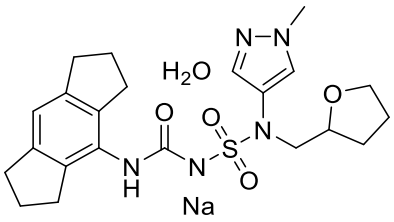
CLAIMS

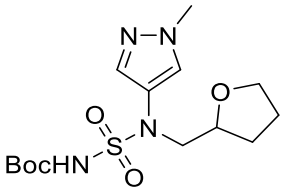
1. A method of preparing Compound No. 10:



(10),

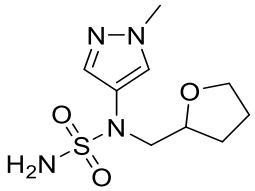
comprising one or more of steps (iv)-(vii):

(iv) reacting Compound No. 5:



(5),

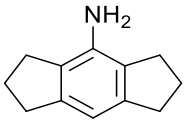
or a salt thereof, with an acid, thereby forming Compound No. 6:



(6),

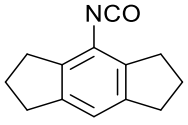
or a salt thereof;

(v) reacting Compound No. 7:



(7),

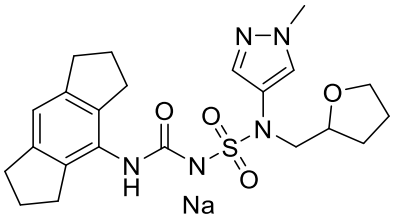
or a salt thereof, with a source of CO, thereby forming Compound No. 8:



(8),

or a salt thereof;

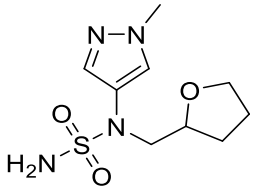
(vi) reacting Compound No. 6 as defined above, or a salt thereof, with Compound No. 8 as defined above, or a salt thereof, thereby forming Compound No. 9:



(9); or

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

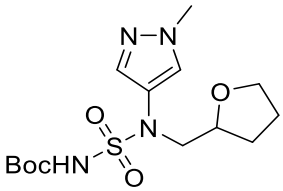
2. A method of preparing Compound No. 6:



(6),

or a salt thereof, comprising:

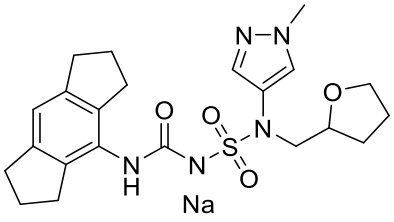
(iii) reacting Compound No. 5:



(5),

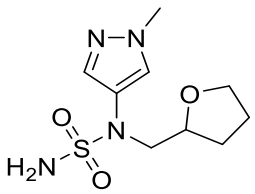
or a salt thereof, with an acid, thereby forming Compound No. 6 as defined above, or a salt thereof.

3. A method of preparing Compound No. 9:



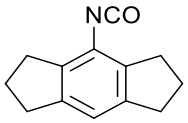
(9), comprising:

(iv) reacting Compound No. 6:



(6),

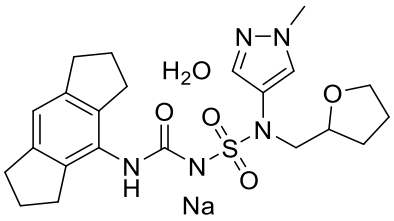
or a salt thereof, with Compound No. 8:



(8),

or a salt thereof, thereby forming Compound No. 9 as defined above.

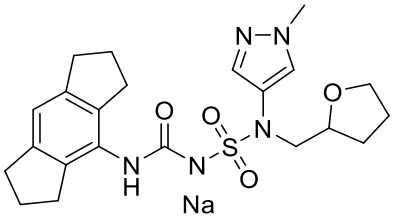
4. A method of preparing Compound No. 10:



(10),

comprising:

(vii) purifying Compound No. 9:



(9),

thereby isolating Compound No. 10 as defined above.

5. The method of claim 1, further comprising steps (i)-(iv):

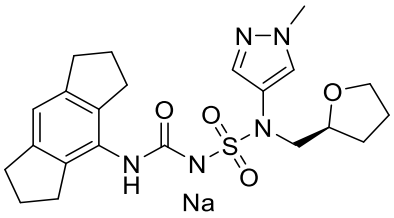
(i) reacting tetrahydrofuran-2-carboxylic acid, with 4-amino-1-methylpyrazole, or a salt thereof, thereby forming N-(1-methyl-1H-pyrazol-4-yl)oxolane-2-carboxamide, or a salt thereof;

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

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

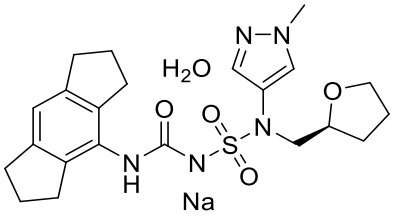
(iv) reacting Compound No. 5 as defined in claim 1 or a salt thereof, with an acid, thereby forming Compound No. 6 as defined in claim 1, or a salt thereof.

6. The method of any one of the preceding claims, wherein Compound No. 9 as defined in claim 1 is Compound No. 9a:



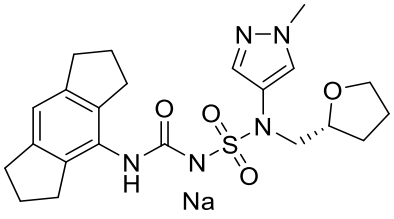
(9a).

7. The method of any one of the preceding claims, wherein Compound No. 10 as defined in claim 1 is Compound No. 10a:



(10a).

8. The method of any one of the preceding claims, wherein Compound No. 9 as defined in claim 1 is Compound No. 9b:



(9b).

9. The method of any one of the preceding claims, wherein in step (iv):

(a) the acid is hydrochloric acid; and/or

(b) the molar ratio of the acid to Compound No. 5 as defined in claim 1, or the salt thereof, is from about 3:1 to about 1:1; and/or

(c) the reacting is performed in the presence of a first solvent to form a first mixture, optionally wherein the first mixture is cooled to a second temperature of about 0±15 °C, about 0±10 °C, or about 0±5 °C, further optionally wherein a second solvent is added to form a second mixture, yet further optionally wherein a base or a buffer is added to the second mixture; and/or

(d) the reacting is performed at a first temperature of about 25±15 °C, about 25±10 °C, or about 25±5 °C; and/or

(e) the reacting is performed for about 26±20 hours, about 26±15 hours, about 26±10 hours, about 26±5 hours, about 26±4 hours, about 26±3 hours, about 26±2 hours, or about 26±1 hours; and/or

(f) Compound No. 6 as defined in claim 1, or the salt thereof, is isolated and/or purified prior to reacting with Compound No. 8 as defined in claim 1, optionally wherein Compound No. 6 as defined in claim 1, or the salt thereof, is at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% pure as measured by HPLC.

10. The method of claim 1, wherein in step (v):

(a) triphosgene is the source of CO; or

(b) the reacting is performed in the presence of a base, optionally wherein the molar ratio of the base to Compound No. 8 as defined in claim 1, or the salt thereof, is from about 3:1 to about 1:1; or

(c) the reacting is performed in the presence of a solvent; or

(d) said step comprises filtering the solution of Compound No. 8 as defined in claim 1, or the salt thereof; or

(e) Compound No. 8 as defined in claim 1, or the salt thereof, is isolated and/or purified prior to reacting with Compound No. 6 as defined in claim 1, or a salt thereof; or

(f) Compound No. 8 as defined in claim 1, or the salt thereof, is not isolated and/or purified prior to reacting with Compound No. 6 as defined in claim 1, or a salt thereof; or

(g) said step yields a solution of Compound No. 8 as defined in claim 1, or the salt thereof; or

(h) said step yields Compound No. 8 as defined in claim 1, or the salt thereof, with purity of at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% as measured by HPLC.

11. The method of claim 1, wherein in step (vi):

(a) the reacting is performed in the presence of a base; or

(b) the reacting is performed in the presence of a first solvent; or

(c) the molar ratio of Compound No. 6 as defined in claim 1, or a salt thereof, to the Compound No. 8 as defined in claim 1, or the salt thereof, is from about 2:1 to about 1:2; or

(d) the reacting comprises partial removal of the first solvent; or

(e) the reacting is performed in the presence of a second solvent; or

(f) the reacting comprises extracting Compound No. 9 as defined in claim 1 using an ether; or

(g) the reacting comprises filtering out Compound No. 9 as defined in claim 1, washing Compound No. 9 as defined in claim 1 with IPA-MTBE, or a combination thereof; or

(h) the reacting is performed at a first temperature of about 25±15 °C, about 25±10 °C, or about 25±5 °C; or

(i) said step comprises filtering Compound No. 9 as defined in claim 1; or

(j) Compound No. 9a or 9b as defined in claim 6 or claim 8 is isolated and/or purified; or

(k) said step yields Compound No. 9 as defined in claim 1 with purity of at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% as measured by HPLC.

12. The method of claim 1, wherein in step (vii):

(a) said step comprises recrystallizing Compound No. 9 as defined in claim 1 in the presence of an organic solvent; or

(b) Compound No. 9 as defined in claim 1 is dissolved in tetrahydrofuran, filtered and washed with tetrahydrofuran to form a first mixture, optionally wherein:

(b)(i) the first mixture of step (vii) is concentrated and ethyl acetate is added to form a second mixture, further optionally wherein:

(b)(ii) the second mixture of step (vii) is concentrated and ethyl acetate and water are added to form a third mixture, yet further optionally wherein:

(b)(iii) the third mixture of step (vii) is heated and then seeded to form a seeded third mixture, or

(b)(iv) wherein the third mixture of step (vii) is heated to a first temperature of about 45±20 °C, about 45±15 °C, about 45±10 °C, about 45±5 °C, about 45±4 °C, about 45±3 °C, about 45±2 °C, or about 45±1 °C and then seeded to form a seeded third mixture, optionally wherein:

(b)(v) after heating to the first temperature, the seeded third mixture of step (vii) is aged for about 1±2 hours, or 1±1 hour, further optionally wherein:

(b)(vi) in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of about 30±20 °C, about 30±15 °C, about 30±10 °C, about 30±5 °C, about 30±4 °C, about 30±3 °C, about 30±2 °C, or about 30±1 °C; or

(b)(vii) wherein in step (vii), after aging the seeded third mixture, the seeded third mixture is cooled to a second temperature of about 30±20 °C, about 30±15 °C, about 30±10 °C, about 30±5 °C, about 30±4 °C, about 30±3 °C, about 30±2 °C, or about 30±1 °C (*e.g.*, about 30 °C) and aged for a time from about 1 hour to about 12 hours, from about 2 hours to about 10 hours, or from about 3 hours to about 6 hours to form a mixture comprising Compound No. 10 as defined in claim 1; optionally wherein:

(b)(viii) in step (vii), n-heptane is added to the mixture comprising Compound No. 10 as defined in claim 1 to form a solid form of Compound No. 10 as defined in claim 1; further optionally wherein:

(b)(ix) in step (vii), the solid form of Compound No. 10 as defined in claim 1 is filtered out and washed, thereby forming substantially pure solid form of Compound No. 10 as defined in claim 1; yet further optionally wherein:

(b)(x) step (vii) yields a specific polymorphic form of Compound No. 10 as defined in claim 1; or

(b)(xi) wherein step (vii) yields polymorphic form (Form 3) of Compound No.10a as defined in claim 7, wherein said Form 3 is characterized by an XRPD pattern comprising signals at 4.4±0.5, 8.4±0.5, and 17.8±0.5 °2θ using Cu Kα radiation; or

(b)(xii) wherein step (vii) yields a solid form of Compound No. 10 as defined in claim 1 with purity of at least about 98%, at least about 98.5%, at least about 99%, at least about 99.1%, at least about 99.2%, at least about 99.3%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, at least about 99.8% as measured by HPLC; or

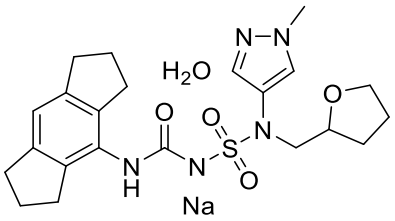
(b)(xiii) wherein step (vii) yields substantially pure polymorphic form (Form 3)

of Compound No. 10a as defined in claim 7, wherein said Form 3 is characterized by an XRPD pattern comprising signals at 4.4±0.5, 8.4±0.5, and 17.8±0.5 °2θ using Cu Kα radiation.

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

14. A pharmaceutical composition comprising Compound No. 10 as defined in claim 1, of any one of the preceding claims, and one or more pharmaceutically acceptable carrier or excipient.

15. Use of Compound No. 10,



(10),

in the manufacture of a medicament for:

(a) preventing or treating a disease in a subject; or

(b) inhibiting inflammasome activity in a subject.