

METHODS OF PREPARING UREA DERIVATIVES

RELATED APPLICATION

[001] This application claims priority to, and the benefit of, U.S. Provisional Patent Application No. 63/600,169 filed November 17, 2023, the entire content of which is hereby incorporated by reference.

BACKGROUND

[002] Autoimmune diseases are associated with the overproduction of proinflammatory factors. One of them is interleukin-1 (IL-1), produced by activated macrophages, monocytes, fibroblasts, and other components of the innate immune system like dendritic cells. IL-1 is involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis (Masters, S. L., et. al., *Annu. Rev. Immunol.* 2009. 27:621–68).

[003] In humans, 22 NLR proteins are divided into four NLR subfamilies according to their N-terminal domains. NLRA contains a CARD-AT domain, NLRB (NAIP) contains a BIR domain, NLRC (including NOD1 and NOD2) contains a CARD domain, and NLRP contains a pyrin domain. Multiple NLR family members are associated with inflammasome formation.

[004] Although inflammasome activation appears to have evolved as an important component of host immunity to pathogens, the NLRP3 inflammasome is unique in its ability to activate in response to endogenous sterile danger signals. Many such sterile signals have been elucidated, and their formation is associated with specific disease states. For example, uric acid crystals found in gout patients are effective triggers of NLRP3 activation. Similarly, cholesterol crystals found in atherosclerotic patients can also promote NLRP3 activation. Recognition of the role of sterile danger signals as NLRP3 activators led to IL-1 and IL-18 being implicated in a diverse range of pathophysiological indications including metabolic, physiologic, inflammatory, hematologic, and immunologic disorders.

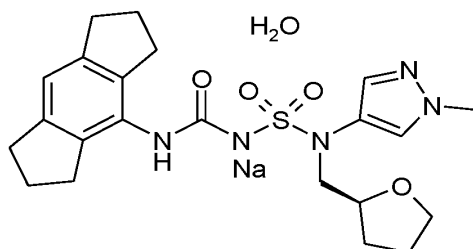
[005] The disclosure arises from a need to provide novel methods of preparing compounds for the specific modulation of NLRP3-dependent cellular processes.

SUMMARY

[006] In some aspects, the present disclosure provides a method of preparing Compound No. 10a or 10b described herein.

[007] In some aspects, the present disclosure provides methods for the efficient preparation of Compound No. 10a.

[008] The chemical name of Compound No. 10a is 1-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-3-[(1-methyl-1H-pyrazol-4-yl)(([(2S)-oxolan-2-yl]methyl)) sulfamoyl]urea, sodium salt, monohydrate:



(Compound No. 10a).

[009] In some aspects, the present disclosure provides a method of preparing Compound No. 10a or 10b, comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5a or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6a or 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a or 6b, or a salt thereof, with Compound No. 8 or a salt thereof, thereby forming Compound No. 9a or 9b; and

(vii) purifying Compound No. 9a or 9b, thereby isolating Compound No. 10a or 10b.

[010] In some aspects, the present disclosure provides a method of preparing Compound No. 10, 10a, or 10b, comprising steps (i)-(vii):

(i) reacting Compound No. 1, 1a, or 1b, with 4-amino-1-methylpyrazole (Compound No. 2) or a salt thereof, thereby forming Compound No. 3, 3a, or 3b, or a salt thereof;

(ii) reacting Compound No. 3, 3a, or 3b, or a salt thereof, with a reducing agent, thereby forming Compound No. 4, 4a, or 4b, or a salt thereof;

(iii) reacting Compound No. 4, 4a, or 4b, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5, 5a, or 5b, or a salt thereof;

(iv) reacting Compound No. 5, 5a, or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6, 6a, or 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6, 6a, or 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9, 9a, or 9b; and

(vii) purifying Compound No. 9, 9a, or 9b, thereby isolating Compound No. 10, 10a, or 10b.

[011] In some aspects, the present disclosure provides a method of preparing Compound No. 10a or 10b, comprising steps (i)-(vii):

(i) reacting Compound No. 1, 1a, or 1b, with 4-amino-1-methylpyrazole (Compound No. 2) or a salt thereof, thereby forming Compound No. 3, 3a, or 3b, or a salt thereof;

(ii) reacting Compound No. 3, 3a, or 3b, or a salt thereof, with a reducing agent, thereby forming Compound No. 4, 4a, or 4b, or a salt thereof;

(iii) reacting Compound No. 4, 4a, or 4b, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5a or 5b, or a salt thereof;

(iv) reacting Compound No. 5a or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6a or 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a or 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a or 9b; and

(vii) purifying Compound No. 9a or 9b, thereby isolating Compound No. 10a or 10b.

[012] In some aspects, the present disclosure provides a method of preparing Compound No. 10a or 10b, comprising steps (i)-(vii):

(i) reacting Compound No. 1, 1a, or 1b, with 4-amino-1-methylpyrazole (Compound No. 2), or a salt thereof, thereby forming Compound No. 3, 3a, or 3b, or a salt thereof;

(ii) reacting Compound No. 3, 3a, or 3b, or a salt thereof, with a reducing agent, thereby forming Compound No. 4, 4a, or 4b, or a salt thereof (*e.g.*, an HCl salt) thereof;

(iii) reacting Compound No. 4, 4a, or 4b, or a salt (*e.g.*, an HCl salt) thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5a or 5b, or a salt thereof;

(iv) reacting Compound No. 5a or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6a or 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a or 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a or 9b; and

(vii) purifying Compound No. 9a or 9b, thereby isolating Compound No. 10a or 10b.

[013] In some aspects, the present disclosure provides a method of preparing Compound No. 10, comprising steps (i)-(vii):

(i) reacting tetrahydrofuran-2-carboxylic acid (*e.g.*, (2S)-tetrahydrofuran-2-carboxylic acid or (2R)-tetrahydrofuran-2-carboxylic acid), with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide (*e.g.*, (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide or (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide), or a salt thereof;

(ii) reacting N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide (*e.g.*, (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide or (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide), or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine (*e.g.*, 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine or 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine), or a salt thereof;

(iii) reacting 1-methyl-N-{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine (*e.g.*, 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine or 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine), or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5, or a salt thereof;

(iv) reacting Compound No. 5, or a salt thereof, with an acid, thereby forming Compound No. 6, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9; and

(vii) purifying Compound No. 9, thereby isolating Compound No. 10.

[014] In some aspects, the present disclosure provides a method of preparing Compound No. 10a or 10b, comprising steps (i)-(vii):

(i) reacting tetrahydrofuran-2-carboxylic acid (*e.g.*, (2S)-tetrahydrofuran-2-carboxylic acid or (2R)-tetrahydrofuran-2-carboxylic acid), with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide (*e.g.*, (2S)-N-(1-methyl-1H-

pyrazol-4-yl)oxolane-2-carboxamide or (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide), or a salt thereof;

(ii) reacting N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide (*e.g.*, (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide or (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide), or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine (*e.g.*, 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine or 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine), or a salt thereof;

(iii) reacting 1-methyl-N-{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine (*e.g.*, 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine or 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine), or a salt thereof, with *tert*-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5a or 5b, or a salt thereof;

(iv) reacting Compound No. 5a or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6a or 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a or 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a or 9b; and

(vii) purifying Compound No. 9a or 9b, thereby isolating Compound No. 10a or 10b.

[015] In some aspects, the present disclosure provides a method of preparing Compound No. 10a, comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5a, or a salt thereof, with an acid, thereby forming Compound No. 6a, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a, or a salt thereof, with Compound No. 8 or a salt thereof, thereby forming Compound No. 9a; and

(vii) purifying Compound No. 9a, thereby isolating Compound No. 10a.

[016] In some aspects, the present disclosure provides a method of preparing Compound No. 10a, comprising steps (i)-(vii):

(i) reacting (2S)-tetrahydrofuran-2-carboxylic acid with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof;

(ii) reacting (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof;

(iii) reacting 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5a, or a salt thereof;

(iv) reacting Compound No. 5a, or a salt thereof, with an acid, thereby forming Compound No. 6a, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a; and

(vii) purifying Compound No. 9a, thereby isolating Compound No. 10a.

[017] In some aspects, the present disclosure provides a method of preparing Compound No. 10b, comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5b, or a salt thereof, with an acid, thereby forming Compound No. 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9b; and

(vii) purifying Compound No. 9b, thereby isolating Compound No. 10b.

[018] In some aspects, the present disclosure provides a method of preparing Compound No. 10b, comprising steps (i)-(vii):

(i) reacting (2R)-tetrahydrofuran-2-carboxylic acid with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof;

(ii) reacting (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof;

(iii) reacting 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5b, or a salt thereof;

(iv) reacting Compound No. 5b, or a salt thereof, with an acid, thereby forming Compound No. 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9b; and

(vii) purifying Compound No. 9b, thereby isolating Compound No. 10b.

[019] In some aspects, the present disclosure provides a compound being prepared by a method described herein.

[020] In some aspects, the present disclosure provides a pharmaceutical composition comprising Compound No. 10a or 10b as described herein, and one or more pharmaceutically acceptable carrier or excipient.

[021] In some aspects, the present disclosure provides a method of inhibiting inflammasome (*e.g.*, the NLRP3 inflammasome) activity (*e.g.*, *in vitro* or *in vivo*), comprising contacting a cell with Compound No. 10a or 10b as described herein (*e.g.*, in an effective amount).

[022] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject Compound No. 10a or 10b as described herein (*e.g.*, in a therapeutically effective amount).

[023] In some aspects, the present disclosure provides Compound No. 10a or 10b as described herein for use in inhibiting inflammasome (*e.g.*, the NLRP3 inflammasome) activity (*e.g.*, *in vitro* or *in vivo*).

[024] In some aspects, the present disclosure provides Compound No. 10a or 10b as described herein for use in treating or preventing a disease or disorder disclosed herein.

[025] In some aspects, the present disclosure provides use of Compound No. 10a or 10b as described herein in the manufacture of a medicament for inhibiting inflammasome (*e.g.*, the NLRP3 inflammasome) activity (*e.g.*, *in vitro* or *in vivo*).

[026] In some aspects, the present disclosure provides use of Compound No. 10a or 10b as described herein in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[027] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

[028] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION

[029] Autoimmune diseases are associated with the overproduction of proinflammatory factors. One of them is interleukin-1 (IL-1), produced by activated macrophages, monocytes, fibroblasts, and other components of the innate immune system like dendritic cells, involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis (Seth L. al. *Rev. Immunol.* 2009. 27:621–68).

[030] Cytokines from the IL-1 family are highly active and as important mediators of inflammation, are primarily associated with acute and chronic inflammation (Sims J. et al. *Nature Reviews Immunology* 10, 89-102 (February 2010)). The overproduction of IL-1 is considered to be an initiator of some autoimmune and autoinflammatory diseases. Autoinflammatory diseases are characterised by recurrent and unprovoked inflammation in the absence of autoantibodies, infection, or antigen-specific T lymphocytes.

[031] Pro-inflammatory cytokines of the IL-1 superfamily include IL-1 α , IL-1 β , IL-18, and IL-36 α , β , λ and are produced in response to pathogens and other cellular stressors as part of a host innate immune response. Unlike many other secreted cytokines, which are processed and released via the standard cellular secretory apparatus consisting of the endoplasmic reticulum and Golgi apparatus, IL-1 family members lack leader sequences required for endoplasmic reticulum entry and thus are retained intracellularly following translation. In addition, IL-1 β , IL-18, and IL-36 α , β , λ are

synthesised as procytokines that require proteolytic activation to become optimal ligands for binding to their cognate receptors on target cells.

[032] In the case of IL-1 α , IL-1 β and IL-18, it is now appreciated that a multimeric protein complex known as an inflammasome is responsible for activating the proforms of IL-1 β and IL-18 and for release of these cytokines extracellularly. An inflammasome complex typically consists of a sensor molecule, such as an NLR (Nucleotide-Oligomerisation Domain (NOD)-like receptor), an adaptor molecule ASC (Apoptosis-associated speck-like protein containing a CARD (Caspase Recruitment Domain)) and procaspase-1. In response to a variety of “danger signals”, including pathogen-associated molecule patterns (PAMPs) and danger associated molecular patterns (DAMPs), subunits of an inflammasome oligomerise to form a supramolecular structure within the cell. PAMPs may include molecules such as peptidoglycan, viral DNA or RNA and bacterial DNA or RNA. DAMPs, on the other hand, consist of a wide range of endogenous or exogenous sterile triggers including monosodium urate crystals, silica, alum, asbestos, fatty acids, ceramides, cholesterol crystals and aggregates of beta-amyloid peptide. Assembly of an inflammasome platform facilitates autocatalysis of procaspase-1 yielding a highly active cysteine protease responsible for activation and release of pro-IL-1 β and pro-IL-18. Thus, release of these highly inflammatory cytokines is achieved only in response to inflammasome sensors detecting and responding to specific molecular danger signals.

[033] In humans, 22 NLR proteins are divided into four NLR subfamilies according to their N-terminal domains. NLRA contains a CARD-AT domain, NLRB (NAIP) contains a BIR domain, NLRC (including NOD1 and NOD2) contains a CARD domain, and NLRP contains a pyrin domain. Multiple NLR family members are associated with inflammasome formation including NLRP1, NLRP3, NLRP6, NLRP7, NLRP12, and NLRC4 (IPAF).

[034] Two other structurally distinct inflammasome structures containing a PYHIN domain (pyrin and HIN domain containing protein) namely Absent in Melanoma 2 (AIM2) and IFN λ -inducible protein 16 (IFI16) (Latz et al., Nat Rev Immunol 2013 13(6) 397-311) serve as intracellular DNA sensors. Pyrin (encoded by the MEFV gene) represents another type of inflammasome platform associated with pro-IL-1 β activation (Chae et al., Immunity 34, 755-768, 2011).

[035] Requiring assembly of an inflammasome platform to achieve activation and release of IL-1 β and IL-18 from monocytes and macrophages ensures their production is carefully orchestrated via a 2-step process. First, the cell must encounter a priming ligand (such as the TLR4 receptor ligand LPS, or an inflammatory cytokine such as TNF α) which leads to NF κ B dependent transcription of

NLRP3, pro-IL-1 β and pro-IL-18. The newly translated procytokines remain intracellular and inactive unless producing cells encounter a second signal leading to activation of an inflammasome scaffold and maturation of procaspase-1.

[036] In addition to proteolytic activation of pro-IL-1 β and pro-IL-18, active caspase-1 also triggers a form of inflammatory cell death known as pyroptosis through cleavage of gasdermin-D. Pyroptosis allows the mature forms of IL-1 β and IL-18 to be externalised along with release of alarmin molecules (compounds that promote inflammation and activate innate and adaptive immunity) such as high mobility group box 1 protein (HMGB1), IL-33, and IL-1 α .

[037] Although inflammasome activation appears to have evolved as an important component of host immunity to pathogens, the NLRP3 inflammasome is unique in its ability activate in response to endogenous and exogenous sterile danger signals. Many such sterile signals have been elucidated, and their formation is associated with specific disease states. For example, uric acid crystals found in gout patients are effective triggers of NLRP3 activation. Similarly, cholesterol crystals found in atherosclerotic patients can also promote NLRP3 activation. Recognition of the role of sterile danger signals as NLRP3 activators led to IL-1 β and IL-18 being implicated in a diverse range of pathophysiological indications including metabolic, physiologic, inflammatory, hematologic and immunologic disorders.

[038] A link to human disease is best exemplified by discovery that mutations in the NLRP3 gene which lead to gain-of-function confer a range of autoinflammatory conditions collectively known as cryopyrin-associated periodic syndromes (CAPS) including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and Neonatal onset multisystem inflammatory disease (NOMID) (Hoffman et al., Nat Genet. 29(3) (2001) 301-305). Likewise, sterile mediator-induced activation of NLRP3 has been implicated in a wide range of disorders including joint degeneration (gout, rheumatoid arthritis, osteoarthritis), cardiometabolic (type 2 diabetes, atherosclerosis, hypertension), Central Nervous System (Alzheimer's Disease, Parkinson's disease, multiple sclerosis), gastrointestinal (Crohn's disease, ulcerative colitis), lung (chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis) and liver (fibrosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis (NASH)). It is further believed that NLRP3 activation promotes kidney inflammation and thus contributes to chronic kidney disease (CKD).

[039] Current treatment options for diseases where IL-1 is implicated as a contributor to pathogenesis include the IL-1 receptor antagonist anakinra, an Fc-containing fusion construct of the

extracellular domains of the IL-1 receptor and IL-1 receptor accessory protein (riloncept) and the anti-IL-1 β monoclonal antibody canakinumab. For example, canakinumab is licensed for CAPS, Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF) and gout.

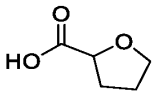
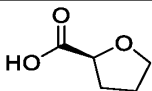
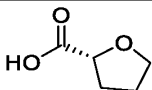
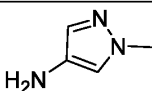
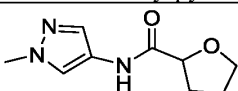
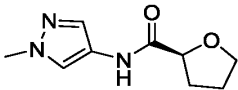
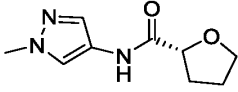
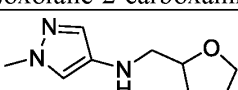
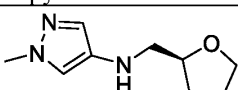
[040] Some small molecules have been reported to inhibit function of the NLRP3 inflammasome. Glyburide, for example, is a specific inhibitor of NLRP3 activation, albeit at micromolar concentrations which are unlikely attainable *in vivo*. Non-specific agents such as parthenolide, Bay 11-7082, and 3,4-methylenedioxy- β -nitrostyrene are reported to impair NLRP3 activation but are expected to possess limited therapeutic utility due to their sharing of a common structural feature consisting of an olefin activated by substitution with an electron withdrawing group; this can lead to undesirable formation of covalent adducts with protein-bearing thiol groups. A number of natural products, for example β -hydroxybutyrate, sulforaphane, quercetin, and salvianolic acid, also are reported to suppress NLRP3 activation. Likewise, numerous effectors/modulators of other molecular targets have been reported to impair NLRP3 activation including agonists of the G-protein coupled receptor TGR5, an inhibitor of sodium-glucose co-transport epigliflozin, the dopamine receptor antagonist A-68930, the serotonin reuptake inhibitor fluoxetine, fenamate non-steroidal anti-inflammatory drugs, and the β -adrenergic receptor blocker nebivolol. Utility of these molecules as therapeutics for the chronic treatment of NLRP3-dependent inflammatory disorders remains to be established. A series of sulphonylurea-containing molecules was previously identified as potent and selective inhibitors of post-translational processing of pro-IL-1 β (Perregaux et al., J Pharmacol. Exp. Ther. 299, 187-197, 2001). The exemplar molecule CP-456,773 from this work was recently characterised as a specific inhibitor of NLRP3 activation (Coll et al., Nat Med 21.3 (2015): 248-255.).

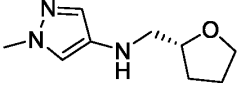
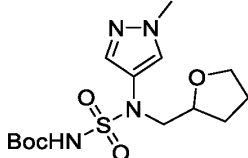
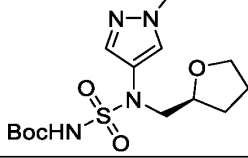
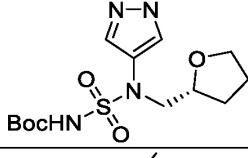
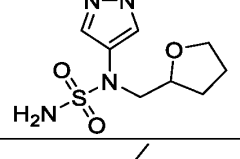
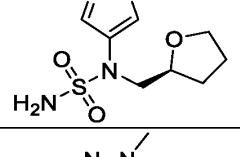
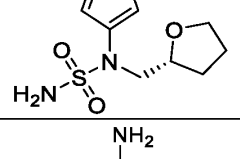
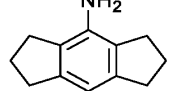
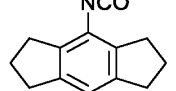
[041] The disclosure relates to methods of preparing compounds useful for the modulation of NLRP3-dependent cellular processes. In some embodiments, methods of preparing compounds with improved physicochemical, pharmacological and pharmaceutical properties to existing NLRP3-modulating compounds are desired.

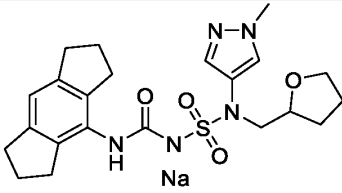
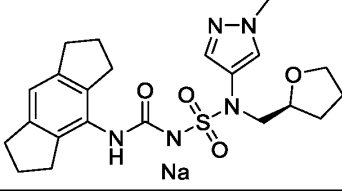
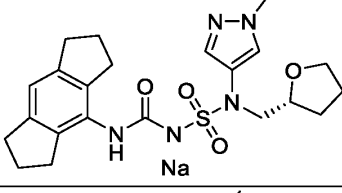
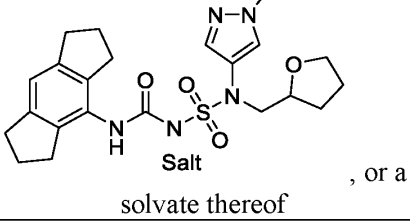
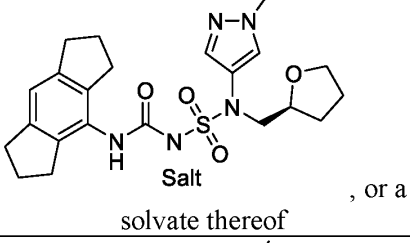
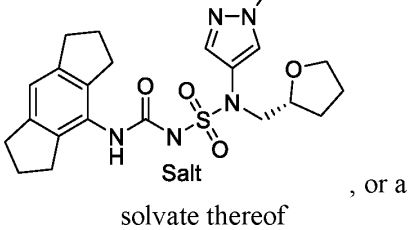
Compounds of the Present Disclosure

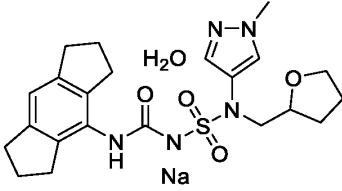
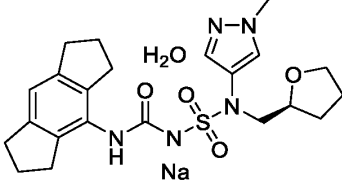
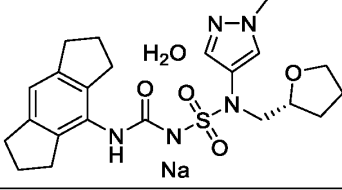
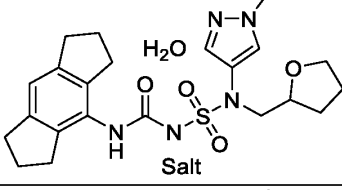
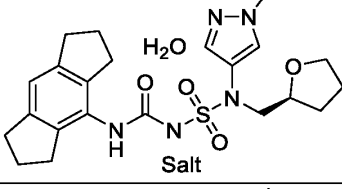
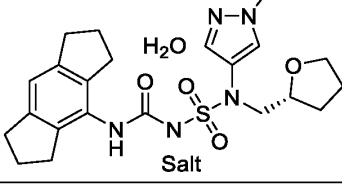
[042] It is understood that the structures of Compound Nos. 1, 1a, 1b, 2, 3, 3a, 3b, 4, 4a, 4b, 5, 5a, 5b, 6, 6a, 6b, 7, 8, 9, 9a, 9b, 9', 9a', 9b', 10, 10a, 10b, 10', 10a', and 10b' are as described in Table 1.

Table 1

Compound No.	Compound Structure
1	 tetrahydrofuran-2-carboxylic acid
1a	 (2S)-tetrahydrofuran-2-carboxylic acid
1b	 (2R)-tetrahydrofuran-2-carboxylic acid
2	 4-amino-1-methylpyrazole
3	 N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide)
3a	 (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide)
3b	 (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide
4	 1-methyl-N-{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine
4a	

Compound No.	Compound Structure
	1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine
4b	 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine)
5	
5a	
5b	
6	
6a	
6b	
7	
8	

Compound No.	Compound Structure
9	
9a	
9b	
9'	
9a'	
9b'	

Compound No.	Compound Structure
10	
10a	
10b	
10'	
10a'	
10b'	

[043] In some embodiments, the salt comprises an alkali metal ion (*e.g.*, Li⁺, Na⁺, or K⁺).

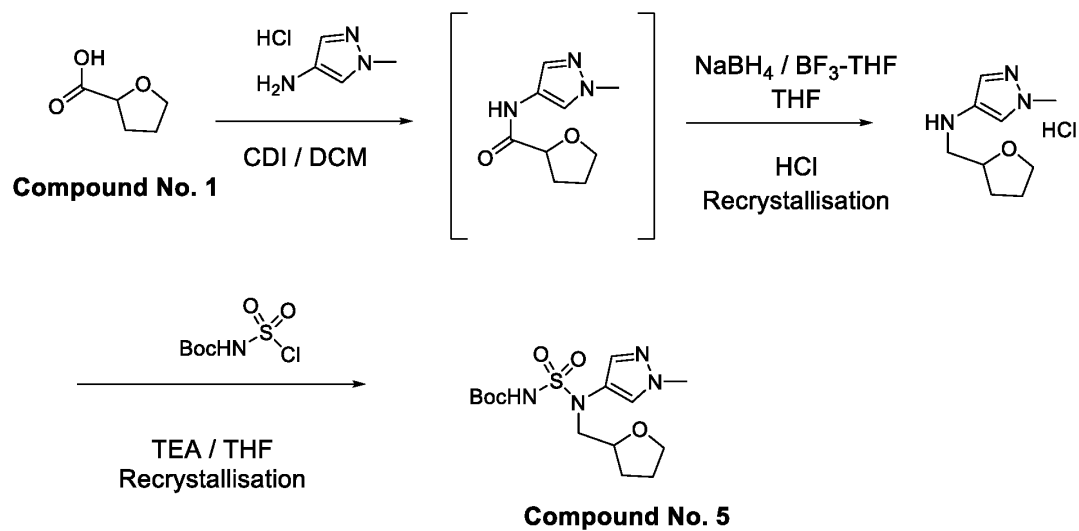
[044] In some embodiments, the salt is the sodium salt.

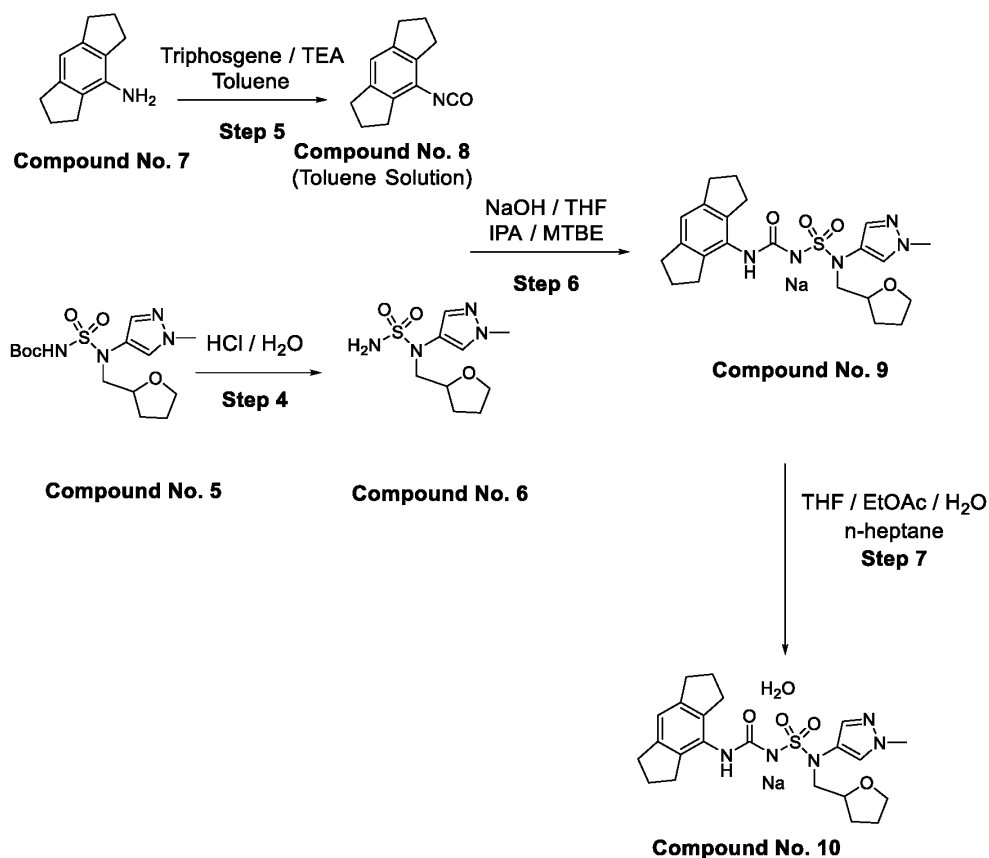
[045] In some embodiments, the salt comprises an alkaline-earth metal ion (*e.g.*, Mg²⁺ or Ca²⁺).

Methods of the Present Disclosure

[046] In some aspects, the present disclosure provides a method of preparing Compound No. 10a or 10b described herein.

[047] In some aspects, the present disclosure provides a method of preparing Compound No. 10a or 10b accordingly to the following scheme:





[048] In some aspects, the present disclosure provides a method of preparing Compound No. 10, 10a, or 10b, comprising steps (i)-(vii):

- (i) reacting Compound No. 1, 1a, or 1b, with 4-amino-1-methylpyrazole (Compound No. 2) or a salt thereof, thereby forming Compound No. 3, 3a, or 3b, or a salt thereof;
- (ii) reacting Compound No. 3, 3a, or 3b, or a salt thereof, with a reducing agent, thereby forming Compound No. 4, 4a, or 4b, or a salt thereof;
- (iii) reacting Compound No. 4, 4a, or 4b, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5, 5a, or 5b, or a salt thereof;
- (iv) reacting Compound No. 5, 5a, or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6, 6a, or 6b, or a salt thereof;
- (v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6, 6a, or 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9, 9a, or 9b; and

(vii) purifying Compound No. 9, 9a, or 9b, thereby isolating Compound No. 10, 10a, or 10b.

[049] In some aspects, the present disclosure provides a method of preparing Compound No. 10a or 10b, comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5a or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6a or 6b, or a salt thereof;

(v) reacting Compound No. 7 or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a or 6b, or a salt thereof, with Compound No. 8 or a salt thereof, thereby forming Compound No. 9a or 9b; and

(vii) purifying Compound No. 9a or 9b, thereby isolating Compound No. 10a or 10b.

[050] In some embodiments, the method of preparing Compound No. 10a or 10b comprises one or more of steps (iv), (v), (vi) and (vii).

[051] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (iv).

[052] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (v).

[053] In some embodiments, the method of preparing Compound No. 10a or 10b comprises steps (iv) and (v).

[054] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (vi).

[055] In some embodiments, the method of preparing Compound No. 10a or 10b comprises steps (iv), (v), and (vi).

[056] In some embodiments, the method of preparing Compound No. 10a or 10b comprises one or more of steps (iv), (v), (vi), and (vii).

[057] In some embodiments, the method comprises steps (iv), (v), (vi), and (vii).

[058] In some aspects, the present disclosure provides a method of preparing Compound No. 10a or 10b, comprising steps (i)-(vii):

(i) reacting tetrahydrofuran-2-carboxylic acid (*e.g.*, (2S)-tetrahydrofuran-2-carboxylic acid or (2R)-tetrahydrofuran-2-carboxylic acid), with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide (*e.g.*, (2S)-N-(1-methyl-1H-

pyrazol-4-yl)oxolane-2-carboxamide or (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide), or a salt thereof;

(ii) reacting N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide (*e.g.*, (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide or (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide), or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine (*e.g.*, 1-methyl-N-{{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine or 1-methyl-N-{{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine), or a salt thereof;

(iii) reacting 1-methyl-N-{{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine (*e.g.*, 1-methyl-N-{{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine or 1-methyl-N-{{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine), or a salt thereof, with *tert*-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5a or 5b, or a salt thereof;

(iv) reacting Compound No. 5a or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6a or 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a or 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a or 9b; and

(vii) purifying Compound No. 9a or 9b, thereby isolating Compound No. 10a or 10b.

[059] In some embodiments, the method of preparing Compound No. 10a or 10b comprises one or more of steps (i), (ii), (iii), (iv), (v), (vi) and (vii).

[060] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (i).

[061] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (ii).

[062] In some embodiments, the method of preparing Compound No. 10a or 10b comprises steps (i) and (ii).

[063] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (iii).

[064] In some embodiments, the method of preparing Compound No. 10a or 10b comprises steps (i), (ii) and (iii).

[065] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (iv).

[066] In some embodiments, the method of preparing Compound No. 10a or 10b comprises steps (i), (ii), (iii) and (iv).

[067] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (v).

[068] In some embodiments, the method of preparing Compound No. 10a or 10b comprises steps (i), (ii), (iii), (iv) and (v).

[069] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (vi).

[070] In some embodiments, the method of preparing Compound No. 10a or 10b comprises steps (i), (ii), (iii), (iv), (v), and (vi).

[071] In some embodiments, the method of preparing Compound No. 10a or 10b comprises step (vii).

[072] In some embodiments, the method of preparing Compound No. 10a or 10b comprises steps (i), (ii), (iii), (iv), (v), (vi) and (vii).

[073] In some embodiments, the method of preparing Compound No. 10a or 10b comprises one or more of steps (i), (ii), (iii), (iv), (v), (vi) and (vii).

[074] In some aspects, the present disclosure provides a method of preparing Compound No. 10a.

[075] In some aspects, the present disclosure provides a method of preparing Compound No. 10a, comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5a, or a salt thereof, with an acid, thereby forming Compound No. 6a, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a; and

(vii) purifying Compound No. 9a, thereby isolating Compound No. 10a.

[076] In some embodiments, the method of preparing Compound No. 10a comprises one or more of steps (iv), (v), (vi) and (vii).

[077] In some embodiments, the method of preparing Compound No. 10a comprises step (iv).

[078] In some embodiments, the method of preparing Compound No. 10a comprises steps (iv) and (v).

[079] In some embodiments, the method of preparing Compound No. 10a comprises step (v).

[080] In some embodiments, the method of preparing Compound No. 10a comprises step (vi).

[081] In some embodiments, the method of preparing Compound No. 10a comprises steps (iv), (v), and (vi).

[082] In some embodiments, the method of preparing Compound No. 10a comprises one or more of steps (iv), (v), (vi), and (vii).

[083] In some aspects, the present disclosure provides a method of preparing Compound No. 10a, comprising steps (i)-(vii):

(i) reacting (2S)-tetrahydrofuran-2-carboxylic acid with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof;

(ii) reacting (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof;

(iii) reacting 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5a, or a salt thereof;

(iv) reacting Compound No. 5a, or a salt thereof, with an acid, thereby forming Compound No. 6a, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a; and

(vii) purifying Compound No. 9a, thereby isolating Compound No. 10a.

[084] In some embodiments, the method of preparing Compound No. 10a comprises one or more of steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[085] In some embodiments, the method of preparing Compound No. 10a comprises step (i).

[086] In some embodiments, the method of preparing Compound No. 10a comprises step (ii).

[087] In some embodiments, the method of preparing Compound No. 10a comprises steps (i) and (ii).

[088] In some embodiments, the method of preparing Compound No. 10a comprises step (iii).

[089] In some embodiments, the method of preparing Compound No. 10a comprises steps (i), (ii), and (iii).

[090] In some embodiments, the method of preparing Compound No. 10a comprises steps (i), (ii), (iii), and (iv).

[091] In some embodiments, the method of preparing Compound No. 10a comprises steps (i), (ii), (iii), (iv), and (v).

[092] In some embodiments, the method of preparing Compound No. 10a comprises steps (i), (ii), (iii), (iv), (v), and (vi).

[093] In some embodiments, the method of preparing Compound No. 10a comprises step (vii).

[094] In some embodiments, the method of preparing Compound No. 10a comprises steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[095] In some aspects, the present disclosure provides a method of preparing Compound No. 10b, comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5b, or a salt thereof, with an acid, thereby forming Compound No. 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9b; and

(vii) purifying Compound No. 9b, thereby isolating Compound No. 10b.

[096] In some embodiments, the method of preparing Compound No. 10b comprises one or more of steps (iv), (v), (vi), and (vii).

[097] In some embodiments, the method of preparing Compound No. 10b comprises step (iv).

[098] In some embodiments, the method of preparing Compound No. 10b comprises steps (iv) and (v).

[099] In some embodiments, the method of preparing Compound No. 10b comprises step (v).

[0100] In some embodiments, the method of preparing Compound No. 10b comprises step (vi).

[0101] In some embodiments, the method of preparing Compound No. 10b comprises steps (iv), (v), and (vi).

[0102] In some embodiments, the method of preparing Compound No. 10b comprises one or more of steps (iv), (v), (vi), and (vii).

[0103] In some aspects, the present disclosure provides a method of preparing Compound No. 10b, comprising steps (i)-(vii):

(i) reacting (2R)-tetrahydrofuran-2-carboxylic acid with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof;

(ii) reacting (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof;

(iii) reacting 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5b, or a salt thereof;

(iv) reacting Compound No. 5b, or a salt thereof, with an acid, thereby forming Compound No. 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9b; and

(vii) purifying Compound No. 9b, thereby isolating Compound No. 10b.

[0104] In some embodiments, the method of preparing Compound No. 10b comprises one or more of steps (i), (ii), (iii), (iv), (v), (vi) and (vii).

[0105] In some embodiments, the method of preparing Compound No. 10b comprises step (i).

[0106] In some embodiments, the method of preparing Compound No. 10b comprises step (ii).

[0107] In some embodiments, the method of preparing Compound No. 10b comprises steps (i) and (ii).

[0108] In some embodiments, the method of preparing Compound No. 10b comprises step (iii).

[0109] In some embodiments, the method of preparing Compound No. 10b comprises steps (i), (ii), and (iii).

[0110] In some embodiments, the method of preparing Compound No. 10b comprises steps (i), (ii), (iii), and (iv).

[0111] In some embodiments, the method of preparing Compound No. 10b comprises steps (i), (ii), (iii), (iv), and (v).

[0112] In some embodiments, the method of preparing Compound No. 10b comprises steps (i), (ii), (iii), (iv), (v), and (vi).

[0113] In some embodiments, the method of preparing Compound No. 10b comprises step (vii).

[0114] In some embodiments, the method of preparing Compound No. 10b comprises steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[0115] In some aspects, the present disclosure provides a method of preparing Compound No. 10a' or 10b', comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5a or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6a or 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a or 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a' or 9b'; and

(vii) purifying Compound No. 9a' or 9b', thereby isolating Compound No. 10a' or 10b'.

[0116] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises one or more of steps (iv), (v), (vi), and (vii).

[0117] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises step (iv).

[0118] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises step (v).

[0119] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises steps (iv) and (v).

[0120] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises step (vi).

[0121] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises steps (iv), (v), and (vi).

[0122] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises one or more of steps (iv), (v), (vi), and (vii).

[0123] In some embodiments, the method comprises steps (iv), (v), (vi), and (vii).

[0124] In some aspects, the present disclosure provides a method of preparing Compound No. 10a' or 10b', comprising steps (i)-(vii):

(i) reacting tetrahydrofuran-2-carboxylic acid (*e.g.*, (2S)-tetrahydrofuran-2-carboxylic acid or (2R)-tetrahydrofuran-2-carboxylic acid), with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide (*e.g.*, (2S)-N-(1-methyl-1H-

pyrazol-4-yl)oxolane-2-carboxamide or (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide), or a salt thereof;

(ii) reacting N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide (*e.g.*, (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide or (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide), or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine (*e.g.*, 1-methyl-N-{{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine or 1-methyl-N-{{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine), or a salt thereof;

(iii) reacting 1-methyl-N-{{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine (*e.g.*, 1-methyl-N-{{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine or 1-methyl-N-{{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine), or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5a or 5b, or a salt thereof;

(iv) reacting Compound No. 5a or 5b, or a salt thereof, with an acid, thereby forming Compound No. 6a or 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a or 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a' or 9b'; and

(vii) purifying Compound No. 9a' or 9b', thereby isolating Compound No. 10a' or 10b'.

[0125] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises one or more of steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[0126] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises step (i).

[0127] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises step (ii).

[0128] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises steps (i) and (ii).

[0129] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises step (iii).

[0130] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises steps (i), (ii), and (iii).

[0131] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises steps (i), (ii), (iii), and (iv).

[0132] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises steps (i), (ii), (iii), (iv), and (v).

[0133] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises steps (i), (ii), (iii), (iv), (v), and (vi).

[0134] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises step (vii).

[0135] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[0136] In some embodiments, the method of preparing Compound No. 10a' or 10b' comprises one or more of steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[0137] In some aspects, the present disclosure provides a method of preparing Compound No. 10a'.

[0138] In some aspects, the present disclosure provides a method of preparing Compound No. 10a', comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5a, or a salt thereof, with an acid, thereby forming Compound No. 6a, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a'; and

(vii) purifying Compound No. 9a', thereby isolating Compound No. 10a'.

[0139] In some embodiments, the method of preparing Compound No. 10a' comprises one or more of steps (iv), (v), (vi), and (vii).

[0140] In some embodiments, the method of preparing Compound No. 10a' comprises step (iv).

[0141] In some embodiments, the method of preparing Compound No. 10a' comprises step (v).

[0142] In some embodiments, the method of preparing Compound No. 10a' comprises steps (iv) and (v).

[0143] In some embodiments, the method of preparing Compound No. 10a' comprises step (vi).

[0144] In some embodiments, the method of preparing Compound No. 10a' comprises steps (iv), (v), and (vi).

[0145] In some embodiments, the method of preparing Compound No. 10a' comprises one or more of steps (iv), (v), (vi), and (vii).

[0146] In some aspects, the present disclosure provides a method of preparing Compound No. 10a', comprising steps (i)-(vii):

(i) reacting (2S)-tetrahydrofuran-2-carboxylic acid with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof;

(ii) reacting (2S)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof;

(iii) reacting 1-methyl-N-{[(2S)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5a, or a salt thereof;

(iv) reacting Compound No. 5a, or a salt thereof, with an acid, thereby forming Compound No. 6a, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6a, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9a'; and

(vii) purifying Compound No. 9a', thereby isolating Compound No. 10a'.

[0147] In some embodiments, the method of preparing Compound No. 10a' comprises one or more of steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[0148] In some embodiments, the method of preparing Compound No. 10a' comprises step (i).

[0149] In some embodiments, the method of preparing Compound No. 10a' comprises step (ii).

[0150] In some embodiments, the method of preparing Compound No. 10a' comprises steps (i) and (ii).

[0151] In some embodiments, the method of preparing Compound No. 10a' comprises step (iii).

[0152] In some embodiments, the method of preparing Compound No. 10a' comprises steps (i), (ii), and (iii).

[0153] In some embodiments, the method of preparing Compound No. 10a' comprises steps (i), (ii), (iii), and (iv).

[0154] In some embodiments, the method of preparing Compound No. 10a' comprises steps (i), (ii), (iii), (iv), and (v).

[0155] In some embodiments, the method of preparing Compound No. 10a' comprises steps (i), (ii), (iii), (iv), (v), and (vi).

[0156] In some embodiments, the method of preparing Compound No. 10a' comprises step (vii).

[0157] In some embodiments, the method of preparing Compound No. 10a' comprises steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[0158] In some aspects, the present disclosure provides a method of preparing Compound No. 10b', comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5b, or a salt thereof, with an acid, thereby forming Compound No. 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6b, or a salt thereof, with Compound No. 8 or a salt thereof, thereby forming Compound No. 9b'; and

(vii) purifying Compound No. 9b', thereby isolating Compound No. 10b'.

[0159] In some embodiments, the method of preparing Compound No. 10b' comprises one or more of steps (iv), (v), (vi), and (vii).

[0160] In some embodiments, the method of preparing Compound No. 10b' comprises step (iv).

[0161] In some embodiments, the method of preparing Compound No. 10b' comprises step (v).

[0162] In some embodiments, the method of preparing Compound No. 10b' comprises steps (iv) and (v).

[0163] In some embodiments, the method of preparing Compound No. 10b' comprises step (vi).

[0164] In some embodiments, the method of preparing Compound No. 10b' comprises steps (iv), (v), and (vi).

[0165] In some embodiments, the method of preparing Compound No. 10b' comprises one or more of steps (iv), (v), (vi), and (vii).

[0166] In some aspects, the present disclosure provides a method of preparing Compound No. 10b', comprising steps (i)-(vii):

(i) reacting (2R)-tetrahydrofuran-2-carboxylic acid with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof;

(ii) reacting (2R)-N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof;

(iii) reacting 1-methyl-N-{[(2R)-oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5b, or a salt thereof;

(iv) reacting Compound No. 5b, or a salt thereof, with an acid, thereby forming Compound No. 6b, or a salt thereof;

(v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;

(vi) reacting Compound No. 6b, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9b'; and

(vii) purifying Compound No. 9b', thereby isolating Compound No. 10b'.

[0167] In some embodiments, the method of preparing Compound No. 10b' comprises one or more of steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[0168] In some embodiments, the method of preparing Compound No. 10b' comprises step (i).

[0169] In some embodiments, the method of preparing Compound No. 10b' comprises step (ii).

[0170] In some embodiments, the method of preparing Compound No. 10b' comprises steps (i) and (ii).

[0171] In some embodiments, the method of preparing Compound No. 10b' comprises step (iii).

[0172] In some embodiments, the method of preparing Compound No. 10b' comprises steps (i), (ii), and (iii).

[0173] In some embodiments, the method of preparing Compound No. 10b' comprises step (iv).

[0174] In some embodiments, the method of preparing Compound No. 10b' comprises steps (i), (ii), (iii), and (iv).

[0175] In some embodiments, the method of preparing Compound No. 10b' comprises step (v).

[0176] In some embodiments, the method of preparing Compound No. 10b' comprises steps (i), (ii), (iii), (iv), and (v).

[0177] In some embodiments, the method of preparing Compound No. 10b' comprises step (vi).

[0178] In some embodiments, the method of preparing Compound No. 10b' comprises steps (i), (ii), (iii), (iv), (v), and (vi).

[0179] In some embodiments, the method of preparing Compound No. 10b' comprises step (vii).

[0180] In some embodiments, the method of preparing Compound No. 10b' comprises steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

[0181] In some embodiments, isolation follows purification.

[0182] In some embodiments, Compound No. 4 or a salt thereof is Compound No. 4a, or a salt thereof.

[0183] In some embodiments, Compound No. 4 or a salt thereof is Compound No. 4b, or a salt thereof.

[0184] In some embodiments, Compound No. 5 or a salt thereof is Compound No. 5a, or a salt thereof.

[0185] In some embodiments, Compound No. 5 or a salt thereof is Compound No. 5b, or a salt thereof.

[0186] In some embodiments, Compound No. 6 or a salt thereof is Compound No. 6a, or a salt thereof.

[0187] In some embodiments, Compound No. 6 or a salt thereof is Compound No. 6b, or a salt thereof.

[0188] In some embodiments, Compound No. 9 is Compound No. 9a.

[0189] In some embodiments, Compound No. 9 is Compound No. 9b.

[0190] In some embodiments, Compound No. 9' is Compound No. 9a'.

[0191] In some embodiments, Compound No. 9' is Compound No. 9b'.

[0192] In some embodiments, Compound No. 10 is Compound No. 10a.

[0193] In some embodiments, Compound No. 10 is Compound No. 10b.

[0194] In some embodiments, Compound No. 10' is Compound No. 10a'.

[0195] In some embodiments, Compound No. 10' is Compound No. 10b'.

Step (iv)

[0196] In some embodiments, in step (iv), the acid is an inorganic acid.

[0197] In some embodiments, in step (iv), the acid is hydrochloric acid.

[0198] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is from about 5:1 to about 1:1.

[0199] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is from about 4:1 to about 1:1.

[0200] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is from about 3:1 to about 1:1.

[0201] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is from about 2:1 to about 1:1.

[0202] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is about 5:1.

[0203] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is about 4:1.

[0204] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is about 3:1.

[0205] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is about 2.5:1.

[0206] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is about 2:1.

[0207] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is about 1.5:1.

[0208] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is about 1.1:1.

[0209] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5a or 5b, or the salt thereof, is about 1:1.

[0210] In some embodiments, in step (iv), the reacting is performed in the presence of a first solvent to form a first mixture. In some embodiments, the first solvent is an inorganic solvent. In some embodiments, the first solvent is a polar protic solvent (*e.g.*, water). In some embodiments, the first solvent is water.

[0211] In some embodiments, in step (iv), the reacting is performed at a first temperature of 25 ± 15 °C, 25 ± 10 °C, or 25 ± 5 °C (*e.g.*, about 25 °C).

[0212] In some embodiments, in step (iv), the reacting is performed at a first temperature of about 25 ± 15 °C, about 25 ± 10 °C, or about 25 ± 5 °C (*e.g.*, about 25 °C).

[0213] In some embodiments, in step (iv), the reacting is performed at a first temperature of about 25 °C.

[0214] In some embodiments, in step (iv), the reacting is performed for 26 ± 20 hours, 26 ± 15 hours, 26 ± 10 hours, 26 ± 5 hours, 26 ± 4 hours, 26 ± 3 hours, 26 ± 2 hours, or 26 ± 1 hours (*e.g.*, about 26 hours).

[0215] In some embodiments, in step (iv), the reacting is performed for about 26 ± 20 hours, about 26 ± 15 hours, about 26 ± 10 hours, about 26 ± 5 hours, about 26 ± 4 hours, about 26 ± 3 hours, about 26 ± 2 hours, or about 26 ± 1 hours (*e.g.*, about 26 hours).

[0216] In some embodiments, in step (iv), the first mixture is cooled to a second temperature of $0\pm 15\text{ }^{\circ}\text{C}$, $0\pm 10\text{ }^{\circ}\text{C}$, or $0\pm 5\text{ }^{\circ}\text{C}$ (e.g., about $0\text{ }^{\circ}\text{C}$).

[0217] In some embodiments, in step (iv), the first mixture is cooled to a second temperature of about $0\pm 15\text{ }^{\circ}\text{C}$, about $0\pm 10\text{ }^{\circ}\text{C}$, or about $0\pm 5\text{ }^{\circ}\text{C}$ (e.g., about $0\text{ }^{\circ}\text{C}$).

[0218] In some embodiments, in step (iv), the first mixture is cooled to a second temperature of about $0\text{ }^{\circ}\text{C}$.

[0219] In some embodiments, in step (iv), the first mixture is cooled to a second temperature of $0\pm 15\text{ }^{\circ}\text{C}$, $0\pm 10\text{ }^{\circ}\text{C}$, or $0\pm 5\text{ }^{\circ}\text{C}$ (e.g., about $0\text{ }^{\circ}\text{C}$) and a second solvent is added to form a second mixture. In some embodiments, in step (iv), the first mixture is cooled to a second temperature of about $0\pm 15\text{ }^{\circ}\text{C}$, about $0\pm 10\text{ }^{\circ}\text{C}$, or about $0\pm 5\text{ }^{\circ}\text{C}$ (e.g., about $0\text{ }^{\circ}\text{C}$) and a second solvent is added to form a second mixture. In some embodiments, the second solvent is an organic solvent. In some embodiments, the second solvent is dichloromethane.

[0220] In some embodiments, in step (iv), a base is added to the second mixture. In some embodiments, the base is sodium hydroxide. In some embodiments, the base is potassium hydroxide.

[0221] In some embodiments, in step (iv), a base is added to the second mixture and pH is adjusted.

[0222] In some embodiments, in step (iv), a buffer is added to the second mixture and pH is adjusted.

[0223] In some embodiments, step (iv) further comprises adding a base to the first mixture, thereby forming Compound No. 6a or 6b or the salt thereof.

[0224] In some embodiments, step (iv) further comprises adding a base to the second mixture, thereby forming Compound No. 6a or 6b or the salt thereof.

[0225] In some embodiments, step (iv) further comprises adding a base or a buffer to the second mixture and adjusting the pH to 8.0 ± 2.0 .

[0226] In some embodiments, step (iv) further comprises adding a base or a buffer to the second mixture and adjusting the pH to about 8.0 ± 2.0 .

[0227] In some embodiments, step (iv) further comprises adding a base or a buffer to the second mixture and adjusting the pH to about 8.0.

[0228] In some embodiments, step (iv) further comprises adding a base or a buffer to the second mixture and adjusting the pH to about 9.0.

[0229] In some embodiments, step (iv) further comprises adding a base to the first mixture and adjusting the pH value to 8.0 ± 2.0 , 8.0 ± 1.5 , 8.0 ± 1.0 , 8.0 ± 0.9 , 8.0 ± 0.8 , 8.0 ± 0.7 , 8.0 ± 0.6 , 8.0 ± 0.5 , 8.0 ± 0.4 , 8.0 ± 0.3 , 8.0 ± 0.2 , or 8.0 ± 0.1 (e.g., about 8.0), thereby forming Compound No. 6a or 6b or the salt thereof.

[0230] In some embodiments, step (iv) further comprises adding a base to the first mixture and adjusting the pH value to about 8.0 ± 2.0 , about 8.0 ± 1.5 , about 8.0 ± 1.0 , about 8.0 ± 0.9 , about 8.0 ± 0.8 , about 8.0 ± 0.7 , about 8.0 ± 0.6 , about 8.0 ± 0.5 , about 8.0 ± 0.4 , about 8.0 ± 0.3 , about 8.0 ± 0.2 , or about 8.0 ± 0.1 (e.g., about 8.0), thereby forming Compound No. 6a or 6b or the salt thereof.

[0231] In some embodiments, step (iv) further comprises adding a base to the first mixture and adjusting the pH value to 9.0 ± 2.0 , 9.0 ± 1.5 , 9.0 ± 1.0 , 9.0 ± 0.9 , 9.0 ± 0.8 , 9.0 ± 0.7 , 9.0 ± 0.6 , 9.0 ± 0.5 , 9.0 ± 0.4 , 9.0 ± 0.3 , 9.0 ± 0.2 , or 9.0 ± 0.1 (e.g., about 9.0), thereby forming Compound No. 6a or 6b or the salt thereof.

[0232] In some embodiments, step (iv) further comprises adding a base to the first mixture and adjusting the pH value to about 9.0 ± 2.0 , about 9.0 ± 1.5 , about 9.0 ± 1.0 , about 9.0 ± 0.9 , about 9.0 ± 0.8 , about 9.0 ± 0.7 , about 9.0 ± 0.6 , about 9.0 ± 0.5 , about 9.0 ± 0.4 , about 9.0 ± 0.3 , about 9.0 ± 0.2 , or about 9.0 ± 0.1 (e.g., about 9.0), thereby forming Compound No. 6a or 6b or the salt thereof.

[0233] In some embodiments, step (iv) further comprises adding a base to the second mixture and adjusting the pH value to 8.0 ± 2.0 , 8.0 ± 1.5 , 8.0 ± 1.0 , 8.0 ± 0.9 , 8.0 ± 0.8 , 8.0 ± 0.7 , 8.0 ± 0.6 , 8.0 ± 0.5 , 8.0 ± 0.4 , 8.0 ± 0.3 , 8.0 ± 0.2 , or 8.0 ± 0.1 (e.g., about 8.0), thereby forming Compound No. 6a or 6b or the salt thereof.

[0234] In some embodiments, step (iv) further comprises adding a base to the second mixture and adjusting the pH value to about 8.0 ± 2.0 , about 8.0 ± 1.5 , about 8.0 ± 1.0 , about 8.0 ± 0.9 , about 8.0 ± 0.8 , about 8.0 ± 0.7 , about 8.0 ± 0.6 , about 8.0 ± 0.5 , about 8.0 ± 0.4 , about 8.0 ± 0.3 , about 8.0 ± 0.2 , or about 8.0 ± 0.1 (e.g., about 8.0), thereby forming Compound No. 6a or 6b or the salt thereof.

[0235] In some embodiments, step (iv) further comprises adding a base to the second mixture and adjusting the pH value to 9.0 ± 2.0 , 9.0 ± 1.5 , 9.0 ± 1.0 , 9.0 ± 0.9 , 9.0 ± 0.8 , 9.0 ± 0.7 , 9.0 ± 0.6 , 9.0 ± 0.5 , 9.0 ± 0.4 , 9.0 ± 0.3 , 9.0 ± 0.2 , or 9.0 ± 0.1 (e.g., about 9.0), thereby forming Compound No. 6a or 6b or the salt thereof.

[0236] In some embodiments, step (iv) further comprises adding a base to the second mixture and adjusting the pH value to about 9.0 ± 2.0 , about 9.0 ± 1.5 , about 9.0 ± 1.0 , about 9.0 ± 0.9 , about 9.0 ± 0.8 , about 9.0 ± 0.7 , about 9.0 ± 0.6 , about 9.0 ± 0.5 , about 9.0 ± 0.4 , about 9.0 ± 0.3 , about 9.0 ± 0.2 , or about 9.0 ± 0.1 (e.g., about 9.0), thereby forming Compound No. 6a or 6b or the salt thereof.

[0237] In some embodiments, step (iv) further comprises adding an inorganic or an organic base to the formed Compound No. 6a or 6b or the salt thereof, thereby adjusting the pH value to a value from about 8.0 to about 9.0.

[0238] In some embodiments, step (iv) further comprises adding K_2CO_3 solution to the formed Compound No. 6a or 6b or the salt thereof, thereby adjusting the pH value to a value from about 8.0 to about 9.0.

[0239] In some embodiments of step (iv), Compound No. 6a or 6b or the salt thereof is isolated and/or purified prior to reacting with Compound No. 8.

[0240] In some embodiments of step (iv), Compound No. 6a or 6b or the salt thereof is not isolated or purified prior to reacting with Compound No. 8.

[0241] In some embodiments, step (iv) yields Compound No. 6a or 6b or the salt thereof with purity of at least about 95% as measured by High-Performance Liquid Chromatography (HPLC).

[0242] In some embodiments, step (iv) yields Compound No. 6a or 6b or the salt thereof with purity of at least about 96% as measured by HPLC.

[0243] In some embodiments, step (iv) yields Compound No. 6a or 6b or the salt thereof with purity of at least about 97% as measured by HPLC.

[0244] In some embodiments, step (iv) yields Compound No. 6a or 6b or the salt thereof with purity of at least about 98% as measured by HPLC.

[0245] In some embodiments, step (iv) yields Compound No. 6a or 6b or the salt thereof with purity of at least about 99% as measured by HPLC.

Step (v)

[0246] In some embodiments, in step (v), a dissociation reaction of phosgene, a reaction between CO_2 with carbon (Boudouard reaction), a reaction of steam and carbon, a high-temperature electrolysis of carbon dioxide with solid oxide electrolyzer cells, or a direct oxidation of carbon in a limited supply of oxygen or air is the source of CO.

[0247] In some embodiments, in step (v), a phosgene derivative is the source of CO.

[0248] In some embodiments, in step (v), triphosgene is the a source of CO.

[0249] In some embodiments, in step (v), the reacting is performed in the presence of a base. In some embodiments, the base is an organic base (*e.g.*, triethylamine (TEA)).

[0250] In some embodiments, in step (v), the reacting is performed in the presence of triethylamine (TEA).

[0251] In some embodiments, in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is from about 3:1 to about 1:1.

[0252] In some embodiments, in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is from about 2:1 to about 1:1.

[0253] In some embodiments, in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is about 3:1.

[0254] In some embodiments, in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is about 2.5:1.

[0255] In some embodiments, in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is about 2.1:1.

[0256] In some embodiments, in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is about 2.0:1.

[0257] In some embodiments, in step (v), the reacting is performed in the presence of a solvent. In some embodiments, the solvent is an aprotic organic solvent (*e.g.*, toluene). In some embodiments, in step (v), the reacting is performed in the presence of toluene.

[0258] In some embodiments, step (v) comprises filtering the solution of Compound No. 8, or the salt thereof (*e.g.*, in toluene).

[0259] In some embodiments of step (v), Compound No. 8, or the salt thereof, is isolated and/or purified prior to reacting with Compound No. 6a or 6b or a salt thereof.

[0260] In some embodiments of step (v), Compound No. 8, or the salt thereof, is not isolated and/or purified prior to reacting with Compound No. 6a or 6b, or a salt thereof.

[0261] In some embodiments, step (v) yields a solution of Compound No. 8, or the salt thereof (*e.g.*, in toluene).

[0262] In some embodiments, step (v) yields Compound No. 8, or the salt thereof, with purity of at least about 95% as measured by HPLC.

[0263] In some embodiments, step (v) yields Compound No. 8, or the salt thereof, with purity of at least about 96% as measured by HPLC.

[0264] In some embodiments, step (v) yields Compound No. 8, or the salt thereof, with purity of at least about 97% as measured by HPLC.

[0265] In some embodiments, step (v) yields Compound No. 8, or the salt thereof, with purity of at least about 98% as measured by HPLC.

[0266] In some embodiments, step (v) yields Compound No. 8, or the salt thereof, with purity of at least about 99% as measured by HPLC.

Step (vi)

[0267] In some embodiments, in step (vi), the reacting is performed in the presence of a base. In some embodiments, the base is an inorganic base (*e.g.*, NaOH).

[0268] In some embodiments, in step (vi), the reacting is performed in the presence of NaOH.

[0269] In some embodiments, in step (vi), the reacting is performed in the presence of a first solvent. In some embodiments, the first solvent is an organic solvent. In some embodiments, the first solvent is an aprotic solvent (*e.g.*, tetrahydrofuran (THF)).

[0270] In some embodiments, in step (vi), the reacting is performed in the presence of tetrahydrofuran (THF).

[0271] In some embodiments, in step (vi), the molar ratio of Compound No. 6a or 6b, or a salt thereof, to the Compound No. 8, or the salt thereof, is from about 2:1 to about 1:2.

[0272] In some embodiments, in step (vi), the molar ratio of Compound No. 6a or 6b, or a salt thereof, to the Compound No. 8, or the salt thereof, is from about 1.5:1 to about 1:1.5.

[0273] In some embodiments, in step (vi), the molar ratio of Compound No. 6a or 6b, or a salt thereof, to the Compound No. 8, or the salt thereof, is about 1:1.

[0274] In some embodiments, in step (vi), the reacting is performed in the presence of an organic solvent.

[0275] In some embodiments, in step (vi), the reacting is performed in the presence of toluene.

[0276] In some embodiments, in step (vi), the reacting comprises removal of the first solvent.

[0277] In some embodiments, in step (vi), the reacting comprises partial removal of the first solvent.

[0278] In some embodiments, in step (vi), the reacting is performed in the presence of a second solvent. In some embodiments, in step (vi), the second solvent is an alcohol. In some embodiments, in step (vi), the second solvent is methanol, ethanol, or isopropanol. In some embodiments, in step (vi), the second solvent is isopropanol (IPA).

[0279] In some embodiments, in step (vi), the reacting comprises extracting Compound No. 9a or 9b using an ether.

[0280] In some embodiments, in step (vi), the reacting comprises extracting Compound No. 9a or 9b using methyl tert-butylether (MTBE).

[0281] In some embodiments, in step (vi), the reacting comprises filtering out Compound No. 9a or 9b.

[0282] In some embodiments, in step (vi), the reacting comprises filtering out Compound No. 9a or 9b and washing Compound No. 9a or 9b with an organic solvent.

[0283] In some embodiments, in step (vi), the reacting comprises filtering out Compound No. 9a or 9b and washing Compound No. 9a or 9b with a mixture of organic solvents.

[0284] In some embodiments, in step (vi), the reacting comprises filtering out Compound No. 9a or 9b and washing Compound No. 9a or 9b with a mixture of an alcohol and an ether.

[0285] In some embodiments, in step (vi), the reacting comprises filtering out Compound No. 9a or 9b and washing Compound No. 9a or 9b with IPA-MTBE.

[0286] In some embodiments, in step (vi), the reacting is performed at a first temperature of 25 ± 15 °C, 25 ± 10 °C, or 25 ± 5 °C (*e.g.*, about 25 °C).

[0287] In some embodiments, in step (vi), the reacting is performed at a first temperature of about 25 ± 15 °C, about 25 ± 10 °C, or about 25 ± 5 °C (*e.g.*, about 25 °C).

[0288] In some embodiments, in step (iv), the reacting is performed for 25 ± 20 hours, 5 ± 2 , 5 ± 4 hours, 5 ± 3 hours, 5 ± 2 hours, or 5 ± 1 hours (*e.g.*, about 5 hours, about 4 hours, about 3 hours, about 2 hours or about 1 hour).

[0289] In some embodiments, in step (iv), the reacting is performed for about 25 ± 20 hours, about 5 ± 2 , about 5 ± 4 hours, about 5 ± 3 hours, about 5 ± 2 hours, or about 5 ± 1 hours (*e.g.*, about 5 hours, about 4 hours, about 3 hours, about 2 hours or about 1 hour).

[0290] In some embodiments, step (vi) comprises filtering Compound No. 9a or 9b.

[0291] In some embodiments, in step (vi), Compound No. 9a or 9b is isolated and/or purified.

[0292] In some embodiments, in step (vi), Compound No. 9a or 9b is not isolated and/or purified.

[0293] In some embodiments, step (vi) yields Compound No. 9a or 9b with purity of at least about 95% as measured by HPLC.

[0294] In some embodiments, step (vi) yields Compound No. 9a or 9b with purity of at least about 96% as measured by HPLC.

[0295] In some embodiments, step (vi) yields Compound No. 9a or 9b with purity of at least about 97% as measured by HPLC.

[0296] In some embodiments, step (vi) yields Compound No. 9a or 9b with purity of at least about 98% as measured by HPLC.

[0297] In some embodiments, step (vi) yields Compound No. 9a or 9b with purity of at least about 99% as measured by HPLC.

Step (vii)

[0298] In some embodiments, step (vii) comprises recrystallizing Compound No. 9a or 9b in the presence of an organic solvent. In some embodiments, the organic solvent comprises n-heptane.

[0299] In some embodiments, step (vii) comprises recrystallizing Compound No. 9a or 9b from tetrahydrofuran, water, and ethyl acetate in the presence of an organic solvent. In some embodiments, the organic solvent comprises n-heptane.

[0300] In some embodiments, in step (vii), Compound No. 9a or 9b is dissolved in tetrahydrofuran.

[0301] In some embodiments, in step (vii), Compound No. 9a or 9b is dissolved in tetrahydrofuran and filtered.

[0302] In some embodiments, in step (vii), Compound No. 9a or 9b is dissolved in about 4 vol of tetrahydrofuran and filtered.

[0303] In some embodiments, in step (vii), Compound No. 9a or 9b is dissolved in tetrahydrofuran, filtered and washed with tetrahydrofuran to form a first mixture.

[0304] In some embodiments, in step (vii), Compound No. 9a or 9b is dissolved in about 4 vol of tetrahydrofuran, filtered and washed with 2 x 1 vol of tetrahydrofuran to form a first mixture.

[0305] In some embodiments, the first mixture of step (vii) is concentrated.

[0306] In some embodiments, the first mixture of step (vii) is concentrated to about 3 volumes.

[0307] In some embodiments, the first mixture of step (vii) is concentrated and ethyl acetate is added to form a second mixture.

[0308] In some embodiments, the first mixture of step (vii) is concentrated to about 3 volumes and ethyl acetate is added to form a second mixture.

[0309] In some embodiments, the first mixture of step (vii) is concentrated to about 3 volumes and about 15 vol of ethyl acetate is added to form a second mixture.

[0310] In some embodiments, the second mixture of step (vii) is concentrated.

[0311] In some embodiments, the second mixture of step (vii) is concentrated and ethyl acetate and water are added to form a third mixture.

[0312] In some embodiments, the second mixture of step (vii) is concentrated to about 10 volumes.

[0313] In some embodiments, the second mixture of step (vii) is concentrated to about 10 volumes and ethyl acetate and water are added to form a third mixture.

[0314] In some embodiments, the second mixture of step (vii) is concentrated to about 10 volumes and about 10 vol of ethyl acetate and about 0.2 vol of water are added to form a third mixture.

[0315] In some embodiments, the third mixture of step (vii) is heated and then seeded to form a seeded third mixture.

[0316] In some embodiments, the third mixture of step (vii) is heated to a first temperature of 45 ± 20 °C, 45 ± 15 °C, 45 ± 10 °C, 45 ± 5 °C, 45 ± 4 °C, 45 ± 3 °C, 45 ± 2 °C, or 45 ± 1 °C (*e.g.*, about 45 °C) and then seeded to form a seeded third mixture.

[0317] In some embodiments, the third mixture of step (vii) is heated to a first temperature of about 45 ± 20 °C, about 45 ± 15 °C, about 45 ± 10 °C, about 45 ± 5 °C, about 45 ± 4 °C, about 45 ± 3 °C, about 45 ± 2 °C, or about 45 ± 1 °C (*e.g.*, about 45 °C) and then seeded to form a seeded third mixture.

[0318] In some embodiments, after heating to the first temperature, the seeded third mixture of step (vii) is aged for 1 ± 2 hours, or 1 ± 1 hour (*e.g.*, about 0.5 hour or about 1 hour).

[0319] In some embodiments, after heating to the first temperature, the seeded third mixture of step (vii) is aged for about 1 ± 2 hours, or 1 ± 1 hour (*e.g.*, about 0.5 hour or about 1 hour).

[0320] In some embodiments, in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of 30 ± 20 °C, 30 ± 15 °C, 30 ± 10 °C, 30 ± 5 °C, 30 ± 4 °C, 30 ± 3 °C, 30 ± 2 °C, or 30 ± 1 °C (*e.g.*, about 30 °C).

[0321] In some embodiments, in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of about 30 ± 20 °C, about 30 ± 15 °C, about 30 ± 10 °C, about 30 ± 5 °C, about 30 ± 4 °C, about 30 ± 3 °C, about 30 ± 2 °C, or about 30 ± 1 °C (*e.g.*, about 30 °C).

[0322] In some embodiments, in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of 30 ± 20 °C, 30 ± 15 °C, 30 ± 10 °C, 30 ± 5 °C, 30 ± 4 °C, 30 ± 3 °C, 30 ± 2 °C, or 30 ± 1 °C (*e.g.*, about 30 °C) and aged for a time from about 1 hour to about 12 hours, from about 2 hours to about 10 hours, or from about 3 hours to about 6 hours to form a mixture comprising Compound No. 10.

[0323] In some embodiments, in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of about 30 ± 20 °C, about 30 ± 15 °C, about 30 ± 10 °C, about 30 ± 5 °C, about 30 ± 4 °C, about 30 ± 3 °C, about 30 ± 2 °C, or about 30 ± 1 °C (*e.g.*, about 30 °C) and aged for a time from about 1 hour to about 12 hours, from about 2 hours to about 10 hours, or from about 3 hours to about 6 hours to form a mixture comprising Compound No. 10.

[0324] In some embodiments, in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of 30 ± 20 °C, 30 ± 15 °C, 30 ± 10 °C, 30 ± 5 °C, 30 ± 4 °C, 30 ± 3 °C, 30 ± 2 °C, or 30 ± 1 °C (*e.g.*, about 30 °C) and aged for about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours to form a mixture comprising Compound No. 10a or 10b.

[0325] In some embodiments, in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of about 30 ± 20 °C, about 30 ± 15 °C, about 30 ± 10 °C, about 30 ± 5 °C, about 30 ± 4 °C, about 30 ± 3 °C, about 30 ± 2 °C, or about 30 ± 1 °C (*e.g.*, about 30 °C) and aged for about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours to form a mixture comprising Compound No. 10a or 10b.

[0326] In some embodiments, in step (vii), n-heptane is added to the mixture comprising Compound No. 10a or 10b to form a solid form of Compound No. 10a or 10b.

[0327] In some embodiments, in step (vii), about 5 vol of n-heptane is added to the mixture comprising Compound No. 10a or 10b to form a solid form of Compound No. 10a or 10b.

[0328] In some embodiments, in step (vii), the solid form of Compound No. 10a or 10b is filtered out and washed, thereby forming substantially pure solid form of Compound No. 10a or 10b.

[0329] In some embodiments, in step (vii), the solid form of Compound No. 10a or 10b is filtered out and washed with a mixture comprising ethyl acetate, heptane, and water, thereby forming substantially pure solid form of Compound No. 10a or 10b.

[0330] In some embodiments, in step (vii), the solid form of Compound No. 10a or 10b is filtered out thereby isolating substantially pure solid form of Compound No. 10a or 10b.

[0331] In some embodiments, in step (vii), the solid form of Compound No. 10a or 10b is filtered out and washed with ethyl acetate-heptane thereby isolating substantially pure solid form of Compound No. 10a or 10b.

[0332] In some embodiments, in step (vii), the solid form of Compound No. 10a or 10b is filtered out and washed with ethyl acetate-heptane containing water thereby isolating substantially pure solid form of Compound No. 10a or 10b.

[0333] In some embodiments, in step (vii), the solid form of Compound No. 10a or 10b is filtered out and washed with 4:1 ethyl acetate-heptane (4 vol) containing 1% v/v water (vs ethyl acetate), thereby forming substantially pure solid form of Compound No. 10a or 10b.

[0334] In some embodiments, in step (vii), the solid form of Compound No. 10a or 10b is dried.

[0335] In some embodiments, step (vii) yields a polymorphic form of Compound No. 10a or 10b.

[0336] In some embodiments, the polymorphic form is a monohydrate of Compound No. 10a or 10b.

[0337] In some embodiments, step (vii) yields polymorphic form (*e.g.*, Form 3) of Compound No. 10a.

- [0338] In some embodiments, Form 3 is a monohydrate Compound No. 10a.
- [0339] In some embodiments, step (vii) yields polymorphic form (Form 3) of Compound No. 10 monohydrate.
- [0340] In some embodiments, Form 3 exhibits high solubility in water, *e.g.*, high aqueous solubility.
- [0341] In some embodiments, the aqueous solubility of Compound No. 10a in Fasted State Simulated Gastric Fluid (FaSSGF; pH is about 1.6) is about 24 µg/mL.
- [0342] In some embodiments, the aqueous solubility of Compound No. 10a in Fed State Simulated Intestinal Fluid (FeSSIF; pH is about 5.0) is about 169 µg/mL.
- [0343] In some embodiments, the aqueous solubility of Compound No. 10a in Fasted State Simulated Intestinal Fluid (FaSSIF; pH is about 6.5) is about 126 µg/mL.
- [0344] In some embodiments, the aqueous solubility of Compound No. 10a in Tris(hydroxymethyl)aminomethane (Tris; pH is about 8.0) is above 300 mg/mL.
- [0345] In some embodiments, the Compound No. 10a (Form 3) exhibits good solubility in methanol, ethanol, acetone, methyl ethyl ketone (MEK), and tetrahydrofuran.
- [0346] In some embodiments, the Compound No. 10a (Form 3) exhibits poor solubility in ethylacetate, isopropylacetate, methyl isobutyl ketone (MIBK), isopropanol and n-heptane.
- [0347] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 98% as measured by HPLC.
- [0348] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 98.5% as measured by HPLC.
- [0349] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 99% as measured by HPLC.
- [0350] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 99.1% as measured by HPLC.
- [0351] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 99.2% as measured by HPLC.
- [0352] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 99.3% as measured by HPLC.
- [0353] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 99.4% as measured by HPLC.
- [0354] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 99.5% as measured by HPLC.

[0355] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 99.6% as measured by HPLC.

[0356] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 99.7% as measured by HPLC.

[0357] In some embodiments, step (vii) yields a solid form of Compound No. 10a or 10b with purity of at least about 99.8% as measured by HPLC.

[0358] In some embodiments, step (vii) yields substantially pure Compound No. 10.

[0359] In some embodiments, step (vii) yields substantially pure polymorphic form (Form 3) of Compound No. 10a.

[0360] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 98% as measured by HPLC.

[0361] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 98.5% as measured by HPLC.

[0362] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 99% as measured by HPLC.

[0363] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 99.1% as measured by HPLC.

[0364] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 99.2% as measured by HPLC.

[0365] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 99.3% as measured by HPLC.

[0366] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 99.4% as measured by HPLC.

[0367] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 99.5% as measured by HPLC.

[0368] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 99.6% as measured by HPLC.

[0369] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 99.7% as measured by HPLC.

[0370] In some embodiments, step (vii) yields a solid form of Compound No. 10a with purity of at least about 99.8% as measured by HPLC.

[0371] In some embodiments, step (vii) yields substantially pure Compound No. 10a.

[0372] In some embodiments, step (vii) yields substantially pure polymorphic form (Form 3) of Compound No. 10a.

[0373] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 98% as measured by HPLC.

[0374] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 98.5% as measured by HPLC.

[0375] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 99% as measured by HPLC.

[0376] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 99.1% as measured by HPLC.

[0377] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 99.2% as measured by HPLC.

[0378] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 99.3% as measured by HPLC.

[0379] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 99.4% as measured by HPLC.

[0380] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 99.5% as measured by HPLC.

[0381] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 99.6% as measured by HPLC.

[0382] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 99.7% as measured by HPLC.

[0383] In some embodiments, step (vii) yields a solid form of Compound No. 10b with purity of at least about 99.8% as measured by HPLC.

[0384] In some embodiments, step (vii) yields substantially pure Compound No. 10b.

[0385] In some embodiments, in-process testing during the synthesis of Compound No. 10a is generated to monitor conversion for each step or completion of drying.

[0386] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 98% as measured by HPLC.

[0387] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 98.5% as measured by HPLC.

- [0388] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 99% as measured by HPLC.
- [0389] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 99.1% as measured by HPLC.
- [0390] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 99.2% as measured by HPLC.
- [0391] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 99.3% as measured by HPLC.
- [0392] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 99.4% as measured by HPLC.
- [0393] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 99.5% as measured by HPLC.
- [0394] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 99.6% as measured by HPLC.
- [0395] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 99.7% as measured by HPLC.
- [0396] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a or 10b with purity of at least about 99.8% as measured by HPLC.
- [0397] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 98% as measured by HPLC.
- [0398] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 98.5% as measured by HPLC.
- [0399] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 99% as measured by HPLC.
- [0400] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 99.1% as measured by HPLC.
- [0401] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 99.2% as measured by HPLC.
- [0402] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 99.3% as measured by HPLC.
- [0403] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 99.4% as measured by HPLC.

- [0404] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 99.5% as measured by HPLC.
- [0405] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 99.6% as measured by HPLC.
- [0406] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 99.7% as measured by HPLC.
- [0407] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10a with purity of at least about 99.8% as measured by HPLC.
- [0408] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 98% as measured by HPLC.
- [0409] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 98.5% as measured by HPLC.
- [0410] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 99% as measured by HPLC.
- [0411] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 99.1% as measured by HPLC.
- [0412] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 99.2% as measured by HPLC.
- [0413] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 99.3% as measured by HPLC.
- [0414] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 99.4% as measured by HPLC.
- [0415] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 99.5% as measured by HPLC.
- [0416] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 99.6% as measured by HPLC.
- [0417] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 99.7% as measured by HPLC.
- [0418] In some embodiments, step (vii) yields at least one solid morphic form of Compound No. 10b with purity of at least about 99.8% as measured by HPLC.

[0419] In some embodiments, in-process testing during the synthesis of Compound No. 10a is generated to monitor conversion for each step or completion of drying. Test Methods for in-process controls (IPC's) are presented in Table 2.

Table 2: IPC Test Methods for the Manufacture of Compound No. 10a

Step / IPC	Test
Step 4: IPC-1	Reaction completion by HPLC
Step 4: IPC-2	Liquor loss by HPLC
Step 5: IPC-1	Reaction completion by HPLC
Step 5: IPC-2	Determine wt% of Compound No. 8 in toluene solution by HPLC
Step 6: IPC-1	Reaction completion by HPLC.
Step 6: IPC-2	Liquor loss by HPLC
Step 7: IPC-1	Liquor loss by HPLC
Step 7: IPC-2	Polymorphic form check
Step 7: IPC-3	Liquor loss by HPLC
Step 7: IPC-4	Residual solvents by Headspace Gas Chromatography (GC-HS)
Step 7: IPC-5	Water content by Karl Fischer (KF)

Compounds Prepared by the Methods

[0420] In some aspects, the present disclosure provides a compound being prepared by a method disclosed herein.

[0421] In some aspects, the present disclosure provides a compound being prepared in large scale according to a method disclosed herein.

[0422] In some aspects, the present disclosure provides a method of preparing Compound No. 5.

[0423] In some aspects, the present disclosure provides a method of preparing Compound No. 5a.

[0424] In some aspects, the present disclosure provides a method of preparing Compound No. 5b.

[0425] In some aspects, the present disclosure provides a method of preparing Compound No. 6.

[0426] In some aspects, the present disclosure provides a method of preparing Compound No. 6a.

[0427] In some aspects, the present disclosure provides a method of preparing Compound No. 6b.

[0428] In some aspects, the present disclosure provides a method of preparing Compound No. 8.

- [0429] In some aspects, the present disclosure provides a method of preparing Compound No. 9.
- [0430] In some aspects, the present disclosure provides a method of preparing Compound No. 9a.
- [0431] In some aspects, the present disclosure provides a method of preparing Compound No. 9b.
- [0432] In some aspects, the present disclosure provides a method of preparing Compound No. 9'.
- [0433] In some aspects, the present disclosure provides a method of preparing Compound No. 9a'.
- [0434] In some aspects, the present disclosure provides a method of preparing Compound No. 9b'.
- [0435] In some aspects, the present disclosure provides a method of preparing Compound No. 10.
- [0436] In some aspects, the present disclosure provides a method of preparing Compound No. 10a.
- [0437] In some aspects, the present disclosure provides a method of preparing Compound No. 10b.
- [0438] In some aspects, the present disclosure provides a method of preparing Compound No. 10'.
- [0439] In some aspects, the present disclosure provides a method of preparing Compound No. 10a'.
- [0440] In some aspects, the present disclosure provides a method of preparing Compound No. 10b'.
- [0441] In some aspects, the present disclosure provides Compound No. 3, or a salt thereof.
- [0442] In some aspects, the present disclosure provides Compound No. 3a, or a salt thereof.
- [0443] In some embodiments, the compound is Compound No. 3a, or a salt thereof, having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.
- [0444] In some embodiments, the compound is Compound No. 3a, or a salt thereof, having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.
- [0445] In some aspects, the present disclosure provides Compound No. 3b, or a salt thereof.
- [0446] In some embodiments, the compound is Compound No. 3b, or a salt thereof, having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.
- [0447] In some embodiments, the compound is Compound No. 3b, or a salt thereof, having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.
- [0448] In some aspects, the present disclosure provides Compound No. 4, or a salt thereof.

[0449] In some aspects, the present disclosure provides Compound No. 4a, or a salt thereof.

[0450] In some embodiments, the compound is Compound No. 4a or a salt thereof having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0451] In some embodiments, the compound is Compound No. 4a, or a salt thereof, having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0452] In some aspects, the present disclosure provides Compound No. 4b, or a salt thereof.

[0453] In some embodiments, the compound is Compound No. 4b, or a salt thereof, having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0454] In some embodiments, the compound is Compound No. 4b, or a salt thereof, having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0455] In some aspects, the present disclosure provides Compound No. 5, or a salt thereof.

[0456] In some aspects, the present disclosure provides Compound No. 5a, or a salt thereof.

[0457] In some embodiments, the compound is Compound No. 5a, or a salt thereof, having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0458] In some embodiments, the compound is Compound No. 5a, or a salt thereof, having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0459] In some aspects, the present disclosure provides Compound No. 5b, or a salt thereof.

[0460] In some embodiments, the compound is Compound No. 5b, or a salt thereof, having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about

97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0461] In some embodiments, the compound is Compound No. 5b, or a salt thereof, having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0462] In some aspects, the present disclosure provides Compound No. 6, or a salt thereof.

[0463] In some aspects, the present disclosure provides Compound No. 6a, or a salt thereof.

[0464] In some embodiments, the compound is Compound No. 6a, or a salt thereof, having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0465] In some embodiments, the compound is Compound No. 6a, or a salt thereof, having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0466] In some aspects, the present disclosure provides Compound No. 6b, or a salt thereof.

[0467] In some embodiments, the compound is Compound No. 6b, or a salt thereof, having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0468] In some embodiments, the compound is Compound No. 6b, or a salt thereof, having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0469] In some aspects, the present disclosure provides Compound No. 8, or a salt thereof.

[0470] In some embodiments, the compound is Compound No. 8, or a salt thereof, having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0471] In some aspects, the present disclosure provides Compound No. 9.

[0472] In some aspects, the present disclosure provides Compound No. 9a.

[0473] In some embodiments, the compound is Compound No. 9a having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0474] In some embodiments, the compound is Compound No. 9a having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0475] In some aspects, the present disclosure provides Compound No. 9b.

[0476] In some embodiments, the compound is Compound No. 9b having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0477] In some embodiments, the compound is Compound No. 9b having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0478] In some embodiments, the compound is:

Compound No. 9;

Compound No. 9a; or

Compound No. 9b having:

(a) an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater; and/or

(b) a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0479] In some aspects, the present disclosure provides Compound No. 9'.

[0480] In some aspects, the present disclosure provides Compound No. 9a'.

[0481] In some embodiments, the compound is Compound No. 9a' having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater,

about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0482] In some embodiments, the compound is Compound No. 9a' having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0483] In some aspects, the present disclosure provides Compound No. 9b'.

[0484] In some embodiments, the compound is Compound No. 9b' having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0485] In some embodiments, the compound is Compound No. 9b' having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0486] In some embodiments, the compound is:

Compound No. 9';

Compound No. 9a'; or

Compound No. 9b' having:

(a) an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater; and/or

(b) a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0487] In some aspects, the present disclosure provides Compound No. 10.

[0488] In some aspects, the present disclosure provides Compound No. 10a.

[0489] In some embodiments, the compound is Compound No. 10a having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0490] In some embodiments, the compound is Compound No. 10a having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0491] In some aspects, the present disclosure provides Compound No. 10b.

[0492] In some embodiments, the compound is Compound No. 10b having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

In some embodiments, the compound is Compound No. 10b having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0493] In some embodiments, the compound is:

Compound No. 10;

Compound No. 10a; or

Compound No. 10b having:

(a) an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater; and/or

(b) a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0494] In some aspects, the present disclosure provides Compound No. 10'.

[0495] In some aspects, the present disclosure provides Compound No. 10a'.

[0496] In some embodiments, the compound is Compound No. 10a' having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0497] In some embodiments, the compound is Compound No. 10a' having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater,

about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0498] In some aspects, the present disclosure provides Compound No. 10b'.

[0499] In some embodiments, the compound is Compound No. 10b' having an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

In some embodiments, the compound is Compound No. 10b' having a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

[0500] In some embodiments, the compound is:

Compound No. 10';

Compound No. 10a'; or

Compound No. 10b' having:

(a) an enantiomeric excess (ee) of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater; and/or

(b) a purity of about 90% or greater, about 95% or greater, about 96% or greater, about 97% or greater, about 98% or greater, about 99% or greater, about 99.5% or greater, about 99.6% or greater, about 99.7% or greater, about 99.8% or greater, or about 99.9% or greater.

Methods of Use

[0501] In some aspects, the present disclosure provides a method of preventing or treating a disease in a subject, comprising administering to the subject Compound No. 10 (*e.g.*, Compound No. 10a or 10b) as described herein.

[0502] In some embodiments, the subject is administered a therapeutically effective amount.

[0503] In some aspects, the present disclosure provides a method of treating a disease in a subject, comprising administering to the subject Compound No. 10 (*e.g.*, Compound No. 10a or 10b) as described herein.

[0504] In some aspects, the present disclosure provides Compound No. 10 (*e.g.*, Compound No. 10a or 10b) as described herein for use in preventing or treating a disease in a subject.

[0505] In some aspects, the present disclosure provides use of Compound No. 10 (*e.g.*, Compound No. 10a or 10b) as described herein in the manufacture of a medicament for preventing or treating a disease in a subject.

[0506] In some aspects, the present disclosure provides use of Compound No. 10 (*e.g.*, Compound No. 10a or 10b) as described herein in the manufacture of a medicament for treating a disease in a subject.

[0507] In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered in a therapeutically effective amount.

[0508] In some embodiments, the disease or disorder is an inflammatory disorder, autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease, or cancer.

[0509] In some aspects, the present disclosure provides a method of inhibiting inflammasome (*e.g.*, the NLRP3 inflammasome) activity in a subject, comprising contacting a cell with Compound No. 10 (*e.g.*, Compound No. 10a or 10b) as described herein.

[0510] In some aspects, the present disclosure provides Compound No. 10 (*e.g.*, Compound No. 10a or 10b) as described herein for use in inhibiting inflammasome (*e.g.*, the NLRP3 inflammasome) activity in a subject.

[0511] In some aspects, the present disclosure provides use of Compound No. 10 (*e.g.*, Compound No. 10a or 10b) as described herein in the manufacture of a medicament for inhibiting inflammasome (*e.g.*, the NLRP3 inflammasome) activity.

[0512] In some embodiments, the subject is an animal.

[0513] In some embodiments, the subject is a mammal.

[0514] In some embodiments, the subject is a human.

[0515] In some embodiments, the subject is a cell.

In some embodiments, the subject is a cell population.

Pharmaceutical Compositions/Formulations

[0516] In some embodiments the present disclosure provides pharmaceutical compositions comprising Compound No. 10 (*e.g.*, Compound No. 10a or 10b), and an excipient, adjuvant, diluent, or carrier (*e.g.*, a pharmaceutically acceptable excipient, adjuvant, diluent, or carrier).

[0517] Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

[0518] Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art. A summary of pharmaceutical compositions described herein may be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington 's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins, 1999), herein incorporated by reference in their entirety.

[0519] A pharmaceutical composition, as used herein, refers to Compound No. 10 (*e.g.*, Compound No. 10a or 10b) and/or an additional therapeutic agent with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. A pharmaceutical composition, as used herein, refers to Compound No. 10 (*e.g.*, Compound No. 10a or 10b) and one or more of the following excipients: microcrystalline cellulose, crospovidone, hypromellose, sodium bicarbonate, hydrophobic colloidal silica, and magnesium stearate.

[0520] In practicing the methods of treatment or use provided herein, therapeutically effective amounts of Compound No. 10 (*e.g.*, Compound No. 10a or 10b) disclosed herein are administered having a disease, disorder, or condition to be treated. In some embodiments, the mammal is a human. The therapeutically effective amounts of the compounds may vary depending on the severity of the disease, the age and relative health of the subject, and other factors.

[0521] Pharmaceutical compositions including Compound No. 10 (*e.g.*, Compound No. 10a or 10b) described herein may be manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

Biological Assays

[0522] Compounds being prepared by the methods described herein can be characterised using a variety of assays known to those skilled in the art to determine whether the compounds have

biological activity. For example, the molecules can be characterised by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

[0523] Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described herein for activity, using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

[0524] Various in vitro or in vivo biological assays may be suitable for detecting the effect of the compounds of the present disclosure. These in vitro or in vivo biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, in vitro cell viability assays, and the assays described herein.

[0525] In some embodiments, the biological assay is a biological assay testing inhibitory activity against IL-1 β release upon NLRP3 activation in peripheral blood mononuclear cells (PBMC).

[0526] In some embodiments, the biological assay is a PBMC IC₅₀ Determination Assay.

[0527] In some embodiments, the compound is tested for their inhibitory activity against IL-1 β release upon NLRP3 activation in blood cells (*e.g.*, peripheral blood mononuclear cells (PBMC)).

[0528] In some embodiments, PBMC is isolated and seeded into the wells of a plate and incubated for a period of time (*e.g.*, for 3 hours with a lipopolysaccharide). Following incubation, the medium is exchanged and the compound added to the well (*e.g.*, a compound of the present disclosure) and the cells may be incubated. Next, the cells are stimulated (*e.g.*, with ATP or nigericin) and the cell culture media are collected for analysis.

[0529] In some embodiments, the release of IL-1 β into the media is determined by a quantitative detection of IL-1 β in the media (*e.g.*, using ELISA).

[0530] In some embodiments, PBMC is isolated (*e.g.*, from buffy coats). Isolated cells are seeded into wells and incubated (*e.g.*, for 3 hours with lipopolysaccharide). The compound is then added and the cells incubated. Next, the cells are stimulated and the media from the wells are collected for analysis.

[0531] In some embodiments, the release of IL-1 β into the media is determined by quantitative detection (*e.g.*, of IL-1 β in media using HTRF®).

Definitions

[0532] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0533] The term “about” is used herein to mean approximately, in the region of, roughly or around. When the term “about” is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 20%, a variance of 10%, a variance of 5%, a variance of 3%, or a variance of 1%.

[0534] As used herein, the term “substantially pure” with reference to a compound indicates that the compound includes less than 10%, less than 5%, less than 3%, less than 1%, less than 0.5%, less than 0.2%, or less than 0.1% by weight of impurities.

[0535] As used herein, the term “a source of CO” refers to an agent that is capable of being a resource of carbon monoxide (CO) during a reaction. In some embodiments, the agent is capable of forming an isocyanate or an equivalent upon reacting with an amine. In some embodiments, a dissociation reaction of phosgene, a reaction between CO₂ with carbon (Boudouard reaction), a reaction of steam and carbon, a high-temperature electrolysis of carbon dioxide with solid oxide electrolyzer cells, or a direct oxidation of carbon in a limited supply of oxygen or air is the source of CO. In some embodiments, the source of CO is a phosgene derivative. In one specific embodiment, the source of CO is triphosgene.

[0536] It is understood that the compounds described herein include the compounds themselves, as well as their salts, and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (*e.g.*, amino) on a substituted benzene compound. Suitable anions may include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (*e.g.*, trifluoroacetate). As used herein, the expressions “one or more of A, B, or C”, “one or more A, B, or C”, “one or more of A, B, and C”, “one or more A, B, and C”, “selected from the group consisting of A, B, and C”, “selected from A, B, and C”, and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, *i.e.*, one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[0537] It is to be understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also

consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0538] It is to be understood that the synthetic processes of the disclosure 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 thereof.

[0539] It is to be understood that Compound No. 10a or 10b 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 which will be apparent to the skilled artisan in light of the teachings herein. 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 Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognised reference textbooks of organic synthesis known to those in the art.

[0540] One of ordinary skill in the art will note that, during the reaction sequences and synthetic scheme described herein, the order of certain steps may be changed, such as the introduction and removal of protecting groups. One of ordinary skill in the art will recognise that certain groups may require protection from the reaction conditions via the use of protecting groups. Protecting groups may also be used to differentiate similar functional groups in molecules. A list of protecting groups and how to introduce and remove these groups can be found in Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999.

[0541] It is to be understood that, unless otherwise stated, any description of a method of treatment or prevention includes use of Compound No. 10a or 10b to provide such treatment or prevention as is described herein. It is to be further understood, unless otherwise stated, any description of a method of treatment or prevention includes use of Compound No. 10a or 10b to prepare a medicament to treat or prevent such a condition. The treatment or prevention includes treatment or prevention of human or non-human animals including rodents and other disease models.

[0542] It is to be understood that, unless otherwise stated, any description of a method of treatment includes use of Compound No. 10a or 10b to provide such treatment as is described herein. It is to be further understood, unless otherwise stated, any description of a method of treatment includes use of Compound No. 10a or 10b to prepare a medicament to treat such a condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[0543] In some embodiments, the term “filtering out” is collecting a solid form of the desired compound by the use of a filter medium.

[0544] As used herein, the term “subject” includes human and non-human animals, as well as cell lines, cell cultures, tissues, and organs. In some embodiments, the subject is a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In some embodiments, the subject is a human.

[0545] As used herein, the term “subject in need thereof” refers to a subject having a disease or having an increased risk of developing the disease. A subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (*i.e.*, a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant disease or disorder disclosed herein (*i.e.*, a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[0546] As used herein, the term “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a

compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term “treat” can also include treatment of a cell *in vitro* or an animal model.

[0547] It is to be understood that Compound No. 10a or 10b, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

[0548] As used herein, the term “preventing” or “prevent,” describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0549] It is to be understood that one skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al.*, *Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna *et al.*, *Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al.*, *The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the disclosure.

[0550] As used herein, the term “pharmaceutical composition” is a formulation containing Compound No. 10a or 10b in a form suitable for administration to a subject. In some embodiments, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intravitreal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with one or more pharmaceutically acceptable carrier, and with any preservatives, buffers, or

propellants that are required. As used herein, the term “pharmaceutically acceptable” refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0551] As used herein, the term “pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims may include both one and more than one such excipient.

[0552] It is to be understood that a pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, intravitreal, oral (*e.g.*, ingestion), inhalation, transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0553] It is to be understood that a compound or pharmaceutical composition of the disclosure can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, a compound of the disclosure may be injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, a disease or disorder disclosed herein) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0554] As used herein, the term “therapeutically effective amount,” refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit

a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0555] As used herein, the term "effective amount," refers to an amount of a pharmaceutical agent to treat or ameliorate an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0556] It is to be understood that, for any compound, the therapeutically effective amount or effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0557] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy.

[0558] The pharmaceutical compositions containing Compound No. 10a or 10b may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or

lyophilising processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carrier comprising excipients and/or auxiliaries that facilitate processing of Compound No. 10a or 10b into preparations that can be used pharmaceutically. The appropriate formulation is dependent upon the route of administration chosen.

[0559] In some embodiments, the pharmaceutical compositions disclosed herein further comprise a pharmaceutically acceptable excipient, such as, for example, a diluent, a carrier, an adjuvant, a binder, a lubricant, a surfactant, a sweetening agent, a flavoring agent, a coating material, a preservative, a dye, a thickener, or a combination thereof.

[0560] It is to be understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0561] It is to be understood that, for the compounds of the present disclosure being capable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[0562] As used herein, the term “pharmaceutically acceptable salts” refers to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making an acid or base salt thereof. Examples of pharmaceutically acceptable salts may include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts may include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts may include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulphonic, acetic, ascorbic, benzene sulphonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulphonic, 1,2-ethane sulphonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, arsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulphonic, maleic, malic, mandelic, methane sulphonic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, succinic, sulphamic, sulphanilic, sulphuric, tannic, tartaric, toluene sulphonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0563] In some embodiments, the salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt. In some embodiments, the salt is a sodium salt.

[0564] In some embodiments, the pharmaceutically acceptable salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt. In some embodiments, the pharmaceutically acceptable salt is a sodium salt. Other examples of pharmaceutically acceptable salts may include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulphonic acid, 2-naphthalenesulphonic acid, 4-toluenesulphonic acid, camphorsulphonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, *e.g.*, 3:1, 2:1, 1:2, or 1:3.

[0565] It is to be understood that all references to pharmaceutically acceptable salts may include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0566] As used herein, Form 2 of Compound No. 10a corresponds to Form 2 disclosed in U.S. Provisional Patent Application No. 63/600,104 filed on November 17, 2023.

[0567] In some embodiments, Form 2 of Compound No. 10a is characterized by an XRPD pattern comprising signals at 4.2 ± 0.5 , 16.7 ± 0.5 , and 16.8 ± 0.5 °2 θ using Cu K α radiation (*e.g.*, 4.2 ± 0.2 , 16.7 ± 0.2 , and 16.8 ± 0.2 °2 θ using Cu K α radiation (*e.g.*, 4.2 ± 0.1 , 16.7 ± 0.1 , and 16.8 ± 0.1 °2 θ using Cu K α radiation (*e.g.*, 4.2, 16.7, and 16.8 °2 θ using Cu K α radiation))).

[0568] In some embodiments, Form 2 of Compound No. 10a is characterized by an XRPD pattern comprising signals at 4.2 ± 0.5 , 8.4 ± 0.5 , 10.2 ± 0.5 , 10.4 ± 0.5 , 13.1 ± 0.5 , 13.5 ± 0.5 , 16.3 ± 0.5 , 16.7 ± 0.5 , 16.8 ± 0.5 , 18.2 ± 0.5 , 18.6 ± 0.5 , 19.3 ± 0.5 , 20.8 ± 0.5 , 21.1 ± 0.5 , 23.0 ± 0.5 , 23.3 ± 0.5 , 23.5 ± 0.5 , 24.3 ± 0.5 , 24.7 ± 0.5 , 25.2 ± 0.5 , 25.3 ± 0.5 , 25.6 ± 0.5 , 26.1 ± 0.5 , 26.6 ± 0.5 , 27.1 ± 0.5 , 28.3 ± 0.5 , 28.9 ± 0.5 , 29.1 ± 0.5 , 29.5 ± 0.5 , 29.8 ± 0.5 , 30.0 ± 0.5 , 30.3 ± 0.5 , 30.7 ± 0.5 , 31.1 ± 0.5 , and 31.7 ± 0.5 °2 θ using Cu K α radiation (*e.g.*, 4.2 ± 0.2 , 8.4 ± 0.2 , 10.2 ± 0.2 , 10.4 ± 0.2 , 13.1 ± 0.2 , 13.5 ± 0.2 , 16.3 ± 0.2 , 16.7 ± 0.2 , 16.8 ± 0.2 , 18.2 ± 0.2 , 18.6 ± 0.2 , 19.3 ± 0.2 , 20.8 ± 0.2 , 21.1 ± 0.2 , 23.0 ± 0.2 , 23.3 ± 0.2 , 23.5 ± 0.2 , 24.3 ± 0.2 , 24.7 ± 0.2 , 25.2 ± 0.2 , 25.3 ± 0.2 , 25.6 ± 0.2 , 26.1 ± 0.2 , 26.6 ± 0.2 , 27.1 ± 0.2 , 28.3 ± 0.2 , 28.9 ± 0.2 , 29.1 ± 0.2 , 29.5 ± 0.2 , 29.8 ± 0.2 , 30.0 ± 0.2 , 30.3 ± 0.2 , 30.7 ± 0.2 , 31.1 ± 0.2 , and 31.7 ± 0.2 °2 θ using Cu K α radiation (*e.g.*, 4.2 ± 0.1 , 8.4 ± 0.1 , 10.2 ± 0.1 , 10.4 ± 0.1 , 13.1 ± 0.1 , 13.5 ± 0.1 ,

16.3±0.1, 16.7±0.1, 16.8±0.1, 18.2±0.1, 18.6±0.1, 19.3±0.1, 20.8±0.1, 21.1±0.1, 23.0±0.1, 23.3±0.1, 23.5±0.1, 24.3±0.1, 24.7±0.1, 25.2±0.1, 25.3±0.1, 25.6±0.1, 26.1±0.1, 26.6±0.1, 27.1±0.1, 28.3±0.1, 28.9±0.1, 29.1±0.1, 29.5±0.1, 29.8±0.1, 30.0±0.1, 30.3±0.1, 30.7±0.1, 31.1±0.1, and 31.7±0.1 °2θ using Cu Kα radiation (*e.g.*, 4.2, 8.4, 10.2, 10.4, 13.1, 13.5, 16.3, 16.7, 16.8, 18.2, 18.6, 19.3, 20.8, 21.1, 23.0, 23.3, 23.5, 24.3, 24.7, 25.2, 25.3, 25.6, 26.1, 26.6, 27.1, 28.3, 28.9, 29.1, 29.5, 29.8, 30.0, 30.3, 30.7, 31.1, and 31.7 °2θ using Cu Kα radiation))).

[0569] In some embodiments, Form 2 of Compound No. 10a is characterized by an endothermic event with an onset at 50±20 °C, 50±15 °C, 50±10 °C, or 50±5 °C (*e.g.*, about 50 °C), as measured by DSC.

[0570] In some embodiments, Form 2 of Compound No. 10a is characterized by an endothermic event with an onset at 144±20 °C, 144±15 °C, 144±10 °C, or 144±5 °C (*e.g.*, about 144 °C), as measured by DSC.

[0571] In some embodiments, Form 2 of Compound No. 10a is characterized by a water uptake (*e.g.*, from 0 % to 90 % RH) of 9.1±0.5 %, 9.1±0.4 %, 9.1±0.3 %, 9.1±0.2 %, 9.1±0.1 %, or 9.1±0.05 % (*e.g.*, about 9.1 %), as measured by GVS.

[0572] In some embodiments, Form 2 of Compound No. 10a is characterized by an uptake (*e.g.*, from 40 % to 70 % RH) of 2.2±0.05 %, 2.2±0.04 %, 2.2±0.03 %, 2.2±0.02 %, or 2.2±0.01 % (*e.g.*, about 2.2 %), as measured by GVS.

[0573] In some embodiments, Form 2 of Compound No. 10a is characterized by an uptake (*e.g.*, from 40 % to 70 % RH) of 6.1±0.05 %, 6.1±0.04 %, 6.1±0.03 %, 6.1±0.02 %, or 6.1±0.01 % (*e.g.*, about 6.1 %), as measured by GVS.

[0574] In some embodiments, Form 2 of Compound No. 10a is characterized by a reversible hysteresis (*e.g.*, from 70 % to 10 % RH), as measured by GVS.

[0575] As used herein, Form 3 of Compound No. 10a corresponds to Form 3 disclosed in U.S. Provisional Patent Application No. 63/600,104 filed on November 17, 2023.

[0576] In some embodiments, Form 3 of Compound No. 10a is characterized by an XRPD pattern comprising signals at 4.4±0.5, 8.4±0.5, and 17.8±0.5 °2θ (*e.g.*, 4.4±0.2, 8.4±0.2, and 17.8±0.2 °2θ using Cu Kα radiation (*e.g.*, 4.4±0.1, 8.4±0.1, and 17.8±0.1 °2θ using Cu Kα radiation (*e.g.*, 4.4, 8.4, and 17.8 °2θ using Cu Kα radiation))).

[0577] In some embodiments, Form 3 of Compound No. 10a is characterized by an XRPD pattern comprising signals at 4.4±0.5, 8.4±0.5, 8.9±0.5, 11.1±0.5, 11.4±0.5, 12.0±0.5, 14.2±0.5, 14.3±0.5, 15.1±0.5, 16.8±0.5, 17.3±0.5, 17.8±0.5, 19.0±0.5, 19.2±0.5, 19.6±0.5, 20.6±0.5, 20.9±0.5,

21.3±0.5, 21.5±0.5, 21.9±0.5, 22.3±0.5, 22.4±0.5, 22.9±0.5, 23.2±0.5, 23.6±0.5, 24.4±0.5, 24.8±0.5, 25.2±0.5, 26.8±0.5, 27.4±0.5, 27.8±0.5, 29.1±0.5, 29.4±0.5, 29.8±0.5, 30.1±0.5, 31.0±0.5, and 31.4±0.5 °2θ using Cu Kα radiation (e.g., 4.4±0.2, 8.4±0.2, 8.9±0.2, 11.1±0.2, 11.4±0.2, 12.0±0.2, 14.2±0.2, 14.3±0.2, 15.1±0.2, 16.8±0.2, 17.3±0.2, 17.8±0.2, 19.0±0.2, 19.2±0.2, 19.6±0.2, 20.6±0.2, 20.9±0.2, 21.3±0.2, 21.5±0.2, 21.9±0.2, 22.3±0.2, 22.4±0.2, 22.9±0.2, 23.2±0.2, 23.6±0.2, 24.4±0.2, 24.8±0.2, 25.2±0.2, 26.8±0.2, 27.4±0.2, 27.8±0.2, 29.1±0.2, 29.4±0.2, 29.8±0.2, 30.1±0.2, 31.0±0.2, and 31.4±0.2 °2θ using Cu Kα radiation (e.g., 4.4±0.1, 8.4±0.1, 8.9±0.1, 11.1±0.1, 11.4±0.1, 12.0±0.1, 14.2±0.1, 14.3±0.1, 15.1±0.1, 16.8±0.1, 17.3±0.1, 17.8±0.1, 19.0±0.1, 19.2±0.1, 19.6±0.1, 20.6±0.1, 20.9±0.1, 21.3±0.1, 21.5±0.1, 21.9±0.1, 22.3±0.1, 22.4±0.1, 22.9±0.1, 23.2±0.1, 23.6±0.1, 24.4±0.1, 24.8±0.1, 25.2±0.1, 26.8±0.1, 27.4±0.1, 27.8±0.1, 29.1±0.1, 29.4±0.1, 29.8±0.1, 30.1±0.1, 31.0±0.1, and 31.4±0.1 °2θ using Cu Kα radiation (e.g., 4.4, 8.4, 8.9, 11.1, 11.4, 12.0, 14.2, 14.3, 15.1, 16.8, 17.3, 17.8, 19.0, 19.2, 19.6, 20.6, 20.9, 21.3, 21.5, 21.9, 22.3, 22.4, 22.9, 23.2, 23.6, 24.4, 24.8, 25.2, 26.8, 27.4, 27.8, 29.1, 29.4, 29.8, 30.1, 31.0, and 31.4 °2θ using Cu Kα radiation))).

[0578] In some embodiments, Form 3 of Compound No. 10a is characterized by a degradation event up to 85±40 °C, 85±30 °C, 85±20 °C, 85±15 °C, 85±10 °C, or 85±5 °C (e.g., up to about 85 °C), as measured by TGA.

[0579] In some embodiments, Form 3 of Compound No. 10a is characterized by a degradation event onset at 85±40 °C, 85±30 °C, 85±20 °C, 85±15 °C, 85±10 °C, or 85±5 °C (e.g., about 85 °C), as measured by TGA.

[0580] In some embodiments, Form 3 of Compound No. 10a is characterized by an endothermic event with an onset at 34±20 °C, 34±15 °C, 34±10 °C, or 34±5 °C (e.g., about 34 °C), as measured by DSC.

[0581] In some embodiments, Form 3 of Compound No. 10a is characterized by an endothermic event with an onset at 102±20 °C, 102±15 °C, 102±10 °C, or 102±5 °C (e.g., about 102 °C), as measured by DSC.

[0582] In some embodiments, Form 3 of Compound No. 10a is characterized by an endothermic event with an onset at 152±20 °C, 152±15 °C, 152±10 °C, or 152±5 °C (e.g., about 152 °C), as measured by DSC.

[0583] In some embodiments, Form 3 of Compound No. 10a is characterized by an uptake (e.g., from 40 % to 80 % RH) of 2.3±0.5 %, 2.3±0.4 %, 2.3±0.3 %, 2.3±0.2 %, 2.3±0.1 %, or 2.3±0.05 % (e.g., about 2.3 %), as measured by GVS.

[0584] In some embodiments, Form 3 of Compound No. 10a is characterized by an uptake (*e.g.*, from 80 % to 90 % RH) of 8.9 ± 0.5 %, 8.9 ± 0.4 %, 8.9 ± 0.3 %, 8.9 ± 0.2 %, 8.9 ± 0.1 %, or 8.9 ± 0.05 % (*e.g.*, about 8.9 %), as measured by GVS.

[0585] In some embodiments, Form 3 of Compound No. 10a is characterized by an uptake (*e.g.*, from 40 % to 80 % RH) of 5.1 ± 0.5 %, 5.1 ± 0.4 %, 5.1 ± 0.3 %, 5.1 ± 0.2 %, 5.1 ± 0.1 %, or 5.1 ± 0.05 % (*e.g.*, about 5.1 %), as measured by GVS.

[0586] In some embodiments, Form 3 of Compound No. 10a is characterized by a reversible hysteresis (*e.g.*, from 70 % to 10 % RH), as measured by GVS.

[0587] In some embodiments, Form 3 of Compound No. 10a is a crystalline solid having one or more of the following characteristics:

- a) a crystal size of $0.300 \times 0.250 \times 0.200$ mm;
- b) a crystal habit of colourless cut rod;
- c) a crystal system of monoclinic;
- d) a space group of $P2_1$;
- e) unit cell dimensions of $a = 10.17100(10)$ Å, $a = 90^\circ$, $b = 12.04740(10)$ Å, $b = 89.8050(10)^\circ$, $c = 20.0561(2)$ Å, $\gamma = 90^\circ$;
- f) a volume of $2457.54(4)$ Å³;
- g) a density (calculated) of 1.350 Mg/m³;
- h) an absorption coefficient of 1.708 mm⁻¹; and/or
- i) $F(000)$ of 1056.

[0588] As used herein, the term “inorganic acids” refers to acids such as, but not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and combinations thereof.

[0589] As used herein the term “organic acids” refers to acids such as, but not limited to: acetic acid; trifluoroacetic acid; phenylacetic acid; propionic acid; stearic acid; lactic acid; ascorbic acid; maleic acid; hydroxymaleic acid; isethionic acid; succinic acid; valeric acid; fumaric acid; malonic acid; pyruvic acid; oxalic acid; glycolic acid; salicylic acid; oleic acid; palmitic acid; lauric acid; a pyranosidyl acid, such as glucuronic acid or galacturonic acid; an alpha-hydroxy acid, such as mandelic acid, citric acid, or tartaric acid; cysteine sulfinic acid; an amino acid, such as aspartic acid, glutaric acid or glutamic acid; an aromatic acid, such as benzoic acid, 2- acetoxibenzoic acid, naphthoic acid, or cinnamic acid; a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid,

methanesulfonic acid, benzenesulfonic acid or ethanesulfonic acid; cysteine sulfonic acid; and combinations thereof.

[0590] As used herein the term “inorganic bases” refers to bases such as, but not limited to, sodium hydroxide, potassium hydroxide, lithium hydroxide, ammonium hydroxide, magnesium hydroxide, sodium carbonate, potassium carbonate, barium hydroxide, calcium hydroxide, ammonia, and combinations thereof.

[0591] As used herein, the term “organic base” refers to an organic compound containing one or more nitrogen atoms, and which acts as a base. Examples of organic bases include, but are not limited to, tertiary amine bases. Examples of organic bases include, but are not limited to, 1,8-Diazabicyclo[5.4.0]undec-7-ene (“DBU”), N-methyl-morpholine (NMM), diisopropylethylamine (DIPEA), triethylamine (TEA), a t-butoxide (*e.g.*, sodium, potassium, calcium or magnesium tert-butoxide).

[0592] As used herein, the term “inorganic solvent” refers to a solvent that does not contain carbon, except for the exceptions noted below. In one embodiment, an inorganic solvent may comprise or consist of water. In another embodiment, an inorganic solvent may comprise nonaqueous solvents. For example and without limitation, an inorganic nonaqueous solvent can include ammonia, sulfur dioxide, sulfuryl chloride, sulfuryl chloride fluoride, phosphoryl chloride, dinitrogen tetroxide, antimony trichloride, bromine pentafluoride, sulfuric acid, nitric acid, phosphorous tribromide, hydrogen fluoride, supercritical carbon dioxide, carbon dioxide, carbon disulfide, various molten salts, and the like.

[0593] As used herein the term “organic solvent” refers to an organic molecule capable of at least partially dissolving another substance (*i.e.*, the solute). Examples of organic solvents that may be used for the present invention include, but are not limited to: hydrocarbon solvents (*e.g.*, n-pentane, n-hexane, n-heptane, n-octane, paraffin, cyclohexane, methylcyclohexane, decahydronaphthalene, mineral oil, crude oils, etc.) which also includes aromatic hydrocarbon solvents (*e.g.*, benzene, toluene, o-xylene, m-xylene, and p-xylene), halogenated hydrocarbon solvents (*e.g.*, carbon tetrachloride, 1,2-dichloroethane, dichloromethane, chloroform, etc.), ester solvents (*e.g.*, ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, ethyl malonate, etc.), ketone solvents (*e.g.*, acetone, methyl ethyl ketone or 2-butanone, methyl isobutyl ketone, cyclohexanone, cyclopentanone, 3-pentanone, etc.), ether solvents (*e.g.*, diethyl ether, dipropyl ether, diphenyl ether, isopropyl ether, tert-butyl methyl ether, tetrahydrofuran, 1,4-dioxane, etc.), amine solvents (*e.g.*, propyl amine, diethylamine, triethylamine, aniline, pyridine), alcohol

solvents (*e.g.*, methanol, ethanol, isopropanol, 1-propanol, 2-methyl-1-propanol, 1-butanol, 2-butanol, 1-pentanol, 3-methyl-1-butanol, tert-butanol, 1-octanol, benzyl alcohol, phenol, trifluoroethanol, glycerol, ethylene glycol, propylene glycol, m-cresol, etc.), acid solvents (*e.g.*, acetic acid, hexanoic acid, etc.), carbon disulfide, nitrobenzene, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, acetonitrile, silicone solvents (*e.g.*, silicone oils, polysiloxanes, cyclosilicones). In some embodiments, the organic solvent may be formed by the combination of two or more organic solvents.

[0594] As used herein, unless otherwise noted, the term “aprotic organic solvent” refers to any solvent that does not yield a proton. Examples of an aprotic organic solvent include, but are not limited to DMF, dioxane, THF, acetonitrile, pyridine, dichloroethane, dichloromethane, MTBE, toluene, and the like.

[0595] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In some embodiments, Compound No. 10a or 10b, is used in pharmaceutical preparations in combination with one or more pharmaceutically acceptable carrier, excipient, or diluent. A suitable pharmaceutically acceptable carrier includes, but is not limited to, inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0596] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0597] In the synthetic scheme described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

[0598] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

[0599] The disclosure having been described, the following examples are offered by way of illustration and not limitation.

EXEMPLARY EMBODIMENTS

[0600] Exemplary Embodiment 1. A method of preparing Compound No. 10, comprising one or more of steps (iv)-(vii):

- (iv) reacting Compound No. 5, or a salt thereof, with an acid, thereby forming Compound No. 6, or a salt thereof;
- (v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;
- (vi) reacting Compound No. 6, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9; or
- (vii) purifying Compound No. 9, thereby isolating Compound No. 10.

[0601] Exemplary Embodiment 2. A method of preparing Compound No. 5, or a salt thereof, comprising:

- (iii) reacting Compound No. 5, or a salt thereof, with an acid, thereby forming Compound No. 6, or a salt thereof.

[0602] Exemplary Embodiment 3. A method of preparing Compound No. 9, comprising:

- (iv) reacting Compound No. 6, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9.

[0603] Exemplary Embodiment 4. A method of preparing Compound No. 10, comprising:

- (vii) purifying Compound No. 9, thereby isolating Compound No. 10.

[0604] Exemplary Embodiment 5. The method of Exemplary Embodiment 1, further comprising steps (i)-(iv):

- (i) reacting tetrahydrofuran-2-carboxylic acid, with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof;
- (ii) reacting N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof;
- (iii) reacting 1-methyl-N-{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5, or a salt thereof; and
- (iv) reacting Compound No. 5 or a salt thereof, with an acid, thereby forming Compound No. 6, or a salt thereof.

[0605] Exemplary Embodiment 6. The method of any one of the preceding Exemplary Embodiments, wherein Compound No. 9 is Compound No. 9a.

[0606] Exemplary Embodiment 7. The method of any one of the preceding Exemplary Embodiments, wherein Compound No. 10 is Compound No. 10a.

[0607] Exemplary Embodiment 8. The method of any one of the preceding Exemplary Embodiments, wherein Compound No. 9 is Compound No. 9b.

[0608] Exemplary Embodiment 9. The method of any one of the preceding Exemplary Embodiments, wherein in step (iv), the acid is hydrochloric acid.

[0609] Exemplary Embodiment 10. The method of any one of the preceding Exemplary Embodiments, wherein in step (iv), the molar ratio of the acid to Compound No. 5, or the salt thereof, is from about 3:1 to about 1:1.

[0610] Exemplary Embodiment 11. The method of any one of the preceding Exemplary Embodiments, wherein in step (iv), the reacting is performed in the presence of a first solvent to form a first mixture.

[0611] Exemplary Embodiment 12. The method of any one of the preceding Exemplary Embodiments, wherein in step (iv), the reacting is performed at a first temperature of about 25 ± 15 °C, about 25 ± 10 °C, or about 25 ± 5 °C.

[0612] Exemplary Embodiment 13. The method of any one of the preceding Exemplary Embodiments, wherein in step (iv), the reacting is performed for about 26 ± 20 hours, about 26 ± 15 hours, about 26 ± 10 hours, about 26 ± 5 hours, about 26 ± 4 hours, about 26 ± 3 hours, about 26 ± 2 hours, or about 26 ± 1 hours.

[0613] Exemplary Embodiment 14. The method of Exemplary Embodiment 11, wherein the first mixture is cooled to a second temperature of about 0 ± 15 °C, about 0 ± 10 °C, or about 0 ± 5 °C.

[0614] Exemplary Embodiment 15. The method of Exemplary Embodiment 11, wherein the first mixture is cooled to a second temperature of about 0 ± 15 °C, about 0 ± 10 °C, or about 0 ± 5 °C and a second solvent is added to form a second mixture.

[0615] Exemplary Embodiment 16. The method of Exemplary Embodiment 15, wherein a base or a buffer is added to the second mixture.

[0616] Exemplary Embodiment 17. The method of any one of the preceding Exemplary Embodiments, wherein in step (iv), Compound No. 6, or the salt thereof, is isolated and/or purified prior to reacting with Compound No. 8.

[0617] Exemplary Embodiment 18. The method of Exemplary Embodiment 17, wherein in step (iv), Compound No. 6, or the salt thereof, is at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% pure as measured by HPLC.

[0618] Exemplary Embodiment 19. The method of Exemplary Embodiment 1, wherein in step (v), triphosgene is the source of CO.

[0619] Exemplary Embodiment 20. The method of Exemplary Embodiment 1, wherein in step (v), the reacting is performed in the presence of a base.

[0620] Exemplary Embodiment 21. The method of Exemplary Embodiment 20, wherein in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is from about 3:1 to about 1:1.

[0621] Exemplary Embodiment 22. The method of Exemplary Embodiment 1, wherein in step (v), the reacting is performed in the presence of a solvent.

[0622] Exemplary Embodiment 23. The method of Exemplary Embodiment 1, wherein step (v) comprises filtering the solution of Compound No. 8, or the salt thereof.

[0623] Exemplary Embodiment 24. The method of Exemplary Embodiment 1, wherein in step (v), Compound No. 8, or the salt thereof, is isolated and/or purified prior to reacting with Compound No. 6, or a salt thereof.

[0624] Exemplary Embodiment 25. The method of Exemplary Embodiment 1, wherein in step (v), Compound No. 8, or the salt thereof, is not isolated and/or purified prior to reacting with Compound No. 6, or a salt thereof.

[0625] Exemplary Embodiment 26. The method of Exemplary Embodiment 1, wherein step (v), yields a solution of Compound No. 8, or the salt thereof.

[0626] Exemplary Embodiment 27. The method of Exemplary Embodiment 1, wherein step (v) yields Compound No. 8, or the salt thereof, with purity of at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% as measured by HPLC.

[0627] Exemplary Embodiment 28. The method of Exemplary Embodiment 1, wherein in step (vi), the reacting is performed in the presence of a base.

[0628] Exemplary Embodiment 29. The method of Exemplary Embodiment 1, wherein in step (vi), the reacting is performed in the presence of a first solvent.

[0629] Exemplary Embodiment 30. The method of Exemplary Embodiment 1, wherein in step (vi), the molar ratio of Compound No. 6, or a salt thereof, to the Compound No. 8, or the salt thereof, is from about 2:1 to about 1:2.

[0630] Exemplary Embodiment 31. The method of Exemplary Embodiment 1, wherein in step (vi), the reacting comprises partial removal of the first solvent.

[0631] Exemplary Embodiment 32. The method of Exemplary Embodiment 1, wherein in step (vi), the reacting is performed in the presence of a second solvent.

[0632] Exemplary Embodiment 33. The method of Exemplary Embodiment 1, wherein in step (vi), the reacting comprises extracting Compound No. 9 using an ether.

[0633] Exemplary Embodiment 34. The method of Exemplary Embodiment 1, wherein in step (vi), the reacting comprises filtering out Compound No. 9, washing Compound No. 9 with IPA-MTBE, or a combination thereof.

[0634] Exemplary Embodiment 35. The method of Exemplary Embodiment 1, wherein in step (vi), the reacting is performed at a first temperature of about 25 ± 15 °C, about 25 ± 10 °C, or about 25 ± 5 °C.

[0635] Exemplary Embodiment 36. The method of Exemplary Embodiment 1, wherein step (vi) comprises filtering Compound No. 9.

[0636] Exemplary Embodiment 37. The method of Exemplary Embodiment 1, wherein in step (vi), Compound No. 9a or 9b is isolated and/or purified.

[0637] Exemplary Embodiment 38. The method of Exemplary Embodiment 1, wherein step (vi) yields Compound No. 9 with purity of at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% as measured by HPLC.

[0638] Exemplary Embodiment 39. The method of Exemplary Embodiment 1, wherein step (vii) comprises recrystallizing Compound No. 9 in the presence of an organic solvent.

[0639] Exemplary Embodiment 40. The method of Exemplary Embodiment 1, wherein in step (vii), Compound No. 9 is dissolved in tetrahydrofuran, filtered and washed with tetrahydrofuran to form a first mixture.

[0640] Exemplary Embodiment 41. The method of Exemplary Embodiment 40, wherein the first mixture of step (vii) is concentrated and ethyl acetate is added to form a second mixture.

[0641] Exemplary Embodiment 42. The method of Exemplary Embodiment 41, wherein the second mixture of step (vii) is concentrated and ethyl acetate and water are added to form a third mixture.

[0642] Exemplary Embodiment 43. The method of Exemplary Embodiment 42, wherein the third mixture of step (vii) is heated and then seeded to form a seeded third mixture.

[0643] Exemplary Embodiment 44. The method of Exemplary Embodiment 42, wherein the third mixture of step (vii) is heated to a first temperature of about 45 ± 20 °C, about 45 ± 15 °C, about 45 ± 10 °C, about 45 ± 5 °C, about 45 ± 4 °C, about 45 ± 3 °C, about 45 ± 2 °C, or about 45 ± 1 °C and then seeded to form a seeded third mixture.

[0644] Exemplary Embodiment 45. The method of Exemplary Embodiment 44, wherein after heating to the first temperature, the seeded third mixture of step (vii) is aged for about 1 ± 2 hours, or 1 ± 1 hour.

[0645] Exemplary Embodiment 46. The method of Exemplary Embodiment 45, wherein in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of about 30 ± 20 °C, about 30 ± 15 °C, about 30 ± 10 °C, about 30 ± 5 °C, about 30 ± 4 °C, about 30 ± 3 °C, about 30 ± 2 °C, or about 30 ± 1 °C.

[0646] Exemplary Embodiment 47. The method of Exemplary Embodiment 45, wherein in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of about 30 ± 20 °C, about 30 ± 15 °C, about 30 ± 10 °C, about 30 ± 5 °C, about 30 ± 4 °C, about 30 ± 3 °C, about 30 ± 2 °C, or about 30 ± 1 °C (*e.g.*, about 30 °C) and aged for a time from about 1 hour to about 12 hours, from about 2 hours to about 10 hours, or from about 3 hours to about 6 hours to form a mixture comprising Compound No. 10.

[0647] Exemplary Embodiment 48. The method of Exemplary Embodiment 47, wherein in step (vii), n-heptane is added to the mixture comprising Compound No. 10 to form a solid form of Compound No. 10.

[0648] Exemplary Embodiment 49. The method of Exemplary Embodiment 48, wherein in step (vii), the solid form of Compound No. 10 is filtered out and washed, thereby forming substantially pure solid form of Compound No. 10.

[0649] Exemplary Embodiment 50. The method of Exemplary Embodiment 49, wherein step (vii) yields a specific polymorphic form of Compound No. 10.

[0650] Exemplary Embodiment 51. The method of Exemplary Embodiment 49, wherein step (vii) yields polymorphic form (Form 3) of Compound No. 10a.

[0651] Exemplary Embodiment 52. The method of Exemplary Embodiment 49, wherein step (vii) yields a solid form of Compound No. 10 with purity of at least about 98%, at least about 98.5%, at least about 99%, at least about 99.1%, at least about 99.2%, at least about 99.3%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, at least about 99.8% as measured by HPLC.

[0652] Exemplary Embodiment 53. The method of Exemplary Embodiment 49, wherein step (vii) yields substantially pure polymorphic form (Form 3) of Compound No. 10a.

[0653] Exemplary Embodiment 54. A compound being prepared by the method of any one of the preceding Exemplary Embodiments.

[0654] Exemplary Embodiment 55. A pharmaceutical composition comprising Compound No. 10, of any one of the preceding Exemplary Embodiments, and one or more pharmaceutically acceptable carrier or excipient.

[0655] Exemplary Embodiment 56. A method of preventing or treating a disease in a subject, comprising administering to the subject Compound No. 10, of any one of the preceding Exemplary Embodiments.

[0656] Exemplary Embodiment 57. Compound No. 10, of any one of the preceding Exemplary Embodiments for use in preventing or treating a disease in a subject.

[0657] Exemplary Embodiment 58. Use of Compound No. 10, of any one of the preceding Exemplary Embodiments in the manufacture of a medicament for preventing or treating a disease in a subject.

[0658] Exemplary Embodiment 59. A method of inhibiting inflammasome activity in a subject, comprising contacting a cell with Compound No. 10, of any one of the preceding Exemplary Embodiments.

[0659] Exemplary Embodiment 60. Compound No. 10, of any one of the preceding Exemplary Embodiments for use in inhibiting inflammasome activity in a subject.

[0660] Exemplary Embodiment 61. Use of Compound No. 10, of any one of the preceding Exemplary Embodiments in the manufacture of a medicament for inhibiting inflammasome activity.

[0661] Exemplary Embodiment 62. The method, compound, or use of any one of the preceding Exemplary Embodiments, wherein the subject is a human.

EXAMPLES

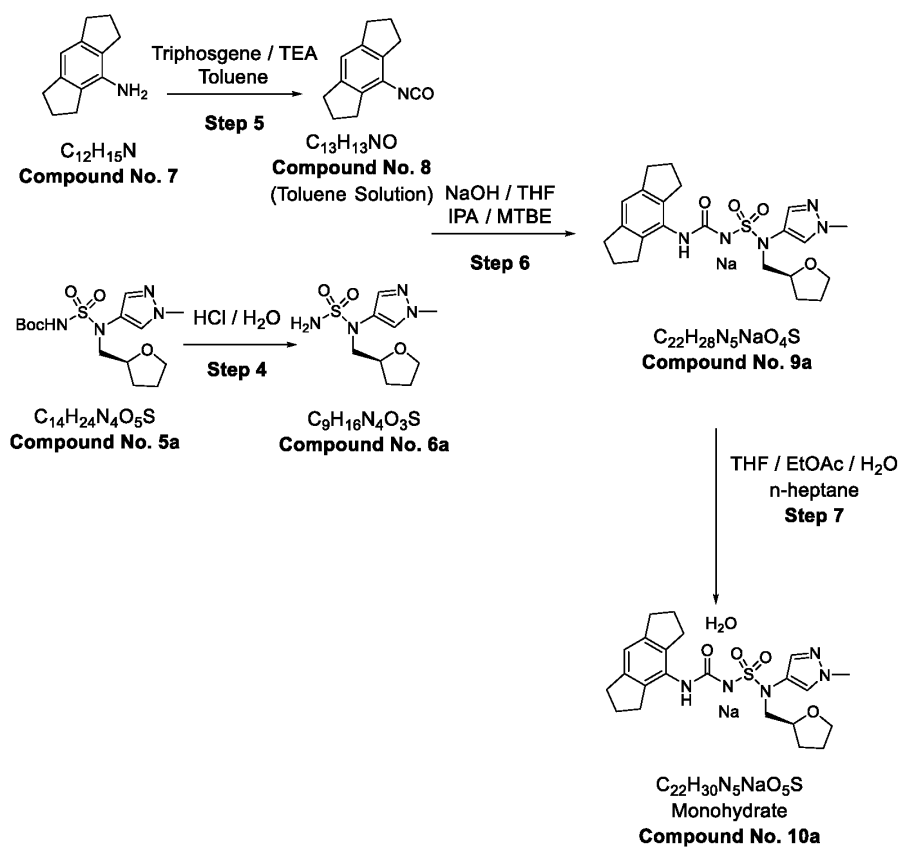
[0662] The disclosure having been described, the following examples are offered by way of illustration and not limitation.

[0663] It is understood that all values presented in the examples are approximate, and are subject to instrumental and/or experimental variations.

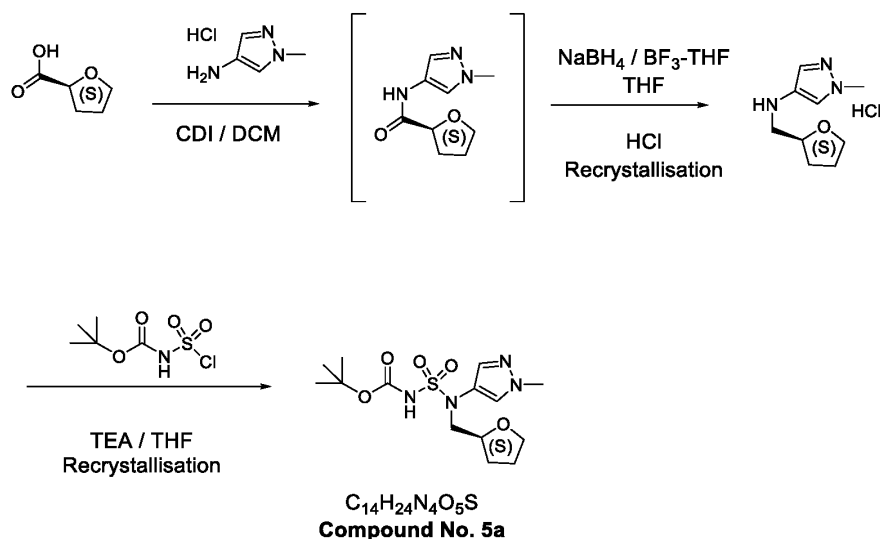
Example 1. Exemplary Synthesis of Compound No. 10a.

[0664] An exemplary synthesis of Compound No. 10a was performed as shown in Scheme 1 and Scheme 2 and the following procedures. The overall synthetic route was a 7-step process, starting from commercially or synthetically available starting materials. Scheme 1 details the four Steps of the manufacturing process. Compound No. 5a was manufactured using the process described in Scheme 2.

Scheme 1: Synthetic Route for Manufacture of Compound No. 10a



Scheme 2: Synthetic Route for Manufacture of Compound No. 5a (Starting Material)



A. Control of Materials

Starting Materials

[0665] There are two characterised starting materials used in the manufacture of Compound No. 10a. 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (Compound No. 7; CAS 63089-56-5) is commercially available substance manufactured to a high specification. The second starting material Compound No. 5a is also manufactured using the process described in **Scheme 2**. The starting materials for the manufacture of Compound No. 5a, (*S*)-tetrahydrofuran-2-carboxylic acid and 4-amino-1-methylpyrazole hydrochloride, are commercially available substances.

[0666] All starting materials are fully synthetic and of non-animal origin, certified as TSE free. The starting materials were supplied with certificates of analysis. All starting materials were qualified and subjected to a use-test prior to entry into the Steps of the process.

[0667] Compound No. 5a, the starting material for Step 4 of the manufacturing process, was manufactured to a very high level of purity ($\geq 99\%$ by HPLC). One parameter in the specification for Compound No. 5a was chiral purity. The specification for the opposite enantiomer in Compound No. 5a was set at ≤ 100 ppm due to toxicological concerns associated with the (*R*)-isomer. In part this was achieved using enantiomerically pure (*S*)-tetrahydrofuran-2-carboxylic acid but the enantiomeric excess was monitored through the individual stages during the manufacture of Compound No. 5a and both intermediates were recrystallised to ensure continued chiral enrichment throughout the synthesis. Batches of Compound No. 5a complied with this specification limit. Analysis for the batches of Compound No. 5a used in the manufacturing process are presented in Table A.

Table A: Compound No. 5a Analysis

Attribute	Batch 1	Batch 2
Batch size	34.23 kg	27.8 kg
Appearance	White Solid	White Solid
Purity (HPLC)	99.9%	99.8%
Impurities (HPLC)	RRT0.762 0.1% Total impurities 0.1%	RRT0.762 0.1% RRT0.949 0.1% Total impurities 0.2%
Chiral purity (HPLC)	≤ 100 ppm	≤ 100 ppm
Assay (Q NMR)	98.8% w/w	97.4% w/w
Water content (KF)	0.03% w/w	0.07% w/w

Note: Identity of Compound No. 5a in Batch 1 and Batch 2 was verified using ^1H NMR, ^{13}C NMR and mass spectroscopy.

[0668] 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (Compound No. 7), the starting material for Step 5 of the manufacturing process, was manufactured to a high level of purity ($\geq 98\%$ by HPLC). Analysis for Compound No. 7 used in the manufacturing process are presented in Table B.

Table B: Compound No. 7 Analysis

Attribute	Batch 1
Appearance	Off-white solid
Purity (HPLC)	100.0% area
Single specified impurities (HPLC)	Impurity 4 (RRT0.96) = 0.1% area Impurity 5 (RRT0.98) = 0.05% area
Single unspecified impurities (HPLC)	Impurity 10 (RRT1.25) = 0.09% area
Total Impurities	0.2% area
Water content (KF)	0.10% w/w
Assay	99.7% w/w
Residual Solvents	Methanol = 79.6 ppm Dichloromethane = ND
Palladium content	0.84 ppm
Metal impurities	Cd, Pb, As, Hg, V, Ni (<LOQ) Co = 0.12 ppm

Note: Identity of Compound No. 7 in Batch 1 was verified using ^1H NMR and mass spectroscopy.

B. Controls of Steps and Intermediates

[0669] The yield and analytical results for intermediates manufactured are presented in Tables C-E.

Table C: Compound No. 6a Analysis

Attribute	Batch 1	Batch 2
Input (Compound No. 5a)	28 kg	33.1 kg
Batch size	17.97 kg	22.68 kg
Yield	88%	92%
Appearance	White Solid	White Solid
Purity (HPLC)	100%	100%
Chiral purity (HPLC)	49 ppm	ND
Assay (HPLC)	98.9% w/w	99.5% w/w

ND = Not detected

Note: Identity of Compound 6a in Batch 1 and Batch 2 was verified using ^1H NMR.

[0670] Compound No. 8 is prepared as a solution in Toluene which is used directly in Step 6, analysis shown in Table D.

Table D: Compound No. 8 Analysis

Attribute	Batch 1	Batch 2
Input (Compound No. 7)	11.83 kg	15.73 kg
Batch size (Assay)	13.58 kg	16.69 kg
Yield	88%	92%
Appearance	Yellow Solution	Yellow Solution
Purity (HPLC)	99.6%	98.8%
Assay (HPLC)	28.4% w/w as solution in toluene	26.7% w/w as solution in toluene

Note: Identity of Compound 8 in Batch 1 and Batch 2 was verified using ¹H NMR.

Table E: Crude Compound No. 9a Analysis

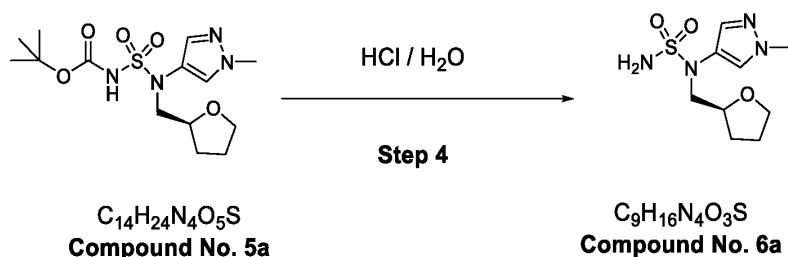
Attribute	Batch 1	Batch 2
Input (Compound No. 6a)	16.8 kg	22.42 kg
Input (Compound No. 8)	47.09 kg (28.4% w/w)	61.00 kg (26.7% w/w)
Batch size	32.28 kg	38.53 kg
Yield	89%	93%
Appearance	White Solid	White Solid
Purity (HPLC)	99.9%	99.8%
Assay (HPLC)	89.0 %w/w	89.8% w/w

Note: Identity of Compound 9a in Batch 1 and Batch 2 was verified using ¹H NMR.

[0671] In-process testing during the synthesis of Compound No. 10a is generated to monitor conversion for each step or completion of drying. The progress of the various reactions was monitored using analytical techniques known in the art (e.g., HPLC, GC, GC-MS, MS, NMR, XRPD, KF)

Step 4: Manufacture of 1-(1-methyl-1H-pyrazol-4-yl)-1-[(2S)-oxolan-2-yl]methyl]sulfonylurea (Compound No. 6a)

[0672] Step 4 was a BOC deprotection of the starting material (Compound No. 5a), using aqueous hydrochloric acid. The reaction conditions for Step 4 are presented in Scheme 3.

Scheme 3: Step 4 – Manufacture of Compound No. 6a

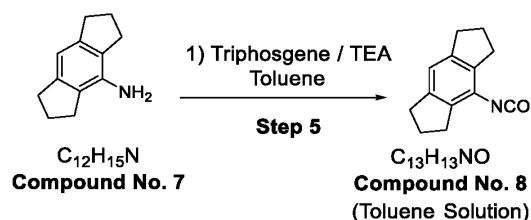
[0673] A solution of aqueous hydrochloric acid was prepared with water (1.1 vol) and conc. hydrochloric acid (5.0 equiv, 1.1 vol). Compound No. 5a (1 equiv.) was added portionwise over approximately 2 h. The mixture was stirred at room temperature for around 24 h. Following reaction completion the mixture was cooled to 0°C. Dichloromethane (2 vol) was added and then the mixture was basified by the addition of 46% sodium hydroxide solution (4.5 equiv.) dropwise over approximately 1 h and maintaining the temperature around 0°C. The mixture was allowed to warm to room temperature and then the pH is finely adjusted to pH 8/9 with 30 wt% K₂CO₃ solution. The layers were separated and the aqueous layer extracted with dichloromethane (2 x 1 vol) [aqueous layer liquor loss: ~0.5 mg/mL, 0.2% loss]. The combined dichloromethane extracts were washed with water (2 x 1 vol) and the combined water washes were further extracted with dichloromethane (1 x 2 vol) [water loss: ~8.0 mg/mL, 2.3% loss]. The dichloromethane solution was now concentrated to around 4 vol (with respect to Compound No. 6). Heptane (6 vol) was added dropwise and the resulting slurry aged at room temperature for around 1 h. The solid was removed by filtration and the filter cake washed with heptane (1 x 1 vol) [Mother liquor loss: ~2.6 mg/mL, 2.1% loss]. The collected solid was dried under vacuum at 20°C for around 20 h.

[0674] An exemplary yield for Step 4 is 90% with purity > 98% by HPLC.

Step 5: Manufacture of 1,2,3,5,6,7-hexahydro-s-indacen-4-isocyanate (Compound No. 8)

[0675] Step 5 involved the treatment of 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (Compound No. 7) with triphosgene to form the corresponding isocyanate, 1,2,3,5,6,7-hexahydro-s-indacen-4-isocyanate (Compound No. 8) as a solution in toluene. A concentrated solution of Compound No. 8 (approx. 30% wt assay) was used directly in Step 6. The reaction conditions for Step 5 are presented in Scheme 5.

Scheme 5: Step 5 – Manufacture of 1,2,3,5,6,7-hexahydro-s-indacen-4-isocyanate (Compound No. 8)



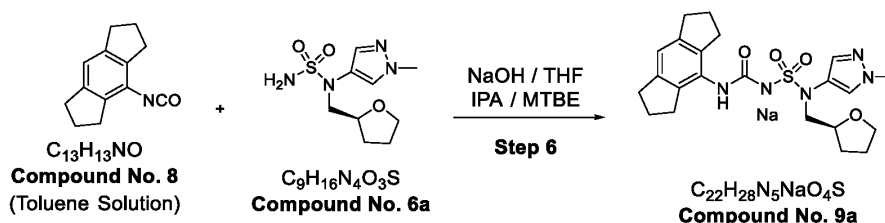
[0676] A solution of 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (Compound No. 7; 1 eq) and triethylamine (2.05 eq) in toluene (6 vol) was treated portionwise with a cooled (0°C) solution of triphosgene (0.34 eq) in toluene (21 vol) over a period of approx. 1 hr while maintaining the temperature below 10°C. The mixture was then warmed to room temperature. After demonstrating reaction completion the mixture, which was a very thick slurry of triethylamine hydrochloride in toluene can be aged at room temperature of up to 24 h. The slurry was filtered and the filtrate collected. The reaction vessel was rinsed with toluene (8 vol) and the rinse was used to wash the filter cake. The combined filtrates were then concentrated to ~4.5 volumes (with respect to Compound No. 7 input). The solution could be stored at ambient temperature before use in Step 6.

[0677] An exemplary wt corrected yield of 1,2,3,5,6,7-hexahydro-s-indacen-4-isocyanate (Compound No. 8) is around 85% and the purity is >98% by HPLC.

Step 6: Manufacture of 1-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-3-[(1-methyl-1H-pyrazol-4-yl)({[(2S)-oxolan-2-yl]methyl}) sulfamoyl]urea, Sodium salt, IPA solvate (Compound No. 9a)

[0678] Step 6 was the final synthetic step in the manufacture of Compound No. 9a prior to a final recrystallisation to prepare the required polymorphic form. The reaction was a sulphonyl urea formation involving the treatment of 1-(1-methyl-1H-pyrazol-4-yl)-1-[(2S)-oxolan-2-yl]methyl]sulfonylurea (Compound No. 6a) as a solution in tetrahydrofuran with 1,2,3,5,6,7-hexahydro-s-indacen-4-isocyanate (Compound No. 8) as a solution in toluene in the presence of sodium hydroxide. The crude Compound No. 9a was isolated as an IPA solvate of the monosodium salt. The reaction conditions for Step 6 are presented in Scheme 6.

Scheme 6: Step 6 –Manufacture of Crude Compound No. 9a

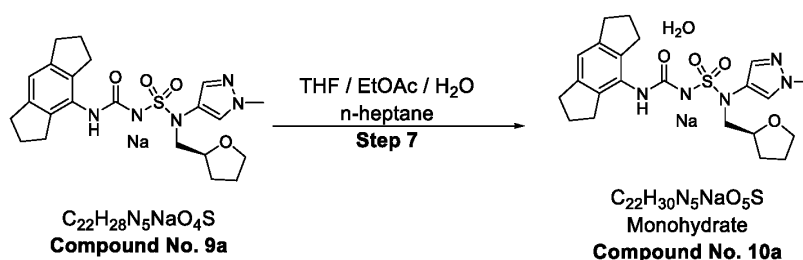


[0679] A solution of Compound No. 6a (1.0 equiv.) in tetrahydrofuran (10 vol) was treated dropwise with concentrated NaOH (46.7 wt%, 1.01 equiv.) while maintaining room temperature. The solution was aged at room temperature for approx. 0.5 h. The toluene solution of Compound No. 8 (1.01 equiv.) was then added over approx. 0.5 h. Following reaction completion the mixture was concentrated to remove tetrahydrofuran (approx. 8 vol of solvent). Isopropylalcohol (IPA; 10 vol) was added and the mixture aged approx. 0.5 h. Methyl *tert*-butylether (MTBE; 5 vol) was then added and the mixture aged for approx. 0.5 h. Having determined a satisfactory conversion the solid was removed by filtration and the filter cake and washed with 2:1 IPA-MTBE (6 vol). The resulting solid was dried at 20-40 °C under vacuum.

[0680] An exemplary wt corrected yield of crude Compound No. 9a is about 90% and the purity is >99% by HPLC.

Step 7: Manufacture of 1-(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)-3-[(1-methyl-1H-pyrazol-4-yl)({[(2S)-oxolan-2-yl]methyl}) sulfamoyl]urea, Sodium salt, Monohydrate (Compound No. 10a)

[0681] The final step of the manufacture of Compound No. 10a is a recrystallisation of crude Compound No. 9a from tetrahydrofuran / water/ ethyl acetate using n-heptane as an anti-solvent. This recrystallisation procedure can be used to upgrade the purity of Compound No. 10a but the primary purpose is to control the polymorphic form of Compound No. 10a (form 3) as the monohydrate for use in clinical trials. The reaction conditions for Step 7 are presented in Scheme 7.

Scheme 7: Step 7 –Manufacture of Purified Compound No. 10a

[0682] Crude Compound No. 9a was dissolved in tetrahydrofuran (THF; 4 vol vs assay). This solution was filtered through celite and washed with THF (2 x 1 vol). This solution was subjected to a final stage clarification then concentrated down to 3 volumes. Ethyl acetate (15 vol) was added and the mixture concentrate to 10 volumes. Further ethyl acetate (10 vol) and water (0.2 vol) was added and the mixture heated to 45°C before seeding (1% wt seed vs assay) and aged for up to 1 h. The mixture is then cooled to 30°C over 0.5 – 1 h. n-Heptane (5 vol) was added The resulting solid was collected by filtration and washed with 4:1 ethyl acetate-heptane (4 vol) containing 1% v/v water (vs ethyl acetate). The solid was dried at 20 °C in a vacuum oven with N₂ sweep.

[0683] An exemplary wt corrected recovery of Compound No. 10a is around 90% and the purity is >99% by HPLC.

Example 2. Properties of Compound No. 10a.

[0684] Compound No. 10a is a white to off-white crystalline powder. It has a single stereogenic centre. Compound No. 10a is a single enantiomer confirmed with the (*S*)-configuration.

[0685] **Polymorphism:** A polymorphism screen on Compound No. 10a revealed a hygroscopic amorphous form and three polymorphic forms. During characterisation a metastable anhydrous Form 1 was obtained on recovery from GVS analysis. In addition, a dihydrate Form 2 was prepared from conversion of the amorphous compound at 25°C / 97% RH and 40°C / 75% RH. Following storage at 60°C / 75% RH the amorphous converted to monohydrate Form 3. When Form 3 is dehydrated a new anhydrous metastable Form 9 was identified. Compound No. 10a exhibits solvated forms with some alcoholic solvents, most notably the IPA solvate which is isolated as an intermediate in the manufacturing process before further processing to the final form.

[0686] Form 2 (dihydrate) and Form 3 (monohydrate) have comparable solid-state properties. The monohydrate (Form 3) is prepared as provided in Example 1. It exhibits a single crystalline/polymorphic form, the sodium salt monohydrate (Form 3).

[0687] Form 2 of Compound No. 10a is characterized by an XRPD pattern comprising signals at 4.2 ± 0.5 , 16.7 ± 0.5 , and 16.8 ± 0.5 $^{\circ}2\theta$ using Cu K α radiation (*e.g.*, 4.2 ± 0.2 , 16.7 ± 0.2 , and 16.8 ± 0.2 $^{\circ}2\theta$ using Cu K α radiation (*e.g.*, 4.2 ± 0.1 , 16.7 ± 0.1 , and 16.8 ± 0.1 $^{\circ}2\theta$ using Cu K α radiation (*e.g.*, 4.2 , 16.7 , and 16.8 $^{\circ}2\theta$ using Cu K α radiation))).

[0688] Form 2 of Compound No. 10a is characterized by an XRPD pattern comprising signals at 4.2 ± 0.5 , 8.4 ± 0.5 , 10.2 ± 0.5 , 10.4 ± 0.5 , 13.1 ± 0.5 , 13.5 ± 0.5 , 16.3 ± 0.5 , 16.7 ± 0.5 , 16.8 ± 0.5 , 18.2 ± 0.5 , 18.6 ± 0.5 , 19.3 ± 0.5 , 20.8 ± 0.5 , 21.1 ± 0.5 , 23.0 ± 0.5 , 23.3 ± 0.5 , 23.5 ± 0.5 , 24.3 ± 0.5 , 24.7 ± 0.5 , 25.2 ± 0.5 , 25.3 ± 0.5 , 25.6 ± 0.5 , 26.1 ± 0.5 , 26.6 ± 0.5 , 27.1 ± 0.5 , 28.3 ± 0.5 , 28.9 ± 0.5 , 29.1 ± 0.5 , 29.5 ± 0.5 , 29.8 ± 0.5 , 30.0 ± 0.5 , 30.3 ± 0.5 , 30.7 ± 0.5 , 31.1 ± 0.5 , and 31.7 ± 0.5 $^{\circ}2\theta$ using Cu K α radiation (*e.g.*, 4.2 ± 0.2 , 8.4 ± 0.2 , 10.2 ± 0.2 , 10.4 ± 0.2 , 13.1 ± 0.2 , 13.5 ± 0.2 , 16.3 ± 0.2 , 16.7 ± 0.2 , 16.8 ± 0.2 , 18.2 ± 0.2 , 18.6 ± 0.2 , 19.3 ± 0.2 , 20.8 ± 0.2 , 21.1 ± 0.2 , 23.0 ± 0.2 , 23.3 ± 0.2 , 23.5 ± 0.2 , 24.3 ± 0.2 , 24.7 ± 0.2 , 25.2 ± 0.2 , 25.3 ± 0.2 , 25.6 ± 0.2 , 26.1 ± 0.2 , 26.6 ± 0.2 , 27.1 ± 0.2 , 28.3 ± 0.2 , 28.9 ± 0.2 , 29.1 ± 0.2 , 29.5 ± 0.2 , 29.8 ± 0.2 , 30.0 ± 0.2 , 30.3 ± 0.2 , 30.7 ± 0.2 , 31.1 ± 0.2 , and 31.7 ± 0.2 $^{\circ}2\theta$ using Cu K α radiation (*e.g.*, 4.2 ± 0.1 , 8.4 ± 0.1 , 10.2 ± 0.1 , 10.4 ± 0.1 , 13.1 ± 0.1 , 13.5 ± 0.1 , 16.3 ± 0.1 , 16.7 ± 0.1 , 16.8 ± 0.1 , 18.2 ± 0.1 , 18.6 ± 0.1 , 19.3 ± 0.1 , 20.8 ± 0.1 , 21.1 ± 0.1 , 23.0 ± 0.1 , 23.3 ± 0.1 , 23.5 ± 0.1 , 24.3 ± 0.1 , 24.7 ± 0.1 , 25.2 ± 0.1 , 25.3 ± 0.1 , 25.6 ± 0.1 , 26.1 ± 0.1 , 26.6 ± 0.1 , 27.1 ± 0.1 , 28.3 ± 0.1 , 28.9 ± 0.1 , 29.1 ± 0.1 , 29.5 ± 0.1 , 29.8 ± 0.1 , 30.0 ± 0.1 , 30.3 ± 0.1 , 30.7 ± 0.1 , 31.1 ± 0.1 , and 31.7 ± 0.1 $^{\circ}2\theta$ using Cu K α radiation (*e.g.*, 4.2 , 8.4 , 10.2 , 10.4 , 13.1 , 13.5 , 16.3 , 16.7 , 16.8 , 18.2 , 18.6 , 19.3 , 20.8 , 21.1 , 23.0 , 23.3 , 23.5 , 24.3 , 24.7 , 25.2 , 25.3 , 25.6 , 26.1 , 26.6 , 27.1 , 28.3 , 28.9 , 29.1 , 29.5 , 29.8 , 30.0 , 30.3 , 30.7 , 31.1 , and 31.7 $^{\circ}2\theta$ using Cu K α radiation))).

[0689] Form 2 of Compound No. 10a is characterized by an endothermic event with an onset at 50 ± 20 $^{\circ}\text{C}$, 50 ± 15 $^{\circ}\text{C}$, 50 ± 10 $^{\circ}\text{C}$, or 50 ± 5 $^{\circ}\text{C}$ (*e.g.*, about 50 $^{\circ}\text{C}$), as measured by DSC.

[0690] Form 2 of Compound No. 10a is characterized by an endothermic event with an onset at 144 ± 20 $^{\circ}\text{C}$, 144 ± 15 $^{\circ}\text{C}$, 144 ± 10 $^{\circ}\text{C}$, or 144 ± 5 $^{\circ}\text{C}$ (*e.g.*, about 144 $^{\circ}\text{C}$), as measured by DSC.

[0691] Form 2 of Compound No. 10a is characterized by a water uptake (*e.g.*, from 0 % to 90 % RH) of 9.1 ± 0.5 %, 9.1 ± 0.4 %, 9.1 ± 0.3 %, 9.1 ± 0.2 %, 9.1 ± 0.1 %, or 9.1 ± 0.05 % (*e.g.*, about 9.1 %), as measured by GVS.

[0692] Form 2 of Compound No. 10a is characterized by an uptake (*e.g.*, from 40 % to 70 % RH) of 2.2 ± 0.05 %, 2.2 ± 0.04 %, 2.2 ± 0.03 %, 2.2 ± 0.02 %, or 2.2 ± 0.01 % (*e.g.*, about 2.2 %), as measured by GVS.

[0693] Form 2 of Compound No. 10a is characterized by an uptake (*e.g.*, from 40 % to 70 % RH) of 6.1 ± 0.05 %, 6.1 ± 0.04 %, 6.1 ± 0.03 %, 6.1 ± 0.02 %, or 6.1 ± 0.01 % (*e.g.*, about 6.1 %), as measured by GVS.

[0694] Form 2 of Compound No. 10a is characterized by a reversible hysteresis (*e.g.*, from 70 % to 10 % RH), as measured by GVS.

[0695] Form 3 of Compound No. 10a is characterized by an XRPD pattern comprising signals at 4.4 ± 0.5 , 8.4 ± 0.5 , and 17.8 ± 0.5 °2 θ (*e.g.*, 4.4 ± 0.2 , 8.4 ± 0.2 , and 17.8 ± 0.2 °2 θ using Cu K α radiation (*e.g.*, 4.4 ± 0.1 , 8.4 ± 0.1 , and 17.8 ± 0.1 °2 θ using Cu K α radiation (*e.g.*, 4.4, 8.4, and 17.8 °2 θ using Cu K α radiation))).

[0696] Form 3 of Compound No. 10a is characterized by an XRPD pattern comprising signals at 4.4 ± 0.5 , 8.4 ± 0.5 , 8.9 ± 0.5 , 11.1 ± 0.5 , 11.4 ± 0.5 , 12.0 ± 0.5 , 14.2 ± 0.5 , 14.3 ± 0.5 , 15.1 ± 0.5 , 16.8 ± 0.5 , 17.3 ± 0.5 , 17.8 ± 0.5 , 19.0 ± 0.5 , 19.2 ± 0.5 , 19.6 ± 0.5 , 20.6 ± 0.5 , 20.9 ± 0.5 , 21.3 ± 0.5 , 21.5 ± 0.5 , 21.9 ± 0.5 , 22.3 ± 0.5 , 22.4 ± 0.5 , 22.9 ± 0.5 , 23.2 ± 0.5 , 23.6 ± 0.5 , 24.4 ± 0.5 , 24.8 ± 0.5 , 25.2 ± 0.5 , 26.8 ± 0.5 , 27.4 ± 0.5 , 27.8 ± 0.5 , 29.1 ± 0.5 , 29.4 ± 0.5 , 29.8 ± 0.5 , 30.1 ± 0.5 , 31.0 ± 0.5 , and 31.4 ± 0.5 °2 θ using Cu K α radiation (*e.g.*, 4.4 ± 0.2 , 8.4 ± 0.2 , 8.9 ± 0.2 , 11.1 ± 0.2 , 11.4 ± 0.2 , 12.0 ± 0.2 , 14.2 ± 0.2 , 14.3 ± 0.2 , 15.1 ± 0.2 , 16.8 ± 0.2 , 17.3 ± 0.2 , 17.8 ± 0.2 , 19.0 ± 0.2 , 19.2 ± 0.2 , 19.6 ± 0.2 , 20.6 ± 0.2 , 20.9 ± 0.2 , 21.3 ± 0.2 , 21.5 ± 0.2 , 21.9 ± 0.2 , 22.3 ± 0.2 , 22.4 ± 0.2 , 22.9 ± 0.2 , 23.2 ± 0.2 , 23.6 ± 0.2 , 24.4 ± 0.2 , 24.8 ± 0.2 , 25.2 ± 0.2 , 26.8 ± 0.2 , 27.4 ± 0.2 , 27.8 ± 0.2 , 29.1 ± 0.2 , 29.4 ± 0.2 , 29.8 ± 0.2 , 30.1 ± 0.2 , 31.0 ± 0.2 , and 31.4 ± 0.2 °2 θ using Cu K α radiation (*e.g.*, 4.4 ± 0.1 , 8.4 ± 0.1 , 8.9 ± 0.1 , 11.1 ± 0.1 , 11.4 ± 0.1 , 12.0 ± 0.1 , 14.2 ± 0.1 , 14.3 ± 0.1 , 15.1 ± 0.1 , 16.8 ± 0.1 , 17.3 ± 0.1 , 17.8 ± 0.1 , 19.0 ± 0.1 , 19.2 ± 0.1 , 19.6 ± 0.1 , 20.6 ± 0.1 , 20.9 ± 0.1 , 21.3 ± 0.1 , 21.5 ± 0.1 , 21.9 ± 0.1 , 22.3 ± 0.1 , 22.4 ± 0.1 , 22.9 ± 0.1 , 23.2 ± 0.1 , 23.6 ± 0.1 , 24.4 ± 0.1 , 24.8 ± 0.1 , 25.2 ± 0.1 , 26.8 ± 0.1 , 27.4 ± 0.1 , 27.8 ± 0.1 , 29.1 ± 0.1 , 29.4 ± 0.1 , 29.8 ± 0.1 , 30.1 ± 0.1 , 31.0 ± 0.1 , and 31.4 ± 0.1 °2 θ using Cu K α radiation (*e.g.*, 4.4, 8.4, 8.9, 11.1, 11.4, 12.0, 14.2, 14.3, 15.1, 16.8, 17.3, 17.8, 19.0, 19.2, 19.6, 20.6, 20.9, 21.3, 21.5, 21.9, 22.3, 22.4, 22.9, 23.2, 23.6, 24.4, 24.8, 25.2, 26.8, 27.4, 27.8, 29.1, 29.4, 29.8, 30.1, 31.0, and 31.4 °2 θ using Cu K α radiation))).

[0697] Form 3 of Compound No. 10a is characterized by a degradation event up to 85 ± 40 °C, 85 ± 30 °C, 85 ± 20 °C, 85 ± 15 °C, 85 ± 10 °C, or 85 ± 5 °C (*e.g.*, up to about 85 °C), as measured by TGA.

[0698] Form 3 of Compound No. 10a is characterized by a degradation event onset at 85 ± 40 °C, 85 ± 30 °C, 85 ± 20 °C, 85 ± 15 °C, 85 ± 10 °C, or 85 ± 5 °C (*e.g.*, about 85 °C), as measured by TGA.

[0699] Form 3 of Compound No. 10a is characterized by an endothermic event with an onset at 34 ± 20 °C, 34 ± 15 °C, 34 ± 10 °C, or 34 ± 5 °C (*e.g.*, about 34 °C), as measured by DSC.

[0700] Form 3 of Compound No. 10a is characterized by an endothermic event with an onset at 102 ± 20 °C, 102 ± 15 °C, 102 ± 10 °C, or 102 ± 5 °C (*e.g.*, about 102 °C), as measured by DSC.

[0701] Form 3 of Compound No. 10a is characterized by an endothermic event with an onset at 152 ± 20 °C, 152 ± 15 °C, 152 ± 10 °C, or 152 ± 5 °C (*e.g.*, about 152 °C), as measured by DSC.

[0702] Form 3 of Compound No. 10a is characterized by an uptake (*e.g.*, from 40 % to 80 % RH) of 2.3 ± 0.5 %, 2.3 ± 0.4 %, 2.3 ± 0.3 %, 2.3 ± 0.2 %, 2.3 ± 0.1 %, or 2.3 ± 0.05 % (*e.g.*, about 2.3 %), as measured by GVS.

[0703] Form 3 of Compound No. 10a is characterized by an uptake (*e.g.*, from 80 % to 90 % RH) of 8.9 ± 0.5 %, 8.9 ± 0.4 %, 8.9 ± 0.3 %, 8.9 ± 0.2 %, 8.9 ± 0.1 %, or 8.9 ± 0.05 % (*e.g.*, about 8.9 %), as measured by GVS.

[0704] Form 3 of Compound No. 10a is characterized by an uptake (*e.g.*, from 40 % to 80 % RH) of 5.1 ± 0.5 %, 5.1 ± 0.4 %, 5.1 ± 0.3 %, 5.1 ± 0.2 %, 5.1 ± 0.1 %, or 5.1 ± 0.05 % (*e.g.*, about 5.1 %), as measured by GVS.

[0705] Form 3 of Compound No. 10a is characterized by a reversible hysteresis (*e.g.*, from 70 % to 10 % RH), as measured by GVS.

[0706] Form 3 of Compound No. 10a is a crystalline solid having one or more of the following characteristics:

- a) a crystal size of $0.300 \times 0.250 \times 0.200$ mm;
- b) a crystal habit of colourless cut rod;
- c) a crystal system of monoclinic;
- d) a space group of $P2_1$;
- e) unit cell dimensions of $a = 10.17100(10)$ Å, $a = 90^\circ$, $b = 12.04740(10)$ Å, $b = 89.8050(10)^\circ$, $c = 20.0561(2)$ Å, $c = 90^\circ$;
- f) a volume of $2457.54(4)$ Å³;
- g) a density (calculated) of 1.350 Mg/m³;
- h) an absorption coefficient or 1.708 mm⁻¹; and/or
- i) $F(000)$ of 1056.

[0707] **Melting Point:** By DSC, Compound No. 10a demonstrates a broad endotherm at 113.7°C with an onset of 70.6°C and an enthalpy of 99.0 J/g followed by a melting endotherm at 163.2°C with an onset of 148.0°C and an enthalpy of 40.1 J/g.

[0708] **Hygroscopicity:** Compound No. 10a is a monohydrate, determined as slightly hygroscopic with water uptake above 95% RH.

[0709] **pKa:** 5.7

[0710] **LogD_{7.4}:** 1.04 (LogD_{2.0} = 3.11; LogD_{11.0} = 0.26)

[0711] **Solubility:** Compound No. 10a (Form 3) is highly soluble in water (> 300 mg/mL); the aqueous solubility of Compound No. 10a over the pH range 1.6-8.5 varies [FaSSGF (pH 1.6) = 24 µg/mL; FeSSIF (pH 5.0) = 169 µg/mL; FaSSIF (pH 6.5) = 126 µg/mL; Tris (pH 8.0) > 300 mg/mL]

[0712] Form 3 exhibits good solubility in methanol, ethanol, acetone, MEK, and tetrahydrofuran but is poorly soluble in ethylacetate, isopropylacetate, MIBK isopropanol and n-heptane.

EQUIVALENTS

[0713] The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms may include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference.

[0714] The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto.

What is claimed is:

1. A method of preparing Compound No. 10, comprising one or more of steps (iv)-(vii):
 - (iv) reacting Compound No. 5, or a salt thereof, with an acid, thereby forming Compound No. 6, or a salt thereof;
 - (v) reacting Compound No. 7, or a salt thereof, with a source of CO, thereby forming Compound No. 8, or a salt thereof;
 - (vi) reacting Compound No. 6, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9; or
 - (vii) purifying Compound No. 9, thereby isolating Compound No. 10.
2. A method of preparing Compound No. 5, or a salt thereof, comprising:
 - (iii) reacting Compound No. 5, or a salt thereof, with an acid, thereby forming Compound No. 6, or a salt thereof.
3. A method of preparing Compound No. 9, comprising:
 - (iv) reacting Compound No. 6, or a salt thereof, with Compound No. 8, or a salt thereof, thereby forming Compound No. 9.
4. A method of preparing Compound No. 10, comprising:
 - (vii) purifying Compound No. 9, thereby isolating Compound No. 10.
5. The method of claim 1, further comprising steps (i)-(iv):
 - (i) reacting tetrahydrofuran-2-carboxylic acid, with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof;
 - (ii) reacting N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof, with a reducing agent, thereby forming 1-methyl-N-{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof;
 - (iii) reacting 1-methyl-N-{[oxolan-2-yl]methyl}-1H-pyrazol-4-amine, or a salt thereof, with tert-butyl N-chlorosulfonylcarbamate, thereby forming Compound No. 5, or a salt thereof; and
 - (iv) reacting Compound No. 5 or a salt thereof, with an acid, thereby forming Compound No. 6, or a salt thereof.

6. The method of any one of the preceding claims, wherein Compound No. 9 is Compound No. 9a.
7. The method of any one of the preceding claims, wherein Compound No. 10 is Compound No. 10a.
8. The method of any one of the preceding claims, wherein Compound No. 9 is Compound No. 9b.
9. The method of any one of the preceding claims, wherein in step (iv), the acid is hydrochloric acid.
10. The method of any one of the preceding claims, wherein in step (iv), the molar ratio of the acid to Compound No. 5, or the salt thereof, is from about 3:1 to about 1:1.
11. The method of any one of the preceding claims, wherein in step (iv), the reacting is performed in the presence of a first solvent to form a first mixture.
12. The method of any one of the preceding claims, wherein in step (iv), the reacting is performed at a first temperature of about 25 ± 15 °C, about 25 ± 10 °C, or about 25 ± 5 °C.
13. The method of any one of the preceding claims, wherein in step (iv), the reacting is performed for about 26 ± 20 hours, about 26 ± 15 hours, about 26 ± 10 hours, about 26 ± 5 hours, about 26 ± 4 hours, about 26 ± 3 hours, about 26 ± 2 hours, or about 26 ± 1 hours.
14. The method of claim 11, wherein the first mixture is cooled to a second temperature of about 0 ± 15 °C, about 0 ± 10 °C, or about 0 ± 5 °C.
15. The method of claim 11, wherein the first mixture is cooled to a second temperature of about 0 ± 15 °C, about 0 ± 10 °C, or about 0 ± 5 °C and a second solvent is added to form a second mixture.

16. The method of claim 15, wherein a base or a buffer is added to the second mixture.
17. The method of any one of the preceding claims, wherein in step (iv), Compound No. 6, or the salt thereof, is isolated and/or purified prior to reacting with Compound No. 8.
18. The method of claim 17, wherein in step (iv), Compound No. 6, or the salt thereof, is at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% pure as measured by HPLC.
19. The method of claim 1, wherein in step (v), triphosgene is the source of CO.
20. The method of claim 1, wherein in step (v), the reacting is performed in the presence of a base.
21. The method of claim 20, wherein in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is from about 3:1 to about 1:1.
22. The method of claim 1, wherein in step (v), the reacting is performed in the presence of a solvent.
23. The method of claim 1, wherein step (v) comprises filtering the solution of Compound No. 8, or the salt thereof.
24. The method of claim 1, wherein in step (v), Compound No. 8, or the salt thereof, is isolated and/or purified prior to reacting with Compound No. 6, or a salt thereof.
25. The method of claim 1, wherein in step (v), Compound No. 8, or the salt thereof, is not isolated and/or purified prior to reacting with Compound No. 6, or a salt thereof.
26. The method of claim 1, wherein step (v), yields a solution of Compound No. 8, or the salt thereof.

27. The method of claim 1, wherein step (v) yields Compound No. 8, or the salt thereof, with purity of at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% as measured by HPLC.
28. The method of claim 1, wherein in step (vi), the reacting is performed in the presence of a base.
29. The method of claim 1, wherein in step (vi), the reacting is performed in the presence of a first solvent.
30. The method of claim 1, wherein in step (vi), the molar ratio of Compound No. 6, or a salt thereof, to the Compound No. 8, or the salt thereof, is from about 2:1 to about 1:2.
31. The method of claim 1, wherein in step (vi), the reacting comprises partial removal of the first solvent.
32. The method of claim 1, wherein in step (vi), the reacting is performed in the presence of a second solvent.
33. The method of claim 1, wherein in step (vi), the reacting comprises extracting Compound No. 9 using an ether.
34. The method of claim 1, wherein in step (vi), the reacting comprises filtering out Compound No. 9, washing Compound No. 9 with IPA-MTBE, or a combination thereof.
35. The method of claim 1, wherein in step (vi), the reacting is performed at a first temperature of about 25 ± 15 °C, about 25 ± 10 °C, or about 25 ± 5 °C.
36. The method of claim 1, wherein step (vi) comprises filtering Compound No. 9.
37. The method of claim 1, wherein in step (vi), Compound No. 9a or 9b is isolated and/or purified.

38. The method of claim 1, wherein step (vi) yields Compound No. 9 with purity of at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% as measured by HPLC.

39. The method of claim 1, wherein step (vii) comprises recrystallizing Compound No. 9 in the presence of an organic solvent.

40. The method of claim 1, wherein in step (vii), Compound No. 9 is dissolved in tetrahydrofuran, filtered and washed with tetrahydrofuran to form a first mixture.

41. The method of claim 40, wherein the first mixture of step (vii) is concentrated and ethyl acetate is added to form a second mixture.

42. The method of claim 41, wherein the second mixture of step (vii) is concentrated and ethyl acetate and water are added to form a third mixture.

43. The method of claim 42, wherein the third mixture of step (vii) is heated and then seeded to form a seeded third mixture.

44. The method of claim 42, wherein the third mixture of step (vii) is heated to a first temperature of about 45 ± 20 °C, about 45 ± 15 °C, about 45 ± 10 °C, about 45 ± 5 °C, about 45 ± 4 °C, about 45 ± 3 °C, about 45 ± 2 °C, or about 45 ± 1 °C and then seeded to form a seeded third mixture.

45. The method of claim 44, wherein after heating to the first temperature, the seeded third mixture of step (vii) is aged for about 1 ± 2 hours, or 1 ± 1 hour.

46. The method of claim 45, wherein in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of about 30 ± 20 °C, about 30 ± 15 °C, about 30 ± 10 °C, about 30 ± 5 °C, about 30 ± 4 °C, about 30 ± 3 °C, about 30 ± 2 °C, or about 30 ± 1 °C.

47. The method of claim 45, wherein in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of about 30 ± 20 °C, about 30 ± 15 °C, about 30 ± 10 °C, about 30 ± 5 °C, about 30 ± 4 °C, about 30 ± 3 °C, about 30 ± 2 °C, or about 30 ± 1 °C (*e.g.*, about 30 °C) and aged for a time from about 1 hour to about 12 hours, from about 2 hours to about 10 hours, or from about 3 hours to about 6 hours to form a mixture comprising Compound No. 10.
48. The method of claim 47, wherein in step (vii), n-heptane is added to the mixture comprising Compound No. 10 to form a solid form of Compound No. 10.
49. The method of claim 48, wherein in step (vii), the solid form of Compound No. 10 is filtered out and washed, thereby forming substantially pure solid form of Compound No. 10.
50. The method of claim 49, wherein step (vii) yields a specific polymorphic form of Compound No. 10.
51. The method of claim 49, wherein step (vii) yields polymorphic form (Form 3) of Compound No. 10a.
52. The method of claim 49, wherein step (vii) yields a solid form of Compound No. 10 with purity of at least about 98%, at least about 98.5%, at least about 99%, at least about 99.1%, at least about 99.2%, at least about 99.3%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, at least about 99.8% as measured by HPLC.
53. The method of claim 49, wherein step (vii) yields substantially pure polymorphic form (Form 3) of Compound No. 10a.
54. A compound being prepared by the method of any one of the preceding claims.
55. A pharmaceutical composition comprising Compound No. 10, of any one of the preceding claims, and one or more pharmaceutically acceptable carrier or excipient.

56. A method of preventing or treating a disease in a subject, comprising administering to the subject Compound No. 10, of any one of the preceding claims.
57. Compound No. 10, of any one of the preceding claims for use in preventing or treating a disease in a subject.
58. Use of Compound No. 10, of any one of the preceding claims in the manufacture of a medicament for preventing or treating a disease in a subject.
59. A method of inhibiting inflammasome activity in a subject, comprising contacting a cell with Compound No. 10, of any one of the preceding claims.
60. Compound No. 10, of any one of the preceding claims for use in inhibiting inflammasome activity in a subject.
61. Use of Compound No. 10, of any one of the preceding claims in the manufacture of a medicament for inhibiting inflammasome activity.
62. The method, compound, or use of any one of the preceding claims, wherein the subject is a human.