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(54) Title: CARBAMATE AND UREA DERIVATIVES

(57) Abstract: Disclosed are carbamate and urea derivatives, pharmaceutical compositions comprising them, and methods of using them.

CARBAMATE AND UREA DERIVATIVES

BACKGROUND OF THE DISCLOSURE

Cross-reference to related applications

[1] This application claims priority from U.S. Application No. 63/015024, filed April 24, 2020, and 63/166083, filed March 25, 2021, the disclosure of each of which is hereby incorporated by reference in its entirety.

Field of the Disclosure

[2] This disclosure relates generally to carbamate- and urea-derived molecules, pharmaceutical compositions comprising them, and methods of using them.

Technical Background

[3] The inflammasome is a large multiprotein complex that plays an important role in both sterile tissue injury and infection. However, due to the potently inflammatory nature of inflammasome-derived mediators, complex regulatory mechanisms have evolved to suppress inflammasome activation in the absence of injury or infection. The importance of such mechanisms is highlighted by activating mutations in the inflammasome pathway that lead to an array of autoinflammatory diseases which can be life threatening. Chronic and acute aberrant activation of the inflammasome pathway also contributes to the pathology of a wide range of arthritic, neurodegenerative, cardiovascular, dermatological, pulmonary and systemic inflammatory conditions.

[4] Assembly of the inflammasome complex is under the control of a 'two-hit' system whereby two independent signals are required for activation. Signal 1 stimulates transcription of inflammasome-related genes, leading to upregulation of the individual components of the inflammasome, as well as the production of the pro-form of the inflammasome substrates interleukin-1β (IL-1β), interleukin-18 (IL-18) and Gasdermin-D within the cytosol. Signal 2 is provided by an array of pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) that are sensed by a family of cytosolic pattern recognition receptors termed nucleotide-binding oligomerization domain-like receptors (NLRs), as well as a few additional inflammasome forming sensors. Binding of the DAMP to its corresponding NLR leads to conformational changes in the NLR allowing self-oligomerization of the receptor. These NLR oligomers then recruits the adapter protein, apoptosis-associated speck-like protein containing a CARD (ASC), nucleating formation of a filament of repeating

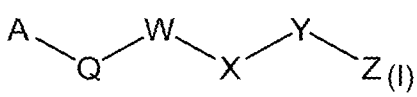
ASC subunits, mediated through the pyrin domain of ASC. The ASC filaments in turn creates a platform for recruitment of caspase-1 leading autocatalytic cleavage and activation, as well nucleating subsequent caspase-1 filament formation mediated through the caspase-1 CARD domain, which is thought to amplify caspase-1 activation. Active caspase-1 then cleaves pro-IL-1β, pro-IL-18 and Gasdermin D into their active forms, releasing the inflammatory mediators from the cell and inducing Gasdermin-D mediated pyroptotic cell death.

[5] Inflammasome formation can be initiated by at least 11 different sensors including Pyrin, numerous NLRs including NLRP1, NLRP3, NLRP6, NLRP7, NLRP12, NLRC4 and NLRC5, the PYHIN family members IFI-16 and AIM2, as well as RIG-I. Conventional approaches to inflammasome inhibition have targeted individual receptors, such as NLRP3, to inhibit a subset of inflammasomes. However, emerging evidence clearly demonstrates that activation of multiple different inflammasome forming receptors is a common pathological feature of many diseases including inflammatory bowel disease, arthritic diseases and neurodegenerative disorders among others. Hence, broader pharmaceutical approaches capable of simultaneously inhibiting multiple species of inflammasomes are needed to address pathological inflammasome-dependent inflammation.

[6] One way to achieve broader inflammasome inhibition is to target the shared components of the inflammasome, such as ASC filaments. Assembly of the inflammasome is induced by a cytosolic sensor (e.g. NLRP3 or AIM2) which detect danger signals associated with infection or sterile injury. Upon sensing these signals, the sensor nucleates formation of long filaments composed of repeating units of the inflammasome adapter protein ASC. These filaments form a scaffold for the recruitment of Caspase-1 leading to autoproteolytic activation of the enzyme. While the inflammasome plays a protective role against infection and injury, aberrant activation of the complex in the absence of infection or injury contributes to a wide range of autoinflammatory conditions. Accordingly, the development of compositions and methods that disrupt assembly of the ASC filament in order to prevent inflammasome driven inflammation is an important challenge.

SUMMARY OF THE DISCLOSURE

[7] One aspect of the disclosure provides compounds having the structural formula:



(I)

and pharmaceutically acceptable salts thereof, and/or solvates or hydrates thereof, wherein:

A is C_1-C_6 alkyl (e.g., t-butyl), -(C_0-C_4 alkyl)-O_{0-1}-cycloalkyl, -(C_0-C_4 alkyl)-O_{0-1}-heterocycloalkyl, -(C_0-C_4 alkyl)-O_{0-1}-aryl, or -(C_0-C_4 alkyl)-O_{0-1}-heteroaryl, or -(C_0-C_2 alkyl)-B-C, wherein B and C are each independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Q and X are -O- or -N(R^A)-, wherein Q and X are not both -O-;

W is C(O) or $S(O)_n$, wherein n is 1 or 2;

Y is a C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, -(C_0-C_2 alkyl)-cycloalkyl, -(C_0-C_2 alkyl)-heterocycloalkyl, -(C_2-C_3 alkenyl)-cycloalkyl, or -(C_2-C_3 alkenyl)-heterocycloalkyl;

Z is absent or -(C_0-C_2 alkyl)-O(R^A) or -(C_0-C_2 alkyl)-N(R^A)(R^B);

wherein

each R^A and R^B is independently H, C_1-C_4 alkyl, or (C_0-C_2)-cyclopropyl;

each alkyl, alkenyl, and alkynyl is unsubstituted, substituted with one or more halogens (e.g., fluorinated or perfluorinated), or substituted with one or two groups independently selected from methyl, ethyl, oxo, acyl, and -C(O)N(R^A)(R^B);

each cycloalkyl has 3-10 ring carbons and is saturated or partially unsaturated, and optionally includes one or two fused and/or bridged cycloalkyl rings, each fused and/or bridged ring having 3-8 ring members, wherein the bridge is bivalent or trivalent, and is substituted with 0-5 R^C or is perfluorinated;

each heterocycloalkyl has 3-10 ring members and 1-4 heteroatoms where each heteroatom is independently boron, nitrogen, oxygen or sulfur and is saturated or partially unsaturated, and optionally includes one or two fused cycloalkyl or aryl rings, and/or one or two bridged cycloalkyl rings, each fused and/or bridged ring each having 3-8 ring members, wherein the bridge is bivalent or trivalent, and is substituted with 0-5 R^C or is perfluorinated;

each aryl is a phenyl or naphthyl, and optionally includes one or two fused cycloalkyl or heterocycloalkyl rings, each fused cycloalkyl or heterocycloalkyl ring having 4-8 ring members, and is substituted with 0-5 R^C or is perfluorinated;

each heteroaryl is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms, where each heteroatom is independently boron, nitrogen, oxygen or sulfur, or is a bicyclic heteroaryl having 1-5 heteroatoms where each heteroatom is independently boron, nitrogen, oxygen, or sulfur, and optionally includes one or two fused cycloalkyl or

heterocycloalkyl rings, each fused cycloalkyl or heterocycloalkyl ring having 4-8 ring members, and wherein the heteroaryl is substituted with 0-5 R^C;

wherein each R^C is independently C_1-C_4 alkyl (e.g., methyl, t-butyl, or -CF_3), -Cl, -F, -Br, -CN, -OR^A, -$C(O)R^A$, -$C(O)NR^BR^A$, -NR^AR^B, SO_3, or $SO_2(C_1$ alkyl).

[8] In another aspect, the disclosure provides pharmaceutical compositions comprising a compound (e.g., a compound of formula (I)) as described herein.

[9] In another aspect, the disclosure provides intermediates useful to prepare the compounds of formula (I).

[10] In another aspect, the disclosure provides methods for treating various diseases, such as inflammation-related diseases to a subject in need thereof. The methods include administering to the subject an effective amount of a compound as described herein (e.g., a compound of formula (I).

[11] In certain embodiments, the diseases that can be treated with the compounds or compositions as described herein include, but are not limited to Adult-Onset Still's Disease (AOSD), Systemic Juvenile Idiopathic Arthritis (sJIA), Macrophage Activation Syndrome (MAS), Autoinflammation with Infantile Enterocolitic (AIFEC), Bullous Pemphigoid, Pemphigus Vulgaris, Idiopathic Pulmonary Fibrosis (IPF), Non-Alcoholic Steatohepatitis (NASH), Systemic Lupus Erythematosus (SLE), Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease, Traumatic Brain Injury (TBI), Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA), Cryopyrin-Associated Periodic Syndromes (CAPS), Vitiligo, Multiple Self-Healing Palmoplantar Carcinoma (MSPC), Autoimmune Addison's Disease, Familial Mediterranean Fever (FMF), Autoimmune Thyroiditis, Stroke, Type 2 Diabetes (T2D), Osteoarthritis, Gout, Atherosclerosis, Hidradenitis Suppurativa, Psoriasis, and Pyrin Diseases.

[12] In another aspect, the disclosure provides methods for treating an inflammatory condition, for example, an inflammatory condition that causes cell death, or release of pro-inflammatory cytokines or other inflammatory mediators, resulting from a coronavirus (e.g., SARS-CoV 2, SARS-CoV, or MERS), viral, bacterial, fungal, parasitic, or other type of infection in a human subject, comprising administering to a subject in need of such treatment a compound as otherwise described herein (e.g., a compound of formula (I)).

[13] In another aspect, the disclosure provides methods for treating an inflammatory condition (e.g., cytokine storm syndrome, or cytokine release syndrome), for example, an inflammatory condition that causes cell death or release of pro-inflammatory cytokines or other inflammatory

mediators, resulting from a cell therapy (e.g., CAR T cell therapy) administered to a human subject, comprising administering to a subject in need of such treatment a compound as otherwise described herein (e.g., a compound of formula (I)).

[14] Other aspects and embodiments of the disclosure are evident in view of the detailed description provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[15] FIG. 1 is a Western blot depicting autoproteolyic cleavage of Caspase-1 when treated with a composition according to the present disclosure.

DETAILED DESCRIPTION

[16] The disclosure provides compounds, pharmaceutical compositions, methods and uses for treating a variety of diseases associated with inhibiting inflammasome formation. Specifically, the compounds are targeted at inhibiting ASC assembly, blocking a structural motif of the inflammasome and preventing cytokine expression. Without wishing to be bound by theory, it is hypothesized that effective binding, and therefore inhibition, can be accomplished by a roughly linear molecule with two distinct motifs: a bulky head group on one end, and a modified alkyl chain on the other. Modifications to these two groups have effectively tuned the observed activity, suggesting a highly tunable family that has demonstrated functionality.

[17] The compounds can be defined generically as with respect to formula (I) as appropriate, or in various subgenera formulae in which A, Q, X, Y, and Z are optionally independently selected from the groups (1a) *et seq.*, (2a) *et seq.*, (3a) *et seq.*, (4a) *et seq.*, and (5a) *et seq.* defined herein below (*e.g.*, wherein the compound is of a structural formula as defined in any combination of the embodiments below):

[18] In certain embodiments of the compounds as otherwise described herein, A is independently selected from the following groups (1a) – (1f):

(1a) t-butyl, -(C_0-C_2 alkyl)-O_{0-1}-cycloalkyl, -(C_0-C_2 alkyl)-O_{0-1}-heterocycloalkyl, -(C_0-C_2 alkyl)-O_{0-1}-aryl, or -(C_0-C_2 alkyl)-O_{0-1}-heteroaryl;

(1b) t-butyl;

(1c) -(C_0-C_1 alkyl)-cycloalkyl, -(C_0-C_1 alkyl)-heterocycloalkyl, -(C_0-C_1 alkyl)-aryl, or -(C_0-C_1 alkyl)-heteroaryl, wherein each cycle is either monocyclic or fused bicyclic;

(1d) phenyl or benzyl;

(1e) -(C_0-C_1 alkyl)-B-C, wherein B is cyclopropyl, cyclobutyl, adamantyl, or phenyl, and C is cyclopropyl, phenyl, tetrazolyl, or morpholinyl;

(1f) -(C_0-C_1 alkyl)-B-C, wherein B is cyclopropyl, adamantyl, or phenyl, and C is cyclopropyl or phenyl.

(1g) cyclobutyl, cyclopentyl, cyclohexyl, or adamantyl;

(1h) A is (C_1 alkyl)-aryl, wherein aryl is monocyclic or fused bicyclic, and the C_1 alkyl is substituted by an unsubstituted methyl or unsubstituted ethyl group.

[19] Each of groups (1a)-(1h) is unsubstituted or substituted as described in connection with formula (I) above.

[20] In certain embodiments of the compounds as otherwise described herein, Q and X are selected from one of the following groups (2a) – (2e):

(2a) Q is -O- and X is -N(R^A)-;

(2b) Q is -N(R^A)- and X is -O-;

(2c) both Q and X are -N(R^A)-;

(2d) as defined in (2a)-(2c), wherein R^A is H or methyl (e.g., H).

(2e) X is -N(H)-.

[21] In certain embodiments of the compounds as otherwise described herein, W is selected from one of the following groups (3a) – (3d):

(3a) C(O);

(3b) S(O) or $S(O)_2$;

(3c) S(O);

(3d) $S(O)_2$.

[22] In certain embodiments of the compounds as otherwise described herein, Y is selected from one of the following groups (4a) – (4g):

(4a) C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

(4b) C_2-C_6 alkyl (e.g., *n*-propyl, *n*-butyl, or *n*-pentyl);

(4c) C_2-C_6 alkenyl;

(4d) C_3-C_6 alkenyl

(4e) C_2-C_6 alkynyl (e.g., but-2-ynyl);

(4f) -(C_0-C_1 alkyl)-cycloalkyl (e.g., -CH_2-cyclopropyl);

(4g) -(C_2-C_3 alkenyl)-cycloalkyl, wherein cycloalkyl is cyclopropyl or cyclobutyl.

[23] Each of groups (4a)-(4g) is unsubstituted or substituted as described in connection with formula (I) above.

[24] Specific examples of C_3-C_6 alkenyl groups in (4d) include but-2-enyl, or 2-methylbut-2-enyl, or 2-fluorobut-2-enyl, or 2,3-difluorobut-2-enyl.

[25] In certain embodiments of the compounds as otherwise described herein, Z is independently selected from one of the following groups (5a) – (5h):

(5a) -(C_0-C_1 alkyl)-O(R^A) or -(C_0-C_1 alkyl)-N(R^A)(R^B);

(5b) -(C_0-C_1 alkyl)-OH or -(C_0-C_1 alkyl)-NH_2;

(5c) OH or NH_2;

(5d) -CH_2-N(R^A)(R^B) (e.g., -CH_2-NH_2);

(5e) -O(R^A) or -N(R^A)(R^B);

(5f) -O(R^A) (e.g., -OH);

(5g) -NH(R^A) (e.g., NH_2 or NH(CH_2CH_3));

(5h) absent.

[26] Each of groups (5a), (5b) and (5d)-(5g) is unsubstituted or substituted as described in connection with formula (I) above.

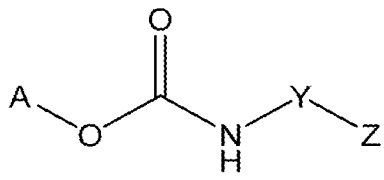
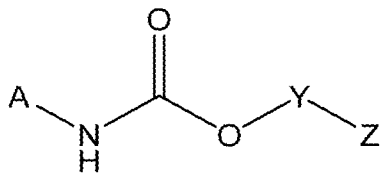
[27] In certain embodiments of the compounds as otherwise described herein, the compound is not *tert*-butyl (4-aminopentyl)carbamate, *tert*-butyl (4-aminobut-2-yn-1-yl)carbamate, tert-butyl (3-hydroxypropyl)carbamate, tert-butyl ethylcarbamate, tert-butyl (3-amino-2-methylpropyl)carbamate, *tert*-butyl but-3-en-1-ylcarbamate, *tert*-butyl (azetidin-3-ylmethyl)carbamate, *tert*-butyl (4-aminobut-2-en-1-yl)carbamate, or *tert*-butyl (4-hydroxybut-2-en-1-yl)carbamate.

[28] In certain embodiments as otherwise described herein, each R^C is independently selected from the group consisting of methyl, ethyl, -CF_3 -F, and –Cl, wherein each methyl and ethyl are

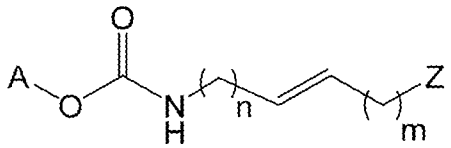
unsubstituted or substituted as described in connection with formula (I) above. For example, in certain embodiments, each R^C is CH_3, $-CH_2CH_3$, $-CF_3$ -F, or -Cl.

[29] In certain embodiments as otherwise described herein, each R^A is independently H, methyl, butenyl, or -(C_{0-2} alkyl)-cyclopropyl. For example, in certain embodiments, each R^A is H or methyl.

[30] In certain embodiments as otherwise described herein, each R^B is H.

[31] In certain embodiments as otherwise described herein, the compound has the structural formula  (I-A) or  (I-B).

[32] For example, in certain embodiments, the compound has the structural formula



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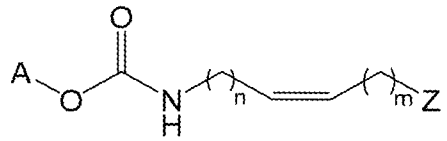

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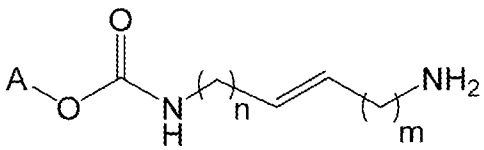

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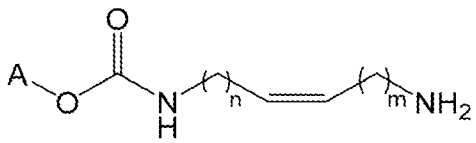

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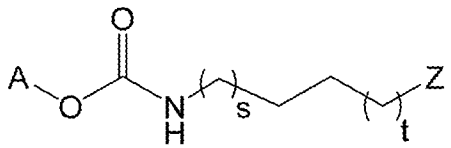

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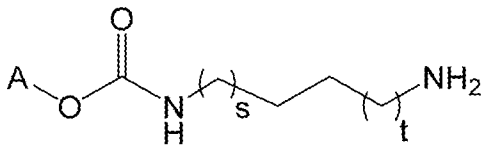

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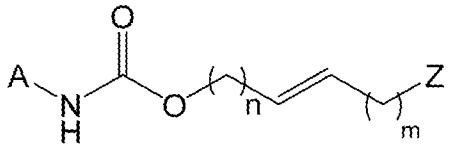

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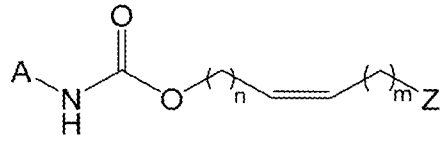

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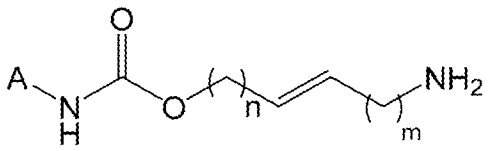

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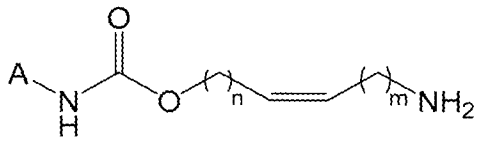

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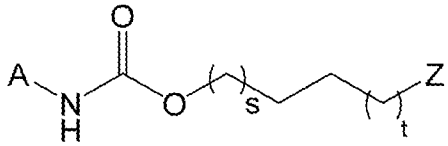

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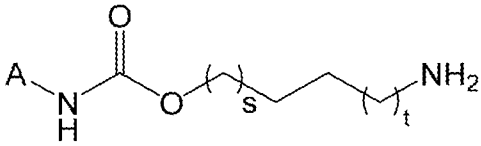


(I-B6)

[33] wherein in each of I-A1, I-A2, I-A3, I-A4, I-A5, I-A6, I-B1, I-B2, I-B3, I-B4, I-B5, and I-B6, n and m are independently 1, 2, or 3 and s and t are independently 0, 1, 2, or 3. Various particular embodiments nos. 1-36 of compounds for use in the methods, compounds and uses of the disclosure include compounds of formula (I), each as defined in each of the following rows (or a pharmaceutically acceptable salt, or a solvate or hydrate thereof), wherein each entry is a group number as defined above:

Table 1

Embodiment	A	Q and X	W	Y	Z
1	(1a)	(2a)	(3a)	(4a)	(5b)
2	(1a)	(2a)	(3a)	(4a)	(5c)
3	(1a)	(2a)	(3a)	(4d)	(5b)
4	(1a)	(2a)	(3a)	(4d)	(5c)
5	(1a)	(2a)	(3a)	(4f)	(5b)
6	(1a)	(2a)	(3a)	(4f)	(5c)
7	(1a)	(2b)	(3a)	(4a)	(5b)
8	(1a)	(2b)	(3a)	(4a)	(5c)
9	(1a)	(2b)	(3a)	(4d)	(5b)
10	(1a)	(2b)	(3a)	(4d)	(5c)
11	(1a)	(2b)	(3a)	(4f)	(5b)
12	(1a)	(2b)	(3a)	(4f)	(5c)
13	(1c)	(2a)	(3a)	(4a)	(5b)
14	(1c)	(2a)	(3a)	(4a)	(5c)
15	(1c)	(2a)	(3a)	(4d)	(5b)
16	(1c)	(2a)	(3a)	(4d)	(5c)
17	(1c)	(2a)	(3a)	(4f)	(5b)
18	(1c)	(2a)	(3a)	(4f)	(5c)
19	(1c)	(2b)	(3a)	(4a)	(5b)

Embodiment	A	Q and X	W	Y	Z
20	(1c)	(2b)	(3a)	(4a)	(5c)
21	(1c)	(2b)	(3a)	(4d)	(5b)
22	(1c)	(2b)	(3a)	(4d)	(5c)
23	(1c)	(2b)	(3a)	(4f)	(5b)
24	(1c)	(2b)	(3a)	(4f)	(5c)
25	(1e)	(2a)	(3a)	(4a)	(5b)
26	(1e)	(2a)	(3a)	(4a)	(5c)
27	(1e)	(2a)	(3a)	(4d)	(5b)
28	(1e)	(2a)	(3a)	(4d)	(5c)
29	(1e)	(2a)	(3a)	(4f)	(5b)
30	(1e)	(2a)	(3a)	(4f)	(5c)
31	(1e)	(2b)	(3a)	(4a)	(5b)
32	(1e)	(2b)	(3a)	(4a)	(5c)
33	(1e)	(2b)	(3a)	(4d)	(5b)
34	(1e)	(2b)	(3a)	(4d)	(5c)
35	(1e)	(2b)	(3a)	(4f)	(5b)
36	(1e)	(2b)	(3a)	(4f)	(5c)

[34] In certain additional embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above, each optionally substituted alkyl, alkenyl, and alkynyl recited in any one of preceding embodiments is unsubstituted.

[35] In certain additional embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and the embodiment described in the paragraph immediately above, each cycloalkyl recited in any one of the preceding embodiments is a 3-7 membered monocyclic cycloalkyl. For example, in certain particular embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and the embodiment described in the paragraph immediately above, each cycloalkyl recited in any one of the preceding embodiments is a cyclopropyl, a cyclobutyl, a cyclopentyl, a cyclopentenyl, a cyclohexyl, or a cyclohexenyl.

[36] In certain additional embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and any embodiment described in the two paragraphs immediately above, each heterocycloalkyl recited in any one of the preceding embodiments is a 4-7 membered monocyclic heterocycloalkyl having 1-2 heteroatoms selected from O, S and N. For example, in certain particular embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and any embodiment described in the two paragraphs immediately above, each heterocycloalkyl recited in any one of the preceding embodiments is a pyrrolidinyl, a tetrahydrofuranyl, a

tetrahydrothienyl, a piperidinyl, a piperazinyl, a morpholinyl, a thiomorpholinyl, a tetrahydro-2H-pyranyl, or a tetrahydro-2H-thiopyranyl. In certain particular embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and any embodiment described in the two paragraphs immediately above, each heterocycloalkyl recited in any one of the preceding embodiments is a pyrrolidine, a piperidine, a piperazine, a tetrahydrofuran, a (1H)dihydropyran, or a morpholine (e.g., each unsubstituted).

[37] In certain additional embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and any embodiment described in the three paragraphs immediately above, each aryl is phenyl.

[38] In certain additional embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and any embodiment described in the four paragraphs immediately above, each heteroaryl is a 5-6 membered monocyclic heteroaryl having 1-3 heteroatoms selected from O, S and N. For example, in certain particular embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and any embodiment described in the four paragraphs immediately above, each heteroaryl is a monocyclic heteroaryl is substituted with 0-3 R^C, e.g., is unsubstituted, substituted with one R^C or substituted with two R^C. In certain particular embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and any embodiment described in the four paragraphs immediately above, each heteroaryl is a furanyl, a thienyl, a pyrrolyl, a pyrazolyl, an imidazolyl, an oxazolyl or a thiazolyl.

[39] In certain additional embodiments, including any of the embodiments described with reference to formula (I) and embodiments 1-36 above and any embodiment described in the paragraphs immediately above, each R^C is independently C_1-C_4 alkyl (e.g., methyl, t-butyl, or -CF_3), -Cl, -F, -Br, -CN, -$N(R^A)(R^B)$, -OR^A, -$C(O)R^A$, or -$C(O)NR^BR^A$. For example, in certain additional embodiments, each R^C is independently methyl, -CF_3, -F-, -CN, -$N(R^A)(R^B)$, -OR^A, or -$C(O)R^A$.

[40] In certain embodiments of the compounds as otherwise described herein, the compound is in the form of a pharmaceutically acceptable salt of a compound as described herein. The person of ordinary skill in the art will appreciate that a variety of pharmaceutically-acceptable salts may be provided, as described in additional detail below. In certain embodiments of the compounds as otherwise described herein, a compound is in the form of a solvate (e.g., a hydrate) of a compound or salt as described herein. The person of ordinary skill in the art will

appreciate that a variety of solvates and/or hydrates may be formed. The person of ordinary skill in the art will appreciate that the phrase "optionally in the form of a pharmaceutically acceptable salt thereof, and/or a solvate or hydrate thereof" includes compounds in the form of solvates and hydrates of base compounds or pharmaceutically acceptable salts as described above. But in certain embodiments as described above, the compound is not in the form of a solvate or hydrate.

Therapeutic Applications

[41] The disclosure also provides methods of treating various diseases, such as inflammatory conditions. These methods include administering to a subject in need of such treatment an effective amount of one or more compounds of the disclosure as described herein (e.g., compounds of formula (I)) or a pharmaceutical composition of the disclosure as described herein.

[42] In certain embodiments, the present disclosure provides for a method of treating an inflammatory condition in a subject thereof, wherein the method includes providing to the subject a compound as otherwise described herein. In certain embodiments as otherwise described herein, the inflammatory condition is an inflammatory bowel disease, an arthritic disease, or a neurodegenerative disorder. In other embodiments, the inflammatory condition is an autoinflammatory syndrome. In still other embodiments, the inflammatory condition is an inflammasome-related condition. Some conditions and/or diseases may be combinations of the above embodiments, or otherwise fall into multiple categories simultaneously.

[43] In certain embodiments, the diseases of the disclosure include, but are not limited to Adult-Onset Still's Disease (AOSD), Systemic Juvenile Idiopathic Arthritis (sJIA), Macrophage Activation Syndrome (MAS), Autoinflammation with Infantile Enterocolitic (AIFEC), Bullous Pemphigoid, Pemphigus Vulgaris, Idiopathic Pulmonary Fibrosis (IPF), Non-Alcoholic Steatohepatitis (NASH), Systemic Lupus Erythematosus (SLE), Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease, Traumatic Brain Injury (TBI), Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA), Cryopyrin-Associated Periodic Syndromes (CAPS), Vitiligo, Multiple Self-Healing Palmoplantar Carcinoma (MSPC), Autoimmune Addison's Disease, Familial Mediterranean Fever (FMF), Autoimmune Thyroiditis, Stroke, Type 2 Diabetes (T2D), Osteoarthritis, Gout, Atherosclerosis, Hidradenitis Suppurativa, Psoriasis, and Pyrin Diseases.

[44] In another aspect, the disclosure provides methods for treating an inflammatory condition, for example, an inflammatory condition that causes cell death, or release of pro-inflammatory

cytokines or other inflammatory mediators, resulting from a coronavirus (e.g., SARS-CoV 2, SARS-CoV, or MERS), viral, bacterial, fungal, parasitic, or other type of infection in a human subject, comprising administering to a subject in need of such treatment a compound as otherwise described herein (e.g., a compound of formula (I)).

[45] In certain embodiments as otherwise described herein, the inflammatory condition may cause at least one of cell death, release of pro-inflammatory cytokines, or other inflammatory mediators.

[46] In certain embodiments as otherwise described herein, the inflammatory condition suitable for treatment by compounds as otherwise described herein includes cytokine storm syndrome, cytokine release syndrome, sepsis, hemophagocytic lymphohistiocytosis, acute lung injury, acute respiratory distress syndrome, or macrophage activation syndrome. Further suitable inflammatory conditions will be apparent to one of skill in the art.

[47] In certain embodiments as otherwise described herein, the inflammatory condition may result from a cell therapy administered to a human subject. For example, a CAR T cell therapy. The inflammatory condition may comprise cytokine storm syndrome, or cytokine release syndrome.

[48] In certain embodiments as otherwise described herein, the inflammatory condition may be treated with a compound as otherwise described herein in co-therapy with at least one of an antiinfective, antimicrobial, antiviral (e.g., remdesivir), monoclonal antibody (e.g., tocilizumab), biologic, immunoglobulin, immunomodulator, anti-inflammatory drug, corticosteroid, small molecule, cell therapy, or other type of prophylactic or therapeutic agent. Such co-therapies may be selected to as to not interfere with the action of the compound of the present disclosure, while treating another aspect of the condition, or alleviating a symptom thereof.

[49] In another aspect, the disclosure provides methods for treating an inflammatory condition (e.g., cytokine storm syndrome, or cytokine release syndrome), for example, an inflammatory condition that causes cell death or release of pro-inflammatory cytokines or other inflammatory mediators, resulting from a cell therapy (e.g., CAR T cell therapy) administered to a human subject, comprising administering to a subject in need of such treatment a compound as otherwise described herein (e.g., a compound of formula (I)).

[50] In certain embodiments as otherwise described herein, a compound as otherwise described herein is administered in co-therapy with at least one of a monoclonal antibody (e.g., tocilizumab), a biologic, an immunoglobulin, an immunomodulatory, an anti-inflammatory drug, a

corticosteroid, a small molecule, a cell therapy, or other type of prophylactic or therapaetuic agent.

[51] Without wishing to be bound by theory, it is presently believed that certain compounds of the present disclosure may aid in the treatment of inflammatory conditions by inhibiting activation of the inflammasome, specifically through binding to the ASC domain, preventing interactions through the pyrin domain (PYD). Accordingly, in certain embodiments, the present disclosure provides for a method for suppressing ASC-filament formation in a subject, wherein the method includes administering a compound as otherwise described herein. In particular, in some embodiments, the inhibition may be through interacting with the apoptosis-associated speck-like protein containing A CARD.

Pharmaceutical Compositions and Dosage Forms

[52] A compound as described herein can usefully be provided in the form of a pharmaceutical composition. Such compositions include the compound according to any one of the preceding aspects or embodiments described herein, together with a pharmaceutically acceptable excipient, diluent, or carrier.

[53] The compounds may be formulated in the pharmaceutical composition per se, or in the form of a hydrate, solvate, or pharmaceutically acceptable salt, as previously described. Typically, such salts are more soluble in aqueous solutions than the corresponding free acids and bases, but salts having lower solubility than the corresponding free acids and bases may also be formed.

[54] The pharmaceutical composition can be, for example, in the form of a tablet, a capsule, or a parenteral formulation, but the person of ordinary skill in the art will appreciate that the compound can be provided in a wide variety of pharmaceutical compositions.

[55] The compounds of the disclosure can be administered, for example, orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing one or more pharmaceutically acceptable carriers, diluents or excipients. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. A medicament including a compound of the disclosure can be provided in any appropriate of the formulations and dosage forms as described herein.

[56] Pharmaceutical compositions can be made using the presently disclosed compounds. For example, in one embodiment, a pharmaceutical composition includes a pharmaceutically

acceptable carrier, diluent or excipient, and compound as described above with reference to any one of the structural formulae.

[57] In the pharmaceutical compositions disclosed herein, one or more compounds of the disclosure may be present in association with one or more pharmaceutically acceptable carriers, diluents or excipients, and, if desired, other active ingredients. The pharmaceutical compositions containing compounds of the disclosure may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[58] Compositions intended for oral use can be prepared according to any suitable method for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by suitable techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed.

[59] Formulations for oral use can also be presented as hard gelatin capsules, wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[60] Formulations for oral use can also be presented as lozenges.

[61] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as a naturally-occurring phosphatide, for example, lecithin, or condensation products of an

alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[62] Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[63] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

[64] Pharmaceutical compositions can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

[65] In some embodiments, the pharmaceutically acceptable carrier, diluent, or excipient is not water. In other embodiments, the water comprises less than 50% of the composition. In some embodiments, compositions comprising less than 50% water have at least 1%, 2%, 3%, 4% or 5% water. In other embodiments, the water content is present in the composition in a trace amount.

[66] In some embodiments, the pharmaceutically acceptable carrier, diluent, or excipient is not alcohol. In other embodiments, the alcohol comprises less than 50% of the composition. In some embodiments, compositions comprising less than 50% alcohol have at least 1%, 2%, 3%, 4% or 5% alcohol. In other embodiments, the alcohol content is present in the composition in a trace amount.

[67] Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative, flavoring, and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils can be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[68] Compounds of the disclosure can also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the compound with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[69] Compounds of the disclosure can also be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[70] The compositions can be formulated in a unit dosage form of the active ingredient. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[71] The compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[72] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of a compound described herein.

[73] The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[74] The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

[75] The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use

as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

[76] The therapeutic dosage of the compounds can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound described herein in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds described herein can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

[77] The compounds described herein can also be formulated in combination with or administered sequentially with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, vaccines, antibodies, immune enhancers, immune suppressants, anti-inflammatory agents and the like.

[78] The person of ordinary skill in the art will formulate a compound as described into pharmaceutical formulations herein. For example, based on the physicochemical properties of the compound, one of ordinary skill in the art will recognize a pharmaceutically effective amount of the compound, and the desired route of administration.

Definitions

[79] Terms used herein may be preceded and/or followed by a single dash, "-", or a double dash, "=", to indicate the bond order of the bond between the named substituent and its parent moiety; a single dash indicates a single bond and a double dash indicates a double bond or a pair of single bonds in the case of a spiro-substituent. In the absence of a single or double dash

it is understood that a single bond is formed between the substituent and its parent moiety; further, substituents are intended to be read "left to right" with reference to the chemical structure referred to unless a dash indicates otherwise. For example, arylalkyl, arylalkyl-, and -alkylaryl indicate the same functionality.

[80] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety can refer to a monovalent radical (e.g., CH_3-CH_2-), in some circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g., -CH_2-CH_2-), which is equivalent to the term "alkylene." Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene. All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). Nitrogens in the presently disclosed compounds can be hypervalent, e.g., an N-oxide or tetrasubstituted ammonium salt. On occasion a moiety may be defined, for example, as -B-$(A)_a$, wherein a is 0 or 1. In such instances, when a is 0 the moiety is -B and when a is 1 the moiety is -B-A.

[81] As used herein, the term "alkyl" includes a saturated hydrocarbon having a designed number of carbon atoms, such as 1 to 10 carbons (i.e., inclusive of 1 and 10), 1 to 8 carbons, 1 to 6 carbons, 1 to 3 carbons, or 1, 2, 3, 4, 5 or 6. Alkyl group may be straight or branched and depending on context, may be a monovalent radical or a divalent radical (i.e., an alkylene group). For example, the moiety "-(C_1-C_6 alkyl)-O-" signifies connection of an oxygen through an alkylene bridge having from 1 to 6 carbons and C_1-C_3 alkyl represents methyl, ethyl, and propyl moieties. Examples of "alkyl" include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, iso-, sec- and tert-butyl, pentyl, and hexyl.

[82] The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached to the parent molecular moiety through an oxygen bridge. Examples of "alkoxy" include, but are not limited to, methoxy, ethoxy, propoxy, and isopropoxy.

[83] The term "alkenyl" as used herein, unsaturated hydrocarbon containing from 2 to 10 carbons (i.e., inclusive of 2 and 10), 2 to 8 carbons, 2 to 6 carbons, or 2, 3, 4, 5 or 6, unless otherwise specified, and containing at least one carbon-carbon double bond. Alkenyl group may be straight or branched and depending on context, may be a monovalent radical or a

divalent radical (i.e., an alkenylene group). For example, the moiety "-(C_2-C_6 alkenyl)-O-" signifies connection of an oxygen through an alkenylene bridge having from 2 to 6 carbons. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl, and 3,7-dimethylocta-2,6-dienyl.

[84] The term "alkynyl" as used herein, unsaturated hydrocarbon containing from 2 to 10 carbons (i.e., inclusive of 2 and 10), 2 to 8 carbons, 2 to 6 carbons, or 2, 3, 4, 5 or 6 unless otherwise specified, and containing at least one carbon-carbon triple bond. Alkynyl group may be straight or branched and depending on context, may be a monovalent radical or a divalent radical (i.e., an alkynylene group). For example, the moiety "-(C_2-C_6 alkynyl)-O-" signifies connection of an oxygen through an alkynylene bridge having from 2 to 6 carbons. Representative examples of alkynyl include, but are not limited to, acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

[85] The term "aryl" represents an aromatic ring system having a single ring (e.g., phenyl) which is optionally fused to other aromatic hydrocarbon rings or non-aromatic cycloalkyl or heterocycloalkyl rings. The aryl ring system is attached to the parent molecular moiety through any atom contained within the ring system. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, indanyl, indenyl, dihydronaphthyl, fluorenyl, tetralinyl, 1,2,3,4-tetrahydronaphthyl, 6,7,8,9-tetrahydro-5*H*-benzo[a]cycloheptenyl, 1H-2,3-dihydrobenzofuranyl and tetrahydroisoquinolinyl. In certain embodiments, aryl is phenyl. In certain embodiments, aryl is phenyl or naphthyl. In certain embodiments, the aryl is (i) phenyl, (ii) naphthyl or (iii) a phenyl ring fused to either a 5 or 6 membered monocyclic cycloalkyl or cycloalkenyl, or a 5 or 6 membered monocyclic heterocycloalkyl. The aryl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups as indicated.

[86] The terms "halogen" or "halo" indicate fluorine, chlorine, bromine, and iodine. In certain embodiments of each and every embodiment as otherwise described herein, the term "halogen" or "halo" refers to fluorine or chlorine. In certain embodiments of each and every embodiment described herein, the term "halogen" or "halo" refers to fluorine. The term "fluorinated" indicates a group (such as alkyl as otherwise described herein) wherein at least one of the carbon-bound hydrogens is substituted by fluorine to form C-F groups. Examples of fluorinated alkyl groups are fluoromethyl, difluoromethyl and trifluoromethyl. Trifluoromethyl is a perfluorinated alkyl

group. The term "perfluorinated " indicates a group (such as alkyl as otherwise described herein) wherein all carbon-bound hydrogens are substituted by fluorine to form C-F groups.

[87] The term "heteroaryl" refers to an aromatic ring or ring system containing at least one aromatic heteroatom selected from boron, nitrogen, oxygen and sulfur in an aromatic ring. Most commonly, the heteroaryl groups will have 1, 2, 3, or 4 heteroatoms. The heteroaryl may be fused to one or more non-aromatic rings, for example, cycloalkyl or heterocycloalkyl rings, wherein the cycloalkyl and heterocycloalkyl rings are described herein. The heteroaryl ring system is bonded to the parent molecular moiety through any atom contained within the ring system. Examples of heteroaryl groups include, but are not limited to, pyridyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, benzo[1,4]oxazinyl, triazolyl, tetrazolyl, isothiazolyl, naphthyridinyl, isochromanyl, chromanyl, isoindolinyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, purinyl, benzodioxolyl, triazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, benzisoxazinyl, benzoxazinyl, benzopyranyl, benzothiopyranyl, chromonyl, chromanonyl, pyridinyl-*N*-oxide, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl *N*-oxide, pyrimidinyl *N*-oxide, pyridazinyl *N*-oxide, pyrazinyl *N*-oxide, quinolinyl *N*-oxide, indolyl *N*-oxide, indolinyl *N*-oxide, isoquinolyl *N*-oxide, quinazolinyl *N*-oxide, quinoxalinyl *N*-oxide, phthalazinyl *N*-oxide, imidazolyl *N*-oxide, isoxazolyl *N*-oxide, oxazolyl *N*-oxide, thiazolyl *N*-oxide, indolizinyl *N*-oxide, indazolyl *N*-oxide, benzothiazolyl *N*-oxide, benzimidazolyl *N*-oxide, pyrrolyl *N*-oxide, oxadiazolyl *N*-oxide, thiadiazolyl *N*-oxide, triazolyl *N*-oxide, tetrazolyl *N*-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide. In certain embodiments, each heteroaryl is selected from pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, isothiazolyl, pyridinyl-*N*-oxide, pyrrolyl *N*-oxide, pyrimidinyl *N*-oxide, pyridazinyl *N*-oxide, pyrazinyl *N*-oxide, imidazolyl *N*-oxide, isoxazolyl *N*-oxide, oxazolyl *N*-oxide, thiazolyl *N*-oxide, pyrrolyl *N*-oxide, oxadiazolyl *N*-oxide, thiadiazolyl *N*-oxide, triazolyl *N*-oxide, and tetrazolyl *N*-oxide. In certain embodiments, heteroaryl groups include pyridyl, pyrimidyl, quinolinyl, indolyl, pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, indazolyl, thiazolyl and benzothiazolyl. The heteroaryl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as indicated.

[88] The term "heterocycloalkyl" refers to a non-aromatic ring or ring system containing at least one heteroatom that is preferably selected from boron, nitrogen, oxygen and sulfur, wherein said heteroatom is in a non-aromatic ring. The heterocycloalkyl may have 1, 2, 3 or 4 heteroatoms. The heterocycloalkyl may be saturated or partially unsaturated (i.e., a heterocycloalkenyl). Heterocycloalkyl includes monocyclic groups of three to eight annular atoms as well as bicyclic and polycyclic ring systems, including bridged and fused systems, wherein each ring includes three to eight annular atoms. The heterocycloalkyl ring is optionally fused and/or bridged to other heterocycloalkyl and/or non-aromatic hydrocarbon rings. In certain embodiments, the heterocycloalkyl groups have from 3 to 7 members in a single ring. In other embodiments, heterocycloalkyl groups have 5 or 6 members in a single ring. In some embodiments, the heterocycloalkyl groups have 3, 4, 5, 6 or 7 members in a single ring. Examples of heterocycloalkyl groups include, but are not limited to, azabicyclo[2.2.2]octyl (in each case also "quinuclidinyl" or a quinuclidine derivative), azabicyclo[3.2.1]octyl, 2,5-diazabicyclo[2.2.1]heptyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, 2-oxazolidonyl, piperazinyl, homopiperazinyl, piperazinonyl, pyrrolidinyl, azepanyl, azetidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, 3,4-dihydroisoquinolin-2(1*H*)-yl, isoindolindionyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, imidazolidonyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide. In certain embodiments, heterocycloalkyl groups include morpholinyl, 3,4-dihydroisoquinolin-2(1*H*)-yl, tetrahydropyranyl, piperidinyl, aza-bicyclo[2.2.2]octyl, γ-butyrolactonyl (i.e., an oxo-substituted tetrahydrofuranyl), γ-butryolactamyl (i.e., an oxo-substituted pyrrolidine), pyrrolidinyl, piperazinyl, azepanyl, azetidinyl, thiomorpholinyl, thiomorpholinyl S,S-dioxide, 2-oxazolidonyl, imidazolidonyl, isoindolindionyl, piperazinonyl. The heterocycloalkyl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as indicated.

[89] The term "cycloalkyl" refers to a non-aromatic carbocyclic ring or ring system, which may be saturated or partially unsaturated (e.g., a cycloalkenyl). The cycloalkyl ring can be optionally fused and/or bridged with a bivalent bridge to other cycloalkyl rings. Certain examples of cycloalkyl groups present in the disclosed compounds have from 3 to 7 members in a single ring, such as having 5 or 6 members in a single ring. In some embodiments, the cycloalkyl groups have 3, 4, 5, 6 or 7 members in a single ring. Examples of cycloalkyl groups include, but

are not limited to, cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, tetrahydronaphthyl norbornanyl, norbornenyl, noborndienyl, and bicyclo[2.2.1]heptanyl. The cycloalkyl groups herein are unsubstituted or, when specified as "optionally substituted", may be substituted in one or more substitutable positions with various groups, as indicated.

[90] Alternatively, a cycloalkyl may be bridged with a trivalent bridge. Examples of trivalently bridged cycloalkyl systems includes adamantanyl.

[91] The term "ring system" encompasses monocycles, as well as fused and/or bridged polycycles.

[92] The term "oxo" means a doubly bonded oxygen, sometimes designated as =O or for example in describing a carbonyl "C(O)" may be used to show an oxo substituted carbon.

[93] The term "substituted," when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent groups as defined below, unless specified otherwise.

[94] As used herein, the phrase "pharmaceutically acceptable salt" refers to both pharmaceutically acceptable acid and base addition salts and solvates. Such pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

[95] One of ordinary skill in the art of medicinal chemistry also will appreciate that the disclosed structures are intended to include isotopically enriched forms of the present compounds. As used herein "isotopes" includes those atoms having the same atomic number but different mass numbers. As is known to those of skill in the art, certain atoms, such as hydrogen occur in different isotopic forms. For example, hydrogen includes three isotopic forms, protium, deuterium and tritium. As will be apparent to those of skill in the art upon consideration of the present compounds, certain compounds can be enriched at a given position with a particular isotope of the atom at that position. For example, compounds having a fluorine atom, may be synthesized in a form enriched in the radioactive fluorine isotope ^{18}F. Similarly, compounds may be enriched in the heavy isotopes of hydrogen: deuterium and tritium; and similarly can be

enriched in a radioactive isotope of carbon, such as ^{13}C. Such isotopic variant compounds undergo different metabolic pathways and can be useful, for example, in studying the ubiquitination pathway and its role in disease. Of course, in certain embodiments, the compound has substantially the same isotopic character as naturally-occurring materials.

[96] One of ordinary skill in the art of chemistry will also appreciate that the disclosed structures, unless otherwise indicated are intended to include all possible stereoisomers of the claimed molecule, including mixtures of certain or all stereoisomers. However, compounds drawn with certain stereochemistry at one or more stereocenters are intended to have the indicated stereochemistry. Compounds and stereocenters drawn with ambiguous stereochemistry are meant to convey any stereoisomer or mixture thereof, e.g., a racemic mixture of compounds or a purified subset of stereoisomers.

[97] As used herein, the terms "individual," "patient," or "subject" are used interchangeably, refers to any animal, including mammals, preferably humans.

[98] As used herein, the phrase "therapeutically effective amount" or "effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

[99] In certain embodiments, an effective amount can be an amount suitable for

(i) inhibiting the progression the disease;
(ii) prophylactic use for example, preventing or limiting development of a disease, condition or disorder in an individual who may be predisposed or otherwise at risk to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;
(iii) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder;
(iv) ameliorating the referenced disease state, for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing or improving the pathology and/or symptomatology) such as decreasing the severity of disease; or
(v) eliciting the referenced biological effect.

[100] As used here, the terms “treatment” and “treating” mean (i) ameliorating the referenced disease state, condition, or disorder (or a symptom thereof), such as, for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing or improving the pathology and/or symptomatology) such as decreasing the severity of disease or symptom thereof, or inhibiting the progression of disease; or (ii) eliciting the referenced biological effect (e.g., inhibiting inflammasome formation or function, or inhibition of IL-1β).

Methods of Preparation

[101] Many general references providing commonly known chemical synthetic schemes and conditions useful for synthesizing the disclosed compounds are available (see, e.g., Smith and March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Fifth Edition, Wiley-Interscience, 2001; or Vogel, A Textbook of Practical Organic Chemistry, Including Qualitative Organic Analysis, Fourth Edition, New York: Longman, 1978).

[102] Compounds as described herein can be purified by any of the means known in the art, including chromatographic means, such as HPLC, preparative thin layer chromatography, flash column chromatography and ion exchange chromatography. Any suitable stationary phase can be used, including normal and reversed phases as well as ionic resins. Most typically the disclosed compounds are purified via silica gel and/or alumina chromatography. See, e.g., Introduction to Modern Liquid Chromatography, 2nd Edition, ed. L. R. Snyder and J. J. Kirkland, John Wiley and Sons, 1979; and Thin Layer Chromatography, ed E. Stahl, Springer-Verlag, New York, 1969.

[103] During any of the processes for preparation of the subject compounds, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups as described in standard works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry,” Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis,” Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie,” Houben-Weyl, 4.sup.th edition, Vol. 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosauren, Peptide, Proteine,” Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and/or in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide and Derivate,” Georg Thieme Verlag, Stuttgart 1974. The

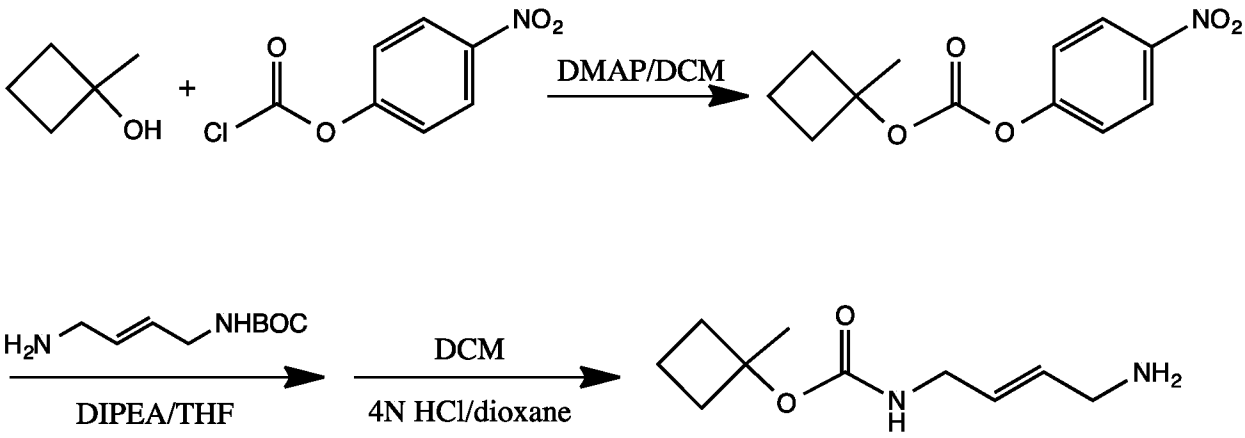
protecting groups may be removed at a convenient subsequent stage using methods known from the art.

[104] A "leaving group" as used herein refers to a moiety of a reactant that is displaced from the first reactant in the chemical reaction. A comprehensive list of suitable leaving groups can be found in J. March, Advanced Organic Chemistry, John Wiley and Sons, N.Y. (2013). Examples of suitable leaving groups include, but are not limited to, halogen (such as Cl or Br), acetoxy, and sulfonyloxy groups (such as methyl sulfonyloxy, trifluoromethylsulfonyloxy ("triflate"), p-toluenesulfonyloxy ("tosylate")).

[105] The compounds disclosed herein can be made using procedures familiar to the person of ordinary skill in the art and as described herein, for example in Schemes 1–5. One of skill in the art can adapt the reaction sequences of schemes and examples as provided herein to fit the desired target molecule. Of course, in certain situations one of skill in the art will use different reagents to affect one or more of the individual steps or to use protected versions of certain of the substituents. Additionally, one skilled in the art would recognize that compounds of the disclosure can be synthesized using different routes altogether. For example, the person of ordinary skill in the art may adapt the procedures described herein and/or other procedures familiar to the person of ordinary skill in the art to make the compounds described herein.

Example 1

Scheme 1: Preparation of Compound 19



Synthesis of 1-Methylcyclobutyl (E)-(4-aminobut-2-en-1-yl)carbamate hydrochloride salt

[106] Step 1: Synthesis of 1-Methylcyclobutyl (4-nitrophenyl) carbonate

[107] To a stirred solution of 1-methylcyclobutan-1-ol (300 mg, 3.48 mmol) in DCM (20 mL) was added DMAP (851 mg, 6.97 mmol) followed by 4-nitrophenyl chloroformate (1.1 g, 5.23 mmol) at 25°C, and stirred the reaction mixture at that temperature for 2h. After completion of the reaction (as judged by TLC), volatiles were removed in vacuo. Crude material thus obtained was purified by combi-flash column chromatography (SiO_2, 12 g, 5% EtOAc/hexane) to give 1-methylcyclobutyl (4-nitrophenyl) carbonate (590 mg, 67%) as light green viscous liquid.

[108] Step 2: Synthesis of tert-butyl (1-methylcyclobutyl) but-2-ene-1,4-diyl(E)-dicarbamate

[109] To a stirred solution of 1-methylcyclobutyl (4-nitrophenyl) carbonate (250 mg, 0.99 mmol) in THF (20 mL) was added DIPEA (0.5 mL, 2.99 mmol) followed by tert-butyl (E)-(4-aminobut-2-en-1-yl)carbamate hydrochloride (244 mg, 1.10 mmol) at 25°C, and the reaction mixture was allowed to heat at 60°C for 4h. After completion of the reaction (as judged by TLC), volatiles were removed in vacuo. Crude material thus obtained was purified by combi-flash column chromatography (SiO_2, 12 g, 10% EtOAc/hexane) to get tert-butyl (1-methylcyclobutyl) but-2-ene-1,4-diyl(E)-dicarbamate (220 mg, 74%) as off white solid.

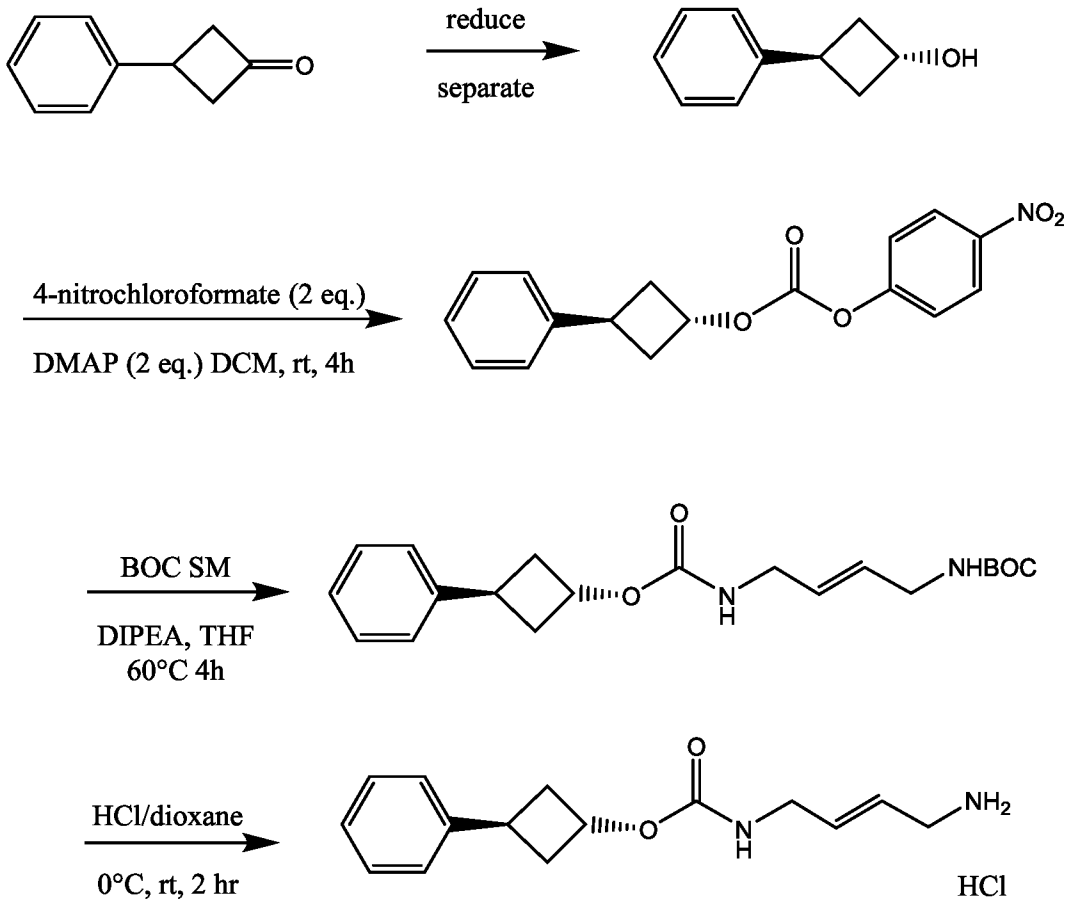
[110] Step 3: 1-Methylcyclobutyl (E)-(4-aminobut-2-en-1-yl)carbamate hydrochloride salt

[111] To a stirred solution of tert-butyl (1-methylcyclobutyl) but-2-ene-1,4-diyl(E)-dicarbamate (**5**) (200 mg, 0.67 mmol) in DCM (15 mL) was added 4(N) HCl in dioxane (1.5 mL, 6 mmol) at 0°C, and the reaction mixture was allowed to stir at 25°C for 4h. After completion of the reaction (as judged by TLC), volatiles were removed in vacuo. Crude material thus obtained was purified by trituration with diethyl ether followed by lyophilization to give 1-methylcyclobutyl (E)-(4-aminobut-2-en-1-yl)carbamate hydrochloride (Compound 19) (109 mg, 69%) as off white solid.

[112] UPLC Column- Column:YMC TRIART C18(33x2.1mm,3µ)-FAF, (mobile phase: 98% [0.05% NH4OAc in water] and 2% [CH3CN] held for 0.75 min, then to 90% [0.05% NH4OAc in water] and 10% [CH3CN] in 1.0 min, further to 2% [0.05% NH4OAc in water] and 98% [CH3CN] in 2.0 min, held this mobile phase composition up to 2.25 min and finally back to initial condition in 5.0 min). Flow =1.5ml/min. Purity is 100%, Rt = 1.67 min. MS Calculated 198.16, MS found: 199.17 [M+H].

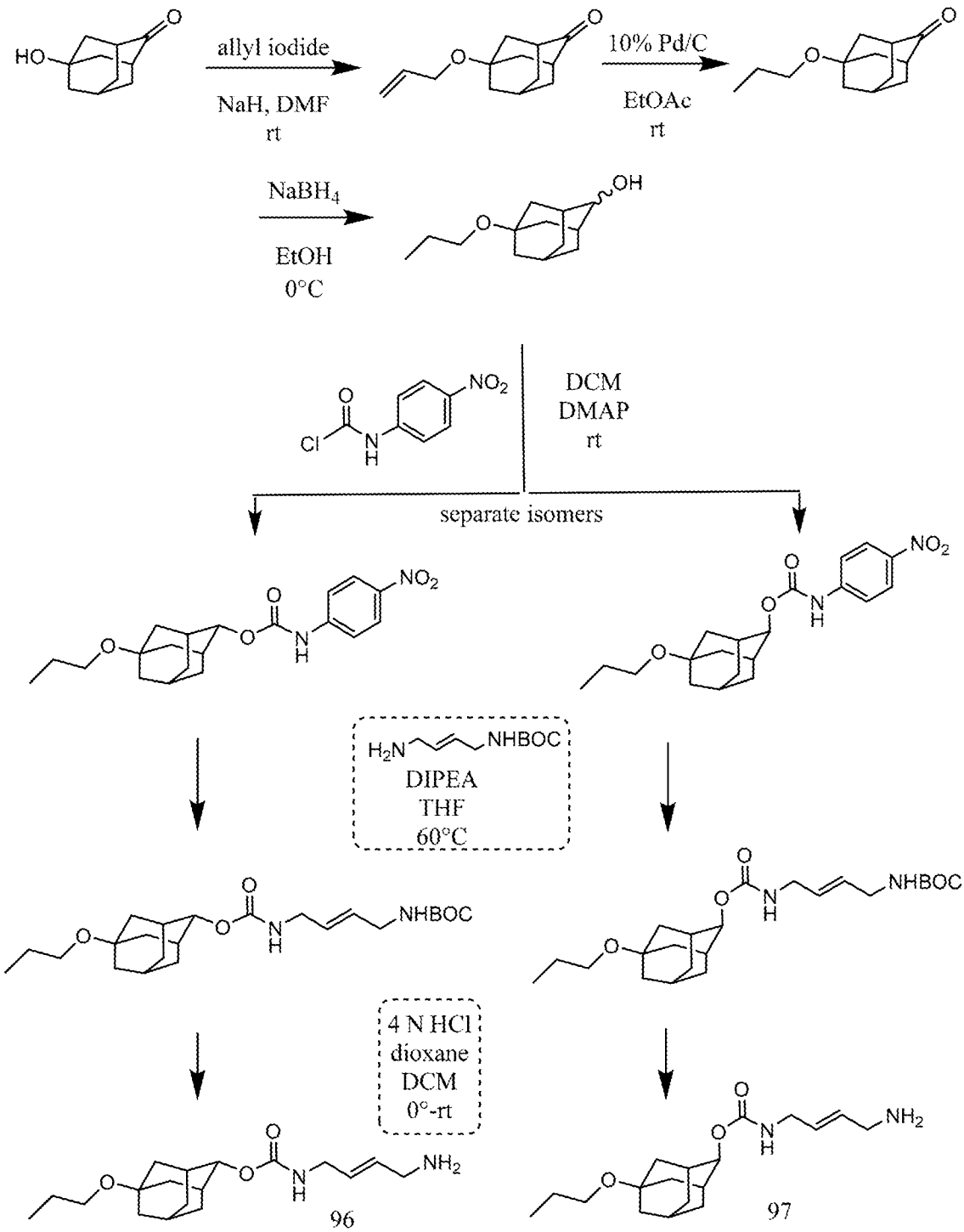
Example 2

Scheme 2: Preparation of Compound 54



Example 3

Scheme 3: Synthesis of Compound 96 and Compound 97



Synthesis of (1R,2r,3S,5s,7s)-5-propoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate hydrochloride (96) and (1R,2s,3S,5s,7s)-5-propoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate hydrochloride (97)

[113] Step 1: Synthesis of (1R,3S,5s,7s)-5-(allyloxy)adamantan-2-one)

[114] To a stirred solution of 5-hydroxyadamantan-2-one (1.00 g, 6.02 mmol) in N,N-dimethylformamide (25.0 mL) was added sodium hydride (289 mg, 2 eq., 12.0 mmol) at 0 °C. Reaction mixture was stirred for 10 min at room temperature and again cooled to 0 °C and added 3-iodoprop-1-ene (660 µL, 1.2 eq., 7.22 mmol). The reaction mixture allowed to stir at room temperature for 3 h, the progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude was purified by silica gel column chromatography using 30% EA/ Hexane as eluents to afford pure compound 5-(prop-2-en-1-yloxy)adamantan-2-one (690 mg, 55%) as gummy colorless liquid.

[115] ^{1}HNMR (400 MHz, DMSO-d_6): δ 5.81-5.87 (m, 1H), 5.17-5.22 (m, 1H), 5.03-5.00 (m, 1H), 3.92-3.93 (m, 2H), 2.44 (s, 2H), 2.23 (s, 1H), 1.89 -1.92 (m, 8H), 1.77-1.80 (m, 2H). LCMS (ES) m/z = 207.1 [M+H]+

[116] Step 2: Synthesis of (1R,3S,5s,7s)-5-propoxyadamantan-2-one

[117] To a stirred solution of 5-(prop-2-en-1-yloxy)adamantan-2-one (600 mg, 2.91 mmol) in ethyl acetate (20.0 mL) after purging with nitrogen was added 10 % palladium on carbon (310 mg) at room temperature. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 2 hr, the progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was filtered through celite bed, the celite bed washed with ethyl acetate. The combined filtrate was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using 40% ethyl acetate/ heptane as eluents to afford pure compound 5-propoxyadamantan-2-one (580 mg, 96%) as gummy dark liquid.

[118] ^{1}HNMR (400 MHz, DMSO-d_6): δ 3.28-3.30 (m, 2H), 2.43-2.48 (m, 2H), 2.22 (s, 1H), 1.77-1.89 (m, 10H), 0.81-0.84 (m, 3H), LCMS (ES) m/z = 209.0 [M+H]+

[119] Step 3: Synthesis of (1R,2r,3S,5s,7s)-5-propoxyadamantan-2-ol

[120] To a stirred solution of 5-propoxyadamantan-2-one (480 mg, 2.30 mmol) in ethanol (10.0 mL) was added sodium borohydride (248 mg, 3 eq., 6.91 mmol) at 0 °C and stirred the solution at the room temperature for 1 hr, the progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, the resulting crude was diluted with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed sequentially with saturated aqueous ammonium chloride and brine solution and then dried over anhydrous magnesium sulfate. The desiccant was filtered off and the solvent was distilled off under reduced pressure to afford compound 5-propoxyadamantan-2-ol (482 mg, 99%) as a gummy liquid.

[121] ^{1}HNMR (400 MHz, DMSO-d_6): δ 4.20-4.56 (m, 1H), 3.49-3.63 (m, 1H), 3.23-3.48 (m, 2H), 1.84-2.01 (m, 2H), 1.66 (s, 1H), 1.41-1.62 (m, 10H), 0.80-0.83 (m, 3H). LCMS (ES) m/z; Not ionized.

[122] Step 4: Synthesis of 4-nitrophenyl ((1R,2r,3S,5s,7s)-5-propoxyadamantan-2-yl) carbonate

[123] To a stirred solution 5-propoxyadamantan-2-ol (480 mg, 2.28 µmol) in dichloromethane (20.00 mL) was added *N*,*N*-dimethylpyridin-4-amine (558 mg, 2 eq., 4.56 µmol) followed by 4-nitrophenyl carbonochloridate (920 mg, 2 eq., 4.56 µmol) at 25 °C and stirred at room temperature for 4 hrs. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (2 x 30 mL), the organic layer dried over sodium sulphate and evaporated the solvent under reduced pressure using a rotavapour. The crude compound was purified by silica gel column chromatography using 15% ethyl acetate/heptane as eluents and followed by prep-HPLC purification to afford 4-nitrophenyl 5-propoxyadamantan-2-yl carbonate (202 mg, 23.58%) (isomer-1/peak 1) as a yellow gummy liquid and 4-nitrophenyl 5-propoxyadamantan-2-yl carbonate (175 mg, 20.42%) (isomer-2/peak 2) as yellow gummy liquid.

[124] Isomer-1: ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.31-8.34 (m, 2H), 7.57-7.60 (m, 2H), 4.84 (s, 1H) 3.25-3.32 (m, 1H), 2.28-2.33 (m, 3H), 2.10 (m, 1H), 1.74-1.87 (m, 9H), 1.38-1.47 (m, 4H), 1.15-1.24 (m, 3H). LCMS (ES) m/z; Not ionized

[125] Isomer-2: ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.31-8.33 (m, 2H), 7.58-7.61 (m, 2H), 4.74 (s, 1H) 3.26-3.31 (m, 2H), 2.34-2.50 (m, 3H), 2.05 (s, 1H), 1.24-1.88 (m, 14H), 0.83-0.86 (m, 3H). LCMS (ES) m/z; Not ionized

[126] Step 5a: Synthesis of tert-butyl N-[(2E)-4-({[(5-propoxyadamantan-2-yl)oxy] carbonyl}amino)but-2-en-1-yl]carbamate (Isomer-1)

[127] To a stirred solution of 4-nitrophenyl 5-propoxyadamantan-2-yl carbonate (isomer-1/peak-1) (200 mg, 533 µmol) in THF (10.0 mL) was added with N,N-Diisopropylethylamine (186 µL, 2 eq., 1.07 mmol) followed by the addition of tert-butyl N-[(2E)-4-aminobut-2-en-1-yl]carbamate hydrochloride (142 mg, 1.2 eq., 639 µmol) under nitrogen atmosphere was allowed to stir for 3 hrs at 65 °C, The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with Ethyl acetate (2 x 20 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure, the crude material was purified by flash column chromatography (silica gel. Size - 24 g, flow rate - 30 mL/min. eluting with a gradient of 0 – 50 % ethyl acetate in heptane to yield tert-butyl N-[(2E)-4-({[(5-propoxyadamantan-2-yl)oxy]carbonyl}amino)but-2-en-1-yl]carbamate (156 mg, 69 %).

[128] ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.19 (s, 1H), 6.89 (s, 1H), 5.48 (s, 2H) 4.60 (s, 1H), 3.51-3.56 (m, 4H), 1.70-2.06 (m, 12H), 1.29-1.47 (m, 14H), 0.83-0.86 (m, 3H). LCMS (ES) m/z; Not ionized.

[129] Step 5b: Synthesis of tert-butyl N-[(2E)-4-({[(5-propoxyadamantan-2-yl)oxy] carbonyl}amino)but-2-en-1-yl]carbamate (Isomer-2)

[130] To a stirred solution of 4-nitrophenyl 5-propoxyadamantan-2-yl carbonate isomer-2/peak 2 (170 mg, 453 µmol) in THF (10.0 mL) was added with N,N-Diisopropylethylamine (158 µL, 2 eq., 906 µmol) followed by the addition of tert-butyl N-[(2E)-4-aminobut-2-en-1-yl]carbamate hydrochloride (142 mg, 1.2 eq., 639 µmol) under nitrogen atmosphere was allowed to stir for 3 h at 65 °C , The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture diluted with water (20 mL) and extracted with Ethyl acetate (2x 20 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to yield crude material. The crude material was purified by flash column chromatography (silica gel. Size - 24 g, flow rate - 30 mL/min) and eluting with a gradient of 0 – 50 % ethyl acetate in heptane to yield tert-butyl N-[(2E)-4-({[(5-propoxyadamantan-2-yl)oxy]carbonyl}amino)but-2-en-1-yl]carbamate (108 mg, 56 %).

[131] ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.25 (s, 1H), 6.93 (s, 1H), 5.47 (s, 2H) 4.50 (s, 1H), 3.51-3.51 (m, 4H), 1.37-2.12 (m, 26H), 0.83-0.86 (m, 3H). LCMS (ES) m/z; Not ionized.

[132] Step 6a: Synthesis of (1R,2r,3S,5s,7s)-5-propoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate hydrochloride (Isomer 1)

[133] To a stirred solution of tert-butyl N-[(2E)-4-({[(5-propoxyadamantan-2-yl)oxy]carbonyl}amino)but-2-en-1-yl]carbamate peak1/isomer-1 (150 mg, 355 µmol) in dichloromethane (3.00 mL) at 0 °C was added 4 M hydrogen chloride in dioxane (3.00 mL) under nitrogen atmosphere. Reaction mixture allowed to stir for 2 hrs at room temperature. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was evaporated under reduced pressure, the resulting crude was washed with diethyl ether and dried under high vacuum to give the desired product 5-propoxyadamantan-2-yl N-[(2E)-4-aminobut-2-en-1-yl]carbamate hydrochloride (isomer-1) (97.0 mg, 76 %).

[134] ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.88 (s, 3H), 7.34-7.36 (m, 1H), 5.75-5.79 (m, 1H), 5.52-5.56 (m, 1H), 4.58 (s, 1H), 3.60 (s, 2H), 3.40 (s, 2H), 2.65-3.30 (m, 2H), 1.34-2.03 (m, 15H), 0.80-0.884 (m, 3H). LCMS (ES) m/z; 323.2 $[M+H]^+$.

[135] Step 6b: Synthesis of (1R,2s,3S,5s,7s)-5-propoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate hydrochloride (Isomer 2)

[136] To a stirred solution of tert-butyl N-[(2E)-4-({[(5-propoxyadamantan-2-yl)oxy]carbonyl}amino)but-2-en-1-yl]carbamate peak2/isomer-2 (105 mg, 248 µmol) in dichloromethane (3.00 mL) at at 0 °C was added 4 M hydrogen chloride in dioxane (3.00 mL) under nitrogen atmosphere. The reaction mixture allowed to stir for 2 hrs at room temperature. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was evaporated under reduced pressure, the resulting crude was washed with diethyl ether and dried under high vacuum to give the desired product 5-propoxyadamantan-2-yl N-[(2E)-4-aminobut-2-en-1-yl]carbamate hydrochloride (isomer-2) (22.0 mg, 27%).

[137] ^{1}HNMR (400 MHz, DMSO-d_6): δ 7.86 (s, 3H), 7.36-7.38 (m, 1H), 5.75-5.79 (m, 1H), 5.52-5.56 (m, 1H), 4.49 (s, 1H), 3.60 (s, 2H), 3.44 (s, 2H), 3.14-3.39 (m, 2H), 1.35-2.05 (m, 15H), 0.80-0.884 (m, 3H). LCMS (ES) m/z; 323 $[M+H]^+$.

Example 4

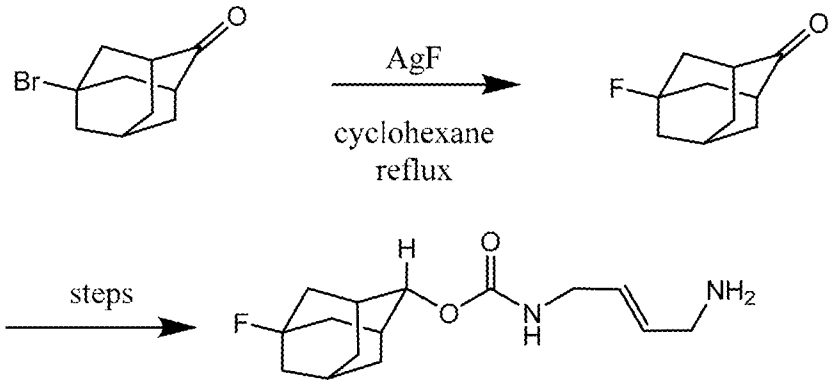
Synthesis of adamantyl-containing compounds

[138] Certain compounds according to the present disclosure include optionally substituted adamantyl groups. For example, Compounds 71–88, 90–107, and 110–116 in Table 2, below, contain optionally substituted adamantyl groups. Such compounds ca be prepared by the person of ordinary skill in the art in light of the present disclosure and reactions known in the art. Suitable reactants for such syntheses include 5-chloro-2-adamantanone; 2-adamantanone-5-

carboxylic acid; 5-bromo-2-adamantanone; 5-hydroxyadamantan-2-one; 1-methyladamantan-2-one; 1-fluoroadamantan-2-one, all of which are readily available.

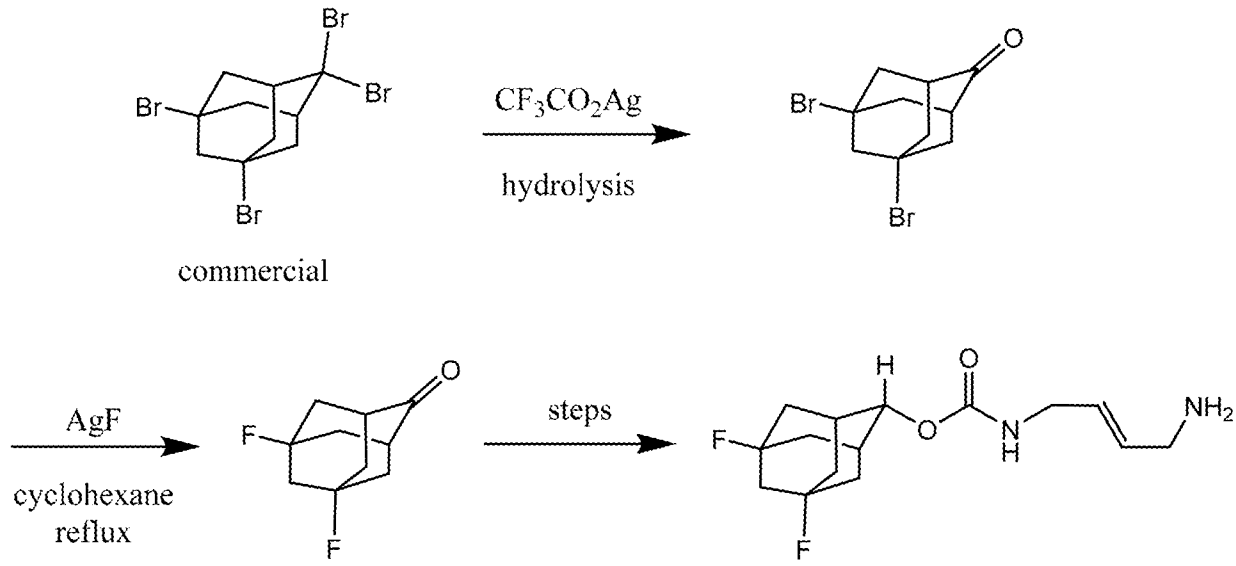
[139] Fluoro compounds 74 and 75 can be prepared using chemistry described in Knoll, Wolfgang; Mieusset, Jean-Luc; Arion, Vladimir B.; Brecker, Lothar; Brinker, Udo H. Organic Letters (2010), 12(10), 2366-2369 (Scheme 4).

[140] Scheme 4



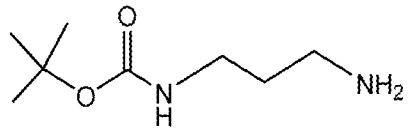
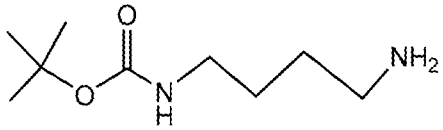
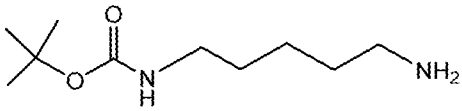
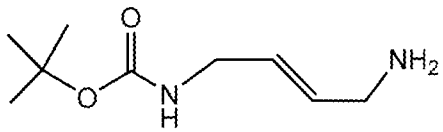
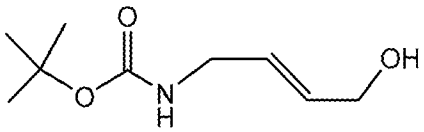
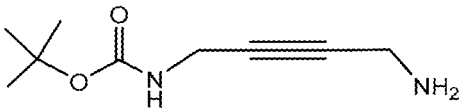
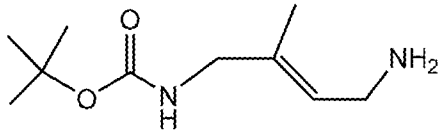
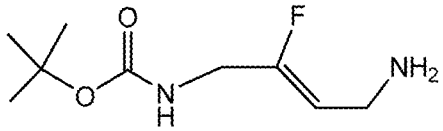
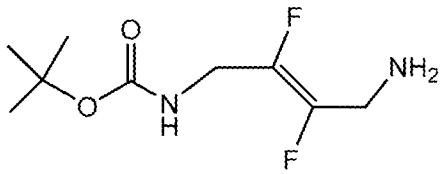
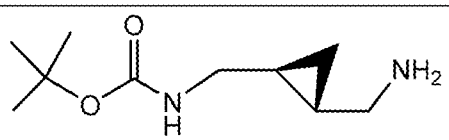
[141] Difluoro compounds, such as compound 106, can be made from the corresponding dibromo species in Sorochinskii, A. E.; Tarasevich, A. S.; Aleksandrov, A. M.; Kukhar, V. P. Zhurnal Organicheskoi Khimii (1981), 17(11), 2339-43 (Scheme 5).

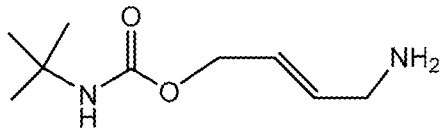
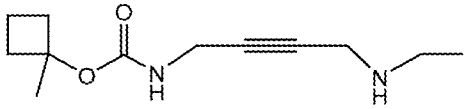
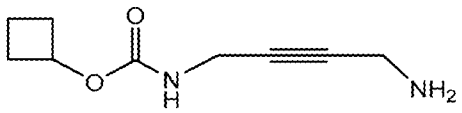
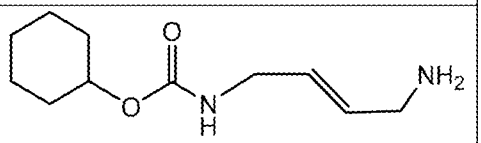
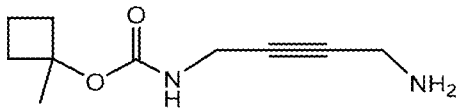
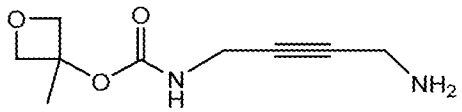
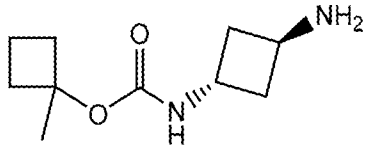
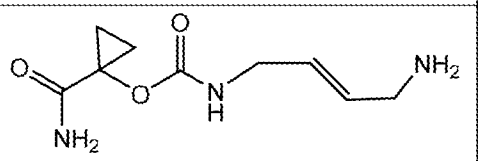
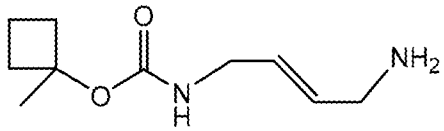
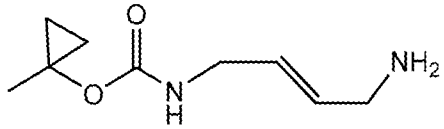
[142] Scheme 5

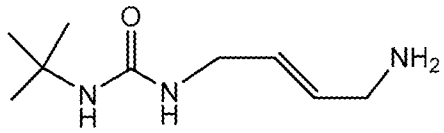
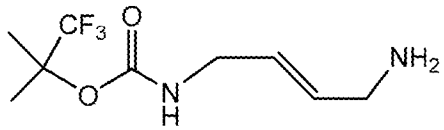
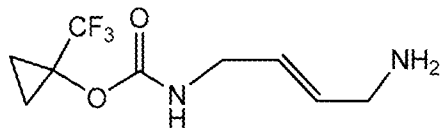
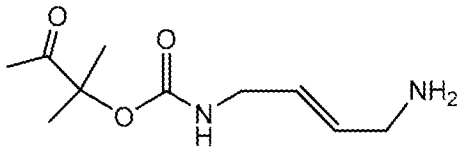
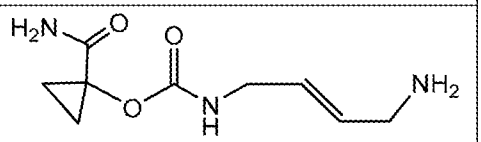
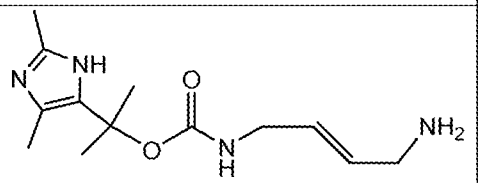
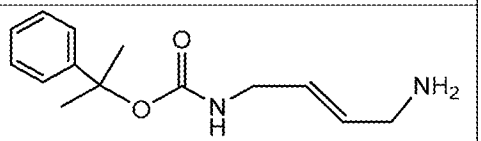
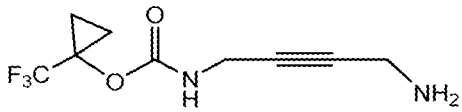
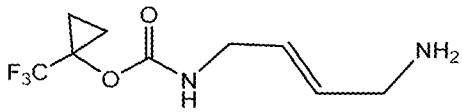
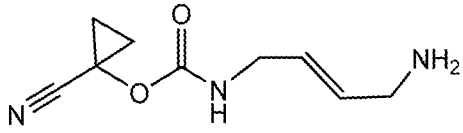


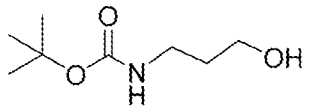
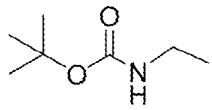
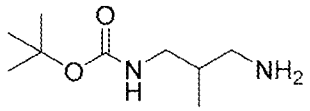
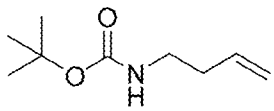
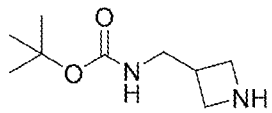
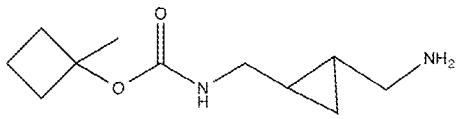
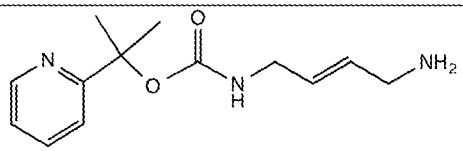
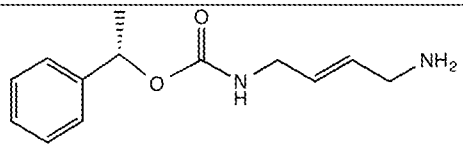
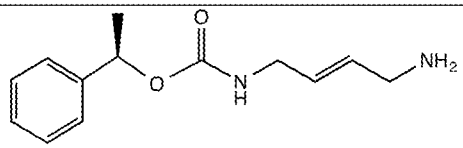
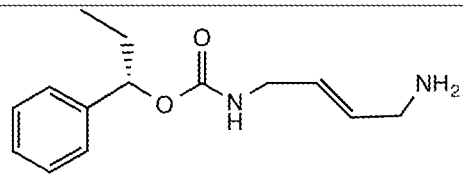
[143] The compounds shown below in Table 2 can be prepared essentially according to procedures known to those of skill in the art in view of Schemes 1–5.

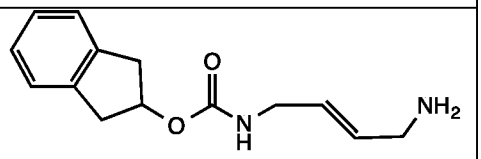
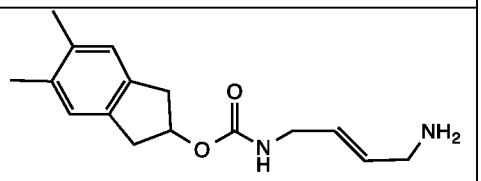
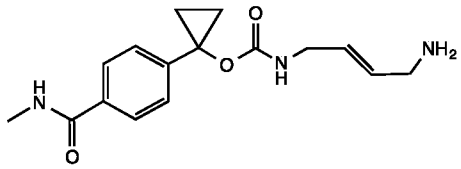
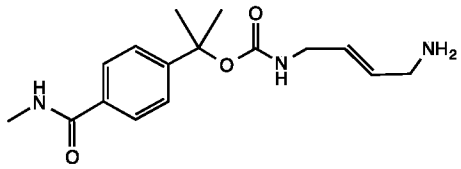
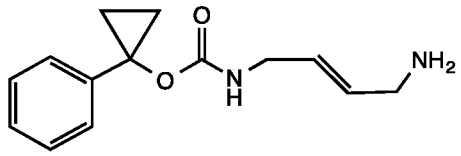
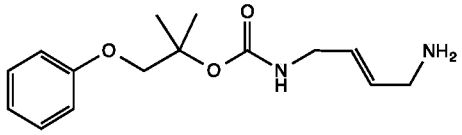
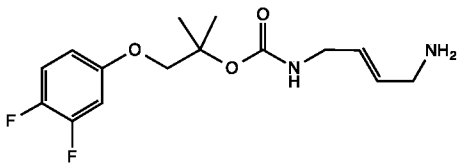
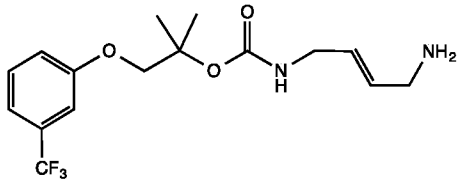
Table 2

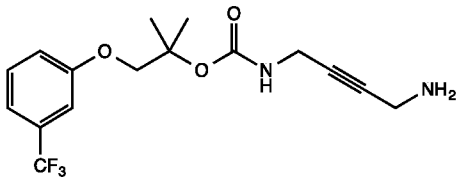
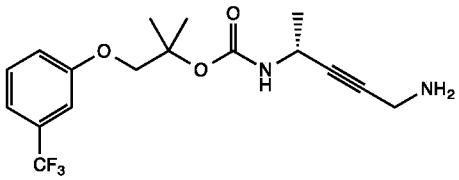
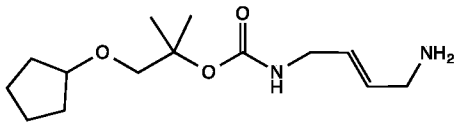
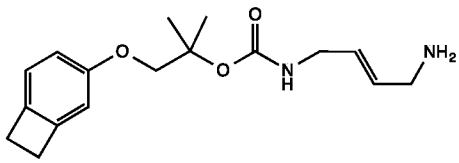
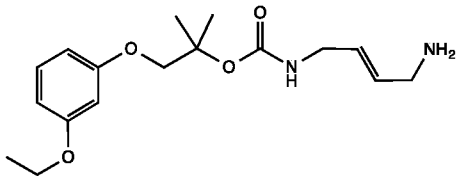
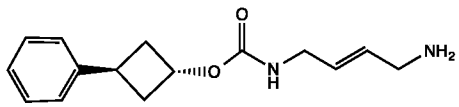
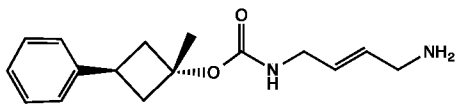
Comp. No.	Name	Structure
1	tert-butyl (3-aminopropyl)carbamate	
2	tert-butyl (4-aminobutyl)carbamate	
3	tert-butyl (5-aminopentyl)carbamate	
4	tert-butyl (4-aminobut-2-en-1-yl)carbamate	
5	tert-butyl (4-hydroxybut-2-en-1-yl)carbamate	
6	tert-butyl (4-aminobut-2-yn-1-yl)carbamate	
7	tert-butyl (4-amino-2-methylbut-2-en-1-yl)carbamate	
8	tert-butyl (4-amino-2-fluorobut-2-en-1-yl)carbamate	
9	tert-butyl (4-amino-2,3-difluorobut-2-en-1-yl)carbamate	
10	tert-butyl ((2-(aminomethyl)cyclopropyl)methyl)carbamate	

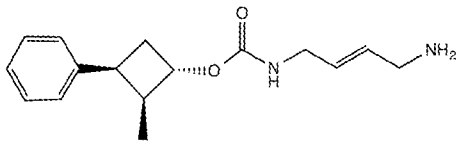
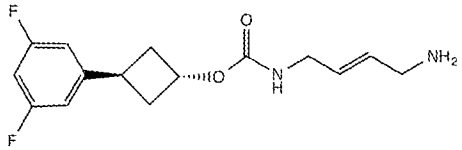
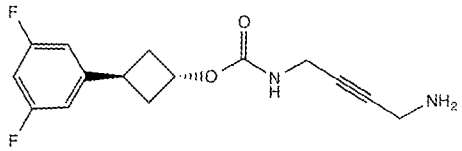
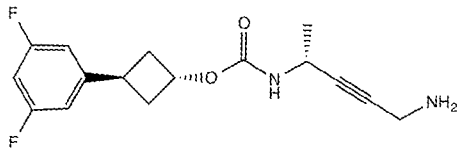
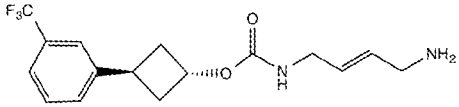
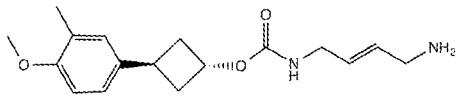
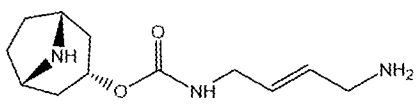
Comp. No.	Name	Structure
11	4-aminobut-2-en-1-yl tert-butylcarbamate	
12	1-methylcyclobutyl (4-(ethylamino)but-2-yn-1-yl)carbamate	
13	cyclobutyl (4-aminobut-2-yn-1-yl)carbamate	
14	cyclohexyl (4-aminobut-2-en-1-yl)carbamate	
15	1-methylcyclobutyl (4-aminobut-2-yn-1-yl)carbamate	
16	3-methyloxetan-3-yl (4-aminobut-2-yn-1-yl)carbamate	
17	1-methylcyclobutyl (3-aminocyclobutyl)carbamate	
18	1-carbamoylcyclopropyl (4-aminobut-2-en-1-yl)carbamate	
19	1-methylcyclobutyl (4-aminobut-2-en-1-yl)carbamate	
20	1-methylcyclopropyl (4-aminobut-2-en-1-yl)carbamate	

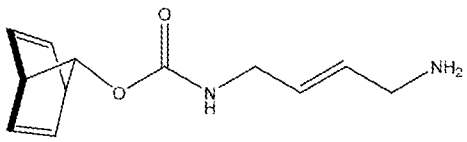
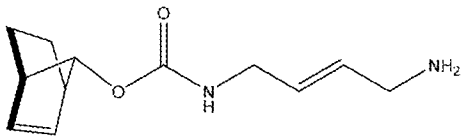
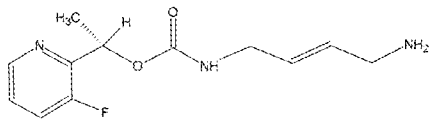
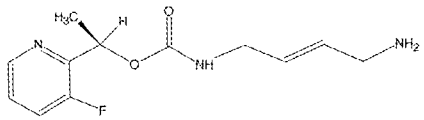
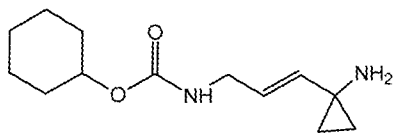
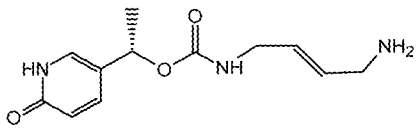
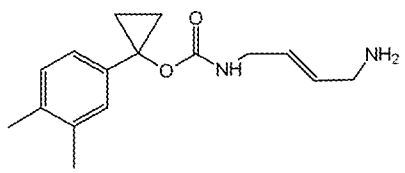
Comp. No.	Name	Structure
21	1-(4-aminobut-2-en-1-yl)-3-(tert-butyl)urea	
22	1,1,1-trifluoro-2-methylpropan-2-yl (4-aminobut-2-en-1-yl)carbamate	
23	1-(trifluoromethyl)cyclopropyl (4-aminobut-2-en-1-yl)carbamate	
24	2-methyl-3-oxobutan-2-yl (4-aminobut-2-en-1-yl)carbamate	
25	1-carbamoylcyclopropyl (4-aminobut-2-en-1-yl)carbamate	
26	2-(2,4-dimethyl-1H-imidazol-5-yl)propan-2-yl (4-aminobut-2-en-1-yl)carbamate	
27	2-phenylpropan-2-yl (4-aminobut-2-en-1-yl)carbamate	
28	1-(trifluoromethyl)cyclopropyl (4-aminobut-2-yn-1-yl)carbamate	
29	1-(trifluoromethyl)cyclopropyl (4-aminobut-2-en-1-yl)carbamate	
30	1-cyanocyclopropyl (4-aminobut-2-en-1-yl)carbamate	

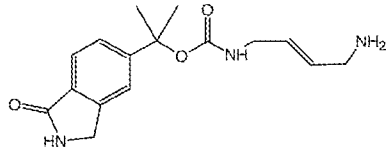
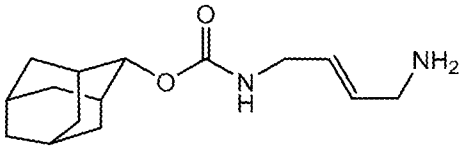
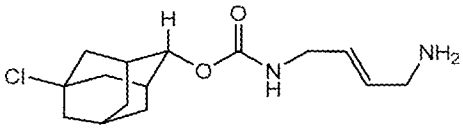
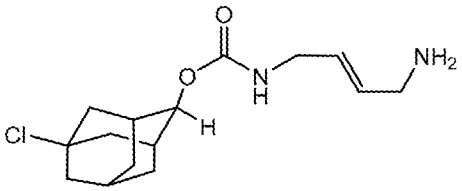
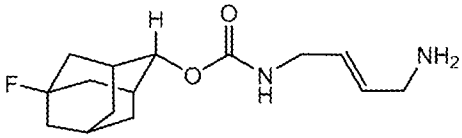
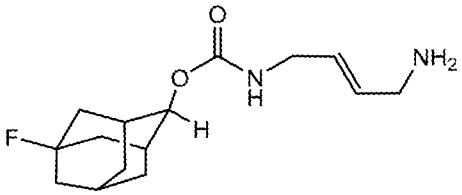
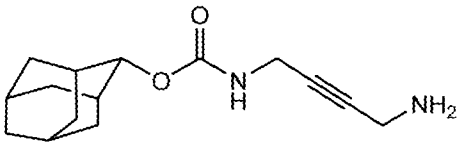
Comp. No.	Name	Structure
31	tert-butyl (3-hydroxypropyl)carbamate	
32	tert-butyl ethylcarbamate	
33	tert-butyl (3-amino-2-methylpropyl)carbamate	
34	tert-butyl but-3-en-1-ylcarbamate	
35	tert-butyl (azetidin-3-ylmethyl)carbamate	
36	1-methylcyclobutyl ((2-(aminomethyl)cyclopropyl)methyl)carbamate	
37	2-(pyridin-2-yl)propan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
38	(S)-1-phenylethyl (E)-(4-aminobut-2-en-1-yl)carbamate	
39	(R)-1-phenylethyl (E)-(4-aminobut-2-en-1-yl)carbamate	
40	(S)-1-phenylpropyl (E)-(4-aminobut-2-en-1-yl)carbamate	

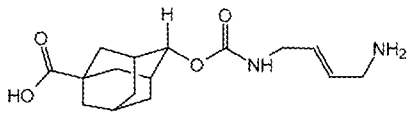
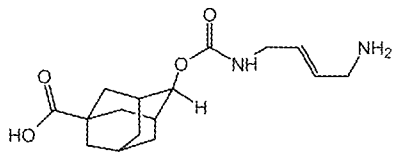
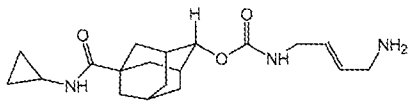
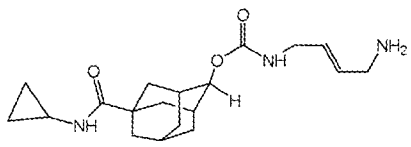
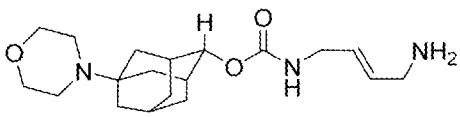
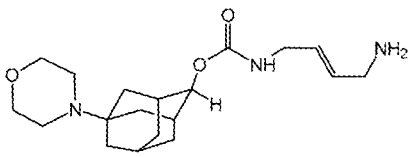
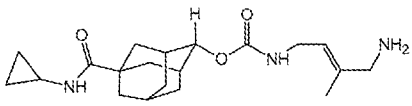
Comp. No.	Name	Structure
41	2,3-dihydro-1H-inden-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
42	5,6-dimethyl-2,3-dihydro-1H-inden-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
43	1-(4-(methylcarbamoyl)phenyl)cyclopropyl (E)-(4-aminobut-2-en-1-yl)carbamate	
44	2-(4-(methylcarbamoyl)phenyl)propan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
45	1-phenylcyclopropyl (E)-(4-aminobut-2-en-1-yl)carbamate	
46	2-methyl-1-phenoxypropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
47	1-(3,4-difluorophenoxy)-2-methylpropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
48	2-methyl-1-(3-(trifluoromethyl)phenoxy)propan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	

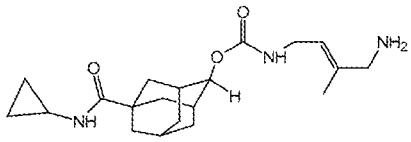
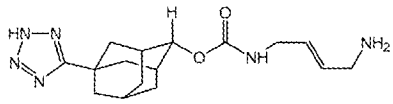
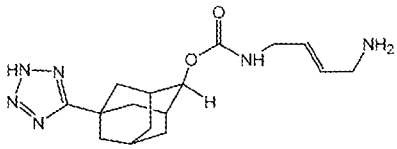
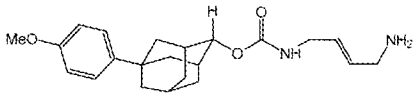
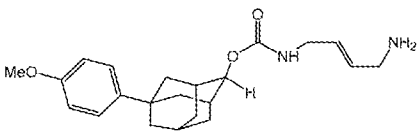
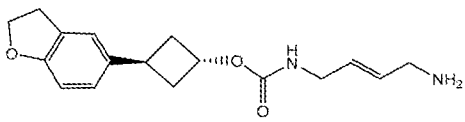
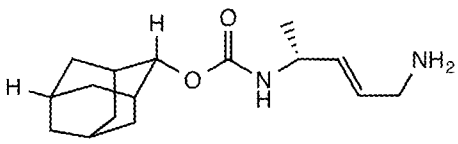
Comp. No.	Name	Structure
49	2-methyl-1-(3-(trifluoromethyl)phenoxy)propan-2-yl (4-aminobut-2-yn-1-yl)carbamate	
50	2-methyl-1-(3-(trifluoromethyl)phenoxy)propan-2-yl (R)-(5-aminopent-3-yn-2-yl)carbamate	
51	1-(cyclopentyloxy)-2-methylpropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
52	1-(bicyclo[4.2.0]octa-1,3,5-trien-3-yloxy)-2-methylpropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
53	1-(3-ethoxyphenoxy)-2-methylpropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
54	(1r,3r)-3-phenylcyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate	
55	(1r,3r)-1-methyl-3-phenylcyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate	

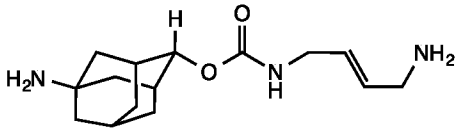
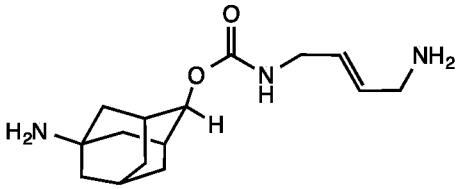
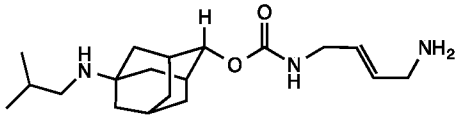
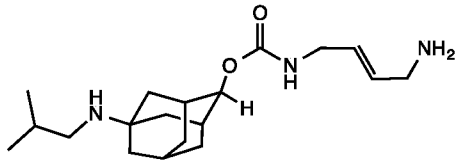
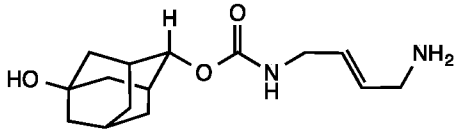
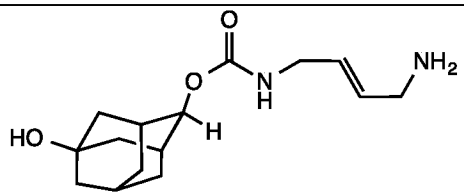
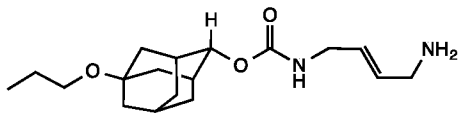
Comp. No.	Name	Structure
56	(1S,2S,3S)-2-methyl-3-phenylcyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate	
57	(1r,3r)-3-(3,5-difluorophenyl)cyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate	
58	(1r,3r)-3-(3,5-difluorophenyl)cyclobutyl (4-aminobut-2-yn-1-yl)carbamate	
59	(1r,3R)-3-(3,5-difluorophenyl)cyclobutyl ((R)-5-aminopent-3-yn-2-yl)carbamate	
60	(1r,3r)-3-(3-(trifluoromethyl)phenyl)cyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate	
61	(1r,3r)-3-(4-methoxy-3-methylphenyl)cyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate	
62	(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl [(2E)-4-aminobut-2-en-1-yl]carbamate	

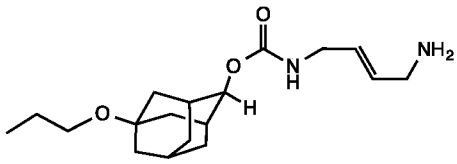
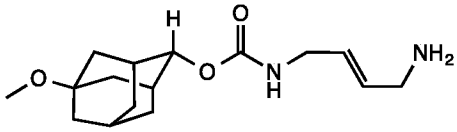
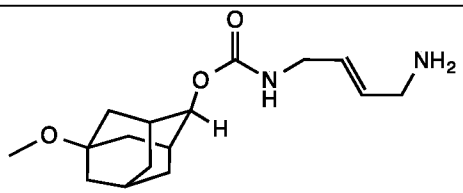
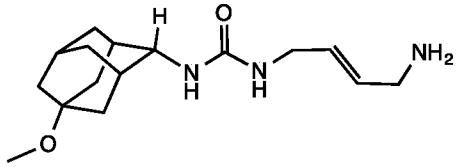
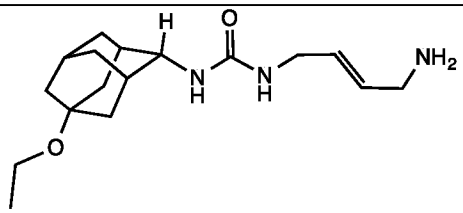
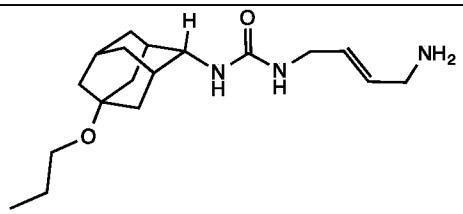
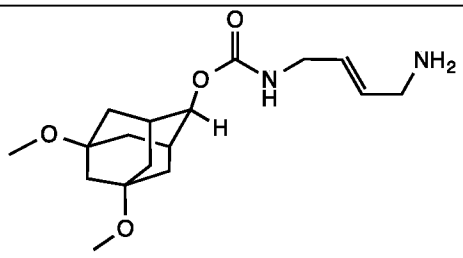
Comp. No.	Name	Structure
63	bicyclo[2.2.1]hepta-2,5-dien-7-yl (E)-(4-aminobut-2-en-1-yl)carbamate	
64	(1R)-bicyclo[2.2.1]hept-2-en-7-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
65	(1S)-1-(3-fluoropyridin-2-yl)ethyl [(2E)-4-aminobut-2-en-1-yl]carbamate	
66	(1R)-1-(3-fluoropyridin-2-yl)ethyl [(2E)-4-aminobut-2-en-1-yl]carbamate	
67	cyclohexyl [(2E)-3-(1-aminocyclopropyl)prop-2-en-1-yl]carbamate	
68	(1S)-1-(6-oxo-1,6-dihydropyridin-3-yl)ethyl [(2E)-4-aminobut-2-en-1-yl]carbamate	
69	1-(3,4-dimethylphenyl)cyclopropyl [(2E)-4-aminobut-2-en-1-yl]carbamate	

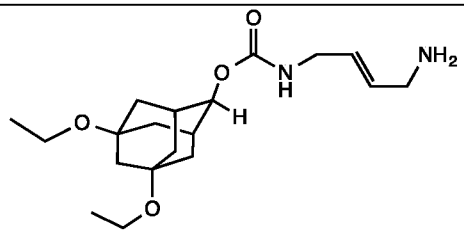
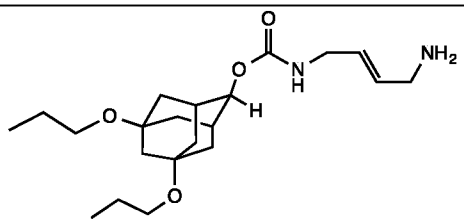
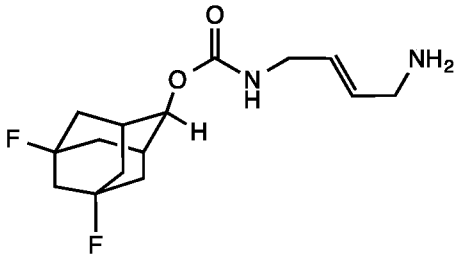
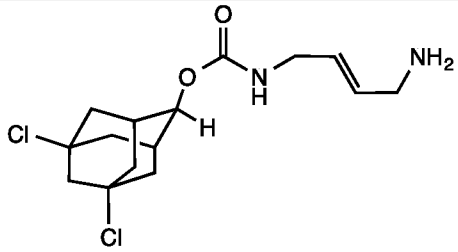
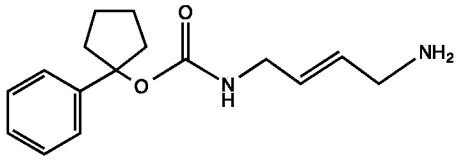
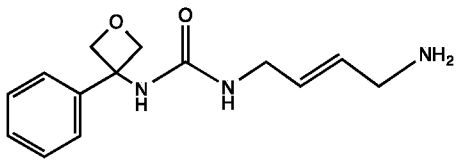
Comp. No.	Name	Structure
70	2-(1-oxo-2,3-dihydro-1H-isoindol-5-yl)propan-2-yl [(2E)-4-aminobut-2-en-1-yl]carbamate	
71	(1R,3S,5r,7r)-adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
72	(1R,2s,3S,5s,7s)-5-chloroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
73	(1R,2r,3S,5s,7s)-5-chloroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
74	(1R,2s,3S,5s,7s)-5-fluoroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
75	(1R,2r,3S,5s,7s)-5-fluoroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
76	(1R,3S,5r,7r)-adamantan-2-yl (4-aminobut-2-yn-1-yl)carbamate	

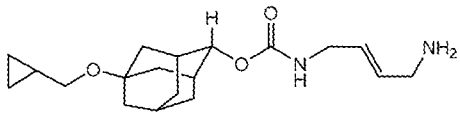
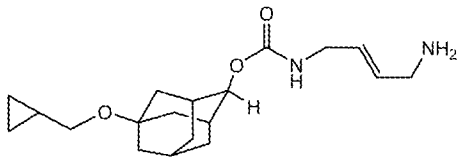
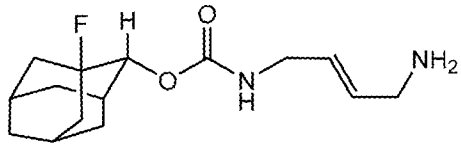
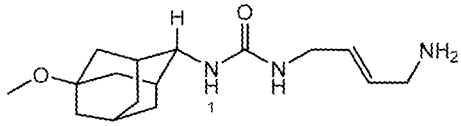
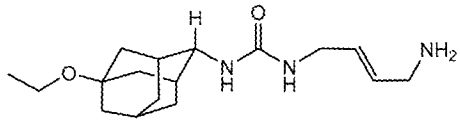
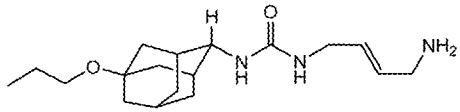
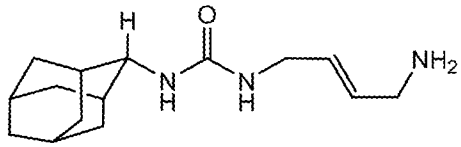
Comp. No.	Name	Structure
77	(1s,3R,4s,5S,7s)-4-((((E)-4-aminobut-2-en-1-yl)carbamoyl)oxy)adamantane-1-carboxylic acid	
78	(1s,3R,4r,5S,7s)-4-((((E)-4-aminobut-2-en-1-yl)carbamoyl)oxy)adamantane-1-carboxylic acid	
79	(1R,2s,3S,5s,7s)-5-(cyclopropylcarbamoyl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
80	(1R,2r,3S,5s,7s)-5-(cyclopropylcarbamoyl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
81	(1R,2s,3S,5s,7s)-5-morpholinoadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
82	(1R,2r,3S,5s,7s)-5-morpholinoadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
83	(1R,2s,3S,5s,7s)-5-(cyclopropylcarbamoyl)adamantan-2-yl ((E)-4-amino-3-methylbut-2-en-1-yl)carbamate	

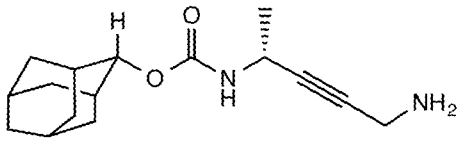
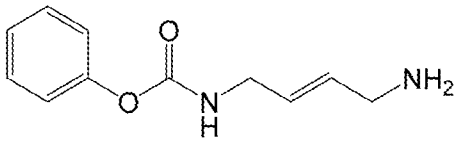
Comp. No.	Name	Structure
84	(1R,2r,3S,5s,7s)-5-(cyclopropylcarbamoyl)adamantan-2-yl ((E)-4-amino-3-methylbut-2-en-1-yl)carbamate	
85	(1R,2s,3S,5s,7s)-5-(2H-tetrazol-5-yl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
86	(1R,2r,3S,5s,7s)-5-(2H-tetrazol-5-yl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
87	(1R,2s,3S,5s,7s)-5-(4-methoxyphenyl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
88	(1R,2r,3S,5s,7s)-5-(4-methoxyphenyl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
89	(1r,3r)-3-(2,3-dihydrobenzofuran-5-yl)cyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate	
90	(1R,3S,5R,7R)-adamantan-2-yl ((R,E)-5-aminopent-3-en-2-yl)carbamate	

Comp. No.	Name	Structure
90	(1R,2s,3S,5s,7s)-5-aminoadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
91	(1R,2r,3S,5s,7s)-5-aminoadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
92	(1R,2s,3S,5s,7*s*)-5-(isobutylamino)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
93	(1R,2*r*,3*S*,5s,7*s*)-5-(isobutylamino)adamantan-2-yl ((*E*)-4-aminobut-2-en-1-yl)carbamate	
94	(1R,2s,3S,5s,7s)-5-hydroxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
95	(1R,2r,3S,5s,7s)-5-hydroxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
96	(1R,2s,3S,5s,7s)-5-propoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	

Comp. No.	Name	Structure
97	(1R,2r,3S,5s,7s)-5-propoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
98	(1R,2s,3S,5s,7s)-5-methoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
99	(1R,2r,3S,5s,7s)-5-methoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
100	1-((E)-4-aminobut-2-en-1-yl)-3-((1R,2r,3S,5s,7s)-5-methoxyadamantan-2-yl)urea	
101	1-((E)-4-aminobut-2-en-1-yl)-3-((1R,2r,3S,5s,7s)-5-ethoxyadamantan-2-yl)urea	
102	1-((E)-4-aminobut-2-en-1-yl)-3-((1R,2r,3S,5s,7s)-5-propoxyadamantan-2-yl)urea	
103	(1R,3S,5s,7s)-5,7-dimethoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	

Comp. No.	Name	Structure
104	(1R,3S,5s,7s)-5,7-diethoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
105	(1R,3S,5s,7s)-5,7-dipropoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
106	(1R,3S,5s,7s)-5,7-difluoroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
107	(1R,3S,5s,7s)-5,7-dichloroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
108	1-phenylcyclopentyl (E)-(4-aminobut-2-en-1-yl)carbamate	
109	(E)-1-(4-aminobut-2-en-1-yl)-3-(3-phenyloxetan-3-yl)urea	

Comp. No.	Name	Structure
110	(1R,2s,3S,5s,7s)-5-(cyclopropylmethoxy)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
111	(1R,2r,3S,5s,7s)-5-(cyclopropylmethoxy)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
112	(1S,2R,3S,5R,7S)-1-fluoroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate	
113	1-((E)-4-aminobut-2-en-1-yl)-3-((1R,2s,3S,5s,7s)-5-methoxyadamantan-2-yl)urea	
114	1-((E)-4-aminobut-2-en-1-yl)-3-((1R,2s,3S,5s,7s)-5-ethoxyadamantan-2-yl)urea	
115	1-((E)-4-aminobut-2-en-1-yl)-3-((1R,2s,3S,5s,7s)-5-propoxyadamantan-2-yl)urea	
116	1-((1R,3S,5r,7r)-adamantan-2-yl)-3-((E)-4-aminobut-2-en-1-yl)urea	

Comp. No.	Name	Structure
117	(1R,3S,5R,7R)-adamantan-2-yl ((R)-5-aminopent-3-yn-2-yl)carbamate	
118	phenyl (E)-(4-aminobut-2-en-1-yl)carbamate	

Biological Methods

[144] Cell Culture: The human monocytic THP-1 cell line was purchased from ATCC (TIB-202). The human monocytic THP-1 ASC-GFP reporter cell line was purchased from Invivogen (thp-ascgfp). Cells were maintained in RPMI media supplemented 10% fetal bovine serum and 100 units of penicillin and streptomycin per mL at a cell density of 2-8 x 10^5 cells/mL.

[145] Human peripheral blood mononuclear cells were isolated from whole blood using Lymphoprep™ density gradient according to the manufacturer's instructions. PBMCs were used fresh.

[146] PMA differentiation of THP-1 cells: For ASC Spec assays, the human monocytic cell line THP-1 ASC-GFP cells were differentiated into a macrophage-like phenotype using Phorbol 12-myristate 13-acetate (PMA). THP-1 cells were suspended at a density of 1-2 x 10^6 cells/mL and supplemented with 100 ng/mL PMA. One hundred thousand cells were seeded into each well of a 96 well plate and incubated for 72 hours. Adherent cells were washed three times with PMA free THP-1 media, then cells were rested for 24 hours in PMA free media.

[147] NLRP3 Inflammasome and pyroptosis assay in THP-1 Cells: THP-1 cells were primed with 300 ng/mL of ultra-pure LPS. One hour later, cells were treated as indicated in figure legend. Three hours post-LPS prime, the NLRP3 inflammasome was activated with 10 μM Nigericin. Two hours later, supernatants were collected and analyzed for IL-1β by ELISA. Pyroptotic cell death was assessed by MTT assay as described below.

[148] Cytotoxicity Assay: THP-1 or PBMCs were treated with a dose titration of the indicated compound for 5 hours after which cell viability was assessed by MTT assay, as described below.

[149] MTT Cell Viability Assay: MTT reagent (0.6 mg/mL in THP-1 culture media) was prepared and 150 μL was added to each well. After 1-2 hours, cells were centrifuged at 500g for 5 minutes to pellet cells and crystals. Supernatants were removed, and formazan crystals were dissolved in 100 μL of isopropanol. Cell viability was assessed by measuring optical density at 560 nm, with a reference wavelength of 670 nm. Viability is expressed as percent signal relative to wells containing untreated cells.

[150] Cell Free Inflammasome Assay: Cell free inflammasome activation and Caspase-1 cleavage was assessed as described previously. Briefly, lysates were prepared from THP-1 by hypotonic lysis to a final protein concentration > 7 mg/mL. Lysates were pretreated for 20 minutes with a final concentration of 1 mM of the indicated compound on ice. Inflammasome activation was induced by incubating samples for 60 minutes at 30°C. Inflammasome activity was assessed through monitoring Caspase-1 cleavage by Western blot.

[151] NLRP3 Inflammasome activation in PBMCs: 2 x 10^5 freshly isolated PBMCs were primed with 300 ng/mL LPS for 1 hour, then treated with a dose titration of the indicated compounds for an additional 2 hours. The NLRP3 inflammasome was then activated by treating cells with 10 μM nigericin for 2 hours. Inflammasome activity was assessed by IL-1β ELISA according to manufacturer's instructions.

[152] AIM2 Inflammasome activation in PBMCs: 2 x 10^5 freshly isolated PBMCs were transfected with poly dA:dT (100 ng/well) using Lipofectamine 2000 (1 μL/well) according to the manufacturer's instructions in order to activate the AIM2 inflammasome. One hour later, cells were treated with a dose titration of the indicated compounds for an additional 17 hours. Inflammasome activity was assessed by IL-1β ELISA according to manufacturer's instructions.

[153] NLRP1 Inflammasome activation in PBMCs: 2 x 10^5 freshly isolated PBMCs were treated with 10 μM Talabostat, a constitutive repressor of the NLRP1 inflammasome. One hour later, cells were treated with a dose titration of the indicated compounds for an additional 17 hours. Inflammasome activity was assessed by IL-1β ELISA according to manufacturer's instructions.

[154] NLRC4 Inflammasome activation PBMCs: 2 x 10^5 freshly isolated PBMCs were transfected with bacterial flagellin protein (100 ng/well) using Lipofectamine 2000 (1 μL/well) according to the manufacturer's instructions in order to activate the NLRC4 inflammasome. One

hour later, cells were treated with a dose titration of the indicated compounds for an additional 17 hours. Inflammasome activity was assessed by IL-1β ELISA according to manufacturer's instructions.

Example 4: Inhibition of Caspase-1 Processing in Cell Free Inflammasome Assay

[155] Inflammasome spontaneously assemble at 30 °C in THP-1 cell lysates with sufficient protein concentrations. This processing is dependent on ASC oligomerization. The indicated compounds, or vehicle control, were added to THP-1 lysates at a final concentration of 1 mM for 20 minutes prior to inflammasome activation. Samples were incubated for 60 minutes at 30°C to activate the inflammasome. Activation of Caspase-1 (Casp-1) through autoproteolytic cleavage was assessed by Western blot. Disappearance of full length Casp-1, along with increased cleaved Casp-1 in the untreated and vehicle control lanes indicates inflammasome activation. As shown in FIG. 1, compound 2 significantly inhibited the conversion of full-length Casp-1 into its active, cleaved form.

Example 5: Cellular Activity Assays

[156] The properties of each compound were assayed in a variety of cellular assays using THP-1 human monocytic cells:

[157] Cytotoxicity was assessed by treating THP-1 cells with a dose titration of the indicated compound for 5 hours, after which cell viability was assessed by MTT assay.

[158] Inflammasome inhibition was assayed in THP-1 cells primed with LPS, then treated with a dose titration of the indicated compound for 2 hours prior to NLRP3 inflammasome activation with Nigericin. IL-1β was assessed in cell supernatants by ELISA to monitor inflammasome activation. Simultaneously, an MTT assay was performed on the cells assess Pyroptosis, a form of inflammasome dependent inflammatory cell death.

[159] ASC oligomerization was monitored using an ASC-GFP THP-1 reporter cell line. Upon inflammasome activation, ASC polymerizes and forms a single large 'Spec' per cell. By tagging ASC with GFP these 'Specs' are readily observable and the percentage of inflammasome containing cells can be assessed. THP-1 ASC-GFP cells were differentiated using PMA overnight, then rested in PMA-free media for one day. Cells were treated with a dose titration of the indicated drug 2 hour prior to NLRP3 inflammasome activation using nigericin. Forty-five minutes after nigericin treatment cells were fixed in 2% paraformaldehyde and imaged on a

fluorescent microscope. The percentage of ASC-GFP Spec positive cells per field was quantified.

Table 3

Compound	Cytotoxicity (CC_{50})	NLRP3 IL-1β (IC_{50})	Protection from Pyroptosis (PD_{50})
2	4380 μM	3440 μM	None
14		13 μM	
31	> 10,000 μM	5700 μM	None
32	> 10,000 μM	10100 μM	None
33	> 10,000 μM	4200 μM	None
34	> 10,000 μM	5720 μM	None
35	> 10,000 μM	5140 μM	None
4	5140 μM	11 μM	4.6 μM
5		1120 μM	1000 μM
36		1000 μM	1000 μM
37		24 μM	20 μM
38		35 μM	46 μM
39		19 μM	26 μM
40		115 μM	200 μM
41		24 μM	25 μM
43		200 μM	200 μM
45		14 μM	21 μM
46		25 μM	129 μM
55		500 μM	
62		>200 μM	

Compound	Cytotoxicity (CC_{50})	NLRP3 IL-1β (IC_{50})	Protection from Pyroptosis (PD_{50})
67		200 μM	200 μM
69		200 μM	200 μM
71		4.0 μM	4.2 μM
72		7.6 μM	11.3 μM
73		6.9 μM	12.3 μM
74		5.2 μM	4.4 μM
75		8.1 μM	6.6 μM
77		200 μM	200 μM
78		200 μM	200 μM
79		200 μM	200 μM
80		200 μM	200 μM
90		200 μM	200 μM
91		200 μM	200 μM
94		15 μM	9.2 μM
95		27 μM	8.2 μM
96		200 μM	200 μM
97		14 μM	15 μM
118		3.8 μM	

Example 6: Inhibition of Multiple Inflammasomes in human PBMCs

[160] The ability of compound 4 to inhibit multiple inflammasomes was assessed in fresh primary human peripheral blood mononuclear cells (PBMCs). A dose titration of compound 4 was added at the same time as the inflammasome stimuli were as follows:

a. NLRP3: LPS prime followed by 2-hour stimulation with nigericin.

b. NLRP1: Overnight treatment with Talabostat (DPP4 inhibitor)

c. NLRC4: Overnight transfection with bacterial flagellin protein

d. AIM2: Overnight transfection with double stranded DNA

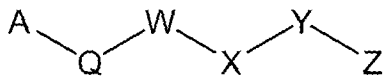
Table 4

Compound	Cytotoxicity (CC_{50})	NLRP3 IL-1β (IC_{50})	NLRP1 IL-1β (IC_{50})	NLRC4 IL-1β (IC_{50})	AIM2 IL-1β (IC_{50})
4	> 1000 μM	6.8 μM	11.3 μM	12.3 μM	7.1 μM

[161] It is to be understood that the embodiments of the invention disclosed herein are illustrative of the principles of the present invention. Other modifications that may be employed are within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations of the present invention may be utilized in accordance with the teachings herein. Accordingly, the present invention is not limited to that precisely as shown and described.

We claim:

1. A compound having the structural formula:



or a pharmaceutically acceptable salt thereof, and/or solvate or hydrate thereof, wherein:

A is C_1-C_6 alkyl (e.g., t-butyl), -(C_0-C_4 alkyl)-O_{0-1}-cycloalkyl, -(C_0-C_4 alkyl)-O_{0-1}-heterocycloalkyl, -(C_0-C_4 alkyl)-O_{0-1}-aryl, or -(C_0-C_4 alkyl)-O_{0-1}-heteroaryl, or -(C_0-C_2 alkyl)-B-C, wherein B and C are each independently cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Q and X are independently -O- or -N(R^A)-, wherein Q and X are not both -O-;

W is C(O) or $S(O)_n$, wherein n is 1 or 2;

Y is a C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, -(C_0-C_2 alkyl)-cycloalkyl, -(C_0-C_2 alkyl)-heterocycloalkyl, -(C_2-C_3 alkenyl)-cycloalkyl, or -(C_2-C_3 alkenyl)-heterocycloalkyl;

Z is absent, -(C_0-C_2 alkyl)-O(R^A) or -(C_0-C_2 alkyl)-N(R^A)(R^B);

wherein

each R^A and R^B is independently H, C_1-C_4 alkyl, or (C_0-C_3 alkyl)-cyclopropyl;

each alkyl, alkenyl, and alkynyl is unsubstituted, substituted with one or more halogens (e.g., fluorinated or perfluorinated), or substituted with one or two groups independently selected from methyl, ethyl, oxo, acyl, and -C(O)N(R^A)(R^B);

each cycloalkyl has 3-10 ring carbons and is saturated or partially unsaturated, and optionally includes one or two fused and/or bridged cycloalkyl rings, each fused and/or bridged ring having 3-8 ring members, wherein the bridge is bivalent or trivalent, and each cycloalkyl is substituted with 0-5 R^C or is perfluorinated;

each heterocycloalkyl has 3-10 ring members and 1-4 heteroatoms where each heteroatom is independently boron, nitrogen, oxygen or sulfur and is saturated or partially

unsaturated, and optionally includes one or two fused cycloalkyl or aryl rings, and/or one or two bridged cycloalkyl rings, each fused and/or bridged ring each having 3-8 ring members, wherein the bridge is bivalent or trivalent, and is substituted with 0-5 R^C or is perfluorinated;

each aryl is a phenyl or naphthyl, and optionally includes one or two fused cycloalkyl or heterocycloalkyl rings, each fused cycloalkyl or heterocycloalkyl ring having 4-8 ring members, and is substituted with 0-5 R^C or is perfluorinated;

each heteroaryl is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms, where each heteroatom is independently boron, nitrogen, oxygen or sulfur, or is a bicyclic heteroaryl having 1-5 heteroatoms where each heteroatom is independently boron, nitrogen, oxygen, or sulfur, and optionally includes one or two fused cycloalkyl or heterocycloalkyl rings, each fused cycloalkyl or heterocycloalkyl ring having 4-8 ring members, and wherein the heteroaryl is substituted with 0-5 R^C;

wherein each R^C is independently C_1-C_4 alkyl (e.g., methyl, t-butyl, or -CF_3), -Cl, -F, -Br, -CN, -OR^A, -C(O)R^A, -C(O)NR^BR^A, -NR^AR^B, -SO_3, or -SO_2(C_1 alkyl).

2. The compound of claim 1, wherein the compound is not tert-butyl (4-aminopentyl) carbamate, tert-butyl (4-aminobut-2-yn-1-yl)carbamate, tert-butyl (3-hydroxypropyl)carbamate, tert-butyl ethylcarbamate, tert-butyl (3-amino-2-methylpropyl)carbamate, tert-butyl but-3-en-1-ylcarbamate, tert-butyl (azetidin-3-ylmethyl)carbamate, tert-butyl (4-aminobut-2-en-1-yl)carbamate, 4-aminobut-2-en-1-yl tert-butylcarbamate, cyclohexyl (4-aminobut-2-en-1-yl)carbamate, or tert-butyl (4-hydroxybut-2-en-1-yl)carbamate.

3. The compound of claim 1 or claim 2, wherein W is C(O).

4. The compound of any of claims 1-3, wherein Q is -O- and X is –N(R^A)-.

5. The compound of claim 4, wherein X is –N(H)-.

6. The compound of any of claims 1-5, wherein A is t-butyl, -(C_0-C_2 alkyl)-O_{0-1}-cycloalkyl, -(C_0-C_2 alkyl)-O_{0-1}-heterocycloalkyl, -(C_0-C_2 alkyl)-O_{0-1}-aryl, or -(C_0-C_2 alkyl)-O_{0-1}-heteroaryl.

7. The compound of any of claims 1-5, wherein A is t-butyl.

8. The compound of any of claims 1-5, wherein A is -(C_0-C_1 alkyl)-cycloalkyl, -(C_0-C_1 alkyl)-heterocycloalkyl, -(C_0-C_1 alkyl)-aryl, or -(C_0-C_1 alkyl)-heteroaryl, wherein each cycle is either monocyclic or fused bicyclic.

9. The compound of any of claims 1-5, wherein A is phenyl or benzyl.

10. The compound of any of claims 1-5, wherein A is (C_1 alkyl)-aryl, wherein aryl is monocyclic or fused bicyclic, and the C_1 alkyl is substituted by an unsubstituted methyl or unsubstituted ethyl group.

11. The compound of any of claims 1-5, wherein A is -(C_0-C_1 alkyl)-B-C, wherein B is cyclopropyl, cyclobutyl, adamantyl, or phenyl, and C is cyclopropyl, phenyl, tetrazolyl or morpholinyl.

12. The compound of any of claims 1-5, wherein A is cyclobutyl, cyclopentyl, cyclohexyl, or adamantyl.

13. The compound of any of claims 1-12, wherein Y is C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl.

14. The compound of any of claims 1-12, wherein Y is C_3-C_6 alkenyl.

15. The compound of any of claims 1-12, wherein Y is -(C_2-C_3 alkenyl)-cyclolalkyl, wherein cycloalkyl is cyclopropyl or cyclobutyl.

16. The compound of any of claims 1-15, wherein Z is absent.

17. The compound of any of claims 1-15, wherein Z is -(C_0-C_1 alkyl)-OH or -(C_0-C_1 alkyl)-NH_2.

18. The compound of any of claims 1-15, wherein Z is -OH or -NH_2.

19. The compound of any of claims 1-18, wherein each R^C is independently -CH_3, -CH_2CH_3, -CF_3, -F, or -Cl.

20. The compound of claim 1, wherein the compound is:

tert-butyl (3-aminopropyl)carbamate;

tert-butyl (4-aminobutyl)carbamate;

tert-butyl (5-aminopentyl)carbamate;

tert-butyl (4-aminobut-2-en-1-yl)carbamate;

tert-butyl (4-hydroxybut-2-en-1-yl)carbamate;

tert-butyl (4-aminobut-2-yn-1-yl)carbamate;

tert-butyl (4-amino-2-methylbut-2-en-1-yl)carbamate;

tert-butyl (4-amino-2-fluorobut-2-en-1-yl)carbamate;

tert-butyl (4-amino-2,3-difluorobut-2-en-1-yl)carbamate;

tert-butyl ((2-(aminomethyl)cyclopropyl)methyl)carbamate;

4-aminobut-2-en-1-yl tert-butylcarbamate;

1-methylcyclobutyl (4-(ethylamino)but-2-yn-1-yl)carbamate;

cyclobutyl (4-aminobut-2-yn-1-yl)carbamate;

cyclohexyl (4-aminobut-2-en-1-yl)carbamate;

1-methylcyclobutyl (4-aminobut-2-yn-1-yl)carbamate;

3-methyloxetan-3-yl (4-aminobut-2-yn-1-yl)carbamate;

1-methylcyclobutyl (3-aminocyclobutyl)carbamate;

1-carbamoylcyclopropyl (4-aminobut-2-en-1-yl)carbamate;

1-methylcyclobutyl (4-aminobut-2-en-1-yl)carbamate;

1-methylcyclopropyl (4-aminobut-2-en-1-yl)carbamate;

1-(4-aminobut-2-en-1-yl)-3-(tert-butyl)urea;

1,1,1-trifluoro-2-methylpropan-2-yl (4-aminobut-2-en-1-yl)carbamate;

1-(trifluoromethyl)cyclopropyl (4-aminobut-2-en-1-yl)carbamate;

2-methyl-3-oxobutan-2-yl (4-aminobut-2-en-1-yl)carbamate;

1-carbamoylcyclopropyl (4-aminobut-2-en-1-yl)carbamate;

2-(2,4-dimethyl-1H-imidazol-5-yl)propan-2-yl (4-aminobut-2-en-1-yl)carbamate;

2-phenylpropan-2-yl (4-aminobut-2-en-1-yl)carbamate;

1-(trifluoromethyl)cyclopropyl (4-aminobut-2-yn-1-yl)carbamate;

1-(trifluoromethyl)cyclopropyl (4-aminobut-2-en-1-yl)carbamate;

1-cyanocyclopropyl (4-aminobut-2-en-1-yl)carbamate;

tert-butyl (3-hydroxypropyl)carbamate;

tert-butyl ethylcarbamate;

tert-butyl (3-amino-2-methylpropyl)carbamate;

tert-butyl but-3-en-1-ylcarbamate;

tert-butyl (azetidin-3-ylmethyl)carbamate;

1-methylcyclobutyl ((2-(aminomethyl)cyclopropyl)methyl)carbamate;

2-(pyridin-2-yl)propan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

(S)-1-phenylethyl (E)-(4-aminobut-2-en-1-yl)carbamate;

(R)-1-phenylethyl (E)-(4-aminobut-2-en-1-yl)carbamate;

(S)-1-phenylpropyl (E)-(4-aminobut-2-en-1-yl)carbamate;

2,3-dihydro-1H-inden-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

5,6-dimethyl-2,3-dihydro-1H-inden-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

1-(4-(methylcarbamoyl)phenyl)cyclopropyl (E)-(4-aminobut-2-en-1-yl)carbamate;

2-(4-(methylcarbamoyl)phenyl)propan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

1-phenylcyclopropyl (E)-(4-aminobut-2-en-1-yl)carbamate;

2-methyl-1-phenoxypropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

1-(3,4-difluorophenoxy)-2-methylpropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

2-methyl-1-(3-(trifluoromethyl)phenoxy)propan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

2-methyl-1-(3-(trifluoromethyl)phenoxy)propan-2-yl (4-aminobut-2-yn-1-yl)carbamate;

2-methyl-1-(3-(trifluoromethyl)phenoxy)propan-2-yl (R)-(5-aminopent-3-yn-2-yl)carbamate;

1-(cyclopentyloxy)-2-methylpropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

1-(bicyclo[4.2.0]octa-1,3,5-trien-3-yloxy)-2-methylpropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

1-(3-ethoxyphenoxy)-2-methylpropan-2-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

(1r,3r)-3-phenylcyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate;

(1r,3r)-1-methyl-3-phenylcyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate;

(1S,2S,3S)-2-methyl-3-phenylcyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate;

(1r,3r)-3-(3,5-difluorophenyl)cyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate;

(1r,3r)-3-(3,5-difluorophenyl)cyclobutyl (4-aminobut-2-yn-1-yl)carbamate;

(1r,3R)-3-(3,5-difluorophenyl)cyclobutyl ((R)-5-aminopent-3-yn-2-yl)carbamate;

(1r,3r)-3-(3-(trifluoromethyl)phenyl)cyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate;

(1r,3r)-3-(4-methoxy-3-methylphenyl)cyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate;

(1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl [(2E)-4-aminobut-2-en-1-yl]carbamate;

bicyclo[2.2.1]hepta-2,5-dien-7-yl (E)-(4-aminobut-2-en-1-yl)carbamate;

(1R)-bicyclo[2.2.1]hept-2-en-7-yl ((E)-4-aminobut-2-en-1-yl)carbamate;

(1S)-1-(3-fluoropyridin-2-yl)ethyl [(2E)-4-aminobut-2-en-1-yl]carbamate;

(1R)-1-(3-fluoropyridin-2-yl)ethyl [(2E)-4-aminobut-2-en-1-yl]carbamate;

cyclohexyl [(2E)-3-(1-aminocyclopropyl)prop-2-en-1-yl]carbamate;

(1S)-1-(6-oxo-1,6-dihydropyridin-3-yl)ethyl [(2E)-4-aminobut-2-en-1-yl]carbamate;

1-(3,4-dimethylphenyl)cyclopropyl [(2E)-4-aminobut-2-en-1-yl]carbamate; or

2-(1-oxo-2,3-dihydro-1H-isoindol-5-yl)propan-2-yl [(2E)-4-aminobut-2-en-1-yl]carbamate.

(1R,3S,5r,7r)-adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-chloroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-chloroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-fluoroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-fluoroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,3S,5r,7r)-adamantan-2-yl (4-aminobut-2-yn-1-yl)carbamate

(1s,3R,4s,5S,7s)-4-((((E)-4-aminobut-2-en-1-yl)carbamoyl)oxy)adamantane-1-carboxylic acid

(1s,3R,4r,5S,7s)-4-((((E)-4-aminobut-2-en-1-yl)carbamoyl)oxy)adamantane-1-carboxylic acid

(1R,2s,3S,5s,7s)-5-(cyclopropylcarbamoyl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-(cyclopropylcarbamoyl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-morpholinoadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-morpholinoadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-(cyclopropylcarbamoyl)adamantan-2-yl ((E)-4-amino-3-methylbut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-(cyclopropylcarbamoyl)adamantan-2-yl ((E)-4-amino-3-methylbut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-(2H-tetrazol-5-yl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-(2H-tetrazol-5-yl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-(4-methoxyphenyl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-(4-methoxyphenyl)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1r,3r)-3-(2,3-dihydrobenzofuran-5-yl)cyclobutyl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,3S,5R,7R)-adamantan-2-yl ((R,E)-5-aminopent-3-en-2-yl)carbamate

(1R,2s,3S,5s,7s)-5-aminoadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-aminoadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-(isobutylamino)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-(isobutylamino)adamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-hydroxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-hydroxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-propoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-propoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2s,3S,5s,7s)-5-methoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,2r,3S,5s,7s)-5-methoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

1-((E)-4-aminobut-2-en-1-yl)-3-((1R,2r,3S,5s,7s)-5-methoxyadamantan-2-yl)urea

1-((E)-4-aminobut-2-en-1-yl)-3-((1R,2r,3S,5s,7s)-5-ethoxyadamantan-2-yl)urea

1-((E)-4-aminobut-2-en-1-yl)-3-((1R,2r,3S,5s,7s)-5-propoxyadamantan-2-yl)urea

(1R,3S,5s,7s)-5,7-dimethoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,3S,5s,7s)-5,7-diethoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,3S,5s,7s)-5,7-dipropoxyadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,3S,5s,7s)-5,7-difluoroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

(1R,3S,5s,7s)-5,7-dichloroadamantan-2-yl ((E)-4-aminobut-2-en-1-yl)carbamate

1-phenylcyclopentyl (E)-(4-aminobut-2-en-1-yl)carbamate

(E)-1-(4-aminobut-2-en-1-yl)-3-(3-phenyloxetan-3-yl)urea

21. A method of treating an inflammatory condition in a subject in need thereof, comprising providing to the subject a compound according to any one of claims 1-20.

22. The method of claim 21, wherein the inflammatory condition is an inflammatory bowel disease, an arthritic disease, or a neurodegenerative disorder.

23. The method of claim 21, wherein the inflammatory condition is an autoinflammatory syndrome.

24. The method of claim 21, wherein the inflammatory condition is an inflammasome-related condition.

25. The method of claim 21, wherein the inflammatory condition is Adult-Onset Still's Disease (AOSD), Systemic Juvenile Idiopathic Arthritis (sJIA), Macrophage Activation Syndrome (MAS), Autoinflammation with Infantile Enterocolitic (AIFEC), Bullous Pemphigoid, Pemphigus Vulgaris, Idiopathic Pulmonary Fibrosis (IPF), Non-Alcoholic Steatohepatitis

(NASH), Systemic Lupus Erythematosus (SLE), Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease, Traumatic Brain Injury (TBI), Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA), Cryopyrin-Associated Periodic Syndromes (CAPS), Vitiligo, Multiple Self-Healing Palmoplantar Carcinoma (MSPC), Autoimmune Addison's Disease, Familial Mediterranean Fever (FMF), Autoimmune Thyroiditis, Stroke, Type 2 Diabetes (T2D), Osteoarthritis, Gout, Atherosclerosis, Hidradenitis Suppurativa, Psoriasis, and Pyrin Diseases.

26. A method for treating an inflammatory condition resulting from a coronavirus (e.g., SARS-CoV 2, SARS-CoV, or MERS), viral, bacterial, fungal, parasitic, or other type of infection in a human subject, comprising administering to a subject in need of such treatment a compound according to any one of claims 1-20.

27. A method according to claim 26, wherein the inflammatory condition causes cell death, or release of pro-inflammatory cytokines or other inflammatory mediators.

28. The method of claim 26 or 27, wherein the inflammatory condition is cytokine storm syndrome, cytokine release syndrome, sepsis, hemophagocytic lymphohistiocytosis, acute lung injury, acute respiratory distress syndrome, or macrophage activation syndrome.

29. The method of any one of claims 26-28, wherein the compound of any one of claim 1-20 is administered in co-therapy with at least one of an antiinfective, antimicrobial, antiviral (e.g., remdesivir), monoclonal antibody (e.g., tocilizumab), biologic, immunoglobulin, immunomodulator, anti-inflammatory drug, corticosteroid, small molecule, cell therapy, or other type of prophylactic or therapeutic agent.

30. A method for treating an inflammatory condition resulting from a cell therapy administered to a human subject, comprising administering to a subject in need of such treatment a compound according to any one of claims 1-20.

31. A method according to 30, wherein the inflammatory condition is cytokine storm syndrome or cytokine release syndrome.

32. A method according to claim 30 or claim 31, wherein the inflammatory condition causes cell death or release of pro-inflammatory cytokines or other inflammatory mediators.

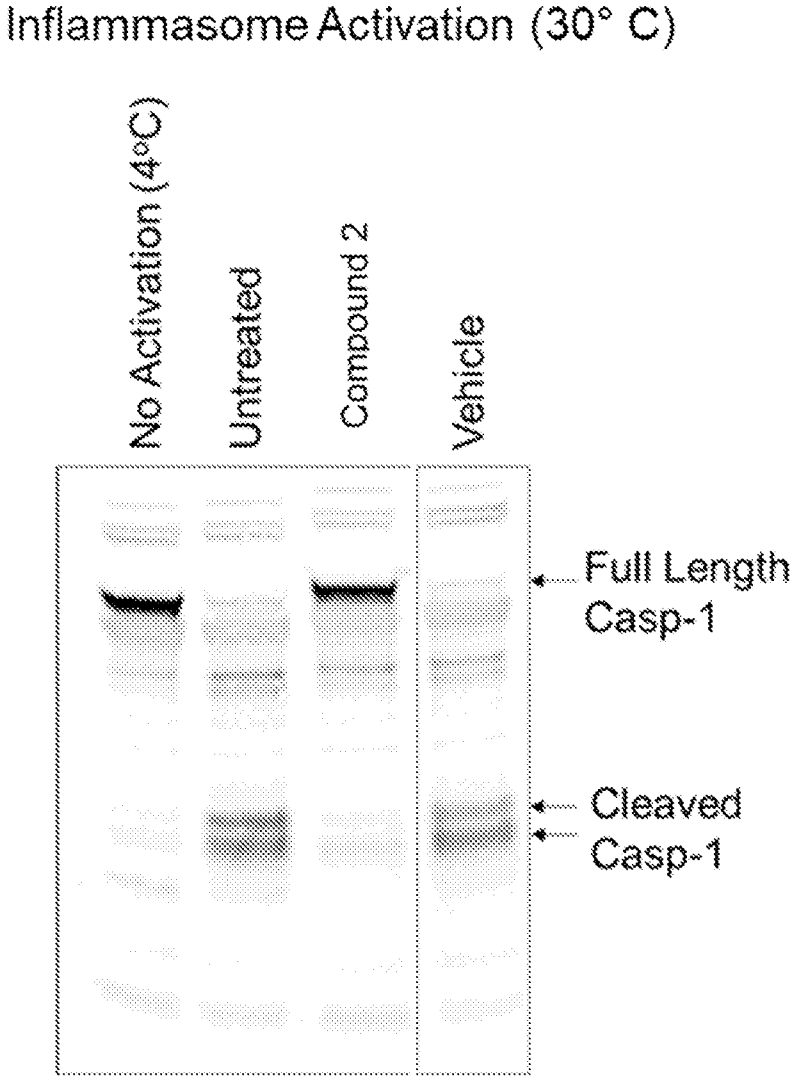
33. The method of any one of claims 30-32, wherein the compound according to any one of claims 1-20 is administered in co-therapy with at least one of a monoclonal antibody (e.g., tocilizumab), a biologic, an immunoglobulin, an immunomodulatory, an anti-inflammatory drug, a corticosteroid, a small molecule, a cell therapy, or other type of prophylactic or therapeutic agent.

34. A method of any one of claims 21-33, wherein the compound is *tert*-butyl (4-aminopentyl)carbamate, *tert*-butyl (4-aminobut-2-yn-1-yl)carbamate, tert-butyl (3-hydroxypropyl)carbamate, tert-butyl ethylcarbamate, tert-butyl (3-amino-2-methylpropyl)carbamate, *tert*-butyl but-3-en-1-ylcarbamate, *tert*-butyl (azetidin-3-ylmethyl)carbamate, *tert*-butyl (4-aminobut-2-en-1-yl)carbamate, or *tert*-butyl (4-hydroxybut-2-en-1-yl)carbamate, or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition comprising a compound of any of claims 1-20 or *tert*-butyl (4-aminopentyl)carbamate, *tert*-butyl (4-aminobut-2-yn-1-yl)carbamate, tert-butyl (3-hydroxypropyl)carbamate, tert-butyl ethylcarbamate, tert-butyl (3-amino-2-methylpropyl)carbamate, *tert*-butyl but-3-en-1-ylcarbamate, *tert*-butyl (azetidin-3-

ylmethyl)carbamate, *tert*-butyl (4-aminobut-2-en-1-yl)carbamate, or *tert*-butyl (4-hydroxybut-2-en-1-yl)carbamate, or a pharmaceutically acceptable salt thereof.

FIG. 1


Inflammasome Activation (30° C)
No Activation (4°C)
Untreated
Compound 2
Vehicle
Full Length Casp-1
Cleaved Casp-1

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C271/12 A61P29/00 C07C271/16 C07C271/18 C07C271/20
C07C271/34 C07C271/52 C07C275/20 C07C317/46
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 171 136 B1 (GENZYME CORP [US]; BRIGHAM & WOMENS HOSPITAL [US]) 22 June 2005 (2005-06-22) claims 1-12,20,21	1,2,13, 21-35
X	US 2 877 263 A (THOMAS GEORGE R) 10 March 1959 (1959-03-10) examples 1-3	1,6,7, 16,20
X	US 4 954 501 A (HERTER ROLF [DE] ET AL) 4 September 1990 (1990-09-04) line 49; example 11 line 24; example 10	1-8,13, 17,18,20
X	US 5 760 273 A (INABA MASASHI [JP] ET AL) 2 June 1998 (1998-06-02) claim 15	1-3,7, 13,16

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 2021	19/07/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/028906

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/274229 A1 (WONG CHI-HUEY [US] ET AL) 17 October 2013 (2013-10-17) figure 11; example 30	1-3,7, 17,18
X	KIM ET AL: "Design, Synthesis, and Biological Activity of 1,3-Disubstituted Ureas as Potent Inhibitors of the Soluble Epoxide Hydrolase of Increased Water Solubility", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 47, no. 8, 17 March 2004 (2004-03-17), pages 2110-2122, XP002396850, ISSN: 0022-2623, DOI: 10.1021/JM030514J page 2112; examples VII,VIII	1-8,17, 18
X	WO 2010/097479 A2 (SYMRISE GMBH & CO KG [DE]; MEYER IMKE [DE] ET AL.) 2 September 2010 (2010-09-02) page 106 - page 123; claim 11	1-6, 8-12,19, 35
X	EP 0 887 079 A1 (PFIZER [US]) 30 December 1998 (1998-12-30) page 30, line 20 - line 30	1-6,8,9, 17,18
X	LALIC GOJKO ET AL: "Scope and Mechanism of Formal S N 2' Substitution Reactions of a Monomeric Imidozirconium Complex with Allylic Electrophiles", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 130, no. 13, 1 April 2008 (2008-04-01), pages 4459-4465, XP55823002, ISSN: 0002-7863, DOI: 10.1021/ja7106096 example 2	1-5,8,9, 13,14, 16-18
X	WO 2020/010451 A1 (TRILLIUM THERAPEUTICS INC [CA]) 16 January 2020 (2020-01-16) paragraph [0195]; example 5	1,2,9, 10, 13-15, 17,18

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-18, 20-34(all partially)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-18, 20-34(all partially)

Present claims 1-18,20-34 relate to an extremely large number of possible compounds/products/methods. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds/products/apparatus/methods claimed, see pages 34-44.
The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1-18,20-34 (PCT Guidelines 9.19 and 9.23).
The search of claims 1-18,20-34 was restricted to those claimed compounds/products which appear to be supported by the examples on pages 34-44 and a generalisation of their structural formulae.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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International application No
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