dimethyl sulfoxide (DMSO), although these agents have limited potency and are nonspecific.

Current treatments for NLRP3-related diseases include biologic agents that target IL-1. These are the recombinant IL-1 receptor antagonist anakinra, the neutralizing IL-1β antibody canakinumab and the soluble decoy IL-1 receptor rilonacept. These approaches have proven successful in the treatment of CAPS, and these biologic agents have been used in clinical trials for other IL-1β-associated diseases.

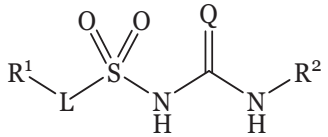
Some diarylsulfonylurea-containing compounds have been identified as cytokine release inhibitory drugs (CRIDs) (Perregaux *et al.*; J. Pharmacol. Exp. Ther. 299, 187-197, 2001). CRIDs are a class of diarylsulfonylurea-containing compounds that inhibit the post-translational processing of IL-1β. Post-translational processing of IL-1β is accompanied by activation of caspase-1 and cell death. CRIDs arrest activated monocytes so that caspase-1 remains inactive and plasma membrane latency is preserved.

Certain sulfonylurea-containing compounds are also disclosed as inhibitors of NLRP3 (see for example, Baldwin *et al.*, J. Med. Chem., 59(5), 1691-1710, 2016; and WO 2016/131098 A1, WO 2017/129897 A1, WO 2017/140778 A1, WO 2017/184604 A1, WO 2017/184623 A1, WO 2017/184624 A1, WO 2018/015445 A1 and WO 2018/136890 A1).

There is a need to provide compounds with improved pharmacological and/or physiological and/or physicochemical properties and/or those that provide a useful alternative to known compounds.

Summary of the Invention

In one aspect, the present disclosure refers to a compound of formula (I):



Formula (I)

wherein:

Q is selected from O or S;

L is a saturated or unsaturated C_1-C_{12} hydrocarbylene group, wherein the

hydrocarbylene group may be straight-chained or branched, or be or include cyclic groups, wherein the hydrocarbylene group may optionally be substituted, and wherein the hydrocarbylene group may optionally include one or more heteroatoms N, O or S in its carbon skeleton;

R^1 is $-NR^3R^4$, $-OR^5$, $-(C=NR^6)R^7$, $-(CO)R^8$, $-CN$, $-N_3$, a quaternary ammonium group or an optionally substituted heterocycle;

R^3, R^4, R^5, R^6, R^7 and R^8 are each independently hydrogen or a saturated or unsaturated C_1-C_{10} hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include cyclic groups, wherein the hydrocarbyl group may optionally be substituted, and wherein the hydrocarbyl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton;

wherein optionally L and R^3, or L and R^4, or R^3 and R^4 together with the nitrogen atom to which they are attached may form a 3- to 12-membered saturated or unsaturated cyclic group, wherein the cyclic group may optionally be substituted;

wherein optionally L and R^5 together with the oxygen atom to which they are attached may form a 3- to 12-membered saturated or unsaturated cyclic group, wherein the cyclic group may optionally be substituted;

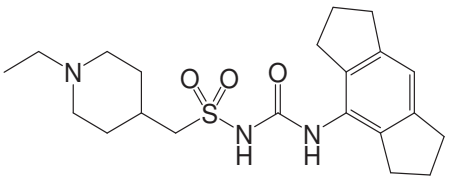
wherein optionally L and R^6, or L and R^7, or R^6 and R^7 together with the -(C=N)– group to which they are attached may form a 3- to 12-membered saturated or unsaturated cyclic group, wherein the cyclic group may optionally be substituted;

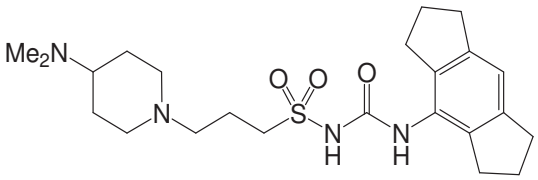
wherein optionally L and R^8 together with the –(C=O)– group to which they are attached may form a 3- to 12-membered saturated or unsaturated cyclic group, wherein the cyclic group may optionally be substituted;

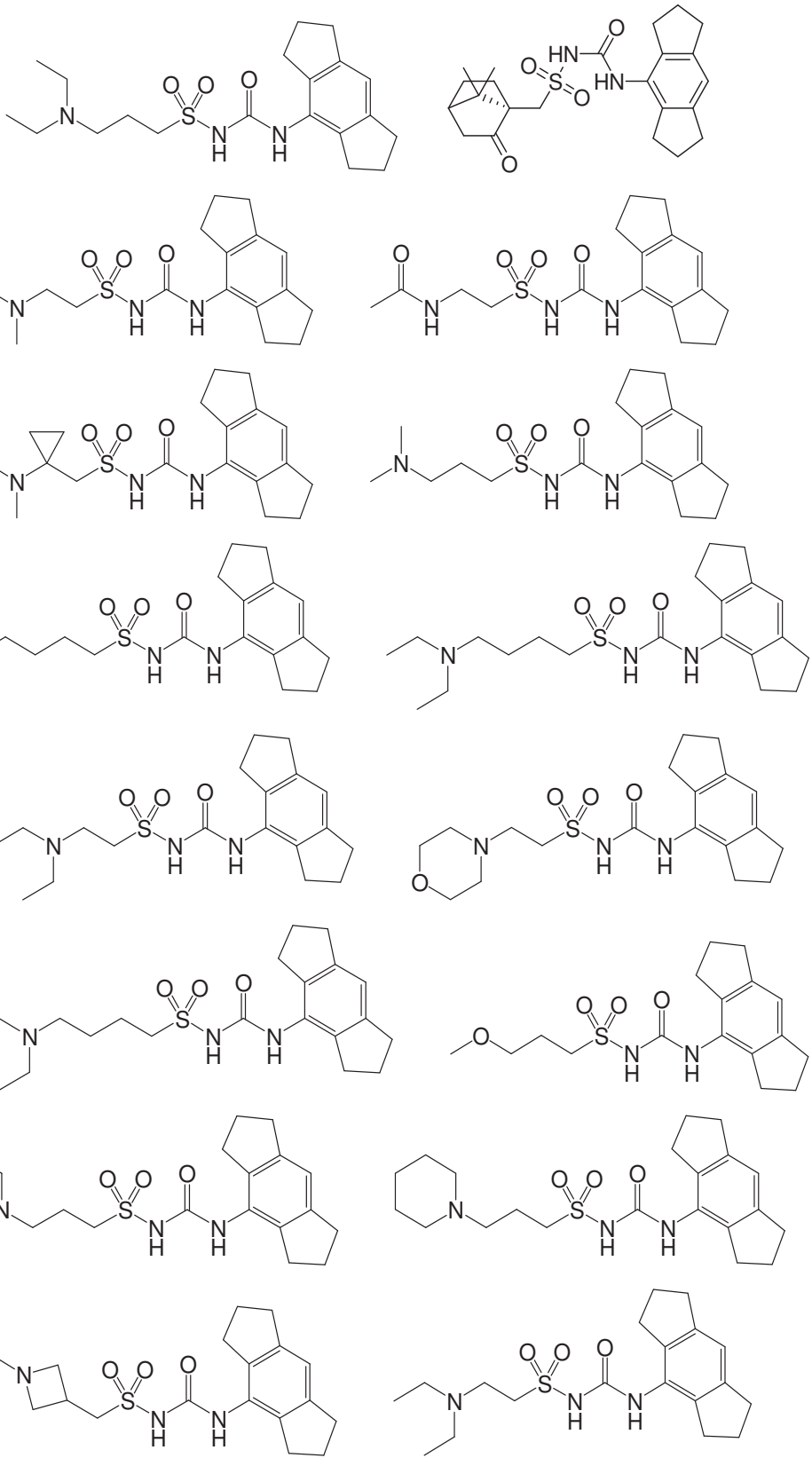
R^2 is a cyclic group substituted at the α-position, wherein R^2 may optionally be further substituted;

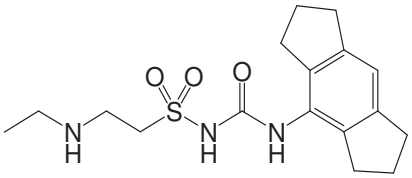
provided that the atom of L which is attached to the sulfur atom of the sulfonylurea group is a carbon atom and is not a ring atom of a heterocyclic or aromatic group.

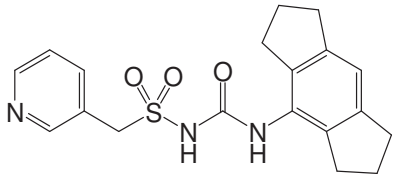
In another aspect, the present disclosure refers to a compound selected from the group consisting of:

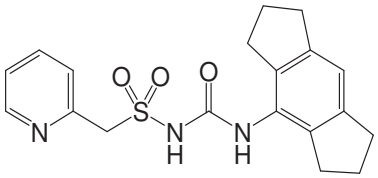


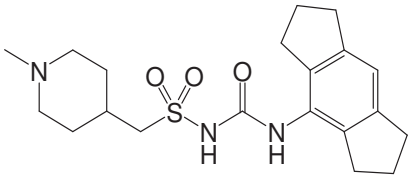


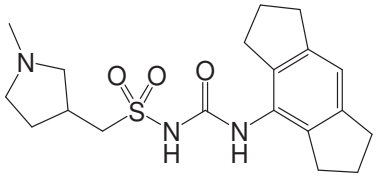


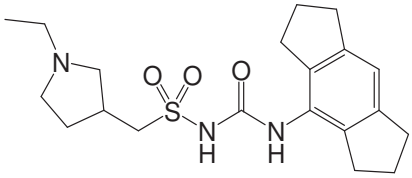


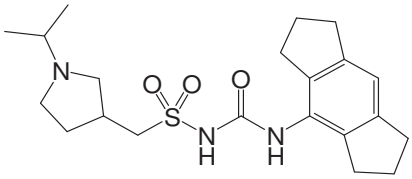


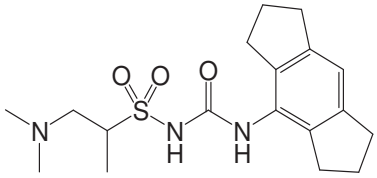


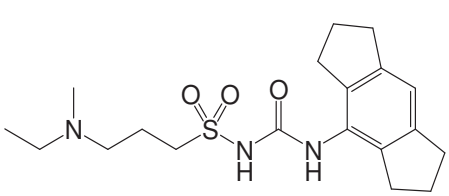


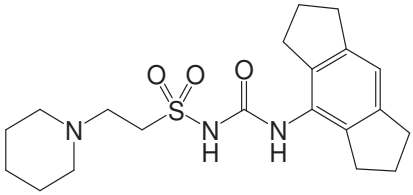


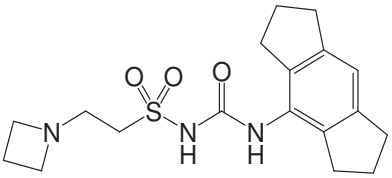


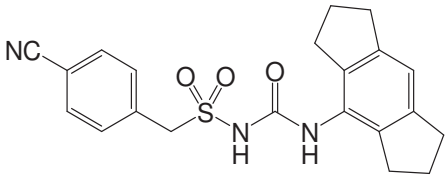


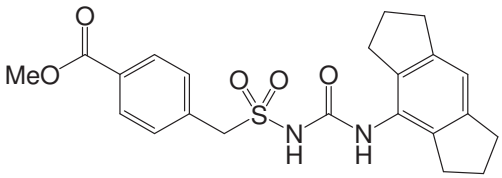


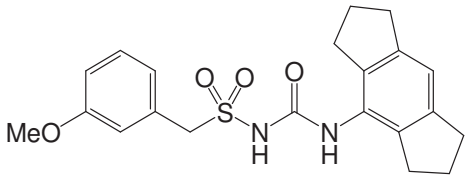


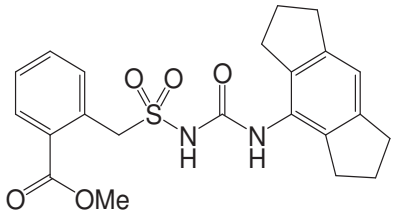


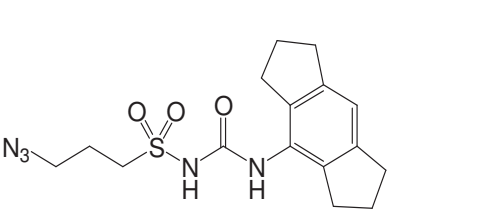


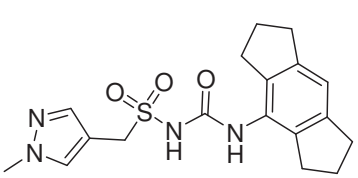


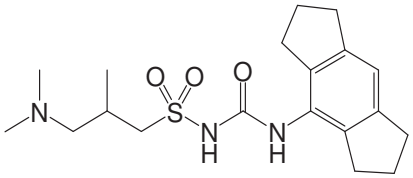


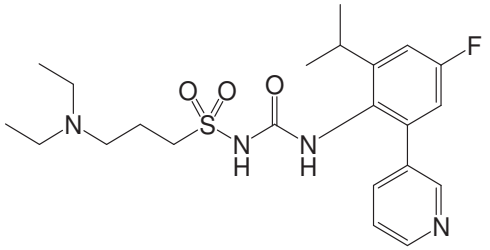


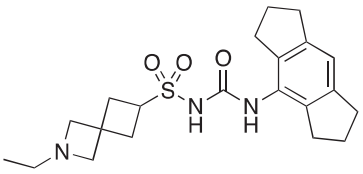


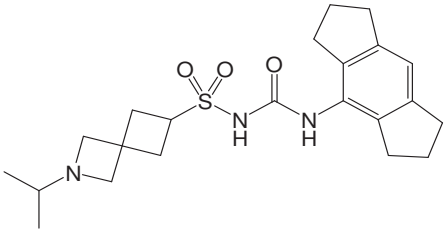


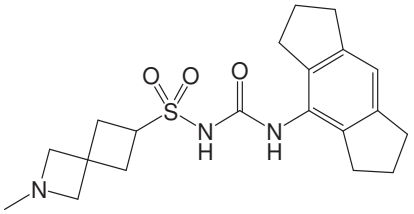


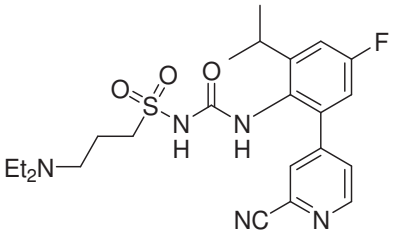


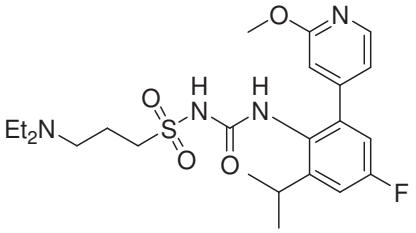




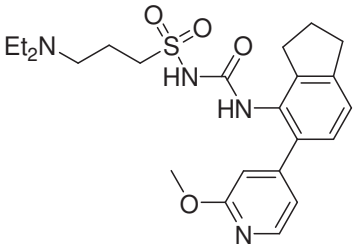


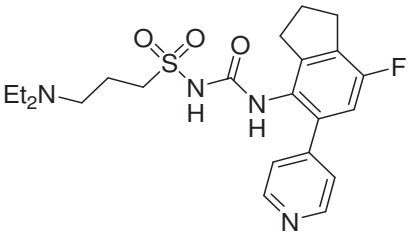


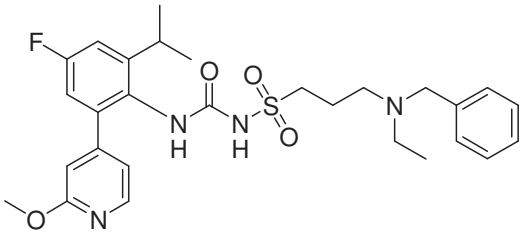


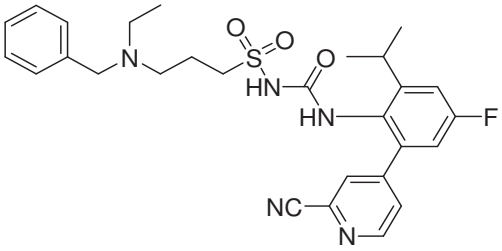


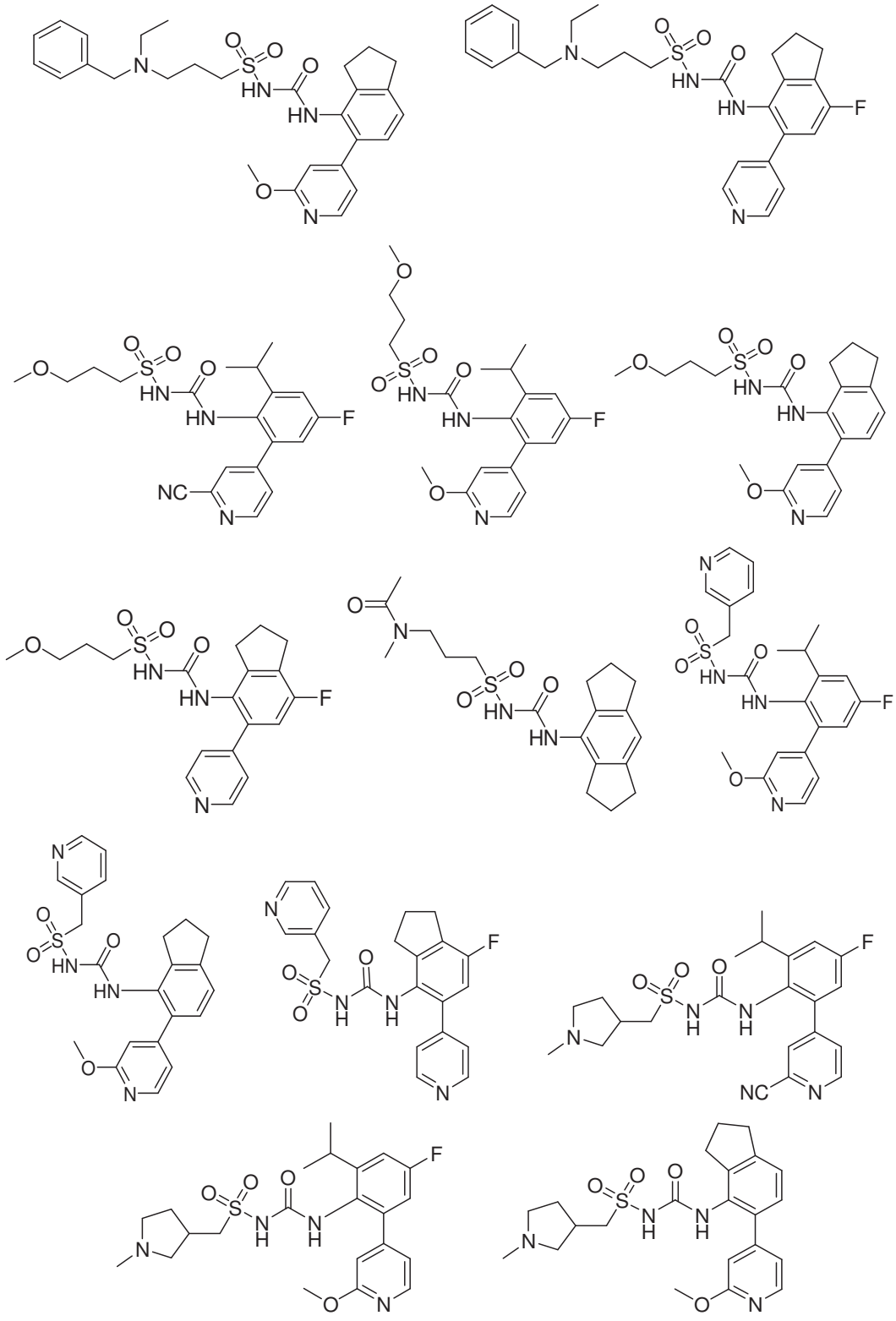
5



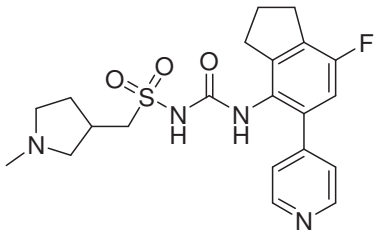


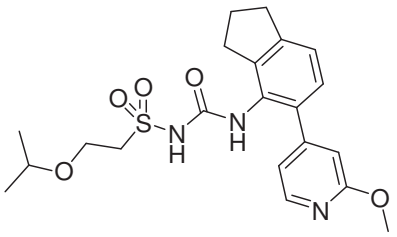


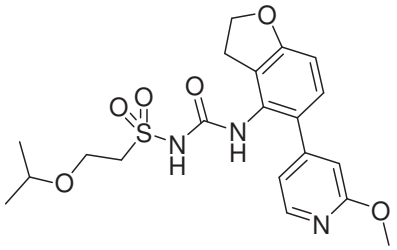


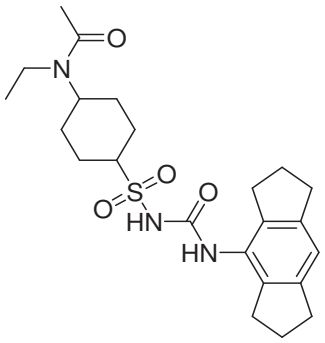


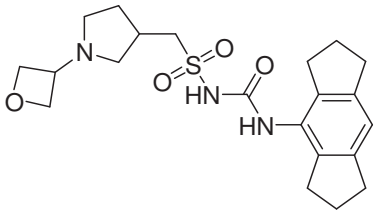
5

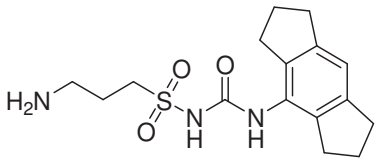


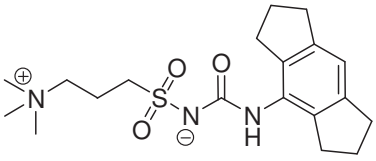


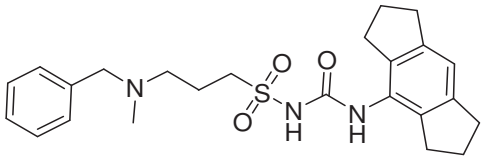


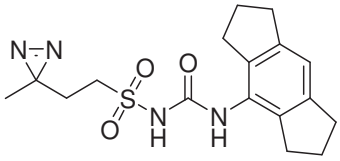


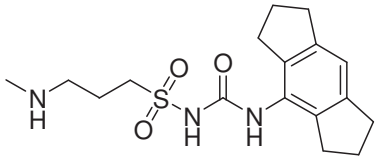




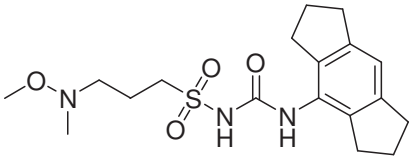


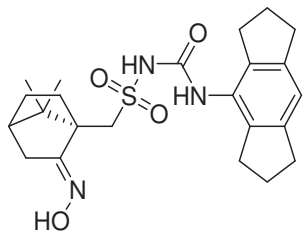


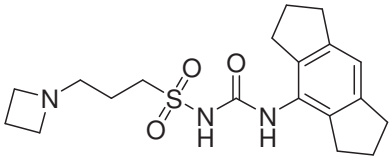


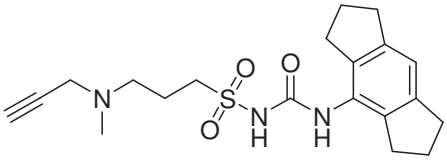


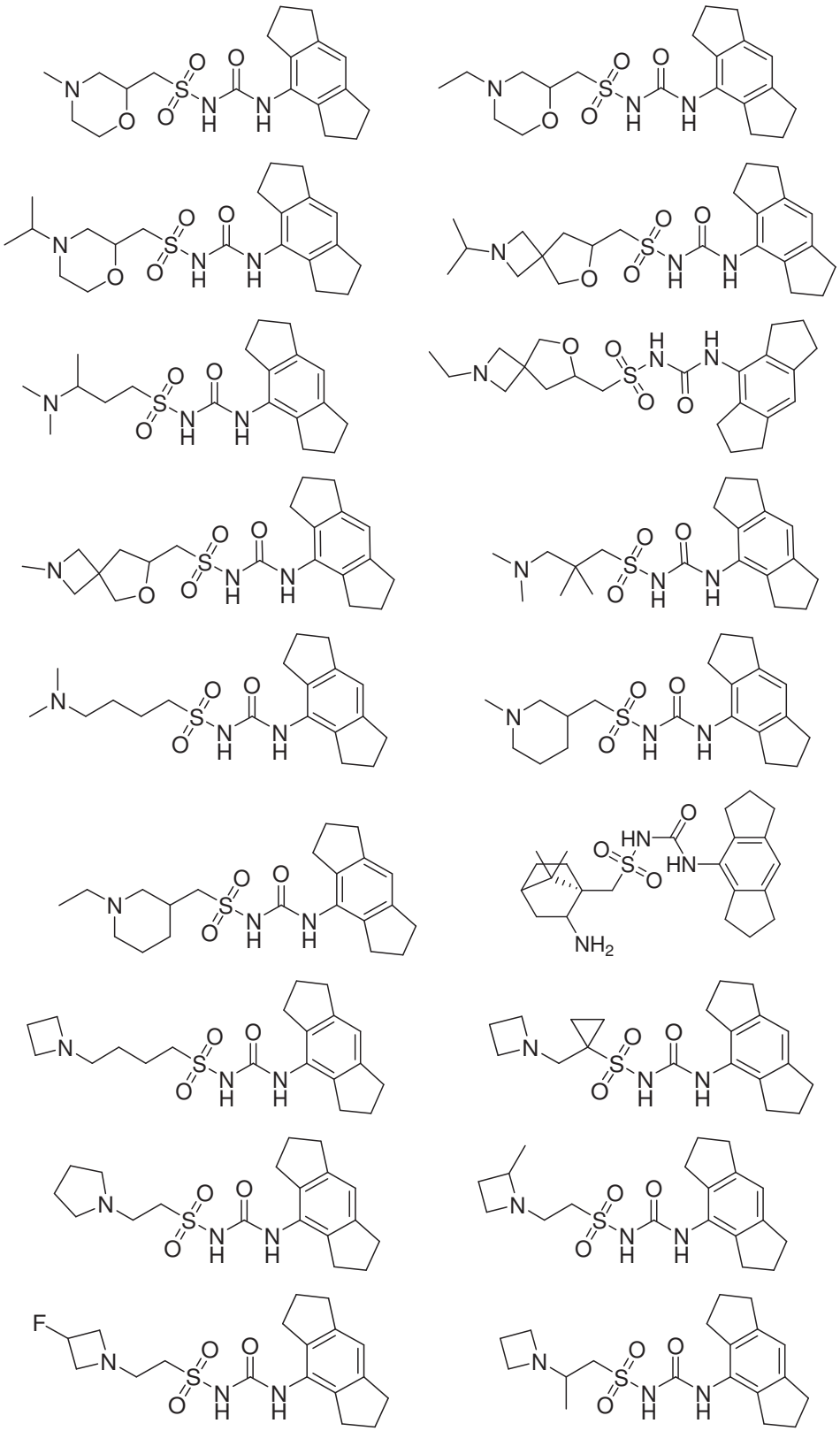
5

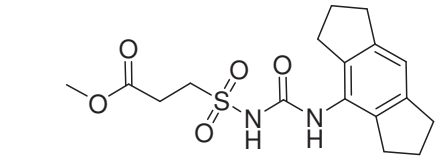


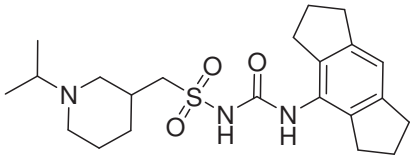


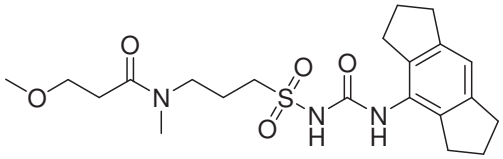


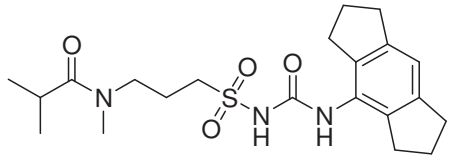


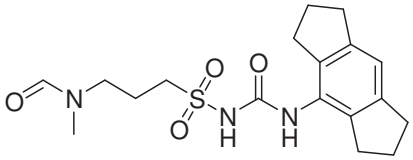


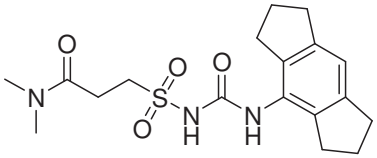


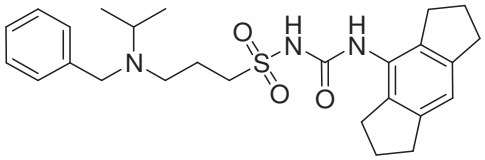


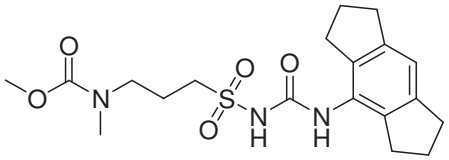


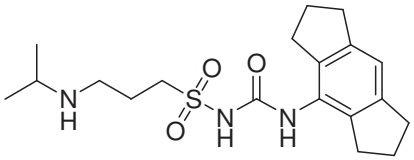


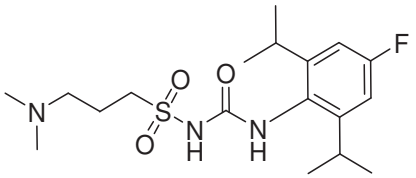




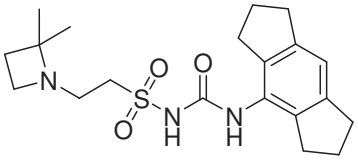


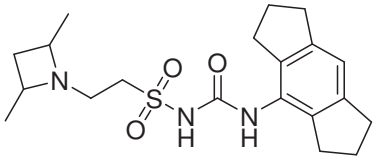


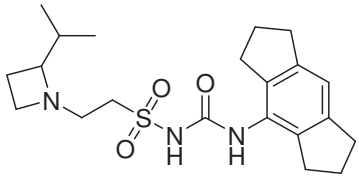


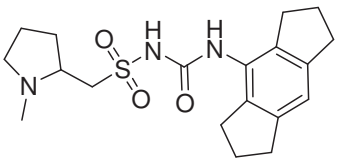


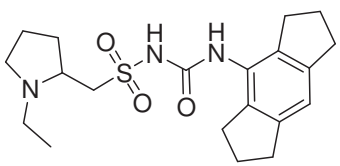
5

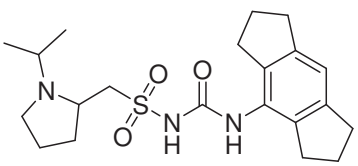


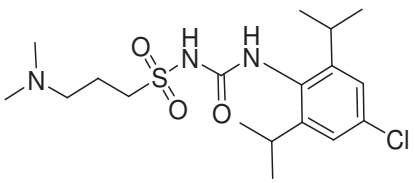


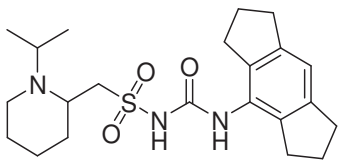


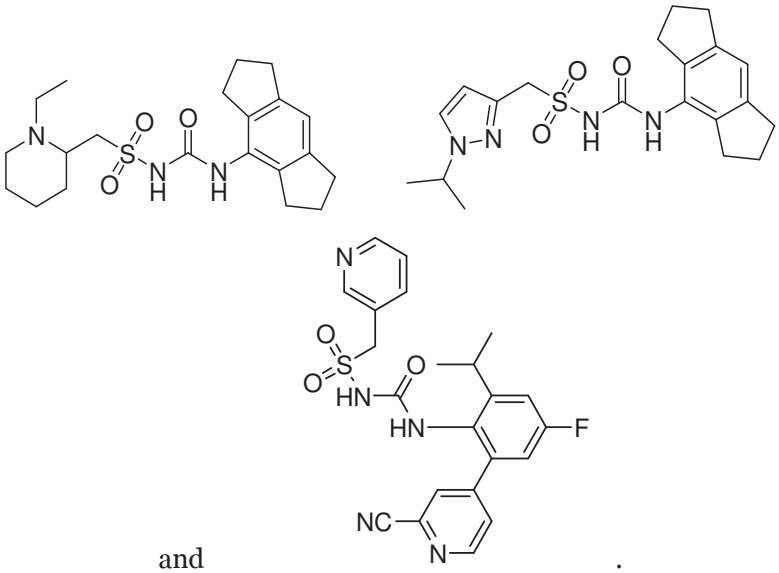












and .

In yet another aspect, the present disclosure refers to a pharmaceutically acceptable salt, solvate or prodrug of a compound as disclosed herein. In a further aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate or prodrug as disclosed herein, and a pharmaceutically acceptable excipient. In still another aspect, the present disclosure refers to a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate or prodrug as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in medicine. In another aspect, the present disclosure refers to a compound, pharmaceutically acceptable salt, solvate, prodrug or pharmaceutical composition as disclosed herein, for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

In a further aspect, the present disclosure refers to a compound, pharmaceutically acceptable salt, solvate, prodrug or pharmaceutical composition as disclosed herein, for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is selected from:

(i) inflammation;

(ii) an auto-immune disease;

(iii) cancer;

(iv) an infection;

(v) a central nervous system disease;

(vi) a metabolic disease;
(vii) a cardiovascular disease;
(viii) a respiratory disease;
(ix) a liver disease;
(x) a renal disease;
(xi) an ocular disease;
(xii) a skin disease;
(xiii) a lymphatic condition;
(xiv) a psychological disorder;
(xv) graft versus host disease; and
(xvi) allodynia; and
(xvii) any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

In a further aspect, the present disclosure refers to a compound, pharmaceutically acceptable salt, solvate, prodrug or pharmaceutical composition as disclosed herein, for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is selected from:

(i) cryopyrin-associated periodic syndromes (CAPS);
(ii) Muckle-Wells syndrome (MWS);
(iii) familial cold autoinflammatory syndrome (FCAS);
(iv) neonatal onset multisystem inflammatory disease (NOMID);
(v) familial Mediterranean fever (FMF);
(vi) pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA);
(vii) hyperimmunoglobulinemia D and periodic fever syndrome (HIDS);
(viii) Tumour Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS);
(ix) systemic juvenile idiopathic arthritis;
(x) adult-onset Still's disease (AOSD);
(xi) relapsing polychondritis;
(xii) Schnitzler's syndrome;
(xiii) Sweet's syndrome;
(xiv) Behcet's disease;
(xv) anti-synthetase syndrome;
(xvi) deficiency of interleukin 1 receptor antagonist (DIRA); and
(xvii) haploinsufficiency of A20 (HA20).

In yet another aspect, the present disclosure refers to a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate or prodrug as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in inhibiting NLRP3.

In still another aspect, the present disclosure refers to the use of a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate or prodrug disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating or preventing a disease, disorder or condition selected from:

(i) inflammation;
(ii) an auto-immune disease;
(iii) cancer;
(iv) an infection;
(v) a central nervous system disease;
(vi) a metabolic disease;
(vii) a cardiovascular disease;
(viii) a respiratory disease;
(ix) a liver disease;
(x) a renal disease;
(xi) an ocular disease;
(xii) a skin disease;
(xiii) a lymphatic condition;
(xiv) a psychological disorder;
(xv) graft versus host disease;
(xvi) allodynia; and
(xvii) any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

In another aspect, the present disclosure refers to the use of a compound as disclosed herein, or a pharmaceutically acceptable salt, solvate or prodrug as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating or preventing a disease, disorder or condition selected from:

(i) cryopyrin-associated periodic syndromes (CAPS);
(ii) Muckle-Wells syndrome (MWS);
(iii) familial cold autoinflammatory syndrome (FCAS);
(iv) neonatal onset multisystem inflammatory disease (NOMID);

(v) familial Mediterranean fever (FMF);

(vi) pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA);

(vii) hyperimmunoglobulinemia D and periodic fever syndrome (HIDS);

(viii) Tumour Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS);

(ix) systemic juvenile idiopathic arthritis;

(x) adult-onset Still's disease (AOSD);

(xi) relapsing polychondritis;

(xii) Schnitzler's syndrome;

(xiii) Sweet's syndrome;

(xiv) Behcet's disease;

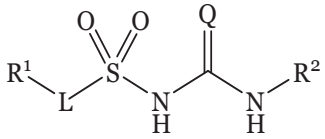
(xv) anti-synthetase syndrome;

(xvi) deficiency of interleukin 1 receptor antagonist (DIRA); and

(xvii) haploinsufficiency of A20 (HA20).

Detailed description

A first aspect of the invention provides a compound of formula (I):



Formula (I)

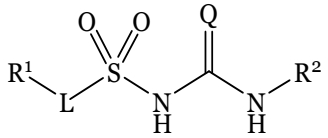
wherein:

Q is selected from O or S;

L is a saturated or unsaturated C_1-C_{12} hydrocarbylene group, wherein the

Claims

1. A compound of formula (I):



Formula (I)

wherein:

Q is selected from O or S;

L is a saturated or unsaturated C_1-C_{12} hydrocarbylene group, wherein the hydrocarbylene group may be straight-chained or branched, or be or include cyclic groups, wherein the hydrocarbylene group may optionally be substituted, and wherein the hydrocarbylene group may optionally include one or more heteroatoms N, O or S in its carbon skeleton;

R^1 is $-NR^3R^4$, $-OR^5$, $-(C=NR^6)R^7$, $-(CO)R^8$, $-CN$, $-N_3$, a quaternary ammonium group or an optionally substituted heterocycle;

R^3, R^4, R^5, R^6, R^7 and R^8 are each independently hydrogen or a saturated or unsaturated C_1-C_{10} hydrocarbyl group, wherein the hydrocarbyl group may be straight-chained or branched, or be or include cyclic groups, wherein the hydrocarbyl group may optionally be substituted, and wherein the hydrocarbyl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton;

wherein optionally L and R^3, or L and R^4, or R^3 and R^4 together with the nitrogen atom to which they are attached may form a 3- to 12-membered saturated or unsaturated cyclic group, wherein the cyclic group may optionally be substituted;

wherein optionally L and R^5 together with the oxygen atom to which they are attached may form a 3- to 12-membered saturated or unsaturated cyclic group, wherein the cyclic group may optionally be substituted;

wherein optionally L and R^6, or L and R^7, or R^6 and R^7 together with the -(C=N)– group to which they are attached may form a 3- to 12-membered saturated or unsaturated cyclic group, wherein the cyclic group may optionally be substituted;

wherein optionally L and R^8 together with the –(C=O)– group to which they are attached may form a 3- to 12-membered saturated or unsaturated cyclic group, wherein the cyclic group may optionally be substituted;

R^2 is a cyclic group substituted at the α-position, wherein R^2 may optionally be further substituted;

provided that the atom of L which is attached to the sulfur atom of the sulfonylurea group is a carbon atom and is not a ring atom of a heterocyclic or aromatic group.

2. A compound as claimed in claim 1, wherein L is a saturated or unsaturated C_1-C_8 hydrocarbylene group, wherein the hydrocarbylene group may be straight-chained or branched, or be or include cyclic groups, and wherein the hydrocarbylene group may optionally be substituted with one or more substituents independently selected from halo, -CN, -$N(R^9)_2$, -OR^9 or oxo (=O) groups, wherein R^9 is independently selected from a hydrogen atom or a C_1-C_3 alkyl group.

3. A compound as claimed in claim 1 or 2, wherein the atom of L which is attached to the sulfur atom of the sulfonylurea group is a carbon atom and is not a ring atom of any cyclic group.

4. A compound as claimed in any one of claims 1 to 3, wherein R^1 is –NR^3R^4, and R^3 and R^4 are each independently hydrogen or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 cycloalkyl, phenyl or benzyl group, each of which may optionally be substituted with one or more substituents independently selected from halo, -CN, -$N(R^9)_2$, -OR^9 or oxo (=O) groups, wherein R^9 is independently selected from a hydrogen atom or a C_1-C_3 alkyl group.

5. A compound as claimed in any one of claims 1 to 3, wherein R^1 is –OR^5, and R^5 is hydrogen or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 cycloalkyl, phenyl or benzyl group, each of which may optionally be substituted with one or more substituents independently selected from halo, -CN, -$N(R^9)_2$, -OR^9 or oxo (=O) groups, wherein R^9 is independently selected from a hydrogen atom or a C_1-C_3 alkyl group.

6. A compound as claimed in any one of claims 1 to 3, wherein R^1 is –$(C{=}NR^6)R^7$, and R^6 and R^7 are each independently hydrogen or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 cycloalkyl, phenyl or benzyl group, each of which may optionally be substituted with one or more substituents independently selected from halo, -CN, -$N(R^9)_2$, -OR^9 or oxo (=O) groups, wherein R^9 is independently selected from a hydrogen atom or a C_1-C_3 alkyl group.

7. A compound as claimed in any one of claims 1 to 3, wherein R^1 is –$(CO)R^8$, and

R^8 is hydrogen or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 cycloalkyl, phenyl or benzyl group, each of which may optionally be substituted with one or more substituents independently selected from halo, -CN, -$N(R^9)_2$, -OR^9 or oxo (=O) groups, wherein R^9 is independently selected from a hydrogen atom or a C_1-C_3 alkyl group.

8. A compound as claimed in any one of claims 1 to 3, wherein R^1 is –(CO)R^8 and, L and R^8 together with the –(C=O)– group to which they are attached form a 4-, 5- or 6-membered saturated cyclic group, wherein the cyclic group may optionally include one further heteroatom N, O or S in its carbon skeleton, and wherein the cyclic group may optionally be substituted with one or more substituents independently selected from halo, -CN, -$N(R^9)_2$, -OR^9, C_1-C_3 alkyl, C_1-C_3 alkylene or oxo (=O) groups, wherein R^9 is independently selected from a hydrogen atom or a C_1-C_3 alkyl group.

9. A compound as claimed in any one of claims 1 to 8, wherein R^2 is an aryl or a heteroaryl group, wherein the aryl or the heteroaryl group is substituted at the α-position, and wherein R^2 may optionally be further substituted.

10. A compound as claimed in claim 9, wherein R^2 is an aryl or a heteroaryl group, wherein the aryl or the heteroaryl group is substituted at the α and α' positions, and wherein R^2 may optionally be further substituted.

11. A compound as claimed in claim 10, wherein R^2 is a fused aryl or a fused heteroaryl group, wherein a first cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring is fused to the aryl or heteroaryl group across the α,β positions and a second cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring is fused to the aryl or heteroaryl group across the α',β' positions, and wherein R^2 may optionally be further substituted.

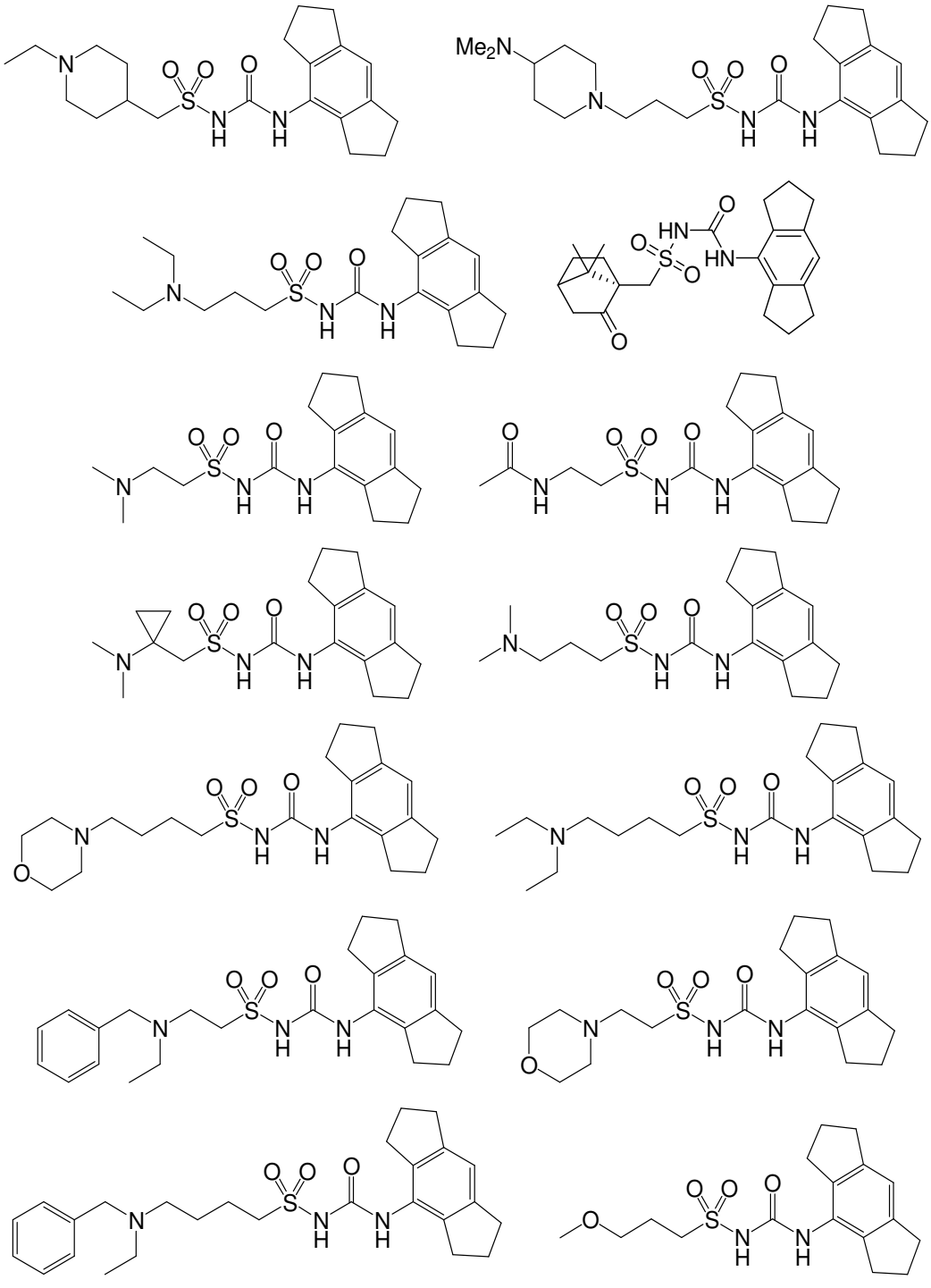
12. A compound as claimed in any one of claims 1 to 8, wherein R^2 is a cyclic group substituted at the α-position with a monovalent heterocyclic group or a monovalent aromatic group, wherein a ring atom of the heterocyclic or aromatic group is directly attached to the α-ring atom of the cyclic group, wherein the heterocyclic or aromatic group may optionally be substituted, and wherein the cyclic group may optionally be further substituted.

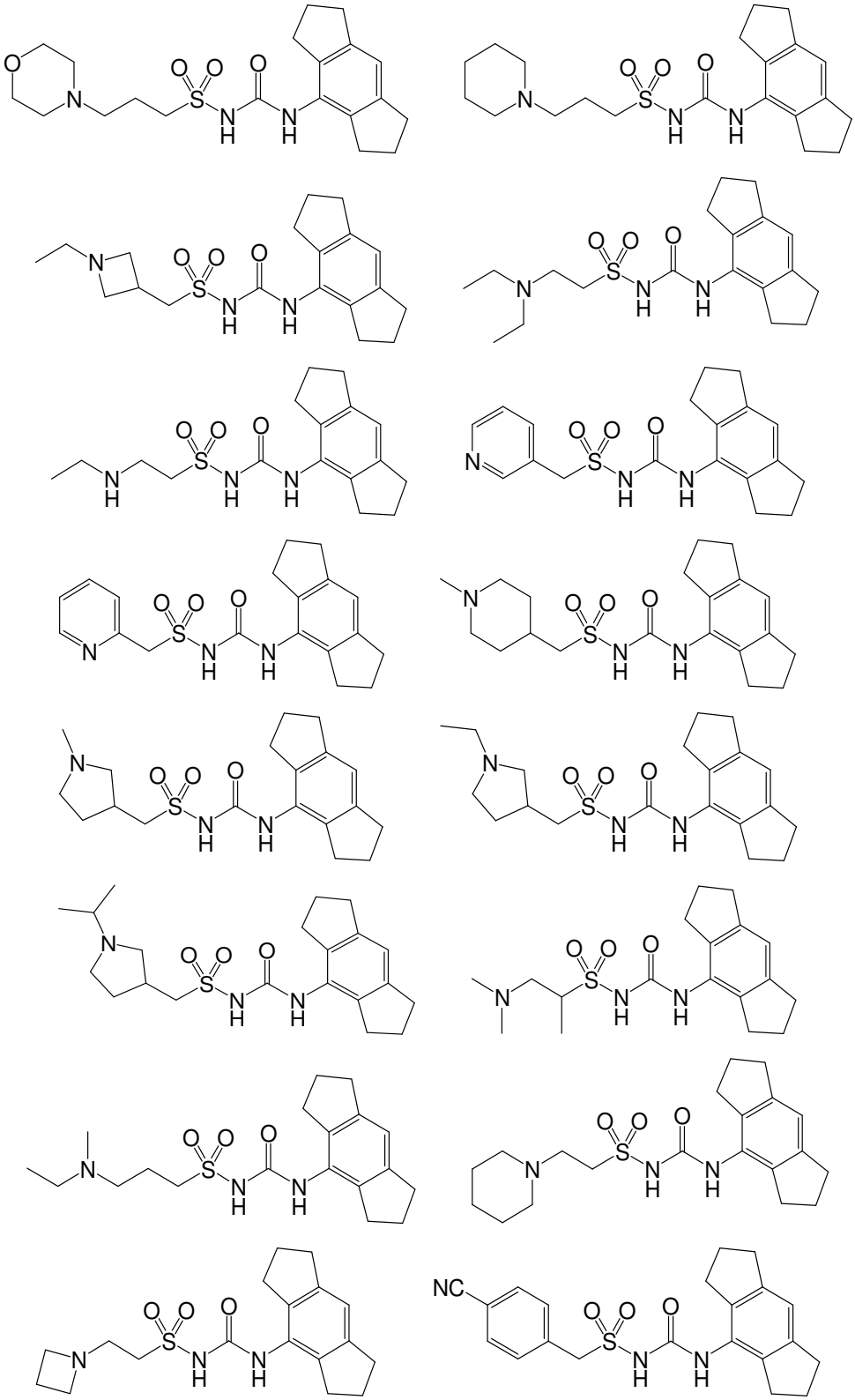
13. A compound as claimed in any one of claims 1 to 8, wherein R^2 is a cyclic group

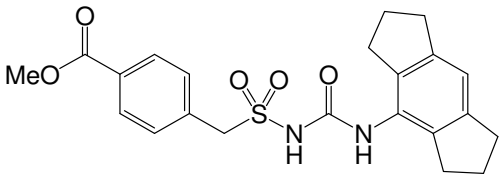
substituted at the α and α' positions, wherein R^2 may optionally be further substituted.

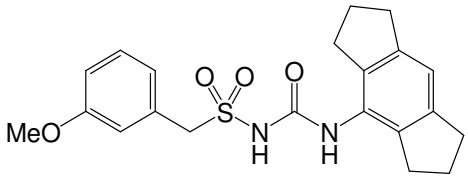
14. A compound as claimed in any one of claims 1 to 13, wherein Q is O.

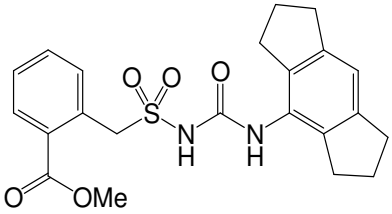
15. A compound selected from the group consisting of:

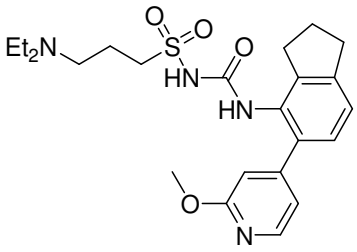


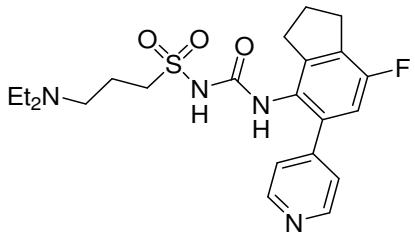


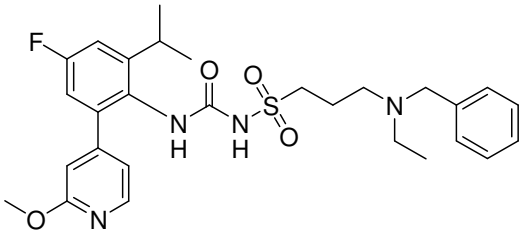


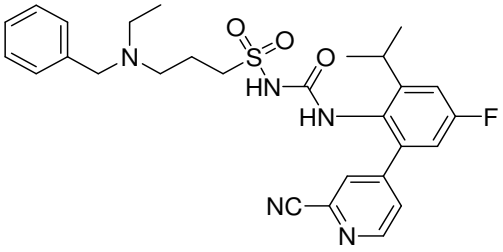


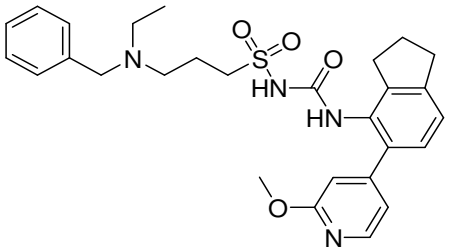


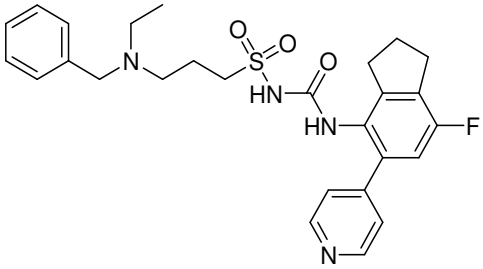


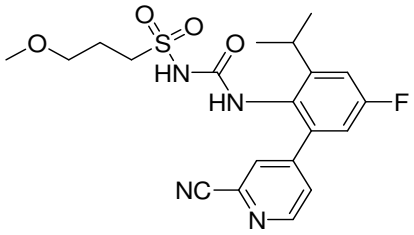


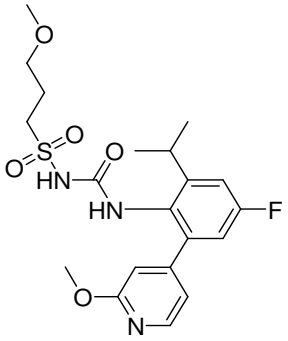


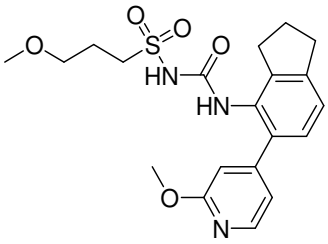


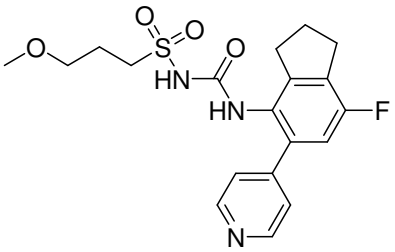


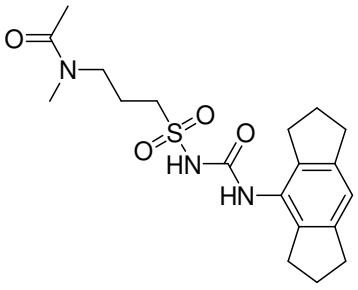


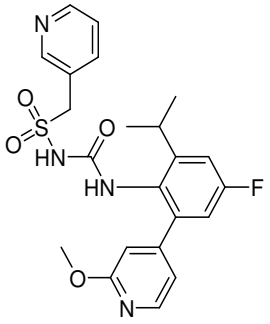




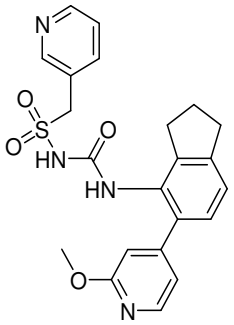


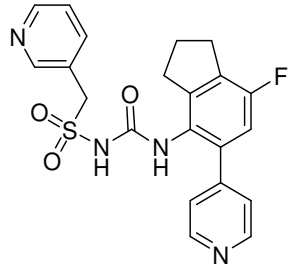


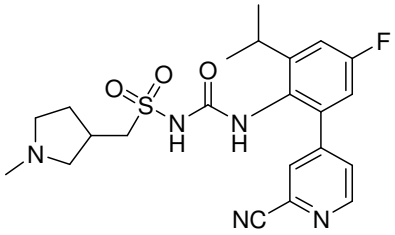


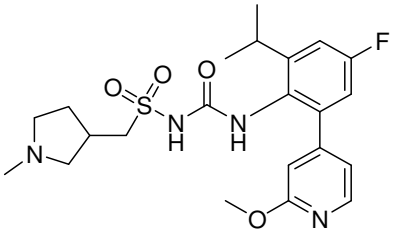


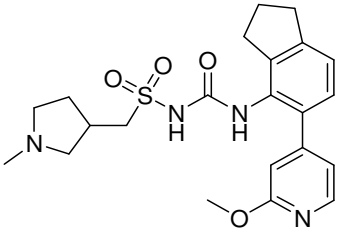
5

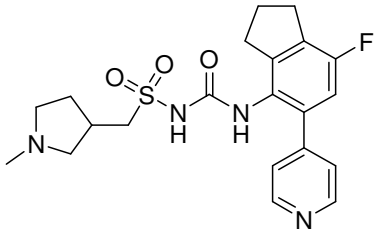


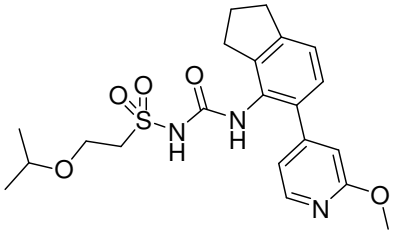


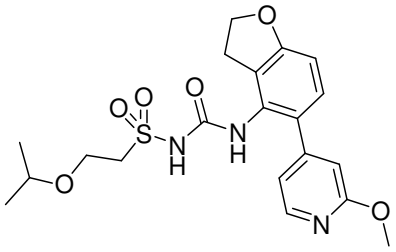


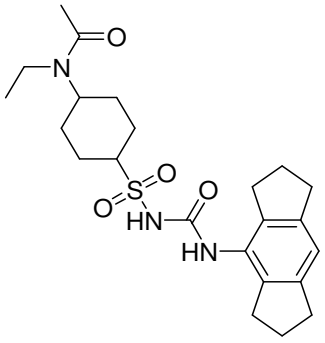


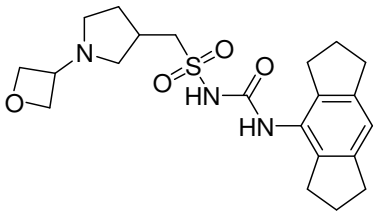


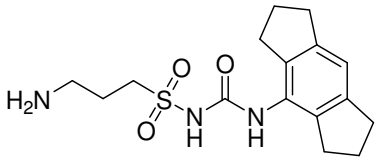




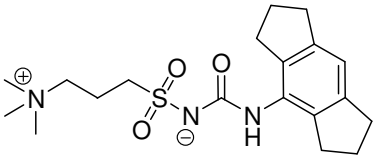


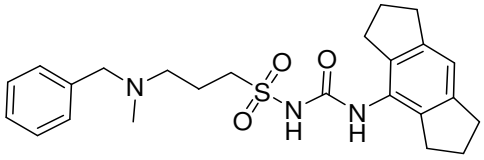


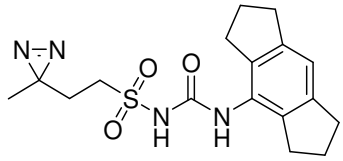


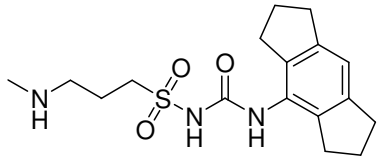


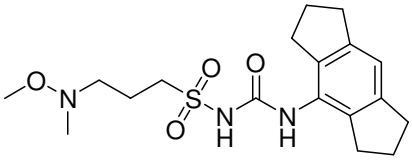
5

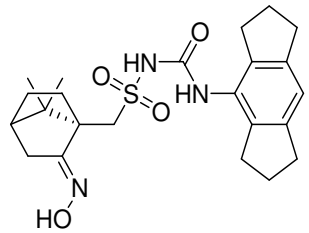


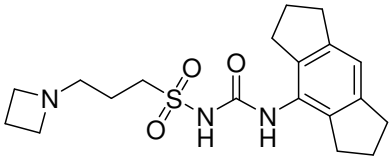


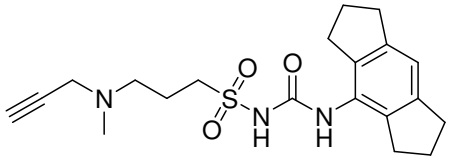


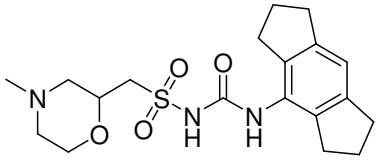


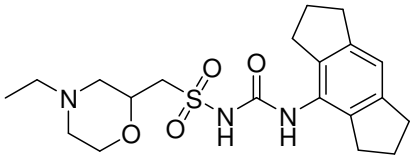


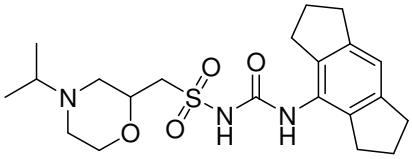


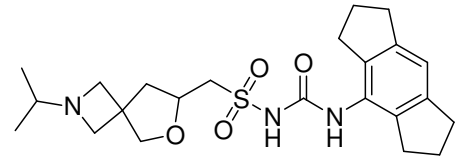


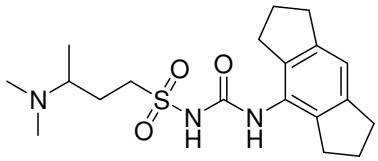


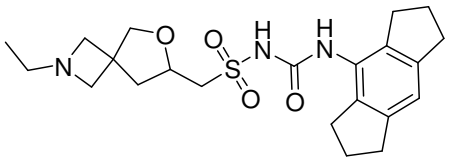


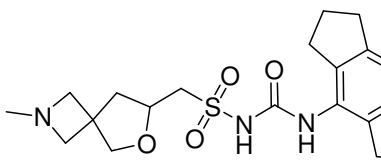


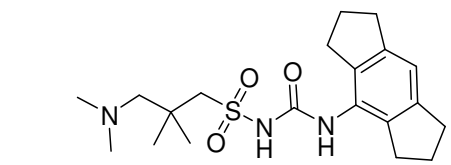


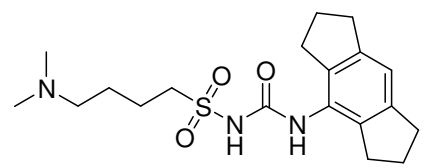


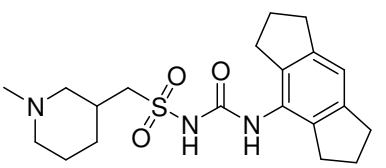


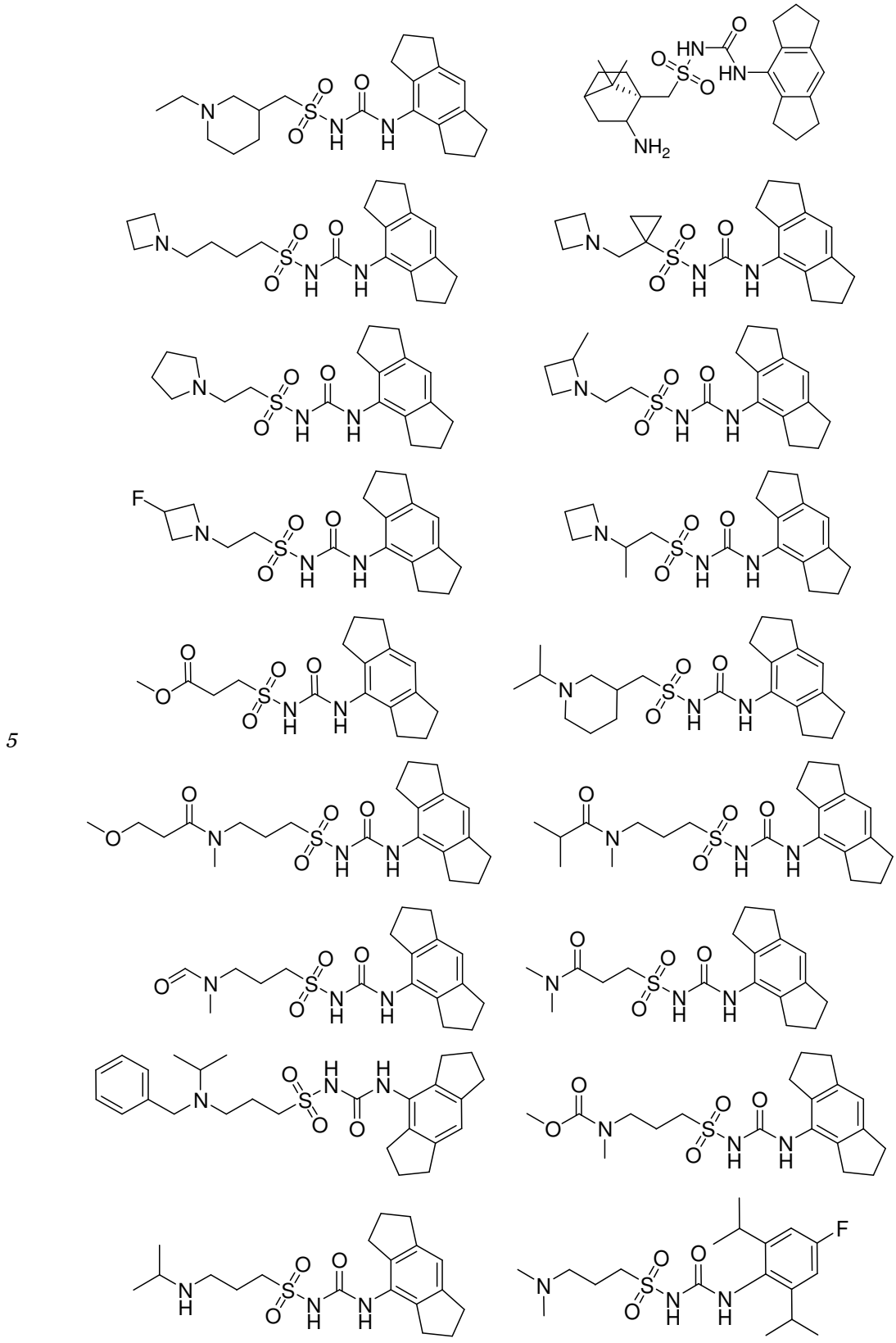


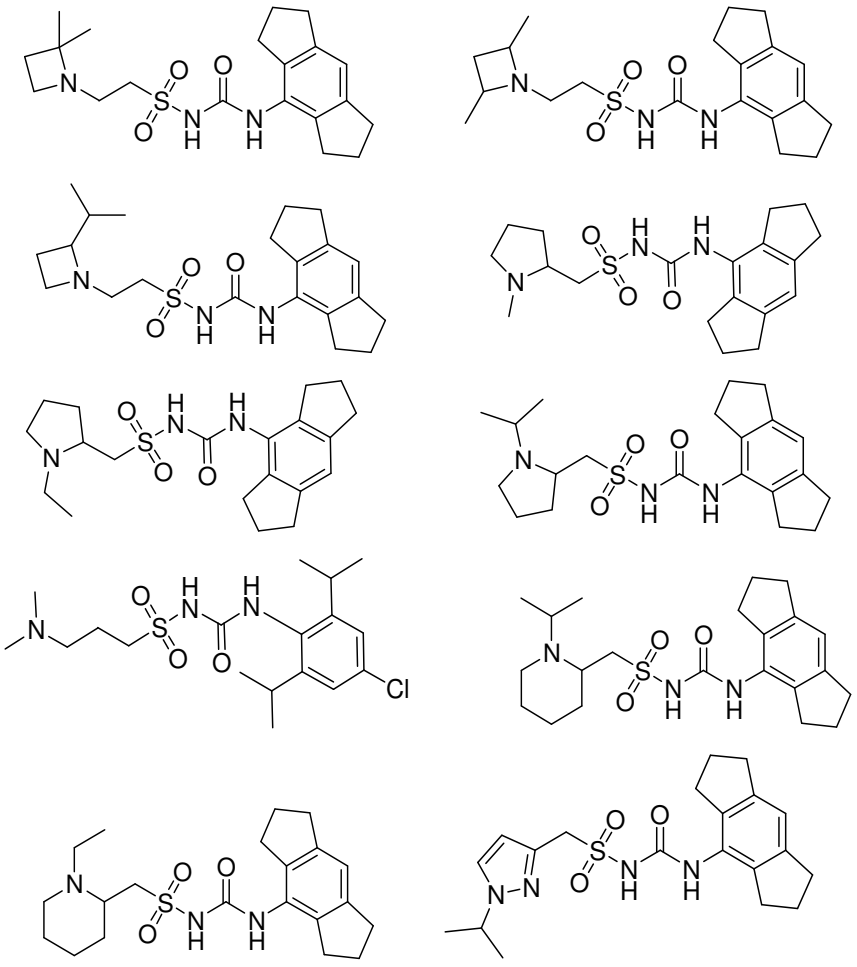


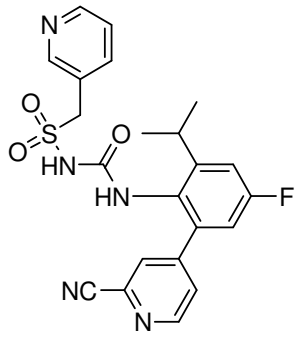










and  .

16. A pharmaceutically acceptable salt, solvate or prodrug of a compound as claimed in any one of claims 1 to 15.

17. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 15, or a pharmaceutically acceptable salt, solvate or prodrug as claimed in claim 16, and a pharmaceutically acceptable excipient.

18. A compound as claimed in any one of claims 1 to 15, or a pharmaceutically acceptable salt, solvate or prodrug as claimed in claim 16, or a pharmaceutical composition as claimed in claim 17, for use in medicine.

19. A compound, pharmaceutically acceptable salt, solvate, prodrug or pharmaceutical composition as claimed in claim 18, for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

20. A compound, pharmaceutically acceptable salt, solvate, prodrug or pharmaceutical composition as claimed in claim 18 or 19, for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is selected from:

(i) inflammation;
(ii) an auto-immune disease;
(iii) cancer;
(iv) an infection;
(v) a central nervous system disease;
(vi) a metabolic disease;
(vii) a cardiovascular disease;
(viii) a respiratory disease;
(ix) a liver disease;
(x) a renal disease;
(xi) an ocular disease;
(xii) a skin disease;
(xiii) a lymphatic condition;
(xiv) a psychological disorder;
(xv) graft versus host disease; and
(xvi) allodynia; and
(xvii) any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

21. A compound, pharmaceutically acceptable salt, solvate, prodrug or pharmaceutical composition as claimed in claim 18 or 19, for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or

condition is selected from:

(i) cryopyrin-associated periodic syndromes (CAPS);
(ii) Muckle-Wells syndrome (MWS);
(iii) familial cold autoinflammatory syndrome (FCAS);
(iv) neonatal onset multisystem inflammatory disease (NOMID);
(v) familial Mediterranean fever (FMF);
(vi) pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA);
(vii) hyperimmunoglobulinemia D and periodic fever syndrome (HIDS);
(viii) Tumour Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS);
(ix) systemic juvenile idiopathic arthritis;
(x) adult-onset Still's disease (AOSD);
(xi) relapsing polychondritis;
(xii) Schnitzler's syndrome;
(xiii) Sweet's syndrome;
(xiv) Behcet's disease;
(xv) anti-synthetase syndrome;
(xvi) deficiency of interleukin 1 receptor antagonist (DIRA); and
(xvii) haploinsufficiency of A20 (HA20).

22. A compound as claimed in any one of claims 1 to 15, or a pharmaceutically acceptable salt, solvate or prodrug as claimed in claim 16, or a pharmaceutical composition as claimed in claim 17, for use in inhibiting NLRP3.

23. Use of a compound as claimed in any one of claims 1 to 15, or a pharmaceutically acceptable salt, solvate or prodrug as claimed in claim 16, or a pharmaceutical composition as claimed in claim 17, in the manufacture of a medicament for treating or preventing a disease, disorder or condition selected from:

(i) inflammation;
(ii) an auto-immune disease;
(iii) cancer;
(iv) an infection;
(v) a central nervous system disease;
(vi) a metabolic disease;
(vii) a cardiovascular disease;
(viii) a respiratory disease;

(ix) a liver disease;
(x) a renal disease;
(xi) an ocular disease;
(xii) a skin disease;
(xiii) a lymphatic condition;
(xiv) a psychological disorder;
(xv) graft versus host disease;
(xvi) allodynia; and
(xvii) any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

24. Use of a compound as claimed in any one of claims 1 to 15, or a pharmaceutically acceptable salt, solvate or prodrug as claimed in claim 16, or a pharmaceutical composition as claimed in claim 17, in the manufacture of a medicament for treating or preventing a disease, disorder or condition selected from:

(i) cryopyrin-associated periodic syndromes (CAPS);
(ii) Muckle-Wells syndrome (MWS);
(iii) familial cold autoinflammatory syndrome (FCAS);
(iv) neonatal onset multisystem inflammatory disease (NOMID);
(v) familial Mediterranean fever (FMF);
(vi) pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA);
(vii) hyperimmunoglobulinemia D and periodic fever syndrome (HIDS);
(viii) Tumour Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS);
(ix) systemic juvenile idiopathic arthritis;
(x) adult-onset Still's disease (AOSD);
(xi) relapsing polychondritis;
(xii) Schnitzler's syndrome;
(xiii) Sweet's syndrome;
(xiv) Behcet's disease;
(xv) anti-synthetase syndrome;
(xvi) deficiency of interleukin 1 receptor antagonist (DIRA); and
(xvii) haploinsufficiency of A20 (HA20).