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.

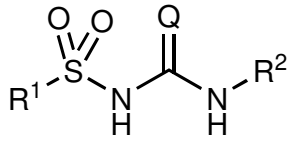
Some diarylsulfonylurea-containing compounds have been identified as cytokine release inhibitory drugs (CRIDs) (Perregaux *et al.*; J. Pharmacol. Exp. Ther. 299, 187-197, 2001). CRIDs are a class of diarylsulfonylurea-containing compounds that inhibit the post-translational processing of IL-1β. Post-translational 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 and WO 2018/015445 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

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



Formula (I)

wherein:

Q is selected from O or S;

R^1 is a non-aromatic heterocyclic group comprising at least one ring nitrogen atom, wherein R^1 is attached to the sulfur atom of the sulfonylurea group by a ring carbon atom, wherein R^1 may optionally be substituted, and wherein when R^1 is a partially aromatic bicyclic, tricyclic or polycyclic group, the ring of R^1 that is directly attached to the sulfur atom of the sulfonylurea group is non-aromatic; and

R^2 is an aryl group substituted at the α and α' positions, wherein R^2 may optionally be further substituted. An example of the disclosure provides a compound of formula (I):

disclosure may be provided as a part of a kit of parts, wherein the kit of parts comprises the pharmaceutical composition of the fourth aspect of the disclosure and one or more further pharmaceutical compositions, wherein the one or more further pharmaceutical compositions each comprise a pharmaceutically acceptable excipient and one or more further active agents.

A fifth aspect of the disclosure provides a compound of the first or second aspect of the disclosure, or a pharmaceutically acceptable salt or solvate of the third aspect of the disclosure, or a pharmaceutical composition of the fourth aspect of the disclosure, for use in medicine. An example of the disclosure provides a compound of the first or second aspect of the disclosure, or a pharmaceutically acceptable salt, solvate or prodrug of the third aspect of the disclosure, or a pharmaceutical composition of the fourth aspect of the disclosure, for use in medicine, and/or for use in the treatment or prevention of a disease, disorder or condition. Typically, the use comprises the administration of the compound, salt, solvate, prodrug or pharmaceutical composition to a subject. In one example, the use comprises the co-administration of one or more further active agents.

In yet another aspect, the present disclosure provides the use of a compound as described herein, or a pharmaceutically acceptable salt or solvate as described herein, or a pharmaceutical composition as described herein, in the manufacture of a medicament for treating or preventing a disease, disorder or condition responsive to NLRP3 inhibition, 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.

significant ($p \leq 0.05$) avoidance of occurrence, delay in onset or reduction in risk as measured by a controlled clinical trial may be deemed a prevention of the disease, disorder or condition. Subjects amenable to prevention include those at heightened risk of a disease, disorder or condition as identified by genetic or biochemical markers. Typically, the genetic or biochemical markers are appropriate to the disease, disorder or condition under consideration and may include for example, inflammatory biomarkers such as C-reactive protein (CRP) and monocyte chemoattractant protein 1 (MCP-1) in the case of inflammation; total cholesterol, triglycerides, insulin resistance and C-peptide in the case of NAFLD and NASH; and more generally IL1β and IL18 in the case of a disease, disorder or condition responsive to NLRP3 inhibition.

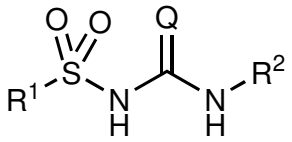
A further example of the disclosure provides the use of a compound of the first or second aspect, or a pharmaceutically effective salt, solvate or prodrug of the third aspect, in the manufacture of a medicament for the treatment or prevention of a disease, disorder or condition. Typically, the treatment or prevention comprises the administration of the compound, salt, solvate, prodrug or medicament to a subject. In one example, the treatment or prevention comprises the co-administration of one or more further active agents.

A further example of the disclosure provides a method of treatment or prevention of a disease, disorder or condition, the method comprising the step of administering an effective amount of a compound of the first or second aspect, or a pharmaceutically acceptable salt, solvate or prodrug of the third aspect, or a pharmaceutical composition of the fourth aspect, to thereby treat or prevent the disease, disorder or condition. In one example, the method further comprises the step of co-administering an effective amount of one or more further active agents. Typically, the administration is to a subject in need thereof.

A further example of the disclosure provides a compound of the first or second aspect of the disclosure, or a pharmaceutically acceptable salt, solvate or prodrug of the third aspect of the disclosure, or a pharmaceutical composition of the fourth aspect of the disclosure, for use in the treatment or prevention of a disease, disorder or condition in an individual, wherein the individual has a germline or somatic non-silent mutation in NLRP3. The

Claims

1. A compound of formula (I):



Formula (I)

wherein:

Q is selected from O or S;

R^1 is a non-aromatic heterocyclic group comprising at least one ring nitrogen atom, wherein R^1 is attached to the sulfur atom of the sulfonylurea group by a ring carbon atom, wherein R^1 may optionally be substituted, and wherein when R^1 is a partially aromatic bicyclic, tricyclic or polycyclic group, the ring of R^1 that is directly attached to the sulfur atom of the sulfonylurea group is non-aromatic; and

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

2. A compound as claimed in claim 1, wherein R^1 is a monocyclic or bicyclic non-aromatic heterocyclic group, wherein R^1 may optionally be substituted.

3. A compound as claimed in claim 2, wherein R^1 is a 4-, 5-, 6- or 7-membered monocyclic non-aromatic heterocyclic group or a 7-, 8-, 9- or 10-membered bicyclic non-aromatic heterocyclic group, wherein R^1 may optionally be substituted.

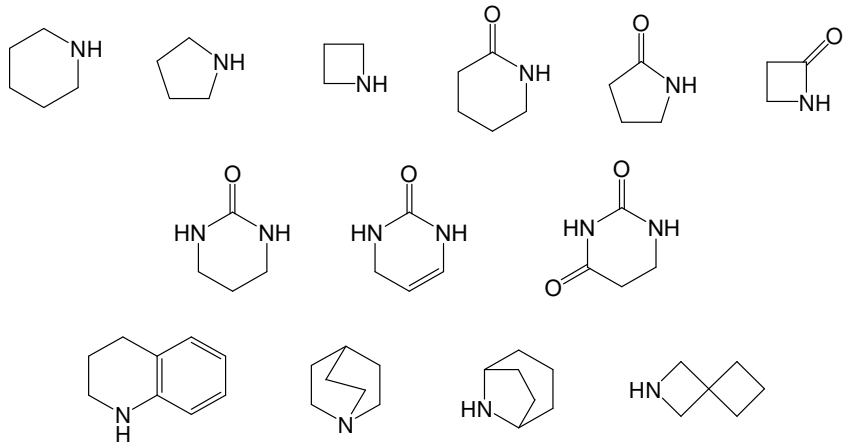
4. A compound as claimed in any one of claims 1 to 3, wherein the non-aromatic heterocyclic group of R^1 is fully saturated.

5. A compound as claimed in any one of claims 1 to 4, wherein R^1 comprises one, two or three ring nitrogen, oxygen or sulfur atoms.

6. A compound as claimed in claim 5, wherein R^1 comprises one or two ring nitrogen or oxygen atoms.

7. A compound as claimed in claim 6, wherein R^1 comprises one or two ring nitrogen atoms.

8. A compound as claimed in any one of claims 1 to 7, wherein R^1 is selected from:



wherein R^1 is attached to the sulfur atom of the sulfonylurea group by a non-aromatic ring carbon atom, and wherein R^1 may optionally be substituted or further substituted.

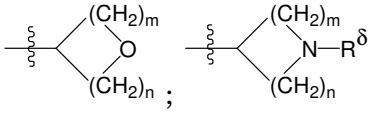
9. A compound as claimed in any one of claims 1 to 8, wherein R^1 is substituted with one or more substituents independently selected from halo; -CN; $-NO_2$; $-N_3$; $-R^\beta$; -OH; $-OR^\beta$; -SH; $-SR^\beta$; $-SOR^\beta$; $-SO_2H$; $-SO_2R^\beta$; $-SO_2NH_2$; $-SO_2NHR^\beta$; $-SO_2N(R^\beta)_2$; $-R^\alpha$-SH; $-R^\alpha$-SR^β; $-R^\alpha$-SOR^β; $-R^\alpha$-SO_2H; $-R^\alpha$-SO_2R^β; $-R^\alpha$-SO_2NH_2; $-R^\alpha$-SO_2NHR^β; $-R^\alpha$-$SO_2N(R^\beta)_2$; $-NH_2$; $-NHR^\beta$; $-N(R^\beta)_2$; $-R^\alpha$-NH_2; $-R^\alpha$-NHR^β; $-R^\alpha$-$N(R^\beta)_2$; -CHO; $-COR^\beta$; -COOH; $-COOR^\beta$; $-OCOR^\beta$; $-R^\alpha$-CHO; $-R^\alpha$-COR^β; $-R^\alpha$-COOH; $-R^\alpha$-$COOR^\beta$; $-R^\alpha$-$OCOR^\beta$; -NH-CHO; $-NR^\beta$-CHO; -NH-COR^β; $-NR^\beta$-COR^β; $-CONH_2$; $-CONHR^\beta$; $-CON(R^\beta)_2$; $-R^\alpha$-NH-CHO; $-R^\alpha$-NR^β-CHO; $-R^\alpha$-NH-COR^β; $-R^\alpha$-NR^β-COR^β; $-R^\alpha$-$CONH_2$; $-R^\alpha$-$CONHR^\beta$; $-R^\alpha$-$CON(R^\beta)_2$; -O-R^α-OH; -O-R^α-OR^β; -O-R^α-NH_2; -O-R^α-NHR^β; -O-R^α-$N(R^\beta)_2$; -NH-R^α-OH; -NH-R^α-OR^β; -NH-R^α-NH_2; -NH-R^α-NHR^β; -NH-R^α-$N(R^\beta)_2$; $-NR^\beta$-R^α-OH; $-NR^\beta$-R^α-OR^β; $-NR^\beta$-R^α-NH_2; $-NR^\beta$-R^α-NHR^β; $-NR^\beta$-R^α-$N(R^\beta)_2$; a C_3-C_7 cycloalkyl group optionally substituted with one or more C_1-C_3 alkyl or C_1-C_3 haloalkyl groups; a C_3-C_7 cycloalkenyl group optionally substituted with one or more C_1-C_3 alkyl or C_1-C_3 haloalkyl groups; a 3- to 7-membered non-aromatic heterocyclic group optionally substituted with one or more C_1-C_6 alkyl or C_1-C_3 haloalkyl groups; oxo (=O); or a C_1-C_4 alkylene bridge;

wherein each $-R^\alpha-$ is independently selected from an alkylene, alkenylene or alkynylene group, wherein the alkylene, alkenylene or alkynylene group contains from 1 to 6 atoms in its backbone, wherein one or more carbon atoms in the backbone of the alkylene, alkenylene or alkynylene group may optionally be replaced by one or more

heteroatoms N, O or S, and wherein the alkylene, alkenylene or alkynylene group may optionally be substituted with one or more halo and/or -R^{β} groups; and

wherein each -R^{β} is independently selected from a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_2-C_6 cyclic group, and wherein any -R^{β} may optionally be substituted with one or more C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_7 cycloalkyl, -O(C_1-C_3 alkyl), halo, -CN, -C≡CH or oxo (=O) groups.

10. A compound as claimed in claim 9, wherein R^1 is substituted on one or more ring nitrogen atoms with a substituent independently selected from halo; -CN; -NO_2; -N_3; -R^{β}; -OH; -OR^{β}; -SH; -SR^{β}; -SOR^{β}; -SO_2H; -SO_2R^{β}; -SO_2NH_2; -SO_2NHR^{β}; -$SO_2N(R^{\beta})_2$; -R^{α}-SH; -R^{α}-SR^{β}; -R^{α}-SOR^{β}; -R^{α}-SO_2H; -R^{α}-SO_2R^{β}; -R^{α}-SO_2NH_2; -R^{α}-SO_2NHR^{β}; -R^{α}-$SO_2N(R^{\beta})_2$; -NH_2; -NHR^{β}; -$N(R^{\beta})_2$; -R^{α}-NH_2; -R^{α}-NHR^{β}; -R^{α}-$N(R^{\beta})_2$; -CHO; -COR^{β}; -COOH; -$COOR^{\beta}$; -$OCOR^{\beta}$; -R^{α}-CHO; -R^{α}-COR^{β}; -R^{α}-COOH; -R^{α}-$COOR^{\beta}$; -R^{α}-$OCOR^{\beta}$; -NH-CHO; -NR^{β}-CHO; -NH-COR^{β}; -NR^{β}-COR^{β}; -$CONH_2$; -$CONHR^{\beta}$; -$CON(R^{\beta})_2$; -R^{α}-NH-CHO; -R^{α}-NR^{β}-CHO; -R^{α}-NH-COR^{β}; -R^{α}-NR^{β}-COR^{β}; -R^{α}-$CONH_2$; -R^{α}-$CONHR^{\beta}$; -R^{α}-$CON(R^{\beta})_2$; a C_3-C_7 cycloalkyl group optionally substituted with one or more C_1-C_3 alkyl or C_1-C_3 haloalkyl groups; a C_3-C_7 cycloalkenyl group optionally substituted with one or more C_1-C_3 alkyl or C_1-C_3 haloalkyl groups;



; ; oxo (=O); or a C_1-C_4 alkylene bridge;

wherein each -R^{α}- is independently selected from an alkylene, alkenylene or alkynylene group, wherein the alkylene, alkenylene or alkynylene group contains from 1 to 6 carbon atoms in its backbone, and wherein the alkylene, alkenylene or alkynylene group may optionally be substituted with one or more halo and/or -R^{β} groups;

wherein each -R^{β} is independently selected from a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_2-C_6 cyclic group, and wherein any -R^{β} may optionally be substituted with one or more C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_7 cycloalkyl, -O(C_1-C_3 alkyl), halo, -CN, -C≡CH or oxo (=O) groups;

wherein each -R^{δ} is independently selected from a C_1-C_6 alkyl or C_1-C_3 haloalkyl group;

wherein each m is independently selected from 1, 2 or 3; and

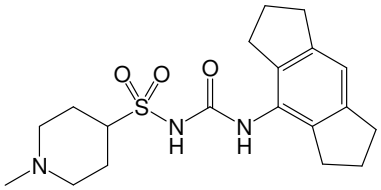
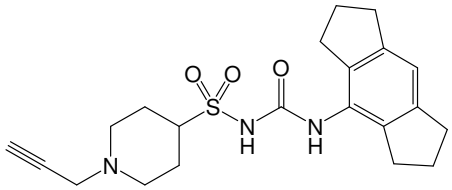
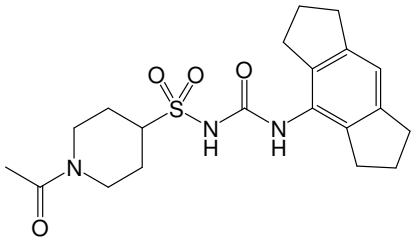
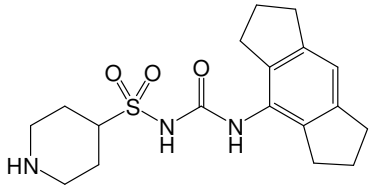
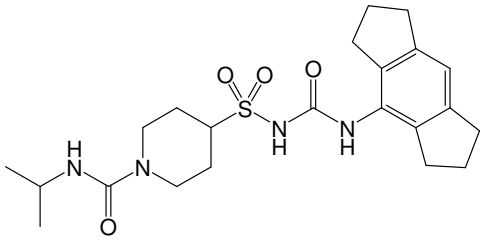
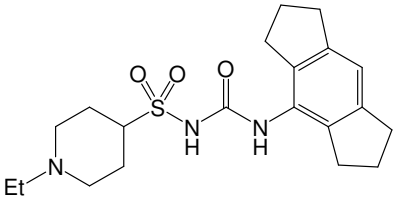
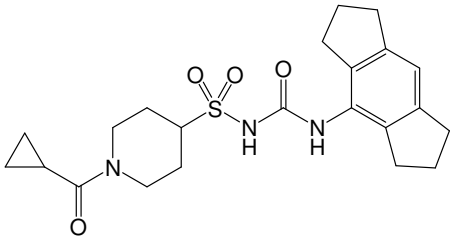
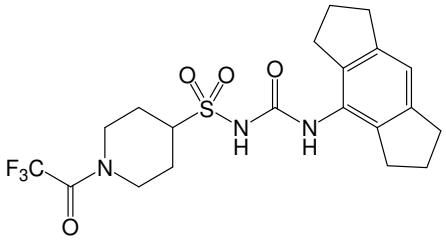
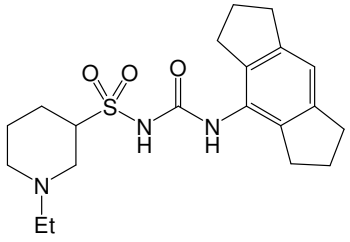
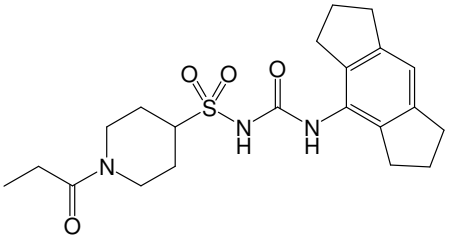
wherein each n is independently selected from 1, 2 or 3.

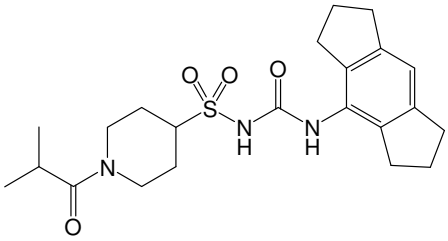
11. A compound as claimed in any one of claims 1 to 10, wherein R^2 is a fused aryl group, wherein a first cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or

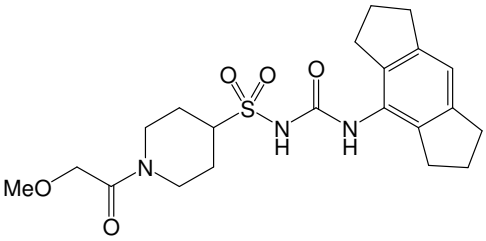
heteroaryl ring is fused to the aryl group across the α,β positions and a second cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring is fused to the aryl group across the α',β' positions, and wherein R^2 may optionally be further substituted.

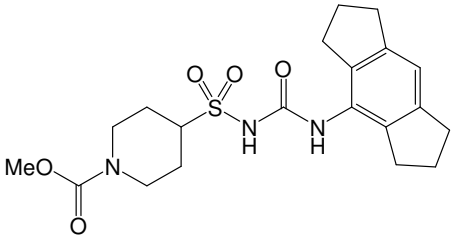
12. A compound as claimed in any one of claims 1 to 11, wherein Q is O.

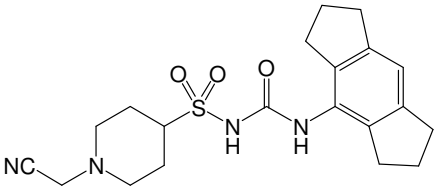
13. A compound selected from the group consisting of:

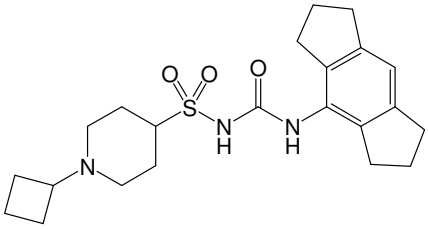











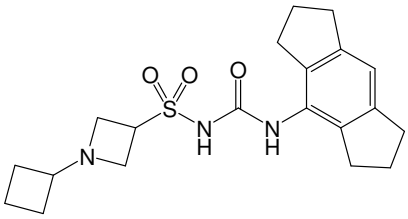


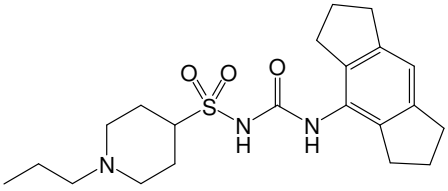


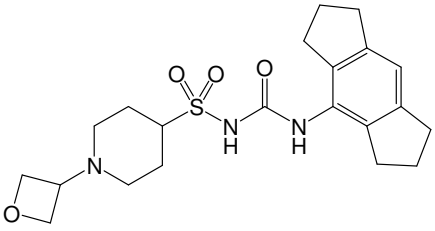


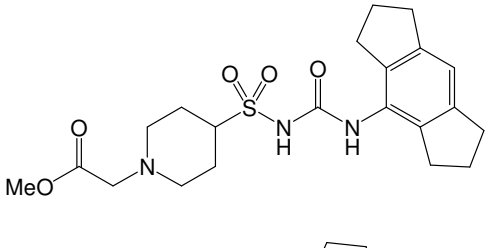


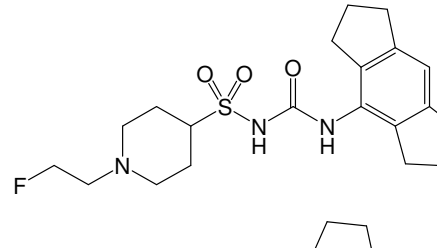


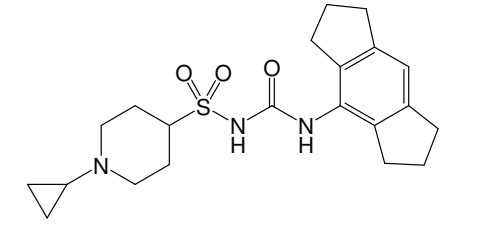


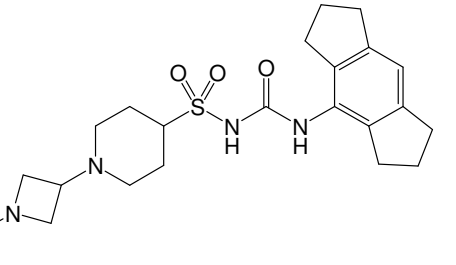


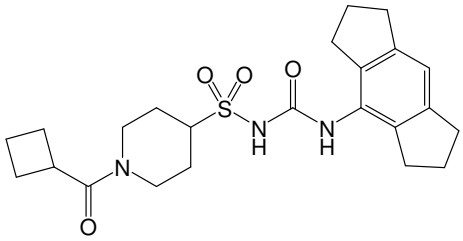


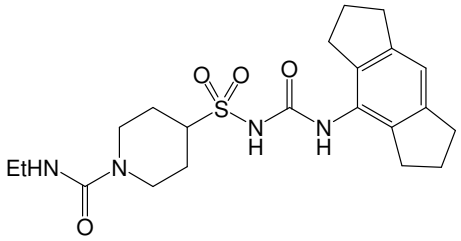


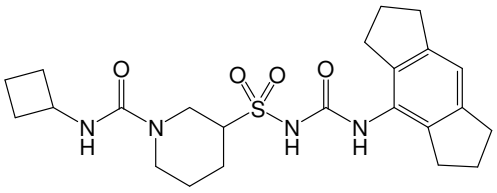


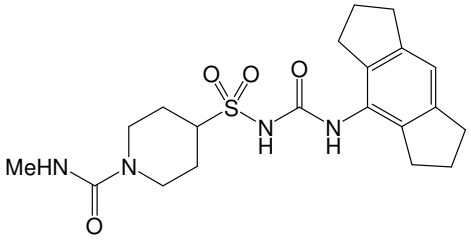


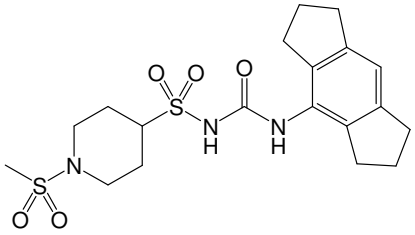


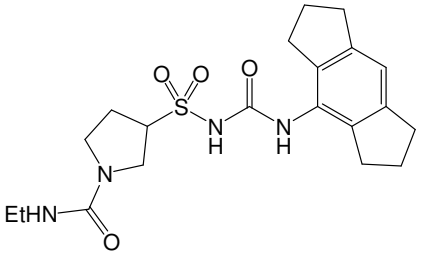


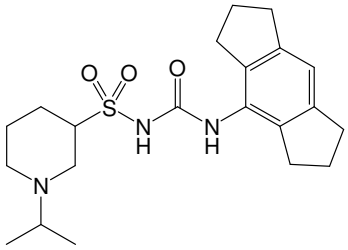

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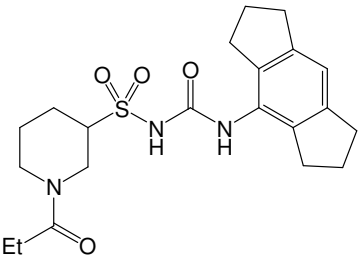


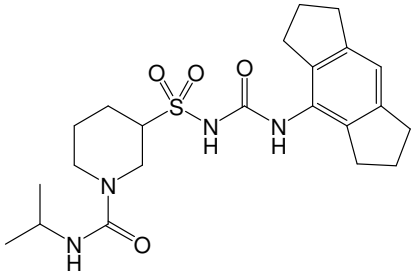

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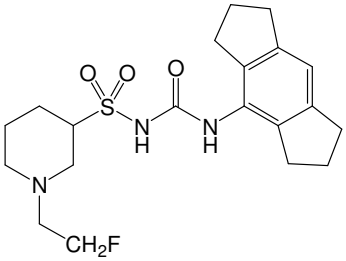


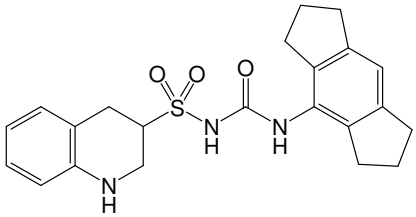

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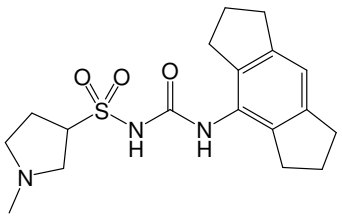


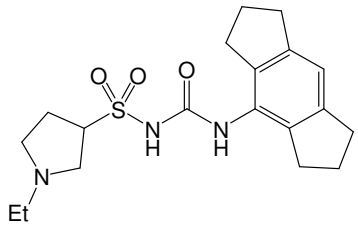

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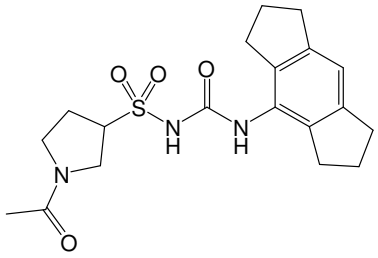


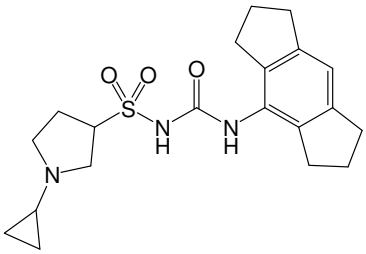

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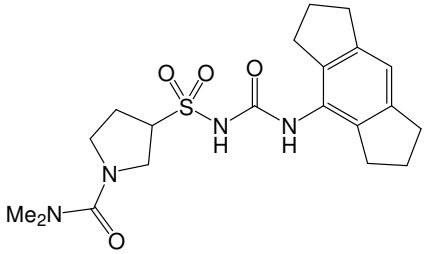


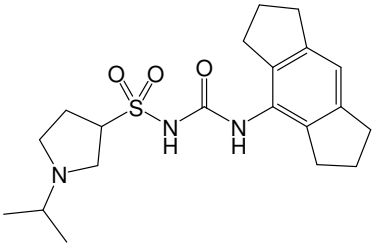


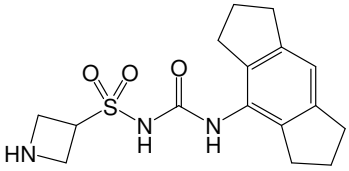

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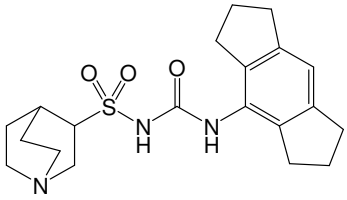

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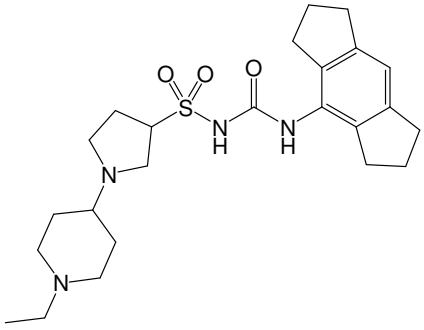

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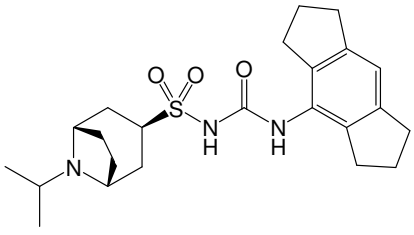

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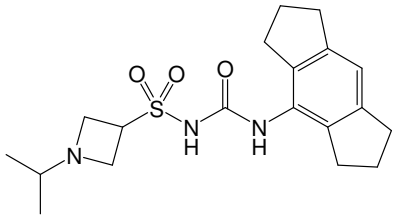

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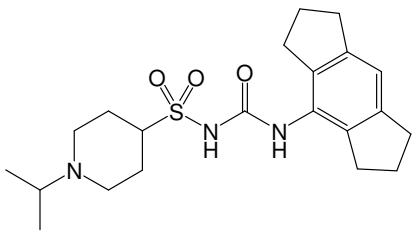

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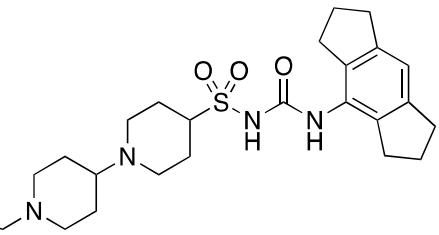

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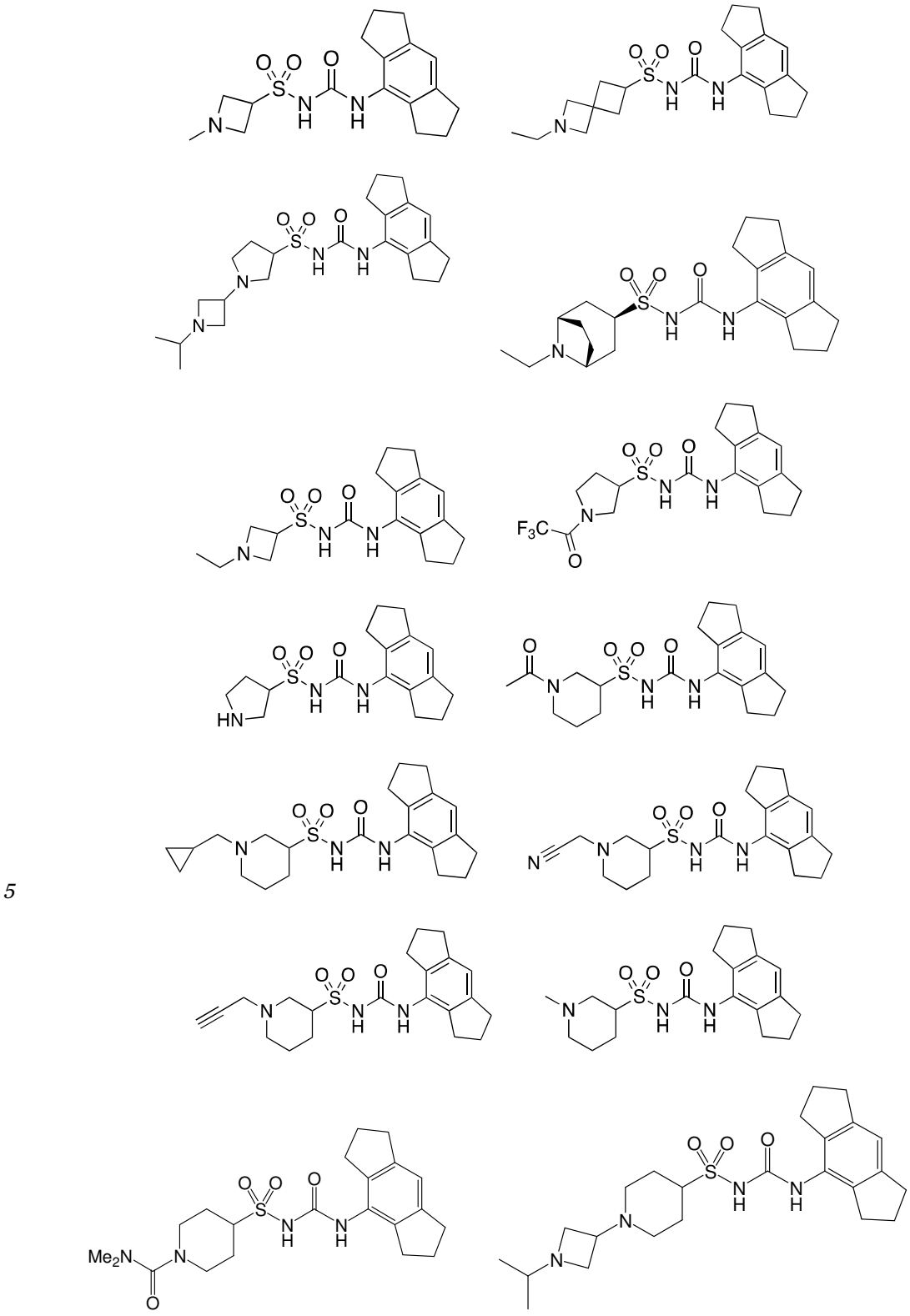

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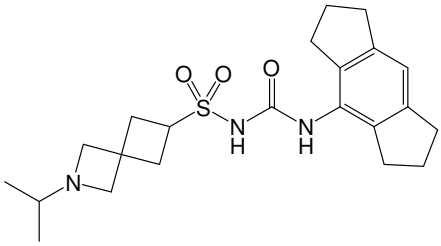

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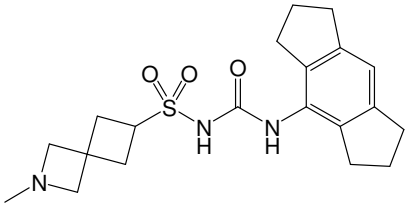
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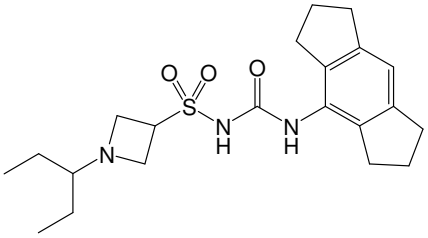

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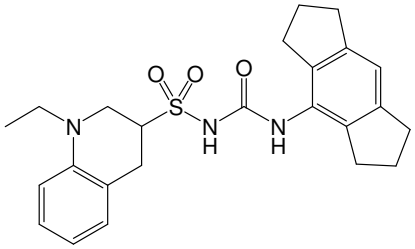

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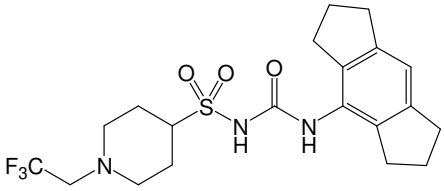


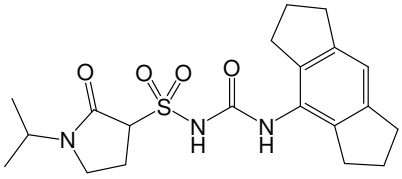


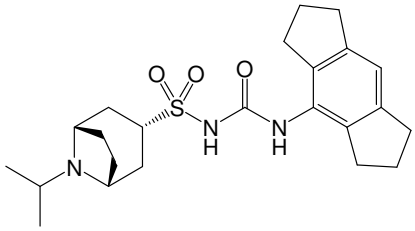


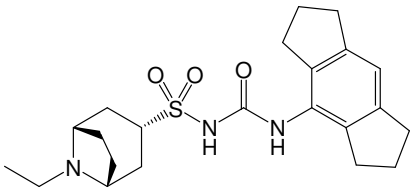


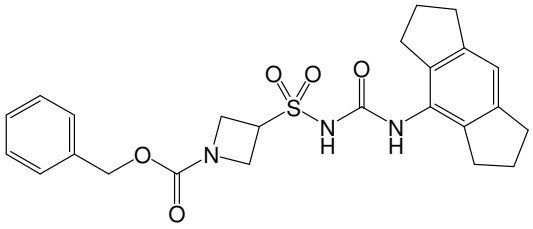


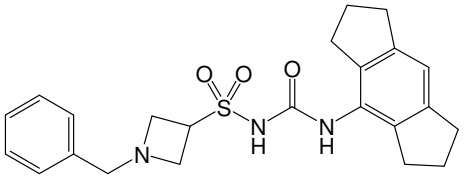




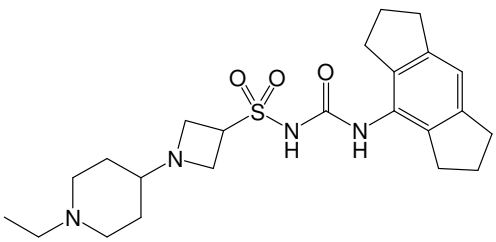


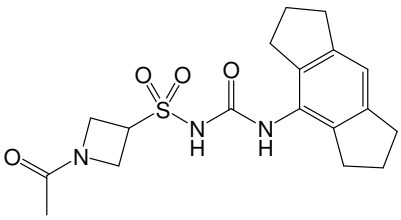


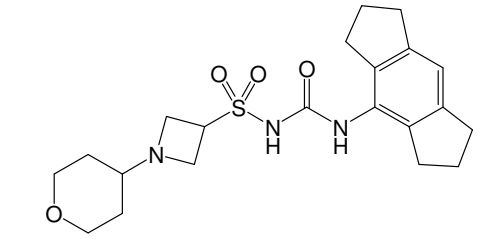


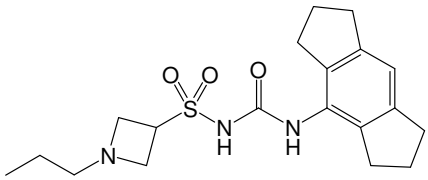


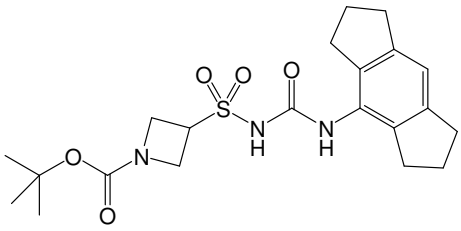
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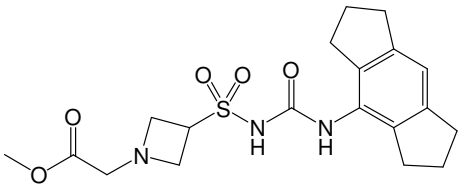


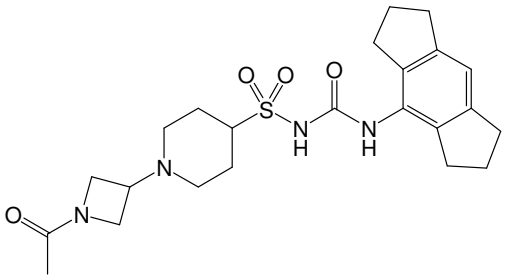


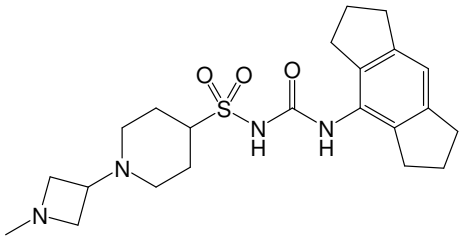


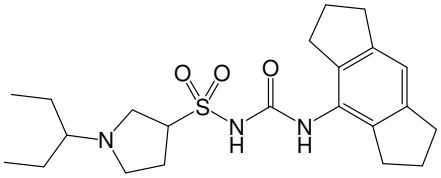


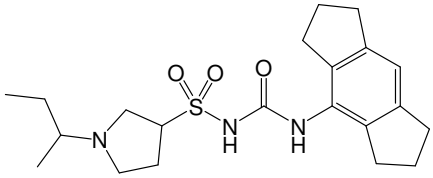


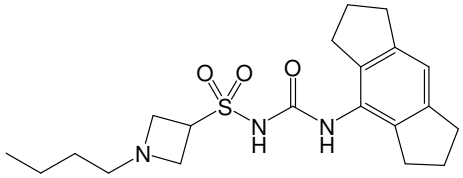


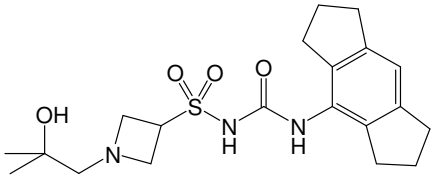




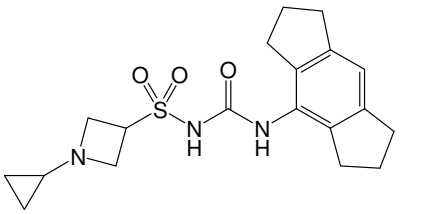


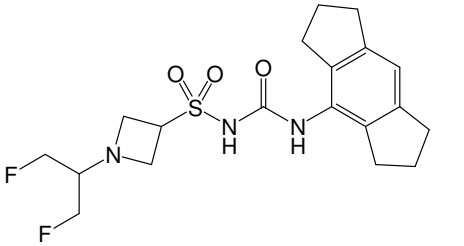


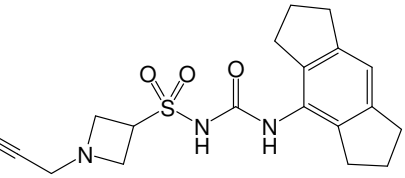


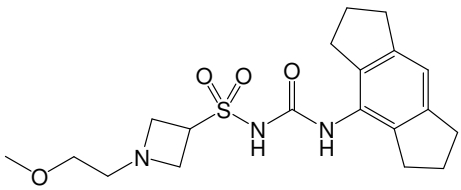


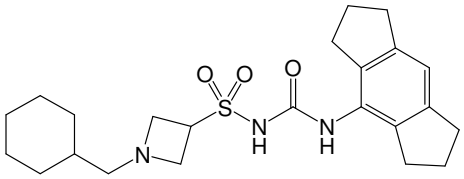
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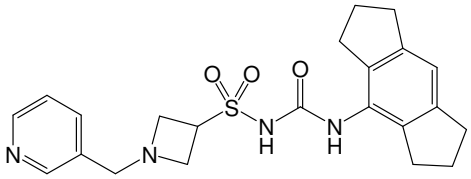


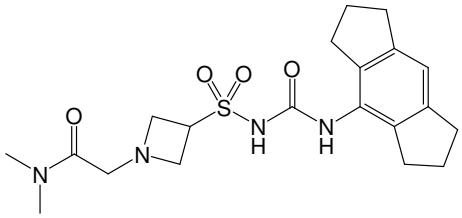


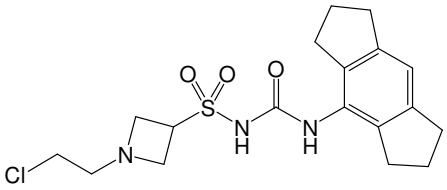


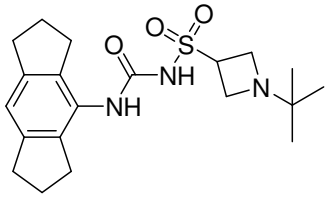


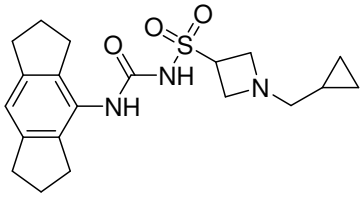


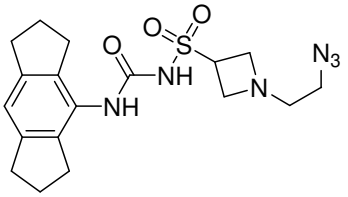


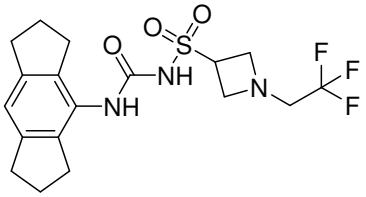


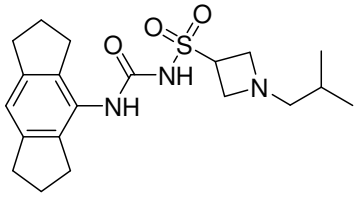


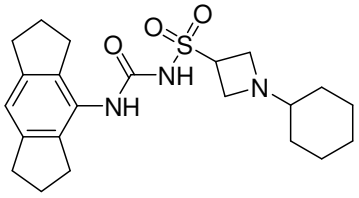




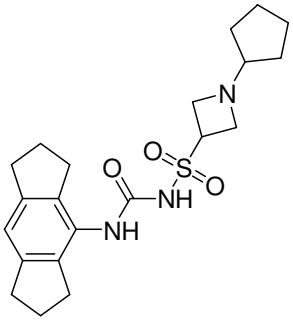


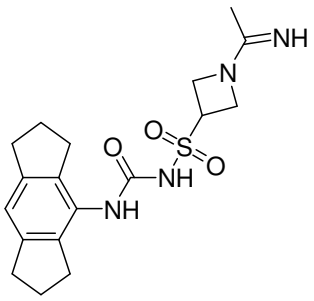


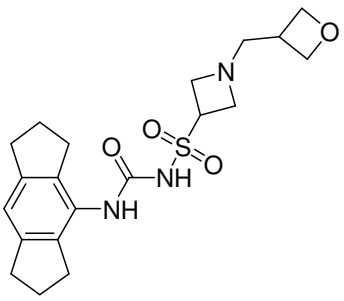


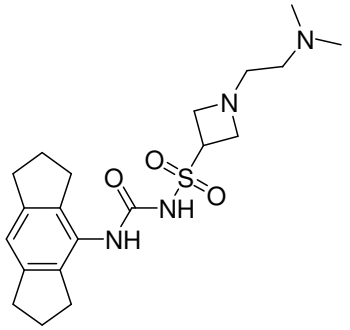
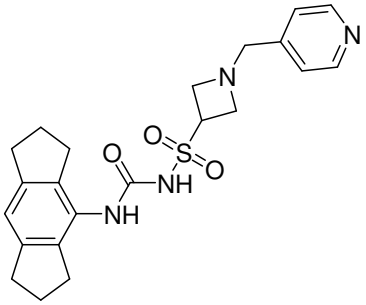
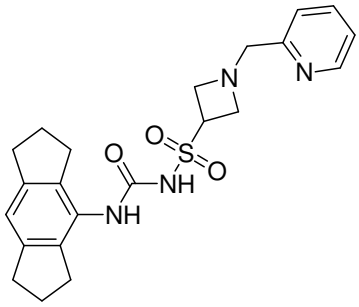
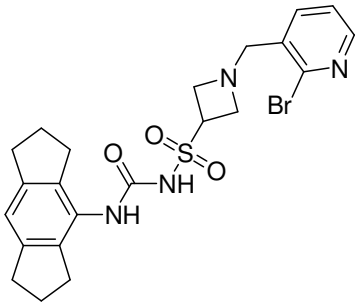
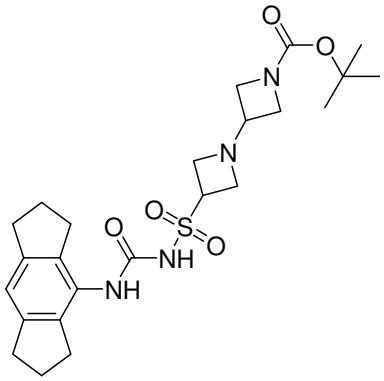
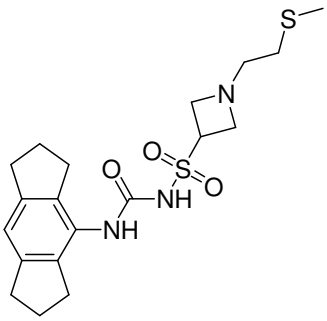
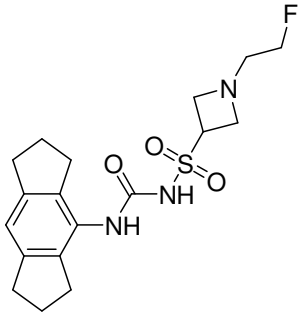
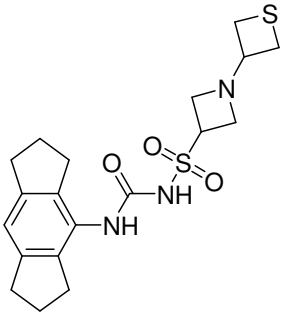
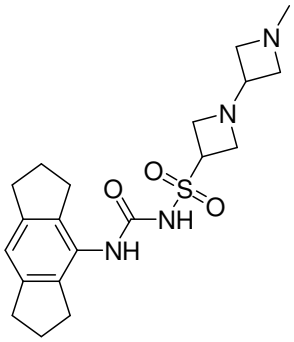


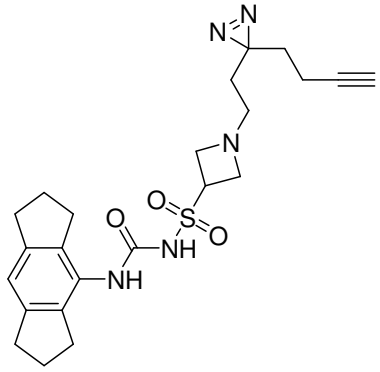
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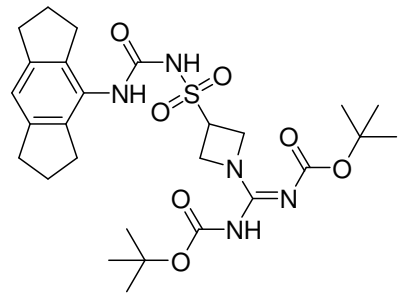


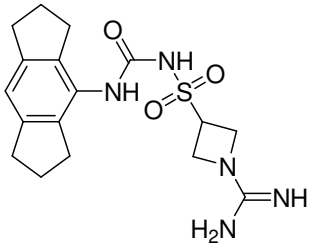


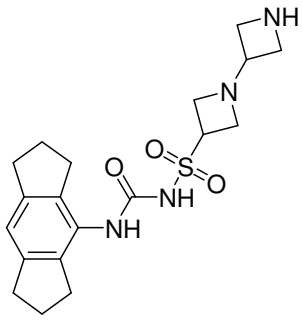


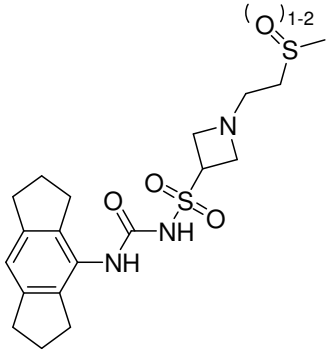










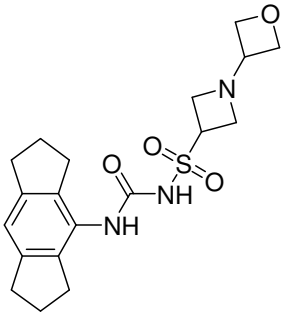


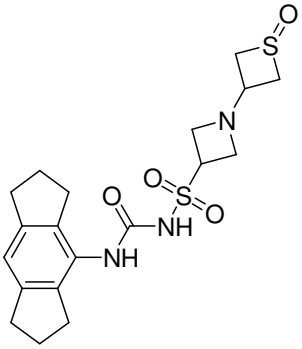


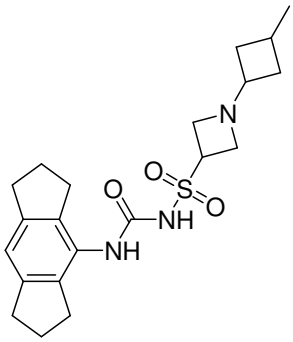


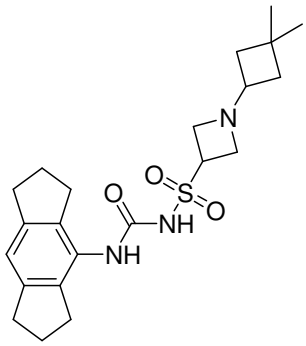


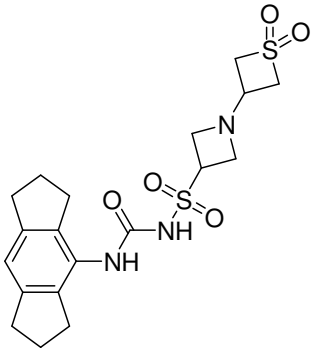


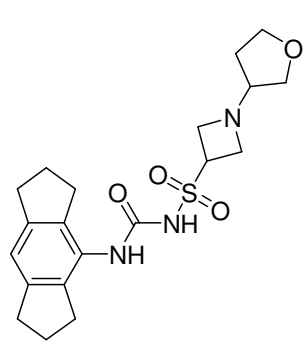


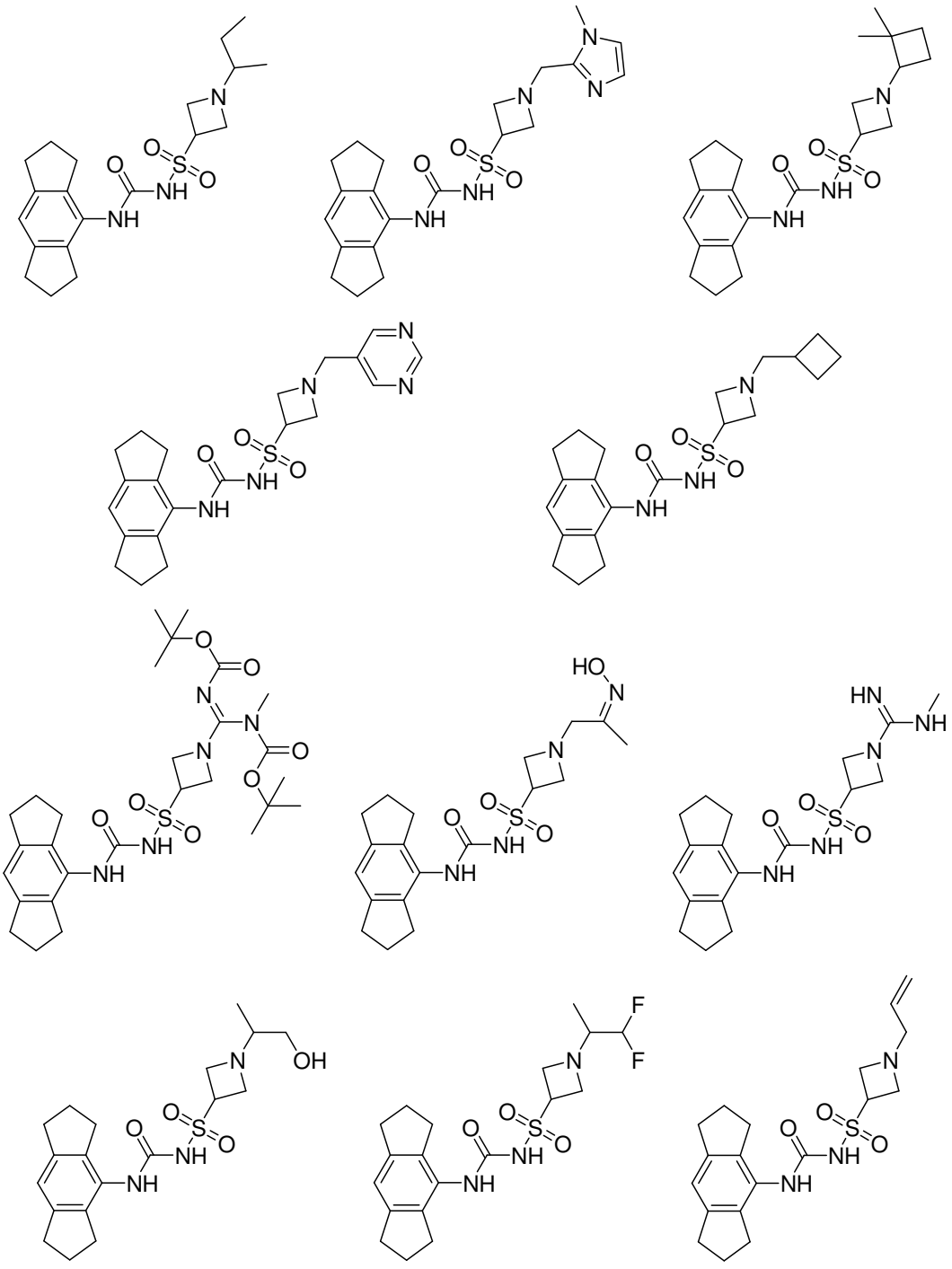


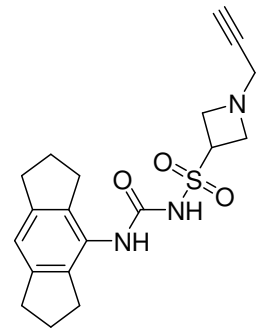


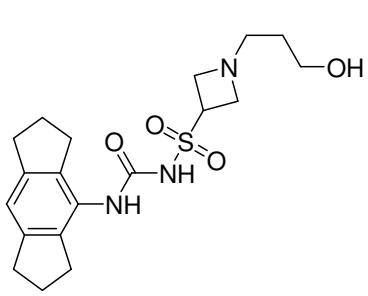


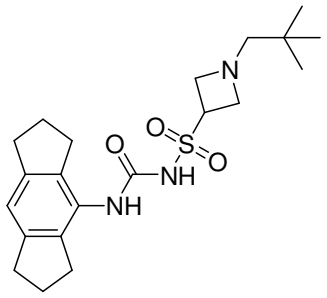


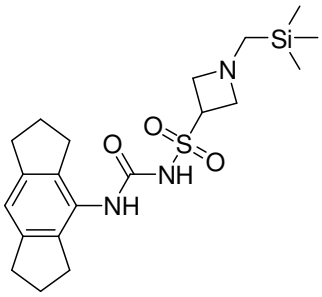


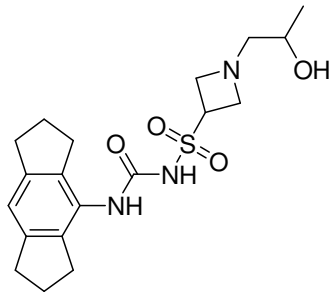


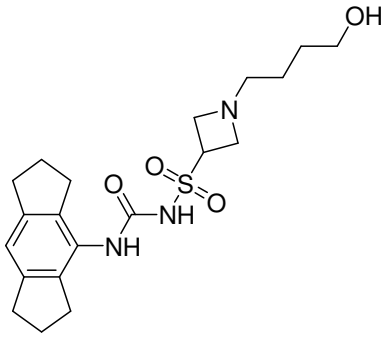


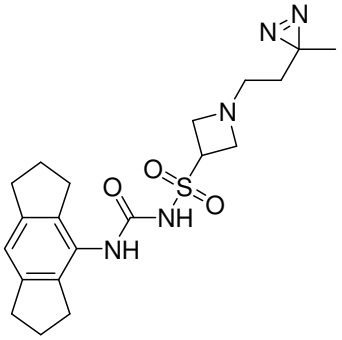


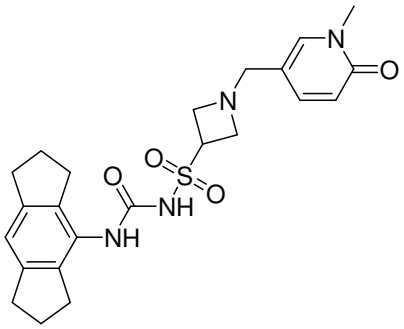


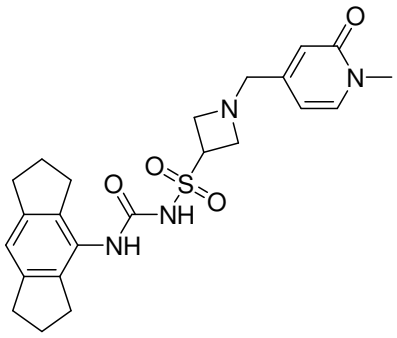


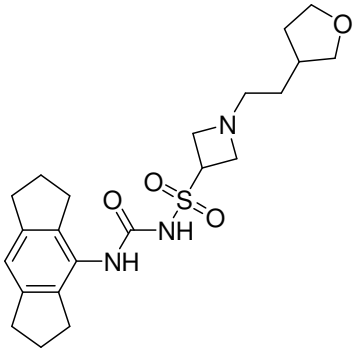


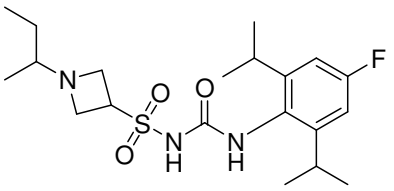


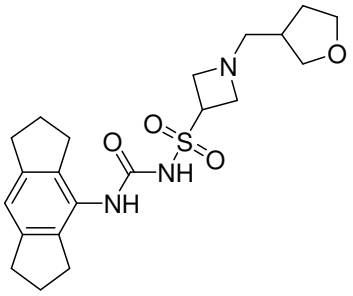


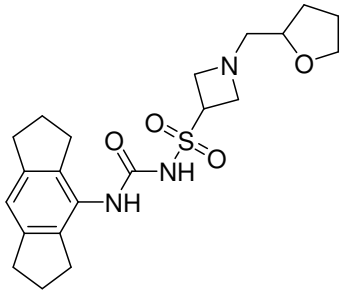


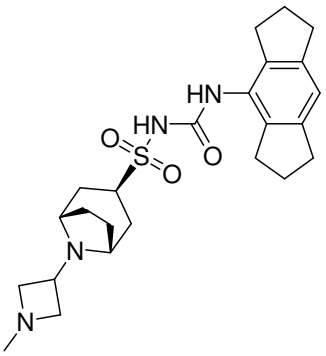


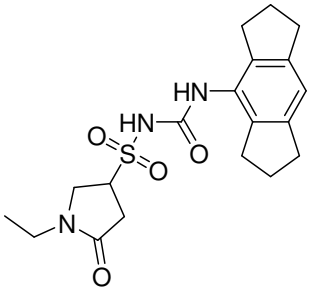


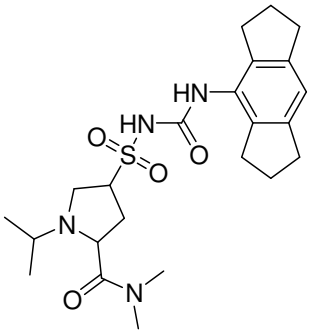


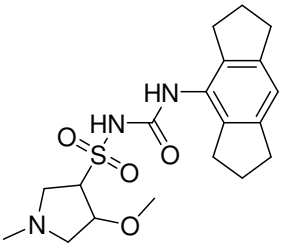


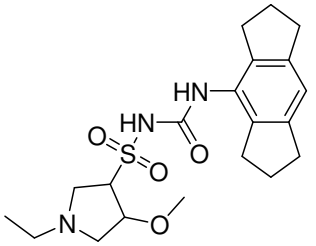


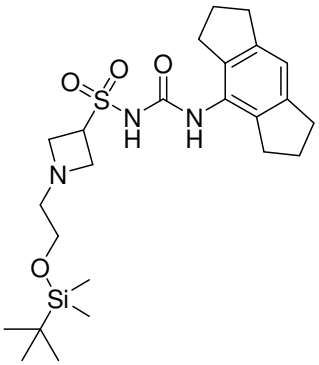


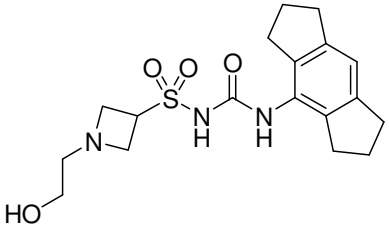


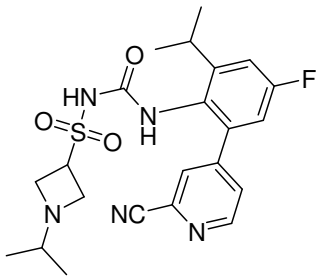


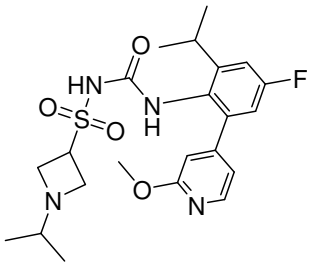


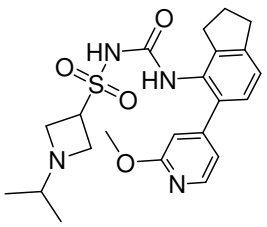


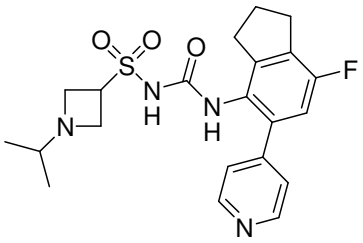


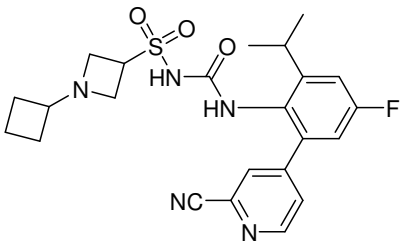


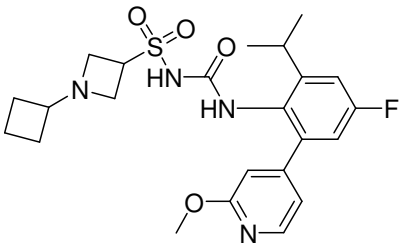


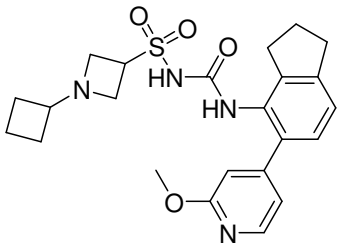


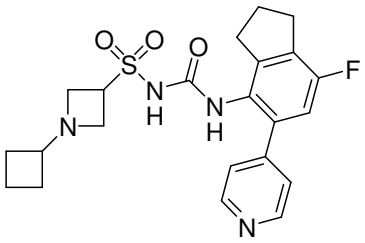


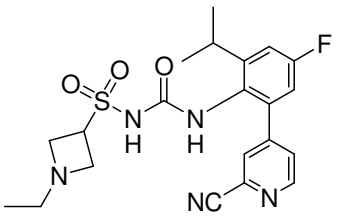


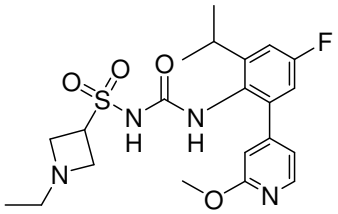


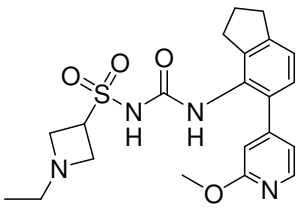


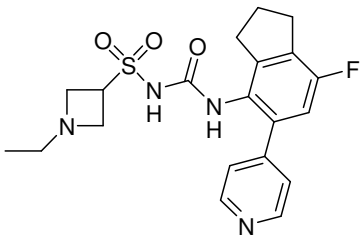


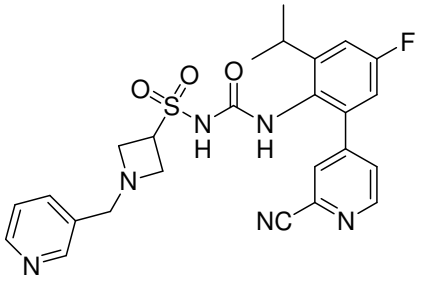


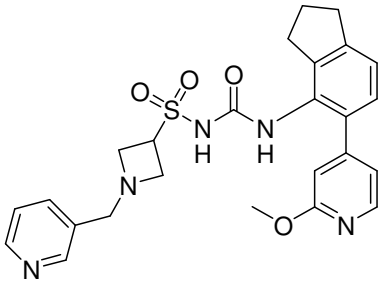


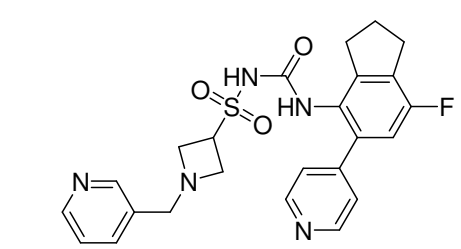


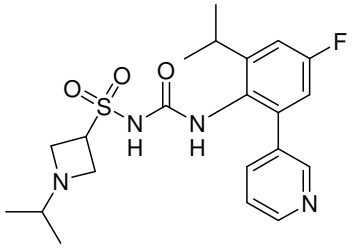


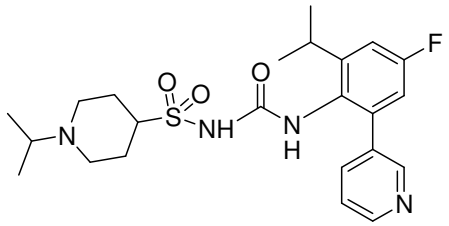


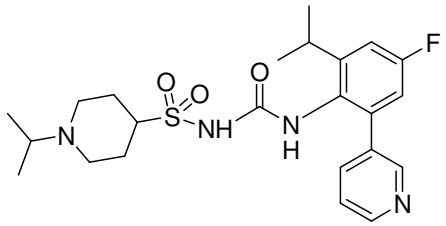


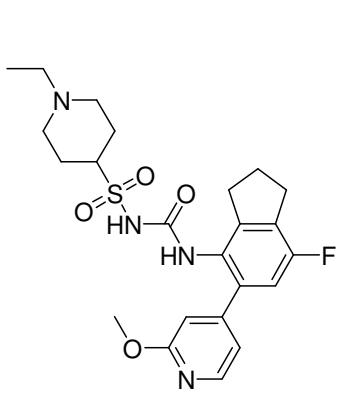


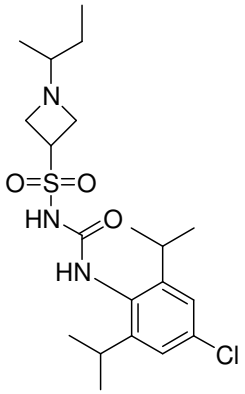


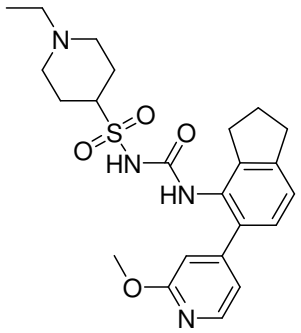


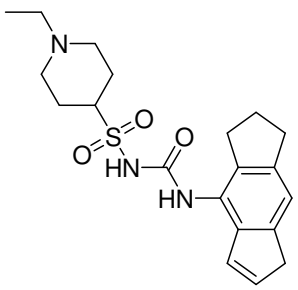


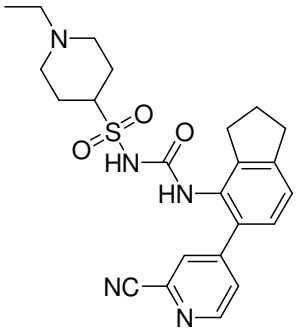


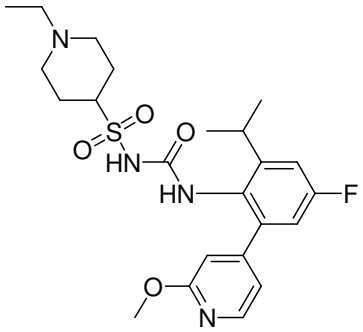


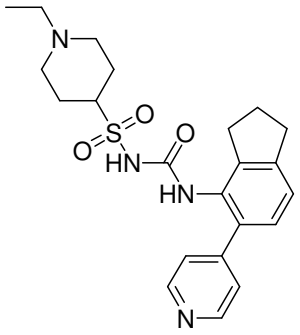


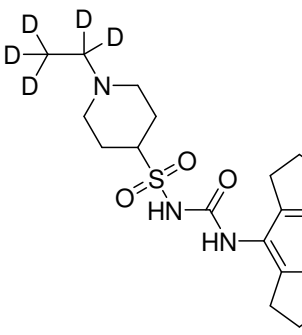


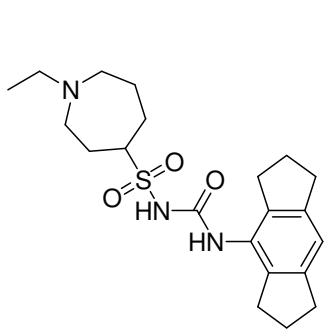


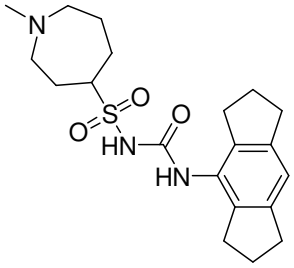








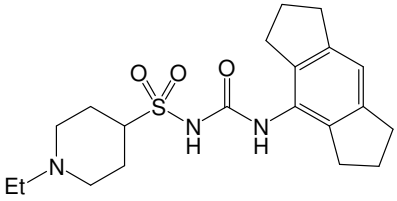




and ,

and pharmaceutically acceptable salts and solvates thereof.

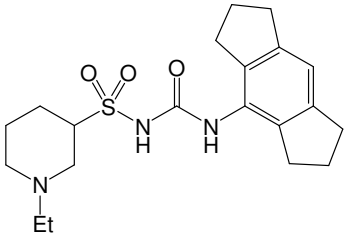
14. A compound selected from the group consisting of:



,

and pharmaceutically acceptable salts and solvates thereof.

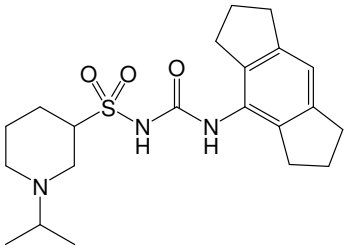
15. A compound selected from the group consisting of:



,

and pharmaceutically acceptable salts and solvates thereof.

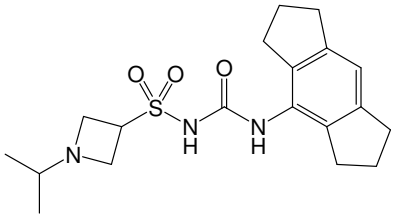
16. A compound selected from the group consisting of:



,

and pharmaceutically acceptable salts and solvates thereof.

17. A compound selected from the group consisting of:



,

and pharmaceutically acceptable salts and solvates thereof.

18. A pharmaceutically acceptable salt or solvate of a compound as claimed in any one of claims 1 to 17.

19. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt or solvate as claimed in claim 18, and a pharmaceutically acceptable excipient.

20. A compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt or solvate as claimed in claim 18, or a pharmaceutical composition as claimed in claim 19, for use in medicine.

21. Use of a compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt or solvate as claimed in claim 18, or a pharmaceutical composition as claimed in claim 19, in the manufacture of a medicament for treating or preventing a disease, disorder or condition responsive to NLRP3 inhibition, 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.

22. Use of a compound as claimed in any one of claims 1 to 17, or a pharmaceutically acceptable salt or solvate as claimed in claim 18, or a pharmaceutical composition as claimed in claim 19, 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).