

METHODS OF PREPARING CARBAMATE DERIVATIVES

RELATED APPLICATION

[001] This application claims priority to International Patent Application No. PCT/CN2022/123712, filed October 5, 2022, 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 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 a compound of Formula (IX) (e.g., Compound No. 9a or 9b) described herein.

[007] In some aspects, the present disclosure provides a method of preparing a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof, comprising one or more of steps (i)-(vii):

(i) contacting Compound No. 1 or a salt thereof, with a hydrogenation agent, thereby forming Compound No. 2 or a salt thereof;

(ii) reacting Compound No. 3, with an esterification agent, thereby forming a compound of Formula (IV) (e.g., Compound No. 4);

(iii) contacting Compound No. 2 or a salt thereof, with the compound of Formula (IV) (e.g., Compound No. 4), thereby forming a compound of Formula (V) (e.g., Compound No. 5) or a salt thereof;

(iv) contacting the compound of Formula (V) (e.g., Compound No. 5) or the salt thereof, with a reducing agent, thereby forming a compound of Formula (VI) (e.g., Compound No. 6a or 6b) or a salt thereof;

(v) contacting Compound No. 7 or a salt thereof, with an CO-generating agent, thereby forming Compound No. 8 or a salt thereof;

(vi) contacting the compound of Formula (VI) (e.g., Compound No. 6a or 6b) or the salt thereof, with Compound No. 8 or a salt thereof, thereby forming a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof; or

(vii) purifying the compound of Formula (IX) (e.g., Compound No. 9a or 9b) or the salt thereof.

[008] In some aspects, the present disclosure provides a method of preparing a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof, comprising steps (i)-(vii):

(i) contacting Compound No. 1 or a salt thereof, with a hydrogenation agent, thereby forming Compound No. 2 or a salt thereof;

(ii) contacting Compound No. 3, with an esterification agent, thereby forming a compound of Formula (IV) (e.g., Compound No. 4);

(iii) contacting Compound No. 2 or a salt thereof, with the compound of Formula (IV) (e.g., Compound No. 4), thereby forming a compound of Formula (V) (e.g., Compound No. 5) or a salt thereof;

(iv) contacting the compound of Formula (V) (e.g., Compound No. 5) or the salt thereof, with a reducing agent, thereby forming a compound of Formula (VI) (e.g., Compound No. 6a or 6b) or a salt thereof;

(v) contacting Compound No. 7 or a salt thereof, with an CO-generating agent, thereby forming Compound No. 8 or a salt thereof;

(vi) contacting the compound of Formula (VI) (e.g., Compound No. 6a or 6b) or the salt thereof, with Compound No. 8 or a salt thereof, thereby forming a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof; and

(vii) purifying the compound of Formula (IX) (e.g., Compound No. 9a or 9b) or the salt thereof.

[009] In some aspects, the present disclosure provides a method of preparing a compound of Formula (V) (e.g., Compound No. 5) or a salt thereof, comprising:

(iii) contacting Compound No. 2 or a salt thereof, with a compound of Formula (IV) (e.g., Compound No. 4), thereby forming a compound of Formula (V) (e.g., Compound No. 5) or a salt thereof.

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

[011] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein, and one or more pharmaceutically acceptable carrier or excipient.

[012] 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 a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein (e.g., in an effective amount).

[013] 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 a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein (e.g., in a therapeutically effective amount).

[014] In some aspects, the present disclosure provides a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein for use in inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*).

[015] In some aspects, the present disclosure provides a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein for use in treating or preventing a disease or disorder disclosed herein.

[016] In some aspects, the present disclosure provides use of a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof 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*).

[017] In some aspects, the present disclosure provides use of a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[018] 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.

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

DETAILED DESCRIPTION

[020] 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).

[021] Cytokines from the IL-1 family are highly active and, as important mediators of inflammation, 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 a mediator 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.

[022] Proinflammatory 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.

[023] 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.

[024] 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).

[025] 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 proIL-1 β activation (Chae et al., Immunity 34, 755-768, 2011).

[026] 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.

[027] 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 .

[028] 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.

[029] 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).

[030] 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 (rilonacept) 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.

[031] 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

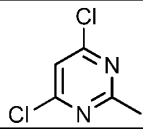
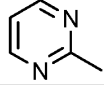
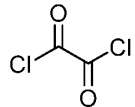
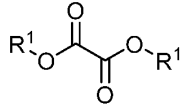
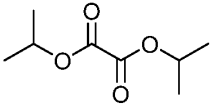
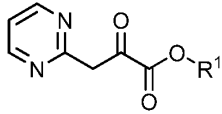
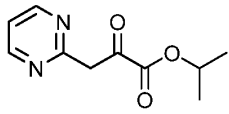
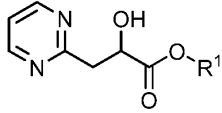
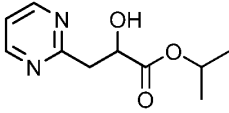
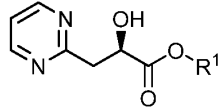
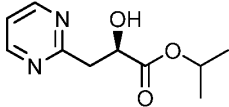
characterised as a specific inhibitor of NLRP3 activation (Coll et al., Nat Med 21.3 (2015): 248-255.).

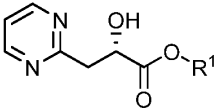
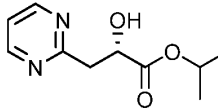
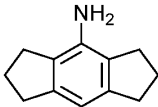
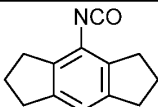
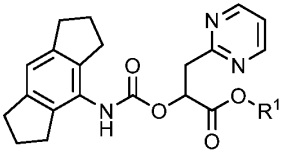
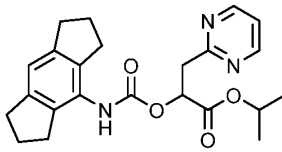
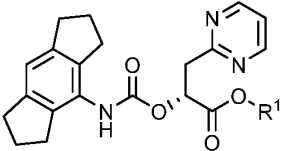
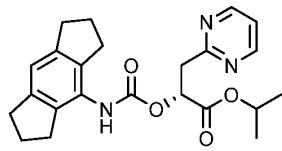
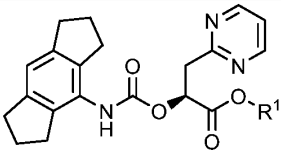
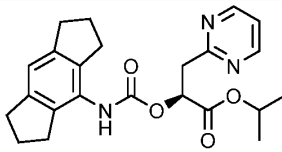
[032] The disclosure relates to methods of preparing compounds useful for the modulation of NLRP3-dependent cellular processes. In some embodiments, methods of preparing compounds with improved physicochemical, pharmacological and pharmaceutical properties to existing NLRP3-modulating compounds are desired.

Compounds of the Present Disclosure

[033] It is understood that the structures of Formulae (IV)-(VI), (VI-a), (VI-b), (IX), (IX-a), and (IX-b), and the structures of Compound Nos. 1-6, 6a, 6b, 7-9, 9a, and 9b are as described in Table I below, wherein R¹ is as described herein.

Table I

Formula No.	Formula Structure	Compound No.	Compound Structure
		1	
		2	
		3	
IV		4	
V		5	
VI		6	
VI-a		6a	

Formula No.	Formula Structure	Compound No.	Compound Structure
VI-b		6b	
		7	
		8	
IX		9	
IX-a		9a	
IX-b		9b	

[034] In some embodiments, each R¹ independently is C₁-C₆ alkyl.

[035] In some embodiments, each R¹ independently is methyl, ethyl, propyl, butyl, pentyl, or hexyl.

[036] In some embodiments, each R¹ independently is methyl, ethyl, or propyl.

[037] In some embodiments, each R¹ is methyl.

[038] In some embodiments, each R¹ is ethyl.

[039] In some embodiments, each R¹ is propyl.

[040] In some embodiments, each R¹ is n-propyl.

[041] In some embodiments, each R¹ is i-propyl.

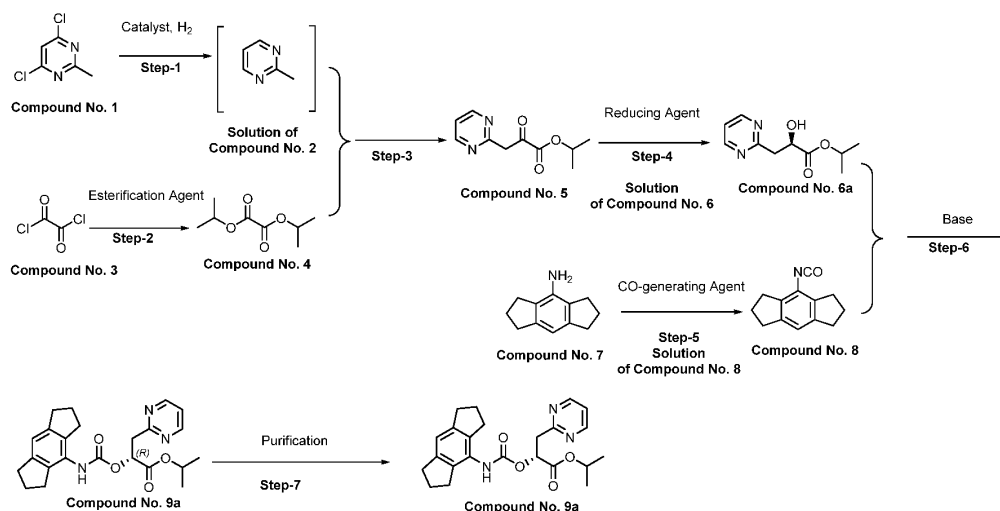
Methods of the Present Disclosure

[042] In some aspects, the present disclosure provides a method of preparing Compound No. 9a or a salt thereof according to the Scheme A.

[043] In some embodiments, Compound No. 1 is dechlorinated to Compound 2 (e.g., via hydrogenation). In some embodiments, Compound No. 3 is converted to Compound No. 4 via an esterification reaction (e.g., in the presence of an esterification agent). In some embodiments, Compound No. 2 is reacted with Compound No. 4 to provide Compound No. 5. In some embodiments, Compound No. 7 is converted to Compound No. 8 (e.g., via reaction with a CO-generating agent). In some embodiments, Compound No. 5 is reduced to Compound No. 6a and reacted with Compound No. 8 to form compound No. 9a. (e.g., in the presence of a base). In some embodiments, Compound No. 9a is purified.

[044] In some embodiments, the method of preparing Compound No. 9a or a salt thereof comprises at least one of the seven steps shown in Scheme A.

Scheme A



[045] In some aspects, the present disclosure provides a method of preparing a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof, comprising one or more of steps (i)-(vii):

- (i) contacting Compound No. 1 or a salt thereof, with a hydrogenation agent, thereby forming Compound No. 2 or a salt thereof;
- (ii) reacting Compound No. 3, with an esterification agent, thereby forming a compound of Formula (IV) (e.g., Compound No. 4);

(iii) contacting Compound No. 2 or a salt thereof, with the compound of Formula (IV) (e.g., Compound No. 4), thereby forming a compound of Formula (V) (e.g., Compound No. 5) or a salt thereof;

(iv) contacting the compound of Formula (V) (e.g., Compound No. 5) or the salt thereof, with a reducing agent, thereby forming a compound of Formula (VI) (e.g., Compound No. 6a or 6b) or a salt thereof;

(v) contacting Compound No. 7 or a salt thereof, with an CO-generating agent, thereby forming Compound No. 8 or a salt thereof;

(vi) contacting the compound of Formula (VI) (e.g., Compound No. 6a or 6b) or the salt thereof, with Compound No. 8 or a salt thereof, thereby forming a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof; or

(vii) purifying the compound of Formula (IX) (e.g., Compound No. 9a or 9b) or the salt thereof.

[046] In some embodiments, the method comprises one or more of steps (iii), (iv), and (vi).

[047] In some embodiments, the method comprises step (iii).

[048] In some embodiments, the method comprises step (iv).

[049] In some embodiments, the method comprises steps (iii) and (iv).

[050] In some embodiments, the method comprises step (vi).

[051] In some embodiments, the method comprises steps (iii), (iv), and (vi).

[052] In some embodiments, the method comprises one or more of steps (iii), (iv), and (vi), and (vii).

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

[054] In some aspects, the present disclosure provides a method of preparing a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof, comprising steps (i)-(vii):

(i) contacting Compound No. 1 or a salt thereof, with a hydrogenation agent, thereby forming Compound No. 2 or a salt thereof;

(ii) contacting Compound No. 3, with an esterification agent, thereby forming a compound of Formula (IV) (e.g., Compound No. 4);

(iii) contacting Compound No. 2 or the salt thereof, with the compound of Formula (IV) (e.g., Compound No. 4), thereby forming a compound of Formula (V) (e.g., Compound No. 5) or a salt thereof;

(iv) contacting the compound of Formula (V) (e.g., Compound No. 5) or the salt thereof, with a reducing agent, thereby forming a compound of Formula (VI) (e.g., Compound No. 6a or 6b) or a salt thereof;

(v) contacting Compound No. 7 or a salt thereof, with an CO-generating agent, thereby forming Compound No. 8 or a salt thereof;

(vi) contacting the compound of Formula (VI) (e.g., Compound No. 6a or 6b) or the salt thereof, with Compound No. 8 or the salt thereof, thereby forming a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof; and

(vii) purifying the compound of Formula (IX) (e.g., Compound No. 9a or 9b) or the salt thereof.

[055] In some embodiments, the compound of Formula (IV) is Compound No. 4.

[056] In some embodiments, the compound of Formula (VI) or a salt thereof is Compound No. 5 or a salt thereof.

[057] In some embodiments, the compound of Formula (VI) or a salt thereof is Compound No. 6 or a salt thereof.

[058] In some embodiments, the compound of Formula (VI) or a salt thereof is a compound of Formula (VI-a) or a salt thereof.

[059] In some embodiments, the compound of Formula (VI) or a salt thereof is Compound No. 6a or a salt thereof.

[060] In some embodiments, the compound of Formula (VI) or a salt thereof is a compound of Formula (VI-b) or a salt thereof.

[061] In some embodiments, the compound of Formula (VI) or a salt thereof is Compound No. 6b or a salt thereof.

[062] In some embodiments, the compound of Formula (IX) or a salt thereof is Compound No. 9.

[063] In some embodiments, the compound of Formula (IX) or a salt thereof is a compound of Formula (IX-a) or a salt thereof.

[064] In some embodiments, the compound of Formula (IX) or a salt thereof is Compound No. 9a or a salt thereof.

[065] In some embodiments, the compound of Formula (IX) or a salt thereof is a compound of Formula (IX-b) or a salt thereof.

[066] In some embodiments, the compound of Formula (IX) or a salt thereof is Compound No. 9b or a salt thereof.

Step (i)

- [067] In some embodiments, in step (i), the hydrogenation agent is hydrogen.
- [068] In some embodiments, in step (i), the hydrogenation agent is an alkene or an alkyne.
- [069] In some embodiments, in step (i), the contacting is performed in the presence of a hydrogenation catalyst.
- [070] In some embodiments, the hydrogenation catalyst is a homogeneous catalyst.
- [071] In some embodiments, the hydrogenation catalyst is a heterogeneous catalyst.
- [072] In some embodiments, the hydrogenation catalyst is a metal catalyst.
- [073] In some embodiments, the hydrogenation catalyst is a nickel catalyst, a platinum catalyst, a palladium catalyst, a rhodium catalyst, or a ruthenium catalyst.
- [074] In some embodiments, the hydrogenation catalyst is a palladium catalyst (e.g., palladium on carbon (Pd/C)).
- [075] In some embodiments, the hydrogenation catalyst is a nickel catalyst (e.g., Raney nickel).
- [076] In some embodiments, in step (i), the contacting is performed in the presence of a base. In some embodiments, the base is an inorganic base (e.g., potassium carbonate (K₂CO₃)).
- [077] In some embodiments, in step (i), the contacting is performed in the presence of a solvent. In some embodiments, the solvent is an organic solvent. In some embodiments, the solvent is an aprotic solvent (e.g., tetrahydrofuran (THF)).
- [078] In some embodiments, in step (i), the contacting is performed at a temperature of 25±15 °C, 25±10 °C, or 25±5 °C (e.g., about 25 °C).
- [079] In some embodiments, in step (i), the contacting is performed for 25±20 hours, 25±15 hours, 25±10 hours, 25±5 hours, 25±4 hours, 25±3 hours, 25±2 hours, or 25±1 hours (e.g., about 25 hours).
- [080] In some embodiments, step (i) comprises filtering a solution of Compound No. 2 or the salt thereof (e.g., in THF).
- [081] In some embodiments, Compound No. 2 or the salt thereof is isolated and/or purified prior to contacting with the compound of Formula (IV) (e.g., Compound No. 4).
- [082] In some embodiments, Compound No. 2 or the salt thereof is not isolated or purified prior to contacting with the compound of Formula (IV) (e.g., Compound No. 4).
- [083] In some embodiments, step (i) yields a solution of Compound No. 2 or the salt thereof (e.g., in THF).

Step (ii)

[084] In some embodiments, in step (ii), the esterification agent is an alcohol.

[085] In some embodiments, the esterification agent is R^1 -OH, wherein R^1 is C_1 - C_6 alkyl.

[086] In some embodiments, the esterification agent is methanol, ethanol, or propanol. In some embodiments, the esterification agent is propanol. In some embodiments, the esterification agent is isopropanol (iPrOH; propan-2-ol).

[087] In some embodiments, in step (ii), the contacting is performed in the presence of an esterification catalyst. In some embodiments, the esterification catalyst is a base catalyst (e.g., 4-dimethylaminopyridine (DMAP)).

[088] In some embodiments, in step (ii), the contacting is performed in the presence of a base. In some embodiments, the base is an organic base (e.g., pyridine).

[089] In some embodiments, in step (ii), the contacting is performed in the presence of a solvent. In some embodiments, the solvent is an organic solvent. In some embodiments, the solvent is an aprotic solvent (e.g., tetrahydrofuran (THF)).

[090] In some embodiments, step (ii) comprises filtering a solution of the compound of Formula (IV) (e.g., Compound No. 4) (e.g., in n-heptane).

Step (iii)

[091] In some aspects, the present disclosure provides a method of preparing a compound of Formula (V) (e.g., Compound No. 5) or a salt thereof, comprising:

(iii) contacting Compound No. 2 or a salt thereof, with a compound of Formula (IV) (e.g., Compound No. 4), thereby forming a compound of Formula (V) (e.g., Compound No. 5) or a salt thereof.

[092] In some embodiments, in step (iii), the contacting is performed in the presence of a salt. In some embodiments, the salt is a potassium salt (e.g., potassium tert-butoxide (tBuOK)).

[093] In some embodiments, in step (iii), the contacting is performed in the presence of an alcohol. In some embodiments, the alcohol is isopropanol (iPrOH; propan-2-ol).

[094] In some embodiments, step (iii) further comprises adding an acid to the formed compound of Formula (V) (e.g., Compound No. 5) or the salt thereof, thereby adjusting the pH value to 7.0 ± 2.0 , 7.0 ± 1.5 , 7.0 ± 1.0 , 7.0 ± 0.9 , 7.0 ± 0.8 , 7.0 ± 0.7 , 7.0 ± 0.6 , 7.0 ± 0.5 , 7.0 ± 0.4 , 7.0 ± 0.3 , 7.0 ± 0.2 , or 7.0 ± 0.1 (e.g., about 7.0).

[095] In some embodiments, the acid is an organic acid (e.g., acetic acid (AcOH)).

[096] In some embodiments, step (iii) further comprises crystalizing the compound of Formula (V) (e.g., Compound No. 5) or the salt thereof in the presence of an organic solvent. In some embodiments, the organic solvent comprises isopropyl acetate and n-heptane.

Step (iv)

[097] In some aspects, the present disclosure provides a method of preparing a compound of Formula (VI) (e.g., Compound No. 6a or 6b) or a salt thereof, comprising:

(iv) contacting a compound of Formula (V) (e.g., Compound No. 5) or a salt thereof, with a reducing agent, thereby forming a compound of Formula (VI) (e.g., Compound No. 6a or 6b) or a salt thereof.

[098] In some embodiments, in step (iv), the reducing agent is a monosaccharide. In some embodiments, the reducing agent is glucose. In some embodiments, the reducing agent is D-glucose. In some embodiments, the reducing agent is L-glucose.

[099] In some embodiments, in step (iv), the contacting is performed in the presence of a reduction catalyst.

[0100] In some embodiments, the reduction catalyst comprises an enzymatic catalyst.

[0101] In some embodiments, the reduction catalyst comprises a molecular catalyst.

[0102] In some embodiments, the reduction catalyst comprises ketoreductase (KRED).

[0103] In some embodiments, the reduction catalyst comprises glutamate dehydrogenase (GDH).

[0104] In some embodiments, the reduction catalyst comprises a dinucleotide phosphate (e.g., as a cofactor).

[0105] In some embodiments, the reduction catalyst comprises nicotinamide adenine dinucleotide phosphate (NADP) as a cofactor.

[0106] In some embodiments, the reduction catalyst comprises ketoreductase (KRED), glutamate dehydrogenase (GDH), and nicotinamide adenine dinucleotide phosphate (NADP).

[0107] In some embodiments, the reduction involves hydride transfer from the reduction catalyst (e.g., NADP cofactor) to the reducing agent (e.g., glucose).

[0108] In some embodiments, the contacting is performed in the presence of a buffering solution. In some embodiments, the buffering solution comprises phosphate (e.g., dipotassium phosphate (K_2HPO_4)). In some embodiments, the buffering solution has a pH value of 7.0 ± 2.0 , 7.0 ± 1.5 , 7.0 ± 1.0 , 7.0 ± 0.9 , 7.0 ± 0.8 , 7.0 ± 0.7 , 7.0 ± 0.6 , 7.0 ± 0.5 , 7.0 ± 0.4 , 7.0 ± 0.3 , 7.0 ± 0.2 , or 7.0 ± 0.1 (e.g., about 7.0).

[0109] In some embodiments, the contacting is performed in the presence of a dipolar aprotic solvent (e.g., dimethyl sulfoxide (DMSO)).

[0110] In some embodiments, step (iv) further comprises extracting the formed compound of Formula (VI) (e.g., Compound No. 6a or 6b) or the salt thereof with an aprotic solvent (e.g., 2-methyltetrahydrofuran (2-MeTHF)).

[0111] In some embodiments, step (iv) yields a solution of the compound of Formula (VI) (e.g., Compound No. 6a or 6b) or the salt thereof (e.g., in 2-methyltetrahydrofuran (2-MeTHF)).

Step (v)

[0112] In some embodiments, in step (v), the CO-generating agent is triphosgene.

[0113] In some embodiments, in step (v), the contacting is performed in the presence of a base. In some embodiments, the base is an organic base (e.g., triethylamine (TEA)).

[0114] In some embodiments, in step (v), the contacting is performed in the presence of a solvent. In some embodiments, the solvent is an aprotic organic solvent (e.g., toluene).

[0115] In some embodiments, step (v) comprises filtering a solution of Compound No. 8 or the salt thereof (e.g., in toluene).

[0116] In some embodiments, step (v) yields a solution of Compound No. 8 or the salt thereof (e.g., in toluene).

Step (vi)

[0117] In some embodiments, in step (vi), the contacting is performed in the presence of a base. In some embodiments, the base is an organic base (e.g., 4-dimethylaminopyridine (DMAP)).

[0118] In some embodiments, in step (vi), the contacting is performed in the presence of a solvent. In some embodiments, the solvent is an aprotic organic solvent. In some embodiments, the solvent comprises 2-methyltetrahydrofuran (2-MeTHF). In some embodiments, the solvent further comprises toluene.

[0119] In some embodiments, step (vi) further comprises washing the formed compound of Formula (IX) (e.g., Compound No. 9a or 9b) or the salt thereof with an acid solution. In some embodiments, the acid solution comprises citric acid (e.g., about 5% citric acid).

[0120] In some embodiments, step (vi) further comprises washing the formed compound of Formula (IX) (e.g., Compound No. 9a or 9b) or the salt thereof with a base solution. In some embodiments, the acid solution comprises sodium bicarbonate (NaHCO_3 ; e.g., about 5% NaHCO_3).

[0121] In some embodiments, step (vi) further comprises crystalizing the compound of Formula (IX) (e.g., Compound No. 9a or 9b) or the salt thereof in the presence of an organic solvent. In some embodiments, the organic solvent comprises isopropyl acetate and n-heptane.

Step (vii)

[0122] In some embodiments, step (vii) comprises crystalizing the compound of Formula (IX) (e.g., Compound No. 9a or 9b) or the salt thereof in the presence of an organic solvent. In some embodiments, the organic solvent comprises isopropyl acetate and n-heptane.

[0123] In some embodiments, the isopropyl acetate and n-heptane are present at a ratio of about 1:1, about 1:2, about 1:3, about 1:4, or about 1:5.

Compounds Being Prepared by the Methods

[0124] In some aspects, the present disclosure provides a compound being prepared by a method disclosed herein.

[0125] In some aspects, the present disclosure provides a compound of Formula (V) or a salt thereof. In some embodiments, the compound is Compound No. 5 or a salt thereof.

[0126] In some embodiments, the compound is Compound No. 5 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.

[0127] In some aspects, the present disclosure provides a compound of Formula (VI) or a salt thereof. In some embodiments, the compound is Compound No. 6 or a salt thereof.

[0128] In some aspects, the present disclosure provides a compound of Formula (VI-a) or a salt thereof. In some embodiments, the compound is Compound No. 6a or a salt thereof.

[0129] 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.

[0130] 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.

[0131] In some aspects, the present disclosure provides a compound of Formula (VI-b) or a salt thereof. In some embodiments, the compound is Compound No. 6b or a salt thereof.

[0132] 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.

[0133] 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.

[0134] In some aspects, the present disclosure provides a compound of Formula (IX) or a salt thereof. In some embodiments, the compound is Compound No. 9 or a salt thereof.

[0135] In some aspects, the present disclosure provides a compound of Formula (IX-a) or a salt thereof. In some embodiments, the compound is Compound No. 9a or a salt thereof.

[0136] In some embodiments, the compound is Compound No. 9a 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.

[0137] In some embodiments, the compound is Compound No. 9a 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.

[0138] In some aspects, the present disclosure provides a compound of Formula (IX-b) or a salt thereof. In some embodiments, the compound is Compound No. 9b or a salt thereof.

[0139] In some embodiments, the compound is Compound No. 9b 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.

[0140] In some embodiments, the compound is Compound No. 9b 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.

Biological Assays

[0141] 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.

[0142] 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.

[0143] 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.

[0144] 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).

[0145] In some embodiments, the biological assay is a PBMC IC₅₀ Determination Assay.

[0146] 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)).

[0147] 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.

[0148] 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).

[0149] 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 be added

and the cells incubated. Next, the cells are stimulated and the media from the wells are collected for analysis.

[0150] 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®).

Pharmaceutical Compositions

[0151] In some aspects, the present disclosure provides pharmaceutical compositions comprising a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein, and one or more pharmaceutically acceptable carrier or excipient.

[0152] The pharmaceutical compositions containing active compounds of the present disclosure 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 lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carrier comprising one or more excipient and/or auxiliary that facilitates processing of the active compound into preparations that can be used pharmaceutically. A person of skill in the art would understand that the appropriate formulation may be dependent upon the route of administration chosen.

[0153] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers may include physiological saline, bacteriostatic water, Cremophor EL (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition.

Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0154] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0155] Oral compositions may include one or more inert diluent or one or more edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0156] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0157] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For

transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0158] The active compounds can be prepared with one or more pharmaceutically acceptable carrier that may protect the compound against rapid elimination from the body, such as a controlled release formulation, including an implant and microencapsulated delivery system. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

[0159] It may be especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0160] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the symptoms of the disease and also preferably causing complete regression of the disease.

[0161] It is understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Methods of Use

[0162] In some aspects, the present disclosure provides a method of preventing or treating a disease in a subject, comprising administering to the subject a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein (e.g., in a therapeutically effective amount).

[0163] In some aspects, the present disclosure provides a method of treating a disease in a subject, comprising administering to the subject a compound of Formula (IX) (e.g., Compound No. 9a or

9b) or a pharmaceutically acceptable salt thereof as described herein (e.g., in a therapeutically effective amount).

[0164] In some aspects, the present disclosure provides a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein for use in preventing or treating a disease in a subject.

[0165] In some aspects, the present disclosure provides a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein for use in treating a disease in a subject.

[0166] In some aspects, the present disclosure provides use of a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein in the manufacture of a medicament for preventing or treating a disease in a subject.

[0167] In some aspects, the present disclosure provides use of a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein in the manufacture of a medicament for treating a disease in a subject.

[0168] In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered in a therapeutically effective amount.

[0169] In some embodiments, the disease or disorder is associated with an implicated inflammasome activity. In some embodiments, the disease or disorder is a disease or disorder in which inflammasome activity is implicated.

[0170] In some embodiments, the disease or disorder is an inflammatory disorder, autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease, or cancer.

[0171] In some embodiments, the disease or disorder is an inflammatory disorder, autoinflammatory disorder and/or an autoimmune disorder.

[0172] In some embodiments, the disease or disorder is selected from cryopyrin-associated autoinflammatory syndrome (CAPS; e.g., familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome/ neonatal-onset multisystem inflammatory disease (NOMID)), familial Mediterranean fever (FMF), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), gout, rheumatoid arthritis, osteoarthritis, Crohn's disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), fibrosis, obesity, type 2 diabetes, multiple sclerosis, dermatological disease (e.g. acne) and neuroinflammation occurring in protein misfolding diseases (e.g., Prion diseases).

- [0173] In some embodiments, the disease or disorder is a neurodegenerative disease.
- [0174] In some embodiments, the disease or disorder is Parkinson's disease or Alzheimer's disease.
- [0175] In some embodiments, the disease or disorder is a dermatological disease.
- [0176] In some embodiments, the dermatological disease is acne.
- [0177] In some embodiments, the disease or disorder is cancer.
- [0178] In some embodiments, the cancer is metastasising cancer, gastrointestinal cancer, skin cancer, non-small-cell lung carcinoma, brain cancer (e.g. glioblastoma) or colorectal adenocarcinoma.
- [0179] In some aspects, the present disclosure provides a method of inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity in a subject (e.g., *in vitro* or *in vivo*), comprising contacting a cell with a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein (e.g., in an effective amount).
- [0180] In some aspects, the present disclosure provides a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein for use in inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity in a subject (e.g., *in vitro* or *in vivo*).
- [0181] In some aspects, the present disclosure provides use of a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof 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*).
- [0182] In some embodiments, the inflammasome is NLRP3 inflammasome.
- [0183] In some embodiments, the subject is an animal.
- [0184] In some embodiments, the subject is a mammal.
- [0185] In some embodiments, the subject is a human.
- [0186] In some embodiments, the subject is a cell.
- [0187] In some embodiments, the subject is a cell population.

Definitions

- [0188] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.
- [0189] As used herein, the term "about" means 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%.

[0190] As used herein, the term “CO-generating agent” refers to an agent that is capable of being a resource of CO during a reaction. In some embodiments, the agent is capable of forming an isocyanate or an equivalent upon reacting with an amine.

[0191] As used herein, “alkyl”, “C₁, C₂, C₃, C₄, C₅ or C₆ alkyl” or “C₁-C₆ alkyl” is intended to include C₁, C₂, C₃, C₄, C₅ or C₆ straight chain (linear) saturated aliphatic hydrocarbon groups and C₃, C₄, C₅ or C₆ branched saturated aliphatic hydrocarbon groups. For example, C₁-C₆ alkyl is intended to include C₁, C₂, C₃, C₄, C₅ and C₆ alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C₁-C₆ for straight chain, C₃-C₆ for branched chain). In some embodiments, a straight chain or branched alkyl has four or fewer carbon atoms.

[0192] 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).

[0193] 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.

[0194] 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.

[0195] 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.

[0196] It is to be understood that a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof 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

[0197] 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.

[0198] It is to be understood that, unless otherwise stated, any description of a method of treatment or prevention includes use of a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a

pharmaceutically acceptable salt thereof 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 a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof to prepare a medicament to treat or prevent such condition. The treatment or prevention includes treatment or prevention of human or non-human animals including rodents and other disease models.

[0199] It is to be understood that, unless otherwise stated, any description of a method of treatment includes use of a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof 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 a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof to prepare a medicament to treat such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[0200] 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.

[0201] 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.

[0202] 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.

[0203] It is to be understood that a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

[0204] As used herein, the term “preventing,” “prevent,” or “protecting against” describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0205] 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.

[0206] As used herein, the term “pharmaceutical composition” is a formulation containing a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof 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, 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.

[0207] 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.

[0208] 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.

[0209] 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, 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.

[0210] 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.

[0211] 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.

[0212] 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.

[0213] 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.

[0214] 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.

[0215] The pharmaceutical compositions containing a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof 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 a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof into preparations that can be used pharmaceutically. The appropriate formulation is dependent upon the route of administration chosen.

[0216] The compound of Formula (IX) (e.g., Compound No. 9a or 9b) or the pharmaceutically acceptable salt thereof can be prepared with one or more pharmaceutically acceptable carrier that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including an implant and microencapsulated delivery system.

[0217] It is to be understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0218] 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.

[0219] 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, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic,

lactobionic, lauryl sulphonc, maleic, malic, mandelic, methane sulphonc, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulphamic, sulphanilic, sulphuric, tannic, tartaric, toluene sulphonc, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0220] 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.

[0221] 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.

[0222] 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.

[0223] 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, a compound of Formula (IX) (*e.g.*, Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof, is used in pharmaceutical preparations in combination with one or more pharmaceutically acceptable carrier 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.

[0224] 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.

[0225] 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.

[0226] 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.

[0227] The disclosure having been described, the following examples are offered by way of illustration and not limitation.

EXEMPLARY EMBODIMENTS

[0228] **Exemplary Embodiment 1.** A method of preparing a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof, comprising one or more of steps (i)-(vii):

(i) contacting Compound No. 1 or a salt thereof, with a hydrogenation agent, thereby forming Compound No. 2 or a salt thereof;

(ii) contacting Compound No. 3, with an esterification agent, thereby forming a compound of Formula (IV);

(iii) contacting Compound No. 2 or the salt thereof, with the compound of Formula (IV), thereby forming a compound of Formula (V) or a salt thereof;

(iv) contacting the compound of Formula (V) or the salt thereof, with a reducing agent, thereby forming a compound of Formula (VI) or a salt thereof;

(v) contacting Compound No. 7 or a salt thereof, with an CO-generating agent, thereby forming Compound No. 8 or a salt thereof;

(vi) contacting the compound of Formula (VI) or the salt thereof, with Compound No. 8 or the salt thereof, thereby forming a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof; or

(vii) purifying the compound of Formula (IX) or the salt thereof.

[0229] **Exemplary Embodiment 2.** A method of preparing a compound of Formula (V) or a salt thereof, comprising:

(iii) contacting Compound No. 2 or a salt thereof, with a compound of Formula (IV), thereby forming a compound of Formula (V) or a salt thereof.

[0230] **Exemplary Embodiment 3.** A method of preparing a compound of Formula (VI) or a salt thereof, comprising:

(iv) contacting a compound of Formula (V) or a salt thereof, with a reducing agent, thereby forming a compound of Formula (VI) or a salt thereof.

[0231] **Exemplary Embodiment 4.** The method of any one of the preceding Exemplary Embodiments, wherein the compound of Formula (IV) is Compound No. 4.

[0232] **Exemplary Embodiment 5.** The method of any one of the preceding Exemplary Embodiments, wherein the compound of Formula (V) or the salt thereof is Compound No. 5 or a salt thereof.

[0233] **Exemplary Embodiment 6.** The method of any one of the preceding Exemplary Embodiments, wherein the compound of Formula (VI) or the salt thereof is Compound No. 6 or a salt thereof.

[0234] **Exemplary Embodiment 7.** The method of any one of the preceding Exemplary Embodiments, wherein the compound of Formula (VI) or the salt thereof is a compound of Formula (VI-a) or a salt thereof;

optionally, wherein the compound of Formula (VI) or the salt thereof is Compound No. 6a or a salt thereof.

[0235] **Exemplary Embodiment 8.** The method of any one of the preceding Exemplary Embodiments, wherein the compound of Formula (VI) or the salt thereof is a compound of Formula (VI-b) or a salt thereof;

optionally, wherein the compound of Formula (VI) or the salt thereof is Compound No. 6b or a salt thereof.

[0236] **Exemplary Embodiment 9.** The method of any one of the preceding Exemplary Embodiments, wherein the compound of Formula (IX) or the salt thereof is Compound No. 9.

[0237] **Exemplary Embodiment 10.** The method of any one of the preceding Exemplary Embodiments, wherein the compound of Formula (IX) or the salt thereof is a compound of Formula (IX-a) or a salt thereof;

optionally, wherein the compound of Formula (IX) or the salt thereof is Compound No. 9a or a salt thereof.

[0238] **Exemplary Embodiment 11.** The method of any one of the preceding Exemplary Embodiments, wherein the compound of Formula (IX) or the salt thereof is a compound of Formula (IX-b) or a salt thereof;

optionally, wherein the compound of Formula (IX) or the salt thereof is Compound No. 9b or a salt thereof.

[0239] **Exemplary Embodiment 12.** The method of any one of the preceding Exemplary Embodiments, wherein in step (i), the hydrogenation agent is hydrogen.

[0240] **Exemplary Embodiment 13.** The method of any one of the preceding Exemplary Embodiments, wherein in step (i), the contacting is performed in the presence of a hydrogenation catalyst;

optionally, wherein the hydrogenation catalyst is Raney nickel.

[0241] **Exemplary Embodiment 14.** The method of any one of the preceding Exemplary Embodiments, wherein in step (i), the contacting is performed in the presence of a base;

optionally, wherein the base is potassium carbonate (K_2CO_3).

[0242] **Exemplary Embodiment 15.** The method of any one of the preceding Exemplary Embodiments, wherein Compound No. 2 or the salt thereof is isolated and/or purified prior to contacting with the compound of Formula (IV).

[0243] **Exemplary Embodiment 16.** The method of any one of the preceding Exemplary Embodiments, wherein Compound No. 2 or the salt thereof is not isolated or purified prior to contacting with the compound of Formula (IV).

[0244] **Exemplary Embodiment 17.** The method of any one of the preceding Exemplary Embodiments, wherein in step (ii), the esterification agent is an alcohol;

optionally, wherein the esterification agent is isopropanol (iPrOH; propan-2-ol).

[0245] **Exemplary Embodiment 18.** The method of any one of the preceding Exemplary Embodiments, wherein in step (ii), the contacting is performed in the presence of an esterification catalyst;

optionally, wherein the esterification catalyst is 4-dimethylaminopyridine (DMAP).

[0246] **Exemplary Embodiment 19.** The method of any one of the preceding Exemplary Embodiments, wherein in step (ii), the contacting is performed in the presence of a base;

optionally, wherein the base is pyridine.

[0247] **Exemplary Embodiment 20.** The method of any one of the preceding Exemplary Embodiments, wherein in step (iii), the contacting is performed in the presence of a salt;

optionally, wherein the salt is potassium tert-butoxide (tBuOK).

[0248] **Exemplary Embodiment 21.** The method of any one of the preceding Exemplary Embodiments, wherein in step (iii), the contacting is performed in the presence of an alcohol;

optionally, wherein the alcohol is isopropanol (iPrOH; propan-2-ol).

[0249] **Exemplary Embodiment 22.** The method of any one of the preceding Exemplary Embodiments, wherein in step (iv), the reducing agent is a monosaccharide;

optionally, wherein the reducing agent is glucose; and

optionally, wherein the reducing agent is D-glucose.

[0250] **Exemplary Embodiment 23.** The method of any one of the preceding Exemplary Embodiments, wherein in step (iv), the contacting is performed in the presence of a reduction catalyst;

optionally, wherein the reduction catalyst comprises ketoreductase (KRED), glutamate dehydrogenase (GDH), and nicotinamide adenine dinucleotide phosphate (NADP).

[0251] **Exemplary Embodiment 24.** The method of any one of the preceding Exemplary Embodiments, wherein in step (v), the CO-generating agent is triphosgene.

[0252] **Exemplary Embodiment 25.** The method of any one of the preceding Exemplary Embodiments, wherein in step (v), the contacting is performed in the presence of a base;

optionally, wherein the base is triethylamine (TEA).

[0253] **Exemplary Embodiment 26.** The method of any one of the preceding Exemplary Embodiments, wherein in step (vi), the contacting is performed in the presence of a base;

optionally, wherein the base is 4-dimethylaminopyridine (DMAP).

[0254] **Exemplary Embodiment 27.** The method of any one of the preceding Exemplary Embodiments, wherein step (vii) comprises crystalizing the compound of Formula (IX) or the salt thereof in the presence of an organic solvent;

optionally, wherein the organic solvent comprises isopropyl acetate and n-heptane; and

optionally, wherein the isopropyl acetate and n-heptane are present at a ratio of about 1:1, about 1:2, about 1:3, about 1:4, or about 1:5.

[0255] **Exemplary Embodiment 28.** A compound being prepared by the method of any one of the preceding Exemplary Embodiments.

[0256] **Exemplary Embodiment 29.** A compound of Formula (V) or a salt thereof;

optionally, wherein the compound is Compound No. 5 or a salt thereof; and

optionally, wherein the compound is Compound No. 5 or the 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.

[0257] **Exemplary Embodiment 30.** A compound of Formula (VI) or a salt thereof;

optionally, wherein the compound is Compound No. 6 or a salt thereof;

optionally, wherein the compound is Compound No. 6a or a salt thereof; and

optionally, wherein the compound is Compound No. 6a or a salt thereof 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.

[0258] **Exemplary Embodiment 31.** A compound of Formula (IX) or a salt thereof;

optionally, wherein the compound is Compound No. 9 or a salt thereof;

optionally, wherein the compound is Compound No. 9a or a salt thereof; and

optionally, wherein the compound is Compound No. 9a or a salt thereof 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.

[0259] **Exemplary Embodiment 32.** A pharmaceutical composition comprising the compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding Exemplary Embodiments, and one or more pharmaceutically acceptable carrier or excipient.

[0260] **Exemplary Embodiment 33.** A method of preventing or treating a disease in a subject, comprising administering to the subject the compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding Exemplary Embodiments.

[0261] **Exemplary Embodiment 34.** The compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding Exemplary Embodiments for use in preventing or treating a disease in a subject.

[0262] **Exemplary Embodiment 35.** Use of the compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding Exemplary Embodiments in the manufacture of a medicament for preventing or treating a disease in a subject.

[0263] **Exemplary Embodiment 36.** A method of inhibiting inflammasome activity in a subject, comprising contacting a cell with the compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding Exemplary Embodiments.

[0264] **Exemplary Embodiment 37.** The compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding Exemplary Embodiments for use in inhibiting inflammasome activity in a subject.

[0265] **Exemplary Embodiment 38.** Use of the compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding Exemplary Embodiments in the manufacture of a medicament for inhibiting inflammasome activity.

[0266] **Exemplary Embodiment 39.** The method, compound, or use of any one of the preceding Exemplary Embodiments, wherein the subject is a human.

EXAMPLES

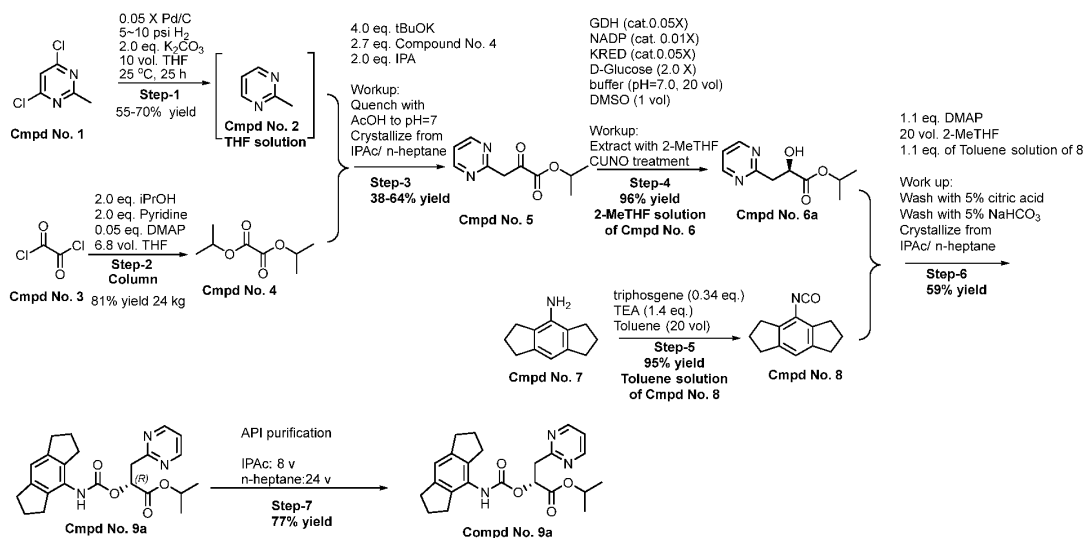
[0267] The disclosure having been described, the following examples are offered by way of illustration and not limitation.

[0268] 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. 9a.

[0269] An exemplary synthesis of Compound No. 9a was performed following the following synthetic scheme and procedures.

Scheme 1



Step 1

[0270] Step 1 was performed using the equipment described in Table 1A and following the procedures described in Table 1B.

Table 1A. Equipment Used in Step 1.

Equip. Name	Equip. Code	Equip. Standard
Reactor	R1	SS/500 L
Diaphragm pump	P1	SS
	P2	SS
	P3	SS
Filter press	F1	SS/Ti
Cartridge filter	Ft1	SS/Ti
Pd/C vessel	X1	SS
Solid feed charger	XL1	SS
Tank	H1	GL

Table 1B. Exemplary Procedures of Step 1.

Charge 10% Pd/C into the solid feed tank of X1 under nitrogen protection
Turn on the process water, rinse the solid tank for at least 5 min, filter the washing water to sewer
Set the jacket temperature of R1 to 20 °C
Check oxygen content.
Charge THF into H1
Charge process water into H1
Charge Compound No. 1 in portions into H1
Charge K ₂ CO ₃ in portions into H1
Stirring H1 for 10-20 min
Charge material in H1 into R1
Charge THF into H1
Adjust R1 batch temperature to 20-30 °C
Charge THF into the solvent feed tank
Transfer the solvent from the solvent feed tank to the solid feed tank and transfer the mixture from the solid feed tank to R1
Charge THF into the solvent feed tank
Transfer the solvent from the solvent feed tank to the solid feed tank and transfer the mixture from the solid feed tank to R1
Charge THF into the solvent feed tank
Transfer the solvent from the solvent feed tank to the solid feed tank and transfer the mixture from the solid feed tank to R1
Stir R1 for 10-20 min
Charge process water into R1
Stir R1 for 10-20 min
Execute the hydrogenation procedure. Increase pressure of hydrogen to 0.03-0.07 MPa
Adjust R1 batch temperature to 20-30 °C
Keep the pressure in R1 at 0.03-0.07 MPa and the temperature at 20-30 °C. Stirring R1 for 5-24 h; check for reaction completion
If complete, adjust R1 batch temperature to 15-25 °C
If not complete, execute further hydrogenation procedure. Increase pressure of hydrogen to 0.03-0.07 MPa
Adjust R1 batch temperature to 20-30 °C
Keep the pressure in R1 at 0.03-0.07 MPa and the temperature at 20-30 °C. Stirring R1 for 1-12 h; check for reaction completion
Adjust R1 batch temperature to 15-25 °C
Blow nitrogen for 5-10 min
Spread two filter clothes into F1
Charge diatomite into F1
Charge MgSO ₄ into F1
Spread a filter cloth on the diatomite and MgSO ₄ as buffer
Charge THF to F1 to moisten the diatomite
Press solvent of F1 out to metal drum flowed by nitrogen, discard the filtrate
Press R1 material by nitrogen from F1, Ft1 to steel-plastic composite drum in portions
Charge THF into R1

Press R1 material by nitrogen from F1, Ft1 to steel-plastic composite drum in portions
Load the filtrate into the steel-plastic drum flowed by nitrogen
Wash H1 with THF

[0271] The product of the step was assessed using the chromatographic conditions shown in Table 1C, and the results are summarized in Table 1D.

Table 1C. Chromatographic Conditions for Assessing Product of Step 1.

Column	DB-624 (30 m×0.32 mm ID×1.8μm, P/N: 123-1334)		
Carrier Gas	N ₂		
Detector	FID		
Detector Temperature	260°C		
Makeup (N ₂) Flow	30 mL/min		
H ₂ Flow	40 mL/min		
Air Flow	400 mL/min		
Control mode	Agilent: Constant Flow		
Flow rate	2.0 mL/min		
Column Temperature Program	Rate (°C/min)	°C	Hold Time (min)
		40	3
	15	240	15
Injector Temperature	220°C		
Split Ratio	10:1		
Diluent	THF		
Needle Wash Solvent	THF		
Run Time	31.3 min		
Inject volume	1 μL		

Table 1D. Assessment of the Products of Step 1.

Batch No	Starting Material	Product				Yield
	Weight (kg)	Gross Wt	Purity (GC)		Assay (GC)	
			Cmpd. No. 2	Impurity		
1	9.90 kg	Filtrate: 69.8 kg Rinse solution: 82.4 kg	86.2% 84.8%	12.2% 13.6%	4.0% 1.2%	66%
2	10.06 kg	Filtrate: 66.8 kg Rinse solution: 84.0 kg	99.2% 88.2%	N.D. 11.5%	4.1% 1.3%	66%
3	9.90 kg	Filtrate: 70.8 kg Rinse solution: 81.2 kg	96.7% 94.1%	3.1% 5.7%	4.7% 0.8%	70%
4	9.66 kg	Filtrate: 74.0 kg Rinse solution: 81.6 kg	82.0% 70.4%	18.0% 29.6%	3.3% 0.8%	55%

Step 2

[0272] Step 2 was performed using the equipment described in Table 2A and following the procedures described in Table 2B.

Table 2A. Equipment Used in Step 2.

Equip. Name	Equip. Code	Equip. Standard
Reactor	R1	GL/2000 L
Diaphragm pump	P1	SS
	P2	SS
	P3	PP/PTFE
	P4	SS
Glove box	XL1	SS
Filter	F1	SS/HL
	Ft1	SS/HL
Vessel	V1	GL
Tank	T1	HDPE
	T2	HDPE
	T3	HDPE
	T4	HDPE
	T5	SS

Table 2B. Exemplary Procedures of Step 2.

Charge 7% NaHCO ₃ (300 kg 3.8 X) into process water (300 kg 3.8 X) to prepare 3.5% NaHCO ₃ solution
Charge THF (250 kg 3.2 X) into R1
Suck pyridine (98 kg 1.26 X) into R1
Suck THF (10 kg) into R1 to rinse pipe
Charge IPA (94 kg 1.21 X) into R1
Charge DMAP (3.9 kg 0.05 X) in portions into R1
Charge THF (254 kg 3.3 X) into R1
Adjust temperature of R1 to -5-5 °C
Suck Compound No. 3 (78 kg 1.00 X) into R1 over 2 h at -5-15 °C
Suck THF (18 kg) into R1 to rinse pipe at -5-15 °C
Adjust temperature of R1 to 20-30 °C
Stir R1 at 20-30 °C for 12-16 h
Adjust temperature of R1 to 5-15 °C
Charge process water (392 kg 5.0 X) into R1 below 25 °C
Adjust temperature of R1 to 15-25 °C
Stir R1 at 15-25 °C for 30-45 min
Settle the batch in R1 at batch temperature 15-25 °C for 30-45 min
Transfer the bottom aqueous phase of R1 to T1/T2
Transfer the organic layer of R1 to new steel and plastic composite drums
Charge all Compound No. 4 aqueous layer (608 kg) into R1
Charge n-heptane (172 kg 2.2 X) into R1
Adjust temperature of R1 to 15-25 °C
Stir R1 at 15-25 °C for 30-60 min

Settle the batch in R1 at batch temperature 15-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to T1/T2
Transfer the organic layer of R1 to new steel and plastic composite drums
Charge all Compound No. 4 aqueous layer (548 kg) into R1
Charge n-heptane (170 kg 2.2 X) into R1
Adjust temperature of R1 to 15-25 °C with batch temperature
Stir R1 at 15-25 °C for 30-60 min
Settle the batch in R1 at batch temperature 15-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to T1/T2
Charge all Compound No. 4 organic layer (806.5 kg) into R1
Charge 3.5% NaHCO ₃ aqueous solution (281 kg 4 X) into R1
Adjust temperature of R1 to 15-25 °C
Stir R1 at 15-25 °C for 30-45 min
Settle the batch in R1 at batch temperature 15-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to T3
Charge 3.5% NaHCO ₃ aqueous solution (281 kg 4 X) into R1
Adjust temperature of R1 to 15-25 °C
Stir R1 at 15-25 °C for 30-60 min
Settle the batch in R1 at batch temperature 15-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to T3
Charge 25% NaCl aqueous solution (236 kg 3.0 X) into R1
Adjust temperature of R1 to 15-25 °C
Stir R1 at 15-25 °C for 30-60 min
Settle the batch in R1 at batch temperature 15-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to T4
Charge 25% NaCl aqueous solution (236 kg 3.0 X) into R1
Adjust temperature of R1 to 15-25 °C
Stir R1 at 15-25 °C for 30-60 min
Settle the batch in R1 at batch temperature 15-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to T4
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of $\leq$ 55 °C, to a volume of 1.0-1.5 X
Adjust temperature of R1 to 20-35 °C
Charge n-heptane (125 kg 1.6 X) into R1
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of $\leq$ 55 °C, to a volume of 1.0-1.5 X
Adjust temperature of R1 to 20-35 °C
Charge n-heptane (218 kg 2.8 X) into R1
Adjust temperature of R1 to 20-35 °C
Stir R1 at 20-35 °C for 0.1-0.5 h
Spread two filter clothes into F1
Charge silica gel (20 kg 0.3 X) into F1
Spread a filter cloth on silica gel to buffer
Charge n-heptane (40 kg) into F1
Press R1 material by nitrogen from F1, Ft1 to T5
Charge n-heptane (238 kg 3.1 X) into R1

Press R1 material by nitrogen from F1, Ft1 to T5
Charge n-heptane (243 kg 3.1 X) into R1
Press R1 material by nitrogen from F1, Ft1 to T5
Charge Compound No. 4 n-heptane solution (798 kg) into R1
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of $\leq 55^{\circ}\text{C}$, to a volume of 1.0-1.5 X
Adjust temperature of R1 to 20-35 $^{\circ}\text{C}$
Charge THF (350 kg 4.5 X) into R1
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of $\leq 55^{\circ}\text{C}$, to a volume of 1.0-1.5 X
Adjust temperature of R1 to 20-35 $^{\circ}\text{C}$
Charge THF (346 kg 4.4 X) into R1
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of $\leq 55^{\circ}\text{C}$, to a volume of 1.0-1.5 X
Adjust R1 to 20-35 $^{\circ}\text{C}$ with batch temperature
Transfer R1 material into new steel and plastic composite drum
Charge THF (23 kg 0.3 X) into R1
Transfer R1 material into new steel and plastic composite drum
Weigh the gross of loaded steel and plastic composite drum calculate the net weight (Compound No. 4, total net = 115.6 kg)
Transfer the Compound No. 4 THF solution and store at ambient conditions
Charge process water (39 kg) to F1
Press solvent of F1 out to plastic drum flowed by nitrogen, discard the filtrate
Load F1 wet cake into fiber drum lined with PE bag

[0273] The product of the step was assessed using the chromatographic conditions shown in Table 2C, and the results are summarized in Table 2D.

Table 2C. Chromatographic Conditions for Assessing Product of Step 2.

Column	Waters Xbridge C18, 4.6 x 150 mm, 3.5 µm, PN: 186003034		
Wavelength	210 nm		
Reference Wavelength	Off		
Column Temperature	20°C		
Flow Rate	1.0 mL/min		
Injector Volume	5 µL		
Needle Wash	ACN		
Mobile Phase A	10 mM CH ₃ COONH ₄ in water		
Mobile Phase B	ACN		
Gradient Program	Time (min)	A%	B%
	Initial	95	5
	10.00	20	80
	13.00	20	80
	14.00	95	5
	19.00	95	5
Run Time	19 min		
Data Acquisition Time	19 min		

Table 2D. Assessment of the Products of Step 2.

Batch No	Starting Material	Product			Yield
	Weight (kg)	Gross Wt	Purity (HPLC)	Assay (HPLC)	
1	78.2 kg	115.6 kg	98%	74.9%	81%

Step 3

[0274] Step 3 was performed using the equipment described in Table 3A and following the procedures described in Table 3B.

Table 3A. Equipment Used in Step 3.

Equip. Name	Equip. Code	Equip. Standard
Reactor	R1	SS/500 L
Diaphragm pump	P1	SS
	P2	SS
	P3	SS
	P4	SS
Glove box	XL1	SS
	XL2	SS
	XL3	SS
Centrifuge	M1	SS
	M2	SS
Mother liquid tank	MV1	GL
	MV2	GL

Equip. Name	Equip. Code	Equip. Standard
Dryer	D1	SS
Bag filter	Fb1	SS/HL shell, PTFE bag
Pipe filter	Ft1	GL SS/HL shell, PTFE core

Table 3B. Exemplary Procedures of Step 3.

Batch No. 1	Batch No. 2
Charge Compound No. 2 THF solution (7.4 kg 1.00 X) into R1	Charge Compound No. 2 THF solution (6.9 kg 0.99 X) into R1
Adjust R1 to -10-5 °C with batch temperature	Adjust R1 to -10-5 °C with batch temperature
Charge Compound No. 4 THF solution (44.3 kg 5.9 X) in portions into R1	Charge Compound No. 4 THF solution (42.0 kg 6.0 X) in portions into R1
Suck IPA (10.0 kg 1.33 X) into R1	Suck IPA (9.5 kg 1.36 X) into R1
Control batch temperature at -10-5 °C and stir for 9-30 min	Control batch temperature at -10-5 °C and stir for 9-30 min
Charge t-BuOK (39.0 kg 5.2 X) in portions into R1 -10-5 °C batch temperature	Charge t-BuOK (36 kg 5.1 X) in portions into R1 -10-5 °C batch temperature
Adjust temperature of R1 to 10-20 °C	Adjust temperature of R1 to 10-20 °C
Control batch temperature at 10-20 °C and stir for 8-18 h	Control batch temperature at 10-20 °C and stir for 8-18 h
Adjust temperature of R1 to 0-10 °C	Adjust temperature of R1 to 0-10 °C
Charge AcOH (16.4 kg 2.2 X) slowly into R1 at batch temperature 0-15 °C, adjust pH = 6-7	Charge AcOH (15.8 kg 2.3 X) slowly into R1 at batch temperature 0-15 °C, adjust pH = 6-7
Adjust temperature of R1 to 10-25 °C	Adjust temperature of R1 to 10-25 °C
Control batch temperature at 10-25 °C and stir for 0.5-2 h	Control batch temperature at 10-25 °C and stir for 0.5-2 h
Spread a centrifuge bag on the centrifuge	Spread a centrifuge bag on the centrifuge
The 1 st centrifuge	The 1 st centrifuge
Charge THF (78 kg 10 X) into the centrifuge (the last load of solvent is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into the mother liquor receiver	Charge THF (80 kg 11 X) into the centrifuge (the last load of solvent is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into the mother liquor receiver
The 2 nd centrifuge	The 2 nd centrifuge
Charge THF (84 kg 11 X) into the centrifuge (the last load is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into the mother liquor receiver	Charge THF (82 kg 12 X) into the centrifuge (the last load is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into the mother liquor receiver
Load solid of the centrifuge into fiber drum/ton bag lined with double PE bags	Load solid of the centrifuge into fiber drum/ton bag lined with double PE bags
Charge THF (72 kg) into R1	Charge THF (88 kg) into R1
Charge all Compound No. 5 first wet cake into R1	Charge all Compound No. 5 first wet cake into R1
Charge THF (90 kg) into R1	Charge THF (81 kg) into R1

Batch No. 1	Batch No. 2
Adjust temperature of R1 to 10-25 °C	Adjust temperature of R1 to 10-25 °C
Control batch temperature at 10-25 °C and stir for 0.5-2 h	Control batch temperature at 10-25 °C and stir for 0.5-2 h
Spread a centrifuge bag on the centrifuge	Spread a centrifuge bag on the centrifuge
The 1 st centrifuge	The 1 st centrifuge
Charge THF (80 kg 11 X) into the centrifuge (the last load of solvent is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into the mother liquor receiver (MV1)	Charge THF (80 kg 11 X) into the centrifuge (the last load of solvent is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into the mother liquor receiver
The last load	The last load
Charge THF (121 kg 16.1 X) into the centrifuge (the last load of solvent is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into the mother liquor receiver (MV1)	Charge THF (82 kg 11.7 X) into the centrifuge (the last load of solvent is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into the mother liquor receiver
Load solid of the centrifuge into fiber drum/ton bag lined with double PE bags	Load solid of the centrifuge into fiber drum/ton bag lined with double PE bags
Wash R1 with process water (60 kg)	Wash R1 with process water (200 kg)
Wash R1 with THF (362 kg)	Wash R1 with THF (302 kg)
Centrifuge the mother liquor from MV1 to MV2	
Rinse MV1 with THF (142 kg) and centrifuge from MV1 to MV2	
Load solid of the centrifuge into fiber drum/ton bag lined with double PE bags	
Charge mother liquid from MV2 into R1	Charge mother liquid from MV1 into R1
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 1-3 X	Concentrate the contents of R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 1-3 X
Charge mother liquid from MV2 into R1	
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 1-3 X	
Rinse MV2 with THF (24 kg) and transfer the rinse solution into R1	Rinse MV1 with THF (46 kg) and transfer the rinse solution into R1
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 1-3 X	Concentrate the contents of R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 1-3 X
Load the material in R1 into SS-plastic composite drums inerted by nitrogen	
Charge THF (21 kg 2.8 X) into R1	Charge THF (4 kg 0.6 X) into R1
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 1-3 X	Concentrate the contents of R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 1-3 X
Load the material in R1 into SS-plastic	Load the material in R1 into SS-plastic

Batch No. 1	Batch No. 2
composite drums inerted by nitrogen	composite drums inerted by nitrogen
Adjust R1 batch temperature to 10-20 °C	Adjust R1 batch temperature to 10-20 °C
Concentrate the contents of R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 1-3 X	
Load the material in R1 into SS-plastic composite drums inerted by nitrogen	
Adjust R1 batch temperature to 10-20 °C	
Charge n-heptane (30 kg 4 X) into R1	Charge n-heptane (26 kg 4 X) into R1
Adjust R1 batch temperature to -5-10 °C over 2-4 h	Adjust R1 batch temperature to -5-10 °C over 4 h
Charge seed (0.07 kg 0.004 X) into R1 at -5-10 °C	Charge seed (0.068 kg 0.004 X) into R1 at -5-10 °C
Stir R1 solution to mix well at batch temperature -5-10 °C for 1-3 h	Stir R1 solution to mix well at batch temperature -5-10 °C for 1-3 h
Charge n-heptane (48 kg 6 X) into R1	Charge n-heptane (42 kg 6 X) into R1
Stir R1 solution to mix well at batch temperature -5-10 °C for 1-5 h	Stir R1 solution to mix well at batch temperature -5-10 °C for 1-5 h
The 1 st load	The 1 st load
Charge n-heptane (22 kg 2.9 X) into the centrifuge (the last load is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into MV2	Charge n-heptane (20 kg 2.9 X) into the centrifuge (the last load is used to rinse the reactor firstly) to rinse wet cake, and transfer the mother liquor into MV1
Load solid of the centrifuge into fiber drum lined with double PE bags	Load solid of the centrifuge into fiber drum lined with double PE bags
Transfer mother liquor into new steel and plastic composite drum from the mother liquor receiver	Transfer mother liquor into new steel and plastic composite drum from the mother liquor receiver
Charge process water (37 kg 4.9 X) into R1	Charge process water (34 kg 4.9 X) into R1
Adjust R1 batch temperature to 10-25 °C	Adjust R1 batch temperature to 10-25 °C
Charge wet cake of H into R1	Charge wet cake of H into R1
Charge process water (72 kg 9.6 X) into R1	Charge process water (68 kg 9.7 X) into R1
Adjust R1 batch temperature to 10-25 °C	Adjust R1 batch temperature to 10-25 °C
Control batch temperature at 10-25 °C and stir for 0.5-3 h	Control batch temperature at 10-25 °C and stir for 0.5-3 h
Transfer to centrifuge	Transfer to centrifuge
Charge process water (58 kg 7.7 X) into the centrifuge (the process water is used to rinse the reactor firstly) to rinse wet cake and transfer the mother liquor into the mother liquor receiver	Charge process water (20 kg 2.9 X) into the centrifuge (the process water is used to rinse the reactor firstly) to rinse wet cake and transfer the mother liquor into the mother liquor receiver
Load solid of the centrifuge into fiber drum lined with double PE bags	Load solid of the centrifuge into fiber drum lined with double PE bags
Transfer mother liquor into new steel and plastic composite drum from the mother liquor receiver	Transfer mother liquor into new steel and plastic composite drum from the mother liquor receiver

Batch No. 1	Batch No. 2
Put H wet cake into drying bag, then put the bag into the layer	Put H wet cake into drying bag, then put the bag into the layer
Adjust the jacket temperature of the dryer to 25-35 °C	Adjust the jacket temperature of the dryer to 25-35 °C
Dry the dryer under reduced pressure at 25-45 °C jacket temperature for 16-24 h	Dry the dryer under reduced pressure at 25-45 °C jacket temperature for 16-24 h
Adjust the dryer jacket temperature to below 35 °C	Adjust the dryer jacket temperature to below 35 °C
Hold for 30 min under nitrogen protection	Hold for 30 min under nitrogen protection
Weigh the prepared double layer of LDPE bags including two cable ties and fiber drum. Pack D1 material into the PE bags (Compound No. 5, total net = 10.95 kg)	Weigh the prepared double layer of LDPE bags including two cable ties and fiber drum. Pack D1 material into the fiber drums (Compound No. 5, total net = 6.15 kg)

[0275] The product of the step was assessed using the chromatographic conditions shown in Table 3C, and the results are summarized in Table 3D.

Table 3C. Chromatographic Conditions for Assessing Product of Step 3.

Column	Waters Xbridge Amide column, 4.6 × 150 mm, 3.5 μm, PN:186004869		
Wavelength	210 nm		
Reference Wavelength	Off (This parameter is only applicable to Agilent and Thermo instruments)		
Column Temperature	20°C		
Flow Rate	1.0 mL/min		
Injection Volume	5 μL		
Needle Wash	ACN: Water = 10:20 (v/v)		
Mobile Phase A	5mM NH ₄ OAc in water (adjust pH to 9.0 with ammonia solution), w/v		
Mobile Phase B	ACN		
Gradient Program	Time (min)	A%	B%
	Initial	20	80
	10.0	40	60
	13.0	40	60
	14.0	20	80
	19.0	20	80
Data Acquisition Time	19 min		
Pump Run Time	19 min		

Table 3D. Assessment of the Products of Step 3.

Batch No	Starting Material	Product			Yield
	Weight (kg, corrected by assay)	Gross Wt	Purity (HPLC)	Assay (HPLC)	
1	7.4 kg	10.95 kg	99.4%	96.2%	64%
2	6.9 kg	6.15 kg	98.3%	93.3%	38%

Step 4

[0276] Step 4 was performed using the equipment described in Table 4A and following the procedures described in Table 4B.

Table 4A. Equipment Used in Step 4.

Equip. Name	Equip. Code	Equip. Standard
Reactor	R1	GL/1000 L
	R2	GL/1000 L
	R3	GL/1000 L
Diaphragm pump	P1	SS
	P2	SS
	P3	SS
	P4	SS
	P5	SS
	P6	PTFE
	P7	SS
Solid feed charger	P8	SS
	XL1	SS
	XL3	SS
	XL4	SS
Glove box	XL5	SS
	XL2	SS
Filter	F1	SS
Chromatographic column	F2	SS
CUNO	Ft2	SS
	Ft3	SS
Pipe filter	Ft1	SS
	Ft4	SS
Tank	T1	SS
	T2	SS
	T3	SS
	T4	SS
	T5	SS

Equip. Name	Equip. Code	Equip. Standard
Vessel	V1	GL
Inline PH	C1	SS

Table 4B. Exemplary Procedures of Step 4.

Charge KOH (24.75 kg 1.46 X) into purified water (106 kg + 116 kg 13.1 X) to prepare 2M KOH solution
Charge 35% HCl (18 kg 1.1 X) into purified water (48 kg + 47 kg 5.6 X) to prepare 2M HCl solution
Charge purified water (176 kg 10 X) into R1
Charge anhydrous K ₂ HPO ₄ (7.2 kg 0.4235 X) in portions into R1
Charge KH ₂ PO ₄ (3.7 kg 0.2176 X) in portions into R1
Charge purified water (176 kg 10 X) into R1
Adjust temperature of R1 to 20-30 °C
Control batch temperature at 20-30 °C and stir it to clear
Charge D-glucose (34.9 kg 2.05 X) in portions into R1
Charge GDH (0.9 kg 0.053 X) in portions into R1
Adjust R1 to 20-30 °C with batch temperature by adjusting the jacket temperature
Control batch temperature at 20-30 °C and stir it to clear
Charge triphosphopyridine nucleotide (0.18 kg 0.011 X) in portions into R1
Charge ketoreductase (KRED; 0.86 kg 0.05 X) in portions into R1
Adjust temperature of R1 to 20-30 °C by adjusting the jacket temperature
Control batch temperature at 20-30 °C and stir for 30-60 min
Charge DMSO (18.4 kg 1.1 X) into R1
Charge Compound No. 5 (16.9 kg 0.99 X) in portions into R1 and keep pH = 6.5-7.1 at 20-30 °C
Charge purified water (18 kg) into R1
Charge 2M KOH aq. (34.00 kg) into R1 via head tank to keep pH = 6.5-7.1
Control batch temperature at 20-30 °C, stir for 3-12 h and keep pH = 6.5-7.1
Charge 2M KOH aq. (11.85 kg) into R1 via head tank to keep pH = 6.5-7.1
Charge 2M HCl aq. (38.40 kg) into R1 via head tank to keep pH = 4.5-5.5
Charge NaCl (45 kg 2.6 X) in portions into R1
Charge 2-MeTHF (150 kg 8.8 X) into R1
Adjust temperature of R1 to 20-30 °C by adjusting the jacket temperature
Control batch temperature at 20-30 °C and stir for 0.5-1 h
Spread two filter cloths into F1
Charge diatomite (34 kg 2 X) into F1
Spread a filter cloth on the diatomite to receive
Charge 2-MeTHF (20 kg) to F1 to rinse the diatomite
Press solvent of F1 out to galvanized steel drums flowed by nitrogen, discard the filtrate
Transfer the material in R1 into T5
Charge 2-MeTHF (146 kg 8.6 X) into R1
Transfer the material in R1 into T5
Load F1 wet cake into fiber drum lined with PE bag
Wash R1 with process water

Charge Compound No. 6a filter solution (836 kg) into R1
Adjust temperature of R1 to 20-30 °C by adjusting the jacket temperature
Stir R1 at 20-30 °C for 30-60 min
Allow R1 to stand for 30-60 min
Transfer R1 aqueous phase into T1
Keep the flow of nitrogen more than 6 m ³ /h and blow the T2 with nitrogen for more than 20 min
Transfer the organic phase of R1 to T2
Charge Compound No. 6a aqueous layer into R1
Charge 2-MeTHF (148 kg 8.7 X) into R1
Adjust temperature of R1 to 20-30 °C by adjusting the jacket temperature
Stir R1 at 20-30 °C for 30-60 min
Allow R1 to stand for 30-60 min at batch temperature 20-30 °C
Keep the flow of nitrogen more than 6 m ³ /h and blow the T1 with nitrogen for more than 20 min
Transfer the aqueous phase of R1 to T1
Keep the flow of nitrogen more than 6 m ³ /h and blow the T2 with nitrogen for more than 20 min
Transfer the aqueous phase of R1 to T2
Charge Compound No. 6a aqueous layer into R1
Charge 2-MeTHF (148 kg 8.7 X) into R1
Adjust temperature of R1 to 20-30 °C by adjusting the jacket temperature
Stir R1 at 20-30 °C for 30-60 min
Allow R1 to stand for 30-60 min at batch temperature 20-30 °C
Keep the flow of nitrogen more than 6 m ³ /h and blow the T1 with nitrogen for more than 20 min
Transfer the aqueous phase of R1 to T1
Keep the flow of nitrogen more than 6 m ³ /h and blow the T2 with nitrogen for more than 20 min
Transfer the aqueous phase of R1 to T2
Charge Compound No. 6a aqueous layer into R1
Charge 2-MeTHF (146 kg 8.6 X) into R1
Adjust temperature of R1 to 20-30 °C by adjusting the jacket temperature
Stir R1 at 20-30 °C for 30-60 min
Allow R1 to stand for 30-60 min at batch temperature 20-30 °C
Keep the flow of nitrogen more than 6 m ³ /h and blow the T1 with nitrogen for more than 20 min
Transfer the aqueous phase of R1 to T1
Keep the flow of nitrogen more than 6 m ³ /h and blow the T2 with nitrogen for more than 20 min
Transfer the aqueous phase of R1 to T2
Wash R1 with 2-MeTHF (188 kg)
Wash R1 with process water
Wash R1 with 2-MeTHF (90 kg)
Wash R3 with 2-MeTHF (200 kg)
Transfer the T2 material into R3
Charge 2-MeTHF (32 kg) into T2
Transfer the T2 material into R3
Concentrate the contents of R3, by distillation under vacuum at an internal temperature of ≤ 45 °C to 1-2 X
Load the material in R3 into SS-plastic composite drums inerted by nitrogen
Charge 2-MeTHF (48 kg 2.8 X) into R3
Concentrate the contents of R3, by distillation under vacuum at an internal temperature of ≤ 45

°C to 1-2 X
Load the material in R3 into SS-plastic composite drums inerted by nitrogen
Adjust temperature of R3 to 20-30 °C by adjusting the jacket temperature
Transfer R3 solution into new plastic-steel drum
Charge 2-MeTHF (10 kg 0.6 X) into R3
Transfer R3 solution into plastic-steel drum (Compound No. 6a 2-MeTHF solution, total net = 34.2 kg)

[0277] The product of the step was assessed using the chromatographic conditions shown in Table 4C, and the results are summarized in Table 4D.

Table 4C. Chromatographic Conditions for Assessing Product of Step 4.

Column	Waters Xbridge Amide column, 4.6 × 150 mm, 3.5 μm, PN:186004869		
Wavelength	210 nm		
Reference Wavelength	Off (This parameter is only applicable to Agilent and Thermo instruments)		
Column temperature	20°C		
Flow rate	1.0 mL/min		
Injection volume	5 μL		
Needle Wash	ACN: Water = 10:20 (v/v)		
Mobile phase A	5mM NH ₄ OAc in water (adjust pH to 9.0 with ammonia solution), w/v		
Mobile phase B	ACN		
Gradient program	Time (min)	A%	B%
	Initial	20	80
	10.0	40	60
	13.0	40	60
	14.0	20	80
	19.0	20	80
Data Acquisition Time	19 min		
Pump Run time	19 min		

Table 4D. Assessment of the Products of Step 4.

Batch No	Starting Material	Product				Yield
	Weight (kg)	Gross Wt	Purity (HPLC)	Chiral Purity (HPLC)	Assay (HPLC)	
1	16.85 kg	34.2 kg	98.1%	100.0%	47.9%	96%

Step 5

[0278] Step 5 was performed using the equipment described in Table 5A and following the procedures described in Table 5B. The product of the step was assessed, and the results are summarized in Table 5C.

Table 5A. Equipment Used in Step 5.

Equip. Name	Equip. Code	Equip. Standard
Reactor	R1	GL/500 L
Diaphragm pump	P1	SS
	P2	SS
	P3	PP/PTFE
	P4	PP/PTFE
Glove box	XL1	Ti/Halar
Centrifuge	F1	HC/HL/SS
Cartridge filter	Ft1	HC, PP/PTFE core
Tank	H1	GL
Tank	V1	GL

Table 5B. Exemplary Procedures of Step 5.

Wash the reactor with toluene (152 kg)
Charge toluene (66kg 3.5 X) into R1
Adjust R1 to 20-30 °C under nitrogen protection
Charge Triphosgene (11.1 kg 0.59 X) into R1
Stir R1 to clear at 20-30 °C under nitrogen protection
Transfer R1 material into H1
Charge toluene (10 kg) into R1
Transfer R1 material into H1
Charge toluene (244 kg 13.0 X) into R1
Charge Compound No. 7 (18.8 kg 1.00 X) into R1
Adjust R1 batch temperature to 20-30 °C under nitrogen protection
Stir R1 to clear at 20-30 °C under nitrogen protection
Add TEA (15.4 kg 0.82 X) slowly into R1 in portions at 20-30 °C under nitrogen protection
Adjust R1 batch temperature to 5-15 °C under nitrogen protection
Add triphosgene toluene solution slowly into R1 via N ₂ pressure in portions below 40 °C NMT 3 h
Charge toluene (15 kg 0.8 X) into R1
Add toluene rinse (15 kg 0.8 X) to R1 slowly via N ₂ pressure in portions below 40 °C
Adjust R1 to 65-75 °C under nitrogen protection
Stir R1 at 65-75 °C for 12-14 h under nitrogen protection
Adjust R1 to 30-40 °C under nitrogen protection
Cool R1 to 10-20 °C under nitrogen protection
Stir R1 at 10-20 °C for 1-2 h under nitrogen protection
Spread two filter clothes into F1

Charge silica gel (10 kg 0.5 X) into F1
Charge diatomite (10 kg 0.5 X) into F1
Charge toluene (40 kg) into F1 to moisten the diatomite and silica gel
Press solvent of F1 out to iron drums flowed by nitrogen, and label pending tag
Press filter R1 material in portions, filter to dryness after loading, transfer the filtrate to V1 blanketed
Charge toluene (161 kg 8.6 X) into R1
Press filter R1 material in portions, filter to dryness after loading, transfer the filtrate to V1 blanketed
Concentrate the contents of R1 by distillation under vacuum at batch temperature $\leq 40^{\circ}\text{C}$ to 3-5 X
Load the material in R1 into H1 inerted by nitrogen
Adjust R1 to below 25°C under nitrogen protection
Transfer R1 material into new steel-plastic compound drums (Compound No. 8 organic solution, total net = 67.0 kg)
Load F1 wet cake into fiber drum lined with PE bag

Table 5C. Assessment of the Products of Step 5.

Batch No	Starting Material	Product			Yield
	Weight (kg)	Gross Wt	Purity (HPLC)	Assay (HPLC)	
1	18.8 kg	67.0 kg	99.8%	30.7%	95%

Step 6

[0279] Step 6 was performed using the equipment described in Table 6A and following the procedures described in Table 6B.

Table 6A. Equipment Used in Step 6.

Equip. Name	Equip. Code	Equip. Standard
Reactor	R1	SS/1000 L
	R2	SS/3000 L
Bag filter	Fb1	SS
Diaphragm pump	P1	SS
	P2	SS
	P3	SS
	P4	SS
	P5	SS
	P6	SS
	P7	SS
	P8	SS
Cartridge filter	Ft1	PP/PTFE
	Ft2	PP/PTFE
Vessel	V1	GL

Equip. Name	Equip. Code	Equip. Standard
Press filter	F1	SS
Glove box	XL1	SS
Solid feed charger	XL2	SS
	XL3	SS
Tank	T1	HDPE
	T2	SS
Centrifuge	M1	SS
Filter dryer	F2	SS/HC
	F3	SS/HC

Table 6B. Exemplary Procedures of Step 6.

Charge sodium citric acid monohydrate (38 kg 2.4 X) into process water (500 kg +148 kg 40.2 X) to prepare 5% citric acid solution
Charge NaHCO ₃ (19 kg 1.2 X) into process water (275 kg + 82 kg 22.2 X) to prepare 5% NaHCO ₃ solution
Charge Compound No. 6a 2-MeTHF solution (16.4 kg, 1.02 X) into R1
Charge 2-MeTHF (254 kg 15.8 X) into R1
Adjust R1 batch temperature to 15-20 °C under nitrogen protection
Stir R1 for 10-30 min under nitrogen protection at 15-20 °C
Charge DMAP (10.5 kg 0.65 X) into R1
Charge 2-MeTHF (8 kg) into R1
Adjust R1 batch temperature to 15-20 °C under nitrogen protection
Stir R1 for 10-30 min under nitrogen protection at 15-20 °C
Adjust R1 batch temperature to 0-10 °C under nitrogen protection
Add Compound No. 8 organic solution (57 kg 3.5 X) into R1 in portions at 0-10 °C
Charge 2-MeTHF (28 kg 1.7 X) into R1
Adjust R1 batch temperature to 18-23 °C under nitrogen protection
Stir R1 at 18-23 °C for 16-20 h
Load the material in R1 into V1 by nitrogen
Charge 2-MeTHF (28 kg 1.7 X) into R1
Load the material in R1 into V1 by nitrogen
Load solid into fiber drum lined with double PE bags
Wash R1 with process water
Load the filtrate from V1 into R1
Charge 2-MeTHF (34 kg) into V1
Load the rinse solution in V1 into R1
Adjust R1 batch temperature to 10-25 °C by adjusting the jacket temperature
Charge 5% citric acid solution (241 kg 15.0 X) into R1
Stir R1 at 10-25 °C with temperature for 20-60 min
Settle the batch in R1 at 10-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to plastic drums
Charge 5% citric acid solution (171 kg 10.6 X) into R1
Stir R1 at 10-25 °C for 20-60 min

Settle the batch in R1 at 10-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to plastic drums
Charge 2-MeTHF (36 kg) into R1
Settle the batch in R1 at 10-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to plastic drums
Charge 25% aq. NaCl (60 kg) into R1
Stir R1 at 10-25 °C for 2-5 min
Settle the batch in R1 at 10-25 °C for 30-60 min
Charge 5% NaHCO ₃ solution (155 kg 9.6 X) into R1
Stir R1 at 10-25 °C for 20-60 min
Settle the batch in R1 at 10-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to plastic drums
Charge process water (144 kg 8.9 X) into R1 at 10-25 °C
Stir R1 at 10-25 °C for 20-60 min
Settle the batch in R1 at 10-25 °C for 30-60 min
Transfer the bottom aqueous phase of R1 to plastic drums
Spread two filter clothes into F1
Charge Na ₂ SO ₄ (50 kg 3.1 X) into F1
Spread a filter cloth on the Na ₂ SO ₄ to receive
Charge 2-MeTHF (22 kg) into F1 to moisten Na ₂ SO ₄
Press solvent of F1 out to galvanized steel drums flowed by nitrogen, discard the filtrate
Circulate the mixture in R1 through F1 and Ft2 for 2-6 h
Transfer the material in R1 into T2
Charge 2-MeTHF (46 kg 2.9 X) into R1
Transfer the material in R1 into T2
Charge 2-MeTHF (44 kg 2.7 X) into F1
Transfer the material in F1 into T2
Wash R1 with 2-MeTHF (172 kg)
Charge Compound No. 9a 2-MeTHF solution into R1
Concentrate the contents of reactor R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 2-3 X
Load F1 wet cake into fiber drum lined with PE bag
Load the material in R1 into iron drums inerted by nitrogen
Charge IPAc (241 kg 15.0 X) into R1
Concentrate the contents of reactor R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 2-3 X
Load the material in R1 into iron drums inerted by nitrogen
Charge IPAc (240 kg 14.9 X) into R1
Concentrate the contents of reactor R1, by distillation under vacuum at an internal temperature of ≤ 45 °C, to a volume of 2-3 X
Load the material in R1 into iron drums inerted by nitrogen
Charge IPAc (130 kg 8.1 X) into R1
Adjust R1 batch temperature to 48-53 °C by adjusting the jacket temperature
Stir R1 to clear at 48-53 °C with batch temperature
Adjust R1 batch temperature to 28-33 °C by adjusting the jacket temperature
Charge n-heptane (260 kg) into R1 at 28-33 °C in 8-9 h

Stir R1 to clear at 28-33 °C with batch temperature for 1-3 h
Adjust R1 batch temperature to 0-10 °C by adjusting the jacket temperature
Stir R1 at 0-10 °C with batch temperature for 5-10 h
Spread centrifuge bag in M1
The 1 st centrifuge
Charge n-heptane (40 kg 2.5 X) to rinse the wet cake (the last solvent is used to rinse the reactor firstly) and transfer the mother liquor into the mother liquor receiver
Load solid of the centrifuge into fiber drum/ton bag lined with double PE bags, the wet cake was divided in two parts for drying.
Transfer mother liquor into plastic-steel composite drums from the mother liquor receiver
Put first Compound No. 9a wet cake into drying bag, then put the bag into the dryer
Adjust the jacket temperature of the dryer to 35-45 °C
Dry F1 material under vacuum, maintaining hot water exchanger temperature at 35-45 °C for 1-3 h
Dry F1 material under vacuum, maintaining hot water exchanger temperature at 40-50 °C for 20-24 h
Adjust the jacket temperature of the dryer to 20-40 °C
Weigh the prepare double layer of antistatic plastic bags including two cable ties and fiber drum, then load the material of dryer into the fiber drums with PE bags (Compound No. 9a, total net = 10.40 kg)
Put the rest Compound No. 9a wet cake into drying bag, then put the bag into the dryer
Adjust the jacket temperature of the dryer to 35-45 °C
Dry F1 material under vacuum, maintaining hot water exchanger temperature at 35-45 °C for 1-3 h
Dry F1 material under vacuum, maintaining hot water exchanger temperature at 40-50 °C for 20-24 h
Adjust the jacket temperature of the dryer to 20-40 °C
Weigh the prepare double layer of antistatic plastic bags including two cable ties and fiber drum, then load the material of dryer into the fiber drums with PE bags (Compound No. 9a, total net = 8.65 kg)

[0280] The product of the step was assessed using the chromatographic conditions shown in Table 6C, and the results are summarized in Table 6D.

Table 6C. Chromatographic Conditions for Assessing Product of Step 6.

Chiral Purity	
Column	CHIRALCEL OJ-RH, 150 mmx 4.6 mm, 5 µm PN:17724
Wavelength	202 nm
Reference wavelength	Off
Column Temperature	35 °C
Flow Rate	1.0 mL/min
Injector Volume	5 µL
Needle Wash Solvent	ACN:Water = 1:1 (v/v)
Mobile Phase A	0.05% H ₃ PO ₄ in water
Mobile Phase B	ACN

Chiral Purity			
Gradient program	Time (min)	A%	B%
	0.00	65	35
	25.00	65	35
Run Time	25 min		
Data Acquisition Time	25 min		

Purity & Assay			
Column	Waters XBridge Phenyl, 4.6 × 150 mm, 3.5 μm PN:186003335		
Wavelength	220 nm		
Reference Wavelength	Off		
Column Temperature	30°C		
Flow Rate	1.0 mL/min		
Injector Volume	5 μL		
Needle Wash	ACN		
Mobile Phase A	0.05% TFA in water: ACN= 900:100, v/v		
Mobile Phase B	0.05% TFA in ACN: water=900:100, v/v		
Gradient Program	Time (min)	A%	B%
	Initial	70	30
	20.00	45	55
	25.00	5	95
	30.00	5	95
	31.00	70	30
	36.00	70	30
Run Time	36 min		
Data Acquisition Time	36 min		

Table 6D. Assessment of the Products of Step 6.

Batch No	Starting Material	Product				Yield
	Weight (kg, corrected by assay)	Gross Wt	Purity (HPLC)	Chiral Purity (HPLC)	Assay (HPLC)	
1	16.4 kg of Compound No. 6a	10.40 kg 8.65 kg	98.8% 98.8%	100% 100%	99.1% 98.7%	59%

Step 7

[0281] Step 7 was performed using the equipment described in Table 7A and following the procedures described in Table 7B.

Table 7A. Equipment Used in Step 7.

Equip. Name	Equip. Code	Equip. Standard
Reactor	R1	GL/1000 L
	R2	SS/2000 L
Cartridge filter	Ft1	SS shell, PTFE core
	Ft2	SS shell, PTFE core
	Ft3	SS shell, PTFE core
	Ft4	SS shell, PTFE core
Glove box	XL1	SS
	XL2	SS
Diaphragm pump	P1	SS
	P2	SS
	P3	SS
	P4	SS
	P5	SS
Filter dryer	FD1	SS/HA
Sieve	XS1	SS

Table 7B. Exemplary Procedures of Step 7.

Wash the reactor with IPAc (150 kg + 77 kg)
Charge IPAc (70 kg 3.7 X) into R1
Charge Compound No. 9a (19.0 kg 1.00 X) into R1
Charge IPAc (68 kg 3.6 X) into R1
Adjust R1 batch temperature to 48-53 °C by adjusting the jacket temperature
Stir R1 at 48-53 °C until the solid is dissolved completely
Transfer the material in R1 into R2
Charge IPAc (16 kg 0.8 X) into R1
Transfer the material in R1 into R2
Adjust R2 batch temperature to 38-43 °C by adjusting the jacket temperature
Charge Compound No. 9a seed (0.124 kg 0.01 X) into R2 at 38-43 °C
Stir R2 at 38-43 °C for 1-2 h
Adjust R2 batch temperature to 28-33 °C by adjusting the jacket temperature over 1-3 h
Stir R2 at 28-33 °C for 1-2 h
Charge n-heptane (362 kg 19.1 X) into R2 at 28-33 °C under nitrogen protection within 8-9 h
Stir R2 at 28-33 °C for 1-3 h
Adjust R2 batch temperature to 0-5 °C by adjusting the jacket temperature over 2-4 h
Stir R2 at 0-5 °C for 8-10 h
Wash FD1 with IPAc (79 kg)
Transfer mother liquor to the filter liquor vessel
Adjust the jacket temperature of FD1 to 0-10 °C
The 1 st filtration
Transfer about half of material in R2 into the filter dryer for filtration, and maintain the batch temperature of R1 at 0-5 °C
Press slowly until no mother liquor comes out obviously. Transfer the filtrate into the filter liquor vessel

Load the mother liquor in mother liquor receiver into iron drums by nitrogen
Charge n-heptane (90 kg 4.7 X) into R2
Adjust R2 jacket temperature to 0-5 °C
Transfer the material in R2 into the filter dryer
Press slowly until no mother liquor comes out obviously. Transfer the filtrate into the filter liquor vessel
Wash R2 with IPAc (79 kg)
Load the mother liquor in mother liquor receiver into new iron drums by nitrogen
Adjust the temperature of FD1 jacket to 30-40 °C
Dry FD1 material under vacuum, maintaining the jacket temperature at 30-40 °C for 5-7 h
Adjust the temperature of FD1 jacket to 40-50 °C
Dry FD1 material under vacuum with stirring, maintaining the jacket temperature at 40-50 °C for 20-24 h
Adjust FD1 jacket temperature to 20-35 °C
Hold FD1 at 20-35 °C for at least 1 h
Install antistatic continuous liner on FD1, open side discharge valve, start agitation and transfer the product in filter dryer to the plastic drum lined with single layer of antistatic LDPE bag
Sieve the material. Load the sieved product to the empty SS drum, weigh the gross weight and record it
After sampling, weigh the gross and calculate the net weight (Purified Compound No. 9a, total net = 14.63 kg)

[0282] The product of the step was assessed using the chromatographic conditions shown in Table 7C, and the results are summarized in Table 7D.

Table 7C. Chromatographic Conditions for Assessing Product of Step 7.

Instrument	Agilent 1260 HPLC with UV detector or equivalent		
Column	CHIRALCEL OJ-RH, 150 mm x 4.6 mm, 5 µm PN:17724		
Wavelength	202 nm		
Reference wavelength	Off		
Column Temperature	35 °C		
Flow Rate	1.0 mL/min		
Injector Volume	5 µL		
Needle Wash Solvent	ACN:Water = 1:1 (v/v)		
Mobile Phase A	0.05% H ₃ PO ₄ in water		
Mobile Phase B	ACN		
Gradient program	Time (min)	A%	B%
	0.00	65	35
	25.00	65	35
Run Time	25 min		
Data Acquisition Time	25 min		

Table 7D. Assessment of the Products of Step 7.

Batch No	Starting Material	Product			Yield
	Weight (kg)	Gross Wt	Purity (HPLC)	Assay (HPLC)	
1	19.0 kg	14.63 kg	99.0%	99.5%	77%

EQUIVALENTS

[0283] 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.

[0284] 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 a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof, comprising one or more of steps (i)-(vii):

(i) contacting Compound No. 1 or a salt thereof, with a hydrogenation agent, thereby forming Compound No. 2 or a salt thereof;

(ii) contacting Compound No. 3, with an esterification agent, thereby forming a compound of Formula (IV);

(iii) contacting Compound No. 2 or the salt thereof, with the compound of Formula (IV), thereby forming a compound of Formula (V) or a salt thereof;

(iv) contacting the compound of Formula (V) or the salt thereof, with a reducing agent, thereby forming a compound of Formula (VI) or a salt thereof;

(v) contacting Compound No. 7 or a salt thereof, with an CO-generating agent, thereby forming Compound No. 8 or a salt thereof;

(vi) contacting the compound of Formula (VI) or the salt thereof, with Compound No. 8 or the salt thereof, thereby forming a compound of Formula (IX) (e.g., Compound No. 9a or 9b) or a salt thereof; or

(vii) purifying the compound of Formula (IX) or the salt thereof.

2. A method of preparing a compound of Formula (V) or a salt thereof, comprising:

(iii) contacting Compound No. 2 or a salt thereof, with a compound of Formula (IV), thereby forming a compound of Formula (V) or a salt thereof.

3. A method of preparing a compound of Formula (VI) or a salt thereof, comprising:

(iv) contacting a compound of Formula (V) or a salt thereof, with a reducing agent, thereby forming a compound of Formula (VI) or a salt thereof.

4. The method of any one of the preceding claims, wherein the compound of Formula (IX) or the salt thereof is:

(a) Compound No. 9;

(b) a compound of Formula (IX-a) or a salt thereof; optionally, wherein the compound of Formula (IX) or the salt thereof is Compound No. 9a or a salt thereof; or

(c) a compound of Formula (IX-b) or a salt thereof; optionally, wherein the compound of Formula (IX) or the salt thereof is Compound No. 9b or a salt thereof.

5. The method of any one of the preceding claims, wherein in step (i), the contacting is performed in the presence of a hydrogenation catalyst;
optionally, wherein the hydrogenation catalyst is Raney nickel.
6. The method of any one of the preceding claims, wherein in step (i), the contacting is performed in the presence of a base;
optionally, wherein the base is potassium carbonate (K_2CO_3).
7. The method of any one of the preceding claims, wherein in step (ii), the esterification agent is an alcohol;
optionally, wherein the esterification agent is isopropanol (iPrOH; propan-2-ol).
8. The method of any one of the preceding claims, wherein in step (ii), the contacting is performed in the presence of an esterification catalyst;
optionally, wherein the esterification catalyst is 4-dimethylaminopyridine (DMAP).
9. The method of any one of the preceding claims, wherein in step (ii), the contacting is performed in the presence of a base;
optionally, wherein the base is pyridine.
10. The method of any one of the preceding claims, wherein in step (iii), the contacting is performed in the presence of a salt;
optionally, wherein the salt is potassium tert-butoxide (tBuOK).
11. The method of any one of the preceding claims, wherein in step (iii), the contacting is performed in the presence of an alcohol;
optionally, wherein the alcohol is isopropanol (iPrOH; propan-2-ol).

12. The method of any one of the preceding claims, wherein in step (iv), the reducing agent is a monosaccharide;
optionally, wherein the reducing agent is glucose; and
optionally, wherein the reducing agent is D-glucose.
13. The method of any one of the preceding claims, wherein in step (iv), the contacting is performed in the presence of a reduction catalyst;
optionally, wherein the reduction catalyst comprises ketoreductase (KRED), glutamate dehydrogenase (GDH), and nicotinamide adenine dinucleotide phosphate (NADP).
14. The method of any one of the preceding claims, wherein in step (v), the CO-generating agent is triphosgene and the contacting is performed in the presence of a base;
optionally, wherein the base is triethylamine (TEA).
15. The method of any one of the preceding claims, wherein in step (vi), the contacting is performed in the presence of a base;
optionally, wherein the base is 4-dimethylaminopyridine (DMAP).
16. The method of any one of the preceding claims, wherein step (vii) comprises crystalizing the compound of Formula (IX) or the salt thereof in the presence of an organic solvent;
optionally, wherein the organic solvent comprises isopropyl acetate and n-heptane; and
optionally, wherein the isopropyl acetate and n-heptane are present at a ratio of about 1:1, about 1:2, about 1:3, about 1:4, or about 1:5.
17. A compound of Formula (IX) or a salt thereof;
optionally, wherein the compound is Compound No. 9 or a salt thereof;
optionally, wherein the compound is Compound No. 9a or a salt thereof; and
optionally, wherein the compound is Compound No. 9a or a salt thereof 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.

18. A pharmaceutical composition comprising the compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding claims, and one or more pharmaceutically acceptable carrier or excipient.

19. A method of inhibiting inflammasome activity in a subject, comprising administering to the subject the compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding claims.

20. A method of preventing or treating a disease in a subject, comprising administering to the subject the compound of Formula (IX), or the pharmaceutically acceptable salt thereof, of any one of the preceding claims.