METHODS OF PREPARING CARBAMATE DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims priority to, and the benefit of, U.S. Provisional Patent Application No. 63/566,096, filed March 15, 2024, 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.

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

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

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

SUMMARY

[006] In some aspects, the present disclosure provides a method of preparing 2-methylpyrimidine salt (Compound No. 3) from 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof, as described herein.

[007] In some aspects, the present disclosure provides a method of preparing 2-methylpyrimidine salt (e.g., Compound No. 3a) from 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof, as described herein.

[008] In some aspects, the present disclosure provides a method for preparing 2-methylpyrimidine salt (e.g., Compound No. 3a), comprising one or more of steps (i) and (ii):

(i) reacting 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof, with a hydrogenating agent, thereby forming 2-methylpyrimidine (Compound No. 2); and

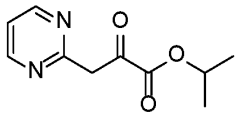
(ii) reacting 2-methylpyrimidine (Compound No. 2), with an acid, thereby forming 2-methylpyrimidine salt (e.g., Compound No. 3a).

[009] In some aspects, the present disclosure provides a method for preparing 2-methylpyrimidine salt (e.g., Compound No. 3a), comprising steps (i) and (ii):

(i) reacting 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof, with a hydrogenating agent, thereby forming 2-methylpyrimidine (Compound No. 2); and

(ii) reacting 2-methylpyrimidine (Compound No. 2), with an acid, thereby forming 2-methylpyrimidine salt (e.g., Compound No. 3a).

[010] In some aspects, the present disclosure provides a method of preparing Compound No. 5 or a salt thereof:



(Compound No. 5),

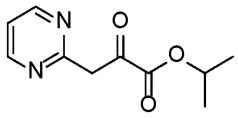
comprising one or more of steps (i)-(iii):

(i) reacting 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof, with a hydrogenating agent, thereby forming 2-methylpyrimidine (Compound No. 2);

(ii) reacting 2-methylpyrimidine (Compound No. 2), with an acid, thereby forming 2-methylpyrimidine salt (e.g., Compound No. 3a); and

(iii) reacting 2-methylpyrimidine salt (e.g., Compound No. 3a), with diisopropyl oxalate (Compound No. 4) or a salt thereof, thereby forming Compound No. 5, or a salt thereof, wherein the reacting is performed in the presence of potassium *tert*-pentoxide.

[011] In some aspects, the present disclosure provides a method of preparing Compound No. 5 or a salt thereof:



(Compound No. 5),

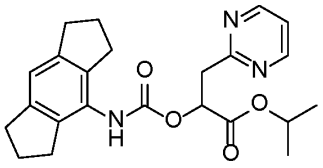
comprising steps (i)-(iii):

(i) reacting 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof, with a hydrogenating agent, thereby forming 2-methylpyrimidine (Compound No. 2);

(ii) reacting 2-methylpyrimidine (Compound No. 2), with an acid, thereby forming 2-methylpyrimidine salt (e.g., Compound No. 3a); and

(iii) reacting 2-methylpyrimidine salt (e.g., Compound No. 3a), with diisopropyl oxalate (Compound No. 4) or a salt thereof, thereby forming Compound No. 5, or a salt thereof, wherein the reacting is performed in the presence of potassium *tert*-pentoxide.

[012] In some aspects, the present disclosure provides a method of preparing Compound No. 9 or a salt thereof:



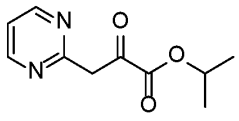
(Compound No. 9),

comprising one or more of steps (i)-(vii):

(i) reacting 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof, with a hydrogenating agent, thereby forming 2-methylpyrimidine (Compound No. 2);

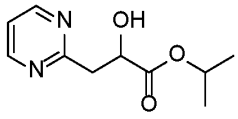
(ii) reacting 2-methylpyrimidine (Compound No. 2), with an acid, thereby forming 2-methylpyrimidine salt (e.g., Compound No. 3a);

(iii) reacting 2-methylpyrimidine salt (e.g., Compound No. 3a), with diisopropyl oxalate (Compound No. 4) or a salt thereof, thereby forming Compound No. 5:



(Compound No. 5), or a salt thereof;

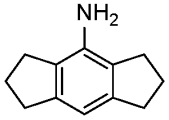
(iv) reacting Compound No. 5, or the salt thereof, with a reducing agent, thereby forming Compound No. 6 (e.g., Compound No. 6a or 6b):



(Compound No. 6),

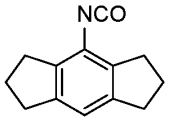
or a salt thereof;

(v) reacting Compound No. 7:



(Compound No. 7),

or a salt thereof, with a source of CO, thereby forming Compound No. 8:



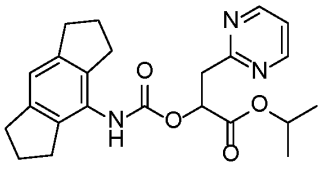
(Compound No. 8),

or a salt thereof;

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

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

[013] In some aspects, the present disclosure provides a method of preparing Compound No. 9 or a salt thereof:



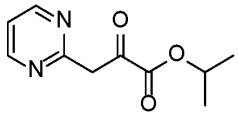
(Compound No. 9),

comprising steps (i)-(vii):

(i) reacting 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof, with a hydrogenating agent, thereby forming 2-methylpyrimidine (Compound No. 2);

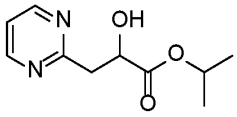
(ii) reacting 2-methylpyrimidine (Compound No. 2), with an acid, thereby forming 2-methylpyrimidine salt (e.g., Compound No. 3a);

(iii) reacting 2-methylpyrimidine salt (e.g., Compound No. 3a), with diisopropyl oxalate (Compound No. 4) or a salt thereof, thereby forming Compound No. 5:



(Compound No. 5), or a salt thereof;

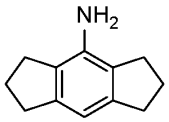
(iv) reacting Compound No. 5, or the salt thereof, with a reducing agent, thereby forming Compound No. 6 (e.g., Compound No. 6a or 6b):



(Compound No. 6),

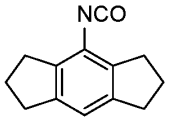
or a salt thereof;

(v) reacting Compound No. 7:



(Compound No. 7),

or a salt thereof, with a source of CO, thereby forming Compound No. 8:



(Compound No. 8),

or a salt thereof;

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

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

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

(iv) reacting Compound No. 5, or a salt thereof, with a reducing agent, thereby forming Compound No. 6 (e.g., Compound No. 6a or 6b), or a salt thereof.

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

[016] In some aspects, the present disclosure provides a pharmaceutical composition comprising Compound No. 9 (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.

[017] In some aspects, the present disclosure provides a method of inhibiting inflammasome (e.g., the NLRP3 inflammasome) activity (e.g., *in vitro* or *in vivo*), comprising contacting a cell with Compound No. 9 (e.g., Compound No. 9a or 9b) or a pharmaceutically acceptable salt thereof as described herein (e.g., in an effective amount).

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

[019] In some aspects, the present disclosure provides Compound No. 9 (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*).

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

[021] In some aspects, the present disclosure provides use of Compound No. 9 (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*) in a subject.

[022] In some aspects, the present disclosure provides use of Compound No. 9 (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.

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

[024] In some aspects, the present disclosure provides Compound No. 9 (e.g., Compound No. 9a or 9b) for use in preventing or treating a disease or for inhibiting inflammasome activity in a subject.

[025] In some aspects, the present disclosure provides a method of inhibiting inflammasome activity in a subject, comprising contacting a cell with Compound No. 9 (e.g., Compound No. 9a or 9b).

[026] 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.

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

DETAILED DESCRIPTION

[028] 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.

[029] Cytokines from the IL-1 family are highly active and, as important mediators of inflammation, are primarily associated with acute and chronic inflammation. The overproduction

of IL-1 is considered to be an initiator of some autoimmune and autoinflammatory diseases. Autoinflammatory diseases are characterised by recurrent and unprovoked inflammation in the absence of autoantibodies, infection, or antigen-specific T lymphocytes.

[030] Proinflammatory cytokines of the IL-1 superfamily include IL-1α, IL-1β, IL-18, and IL-36α, 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-1β, IL-18, and IL-36α, β, λ are synthesised as procytokines that require proteolytic activation to become optimal ligands for binding to their cognate receptors on target cells.

[031] In the case of IL-1α, IL-1β and IL-18, it is now appreciated that a multimeric protein complex known as an inflammasome is responsible for activating the proforms of IL-1β and IL-18 and for release of these cytokines extracellularly. An inflammasome complex typically consists of a sensor molecule, such as an NLR (Nucleotide-Oligerimisation 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-1β 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.

[032] 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).

[033] Two other structurally distinct inflammasome structures containing a PYHIN domain (pyrin and HIN domain containing protein) namely Absent in Melanoma 2 (AIM2) and IFNλ-

inducible protein 16 (IFI16) serve as intracellular DNA sensors. Pyrin (encoded by the MEFV gene) represents another type of inflammasome platform associated with pro-IL-1β activation.

[034] Requiring assembly of an inflammasome platform to achieve activation and release of IL-1β 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 TNFα) which leads to NF-KB dependent transcription of NLRP3, pro-IL-1β 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.

[035] In addition to proteolytic activation of pro-IL-1β 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-1β 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-1α.

[036] 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-1β and IL-18 being implicated in a diverse range of pathophysiological indications including metabolic, physiologic, inflammatory, hematologic and immunologic disorders.

[037] 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. 2001, 29(3) 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).

[038] 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-1β 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.

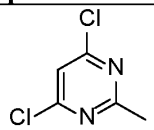
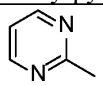
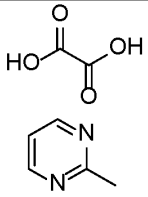
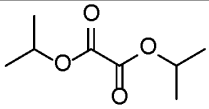
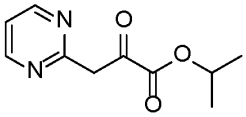
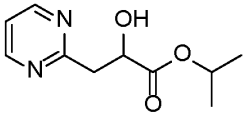
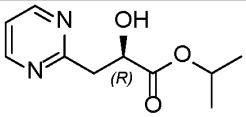
[039] Some small molecules have been reported to inhibit function of the NLRP3 inflammasome. Glyburide, for example, is a specific inhibitor of NLRP3 activation, albeit at micromolar concentrations which are unlikely attainable *in vivo*. Non-specific agents such as parthenolide, Bay 11-7082, and 3,4-methylenedioxy-β-nitrostyrene 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-1β. The exemplar molecule CP-456,773 from this work was recently characterised as a specific inhibitor of NLRP3 activation (Coll et al., Nature Medicine 2015, 21, 248-255).

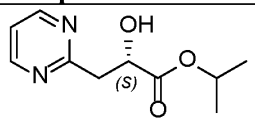
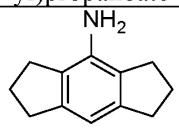
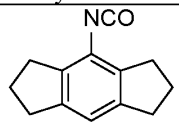
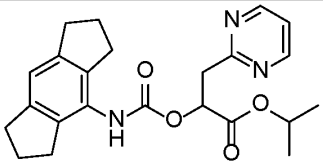
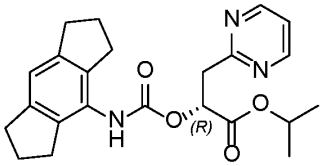
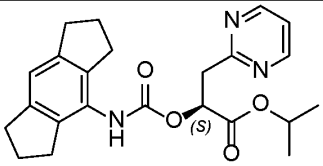
[040] The disclosure relates to methods of preparing compounds useful for the modulation of NLRP3-dependent cellular processes. In some embodiments, methods of preparing compounds with improved physicochemical, pharmacological and pharmaceutical properties to existing NLRP3-modulating compounds are desired.

Compounds of the Present Disclosure

[041] It is understood that the structures of Compound Nos. 1-3, 3a, 4-6, 6a, 6b, 7-9, 9a, and 9b are as described in Table I below.

Table I

Compound No.	Compound Structure
1	 4,6-dichloro-2-methylpyrimidine
2	 2-methylpyrimidine
3	 salt 2-methylpyrimidine salt
3a	 2-methylpyrimidine oxalate
4	 diisopropyl oxalate
5	 isopropyl 2-oxo-3-(pyrimidin-2-yl)propanoate
6	 isopropyl 2-hydroxy-3-(pyrimidin-2-yl)propanoate
6a	 isopropyl (R)-2-hydroxy-3-(pyrimidin-2-yl)propanoate

Compound No.	Compound Structure
6b	 isopropyl (S)-2-hydroxy-3-(pyrimidin-2-yl)propanoate
7	 1,2,3,5,6,7-hexahydro-s-indacen-4-amine
8	 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene
9	 isopropyl 2-(((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)oxy)-3-(pyrimidin-2-yl)propanoate
9a	 isopropyl (R)-2-(((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)oxy)-3-(pyrimidin-2-yl)propanoate
9b	 isopropyl (S)-2-(((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)oxy)-3-(pyrimidin-2-yl)propanoate

Methods of the Present Disclosure

[042] Without wishing to be bound by theory, it is understood that the methods of the present disclosure could carry various potential advantages, e.g., as compared to previously known methods.

[043] For example, a method of the present disclosure could involve use of catalytic hydrogen transfer (e.g., in step (i)), which is not normally recognised for de-chlorination. Such hydrogen transfer conditions could lead to a more controlled reduction and critically substantially no over-reduction bi-products, and could thereby result in a higher yield and a cleaner product. For another example, in a method of the present disclosure, the preparation of Compound No. 3 (e.g., Compound No. 3a) could be novel over previously known method, and could provide a solid isolated product in high purity and/or high yield. The synthesized Compound No. 3 (e.g., Compound No. 3a) could then be used directly in the next step.

[044] For another example, a method of the present disclosure could involve the use of oxalate salt (e.g., Compound No. 3a) in step (iii), and/or the use of potassium *tert*-pentoxide as a base (e.g., in place of potassium *tert*-butoxide), such method could avoid the formation of the *tert*-butyl ester impurity, which was previously known to be difficult to purge and persisted in prepared product (e.g., Compound No. 9a). Even if assuming a *tert*-pentyl ester impurity could be formed during the step (iii), such impurity could be more lipophilic than the *tert*-butyl ester, thereby could be more readily purged from the step (iii) and not persist in the prepared product (e.g., Compound No. 9a).Thus, the method could yield a product of higher purity in the downstream processing, e.g., due to indicating that impurities resulting from the method are more efficient to be purged than in other methods.

[045] In some aspects, the present disclosure provides a method of preparing Compound No. 3 (e.g., Compound No. 3a) described herein.

[046] In some embodiments, the method comprises one or more of steps (i)-(ii):

(i) reacting Compound No. 1 or a salt thereof, with a hydrogenating agent, thereby forming Compound No. 2; and

(ii) reacting Compound No. 2, with an acid, thereby forming Compound No. 3 (e.g., Compound No. 3a).

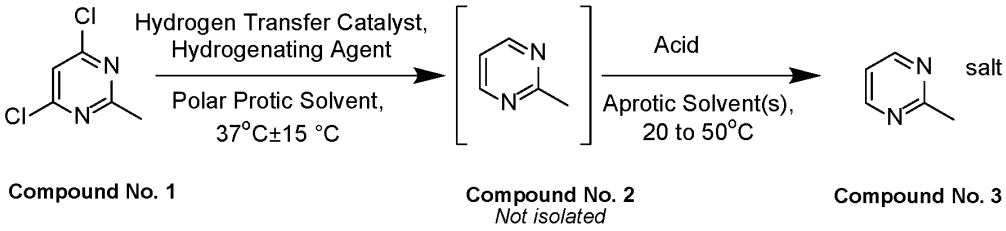
[047] In some embodiments, the method comprises step (i).

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

[049] In some embodiments, the method comprises steps (i) and (ii).

[050] In some embodiments, the method comprises one or more steps according to Scheme A.

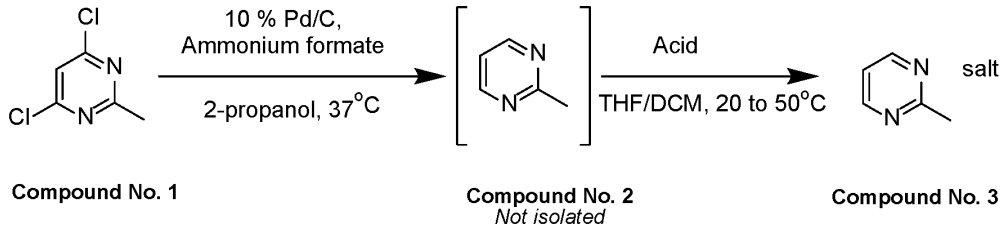
Scheme A



Compound No. 1 **Compound No. 2** *Not isolated* **Compound No. 3**

[051] In some embodiments, the method comprises one or more steps according to Scheme A-1.

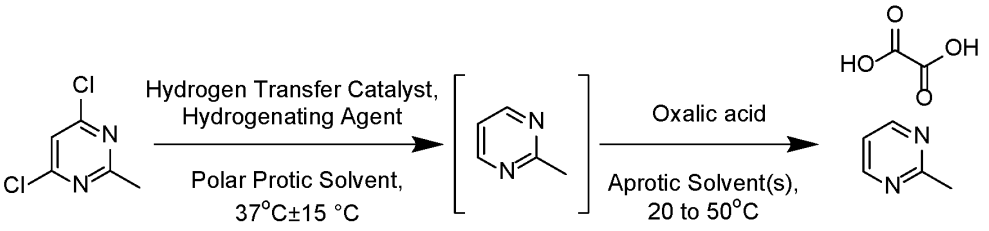
Scheme A-1



Compound No. 1 **Compound No. 2** *Not isolated* **Compound No. 3**

[052] In some embodiments, the method comprises one or more steps according to Scheme A-2.

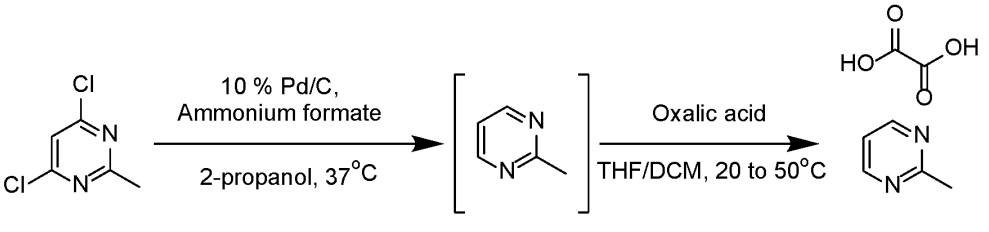
Scheme A-2



Compound No. 1 **Compound No. 2** *Not isolated* **Compound No. 3a**

[053] In some embodiments, the method comprises one or more steps according to Scheme A-3.

Scheme A-3



Compound No. 1 **Compound No. 2** *Not isolated* **Compound No. 3a**

[054] In some embodiments, the present disclosure provides a method of preparing Compound No. 5, or a salt thereof, described herein.

[055] In some embodiments, the methods comprises one or more of steps (i)-(iii):

(i) reacting Compound No. 1 or a salt thereof, with a hydrogenating agent, thereby forming Compound No. 2; and

(ii) reacting Compound No. 2, with an acid, thereby forming Compound No. 3 (e.g., Compound No. 3a); and

(iii) reacting Compound No. 3 (e.g., Compound No. 3a), with Compound No. 4 or a salt thereof, thereby forming Compound No. 5 or a salt thereof.

[056] In some embodiments, the method comprises step (i).

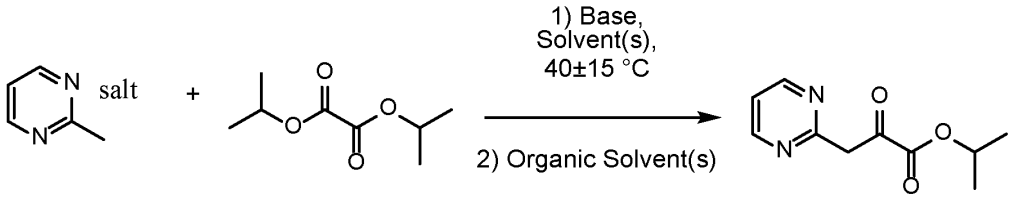
[057] In some embodiments, the method comprises step (ii).

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

[059] In some embodiments, the method comprises steps (i)-(iii).

[060] In some embodiments, the method comprises one or more steps according to Scheme B.

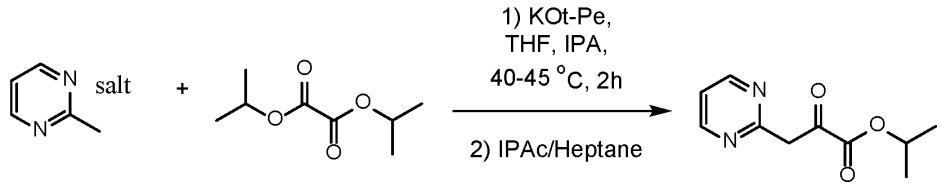
Scheme B



Compound No. 3 **Compound No. 4** **Compound No. 5**

[061] In some embodiments, the method comprises one or more steps according to Scheme B-1.

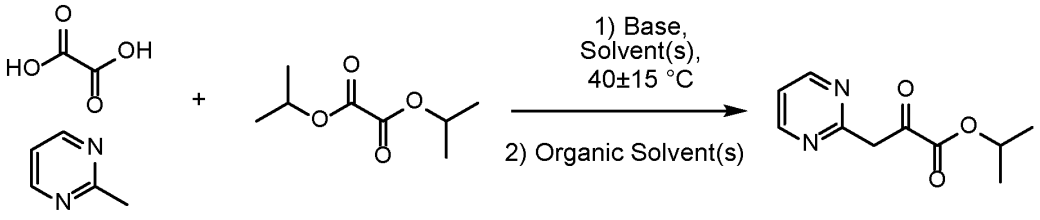
Scheme B-1



Compound No. 3 **Compound No. 4** **Compound No. 5**

[062] In some embodiments, the method comprises one or more steps according to Scheme B-2.

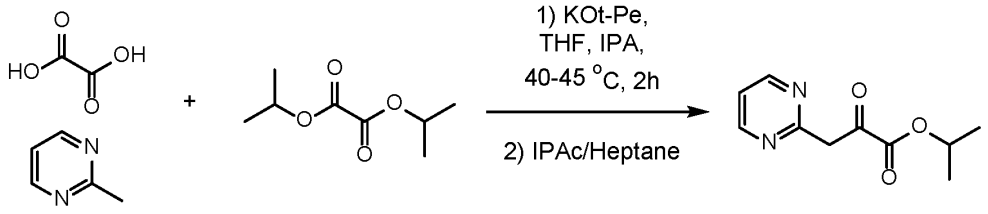
Scheme B-2



Compound No. 3a **Compound No. 4** **Compound No. 5**

[063] In some embodiments, the method comprises one or more steps according to Scheme B-3.

Scheme B-3



Compound No. 3a **Compound No. 4** **Compound No. 5**

[064] In some embodiments, the present disclosure provides a method of preparing Compound No. 6 (e.g., Compound No. 6a or 6b), or a salt thereof, comprising one or more of steps (i)-(iv):

(i) reacting Compound No. 1 or a salt thereof, with a hydrogenating agent, thereby forming Compound No. 2; and

(ii) reacting Compound No. 2, with an acid, thereby forming Compound No. 3 (e.g., Compound No. 3a); and

(iii) reacting Compound No. 3 (e.g., Compound No. 3a), with Compound No. 4 or a salt thereof, thereby forming Compound No. 5 or a salt thereof; and

(iv) reacting Compound No. 5, or a salt thereof, with a reducing agent, thereby forming Compound No. 6 (e.g., Compound No. 6a or 6b), or a salt thereof.

[065] In some embodiments, the method comprises step (i).

[066] In some embodiments, the method comprises step (ii).

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

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

[069] In some embodiments, the method comprises steps (i)-(iv).

[070] In some embodiments, the present disclosure provides a method of preparing Compound No. 9 (e.g., Compound No. 9a or 9b), or a salt thereof, described herein.

[071] In some embodiments, the method comprises one or more of steps (i)-(vii):

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

(ii) reacting Compound No. 2, with an acid, thereby forming Compound No. 3 (e.g., Compound No. 3a);

(iii) reacting Compound No. 3 (e.g., Compound No. 3a), with Compound No. 4 or a salt thereof, thereby forming Compound No. 5 or a salt thereof;

(iv) reacting Compound No. 5, or the salt thereof, with a reducing agent, thereby forming Compound No. 6 (e.g., Compound No. 6a or 6b) or a salt thereof;

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

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

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

[072] In some embodiments, the method comprises step (i).

[073] In some embodiments, the method comprises step (ii).

[074] In some embodiments, the method comprises step (i) and (ii).

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

[076] In some embodiments, the comprises steps (i), (ii), and (iii).

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

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

[079] In some embodiments, the method comprises step (v).

[080] In some embodiments, the method comprises steps (i), (ii), (iii), (iv), and (v).

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

[082] In some embodiments, the method comprises steps (i), (ii), (iii), (iv), (v), and (vi).

[083] In some embodiments, the method comprises step (vii).

[084] In some embodiments, the method comprises steps (i), (ii), (iii), (iv), (v), (vi), and (vii).

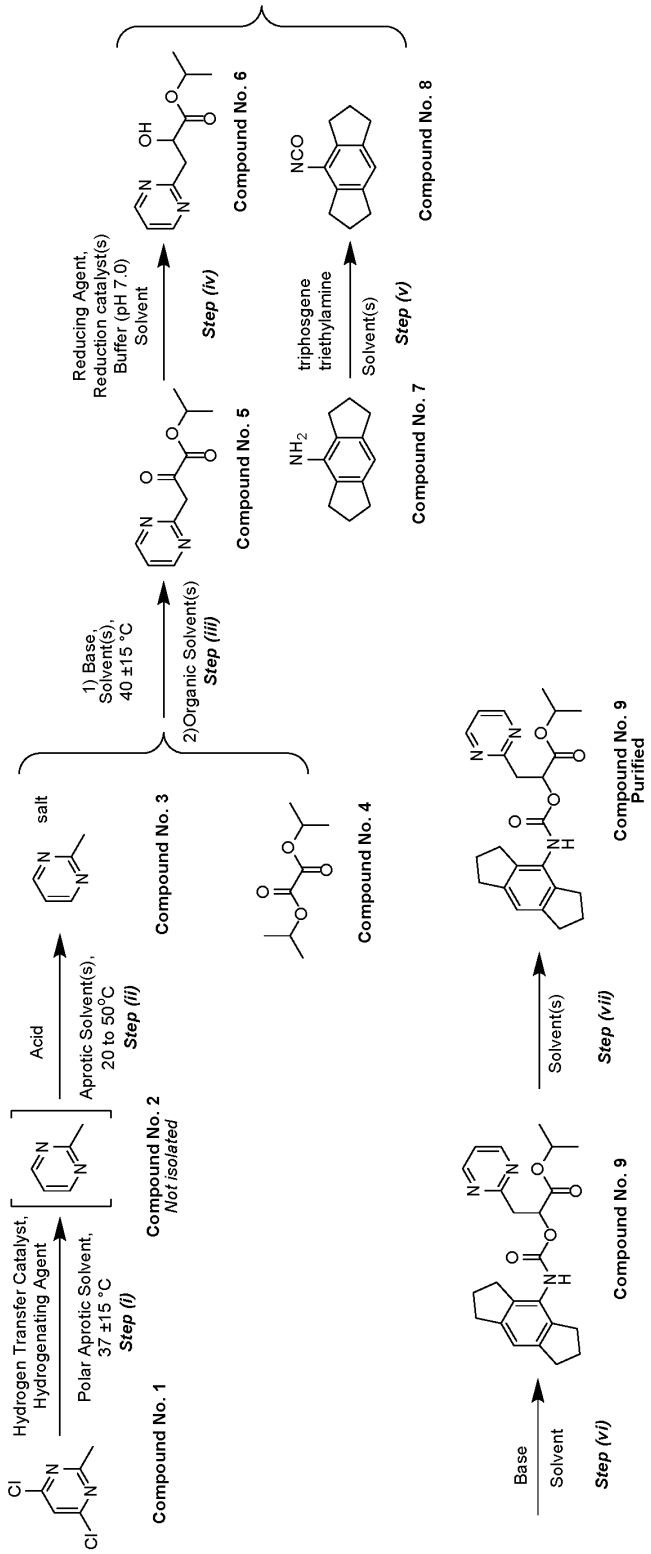
[085] In some embodiments, the method comprises one or more steps according to Scheme C.

[086] In some embodiments, the method comprises one or more steps according to Scheme C-1.

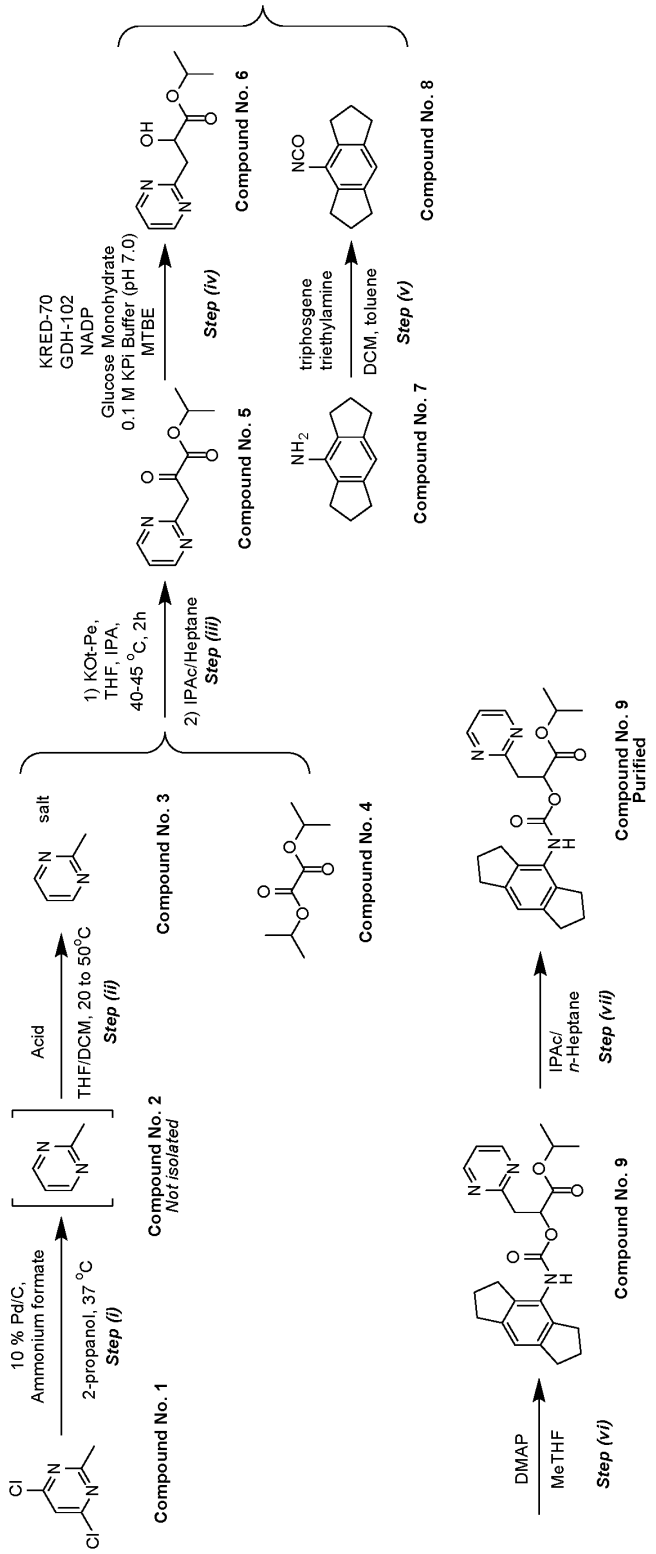
[087] In some embodiments, the method comprises one or more steps according to Scheme C-2.

[088] In some embodiments, the method comprises one or more steps according to Scheme C-3.

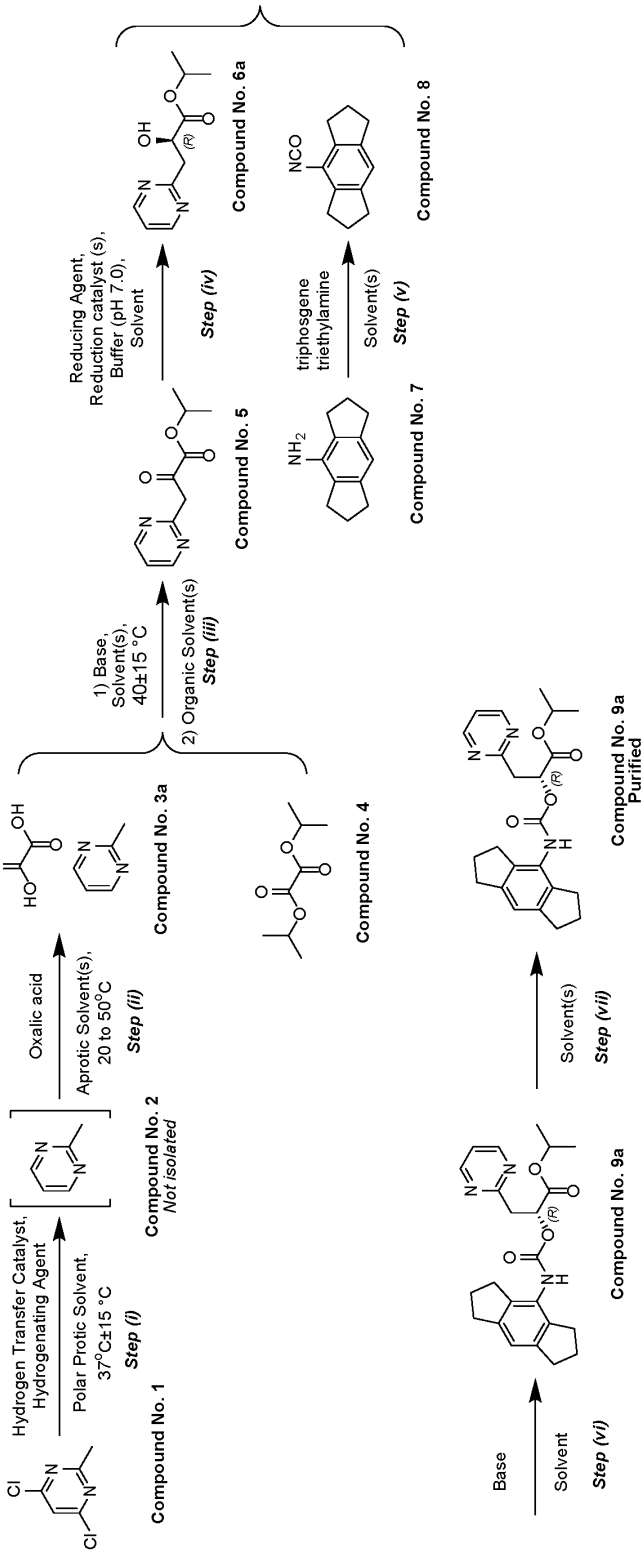
Scheme C


Hydrogen Transfer Catalyst, Hydrogenating Agent
Polar Aprotic Solvent, 37 ±15 °C
Step (i)
Compound No. 1
Compound No. 2
Not isolated
Acid
Aprotic Solvent(s), 20 to 50°C
Step (ii)
salt
Compound No. 3
1) Base, Solvent(s), 40 ±15 °C
2)Organic Solvent(s)
Step (iii)
Compound No. 4
Reducing Agent, Reduction catalyst(s) Buffer (pH 7.0) Solvent
Step (iv)
Compound No. 5
Compound No. 6
triphosgene triethylamine
Solvent(s)
Step (v)
Compound No. 7
Compound No. 8
Base
Solvent
Step (vi)
Compound No. 9
Solvent(s)
Step (vii)
Compound No. 9 Purified

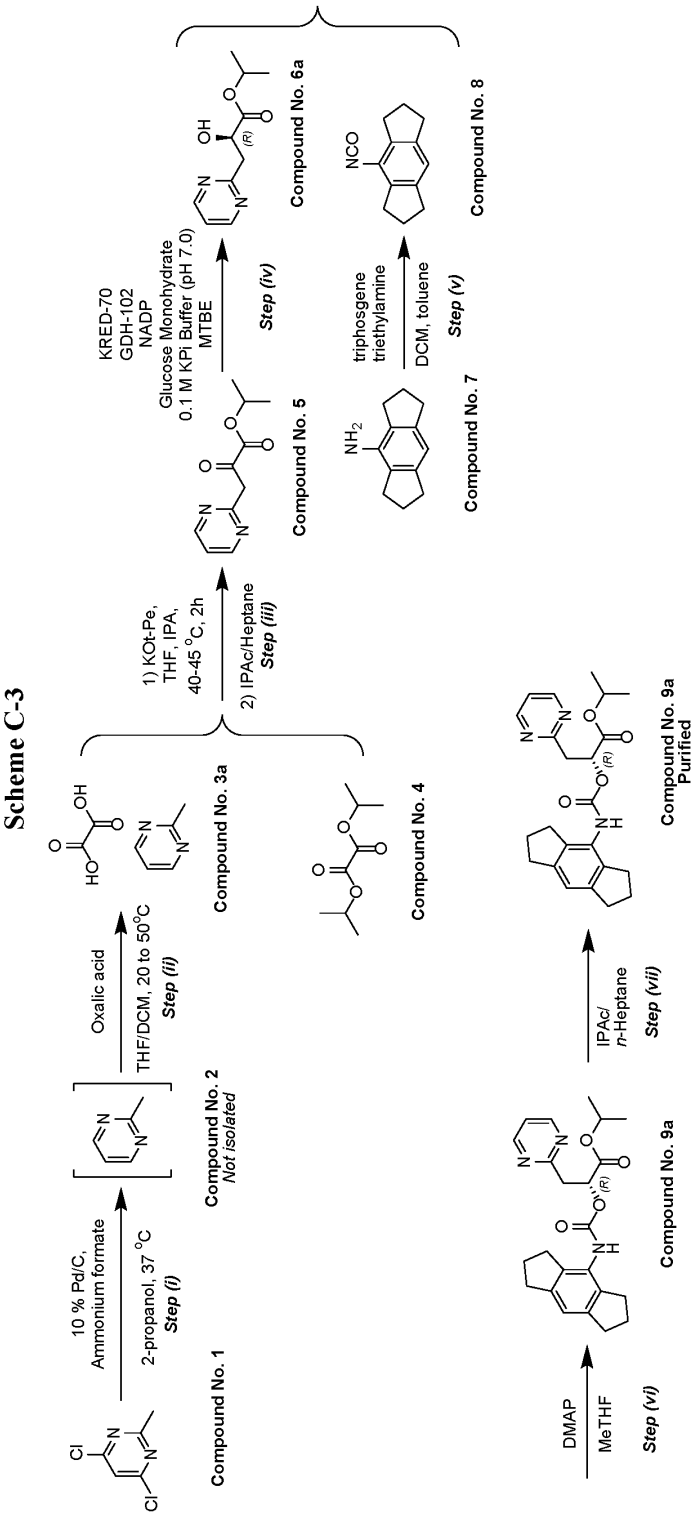
Scheme C-1


Cl
Cl
Compound No. 1
10 % Pd/C,
Ammonium formate
2-propanol, 37 °C
Step (i)
Compound No. 2
Not isolated
Acid
THF/DCM, 20 to 50°C
Step (ii)
salt
Compound No. 3
Compound No. 4
1) KOt-Pe,
THF, IPA,
40-45 °C, 2h
2) IPAc/Heptane
Step (iii)
Compound No. 5
KRED-70
GDH-102
NADP
Glucose Monohydrate
0.1 M KPi Buffer (pH 7.0)
MTBE
Step (iv)
Compound No. 6
NH2
Compound No. 7
triphosgene
triethylamine
DCM, toluene
Step (v)
NCO
Compound No. 8
DMAP
MeTHF
Step (vi)
Compound No. 9
IPAc/
n-Heptane
Step (vii)
Compound No. 9
Purified

Scheme C-2


Hydrogen Transfer Catalyst, Hydrogenating Agent
Polar Protic Solvent, 37°C±15 °C
Step (i)
Compound No. 1
Compound No. 2
Not isolated
Oxalic acid
Aprotic Solvent(s), 20 to 50°C
Step (ii)
Compound No. 3a
1) Base, Solvent(s), 40±15 °C
2) Organic Solvent(s)
Step (iii)
Compound No. 4
Compound No. 5
Reducing Agent, Reduction catalyst (s), Buffer (pH 7.0), Solvent
Step (iv)
Compound No. 6a
triphosgene triethylamine
Solvent(s)
Step (v)
Compound No. 7
Compound No. 8
Base
Solvent
Step (vi)
Compound No. 9a
Solvent(s)
Step (vii)
Compound No. 9a Purified

Scheme C-3


Cl
N
N
Cl
Compound No. 1
10 % Pd/C,
Ammonium formate
2-propanol, 37 °C
Step (i)
Compound No. 2
Not isolated
Oxalic acid
THF/DCM, 20 to 50°C
Step (ii)
HO
OH
O
N
N
Compound No. 3a
O
O
O
O
Compound No. 4
1) KOt-Pe,
THF, IPA,
40-45 °C, 2h
2) IPAc/Heptane
Step (iii)
KRED-70
GDH-102
NADP
Glucose Monohydrate
0.1 M KPi Buffer (pH 7.0)
MTBE
Step (iv)
Compound No. 5
Compound No. 6a
NH2
Compound No. 7
triphosgene
triethylamine
DCM, toluene
Step (v)
NCO
Compound No. 8
DMAP
MeTHF
Step (vi)
Compound No. 9a
IPAc/
n-Heptane
Step (vii)
Compound No. 9a
Purified

Step (i)

[089] In some embodiments, in step (i), the hydrogenating agent is hydrogen or ammonium formate.

[090] In some embodiments, in step (i), the hydrogenating agent is hydrogen.

[091] In some embodiments, in step (i), the hydrogenating agent is ammonium formate.

[092] In some embodiments, step (i) is performed in the presence of a hydrogen transfer catalyst.

[093] In some embodiments, in step (i), the hydrogen transfer catalyst is a nickel catalyst, a platinum catalyst, a palladium catalyst, a rhodium catalyst, or a ruthenium catalyst.

[094] In some embodiments, in step (i), the hydrogen transfer catalyst is a nickel catalyst (e.g., Raney nickel).

[095] In some embodiments, in step (i), the hydrogen transfer catalyst is a platinum catalyst.

[096] In some embodiments, in step (i), the hydrogen transfer catalyst is a palladium catalyst (e.g., palladium on carbon (Pd/C)).

[097] In some embodiments, in step (i), the hydrogen transfer catalyst is a rhodium catalyst.

[098] In some embodiments, in step (i), the hydrogen transfer catalyst is a ruthenium catalyst.

[099] In some embodiments, in step (i), the reacting is performed in the presence of a solvent or a mixture of solvents. In some embodiments, the solvent is an organic solvent or a mixture of organic solvents. In some embodiments, the solvent is a polar protic solvent (e.g., methanol, 2-propanol, or a mixture thereof).

[0100] In some embodiments, in step (i), the reacting is conducted at a temperature of 35±15 °C, 35±10 °C, or 35±5 °C (e.g., about 35 °C).

[0101] In some embodiments, in step (i), the reacting is conducted at a temperature of 36±15 °C, 36±10 °C, or 36±5 °C (e.g., about 36 °C).

[0102] In some embodiments, in step (i), the reacting is conducted at a temperature of 37±15 °C, 37±10 °C, or 37±5 °C (e.g., about 37 °C).

[0103] In some embodiments, in step (i), the reacting is conducted at a temperature of 38±15 °C, 38±10 °C, or 38±5 °C (e.g., about 38 °C).

[0104] In some embodiments, in step (i), the reacting is conducted at a temperature of 39±15 °C, 39±10 °C, or 39±5 °C (e.g., about 39 °C).

[0105] In some embodiments, in step (i), the reacting is conducted at a temperature of 40±15 °C, 40±10 °C, or 40±5 °C (e.g., about 40 °C).

[0106] In some embodiments, in step (i), the reacting is performed for 5±10 hours, 5±9 hours, 5±8 hours, 5±7 hours, 5±6 hours, 5±5 hours, 5±4 hours, 5±3 hours, 5±2 hours, or 5±1 hours (e.g., about 5 hours).

[0107] In some embodiments, in step (i), the reacting is performed for 6±10 hours, 6±9 hours, 6±8 hours, 6±7 hours, 6±6 hours, 6±5 hours, 6±4 hours, 6±3 hours, 6±2 hours, or 6±1 hours (e.g., about 6 hours).

[0108] In some embodiments, in step (i), the reacting is performed for 7±10 hours, 7±9 hours, 7±8 hours, 7±7 hours, 7±6 hours, 7±5 hours, 7±4 hours, 7±3 hours, 7±2 hours, or 7±1 hours (e.g., about 7 hours).

[0109] In some embodiments, in step (i), the reacting is performed for 8±10 hours, 8±9 hours, 8±8 hours, 8±7 hours, 8±6 hours, 8±5 hours, 8±4 hours, 8±3 hours, 8±2 hours, or 8±1 hours (e.g., about 8 hours).

[0110] In some embodiments, in step (i), the 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof to hydrogenating agent ratio is from about 5:1 to about 1:5.

[0111] In some embodiments, in step (i), the 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof to hydrogenating agent ratio is from about 4:1 to about 1:4.

[0112] In some embodiments, in step (i), the 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof to hydrogenating agent ratio is from about 3:1 to about 1:3.

[0113] In some embodiments, in step (i), the 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof to hydrogenating agent ratio is from about 2:1 to about 1:2.

[0114] In some embodiments, in step (i), the 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof to hydrogenating agent ratio is from about 1:1 to about 1:4.

[0115] In some embodiments, in step (i), the 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof to hydrogenating agent ratio is about 1:1.

[0116] In some embodiments, in step (i), the 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof to hydrogenating agent ratio is about 1:2.

[0117] In some embodiments, in step (i), the 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof to hydrogenating agent ratio is about 1:3.

[0118] In some embodiments, in step (i), the 4,6-dichloro-2-methylpyrimidine (Compound No. 1) or a salt thereof to hydrogenating agent ratio is about 1:4.

[0119] In some embodiments, in step (i), 2-methylpyrimidine (Compound No. 2) is not isolated or purified prior to step (ii) (e.g., prior to reacting with the acid).

[0120] In some embodiments, in step (i), a mixture comprising 2-methylpyrimidine (Compound No. 2) is formed.

[0121] In some embodiments, in step (i), the mixture comprising 2-methylpyrimidine (Compound No. 2) is acidified (e.g., with an aqueous solution of hydrochloric acid).

[0122] In some embodiments, in step (i), the acidified mixture is washed with an organic solvent (e.g., methyl tert-butyl ether).

[0123] In some embodiments, in step (i), a polar solvent (e.g., dichloromethane) is added to the washed mixture.

[0124] In some embodiments, in step (i), the mixture is basified (e.g., with an aqueous solution of potassium carbonate).

[0125] In some embodiments, in step (i), the mixture is basified to a pH of at least about 7.5.

[0126] In some embodiments, in step (i), the mixture is basified to a pH of at least about 8.

[0127] In some embodiments, in step (i), the mixture is basified to a pH of at least about 8.5.

[0128] In some embodiments, in step (i), the mixture is basified to a pH of at least about 9.

[0129] In some embodiments, in step (i), 2-methylpyrimidine (Compound No. 2) is extracted from the basified mixture in the polar solvent (e.g., dichloromethane).

Step (ii)

[0130] In some embodiments, in step (ii), the acid is an organic acid (e.g., oxalic acid).

[0131] In some embodiments, in step (ii), the acid is oxalic acid.

[0132] In some embodiments, in step (ii), the reacting is performed in the presence of an aprotic solvent (e.g., dichloromethane (DCM), tetrahydrofuran (THF), or a mixture thereof).

[0133] In some embodiments, in step (ii), the reacting is performed in the presence of tetrahydrofuran (THF).

[0134] In some embodiments, step (ii) is conducted at a temperature from about -20 °C to about 60 °C to form a second mixture.

[0135] In some embodiments, step (ii) is conducted at a temperature from about 20 °C to about 50 °C to form a second mixture.

[0136] In some embodiments, step (ii) is conducted at a temperature from about 30 °C to about 50 °C to form a second mixture.

[0137] In some embodiments, step (ii) is conducted at a temperature from about 40 °C to about 50 °C to form a second mixture.

[0138] In some embodiments, step (ii) is conducted at a temperature of about 20 °C to form a second mixture.

[0139] In some embodiments, step (ii) is conducted at a temperature of about 25 °C to form a second mixture.

[0140] In some embodiments, step (ii) is conducted at a temperature of about 30 °C to form a second mixture.

[0141] In some embodiments, step (ii) is conducted at a temperature of about 35 °C to form a second mixture.

[0142] In some embodiments, step (ii) is conducted at a temperature of about 40 °C to form a second mixture.

[0143] In some embodiments, step (ii) is conducted at a temperature of about 45 °C to form a second mixture.

[0144] In some embodiments, step (ii) is conducted at a temperature of about 50 °C to form a second mixture.

[0145] In some embodiments, in step (ii), the second mixture is subjected to a temperature cycling procedure.

[0146] In some embodiments, in step (ii), the second mixture is subjected to a temperature cycling procedure comprises the steps of (a) cooling the second mixture to about 20 °C over about 1 hour and agitating for about 15 minutes, (b) heating back to about 45 °C and agitating for at least about 30 minutes, (c) cooling from about 45 °C to about 20 °C over about 1 hour and agitating for about 15 minutes, (d) heating back to about 45 °C and agitating for at least about 30 minutes, (e) cooling from about 45 °C to about -10 °C over about 4 hours, and (f) stirring for at least about 13 hours at about -10 °C.

[0147] In some embodiments, step (ii) further comprises isolating the 2-methylpyrimidine salt (Compound No. 3).

[0148] In some embodiments, step (ii) further comprises isolating the 2-methylpyrimidine salt (e.g., Compound No. 3a).

[0149] In some embodiments, step (ii) further comprises isolating 2-methylpyrimidine oxalate (Compound No. 3a).

[0150] In some embodiments, step (ii) further comprises drying the 2-methylpyrimidine salt (Compound No. 3).

[0151] In some embodiments, step (ii) further comprises drying the 2-methylpyrimidine salt (e.g., Compound No. 3a).

[0152] In some embodiments, step (ii) further comprises drying 2-methylpyrimidine oxalate (Compound No. 3a).

[0153] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 98% by area as measured by HPLC (High-performance liquid chromatography).

[0154] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 98.5% by area as measured by HPLC.

[0155] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 99% by area as measured by HPLC.

[0156] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 99.1% by area as measured by HPLC.

[0157] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 99.2% by area as measured by HPLC.

[0158] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 99.3% by area as measured by HPLC.

[0159] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 99.4% by area as measured by HPLC.

[0160] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 99.5% by area as measured by HPLC.

[0161] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 99.6% by area as measured by HPLC.

[0162] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 99.7% by area as measured by HPLC.

[0163] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) has a purity of at least about 99.8% by area as measured by HPLC.

[0164] In some embodiments, in step (ii), 2-methylpyrimidine oxalate (Compound No. 3a) has a purity of at least about 98%, at least about 98.5%, at least about 99%, at least about 99.1%, at least about 99.2%, at least about 99.3%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, or at least about 99.8% by area as measured by HPLC.

[0165] In some embodiments, in step (ii), the yield of 2-methylpyrimidine salt (e.g., Compound No. 3a) is at least about 50%.

[0166] In some embodiments, in step (ii), the yield of 2-methylpyrimidine salt (e.g., Compound No. 3a) is at least about 55%.

[0167] In some embodiments, in step (ii), the yield of 2-methylpyrimidine salt (e.g., Compound No. 3a) is at least about 60%.

[0168] In some embodiments, in step (ii), the yield of 2-methylpyrimidine salt (e.g., Compound No. 3a) is at least about 65%.

[0169] In some embodiments, in step (ii), the yield of 2-methylpyrimidine salt (e.g., Compound No. 3a) is at least about 69%.

[0170] In some embodiments, in step (ii), the yield of 2-methylpyrimidine salt (e.g., Compound No. 3a) is at least about 70%.

[0171] In some embodiments, in step (ii), the yield of 2-methylpyrimidine salt (e.g., Compound No. 3a) is at least about 75%.

[0172] In some embodiments, in step (ii), the yield of 2-methylpyrimidine salt (e.g., Compound No. 3a) is at least about 80%.

[0173] In some embodiments, in step (ii), the yield of 2-methylpyrimidine salt (e.g., Compound No. 3a) is at least about 85%.

[0174] In some embodiments, in step (ii), the yield of 2-methylpyrimidine oxalate (Compound No. 3a) is at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 69%, at least about 70%, at least about 75%, at least about 80%, or at least about 85%.

[0175] In some embodiments, in step (ii), the 2-methylpyrimidine salt is 2-methylpyrimidine oxalate.

[0176] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) comprises less than about 5% of impurities by area as measured by HPLC.

[0177] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) comprises less than about 4% of impurities by area as measured by HPLC.

[0178] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) comprises less than about 3% of impurities by area as measured by HPLC.

[0179] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) comprises less than about 2% of impurities by area as measured by HPLC.

[0180] In some embodiments, in step (ii), the 2-methylpyrimidine salt (e.g., Compound No. 3a) comprises less than about 1% of impurities by area as measured by HPLC.

[0181] In some embodiments, in step (ii), 2-methylpyrimidine oxalate (Compound No. 3a) comprises less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% of impurities by area as measured by HPLC.

[0182] In some embodiments, in step (ii), the impurities comprise 2-propanol.

[0183] In some embodiments, in step (ii), the impurities comprise 4, 6-dichloro-2-methylpyrimidine.

[0184] In some embodiments, in step (ii), the impurities comprise 2-propanol; 4, 6-dichloro-2-methylpyrimidine; or a mixture thereof.

[0185] In some embodiments, in step (ii), the impurities comprise less than about 5.5% of 2-propanol.

[0186] In some embodiments, in step (ii), the impurities comprise less than about 0.1% of 4, 6-dichloro-2-methylpyrimidine.

[0187] In some embodiments, in step (ii), the impurities comprise about 4.9% of 2-propanol; about 0.03% of 4, 6-dichloro-2-methylpyrimidine; or a mixture thereof.

Step (iii)

[0188] In some embodiments, in step (iii), the reacting is performed in the presence of a base. In some embodiments, the base is potassium *tert*-pentoxide.

[0189] In some embodiments, step (iii) results in less than about 1.0% of tert-pentyl ester by area as measured by HPLC.

[0190] In some embodiments, step (iii) results in less than about 0.9% of tert-pentyl ester by area as measured by HPLC.

[0191] In some embodiments, step (iii) results in less than about 0.8% of tert-pentyl ester by area as measured by HPLC.

[0192] In some embodiments, step (iii) results in less than about 0.7% of tert-pentyl ester by area as measured by HPLC.

[0193] In some embodiments, step (iii) results in less than about 0.6% of tert-pentyl ester by area as measured by HPLC.

[0194] In some embodiments, step (iii) results in less than about 0.5% of tert-pentyl ester by area as measured by HPLC.

[0195] In some embodiments, step (iii) results in less than about 0.4% of tert-pentyl ester by area as measured by HPLC.

[0196] In some embodiments, step (iii) results in less than about 0.3% of tert-pentyl ester by area as measured by HPLC.

[0197] In some embodiments, step (iii) results in less than about 0.2% of tert-pentyl ester by area as measured by HPLC.

[0198] In some embodiments, step (iii) results in less than about 0.1% of tert-pentyl ester by area as measured by HPLC.

[0199] In some embodiments, step (iii) is conducted at a temperature of 30±15 °C, 30±10 °C, or 30±5 °C (e.g., about 30°C).

[0200] In some embodiments, step (iii) is conducted at a temperature of 40±15 °C, 40±10 °C, or 40±5 °C (e.g., about 40°C).

[0201] In some embodiments, step (iii) is conducted at a temperature of 50±15 °C, 50±10 °C, or 50±5 °C (e.g., about 50°C).

[0202] In some embodiments, step (iii) is performed in the presence of a polar solvent.

[0203] In some embodiments, step (iii) is performed in the presence of an aprotic solvent.

[0204] In some embodiments, step (iii) is performed in the presence of a polar solvent, an aprotic solvent, or a mixture thereof. In some embodiments, step (iii) is performed in the presence of THF, isopropyl alcohol (IPA), or a mixture thereof.

[0205] In some embodiments, step (iii), further comprises isolating Compound No. 5, or a salt thereof.

[0206] In some embodiments, in step (iii), a mixture comprising Compound No. 5, or a salt thereof, is formed.

[0207] In some embodiments, in step (iii), the mixture comprising Compound No. 5, or a salt thereof, is washed with an aqueous solution (e.g., aqueous potassium bicarbonate solution).

[0208] In some embodiments, in step (iii), the mixture comprising Compound No. 5, or a salt thereof, is further washed with water.

[0209] In some embodiments, in step (iii), an organic solvent (e.g., isopropyl acetate, heptane, or a mixture thereof) is added to the washed mixture to form a suspension.

[0210] In some embodiments, in step (iii), Compound No. 5, or a salt thereof, is isolated by filtration.

[0211] In some embodiments, in step (iii), Compound No. 5, or a salt thereof has a purity of at least about 90% by area as measured by HPLC.

[0212] In some embodiments, in step (iii), Compound No. 5, or a salt thereof has a purity of at least about 92% by area as measured by HPLC.

[0213] In some embodiments, in step (iii), Compound No. 5, or a salt thereof has a purity of at least about 94% by area as measured by HPLC.

[0214] In some embodiments, in step (iii), Compound No. 5, or a salt thereof has a purity of at least about 96% by area as measured by HPLC.

[0215] In some embodiments, in step (iii), Compound No. 5, or a salt thereof has a purity of at least about 98% by area as measured by HPLC.

[0216] In some embodiments, in step (iii), Compound No. 5, or a salt thereof has a purity of at least about 99% by area as measured by HPLC.

[0217] In some embodiments, in step (iii), the yield of Compound No. 5, or a salt thereof is at least about 60%.

[0218] In some embodiments, in step (iii), the yield of Compound No. 5, or a salt thereof is at least about 65%.

[0219] In some embodiments, in step (iii), the yield of Compound No. 5, or a salt thereof is at least about 70%.

[0220] In some embodiments, in step (iii), the yield of Compound No. 5, or a salt thereof is at least about 75%.

[0221] In some embodiments, in step (iii), the yield of Compound No. 5, or a salt thereof is at least about 80%.

[0222] In some embodiments, in step (iii), the yield of Compound No. 5, or a salt thereof is at least about 85%.

[0223] In some embodiments, in step (iii), the yield of Compound No. 5, or a salt thereof is at least about 90%.

Step (iv)

[0224] In some embodiments, in step (iv), the reducing agent is a monosaccharide.

[0225] In some embodiments, in step (iv), the reducing agent is glucose monohydrate.

[0226] In some embodiments, step (iv) is performed in the presence of a reduction catalyst.

[0227] In some embodiments, step (iv) is performed in the presence of a reduction catalyst, wherein the reduction catalyst is an enzymatic catalyst.

[0228] In some embodiments, step (iv) is performed in the presence of a reduction catalyst, wherein the reduction catalyst is a dinucleotide phosphate.

[0229] In some embodiments, step (iv) is performed in the presence of a reduction catalyst, wherein the reduction catalyst is an enzymatic catalyst, a dinucleotide phosphate, or a mixture thereof.

[0230] In some embodiments, in step (iv), the enzymatic catalyst is ketoreductase (KRED).

[0231] In some embodiments, in step (iv), the enzymatic catalyst is glutamate dehydrogenase (GDH).

[0232] In some embodiments, in step (iv), the enzymatic catalyst is ketoreductase (KRED), glutamate dehydrogenase (GDH), or a mixture thereof.

[0233] In some embodiments, in step (iv), the enzymatic catalyst is ketoreductase (KRED), glutamate dehydrogenase (GDH), or a mixture thereof, and wherein the dinucleotide phosphate is nicotinamide adenine dinucleotide phosphate (NADP).

[0234] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5, or the salt thereof, is from about 4:1 to about 1:4.

[0235] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5, or the salt thereof, is from about 3:1 to about 1:3.

[0236] In some embodiments, in step (iv), the molar ratio of the acid to Compound No. 5, or the salt thereof, is from about 2:1 to about 1:2.

[0237] In some embodiments, in step (iv), Compound No. 6 (e.g., Compound No. 6a or 6b), or the salt thereof, is isolated prior to reacting with Compound No. 8 or a salt thereof.

[0238] In some embodiments, in step (iv), the reacting is performed in the presence of a buffering solution. In some embodiments, the buffering solution comprises phosphate (e.g., dipotassium phosphate (K_2HPO_4) or monopotassium phosphate (KH_2PO_4)).

[0239] In some embodiments, in step (iv), the reacting is performed at a pH of about 7.

[0240] 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).

[0241] In some embodiments, the contacting is performed in the presence of a polar aprotic solvent (e.g., methyl *t*-butyl ether (MTBE)).

[0242] In some embodiments, step (iv) further comprises extracting the formed Compound No. 6 (e.g., Compound No. 6a or 6b) or the salt thereof.

[0243] In some embodiments, step (iv) yields a solution of Compound No. 6 (e.g., Compound No. 6a or 6b) or the salt thereof.

Step (v)

[0244] In some embodiments, in step (v), the source of CO is triphosgene.

[0245] In some embodiments, in step (v), the reacting is performed in the presence of a base. In some embodiments, the base is an organic base (e.g., triethylamine (TEA)).

[0246] 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, dichloromethane (DCM), or a mixture thereof).

[0247] In some embodiments, in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is from about 3:1 to about 1:3.

[0248] In some embodiments, step (v) comprises filtering a solution of Compound No. 8 or the salt thereof (e.g., in toluene).

[0249] In some embodiments, step (v) yields a solution of Compound No. 8 or the salt thereof (e.g., in toluene).

Step (vi)

[0250] In some embodiments, in step (vi), the reacting is performed in the presence of a base. In some embodiments, the base is an organic base (e.g., 4-dimethylaminopyridine (DMAP)).

[0251] In some embodiments, in step (vi), the reacting is performed in the presence of a solvent. In some embodiments, the solvent is an aprotic organic solvent. In some embodiments, the solvent comprises methyltetrahydrofuran (MeTHF).

[0252] In some embodiments, step (vi) is performed in the presence of an organic base, an aprotic solvent, or a mixture thereof.

[0253] In some embodiments, in step (vi), the molar ratio of Compound No. 6 (e.g., Compound No. 6a or 6b), or a salt thereof, to the Compound No. 8, or the salt thereof, is from about 3:1 to about 1:3.

[0254] In some embodiments, in step (vi), Compound No. 9 (e.g., Compound No. 9a or 9b), or a salt thereof, is isolated.

Step (vii)

[0255] In some embodiments, step (vii) comprises crystallizing Compound No. 9 (e.g., Compound No. 9a or 9b), or a salt thereof, in the presence of at least one organic solvent. In some embodiments, the at least one organic solvent is isopropyl acetate (IPAc), n-heptane, or a mixture thereof.

[0256] In some embodiments, step (vii) further comprises isolating Compound No. 9 (e.g., Compound No. 9a or 9b) or a salt thereof.

[0257] In some embodiments, in step (vii), Compound No. 9 (e.g., Compound No. 9a or 9b), or a salt thereof, has a purity of at least about 99.0 % by area as measured by HPLC.

[0258] In some embodiments, in step (vii), Compound No. 9 (e.g., Compound No. 9a or 9b), or a salt thereof, has a purity of at least about 99.5 % by area as measured by HPLC.

Compounds Prepared by the Methods

[0259] In some embodiments, the present disclosure provides a compound being prepared by a method disclosed herein.

[0260] In some embodiments, the present disclosure provides a compound being prepared in large scale according to a method disclosed herein.

[0261] In some embodiments, the present disclosure provides a method of preparing Compound No. 2.

[0262] In some embodiments, the present disclosure provides a method of preparing Compound No. 3.

[0263] In some embodiments, the present disclosure provides a method of preparing Compound No. 3a.

[0264] In some embodiments, the present disclosure provides a method of preparing Compound No. 5 or a salt thereof.

[0265] In some embodiments, the present disclosure provides a method of preparing Compound No. 6 or a salt thereof.

[0266] In some embodiments, the present disclosure provides a method of preparing Compound No. 6a or a salt thereof.

[0267] In some embodiments, the present disclosure provides a method of preparing Compound No. 6b or a salt thereof.

[0268] In some embodiments, the present disclosure provides a method of preparing Compound No. 8 or a salt thereof.

[0269] In some embodiments, the present disclosure provides a method of preparing Compound No. 9 or a salt thereof.

[0270] In some embodiments, the present disclosure provides a method of preparing Compound No. 9a or a salt thereof.

[0271] In some embodiments, the present disclosure provides a method of preparing Compound No. 9b or a salt thereof.

[0272] In some embodiments, the present disclosure provides Compound No. 3.

[0273] In some embodiments, the compound is Compound No. 3 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.

[0274] In some embodiments, the compound is Compound No. 3 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.

[0275] In some embodiments, the present disclosure provides Compound No. 3a.

[0276] In some embodiments, the compound is Compound No. 3a 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.

[0277] In some embodiments, the compound is Compound No. 3a 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.

[0278] In some embodiments, the compound is:

Compound No. 3; or

Compound No. 3a 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.

[0279] In some embodiments, the present disclosure provides Compound No. 5 or a salt thereof.

[0280] In some embodiments, the compound is Compound No. 5, 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.

[0281] 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.

[0282] In some embodiments, the present disclosure provides Compound No. 6, or a salt thereof.

[0283] In some embodiments, the compound is Compound No. 6, 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.

[0284] In some embodiments, the compound is Compound No. 6, 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.

[0285] In some embodiments, the present disclosure provides Compound No. 6a, or a salt thereof.

[0286] 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.

[0287] 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.

[0288] In some embodiments, the present disclosure provides Compound No. 6b, or a salt thereof.

[0289] 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.

[0290] 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.

[0291] In some embodiments, the present disclosure provides Compound No. 9, or a salt thereof.

[0292] In some embodiments, the compound is Compound No. 9, 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.

[0293] In some embodiments, the compound is Compound No. 9, 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.

[0294] In some embodiments, the present disclosure provides Compound No. 9a, or a salt thereof.

[0295] 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.

[0296] 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.

[0297] In some embodiments, the present disclosure provides Compound No. 9b, or a salt thereof.

[0298] 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.

[0299] 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.

[0300] In some embodiments, the present disclosure provides a compound prepared by a method as described herein.

Methods of Use

[0301] In some embodiments, the present disclosure provides a method of preventing or treating a disease in a subject, comprising administering to the subject Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, as described herein.

[0302] In some embodiments, the present disclosure provides Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, for use in preventing or treating a disease or for inhibiting inflammasome activity in a subject.

[0303] In some embodiments, the present disclosure provides use Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for preventing or treating a disease or for inhibiting inflammasome activity in a subject.

[0304] In some embodiments, the present disclosure provides a method of inhibiting inflammasome activity in a subject, comprising contacting a cell with Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof.

[0305] In some embodiments, the subject is administered a therapeutically effective amount of Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof.

[0306] In some embodiments, the present disclosure provides a method of treating a disease in a subject, comprising administering to the subject Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, as described herein.

[0307] In some embodiments, the present disclosure provides Compound No. 9 (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.

[0308] In some embodiments, the present disclosure provides use of Compound No. 9 (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.

[0309] In some embodiments, the present disclosure provides use of Compound No. 9 (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.

[0310] In some embodiments, the compound or the pharmaceutically acceptable salt thereof is administered in a therapeutically effective amount.

[0311] In some embodiments, the disease or disorder is an inflammatory disorder, autoinflammatory disorder, an autoimmune disorder, a neurodegenerative disease, or cancer.

[0312] In some embodiments, the present disclosure provides a method of inhibiting inflammasome (*e.g.*, the NLRP3 inflammasome) activity in a subject, comprising contacting a cell with Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, as described herein. In some embodiments, the present disclosure provides Compound No. 9 (e.g., Compound No. 9a or 9b), or a salt thereof, as described herein for use in inhibiting inflammasome (*e.g.*, the NLRP3 inflammasome) activity in a subject.

[0313] In some embodiments, the present disclosure provides use of Compound No. 9 (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.

[0314] In some embodiments, the subject is an animal.

[0315] In some embodiments, the subject is a mammal.

[0316] In some embodiments, the subject is a human.

[0317] In some embodiments, the subject is a cell.

[0318] In some embodiments, the subject is a cell population.

Pharmaceutical Compositions/Formulations

[0319] In some embodiments, the present disclosure provides pharmaceutical compositions comprising Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, and an excipient, adjuvant, diluent, or carrier (e.g., a pharmaceutically acceptable excipient, adjuvant, diluent, or carrier.

[0320] In some embodiments, the present disclosure provides pharmaceutical compositions comprising Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, and one or more of a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, a pharmaceutically acceptable adjuvant, or a pharmaceutically acceptable excipient.

[0321] Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

[0322] Proper formulation is dependent upon the route of administration chosen. Any of the well- known techniques, carriers, and excipients may be used as suitable and as understood in the art. A summary of pharmaceutical compositions described herein may be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington ‘s Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins, 1999), herein incorporated by reference in their entirety.

[0323] A pharmaceutical composition, as used herein, refers to Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, and/or an additional therapeutic agent with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. A pharmaceutical composition, as used herein, refers to Compound No. 9 (e.g., Compound No. 9a or 9b), or a salt thereof, and one or more of the following excipients: microcrystalline cellulose, crospovidone, Hypromellose, sodium bicarbonate, hydrophobic colloidal silica, and magnesium stearate.

[0324] In practicing the methods of treatment or use provided herein, therapeutically effective amounts of Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, disclosed herein are administered having a disease, disorder, or condition to be treated. In some embodiments, the mammal is a human.

The therapeutically effective amounts of the compounds may vary depending on the severity of the disease, the age and relative health of the subject, and other factors.

[0325] Pharmaceutical compositions including Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, described herein may be manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing,

dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

Biological Assays

[0326] 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.

[0327] 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.

[0328] 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.

[0329] In some embodiments, the biological away is a biological away testing inhibitory activity against IL-1β release upon NLRP3 activation in peripheral blood mononuclear cells (PBMC).

[0330] In some embodiments, the biological assay is a PBMC IC50 Determination Assay.

[0331] In some embodiments, the compound is tested for its inhibitory activity against IL-1β release upon NLRP3 activation in blood cells (e.g., peripheral blood mononuclear cells (PBMC)).

[0332] 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.

[0333] In some embodiments, the release of IL-1β into the media is determined by a quantitative detection of IL-1β in the media (e.g., using ELISA).

[0334] 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.

[0335] In some embodiments, the release of IL-1β into the media is determined by quantitative detection (e.g., of IL-1β in media using HTRF®).

Definitions

[0336] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0337] The term “about” is used herein to mean approximately, in the region of, roughly or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%, a variance of 10%, a variance of 5%, a variance of 3%, or a variance of 1%.

[0338] As used herein, the term “substantially pure” with reference to a compound indicates that the compound includes less than 10%, less than 5%, less than 3%, less than 1%, less than 0.5%, less than 0.2%, or less than 0.1% by weight of impurities.

[0339] As used herein, the term “a source of CO” refers to an agent that is capable of being a resource of carbon monoxide (CO) during a reaction. In some embodiments, the agent is capable of forming an isocyanate or an equivalent upon reacting with an amine. In some embodiments, a dissociation reaction of phosgene, a reaction between CO_2 with carbon (Boudouard reaction), a reaction of steam and carbon, a high-temperature electrolysis of carbon dioxide with solid oxide electrolyzer cells, or a direct oxidation of carbon in a limited supply of oxygen or air is the source of CO. In some embodiments, the source of CO is a phosgene derivative. In one specific embodiment, the source of CO is triphosgene.

[0340] 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).

[0341] 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.

[0342] 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.

[0343] 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.

[0344] It is to be understood that Compound No. 3 (e.g., Compound No. 3a) and Compound No. 9 (e.g., Compound No. 9a or 9b), or a 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.

[0345] 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.

[0346] It is to be understood that, unless otherwise stated, any description of a method of treatment or prevention includes use of Compound No. 9 (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 Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, to prepare a medicament to treat or prevent such a condition. The treatment or prevention includes treatment or prevention of human or non-human animals including rodents and other disease models.

[0347] It is to be understood that, unless otherwise stated, any description of a method of treatment includes use of Compound No. 9 (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 Compound No. 9 (e.g., Compound No. 9a or 9b), or a pharmaceutically acceptable salt thereof, to prepare a medicament to treat such a condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[0348] In some embodiments, the term "filtering out" is collecting a solid form of the desired compound by the use of a filter medium.

[0349] 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.

[0350] 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.

[0351] 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.

[0352] It is to be understood that Compound No. 9 (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.

[0353] As used herein, the term "preventing," or "prevent," describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0354] 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.

[0355] As used herein, the term "pharmaceutical composition" is a formulation containing Compound No. 9 (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, intravitreal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with one or more pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0356] 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.

[0357] 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.

[0358] It is to be understood that a pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.,* intravenous, intradermal, subcutaneous, intravitreal, oral (*e.g.*, ingestion), inhalation, transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0359] 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.

[0360] 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.

[0361] 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.

[0362] 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.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (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, LD_{50}/ED_{50}. 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.

[0363] 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.

[0364] The pharmaceutical compositions containing Compound No. 9 (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 Compound No. 9 (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.

[0365] In some embodiments, the pharmaceutical compositions disclosed herein further comprise a pharmaceutically acceptable excipient, such as, for example, a diluent, a carrier, an adjuvant, a binder, a lubricant, a surfactant, a sweetening agent, a flavoring agent, a coating material, a preservative, a dye, a thickener, or a combination thereof.

[0366] It is to be understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0367] 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.

[0368] As used herein, the term “pharmaceutically acceptable salts” refers to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making an acid or base salt thereof. Examples of pharmaceutically acceptable salts may include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts may include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts may include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulphonic, acetic, ascorbic, benzene sulphonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulphonic, 1,2-ethane sulphonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, arsanilic, hexylresorcinic,

hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulphonic, maleic, malic, mandelic, methane sulphonic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, succinic, sulphamic, sulphanilic, sulphuric, tannic, tartaric, toluene sulphonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0369] In some embodiments, the salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt. In some embodiments, the salt is a sodium salt.

[0370] In some embodiments, the pharmaceutically acceptable salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt. In some embodiments, the pharmaceutically acceptable salt is a sodium salt. Other examples of pharmaceutically acceptable salts may include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulphonic acid, 2-naphthalenesulphonic acid, 4-toluenesulphonic acid, camphorsulphonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

[0371] 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.

[0372] As used herein, the term “inorganic acids” refers to acids such as, but not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and combinations thereof.

[0373] As used herein the term “organic acids” refers to acids such as, but not limited to: acetic acid; trifluoroacetic acid; phenylacetic acid; propionic acid; stearic acid; lactic acid; ascorbic acid; maleic acid; hydroxymaleic acid; isethionic acid; succinic acid; valeric acid; fumaric acid; malonic acid; pyruvic acid; oxalic acid; glycolic acid; salicylic acid; oleic acid; palmitic acid;

lauric acid; a pyranosidyl acid, such as glucuronic acid or galacturonic acid; an alpha-hydroxy acid, such as mandelic acid, citric acid, or tartaric acid; cysteine sulfinic acid; an amino acid, such as aspartic acid, glutaric acid or glutamic acid; an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic acid; a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, benzenesulfonic acid or ethanesulfonic acid; cysteine sulfonic acid; and combinations thereof.

[0374] As used herein the term "inorganic bases" refers to bases such as, but not limited to, sodium hydroxide, potassium hydroxide, lithium hydroxide, ammonium hydroxide, magnesium hydroxide, sodium carbonate, potassium carbonate, barium hydroxide, calcium hydroxide, ammonia, and combinations thereof.

[0375] As used herein, the term "organic base" refers to an organic compound containing one or more nitrogen atoms, and which acts as a base. Examples of organic bases include, but are not limited to, tertiary amine bases. Examples of organic bases include, but are not limited to, 1,8-Diazabicyclo[5.4.0]undec-7-ene ("DBU"), N-methyl-morpholine (NMM), 4-dimethylaminopyridine (DMAP), diisopropylethylamine (DIPEA), triethylamine (TEA), a t-butoxide (e.g., sodium, potassium, calcium or magnesium tert- butoxide).

[0376] As used herein, the term "inorganic solvent" refers to a solvent that does not contain carbon, except for the exceptions noted below. In one embodiment, an inorganic solvent may comprise or consist of water. In another embodiment, an inorganic solvent may comprise nonaqueous solvents. For example and without limitation, an inorganic nonaqueous solvent can include ammonia, sulfur dioxide, sulfuryl chloride, sulfuryl chloride fluoride, phosphoryl chloride, dinitrogen tetroxide, antimony trichloride, bromine pentafluoride, sulfuric acid, nitric acid, phosphorous tribromide, hydrogen fluoride, supercritical carbon dioxide, carbon dioxide, carbon disulfide, various molten salts, and the like.

[0377] As used herein the term "organic solvent" refers to an organic molecule capable of at least partially dissolving another substance (i.e., the solute). Examples of organic solvents that may be used for the present invention include, but are not limited to: hydrocarbon solvents (e.g., n-pentane, n-hexane, n-heptane, n-octane, paraffin, cyclohexane, methylcyclohexane, decahydronaphthalene, mineral oil, crude oils, etc.) which also includes aromatic hydrocarbon solvents (e.g., benzene, toluene, o-xylene, m-xylene, and p-xylene), halogenated hydrocarbon solvents (e.g., carbon tetrachloride, 1,2-dichloroethane, dichloromethane, chloroform, etc.), ester solvents (e.g., ethyl formate, methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, ethyl malonate, etc.), ketone solvents (e.g., acetone, methyl ethyl ketone or 2-butanone, methyl isobutyl ketone, cyclohexanone, cyclopentanone, 3-pentanone, etc.), ether

solvents (e.g., diethyl ether, dipropyl ether, diphenyl ether, isopropyl ether, tert-butyl methyl ether, tetrahydrofuran, 1,4-dioxane, etc.), amine solvents (e.g., propyl amine, diethylamine, triethylamine, aniline, pyridine), alcohol solvents (e.g., methanol, ethanol, isopropanol, 1-propanol, 2-propanol, 2-methyl-1-propanol, 1-butanol, 2-butanol, 1-pentanol, 3-methyl-1-butanol, tert-butanol, 1-octanol, benzyl alcohol, phenol, trifluoroethanol, glycerol, ethylene glycol, propylene glycol, m-cresol, etc.), acid solvents (e.g., acetic acid, hexanoic acid, etc.), carbon disulfide, nitrobenzene, N,N-dimethylformamide, N,N,-dimethylacetamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, acetonitrile, silicone solvents (e.g., silicone oils, polysiloxanes, cyclosilicones). In some embodiments, the organic solvent may be formed by the combination of two or more organic solvents.

[0378] As used herein, unless otherwise noted, the term "aprotic organic solvent" refers to any solvent that does not yield a proton. Examples of an aprotic organic solvent include, but are not limited to DMF, dioxane, THF, methyltetrahydrofuran, acetonitrile, pyridine, dichloroethane, dichloromethane, MTBE, toluene, and the like.

[0379] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In some embodiments, Compound No. 9 (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, excipient, or diluent. A suitable pharmaceutically acceptable carrier includes, but is not limited to, inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0380] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other cafeatures 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.

[0381] 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.

[0382] 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.

[0383] The disclosure having been described, the following examples are offered by way of illustration and not limitation.

EXEMPLARY EMBODIMENTS

[0384] Exemplary Embodiment 1. A method of preparing 2-methylpyrimidine salt from 4,6-dichloro-2-methylpyrimidine.

[0385] Exemplary Embodiment 2. The method of Exemplary Embodiment 1, comprising steps (i) and (ii):

(i) reacting 4,6-dichloro-2-methylpyrimidine, with a hydrogenating agent, thereby forming 2-methylpyrimidine; and

(ii) reacting 2-methylpyrimidine, with an acid, thereby forming 2-methylpyrimidine salt.

[0386] Exemplary Embodiment 3. The method of Exemplary Embodiment 2, wherein step (i) is performed in the presence of a hydrogen transfer catalyst.

[0387] Exemplary Embodiment 4. The method of Exemplary Embodiment 3, wherein the hydrogen transfer catalyst is a nickel catalyst, a platinum catalyst, a palladium catalyst, a rhodium catalyst, or a ruthenium catalyst.

[0388] Exemplary Embodiment 5. The method of Exemplary Embodiment 2, wherein the hydrogenating agent is ammonium formate.

[0389] Exemplary Embodiment 6. The method of Exemplary Embodiment 2, wherein the 4,6-dichloro-2-methylpyrimidine to hydrogenating agent ratio is from about 1:1 to about 1:4.

[0390] Exemplary Embodiment 7. The method of Exemplary Embodiment 2, wherein step (i) is conducted at a temperature of 37±15 °C, 37±10 °C, or 37±5 °C.

[0391] Exemplary Embodiment 8. The method of Exemplary Embodiment 2, wherein in step (i), a mixture comprising 2-methylpyrimidine is formed.

[0392] Exemplary Embodiment 9. The method of Exemplary Embodiment 8, wherein a polar solvent is added to the mixture comprising 2-methylpyrimidine to from a first mixture prior to reacting with the acid of step (ii).

[0393] Exemplary Embodiment 10. The method of Exemplary Embodiment 8, wherein the first mixture is basified to a pH of at least about 8.

[0394] Exemplary Embodiment 11. The method of Exemplary Embodiment 2, wherein in step (ii), the acid is oxalic acid.

[0395] Exemplary Embodiment 12. The method of Exemplary Embodiment 2, wherein in step (ii), the reacting is performed in the presence of an aprotic solvent.

[0396] Exemplary Embodiment 13. The method of Exemplary Embodiment 12, wherein the aprotic solvent is tetrahydrofuran.

[0397] Exemplary Embodiment 14. The method of any one of Exemplary Embodiments 2 and 11-13, wherein step (ii) is conducted at a temperature from about 20 °C to about 50 °C to form a second mixture.

[0398] Exemplary Embodiment 15. The method of Exemplary Embodiment 14, wherein the second mixture is subjected to a temperature cycling procedure.

[0399] Exemplary Embodiment 16. The method of Exemplary Embodiment 15, wherein the temperature cycling procedure comprises the steps of (a) cooling the second mixture to about 20 °C over about 1 hour and agitating for about 15 minutes, (b) heating back to about 45 °C and agitating for at least about 30 minutes, (c) cooling from about 45 °C to about 20 °C over about 1 hour and agitating for about 15 minutes, (d) heating back to about 45 °C and agitating for at least about 30 minutes, (e) cooling from about 45 °C to about -10 °C over about 4 hours, and (f) stirring for at least about 13 hours at about -10 °C.

[0400] Exemplary Embodiment 17. The method of any one of Exemplary Embodiments 2 and 11-16, wherein step (ii) further comprises isolating the 2-methylpyrimidine salt.

[0401] Exemplary Embodiment 18. The method of any one of Exemplary Embodiments 2 and 11-17, wherein step (ii) further comprises drying the 2-methylpyrimidine salt.

[0402] Exemplary Embodiment 19. The method of any one of Exemplary Embodiments 2 and 11-18, wherein the 2-methylpyrimidine salt has a purity of at least about 98%, at least about 98.5%, at least about 99%, at least about 99.1%, at least about 99.2%, at least about 99.3%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, or at least about 99.8% by area as measured by HPLC.

[0403] Exemplary Embodiment 20. The method of any one of Exemplary Embodiments 2 and 11-19, wherein the yield of 2-methylpyrimidine salt is at least about 50%, at least about 55%, at

least about 60%, at least about 65%, at least about 69%, at least about 70%, at least about 75%, at least about 80%, or at least about 85%.

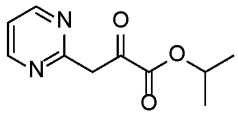
[0404] Exemplary Embodiment 21. The method of any one of Exemplary Embodiments 2 and 17-20, wherein the 2-methylpyrimidine salt is 2-methylpyrimidine oxalate.

[0405] Exemplary Embodiment 22. The method of any one of Exemplary Embodiments 2 and 17-21, wherein the 2-methylpyrimidine salt comprises less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% of impurities by area as measured by HPLC.

[0406] Exemplary Embodiment 23. The method of Exemplary Embodiment 22, wherein the impurities comprise 2-propanol; 4, 6-dichloro-2-methylpyrimidine; or a mixture thereof.

[0407] Exemplary Embodiment 24. The method of Exemplary Embodiment 22 or Exemplary Embodiment 23, wherein the impurities comprise about 4.9% of 2-propanol; about 0.03% of 4, 6-dichloro-2-methylpyrimidine; or a mixture thereof.

[0408] Exemplary Embodiment 25. A method of preparing Compound No. 5 or a salt thereof:



(Compound No. 5),

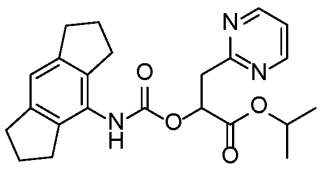
comprising steps (i)-(iii):

(i) reacting 4,6-dichloro-2-methylpyrimidine, with a hydrogenating agent, thereby forming 2-methylpyrimidine;

(ii) reacting 2-methylpyrimidine, with an acid, thereby forming 2-methylpyrimidine salt; and

(iii) reacting 2-methylpyrimidine salt, with diisopropyl oxalate, thereby forming Compound No. 5, or a salt thereof, wherein the reacting is performed in the presence of potassium *tert*-pentoxide.

[0409] Exemplary Embodiment 26. A method of preparing Compound No. 9 or a salt thereof:



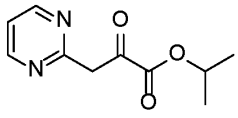
(Compound No. 9),

comprising one or more of steps (i)-(vii):

(i) reacting 4,6-dichloro-2-methylpyrimidine, with a hydrogenating agent, thereby forming 2-methylpyrimidine;

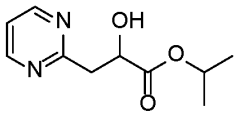
(ii) reacting 2-methylpyrimidine, with an acid, thereby forming 2-methylpyrimidine salt;

(iii) reacting 2-methylpyrimidine salt, with diisopropyl oxalate, thereby forming Compound No. 5:



(Compound No. 5), or a salt thereof;

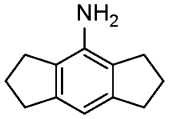
(iv) reacting Compound No. 5, or the salt thereof, with a reducing agent, thereby forming Compound No. 6:



(Compound No. 6),

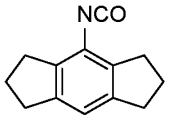
or a salt thereof;

(v) reacting Compound No. 7:



(Compound No. 7),

or a salt thereof, with a source of CO, thereby forming Compound No. 8:



(Compound No. 8),

or a salt thereof;

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

(vii) purifying Compound No. 9 or the salt thereof.

[0410] Exemplary Embodiment 27. A method of preparing Compound No. 6, or a salt thereof, comprising:

(iv) reacting Compound No. 5, or a salt thereof, with a reducing agent, thereby forming Compound No. 6, or a salt thereof.

[0411] Exemplary Embodiment 28. The method of Exemplary Embodiment 26, wherein step (i) is performed in the presence of a hydrogen transfer catalyst.

[0412] Exemplary Embodiment 29. The method of Exemplary Embodiment 26, wherein the hydrogenating agent is ammonium formate.

[0413] Exemplary Embodiment 30. The method of Exemplary Embodiment 26, wherein 4,6-dichloro-2-methylpyrimidine to hydrogenating agent ratio is from about 1:1 to about 1:4.

[0414] Exemplary Embodiment 31. The method of Exemplary Embodiment 26, wherein in step (ii), 2-methylpyrimidine is dissolved in a polar solvent prior to reacting with the acid.

[0415] Exemplary Embodiment 32. The method of Exemplary Embodiment 26 or Exemplary Embodiment 31, wherein step (ii) further comprises isolating the 2-methylpyrimidine salt.

[0416] Exemplary Embodiment 33. The method of Exemplary Embodiment 26, wherein step (iii) is performed in the presence of a base.

[0417] Exemplary Embodiment 34. The method of Exemplary Embodiment 33, wherein the base in step (iii) is potassium *tert*-pentoxide.

[0418] Exemplary Embodiment 35. The method of any one of Exemplary Embodiments 26, 33, and 34, wherein step (iii) results in less than about 0.3% of tert-pentyl ester by area as measured by HPLC.

[0419] Exemplary Embodiment 36. The method of any one of Exemplary Embodiments 26 and 33-35, wherein step (iii) is conducted at a temperature of 40±15 °C, 40±10 °C, or 40±5 °C.

[0420] Exemplary Embodiment 37. The method of any one of Exemplary Embodiments 26 and 33-36, wherein step (iii) is performed in the presence of a polar solvent, an aprotic solvent, or a mixture thereof.

[0421] Exemplary Embodiment 38. The method of any one of Exemplary Embodiments 26 and 33-37, wherein in step (iii), further comprises isolating Compound No. 5, or a salt thereof.

[0422] Exemplary Embodiment 39. The method of any one of Exemplary Embodiments 26 and 33-38, wherein in step (iii), Compound No. 5, or a salt thereof has a purity of at least about 90%, at least about 92%, at least about 94%, at least about 96%, at least about 98%, or at least about 99% by area as measured by HPLC.

[0423] Exemplary Embodiment 40. The method of any one of Exemplary Embodiments 26-39, wherein in step (iv), the reducing agent is a monosaccharide.

[0424] Exemplary Embodiment 41. The method of any one of Exemplary Embodiments 26-40, wherein step (iv) is performed in the presence of a reduction catalyst, wherein the reduction catalyst is an enzymatic catalyst, a dinucleotide phosphate, or a mixture thereof.

[0425] Exemplary Embodiment 42. The method of Exemplary Embodiment 41, wherein the enzymatic catalyst is ketoreductase (KRED), glutamate dehydrogenase (GDH), or a mixture thereof, and wherein the dinucleotide phosphate is nicotinamide adenine dinucleotide phosphate (NADP).

[0426] Exemplary Embodiment 43. The method of any one of Exemplary Embodiments 26-42, wherein in step (iv), the molar ratio of the acid to Compound No. 5, or the salt thereof, is from about 3:1 to about 1:3.

[0427] Exemplary Embodiment 44. The method of any one of Exemplary Embodiments 26-43, wherein in step (iv), Compound No. 6, or the salt thereof, is isolated prior to reacting with Compound No. 8 or a salt thereof.

[0428] Exemplary Embodiment 45. The method of Exemplary Embodiment 26, wherein in step (v), the source of CO is triphosgene.

[0429] Exemplary Embodiment 46. The method of any one of Exemplary Embodiments 26 and 28-45, wherein in step (v), the reacting is performed in the presence of a base.

[0430] Exemplary Embodiment 47. The method of Exemplary Embodiment 46, wherein in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is from about 3:1 to about 1:3.

[0431] Exemplary Embodiment 48. The method of any one of Exemplary Embodiments 26 and 28-47, wherein step (v) is performed in the presence of toluene, dichloromethane, or a mixture thereof.

[0432] Exemplary Embodiment 49. The method of any one of Exemplary Embodiments 26 and 28-48, wherein in step (vi), the molar ratio of Compound No. 6, or a salt thereof, to the Compound No. 8, or the salt thereof, is from about 3:1 to about 1:3.

[0433] Exemplary Embodiment 50. The method of Exemplary Embodiment 26, wherein step (vii) further comprises crystallizing Compound No. 9, or the salt thereof, in the presence of at least one organic solvent.

[0434] Exemplary Embodiment 51. The method of any one of Exemplary Embodiments 26 and 28-50, wherein step (vii) further comprises isolating Compound No. 9 or the salt thereof.

[0435] Exemplary Embodiment 52. The method of any one of Exemplary Embodiments 26 and 28-51, wherein step (vii), Compound No. 9 or the salt thereof has a purity of at least about 99.5% by area as measured by HPLC.

[0436] Exemplary Embodiment 53. A compound being prepared by the method of any one of the preceding Exemplary Embodiments.

[0437] Exemplary Embodiment 54. A pharmaceutical composition comprising Compound No. 9, or the salt thereof, of any one of Exemplary Embodiments 26 and 28-52, and one or more pharmaceutically acceptable carrier, diluent, adjuvant, or excipient.

[0438] Exemplary Embodiment 55. A method of preventing or treating a disease in a subject, comprising administering to the subject Compound No. 9, or the salt thereof, of any one of Exemplary Embodiments 26 and 28-52.

[0439] Exemplary Embodiment 56. Compound No. 9, or the salt thereof, of any one of Exemplary Embodiments 26 and 28-52 for use in preventing or treating a disease or for inhibiting inflammasome activity in a subject.

[0440] Exemplary Embodiment 57. Use of Compound No. 9, or the salt thereof, of any one of Exemplary Embodiments 26 and 28-52 in the manufacture of a medicament for preventing or treating a disease or for inhibiting inflammasome activity in a subject.

[0441] Exemplary Embodiment 58. A method of inhibiting inflammasome activity in a subject, comprising contacting a cell with Compound No. 9, or the salt thereof, of any one of Exemplary Embodiments 26 and 28-52.

[0442] Exemplary Embodiment 59. The method, compound, or use of any one of the preceding Exemplary Embodiments, wherein the subject is a human.

EXAMPLES

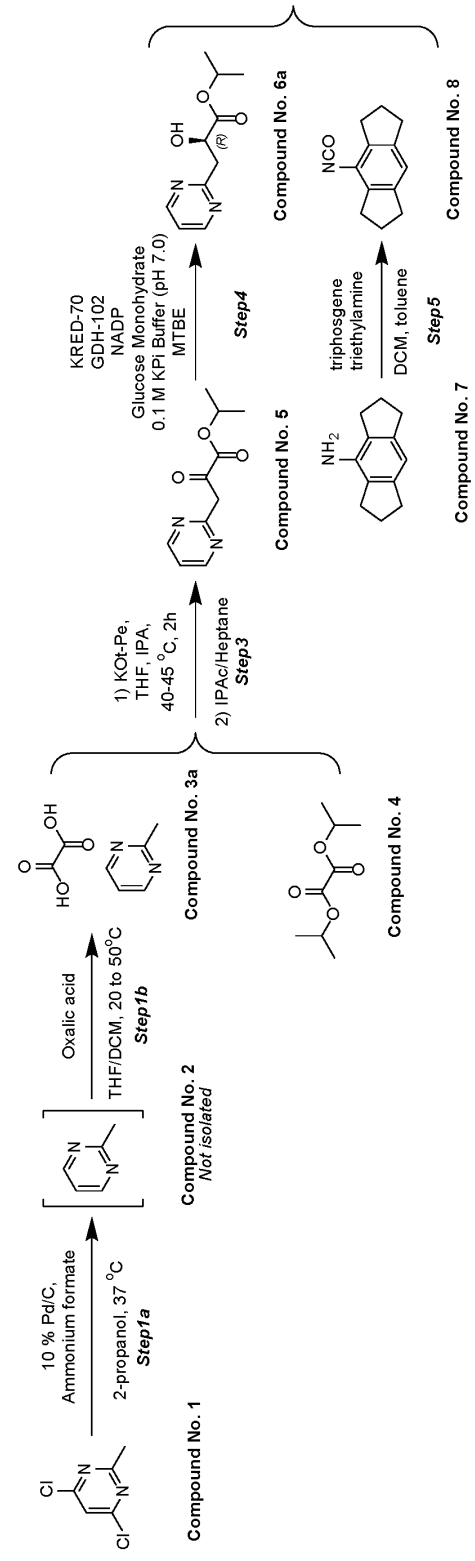
[0443] The disclosure having been described, the following examples are offered by way of illustration and not limitation.

[0444] 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.

[0445] An exemplary synthesis of Compound No. 9a was performed as shown in Scheme 1, Scheme 2, and Scheme 3 and the following procedures. The overall synthetic route was a 7-step process, starting from commercially or synthetically available starting materials.

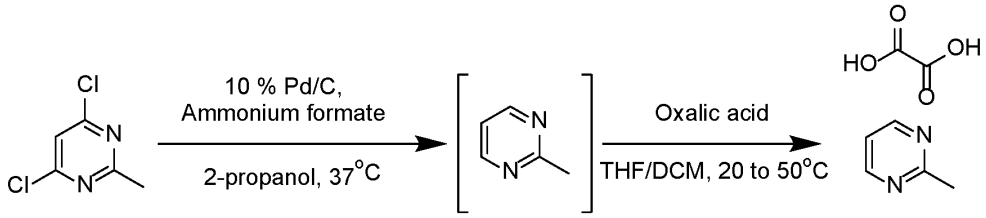
Scheme 1: Compound No. 9a Manufacturing Process



Example 2. Exemplary Synthesis of Compound No. 3a.

[0446] An exemplary synthesis of Compound No. 3a was performed as shown in Scheme 2.

Scheme 2: Compound No. 3a Manufacturing Process



Compound No. 1 | Compound No. 2 *Not isolated* | Compound No. 3a

Process Description

[0447] Palladium on Carbon catalyst [10% type 487 paste (10.50 g, 0.1wt. based on 47.6% dry basis)] was added to an inerted vessel containing 4, 6-dichloro-2-methylpyrimidine (50 g, 307 mmol, 1 eq). 2-Propanol (375 mL, 7.5 vol) was added and the mixture stirred at 20-25 °C for 10 min. The mixture was then gently heated to 35 - 40 °C over approximately 40 min.

[0448] A solution of ammonium formate (42.6 g, 675 mmol, 2.2 eq) in methanol (175 mL, 3.5 vol) and water (16.65 mL, 0.33 vol) was cautiously added over at least 5 hours. The mixture was then maintained at 35 - 40 °C and stirred for at least a further 2 hours. **IPC 1: Reaction completion by HPLC**. Target is less than or equals to 2 area% of 4, 6-dichloro-2-methylpyrimidine remaining with respect to Step 1 product.

[0449] The catalyst was removed by filtration through a pad of Celite and the filter cake was washed with 2-propanol (125 mL, 2.5 vol). 2-Methylpyrimidine product content of 2-propanol solution was determined by NMR Assay. This was used to calculate the later charges for both reagents and solvents).

[0450] The resulting solution of 2-methylpyrimidine (24.57 g, 261 mmol, 1 eq) was added over at least 30 min at 20 - 25 °C to stirred 2M aqueous hydrochloric acid (261 mL, 522 mmol, 2 eq, 10.5 vol). The solution was then concentrated by distillation in vacuo to 10.5 vol keeping the internal temperature around 45-60 °C. The mixture was cooled to 20 - 25 °C. Content of 2-propanol (determined by NMR): target is less than or equals to 1.22% and methanol: target is less than or equals to 2.30%.

[0451] MTBE (171.99 mL, 7 vol) was added and the mixture was agitated at 20 to 25 °C for at least 15 minutes then allowed to settle for at least 30 minutes. The layers were separated the aqueous layer containing the product was collected. Dichloromethane (171.99 mL, 7 vol) was added and the mixture was agitated for at least 15 min. The mixture was then slowly basified with 30%w/w aqueous potassium carbonate solution (103 mL, 287 mmol, 1.1 eq, 4.2 vol)

ensuring the internal temperature does not exceed 25 °C. The mixture was agitated at 20 to 25 °C for at least 15 minutes and was allowed to settle over at least 30 minutes. Target basic pH is greater than 8.

[0452] The organic layer containing the product was separated and the aqueous portion was extracted with dichloromethane (2 x 171.99 mL, 7 vol). Target 3.5%w/w of product in DCM layer - mass of DCM layer 690 g - 24.15 g of product.

[0453] Oxalic acid (35.3 g, 392 mmol) was dissolved in THF (127.76 mL, 5.2 vol) at 20 - 25°C. The combined DCM solution (containing 2-methylpyrimidine) was then added over at least 2 hours with vigorous mixing. The mixture was heated to 45 °C and was agitated for at least 30 min.

[0454] **The following temperature cycling was used to aid filtration.** The reactor contents were cooled from 45 °C over 1 hour to 20 °C and were agitated for 15 min. The reactor contents were heated back to 45 °C and were agitated for at least 30 min. The reactor contents were again cooled from 45 °C over 1 hour to 20 °C and were agitate for 15 min. The reactor contents were once again heated back to 45 °C and were agitated for at least 30 min. The reactor contents were now cooled from 45 °C over 4 hours to -10 °C. The mixture was stirred for at least 13 hours at -10 °C.

[0455] The solid (now the 1:1.5 oxalate salt of 2-methylpyrimidine) was removed by filtration, washed with cold DCM (86 mL, 3.5 vol) and the filter cake was pulled dry for 3 hours. Wet cake purity was measured by HPLC. Target is at least 99 area%.

[0456] The white solid was dried under vacuum at 25 °C for at least 16 hours (47.33 g, 69% yield). **IPC 4: Water content by KF.** Target is less than or equals to 5.0 %w/w. If the target was not met continue drying for up to 24 hours.

[0457] The results obtained are provided in Table 1.

Table 1. Summary of the Results for Manufacture of Compound No. 3a

Input	Output	Yield
33.0 kg	31.07 kg	67%

[0458] The results of the In Process Control analyses are provided in Table 2.

Table 2. Summary of In Process Control Results for Manufacture of Compound No. 3a

IPC	Test	Target	Results
1	Reaction completion by HPLC	Less than or equals to 2% area 4, 6-dichloro-2-methylpyrimidine	0.03%
2	Product content of 2-propanol solution by NMR assay	Reported result % w/w	4.9%

IPC	Test	Target	Results
3	Wet cake purity by HPLC	At least 99% area of Compound No. 3a	100%
4	Water content by KF	Less than or equals to 5.0% w/w	2.2%

[0459] The results of the isolated intermediate analyses are provided in Table 3.

Table 3. Summary of Isolated Intermediate Release Results for the synthesis of Compound No. 3a

Attribute	Specification Limit	Results
Water content by KF	≤5% w/w	1.2%
Appearance	White to yellow solid	White Solid
Identification by ^{1}H NMR ($CDCl_3$)	Conforms to Reference Material	Conforms
Purity by HPLC	At least 99% area of Compound No. 3a	100%

[0460] The result of the Isolated Intermediate Release HPLC purity analysis for the synthesis of Compound No. 3a is provided in Table 4.

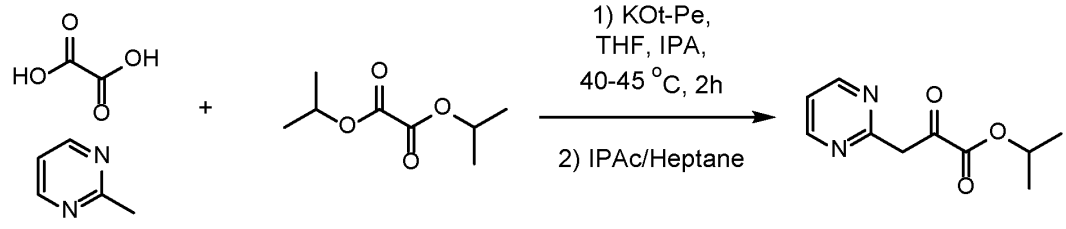
Table 4. Result of the release analysis HPLC purity for the synthesis of Compound No. 3a

Name	Retention Time	Area	% Area
Compound No. 3a	3.933	3141867	100.00
4-chloro-2-methylpyrimidine	5.700		
4,6-Dichloro-2-methylpyrimidin	7.600		

Example 3. Exemplary Synthesis of Compound No. 5.

[0461] An exemplary synthesis of Compound No. 5 was performed as shown in Scheme 3.

Scheme 3: Compound No. 5 Manufacturing Process



Compound No. 3a **Compound No. 4** **Compound No. 5**

[0462] A solution of potassium tert-pentoxide [2M in THF (7.63 L, 3.5 eq)] was added over at least 4 hours to a stirred suspension of 2-methylpyrimidine oxalate (1 kg, 1 eq), diisopropyl oxalate (1.25 kg, 1.65 eq) and 2-propanol (0.90 L, 2.7 eq) in THF (1.0 L, 1 vol) keeping internal temperature below 50 °C. The reaction mixture was stirred for at least 2 hours at 40-45 °C. **IPC**

1: Reaction completion by HPLC. Target is less than or equals to 2% area of 2-methylpyrimidine remaining.

[0463] The suspension was cooled to 0-10 °C before quenching with a solution of acetic acid (0.90 L, 3.6 eq) in water (8.0 L, 8 vol) maintaining the internal temp below 30 °C (Target is less than 25 °C). The temperature was adjusted to 15-25 °C and the mixture was stirred for at least 15 minutes. The resulting biphasic solution was concentrated to 12 vol keeping the temp <45 °C. Isopropyl acetate (6.0 L, 6 vol) was added and once again the biphasic mixture was concentrated to 12 vol keeping the temp less than 45 °C. Further isopropyl acetate (5.0 L, 5 vol) was added and again the biphasic mixture was concentrated to 12 vol keeping the temp less than 45°C. Further isopropyl acetate (5.0 L, 5 vol) was added and again the biphasic mixture was concentrated to 12 vol keeping the temp less than 45°C. Solvent swap completion was determined by NMR. Target is less than or equals to 2 %w/w THF with respect to isopropyl acetate.

[0464] The mixture was cooled to 20-25 °C and was stirred for 15 minutes before the layers are separated. The organic layer was washed with 20% w/w aqueous potassium bicarbonate solution (7.0 L, 7 vol) and then water (5.0 L, 5 vol). Additional isopropyl acetate (5.0 L, 5 vol) was added before the solution was concentrated to 2 vol *in vacuo* keeping the temperature below 40°C. Heptane (13.0 L, 13 vol) was added and the mixture was stirred at 35-45 °C for 20 minutes. The resulting suspension was slowly cooled to 0-10 °C over 3 hours and then stirred at 0-10 °C for a further 2 hours. The solid was removed by filtration and the filter cake was washed with cold heptane (2 x 2.0 L, 2 vol). **Check 1**: **Wet cake purity by HPLC**. Target is at least 96 area%.

[0465] The cake was pulled dry for 2 hours and then dried under vacuum for at least 16 hours at 20-25 °C. **IPC 3**: **Loss on drying.** Target is less than1%.

[0466] The results obtained are provided in Table 5.

Table 5. Summary of Results for Manufacture of Compound No. 5

Input	Output	Yield
31.08 kg	22.49 kg	80%

[0467] The results of the In Process Control analyses are provided in Table 6.

Table 6. Summary of In Process Control Results for Compound No. 5

IPC	Test	Target	Results
1	Reaction completion by HPLC	Less than or equals to 2% area Compound No. 3a	0.30%
2/1	Solvent swap completion by NMR	Less than or equals to 2% w/w THF wrt isopropyl acetate	2.3%

2/2	Solvent swap completion by NMR	Less than or equals to 2% w/w THF wrt isopropyl acetate	≤ 2%
3	Loss on drying at 30°C under vacuum	Less than 1% w/w	0.12%

[0468] The results of the isolated intermediate analyses are provided in Table 7.

Table 7. Summary of Isolated Intermediate Release Results for the synthesis of Compound No. 5

Attribute	Specification Limit	Results
Appearance	Green to Yellow to Orange solid	Dark yellow solid
Identification by ^{1}H NMR ($CDCl_3$)	Conforms to Reference Material	Conforms
Residual solvents by GC-HS	Isopropyl alcohol Less than or equals to 5000ppm	142 ppm
Purity by HPLC	At least 96% area of Compound No. 5	96.2%

[0469] The result of the Isolated Intermediate Release HPLC purity analysis for the synthesis of Compound No. 5 is provided in Table 8 (RRT means relative retention time).

Table 8. Result of the release analysis HPLC for the synthesis of Compound No. 5

Name	Retention Time	Area	% Area
Compound No. 3a	4.124		
RRT~ 0.588	5.409	48484	0.33
RRT~ 0.605	5.569	70358	0.48
RRT~ 0.682	6.280	118844	0.81
RRT~ 0.743	6.839	41426	0.28
RRT~ 0.811	7.471	22424	0.15
Compound No. 5	9.207	14045060	95.97
RRT~ 1.039	9.564	84794	0.58
RRT~ 1.067	9.820	21337	0.15
RRT~ 1.157	10.654	143435	0.98
RRT~ 1.212	11.161	38271	0.26

EQUIVALENTS

[0470] 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.

[0471] 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.

CLAIMS

What is claimed is:

1. A method of preparing 2-methylpyrimidine salt from 4,6-dichloro-2-methylpyrimidine.

2. The method of claim 1, comprising steps (i) and (ii):

(i) reacting 4,6-dichloro-2-methylpyrimidine, with a hydrogenating agent, thereby forming 2-methylpyrimidine; and

(ii) reacting 2-methylpyrimidine, with an acid, thereby forming 2-methylpyrimidine salt.

3. The method of claim 2, wherein step (i) is performed in the presence of a hydrogen transfer catalyst.

4. The method of claim 3, wherein the hydrogen transfer catalyst is a nickel catalyst, a platinum catalyst, a palladium catalyst, a rhodium catalyst, or a ruthenium catalyst.

5. The method of claim 2, wherein the hydrogenating agent is ammonium formate.

6. The method of claim 2, wherein the 4,6-dichloro-2-methylpyrimidine to hydrogenating agent ratio is from about 1:1 to about 1:4.

7. The method of claim 2, wherein step (i) is conducted at a temperature of 37±15 °C, 37±10 °C, or 37±5 °C.

8. The method of claim 2, wherein in step (i), a mixture comprising 2-methylpyrimidine is formed.

9. The method of claim 8, wherein a polar solvent is added to the mixture comprising 2-methylpyrimidine to from a first mixture prior to reacting with the acid of step (ii).

10. The method of claim 8, wherein the first mixture is basified to a pH of at least about 8.

11. The method of claim 2, wherein in step (ii), the acid is oxalic acid.

12. The method of claim 2, wherein in step (ii), the reacting is performed in the presence of an aprotic solvent.

13. The method of claim 12, wherein the aprotic solvent is tetrahydrofuran.

14. The method of any one of claims 2 and 11-13, wherein step (ii) is conducted at a temperature from about 20 °C to about 50 °C to form a second mixture.

15. The method of claim 14, wherein the second mixture is subjected to a temperature cycling procedure.

16. The method of claim 15, wherein the temperature cycling procedure comprises the steps of (a) cooling the second mixture to about 20 °C over about 1 hour and agitating for about 15 minutes, (b) heating back to about 45 °C and agitating for at least about 30 minutes, (c) cooling from about 45 °C to about 20 °C over about 1 hour and agitating for about 15 minutes, (d) heating back to about 45 °C and agitating for at least about 30 minutes, (e) cooling from about 45 °C to about -10 °C over about 4 hours, and (f) stirring for at least about 13 hours at about -10 °C.

17. The method of any one of claims 2 and 11-16, wherein step (ii) further comprises isolating the 2-methylpyrimidine salt.

18. The method of any one of claims 2 and 11-17, wherein step (ii) further comprises drying the 2-methylpyrimidine salt.

19. The method of any one of claims 2 and 11-18, wherein the 2-methylpyrimidine salt has a purity of at least about 98%, at least about 98.5%, at least about 99%, at least about 99.1%, at least about 99.2%, at least about 99.3%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, or at least about 99.8% by area as measured by HPLC.

20. The method of any one of claims 2 and 11-19, wherein the yield of 2-methylpyrimidine salt is at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 69%, at least about 70%, at least about 75%, at least about 80%, or at least about 85%.

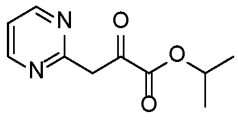
21. The method of any one of claims 2 and 17-20, wherein the 2-methylpyrimidine salt is 2-methylpyrimidine oxalate.

22. The method of any one of claims 2 and 17-21, wherein the 2-methylpyrimidine salt comprises less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% of impurities by area as measured by HPLC.

23. The method of claim 22, wherein the impurities comprise 2-propanol; 4, 6-dichloro-2-methylpyrimidine; or a mixture thereof.

24. The method of claim 22 or claim 23, wherein the impurities comprise about 4.9% of 2-propanol; about 0.03% of 4, 6-dichloro-2-methylpyrimidine; or a mixture thereof.

25. A method of preparing Compound No. 5 or a salt thereof:



(Compound No. 5),

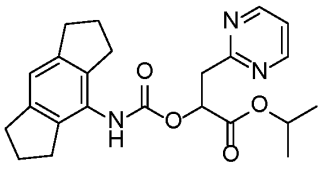
comprising steps (i)-(iii):

(i) reacting 4,6-dichloro-2-methylpyrimidine, with a hydrogenating agent, thereby forming 2-methylpyrimidine;

(ii) reacting 2-methylpyrimidine, with an acid, thereby forming 2-methylpyrimidine salt; and

(iii) reacting 2-methylpyrimidine salt, with diisopropyl oxalate, thereby forming Compound No. 5, or a salt thereof, wherein the reacting is performed in the presence of potassium *tert*-pentoxide.

26. A method of preparing Compound No. 9 or a salt thereof:



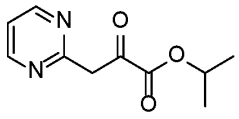
(Compound No. 9),

comprising one or more of steps (i)-(vii):

(i) reacting 4,6-dichloro-2-methylpyrimidine, with a hydrogenating agent, thereby forming 2-methylpyrimidine;

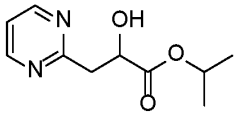
(ii) reacting 2-methylpyrimidine, with an acid, thereby forming 2-methylpyrimidine salt;

(iii) reacting 2-methylpyrimidine salt, with diisopropyl oxalate, thereby forming Compound No. 5:



(Compound No. 5), or a salt thereof;

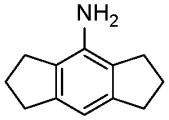
(iv) reacting Compound No. 5, or the salt thereof, with a reducing agent, thereby forming Compound No. 6:



(Compound No. 6),

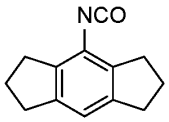
or a salt thereof;

(v) reacting Compound No. 7:



(Compound No. 7),

or a salt thereof, with a source of CO, thereby forming Compound No. 8:



(Compound No. 8),

or a salt thereof;

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

(vii) purifying Compound No. 9 or the salt thereof.

27. A method of preparing Compound No. 6, or a salt thereof, comprising:

(iv) reacting Compound No. 5, or a salt thereof, with a reducing agent, thereby forming Compound No. 6, or a salt thereof.

28. The method of claim 26, wherein step (i) is performed in the presence of a hydrogen transfer catalyst.

29. The method of claim 26, wherein the hydrogenating agent is ammonium formate.

30. The method of claim 26, wherein 4,6-dichloro-2-methylpyrimidine to hydrogenating agent ratio is from about 1:1 to about 1:4.

31. The method of claim 26, wherein in step (ii), 2-methylpyrimidine is dissolved in a polar solvent prior to reacting with the acid.

32. The method of claim 26 or claim 31, wherein step (ii) further comprises isolating the 2-methylpyrimidine salt.

33. The method of claim 26, wherein step (iii) is performed in the presence of a base.

34. The method of claim 33, wherein the base in step (iii) is potassium *tert*-pentoxide.

35. The method of any one of claims 26, 33, and 34, wherein step (iii) results in less than about 0.3% of tert-pentyl ester by area as measured by HPLC.

36. The method of any one of claims 26 and 33-35, wherein step (iii) is conducted at a temperature of 40±15 °C, 40±10 °C, or 40±5 °C.

37. The method of any one of claims 26 and 33-36, wherein step (iii) is performed in the presence of a polar solvent, an aprotic solvent, or a mixture thereof.

38. The method of any one of claims 26 and 33-37, wherein in step (iii), further comprises isolating Compound No. 5, or a salt thereof.

39. The method of any one of claims 26 and 33-38, wherein in step (iii), Compound No. 5, or a salt thereof has a purity of at least about 90%, at least about 92%, at least about 94%, at least about 96%, at least about 98%, or at least about 99% by area as measured by HPLC.

40. The method of any one of claims 26-39, wherein in step (iv), the reducing agent is a monosaccharide.

41. The method of any one of claims 26-40, wherein step (iv) is performed in the presence of a reduction catalyst, wherein the reduction catalyst is an enzymatic catalyst, a dinucleotide phosphate, or a mixture thereof.

42. The method of claim 41, wherein the enzymatic catalyst is ketoreductase (KRED), glutamate dehydrogenase (GDH), or a mixture thereof, and wherein the dinucleotide phosphate is nicotinamide adenine dinucleotide phosphate (NADP).

43. The method of any one of claims 26-42, wherein in step (iv), the molar ratio of the acid to Compound No. 5, or the salt thereof, is from about 3:1 to about 1:3.

44. The method of any one of claims 26-43, wherein in step (iv), Compound No. 6, or the salt thereof, is isolated prior to reacting with Compound No. 8 or a salt thereof.

45. The method of claim 26, wherein in step (v), the source of CO is triphosgene.

46. The method of any one of claims 26 and 28-45, wherein in step (v), the reacting is performed in the presence of a base.

47. The method of claim 46, wherein in step (v), the molar ratio of the base to Compound No. 8, or the salt thereof, is from about 3:1 to about 1:3.

48. The method of any one of claims 26 and 28-47, wherein step (v) is performed in the presence of toluene, dichloromethane, or a mixture thereof.

49. The method of any one of claims 26 and 28-48, wherein in step (vi), the molar ratio of Compound No. 6, or a salt thereof, to the Compound No. 8, or the salt thereof, is from about 3:1 to about 1:3.

50. The method of claim 26, wherein step (vii) further comprises crystallizing Compound No. 9, or the salt thereof, in the presence of at least one organic solvent.

51. The method of any one of claims 26 and 28-50, wherein step (vii) further comprises isolating Compound No. 9 or the salt thereof.

52. The method of any one of claims 26 and 28-51, wherein step (vii), Compound No. 9 or the salt thereof has a purity of at least about 99.5% by area as measured by HPLC.

53. A compound being prepared by the method of any one of the preceding claims.

54. A pharmaceutical composition comprising Compound No. 9, or the salt thereof, of any one of claims 26 and 28-52, and one or more pharmaceutically acceptable carrier, diluent, adjuvant, or excipient.

55. A method of preventing or treating a disease in a subject, comprising administering to the subject Compound No. 9, or the salt thereof, of any one of claims 26 and 28-52.

56. Compound No. 9, or the salt thereof, of any one of claims 26 and 28-52 for use in preventing or treating a disease or for inhibiting inflammasome activity in a subject.

57. Use of Compound No. 9, or the salt thereof, of any one of claims 26 and 28-52 in the manufacture of a medicament for preventing or treating a disease or for inhibiting inflammasome activity in a subject.

58. A method of inhibiting inflammasome activity in a subject, comprising contacting a cell with Compound No. 9, or the salt thereof, of any one of claims 26 and 28-52.

59. The method, compound, or use of any one of the preceding claims, wherein the subject is a human.