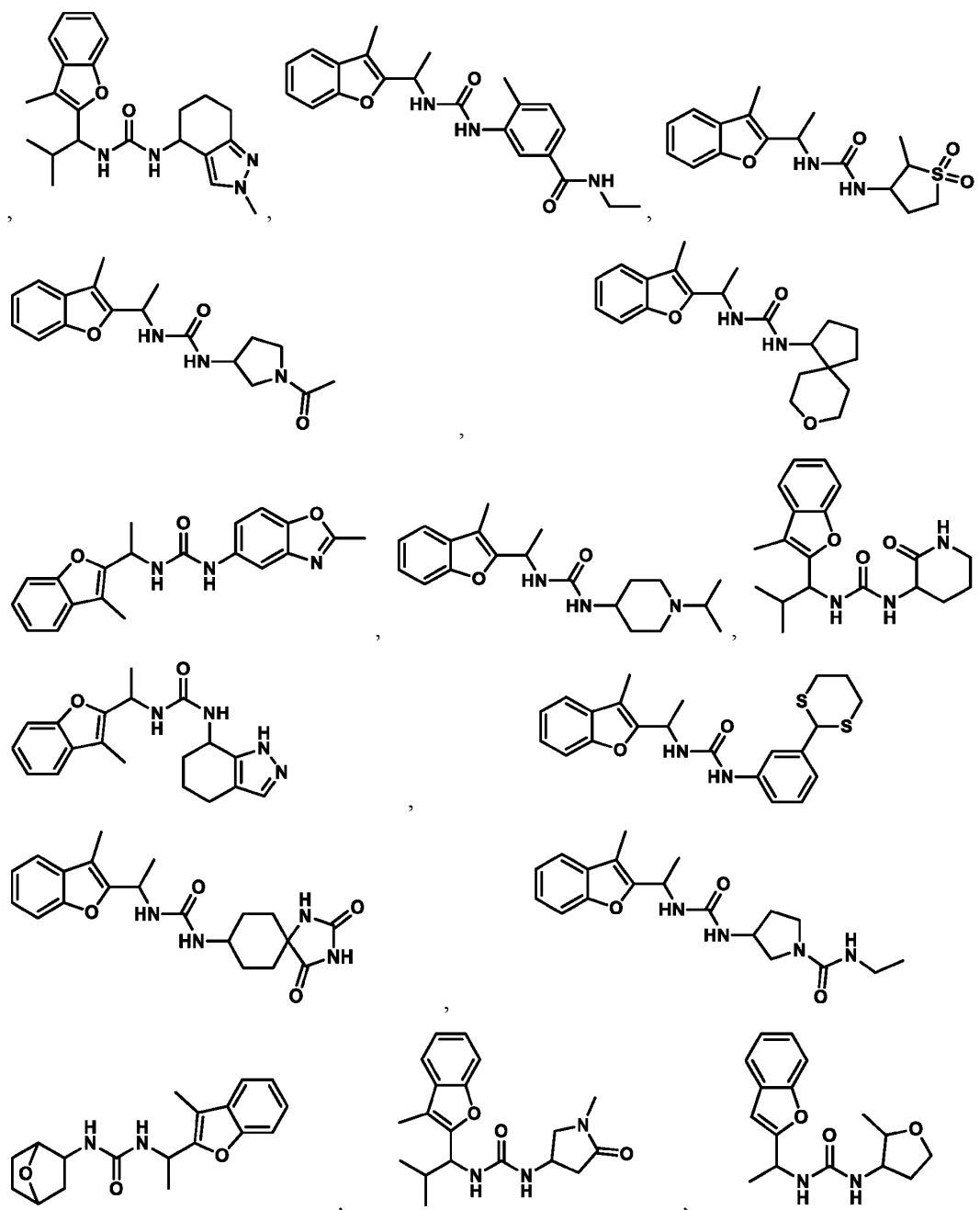


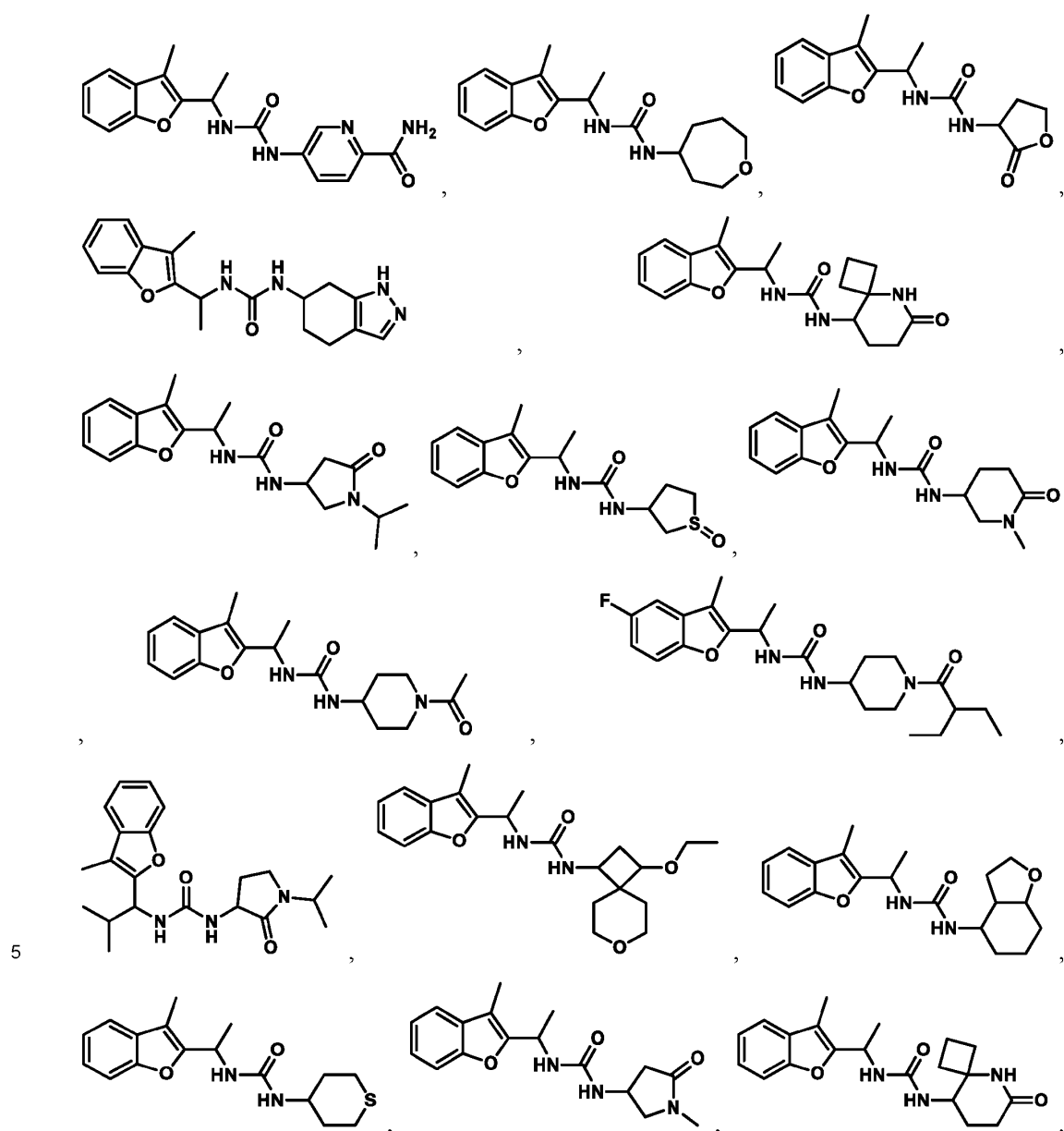


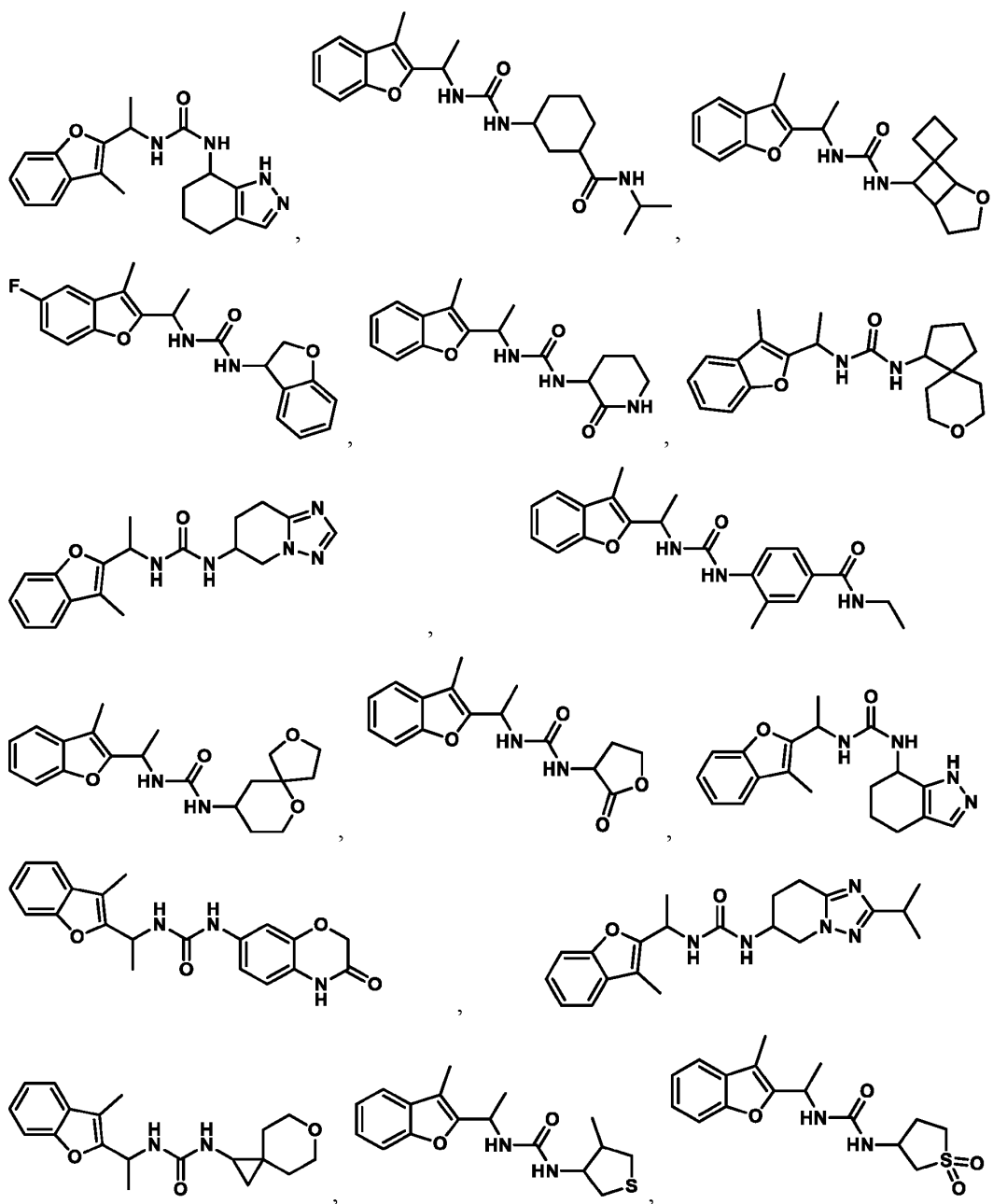
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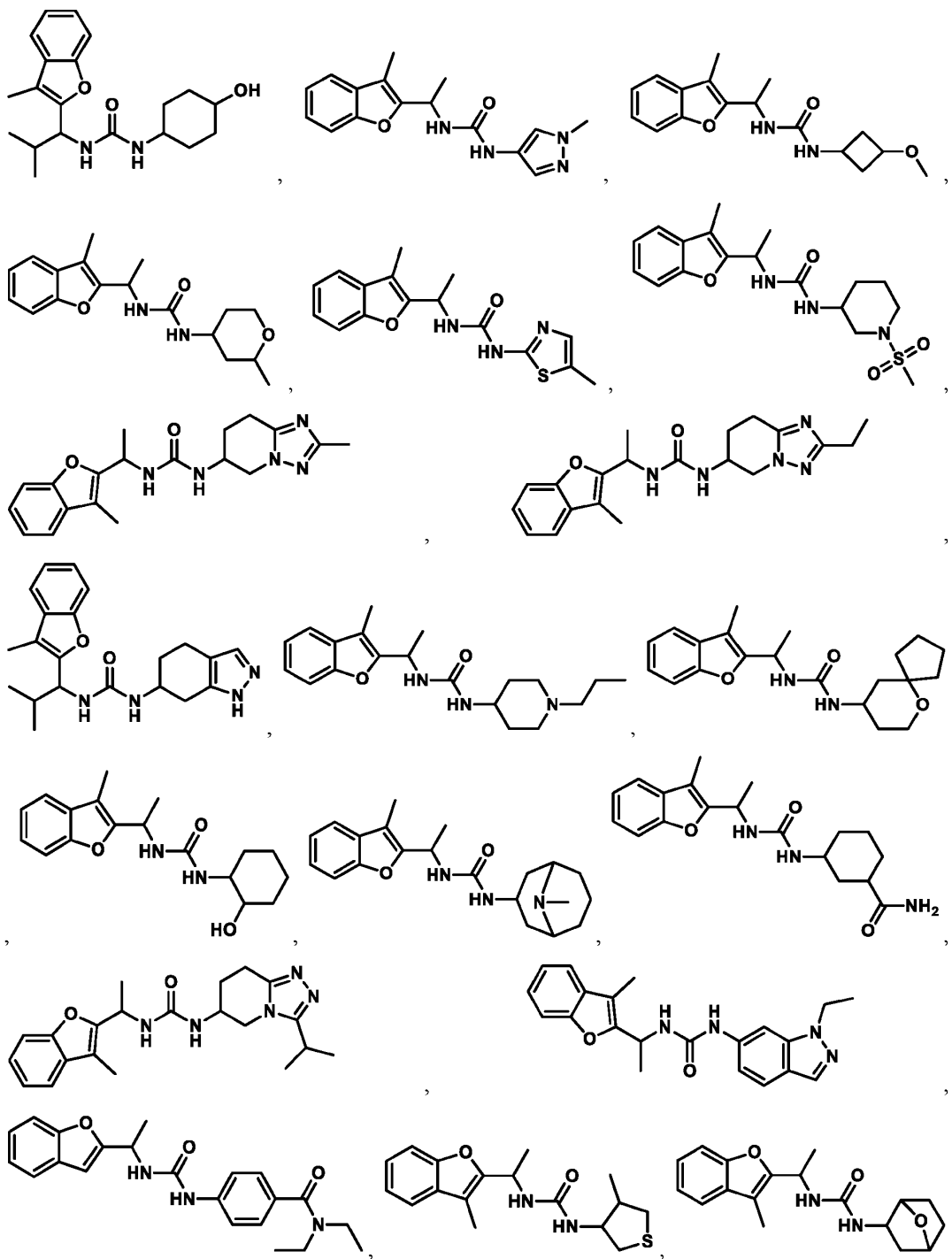


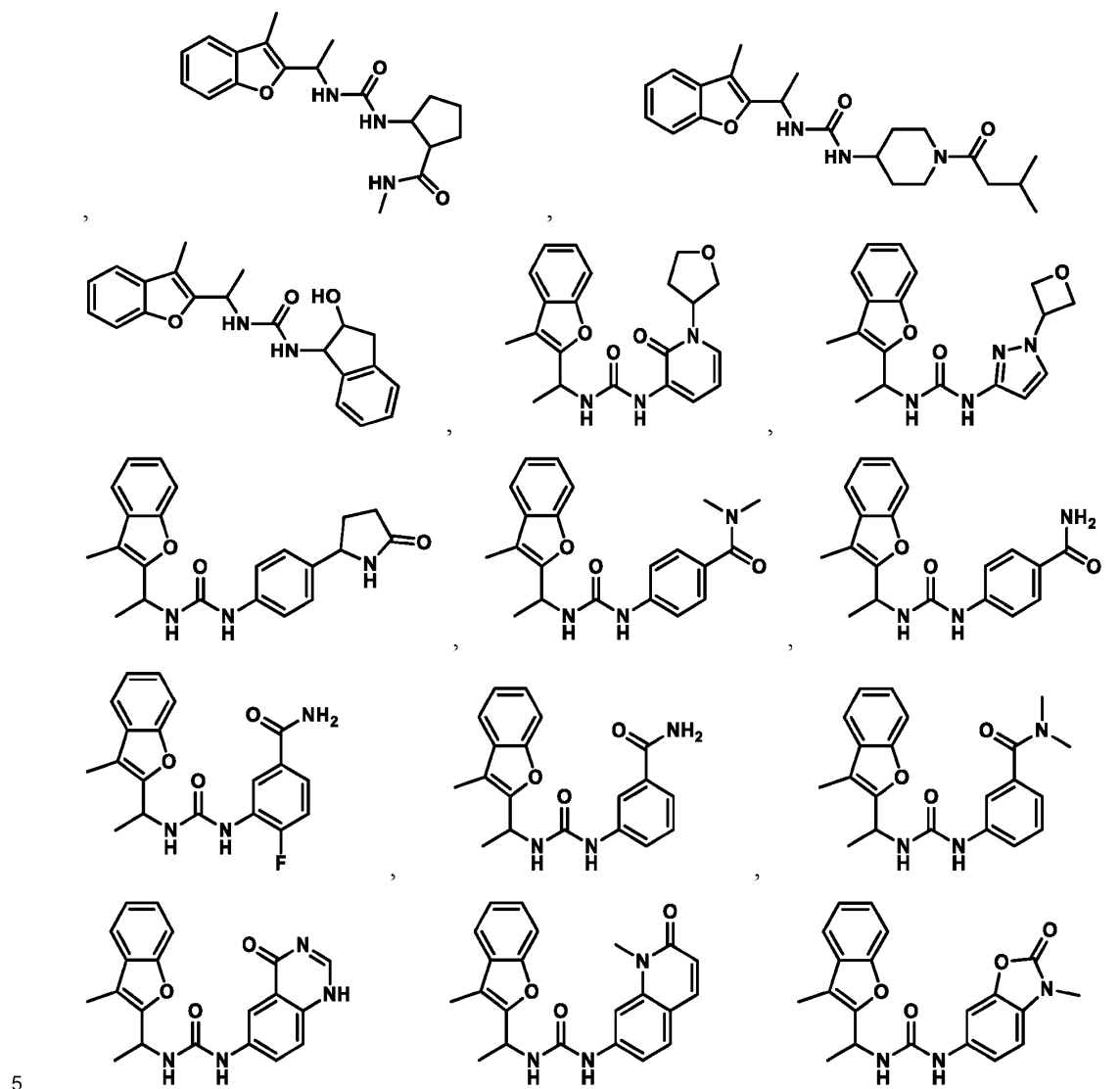


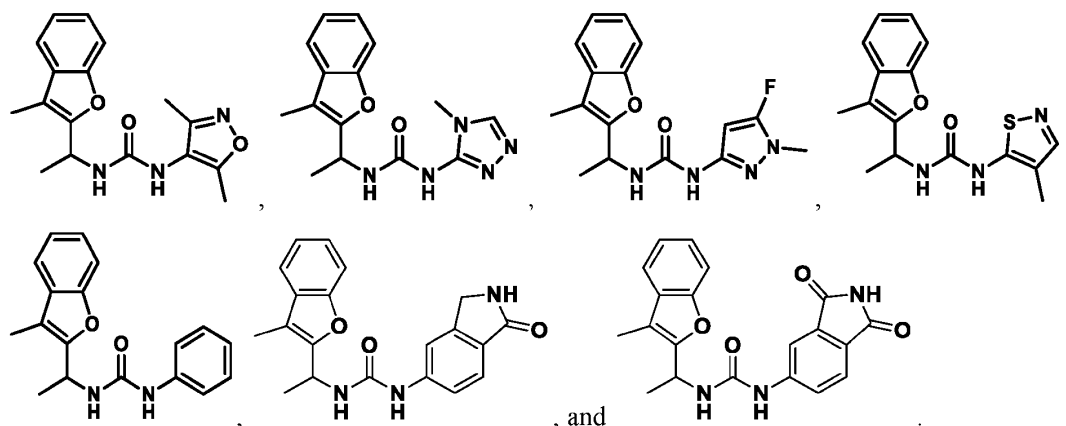






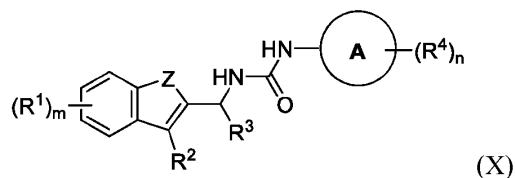






In some embodiments, when Z is NR^x and R^3 is methyl, Ring A is not phenyl.

In some embodiments, the compound of Formula (I) is a compound of Formula (X):



5

or a salt and/or solvate thereof, wherein:

Z is O or NR^x ;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each R^1 is an independently selected halogen;

10

m is 0, 1, 2, or 3;

R^2 is halogen, C1-C6 alkyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

15

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

each R^4 is independently selected from the group consisting of: halogen, C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-\text{CO}_2\text{H}$, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$, $-\text{C}(=\text{O})\text{NR}^{\text{C}}\text{R}^{\text{D}}$, $-\text{SO}_2(\text{NR}^{\text{E}}\text{R}^{\text{F}})$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{S}(=\text{O})(=\text{NH})(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})(\text{C1-C6 alkyl})$, $-\text{CO}_2(\text{C1-C6 alkyl})$, 5-6 membered heteroaryl optionally substituted

20

with C1-C6 alkyl, and a 3-6 membered heterocyclyl or 3-6 membered cycloalkyl each optionally substituted with 1 or 2 independently selected R^G;

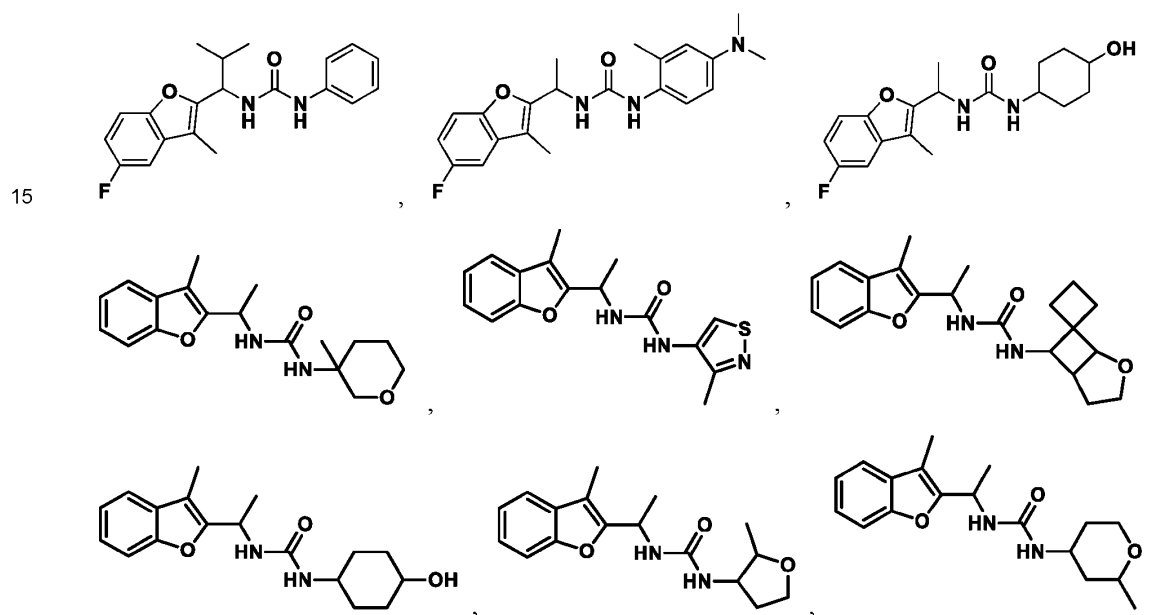
n is 0, 1, or 2;

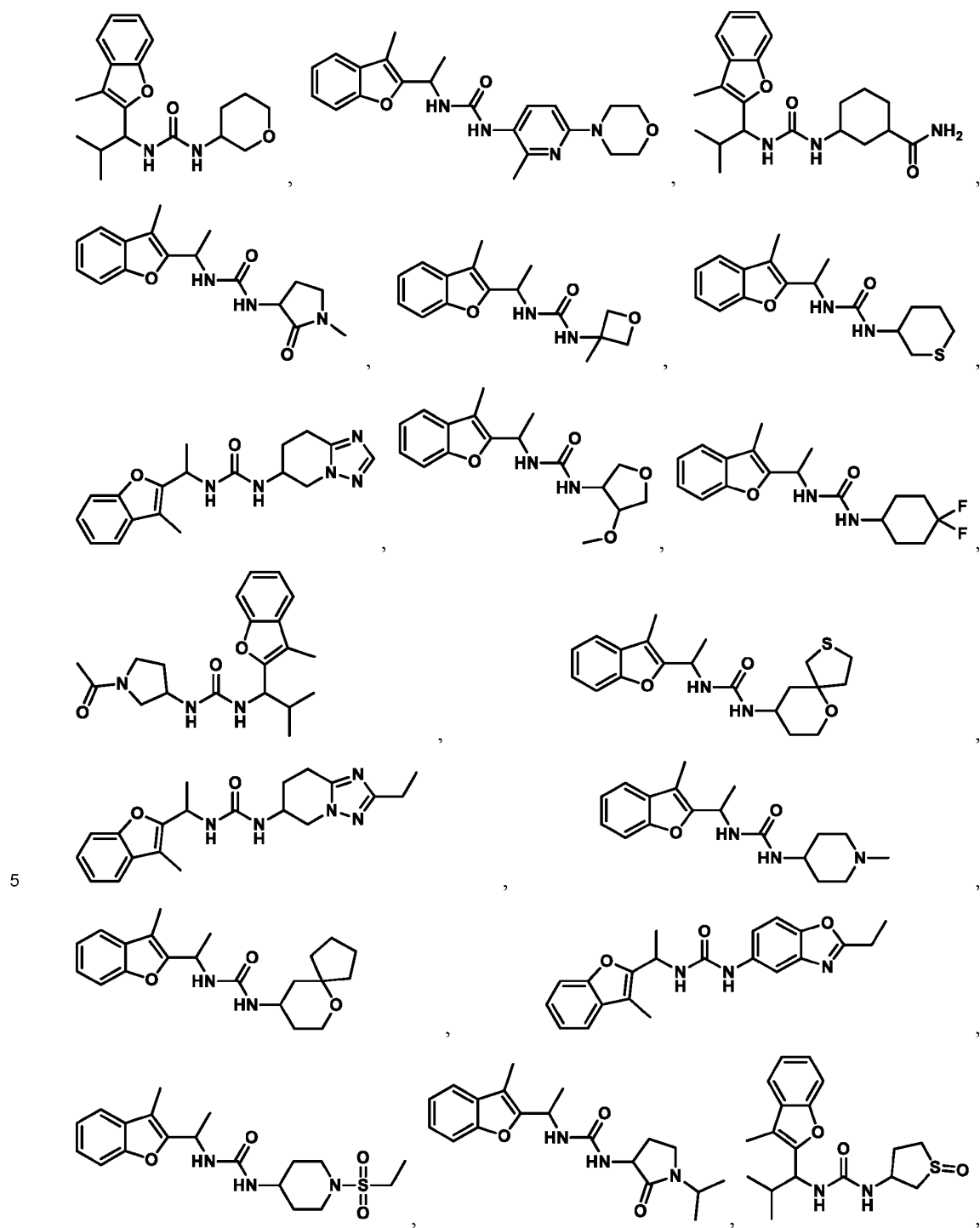
each R^A, R^{A1}, R^B, R^{B1}, R^C, R^{C1}, R^D, R^{D1}, R^E, and R^F is independently hydrogen, 4-6 membered heterocyclyl, C1-C6 haloalkyl, -C(=O)(C1-C6 alkyl), -SO₂(C1-C6 alkyl), 3-6 membered cycloalkyl optionally substituted with hydroxyl, or C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, -C(=O)NR^{B2}R^{C2}, 5-6 membered heteroaryl, 3-6 membered cycloalkyl, SO₂(C1-C6 alkyl), -SO₂(NH₂); or

R^C and R^D, together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

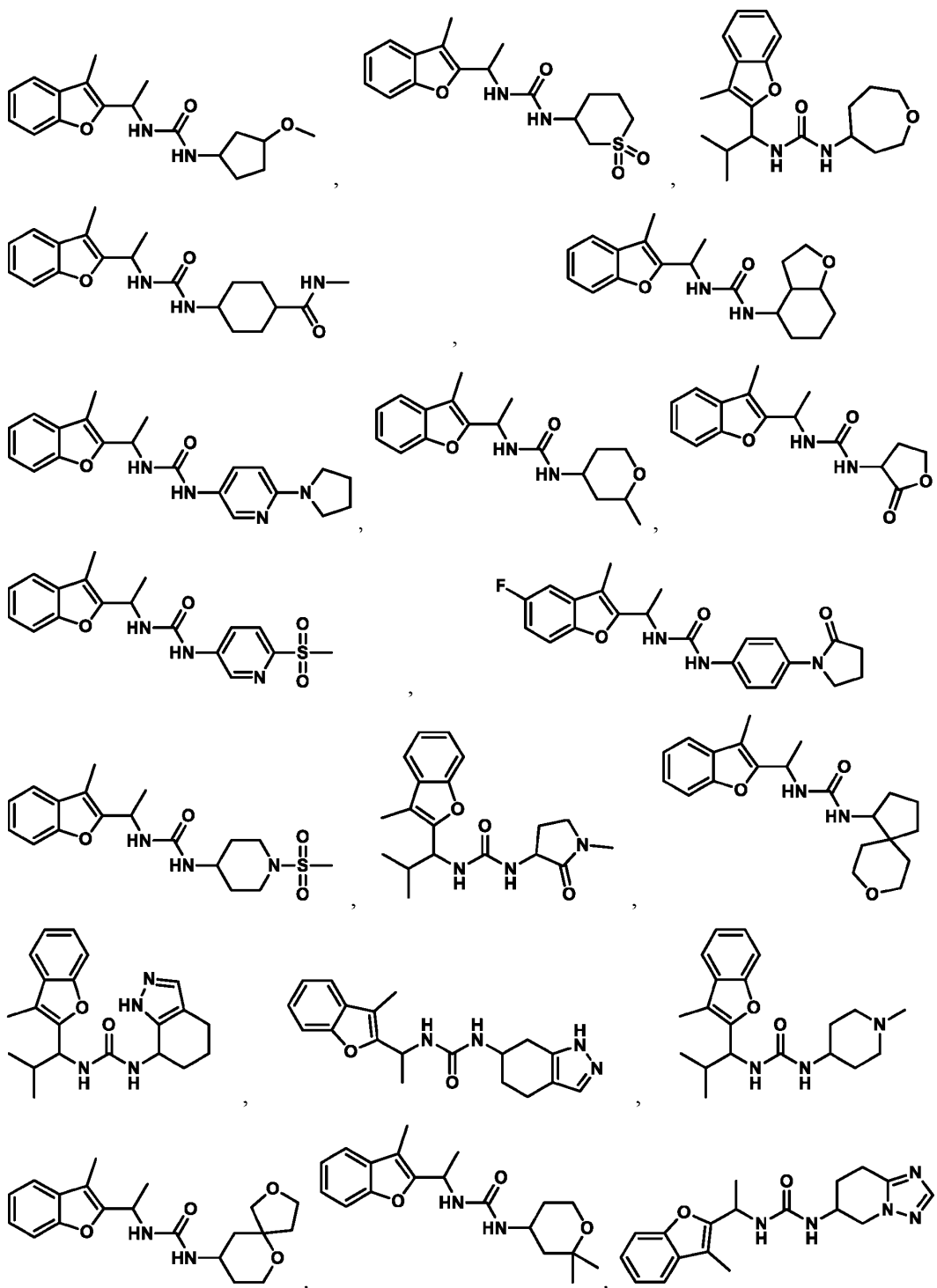
each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, -NR^{A1}R^{B1}, -C(=O)NR^{C1}R^{D1}, -CO₂(C1-C6 alkyl), C1-C6 haloalkyl, C3-C6 cycloalkyl, and -CO₂H; and

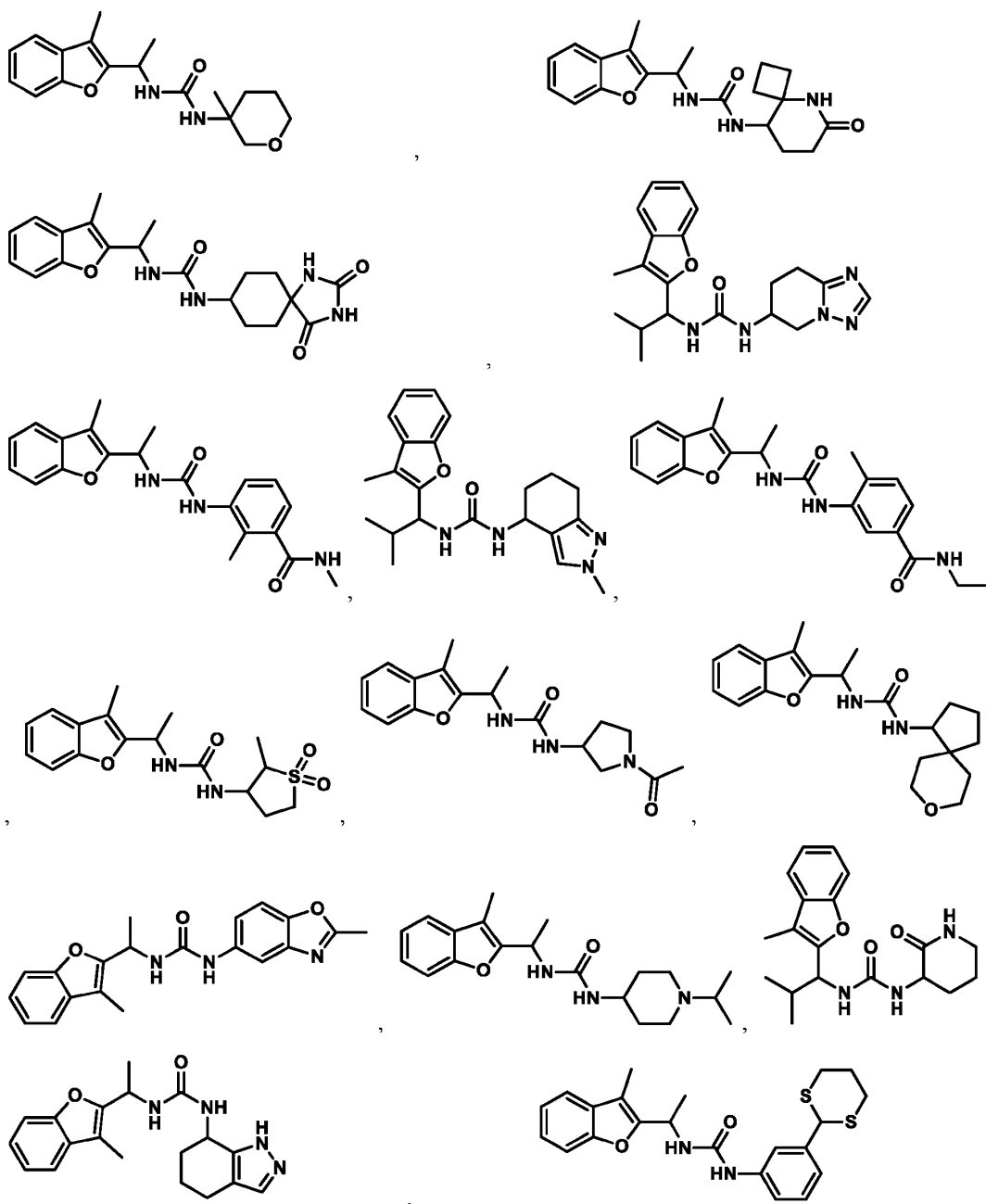
wherein the compound is not a compound selected from the group consisting of:

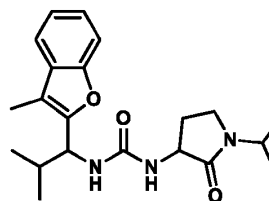
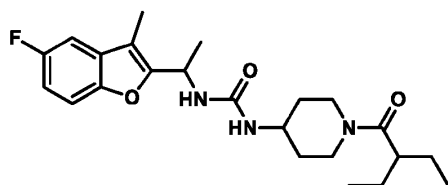
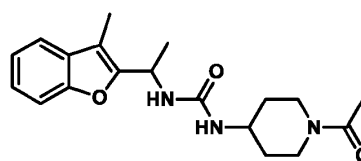
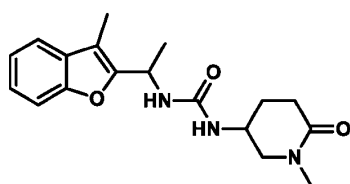
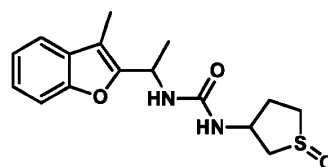
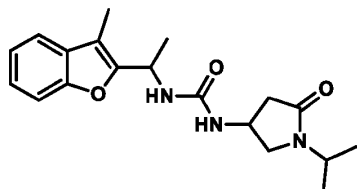
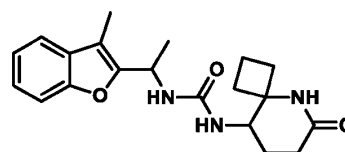
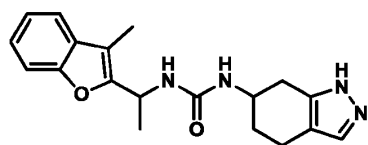
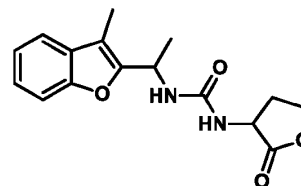
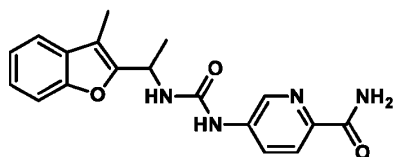
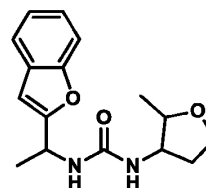
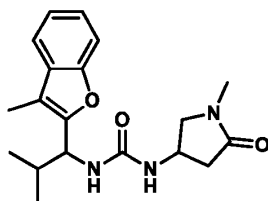
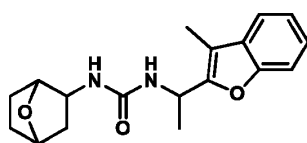
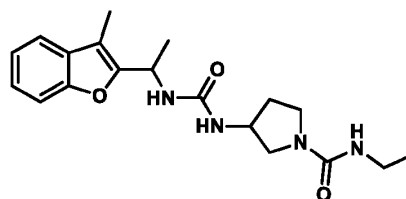
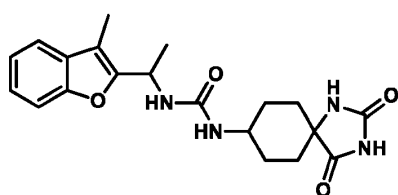


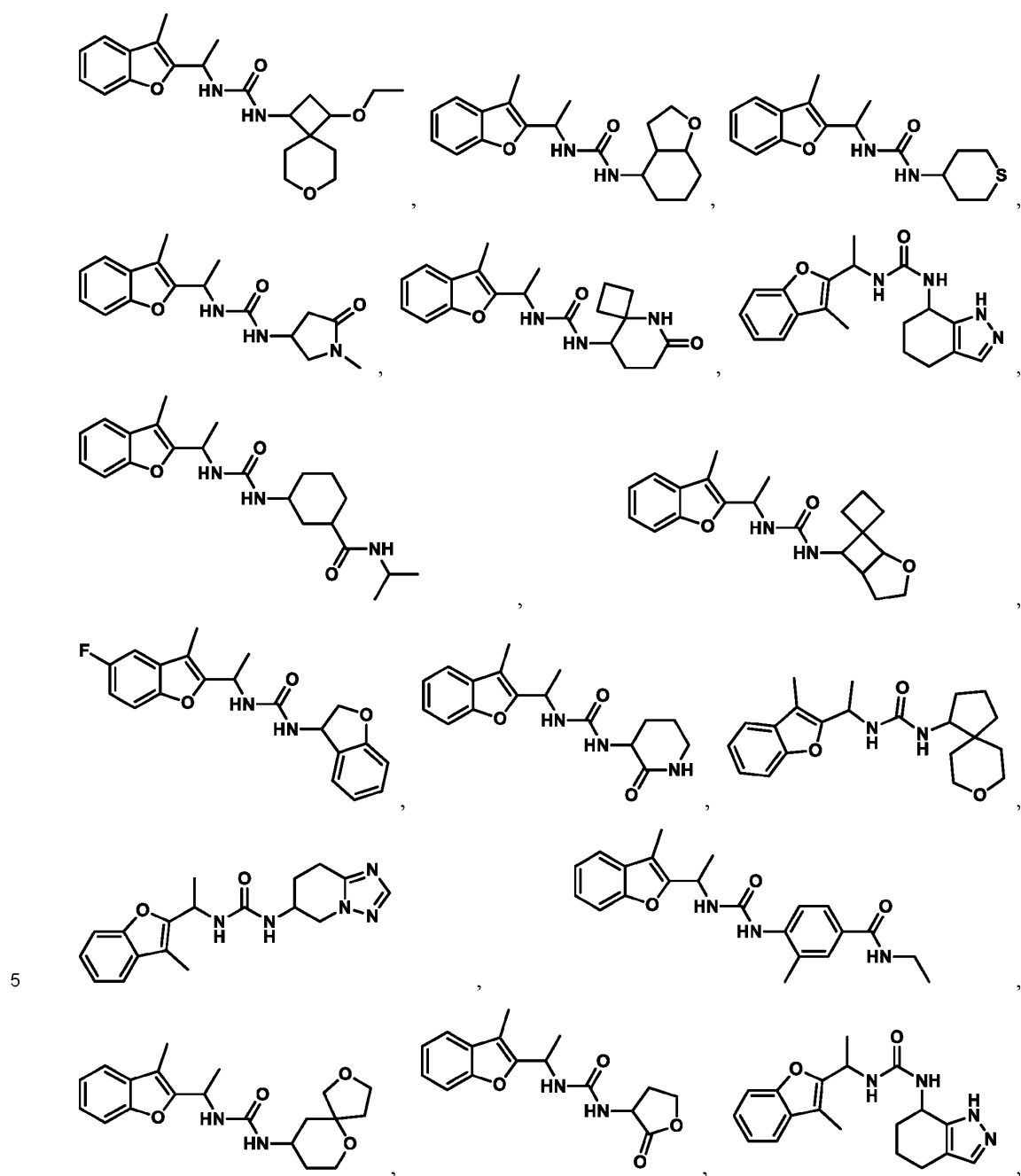


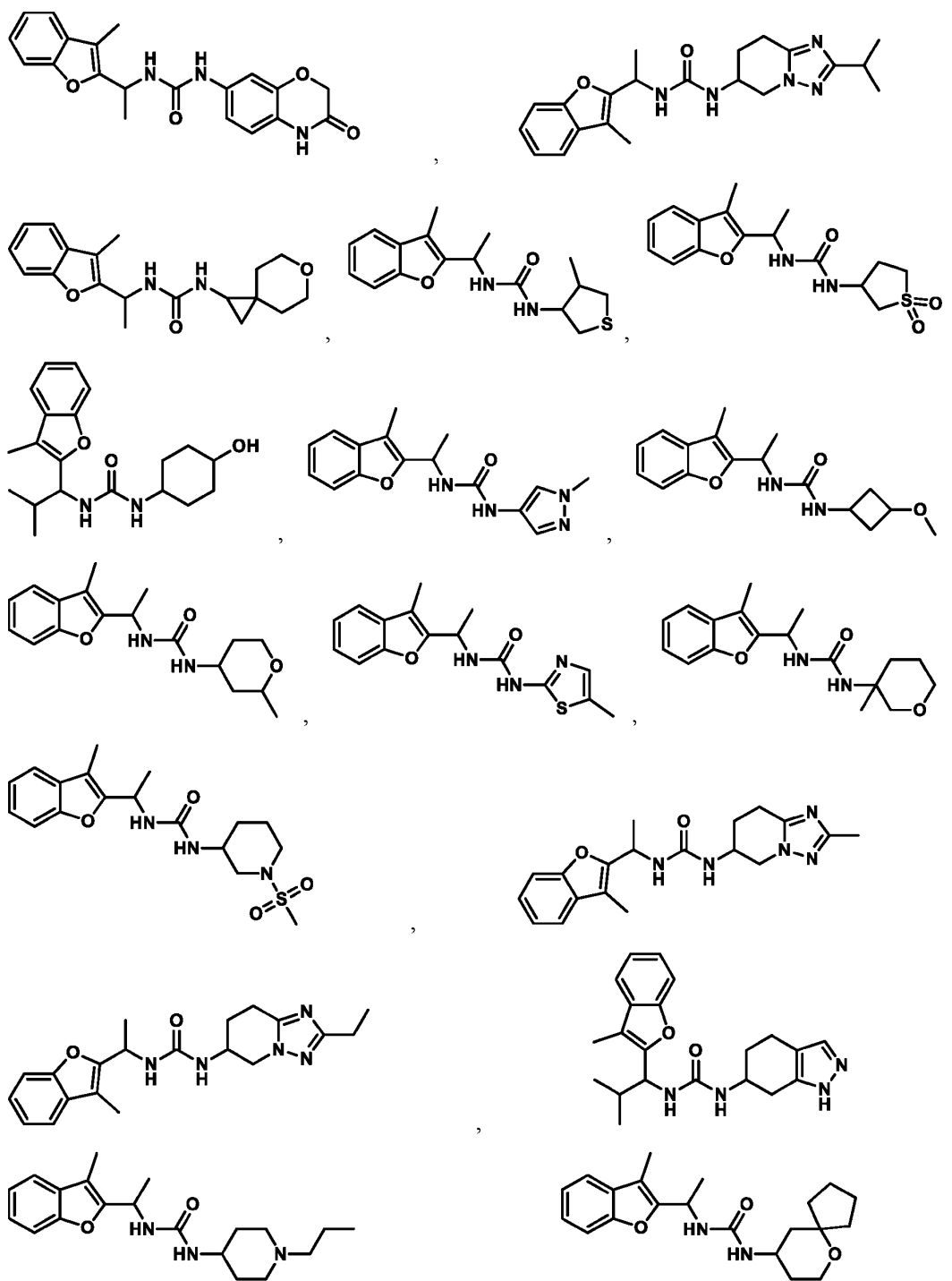


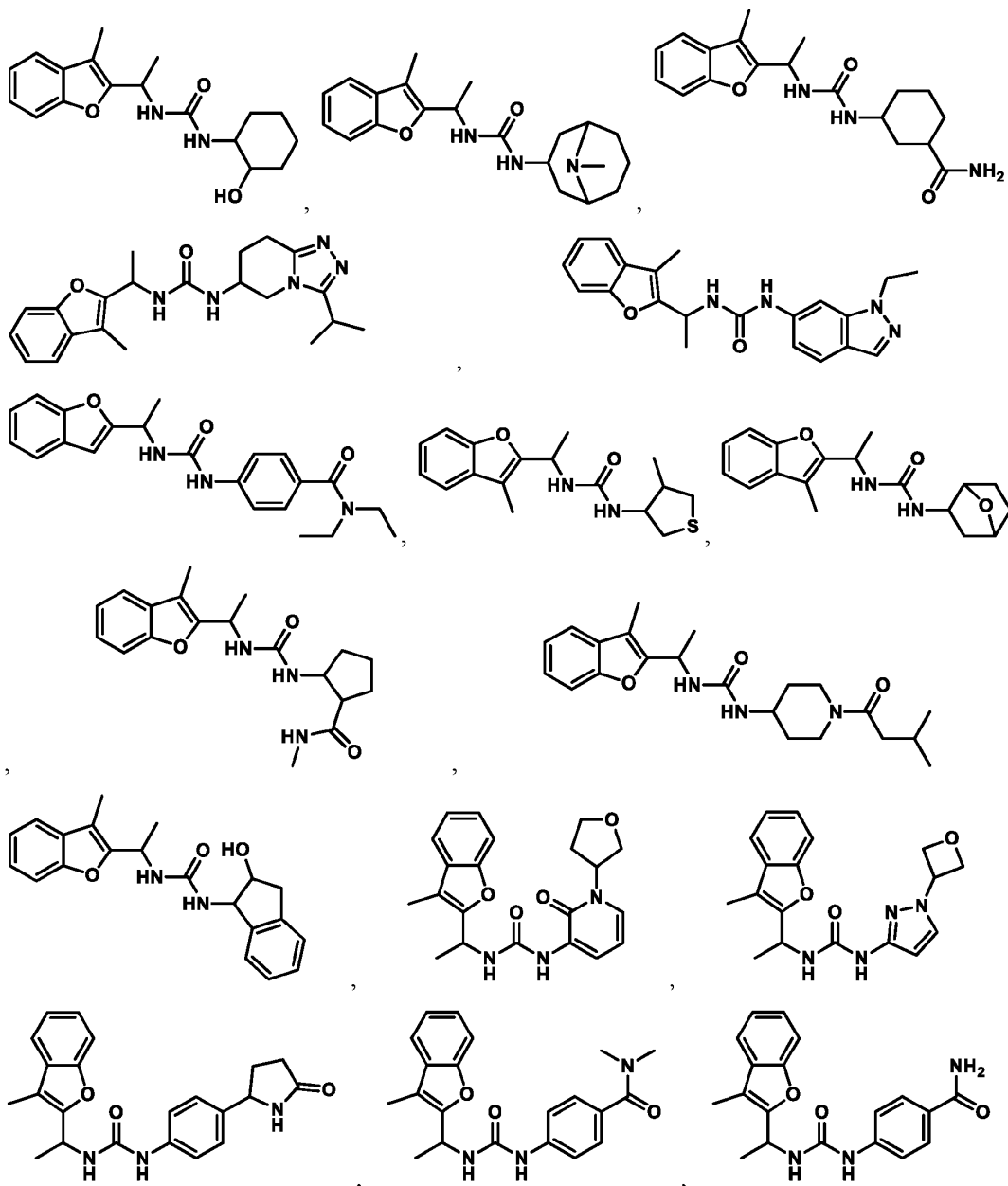


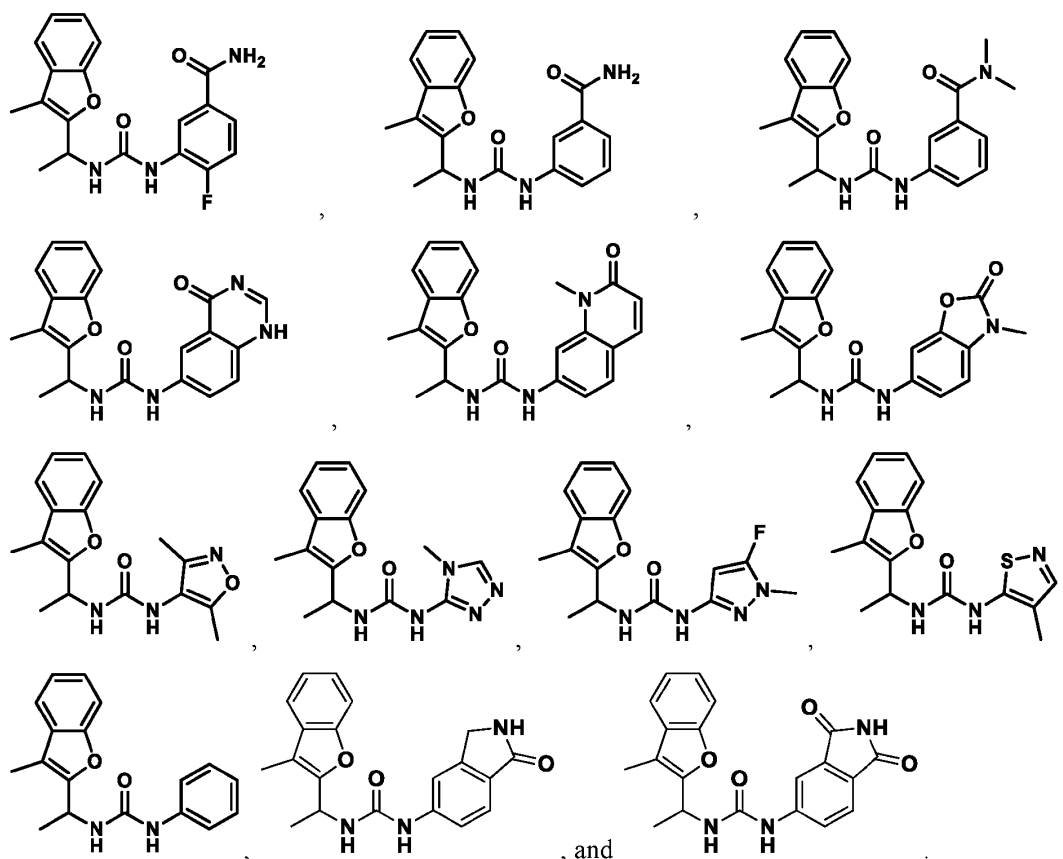






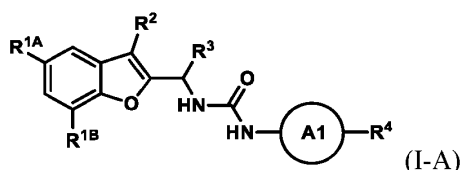






In some embodiments, the compounds described herein are not compounds that are selected from the group of compounds that are not a compound of Formula (I) described above (i.e., the "excluded compounds"). In some embodiments, the excluded compounds are flat structures, as indicated above. In some embodiments, the excluded compounds are specific stereoisomers, e.g. specific enantiomers or diastereomers. In some embodiments, the excluded compounds are R isomers. In some embodiments, the excluded compounds are S isomers. In some embodiments, one or more of the excluded compounds are R isomers, and the remaining excluded compounds are S isomers. In some embodiments, the excluded compounds are R isomers. In some embodiments, one or more of the excluded compounds are S isomers, and the remaining excluded compounds are S isomers.

In some embodiments, the compound of Formula (I) is Formula (I-A):



or a salt and/or solvate thereof, wherein:

R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

5 R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A1 is a 6 membered heteroaryl;

10 R^4 is independently selected from the group consisting of: C1-C6 alkyl optionally substituted with $-NR^A R^B$, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-CO_2H$, $-NR^A R^B$, $-C(=O)NR^C R^D$, $-SO_2(NR^E R^F)$, $-SO_2(C1-C6 \text{ alkyl})$, $-S(=O)(=NH)(C1-C6 \text{ alkyl})$, $-C(=O)(C1-C6 \text{ alkyl})$, $-CO_2(C1-C6 \text{ alkyl})$, 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl, 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G , and 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected R^G ;

15 wherein R^4 is bonded to the position of Ring A1 that is *para* to the N atom of the urea moiety;

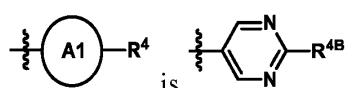
20 each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen, 4-6 membered heterocyclyl, C1-C6 haloalkyl, 3-6 membered cycloalkyl optionally substituted with hydroxyl, or C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, 3-6 membered cycloalkyl, $-SO_2(C1-C6 \text{ alkyl})$, and $-SO_2(NH_2)$; or

R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

25 each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1} R^{B1}$, $-C(=O)NR^{C1} R^{D1}$, $-CO_2(C1-C6 \text{ alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-CO_2H$.

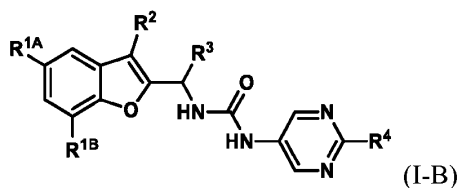
In some embodiments, Ring A1 is pyrimidinyl, pyridyl, or pyrazolyl. In some embodiments, Ring A1 is pyrimidinyl. In some embodiments, Ring A1 is pyridyl. In some embodiments, Ring A1 is pyrazolyl.

In some embodiments, Ring A1 is 5-pyrimidinyl, 3-pyridyl, or 4-pyrazolyl. In some
5 embodiments, Ring A1 is 5-pyrimidinyl. In some embodiments, Ring A1 is 3-pyridyl. In some
embodiments, Ring A1 is 4-pyrazolyl.

In some embodiments of Formula (I-A), , wherein: R^{4B} is
selected from -NR^AR^B and 4-6 membered heterocyclyl comprising one nitrogen ring member and
optionally substituted with 1-2 independently selected R^{G1}; wherein R^{G1} is selected from fluoro,
10 hydroxyl, and C1-C6 alkyl.

In some embodiments of Formula (I-A), R^A and R^B are each hydrogen.

In some embodiments, the compound of Formula (I) is Formula (I-B):



or a salt and/or solvate thereof, wherein:

15 R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R² is a C1-C6 alkyl or a C1-C6 haloalkyl;

R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with
1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

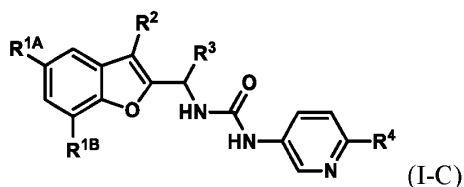
20 R⁴ is independently selected from the group consisting of: C1-C6 alkyl optionally
substituted with -NR^AR^B, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, -CO₂H, -NR^AR^B, -
C(=O)NR^CR^D, -SO₂(NR^ER^F), -SO₂(C1-C6 alkyl), -S(=O)(=NH)(C1-C6 alkyl), -C(=O)(C1-C6
alkyl), -CO₂(C1-C6 alkyl), 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl, 3-6
membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G, and 3-6
25 membered cycloalkyl optionally substituted with 1 or 2 independently selected R^G;

each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen, 4-6 membered heterocyclyl, C1-C6 haloalkyl, 3-6 membered cycloalkyl optionally substituted with hydroxyl, or C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, 3-6 membered cycloalkyl, $-\text{SO}_2(\text{C1-C6 alkyl})$, and $-\text{SO}_2(\text{NH}_2)$; or

5 R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-\text{NR}^{A1}\text{R}^{B1}$, $-\text{C}(=\text{O})\text{NR}^{C1}\text{R}^{D1}$, $-\text{CO}_2(\text{C1-C6 alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-\text{CO}_2\text{H}$.

10 In some embodiments, the compound of Formula (I) is Formula (I-C):



or a salt and/or solvate thereof, wherein:

R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

15 R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

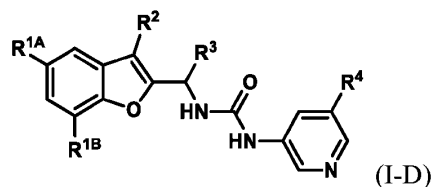
R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-\text{CO}_2\text{H}$, $-\text{NR}^A\text{R}^B$, $-\text{C}(=\text{O})\text{NR}^C\text{R}^D$, $-\text{SO}_2(\text{NR}^E\text{R}^F)$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{S}(=\text{O})(=\text{NH})(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})(\text{C1-C6 alkyl})$, $-\text{CO}_2(\text{C1-C6 alkyl})$, 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G ;

each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen or C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl; or

25 R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

each R^G is independently selected from the group consisting of: fluoro, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-\text{NR}^{A1}\text{R}^{B1}$, $-\text{C}(=\text{O})\text{NR}^{C1}\text{R}^{D1}$, and $-\text{CO}_2\text{H}$.

In some embodiments, the compound of Formula (I) is Formula (I-D):



or a salt and/or solvate thereof, wherein:

R^{1A} is halogen;

5 R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

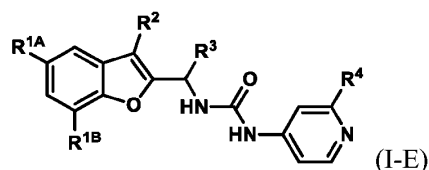
R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-\text{CO}_2\text{H}$, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$, $-\text{C}(=\text{O})\text{NR}^{\text{C}}\text{R}^{\text{D}}$, $-\text{SO}_2(\text{NR}^{\text{E}}\text{R}^{\text{F}})$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{S}(=\text{O})(=\text{NH})(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})(\text{C1-C6 alkyl})$, $-\text{CO}_2(\text{C1-C6 alkyl})$, 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^{G} ;

15 each R^{A} , R^{A1} , R^{B} , R^{B1} , R^{C} , R^{C1} , R^{D} , R^{D1} , R^{E} , and R^{F} is independently hydrogen or C1-C6 alkyl, C1-C6 haloalkyl; or

R^{C} and R^{D} , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

20 each R^{G} is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-\text{C}(=\text{O})\text{NR}^{\text{C1}}\text{R}^{\text{D1}}$, $-\text{CO}_2(\text{C1-C6 alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-\text{CO}_2\text{H}$.

In some embodiments, the compound of Formula (I) is Formula (I-E):



or a salt and/or solvate thereof, wherein:

R^{1A} is halogen;

25 R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

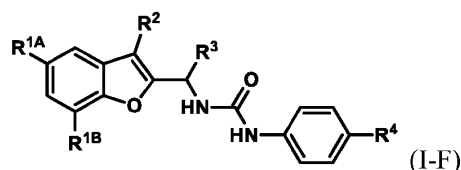
R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-\text{CO}_2\text{H}$, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$, $-\text{C}(=\text{O})\text{NR}^{\text{C}}\text{R}^{\text{D}}$, $-\text{SO}_2(\text{NR}^{\text{E}}\text{R}^{\text{F}})$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{S}(=\text{O})(=\text{NH})(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})(\text{C1-C6 alkyl})$, $-\text{CO}_2(\text{C1-C6 alkyl})$, 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^{G} ;

each R^{A} , R^{A1} , R^{B} , R^{B1} , R^{C} , R^{C1} , R^{D} , R^{D1} , R^{E} , and R^{F} is independently hydrogen or C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl; or

R^{C} and R^{D} , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

each R^{G} is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-\text{C}(=\text{O})\text{NR}^{\text{C1}}\text{R}^{\text{D1}}$, $-\text{CO}_2(\text{C1-C6 alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-\text{CO}_2\text{H}$.

In some embodiments, the compound of Formula (I) is Formula (I-F):



or a salt and/or solvate thereof, wherein:

$R^{1\text{A}}$ is halogen;

$R^{1\text{B}}$ is halogen or absent (the phenyl ring is monosubstituted with $R^{1\text{A}}$);

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

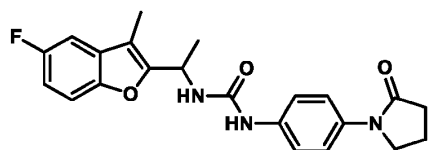
R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-\text{CO}_2\text{H}$, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$, $-\text{C}(=\text{O})\text{NR}^{\text{C}}\text{R}^{\text{D}}$, $-\text{SO}_2(\text{NR}^{\text{E}}\text{R}^{\text{F}})$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{S}(=\text{O})(=\text{NH})(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})(\text{C1-C6 alkyl})$, $-\text{CO}_2(\text{C1-C6 alkyl})$, 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^{G} ;

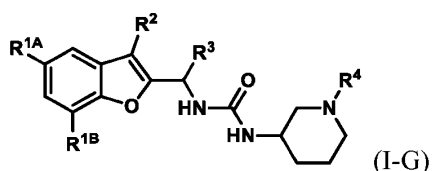
each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen or C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl; or

R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

5 each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $-C(=O)NR^{C1}R^{D1}$, $-CO_2$ (C1-C6 alkyl), C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-CO_2H$; and wherein the compound is not



In some embodiments, the compound of Formula (I) is Formula (I-G):



10

or a salt and/or solvate thereof, wherein:

R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

15 R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-CO_2H$, $-NR^A R^B$, $-C(=O)NR^C R^D$, $-SO_2(NR^E R^F)$, $-SO_2$ (C1-C6 alkyl), $-S(=O)(=NH)$ (C1-C6 alkyl), $-C(=O)$ (C1-C6 alkyl), $-CO_2$ (C1-C6 alkyl), 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G ;

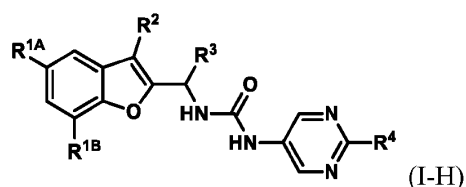
20

each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen or C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl; or

25 R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $-C(=O)NR^{C1}R^{D1}$, $-CO_2(C1-C6 \text{ alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-CO_2H$.

In some embodiments, the compound of Formula (I) is Formula (I-H):



or a salt and/or solvate thereof, wherein:

R^{1A} is halogen;

R^{1B} is halogen, cyano, cyclopropyl, or absent (the phenyl ring is monosubstituted with R^{1A});

10 R^2 is a C1-C6 alkyl or C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl or a C1-C6 haloalkyl;

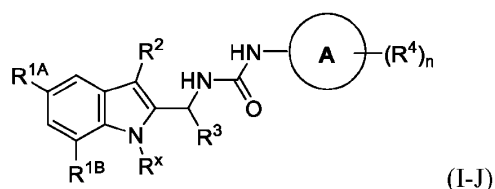
R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl, C1-C6 haloalkyl, $-NR^A R^B$, and 3-9 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G ;

15 each R^A , R^B , R^{C1} , and R^{D1} is independently hydrogen, 4-6 membered heterocyclyl, C1-C6 alkyl optionally substituted with hydroxyl or $-C(=O)NR^{B2}R^{C2}$, $-C(=O)O(C1-C6 \text{ alkyl})$, or C1-C6 haloalkyl;

each R^{A2} , R^{B2} , and R^{C2} is independently hydrogen or C1-C6 alkyl;

20 each R^G is independently selected from the group consisting of: fluoro, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, $=NR^{A2}$, $-C(=O)NR^{C1}R^{D1}$, C1-C6 haloalkoxy, $-SO_2(C1-C6 \text{ alkyl})$, and $-CO_2H$.

In some embodiments, the compound of Formula (I) is Formula (I-J):



or a salt and/or solvate thereof, wherein:

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

5 R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A1 is a 6 membered heteroaryl;

R^4 is independently selected from the group consisting of: C1-C6 alkyl optionally substituted with $-NR^A R^B$, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-CO_2H$, $-NR^A R^B$, -
10 $C(=O)NR^C R^D$, $-SO_2(NR^E R^F)$, $-SO_2(C1-C6 \text{ alkyl})$, $-S(=O)(=NH)(C1-C6 \text{ alkyl})$, $-C(=O)(C1-C6 \text{ alkyl})$, $-CO_2(C1-C6 \text{ alkyl})$, 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl, 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G , and 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected R^G ;

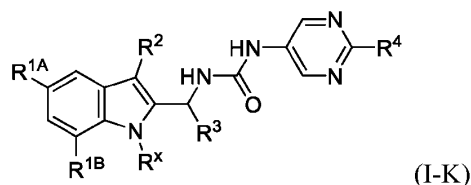
wherein R^4 is bonded to the position of Ring A1 that is *para* to the N atom of the urea moiety;
15 moiety;

each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen, 4-6 membered heterocyclyl, C1-C6 haloalkyl, 3-6 membered cycloalkyl optionally substituted with hydroxyl, or C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, 3-6 membered cycloalkyl, $-SO_2(C1-C6 \text{ alkyl})$, and $-SO_2(NH_2)$; or

20 R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1} R^{B1}$, $-C(=O)NR^{C1} R^{D1}$, $-CO_2(C1-C6 \text{ alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-CO_2H$.

25 In some embodiments, the compound of Formula (I) is Formula (I-K):



or a salt and/or solvate thereof, wherein:

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with
5 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

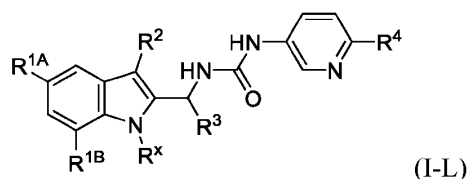
R^4 is independently selected from the group consisting of: C1-C6 alkyl optionally substituted with $-NR^A R^B$, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-CO_2H$, $-NR^A R^B$, $-C(=O)NR^C R^D$, $-SO_2(NR^E R^F)$, $-SO_2(C1-C6 \text{ alkyl})$, $-S(=O)(=NH)(C1-C6 \text{ alkyl})$, $-C(=O)(C1-C6 \text{ alkyl})$, $-CO_2(C1-C6 \text{ alkyl})$, 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl, 3-6
10 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G , and 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected R^G ;

each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen, 4-6 membered heterocyclyl, C1-C6 haloalkyl, 3-6 membered cycloalkyl optionally substituted with hydroxyl, or C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from
15 hydroxyl, 3-6 membered cycloalkyl, $-SO_2(C1-C6 \text{ alkyl})$, and $-SO_2(NH_2)$; or

R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1} R^{B1}$, $-C(=O)NR^{C1} R^{D1}$, $-CO_2(C1-C6 \text{ alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-CO_2H$.
20

In some embodiments, the compound of Formula (I) is Formula (I-L):



or a salt and/or solvate thereof, wherein:

R^X is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

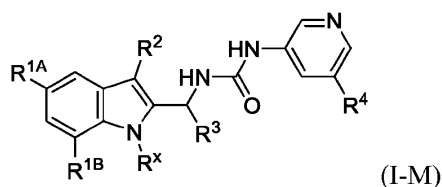
R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-\text{CO}_2\text{H}$, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$, $-\text{C}(=\text{O})\text{NR}^{\text{C}}\text{R}^{\text{D}}$, $-\text{SO}_2(\text{NR}^{\text{E}}\text{R}^{\text{F}})$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{S}(=\text{O})(=\text{NH})(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})(\text{C1-C6 alkyl})$, $-\text{CO}_2(\text{C1-C6 alkyl})$, 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^{G} ;

each R^{A} , R^{A1} , R^{B} , R^{B1} , R^{C} , R^{C1} , R^{D} , R^{D1} , R^{E} , and R^{F} is independently hydrogen or C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl; or

R^{C} and R^{D} , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

each R^{G} is independently selected from the group consisting of: fluoro, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-\text{NR}^{\text{A1}}\text{R}^{\text{B1}}$, $-\text{C}(=\text{O})\text{NR}^{\text{C1}}\text{R}^{\text{D1}}$, and $-\text{CO}_2\text{H}$.

In some embodiments, the compound of Formula (I) is Formula (I-M):



or a salt and/or solvate thereof, wherein:

R^{x} is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

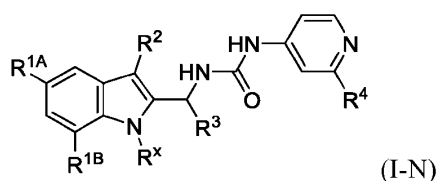
R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-\text{CO}_2\text{H}$, $-\text{NR}^{\text{A}}\text{R}^{\text{B}}$, $-\text{C}(=\text{O})\text{NR}^{\text{C}}\text{R}^{\text{D}}$, $-\text{SO}_2(\text{NR}^{\text{E}}\text{R}^{\text{F}})$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{S}(=\text{O})(=\text{NH})(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})(\text{C1-C6 alkyl})$, $-\text{CO}_2(\text{C1-C6 alkyl})$, 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^{G} ;

each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen or C1-C6 alkyl, C1-C6 haloalkyl; or

R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

5 each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $-C(=O)NR^{C1}R^{D1}$, $-CO_2$ (C1-C6 alkyl), C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-CO_2H$.

In some embodiments, the compound of Formula (I) is Formula (I-N):



10 or a salt and/or solvate thereof, wherein:

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

15 R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

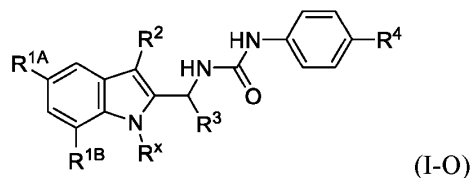
R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-CO_2H$, $-NR^A R^B$, $-C(=O)NR^C R^D$, $-SO_2(NR^E R^F)$, $-SO_2$ (C1-C6 alkyl), $-S(=O)(=NH)$ (C1-C6 alkyl), $-C(=O)$ (C1-C6 alkyl), $-CO_2$ (C1-C6 alkyl), 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G ;

each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen or C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl; or

25 R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $-C(=O)NR^{C1}R^{D1}$, $-CO_2$ (C1-C6 alkyl), C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-CO_2H$.

In some embodiments, the compound of Formula (I) is Formula (I-O):



or a salt and/or solvate thereof, wherein:

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

5 R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

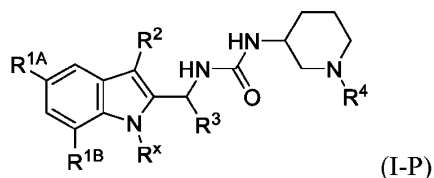
10 R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-\text{CO}_2\text{H}$, $-\text{NR}^A\text{R}^B$, $-\text{C}(=\text{O})\text{NR}^C\text{R}^D$, $-\text{SO}_2(\text{NR}^E\text{R}^F)$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{S}(=\text{O})(=\text{NH})(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})(\text{C1-C6 alkyl})$, $-\text{CO}_2(\text{C1-C6 alkyl})$, 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G ;

15 each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen or C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl; or

R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

20 each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-\text{NR}^{A1}\text{R}^{B1}$, $-\text{C}(=\text{O})\text{NR}^{C1}\text{R}^{D1}$, $-\text{CO}_2(\text{C1-C6 alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-\text{CO}_2\text{H}$.

In some embodiments, the compound of Formula (I) is Formula (I-P):



or a salt and/or solvate thereof, wherein:

25 R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

R^{1A} is halogen;

R^{1B} is halogen or absent (the phenyl ring is monosubstituted with R^{1A});

R^2 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with
5 1 or 2 fluoro;

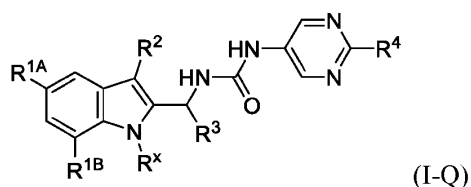
R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-\text{CO}_2\text{H}$, $-\text{NR}^A\text{R}^B$, $-\text{C}(=\text{O})\text{NR}^C\text{R}^D$, $-\text{SO}_2(\text{NR}^E\text{R}^F)$, $-\text{SO}_2(\text{C1-C6 alkyl})$, $-\text{S}(=\text{O})(=\text{NH})(\text{C1-C6 alkyl})$, $-\text{C}(=\text{O})(\text{C1-C6 alkyl})$, $-\text{CO}_2(\text{C1-C6 alkyl})$, 5-6 membered heteroaryl, and 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently
10 selected R^G ;

each R^A , R^{1A} , R^B , R^{1B} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently hydrogen or C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl; or

R^C and R^D , together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl;

15 each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl, C1-C6 alkoxy, $-\text{NR}^A\text{R}^{B1}$, $-\text{C}(=\text{O})\text{NR}^{C1}\text{R}^{D1}$, $-\text{CO}_2(\text{C1-C6 alkyl})$, C1-C6 haloalkyl, C3-C6 cycloalkyl, and $-\text{CO}_2\text{H}$.

In some embodiments, the compound of Formula (I) is Formula (I-Q):



20 or a salt and/or solvate thereof, wherein:

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

R^{1A} is halogen;

R^{1B} is halogen, cyano, cyclopropyl, or absent (the phenyl ring is monosubstituted with
25 R^{1A});

R^2 is a C1-C6 alkyl or C1-C6 haloalkyl;

R^3 is a C1-C6 alkyl or a C1-C6 haloalkyl;

R^4 is independently selected from the group consisting of: C1-C6 alkyl, C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6

cycloalkyl, C1-C6 haloalkyl, $-NR^A R^B$, and 3-9 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G ;

each R^A , R^B , R^{C1} , and R^{D1} is independently hydrogen, 4-6 membered heterocyclyl, C1-C6 alkyl optionally substituted with hydroxyl or $-C(=O)NR^{B2}R^{C2}$, $-C(=O)O(C1-C6 \text{ alkyl})$, or C1-C6 haloalkyl;

each R^{A2} , R^{B2} , and R^{C2} is independently hydrogen or C1-C6 alkyl;

each R^G is independently selected from the group consisting of: fluoro, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, $=NR^{A2}$, $-C(=O)NR^{C1}R^{D1}$, C1-C6 haloalkoxy, $-SO_2(C1-C6 \text{ alkyl})$, and $-CO_2H$.

In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

In some embodiments, each R^1 is an independently selected halogen. In some embodiments, each R^1 is independently selected from fluoro and chloro. In some embodiments, each R^1 is independently selected from fluoro and bromo. In some embodiments, each R^1 is fluoro. In some embodiments, at least one R^1 is an independently selected halogen. In some embodiments, at least one R^1 is independently selected from fluoro and chloro. In some embodiments, at least one R^1 is fluoro.

In some embodiments, at least one R^1 is cyano. In some embodiments, at least one R^1 is hydroxyl. In some embodiments, at least one R^1 is C1-C6 alkyl optionally substituted with hydroxyl. In some embodiments, at least one R^1 is C1-C6 alkyl substituted with hydroxyl. In some embodiments, at least one R^1 is C1-C3 alkyl substituted with hydroxyl. In some embodiments, at least one R^1 is hydroxymethyl. In some embodiments, at least one R^1 is unsubstituted C1-C6 alkyl. In some embodiments, at least one R^1 is methyl. In some embodiments, at least one R^1 is C3-C6 cycloalkyl. In some embodiments, at least one R^1 is cyclopropyl.

In some embodiments, m is 2; one R^1 is halogen; and the other R^1 is C1-C6 alkyl. In some embodiments, m is 2; one R^1 is fluoro; and the other R^1 is methyl. In some embodiments, m is 2; one R^1 is halogen; and the other R^1 is C3-C6 cycloalkyl. In some embodiments, m is 2; one R^1 is halogen; and the other R^1 is cyclopropyl. In some embodiments, m is 2; one R^1 is fluoro; and the other R^1 is cyano. In some embodiments, m is 2; one R^1 is halogen; and the other R^1 is halogen. In some embodiments, m is 2; one R^1 is fluoro; and the other R^1 is fluoro.

In some embodiments, R² is hydroxyl. In some embodiments, R² is C1-C6 alkyl optionally substituted with hydroxyl. In some embodiments, R² is C1-C6 alkyl substituted with hydroxyl. In some embodiments, R² is C1-C3 alkyl substituted with hydroxyl. In some embodiments, R² is hydroxymethyl. In some embodiments, R² is an unsubstituted C1-C6 alkyl. In some embodiments, R² is unsubstituted C1-C3 alkyl. In some embodiments, R² is methyl.

In some embodiments, R² is a C1-C6 haloalkyl. In some embodiments, R² is a C1-C3 haloalkyl. In some embodiments, R² is difluoromethyl. In some embodiments, R² is trifluoromethyl.

In some embodiments, R² is halogen. In some embodiments, R² is fluoro. In some embodiments, R² is chloro.

In some embodiments, R² is C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro. In some embodiments, R² is C3-C6 cycloalkyl substituted with 1 or 2 fluoro. In some embodiments, R² is C3-C6 cycloalkyl substituted with 1 fluoro. In some embodiments, R² is C3-C6 cycloalkyl substituted with 2 fluoro. In some embodiments, R² is C3-C4 cycloalkyl substituted with 1 fluoro. In some embodiments, R² is C3-C4 cycloalkyl substituted with 2 fluoro. In some embodiments, R² is an unsubstituted C3-C6 cycloalkyl.

In some embodiments, R³ is a C1-C6 alkyl. In some embodiments, R³ is a C1-C3 alkyl. In some embodiments, R³ is methyl, ethyl, t-butyl, or isopropyl. In some embodiments, R³ is methyl, ethyl, or isopropyl. In some embodiments, R³ is methyl. In some embodiments, R³ is ethyl. In some embodiments, R³ is isopropyl.

In some embodiments, R³ is a C1-C6 haloalkyl. In some embodiments, R³ is a C1-C3 haloalkyl. In some embodiments, R³ is difluoromethyl. In some embodiments, R³ is trifluoromethyl.

In some embodiments, R³ is C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl. In some embodiments, R³ is C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 or 2 fluoro. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 fluoro. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 fluoro at the position of the C3-C6 cycloalkyl that is bonded to the methine of Formula (I). In some embodiments, R³ is 2,2-difluorocyclopropyl or 3,3-difluorocyclopropyl. In some embodiments, R³ is C3-C6 cycloalkyl optionally substituted with 1 or 2 methyl. In some embodiments, R³ is C3-

C6 cycloalkyl substituted with 1 or 2 methyl. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 methyl. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 methyl at the position of the C3-C6 cycloalkyl that is bonded to the methine of Formula (I). In some embodiments, R³ is an unsubstituted C3-C6 cycloalkyl. In some embodiments, the R³ C3-C6 cycloalkyl is cyclopropyl. In some embodiments, R³ is cyclopropyl. In some embodiments, R³ is cyclobutyl. In some embodiments, R³ is cyclopentyl. In some embodiments, R³ is cyclohexyl.

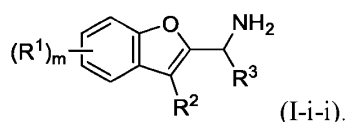
In some embodiments, R' is C1-C6 alkyl. In some embodiments, R' is C1-C4 alkyl. In some embodiments, R' is C1-C3 alkyl. In some embodiments, R' is isopropyl. In some embodiments, R' is methyl. In some embodiments, R' is ethyl. In some embodiments, R' is n-propyl.

In some embodiments, R' is C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl or C1-6 alkoxy. In some embodiments, R' is C6-C10 aryl substituted with 1-3 independently selected C1-6 alkyl or C1-6 alkoxy. In some embodiments, R' is C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl. In some embodiments, R' is C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkoxy. In some embodiments, R' is C6-C10 aryl substituted with 1-3 independently selected C1-6 alkyl. In some embodiments, R' is C6-C10 aryl substituted with 1-3 independently selected C1-6 alkoxy.

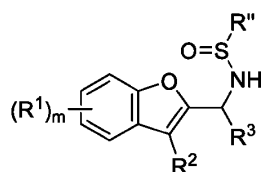
In some embodiments, R'' is C1-C6 alkyl. In some embodiments, R'' is C1-C4 alkyl. In some embodiments, R'' is C1-C3 alkyl. In some embodiments, R'' is isopropyl. In some embodiments, R'' is methyl. In some embodiments, R'' is ethyl. In some embodiments, R'' is n-propyl.

In some embodiments, Hal is selected from chloro, bromo, and iodo. In some embodiments, Hal is selected from chloro, bromo, and trifluoromethyl. In some embodiments, Hal is chloro. In some embodiments, Hal is bromo. In some embodiments, Hal is iodo. In some embodiments, Hal is trifluoromethanesulfonyl.

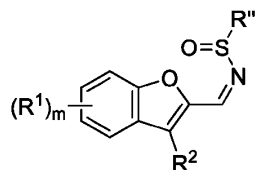
In some embodiments, the compound of Formula (I-i) is a compound of Formula (I-i-i):



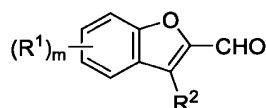
In some embodiments, the compound of Formula (I-iii) is a compound of Formula (I-iii-i)



In some embodiments, the compound of Formula (I-iv) is a compound of Formula (I-iv-i)

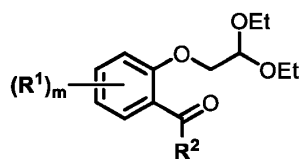


In some embodiments, the compound of Formula (I-v) is a compound of Formula (I-v-i)

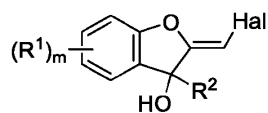


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In some embodiments, the compound of Formula (I-vi) is a compound of Formula (I-vi-i)



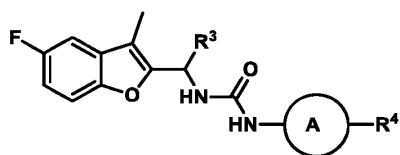
In some embodiments, the compound of Formula (I-viii) is a compound of Formula (I-viii-i)



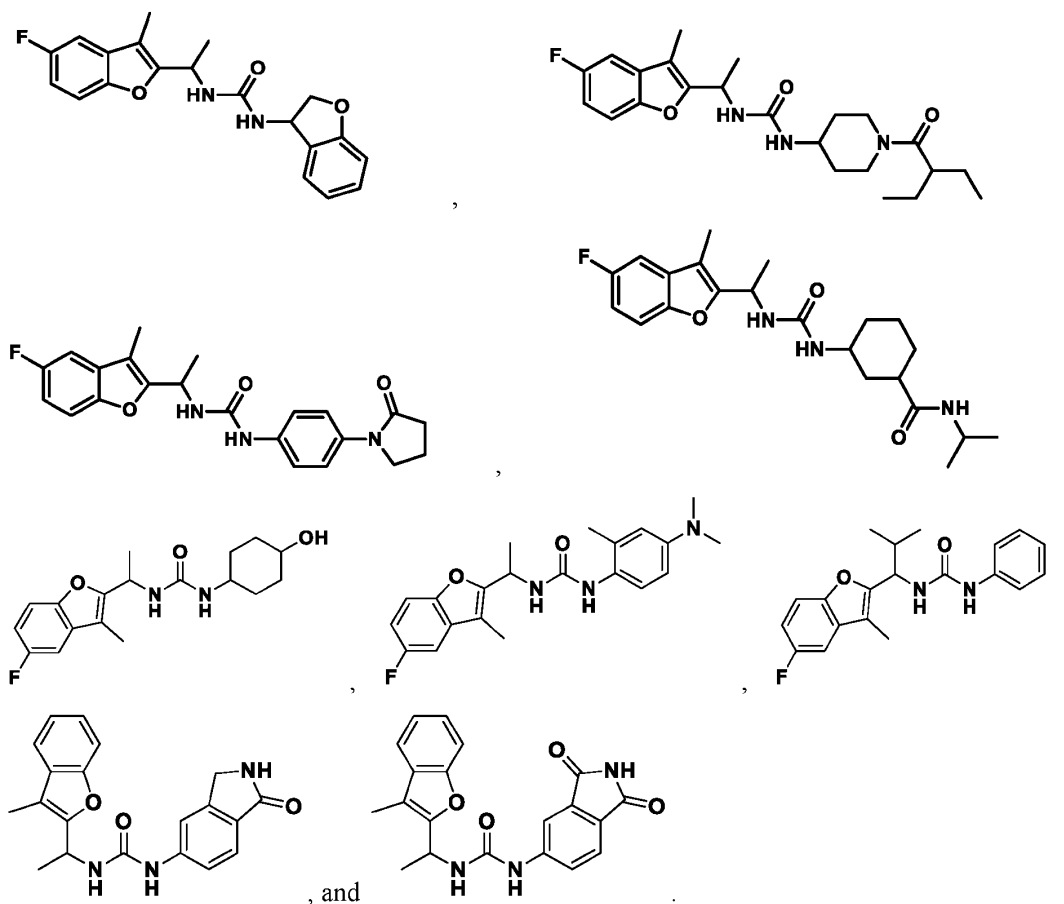
i)

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In some embodiments, the compound of Formula (I) is

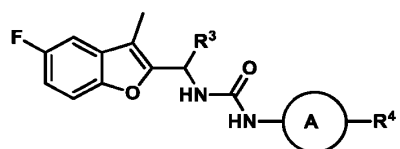


or a salt and/or solvate thereof, wherein R³, R⁴, and Ring A are as described herein; and wherein the compound is not a compound selected from the group consisting of:

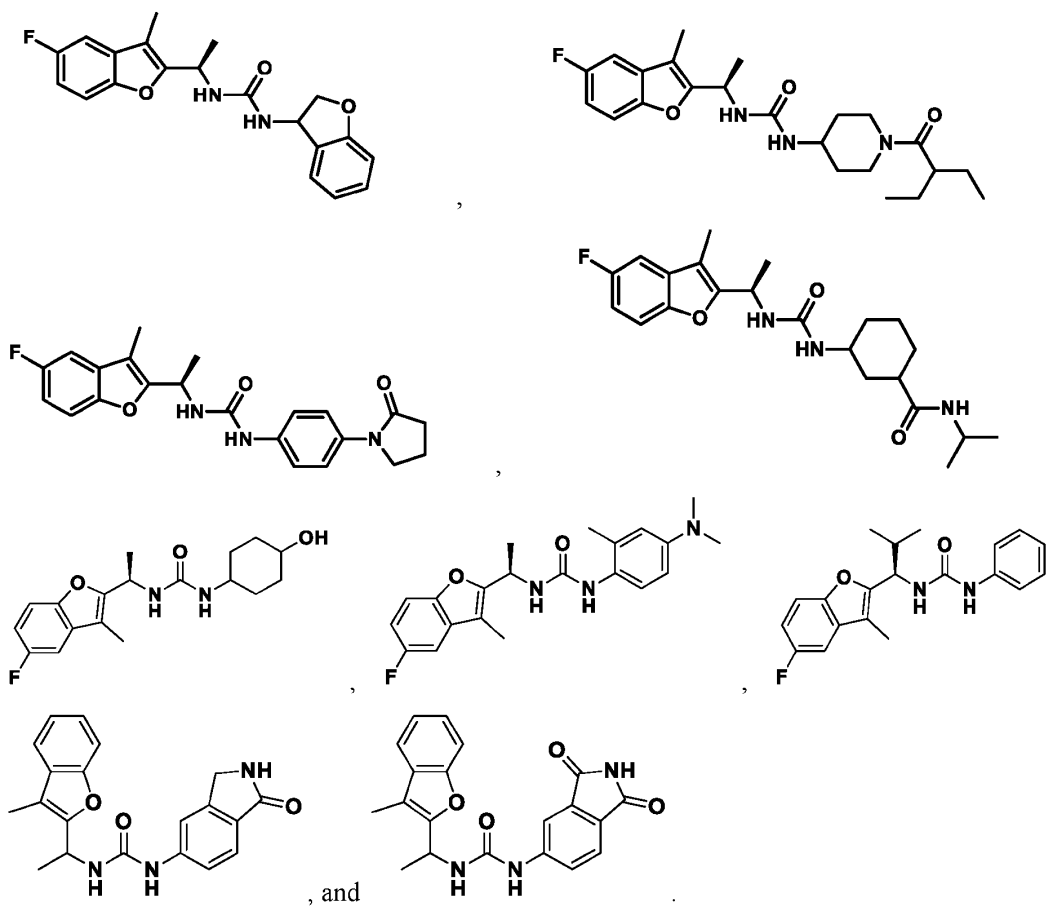


5

In some embodiments, the compound of Formula (I) is

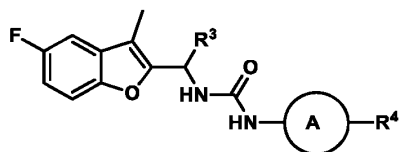


or a salt and/or solvate thereof, wherein R^3 , R^4 , and Ring A are as described herein; and wherein the compound is not a compound selected from the group consisting of:

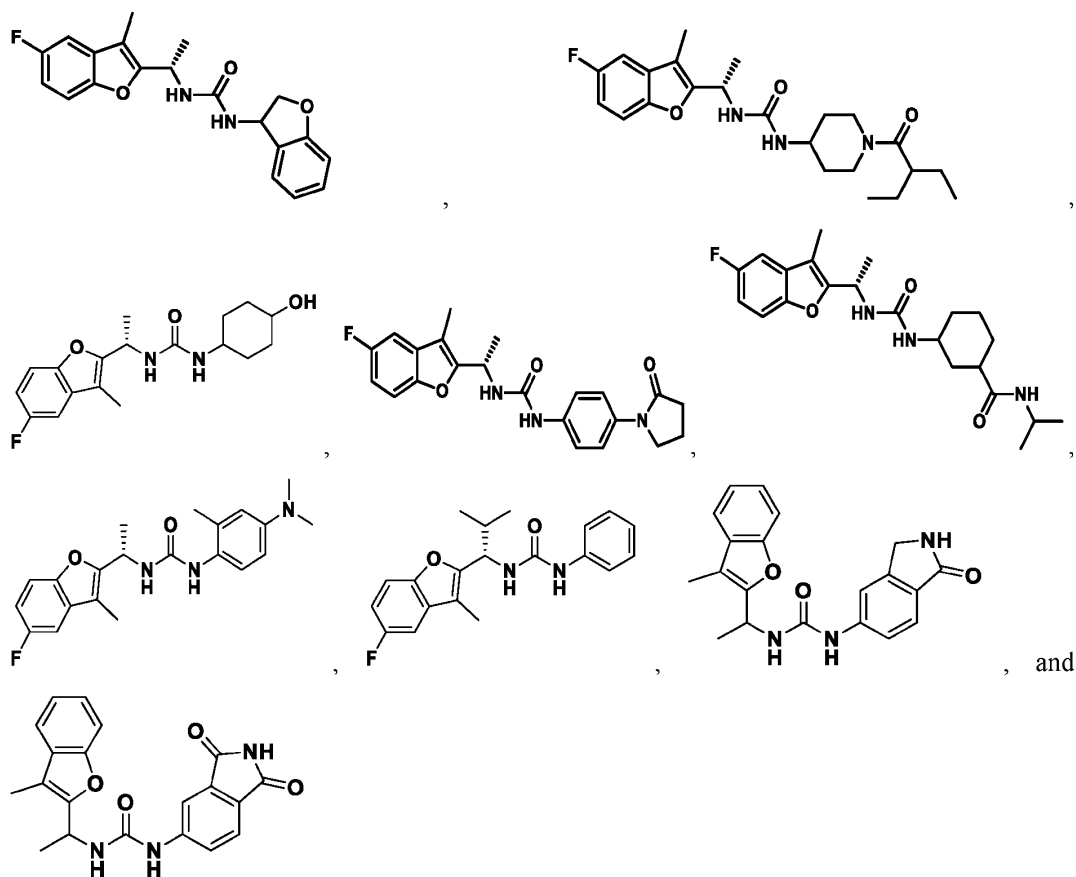


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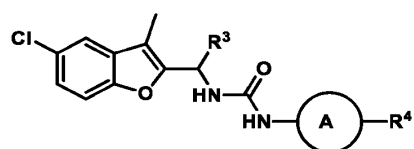
In some embodiments, the compound of Formula (I) is



or a salt and/or solvate thereof, wherein R^3 , R^4 , and Ring A are as described herein; and wherein the compound is not a compound selected from the group consisting of:

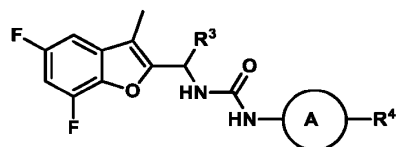


5 In some embodiments, the compound of Formula (I) is



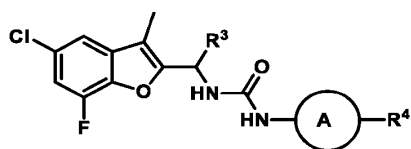
or a salt and/or solvate thereof, wherein R³, R⁴, and Ring A are as described herein.

In some embodiments, the compound of Formula (I) is



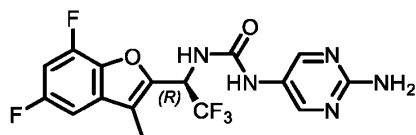
10 or a salt and/or solvate thereof, wherein R^3 , R^4 , and Ring A are as described herein.

In some embodiments, the compound of Formula (I) is



or a salt and/or solvate thereof, wherein R^3 , R^4 , and Ring A are as described herein.

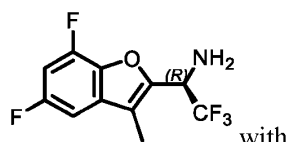
Some embodiments provide a process of preparing Compound 1:



(1), or a salt and/or solvate thereof;

5

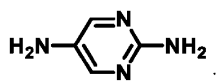
comprising contacting



with

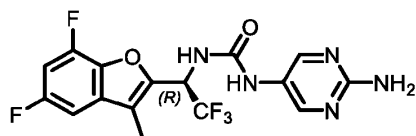
(i) a carbonyl equivalent or an isocyanate-forming reagent; and

(ii) pyrimidine-2,5-diamine having the structure



to form Compound 1.

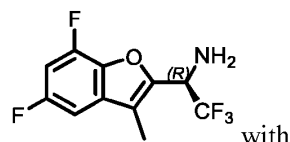
Some embodiments provide Compound 1:



10

(1), or a salt and/or solvate thereof;

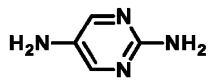
prepared by a process comprising contacting



with

(i) a carbonyl equivalent or an isocyanate-forming reagent; and

(ii) pyrimidine-2,5-diamine having the structure



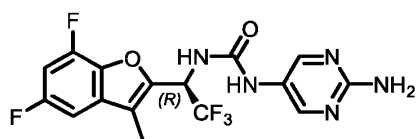
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In some embodiments, the carbonyl equivalent or isocyanate-forming reagent is a carbonyl equivalent. In some embodiments, the carbonyl equivalent is $R'OC(O)Cl$, wherein R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl, nitro, or C1-6 alkoxy. In some embodiments, the carbonyl equivalent is selected from the

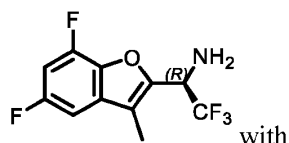
group consisting of: phenyl chloroformate, phosgene, trichloromethyl chloroformate (i.e., diphosgene), bis(trichloromethyl) carbonate (i.e., triphosgene), 4-nitrophenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester. In some embodiments, the carbonyl equivalent is phenyl chloroformate.

In some embodiments, the carbonyl equivalent or isocyanate-forming reagent is an or isocyanate-forming reagent. In some embodiments, the isocyanate-forming reagent is selected from the group consisting of: phosgene (toluene solution), trichloromethyl chloroformate (diphosgene), bis(trichloromethyl) carbonate (triphosgene), 4-nitrophenyl chloroformate, phenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester.

Some embodiments provide a process of preparing Compound 1:



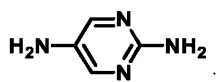
(1), or a salt and/or solvate thereof;



comprising contacting with

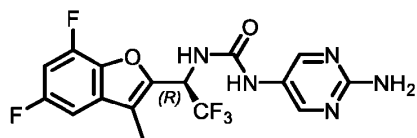
(i) a carbonyl equivalent; and

(ii) pyrimidine-2,5-diamine having the structure

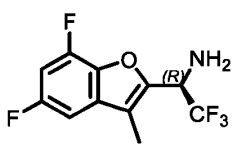


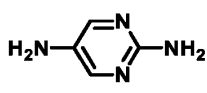
to form Compound 1.

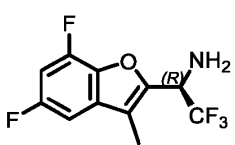
Some embodiments provide Compound 1:

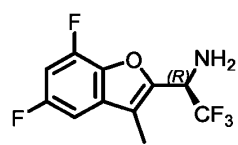


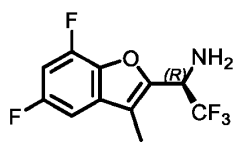
(1), or a salt and/or solvate thereof;

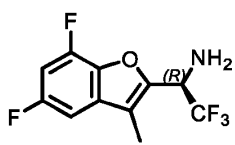
prepared by a process comprising contacting  with
 (i) a carbonyl equivalent; and

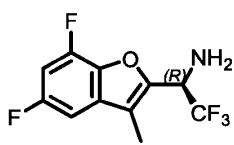
(ii) pyrimidine-2,5-diamine having the structure .

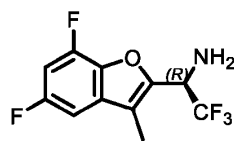
In some embodiments, contacting  with the carbonyl equivalent and
 5 pyrimidine-2,5-diamine to form Compound 1 comprises adding the carbonyl equivalent to

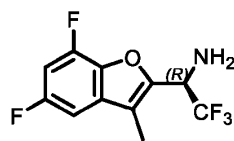
 and a base to form mixture 1, then adding pyrimidine-2,5-diamine to mixture
 1 to form mixture 2.

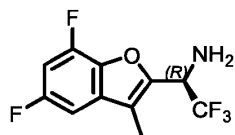
In some embodiments, the molar ratio of the carbonyl equivalent to  is about 1.0 to about 4.0 (e.g., about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4,
 10 about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3). In some

embodiments, the molar ratio of the carbonyl equivalent to  is about 1.05. In

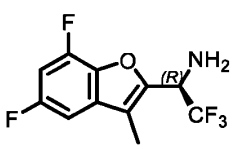
some embodiments, the molar ratio of the carbonyl equivalent to  is about
 1.3.

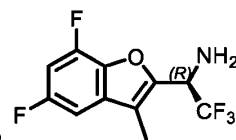


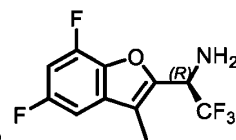
In some embodiments, the molar ratio of the base to  is about 1.0 to about 5.0 (e.g., about 2.0 to about 5.0, about 2.0 to about 4.0, about 2.5 to about 3.5, about 3.0, or about 3.5). In some embodiments, the molar ratio of the sodium bicarbonate to

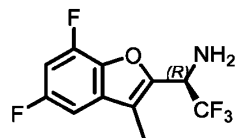


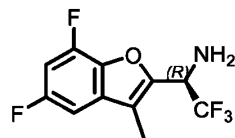
is about 3.0. In some embodiments, the molar ratio of the sodium

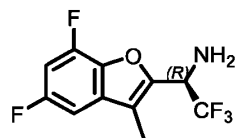
5 bicarbonate to  is about 3.5.

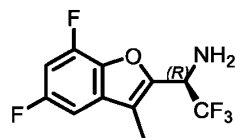


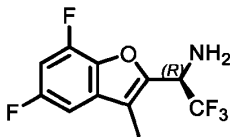
In some embodiments, adding the carbonyl equivalent to  and a base to form mixture 1 is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is 10 tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.

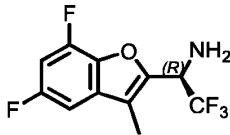


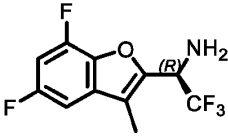
In some embodiments, adding the carbonyl equivalent to  and the base to form mixture 1 is performed under an inert atmosphere. In some embodiments, the adding is performed under nitrogen. In some embodiments, the adding is performed under argon.

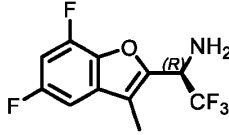


15 In some embodiments, adding the carbonyl equivalent to  and the base is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 2 °C, or

about 0 °C). In some embodiments, adding the carbonyl equivalent to  is performed at about 0 °C to about 5 °C. In some embodiments, adding the carbonyl equivalent to

 is performed at about 0 °C to about 2 °C. In some embodiments, adding the

carbonyl equivalent to  is performed at about 0 °C.

5 In some embodiments, after adding the carbonyl equivalent to  and the base, mixture 1 is agitated for about 1 hour to about 7 days (e.g., about 1 hour to about 2 days, about 5 hours to about 1 day, about 10 hours to about 18 hours, about 10 hours to about 14 hours, about 14 hours to about 18 hours, about 12 hours to about 16 hours, about 14 hours to about 16 hours, or about 16 hours).

10 In some embodiments, adding pyrimidine-2,5-diamine to mixture 1 to form mixture 2 comprises adding a second base to mixture 1 and pyrimidine-2,5-diamine to mixture 1. In some embodiments, adding pyrimidine-2,5-diamine to mixture 1 to form mixture 2 comprises adding a second base to mixture 1 then pyrimidine-2,5-diamine to mixture 1. In some embodiments, adding the compound of Formula (I-ii) to mixture 1 to form mixture 2 comprises adding the compound of

15 Formula (I-ii) to mixture 1 then the second base to mixture 1. In some embodiments, the second base is selected from N,N-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene (DBU), and 1,5-diazabicyclo(4.3.0)non-5-ene (DBN). In some embodiments, the second base is triethylamine. In some embodiments, the second base is N,N-diisopropylethylamine.

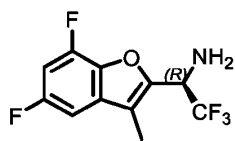
20 In some embodiments, adding a second base to mixture 1 and pyrimidine-2,5-diamine to mixture 1 is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 2 °C, or about 0 °C). In some embodiments, adding a second base to mixture 1 and

pyrimidine-2,5-diamine to mixture 1 is performed at about 0 °C to about 5 °C. In some embodiments, adding a second base to mixture 1 and pyrimidine-2,5-diamine to mixture 1 is performed at about 0 °C to about 2 °C. In some embodiments, adding a second base to mixture 1 and the compound of Formula (I-ii) to mixture 1 is performed at about 0 °C.

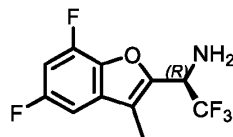
5 In some embodiments, after forming mixture 2, mixture 2 is warmed to about 20 °C to about 90 °C (e.g., about 20 °C to about 60 °C, about 20 °C to about 50 °C, about 20 °C to about 40 °C, about 25 °C to about 35 °C, or about 30 °C) over about 15 minutes to about 5 hours (e.g., about 1 hour to about 3 hours, or about 2 hours); then agitated at about 20 °C to about 90 °C (e.g., about 20 °C to about 60 °C, about 20 °C to about 50 °C, about 20 °C to about 40 °C, about 25 °C to about 35 °C, or about 30 °C) for about 1 hour to about 7 days (e.g., about 1 hour to about 2 days, about 5 hours to about 1 day, about 10 hours to about 18 hours, about 10 hours to about 14 hours, about 14 hours to about 18 hours, about 12 hours to about 16 hours, about 14 hours to about 16 hours, or about 16 hours) to form Compound 1.

15 In some embodiments, warming then agitating mixture 2 to form Compound 1 comprises adding an aqueous base and a workup solvent after the warming and agitating. In some embodiments, the aqueous base is aqueous sodium bicarbonate. In some embodiments, the aqueous base is 5% w/w aqueous sodium bicarbonate. In some embodiments, the workup solvent is isopropyl acetate or isopropyl alcohol. In some embodiments, the solvent is isopropyl acetate.

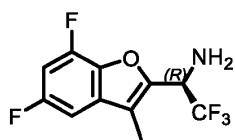
20 In some embodiments, the process comprises recrystallizing Compound 1 from a solvent. In some embodiments, the process comprises Compound 1 from a solvent after adding the aqueous base and the workup solvent. In some embodiments, the solvent is a mixture of isopropyl acetate and heptane. In some embodiments, the ratio of isopropyl acetate to heptane is about 6:1 to about 1:10 (e.g., about 6:1 to about 4:2, about 1:7 to about 3:7, about 4:6 to about 6:4, about 4:2 to about 3:1, about 2:7, about 1:1, or about 5:2). In some embodiments, after recrystallizing Compound 1, 25 Compound 1 is rinsed with a mixture of isopropyl acetate and heptane, then water, then a mixture of isopropyl acetate and heptane. In some embodiments, after rinsing Compound 1, Compound 1 is dried. In some embodiments, drying Compound 1 comprises drying Compound 1 at a pressure lesser than atmospheric pressure. In some embodiments, drying Compound 1 comprises drying Compound 1 at ambient temperature.



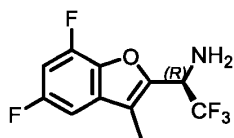
In some embodiments, contacting with the carbonyl equivalent and



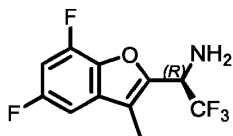
pyrimidine-2,5-diamine to form Compound 1 comprises adding to the carbonyl equivalent and a base to form mixture 1', then adding pyrimidine-2,5-diamine to mixture



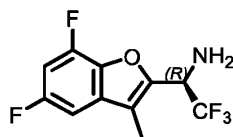
1' to form mixture 2'. In some embodiments, is in the form of a salt. In



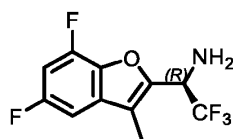
5 some embodiments, is in the form of a salt, and contacting



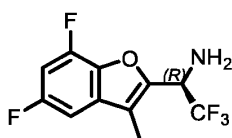
with the carbonyl equivalent and pyrimidine-2,5-diamine to form



Compound 1 comprises adding to the carbonyl equivalent and a base to form mixture 1', then adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2'.

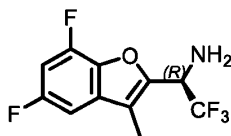


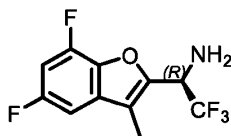
In some embodiments, salt is a hydrochloride salt.

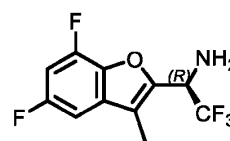


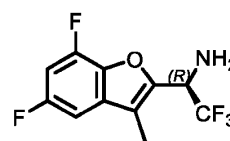
10 In some embodiments, adding to the carbonyl equivalent and a base to form mixture 1' is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran,

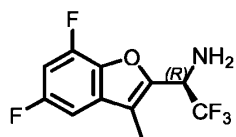
acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.

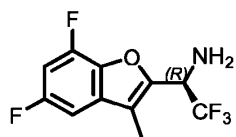


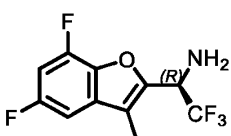
In some embodiments, adding  to the carbonyl equivalent and a base to form mixture 1' is performed under an inert atmosphere. In some embodiments, the contacting is performed under nitrogen. In some embodiments, the contacting is performed under argon.

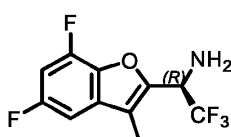


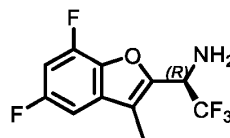
In some embodiments, the molar ratio of the carbonyl equivalent to  is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3, about 2.0). In some embodiments, the molar ratio of the carbonyl equivalent to

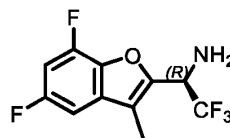


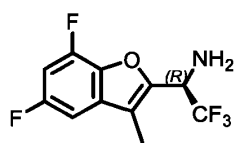
 is about 1.05. In some embodiments, the molar ratio of the carbonyl

equivalent to  is about 1.3. In some embodiments, the molar ratio of the

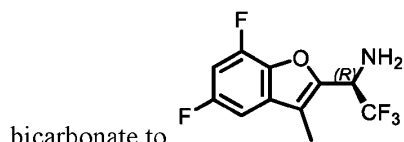
carbonyl equivalent to  is about 2.0.



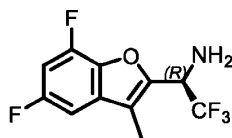
In some embodiments, the molar ratio of the base to  is about 1.0 to about 5.0 (e.g., about 2.0 to about 5.0, about 2.0 to about 4.0, about 2.5 to about 3.5, about 3.0, or about 3.5. In some embodiments, the molar ratio of the sodium bicarbonate to



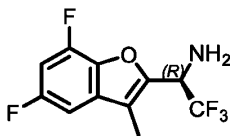
is about 3.0. In some embodiments, the molar ratio of the sodium



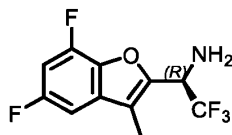
bicarbonate to is about 3.5.



In some embodiments, adding to the carbonyl equivalent and a base to form mixture 1' is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.

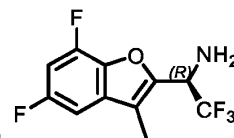


In some embodiments, adding to the carbonyl equivalent and a base to form mixture 1' is performed under an inert atmosphere. In some embodiments, the adding is performed under nitrogen. In some embodiments, the adding is performed under argon.



In some embodiments, adding to the carbonyl equivalent and a base is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or

about 0 °C). In some embodiments, adding the carbonyl equivalent to is performed at about 5 °C or lower.



In some embodiments, adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2' comprises adding a third base to mixture 1' and pyrimidine-2,5-diamine to mixture 1'. In some embodiments, adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2' comprises adding a third base to mixture 1' then pyrimidine-2,5-diamine to mixture 1'. In some embodiments, adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2' comprises adding aqueous sodium chloride to mixture 1', a third base to mixture 1', and pyrimidine-2,5-diamine to mixture 1'. In some embodiments, adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2' comprises adding aqueous sodium chloride to mixture 1', a third base to mixture 1', then pyrimidine-2,5-diamine to mixture 1'. In some embodiments, the third base is selected from N,N-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene (DBU), and 1,5-diazabicyclo(4.3.0)non-5-ene (DBN). In some embodiments, the third base is triethylamine. In some embodiments, the third base is N,N-diisopropylethylamine.

In some embodiments, the molar ratio of pyrimidine-2,5-diamine to Compound 1 is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.15, about 1.2, about 1.3, about 2.0, or about 3.0). In some embodiments, the molar ratio of pyrimidine-2,5-diamine to Compound 1 is about 1.15.

In some embodiments, the molar ratio of the third base to Compound 1 is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.15, about 1.2, about 1.3, about 2.0, or about 3.0). In some embodiments, the molar ratio of the third base to Compound 1 is about 2.0.

In some embodiments, adding aqueous sodium chloride to mixture 1', the third base to mixture 1', and pyrimidine-2,5-diamine is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C). In some embodiments, adding aqueous sodium chloride to mixture 1', the third base to mixture 1', and pyrimidine-2,5-diamine is performed at about 0 °C to about 5 °C.

In some embodiments, after forming mixture 2, mixture 2 is agitated at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C) for about 1 hour to about 7 days (e.g., about 1 hour to about 4 days, about 5 hours to about 4 day, about 12 hours to about 3 days, about 1 day to about 3 days, about 24 hours to about 36 hours, about 30 hours to about 40

hours, about 10 hours to about 18 hours, about 10 hours to about 14 hours, about 14 hours to about 18 hours, about 12 hours to about 16 hours, about 14 hours to about 16 hours, or about 16 hours) to form Compound 1.

In some embodiments, the process comprises adding water and an extraction solvent to mixture 2' after agitating mixture 2' to form mixture 3'. In some embodiments, the extraction solvent is ethyl acetate or isopropyl acetate. In some embodiments, the extraction solvent is isopropyl acetate. In some embodiments, the process comprises agitating and/or shaking mixture 3'. In some embodiments, the process comprises separating an organic liquid from mixture 3'. In some embodiments, the process comprises adding an aqueous base to the organic liquid to form mixture 4'. In some embodiments, the aqueous base is aqueous sodium bicarbonate. In some embodiments, the aqueous sodium bicarbonate is 5% w/w aqueous sodium bicarbonate. In some embodiments, the process comprises separating the organic liquid from mixture 4'. In some embodiments, the process comprises reducing the volume of the organic liquid at a pressure lesser than atmospheric pressure. In some embodiments, the process comprises adding an anti-solvent to the organic liquid to form a slurry. In some embodiments, the anti-solvent is hexanes or heptane. In some embodiments, the anti-solvent is heptane. In some embodiments, the process comprises filtering the slurry to provide a solid. In some embodiments, the process comprises dissolving the solid in isopropanol and adding water to the dissolved solid to form a slurry. In some embodiments, the slurry is cooled. In some embodiments, the slurry is filtered. In some embodiments, the slurry is dried at a pressure lesser than atmospheric pressure to provide Compound 1.

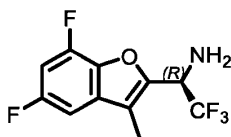
In some embodiments, Compound 1 is precipitated from tetrahydrofuran and heptane. In some embodiments, Compound 1 is precipitated from isopropanol and water. In some embodiments, Compound 1 is precipitated from tetrahydrofuran and heptane, then precipitated from isopropanol and water. In some embodiments, after precipitating Compound 1, Compound 1 is dried. In some embodiments, drying Compound 1 comprises drying Compound 1 at a pressure lesser than atmospheric pressure. In some embodiments, drying Compound 1 comprises drying Compound 1 at about 25 °C to about 70 °C (e.g., about 20 °C to about 25 °C, about 30 °C to about 60 °C, about 40 °C to about 50 °C, or about 45 °C). In some embodiments, drying Compound 1 comprises drying Compound 1 at about 45 °C. In some embodiments, drying Compound 1

comprises drying Compound 1 at a pressure lesser than atmospheric pressure at about 20 °C to about 25 °C.

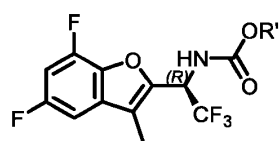
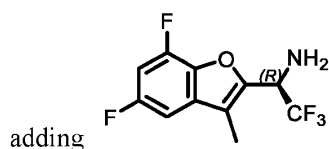
In some embodiments, the carbonyl equivalent is selected from the group consisting of: phenyl chloroformate, phosgene, trichloromethyl chloroformate (i.e., diphosgene), bis(trichloromethyl) carbonate (i.e., triphosgene), 4-nitrophenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester.

In some embodiments, the carbonyl equivalent is phenyl chloroformate.

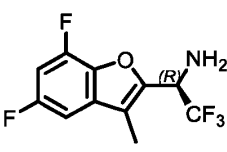
In some embodiments, the carbonyl equivalent is R'OC(O)Cl, wherein R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl, nitro, or C1-6 alkoxy. In some embodiments, R' is phenyl. In some embodiments, R' is para-nitrophenyl.

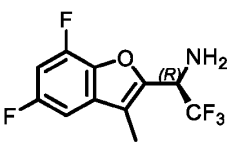


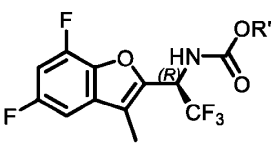
In some embodiments, contacting with R'OC(O)Cl and pyrimidine-2,5-diamine to form Compound 1 comprises:
combining R'OC(O)Cl with a base;

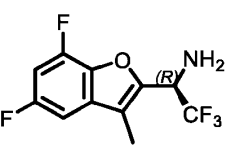


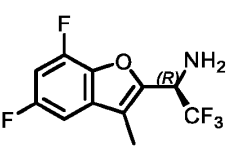
to the mixture of R'OC(O)Cl and the base to form

In some embodiments, contacting  with R'OC(O)Cl and pyrimidine-

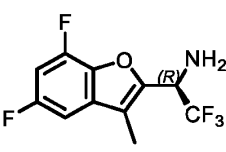
2,5-diamine to form Compound 1 comprises adding  to a mixture of

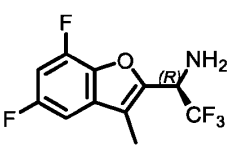
R'OC(O)Cl and a base to form .

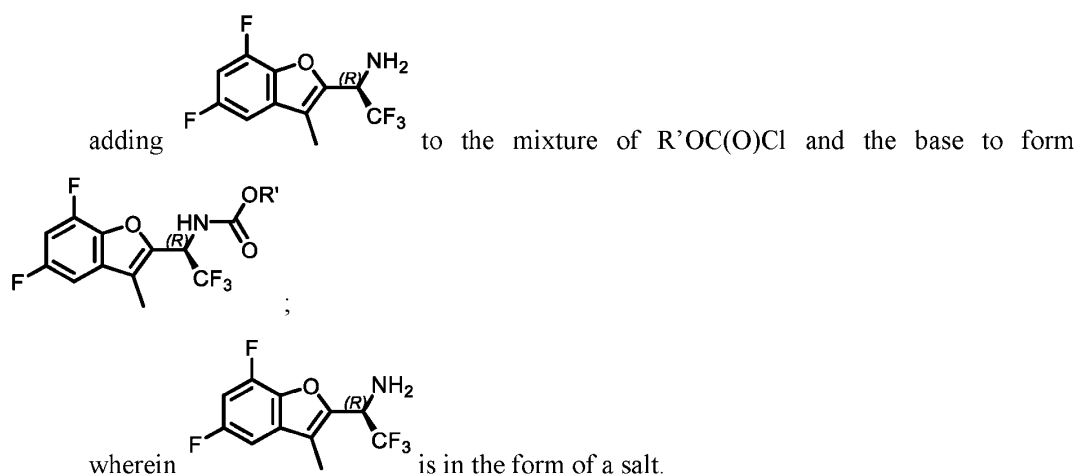
In some embodiments,  is added as a solution or slurry in a solvent.

5 In some embodiments,  is added as a solution in a solvent.

In some embodiments, the mixture of R'OC(O)Cl and the base is a solution or slurry in a solvent. In some embodiments, the mixture of R'OC(O)Cl and the base is a solution in a solvent.

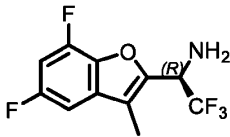
In some embodiments,  is in the form of a salt. In some embodiments, the salt is a hydrochloride salt.

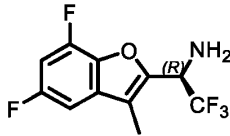
10 In some embodiments, contacting  with R'OC(O)Cl and pyrimidine-2,5-diamine to form Compound 1 comprises:
combining R'OC(O)Cl with a base;

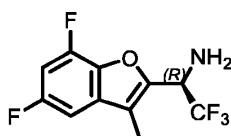


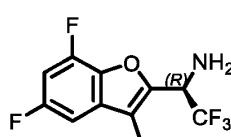
In some embodiments, combining R'OC(O)Cl with a base comprises combining the base with a solvent, then adding the R'OC(O)Cl. In some embodiments, combining the base with a solvent, then adding the R'OC(O)Cl comprises adding the R'OC(O)Cl to the base and solvent at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C), then adding the R'OC(O)Cl.

In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water. In some embodiments, when the base is combined with the solvent then R'OC(O)Cl added, (i) water is added to the base to form an aqueous base, (ii) tetrahydrofuran is added to the aqueous base, then (iii) R'OC(O)Cl is added to the tetrahydrofuran and aqueous base.

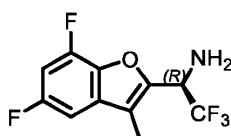
In some embodiments, adding  to the mixture of R'OC(O)Cl and the base is performed at about -10 °C to about 20 °C (e.g., about -5 °C to about 5 °C, about 0 °C to about 10 °C, about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C). In some embodiments, adding the compound of Formula (I-i) to the mixture of R'OC(O)Cl and the base is

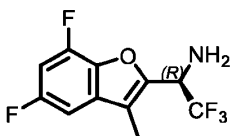
performed at about -5 °C to about 5 °C. In some embodiments, adding  to the mixture of R'OC(O)Cl and the base is performed at about 0 °C to about 5 °C. In some

embodiments, adding  to the mixture of R'OC(O)Cl and the base is performed

at lesser than 5 °C. In some embodiments,  is added to the mixture of

5 R'OC(O)Cl and the base as a solution in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination
10 of tetrahydrofuran and water.

In some embodiments,  is added to the mixture of R'OC(O)Cl and the base over a time period of about 15 minutes to about 48 hours (e.g., about 15 minutes to about 2 hours, about 18 hours to about 30 hours, about 18 hours to about 24 hours, about 15 minutes to about 24 hours, about 1 hour to about 7 hours, about 1 hour to about 5 hours, about 2 hours to about 4 hours, about 3 hours to about 7 hours, about 24 hours, about 21 hours, about 18 hours,
15 about 16 hours, about 12 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, or about 1 hour).

In some embodiments, adding  to the mixture of R'OC(O)Cl and the base forms mixture 3. In some embodiments, mixture 3 is agitated for about 15 minutes to about

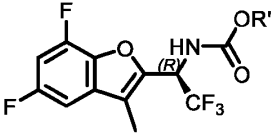
48 hours (e.g., about 15 minutes to about 2 hours, about 18 hours to about 30 hours, about 18 hours to about 24 hours, about 15 minutes to about 24 hours, about 1 hour to about 7 hours, about 1 hour to about 5 hours, about 2 hours to about 4 hours, about 3 hours to about 7 hours, about 24 hours, about 21 hours, about 18 hours, about 16 hours, about 12 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, or about 1 hour). In some embodiments, mixture 3 is agitated at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C).

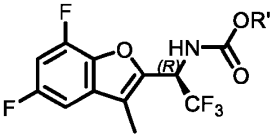
In some embodiments, agitating mixture 3 forms a biphasic mixture comprising an organic phase and an aqueous phase. In some embodiments, the organic phase is separated from the aqueous phase. In some embodiments, the organic phase was washed with an aqueous base. In some embodiments, the aqueous base is aqueous sodium bicarbonate. In some embodiments, the organic phase is concentrated at a pressure lesser than atmospheric pressure. In some embodiments, after concentrating the organic phase, an anti-solvent is added to the concentrated organic phase to form mixture 4. In some embodiments, the anti-solvent is hexane or heptane. In some embodiments, the anti-solvent is heptane.

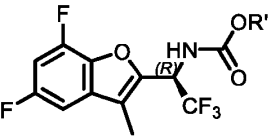
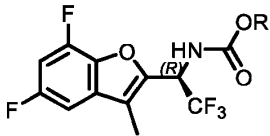
In some embodiments, after adding the anti-solvent, mixture 4 is agitated at about 20 °C to about 80 °C (e.g., about 30 °C to about 70 °C, about 30 °C to about 60 °C, about 40 °C to about 50 °C, about 20 °C to about 50 °C, about 40 °C to about 80 °C, about 20 °C to about 80 °C, about 20 °C to about 80 °C, about 40 °C, or about 50 °C). In some embodiments, after adding the anti-solvent, mixture 4 is agitated at about 40 °C to about 50 °C. In some embodiments, the agitating is performed for about 1 minute to about 24 hours (e.g., about 1 minute to about 60 minutes, about 10 minutes, to about 50 minutes, about 15 minutes to about 45 minutes, about 20 minutes to about 40 minutes, about 25 minutes to about 35 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 1 minute to about 2 hours, or about 15 minutes to about 4 hours). In some embodiments, the agitating is performed for about 30 minutes.

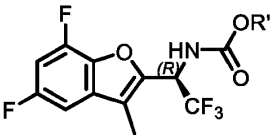
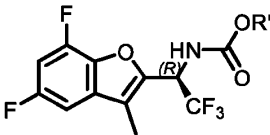
In some embodiments, after adding the anti-solvent, mixture 4 is stood and/or agitated for about 10 minutes to about 48 hours (e.g. about 6 hours to about 24 hours, about 12 hours to about 24 hours, about 16 hours to about 20 hours, about 18 hours to about 30 hours, about 24 hours to about 48 hours, or about 18 hours). In some embodiments, the standing and/or agitating is performed at about -20 °C to about 15 °C (e.g., about -15 °C to about 5 °C, about -10 °C to about 0 °C, about -10 °C, about -5 °C, or about 0 °C).

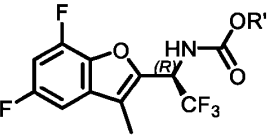
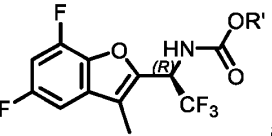
In some embodiments, after adding the anti-solvent, mixture 4 is concentrated at a pressure lesser than atmospheric pressure. In some embodiments, after concentrating mixture 4, a slurry is

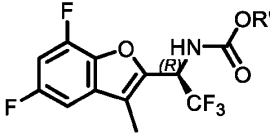
formed. In some embodiments, the slurry is filtered to provide . In some

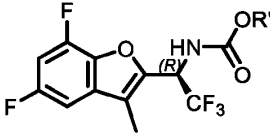
embodiments,  is rinsed with hexane or heptane (e.g., heptane). In some

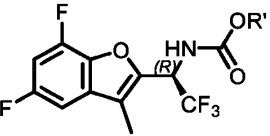
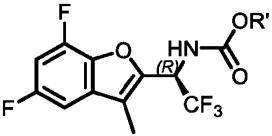
5  ,  is dried. In some

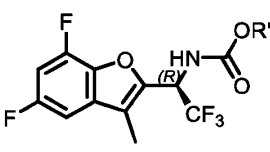
embodiments, drying  comprises drying  at a pressure lesser than atmospheric pressure. In some embodiments, drying

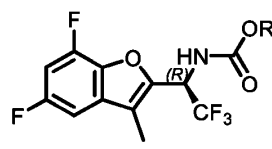
 comprises drying  at about 25 °C to about 70 °C (e.g., about 30 °C to about 60 °C, about 40 °C to about 50 °C, about 40 °C to about 45 °C, about 45

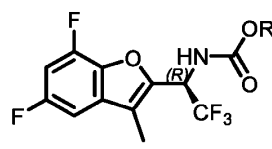
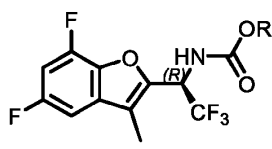
10 °C to about 50 °C, or about 45 °C). In some embodiments, drying 

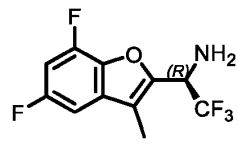
comprises drying  at about 45 °C. In some embodiments, drying

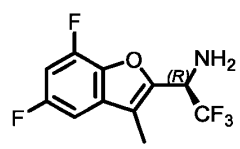
 comprises drying  at about 40 °C to about 45

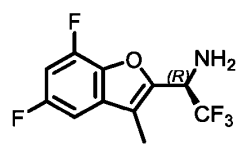
°C. In some embodiments, drying  comprises drying

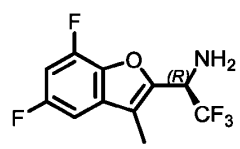
 at about 45 °C to about 50 °C. In some embodiments, drying

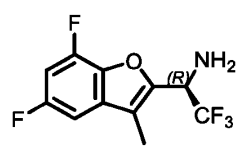
 comprises drying  under an inert atmosphere (e.g., under nitrogen).

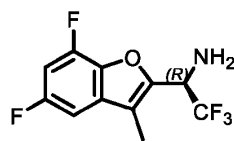
5 In some embodiments, the molar ratio of the R'OC(O)Cl to  is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3, about 2.0, or about 3.0). In some embodiments, the molar ratio of the R'OC(O)Cl to

 is about 1.05. In some embodiments, the molar ratio of the R'OC(O)Cl to

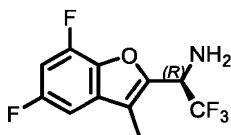
10  is about 1.3. In some embodiments, the molar ratio of the R'OC(O)Cl to

 is about 2.0. In some embodiments, the molar ratio of the R'OC(O)Cl to

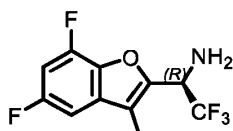
 is about 3.0.



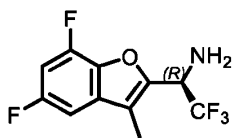
In some embodiments, the molar ratio of the base to is about 1.0 to about 5.0 (e.g., about 1.0 to about 3.0, about 2.0 to about 5.0, about 2.0 to about 4.0, about 2.5 to about 3.5, about 2.0, about 2.2, about 3.0, or about 3.5. In some embodiments, the molar ratio of



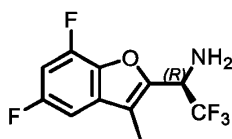
the sodium bicarbonate to is about 2.0. In some embodiments, the molar



ratio of the sodium bicarbonate to is about 2.2. In some embodiments, the

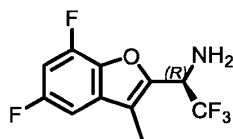


molar ratio of the sodium bicarbonate to is about 3.0. In some embodiments,

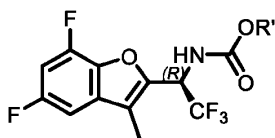


the molar ratio of the sodium bicarbonate to is about 3.5.

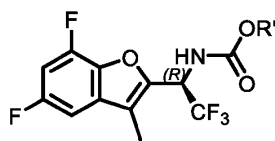
In some embodiments, the base is selected from sodium bicarbonate, potassium carbonate, potassium phosphate, sodium carbonate, potassium bicarbonate, N,N-diisopropylethylamine, triethylamine, trimethylamine, and citric acid. In some embodiments, the base is sodium bicarbonate.



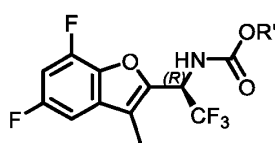
In some embodiments, contacting with $R'OC(O)Cl$ and pyrimidine-2,5-diamine to form Compound 1 comprises:



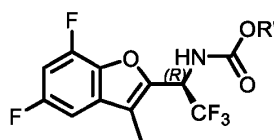
contacting with pyrimidine-2,5-diamine to form Compound 1.



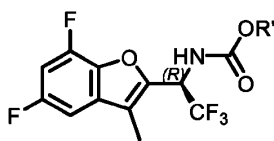
In some embodiments, contacting with pyrimidine-2,5-diamine to form Compound 1 is performed in the presence of a third base. In some embodiments, the third base is selected from N,N-diisopropylethylamine (DIPEA), triethylamine (TEA), 1,8-diazabicycloundec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), sodium bicarbonate, potassium carbonate, and potassium phosphate. In some embodiments, the third base is triethylamine. In some embodiments, the third base is N,N-diisopropylethylamine.



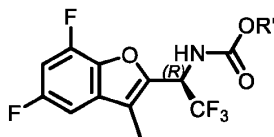
In some embodiments, contacting with pyrimidine-2,5-diamine



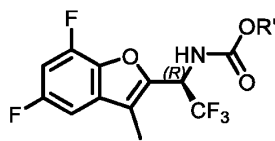
to form Compound 1 comprises adding to pyrimidine-2,5-diamine. In



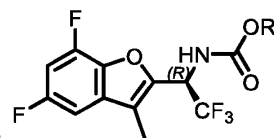
some embodiments, contacting with pyrimidine-2,5-diamine to form



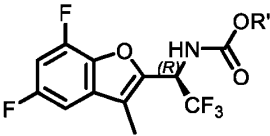
Compound 1 comprises adding to pyrimidine-2,5-diamine in the absence of a base.

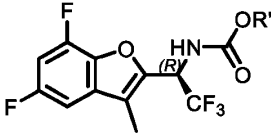


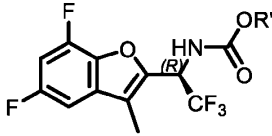
In some embodiments, contacting with pyrimidine-2,5-diamine

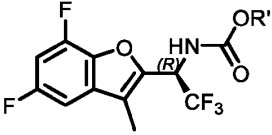


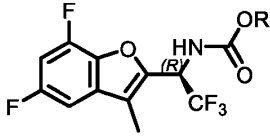
to form Compound 1 comprises adding pyrimidine-2,5-diamine to . In

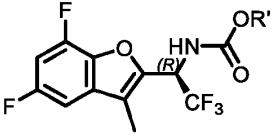
some embodiments, contacting  with pyrimidine-2,5-diamine to form

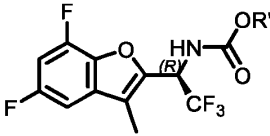
Compound 1 comprises adding pyrimidine-2,5-diamine to ; then adding

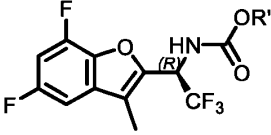
a solvent to the mixture of pyrimidine-2,5-diamine and . In some embodiments, the solvent is N,N-dimethylacetamide.

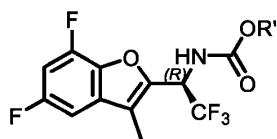
5 In some embodiments, contacting  with pyrimidine-2,5-diamine

to form Compound 1 comprises adding pyrimidine-2,5-diamine to  in the absence of a base.

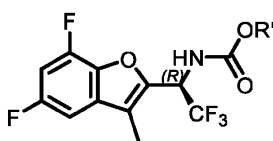
In some embodiments, contacting  with pyrimidine-2,5-diamine to form Compound 1 is performed in N,N-dimethylacetamide. In some embodiments, contacting

10  with pyrimidine-2,5-diamine to form Compound 1 is performed under an

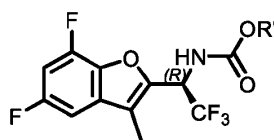
inert atmosphere. In some embodiments, contacting  with pyrimidine-2,5-diamine to form Compound 1 is performed under nitrogen. In some embodiments, contacting



with pyrimidine-2,5-diamine to form Compound 1 is performed under argon. In some embodiments, the N-N-dimethylacetamide comprises less than 2% water by volume (e.g., less than 1.5% water by volume, less than 1% water by volume, less than 0.5% water by volume, less than 0.3% water by volume, less than 0.2% water by volume, less than 0.1% water by volume, less than 0.05% water by volume, or less than 0.02% water by volume). In some
 5 embodiments, the N-N-dimethylacetamide comprises less than 0.3% water by volume.



In some embodiments, after adding to pyrimidine-2,5-diamine or



after adding pyrimidine-2,5-diamine to , mixture 5 is formed. In some
 10 embodiments, mixture 5 is agitated. In some embodiments, mixture 5 is agitated for about 1
 minute to about 48 hours (e.g., 1 minute to about 24 hours, 1 minute to about 12 hours, 1 minute
 to about 6 hours, 1 minute to about 3 hours, about 30 minutes to about 1.5 hours, about 8 hours to
 about 24 hours, about 12 hours to about 13 hours, about 3 hours, or about 1 hour). In some
 15 embodiments, mixture 5 is agitated for about 12 hours to about 13 hours. In some embodiments,
 mixture 5 is agitated for about 3 hours. In some embodiments, mixture 5 is agitated for about 1
 hour. In some embodiments, mixture 5 is agitated at about 10 °C to about 90 °C (e.g., about 10 °C
 to about 90 °C, about 20 °C to about 80 °C, about 30 °C to about 70 °C, about 30 °C to about 60
 °C, about 35 °C to about 60 °C, about 40 °C to about 55 °C, about 45 °C to about 50 °C, about 45
 °C, about 50 °C, or about 55°C).

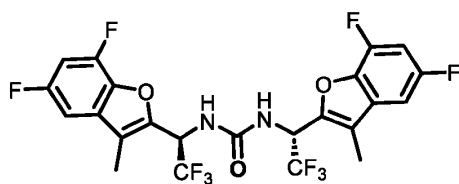
In some embodiments, after agitating mixture 5, the process comprises adding water to
 20 mixture 5 to form mixture 5'. In some embodiments, the process comprises agitating mixture 5'.
 In some embodiments, the process comprises agitating mixture 5' for about 1 minute to about 48
 hours (e.g., 1 minute to about 24 hours, 1 minute to about 12 hours, 1 minute to about 6 hours, 1
 minute to about 3 hours, about 30 minutes to about 1.5 hours, about 1 hour to about 5 hours, about
 2 hours to about 4 hours, about 8 hours to about 24 hours, about 12 hours to about 13 hours, about

3 hours, or about 1 hour). In some embodiments, the process comprises agitating mixture 5' for about 12 hours to about 13 hours. In some embodiments, the process comprises agitating mixture 5' for about 3 hours. In some embodiments, the process comprises agitating mixture 5' for about 1 hour.

5 In some embodiments, after agitating mixture 5', a slurry is formed. In some embodiments, the slurry is filtered to provide Compound 1. In some embodiments, Compound 1 is washed with water. In some embodiments, Compound 1 is dried at a pressure lesser than atmospheric pressure.

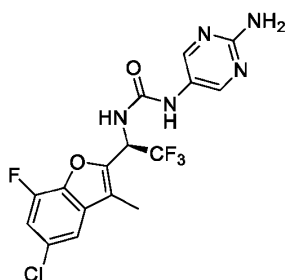
In some embodiments, Compound 1 is recrystallized from a solvent. In some embodiments, the solvent is a mixture of isopropyl alcohol and water. In some embodiments, the solvent is a mixture of isopropyl acetate and heptane. In some embodiments, the ratio of isopropyl alcohol to water is about 1:3 to about 1:1 (e.g., about 1:2). In some embodiments, the ratio of isopropyl acetate to heptane is about 6:1 to about 4:2 (e.g., about 5:2). In some embodiments, after recrystallizing Compound 1, Compound 1 is rinsed with a mixture of isopropyl acetate and heptane, then water, then a mixture of isopropyl acetate and heptane. In some embodiments, after rinsing Compound 1, Compound 1 is dried. In some embodiments, drying Compound 1 comprises drying Compound 1 at a pressure lesser than atmospheric pressure. In some embodiments, drying Compound 1 comprises drying Compound 1 at ambient temperature.

In some embodiments, Compound 1 has a purity of at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 98%, at least 99%, about 98%, about 98.5%, about 99%, about 99.5%). In some embodiments, less than 10% (e.g., less than 7%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, less than 0.1%, less than 0.6%, about 1%, about 1.3%, about 0.05%, or no detectable amount) of Impurity 1 is present as an impurity with Compound 1.



(Impurity 1).

25 In some embodiments, less than 10% (e.g., less than 7%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, less than 0.1%, less than 0.6%, about 1%, about 1.3%, about 0.05%, or no detectable amount) of Impurity 2 is present as an impurity with Compound 1.



(Impurity 2).

In some embodiments, the process comprises preparing a crystalline hemihydrate Form 1 by a method comprising:

- (a) dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof in isopropanol to form a solution;
- (b) adding water to the solution to form a mixture;
- (c) reducing the temperature of the mixture then maintaining the temperature for a first period of time;
- (d) increasing the temperature of the mixture then maintaining the temperature for a second period of time;
- (e) reducing the temperature of the mixture then maintaining the temperature for a third period of time; and
- (f) isolating Form 1 from the mixture.

In some embodiments, Form 1 has one or more characteristics described below.

In some embodiments, the XRPD pattern of Form 1 has a peak at 6.4 ± 0.2 degrees 2θ . In some embodiments, the peak at 6.4 ± 0.2 degrees 2θ has the highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 15.8 ± 0.2 degrees 2θ . In some embodiments, the peak at 15.8 ± 0.2 degrees 2θ has the second relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 18.3 ± 0.2 degrees 2θ . In some embodiments, the peak at 18.3 ± 0.2 degrees 2θ has the third highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 22.3 ± 0.2 degrees 2θ . In some embodiments, the peak at 22.3 ± 0.2 degrees 2θ has the fourth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 20.8 ± 0.2 degrees 2θ . In some embodiments, the peak at 20.8 ± 0.2 degrees 2θ has the fifth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 19.3 ± 0.2 degrees 2θ . In some embodiments, the peak at 19.3 ± 0.2 degrees 2θ has the sixth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 24.0 ± 0.2 degrees 2θ . In some embodiments, the peak at 24.0 ± 0.2 degrees 2θ has the seventh highest relative intensity.

5 In some embodiments, the XRPD pattern of Form 1 has a peak at 26.9 ± 0.2 degrees 2θ . In some embodiments, the peak at 26.9 ± 0.2 degrees 2θ has the eighth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 14.6 ± 0.2 degrees 2θ . In some embodiments, the peak at 14.6 ± 0.2 degrees 2θ has the ninth highest relative intensity.

10 In some embodiments, the XRPD pattern of Form 1 has a peak at 31.3 ± 0.2 degrees 2θ . In some embodiments, the peak at 31.3 ± 0.2 degrees 2θ has the tenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 28.3 ± 0.2 degrees 2θ . In some embodiments, the peak at 28.3 ± 0.2 degrees 2θ has the eleventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 29.2 ± 0.2 degrees 2θ . In some embodiments, the peak at 29.2 ± 0.2 degrees 2θ has the twelfth highest relative intensity.

15 In some embodiments, the XRPD pattern of Form 1 has a peak at 22.8 ± 0.2 degrees 2θ . In some embodiments, the peak at 22.8 ± 0.2 degrees 2θ has the thirteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 28.0 ± 0.2 degrees 2θ . In some embodiments, the peak at 28.0 ± 0.2 degrees 2θ has the fourteenth highest relative intensity.

20 In some embodiments, the XRPD pattern of Form 1 has a peak at 25.3 ± 0.2 degrees 2θ . In some embodiments, the peak at 25.3 ± 0.2 degrees 2θ has the fifteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 21.5 ± 0.2 degrees 2θ . In some embodiments, the peak at 21.5 ± 0.2 degrees 2θ has the sixteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 19.9 ± 0.2 degrees 2θ . In some embodiments, the peak at 19.9 ± 0.2 degrees 2θ has the seventeenth highest relative intensity.

25 In some embodiments, the XRPD pattern of Form 1 has a peak at 27.6 ± 0.2 degrees 2θ . In some embodiments, the peak at 27.6 ± 0.2 degrees 2θ has the eighteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 20.5 ± 0.2 degrees 2θ . In some embodiments, the peak at 20.5 ± 0.2 degrees 2θ has the nineteenth highest relative intensity.

30 In some embodiments, the XRPD pattern of Form 1 has a peak at 21.8 ± 0.2 degrees 2θ . In some embodiments, the peak at 21.8 ± 0.2 degrees 2θ has the twentieth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 25.1 ± 0.2 degrees 2θ . In some embodiments, the peak at 25.1 ± 0.2 degrees 2θ has the twenty-first highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at 25.8 ± 0.2 degrees 2θ . In some embodiments, the peak at 25.8 ± 0.2 degrees 2θ has the twenty-second highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has peaks (± 0.2 degrees 2θ) at 6.4, 15.8, and 18.3.

In some embodiments, the XRPD pattern of Form 1 has peaks (± 0.2 degrees 2θ) at 6.4, 15.8, 18.3, 22.3, 20.8, 19.3, 24.0, 26.9, 14.6, and 31.3.

In some embodiments, the XRPD pattern of Form 1 has peaks (± 0.2 degrees 2θ) at 6.4, 15.8, 18.3, 22.3, 20.8, 19.3, 24.0, 26.9, 14.6, 31.3, 28.3, 29.2, 22.8, 28.0, 25.3, 21.5, 19.9, 27.6, 20.5, 21.8, 25.1, and 25.8.

In some embodiments, Form 1 is characterized by an XRPD pattern substantially the same as that shown in FIG. 1.

Form 1 can also have one or more of the following characteristics.

In some embodiments, Form 1 has a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 0.5% to about 5% (e.g., about 1% to about 3%, about 2% to about 3%, or about 2.3%) at about 70 °C to about 140 °C (e.g., about 90 °C to about 130 °C, about 90 °C to about 120 °C, about 90 °C to about 115 °C, about 100 °C to about 140 °C, about 110 °C to about 140 °C, about 100 °C to about 120 °C, about 105 °C to about 120 °C, about 109 °C to about 115 °C, about 75 °C to about 125 °C, about 85 °C to about 113 °C, about 85 °C to about 105 °C, or about 112 °C). In some embodiments, the Form 1 has a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 2.3% at about 112.5 °C. In some embodiments, Form 1 has a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 2.3% at about 85 °C to about 113 °C.

In some embodiments, Form 1 has a TGA curve characterized by a weight loss of about 5% to about 30% (e.g., about 5% to about 27%, about 5% to about 25%, about 5% to about 22%, about 10% to about 25%, about 20% to about 22%, about 14% to about 20%, or about 17.6%) at about 150 °C to about 250 °C (e.g., about 230 to about 260 °C about 230 °C to about 250 °C, about 162 °C to about 248 °C, about 230 °C to about 240 °C, about 240 °C to about 260 °C, about 240 °C to about 250 °C, about 242 °C to about 248 °C, or about 245 °C). In some embodiments,

Form 1 has a TGA curve characterized by a weight loss of about 17.6% at about 245 °C. In some embodiments, the Form 1 has a TGA curve characterized by a weight loss of about 17.6% at about 162 °C to about 248 °C.

In some embodiments, the Form 1 has a TGA curve that is substantially the same as that shown in FIG. 2. In some embodiments, the crystalline form is Form 1 having a Thermal Gravimetric/Differential Scanning Calorimetry (TG/DSC) thermogram that is substantially the same as that shown in FIG. 2.

In some embodiments, the Form 1 has a differential scanning calorimetry (DSC) first heat cycle thermogram having an endothermic event having an onset temperature of about 105 °C and a peak of about 129 °C, an endothermic event having an onset temperature of about 158 °C and a peak of about 162 °C and an endothermic event having an onset temperature of about 174 °C and a peak of about 177 °C.

In some embodiments, the Form 1 has a Differential Scanning Calorimetry (DSC) thermogram that is substantially the same as that shown in FIG. 3.

In some embodiments, the Form 1 has a DSC first cooling cycle thermogram characterized by a single exothermic event at with an onset temperature of 151 °C and a peak temperature of 147 °C.

In some embodiments, the Form 1 has a DSC first cooling cycle thermogram substantially the same as that shown in FIG. 4.

In some embodiments, the Form 1 is a hemihydrate.

In some embodiments, the enantiomeric excess (ee) of crystalline Form 1 is at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 97%, at least 98%, at least 99%, or about 100%).

In some embodiments, the Form 1 is substantially pure.

In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof comprises the free base of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof is the free base of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-

trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof comprises amorphous (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof is amorphous (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof comprises the free base amorphous form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof is the free base amorphous form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof comprises Form 1*. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof is Form 1*.

In some embodiments, the dissolving in step (a) is performed at about 40 °C to 60 °C (e.g., about 45 °C to about 55 °C, or about 50 °C). In some embodiments, the dissolving in step (a) is performed at about 50 °C.

In some embodiments, the solution formed in step (a) has a concentration of about 0.08 g/mL to about 1.65 g/mL (e.g., about 0.09 g/mL to about 1.55 g/mL, about 0.1 g/mL to about 0.145 g/mL, about 0.1 g/mL to about 0.135 g/mL, about 0.12 g/mL to about 0.13 g/mL, or about 0.125 g/mL). In some embodiments, the solution formed in step (a) has a concentration of about 0.125 g/mL.

In some embodiments, step (a) comprises cooling the solution to about 30 °C to 50 °C (e.g., about 35 °C to about 45 °C, or about 40 °C). In some embodiments, step (a) comprises cooling the solution to about 40 °C. In some embodiments, the cooling is performed at about 0.1 °C per minute to about 5 °C per minute (e.g., about 0.5 °C per minute to about 2 °C per minute, or about 1 °C per minute). In some embodiments, the cooling is performed at about 1 °C per minute.

In some embodiments, the volume/volume ratio of water added to the solution in step (b) to the isopropanol used in the dissolving in step (a) is about 2:1 to about 6:1 (e.g., about 3:1 to about 5:1, or about 4:1). In some embodiments, the volume/volume ratio of water added to the solution in step (b) to the isopropanol used in the dissolving in step (a) is about 4:1.

5 In some embodiments, about $1/8^{\text{th}}$ to about $1/32^{\text{nd}}$ of the water is added to the solution per hour. $1/16^{\text{th}}$ of the water is added to the solution per hour. In some embodiments, about $1/16^{\text{th}}$ of the water is added to the solution per hour.

In some embodiments, the temperature of the mixture in step (c) is reduced to about 1 °C to about 15 °C (e.g., about 1 °C to about 10 °C, about 2 °C to about 8 °C, about 3 °C to about 7 °C, or about 5 °C). In some embodiments, the temperature of the mixture in step (c) is reduced to about 5 °C. In some embodiments, the first period of time is about 1 minute to about 24 hours (e.g., about 1 minute to about 18 hours, about 1 minute to about 12 hours, about 1 minute to about 6 hours, about 1 minute to about 3 hours, about 1 minute to about 2 hours, about 1 minute to about 30 minutes, about 1 minute to about 5 minutes, about 30 minutes to about 1.5 hours, about 45 minutes to about 1.25 hours, about 1 minute, or about 1 hour). In some embodiments, the first period of time is about 1 hour. In some embodiments, the first period of time is about 1 minute.

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In some embodiments, the temperature of the mixture in step (d) is increased to about 25 °C to about 60 °C (e.g., about 25 °C to about 50 °C, about 30 °C to about 60 °C, about 30 °C to about 50 °C, about 35 °C to about 45 °C, or about 5 °C). In some embodiments, the temperature of the mixture in step (c) is increased to about 40 °C. In some embodiments, the second period of time is about 1 minute to about 24 hours (e.g., about 1 minute to about 18 hours, about 1 minute to about 12 hours, about 1 minute to about 6 hours, about 1 minute to about 3 hours, about 1 minute to about 2 hours, about 1 minute to about 30 minutes, about 1 minute to about 5 minutes, about 30 minutes to about 1.5 hours, about 45 minutes to about 1.25 hours, about 1 minute, or about 1 hour). In some embodiments, the second period of time is about 1 hour. In some embodiments, the second period of time is about 1 minute.

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In some embodiments, the temperature of the mixture in step (e) is reduced to about 1 °C to about 15 °C (e.g., about 1 °C to about 10 °C, about 2 °C to about 8 °C, about 3 °C to about 7 °C, or about 5 °C). In some embodiments, the temperature of the mixture in step (e) is reduced to about 5 °C. In some embodiments, the third period of time is about 1 minute to about 24 hours (e.g., about 1 minute to about 18 hours, about 1 minute to about 12 hours, about 1 minute to about

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6 hours, about 1 minute to about 3 hours, about 1 minute to about 2 hours, about 1 minute to about 30 minutes, about 1 minute to about 5 minutes, about 30 minutes to about 1.5 hours, about 45 minutes to about 1.25 hours, about 6 hours to about 18 hours, about 6 hours to about 24 hours, about 9 hours to about 15 hours, about 9 hours to about 14 hours, about 10 hours to about 12 hours, about 10.5 hours to about 11.5 hours, about 11 hours, about 12 hours, about 1 hour, or about 1 minute). In some embodiments, the third period of time is about 11 hours. In some embodiments, the third period of time is about 11 hours.

In some embodiments, step (f) comprises filtering the mixture to provide Form 1. In some embodiments, step (f) comprises filtering the mixture to provide a solid; and rinsing the solid to provide Form 1. In some embodiments, rinsing the solid to provide Form 1 comprises drying the solid after the rinsing to provide Form 1. In some embodiments, the rinsing the solid comprises rinsing the solid with a solvent. In some embodiments, the solvent comprises an alcohol. In some embodiments, the alcohol is methanol, ethanol, and/or isopropanol. In some embodiments, the solvent comprises water. In some embodiments, the solvent comprises an alcohol and water. In some embodiments, the solvent comprises methanol and water. In some embodiments, the solvent is methanol and water.

In some embodiments, step (f) comprises:

filtering the mixture to provide a solid;

rinsing the solid with methanol and water; and

drying the solid to provide Form 1.

In some embodiments, the drying is performed for about 1 minute to about 16 hours (e.g., about 1 minute to about 14 hours, about 1 minute to about 12 hours, about 1 minute to about 8 hours, about 1 minute to about 4 hours, about 1 minute to about 2 hours, about 1 minute to about 1 hour, or about 1 minute to about 30 minutes). In some embodiments, drying the solid comprises drying the solid at a pressure lesser than atmospheric pressure. In some embodiments, the drying is performed at a temperature of about 25 °C to about 100 °C (e.g., about 25 °C to about 80 °C, about 35 °C to about 80 °C, about 45 °C to about 70 °C, about 45 °C to about 60 °C).

In some embodiments, the process comprises preparing a crystalline hemihydrate Form 1 by a method comprising:

dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof in methanol to form a solution;

adding water to the solution to form a first mixture;

adding (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 to the first mixture to form a second mixture; and

isolating a solid from the third mixture to provide Form 1.

5 In some embodiments, the process comprises preparing a crystalline hemihydrate Form 1 by a method comprising:

(a) dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof in methanol to form a solution;

(b) adding water to the solution to form a first mixture;

10 (c) adding (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 to the first mixture to form a second mixture;

(d) agitating the second mixture;

(e) adding water to the second mixture to form a third mixture;

(f) agitating the third mixture; and

15 (g) isolating Form 1 from the third mixture.

In some embodiments, the solution formed in step (a) has a concentration of about 0.03 g/mL to about 1 g/mL (e.g., about 0.03 g/mL to about 0.5 g/mL, about 0.05 g/mL to about 0.3 g/mL, about 0.1 g/mL to about 0.2 g/mL, about 0.13 g/mL to about 0.18 g/mL, or about 0.16 g/mL). In some embodiments, the solution formed in step (a) has a concentration of about 0.16 g/mL.

20 In some embodiments, dissolving the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a salt and/or solvate thereof in methanol to form a solution comprises dissolving the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea in a first portion of methanol to form an unfiltered solution, filtering the unfiltered solution through a filter to provide a filtrate, then rinsing the filter with a second portion of methanol to provide a rinse that is combined with the filtrate to provide the solution. In some embodiments, the filtering is a polish filtering. In some embodiments, the filter has a pore size of about 0.2 microns. In some embodiments, the weight of the first portion of methanol is about 4 to about 8 times (e.g., about 5 to about 8 times, about 6 to about 7 times, or about 6.3 times (e.g., about 6.3 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that

is dissolved. In some embodiments, the weight of the first portion of methanol is about 4 to about 8 times (e.g., about 0.5 to about 3 times, about 1 to about 3 times, or about 1.6 times (e.g., about 1.6 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved.

5 In some embodiments, the solution is cooled to about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C, about 20 °C to about 25 °C, about 17 °C to about 23 °C, about 15 °C, about 20 °C, or about 25 °C (e.g., about 15 °C to about 25 °C)) before adding the water in step (b). In some embodiments, the water added in step (b) is purified water. In some embodiments, adding the water in step (b) comprises filtering the water
10 through a filter, then adding the water to form the first mixture. In some embodiments, the water added in step (b) is about 0.1 to about 2 times (e.g., about 0.1 to about 1.5 times, about 0.1 to about 1 times, about 0.3 to about 0.7 times, or about 0.5 times (e.g., about 0.5 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved in step (a).

15 In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 added in step (c) is about 0.1% to about 20% by weight (e.g., about 0.1% to about 15% by weight, about 0.1% to about 10% by weight, about 0.1% to about 5% by weight, about 0.1% to about 3% by weight, about 0.5% to about 3% by weight, about 0.7% to about 2.5% by weight, about 0.7% to about 1.3% by weight, or about
20 1% by weight (e.g., about 1% by weight)) of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved in step (a).

In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 added in step (c) is prepared by Method 1 described herein. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-
25 3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 added in step (c) is prepared by Method 2 described herein.

In some embodiments, the agitating in step (d) is performed at about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C, about 20 °C to about 25 °C, about 17 °C to about 23 °C, about 15 °C, about 20 °C, or about 25 °C (e.g., about
30 15 °C to about 25 °C)). In some embodiments, the agitating in step (d) is performed for about 1 minute to about 24 hours (e.g., about 1 minute to about 18 hours, about 1 minute to about 12 hours,

about 1 minute to about 8 hours, about 1 minute to about 6 hours, about 30 minutes to about 6 hours, about 1 hour to about 5 hours, about 2 hours to about 4 hours, about 2.5 hours to about 3.5 hours, or about 3 hours (e.g., about 3 hours)).

5 In some embodiments, the water added in step (e) is purified water. In some embodiments, adding the water in step (e) comprises filtering the water through a filter, then adding the water to form the third mixture. In some embodiments, the water added in step (e) is about 0.1 to about 20 times (e.g., about 0.1 to about 15 times, about 0.1 to about 10 times, about 1 to about 9 times, about 3 to about 7 times, about 4 to about 5 times, or about 4.5 times (e.g., about 4.5 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved in step (a). In some embodiments, the water added in step (e) 10 is added over a period of about 1 second to about 48 hours (e.g., about 1 minute to about 24 hours, about 1 minute to about 18 hours, about 1 hour to about 12 hours, about 4 hours to about 12 hours, about 6 hours to about 10 hours, about 7 hours to about 9 hours, or about 8 hours (e.g., about 8 hours)).

15 In some embodiments, the agitating in step (f) is performed at about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C, about 20 °C to about 25 °C, about 17 °C to about 23 °C, about 15 °C, about 20 °C, or about 25 °C (e.g., about 15 °C to about 25 °C)). In some embodiments, the agitating in step (f) is performed for about 1 minute to about 48 hours (e.g., about 1 minute to about 36 hours, about 1 minute to about 24 hours, 20 about 4 hours to about 24 hours, about 8 hours to about 20 hours, about 12 hours to about 20 hours, about 14 hours to about 18 hours, about 15 hours to about 17 hours, or about 16 hours (e.g., about 16 hours)).

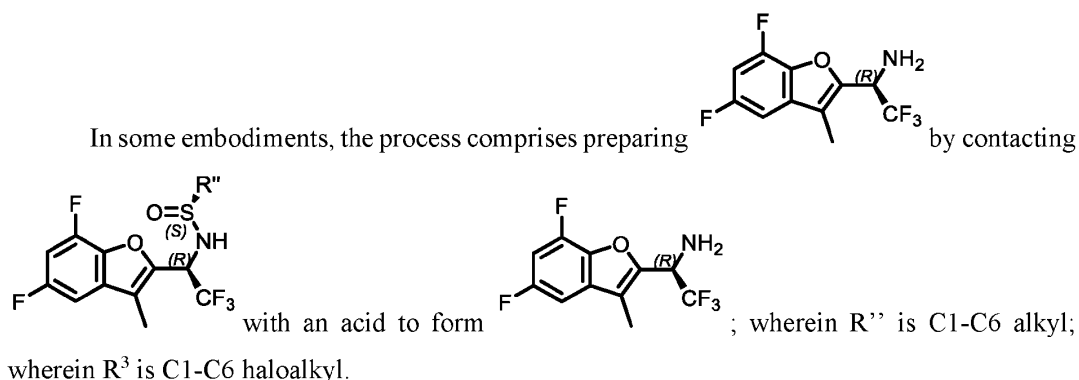
In some embodiments, step (f) comprises filtering the mixture to provide Form 1. In some embodiments, step (f) comprises filtering the mixture to provide a solid; and rinsing the solid to provide Form 1. In some embodiments, rinsing the solid to provide Form 1 comprises drying the solid after the rinsing to provide Form 1. In some embodiments, the rinsing the solid comprises rinsing the solid with a solvent. In some embodiments, the solvent comprises an alcohol. In some 25 embodiments, the alcohol is methanol, ethanol, and/or isopropanol. In some embodiments, the solvent comprises water. In some embodiments, the solvent comprises an alcohol and water. In some 30 embodiments, the solvent comprises methanol and water. In some embodiments, the solvent is methanol and water.

In some embodiments, isolating Form 1 from the third mixture comprises:

- (i) filtering the third mixture to provide a solid;
- (ii) rinsing the solid with methanol and water; and
- (iii) drying the solid to provide Form 1.

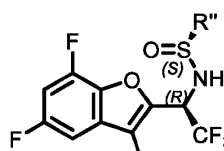
5 In some embodiments, the weight of the methanol and water is about 0.5 to about 5 times (e.g., about 0.5 to about 4 times, about 0.5 to about 3 times, about 1 to about 3 times, about 1.5 to about 2.1 times, or about 1.8 times (e.g., about 1.8 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved in step (a). In some embodiments, the ratio of methanol to water is about 1:100 to
 10 about 100:1 (e.g., about 20:80 to about 90:10, about 30:70 to about 90:10, about 50:50 to about 80:20, about 55:45 to about 65:35, or about 61:39 (e.g., about 61:39)).

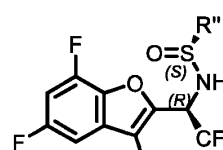
In some embodiments, drying the solid comprises drying the solid at about 30 °C to about 60 °C (e.g., about 30 °C to about 50 °C, about 35 °C to about 45 °C, about 35 °C to about 40 °C, about 40 °C to about 45 °C, about 35 °C, about 40 °C, or about 45 °C (e.g., about 35 °C to about
 15 45 °C)). In some embodiments, drying the solid comprises drying the solid at a pressure lesser than atmospheric pressure. In some embodiments, drying the solid comprises drying the solid under an inert gas (e.g., nitrogen or argon (e.g., nitrogen)). In some embodiments, drying the solid comprises drying the solid until the solid includes about 1% to about 4% (e.g., about 1.5% to about 3.2% or about 2% to about 2.6% (e.g., about 2% to about 2.6%)) by weight of water. In some
 20 embodiments, the Form 1 obtained in step (g) includes about 1% to about 4% (e.g., about 1.5% to about 3.2% or about 2% to about 2.6% (e.g., about 2% to about 2.6%)) by weight of water.



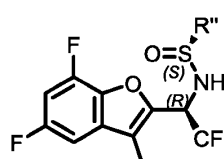
25 In some embodiments, the acid is hydrogen chloride. In some embodiments, the acid is a solution of hydrogen chloride in ethyl acetate, diethyl ether, or 1,4-dioxane. In some embodiments,

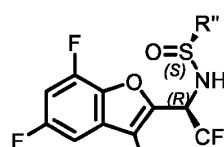
the acid is a solution of hydrogen chloride in ethyl acetate. In some embodiments, the acid is a 1 molar solution of hydrogen chloride in ethyl acetate.

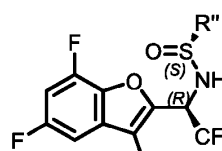
In some embodiments, the contacting comprises adding  to the acid.

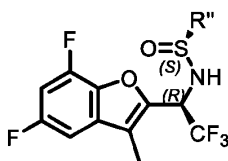
In some embodiments, the contacting comprises adding the acid to . In some

embodiments, the adding is performed at about 0 °C to about 30 °C (e.g., about 0 °C to about 25 °C, about 0 °C to about 20 °C, about 0 °C to 10 °C, or about 5 °C to about 15 °C). In some embodiments, the agitating is performed at about 0 °C to about 10 °C. In some embodiments, the agitating is performed at about 5 °C to about 15 °C. In some embodiments, the contacting

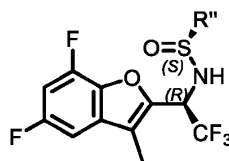
comprises agitating  with the acid for about 5 minutes to about 24 hours (e.g., about 5 minutes to about 10 hours, about 5 minutes to about 5 hours, about 5 minutes to about 3 hours, about 30 minutes to about 1.5 hours, about 3 hours, or about 1 hour) to form mixture 6. In

some embodiments, the contacting comprises agitating  with the acid for about 3 hours to form mixture 6. In some embodiments, the contacting comprises agitating

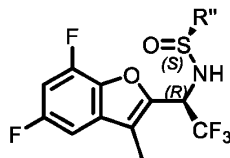
 with the acid for about 1 hour to form mixture 6. In some embodiments, the



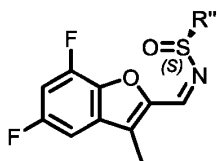
contacting comprises agitating with the acid for at least 1 hour to form mixture 6. In some embodiments, the agitating is performed at about 0 °C to about 30 °C (e.g., about 0 °C to about 25 °C, about 0 °C to about 20 °C, about 0 °C to 10 °C, or about 5 °C to about 15 °C). In some embodiments, the agitating is performed at about 5 °C to about 15 °C. In some
 5 embodiments, the contacting comprises adding heptane or hexanes (e.g., heptane) to mixture 6. In some embodiments, after adding the heptane or hexanes (e.g., heptane) to mixture 6, the mixture is cooled to about -20 °C to about 0 °C (e.g., about -15 °C to about -5 °C, or about -10 °C (e.g., about -15 °C to about -5 °C)) over about 5 minutes to about 48 hours (e.g., about 5 minutes to about 24 hours, about 3 hours to about 9 hours, about 24 hours, or about 6 hours (e.g., about 6
 10 hours)) then agitated or permitted to stand (e.g., agitated) for about 10 hours to about 2 days (e.g., about 12 hours to about 24 hours, about 14 hours to about 22 hours, about 18 hours to about 30 hours, about 22 hours to about 26 hours, about 24 hours, or about 18 hours (e.g., about 24 hours))



to form a solid. In some embodiments, the solid is filtered to provide



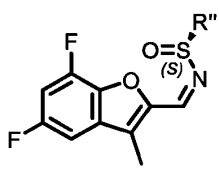
In some embodiments, the process comprises preparing by contacting

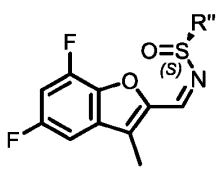


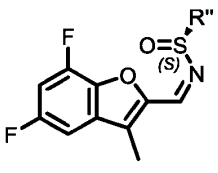
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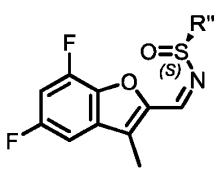
with a trifluoromethylating reagent to form ; wherein R''

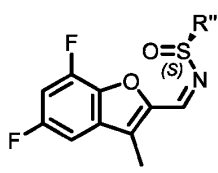
is C1-C6 alkyl.

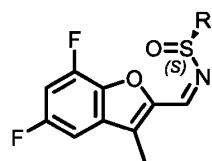
In some embodiments, the C=N double bond in  has E geometry. In

some embodiments, the C=N double bond in  has Z geometry.

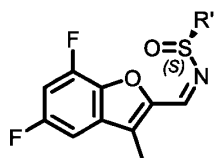
In some embodiments, the molar ratio of the trifluoromethylating reagent to  is about 1.0 to about 6.0 (e.g., about 1.0 to about 5.0, about 1.0 to about 4.0, about 2.0 to about 4.0, about 1.0 to about 5.0, about 2.5 to about 3.5, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3, about 2.0, about 2.5, about 3.0, or about 3.5). In some

embodiments, the molar ratio of the trifluoromethylating reagent to  is about 3.0.

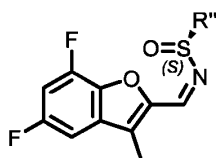
In some embodiments, the molar ratio of the phase transfer reagent to  is about 0.8 to about 6.0 (e.g., about 1.0 to about 5.0, about 1.0 to about 4.0, about 2.0 to about 4.0, about 1.0 to about 5.0, about 2.5 to about 3.5, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 0.8, about 0.9, about 0.95, about 1.0, about 1.05, about 1.1, about 1.2, about 1.3, about 2.0, about 2.5, about 3.0, or about 3.5).



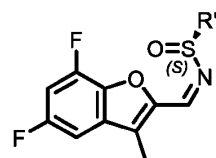
In some embodiments, the molar ratio of the phase transfer reagent to is about 1.0.



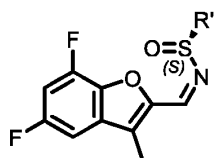
In some embodiments, contacting with the trifluoromethylating



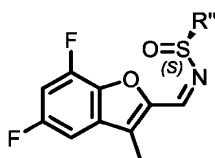
reagent comprises contacting with the trifluoromethylating reagent and a



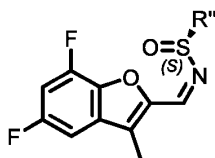
5 phase transfer reagent. In some embodiments, contacting with the trifluoromethylating reagent and the phase transfer reagent forms mixture 7.



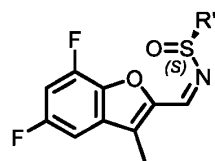
In some embodiments, contacting with the trifluoromethylating reagent and the phase transfer reagent comprises adding the phase transfer reagent to

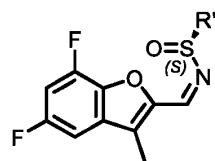


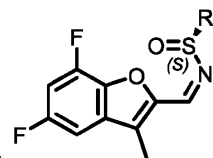
, then adding the trifluoromethylating reagent to the mixture of

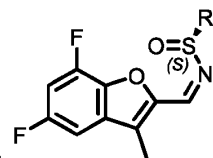


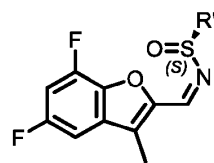
10 and the phase transfer reagent.

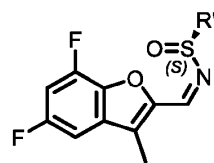


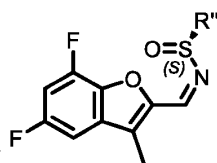
In some embodiments, the phase transfer reagent is added to  at about 5 °C to about 40 °C (e.g., about 10 °C to about 35 °C, about 15 °C to about 25 °C, about 15 °C to

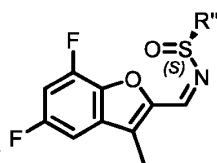


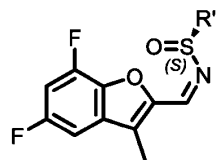
about 20 °C). In some embodiments, the phase transfer reagent is added to  at about 15 °C to about 20 °C.

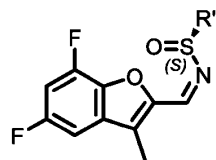


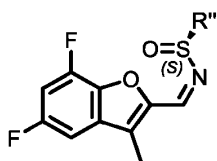
5 In some embodiments, after adding the phase transfer reagent to , the



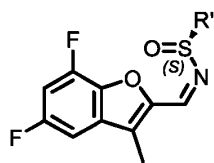
mixture of  and the phase transfer reagent is cooled to about -40 °C to about 0 °C (e.g., -30 °C to about -5 °C, -25 °C to about -10 °C, -20 °C to about -15 °C). In some



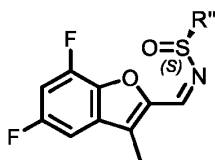
embodiments, after adding the phase transfer reagent to , the mixture of



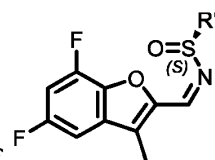
and the phase transfer reagent is cooled to about -20 °C to about -15 °C.



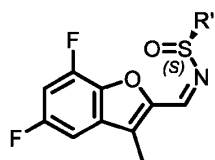
In some embodiments, after cooling the mixture of



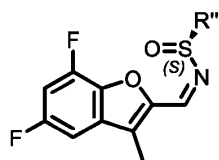
transfer reagent, the mixture of



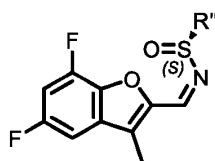
and the phase transfer reagent is agitated for about 5 minutes to about 3 hours (e.g., about 5 minutes to about 2 hours, about 30 minutes to about 1.5 hours, or about 1 hour). In some embodiments, after cooling the mixture of



and the phase transfer reagent, the mixture of

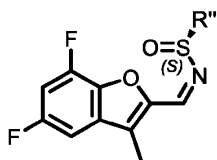


and the phase transfer reagent is performed at about -40 °C to about 0 °C (e.g., -30 °C to about -5 °C, -25 °C to about -10 °C, -20 °C to about -15 °C). In some embodiments,

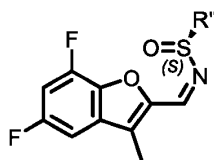


adding the trifluoromethylating reagent to the mixture of

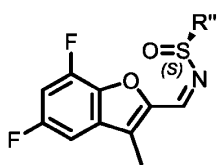
In some embodiments, the trifluoromethylating reagent is added to the mixture of



and the phase transfer reagent dropwise.

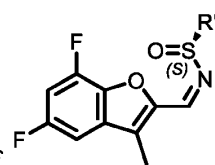


In some embodiments, contacting with the trifluoromethylating reagent and the phase transfer reagent comprises adding the trifluoromethylating reagent to



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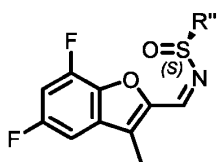
, then adding the phase transfer reagent to the mixture of and the trifluoromethylating reagent.



In some embodiments, contacting with the trifluoromethylating reagent and the phase transfer reagent is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, benzene, toluene, xylene, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent comprises toluene, xylene, or benzene. In some embodiments, the solvent comprises toluene. In some embodiments, the solvent is toluene.

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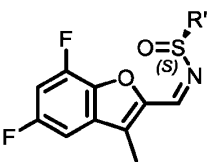
In some embodiments, the process comprises adding the trifluoromethylating reagent to



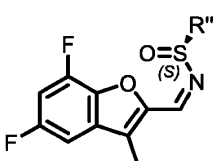
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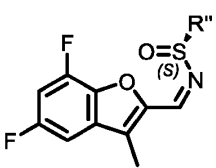
at about -78 °C to about 25 °C (e.g., about -78 °C to about 0 °C, about -78 °C to about -5 °C, about -50 °C to about 10 °C, about -40 °C to about 0 °C, about -30 °C to about 0 °C,

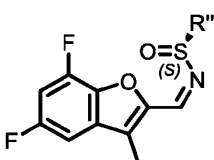
about -20 °C to about -10 °C, about -20 °C, or about -10 °C). In some embodiments, the

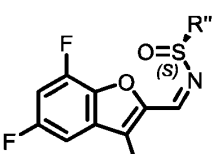
trifluoromethylating reagent is added to  at about -20 °C to about -10 °C.

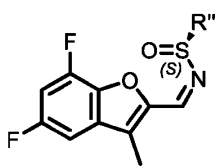
In some embodiments, the process comprises adding the trifluoromethylating reagent to

 over about 1 minute to about 24 hours (e.g., about 1 minute to about 12 hours,
 5 about 12 hours to about 24 hours, about 6 hours to about 12 hours, about 1 minute to about 12
 hours, about 1 minute to about 9 hours, about 1 minute to about 6 hours, about 1 minute to about
 4 hours, about 1 minute to about 3 hours, about 1 minute to about 2 hours, about 30 minutes to
 about 1.5 hours, about 45 minutes to about 1.25 hours, or about 1 hour. In some embodiments, the

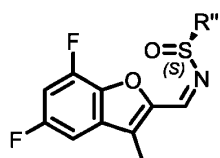
process comprises adding the trifluoromethylating reagent to  over about 1
 10 hour.

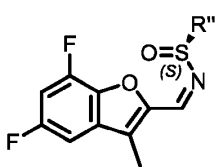
In some embodiments, the process comprises agitating , the
 trifluoromethylating reagent, and the phase transfer reagent after adding the phase transfer reagent.

In some embodiments, the process comprises agitating , the
 trifluoromethylating reagent, and the phase transfer reagent at about -78 °C to about 25 °C (e.g.,
 15 about -78 °C to about 0 °C, about -78 °C to about -5 °C, about -50 °C to about 10 °C, about -40 °C
 to about 0 °C, about -30 °C to about 0 °C, about -20 °C to about -10 °C, about -20 °C, or about -10

°C). In some embodiments, the phase transfer reagent is added to  at about -20 °C to about -10 °C.

In some embodiments, adding the phase transfer reagent to the mixture of

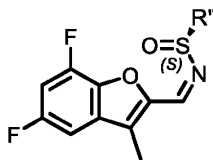
 and the trifluoromethylating reagent comprises adding the phase transfer

5 reagent to the mixture of  and the trifluoromethylating reagent in several portions. In some embodiments, the several portions are 7 to 13 portions. In some embodiments, the several portions are 9 to 11 portions. In some embodiments, the several portions are 10 portions. In some embodiments, the 10 portions are 10 portions that are substantially the same in weight.

10 In some embodiments, the process comprises adding water or an aqueous acid to mixture 7. In some embodiments, the process comprises adding an aqueous acid to mixture 7 to form mixture 8. In some embodiments, the aqueous acid is aqueous ammonium chloride (e.g., 10% aqueous ammonium chloride by weight). In some embodiments, adding the water or aqueous acid to mixture 7 is performed at about -10 °C to about 25 °C (e.g., about -5 °C to about 5 °C).

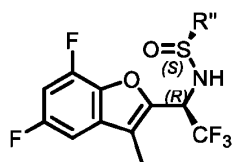
15 In some embodiments, the process comprises adding a solvent to mixture 8 to form mixture 9. In some embodiments, mixture 9 is biphasic. In some embodiments, mixture 9 comprises an organic phase and an aqueous phase. In some embodiments, the organic phase is separated from mixture 9 and concentrated under at a pressure lesser than atmospheric pressure. In some embodiments, the solvent is dichloromethane, chloroform, ethyl acetate, or diethyl ether. In some
20 embodiments, the solvent is ethyl acetate. In some embodiments, concentrating the organic phase

at a pressure lesser than atmospheric pressure provides a residue. In some embodiments, the

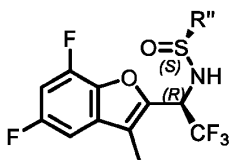


residue is purified using silica gel to provide

In some embodiments, the process comprises adding water and/or aqueous base to mixture 8 to form mixture 9'. In some embodiments, mixture 9' comprises an organic phase and an aqueous phase. In some embodiments, the process comprises separating the organic phase from mixture 9'. In some embodiments, the process comprises distilling the organic phase to provide a distillate. In some embodiments, the process comprises passing the distillate through carbon (e.g., activated carbon). In some embodiments, the process comprises reducing the volume of the distillate under a pressure lesser than atmospheric pressure to form a concentrate after passing the distillate through carbon. In some embodiments, the process comprises adding water to the concentrate, then reducing the volume of the mixture of water and concentrate to form mixture 9''. In some embodiments, the process comprises adding an anti-solvent to mixture 9'', then reducing the volume of mixture 9'' to form mixture 9'''. In some embodiments, the anti-solvent is heptane. In some embodiments, the process comprises adding a portion (e.g., a previously prepared portion)



of to mixture 9''' to form a precipitate. In some embodiments, the

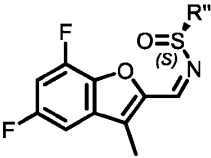


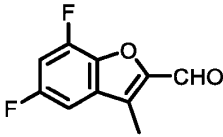
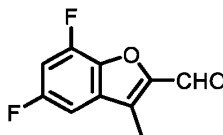
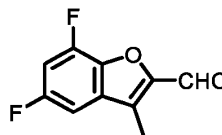
precipitate is filtered and dried to form

In some embodiments, the trifluoromethylating reagent is selected from TMSCF₃, [(Trifluoromethyl)thio]benzene, potassium trimethoxy(trifluoromethyl)borate, Et₃GeNa/C₆H₅SCF₃, N,N-dimethyl-(1-phenyl-2,2,2-trifluoroethoxytrimethylsilyl)-amine, S-(trifluoromethyl)dibenzothiophenium tetrafluoroborate, (SP-4-1)-tetrakis(trifluoromethyl)cuprate(1-), (SP-4-1)-tetrakis(trifluoromethyl)argentate(1-), [(1,1,2,2,2-pentafluoroethyl)sulfonyl]benzene, 5-(trifluoromethyl)-thianthrenium, 1,1,1-

trifluoromethanesulfonate (1:1). In some embodiments, the trifluoromethylating reagent is TMSCF_3 .

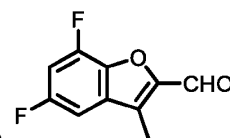
In some embodiments, the phase transfer reagent is selected from tetrabutylammonium acetate, tetrabutylphosphonium bromide, triethylbenzylammonium chloride, decyltrimethylammonium bromide, tetraethylammonium trifluoromethanesulfonate, benzyldodecyldimethylammonium chloride, benzyldimethyltetradecylammonium chloride, benzylcholine bromide, benzyldimethylphenylammonium chloride, benzyltributylammonium bromide, 1,1'-(butane-1,4-diyl)bis[4-aza-1-azoniabicyclo[2.2.2]octane] dibromide, ethylhexadecyldimethylammonium bromide, decamethonium bromide, tetrapropylammonium iodide, tetrahexylammonium iodide, tetra(decyl)ammonium bromide, tetraamylammonium chloride, and dimethyldipalmitylammonium bromide. In some embodiments, the phase transfer reagent is tetrabutylammonium acetate.

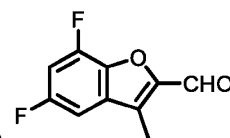
In some embodiments, the process comprises preparing  by contacting

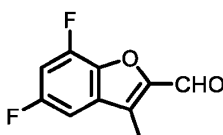
 with $\text{H}_2\text{N}-\text{S}(=\text{O})-\text{R}''$; wherein R'' is C1-C6 alkyl. In some embodiments, contacting  with $\text{H}_2\text{N}-\text{S}(=\text{O})-\text{R}''$ comprises contacting  with $\text{H}_2\text{N}-\text{S}(=\text{O})-\text{R}''$ and a condensing base. In some embodiments, the condensing base is selected from sodium bicarbonate, potassium carbonate, potassium phosphate, sodium carbonate, potassium bicarbonate, N,N-diisopropylethylamine, triethylamine, and citric acid. In some embodiments, the condensing base is potassium carbonate.

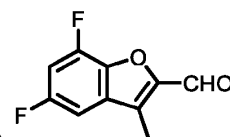
In some embodiments, the contacting is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-

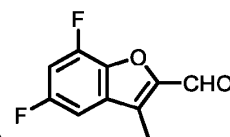
dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is ethyl acetate. In some embodiments, the solvent is tetrahydrofuran.

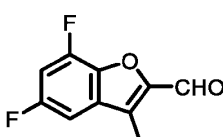


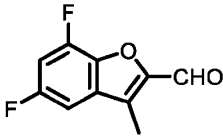
In some embodiments, the molar ratio of the condensing base to  is about 0.8 to about 6.0 (e.g., about 1.0 to about 5.0, about 1.0 to about 4.0, about 2.0 to about 4.0, about 1.0 to about 5.0, about 2.5 to about 3.5, about 1.0 to about 2.0, about 1.3 to about 1.7, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 0.8, about 0.9, about 0.95, about 1.0, about 1.05, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 2.0, about 2.5, about 3.0, or about 3.5). In some embodiments, the molar ratio of

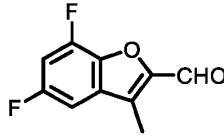
the condensing base to  is about 1.5.

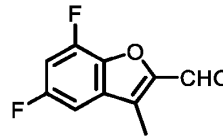


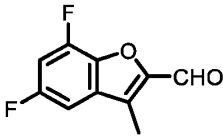
In some embodiments, the molar ratio of the condensing base to  is about 0.8 to about 6.0 (e.g., about 1.0 to about 5.0, about 1.0 to about 4.0, about 2.0 to about 4.0, about 1.0 to about 5.0, about 2.5 to about 3.5, about 1.0 to about 2.0, about 1.3 to about 1.7, about 1.0 to about 1.5, about 1.0 to about 1.4, about 0.8 to about 1.2, about 0.9 to about 1.1, about 1.0 to about 1.1, about 1.2 to about 1.4, about 0.95 to about 1.05, about 1.0 to about 1.04, about 0.8, about 0.9, about 0.95, about 1.0, about 1.02, about 1.05, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 2.0, about 2.5, about 3.0, or about 3.5). In some embodiments, the molar

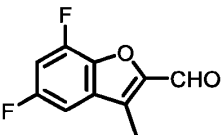
ratio of the condensing base to  is about 1.02.

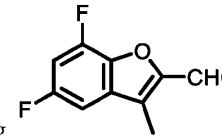
In some embodiments, contacting  with $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ and the condensing base is performed at about 25 °C to about 80 °C (e.g., about 25 °C to about 70 °C, about 25 °C to about 60 °C, about 35 °C to about 50 °C, about 35 °C to about 45 °C, about 35 °C, about

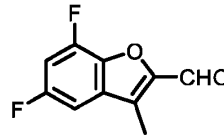
40 °C, or about 45 °C). In some embodiments, contacting  with $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ and the condensing base is performed at about 35 °C to about 45 °C.

In some embodiments, contacting  with $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ and the condensing base is performed at about 25 °C to about 80 °C (e.g., about 25 °C to about 70 °C, about 25 °C to about 60 °C, about 35 °C to about 50 °C, about 35 °C to about 45 °C, about 35 °C, about 40 °C, or about 45 °C).

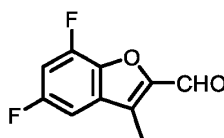
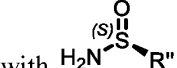
In some embodiments, contacting  with $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ and the

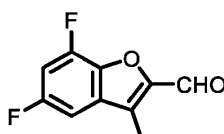
condensing base comprises agitating  with $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ and the condensing

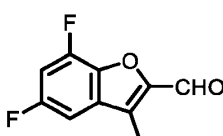
base. In some embodiments, agitating  with $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ and the condensing

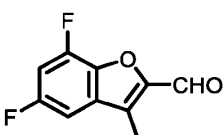
base comprises agitating  with $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ and the condensing base for about 1 hour to about 48 hours (e.g., about 2 hours to about 36 hours, about 2 hours to about 24 hours,

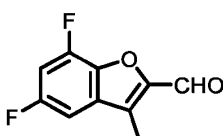
about 2 hours to about 12 hours, about 6 hours to about 24 hours, about 9 hours to about 19 hours, about 11 hours to about 17 hours, about 13 hours to about 15 hours, about 13.5 hours to about 14.5

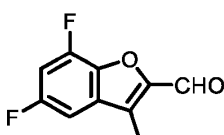
hours, or about 14 hours). In some embodiments, agitating  with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{||}}{\text{S}}}-\text{R}''$ 

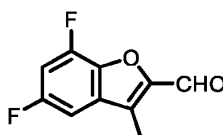
and the condensing base comprises agitating  with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{||}}{\text{S}}}-\text{R}''$ and the
5 condensing base for about 14 hours.

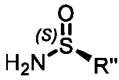
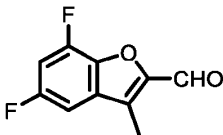
In some embodiments, contacting  with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{||}}{\text{S}}}-\text{R}''$ and a condensing

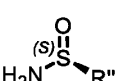
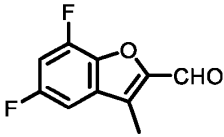
base comprises adding the $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{||}}{\text{S}}}-\text{R}''$ to , then adding the condensing base

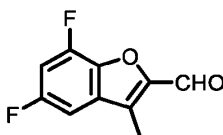
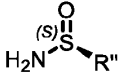
to the mixture of $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{||}}{\text{S}}}-\text{R}''$ and .

In some embodiments, adding the $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{||}}{\text{S}}}-\text{R}''$ to  is performed at
10 about 5 °C to about 40 °C (e.g., about 10 °C to about 35 °C, about 15 °C to about 25 °C, about 15

°C to about 20 °C). In some embodiments adding the $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{||}}{\text{S}}}-\text{R}''$ to  is
performed at about 15 °C to about 20 °C.

In some embodiments, adding the condensing base to the mixture of  and  is performed at about 5 °C to about 40 °C (e.g., about 10 °C to about 35 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C). In some embodiments adding the

condensing base to the mixture of  and  is performed at about 15 °C to about 20 °C.

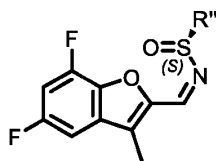
In some embodiments, contacting  with  and a condensing base provides mixture 10. In some embodiments, mixture 10 is agitated for about 15 minutes to about 48 hours (e.g., about 15 minutes to about 24 hours, about 15 minutes to about 16 hours, about 15 minutes to about 10 hours, about 2 hours to about 8 hours, about 3 hours to about 7 hours, about 4 hours to about 6 hours, or about 5 hours). In some embodiments, mixture 10 is agitated for about 15 minutes to about 5 hours. In some embodiments, agitating mixture 10 is performed at about 25 °C to about 110 °C (e.g., 40 °C to about 80 °C, 50 °C to about 70 °C, 55 °C to about 65 °C, or about 60 °C). In some embodiments, agitating mixture 10 is performed at about 60 °C.

In some embodiments, after agitating mixture 10, mixture 10 is cooled to about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, or about 20 °C). In some embodiments, after agitating mixture 10, mixture 10 is cooled to about 20 °C. In some embodiments, after agitating mixture 10, mixture 10 is cooled to about 15 °C to about 25 °C.

In some embodiments, cooling mixture 10 comprises forming a slurry. In some embodiments, the process comprises filtering the slurry to provide a solution. In some embodiments, the process comprises reducing the volume of the solution under a pressure lesser than atmospheric pressure. In some embodiments, the process comprises (i) adding a solvent to the solution; (ii) reducing the volume of the solution under a pressure lesser than atmospheric pressure; optionally (iii) adding a solvent to the solution; and optionally (iv) reducing the volume

of the solution under a pressure lesser than atmospheric pressure to form a concentrate. In some embodiments, the solvent is methanol, ethanol, or isopropanol. In some embodiments, the solvent is ethanol. In some embodiments, steps (iii) and (iv) are required. In some embodiments, the process comprises cooling the concentrate to about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, or about 20 °C). In some embodiments, the process comprises cooling the concentrate to about 15 °C to about 25 °C. In some embodiments, the process comprises adding water to the concentrate after cooling the concentrate to form mixture 10'. In some embodiments, the process comprises agitating mixture 10' for about 1 hour to about 48 hours (e.g., about 2 hours to about 36 hours, about 2 hours to about 24 hours, about 2 hours to about 12 hours, about 6 hours to about 24 hours, about 9 hours to about 19 hours, about 11 hours to about 17 hours, about 13 hours to about 15 hours, about 13.5 hours to about 14.5 hours, or about 14 hours). In some embodiments, the process comprises agitating mixture 10' for about 14 hours. In some embodiments, after agitating mixture 10', a slurry is formed. In some embodiments, the slurry is filtered to provide the compound of Formula (I-v).

In some embodiments, the process comprises concentrating mixture 10 at a pressure lesser



than atmospheric pressure to provide

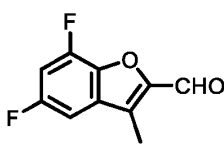
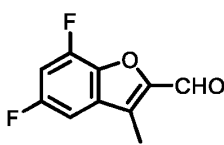
after cooling mixture 10.

In some embodiments, the process comprises

In some embodiments, contacting the compound of Formula (I-v) with $\text{H}_2\text{N}-\text{S}(=\text{O})_2-\text{R}''$ and a

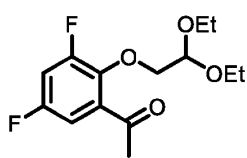
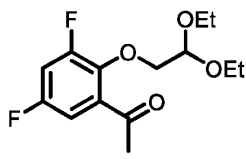
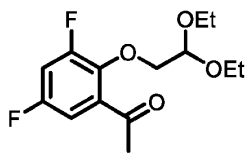
condensing base comprises adding the $\text{H}_2\text{N}-\text{S}(=\text{O})_2-\text{R}''$ to the compound of Formula (I-v), then adding

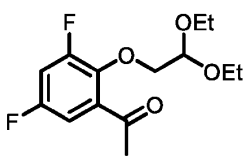
the condensing base to the mixture of $\text{H}_2\text{N}-\text{S}(=\text{O})_2-\text{R}''$ and the compound of Formula (I-v).

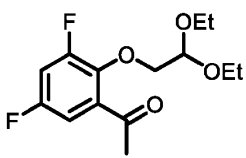
In some embodiments, the process comprises preparing  by contacting  with an acid.

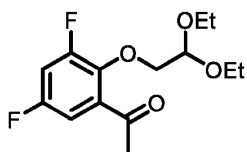
In some embodiments, the acid is a protic acid. In some embodiments, the acid is a Lewis acid. In some embodiments, the acid is selected from acetic acid, hydrogen chloride, sulfuric acid, phosphoric acid, nitric acid, aluminum chloride, zinc chloride, trimethylaluminum, iron (III) bromide, and boron trifluoride (e.g., boron trifluoride dietherate).

In some embodiments, the acid is acetic acid.

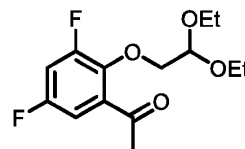
In some embodiments, contacting  with an acid comprises adding  to the acid. In some embodiments, contacting  with

an acid comprises contacting  with the acid in a solvent. In some embodiments, the solvent is acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is N,N-dimethylformamide. In some embodiments,

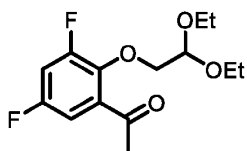
adding  to the acid forms mixture 11. In some embodiments, after adding



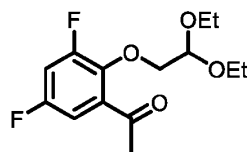
to the acid, mixture 11 is heated at about 80 °C to about 160 °C (e.g., about 90 °C to about 150 °C, about 100 °C to about 140 °C, about 110 °C to about 130 °C, about 115 °C



to about 125 °C, or about 120 °C). In some embodiments, after adding to the acid, mixture 11 is heated at about 120 °C. In some embodiments, after adding



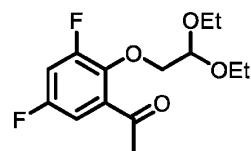
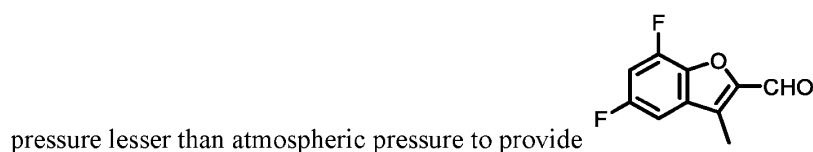
5 to the acid, mixture 11 is agitated for about 15 minutes to about 2 days (e.g., about 30 minutes to about 24 hours, about 2 hours to about 16 hours, about 4 hours to about 12 hours, about 6 hours to about 10 hours, about 7 hours to about 9 hours, or about 8 hours). In some



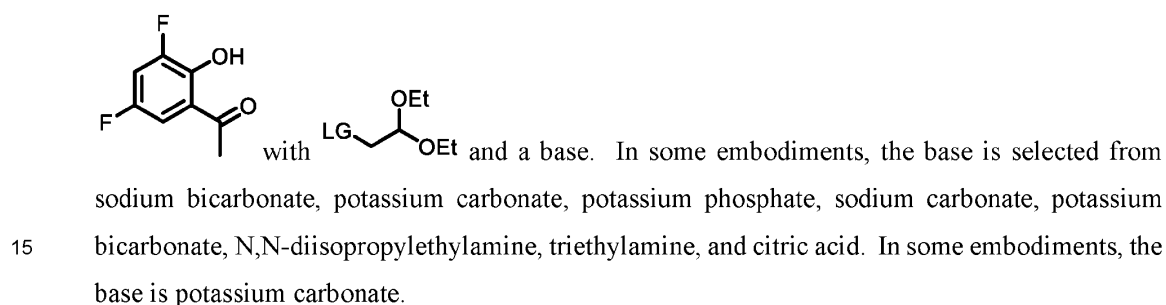
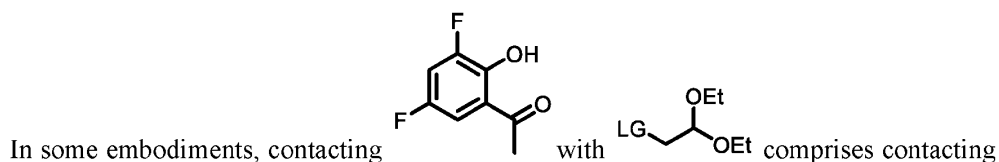
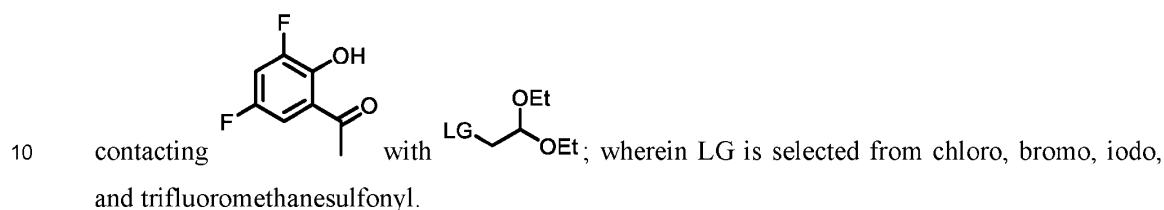
embodiments, after adding to the acid, mixture 11 is agitated for about 8 hours.

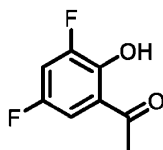
10 In some embodiments, after agitating mixture 11, water is added to mixture 11. In some embodiments, after adding water to mixture 11, a solvent is added to mixture 11 to form mixture 12. In some embodiments, mixture 12 is biphasic. In some embodiments, mixture 12 comprises an organic phase and an aqueous phase. In some embodiments, the organic phase is isolated and washed with an aqueous base. In some embodiments, the aqueous base is aqueous potassium carbonate (e.g., 15% aqueous potassium carbonate by weight). In some embodiments, after washing the organic phase with the aqueous base, the organic phase is agitated with water and Na₂S₂O₄. In some embodiments, the organic phase is agitated with water and Na₂S₂O₄ for about 5 minutes to about 2 days (e.g., about 1 hour to about 24 hours, about 4 hours to about 18 hours, about 6 hours to about 10 hours, or about 8 hours). In some embodiments, the organic phase is agitated with water and Na₂S₂O₄ for about 8 hours. In some embodiments, agitating the organic

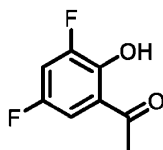
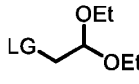
phase with water and $\text{Na}_2\text{S}_2\text{O}_4$ forms a solid. In some embodiments, the solid is separated from the solvent and water. In some embodiments, the solid is combined with ethyl acetate to form a solution, and the pH of the solution is adjusted to about 8 to about 11 (e.g., about 9 to about 10, about 9, or about 10) and then agitated for about 5 minutes to about 1 day (e.g., about 1 hour to about 10 hours, about 3 hours to about 7 hours, about 4 hours to about 6 hours, or about 5 hours) to form a biphasic mixture. In some embodiments, the biphasic mixture comprises an organic phase and an aqueous phase. In some embodiments, the organic phase concentrated under at a

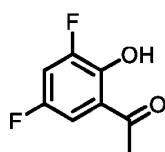


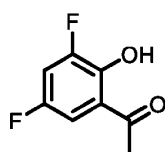
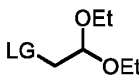
In some embodiments, the process comprises preparing

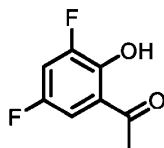


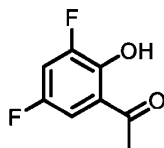
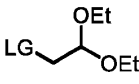


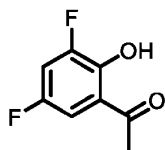
In some embodiments, contacting  with  and a base is performed in a solvent. In some embodiments, the solvent is acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is N,N-dimethylformamide.

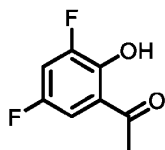
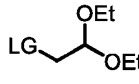


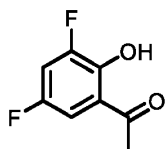
In some embodiments, contacting  with  and a base comprises

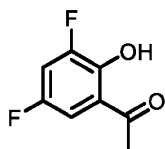
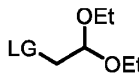


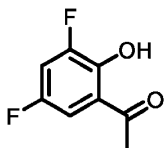
contacting  with , a base, and sodium iodide.

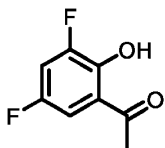
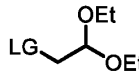


In some embodiments, contacting  with , a base, and sodium iodide is performed at about 80 °C to about 160 °C (e.g., about 90 °C to about 150 °C, about 100 °C to about 140 °C, about 110 °C to about 130 °C, about 115 °C to about 125 °C, or about 120 °C).



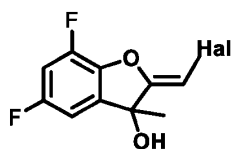
In some embodiments, contacting  with , a base, and sodium iodide is performed at about 120 °C.



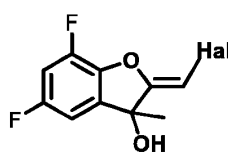
In some embodiments, adding  to , a base, and sodium iodide forms mixture 13. In some embodiments, mixture 13 is agitated for about 15 minutes to about 2 days (e.g., about 30 minutes to about 24 hours, about 2 hours to about 16 hours, about 2 hours to

about 8 hours, about 3 hours to about 7 hours, about 4 hours to about 6 hours, or about 5 hours). In some embodiments, mixture 13 is agitated for about 5 hours.

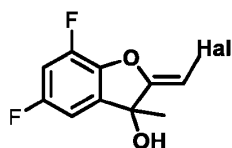
In some embodiments, the process comprises preparing the compound of Formula (I-v) by



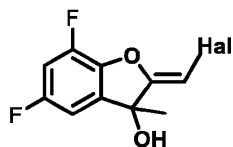
contacting a compound of with an acid; wherein Hal is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl. In some embodiments, Hal is chloro. In some embodiments, the acid is sulfuric acid, hydrogen chloride, nitric acid, phosphoric acid, or hydrogen bromide. In some embodiments, the acid is sulfuric acid.



In some embodiments, contacting with the acid is performed in a solvent. In some embodiments, the solvent comprises methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether.

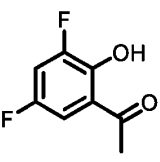


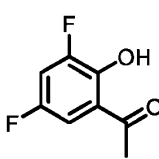
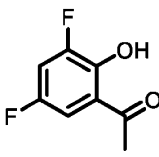
In some embodiments, contacting with the acid is performed at about 10 °C to about 60 °C (e.g., about 15 °C to about 55 °C, about 15 °C to about 35 °C, about 20 °C to about 30 °C, about 23 °C to about 27 °C, or about 25 °C). In some embodiments, contacting



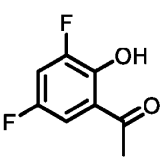
with the acid is performed at about 25 °C.

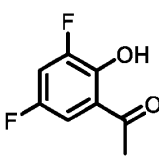
In some embodiments, the process comprises preparing the compound of Formula (I-viii)

by contacting  with . In some embodiments, Z is O. In some embodiments, R² is C1-C6 alkyl. In some embodiments, R² is methyl.

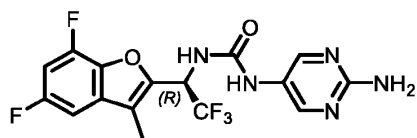
In some embodiments, contacting  with  comprises contacting  with  and a base. In some embodiments, the base is potassium tert-butoxide. In some embodiments, the contacting is performed in a solvent.

In some embodiments, the solvent comprises methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether.

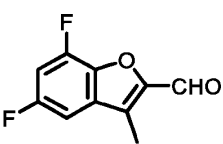
In some embodiments, contacting  with  and a base is performed at about 10 °C to about 60 °C (e.g., about 15 °C to about 55 °C, about 15 °C to about 35 °C, about 20 °C to about 30 °C, about 23 °C to about 27 °C, or about 25 °C). In some embodiments, contacting

 with  and a base is performed at about 25 °C.

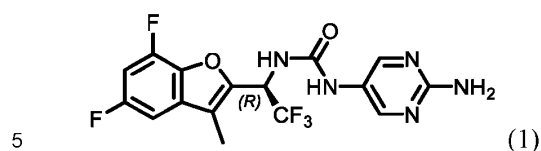
Some embodiments provide a process of preparing Compound 1, having the structure:

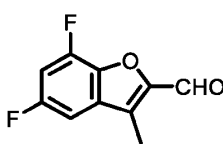


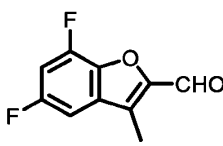
(1), or a salt and/or solvate thereof;

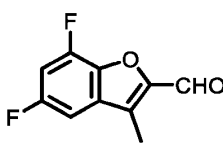
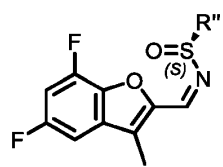
comprising reacting  to form Compound 1.

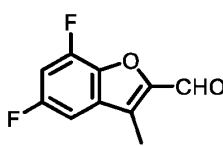
Some embodiments Compound 1, having the structure:

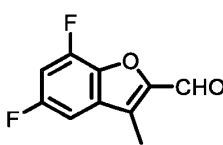


prepared by a process comprising reacting  to form Compound 1.

In some embodiments, reacting  to form Compound 1 comprises

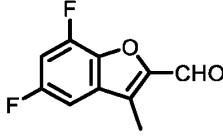
contacting  with $\text{H}_2\text{N}-\text{S}^{(s)}(\text{O})-\text{R}''$ to form ; wherein R'' is C1-C6 alkyl.

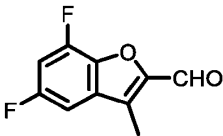
10 In some embodiments, contacting  with $\text{H}_2\text{N}-\text{S}^{(s)}(\text{O})-\text{R}''$ comprises

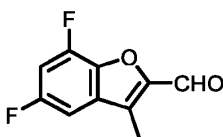
contacting  with $\text{H}_2\text{N}-\text{S}^{(s)}(\text{O})-\text{R}''$ and a condensing base. In some embodiments,

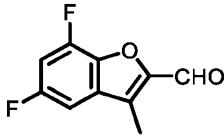
the condensing base is selected from sodium bicarbonate, potassium carbonate, potassium phosphate, sodium carbonate, potassium bicarbonate, N,N-diisopropylethylamine, triethylamine, and citric acid. In some embodiments, the condensing base is potassium carbonate.

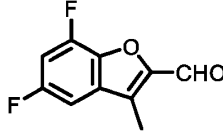
In some embodiments, the contacting is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is ethyl acetate.

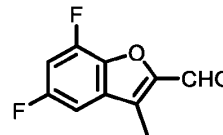
In some embodiments, contacting  with $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ and a condensing

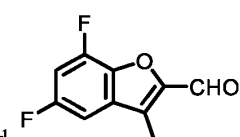
base comprises adding the $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ to , then adding the condensing base

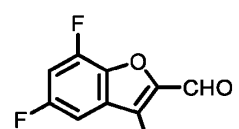
to the mixture of $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ and .

In some embodiments, adding the $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ to  is performed at about 5 °C to about 40 °C (e.g., about 10 °C to about 35 °C, about 15 °C to about 25 °C, about 15

°C to about 20 °C). In some embodiments adding the $\text{H}_2\text{N}-\overset{\text{(S)}}{\overset{\text{O}}{\parallel}}\text{S}-\text{R}''$ to  is performed at about 15 °C to about 20 °C.

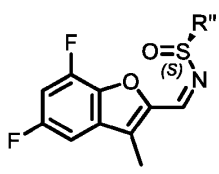
In some embodiments, adding the condensing base to the mixture of $\text{H}_2\text{N}-\text{S}^{(S)}(\text{O})-\text{R}''$ and  is performed at about 5 °C to about 40 °C (e.g., about 10 °C to about 35 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C). In some embodiments adding the

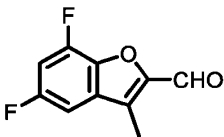
condensing base to the mixture of $\text{H}_2\text{N}-\text{S}^{(S)}(\text{O})-\text{R}''$ and  is performed at about 15 °C to about 20 °C.

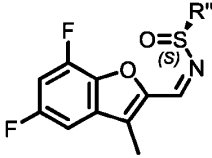
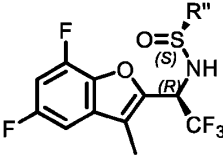
In some embodiments, contacting  with $\text{H}_2\text{N}-\text{S}^{(S)}(\text{O})-\text{R}''$ and a condensing base provides mixture 10. In some embodiments, mixture 10 is agitated for about 15 minutes to about 48 hours (e.g., about 15 minutes to about 24 hours, about 15 minutes to about 16 hours, about 15 minutes to about 10 hours, about 2 hours to about 8 hours, about 3 hours to about 7 hours, about 4 hours to about 6 hours, or about 5 hours). In some embodiments, mixture 10 is agitated for about 15 minutes to about 5 hours. In some embodiments, agitating mixture 10 is performed at about 25 °C to about 110 °C (e.g., 40 °C to about 80 °C, 50 °C to about 70 °C, 55 °C to about 65 °C, or about 60 °C). In some embodiments, agitating mixture 10 is performed at about 60 °C.

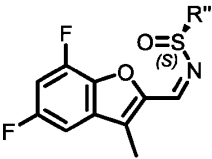
In some embodiments, after agitating mixture 10, mixture 10 is cooled to about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, or about 20 °C). In some embodiments, after agitating mixture 10, mixture 10 is cooled to about 20 °C.

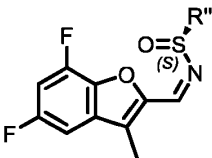
After cooling mixture 10, mixture 10 is concentrated at a pressure lesser than atmospheric

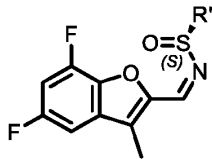
pressure to provide .

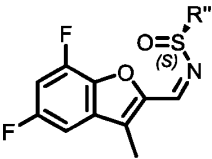
In some embodiments, reacting  to form Compound 1 comprises contacting

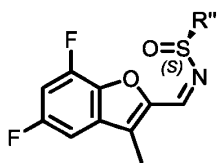
 with a trifluoromethylating reagent to form ; wherein R'' is C1-C6 alkyl.

In some embodiments, contacting  with the trifluoromethylating

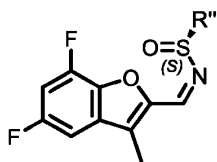
5 reagent comprises contacting  with the trifluoromethylating reagent and a

phase transfer reagent. In some embodiments, contacting  with the trifluoromethylating reagent and the phase transfer reagent forms mixture 7.

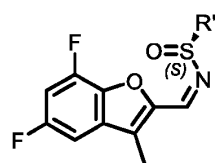
In some embodiments, contacting  with the trifluoromethylating reagent and the phase transfer reagent comprises adding the phase transfer reagent to



, then adding the trifluoromethylating reagent to the mixture of

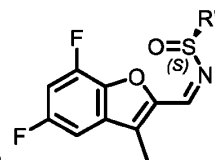


and the phase transfer reagent.

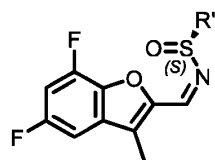


In some embodiments, the phase transfer reagent is added to at about 5 °C to about 40 °C (e.g., about 10 °C to about 35 °C, about 15 °C to about 25 °C, about 15 °C to

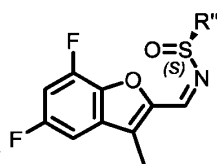
about 20 °C). In some embodiments, the phase transfer reagent is added to at about 15 °C to about 20 °C.

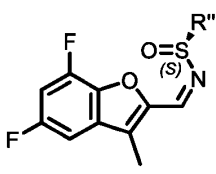


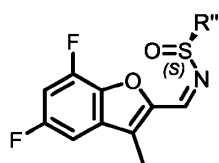
In some embodiments, after adding the phase transfer reagent to , the



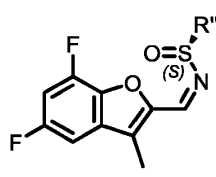
mixture of and the phase transfer reagent is cooled to about -40 °C to about 0 °C (e.g., -30 °C to about -5 °C, -25 °C to about -10 °C, -20 °C to about -15 °C). In some

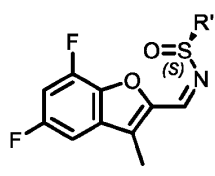


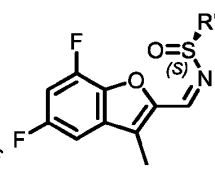
embodiments, after adding the phase transfer reagent to , the mixture of

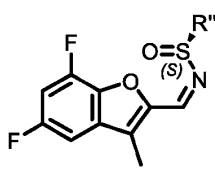


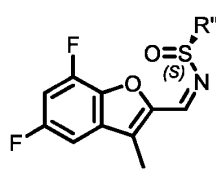
and the phase transfer reagent is cooled to about -20 °C to about -15 °C.

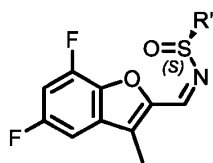
In some embodiments, after cooling the mixture of  and the phase

transfer reagent, the mixture of  and the phase transfer reagent is agitated for
5 about 5 minutes to about 3 hours (e.g., about 5 minutes to about 2 hours, about 30 minutes to about

1.5 hours, or about 1 hour). In some embodiments, after cooling the mixture of 

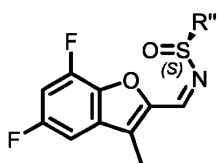
and the phase transfer reagent, the mixture of  and the phase transfer reagent
is agitated for about 1 hour.

In some embodiments, adding the trifluoromethylating reagent to the mixture of 
10 and the phase transfer reagent is performed at about -40 °C to about 0 °C (e.g.,
-30 °C to about -5 °C, -25 °C to about -10 °C, -20 °C to about -15 °C). In some embodiments,



adding the trifluoromethylating reagent to the mixture of and the phase transfer reagent is performed at about -20 °C to about -15 °C.

In some embodiments, the trifluoromethylating reagent is added to the mixture of



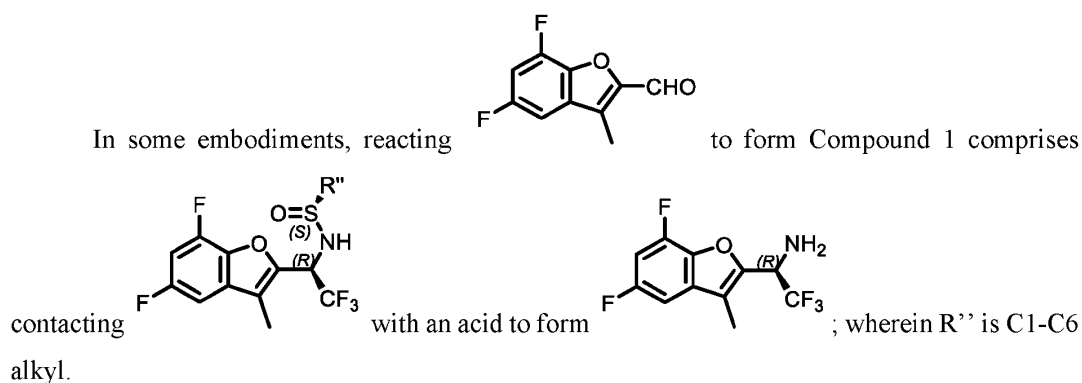
and the phase transfer reagent dropwise.

5 In some embodiments, the process comprises adding water or an aqueous acid to mixture 7. In some embodiments, the process comprises adding an aqueous acid to mixture 7 to form mixture 8. In some embodiments, the aqueous acid is aqueous ammonium chloride (e.g., 10% aqueous ammonium chloride by weight).

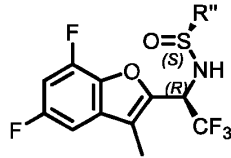
In some embodiments, the process comprises adding a solvent to mixture 8 to form mixture 9. In some embodiments, mixture 9 is biphasic. In some embodiments, mixture 9 comprises an organic phase and an aqueous phase. In some embodiments, the organic phase is isolated and concentrated under at a pressure lesser than atmospheric pressure. In some embodiments, the solvent is dichloromethane, chloroform, ethyl acetate, or diethyl ether. In some embodiments, the solvent is ethyl acetate. In some embodiments, concentrating the organic phase at a pressure lesser than atmospheric pressure provides a residue. In some embodiments, the residue is purified using silica gel to provide the compound of Formula (I-iv).

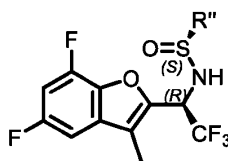
In some embodiments, the trifluoromethylating reagent is selected from TMSCF₃, [(Trifluoromethyl)thio]benzene, potassium trimethoxy(trifluoromethyl)borate, Et₃GeNa/C₆H₅SCF₃, N,N-dimethyl-(1-phenyl-2,2,2-trifluoroethoxytrimethylsilyl)-amine, S-(trifluoromethyl)dibenzothiophenium tetrafluoroborate, (SP-4-1)-tetrakis(trifluoromethyl)cuprate(1-), (SP-4-1)-tetrakis(trifluoromethyl)argentate(1-), [(1,1,2,2,2-pentafluoroethyl)sulfonyl]benzene, 5-(trifluoromethyl)-thianthrenium, 1,1,1-trifluoromethanesulfonate (1:1). In some embodiments, the trifluoroalkylating reagent is a trifluoromethylating reagent. In some embodiments, the trifluoromethylating reagent is TMSCF₃.

In some embodiments, the phase transfer reagent is selected from tetrabutylammonium acetate, tetrabutylphosphonium bromide, triethylbenzylammonium chloride, decyltrimethylammonium bromide, tetraethylammonium trifluoromethanesulfonate, benzyldecyldimethylammonium chloride, benzyltrimethyltetradecylammonium chloride, benzoylcholine bromide, benzyltrimethylphenylammonium chloride, benzyltributylammonium bromide, 1,1'-(butane-1,4-diyl)bis[4-aza-1-azoniabicyclo[2.2.2]octane] dibromide, ethylhexadecyldimethylammonium bromide, decamethonium bromide, tetrapropylammonium iodide, tetrahexylammonium iodide, tetra(decyl)ammonium bromide, tetraamylammonium chloride, and dimethyldipalmitylammonium bromide. In some embodiments, the phase transfer reagent is tetrabutylammonium acetate.

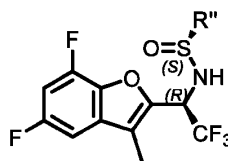


In some embodiments, the acid is hydrogen chloride. In some embodiments, the acid is a solution of hydrogen chloride in ethyl acetate, diethyl ether, or 1,4-dioxane. In some embodiments, the acid is a solution of hydrogen chloride in ethyl acetate. In some embodiments, the acid is a 1 molar solution of hydrogen chloride in ethyl acetate.

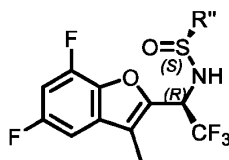
In some embodiments, the contacting comprises adding  to the acid. In some embodiments, the adding is performed at about 0 °C to about 30 °C (e.g., about 0 °C to about 25 °C, about 0 °C to about 20 °C, about 0 °C to 10 °C, or about 5 °C to about 15 °C). In some embodiments, the agitating is performed at about 0 °C to about 10 °C. In some embodiments, the



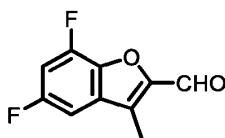
contacting comprises agitating with the acid for about 5 minutes to about 24 hours (e.g., about 5 minutes to about 10 hours, about 5 minutes to about 5 hours, about 5 minutes to about 3 hours, about 30 minutes to about 1.5 hours, or about 1 hour) to form mixture 6. In some



embodiments, the contacting comprises agitating with the acid for about 1 hour to form mixture 6. In some embodiments, the agitating is performed at about 0 °C to about 30 °C (e.g., about 0 °C to about 25 °C, about 0 °C to about 20 °C, about 0 °C to 10 °C, or about 5 °C to about 15 °C). In some embodiments, the agitating is performed at about 5 °C to about 15 °C. In some embodiments, the contacting comprises adding heptane or hexanes (e.g., heptane) to mixture 6. In some embodiments, after adding the heptane or hexanes (e.g., heptane) to mixture 6, the mixture is cooled to about -20 °C to about 0 °C (e.g., -15 °C to about -5 °C, or about -10 °C) over about 5 minutes to about 24 hours (e.g., about 3 hours to about 9 hours, or about 6 hours) then agitated or permitted to stand (e.g., agitated) for about 10 hours to about 2 days (e.g., about 12 hours to about 24 hours, about 14 hours to about 22 hours, about 18 hours to about 30 hours, about 22 hours to about 26 hours, about 24 hours, or about 18 hours) to form a solid. In some

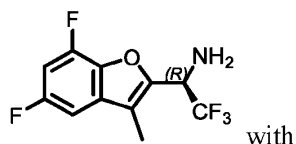


embodiments, the solid is filtered to provide



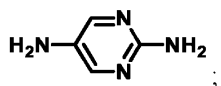
In some embodiments, reacting

to form Compound 1 comprises contacting

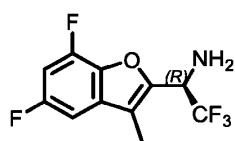


(i) a carbonyl equivalent; and

(ii) pyrimidine-2,5-diamine having the structure
to form Compound 1.



In some embodiments, contacting
5 pyrimidine-2,5-diamine to form Compound 1 comprises adding the carbonyl equivalent to



and a base to form mixture 1, then adding pyrimidine-2,5-diamine to mixture
1 to form mixture 2.

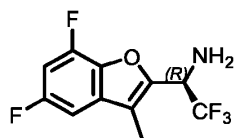
In some embodiments, the molar ratio of the carbonyl equivalent to
is about 1.0 to about 4.0 (e.g., about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4,
10 about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3). In some

embodiments, the molar ratio of the carbonyl equivalent to
is about 1.05. In

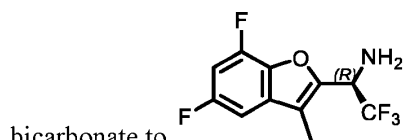
some embodiments, the molar ratio of the carbonyl equivalent to
is about
1.3.

In some embodiments, the molar ratio of the base to
is about 1.0 to
15 about 5.0 (e.g., about 2.0 to about 5.0, about 2.0 to about 4.0, about 2.5 to about 3.5, about 3.0, or

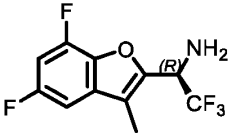
about 3.5. In some embodiments, the molar ratio of the sodium bicarbonate to

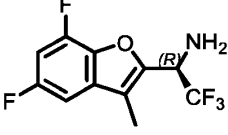


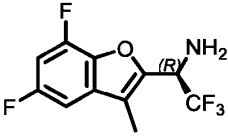
is about 3.0. In some embodiments, the molar ratio of the sodium

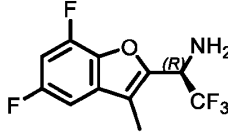


bicarbonate to is about 3.5.

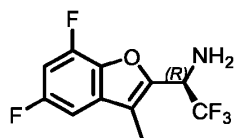
In some embodiments, adding the carbonyl equivalent to  and a base to form mixture 1 is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.

In some embodiments, adding the carbonyl equivalent to  and the base to form mixture 1 is performed under an inert atmosphere. In some embodiments, the adding is performed under nitrogen. In some embodiments, the adding is performed under argon.

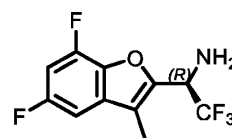
In some embodiments, adding the carbonyl equivalent to  and the base is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 2 °C, or

about 0 °C). In some embodiments, adding the carbonyl equivalent to  is

performed at about 0 °C to about 5 °C. In some embodiments, adding the carbonyl equivalent to



is performed at about 0 °C to about 2 °C.



In some embodiments, after adding the carbonyl equivalent to the base, mixture 1 is agitated for about 1 hour to about 7 days (e.g., about 1 hour to about 2 days, about 5 hours to about 1 day, about 10 hours to about 18 hours, about 10 hours to about 14 hours, about 14 hours to about 18 hours, about 12 hours to about 16 hours, about 14 hours to about 16 hours, or about 16 hours).

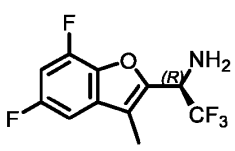
In some embodiments, adding pyrimidine-2,5-diamine to mixture 1 to form mixture 2 comprises adding a second base to mixture 1 and pyrimidine-2,5-diamine to mixture 1. In some embodiments, adding pyrimidine-2,5-diamine to mixture 1 to form mixture 2 comprises adding a second base to mixture 1 then pyrimidine-2,5-diamine to mixture 1. In some embodiments, the second base is selected from N,N-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene (DBU), and 1,5-diazabicyclo(4.3.0)non-5-ene (DBN). In some embodiments, the second base is triethylamine. In some embodiments, the second base is N,N-diisopropylethylamine.

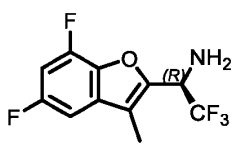
In some embodiments, adding a second base to mixture 1 and pyrimidine-2,5-diamine to mixture 1 is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 2 °C, or about 0 °C). In some embodiments, adding a second base to mixture 1 and pyrimidine-2,5-diamine to mixture 1 is performed at about 0 °C to about 5 °C. In some embodiments, adding a second base to mixture 1 and pyrimidine-2,5-diamine to mixture 1 is performed at about 0 °C to about 2 °C.

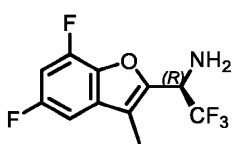
In some embodiments, after forming mixture 2, mixture 2 is warmed to about 20 °C to about 60 °C (e.g., about 20 °C to about 50 °C, about 20 °C to about 40 °C, about 25 °C to about 35 °C, or about 30 °C) over about 15 minutes to about 5 hours (e.g., about 1 hour to about 3 hours, or about 2 hours); then agitated at about 20 °C to about 60 °C (e.g., about 20 °C to about 50 °C, about 20 °C to about 40 °C, about 25 °C to about 35 °C, or about 30 °C) for about 1 hour to about 7 days (e.g., about 1 hour to about 2 days, about 5 hours to about 1 day, about 10 hours to about 18 hours,

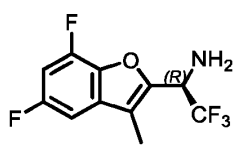
about 10 hours to about 14 hours, about 14 hours to about 18 hours, about 12 hours to about 16 hours, about 14 hours to about 16 hours, or about 16 hours) to form Compound 1.

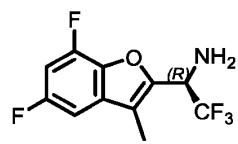
In some embodiments, Compound 1 is recrystallized from a solvent. In some embodiments, the solvent is a mixture of isopropyl acetate and heptane. In some embodiments, the ratio of isopropyl acetate to heptane is about 6:1 to about 4:2 (e.g., about 5:2). In some embodiments, after recrystallizing Compound 1, Compound 1 is rinsed with a mixture of isopropyl acetate and heptane, then water, then a mixture of isopropyl acetate and heptane. In some embodiments, after rinsing Compound 1, Compound 1 is dried. In some embodiments, drying Compound 1 comprises drying Compound 1 at a pressure lesser than atmospheric pressure. In some embodiments, drying Compound 1 comprises drying Compound 1 at ambient temperature.

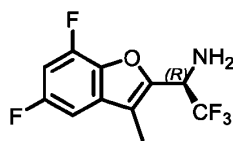
In some embodiments, contacting  with the carbonyl equivalent and

pyrimidine-2,5-diamine to form Compound 1 comprises adding  to the carbonyl equivalent and a base to form mixture 1', then adding pyrimidine-2,5-diamine to mixture

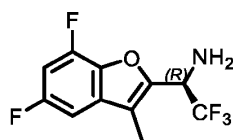
1' to form mixture 2'. In some embodiments,  is in the form of a salt. In

some embodiments,  is in the form of a salt, and contacting

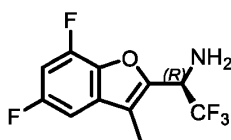
 with the carbonyl equivalent and pyrimidine-2,5-diamine to form



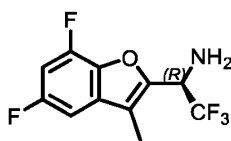
Compound 1 comprises adding to the carbonyl equivalent and a base to form mixture 1', then adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2'.



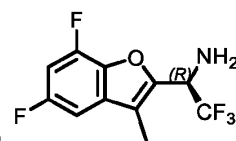
In some embodiments, salt is a hydrochloride salt.



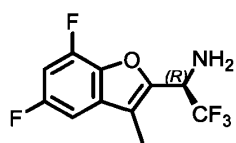
In some embodiments, adding to the carbonyl equivalent and a base to form mixture 1' is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.



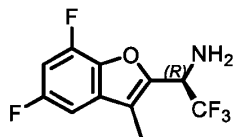
In some embodiments, adding to the carbonyl equivalent and a base to form mixture 1' is performed under an inert atmosphere. In some embodiments, the contacting is performed under nitrogen. In some embodiments, the contacting is performed under argon.



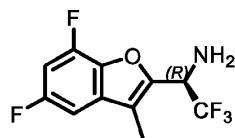
In some embodiments, the molar ratio of the carbonyl equivalent to is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3, about 2.0). In some embodiments, the molar ratio of the carbonyl equivalent to



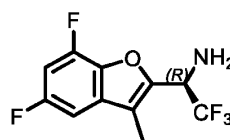
is about 1.05. In some embodiments, the molar ratio of the carbonyl



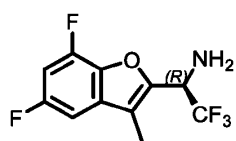
equivalent to is about 1.3. In some embodiments, the molar ratio of the



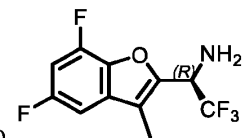
carbonyl equivalent to is about 2.0.



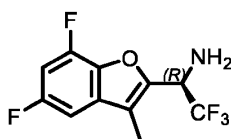
In some embodiments, the molar ratio of the base to is about 1.0 to about 5.0 (e.g., about 2.0 to about 5.0, about 2.0 to about 4.0, about 2.5 to about 3.5, about 3.0, or about 3.5. In some embodiments, the molar ratio of the sodium bicarbonate to



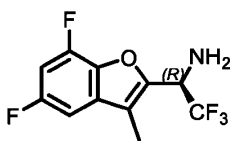
is about 3.0. In some embodiments, the molar ratio of the sodium



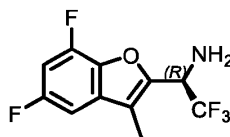
bicarbonate to is about 3.5.



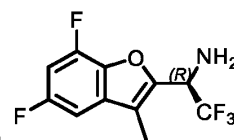
In some embodiments, adding to the carbonyl equivalent and a base to form mixture 1' is performed in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.



In some embodiments, adding to the carbonyl equivalent and a base to form mixture 1' is performed under an inert atmosphere. In some embodiments, the adding is performed under nitrogen. In some embodiments, the adding is performed under argon.



In some embodiments, adding to the carbonyl equivalent and a base is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or



about 0 °C). In some embodiments, adding the carbonyl equivalent to is performed at about 5 °C or lower.

In some embodiments, adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2' comprises adding a third base to mixture 1' and pyrimidine-2,5-diamine to mixture 1'. In some
 10 embodiments, adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2' comprises adding a third base to mixture 1' then pyrimidine-2,5-diamine to mixture 1'. In some embodiments, adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2' comprises adding aqueous sodium chloride to mixture 1', a third base to mixture 1', and pyrimidine-2,5-diamine to mixture 1'. In
 15 some embodiments, adding pyrimidine-2,5-diamine to mixture 1' to form mixture 2' comprises adding aqueous sodium chloride to mixture 1', a third base to mixture 1', then pyrimidine-2,5-diamine to mixture 1'. In some embodiments, the third base is selected from N,N-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene (DBU), and 1,5-diazabicyclo(4.3.0)non-5-ene (DBN). In some embodiments, the third base is triethylamine. In
 20 some embodiments, the third base is N,N-diisopropylethylamine.

In some embodiments, adding aqueous sodium chloride to mixture 1', the third base to mixture 1', and pyrimidine-2,5-diamine is performed at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C). In some embodiments, adding aqueous sodium chloride to mixture 1', the third base to mixture 1', and pyrimidine-2,5-diamine is performed at about 0 °C to about 5 °C.

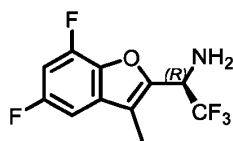
In some embodiments, after forming mixture 2, mixture 2 is agitated at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C) for about 1 hour to about 7 days (e.g., about 1 hour to about 4 days, about 5 hours to about 4 day, about 12 hours to about 3 days, about 1 day to about 3 days, about 24 hours to about 36 hours, about 30 hours to about 40 hours, about 10 hours to about 18 hours, about 10 hours to about 14 hours, about 14 hours to about 18 hours, about 12 hours to about 16 hours, about 14 hours to about 16 hours, or about 16 hours) to form Compound 1.

In some embodiments, Compound 1 is precipitated from tetrahydrofuran and heptane. In some embodiments, Compound 1 is precipitated from isopropanol and water. In some embodiments, Compound 1 is precipitated from tetrahydrofuran and heptane, then precipitated from isopropanol and water. In some embodiments, after precipitating Compound 1, Compound 1 is dried. In some embodiments, drying Compound 1 comprises drying Compound 1 at a pressure lesser than atmospheric pressure. In some embodiments, drying Compound 1 comprises drying Compound 1 at about 25 °C to about 70 °C (e.g., about 20 °C to about 25 °C, about 30 °C to about 60 °C, about 40 °C to about 50 °C, or about 45 °C). In some embodiments, drying Compound 1 comprises drying Compound 1 at about 45 °C. In some embodiments, drying Compound 1 comprises drying Compound 1 at a pressure lesser than atmospheric pressure at about 20 °C to about 25 °C.

In some embodiments, the carbonyl equivalent is selected from the group consisting of: phenyl chloroformate, phosgene, trichloromethyl chloroformate (i.e., diphosgene), bis(trichloromethyl) carbonate (i.e., triphosgene), 4-nitrophenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester.

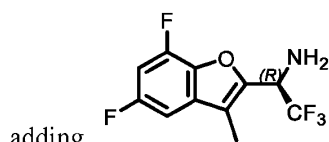
In some embodiments, the carbonyl equivalent is phenyl chloroformate.

In some embodiments, the carbonyl equivalent is R'OC(O)Cl, wherein R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl, nitro, or C1-6 alkoxy. In some embodiments, R' is phenyl. In some embodiments, R' is para-nitrophenyl.

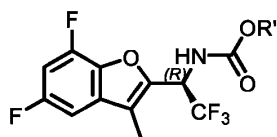


In some embodiments, contacting
2,5-diamine to form Compound 1 comprises:

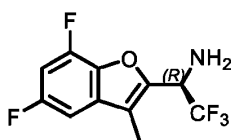
combining $R'OC(O)Cl$ with a base;



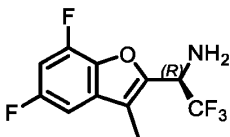
adding to the mixture of $R'OC(O)Cl$ and the base to form



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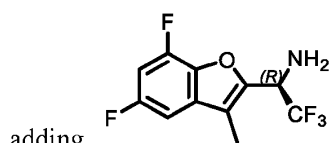


In some embodiments,
the salt is a hydrochloride salt.

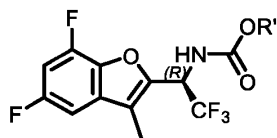


In some embodiments, contacting
2,5-diamine to form Compound 1 comprises:

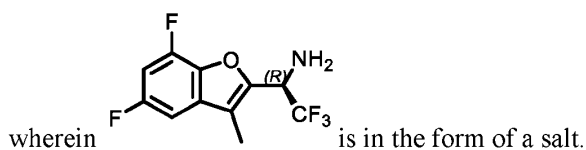
combining $R'OC(O)Cl$ with a base;



adding to the mixture of $R'OC(O)Cl$ and the base to form

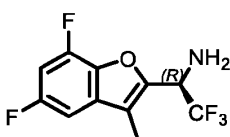


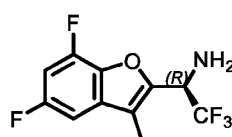
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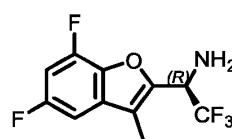


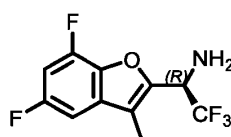
In some embodiments, combining $R'OC(O)Cl$ with a base comprises combining the base with a solvent, then adding the $R'OC(O)Cl$. In some embodiments, combining the base with a solvent, then adding the $R'OC(O)Cl$ comprises adding the $R'OC(O)Cl$ to the base and solvent at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C), then adding the $R'OC(O)Cl$.

In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.

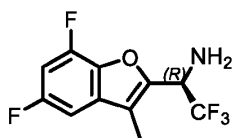
In some embodiments, adding  to the mixture of $R'OC(O)Cl$ and the base is performed at about 0 °C to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about

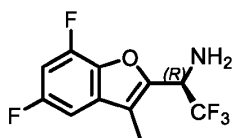
5 °C, or about 0 °C). In some embodiments, adding  to the mixture of $R'OC(O)Cl$ and the base is performed at about 0 °C to about 5 °C. In some embodiments, adding

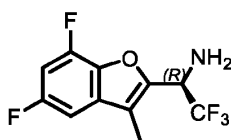
 to the mixture of $R'OC(O)Cl$ and the base is performed at lesser than 5 °C.

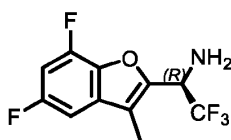
In some embodiments,  is added to the mixture of $R'OC(O)Cl$ and the base as a solution in a solvent. In some embodiments, the solvent comprises acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-

dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is a combination of tetrahydrofuran and water.



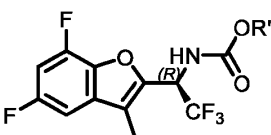
In some embodiments,  is added to the mixture of R'OC(O)Cl and the
 5 base over a time period of about 15 minutes to about 48 hours (e.g., about 15 minutes to about 2 hours, about 18 hours to about 30 hours, about 18 hours to about 24 hours, about 15 minutes to about 24 hours, about 1 hour to about 7 hours, about 1 hour to about 5 hours, about 2 hours to about 4 hours, about 3 hours to about 7 hours, about 24 hours, about 21 hours, about 18 hours, about 16 hours, about 12 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, or
 10 about 1 hour).

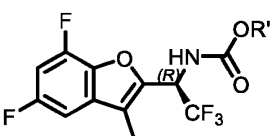


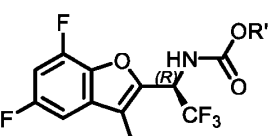
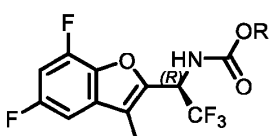
In some embodiments, adding  to the mixture of R'OC(O)Cl and the
 base forms mixture 3. In some embodiments, mixture 3 is agitated for about 15 minutes to about
 48 hours (e.g., about 15 minutes to about 2 hours, about 18 hours to about 30 hours, about 18 hours
 to about 24 hours, about 15 minutes to about 24 hours, about 1 hour to about 7 hours, about 1 hour
 15 to about 5 hours, about 2 hours to about 4 hours, about 3 hours to about 7 hours, about 24 hours, about 21 hours, about 18 hours, about 16 hours, about 12 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, or about 1 hour). In some embodiments, mixture 3 is agitated at about 0 to about 10 °C (e.g., about 0 °C to about 5 °C, about 0 °C to about 5 °C, or about 0 °C).

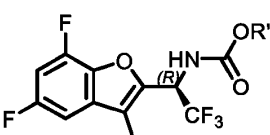
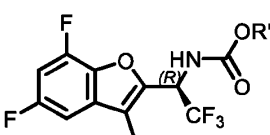
In some embodiments, agitating mixture 3 forms a biphasic mixture comprising an organic
 20 phase and an aqueous phase. In some embodiments, the organic phase is separated from the aqueous phase. In some embodiments, the organic phase was washed with an aqueous base. In some embodiments, the aqueous base is aqueous sodium bicarbonate. In some embodiments, the organic phase is concentrated at a pressure lesser than atmospheric pressure. In some
 25 embodiments, after concentrating the organic phase, an anti-solvent is added to the concentrated organic phase to form mixture 4. In some embodiments, the anti-solvent is hexane or heptane. In some embodiments, the anti-solvent is heptane.

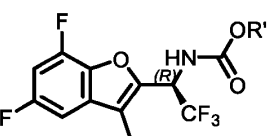
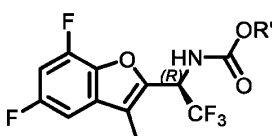
In some embodiments, after adding the anti-solvent, mixture 4 is concentrated at a pressure lesser than atmospheric pressure. In some embodiments, after concentrating mixture 4, a slurry is

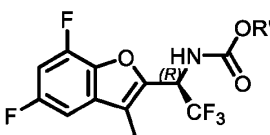
formed. In some embodiments, the slurry is filtered to provide . In some

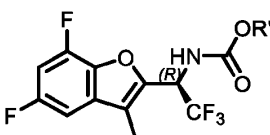
embodiments,  is rinsed with hexane or heptane (e.g., heptane). In some

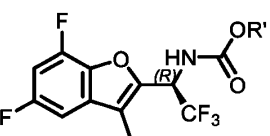
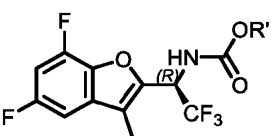
5  ,  is dried. In some

embodiments, drying  comprises drying  at a pressure lesser than atmospheric pressure. In some embodiments, drying

 comprises drying  at about 25 °C to about 70 °C (e.g., about 30 °C to about 60 °C, about 40 °C to about 50 °C, about 40 °C to about 45 °C, about 45

10 °C to about 50 °C, or about 45 °C). In some embodiments, drying 

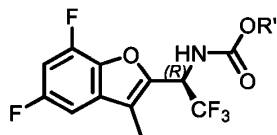
comprises drying  at about 45 °C. In some embodiments, drying

 comprises drying  at about 40 °C to about 45

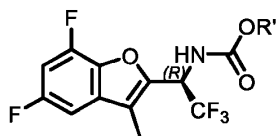
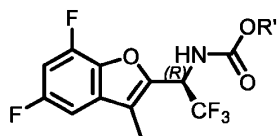
°C. In some embodiments, drying



comprises drying



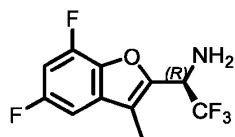
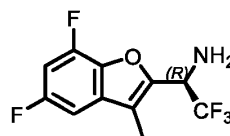
at about 45 °C to about 50 °C. In some embodiments, drying



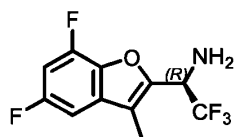
comprises drying under an inert atmosphere

(e.g., under nitrogen).

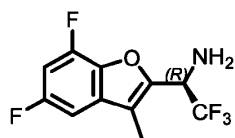
In some embodiments, the molar ratio of the $R'OC(O)Cl$ to $FeCl_3$ is about 1.0 to about 4.0 (e.g., about 1.0 to about 3.0, about 1.0 to about 2.0, about 1.0 to about 1.5, about 1.0 to about 1.4, about 1.0 to about 1.1, about 1.2 to about 1.4, about 1.05, about 1.1, about 1.2, about 1.3, about 2.0). In some embodiments, the molar ratio of the $R'OC(O)Cl$ to



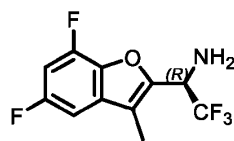
is about 1.05. In some embodiments, the molar ratio of the R'OC(O)Cl to



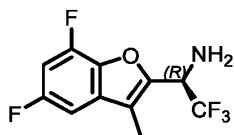
is about 1.3. In some embodiments, the molar ratio of the R'OC(O)Cl to



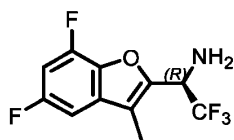
is about 2.0.



In some embodiments, the molar ratio of the base to is about 1.0 to about 5.0 (e.g., about 1.0 to about 3.0, about 2.0 to about 5.0, about 2.0 to about 4.0, about 2.5 to about 3.5, about 2.2, about 3.0, or about 3.5. In some embodiments, the molar ratio of the sodium

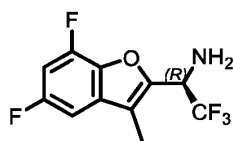


bicarbonate to is about 3.0. In some embodiments, the molar ratio of the

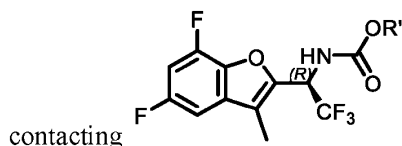


sodium bicarbonate to is about 3.5.

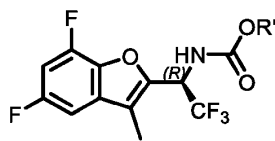
In some embodiments, the base is selected from sodium bicarbonate, potassium carbonate, potassium phosphate, sodium carbonate, potassium bicarbonate, N,N-diisopropylethylamine, triethylamine, trimethylamine, and citric acid. In some embodiments, the base is sodium bicarbonate.



In some embodiments, contacting with R'OC(O)Cl and pyrimidine-2,5-diamine to form Compound 1 comprises:

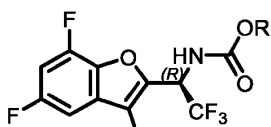


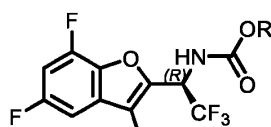
contacting with pyrimidine-2,5-diamine to form Compound 1.

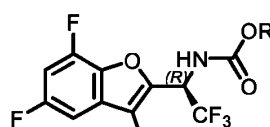


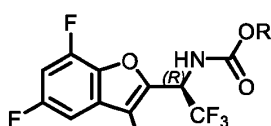
In some embodiments, contacting with pyrimidine-2,5-diamine to form Compound 1 is performed in the presence of a third base. In some embodiments, the third base is selected from N,N-diisopropylethylamine (DIPEA), triethylamine (TEA), 1,8-diazabicycloundec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), sodium bicarbonate,

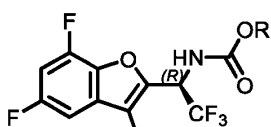
potassium carbonate, and potassium phosphate. In some embodiments, the third base is triethylamine. In some embodiments, the third base is N,N-diisopropylethylamine.

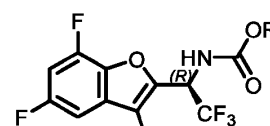
In some embodiments, contacting  with pyrimidine-2,5-diamine

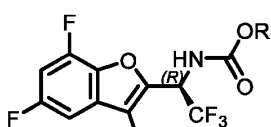
to form Compound 1 comprises adding  to pyrimidine-2,5-diamine. In

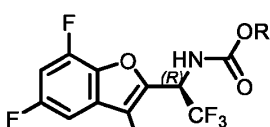
5 some embodiments, contacting  with pyrimidine-2,5-diamine to form

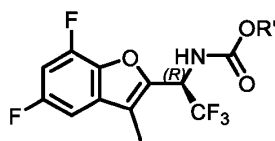
Compound 1 comprises adding  to pyrimidine-2,5-diamine in the absence of a base.

In some embodiments, contacting  with pyrimidine-2,5-diamine

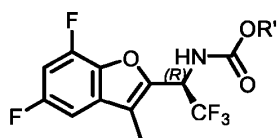
to form Compound 1 comprises adding pyrimidine-2,5-diamine to 

10 In some embodiments, contacting  with pyrimidine-2,5-diamine

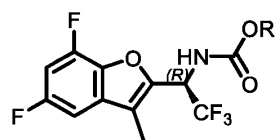
to form Compound 1 comprises adding pyrimidine-2,5-diamine to  in the absence of a base.



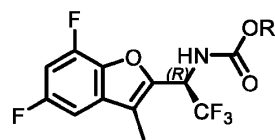
In some embodiments, contacting with pyrimidine-2,5-diamine to form Compound 1 is performed in N,N-dimethylacetamide. In some embodiments, contacting



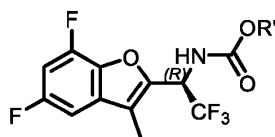
with pyrimidine-2,5-diamine to form Compound 1 is performed under an



inert atmosphere. In some embodiments, contacting with pyrimidine-2,5-diamine to form Compound 1 is performed under nitrogen. In some embodiments, the N,N-dimethylacetamide comprises less than 2% water by volume (e.g., less than 1.5% water by volume, less than 1% water by volume, less than 0.5% water by volume, less than 0.3% water by volume, less than 0.2% water by volume, less than 0.1% water by volume, less than 0.05% water by volume, or less than 0.02% water by volume). In some embodiments, the N,N-dimethylacetamide

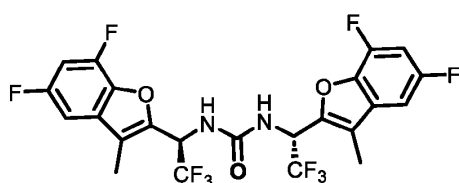


In some embodiments, after adding to pyrimidine-2,5-diamine or



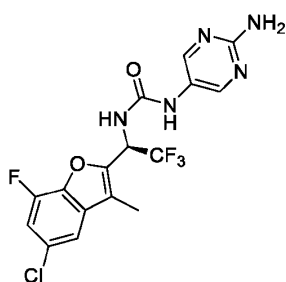
after adding pyrimidine-2,5-diamine to , mixture 5 is formed. In some embodiments, mixture 5 is agitated for about 1 minute to about 48 hours (e.g., 1 minute to about 24 hours, 1 minute to about 12 hours, 1 minute to about 6 hours, 1 minute to about 3 hours, about 30 minutes to about 1.5 hours, about 8 hours to about 24 hours, about 12 hours to about 13 hours, about 3 hours, or about 1 hour). In some embodiments, mixture 5 is agitated for about 12 hours to about 13 hours. In some embodiments, mixture 5 is agitated for about 3 hours. In some embodiments, mixture 5 is agitated for about 1 hour.

In some embodiments, Compound 1 has a purity of at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 98%, at least 99%, about 98%, about 98.5%, about 99%, about 99.5%). In some embodiments, less than 10% (e.g., less than 7%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, less than 0.1%, less than 0.6%, about 1%, about 1.3%, about 0.05%, or no detectable amount) of Impurity 1 is present as an impurity with Compound 1.



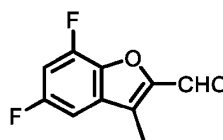
(Impurity 1).

In some embodiments, less than 10% (e.g., less than 7%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5%, less than 0.2%, less than 0.1%, less than 0.6%, about 1%, about 1.3%, about 0.05%, or no detectable amount) of Impurity 2 is present as an impurity with Compound 1.

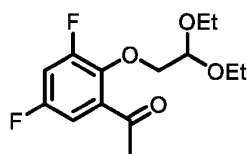


(Impurity 2).

In some embodiments, the process comprises preparing



by contacting

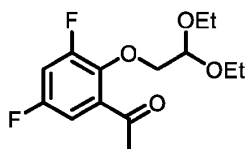


with an acid.

In some embodiments, the acid is a protic acid. In some embodiments, the acid is a Lewis acid. In some embodiments, the acid is selected from acetic acid, hydrogen chloride, sulfuric acid,

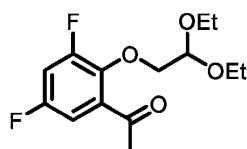
phosphoric acid, nitric acid, aluminum chloride, zinc chloride, trimethylaluminum, iron (III) bromide, and boron trifluoride (e.g., boron trifluoride dietherate).

In some embodiments, the acid is acetic acid.



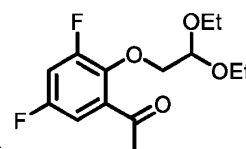
In some embodiments, contacting

with an acid comprises adding

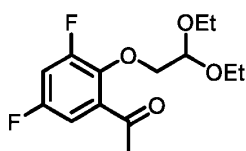


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to the acid. In some embodiments, contacting



with

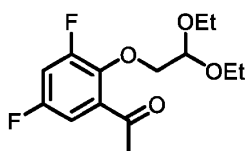


an acid comprises contacting

with the acid in a solvent. In some

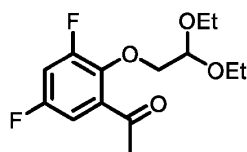
embodiments, the solvent is acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is N,N-dimethylformamide. In some embodiments,

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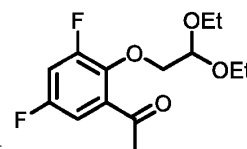


adding

to the acid forms mixture 11. In some embodiments, after adding



to the acid, mixture 11 is heated at about 80 °C to about 160 °C (e.g., about 90 °C to about 150 °C, about 100 °C to about 140 °C, about 110 °C to about 130 °C, about 115 °C

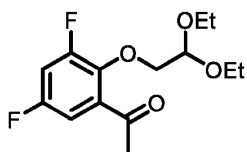


to about 125 °C, or about 120 °C). In some embodiments, after adding

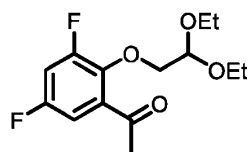
to

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the acid, mixture 11 is heated at about 120 °C. In some embodiments, after adding



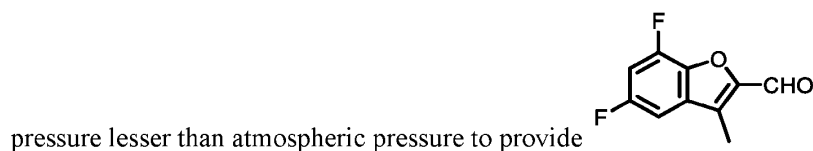
to the acid, mixture 11 is agitated for about 15 minutes to about 2 days (e.g., about 30 minutes to about 24 hours, about 2 hours to about 16 hours, about 4 hours to about 12 hours, about 6 hours to about 10 hours, about 7 hours to about 9 hours, or about 8 hours). In some



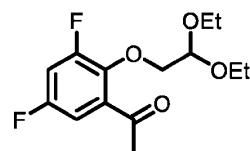
embodiments, after adding to the acid, mixture 11 is agitated for about 8 hours.

In some embodiments, after agitating mixture 11, water is added to mixture 11. In some embodiments, after adding water to mixture 11, a solvent is added to mixture 11 to form mixture 12. In some embodiments, mixture 12 is biphasic. In some embodiments, mixture 12 comprises an organic phase and an aqueous phase. In some embodiments, the organic phase is isolated and washed with an aqueous base. In some embodiments, the aqueous base is aqueous potassium carbonate (e.g., 15% aqueous potassium carbonate by weight). In some embodiments, after washing the organic phase with the aqueous base, the organic phase is agitated with water and $\text{Na}_2\text{S}_2\text{O}_4$. In some embodiments, the organic phase is agitated with water and $\text{Na}_2\text{S}_2\text{O}_4$ for about 5 minutes to about 2 days (e.g., about 1 hour to about 24 hours, about 4 hours to about 18 hours, about 6 hours to about 10 hours, or about 8 hours). In some embodiments, the organic phase is agitated with water and $\text{Na}_2\text{S}_2\text{O}_4$ for about 8 hours. In some embodiments, agitating the organic phase with water and $\text{Na}_2\text{S}_2\text{O}_4$ forms a solid. In some embodiments, the solid is separated from the solvent and water. In some embodiments, the solid is combined with ethyl acetate to form a solution, and the pH of the solution is adjusted to about 8 to about 11 (e.g., about 9 to about 10, about 9, or about 10) and then agitated for about 5 minutes to about 1 day (e.g., about 1 hour to about 10 hours, about 3 hours to about 7 hours, about 4 hours to about 6 hours, or about 5 hours) to form a biphasic mixture. In some embodiments, the biphasic mixture comprises an organic

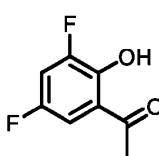
phase and an aqueous phase. In some embodiments, the organic phase concentrated under at a



In some embodiments, the process comprises preparing



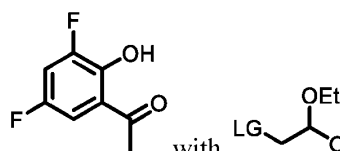
contacting



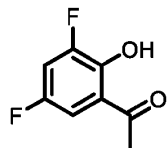
with $\text{LG}-\text{CH}_2-\text{CH}(\text{OEt})_2$; wherein LG is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl.

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In some embodiments, contacting



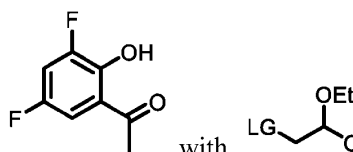
with $\text{LG}-\text{CH}_2-\text{CH}(\text{OEt})_2$ comprises contacting



with $\text{LG}-\text{CH}_2-\text{CH}(\text{OEt})_2$ and a base. In some embodiments, the base is selected from sodium bicarbonate, potassium carbonate, potassium phosphate, sodium carbonate, potassium bicarbonate, N,N-diisopropylethylamine, triethylamine, and citric acid. In some embodiments, the

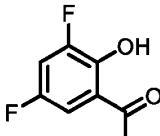
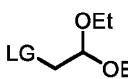
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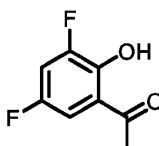
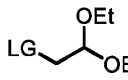
In some embodiments, contacting

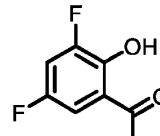
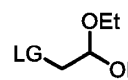


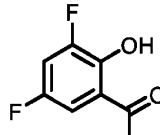
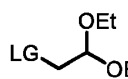
with $\text{LG}-\text{CH}_2-\text{CH}(\text{OEt})_2$ and a base is performed in a solvent. In some embodiments, the solvent is acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is N,N-dimethylformamide.

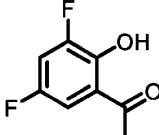
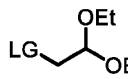
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In some embodiments, contacting  with  and a base comprises

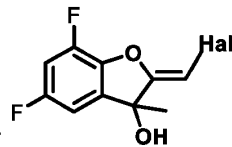
contacting  with , a base, and sodium iodide.

In some embodiments, contacting  with , a base, and sodium iodide is performed at about 80 °C to about 160 °C (e.g., about 90 °C to about 150 °C, about 100 °C to about 140 °C, about 110 °C to about 130 °C, about 115 °C to about 125 °C, or about 120 °C).

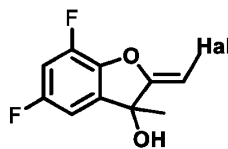
In some embodiments, contacting  with , a base, and sodium iodide is performed at about 120 °C.

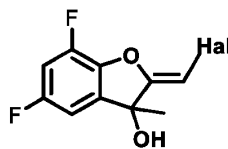
In some embodiments, adding  to , a base, and sodium iodide forms mixture 13. In some embodiments, mixture 13 is agitated for about 15 minutes to about 2 days (e.g., about 30 minutes to about 24 hours, about 2 hours to about 16 hours, about 2 hours to about 8 hours, about 3 hours to about 7 hours, about 4 hours to about 6 hours, or about 5 hours). In some embodiments, mixture 13 is agitated for about 5 hours.

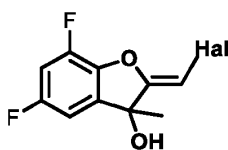
In some embodiments, the process comprises preparing the compound of Formula (I-v) by

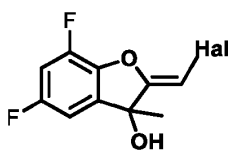
contacting a compound of  with an acid; wherein Hal is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl. In some embodiments, Hal is chloro. In some

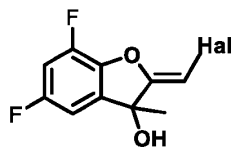
embodiments, the acid is sulfuric acid, hydrogen chloride, nitric acid, phosphoric acid, or hydrogen bromide. In some embodiments, the acid is sulfuric acid.



In some embodiments, contacting  with the acid is performed in a solvent. In some embodiments, the solvent comprises methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some
 10 embodiments, the solvent is methyl tert-butyl ether.

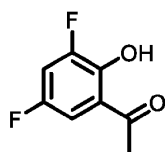


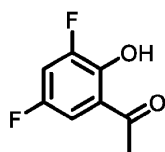
In some embodiments, contacting  with the acid is performed at about 10 °C to about 60 °C (e.g., about 15 °C to about 55 °C, about 15 °C to about 35 °C, about 20 °C to about 30 °C, about 23 °C to about 27 °C, or about 25 °C). In some embodiments, contacting

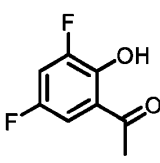


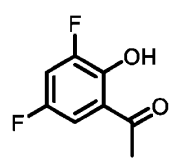
15 with the acid is performed at about 25 °C.

In some embodiments, the process comprises preparing the compound of Formula (I-viii)

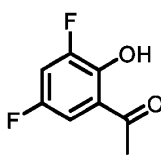


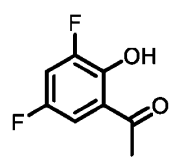
by contacting  with . In some embodiments, Z is O. In some embodiments, R² is C1-C6 alkyl. In some embodiments, R² is methyl.

In some embodiments, contacting  with  comprises contacting

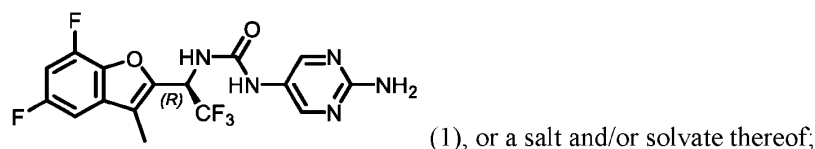
 with  and a base. In some embodiments, the base is potassium tert-butoxide. In some embodiments, the contacting is performed in a solvent.

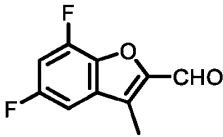
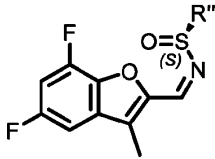
In some embodiments, the solvent comprises methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropyl alcohol, methanol, ethanol, tetrahydrofuran, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether.

In some embodiments, contacting  with  and a base is performed at about 10 °C to about 60 °C (e.g., about 15 °C to about 55 °C, about 15 °C to about 35 °C, about 20 °C to about 30 °C, about 23 °C to about 27 °C, or about 25 °C). In some embodiments, contacting

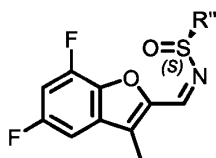
 with  and a base is performed at about 25 °C.

Some embodiments provide a process of preparing Compound 1, having the structure:

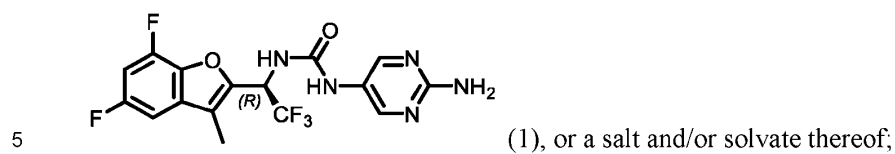


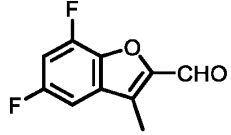
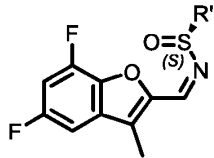
comprising contacting  with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{O}}{\text{S}}^{(S)}}-\text{R}''$ to form ,

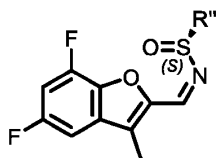
wherein R'' is C1-C6 alkyl; and

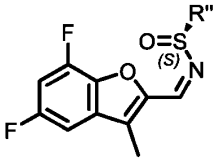
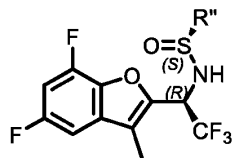
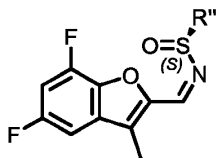
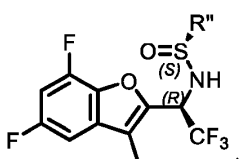
reacting  to form Compound 1.

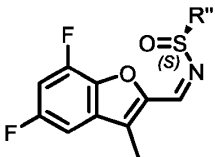
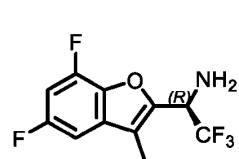
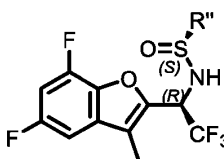
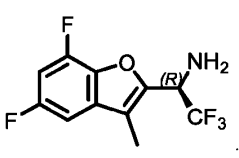
Some embodiments provide Compound 1, having the structure:

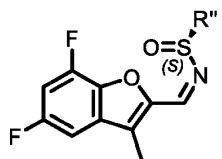
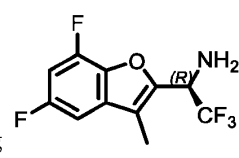


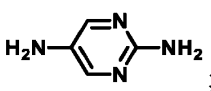
prepared by a process comprising contacting  with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{O}}{\text{S}}^{(S)}}-\text{R}''$ to form , wherein R'' is C1-C6 alkyl; and

reacting  to form Compound 1.

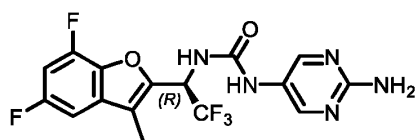
In some embodiments, reacting  to form Compound 1 comprises preparing  by contacting  with a trifluoromethylating reagent to form ; wherein R'' is C1-C6 alkyl.

In some embodiments, reacting  to form Compound 1 comprises preparing  by contacting  with an acid to form .

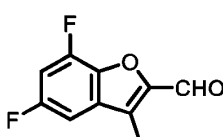
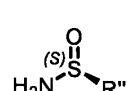
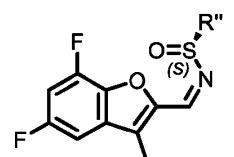
In some embodiments, reacting  to form Compound 1 comprises contacting  with (i) a carbonyl equivalent; and

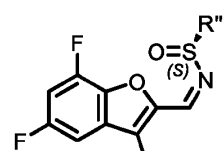
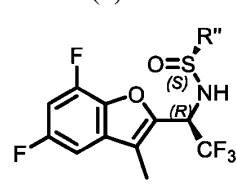
(ii) pyrimidine-2,5-diamine having the structure  ;
to form Compound 1.

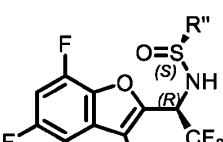
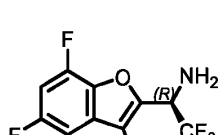
Some embodiments provide a process of preparing Compound 1, having the structure:

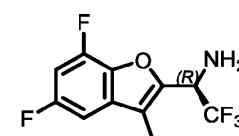
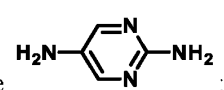


(1), or a salt and/or solvate thereof, comprising:

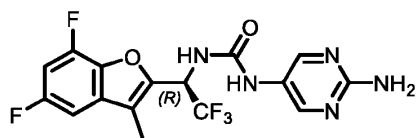
5 (a) contacting  with  to form  ,
wherein R'' is C1-C6 alkyl;

(b) contacting  with a trifluoromethylating reagent to form  ;

(c) contacting  with HCl to form  ; and

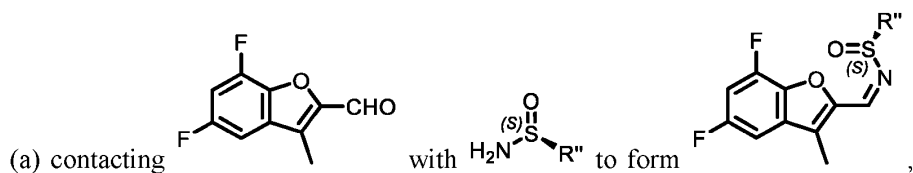
10 (d) contacting  with (i) a carbonyl equivalent; and (ii) pyrimidine-2,5-diamine having the structure  ;
to form Compound 1.

Some embodiments provide Compound 1, having the structure:



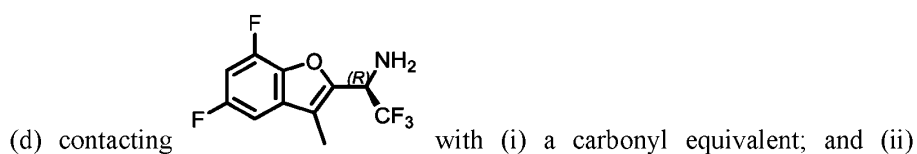
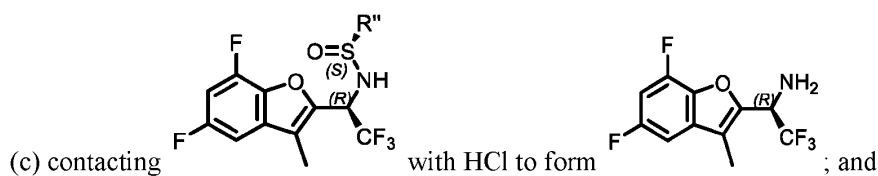
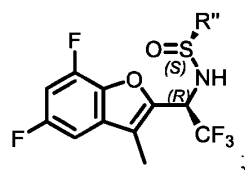
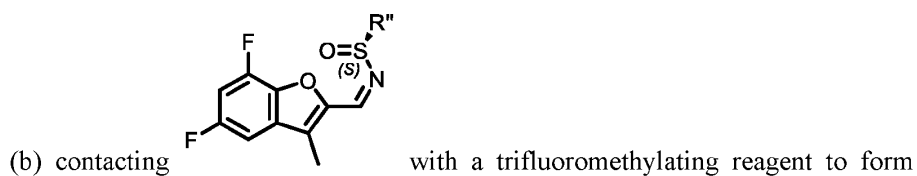
(1), or a salt and/or solvate thereof; prepared by a process

comprising:



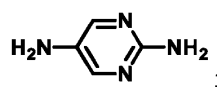
5

wherein R'' is C1-C6 alkyl;



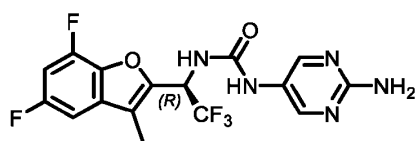
10

pyrimidine-2,5-diamine having the structure

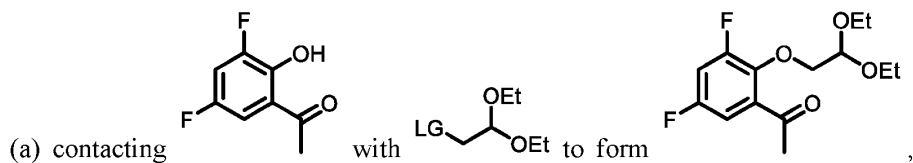


to form Compound 1.

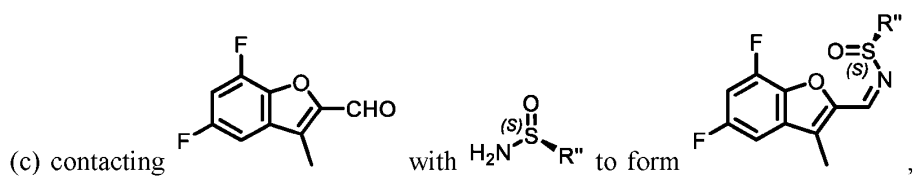
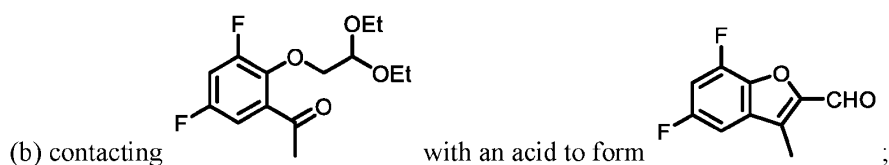
Some embodiments provide a process of preparing Compound 1, having the structure:



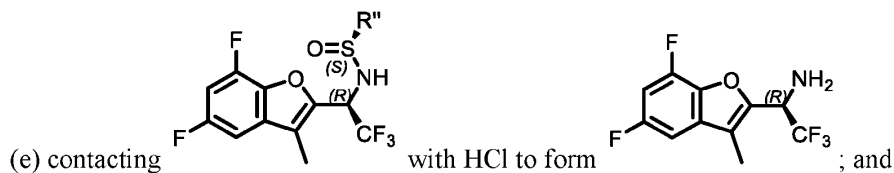
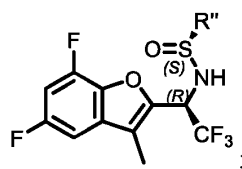
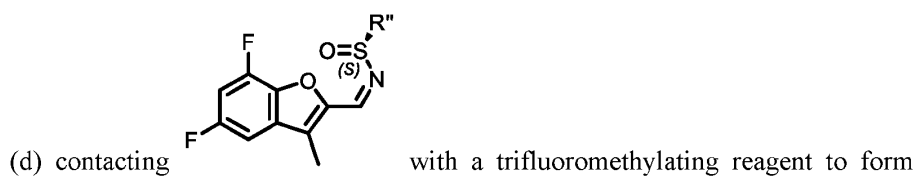
(1), or a salt and/or solvate thereof; comprising:

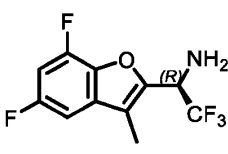


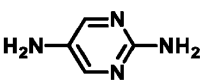
wherein LG is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;



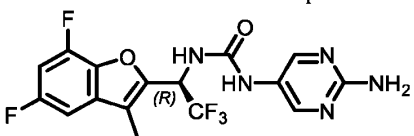
wherein R'' is C1-C6 alkyl;



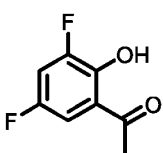
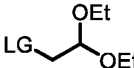
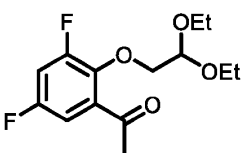
(f) contacting  with (i) a carbonyl equivalent; and (ii)

pyrimidine-2,5-diamine having the structure  ;
to form Compound 1.

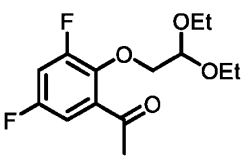
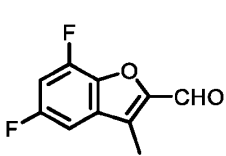
Some embodiments provide Compound 1, having the structure:

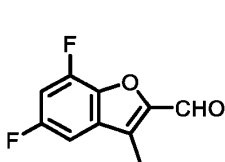
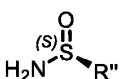
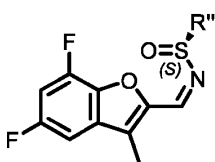
5  (1), or a salt and/or solvate thereof;

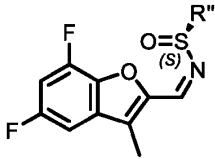
prepared by a process comprising:

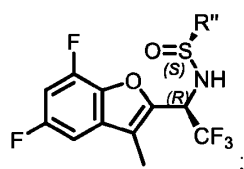
(a) contacting  with  to form  ,

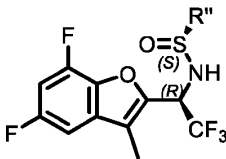
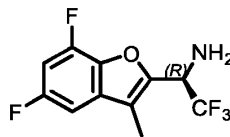
wherein LG is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;

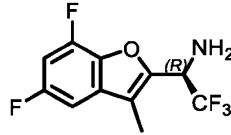
(b) contacting  with an acid to form  ;

10 (c) contacting  with  to form  ,
wherein R'' is C1-C6 alkyl;

(d) contacting  with a trifluoromethylating reagent to form

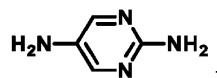


(e) contacting  with HCl to form ; and

(f) contacting  with (i) a carbonyl equivalent; and (ii)

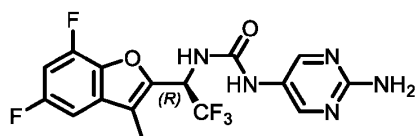
5

pyrimidine-2,5-diamine having the structure

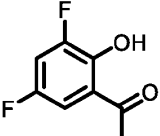
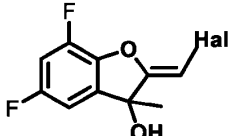


to form Compound 1.

Some embodiments provide a process of preparing Compound 1, having the structure:

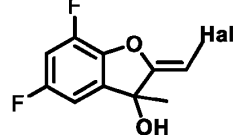
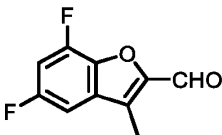


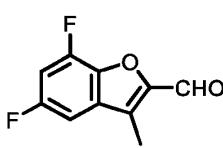
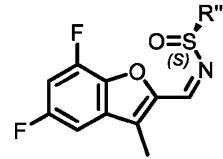
(1), or a salt and/or solvate thereof; comprising:

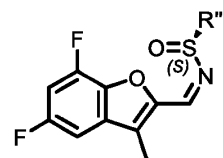
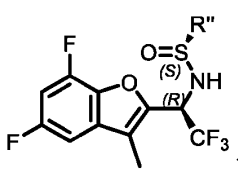
(a) contacting  with  to form  ,

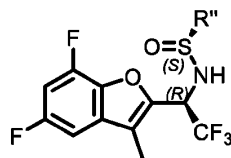
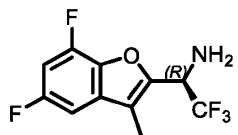
10

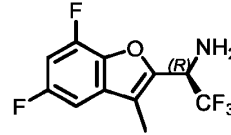
wherein Hal is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;

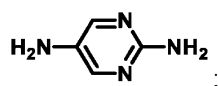
(b) contacting  with an acid to form  ;

(c) contacting  with $\text{H}_2\text{N}-\overset{\text{O}}{\underset{\text{(S)}}{\parallel}}\text{S}-\text{R}''$ to form ,
wherein R'' is C1-C6 alkyl;

(d) contacting  with a trifluoromethylating reagent to form ;

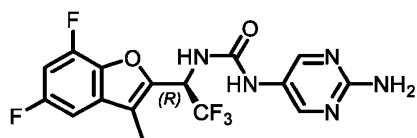
5 (e) contacting  with HCl to form ; and

(f) contacting  with (i) $\text{R}'\text{OC(O)Cl}$, wherein R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl or C1-6 alkoxy; and (ii) pyrimidine-2,5-diamine having the structure

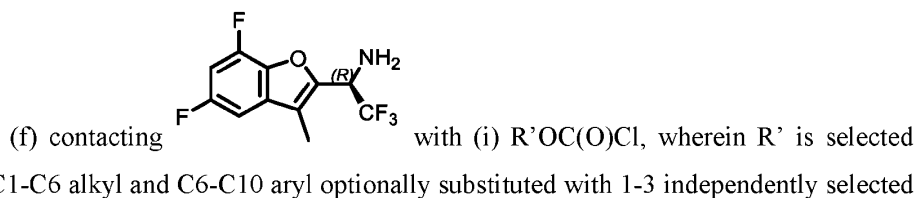
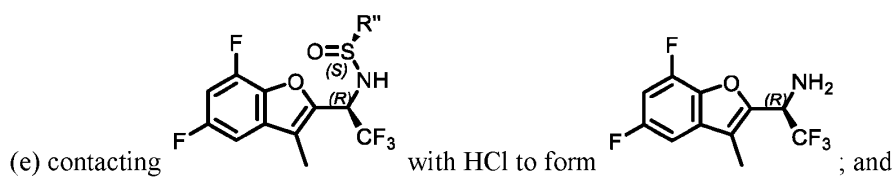
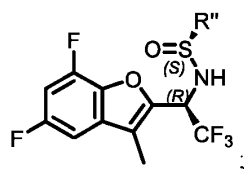
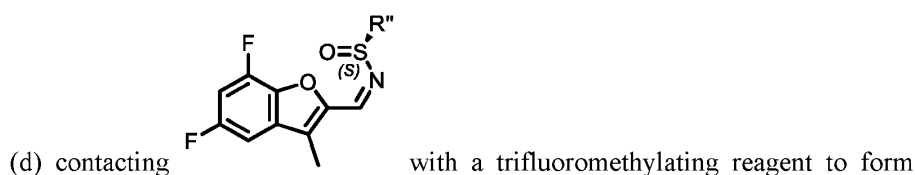
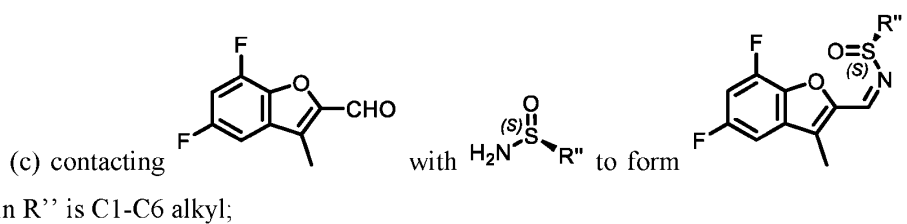
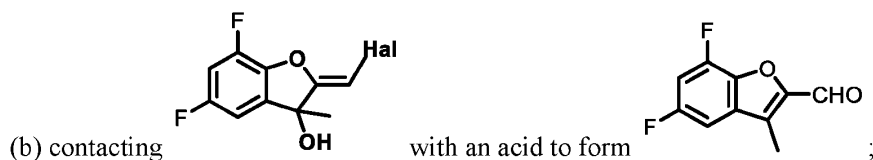
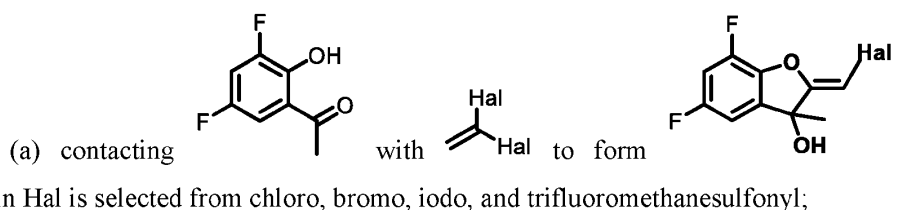


10 to form Compound 1.

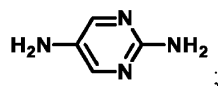
Some embodiments provide Compound 1, having the structure:



(1), or a salt and/or solvate thereof; prepared by a process comprising:



C1-6 alkyl or C1-6 alkoxy; and (ii) pyrimidine-2,5-diamine having the structure



to form Compound 1.

In some embodiments, the process comprises preparing pyrimidine-2,5-diamine by contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen. In some embodiments, the palladium on carbon is palladium adsorbed to carbon. In some embodiments, contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen forms mixture 14. In some embodiments, In some embodiments, contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen is performed at a pressure of about 15 to about 90 psi (e.g., about 25 to about 70 psi, about 55 to about 75 psi, about 60 to about 70 psi, about 35 to about 55 psi, about 40 to about 50 psi, about 60 to about 80 psi, about 65 to about 75 psi, about 40 psi, about 50 psi, about 60 psi, about 70 psi, or about 80 psi). In some embodiments, contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen is performed at a pressure of about 40 to about 50 psi. In some embodiments, contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen is performed at a pressure of about 60 to about 70 psi. In some embodiments, contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen is performed at a pressure of about 70 psi.

In some embodiments, contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen comprises contacting 5-nitropyrimidine-2-amine with palladium on carbon in a solvent under an atmosphere of hydrogen. In some embodiments, the solvent comprises acetonitrile, tetrahydrofuran, methanol, ethanol, isopropanol, or any combination thereof. In some embodiments, the solvent is acetonitrile, tetrahydrofuran, methanol, ethanol, isopropanol, or any combination thereof. In some embodiments, the solvent comprises tetrahydrofuran and methanol.

In some embodiments, the palladium on carbon comprises water. In some embodiments, the palladium on carbon comprises about 40% to about 60% water (e.g., about 45% to about 55% water or about 50% by weight water). In some embodiments, the palladium on carbon comprises water. In some embodiments, the palladium on carbon comprises about 50% by weight water.

In some embodiments, the palladium on carbon is about 5% to about 20% (e.g., about 5%, about 8% to about 12%, about 9% to about 11%, about 10%, about 13% to about 17%, about 14% to about 16%, about 15%, or about 20%) weight/weight palladium on carbon. In some embodiments, the palladium on carbon is about 10% weight/weight palladium on carbon. In some
5 embodiments, the palladium on carbon is about 15% weight/weight palladium on carbon.

In some embodiments, the weight percentage of the palladium in the palladium on carbon to the 5-nitropyrimidine-2-amine is about 1% to about 50% (e.g., about 1% to about 40%, about 1% to about 30%, about 1% to about 20%, about 5% to about 25%, about 10% to about 50%, about 8% to about 12%, about 13% to about 17%, about 10%, about 15%, or about 20%). In some
10 embodiments, the weight percentage of the palladium in the palladium on carbon to the 5-nitropyrimidine-2-amine is about 10%. In some embodiments, the weight percentage of the palladium in the palladium on carbon to the 5-nitropyrimidine-2-amine is about 20%.

In some embodiments, contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen comprises agitating the 5-nitropyrimidine-2-amine with the
15 palladium on carbon under the atmosphere of hydrogen. In some embodiments, the agitating is performed for about 1 minute to about 48 hours (e.g., about 1 minute to about 12 hours, about 30 minutes to about 1.5 hours, about 30 minutes to about 6 hours, about 1 hour to about 4 hours, about 2.5 hours to about 3.5 hours, about 3.5 hours to about 4.5 hours, about 1 hour to about 6 hours, about 2 hours to about 4 hours, about 3 hours to about 5 hours, about 1 hour, about 2 hours, about
20 3 hours, about 4 hours, about 5 hours, or about 6 hours). In some embodiments, the agitating is performed for about 1 hour. In some embodiments, the agitating is performed for about 2 hours. In some embodiments, the agitating is performed for at least about 4 hours.

In some embodiments, the agitating is performed at about 20 °C to about 90 °C (e.g., about 30 °C to about 80 °C, about 40 °C to about 70 °C, about 35 °C to about 55 °C, about 40 °C to about
25 55 °C, about 40 °C to about 50 °C, about 50 °C to about 60 °C, about 60 °C to about 70 °C, about 35 °C, about 40 °C, about 45 °C, about 50 °C, about 55 °C, about 60 °C, or about 70 °C).

In some embodiments, the process comprises filtering mixture 14 (e.g., through a layer of diatomaceous earth) to form a filtrate. In some embodiments, the process comprises reducing the volume of the filtrate at a pressure lesser than atmospheric pressure to form a concentrate. In some
30 embodiments, the process comprises adding a solvent to the concentrate to form mixture 14'. In some embodiments, the solvent is isopropyl acetate. In some embodiments, the process comprises

cooling mixture 14' to about -10 °C to about 20 °C (e.g., about -5 °C to about 5 °C, about 0 °C to about 10 °C, about 0 °C to about 5 °C, about 0 °C to about 2 °C, or about 0 °C). In some embodiments, a precipitate forms in mixture 14' after cooling. In some embodiments, the process comprises filtering mixture 14' to provide pyrimidine-2,5-diamine.

5 In some embodiments, the process comprises dissolving the pyrimidine-2,5-diamine in a solvent to form a slurry. In some embodiments, the solvent comprises methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropanol, methanol, ethanol, tetrahydrofuran, acetonitrile, water, or any combination thereof. In some embodiments, the solvent is methyl tert-butyl ether, acetone, chloroform, ethyl acetate, dichloromethane, isopropanol,
10 methanol, ethanol, tetrahydrofuran, acetonitrile, water, or any combination thereof. In some embodiments, the solvent comprises isopropanol and water. In some embodiments, the solvent is isopropanol and water. In some embodiments, the solvent comprises about 40% to about 99% isopropanol and about 1% to about 40% water (e.g., about 70% to about 97% isopropanol and about 3% to about 30% water; about 80% to about 95% isopropanol and about 5% to about 20%
15 water; or about 90% isopropanol and about 10% water). In some embodiments, the solvent comprises about 90% isopropanol and about 10% water. In some embodiments, the slurry is heated at about 30 °C to about 90 °C (e.g., about 40 °C to about 90 °C, about 50 °C to about 80 °C, about 55 °C to about 75 °C, about 60 °C to about 70 °C, about 50 °C to about 60 °C, about 70 °C to about 80 °C, about 60 °C, about 65 °C, or about 70 °C). In some embodiments, the slurry is
20 heated at about 60 °C to about 70 °C. In some embodiments, the slurry is heated for about 1 minute to about 48 hours (e.g., about 1 minute to about 36 hours, about 1 minute to about 24 hours, about 1 minute to about 2 hours, about 1 hour to about 12 hours, about 30 minutes to about 1.5 hours, about 45 minutes to about 1.25 hours, or about 1 hour). In some embodiments, the slurry is heated for about 1 hour. In some embodiments, the process comprises cooling the slurry after heating the
25 slurry. In some embodiments, cooling the slurry comprises cooling the slurry at about -20 °C to about 30 °C (e.g., about -10 °C to about 20 °C, about -5 °C to about 15 °C, about 0 °C to about 10 °C, about 0 °C, about 5 °C, or about 10 °C). In some embodiments, cooling the slurry comprises cooling the slurry to about 0 °C to about 10 °C. In some embodiments, cooling the slurry comprises cooling the slurry for about 1 minute to about 72 hours (e.g., about 1 minute to about 48 hours,
30 about 1 hour to about 36 hours, about 2 hours to about 24 hours, about 3 hours to about 18 hours, about 4 hours to about 12 hours, about 6 hours to about 10 hours, about 7 hours to about 9 hours,

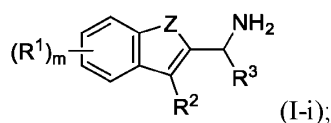
about 7.5 hours to about 8.5 hours, about 8 hours, at least 1 hour, at least 4 hours, at least 6 hours, at least 8 hours, at least 10 hours, or at least 12 hours). In some embodiments, cooling the slurry comprises cooling the slurry for at least 8 hours. In some embodiments, the process comprises filtering the slurry after cooling the slurry to provide recrystallized pyrimidine-2,5-diamine. In some embodiments, the process comprises drying the recrystallized pyrimidine-2,5-diamine at a pressure lesser than atmospheric pressure. In some embodiments, the process comprises heating the recrystallized pyrimidine-2,5-diamine at a temperature of about 20 °C to about 70 °C (e.g., about 30 °C to about 60 °C, about 40 °C to about 50 °C, about 40 °C, or about 50 °C). In some embodiments, the process comprises heating the recrystallized pyrimidine-2,5-diamine at a temperature of about 40 °C to about 50 °C.

In some embodiments of the compounds, methods, and processes described herein, Formula (I) is present in the form of a salt. In some embodiments of the compounds, methods, and processes described herein, Formula (I) is present in the form of a solvate. In some embodiments of the compounds, methods, and processes described herein, Formula (I) is present in the form of a salt of a solvate. In some embodiments of the compounds, methods, and processes described herein, Compound 1 is present in the form of a salt. In some embodiments of the compounds, methods, and processes described herein, Compound 1 is present in the form of a solvate. In some embodiments of the compounds, methods, and processes described herein, Compound 1 is present in the form of a salt of a solvate. In some embodiments, the salt is a pharmaceutically acceptable salt. In some embodiments, the solvate is a pharmaceutically acceptable solvate.

In some embodiments, Compound 1 is present in the form of a solvate. In some embodiments, Compound 1 is present in the form of a free base solvate. In some embodiments, Compound 1 is present in the form of a hydrate. In some embodiments, Compound 1 is present in the form of a free base hydrate. In some embodiments, Compound 1 is present in the form of a hemihydrate. In some embodiments, Compound 1 is present in the form of a free base hemihydrate.

Compounds

Some embodiments provide a compound of Formula (I-i):



wherein:

Z is O or NR^x;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

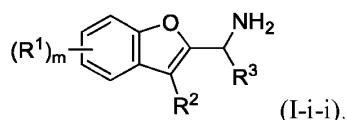
5 each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

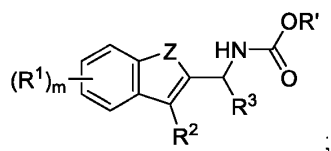
R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro; and

10 R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl.

In some embodiments, the compound of Formula (I-i) is a compound of Formula (I-i-i):



Some embodiments provide a compound of Formula (I-i-a)



15

wherein:

Z is O or NR^x;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

20 each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

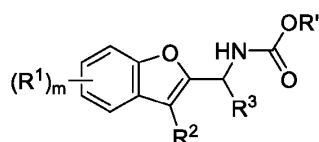
m is 0, 1, 2, or 3;

R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

25 R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl; and

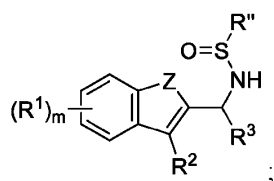
R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl or C1-6 alkoxy.

In some embodiments, the compound of Formula (I-i-a) is a compound of Formula (I-i-a-i)



5

Some embodiments provide a compound of Formula (I-iii)



wherein:

Z is O or NR^x;

10

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

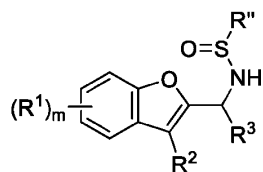
15

R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl; and

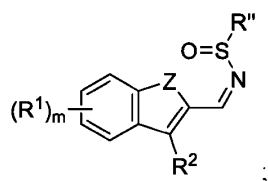
R'' is C1-C6 alkyl.

In some embodiments, the compound of Formula (I-iii) is a compound of Formula (I-iii-i)



20

Some embodiments provide a compound of Formula (I-iv)



wherein:

Z is O or NR^x ;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

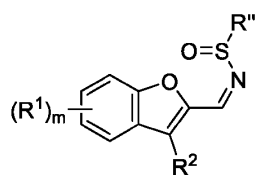
5 each R^1 is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

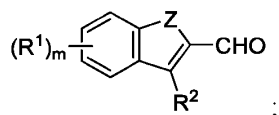
R^2 is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro; and

10 R'' is C1-C6 alkyl.

In some embodiments, the compound of Formula (I-iv) is a compound of Formula (I-iv-i)



Some embodiments provide a compound of Formula (I-v)



15 wherein:

Z is O or NR^x ;

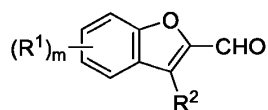
R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each R^1 is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

20 m is 0, 1, 2, or 3; and

R^2 is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro.

In some embodiments, the compound of Formula (I-v) is a compound of Formula (I-v-i)



In some embodiments, is . In some embodiments,

is . In some embodiments, is .

In some embodiments, is . In some embodiments,

is . In some embodiments, is .

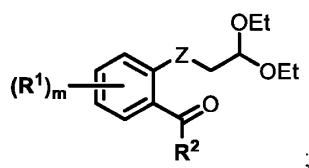
In some embodiments, is . In some embodiments,

is . In some embodiments, is

. In some embodiments, is . In some

embodiments, is or .

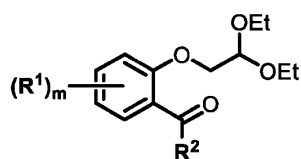
Some embodiments provide a compound of Formula (I-vi)



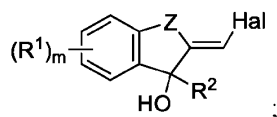
wherein:

R^2 is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro.

5 In some embodiments, the compound of Formula (I-vi) is a compound of Formula (I-vi-i)



Some embodiments provide a compound of Formula (I-viii)



wherein:

10 Z is O or NR^x ;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

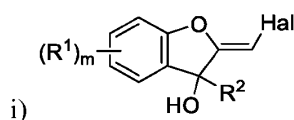
each R^1 is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

15 R^2 is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro; and

Hal is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl.

In some embodiments, the compound of Formula (I-viii) is a compound of Formula (I-viii-i)



20 In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, m is 3.

In some embodiments, each R^1 is an independently selected halogen. In some embodiments, each R^1 is independently selected from fluoro and chloro. In some embodiments, each R^1 is independently selected from fluoro and bromo. In some embodiments, each R^1 is fluoro. In some embodiments, at least one R^1 is an independently selected halogen. In some embodiments, at least one R^1 is independently selected from fluoro and chloro. In some embodiments, at least one R^1 is fluoro.

In some embodiments, at least one R^1 is cyano. In some embodiments, at least one R^1 is hydroxyl. In some embodiments, at least one R^1 is C1-C6 alkyl optionally substituted with hydroxyl. In some embodiments, at least one R^1 is C1-C6 alkyl substituted with hydroxyl. In some embodiments, at least one R^1 is C1-C3 alkyl substituted with hydroxyl. In some embodiments, at least one R^1 is hydroxymethyl. In some embodiments, at least one R^1 is unsubstituted C1-C6 alkyl. In some embodiments, at least one R^1 is methyl. In some embodiments, at least one R^1 is C3-C6 cycloalkyl. In some embodiments, at least one R^1 is cyclopropyl.

In some embodiments, m is 2; one R^1 is halogen; and the other R^1 is C1-C6 alkyl. In some embodiments, m is 2; one R^1 is fluoro; and the other R^1 is methyl. In some embodiments, m is 2; one R^1 is halogen; and the other R^1 is C3-C6 cycloalkyl. In some embodiments, m is 2; one R^1 is halogen; and the other R^1 is cyclopropyl. In some embodiments, m is 2; one R^1 is fluoro; and the other R^1 is cyano. In some embodiments, m is 2; one R^1 is halogen; and the other R^1 is halogen. In some embodiments, m is 2; one R^1 is fluoro; and the other R^1 is fluoro.

In some embodiments, R^2 is hydroxyl. In some embodiments, R^2 is C1-C6 alkyl optionally substituted with hydroxyl. In some embodiments, R^2 is C1-C6 alkyl substituted with hydroxyl. In some embodiments, R^2 is C1-C3 alkyl substituted with hydroxyl. In some embodiments, R^2 is hydroxymethyl. In some embodiments, R^2 is an unsubstituted C1-C6 alkyl. In some embodiments, R^2 is unsubstituted C1-C3 alkyl. In some embodiments, R^2 is methyl.

In some embodiments, R^2 is a C1-C6 haloalkyl. In some embodiments, R^2 is a C1-C3 haloalkyl. In some embodiments, R^2 is difluoromethyl. In some embodiments, R^2 is trifluoromethyl.

In some embodiments, R^2 is halogen. In some embodiments, R^2 is fluoro. In some embodiments, R^2 is chloro.

In some embodiments, R^2 is C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro. In some embodiments, R^2 is C3-C6 cycloalkyl substituted with 1 or 2 fluoro. In some embodiments,

R² is C3-C6 cycloalkyl substituted with 1 fluoro. In some embodiments, R² is C3-C6 cycloalkyl substituted with 2 fluoro. In some embodiments, R² is C3-C4 cycloalkyl substituted with 1 fluoro. In some embodiments, R² is C3-C4 cycloalkyl substituted with 2 fluoro. In some embodiments, R² is an unsubstituted C3-C6 cycloalkyl.

5 In some embodiments, R³ is a C1-C6 alkyl. In some embodiments, R³ is a C1-C3 alkyl. In some embodiments, R³ is methyl, ethyl, t-butyl, or isopropyl. In some embodiments, R³ is methyl, ethyl, or isopropyl. In some embodiments, R³ is methyl. In some embodiments, R³ is ethyl. In some embodiments, R³ is isopropyl.

10 In some embodiments, R³ is a C1-C6 haloalkyl. In some embodiments, R³ is a C1-C3 haloalkyl. In some embodiments, R³ is difluoromethyl. In some embodiments, R³ is trifluoromethyl.

In some embodiments, R³ is C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl. In some embodiments, R³ is C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 or 2 fluoro. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 fluoro. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 fluoro at the position of the C3-C6 cycloalkyl that is bonded to the methine of Formula (I). In some embodiments, R³ is 2,2-difluorocyclopropyl or 3,3-difluorocyclopropyl. In some embodiments, R³ is C3-C6 cycloalkyl optionally substituted with 1 or 2 methyl. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 or 2 methyl. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 methyl. In some embodiments, R³ is C3-C6 cycloalkyl substituted with 1 methyl at the position of the C3-C6 cycloalkyl that is bonded to the methine of Formula (I). In some embodiments, R³ is an unsubstituted C3-C6 cycloalkyl. In some embodiments, the R³ C3-C6 cycloalkyl is cyclopropyl. In some embodiments, R³ is cyclopropyl. In some embodiments, R³ is cyclobutyl. In some embodiments, R³ is cyclopentyl. In some embodiments, R³ is cyclohexyl.

25 In some embodiments, R' is C1-C6 alkyl. In some embodiments, R' is C1-C4 alkyl. In some embodiments, R' is C1-C3 alkyl. In some embodiments, R' is isopropyl. In some embodiments, R' is methyl. In some embodiments, R' is ethyl. In some embodiments, R' is n-propyl.

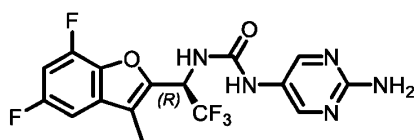
30 In some embodiments, R' is C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl or C1-6 alkoxy. In some embodiments, R' is C6-C10 aryl substituted with 1-

3 independently selected C1-6 alkyl or C1-6 alkoxy. In some embodiments, R' is C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl. In some embodiments, R' is C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkoxy. In some embodiments, R' is C6-C10 aryl substituted with 1-3 independently selected C1-6 alkyl. In some
 5 embodiments, R' is C6-C10 aryl substituted with 1-3 independently selected C1-6 alkoxy.

In some embodiments, R'' is C1-C6 alkyl. In some embodiments, R'' is C1-C4 alkyl. In some embodiments, R'' is C1-C3 alkyl. In some embodiments, R'' is isopropyl. In some embodiments, R'' is methyl. In some embodiments, R'' is ethyl. In some embodiments, R'' is n-propyl.

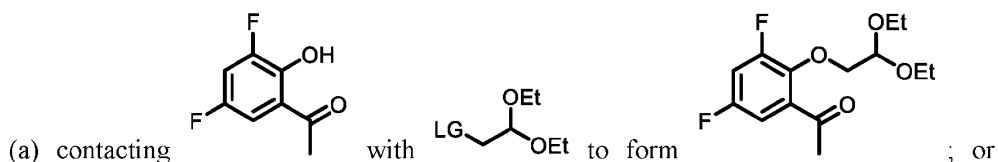
10 In some embodiments, Hal is selected from chloro, bromo, and iodo. In some embodiments, Hal is selected from chloro, bromo, and trifluoromethyl. In some embodiments, Hal is chloro. In some embodiments, Hal is bromo. In some embodiments, Hal is iodo. In some embodiments, Hal is trifluoromethanesulfonyl.

Some embodiments provide a process of preparing Compound 1, having the structure:

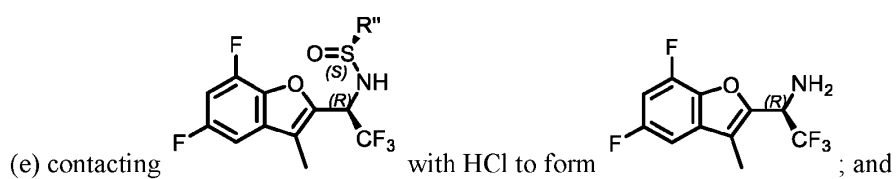
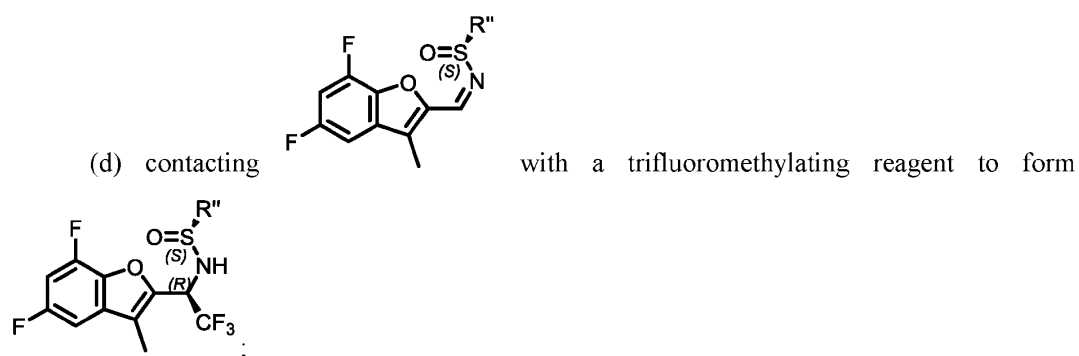
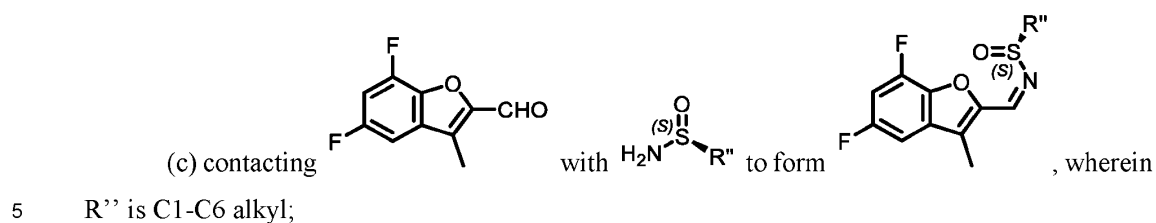
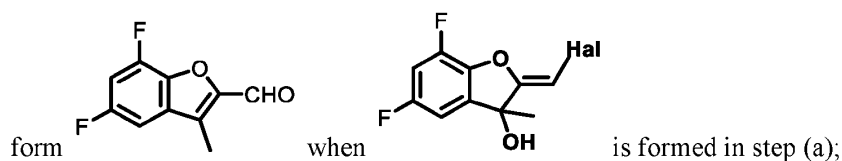
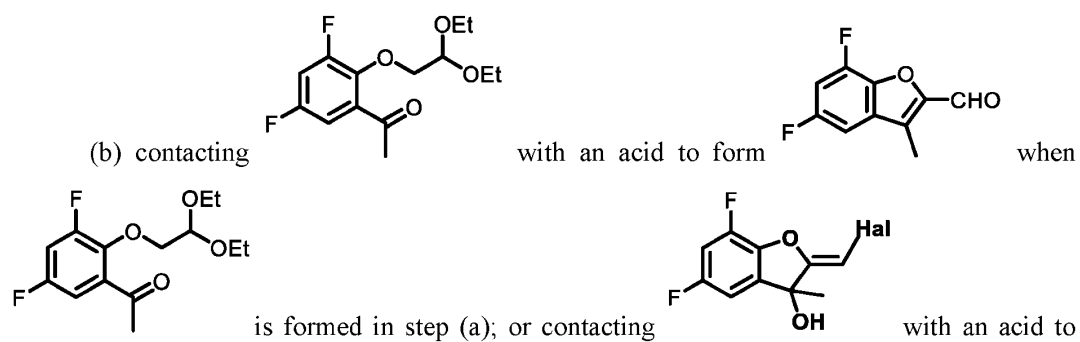


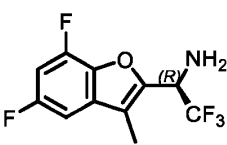
(1), or a salt and/or solvate thereof;

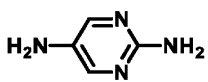
comprising:



contacting with to form ; wherein LG is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl; and wherein Hal is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;

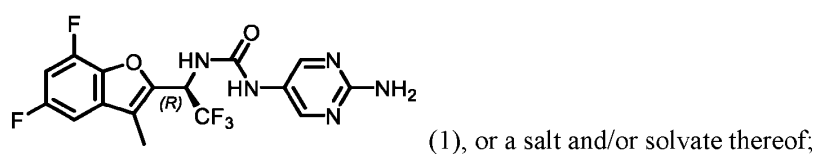


(f) contacting  with (i) a carbonyl equivalent; and (ii) pyrimidine-2,5-

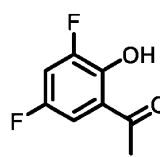
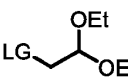
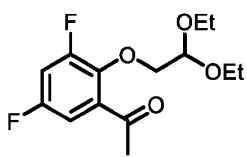
diamine having the structure  ;

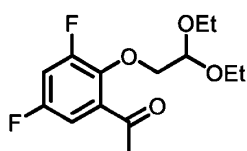
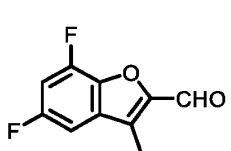
to form Compound 1; wherein the pyrimidine-2,5-diamine is formed by contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen.

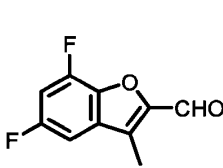
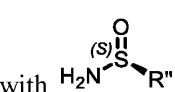
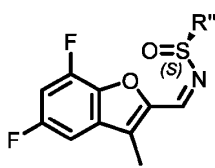
5 Some embodiments provide a process of preparing Compound 1, having the structure:

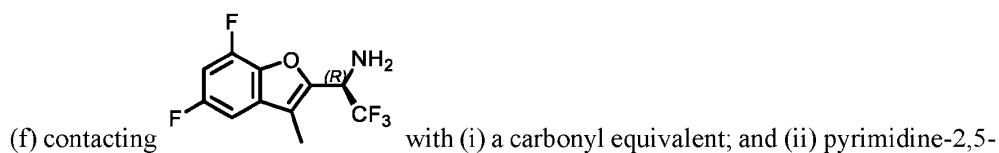
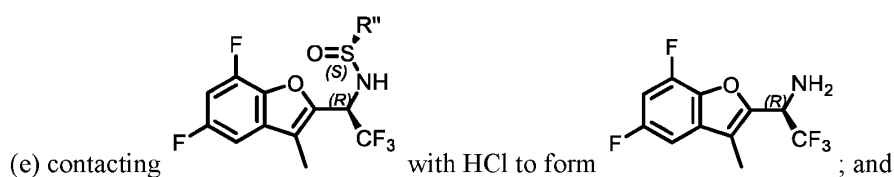
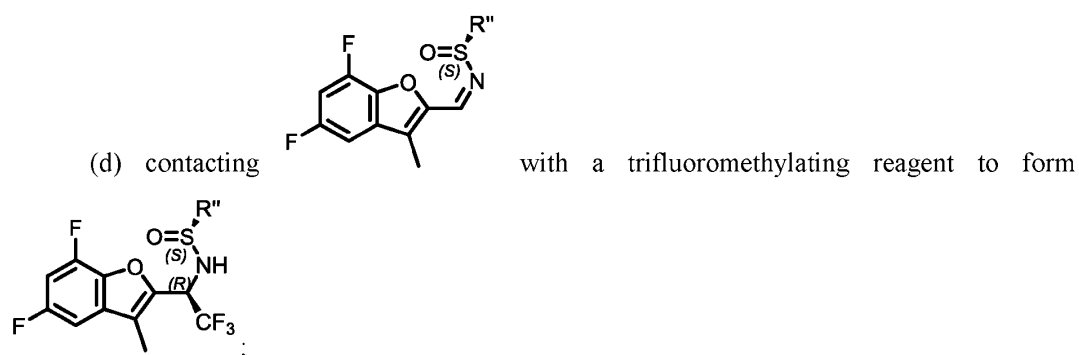


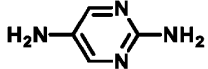
comprising:

(a) contacting  with  to form  , wherein LG is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;

10 (b) contacting  with an acid to form  ;

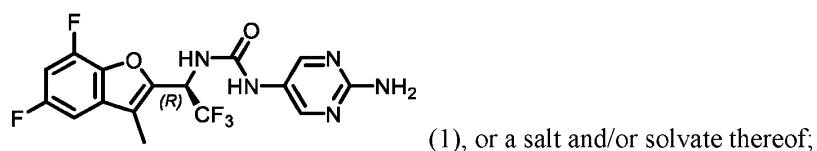
(c) contacting  with  to form  , wherein R'' is C1-C6 alkyl;



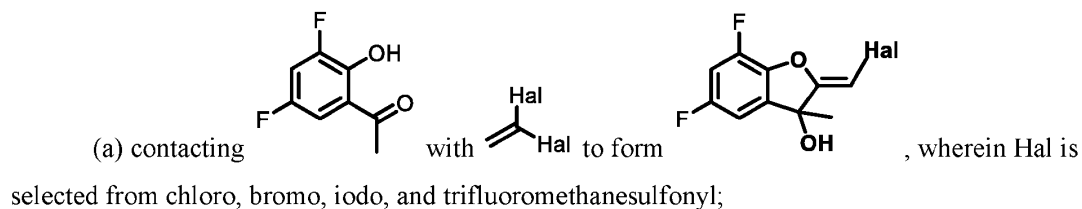
5 diamine having the structure ;

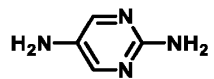
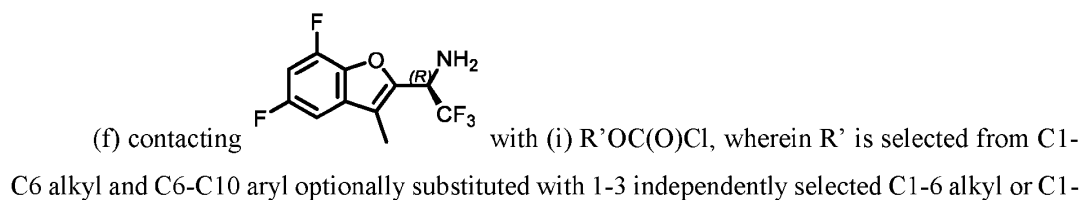
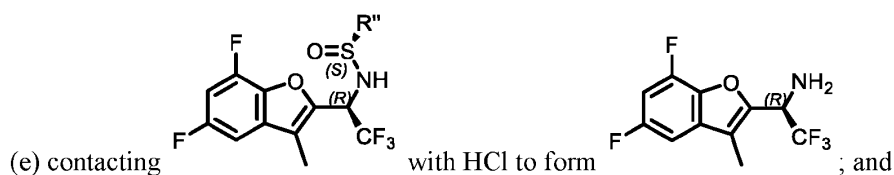
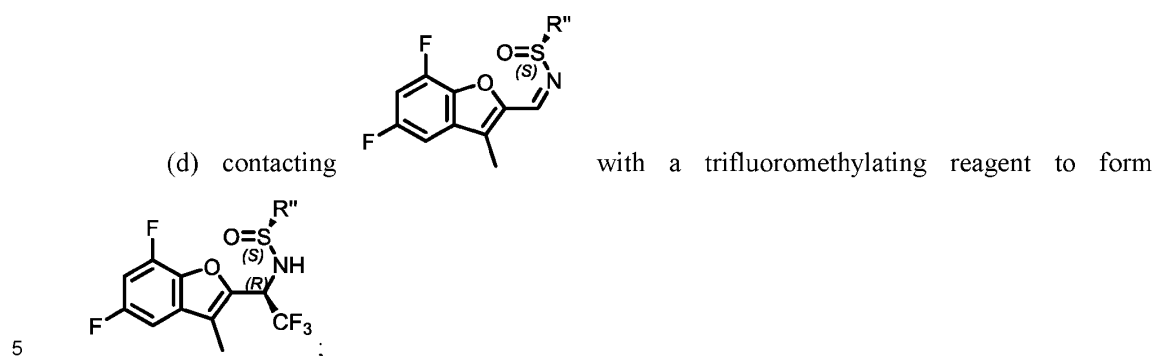
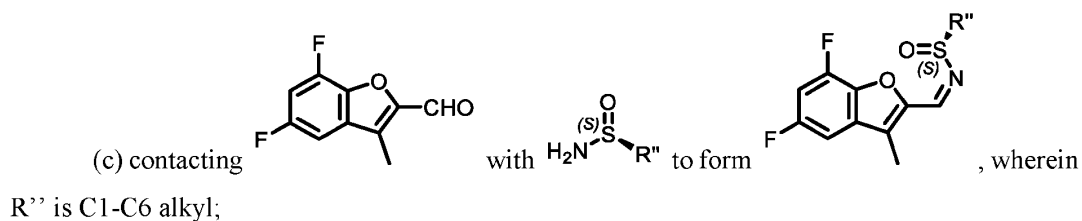
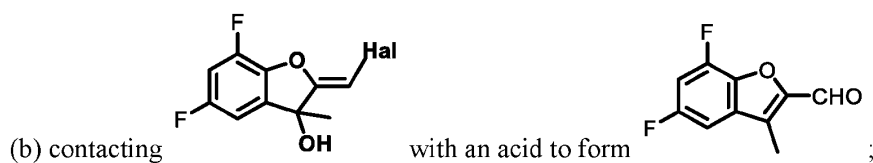
to form Compound 1; wherein the pyrimidine-2,5-diamine is formed by contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen.

Some embodiments provide a process of preparing Compound 1, having the structure:

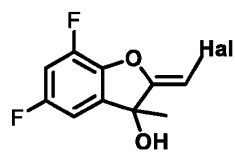


10 comprising:

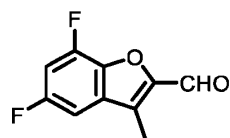




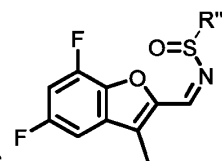
to form Compound 1; wherein the pyrimidine-2,5-diamine is formed by contacting 5-nitropyrimidine-2-amine with palladium on carbon under an atmosphere of hydrogen.



Some embodiments provide a compound having the structure

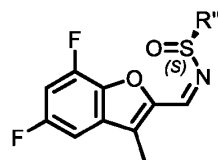


Some embodiments provide a compound having the structure



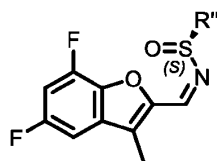
Some embodiments provide a compound having the structure

Some



embodiments provide a compound having the structure

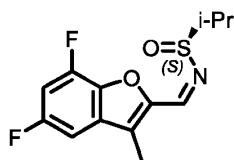
Some embodiments



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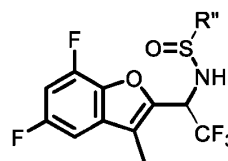
provide a compound having the structure

Some embodiments provide a



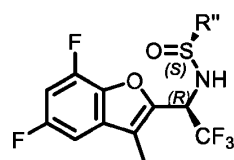
compound having the structure

Some embodiments provide a compound having the structure



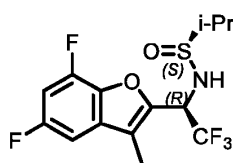
. Some

embodiments provide a compound having the structure

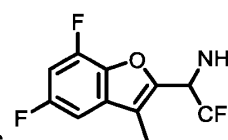


. Some embodiments

provide a compound having the structure

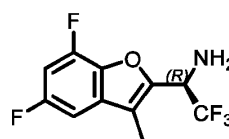


Some embodiments provide a compound having the structure

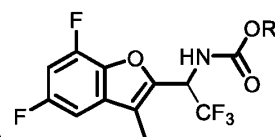


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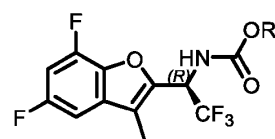
5 embodiments provide a compound having the structure



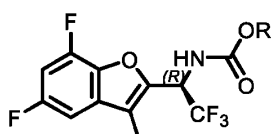
Some embodiments provide a compound having the structure

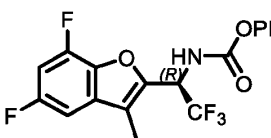


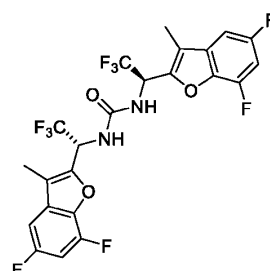
Some embodiments provide a compound having the structure

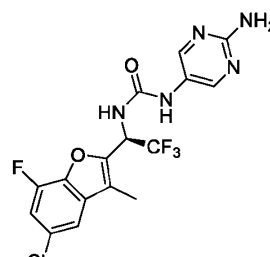


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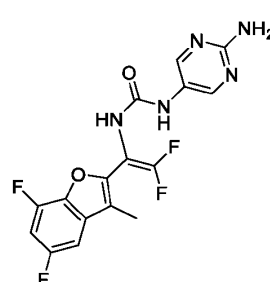
embodiments provide a compound having the structure . Some

embodiments provide a compound having the structure .

Some embodiments provide a compound having the structure .

Some embodiments provide a compound having the structure .

5

Some embodiments provide a compound having the structure .

EXAMPLES

Compound Preparation

The compounds disclosed herein can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared

intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or in light of the teachings herein. The synthesis of the compounds disclosed herein can be achieved by generally following the schemes provided herein, with modification for specific desired substituents.

5 Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*,
10 John Wiley and Sons (1994); Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; and Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999, are useful and recognized reference textbooks of organic synthesis known
15 to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present disclosure.

 The synthetic processes disclosed herein can tolerate a wide variety of functional groups; therefore, various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt and/or
20 solvate thereof.

Materials and Methods

 The compounds provided herein, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible
25 synthetic routes.

 The reactions for preparing the compounds provided herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can
30 range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction

can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of the compounds provided herein can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Protecting Group Chemistry, 1st Ed., Oxford University Press, 2000; March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th Ed., Wiley-Interscience Publication, 2001; and Petursson, S. et al., "Protecting Groups in Carbohydrate Chemistry," J. Chem. Educ., 74(11), 1297 (1997).

X-ray Powder Diffraction (XRPD):

XRPD analysis was carried out on a PANalytical X'pert pro with PIXcel detector (128 channels), scanning the samples between 3 and 35° 2 θ . The material was gently ground to release any agglomerates and loaded onto a multi-well plate with Mylar polymer film to support the sample. The multi-well plate was then placed into the diffractometer and analyzed using Cu K radiation ($\alpha_1 \lambda = 1.54060 \text{ \AA}$; $\alpha_2 = 1.54443 \text{ \AA}$; $\beta = 1.39225 \text{ \AA}$; $\alpha_1 : \alpha_2$ ratio = 0.5) running in transmission mode (step size 0.0130° 2 θ , step time 18.87s) using 40 kV / 40 mA generator settings. XRPD analysis that used the longer basic batch method was carried out on a PANalytical X'pert pro with PIXcel detector (128 channels), scanning the samples between 3 and 35° 2 θ . The material was gently ground to release any agglomerates and loaded onto a multi-well plate with Mylar polymer film to support the sample. The multi-well plate was then placed into the diffractometer and analyzed using Cu K radiation ($\alpha_1 \lambda = 1.54060 \text{ \AA}$; $\alpha_2 = 1.54443 \text{ \AA}$; $\beta = 1.39225 \text{ \AA}$; $\alpha_1 : \alpha_2$ ratio = 0.5) running in transmission mode (step size 0.0130° 2 θ , step time 68.595s) using 40 kV / 40 mA generator settings. Data were visualized and images generated using the HighScore Plus 4.7 desktop application (PANalytical, 2017).

Thermogravimetric Analysis/ Differential Scanning Calorimetry (TGA/DSC):

Material (3 – 10 mg of mg) was added into a pre-tared open aluminum pan and loaded into a TA Instruments Discovery SDT 650 Auto-Simultaneous DSC and held at room temperature. The sample was then heated at a rate of 10 °C/min from 30 – 400 °C during which time the change in

sample weight was recorded along with the heat flow response (DSC). Nitrogen was used as the sample purge gas, at a flow rate of 200 cm³/min.

Differential Scanning Calorimetry (DSC):

5 Material (1 – 5 mg) was weighed into an aluminum DSC pan and sealed non-hermetically with an aluminum lid. The sample pan was then loaded into a TA Instruments Discovery DSC 2500 differential scanning calorimeter equipped with a RC90 cooler. The sample and reference were heated to 210 °C at a scan rate of 10°C/min and the resulting heat flow response monitored. The sample was cooled to -80°C and then reheated again to 210 °C all at 10 °C/min. Nitrogen was
10 used as the purge gas, at a flow rate of 50 cm³/min.

Abbreviations

Abbreviation	Meaning
ACN	Acetonitrile
AcOH	Acetic acid
Aq.	Aqueous
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DMF	N,N-dimethylformamide
DMAc/DMA	Dimethylacetamide
DMSO	Dimethylsulfoxide
EtOAc	Ethyl acetate
EtOH	Ethanol
HPLC	High-performance liquid chromatography
h	Hour(s)
i-PrOH	Isopropanol
iPAc	Isopropyl acetate
KF	Karl Fischer titration
MeOH	Methanol
min	Minute(s)
MTBE	Methyl tert-butyl ether
NaOH	Sodium hydroxide
Pd/C	Palladium on carbon
RT or rt	Room temperature
RRT	Relative retention time
THF	Tetrahydrofuran
TEA	Triethylamine

t-BuOK	Potassium tert-butoxide
TBAT	Tetrabutyl ammonium acetate (Bu ₄ OAc)
TMS	Trimethylsilyl
UPLC	Ultra performance liquid chromatography
XRPD	X-ray powder diffraction

Introduction

An improved route for the synthesis of Compound 1 was developed in order to ensure higher standards for Identity, Strength, Quality, and Purity of Active Pharmaceutical Ingredient (API) according to Good Manufacturing practices (cGMP). The route in Scheme 1 below, was executed on a 300 g scale and the cGMP route, which is shown in Scheme 2 below, was executed on about 11 kg scale.

The specification for Compound 1, Form 1 hemihydrate (the “API” as referred to herein) were : ≥ 97.0 % (area/area or “a/a”), 97.0-103.0 % (weight/weight, “w/w”), unknown individual impurity ≤ 0.15 % (a/a), total impurities ≤ 3.0 % (a/a) by UPLC and the chiral purity ≥ 98.0 % (a/a) by HPLC. The cGMP scale up campaign was successfully executed over 3 months to deliver 10.87 kg API with purity of 99.9 % (a/a), 99.6 % (w/w) and 0.1 % Impurity 2 as a single impurity by UPLC. The chiral purity was 100.0% (a/a) by HPLC.

Several challenges were overcome in order to successfully execute a multi-kilogram synthesis of Compound 1, Form 1 hemihydrate that adhered to cGMP requirements and guidance standards. These included:

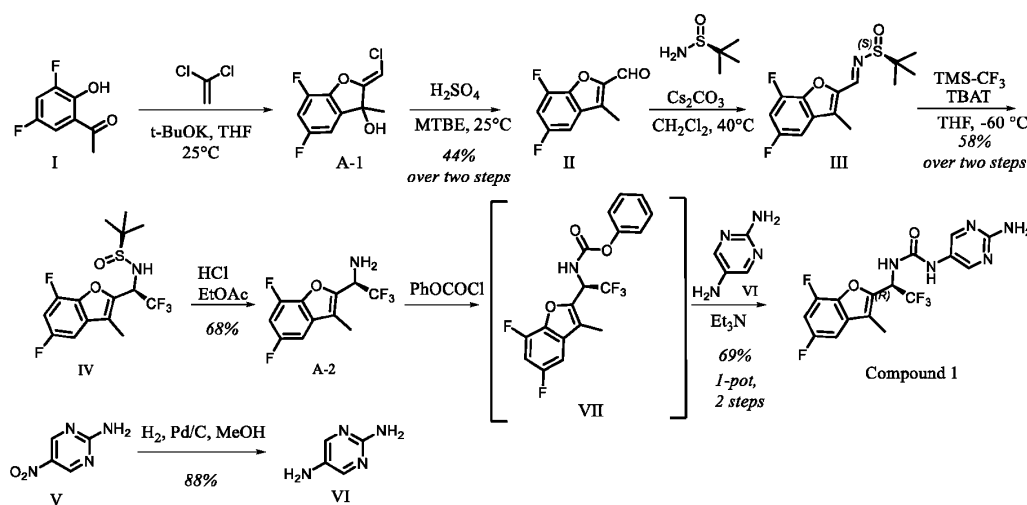
1. Production of Intermediate VI (see Scheme 1). The main issue was the capacity of the hydrogenator required to run the reaction in a single batch run. An alternative approach to catalytic hydrogenation was explored to reduce 5-nitropyrimidin-2-amine via the hydrogen transfer from formic acid (see **Example 1**). While it was found that the hydrogen transfer conditions successfully transformed V into VI, the removal of salts and extraction of VI from the aqueous work up was difficult due to the high solubility of VI in water. Accordingly, it was decided to use hydrogenation with hydrogen gas for the production of VI. Given the size of the hydrogenator vessel (20 L) available at the cGMP manufacturing facility, this approach required 6 batch runs to produce sufficient intermediate VI for API delivery.

2. Production of Intermediate A-2. As executed in Route A, it was found that there was significant reduction in yield during the freebasing of the HCl salt intermediate. Accordingly, it

was decided to isolate and use the HCl salt (B-2) for subsequent reactions (see Scheme 2), and not the free base form (A-2).

3. Production of the carbamate VII. Shown in brackets in Route A to indicate *in-situ* formation via reaction of free base form A-2 with phenyl chloroformate, there was a significant level of Impurity 1 (i.e. up to 10 %) observed when the transformation was carried out in this manner. Accordingly, an alternative approach was taken to generate the free base form A-2 *in-situ* from the HCl salt B-2, which would then rapidly react with phenyl chloroformate to form Intermediate VII. The carbamate was then isolated as a pure crystalline solid. Condensation between pure VII and pure VI then produced Compound 1 with no detected levels of Impurity 1 observed (see **Table E7** for the structure of Impurity 1 and other impurities).

4. The presence of Impurity 2. Seen in both routes, the identity of this impurity was not clearly established. Impurity 2 was eventually isolated by preparative HPLC from a GLP batch of Compound 1 that contained 0.5 % of this impurity. The chemical structure of Impurity 2 was then elucidated through NMR and LC-MS to be (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5-chloro-7-fluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (see **Table E7**). Thus, this impurity was identified and quantified in the final API in order to meet cGMP requirements.

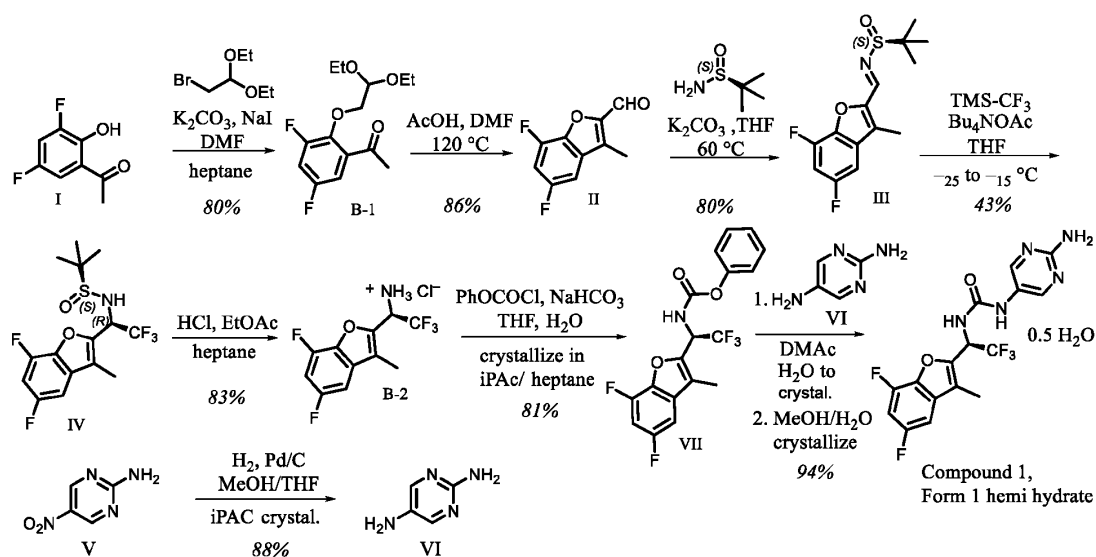


Scheme 1: Route A (GLP, 300 g scale)

Summary of Route A

Compound 1 was prepared on 300 g scale via the route shown in Scheme 1. Starting with commercially available 1-(3,5-difluoro-2-hydroxyphenyl)ethan-1-one (I), condensation with 1,1-

dichloroethene under basic conditions yielded intermediate A-1, which was dehydrated/aromatized by treatment with sulfuric acid to give 5,7-difluoro-3-methylbenzofuran-2-carbaldehyde (II). Formation of (S,E)-N-((5,7-difluoro-3-methylbenzofuran-2-yl)methylene)-2-methylpropane-2-sulfinamide (III) was achieved by treating intermediate (II) with commercially available (S)-2-methylpropane-2-sulfinamide under base catalysis. Enantioselective addition of the trifluoromethyl group was accomplished by treatment of intermediate III with trifluoromethyltrimethylsilane with catalytic tetrabutylammonium bromide under reduced temperature. Removal of the tert-butylsulfiny group of IV was accomplished by treatment with HCl, followed by treatment with base to give freebase Intermediate A-2. Treatment of A-2 with phenyl chloroformate gave the corresponding phenol carbamate (shown in brackets to indicate *in-situ* formation), which was condensed with pyrimidine-2,5-diamine (VI) in the presence of triethylamine to give Compound 1. As noted above, Route A suffered a couple of issues: (1) an appreciable loss of A-2 during the freebase procedure, and (2) the introduction of Impurity 1 (i.e., up to 10 %) presumably caused by hydrolysis of the intermediate phenol carbamate (shown in brackets) back to intermediate A-2, which reacts with the phenol carbamate to result in a symmetrical urea (Impurity 1, **Table E7**).



Scheme 2: Route B (cGMP, 11 kg scale)

Summary of Route B

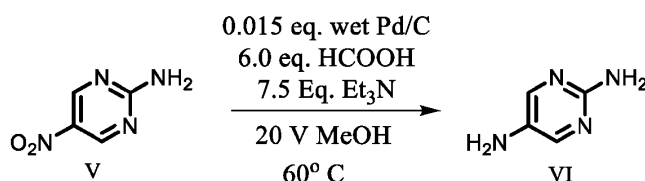
Compound 1 was prepared on 10.9 kg scale under cGMP protocols using the route shown in Scheme 2. Route B began with *O*-alkylation of commercially available 1-(3,5-difluoro-2-hydroxyphenyl)ethan-1-one (I) to afford Intermediate B-1, which was treated with acetic acid to give Intermediate II. Aldehyde II was condensed with optically pure commercially available (S)-2-methylpropane-2-sulfinamide under base catalysis to give Intermediate III. Enantioselective addition of the trifluoromethyl group was accomplished by treatment of intermediate III with trifluoromethyltrimethylsilane in the presence of catalytic tetrabutylammonium acetate under reduced temperature to give Intermediate IV. Removal of the tert-butylsulfinyl group of IV was accomplished by treatment with HCl to afford Intermediate B-2, a stable and crystalline hydrochloride salt. The requisite intermediate VI was prepared by catalytic hydrogenation of commercially available 5-nitropyrimidin-2-amine (V). The phenol carbamate (Intermediate VII) was prepared by reacting B-2 with phenyl chloroformate under modified Schotten-Baumann conditions; the Intermediate VII was subsequently isolated as a crystalline solid. The final step involved condensation of Intermediate VII with pyrimidine-2,5-diamine (VI) to give Compound 1 in crystalline form. Compound 1, Form 1 hemi-hydrate (0.5 molar equivalents of water) was obtained via crystallization of Compound 1 from methanol-water.

A comparison of Route B with Route A indicates several key differences, which resulted in significant improvements in the process. These key differences include:

- (1) Route B used a different method of preparation of aldehyde Intermediate II,
- (2) Route B included isolation of Intermediate B-2 (hydrochloride salt), and
- (3) Route B included isolation of the intermediate carbamate (VII).

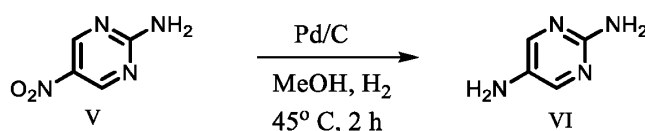
These differences, as discussed in the foregoing and detailed herein resulted in increased overall yield and a reduction in the level of impurities, in particular the complete elimination of Impurity 1 and a significant reduction in the amount of Impurity 2. For reference, a summary of putative impurities potentially present in the final API (either due to side-reactions or unreacted starting materials) is provided in **Table E7**. The following examples serve to illustrate optimization of Route B (cGMP synthesis) to give Compound 1, Form 1 hemihydrate.

Example 1. Preparation of pyrimidine-2, 5-diamine by transfer hydrogenation



Into a reaction flask were added all components in the relative amounts indicated. Upon reaction completion, Pd/C was filtered, and the volatiles were removed under vacuum. The crude mixture was redissolved in DCM and water was added to wash out HCOOH, TEA and salt. It was found the majority of the product remained in the aqueous layer. An attempt using NaOH to make the aqueous layer basic (pH 14) followed by DCM to extract the product failed to effectively extract the product (VI) from the aqueous layer.

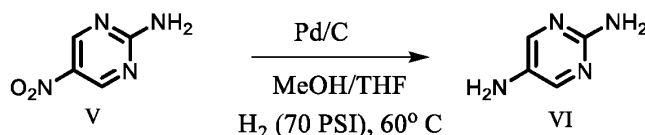
Example 2. Preparation of pyrimidine-2,5-diamine by catalytic hydrogenation in methanol



To a 300 mL Parr reactor was charged 10 g (1.0 eq) 5-nitropyrimidin-2-amine, Pd/C (1 g, 10 % w/w, 50 % wet in water) and MeOH (130 mL, 13 Volumes, herein referred to as “V”). The resulting mixture was hydrogenated at 60-70 psi H₂ at 45°C for 2 hours to achieve reaction completion. The catalyst was filtered through a Celite pad followed by MeOH (50 mL, 5 V) wash. MeOH was then swapped to isopropyl acetate (50 mL, 5 V) at 60-70°C. The slurry was slowly cooled to below 0°C over 3 hours and then aged overnight. The solid was filtered and washed with isopropyl acetate (15 mL, 1.5 V). The wet cake was dried in a vacuum oven at 50°C with a nitrogen bleed overnight to afford 6.6 g (84.2 %) of the title compound as a yellow crystalline solid.

Notes: (1). The procedure of **Example 2** was successfully scaled up using 85 g 5-nitropyrimidin-2-amine in a 2 L Parr reactor to produce 57.1 g (85.5 % yield) of the title compound as a yellow crystalline solid with HPLC purity of 100.0 %; and (2) The solubility of 5-nitropyrimidin-2-amine was observed to very poor in MeOH (i.e. not completely soluble in 30 V MeOH at 60°C). As a result, the above hydrogenation conditions were modified to add THF to the solvent mixture. (14 V THF) with 10 V MeOH at 60°C. Also, the catalyst loading was increased from 0.1 X to 0.25 X in order to achieve completion of the reaction within 2 hours so that 2 runs per day could be achieved when run on a larger scale.

Example 3. Preparation of pyrimidine-2,5-diamine by catalytic hydrogenation in methanol-tetrahydrofuran with increased catalyst loading



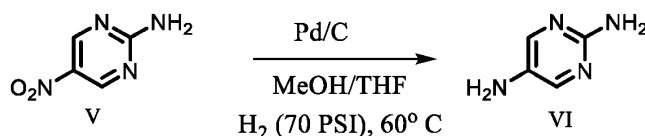
5 Protocol:

Using a 2 L Parr hydrogenator:

1. Charge 5-nitropyrimidin-2-amine (35 g, 1.0 X).
2. Charge THF (490 mL, 14 V).
3. Charge MeOH (350 mL, 10 V).
- 10 4. Heat the contents to 55-65°C to obtain a clear solution.
5. Cool the contents to 40-50°C.
6. Charge Pd/C (8.75 g or 0.25 X, 10 % w/w, 50 % water).
7. Purge with nitrogen 3 times and hydrogenate at 60°C under 70 psi H₂ pressure.
8. Monitor reaction; typically complete after 2 hours.
- 15 9. Filter Pd/C through the Celite pad.
10. Rinse Parr reactor with MeOH (105 mL, 3 V) and wash the Celite cake with rinse.
11. Concentrate the filtrate under reduced pressure at 40-60°C to about 105 mL (3 V).
12. Add isopropyl acetate (175 mL, 5 V).
13. Concentrate the batch to about 105 mL (3 V).
- 20 14. The cool the slurry to room temperature and held for 3 hours.
15. Filter the solid and wash the cake with isopropyl acetate (35 mL, 1 V).
16. Dry the wet cake in a vacuum oven at 50°C with a nitrogen bleed overnight (18 h).
17. Dry cake yield was 23.8 g (86.5 %) of pyrimidine-2,5-diamine as a pale yellow crystalline solid.

25

Example 4. cGMP manufacturing protocol for preparation of pyrimidine-2,5-diamine by catalytic hydrogenation in methanol-tetrahydrofuran



The production of Intermediate VI was executed via 12 hydrogenation runs in an 18 L Parr reactor in 2 separate batch records (VI-B1 and VI-B2, 6 runs per batch) using the modified procedure shown in **Example 3**. Each hydrogenation run used 0.6 kg 5-nitropyrimidin-2-amine, 0.15 kg Pd/C (10 % w/w, 50 % wet) in 6 L MeOH and 8.4 L THF at 70 psi H₂ and 60°C. Upon the reaction completion, the catalyst was filtered through a Celite pad. The hydrogenator was rinsed with 2.4 L MeOH and the rinse was used to wash the Celite/catalyst cake. For each batch record, a combined filtrate obtained from 6 runs was subjected to a solvent swap from MeOH/THF to IPA in which the product was crystallized out and isolated by filtration. The wet cake was dried at 45°C in a vacuum oven with a nitrogen bleed until all residual solvents met the specification. For VI-B1, 2.425 kg VI was obtained in 85.2 % yield with a HPLC purity of 98.7 % (a/a) and assay of 99.4 % (w/w). For VI-B2, 2.665 kg VI was obtained in 91.3 % yield with a HPLC purity of 99.4 % (a/a) and assay of 96.9 % (w/w).

Equipment

Reactor 1 (R1): 18L, Stainless Steel, 1-20V, 14 L max working volume (15.56 V), Temp Range: 15-60°C Pressure Range: 60-70 psi.

Reactor 2 (R2): Glass, 1-13 V (59 L) for combined work up. Temp Range: -5-60 °C.

Vacuum oven (D1): Temp Range: 40-50 °C

Tray (T1, T2, T3): Hastelloy

Protocol:

1. Prepared Hydrogenation Reactor R1 by charging nitrogen and pulling vacuum.
2. Prepared Reactor R2 with reflux condenser and charging with nitrogen as needed.
3. Charged 0.60 kg of 5-Nitropyrimidin-2-amine (target range: 0.59 – 0.61 kg) into Reactor R1.
4. Charged 7.52 kg of THF (target range: 7.1 – 7.9 kg, ~14V) into Reactor R1
5. Charged 4.75 kg of Methanol (target range: 4.51 – 5.00 kg, ~10V) into Reactor R1.
6. Turned on agitation to 280 RPM and adjusted temperature of Reactor R1 to 52°C in order to dissolve material.

7. Adjusted temperature of Reactor R1 to 45°C and degassed headspace with nitrogen in preparation for Pd/C charge.
8. Charged 0.15 kg of Pd/C (target range: 0.14 – 0.16 kg, 0.25X) into Reactor R1.
9. Sealed Reactor R1 and slowly charged Hydrogen gas to a pressure of 60 psi. Carefully adjusted temperature of Reactor R1 to 50-70°C and held with constant agitation for 1 hour at 60-70 psi.
10. Checked mixture from Reactor R1 to test reaction conversion. Starting material gone.
11. Carefully purged Reactor R1 by charging nitrogen and pulling vacuum.
12. Prepared 0.15 kg of Celite (target range: 0.14 – 0.16, 0.25X) on filter funnel and pre-wetted filter bed with methanol.
13. Filtered contents of Reactor R1 through Celite filter bed with contents warmed at 41°C.
14. Charged 1.87 kg of Methanol (target range: 1.8 – 2.0 kg, 3.2X) into Reactor R1 to rinse reactor and heated rinse to 48°C.
15. Transferred rinse from Reactor R1 to wash Celite filter bed. Cake wash combined with mother liquor and transferred into Reactor R2.
- Steps 1-14 were repeated on other 5 run/lots and combined lots were transferred to R2 for batch VI-B1.
- Combined work up, filtration, and drying for batch VI-B1
15. Established new unit value, Y = 3.60 kg of 5-Nitropyrimidin-2-amine total charged for VI-B1.
16. Concentrated contents of Reactor R2 from ~50 L to ~9 L (target ~2.5 V) under vacuum maintaining temperature <60°C.
17. Stopped distillation then slowly cooled contents of Reactor R2 from 45°C to 0°C over 3 hr, 1 min.
18. Held contents of Reactor R2 at 0°C for 17 hr, 18 min with constant agitation.
19. Filtered contents of Reactor R2.
20. Charged 3.07 kg of isopropyl acetate (target range: 3.0 – 3.3 kg, ~1 V) into Reactor R2 to rinse Reactor.
21. Transferred rinse from Reactor R2 to wash wet cake in filter funnel.
22. Loaded wet cake from filter funnel into Hastelloy trays. Net weight: 2.69 kg
23. Dried material in vacuum oven at 40-50°C under vacuum and nitrogen bleed for 1 day 1 hr 26 min.
24. Check water content of each tray by KF; results failed to meet criteria.
25. Continued to dry material for an additional 21 hr 27 min at 47°C.

26. Check water content of each tray by KF; results passed criteria (KF for Water ≤ 0.5 % (w/w); result 0.4 %)

27. Pulled 5.0 g retain sample.

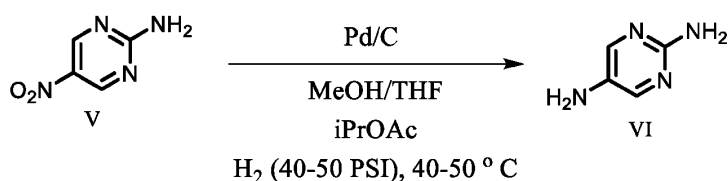
28. Packaged bulk and stored for use in next production step. Total net for VI-B1: 2.425 kg

5 Steps 1-28 were repeated for additional six runs and these lots were combined to give VI-B2 to obtain a total net for batch VI-B2 of 2.665 kg of Intermediate VI; the analytical test result and pass criteria for each batch are shown in **Table E1**.

Table E1. Analytical results for cGMP batches VI-B1 and VI-B2

Test/criteria	Result for VI-B1	Result for VI-B2
KF for Water ≤ 0.5 % (w/w)	0.4 % (w/w)	0.5 % (w/w)
HPLC Purity ≥ 98.0 % (a/a)	98.7 % (a/a)	99.4 % (a/a)
A HPLC Assay; Report Result (% w/w)	99.4 % (a/a)	96.9% (a/a)
Residual Solvents: THF, MeOH, IPAc; Report Result (ppm)	MeOH: 1638 ppm THF: < 909 ppm IPAc: 1356 ppm	MeOH: 1096 ppm THF: 1547 ppm IPAc: <498 ppm
Pd content; Report Results (ppm)	0.54 ppm	< 0.02 ppm
Appearance; Report Results	Yellow Solid Crystals	Yellow Solid Crystals

Example 5. Alternative cGMP manufacturing protocol for preparation of pyrimidine-2,5-diamine by catalytic hydrogenation in methanol-tetrahydrofuran



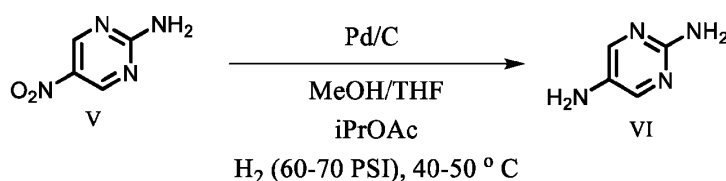
15 Starting material 5-nitropyrimidin-2-amine (1 eq) was hydrogenated under 40–50 psi hydrogen gas pressure in the presence of palladium-on-carbon catalyst (15% w/w, 10% Pd loading, 50% water-wet) in a mixture of tetrahydrofuran (12 vols) and methanol (12 vols) at 40–50 °C for at least 4 hours until in-process control by HPLC indicated <0.5% 5-nitropyrimidin-2-amine remaining versus Intermediate VI. The reaction mixture was filtered through a bed of celite (1.5
20 wt eq) to remove the catalyst followed by a rinse of methanol (3 vols). The mixture was distilled under vacuum to a concentrate (~2.5 vols). Isopropyl acetate (5 vols) was added and distilled

under vacuum to a concentrate (~2.5 vols). The solution was cooled to -5 to 5 °C over three hours to effect crystallization. The batch was filtered, and the cake washed with isopropyl acetate (3 vols) cooled to 0-10 °C. The isolated solids were dried at 40-50 °C under vacuum with nitrogen sweep to constant weight. In-process control for purity of Intermediate VI by HPLC was conducted; if the purity did not meet the acceptance criteria for Intermediate VI, an optional recrystallization was performed as described below.

Optional Recrystallization

Intermediate VI is dissolved in a mixture of isopropanol (18 vols) and water (2 vols). The slurry is heated to 60-70 °C and held for about 1 hour. The mixture is cooled to 0-10 °C at a rate of 10 °C/hour then held at 0-10 °C for at least 8 hours. The batch is filtered, the filter cake washed twice with isopropanol-water solution at 0-10 °C (2 vols, 9:1). The wet cake is dried at 40-50 °C under vacuum with nitrogen sweep to constant weight to afford Intermediate VI in approximately 56% yield.

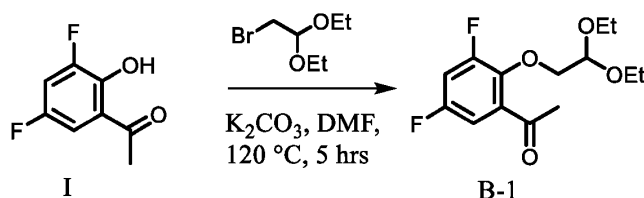
Example 6. Second alternative cGMP manufacturing protocol for preparation of pyrimidine-2,5-diamine by catalytic hydrogenation in methanol-tetrahydrofuran



Commercially available 5-nitropyrimidin-2-amine is hydrogenated under 60-70 psi hydrogen gas pressure in the presence of palladium-on-carbon catalyst (10 wt%, 10% Pd loading, 50% water-wet) in a mixture of tetrahydrofuran (12.5 wt eq) and methanol (8 wt eq) at 50-60 °C for at least 1 hour until in-process control by HPLC indicates < 0.5% 5-nitropyrimidin-2-amine remaining versus Intermediate VI. The reaction mixture is filtered through a bed of celite (1.5 wt eq) to remove the catalyst followed by a rinse of methanol (3.2 wt eq). The mixture is distilled under vacuum to a concentrate (~2.5 vols). Isopropyl acetate (4.4 wt eq) is added and distilled under vacuum to a concentrate (~2.5 vols). The solution is cooled to -5 to 5 °C over three hours to effect crystallization. The batch is filtered, and the cake washed with isopropyl acetate (0.9 wt eq) cooled

to 0–10 °C. The isolated solids are dried at 40–50 °C under vacuum with nitrogen sweep to constant weight. Intermediate VI is isolated in approximately 85% yield.

Example 7. Preparation of 1-(2-(2,2-diethoxyethoxy)-3,5-difluorophenyl)ethan-1-one

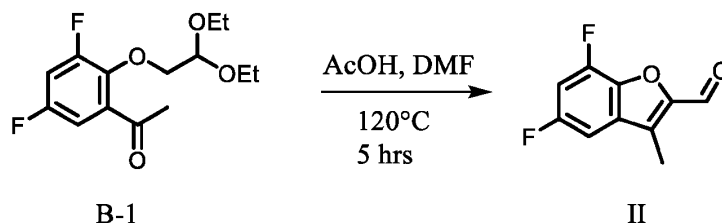


Protocol:

Using a 500 L reactor (R1) with mechanical stirrer and temperature controller under nitrogen atmosphere:

1. Charge DMF (256 kg) into R1 at 15–20 °C.
- 10 2. Charge with 1-(3,5-difluoro-2-hydroxyphenyl)ethan-1-one (I; 27.0 kg, 156 mol) into R1 at 15–20 °C.
3. Charge with 2-bromo-1,1-diethoxyethane (32.4 kg, 163 mol) into R1 at 15–20 °C.
4. Charge K₂CO₃ (43.4 kg, 312 mol) into R1 at 15–20 °C.
5. Charge NaI (2.35 kg, 15.6 mol) into R1 at 15–20 °C.
- 15 6. The reaction was heated to 120 °C and stirred at 120 °C for 8 hrs.
7. A sample was taken and diluted with ACN for monitoring. HPLC showed 79.0 % of B-1 was detected.
8. The reaction mixture of R1 was cooled to 20 °C with circulating glycol (7 °C).
9. Charge H₂O 1000 kg into R2 at 15–20 °C.
- 20 10. The reaction mixture from R1 was transferred into R2 under stirring at 15–20 °C
11. Charge EtOAc (180 kg) into R2 and stirred at 20 °C for 0.5 h, then stand for 20 min, separated organic phase. The aqueous phase was extracted again with EtOAc (180 kg).
12. Combine the organic phase and washed with 15 % aq. NaCl (200 kg) 2 times
13. The organic phase was continuously concentrated via vacuum distillation at 50 °C to give B-
- 25 1 (43.6 kg, purity = 83.2 %) as a brown oil.

Example 8. Preparation of 5,7-difluoro-3-methylbenzofuran-2-carbaldehyde



Protocol:

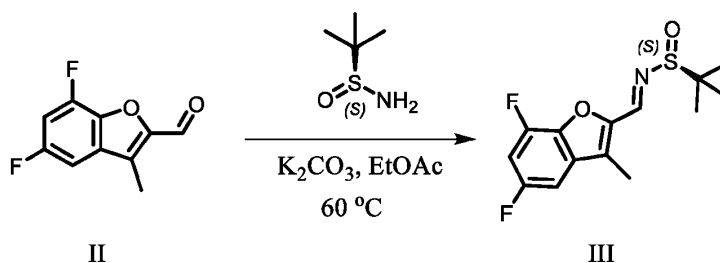
Using a 1000 L reactor (R1) with mechanical stirrer and temperature control under N₂ protection:

- 5 1. Charge AcOH (430 kg) into R1 at 15-20 °C.
2. Charge 1-(2-(2,2-diethoxyethoxy)-3,5-difluorophenyl)ethan-1-one (B-1; 43.0 kg, 149 mol) into R1 at 15-20 °C.
3. Charge DMF (10.9 kg, 149 mol) into R1 at 15-20 °C.
4. The reaction was heated to 120 °C and stirred at 120°C for 8 h.
- 10 5. A sample was taken and diluted with ACN for monitoring. HPLC showed indicated 73.1 % of 5,7-difluoro-3-methylbenzofuran-2-carbaldehyde (II) was detected.
6. The reaction mixture of R1 was cooled to 20 °C with circulating glycol (7 °C).
7. Charge H₂O 1000 kg into R2 at 15-20 °C.
8. The reaction mixture from R1 was pour into R2 under stirring at 15-20 °C
- 15 9. Charge EtOAc (180 kg) into R2 and stirred at 20 °C for 0.5 h, then stand for 20 min, separated organic phase. The aqueous phase was extracted again with EtOAc (180 kg).
10. Combine the organic phase and washed with 15 % aq. K₂CO₃ (100 kg) 2 X.
11. Charge the organic phase (400 kg) into R1 at 15-20 °C.
12. Charge H₂O (300 kg) into R1 at 15-20 °C.
- 20 13. Charge Na₂S₂O₄ (75 kg) into R1 at 15-20 °C under stirring and stirred for 8 hrs. (pale yellow solids were precipitated).
15. The solid was filtered and the filter cake was washed with EtOAc (50 kg).
15. The filtrate was separated and the aqueous phase was washed with EtOAc (50 kg) 2 X.
16. Charge the aqueous phase and the cake into R1 at 15-20 °C.
- 25 17. Charge EtOAc (180 kg) into R1 under stirring at 15-20 °C.
18. The pH of the solution in R1 was adjusted to 9-10 with K₂CO₃ (solid) and stirred for 5 h at 15-20 °C.

19. The solution of R1 was separated and the organic phase was collected.
20. The aqueous phase was extracted with EtOAc (90 kg).
21. The organic phases were combined and washed with 15 % aq. NaCl (100 kg) 2X.
22. The organic phase was continuously concentrated via vacuum distillation at 50 °C to give
- 5 5,7-difluoro-3-methylbenzofuran-2-carbaldehyde (19.2 kg, purity = 99.2 %) as light yellow solid and confirmed by HPLC.

Example 9. Preparation of (S,Z)-N-((5,7-difluoro-3-methylbenzofuran-2-yl)methylene)-2-methylpropane-2-sulfonamide

10



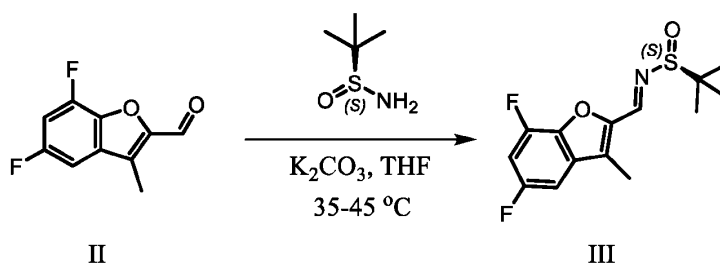
Protocol:

- Using a 1000 mL reactor (R1) with mechanical stirrer and temperature control under N₂ protection:
- 15 1. Charge EtOAc (170 kg) into R1 at 15-20 °C.
2. Charge 5,7-difluoro-3-methylbenzofuran-2-carbaldehyde (II; 19.0 kg, 96.8 mol) into R1 at 15-20 °C.
3. Charge (S)-2-methylpropane-2-sulfonamide (11.9 kg, 98.7 mol) into R1 at 15-20 °C.
4. Charge K₂CO₃ (20.0 kg, 145 mol) into R1 at 15-20 °C.
- 20 5. The reaction was heated to 60 °C and stirred at 60 °C for 5 hrs.
6. A sample was taken and diluted with ACN for monitoring. HPLC showed indicated 97.7 % of (S,Z)-N-((5,7-difluoro-3-methylbenzofuran-2-yl)methylene)-2-methylpropane-2-sulfonamide was detected.
7. The reaction mixture of R1 was cooled to 20 °C with circulating glycol (7 °C).
- 25 8. The solution of the reaction mixture was filtered with a pad of celite (20 kg) to remove (K₂CO₃) and the cake was washed with EtOAc (30 kg).

9. The organic phase was combined and washed with 15 % aq NaCl (100 kg) for twice.
10. The organic phase was continuously concentrated via vacuum distillation at 50 °C to give (S,Z)-N-((5,7-difluoro-3-methylbenzofuran-2-yl)methylene)-2-methylpropane-2-sulfinamide (25.1 kg, purity = 99.2 %) as light brown solid confirmed by HPLC.

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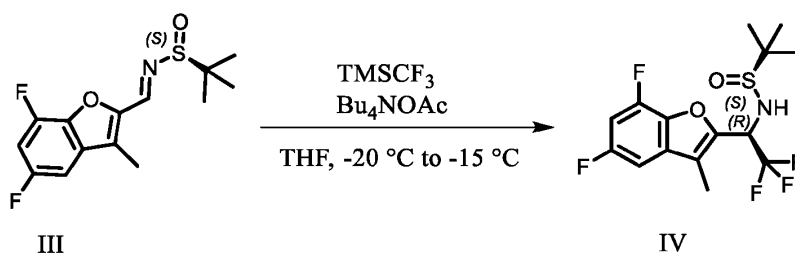
Example 10. cGMP Preparation of (S,Z)-N-((5,7-difluoro-3-methylbenzofuran-2-yl)methylene)-2-methylpropane-2-sulfinamide



10 Intermediate II (1 eq) was reacted with (S)-2-methylpropane-2-sulfinamide (1.02 eq) in the presence of potassium carbonate (1.5 eq) in THF (10 vols) at 35–45 °C for at least 14 hours until in-process control by HPLC indicated <3% Intermediate II remained versus Intermediate III. The reaction mixture was cooled to 15–25 °C then filtered. The mixture was distilled under vacuum to a concentrate (~3 vols) before ethanol (10 vols) was added and the batch distilled under vacuum to a concentrate (~3 vols). Ethanol (10 vols) was added, and the batch distilled under vacuum to a final concentrate (~5 vols). The solution was cooled to 15–25 °C, water (5 vols) was added, and the slurry was stirred for at least 14 hours. The batch was filtered, and the cake twice washed with ethanol–water (2 vols, 1:1). The isolated solids were dried at 40–50 °C under vacuum with nitrogen sweep to constant weight. Intermediate III was isolated in approximately 88% yield.

20

Example 11. Preparation of (S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide

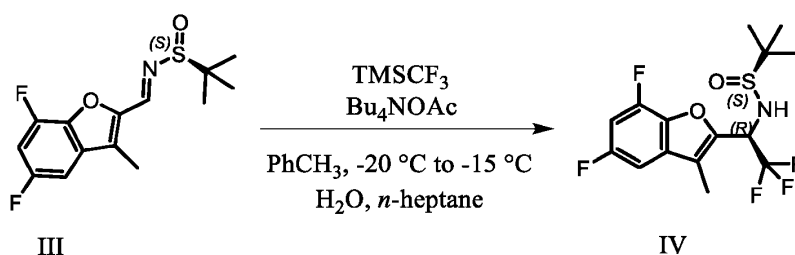
Protocol:

Using a 1000 L reactor (R1) with mechanical stirrer and temperature control under N₂ protection:

1. Charge THF (224 kg) into R1 at 15-20 °C.
- 5 2. Charge (S,Z)-N-((5,7-difluoro-3-methylbenzofuran-2-yl)methylene)-2-methylpropane-2-sulfonamide (III; 25.0 kg, 83.6 mol) into R1 at 15-20 °C.
3. Charge tetrabutylammonium acetate (25.1 kg 83.6 mol) into R1 at 15-20 °C.
4. The reaction was cooled to -20 °C to about -15 °C and stirred at -20 °C to about -15 °C for 1 hrs.
- 10 5. Charge TMSCF₃ (35.6 kg, 250 mol) dropwise at -20 °C to about -15 °C. (Keep the temperature below -15 °C)
6. A sample was taken and diluted with ACN for monitoring. HPLC showed 71.1 % of (S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfonamide was detected.
- 15 7. The reaction mixture was added to a solution of 10 % aq.NH₄Cl (1000 kg) in R2 at 0~5 °C under stirring.
8. The solution was extracted with EtOAc (180 kg×2) and the organic phase was wash with 15 % aq.NaCl 200 kg 2X.
9. The organic phase was continuously concentrated via vacuum distillation at 50 °C to give
- 20 crude (S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfonamide (52 kg) as light brown oil.
10. The crude was purified by column chromatography to obtain (S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfonamide (13.1 kg, 97.67 %, 42.5 % yield) as yellow solid.
- 25 Single diastereomer: HPLC purity (220 nM): 97.67 % (a/a); Chiral purity by SFC: % ee = 100 %
LC/MS: exact mass 369.08; *m/z* = 369.9 [M+H]⁺; ¹H NMR: (400 MHz, CHLOROFORM-d₆) δ

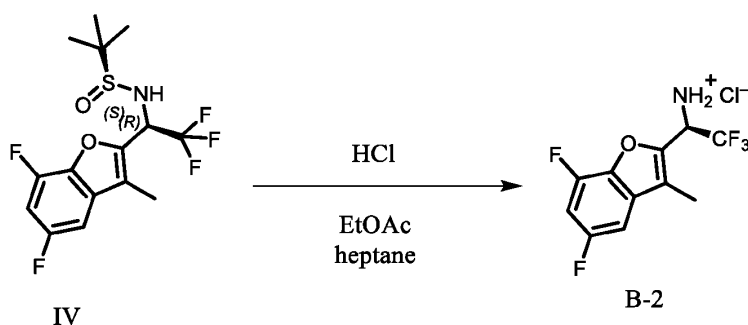
= 6.99 (dd, $J = 2.4, 7.6$ Hz, 1H), 6.91 - 6.84 (m, 1H), 5.04 (quin, $J = 7.2$ Hz, 1H), 4.29 (br d, $J = 8.0$ Hz, 1H), 2.28 (s, 3H), 1.299 (m, 9H). ^{19}F NMR $\delta = -74.288$ ppm.

Example 12. Preparation of (S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide



Intermediate III (1 eq) was dissolved in toluene (10 vols) and cooled to -20 to -10 $^\circ\text{C}$. Trimethyl(trifluoromethyl)silane (3 eq) was added over at least 1 hour before tetrabutylammonium acetate (1 eq) was added as a solid in ten equal portions maintaining the internal reaction temperature below -10 $^\circ\text{C}$. The reaction was stirred at -20 to -10 $^\circ\text{C}$ for at least 3 hours until in-process control by HPLC indicated $<0.5\%$ Intermediate III remained versus Intermediate IV. The reaction mixture was quenched into 10 wt% ammonium hydrochloride aqueous solution (20 vols) at -5 to 5 $^\circ\text{C}$. The lower aqueous layer was removed, and the organic layer was washed sequentially with water (5 vols), 5 wt% aqueous sodium bicarbonate (10 vols) twice, and water (5 vols) twice. The organic layer was co-distilled with toluene (10 vols) twice before filtering through a cartridge containing activated carbon. The mixture was distilled under vacuum to a concentrate (~ 5 vols). Water (3 vols) was added, and the mixture was distilled under vacuum to a concentrate (~ 3 vols). n-Heptane (5 vols) was added, and the batch distilled under vacuum to a concentrate (~ 3 vols). n-Heptane (3 vols) was added and IPC for the residual toluene demonstrated $<1\%$ by GC. The mixture was seeded with Intermediate IV (0.003 wt eq) and stirred for at least 24 hours at 20 $^\circ\text{C}$. The batch was filtered, and the cake washed with 1:1 n-heptane–water (2 vols). The isolated solids were dried at 25 – 35 $^\circ\text{C}$ under vacuum with nitrogen sweep to constant weight. Intermediate IV was isolated in approximately 50% yield.

Example 13. Preparation of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt



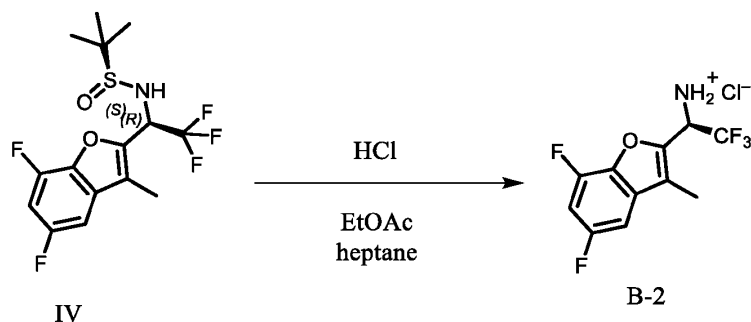
5 Protocol:

Using a dry 2.0 L reactor (R1) with mechanical stirrer and temperature control under N₂ protection:

1. Charged 1M HCl in EtOAc (570 mL, 2.1 eq, 5.7 V).
2. Cooled the content to 0-10°C.
- 10 3. Charged (S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfonamide (IV; 100.0 g, 1.0 eq).
4. Adjusted the batch temperature to 5-15°C.
5. HPLC analysis after 1 hour revealed 99.2 % conversion.
6. Slowly added heptane (1.5 L, 15.0 V) over 3 hours at 5-15°C.
- 15 7. Slowly cooled to -10°C over 6 hours.
8. Agitated at -10°C for 18 hours.
9. Filtered the solid and washed the filter cake with heptane (400 mL, 4.0 V).
10. Dried the wet cake at 50°C in a vacuum oven with a nitrogen bleed for 18 hours.
11. Dry cake was weighed at 75.1 g (95 % yield).

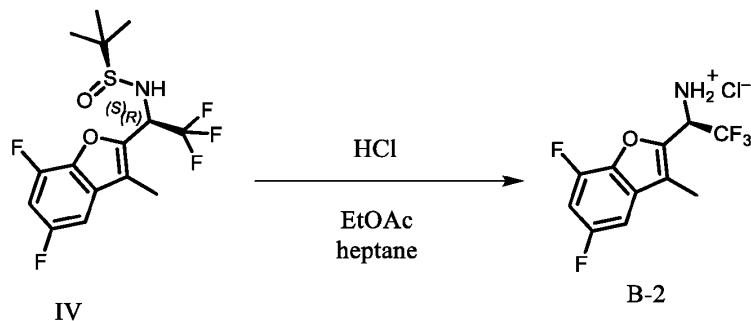
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Example 14. cGMP preparation of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt



Intermediate IV (1 eq) was treated with a solution of hydrogen chloride in ethyl acetate (~1M, 2.5 eq, ~6 vol) at 5–15 °C for at least 3 hours until in-process control indicated <1% Intermediate IV remaining versus Intermediate B-2. n-Heptane (15 vols) is added, the mixture cooled to –15 to –5 °C over 6 hours before being held at –15 to –5 °C for at least 24 hours to complete crystallization. The batch was filtered, and the filter cake washed twice with n-heptane (1 vol). The cake was dried at 40–50 °C under vacuum with nitrogen sweep for at least 16 hours until constant weight. Intermediate B-2 was isolated in approximately 70% yield.

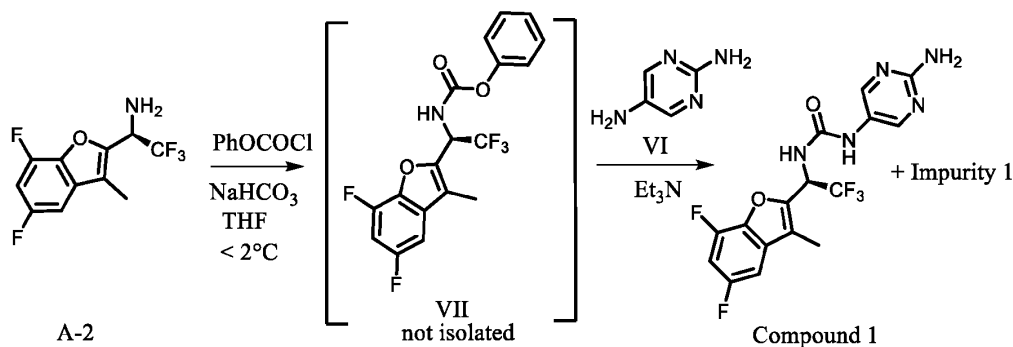
Example 15. Alternative cGMP preparation of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt



Intermediate IV was treated with a solution of hydrogen chloride in ethyl acetate (approx. 1 molar, 5 wt eq) at 5–15 °C for at least 1 hour until in-process control indicated < 1 area% Intermediate IV remaining versus Intermediate B-2. n-Heptane (10 wt eq) was added, and the mixture was cooled to –15 to –5 °C and held for at least 24 hours to complete crystallization. The batch was filtered, and the filter cake washed with n-heptane (2 x 1.4 wt eq). The cake was dried at 40–50 °C under vacuum with nitrogen sweep for at least 16 hours until constant weight. Intermediate B-2 was isolated in approximately 80% yield.

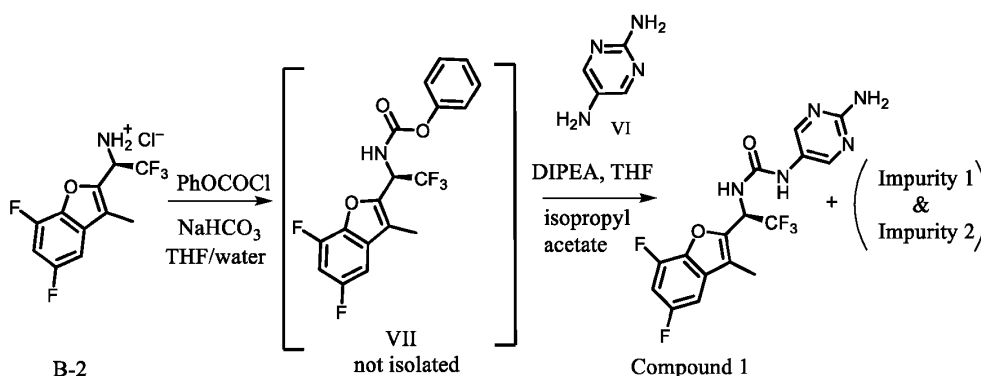
Example 16. Preparation of Compound 1 from (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine via one-pot tandem carbamate formation/condensation with pyrimidine-2,5-diamine

5



To a slurry of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine (A-2; 10 g, 1.0 eq) and NaHCO₃ (8.36 g, 3.0 eq) in 120 mL THF at 0°C under nitrogen was slowly added phenyl chloroformate (6.5 mL, 1.05 eq) while maintaining the batch temperature below 2°C. The resulting mixture was agitated at 0°C overnight to achieve 99.2 % conversion. TEA (9.2 mL, 2.0 eq) was slowly added while maintaining the batch temperature below 2°C. After 15 minutes, pyrimidine-2,5-diamine was added over 20 minutes. The reaction was then allowed to warm up to 30°C over 2 hours and was held at 30°C overnight to achieve completion. The workup was done by first quenching with 5 % NaHCO₃ (50 mL, 5V) and isopropyl acetate (100 mL, 10V) was used to extract the product. The product was crystallized from isopropyl acetate (40 mL, 4V) and heptane (140 mL, 14 V). The product was filtered and sequentially washed with 20 % IPAc/heptane (50 mL, 5 V), water (50 mL, 5 V) and then 20 % isopropyl acetate /heptane (50 mL, 5 V). After drying under vacuum at ambient temperature overnight, 11.5g (76 %) crude Compound 1 was obtained as an off-white solid with a HPLC purity of 98.6 % (peak area) with 1.3 % (peak area) 1,3-bis((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Impurity 1).

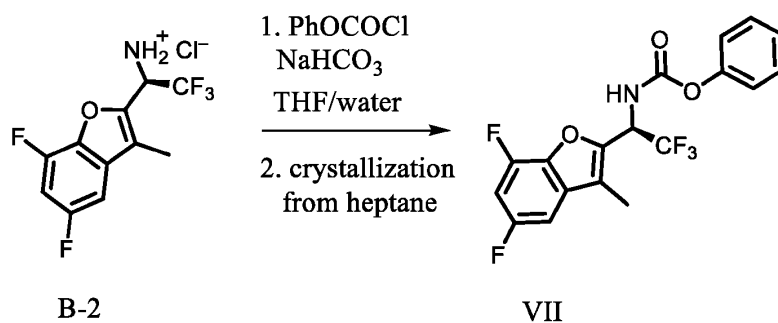
Example 17. Preparation of Compound 1 from (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt via one-pot tandem carbamate formation/condensation with pyrimidine-2,5-diamine



To a mixture of phenyl chloroformate (2.75 mL, 1.3 eq) and NaHCO₃ (4.9 g, 3.5 eq) in 50 mL (10 V) THF and 10 mL (2 V) water at 0°C under nitrogen was slowly added a solution of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt (B-2; 5.0 g, 1.0 eq) in 10 mL (2 V) THF and 5 mL (1 V) water over 1 hour while maintaining the batch temperature below 5°C. It was found that the reaction was clean and addition controlled, meaning that the reaction was completed upon completion of B-2 addition. Brine (10 % aq. NaCl, 20 mL, 4V) was added, and the batch was settled for layer separation. HPLC analysis of the aqueous layer revealed no loss of the intermediate carbamate (VII). DIPEA (5.8 mL, 2.0 eq) was added followed by a solution of pyrimidine-2,5-diamine (VI; 2.1 g, 1.15 eq) over an hour at 0- 10°C. The resulting mixture was agitated at 0-10°C under nitrogen overnight to give about 80 % conversion. The reaction was aged another day to achieve completion. The workup was done by first adding 20 mL water (4 V), settling and separating the layers. THF was partially removed from the organic layer under rotovap to about 25 mL (5V). The product in the aqueous layer was back-extracted using isopropyl acetate (50 mL, 10 V). The combined organic layer (5 V THF + 10 V isopropyl acetate) was washed with 5 % NaHCO₃ (25 mL, 5 V) to remove residual phenol and then 10 % brine (25 mL, 5 V). The final organic layer was concentrated to 10 mL (2 V) to afford a slurry and heptane (50 mL, 10 V) was slowly added as anti-solvent. After agitating at ambient temperature for few hours, the product was filtered and sequentially washed heptane (10 mL, 2 V). The wet cake was redissolved in isopropanol (30 mL, 6 V) and then concentrated at 45°C to about 15 mL (3V). Water (50 mL, 10V) was slowly added to afford a white slurry. The slurry was cooled to 0-10°C and was agitating at 0-10°C for few hours. The solid was filtered and washed with water (10 mL, 2 V). The wet cake was dried at 45°C in a vacuum oven with nitrogen bleed overnight to afford 5.3 g (78 %) of Compound 1 with an HPLC purity of 99.45 % (peak area) with 0.05 % (peak area) Impurity 1.

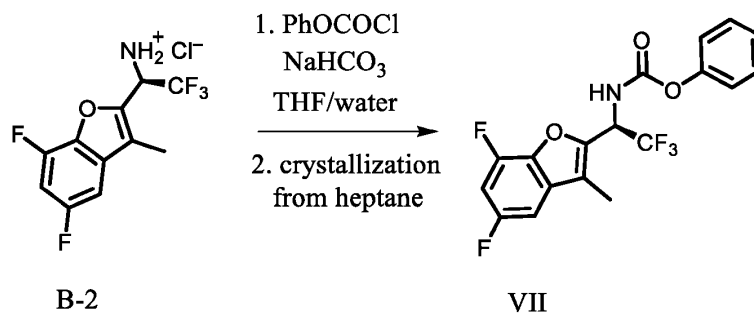
An additional impurity was observed at 0.50 % (peak area) as well; Impurity 2, identified as (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5-chloro-7-fluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (see **Table E7**) presumably formed under conditions of elevated chloride ion concentration as an exchange reaction of a chloride with one of the fluorines on the benzofuran ring). In repeat runs of this procedure, Impurity 1 was consistently obtained at a higher level (> 1.0 % peak area). Accordingly, it was concluded that in order to control levels of impurities, it was best to isolate the intermediate carbamate (VII) and then in a separate reaction condense it with VI to produce Compound 1.

Example 18. Preparation of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate



To a mixture of 15.2 g NaHCO₃ (3.0 eq) in 30 mL water and 120 mL THF at 0-5°C was added 10 mL phenyl chloroformate (1.3 eq) followed by slow addition of a solution of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt (B-2; 20 g, 1.0 eq) in 20 mL water and 40 mL THF over an hour. HPLC analysis revealed the reaction completion after 21 hours (i.e. 0.1 % B-2 remained). Water (50 mL) was added to completely dissolve NaHCO₃ and the batch was settled to cut the aqueous layer to waste. The organic layer was then washed with 100 mL 5 % NaHCO₃ aq. and THF was then displaced by heptane (100 mL) in which phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate (VII) was crystallized out as a white solid. Crude product was filtered and washed with 30 mL heptane. The wet cake was dried at 45-50°C in a vacuum oven with a nitrogen bleed overnight to afford 18.1 g (71 %) of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate as a white crystalline solid. The yield was later optimized to 80-90 % and the optimized procedure is shown in **Example 13**.

Example 19. Preparation of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate; an optimized procedure

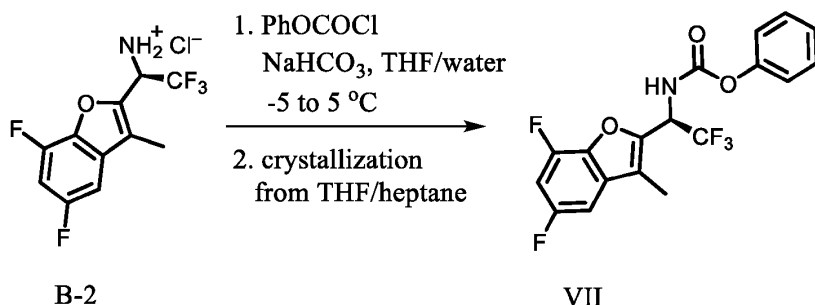


Protocol:

Using a 2 L jacketed flask with temperature control and nitrogen protection:

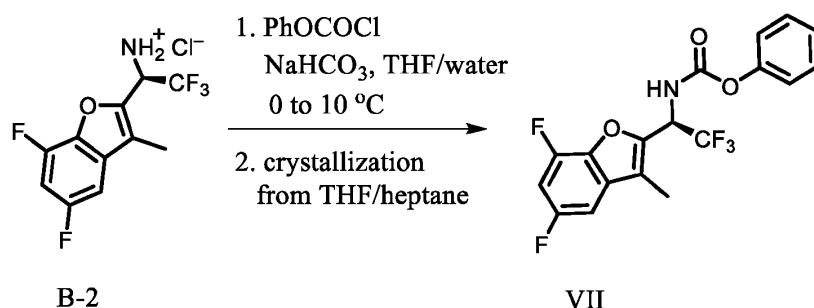
1. Charge NaHCO₃ (42.0 g, 3.0 eq).
2. Charge H₂O (100 mL, 2.0 V).
3. Charge THF (400 mL, 8.0 V).
4. Cool the content to 0-5°C.
5. Charge phenyl chloroformate (42 mL, 2.0 eq) at 0-5°C.
6. Slowly add a solution of 50.0 g (1.0 eq) (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride (B-2) in water (50 mL, 1.0 V) and THF (100 mL, 2.0 V) over 3 hours at 0-5°C.
7. HPLC analysis revealed 0.15 % B-2 after 2 hours.
8. Settle and separate the layers.
9. Concentrate the organic layer under reduced pressure at below 40°C to 150 mL (3 V).
10. Add heptane (300 mL, 6.0 V).
11. Concentrate under reduced pressure at below 40°C to about 150 mL (3 V).
12. Cool the slurry to -10°C and held at -10°C overnight (18 hours).
13. Filter and wash the cake with heptane (100 mL, 2 V).
14. Dry the wet cake at 40-45°C in a vacuum oven with a nitrogen bleed for 18 hours.
15. Dry cake weighed at 54.0 g (84.5 % yield) of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate as an off-white crystalline solid.

Example 20. cGMP preparation of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate



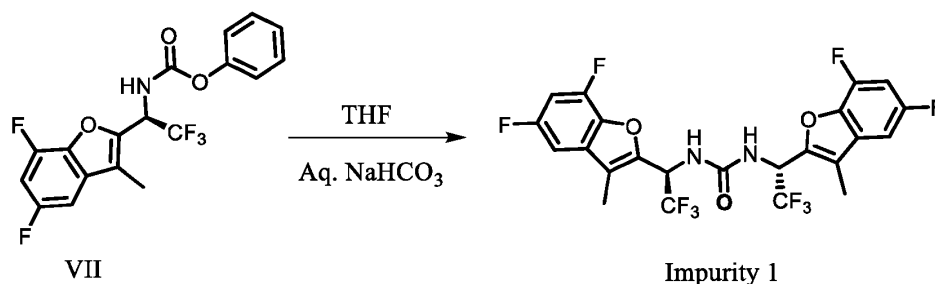
A solution of Intermediate B-2 (1 eq) in tetrahydrofuran (2 vols) and water (1 vol) was added to sodium bicarbonate (2 eq) and phenyl chloroformate (3 eq) in a mixture of tetrahydrofuran (8 vols) and water (2 vols) at -5 to 5 °C. The reaction mixture was agitated for approximately 3 hours before in-process control indicated $<0.5\%$ Intermediate B-2 versus Intermediate VII remaining. The lower aqueous layer was removed, and the organic layer distilled below 50 °C under vacuum to approximately 3 volumes. n-Heptane (6 vols) was added, and the mixture stirred at 40 – 50 °C for at least 30 minutes before the lower aqueous layer was removed. The organic layer was distilled at 35 – 50 °C under vacuum to approximately 3 volumes and polish filtered. The solution was heated to 40 – 50 °C before n-heptane (6 vols) was added and the solution distilled at 35 – 50 °C under vacuum to approximately 5 volumes, before IPC demonstrates residual tetrahydrofuran $\leq 0.2\%$ by GC. The mixture was cooled to -10 to 0 °C over at least 2 hours then stirred at -10 to 0 °C for at least 18 hours. The batch was filtered, the filter cake was washed with to n-heptane (4 vols) at -10 to 0 °C and dried at 40 – 50 °C under vacuum with nitrogen sweep to constant weight. Intermediate VII was isolated in approximately 95% yield.

Example 21. Alternative cGMP preparation of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate



A solution of Intermediate B-2 (1 eq) in tetrahydrofuran (1.8 wt eq) and water (1 wt eq) was added to sodium bicarbonate (2.2 mol eq) and phenyl chloroformate (2.0 mol eq) in a mixture of tetrahydrofuran (6.2 wt eq) and water (2 wt eq) at 0–10 °C. The reaction mixture was agitated for approximately 1 hour before in-process control indicated < 0.5 area% Intermediate B-2 remaining. The lower aqueous layer was removed, and the organic layer distilled below 50 °C under vacuum to approximately 3 volumes. n-Heptane (3.4 wt eq) was added, and the mixture stirred at 40–50 °C for at least 30 minutes before the lower aqueous layer was removed. The organic layer was distilled at 35–50 °C under vacuum to approximately 3 volumes before n-heptane (3.4 wt eq) was added and the solution distilled at 35–50 °C under vacuum to approximately 3 volumes. n-Heptane (1.4 wt eq) was added, and the solution was cooled to 35–40 °C before Intermediate VII seed (0.5 mole eq) was added. The mixture was distilled to approximately 4 volumes before being cooled to –10 to 0 °C, over at least 3 hours. The batch was filtered and dried at 40–50 °C under vacuum with nitrogen sweep to constant weight. Intermediate VII was isolated in approximately 80% yield.

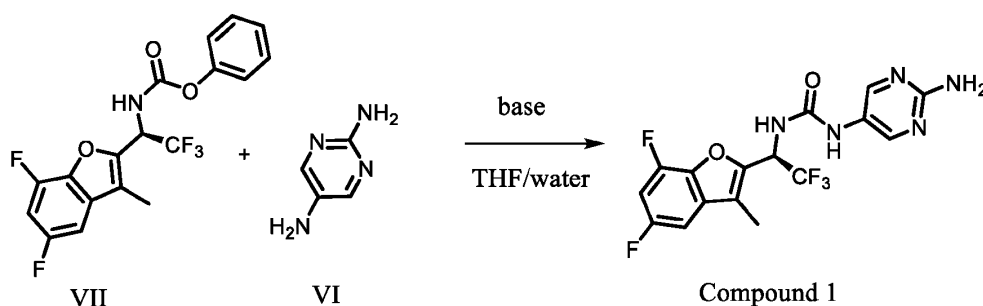
Example 22. Preparation of 1,3-bis((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Impurity 1)



A solution of phenyl (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate (VII) in THF was treated with 5 % aqueous NaHCO₃ to neutral pH then

kept in the refrigerator to afford 31 % 1,3-bis((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Impurity 1) over the weekend and then 65 % of Impurity 1 after another 3 days at room temperature. Since Impurity 1 is not soluble in THF/heptane while carbamate VII is, the isolation of Impurity 1 from the THF solution containing VII/Impurity 1 (35 %/ 65 %) was accomplished by crystallization in THF/heptane to obtain 1,3-bis((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Impurity 1) as a white crystalline solid.

Example 23. Base screen for preparation of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1) from pyrimidine-2,5-diamine (VI) and Carbamate VII



Pyrimidine-2,5-diamine (VI) is highly soluble in water, while phenyl (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethylcarbamate (VII) has limited stability in aqueous media. Thus, it was anticipated that the selection of base might have an effect on the efficiency of the desired urea formation relative to the side-reactions that lead to Impurity 1 or other possible impurities. A base screening was performed in THF/water solvent system in the following protocol:

To a mixture of 80 mg (1.1 eq) pyrimidine-2,5-diamine (VI) and base (3.0 eq) in THF (2 mL) and water (2 mL) at ambient temperature was added dropwise a solution of 250 mg (1.0 eq) phenyl (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethylcarbamate (VII) in THF (2 mL). The resulting mixture was agitated at ambient temperature and samples were taken at 1 hour, 4 hours and 20 hours for HPLC analysis. The results are summarized in **Table E2**.

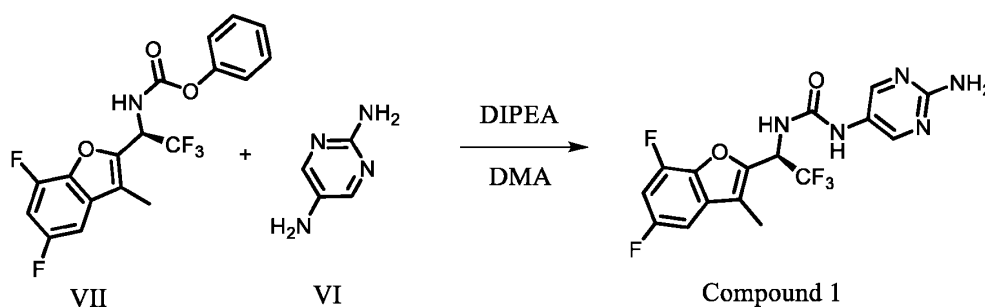
Table E2. Effect of base on relative percentage (peak area %) of compounds in reaction mixture

base	% A-2	% Compound 1	% Impurity 2	% VII	% Impurity 1
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NaHCO ₃	4.88% (1h)	68.73% (1h)	0.21% (1h)	20.97% (1h)	5.21% (1h)
	7.79% (4h)	82.05% (4h)	0.26% (4h)	0.00% (4h)	9.17% (4h)
	2.91% (20h)	84.77% (20h)	0.25% (20h)	0.00% (20h)	11.22% (20h)
K ₂ CO ₃	8.07% (1h)	87.21% (1h)	0.25% (1h)	3.29% (1h)	1.18% (1h)
	7.47% (4h)	88.53% (4h)	0.23% (4h)	0.00% (4h)	2.17% (4h)
	7.59% (20h)	85.57% (20h)	0.17% (20h)	0.00% (20h)	2.19% (20h)
K ₃ PO ₄	29.57% (1h)	69.94% (1h)	0.16% (1h)	0.00% (1h)	0.34% (1h)
	27.23% (4h)	61.07% (4h)	0.21% (4h)	0.00% (4h)	0.42% (4h)
	26.86% (20h)	58.37% (20h)	0.27% (20h)	0.00% (20h)	0.51% (20h)
DIPEA	8.34% (1h)	79.28% (1h)	0.23% (1h)	8.11% (1h)	4.05% (1h)
	4.62% (4h)	87.11% (4h)	0.25% (4h)	0.29% (4h)	6.97% (4h)
	2.61% (20h)	87.63% (20h)	0.22% (20h)	0.00% (20h)	7.90% (20h)
TEA	15.19% (1h)	73.19% (1h)	0.22% (1h)	0.64% (1h)	10.24% (1h)
	8.05% (4h)	76.95% (4h)	0.24% (4h)	0.00% (4h)	13.84% (4h)
	7.29% (20h)	76.65% (20h)	0.19% (20h)	0.00% (20h)	15.00% (20h)

As shown in **Table E2**, for the inorganic bases, the trend was identified that the weaker base (NaHCO₃) the more Impurity 1 (11.22 % at 20 h) and the stronger base (K₃PO₄) the less Impurity 1 (2.19 % at 20 h). However, more A-2 was obtained with the stronger base as a result of the hydrolysis, e.g., 29.57 % at 1 h. For the organic base, DIPEA outperformed TEA under the same conditions.

Example 24. Preparation of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1) from pyrimidine-2,5-diamine (VI) and Carbamate VII in DMA



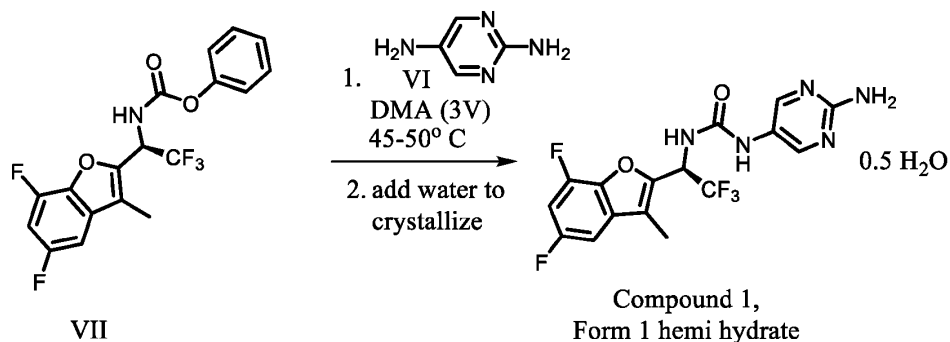
It was found that pyrimidine-2,5-diamine is highly soluble in *N,N*-dimethylacetamide (DMA) and it was anticipated that the formation of Impurity 1 would be reduced if the urea formation is run under anhydrous conditions. Indeed, condensation of carbamate VII with

pyrimidine-2,5-diamine (VI) in anhydrous DMA cleanly produced the desired Compound 1 in the presence of DIPEA in the following procedure:

A mixture of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate (VII; 0.5 g, 1.0 eq), pyrimidine-2,5-diamine (VI; 0.15 g, 1.1 eq) and DIPEA (0.5 mL, 2.2 eq) in 5 mL (10 V) anhydrous DMA was agitated at ambient temperature under nitrogen. HPLC analysis after 1 hour revealed 99.7 % (peak area) pure Compound 1, with 0.3 % (Peak area) Impurity 2, and no detectable level of Impurity 1.

The above reaction conditions were tested in the absence of DIPEA and it was found that the reaction was clean but slower than observed in the presence of DIPEA. In particular, for a 5 g scale reaction, there was 72 % conversion after 3 hours at ambient temperature and 100 % conversion after 18 hours. Accordingly, it was concluded that DIPEA catalysis was preferred.

Example 25. Preparation of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1, Form 1 hemihydrate) from pyrimidine-2,5-diamine (VI) and Carbamate VII in DMA with crystallizations



Protocol:

1. Under nitrogen at room temperature, charge pyrimidine-2,5-diamine (VI; 6.3 g, 1.1 eq).
2. Charge phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate (VII; 20.0 g, 1.0 eq).
3. Charge anhydrous DMA (60 mL, 3 V).
4. Agitate at 45-50°C.
5. HPLC analysis showed completion after 3 hours.
6. Cool to room temperature.

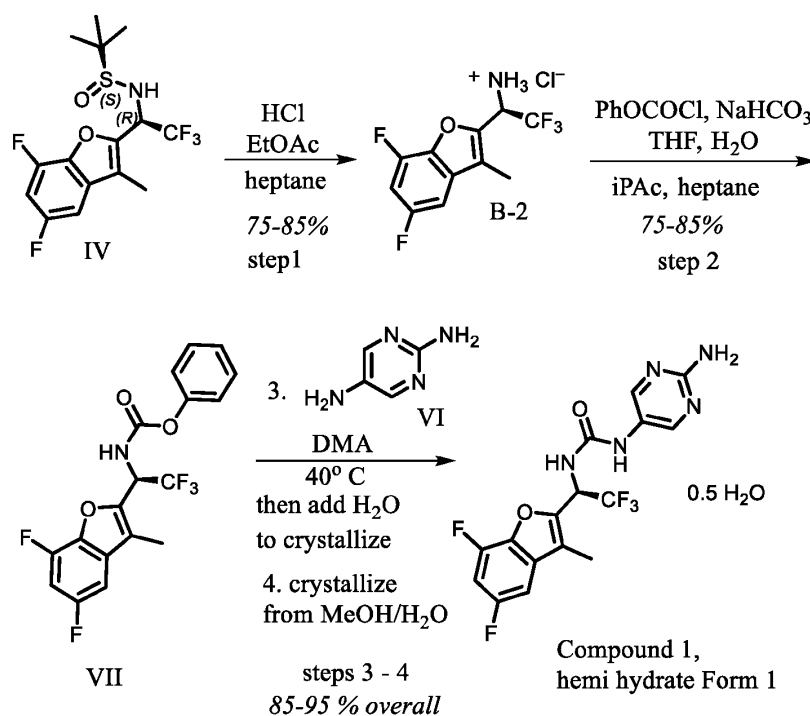
7. Add slowly 200 mL (10 V) water over 2 hours.
8. Agitate the slurry at room temperature for another 3 hours.
9. Filter and wash the cake with 80 mL (4 V) water.
10. Dry at 40°C in a vacuum oven with a nitrogen bleed overnight (22 h).
- 5 11. Dry cake weight at 20.1 g (98.6 % yield) crude Compound 1 as a white solid.
12. HPLC analysis revealed 99.11 % (peak area) Compound 1 with 0.39 % (peak area) Impurity 2, and 0.04 % (peak area) Impurity 1, plus two unknown impurities at RRT 1.16 = 0.14 % (peak area) and RRT 1.32 = 0.11 % Peak area).
13. Redissolve the crude API in isopropyl alcohol (80 mL, 5 V) at 50-60°C.
- 10 14. Concentrate to 50 mL (2.5V) at 40-60°C.
15. Cool to 20-30°C.
16. Slowly add 150 mL water (7.5 V) over 2 hours.
17. Agitate at 20-30°C for 3 hours.
18. Filter and wash the filter cake with water (80 mL, 4 V).
- 15 19. Dry at 40°C vacuum oven with a nitrogen bleed for 20h to afford 19.5 g (97 % yield) of Compound 1.

HPLC (% peak area) = 99.06 % Compound 1, 0.38 % Impurity 2, 0.05 % Impurity 1 and chiral purity of 100.0 %; KF = 2.5% (w/w) water; and XRPD = Form 1. FIG. 1 depicts the XRPD diffractogram of Compound 1, Form 1 hemi hydrate. FIG. 2 Depicts the TG/DSC thermogram of Form 1. FIG. 3 Depicts the DSC thermogram (first heat cycle) of Form 1. FIG. 4 Depicts the DSC thermogram (first cool cycle) of Form 1.

20

Example 26. cGMP synthesis of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1, Form 1 hemihydrate) from 5 pyrimidine-2,5-diamine (VI) and (S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (IV)

25



NOTE: Stoichiometry and operational parameters are all approximate. All solvent charges are weight based and +/- 10 %

Overview of Synthetic steps

5 *Step 1. Preparation of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt*

(S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfonamide (IV) was treated with a solution of hydrogen chloride in ethyl acetate (approx. 1 molar, 5 wt eq) at 5–15 °C for at least 1 hour until IPC indicated < 1 area % IV remaining versus title compound. *n*-Heptane (10 wt eq) was added, the mixture cooled to –15 to –5 °C and held for at least 24 hours to complete crystallization. The batch was filtered, and the filter cake washed with *n*-heptane (2 x 1.4 wt eq). The cake was dried at 40–50 °C under vacuum with nitrogen sweep for at least 16 hours until constant weight. (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt (B-2) was isolated in approximately 80 % yield.

Step 2. Preparation of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate

A solution of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt (B-2; 1 eq) in THF (1.8 wt eq) and water (1 wt eq) was added to sodium bicarbonate (2.2 mol eq) and phenyl chloroformate (2.0 mol eq) in a mixture of THF (6.2 wt eq) and water (2 wt eq) at 0–10 °C. The reaction mixture was agitated for approximately 1 hour until HPLC monitoring indicated < 0.5 area % starting material remaining. The lower aqueous layer was removed, and the organic layer distilled below 50 °C under vacuum to approximately 3 volumes. *n*-Heptane (3.4 wt eq) was added, and the mixture stirred at 40–50 °C for at least 30 minutes before the lower aqueous layer was removed. The organic layer was distilled at 35–50 °C under vacuum to approximately 3 volumes before *n*-heptane (3.4 wt eq) was added and the solution distilled at 35–50 °C under vacuum to approximately 3 volumes. *n*-Heptane (1.4 wt eq) was added, and the solution was cooled to 35–40 °C before Intermediate VII seed (0.5 mole eq) was added. The mixture was distilled to approximately 4 volumes before being cooled to –10 to 0 °C over at least 3 hours. The batch was filtered and dried at 40–50 °C under vacuum with nitrogen sweep to constant weight. The title compound was isolated in approximately 80 % yield.

Step 3. Preparation of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea

A mixture of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate (VII; 1 eq) and pyrimidine-2,5-diamine (VI; 1.1 eq) in DMAc (2.8 wt eq) was heated at 35–45 °C for approximately 6 hours until HPLC monitoring indicated VII was <0.5 area %. The batch was cooled to 15–25 °C and purified water (12 wt eq) added slowly. The batch was agitated for approximately 6 hours before being filtered and washed twice with water (2 wt eq and 5 wt eq). The product was dried at 35–45 °C under vacuum to constant weight.

Step 4. Preparation of Compound 1 base hemi-hydrate Form 1

The intermediate product from Step 3 was dissolved in methanol (6.3 wt eq) at 20–30 °C before being polish-filtered through a 0.2-micron filter followed by a reactor rinse (1.6 wt eq). The batch was cooled to 15–25 °C before purified water (0.5 wt eq) was added via a 0.2-micron filter followed by addition of Compound 1 free base hemi-hydrate Form 1 seed (0.01 wt eq). The

mixture was agitated at 15–25 °C for approximately 3 hours before purified water (4.5 wt eq) was added via a 0.2-micron filter over a period of approximately 8 hours. The batch was then agitated 15–25 °C for approximately 16 hours to effect crystallization completion. The batch was filtered and washed with a pre-mixed solution of methanol (1.1 wt eq) and purified water (0.7 wt eq) via a 0.2-micron filter. Product was dried at 35–45 °C under vacuum with nitrogen sweep for at least 24 hours until constant weight and KF indicates water content of 2.0–2.6 wt %. Compound 1 base hemi-hydrate Form 1 was discharged to double LDPE liner-bags in a HDPE drum. The expected yield was approximately 90 %.

cGMP Protocols

Step 1. Preparation of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt

The conversion of (S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (IV, from **Example 8**; 16.00 kg, 1.0 eq) to (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt (B-2) was accomplished using 1M HCl in EtOAc. First, the deprotection reaction was performed at 5–10°C using 2.1 eq HCl (1M in EtOAc, 97.18 kg) overnight (i.e. 11 hours) to achieve the completion at which stage the desired salt crystallized out of the solution. Heptane (164.06 kg) was slowly added as an anti-solvent over 3 hours to maximize the yield. The resulting slurry was agitated at 5–10°C over the weekend. The product was filtered using the filter-dryer and the filtercake was washed with heptane (44.66 kg). The wet cake was dried under vacuum with a nitrogen bleed and intermittent agitation at the jacket temperature of 50°C for 24 hours to afford 11.51 kg (83.2 %) of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt with a UPLC purity of 99.7% (peak area), assay of 94.5 % (w/w) and HPLC chiral purity of 99.4 % (peak area).

Equipment

Reactor 1 (RI): 400 L, Glass, 23 V, Temp Range: -15 – 15°C, Pressure Range: Full Vacuum to Atmospheric

Receiver (VI): Glass-Lined or Hastelloy; As Needed

Filter Dryer (DI): Max Temp: 50°C, Pressure Range: Full Vacuum to Atmospheric

Protocol:

1. Prepared R1 by charging nitrogen and pulling vacuum and repeating as needed to maintain under nitrogen during the process.
- 5 2. Charged 97.18 kg of HCl Solution 1.0 M in EtOAc (charging range: 94.31 – 100.04 kg) into R1.
3. Turned on agitation and cooled contents of R1 to 8°C.
4. Charged 12.86 kg into R1 (charging range 12.77 – 13.03 kg).
5. Charged 3.10 kg of (S)-N-((R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)-
- 10 2-methylpropane-2-sulfinamide (IV) into (charging range 3.07 – 3.13 kg).
6. Held contents of R1 at 5-10°C overnight for ~11 hr.
7. Took sample of mixture from R1 to test reaction conversion. Result passed criteria (SM not detected).
8. Charged 164.06 kg of heptane into R1 slowly over 3 hr 11 min while maintaining temperature
- 15 of R1 5-7°C.
9. Slowly cooled contents of R1 from 7°C to -11°C over 6 hours.
10. Held contents of R1 at -11 to -10°C for 2 days 7 hr 28 min.
11. Filtered contents of R1 through Filter D1 with filtrate sent to V1. The jacket of the filter dryer was set to 0°C.
- 20 12. Drained filtrate from V1 and weighed 184.20 kg.
13. Charged 22.26 kg of heptane into R1 to rinse reactor walls and impeller blades and then transferred contents to wash wet cake in filter dryer with filtrate sent to receiver.
14. Charged 22.40 kg of heptane into R1 to rinse reactor walls and impeller blades and then transferred contents to wash wet cake in filter dryer with filtrate sent to receiver.
- 25 15. Drained contents of V1 to a closed top HDPE drum. Net weight: 49.60 kg.
16. Held material in filter dryer over night for 17 hr 10 min with a jacket temperature of 50°C and an internal temp of ~27°C.
17. Continued to dry and turned on agitation in the filter dry intermittently for another 23 hr 50 min.
- 30 18. Took Sample of material from filter dryer. Results passed criteria (see **Table E3**).
19. Packaged bulk material for use in next production step. Net weight packaged: 11.26 kg.

Table E3. Analytical results for cGMP batch of Intermediate B-2

Test/criteria	Result for B-2 cGMP batch
HPLC Purity ≥ 99.0 % (a/a)	99.7 % (a/a)
HPLC Assay: 90.0- 100.0 % (w/w)	94.5 % (w/w)
Residual Solvents by GC: Heptane ≤ 5000 ppm Ethyl Acetate ≤ 5000 ppm	Heptane: 4236 ppm Ethyl Acetate: < LOQ (100 ppm)
Residual Impurity 5 by GC: Report Result (ppm)	7022 ppm
Visual Appearance: White to yellow solid	White solid
Chiral purity by HPLC ≥ 99.0 % (a/a)	99.4 % (a/a)

Step 3. Preparation of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate

The conversion of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt (B-2; 11.24 kg, 1.0 eq) to phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate (VII) was done using phenyl chloroformate (17.72 kg) in the presence of NaHCO₃ (8.62 kg) in THF (90.24 kg) and water (33.80 kg). Upon the reaction completion, the reaction mixture was settled and the layers were separated. THF was swapped to heptane via vacuum distillation at below 50°C. The resulting slurry in heptane (45 L, 4 V) was cooled to 0°C and was agitated at 0°C for about 10 hours. The product was filtered in the filter-dryer and the filtercake was washed using the cold mother liquor. The wet cake was dried under vacuum with a nitrogen bleed and intermittent agitation at the jacket temperature of 50° C until KF ≤ 0.5 % (w/w). The dry cake was 13.10 kg (80.6 %) VII with a UPLC purity of 98.2 % (peak area) and assay of 83.5 % (w/w).

Equipment

Reactor 1 (R1): Hastelloy, 16V, temp range: -10 – 50°C, pressure range: full vacuum to atmospheric

Reactor 2 (R2): glass, 3 V, temp range: 20 – 30°C, pressure range: full vacuum to atmospheric

Reciever (V1): Hastelloy; As Needed

Reciever (V2): glass-lined; as Needed

Filter Dryer (DI): Max Temp: 50°C, Pressure Range: Full Vacuum to Atmospheric

Protocol:

1. Prepared R1 and R2, as well as V1 and V2, and D1 by charging nitrogen and pulling vacuum and repeating as needed to maintain under nitrogen during the process.
- 5 2. Charged 11.24 kg of (R)-1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethan-1-amine, hydrochloride salt (B-2) into R2 followed by 11.30 kg of purified water followed by 20.04 kg of THF into R2.
3. Charged 8.62 kg of sodium bicarbonate (target range: 8.35 – 8.87 kg) into R1.
4. Charged 22.50 kg of purified water (target range: 21.39 – 23.65 kg) into R1.
- 10 5. Charged 70.2 kg of THF (target range: 66.55 – 73.53 kg) into R1 and turned on agitation.
6. Cooled contents of R1 from 20°C to 3°C
7. Charged 11.72 kg of phenyl chloroformate slowly over 19 min while maintaining temperature at 1-3°C.
8. Slowly transferred solution of B-2 from R2 to R1 over 3 hr 5 min while maintaining temperature of R1 at 1-2°C.
- 15 9. Charged 10.0 kg of THF into R2 to rinse reaction. Transferred rinse from R2 to R1 slowly while maintaining temperature at 1-2°C.
10. Agitated contents of R1 for 1 hour 25 min.
11. Took sample of mixture from R1 to test reaction conversion. Results failed criteria: 47.4 %
(peak area).
- 20 12. Charged 3.00 kg of phenyl chloroformate into R1 carefully while maintaining temperature 3-6°C and held contents of R1 at 4-6°C for 1 hour with constant agitation.
13. Took Sample of mixture from R1 to test reaction conversion. Results failed criteria: 5.89 %
(peak area).
- 25 14. Charged 3.00 kg of phenyl chloroformate into R1 carefully while maintaining temperature 4°C and held contents of R1 at 4°C for 12 hr 10 min with constant agitation.
15. Took sample of mixture from R1 to test reaction conversion. Results passed criteria: 0.05 %
(peak area).
16. Stopped agitation in R1 for 30 min and allowed phases to separate. Transferred bottom aqueous
30 layer to V1 and drain contents of V1 into drum. Net weight of aqueous layer: 39.0 kg. 17.

- Concentrated contents of R1 while maintaining temperature < 50°C targeting final volume of ~34L. Collected a total of 68.6 kg of distillate.
18. Charged 38.6 kg of heptane into R1 and adjusted temperature to 48°C.
19. Agitated contents of R1 for 15 min, then stopped agitation and held of 30 min to allow phases to separate.
20. Transferred bottom aqueous layer to V1 and drain contents of V1 into drum. Net weight of aqueous layer: 3.8 kg.
21. Concentrated contents of R1 while maintaining temperature < 50°C targeting final volume of ~34L. Collected a total of 34.4 kg of distillate.
22. Charged 38.6 kg of heptane into R1.
23. Concentrated contents of R1 while maintaining temperature < 50°C targeting final volume of ~56L. Collected a total of 19.6 kg of distillate.
24. Adjusted temperature of R1 from 46°C to 40°C.
25. Took sample of mixture from R1 to test for residual THF. Results passed criteria.
26. Verified solution in R1 was clear then charged 56.5 g of VII crystal seeds into R1. Following seed charge, seeds were observed to persist in solution.
27. Agitated contents in R1 for 2 hours at 38°C.
28. Concentrated contents of R1 while maintaining temperature 25-40°C targeting final volume of ~45L. Collected a total of 8.0 kg of distillate.
29. Adjusted temperature of R1 from 28°C to 37°C.
30. Adjusted Temperature of R1 adjusted to 25°C.
31. Charged 19.28 kg of heptane into R1 slowly over 2 hours at ambient temperature.
32. Slowly cooled contents of R1 from 20°C to 0°C over 9 hours 41 min with constant agitation.
33. Filtered contents of R1 through D1 with filtrate sent to V1. The jacket of the filter dryer was set to -10-0°C.
34. The filtrate was used to rinse R1 and V2 which was transferred to wash the wetcake in D1.
35. All filtrate was collected in HDPE drum. Net Weight: 28. kg
36. Material was held in the filter-dryer with a jacket temperature of 50°C for 3 days 16 hr 18 min.
37. Took sample of material from filter dryer to test water content. Results failed criteria: 0.6 % w/w

38. Held product in D1 for an additional ~17 hr. Took sample of material from filter dryer to test water content. Results passed criteria: 0.5 % w/w.
39. Took sample of material from filter dryer to test purity and assay. Results failed to reach criteria (see **Table E4**). Approved to move forward.
- 5 40. Packaged 13.05 kg of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate (VII). Total yield: 13.10 kg before sampling.

Table E4. Analytical results for cGMP batch of Intermediate VII

Test/criteria	Result for VII cGMP batch
Water content by KF ≤ 0.5 % (w/w)	0.5 % (w/w), Pass
Appearance: Report Result	Off-white solid
Purity by UPLC ≥ 99.0 % (a/a)	98.2 % (a/a), Fail
UPLC ≥ 90.0 % (w/w)	83.5 % (w/w), Fail

10 *Steps 4-5. Preparation of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1), hemi-hydrate Form 1*

Compound 1, hemi-hydrate Form 1 was prepared from phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate (VII; 13.02 kg) and pyrimidine-2,5-diamine (VI; 4.06 kg from combined VI-B1 and VI-B1 batches of **Example 4**) in DMA at 40°C.

15 First, a mixture of VII (13.02 kg) and VI (4.06 kg) in DMA (36.46 kg) was agitated at 40°C overnight (i.e. 12 hours 36 minutes) to achieve the completion. The reaction mixture was cooled to 20°C followed by slow addition of water (156.6 kg) to crystallize the product out of solution. The solid was filtered in the filter-dryer with agitator and the filter cake was washed with water. The wet cake was dried under vacuum with a nitrogen bleed and intermittent agitation at the jacket

20 temperature up to 65°C for 18 hours to afford 13.16 kg crude Compound 1 containing 13.5 % (w/w) water. Secondly, the crude Compound 1 was dissolved in MeOH (74.2 kg) followed by polish filtration using an in-line cartridge filter in which another 18.6 kg MeOH was used as a rinse. To this MeOH solution was added 4.41 kg water and then 115.9 g of Compound 1 hemi-hydrate Form 1 seeds. The resulting mixture was agitated at 20°C for 3 hours and water (53.32 kg)

25 was slowly added over 8 hours to maximize the yield. After agitating at 20°C overnight (17 hours), the solid was filtered in the filter-dryer and the filter cake was washed with a pre-mixed 20.4 kg MeOH:water (2:1). The wet cake was dried under vacuum with a nitrogen bleed and intermittent

agitation at the jacket temperature of 40°C for 45 hours to afford 10.87 kg Compound 1 with a UPLC purity of 99.9 % (peak area), assay of 100.4 % (w/w) and HPLC chiral purity of 100.0 (peak area or ee).

5 Equipment

Reactor 1 (R1): Hastelloy, 14 V, temp range: 15 – 45°C, pressure range: full vacuum to atmospheric

Reactor 1 (R2): glass-lined; as Needed

Receiver (V1): Hastelloy; As Needed

10 Filter Dryer (D1): Max Temp: 50°C, Pressure Range: Full Vacuum to Atmospheric

Protocol:

1. Charged 13.02 kg of phenyl (R)-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)carbamate (VII) into R1.
- 15 2. Charged 4.06 kg of pyrimidine-2,5-diamine (VI) into R1.
3. Charged 36.46 kg of N,N-Dimethylacetamide into R1.
4. Turned on agitation and adjusted temperature of R1 to 40°C.
5. Held contents of R1 at ~40°C overnight for 12 hr 36 min with constant agitation.
6. Took sample of mixture from R1 to test reaction conversion. Results passed criteria.
- 20 7. Cooled contents of R1 from 40°C to 19°C.
8. Charged 156.6 kg of water slowly over 3 hours into R1 then held for 6 hours 5 min at 19-20°C with constant agitation.
9. Transferred contents from R1 to D1 to filter contents with filtrate sent to V1.
10. Rinsed R1 with 26.4 kg of water and transferred rinse to wash wetcake in D1.
- 25 11. Cleaned R1 with methanol as needed – 14.0 kg – and transferred to waste.
12. Charged 67.2 kg of water directly into D1 and slurried with agitation in D1 for 1 hour. Then filtered contents with filtrate sent to V1.
13. Held product in filter dryer under vacuum with jacket temperature set at 40-60°C with intermittent agitation for 11 hours 22 min
- 30 14. Charged 68.4 kg of water directly into D1 and slurried cake for 1 hour. Then filtered contents of D1 with filtrate sent to V1.

15. Charged 62.4 kg of water directly into D1 and slurried cake for 1 hour. Then filtered contents of D1 with filtrate sent to V1.
16. Held product in filter dryer under vacuum with jacket temperature set at 40-65°C with intermittent agitation for 17 hours 52 min.
- 5 17. Took sample of material from filter dryer to test water content. Results failed criteria. Result: 15.3 % w/w.
18. Held product in filter dryer under vacuum for 50 min with jacket temperature set at ~65°C with intermittent agitation.
19. Took sample of material from filter dryer to test water content. Results failed criteria. Result:
- 10 13.5 % w/w.
20. Transferred filter cake from D1 into clean tared container. Net weight: 13.16 kg.
21. Established new unit value, Y = 11.67 kg based on the assay-corrected amount of Compound 1.
22. Charged 13.11 kg of Compound 1 from packaged into R1.
- 15 23. Charged 74.2 kg of methanol into R1.
24. Turned on agitation and adjusted temperature to 22°C. Held contents at 22-24°C for ~ 1 hr.
25. Visually confirmed contents in R1 were fully dissolved before proceeding.
26. Performed polish filtration by transferring contents of R1 to R2 with vacuum through in-line cartridge filter.
- 20 27. Rinsed R1 with 18.6 kg of methanol and transferred rinse to R1 through in-line cartridge filter.
28. Cleaned R1 using methanol as needed.
29. Pre-mixed solution of methanol-water in R1: Charged 12.4 kg of methanol into R1 via in-line cartridge filter. Then charged 8.0 kg of water into R1 via in-line cartridge filter.
- 25 30. Agitated contents of R1 for 23 min at 21-24°C.
31. Turned on agitation in R2
32. Charged 4.41 kg of water into R2 via in-line cartridge filter.
33. Charged 115.9 g of Compound 1 hemi-hydrate Form 1 seeds into R2.
34. Agitated R2 for 3 hours at 20-21°C.
- 30 35. Charged 53.32 kg of water through cartridge filter slowly over 8 hours.
36. Held contents of R2 at 17-21°C for ~17 hours with constant agitation.

37. Transferred contents from R2 to D1 to filter contents.
38. Transferred contents of R1 (MeOH:water 2:1 Solution) to rinse R2 and transferred rinse to slurry wash wetcake in D1.
39. Held product in the filter-dryer with a jacket temperature of 40°C for 1 day 20 hr 36 min with intermittent agitation.
40. Took sample of material from filter dryer to test water content and residual solvents. Results Passed Criteria.
41. Took sample of material from filter dryer to test purity and assay. Results passed criteria (see **Table E5**).
42. Packaged bulk material from filter dryer into tared clean container (HDPE drum lined with double bags of PE continuous liner). Pulled samples as needed for release testing from bulk packaged material. Packaged product net weight: 10.58 kg. New weight before sampling: 10.87 kg.

Table E5. Analytical results for cGMP batch of Compound 1, Form 1

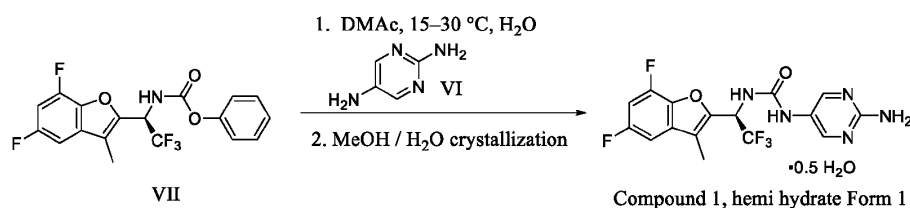
Test/criteria	Result for cGMP batch
Water content in hemi-hydrate Form 1, $2.0 \% \leq \text{KF} \leq 2.6 \%$ (w/w)	2.2 % (w/w)
Residual solvents by GC: MeOH ≤ 3000 ppm, DMA ≤ 1090 ppm	MeOH: 1633 ppm DMA: < LOQ (100 ppm)
Purity of hemi-hydrate Form 1 $\geq 98.0 \%$ (a/a), UPLC	99.9 % (a/a)
Assay of hemi-hydrate Form 1 Report Result, UPLC	100.4 % (w/w)

Example 27. Alternative Procedure for Preparation of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1, Form 1 hemihydrate)

The intermediate product (2.5 g) was dissolved in 20 mL (8 vol.) of 2-propanol at 50 °C in a 100 mL temperature-controlled reactor. Once dissolved, the mixture was cooled to 40 °C at 1 °C/min. At 40 °C, 80 mL (32 vol.) of water was added to the mixture at 5 mL/h (2 vol. per hour). After antisolvent addition was complete, the mixture was cooled to 5 °C at 0.2 °C/min. The mixture was temperature cycled between 5 °C and 40 °C with a temperature ramp of 0.1 °C/min and 1 hour holds between steps for 1 cycle before returning to 5 °C. After about 11 h at 5 °C, the experiment was isolated via Buchner filtration and analyzed by XRPD. The isolated

solids were dried under vacuum at 40 °C for about 18 h, then under vacuum at ambient temperature for a further 65 h.

Example 28. Alternative cGMP Procedure for Preparation of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1, Form 1 hemihydrate)



A solution of Intermediate VII (1 eq) in dimethylacetamide (3 vols) is added to a slurry of 5-aminopyrimidin-2-amine (1.1 eq) in dimethylacetamide (2 vols) at 15–30 °C over approximately 1 hour. The reaction mixture is stirred for at least 4 hours before in-process control indicates $\leq 0.5\%$ Intermediate VII versus Compound 1 hemihydrate Form 1 remaining. The batch is then charged with water (24 vols) over 2 hours. The slurry is stirred for at least 6 hours at 15–30 °C and filtered. The filter cake is washed with water (6 vols) and dried at 40–50 °C under vacuum with nitrogen sweep for at least 24 hours until constant weight. The batch was dissolved in methanol (8 vols) at 15–30 °C, and polish filtered through a cartridge containing activated carbon. The resulting solution was charged with water (0.6 vol) and seeded with Compound 1 free base hemi-hydrate Form 1 seed (0.005 wt eq). Water (5 vols) was added over 12 hours and the obtained slurry was stirred for at least 16 hours before being filtered. The filter cake was washed with water (6 vols) and dried at 40–50 °C under vacuum with nitrogen sweep for at least 24 hours until constant weight to afford STX-478 free base hemi-hydrate Form 1 in 85% yield.

Example 29. General properties of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1, Form 1 hemihydrate)

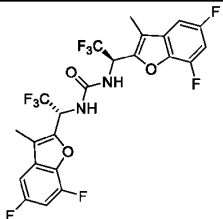
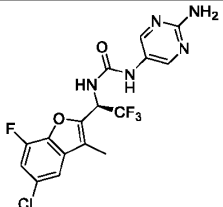
FIG. 1 depicts the XRPD diffractogram of Compound 1, Form 1 hemi hydrate. FIG. 2 Depicts the TG/DSC thermogram of Form 1. FIG. 3 Depicts the DSC thermogram (first heat cycle) of Form 1. FIG. 4 Depicts the DSC thermogram (first cool cycle) of Form 1.

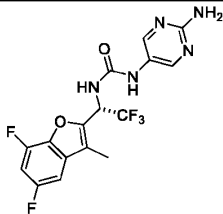
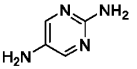
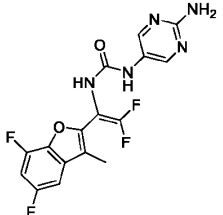
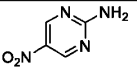
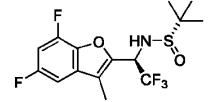
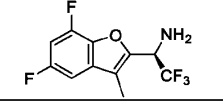
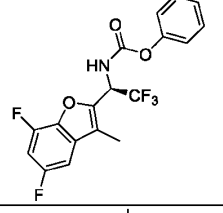
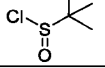
Other properties of Compound 1 free base hemi-hydrate Form 1 are presented in **Table E6**.

Table E6. General properties of Compound 1 free base hemi-hydrate Form 1

Property	Description
Physical state	Crystalline solid
Optical activity	Single enantiomer, (<i>R</i>)-configuration
Melting range	178.6 °C onset; 180.5 °C sharp peak (endotherms at 123 °C and 166 °C (dehydration and possible form change))
Hygroscopicity	Non-hygroscopic
Organic solubility (mg/mL)	4:1 acetonitrile-water >1 Methanol 200 Ethanol 90 Isopropanol 70 Acetone 130 MTBE 9 Heptane <10 Dichloromethane <10 Dimethyl acetamide >500
Aqueous solubility (µg/mL)	0.1N HCl (pH 2) 29 25mM NaOAc (pH 4) 7 PBS/Blank FaSSIF (pH 6.5) 5 Water 8
pKa	2.6
Log P	3.5
Log D _{7.4}	3.6
Permeability, Papp (A-B), Caco-2	13 (10 ⁻⁶ cm/s)

Table E7. Identified and potential impurities in Compound 1, Form 1 hemihydrate

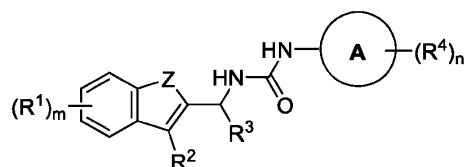
Impurity	Structure	Route A*	Route B*
Impurity 1		1.38 %	Not detected
Impurity 2		0.58 %	0.11 %

Impurity	Structure	Route A*	Route B*
Impurity 3		Not detected	Not detected
Intermediate VI		-	<LOQ**
Impurity 4		-	Not detected
Intermediate V		-	Not detected
Intermediate IV		Not detected	Not detected
A-2		Not detected	Not detected
Intermediate VII		Not detected	Not detected
Impurity 5		-	N/A
Impurity 6		-	<LOQ

*% peak area; **LOQ= level of quantitation

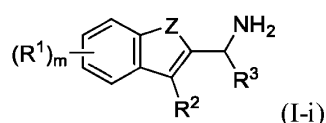
WHAT IS CLAIMED IS:

1. A process of preparing a compound of Formula (I):



(I), or a salt and/or solvate thereof;

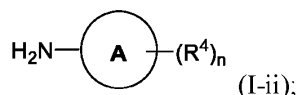
- 5 comprising contacting a compound of Formula (I-i):



with

(i) a carbonyl equivalent; and

(ii) a compound of Formula (I-ii)



10

to form the compound of Formula (I), wherein:

Z is O or NR^x;

R^x is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

15 each R¹ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

R² is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

20 R³ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

each R⁴ is independently selected from the group consisting of:

(i) halogen,

- (ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or $-NR^A R^B$,
 (iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,
 (iv) C1-C6 haloalkyl,
 5 (v) hydroxyl,
 (vi) cyano,
 (vii) $-CO_2H$,
 (viii) $-NR^A R^B$,
 (ix) $=NR^{A2}$,
 10 (x) $-C(=O)NR^C R^D$,
 (xi) $-SO_2(NR^E R^F)$,
 (xii) $-SO_2(C1-C6 \text{ alkyl})$,
 (xiii) $-S(=O)(=NH)(C1-C6 \text{ alkyl})$,
 (xiv) $-C(=O)(C1-C6 \text{ alkyl})$,
 15 (xv) $-CO_2(C1-C6 \text{ alkyl})$,
 (xvi) 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl,
 (xvii) 3-9 membered heterocyclyl optionally substituted with 1 or 2 independently selected R^G , and
 (xviii) 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected R^G ;
 20 n is 0, 1, or 2;
 each R^A , R^{A1} , R^B , R^{B1} , R^C , R^{C1} , R^D , R^{D1} , R^E , and R^F is independently
 (i) hydrogen,
 (ii) hydroxyl,
 25 (iii) 4-6 membered heterocyclyl,
 (iv) C1-C6 haloalkyl,
 (v) $-C(=O)(C1-C6 \text{ alkyl})$,
 (vi) $-C(=O)O(C1-C6 \text{ alkyl})$,
 (vii) $-SO_2(C1-C6 \text{ alkyl})$,
 30 (viii) 3-6 membered cycloalkyl optionally substituted with hydroxyl, or

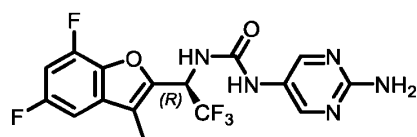
(ix) C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, $-C(=O)NR^{B2}R^{C2}$, 5-6 membered heteroaryl, 3-6 membered cycloalkyl, $-SO_2(C1-C6$ alkyl), $-CO_2H$, and $-SO_2(NH_2)$; or

R^C and R^D , together with the nitrogen atom to which they are attached form a 4-10 membered heterocyclyl optionally substituted with 1-2 substituents independently selected from hydroxyl, halogen, $-C(=O)NR^{B1}R^{C1}$, $-SO_2(C1-C6$ alkyl), $-CO_2H$, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, and C1-C6 haloalkoxy;

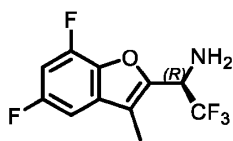
each R^{A2} , R^{B2} , and R^{C2} is independently hydrogen or C1-C6 alkyl; and

each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $=NR^{A2}$, $-C(=O)NR^{C1}R^{D1}$, $-CO_2(C1-C6$ alkyl), C1-C6 haloalkyl, C3-C6 cycloalkyl, C1-C6 haloalkoxy, $-SO_2(C1-C6$ alkyl), and $-CO_2H$.

2. A process of preparing Compound 1, having the structure:



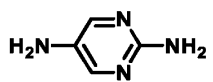
(1), or a salt and/or solvate thereof;



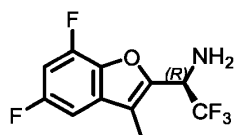
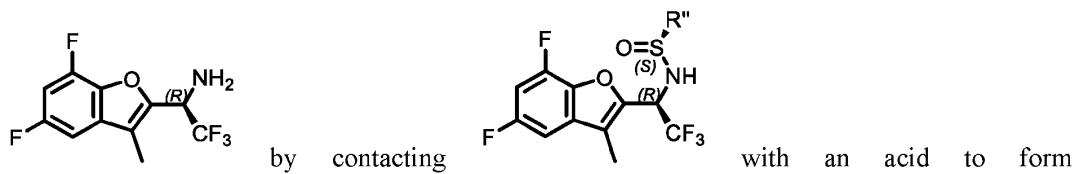
comprising contacting with

(i) a carbonyl equivalent; and

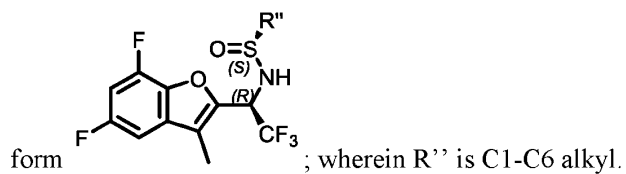
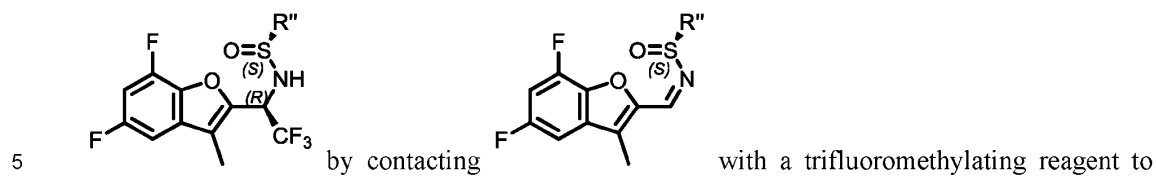
(ii) pyrimidine-2,5-diamine having the structure to form Compound 1.



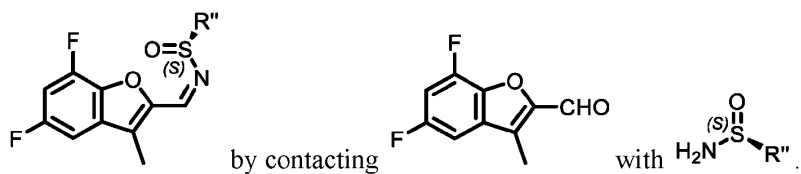
3. The process of claim 2, wherein the process comprises preparing



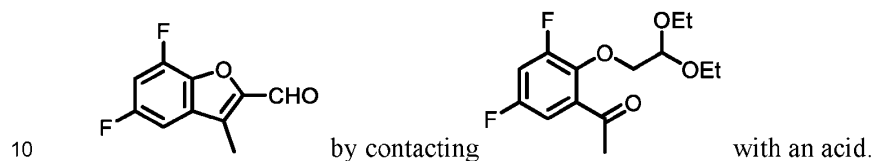
4. The process of claim 3, wherein the process comprises preparing



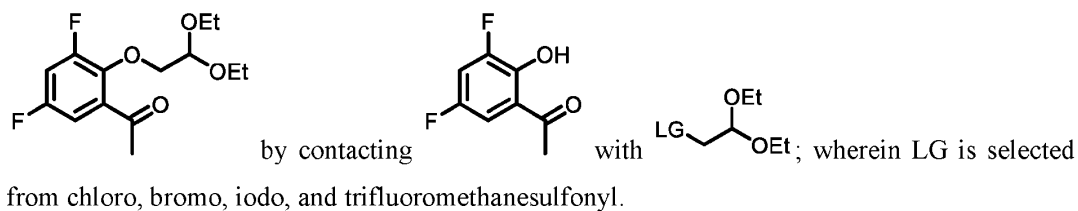
5. The process of claim 3 or 4, wherein the process comprises preparing



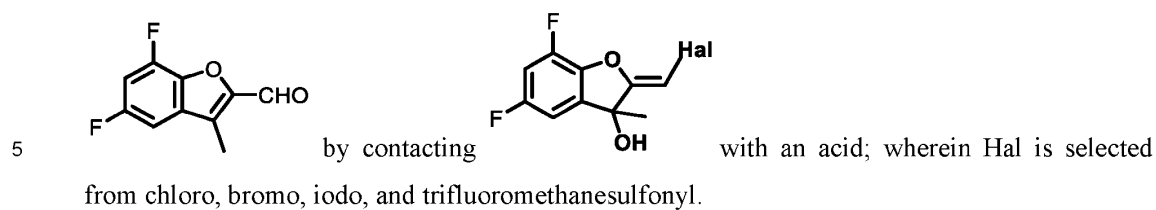
6. The process of claim 5, wherein the process comprises preparing



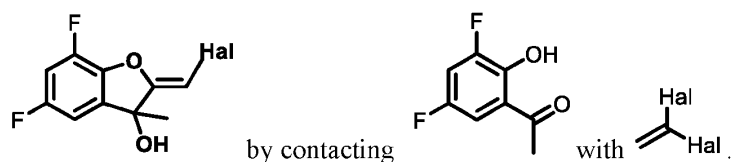
7. The process of claim 6, wherein the process comprises preparing



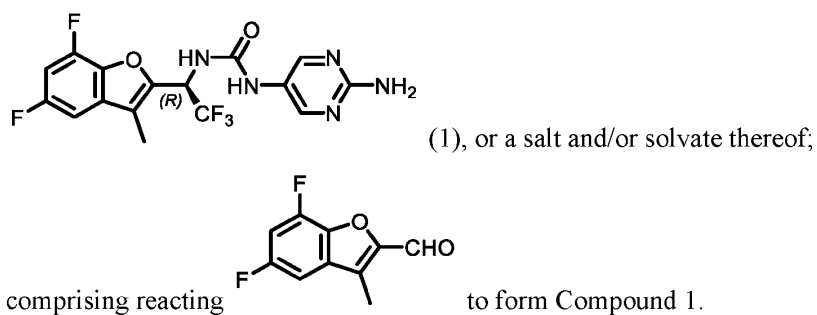
8. The process of claim 5, wherein the process comprises preparing

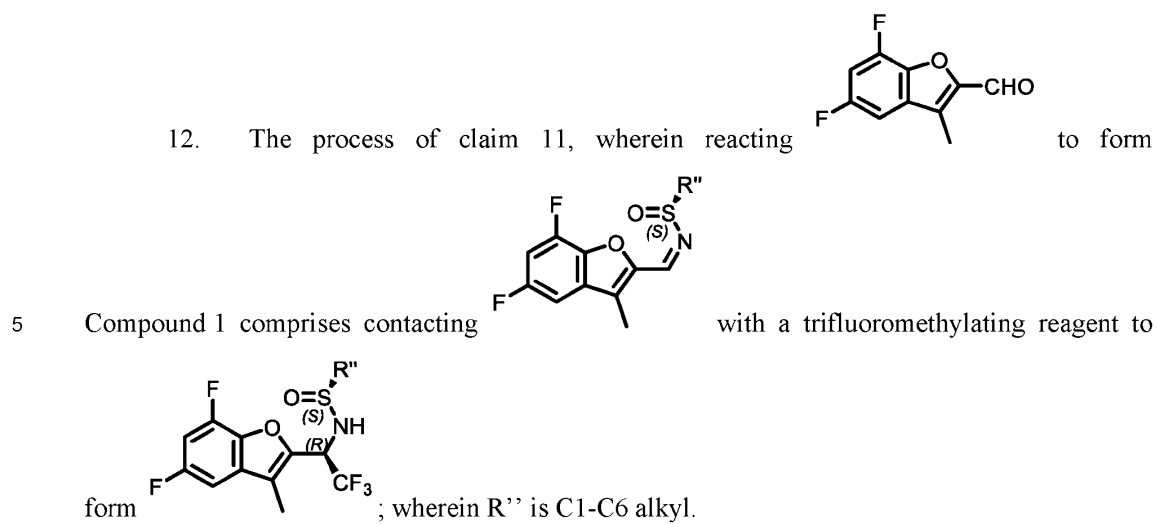
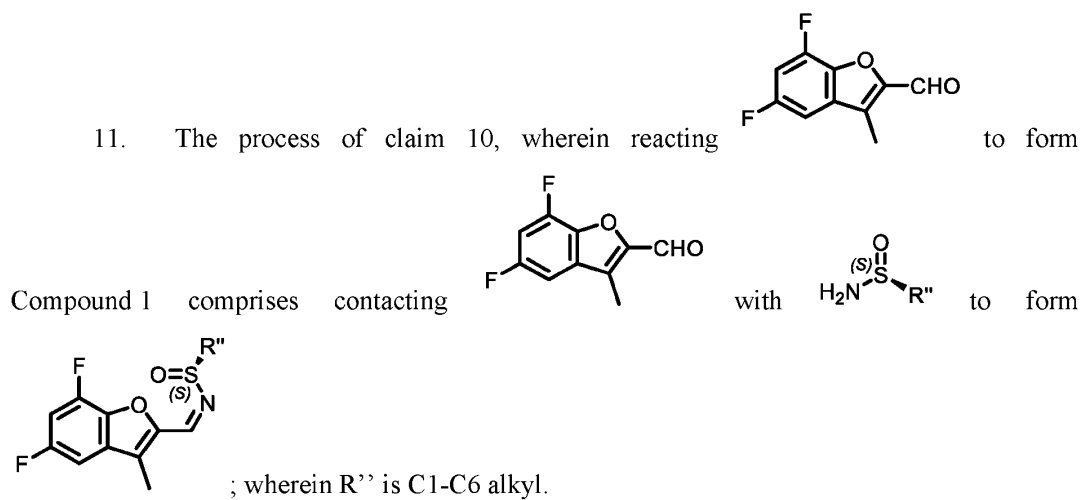


9. The process of claim 8, wherein the process comprises preparing

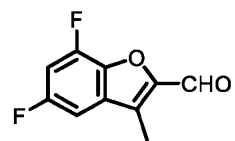


10. A process of preparing Compound 1, having the structure:



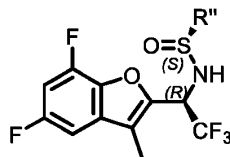


13. The process of claim 12, wherein reacting

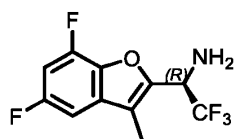


to form

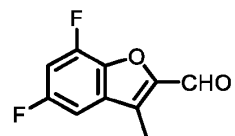
Compound 1 comprises contacting



with an acid to form



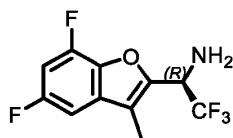
14. The process of claim 10, wherein reacting



to form

5

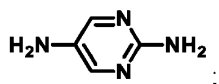
Compound 1 comprises contacting



with

(i) a carbonyl equivalent; and

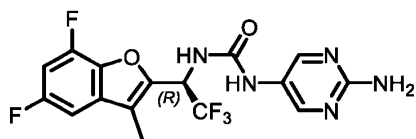
(ii) pyrimidine-2,5-diamine having the structure



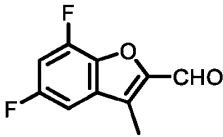
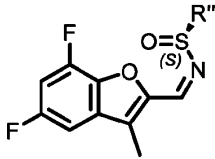
to form Compound 1.

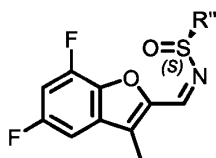
10

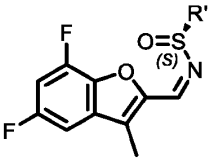
15. A process of preparing Compound 1, having the structure:

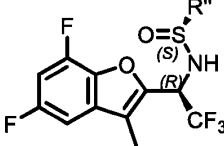
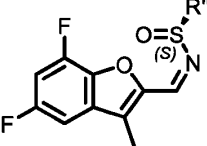


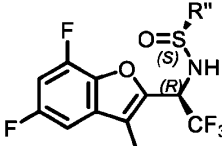
(1), or a salt and/or solvate thereof;

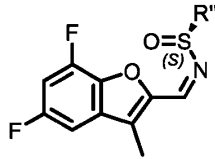
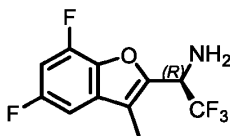
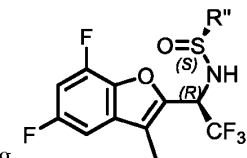
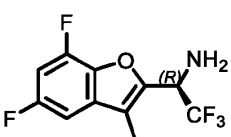
comprising contacting  with $\text{H}_2\text{N}-\overset{\text{O}}{\overset{\text{O}}{\text{S}}}(\text{S})-\text{R}''$ to form ,
 wherein R'' is C1-C6 alkyl; and

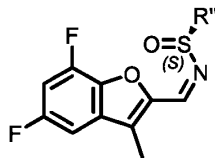
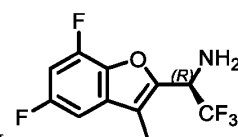
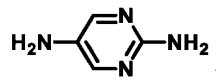
reacting  to form Compound 1.

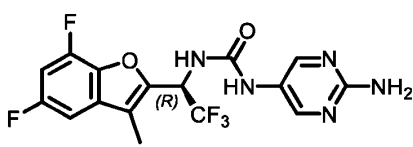
16. The process of claim 15, wherein reacting  to form Compound

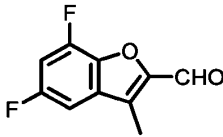
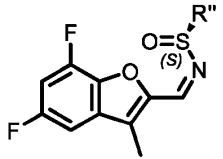
1 comprises preparing  by contacting  with a

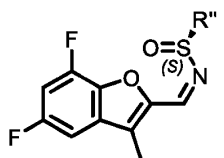
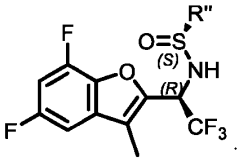
trifluoromethylating reagent to form ; wherein R'' is C1-C6 alkyl.

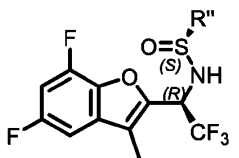
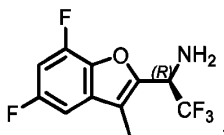
17. The process of any one of claims 15-16, wherein reacting  to form Compound 1 comprises preparing  by contacting  with an acid to form .

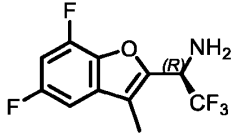
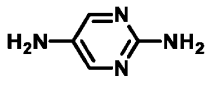
18. The process of any one of claims 15-17, wherein reacting  to form Compound 1 comprises contacting  with (i) a carbonyl equivalent; and (ii) pyrimidine-2,5-diamine having the structure ; to form Compound 1.

19. A process of preparing Compound 1, having the structure:  (1), or a salt and/or solvate thereof; comprising:

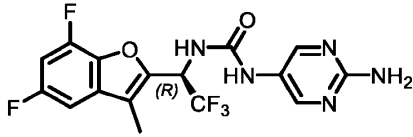
(a) contacting  with $\text{H}_2\text{N}-\overset{\text{(S)}}{\text{S}}(\text{R}'')\text{R}''$ to form , wherein R'' is C1-C6 alkyl;

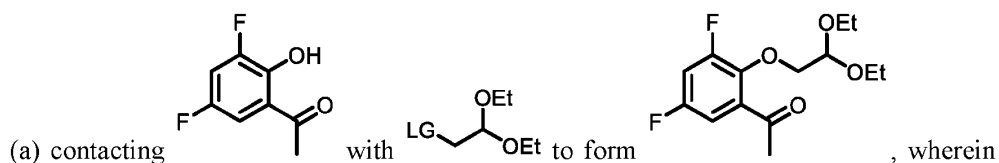
(b) contacting  with a trifluoromethylating reagent to form ;

5 (c) contacting  with HCl to form ; and

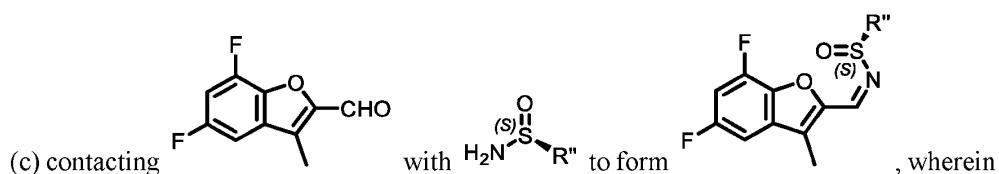
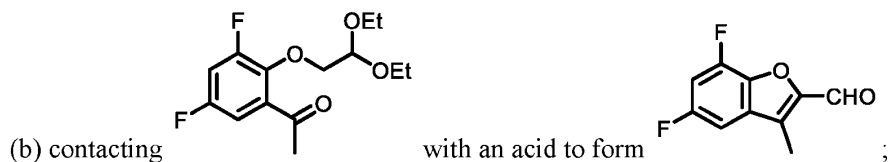
(d) contacting  with (i) a carbonyl equivalent; and (ii) pyrimidine-2,5-diamine having the structure ; to form Compound 1.

20. A process of preparing Compound 1, having the structure:

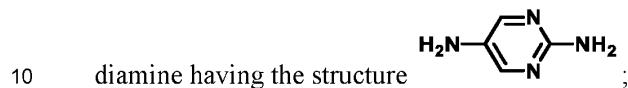
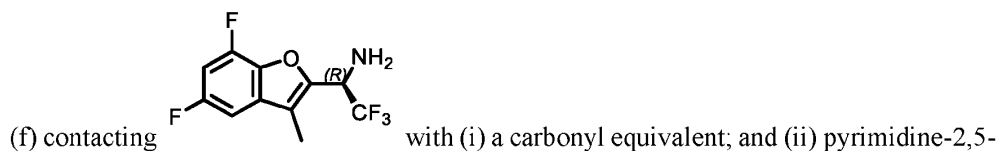
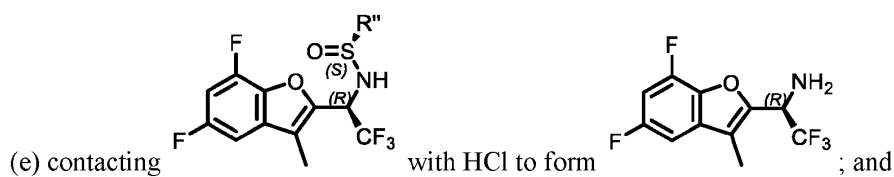
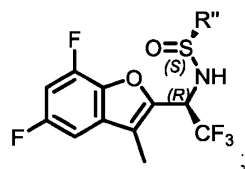
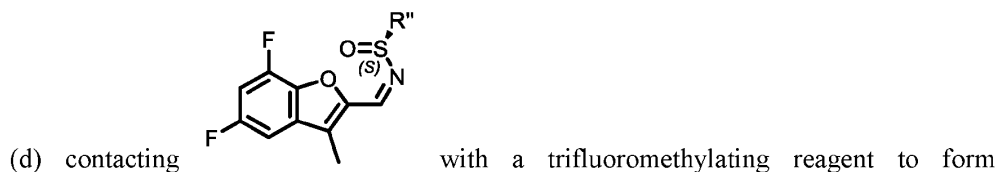
10  (1), or a salt and/or solvate thereof; comprising:



LG is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;

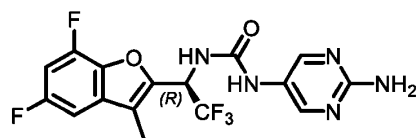


5 R'' is C1-C6 alkyl;



to form Compound 1.

21. A process of preparing Compound 1, having the structure:



(1), or a salt and/or solvate thereof;

comprising:

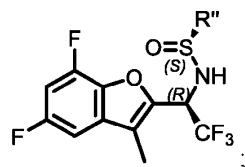
(a) contacting with to form , wherein Hal is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;

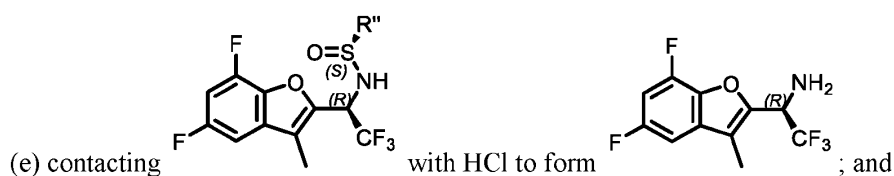
(b) contacting with an acid to form ;

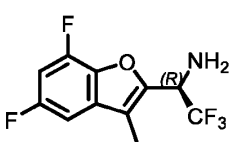
(c) contacting with to form , wherein

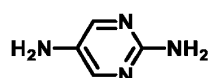
10 R'' is C1-C6 alkyl;

(d) contacting with a trifluoromethylating reagent to form





(f) contacting  with (i) R'OC(O)Cl, wherein R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl or C1-

6 alkoxy; and (ii) pyrimidine-2,5-diamine having the structure ;

5 to form Compound 1.

22. The process of any one of claims 1-21, wherein the carbonyl equivalent is R'OC(O)Cl, wherein R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl, nitro, or C1-6 alkoxy.

23. The process of any one of claims 1-22, wherein the carbonyl equivalent is selected from the group consisting of: phenyl chloroformate, phosgene, trichloromethyl chloroformate (i.e., diphosgene), bis(trichloromethyl) carbonate (i.e., triphosgene), 4-nitrophenyl chloroformate, bis(2,5-dioxopyrrolidin-1-yl) carbonate, 1,1'-carbonyldiimidazole, 2,2,2-trifluoroethyl chloroformate, 2,2,2-trichloroethyl chloroformate, dimethyl carbonate, carbonochloridic acid, and 1-methylethenyl ester.

15 24. The process of any one of claims 1-23, wherein the carbonyl equivalent is phenyl chloroformate.

25. The process of any one of claims 3-24, wherein the acid is HCl.

26. The process of any one of claims 4-25, wherein the trifluoromethylating reagent is TMSCF₃.

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