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.

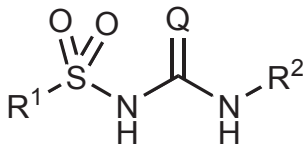
Some diarylsulfonylurea-containing compounds have been identified as cytokine release inhibitory drugs (CRIDs) (Perregaux *et al.*; J. Pharmacol. Exp. Ther. 299, 187-197, 2001). CRIDs are a class of diarylsulfonylurea-containing compounds that inhibit the post-translational processing of IL-1β. Post-translational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

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

In the context of the present specification, a "hydrocarbyl" substituent group or a hydrocarbyl moiety in a substituent group only includes carbon and hydrogen atoms but, unless stated otherwise, does not include any heteroatoms, such as N, O or S, in its carbon skeleton. A hydrocarbyl group/moiety may be saturated or unsaturated (including aromatic), and may be straight-chained or branched, or be or include cyclic groups wherein, unless stated otherwise, the cyclic group does not include any heteroatoms, such as N, O or S, in its carbon skeleton. Examples of hydrocarbyl groups include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl and aryl groups/moieties and combinations of all of these groups/moieties. Typically a hydrocarbyl group is a C_1-C_{20} hydrocarbyl group. More typically a hydrocarbyl group is a C_1-C_{15} hydrocarbyl group. More typically a hydrocarbyl group is a C_1-C_{10} hydrocarbyl group. A "hydrocarbylene" group is similarly defined as a divalent hydrocarbyl group.

In the context of the present specification, unless otherwise stated, an "alkyl" substituent group or an alkyl moiety in a substituent group may be linear or branched. Examples of alkyl groups/moieties include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl and *n*-pentyl groups/moieties. Unless stated otherwise, the term "alkyl" does not include "cycloalkyl". Typically an alkyl group is a C_1-C_{12} alkyl group. More typically an alkyl group is a C_1-C_6 alkyl group. An "alkylene" group is similarly defined as a divalent alkyl group.

An "alkenyl" substituent group or an alkenyl moiety in a substituent group refers to an unsaturated alkyl group or moiety having one or more carbon-carbon double bonds. Examples of alkenyl groups/moieties include ethenyl, propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 1-hexenyl, 1,3-butadienyl, 1,3-pentadienyl, 1,4-pentadienyl and 1,4-hexadienyl groups/moieties. Unless stated otherwise, the term "alkenyl" does not include "cycloalkenyl". Typically an alkenyl group is a C_2-C_{12} alkenyl group. More typically an alkenyl group is a C_2-C_6 alkenyl group. An "alkenylene" group is similarly defined as a divalent alkenyl group.

An "alkynyl" substituent group or an alkynyl moiety in a substituent group refers to an unsaturated alkyl group or moiety having one or more carbon-carbon triple bonds.

Examples of alkynyl groups/moieties include ethynyl, propargyl, but-1-ynyl and but-2-ynyl. Typically an alkynyl group is a C_2-C_{12} alkynyl group. More typically an alkynyl group is a C_2-C_6 alkynyl group. An "alkynylene" group is similarly defined as a divalent alkynyl group.

A "cyclic" substituent group or a cyclic moiety in a substituent group refers to any hydrocarbyl ring, wherein the hydrocarbyl ring may be saturated or unsaturated (including aromatic) and may include one or more heteroatoms, e.g. N, O or S, in its carbon skeleton. Examples of cyclic groups include cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl groups as discussed below. A cyclic group may be monocyclic, bicyclic (e.g. bridged, fused or spiro), or polycyclic. Typically, a cyclic group is a 3- to 12-membered cyclic group, which means it contains from 3 to 12 ring atoms. More typically, a cyclic group is a 3- to 7-membered monocyclic group, which means it contains from 3 to 7 ring atoms.

As used herein, where it is stated that a cyclic group is monocyclic, it is to be understood that the cyclic group is not substituted with a divalent bridging substituent (e.g. -O-, -S-, -NH-, -N(R^β)- or -R^α-) so as to form a bridged, fused or spiro substituent. However, unless stated otherwise, a substituted monocyclic group may be substituted with one or more monovalent cyclic groups. Similarly, where it is stated that a group is bicyclic, it is to be understood that the cyclic group including any bridged, fused or spiro divalent bridging substituents attached to the cyclic group, but excluding any monovalent cyclic substituents, is bicyclic.

A "heterocyclic" substituent group or a heterocyclic moiety in a substituent group refers to a cyclic group or moiety including one or more carbon atoms and one or more heteroatoms, e.g. N, O or S, in the ring structure. Examples of heterocyclic groups include heteroaryl groups as discussed below and non-aromatic heterocyclic groups such as azetidinyl, azetinyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydrothiophenyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxetanyl, thietanyl, pyrazolidinyl, imidazolidinyl, dioxolanyl, oxathiolanyl, thianyl, and dioxanyl groups.

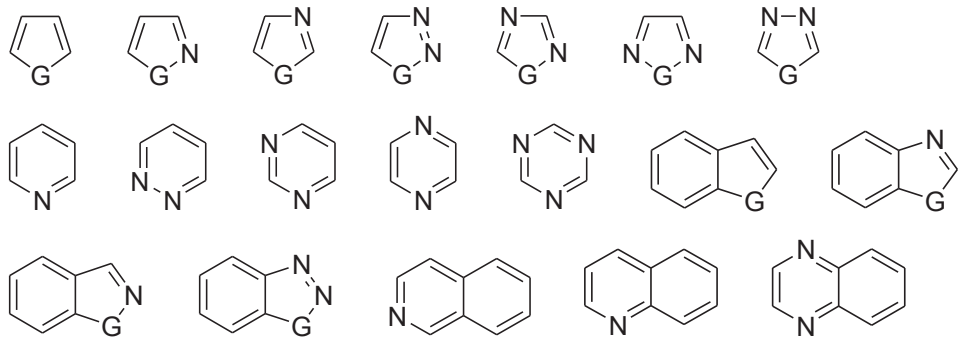
A "cycloalkyl" substituent group or a cycloalkyl moiety in a substituent group refers to a saturated hydrocarbyl ring containing, for example, from 3 to 7 carbon atoms, examples of which include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Unless

stated otherwise, a cycloalkyl substituent group or moiety may include monocyclic, bicyclic or polycyclic hydrocarbyl rings.

A “cycloalkenyl” substituent group or a cycloalkenyl moiety in a substituent group refers to a non-aromatic unsaturated hydrocarbyl ring having one or more carbon-carbon double bonds and containing, for example, from 3 to 7 carbon atoms, examples of which include cyclopent-1-en-1-yl, cyclohex-1-en-1-yl and cyclohex-1,3-dien-1-yl. Unless stated otherwise, a cycloalkenyl substituent group or moiety may include monocyclic, bicyclic or polycyclic hydrocarbyl rings.

An “aryl” substituent group or an aryl moiety in a substituent group refers to an aromatic hydrocarbyl ring. The term “aryl” includes monocyclic aromatic hydrocarbons and polycyclic fused ring aromatic hydrocarbons wherein all of the fused ring systems (excluding any ring systems which are part of or formed by optional substituents) are aromatic. Examples of aryl groups/moieties include phenyl, naphthyl, anthracenyl and phenanthrenyl. Unless stated otherwise, the term “aryl” does not include “heteroaryl”.

A “heteroaryl” substituent group or a heteroaryl moiety in a substituent group refers to an aromatic heterocyclic group or moiety. The term “heteroaryl” includes monocyclic aromatic heterocycles and polycyclic fused ring aromatic heterocycles wherein all of the fused ring systems (excluding any ring systems which are part of or formed by optional substituents) are aromatic. Examples of heteroaryl groups/moieties include the following:



wherein G = O, S or NH.

Unless stated otherwise, where a cyclic group or moiety is stated to be non-aromatic, such as a cycloalkyl, cycloalkenyl or non-aromatic heterocyclic group, it is to be understood that the group or moiety, excluding any ring systems which are part of or

formed by optional substituents, is non-aromatic. Similarly, where a cyclic group or moiety is stated to be aromatic, such as an aryl or a heteroaryl group, it is to be understood that the group or moiety, excluding any ring systems which are part of or formed by optional substituents, is aromatic. Typically, a cyclic group or moiety is considered non-aromatic, when it does not have any tautomers that are aromatic. Typically, when a cyclic group or moiety has a tautomer that is aromatic, it is considered aromatic, even if it has tautomers that are not aromatic.

For the purposes of the present specification, where a combination of moieties is referred to as one group, for example, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl, the last mentioned moiety contains the atom by which the group is attached to the rest of the molecule. An example of an arylalkyl group is benzyl.

For the purposes of the present specification, in an optionally substituted group or moiety:

(i) each hydrogen atom may optionally be replaced by a group independently selected from halo; -CN; -NO_2; -N_3; -R^β; -OH; -OR^β; -R^α-halo; -R^α-CN; -R^α-NO_2; -R^α-N_3; -R^α-R^β; -R^α-OH; -R^α-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-$SO_2N(R^\beta)_2$; -$Si(R^\beta)_3$; -O-$Si(R^\beta)_3$; -R^α-$Si(R^\beta)_3$; -R^α-O-$Si(R^\beta)_3$; -NH_2; -NHR^β; -$N(R^\beta)_2$; -$N(O)(R^\beta)_2$; -$N^+(R^\beta)_3$; -R^α-NH_2; -R^α-NHR^β; -R^α-$N(R^\beta)_2$; -R^α-$N(O)(R^\beta)_2$; -R^α-$N^+(R^\beta)_3$; -CHO; -COR^β; -COOH; -$COOR^\beta$; -$OCOR^\beta$; -R^α-CHO; -R^α-COR^β; -R^α-COOH; -R^α-$COOR^\beta$; -R^α-$OCOR^\beta$; -$C(=NH)R^\beta$; -$C(=NH)NH_2$; -$C(=NH)NHR^\beta$; -$C(=NH)N(R^\beta)_2$; -$C(=NR^\beta)R^\beta$; -$C(=NR^\beta)NHR^\beta$; -$C(=NR^\beta)N(R^\beta)_2$; -$C(=NOH)R^\beta$; -$C(N_2)R^\beta$; -R^α-$C(=NH)R^\beta$; -R^α-$C(=NH)NH_2$; -R^α-$C(=NH)NHR^\beta$; -R^α-$C(=NH)N(R^\beta)_2$; -R^α-$C(=NR^\beta)R^\beta$; -R^α-$C(=NR^\beta)NHR^\beta$; -R^α-$C(=NR^\beta)N(R^\beta)_2$; -R^α-$C(=NOH)R^\beta$; -R^α-$C(N_2)R^\beta$; -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-$CON(R^\beta)_2$; -O-R^α-OH; -O-R^α-OR^β; -O-R^α-NH_2; -O-R^α-NHR^β; -O-R^α-$N(R^\beta)_2$; -O-R^α-$N(O)(R^\beta)_2$; -O-R^α-$N^+(R^\beta)_3$; -NH-R^α-OH; -NH-R^α-OR^β; -NH-R^α-NH_2; -NH-R^α-NHR^β; -NH-R^α-$N(R^\beta)_2$; -NH-R^α-$N(O)(R^\beta)_2$; -NH-R^α-$N^+(R^\beta)_3$; -NR^β-R^α-OH; -NR^β-R^α-OR^β; -NR^β-R^α-NH_2; -NR^β-R^α-NHR^β; -NR^β-R^α-$N(R^\beta)_2$; -NR^β-R^α-$N(O)(R^\beta)_2$; -NR^β-R^α-$N^+(R^\beta)_3$; -$N(O)R^\beta$-R^α-OH; -$N(O)R^\beta$-R^α-OR^β; -$N(O)R^\beta$-R^α-NH_2; -$N(O)R^\beta$-R^α-NHR^β; -$N(O)R^\beta$-R^α-$N(R^\beta)_2$; -$N(O)R^\beta$-R^α-$N(O)(R^\beta)_2$; -$N(O)R^\beta$-R^α-$N^+(R^\beta)_3$; -$N^+(R^\beta)_2$-R^α-OH; -$N^+(R^\beta)_2$-R^α-OR^β; -$N^+(R^\beta)_2$-R^α-NH_2; -$N^+(R^\beta)_2$-R^α-NHR^β; -$N^+(R^\beta)_2$-R^α-$N(R^\beta)_2$; or -$N^+(R^\beta)_2$-R^α-$N(O)(R^\beta)_2$; and/or

(ii) any two hydrogen atoms attached to the same atom may optionally be replaced by a π-bonded substituent independently selected from oxo (=O), =S, =NH or =NR^{β}; and/or

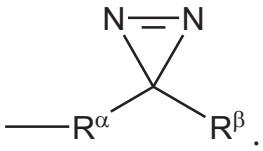
(iii) any two hydrogen atoms attached to the same or different atoms, within the same optionally substituted group or moiety, may optionally be replaced by a bridging substituent independently selected from -O-, -S-, -NH-, -N=N-, -$N(R^{\beta})$-, -$N(O)(R^{\beta})$-, -$N^{+}(R^{\beta})_2$- or -R^{α}-;

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 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, wherein one or more -CH_2- groups in the backbone of the alkylene, alkenylene or alkynylene group may optionally be replaced by one or more -$N(O)(R^{\beta})$- or -$N^{+}(R^{\beta})_2$- groups, 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, or wherein any two or three -R^{β} attached to the same nitrogen atom may, together with the nitrogen atom to which they are attached, form a C_2-C_7 cyclic group, and wherein any -R^{β} may optionally be substituted with one or more C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halocycloalkyl, -O(C_1-C_4 alkyl), -O(C_1-C_4 haloalkyl), -O(C_3-C_7 cycloalkyl), -O(C_3-C_7 halocycloalkyl), -CO(C_1-C_4 alkyl), -CO(C_1-C_4 haloalkyl), -COO(C_1-C_4 alkyl), -COO(C_1-C_4 haloalkyl), halo, -OH, -NH_2, -CN, -C≡CH, oxo (=O), or 4- to 6-membered heterocyclic group.

Typically, the compounds of the present disclosure comprise at most one quaternary ammonium group such as -$N^{+}(R^{\beta})_3$ or -$N^{+}(R^{\beta})_2$-.

Where reference is made to a -R^{α}-$C(N_2)R^{\beta}$ group, what is intended is:



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Typically, in an optionally substituted group or moiety:

(i) each hydrogen atom may optionally be replaced by a group independently selected from halo; -CN; -NO_2; -N_3; -R^{β}; -OH; -OR^{β}; -SH; -SR^{β}; -SOR^{β}; -SO_2H; -SO_2R^{β};

$-SO_2NH_2$; $-SO_2NHR^\beta$; $-SO_2N(R^\beta)_2$; $-R^\alpha$-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; or 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; and/or

(ii) any two hydrogen atoms attached to the same carbon atom may optionally be replaced by a π-bonded substituent independently selected from oxo (=O), =S, =NH or $=NR^\beta$; and/or

(iii) any two hydrogen atoms attached to the same or different atoms, within the same optionally substituted group or moiety, may optionally be replaced by a bridging substituent independently selected from -O-, -S-, -NH-, $-N(R^\beta)$- or $-R^\alpha$-;

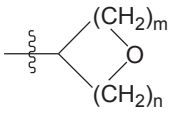
wherein each $-R^\alpha$- is independently selected from an alkylene, alkenylene or alkynylene group, wherein the alkylene, alkenylene or alkynylene group contains from 1 to 6 atoms in its backbone, wherein one or more carbon atoms in the backbone of the alkylene, alkenylene or alkynylene group may optionally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

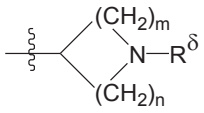
wherein each $-R^\beta$ is independently selected from a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_2-C_6 cyclic group, and wherein any $-R^\beta$ may optionally be substituted with one or more C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_7 cycloalkyl, -O(C_1-C_3 alkyl), halo, -CN, -C≡CH or oxo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

Typically, in an optionally substituted group or moiety:

(i) each hydrogen atom may optionally be replaced by a group 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^{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;



; or


; and/or

(ii) any two hydrogen atoms attached to the same carbon atom may optionally be replaced by a π-bonded substituent independently selected from (oxo) =O, =S, =NH or =NR^{β}; and/or

(iii) any two hydrogen atoms attached to the same or different atoms, within the same optionally substituted group or moiety, may optionally be replaced by a bridging substituent independently selected from -O-, -S-, -NH-, -N(R^{β})- or -R^{α}-;

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.

Typically a substituted group comprises 1, 2, 3 or 4 substituents, more typically 1, 2 or 3 substituents, more typically 1 or 2 substituents, and more typically 1 substituent.

Unless stated otherwise, any divalent bridging substituent (e.g. -O-, -S-, -NH-, -N(R^{β})-, -N(O)(R^{β})-, -N^{+}(R^{β})$_2$- or -R^{α}-) of an optionally substituted group or moiety (e.g. R^1) must only be attached to the specified group or moiety and may not be attached to a second group or moiety (e.g. R^2), even if the second group or moiety can itself be optionally substituted.

The term “halo” includes fluoro, chloro, bromo and iodo.

Unless stated otherwise, any reference to an element is to be considered a reference to all isotopes of that element. Thus, for example, unless stated otherwise any reference to hydrogen is considered to encompass all isotopes of hydrogen including deuterium and tritium.

Where reference is made to a hydrocarbyl or other group including one or more heteroatoms N, O or S in its carbon skeleton, or where reference is made to a carbon atom of a hydrocarbyl or other group being replaced by an N, O or S atom, what is intended is that:



;

$-CH_2-$ is replaced by $-NH-$, $-O-$ or $-S-$;

$-CH_3$ is replaced by $-NH_2$, $-OH$, or $-SH$;

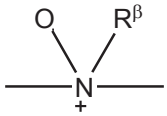
$-CH=$ is replaced by $-N=$;

$CH_2=$ is replaced by $NH=$, $O=$ or $S=$; or

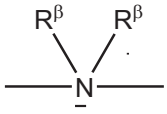
$CH\equiv$ is replaced by $N\equiv$;

provided that the resultant group comprises at least one carbon atom. For example, methoxy, dimethylamino and aminoethyl groups are considered to be hydrocarbyl groups including one or more heteroatoms N, O or S in their carbon skeleton.

Where reference is made to a $-CH_2-$ group in the backbone of a hydrocarbyl or other group being replaced by a $-N(O)(R^\beta)-$ or $-N^+(R^\beta)_2-$ group, what is intended is that:

$-CH_2-$ is replaced by 

; or

$-CH_2-$ is replaced by 

.

In the context of the present specification, unless otherwise stated, a C_x-C_y group is defined as a group containing from x to y carbon atoms. For example, a C_1-C_4 alkyl group is defined as an alkyl group containing from 1 to 4 carbon atoms. Optional

substituents and moieties are not taken into account when calculating the total number of carbon atoms in the parent group substituted with the optional substituents and/or containing the optional moieties. For the avoidance of doubt, replacement heteroatoms, e.g. N, O or S, are not to be counted as carbon atoms when calculating the number of carbon atoms in a C_x-C_y group. For example, a morpholinyl group is to be considered a C_4 heterocyclic group, not a C_6 heterocyclic group.

For the purposes of the present specification, where it is stated that a first atom or group is "directly attached" to a second atom or group it is to be understood that the first atom or group is covalently bonded to the second atom or group with no intervening atom(s) or groups being present. So, for example, for the group $(C=O)N(CH_3)_2$, the carbon atom of each methyl group is directly attached to the nitrogen atom and the carbon atom of the carbonyl group is directly attached to the nitrogen atom, but the carbon atom of the carbonyl group is not directly attached to the carbon atom of either methyl group.

R^1 is a non-aromatic heterocyclic group which may optionally be substituted. For the avoidance of doubt, it is noted that it is a ring atom of the non-aromatic heterocyclic group of R^1 that is directly attached to the sulfur atom of the sulfonylurea group, not any optional substituent.

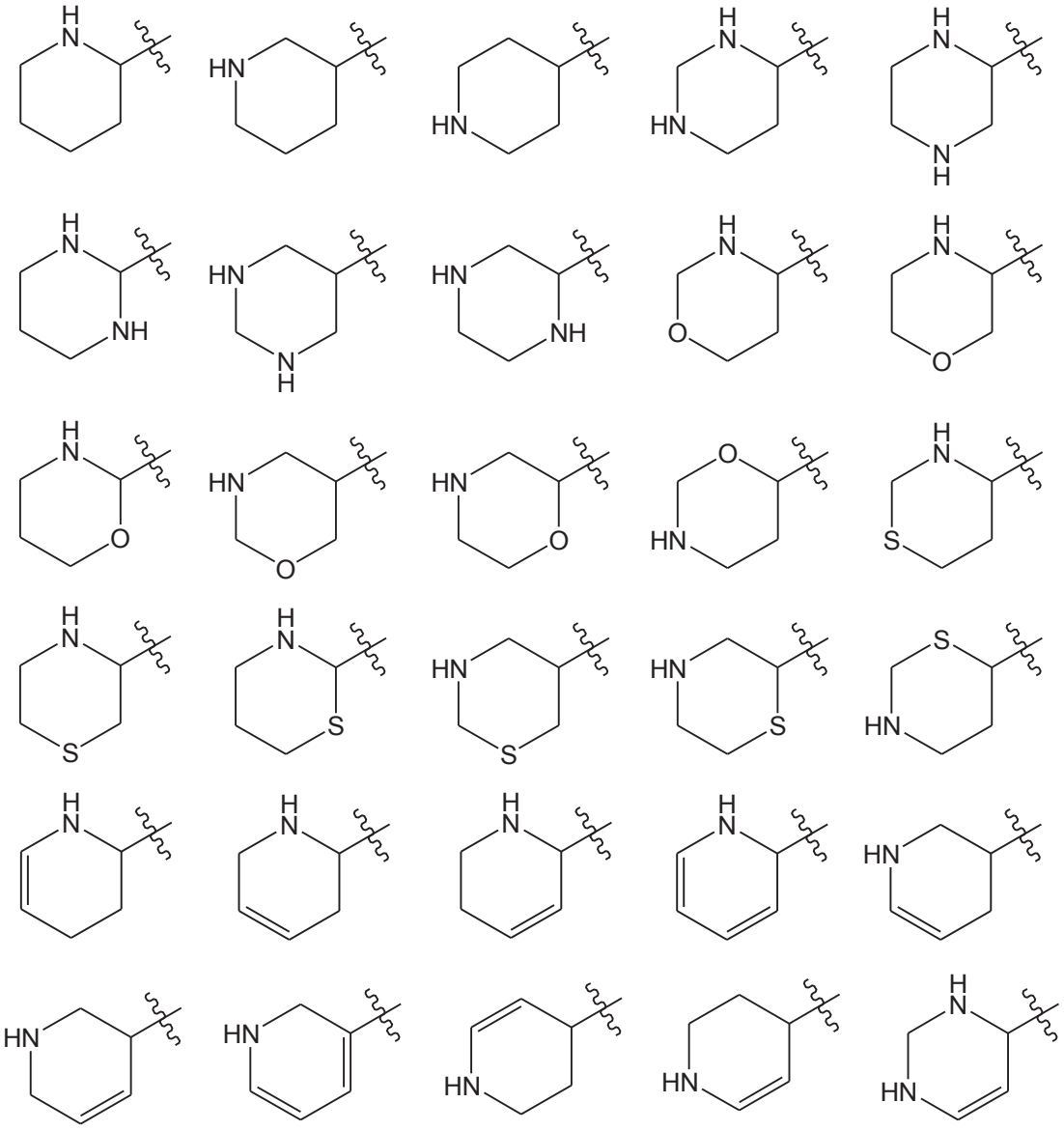
R^1 is a non-aromatic heterocyclic group which may be monocyclic, bicyclic (including bridged, fused and spiro), tricyclic or polycyclic. The bicyclic, tricyclic and polycyclic ring structures may be partially aromatic. For the avoidance of doubt, it is noted that when R^1 is a partially aromatic bicyclic, tricyclic or polycyclic group, the ring of R^1 that is directly attached to the sulfur atom of the sulfonylurea group is non-aromatic. For the avoidance of doubt, it is also noted that when R^1 is a bicyclic, tricyclic or polycyclic group, the at least one ring nitrogen atom of R^1 is in a non-aromatic ring, but not necessarily in the non-aromatic ring of R^1 that is directly attached to the sulfur atom of the sulfonylurea group. In one example, when R^1 is a bicyclic, tricyclic or polycyclic group, the at least one ring nitrogen atom of R^1 is in the non-aromatic ring of R^1 that is directly attached to the sulfur atom of the sulfonylurea group.

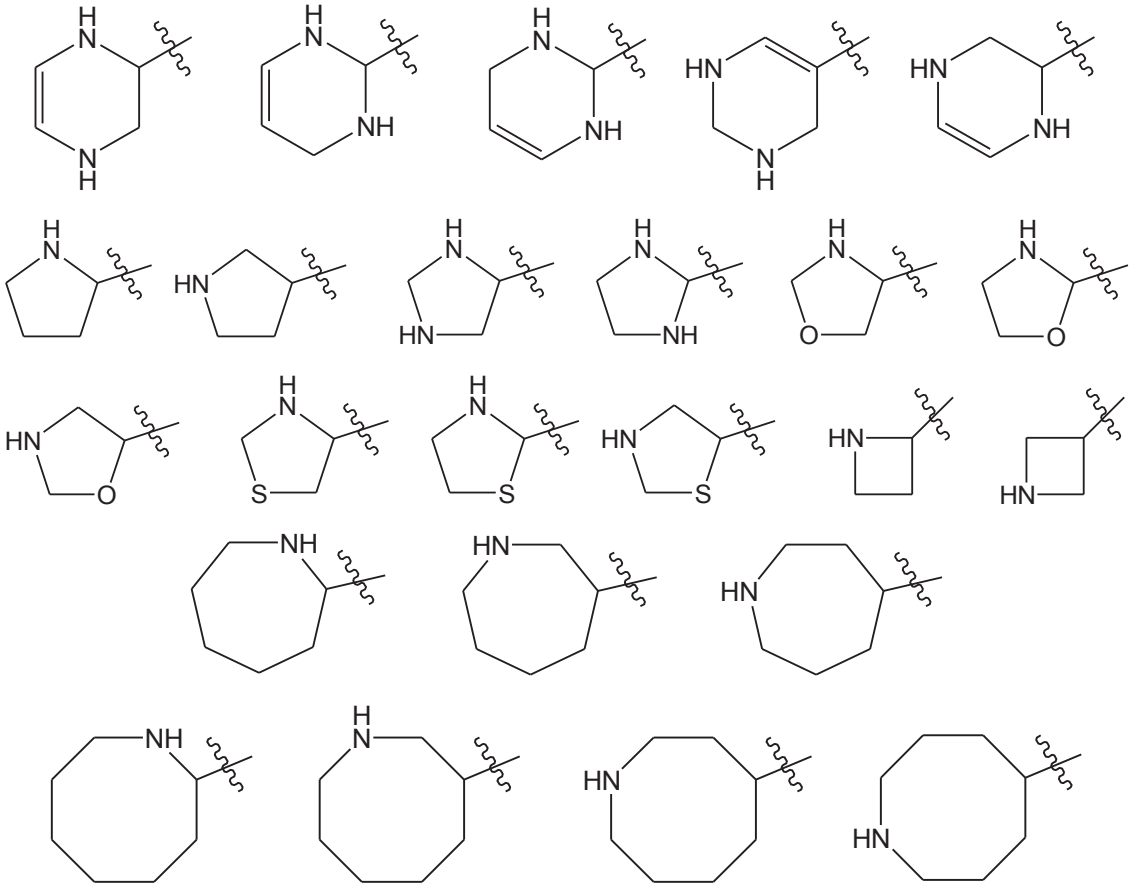
Typically R^1 is monocyclic or bicyclic. In one example, R^1 is a 4-, 5-, 6- or 7-membered monocyclic ring or a 7-, 8-, 9- or 10-membered bicyclic ring, wherein R^1 may optionally be substituted. In one example, R^1 is a 4-, 5- or 6-membered monocyclic ring or a 7-, 8-,

9- or 10-membered bicyclic ring, wherein R^1 may optionally be substituted.

The non-aromatic heterocyclic group of R^1 may be fully saturated or partially unsaturated. In one example, the non-aromatic heterocyclic group of R^1 is fully saturated.

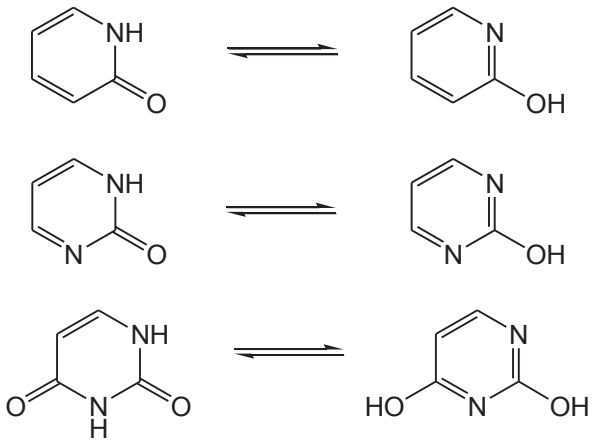
In one example, the non-aromatic heterocyclic group of R^1 is monocyclic. Where the non-aromatic heterocyclic group of R^1 is monocyclic, it may optionally be substituted with any monovalent substituent or any divalent π-bonded substituent, such as those defined above, but may not be substituted with a divalent bridging substituent (e.g. -O-, -S-, -NH-, -N(R^β)- or -R^α-) so as to form a bridged, fused or spiro substituent. Examples of monocyclic non-aromatic heterocyclic groups include:

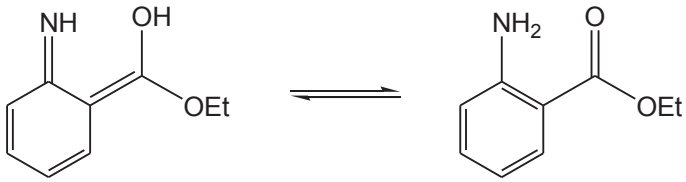




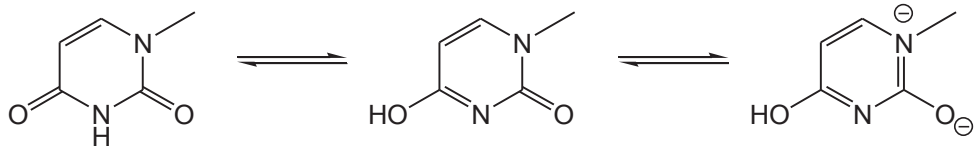
The non-aromatic heterocyclic group of R^1 may comprise one or more double bonds in the heterocyclic ring, provided the heterocyclic ring is non-aromatic. The non-aromatic heterocyclic group of R^1 does not have any tautomers that are aromatic.

The following are considered aromatic heterocyclic groups, because they have an aromatic tautomer:



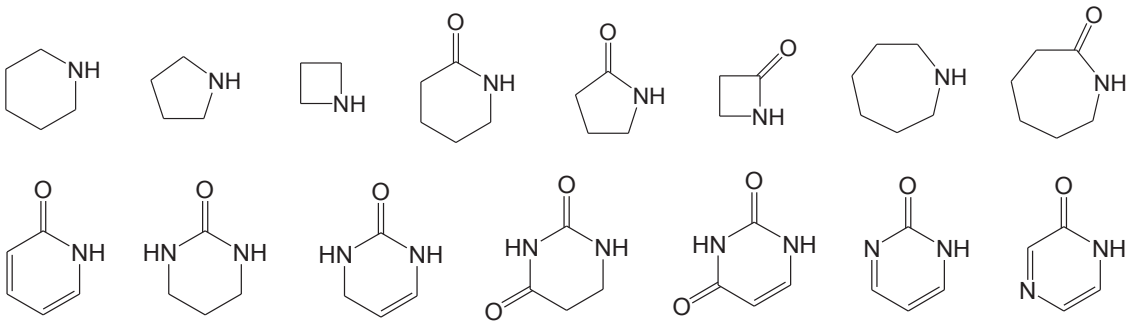


For the avoidance of doubt, the term "non-aromatic heterocyclic group" does not exclude heterocyclic groups or moieties which may possess aromatic character only by virtue of mesomeric charge separation. For example, the following is considered a non-aromatic heterocyclic group, because it does not have an aromatic tautomer:

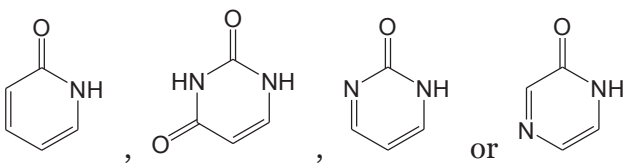


because the last shown tautomer is not taken into consideration because of mesomeric charge separation.

In one example, the non-aromatic heterocyclic group of R^1 is monocyclic and is selected from:

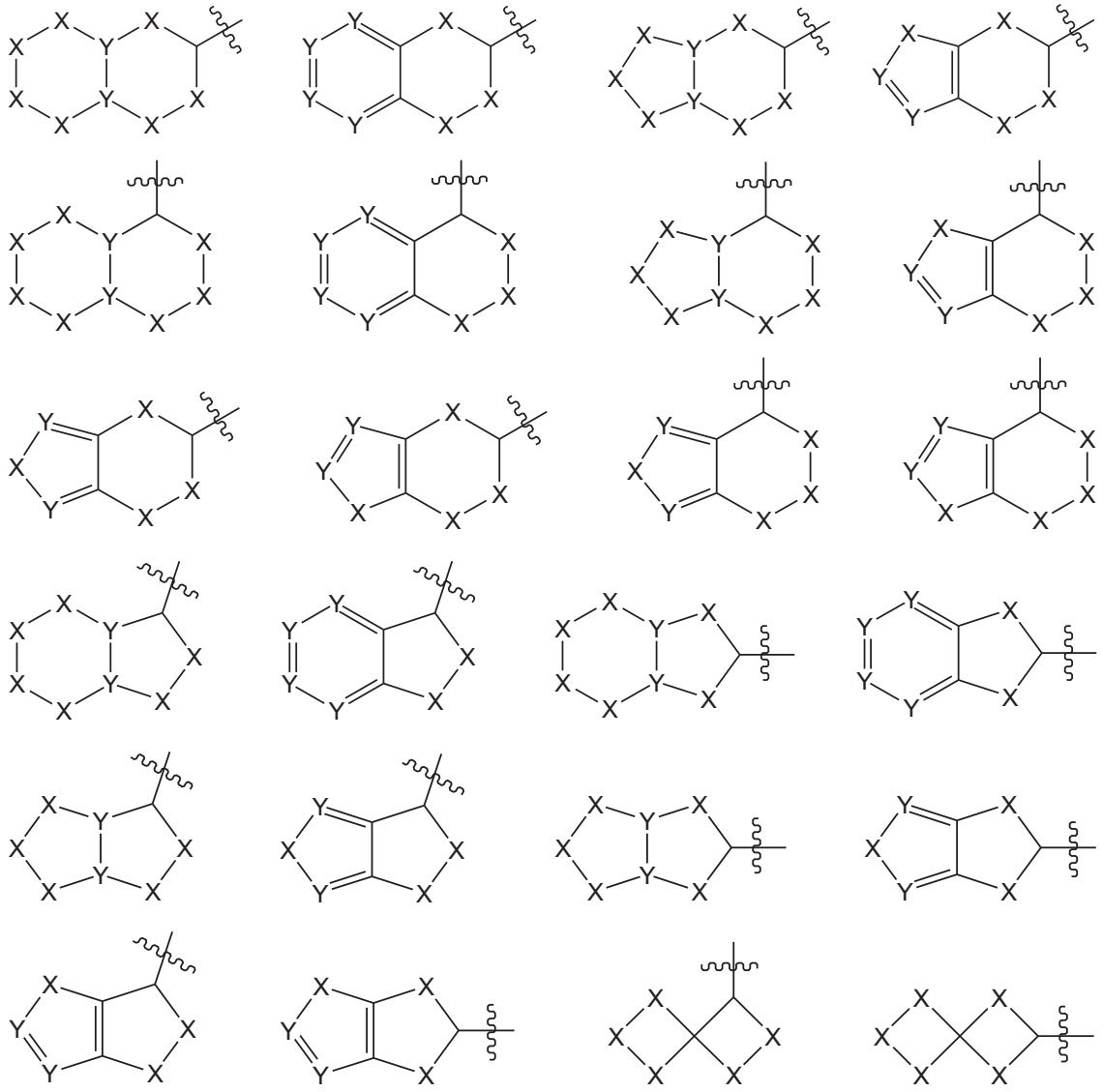


wherein R^1 may optionally be substituted or further substituted. Such non-aromatic heterocyclic R^1 groups are attached to the sulfur atom of the sulfonylurea group by any suitable ring carbon atom. Where the non-aromatic heterocyclic group of R^1 is monocyclic and is selected from:



, , or , at least one ring nitrogen atom which is adjacent to a carbonyl group is substituted, so that the non-aromatic heterocyclic group of R^1 does not have any tautomers that are aromatic.

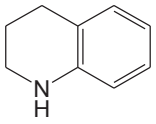
In another example, the non-aromatic heterocyclic group of R^1 may be substituted with one or more fused cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl rings such that the resultant group is bicyclic, tricyclic or polycyclic. For example, the non-aromatic heterocyclic group of R^1 may optionally be substituted with $-R^{\alpha}-$ as defined above. The resultant group may optionally be further substituted with any monovalent substituent or any divalent π-bonded substituent, such as those defined above. Typically in such an example, the resultant group is bicyclic or tricyclic, most typically bicyclic. Examples of such resultant bicyclic groups include:



wherein each X is independently CH_2, NH, O or S, and each Y is independently CH or N, and wherein the at least one ring nitrogen atom of R^1 is in a non-aromatic ring, and provided that non-aromatic heteroatoms are not adjacent each other. Typically such bicyclic groups comprise 1, 2 or 3 ring heteroatoms N, O or S. In one example, the at

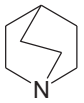
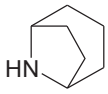
least one ring nitrogen atom of R^1 is in the non-aromatic ring of R^1 that is directly attached to the sulfur atom of the sulfonylurea group.

In one example, the non-aromatic heterocyclic group of R^1 is a fused bicyclic ring. For example, the non-aromatic heterocyclic group of R^1 may be:

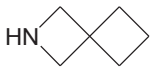


, wherein R^1 may optionally be substituted. Such a non-aromatic heterocyclic R^1 group is attached to the sulfur atom of the sulfonylurea group by any suitable non-aromatic ring carbon atom.

In another example, the non-aromatic heterocyclic group of R^1 is a bridged bicyclic ring. For example, the non-aromatic heterocyclic group of R^1 may be:

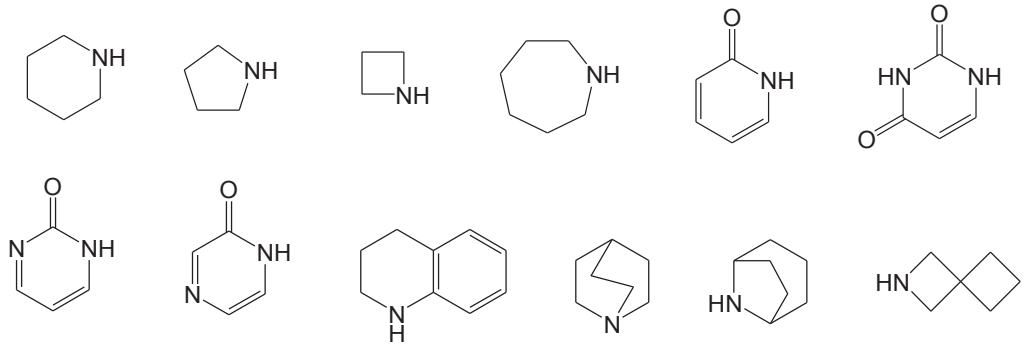
 or  , wherein R^1 may optionally be substituted. Such non-aromatic heterocyclic R^1 groups are attached to the sulfur atom of the sulfonylurea group by any suitable ring carbon atom.

In yet another example, the non-aromatic heterocyclic group of R^1 is a spiro bicyclic ring. For example, the non-aromatic heterocyclic group of R^1 may be:



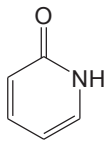
, wherein R^1 may optionally be substituted. Such a non-aromatic heterocyclic R^1 group is attached to the sulfur atom of the sulfonylurea group by any suitable ring carbon atom.

In one example, the non-aromatic heterocyclic group of R^1 is selected from:



wherein R^1 may optionally be substituted or further substituted. Such non-aromatic heterocyclic R^1 groups are attached to the sulfur atom of the sulfonylurea group by any

suitable non-aromatic ring carbon atom. Where the non-aromatic heterocyclic group of R^1 is selected from:



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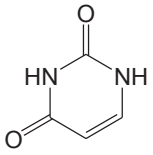

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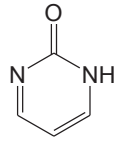
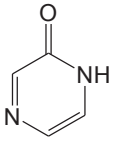
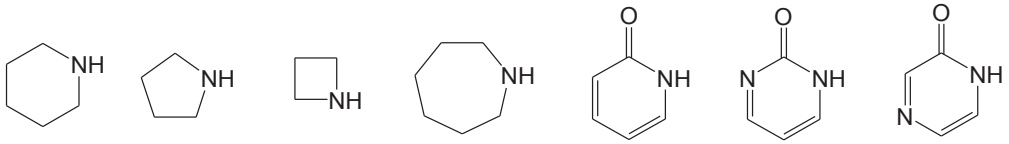


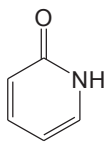
or


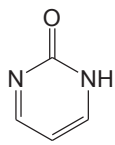
, at least one ring nitrogen atom which is adjacent to a carbonyl group is substituted, so that the non-aromatic heterocyclic group of R^1 does not have any tautomers that are aromatic.

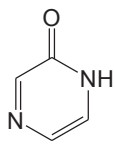
In one example, the non-aromatic heterocyclic group of R^1 is selected from:



wherein R^1 may optionally be substituted or further substituted. Such non-aromatic heterocyclic R^1 groups are attached to the sulfur atom of the sulfonylurea group by any suitable ring carbon atom. Where the non-aromatic heterocyclic group of R^1 is selected from:

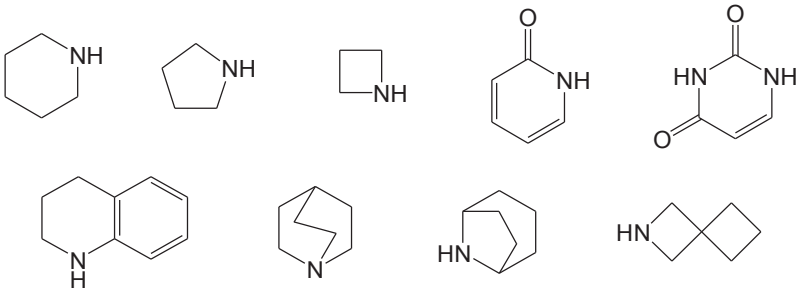


,


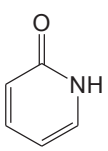
or


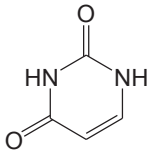
, at least one ring nitrogen atom which is adjacent to a carbonyl group is substituted, so that the non-aromatic heterocyclic group of R^1 does not have any tautomers that are aromatic.

In one example, the non-aromatic heterocyclic group of R^1 is selected from:



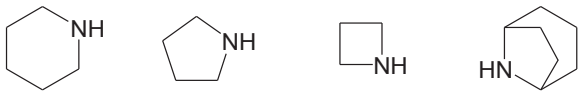
wherein R^1 may optionally be substituted or further substituted. Such non-aromatic heterocyclic R^1 groups are attached to the sulfur atom of the sulfonylurea group by any suitable non-aromatic ring carbon atom. Where the non-aromatic heterocyclic group of R^1 is selected from:



or 

, at least one ring nitrogen atom is substituted, so that the non-aromatic heterocyclic group of R^1 does not have any tautomers that are aromatic.

In one example, the non-aromatic heterocyclic group of R^1 is selected from:



wherein R^1 may optionally be substituted or further substituted. Such non-aromatic heterocyclic R^1 groups are attached to the sulfur atom of the sulfonylurea group by any suitable ring carbon atom.

R^1 is a non-aromatic heterocyclic group comprising at least one ring nitrogen atom. In one example, R^1 comprises one, two or three ring nitrogen, oxygen or sulfur atoms. In another example, R^1 comprises one or two ring nitrogen or oxygen atoms. In another example, R^1 comprises one or two ring nitrogen atoms. In yet another example, R^1 comprises one ring nitrogen atom.

R^1 may optionally be substituted with one or more substituents, such as those defined above.

In one example, R^1 is substituted with one or more (such as one, two or three) substituents independently selected from halo; -CN; $-NO_2$; $-N_3$; $-R^\beta$; -OH; $-OR^\beta$; $-R^\alpha$-halo; $-R^\alpha$-CN; $-R^\alpha$-NO_2; $-R^\alpha$-N_3; $-R^\alpha$-R^β; $-R^\alpha$-OH; $-R^\alpha$-OR^β; -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; $-R^\alpha$-$SO_2N(R^\beta)_2$; $-Si(R^\beta)_3$; $-O-Si(R^\beta)_3$; $-R^\alpha$-$Si(R^\beta)_3$; $-R^\alpha$-$O-Si(R^\beta)_3$; $-NH_2$; $-NHR^\beta$; $-N(R^\beta)_2$; $-N(O)(R^\beta)_2$; $-N^+(R^\beta)_3$; $-R^\alpha$-NH_2; $-R^\alpha$-NHR^β; $-R^\alpha$-$N(R^\beta)_2$; $-R^\alpha$-$N(O)(R^\beta)_2$; $-R^\alpha$-$N^+(R^\beta)_3$; -CHO; $-COR^\beta$; -COOH; $-COOR^\beta$; $-OCOR^\beta$; $-R^\alpha$-CHO; $-R^\alpha$-COR^β; $-R^\alpha$-COOH; $-R^\alpha$-$COOR^\beta$; $-R^\alpha$-$OCOR^\beta$; $-C(=NH)R^\beta$; $-C(=NH)NH_2$; $-C(=NH)NHR^\beta$; $-C(=NH)N(R^\beta)_2$; $-C(=NR^\beta)R^\beta$; $-C(=NR^\beta)NHR^\beta$; $-C(=NR^\beta)N(R^\beta)_2$; $-C(=NOH)R^\beta$; $-C(N_2)R^\beta$; $-R^\alpha$-$C(=NH)R^\beta$; $-R^\alpha$-$C(=NH)NH_2$; $-R^\alpha$-$C(=NH)NHR^\beta$; $-R^\alpha$-$C(=NH)N(R^\beta)_2$; $-R^\alpha$-$C(=NR^\beta)R^\beta$; $-R^\alpha$-$C(=NR^\beta)NHR^\beta$; $-R^\alpha$-$C(=NR^\beta)N(R^\beta)_2$; $-R^\alpha$-$C(=NOH)R^\beta$; $-R^\alpha$-$C(N_2)R^\beta$; -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;

$-R^{\alpha}-NH-COR^{\beta}$; $-R^{\alpha}-NR^{\beta}-COR^{\beta}$; $-R^{\alpha}-CONH_2$; $-R^{\alpha}-CONHR^{\beta}$; $-R^{\alpha}-CON(R^{\beta})_2$; $-O-R^{\alpha}-OH$; $-O-R^{\alpha}-OR^{\beta}$; $-O-R^{\alpha}-NH_2$; $-O-R^{\alpha}-NHR^{\beta}$; $-O-R^{\alpha}-N(R^{\beta})_2$; $-O-R^{\alpha}-N(O)(R^{\beta})_2$; $-O-R^{\alpha}-N^{+}(R^{\beta})_3$; $-NH-R^{\alpha}-OH$; $-NH-R^{\alpha}-OR^{\beta}$; $-NH-R^{\alpha}-NH_2$; $-NH-R^{\alpha}-NHR^{\beta}$; $-NH-R^{\alpha}-N(R^{\beta})_2$; $-NH-R^{\alpha}-N(O)(R^{\beta})_2$; $-NH-R^{\alpha}-N^{+}(R^{\beta})_3$; $-NR^{\beta}-R^{\alpha}-OH$; $-NR^{\beta}-R^{\alpha}-OR^{\beta}$; $-NR^{\beta}-R^{\alpha}-NH_2$; $-NR^{\beta}-R^{\alpha}-NHR^{\beta}$; $-NR^{\beta}-R^{\alpha}-N(R^{\beta})_2$; $-NR^{\beta}-R^{\alpha}-N(O)(R^{\beta})_2$; $-NR^{\beta}-R^{\alpha}-N^{+}(R^{\beta})_3$; $-N(O)R^{\beta}-R^{\alpha}-OH$; $-N(O)R^{\beta}-R^{\alpha}-OR^{\beta}$; $-N(O)R^{\beta}-R^{\alpha}-NH_2$; $-N(O)R^{\beta}-R^{\alpha}-NHR^{\beta}$; $-N(O)R^{\beta}-R^{\alpha}-N(R^{\beta})_2$; $-N(O)R^{\beta}-R^{\alpha}-N(O)(R^{\beta})_2$; $-N(O)R^{\beta}-R^{\alpha}-N^{+}(R^{\beta})_3$; $-N^{+}(R^{\beta})_2-R^{\alpha}-OH$; $-N^{+}(R^{\beta})_2-R^{\alpha}-OR^{\beta}$; $-N^{+}(R^{\beta})_2-R^{\alpha}-NH_2$; $-N^{+}(R^{\beta})_2-R^{\alpha}-NHR^{\beta}$; $-N^{+}(R^{\beta})_2-R^{\alpha}-N(R^{\beta})_2$; or $-N^{+}(R^{\beta})_2-R^{\alpha}-N(O)(R^{\beta})_2$;

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, wherein one or more $-CH_2-$ groups in the backbone of the alkylene, alkenylene or alkynylene group may optionally be replaced by one or more $-N(O)(R^{\beta})-$ or $-N^{+}(R^{\beta})_2-$ groups, and wherein the alkylene, alkenylene or alkynylene group may optionally be substituted with one or more halo and/or $-R^{\beta}$ groups; and

wherein each $-R^{\beta}$ 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, or wherein any two or three $-R^{\beta}$ attached to the same nitrogen atom may, together with the nitrogen atom to which they are attached, form a C_2-C_7 cyclic group, and wherein any $-R^{\beta}$ may optionally be substituted with one or more C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 halocycloalkyl, $-O(C_1$-C_4 alkyl), $-O(C_1$-C_4 haloalkyl), $-O(C_3$-C_7 cycloalkyl), $-O(C_3$-C_7 halocycloalkyl), $-CO(C_1$-C_4 alkyl), $-CO(C_1$-C_4 haloalkyl), $-COO(C_1$-C_4 alkyl), $-COO(C_1$-C_4 haloalkyl), halo, -OH, $-NH_2$, -CN, $-C{\equiv}CH$, oxo (=O), or 4- to 6-membered heterocyclic group.
Typically, R^1 is substituted on one or more ring nitrogen atoms with such a substituent.

In another example, R^1 is substituted with one or more (such as one, two or three) substituents independently selected from halo; -CN; $-NO_2$; $-N_3$; $-R^{\beta}$; -OH; $-OR^{\beta}$; -SH; $-SR^{\beta}$; $-SO_2R^{\beta}$; $-NH_2$; $-NHR^{\beta}$; $-N(R^{\beta})_2$; -CHO; $-COR^{\beta}$; -COOH; $-COOR^{\beta}$; $-OCOR^{\beta}$; $-R^{\alpha}-CHO$; $-R^{\alpha}-COR^{\beta}$; $-R^{\alpha}-COOH$; $-R^{\alpha}-COOR^{\beta}$; $-R^{\alpha}-OCOR^{\beta}$; -NH-CHO; $-NR^{\beta}-CHO$; $-NH-COR^{\beta}$; $-NR^{\beta}-COR^{\beta}$; $-CONH_2$; $-CONHR^{\beta}$; $-CON(R^{\beta})_2$; $-R^{\alpha}-NH-CHO$; $-R^{\alpha}-NR^{\beta}-CHO$; $-R^{\alpha}-NH-COR^{\beta}$; $-R^{\alpha}-NR^{\beta}-COR^{\beta}$; $-R^{\alpha}-CONH_2$; $-R^{\alpha}-CONHR^{\beta}$; $-R^{\alpha}-CON(R^{\beta})_2$; $-O-R^{\alpha}-OH$; $-O-R^{\alpha}-OR^{\beta}$; $-O-R^{\alpha}-NH_2$; $-O-R^{\alpha}-NHR^{\beta}$; $-O-R^{\alpha}-N(R^{\beta})_2$; $-NH-R^{\alpha}-OH$; $-NH-R^{\alpha}-OR^{\beta}$; $-NH-R^{\alpha}-NH_2$; $-NH-R^{\alpha}-NHR^{\beta}$; $-NH-R^{\alpha}-N(R^{\beta})_2$; $-NR^{\beta}-R^{\alpha}-OH$; $-NR^{\beta}-R^{\alpha}-OR^{\beta}$; $-NR^{\beta}-R^{\alpha}-NH_2$; $-NR^{\beta}-R^{\alpha}-NHR^{\beta}$; $-NR^{\beta}-R^{\alpha}-N(R^{\beta})_2$; a C_3-C_7 cycloalkyl group optionally

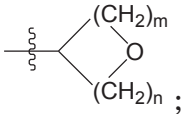
substituted with one or more C_1-C_3 alkyl or C_1-C_3 haloalkyl groups; a C_3-C_7 cycloalkenyl group optionally substituted with one or more C_1-C_3 alkyl or C_1-C_3 haloalkyl groups; a 3- to 7-membered non-aromatic heterocyclic group optionally substituted with one or more C_1-C_6 alkyl or C_1-C_3 haloalkyl groups; oxo (=O); or a C_1-C_4 alkylene bridge;

wherein each -R^{α}- 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.

Typically, R^1 is substituted on one or more ring nitrogen atoms with such a substituent.

In another example, R^1 is substituted with one or more (such as one, two or three) substituents independently selected from halo; -CN; -NO_2; -N_3; -R^{β}; -OH; -OR^{β}; -SH; -SR^{β}; -SO_2R^{β}; -NH_2; -NHR^{β}; -N(R^{β})$_2$; -CHO; -COR^{β}; -COOH; -COOR^{β}; -OCOR^{β}; -R^{α}-CHO; -R^{α}-COR^{β}; -R^{α}-COOH; -R^{α}-COOR^{β}; -R^{α}-OCOR^{β}; -NH-CHO; -NR^{β}-CHO; -NH-COR^{β}; -NR^{β}-COR^{β}; -$CONH_2$; -CONHR^{β}; -CON(R^{β})$_2$; -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^{β}; -R^{α}-CON(R^{β})$_2$; 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;



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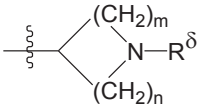


; oxo (=O); or a C_1-C_4 alkylene bridge;

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;

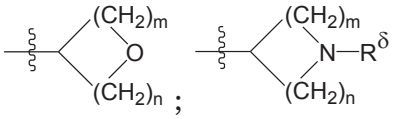
wherein each -R^{δ} is independently selected from a C_1-C_6 alkyl or C_1-C_3 haloalkyl group;

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

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

Typically, R^1 is substituted on one or more ring nitrogen atoms with such a substituent.

In another example, R^1 is substituted with one or more (such as one, two or three) substituents independently selected from halo; -CN; -N_3; -R^{β}; -SO_2R^{β}; -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}; -$COOR^{\beta}$; -$OCOR^{\beta}$; -R^{α}-CHO; -R^{α}-COR^{β}; -R^{α}-$COOR^{\beta}$; -R^{α}-$OCOR^{\beta}$; -NH-CHO; -NR^{β}-CHO; -NH-COR^{β}; -NR^{β}-COR^{β}; -$CONH_2$; -$CONHR^{\beta}$; -$CON(R^{\beta})_2$;



; ; or oxo (=O);

wherein each -R^{α}- is independently selected from a C_1-C_3 alkylene group;

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

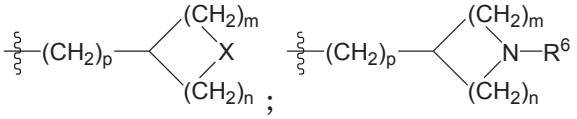
wherein each -R^{δ} is independently selected from a C_1-C_6 alkyl group;

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

wherein each n is independently selected from 1 or 2.

Typically, R^1 is substituted on one or more ring nitrogen atoms with such a substituent.

In one example, R^1 is substituted with one or more (such as one, two or three) substituents independently selected from halo; C_1-C_6 alkyl; C_1-C_6 haloalkyl; C_2-C_6 alkenyl; C_2-C_6 haloalkenyl; C_2-C_6 alkynyl; C_2-C_6 haloalkynyl; -R^5-CN; -R^5-N_3; -R^5-NO_2; -R^5-$N(R^6)_2$; -R^5-OR^6; -R^5-SR^6; -R^5-$Si(R^6)_3$; -R^5-O-$Si(R^6)_3$; -R^5-COR^6; -R^5-$COOR^6$; -R^5-CO-R^5-OR^6; -R^5-$CON(R^6)_2$; -R^5-CO-R^5-$N(R^6)_2$; -R^5-$C(=NR^6)R^6$; -R^5-$C(=NR^6)N(R^6)_2$; -R^5-C(=NOH)R^6; -R^5-SO_2R^6; -R^5-phenyl; -R^5-(Het);



; ; oxo (=O); -CH_2CH_2-; -$CH_2CH_2CH_2$-; -$CH_2CH_2CH_2CH_2$-; -CH=CH-CH=CH_2-; or -R^5-(C_3-C_6 cycloalkyl) wherein the C_3-C_6 cycloalkyl group is optionally substituted with one or two substituents independently selected from C_1-C_3 alkyl; wherein

R^5 is independently selected from a bond or C_1-C_5 alkylene;

R^6 is independently selected from hydrogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_6 cycloalkyl, -CO-(C_1-C_3 alkyl), -COO-(C_1-C_4 alkyl) or benzyl;

Het is selected from a pyridinyl, 2-oxo-1,2-dihydropyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl or diazirinyl group, each of which may optionally be substituted with one or two substituents independently selected from halo, C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl;

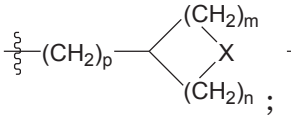
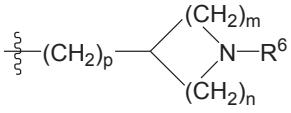
X is selected from O, S, SO or SO_2;

m is 1, 2 or 3;

n is 1, 2 or 3; and

p is 0, 1 or 2.

Typically, R^1 is substituted on one or more ring nitrogen atoms with such a substituent.

In one example, R^1 is substituted on one or more (such as one, two or three) ring nitrogen atoms with a substituent independently selected from halo; C_1-C_6 alkyl; C_1-C_6 haloalkyl; C_2-C_6 alkenyl; C_2-C_6 haloalkenyl; C_2-C_6 alkynyl; C_2-C_6 haloalkynyl; -R^5-CN; -R^5-N_3; -R^5-NO_2; -R^5-$N(R^6)_2$; -R^5-OR^6; -R^5-SR^6; -R^5-$Si(R^6)_3$; -R^5-O-$Si(R^6)_3$; -R^5-COR^6; -R^5-$COOR^6$; -R^5-CO-R^5-OR^6; -R^5-$CON(R^6)_2$; -R^5-CO-R^5-$N(R^6)_2$; -R^5-$C(=NR^6)R^6$; -R^5-$C(=NR^6)N(R^6)_2$; -R^5-$C(=NOH)R^6$; -R^5-SO_2R^6; -R^5-phenyl; -R^5-(Het);  ;  ; oxo (=O); -CH_2CH_2-; -$CH_2CH_2CH_2$-; -$CH_2CH_2CH_2CH_2$-; or -R^5-(C_3-C_6 cycloalkyl) wherein the C_3-C_6 cycloalkyl group is optionally substituted with one or two substituents independently selected from C_1-C_3 alkyl; wherein

R^5 is independently selected from a bond or C_1-C_5 alkylene;

R^6 is independently selected from hydrogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_6 cycloalkyl, -CO-(C_1-C_3 alkyl), -COO-(C_1-C_4 alkyl) or benzyl;

Het is selected from a pyridinyl, 2-oxo-1,2-dihydropyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl or diazirinyl group, each of which may optionally be substituted with one or two substituents independently selected from halo, C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl;

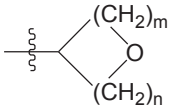
X is selected from O, S, SO or SO_2;

m is 1, 2 or 3;

n is 1, 2 or 3; and

p is 0, 1 or 2.

In one example, R^1 is substituted on one or more (such as one, two or three) ring nitrogen atoms with a substituent independently selected from halo; C_1-C_6 alkyl; C_1-C_6 haloalkyl; C_2-C_6 alkenyl; C_2-C_6 haloalkenyl; C_2-C_6 alkynyl; C_2-C_6 haloalkynyl; -R^5-CN; -R^5-N_3; -R^5-NO_2; -R^5-$N(R^6)_2$; -R^5-OR^6; -R^5-COR^6; -R^5-$COOR^6$; -R^5-CO-R^5-OR^6; -R^5-$CON(R^6)_2$; -R^5-CO-R^5-$N(R^6)_2$; -R^5-SO_2R^6; -R^5-phenyl; -R^5-pyridinyl; -R^5-(C_3-C_6 cycloalkyl);



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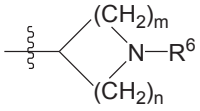


; oxo (=O); -$CH_2CH_2CH_2$-; or -$CH_2CH_2CH_2CH_2$-; wherein

R^5 is independently selected from a bond or C_1-C_5 alkylene;

R^6 is independently selected from hydrogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_6 cycloalkyl, -CO-(C_1-C_3 alkyl) or benzyl;

m is 1, 2 or 3; and

n is 1, 2 or 3.

In one example, R^1 is substituted on one or more (such as one, two or three) ring carbon atoms with a substituent independently selected from oxo (=O); -CH_2CH_2-; -$CH_2CH_2CH_2$-; -$CH_2CH_2CH_2CH_2$-; -CH=CH-CH=CH_2-; -OR^7 or -$CON(R^7)_2$; wherein R^7 is independently selected from hydrogen or C_1-C_3 alkyl.

In one example, R^1 is substituted on one or more (such as one, two or three) ring carbon atoms with a substituent independently selected from oxo (=O); -$CH_2CH_2CH_2$-; -$CH_2CH_2CH_2CH_2$-; or -CH=CH-CH=CH_2-.

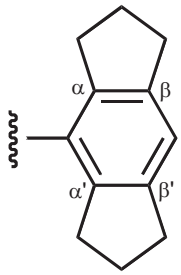
In one example of any of the above example s, R^1 contains from 4 to 25 atoms other than hydrogen. More typically, R^1 contains from 4 to 20 atoms other than hydrogen. More typically, R^1 contains from 4 to 17 atoms other than hydrogen.

R^2 is a cyclic group substituted at the α-position, wherein R^2 may optionally be further substituted. For the avoidance of doubt, it is noted that it is a ring atom of the cyclic group of R^2 that is directly attached to the nitrogen atom of the urea or thiourea group, not any substituent.

In one example of the first aspect of the disclosure, 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. Typically, R^2 is a phenyl or a 5- or 6-membered

heteroaryl group, wherein the phenyl or the heteroaryl group is substituted at the α-position, and wherein R^2 may optionally be further substituted. Typically, 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. Typically, R^2 is a phenyl or a 5- or 6-membered heteroaryl group, wherein the phenyl or the heteroaryl group is substituted at the α and α' positions, and wherein R^2 may optionally be further substituted. For example, R^2 may be a phenyl group substituted at the 2- and 6-positions or a phenyl group substituted at the 2-, 4- and 6-positions.

As used herein, the nomenclature α, β, α', β' refers to the position of the atoms of a cyclic group, such as $-R^2$, relative to the point of attachment of the cyclic group to the remainder of the molecule. For example, where $-R^2$ is a 1,2,3,5,6,7-hexahydro-s-indacen-4-yl moiety, the α, β, α' and β' positions are as follows:



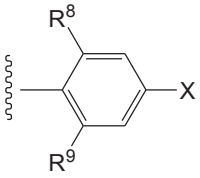
In another example, R^2 is a cyclic group substituted at the α and α' positions, wherein R^2 may optionally be further substituted. For example, R^2 may be a cycloalkyl, cycloalkenyl or non-aromatic heterocyclic group substituted at the α and α' positions.

In any of the above examples, typical substituents at the α and/or α' positions of the parent cyclic group of R^2 comprise a carbon atom. For example, typical substituents at the α and/or α' positions of the parent cyclic group of R^2 may be independently selected from $-R^4$, $-OR^4$ and $-COR^4$ groups, wherein each R^4 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 each R^4 is optionally further substituted with one or more halo groups. More typically, the substituents at the α and/or α' positions are independently selected from alkyl and cycloalkyl groups, such as C_3-C_6 branched alkyl and C_3-C_6 cycloalkyl groups, e.g. isopropyl, cyclopropyl, cyclohexyl or t-butyl groups, wherein the alkyl and cycloalkyl groups are optionally further substituted with one or more fluoro and/or chloro groups.

In one example of any of the above example s, each substituent at the α and α' positions

comprises a carbon atom.

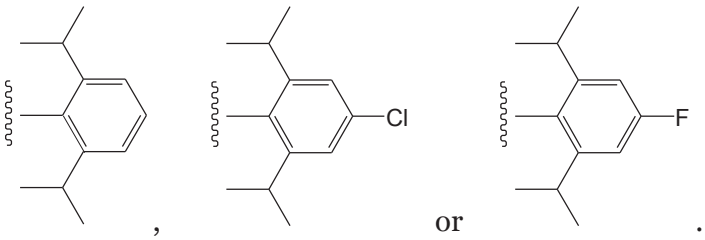
In one example, -R^2 has a formula selected from:



,

wherein R^8 and R^9 are independently selected from C_1-C_4 alkyl, and X is hydrogen or halo.

Typically, -R^2 has a formula selected from:



, or .

Other typical substituents at the α and/or α' positions of the parent cyclic group of R^2 may include cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl rings which are fused to the parent cyclic group across the α,β and/or α',β' positions respectively. Such fused cyclic groups are described in greater detail below.

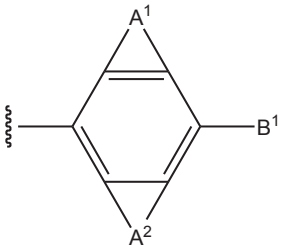
In one example, R^2 is a fused aryl or a fused heteroaryl group, wherein the aryl or heteroaryl group is fused to one or more cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl rings, wherein R^2 may optionally be further substituted.

In another example, R^2 is a fused aryl or a fused heteroaryl group, wherein the aryl or heteroaryl group is fused to two or more independently selected cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl rings, wherein R^2 may optionally be further substituted. Typically, the two or more cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl rings are each ortho-fused to the aryl or heteroaryl group, i.e. each fused cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring has only two atoms and one bond in common with the aryl or heteroaryl group. Typically, R^2 is tricyclic.

In yet another example, 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, wherein R^2 may optionally be further substituted.

In one example, $-R^2$ has a formula selected from:



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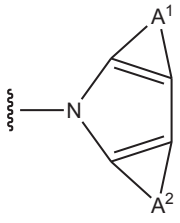

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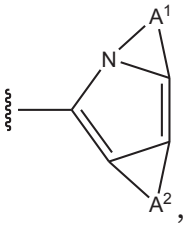

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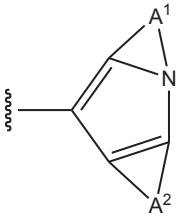
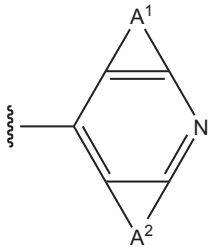


or


,

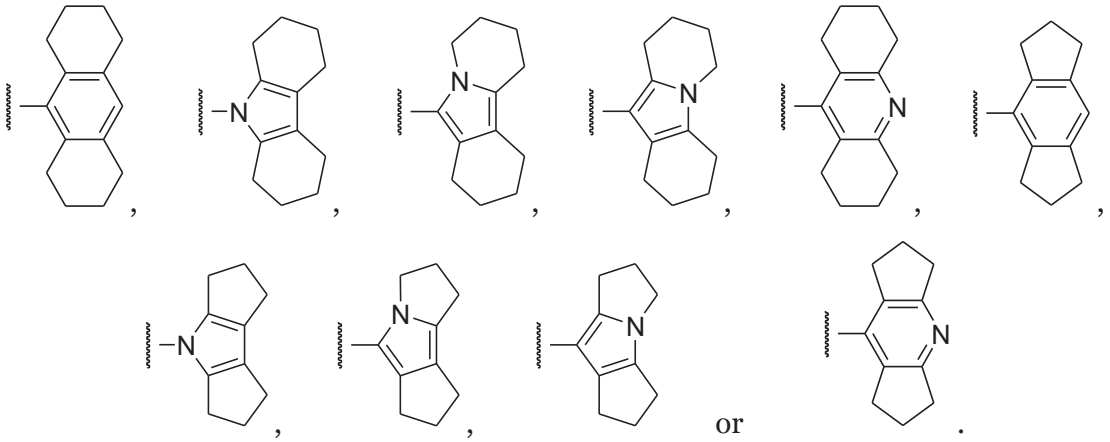
wherein A^1 and A^2 are each independently selected from an optionally substituted alkylene or alkenylene group, wherein one or more carbon atoms in the backbone of the alkylene or alkenylene group may optionally be replaced by one or more heteroatoms N, O or S, and wherein B^1 is hydrogen or any optional substituent. B^1 and any optional substituent attached to A^1 or A^2 may together with the atoms to which they are attached form a further fused cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which may itself be optionally substituted. Similarly, any optional substituent attached to A^1 and any optional substituent attached to A^2 may also together with the atoms to which they are attached form a further fused cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which may itself be optionally substituted.

Typically, B^1 is hydrogen or a halo, hydroxyl, -CN, $-NO_2$, $-B^2$ or $-OB^2$ group, wherein B^2 is a C_1-C_4 alkyl group which may optionally be halo-substituted.

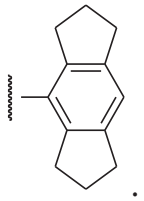
Typically, any ring containing A^1 or A^2 is a 5- or 6-membered ring. Typically, A^1 and A^2 are unsubstituted or substituted with one or more halo, hydroxyl, -CN, $-NO_2$, $-B^3$ or $-OB^3$ groups, wherein B^3 is a C_1-C_4 alkyl group which may optionally be halo-

substituted.

In a further example, -R^2 has a formula selected from:



Typically, -R^2 has the formula:



Yet other typical substituents at the α-position of the parent cyclic group of R^2 may include monovalent heterocyclic groups and monovalent aromatic groups, wherein a ring atom of the heterocyclic or aromatic group is directly attached via a single bond to the α-ring atom of the parent cyclic group, wherein the heterocyclic or aromatic group may optionally be substituted, and wherein the parent cyclic group may optionally be further substituted. Such R^2 groups are described in greater detail below.

In one example, the α-substituted parent cyclic group of R^2 is a 5- or 6-membered cyclic group, wherein the cyclic group may optionally be further substituted. In one example, the α-substituted parent cyclic group of R^2 is an aryl or a heteroaryl group, all of which may optionally be further substituted. In one example, the α-substituted parent cyclic group of R^2 is a phenyl or a 5- or 6-membered heteroaryl group, all of which may optionally be further substituted. In one example, the α-substituted parent cyclic group of R^2 is a phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl or oxadiazolyl group, all of which may optionally be further substituted. In one example,

the α-substituted parent cyclic group of R^2 is a phenyl group, which may optionally be further substituted.

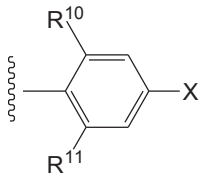
In one example, the α-substituted parent cyclic group of R^2 is substituted at the α and α' positions, and may optionally be further substituted. For example, the α-substituted parent cyclic group of R^2 may be a phenyl group substituted at the 2- and 6-positions or a phenyl group substituted at the 2-, 4- and 6-positions.

In one example, R^2 is a parent cyclic group substituted at the α-position with a monovalent heterocyclic group or a monovalent aromatic group, wherein the heterocyclic or aromatic group may optionally be substituted, and wherein the parent cyclic group may optionally be further substituted. In one example, the monovalent heterocyclic or aromatic group at the α-position is phenyl or a 5- or 6-membered heterocyclic group, all of which may optionally be substituted. In one example, the monovalent heterocyclic or aromatic group at the α-position is a phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, azetinyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, 1,3-dioxolanyl, 1,2-oxathiolanyl, 1,3-oxathiolanyl, piperidinyl, tetrahydropyranyl, thianyl, piperazinyl, 1,4-dioxanyl, morpholinyl or thiomorpholinyl group, all of which may optionally be substituted. In one example, the monovalent heterocyclic or aromatic group at the α-position is a phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, piperidinyl or tetrahydropyranyl group, all of which may optionally be substituted. In one example, the monovalent heterocyclic or aromatic group at the α-position is a phenyl, pyridinyl, pyrimidinyl, pyrazolyl, imidazolyl, isoxazolyl, thiazolyl or tetrahydropyranyl group, all of which may optionally be substituted. In one example, the monovalent heterocyclic or aromatic group at the α-position is a phenyl, pyridinyl, pyrimidinyl or pyrazolyl group, all of which may optionally be substituted with one or two substituents independently selected from halo, -OH, $-NH_2$, -CN, $-NO_2$, $-B^4$, $-OB^4$, $-NHB^4$ or $-N(B^4)_2$, wherein B^4 is independently selected from a C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl group all of which may optionally be halo-substituted. In one example, the monovalent heterocyclic or aromatic group at the α-position is an unsubstituted phenyl, pyridinyl, pyrimidinyl or pyrazolyl group. In one example, the monovalent heterocyclic group at the α-position is a pyridin-2-yl, pyridin-3-yl or pyridin-4-yl group, all of which may optionally be

substituted with one or two substituents independently selected from halo, -OH, $-NH_2$, -CN, $-NO_2$, $-B^4$, $-OB^4$, $-NHB^4$ or $-N(B^4)_2$, wherein B^4 is independently selected from a C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl group all of which may optionally be halo-substituted. In one example, the monovalent heterocyclic group at the α-position is an unsubstituted pyridin-3-yl group or a pyridin-4-yl group optionally substituted with one or two substituents independently selected from halo, -OH, $-NH_2$, -CN, $-NO_2$, $-B^4$, $-OB^4$, $-NHB^4$ or $-N(B^4)_2$, wherein B^4 is independently selected from a C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl group all of which may optionally be halo-substituted. Alternatively, any of these the monovalent heterocyclic groups at the α-position may optionally be substituted with one or two substituents independently selected from halo, -OH, $-NH_2$, -CN, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 haloalkyl, $-OB^8$ or $-N(B^8)_2$, wherein B^8 is independently selected from C_1-C_4 alkyl which may optionally be halo-substituted.

In one example, R^2 is a parent cyclic group substituted at the α-position with a monovalent heterocyclic group or a monovalent aromatic group, wherein the heterocyclic or aromatic group may optionally be substituted, and wherein the parent cyclic group may optionally be further substituted. In one example, such further substituents are in the α' position of the α-substituted parent cyclic group of R^2. Such further substituents may be independently selected from halo, $-R^\delta$, $-OR^\delta$ or $-COR^\delta$ groups, wherein each R^δ 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 each R^δ is optionally further substituted with one or more halo groups. Typically, such further substituents on the α-substituted parent cyclic group of R^2 are independently selected from halo, C_1-C_6 alkyl (in particular C_3-C_6 branched alkyl) or C_3-C_6 cycloalkyl groups, e.g. fluoro, chloro, isopropyl, cyclopropyl, cyclohexyl or t-butyl groups, wherein the alkyl and cycloalkyl groups are optionally further substituted with one or more fluoro and/or chloro groups.

In one example, $-R^2$ has a formula selected from:



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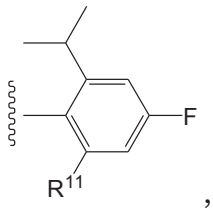
wherein R^{10} is C_1-C_4 alkyl, R^{11} is a 5- or 6-membered, optionally substituted heterocyclic or aromatic group, and X is hydrogen or halo. In one example, the optional substituents on the heterocyclic or aromatic group are selected from halo, -OH, $-NH_2$,

-CN, $-NO_2$, $-B^5$, $-OB^5$, $-NHB^5$ or $-N(B^5)_2$, wherein B^5 is independently selected from a C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl group all of which may optionally be halo-substituted. Alternatively, the optional substituents on the heterocyclic or aromatic group are selected from halo, -OH, $-NH_2$, -CN, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 haloalkyl, $-OB^8$ or $-N(B^8)_2$, wherein B^8 is independently selected from C_1-C_4 alkyl which may optionally be halo-substituted.

Typically, $-R^2$ has a formula selected from:



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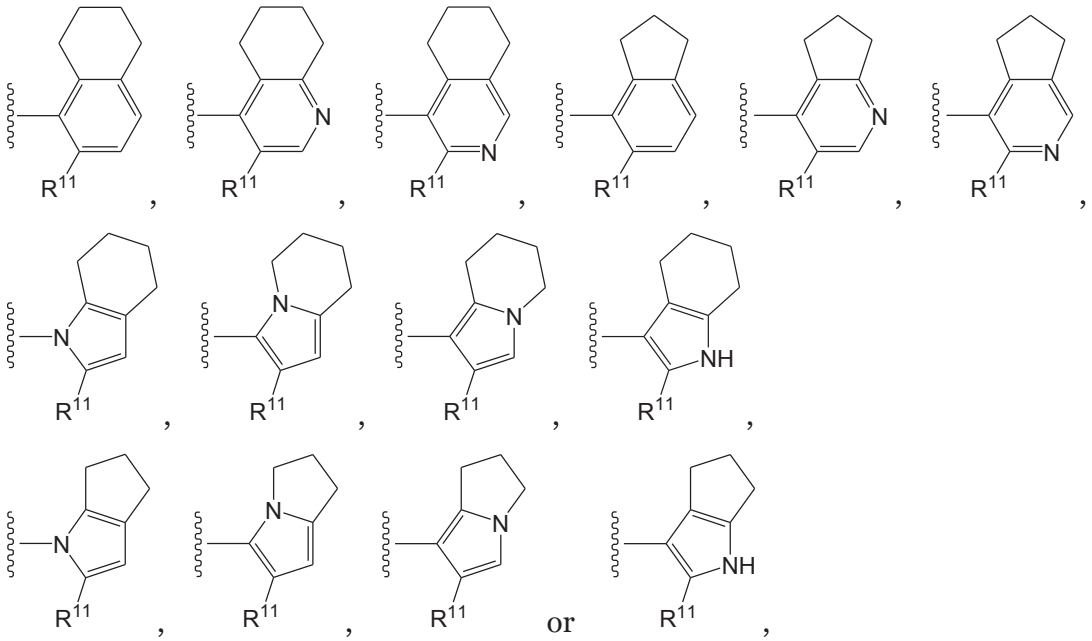
wherein R^{11} is a 5- or 6-membered, optionally substituted heterocyclic or aromatic group. In one example, the optional substituents on the heterocyclic or aromatic group are selected from halo, -OH, $-NH_2$, -CN, $-NO_2$, $-B^6$, $-OB^6$, $-NHB^6$ or $-N(B^6)_2$, wherein B^6 is independently selected from a C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl group all of which may optionally be halo-substituted. Alternatively, the optional substituents on the heterocyclic or aromatic group are selected from halo, -OH, $-NH_2$, -CN, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 haloalkyl, $-OB^8$ or $-N(B^8)_2$, wherein B^8 is independently selected from C_1-C_4 alkyl which may optionally be halo-substituted.

In one example, R^2 is a parent cyclic group substituted at the α-position with a monovalent heterocyclic group or a monovalent aromatic group, wherein the heterocyclic or aromatic group may optionally be substituted, and wherein the parent cyclic group may optionally be further substituted. The further substituents on the α-substituted parent cyclic group of R^2 also include cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl rings which are fused to the α-substituted parent cyclic group of R^2. Typically, the cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl rings are ortho-fused to the α-substituted parent cyclic group of R^2, i.e. each fused cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring has only two atoms and one bond in common with the α-substituted parent cyclic group of R^2. Typically, the cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl rings are ortho-fused to the α-substituted parent cyclic group of R^2 across the α',β' positions.

In one example, -R^2 has a formula selected from:



wherein R^{11} is a 5- or 6-membered, optionally substituted heterocyclic or aromatic group. In one example, the optional substituents on the heterocyclic or aromatic group are selected from halo, -OH, -NH_2, -CN, -NO_2, -B^7, -OB^7, -NHB^7 or -$N(B^7)_2$, wherein B^7 is independently selected from a C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl group all of which may optionally be halo-substituted. Alternatively, the optional substituents on the heterocyclic or aromatic group are selected from halo, -OH, -NH_2, -CN, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 haloalkyl, -OB^8 or -$N(B^8)_2$, wherein B^8 is independently selected from C_1-C_4 alkyl which may optionally be halo-substituted.

In one example, R^2 is phenyl or a 5- or 6-membered heteroaryl group (such as phenyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl); wherein

(i) the phenyl or 5- or 6-membered heteroaryl group is substituted at the α position with a substituent selected from -R^4, -OR^4 and -COR^4, wherein R^4 is 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 R^4 is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted at the α' position with a substituent selected from -R^{14}, -OR^{14} and -COR^{14}, wherein R^{14} is 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 R^{14} is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted (typically with one, two or three substituents independently selected from halo, -NO_2, -CN, -$COOR^{15}$, -$CONH_2$, -$CONHR^{15}$ or -$CON(R^{15})_2$, wherein each -R^{15} is

independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group); or

(ii) the phenyl or 5- or 6-membered heteroaryl group is substituted with a cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which is fused to the parent phenyl or 5- or 6-membered heteroaryl group across the α,β positions and which is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted at the α' position with a substituent selected from -R^4, -OR^4 and -COR^4, wherein R^4 is 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 R^4 is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted (typically with one or two substituents independently selected from halo, -NO_2, -CN, -$COOR^{15}$, -$CONH_2$, -$CONHR^{15}$ or -$CON(R^{15})_2$, wherein each -R^{15} is independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group); or

(iii) the phenyl or 5- or 6-membered heteroaryl group is substituted with a first cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which is fused to the parent phenyl or 5- or 6-membered heteroaryl group across the α,β positions and which is optionally substituted with one or more halo groups; and

the phenyl or 5- or 6-membered heteroaryl group is substituted with a second cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which is fused to the parent phenyl or 5- or 6-membered heteroaryl group across the α',β' positions and which is optionally substituted with one or more halo groups; and

optionally the phenyl group is further substituted (typically with a substituent selected from halo, -NO_2, -CN, -$COOR^{15}$, -$CONH_2$, -$CONHR^{15}$ or -$CON(R^{15})_2$, wherein each -R^{15} is independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group); or

(iv) the phenyl or 5- or 6-membered heteroaryl group is substituted at the α-position with a monovalent heterocyclic group or a monovalent aromatic group selected from phenyl, pyridinyl, pyrimidinyl, pyrazolyl, imidazolyl, triazolyl or tetrahydropyranyl, wherein the monovalent heterocyclic or aromatic group may optionally be substituted with one or two substituents independently selected from halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -R^{12}-OR^{13}, -R^{12}-$N(R^{13})_2$, -R^{12}-CN or -R^{12}-C≡CR^{13}, and wherein a ring atom of the monovalent heterocyclic or aromatic group is directly attached to the α-ring atom of the parent phenyl or 5- or 6-membered heteroaryl group; wherein R^{12} is independently selected from a bond or a C_1-C_3 alkylene group; and R^{13} is independently selected from hydrogen or a C_1-C_3 alkyl or C_1-C_3 haloalkyl group; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted at the α' position with a substituent selected from -R^4, -OR^4 and -COR^4,

wherein R^4 is 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 R^4 is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted (typically with one, two or three substituents independently selected from halo, $-NO_2$, -CN, $-COOR^{15}$, $-CONH_2$, $-CONHR^{15}$ or $-CON(R^{15})_2$, wherein each $-R^{15}$ is independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group); or

(v) the phenyl or 5- or 6-membered heteroaryl group is substituted at the α-position with a monovalent heterocyclic group or a monovalent aromatic group selected from phenyl, pyridinyl, pyrimidinyl, pyrazolyl, imidazolyl, triazolyl or tetrahydropyranyl, wherein the monovalent heterocyclic or aromatic group may optionally be substituted with one or two substituents independently selected from halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, $-R^{12}$-OR^{13}, $-R^{12}$-$N(R^{13})_2$, $-R^{12}$-CN or $-R^{12}$-$C{\equiv}CR^{13}$, and wherein a ring atom of the monovalent heterocyclic or aromatic group is directly attached to the α-ring atom of the parent phenyl or 5- or 6-membered heteroaryl group; wherein R^{12} is independently selected from a bond or a C_1-C_3 alkylene group; and R^{13} is independently selected from hydrogen or a C_1-C_3 alkyl or C_1-C_3 haloalkyl group; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted with a cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which is fused to the parent phenyl or 5- or 6-membered heteroaryl group across the α',β' positions and which is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted (typically with one or two substituents independently selected from halo, $-NO_2$, -CN, $-COOR^{15}$, $-CONH_2$, $-CONHR^{15}$ or $-CON(R^{15})_2$, wherein each $-R^{15}$ is independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group).

In the example directly above, where a group or moiety is optionally substituted with one or more halo groups, it may be substituted for example with one, two, three, four, five or six halo groups.

In one example of any of the above example s, R^2 contains from 15 to 50 atoms. More typically, R^2 contains from 20 to 40 atoms. Most typically, R^2 contains from 25 to 35 atoms.

In another example of any of the above example s, R^2 contains from 10 to 50 atoms other than hydrogen. More typically, R^2 contains from 10 to 40 atoms other than

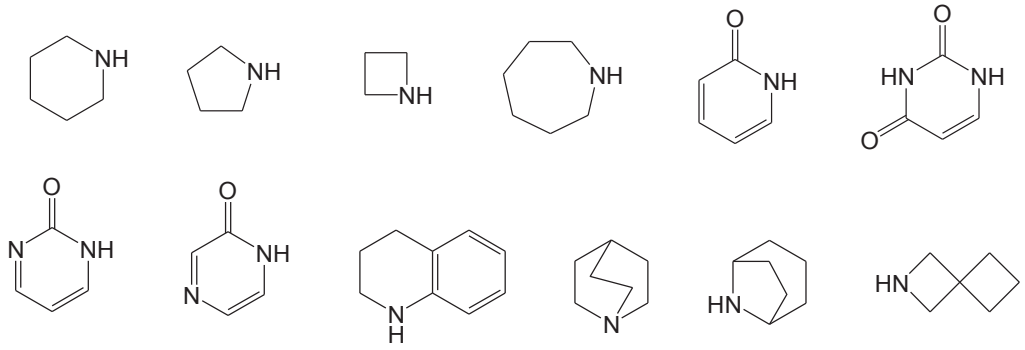
hydrogen. More typically, R^2 contains from 10 to 35 atoms other than hydrogen. Most typically, R^2 contains from 12 to 30 atoms other than hydrogen.

Q is selected from O or S. In one example of the first aspect of the disclosure, Q is O.

In one specific example, the disclosure provides a compound of formula (I), wherein:

Q is O;

R^1 is a non-aromatic heterocyclic group selected from:



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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; and

R^2 is phenyl or a 5- or 6-membered heteroaryl group; wherein

(i) the phenyl or 5- or 6-membered heteroaryl group is substituted at the α position with a substituent selected from $-R^4$, $-OR^4$ and $-COR^4$, wherein R^4 is 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 R^4 is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted at the α' position with a substituent selected from $-R^{14}$, $-OR^{14}$ and $-COR^{14}$, wherein R^{14} is 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 R^{14} is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted (typically with one, two or three substituents independently selected from halo, $-NO_2$, -CN, $-COOR^{15}$, $-CONH_2$, $-CONHR^{15}$ or $-CON(R^{15})_2$, wherein each $-R^{15}$ is independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group); or

(ii) the phenyl or 5- or 6-membered heteroaryl group is substituted with a cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which is fused to the parent phenyl or 5- or 6-membered heteroaryl group across the α,β positions and which is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further

substituted at the α' position with a substituent selected from -R^4, -OR^4 and -COR^4, wherein R^4 is 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 R^4 is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted (typically with one or two substituents independently selected from halo, -NO_2, -CN, -$COOR^{15}$, -$CONH_2$, -$CONHR^{15}$ or -$CON(R^{15})_2$, wherein each -R^{15} is independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group); or

(iii) the phenyl or 5- or 6-membered heteroaryl group is substituted with a first cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which is fused to the parent phenyl or 5- or 6-membered heteroaryl group across the α,β positions and which is optionally substituted with one or more halo groups; and

the phenyl or 5- or 6-membered heteroaryl group is substituted with a second cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which is fused to the parent phenyl or 5- or 6-membered heteroaryl group across the α',β' positions and which is optionally substituted with one or more halo groups; and

optionally the phenyl group is further substituted (typically with a substituent selected from halo, -NO_2, -CN, -$COOR^{15}$, -$CONH_2$, -$CONHR^{15}$ or -$CON(R^{15})_2$, wherein each -R^{15} is independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group); or

(iv) the phenyl or 5- or 6-membered heteroaryl group is substituted at the α-position with a monovalent heterocyclic group or a monovalent aromatic group selected from phenyl, pyridinyl, pyrimidinyl, pyrazolyl, imidazolyl, triazolyl or tetrahydropyranyl, wherein the monovalent heterocyclic or aromatic group may optionally be substituted with one or two substituents independently selected from halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -R^{12}-OR^{13}, -R^{12}-$N(R^{13})_2$, -R^{12}-CN or -R^{12}-C≡CR^{13}, and wherein a ring atom of the monovalent heterocyclic or aromatic group is directly attached to the α-ring atom of the parent phenyl or 5- or 6-membered heteroaryl group; wherein R^{12} is independently selected from a bond or a C_1-C_3 alkylene group; and R^{13} is independently selected from hydrogen or a C_1-C_3 alkyl or C_1-C_3 haloalkyl group; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted at the α' position with a substituent selected from -R^4, -OR^4 and -COR^4, wherein R^4 is 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 R^4 is optionally substituted with one or more halo groups; and

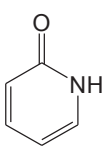
optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted (typically with one, two or three substituents independently selected from halo, -NO_2, -CN, -$COOR^{15}$, -$CONH_2$, -$CONHR^{15}$ or -$CON(R^{15})_2$, wherein each -R^{15} is independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group); or

(v) the phenyl or 5- or 6-membered heteroaryl group is substituted at the α-position with a monovalent heterocyclic group or a monovalent aromatic group selected from phenyl, pyridinyl, pyrimidinyl, pyrazolyl, imidazolyl, triazolyl or tetrahydropyranyl, wherein the monovalent heterocyclic or aromatic group may optionally be substituted with one or two substituents independently selected from halo, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -R^{12}-OR^{13}, -R^{12}-$N(R^{13})_2$, -R^{12}-CN or -R^{12}-C≡CR^{13}, and wherein a ring atom of the monovalent heterocyclic or aromatic group is directly attached to the α-ring atom of the parent phenyl or 5- or 6-membered heteroaryl group; wherein R^{12} is independently selected from a bond or a C_1-C_3 alkylene group; and R^{13} is independently selected from hydrogen or a C_1-C_3 alkyl or C_1-C_3 haloalkyl group; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted with a cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring which is fused to the parent phenyl or 5- or 6-membered heteroaryl group across the α',β' positions and which is optionally substituted with one or more halo groups; and

optionally the phenyl or 5- or 6-membered heteroaryl group is further substituted (typically with one or two substituents independently selected from halo, -NO_2, -CN, -$COOR^{15}$, -$CONH_2$, -$CONHR^{15}$ or -$CON(R^{15})_2$, wherein each -R^{15} is independently selected from a C_1-C_4 alkyl or C_1-C_4 haloalkyl group);

provided that when the non-aromatic heterocyclic group of R^1 is selected from:



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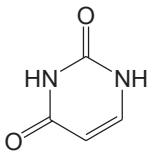

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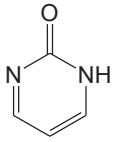
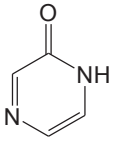


or


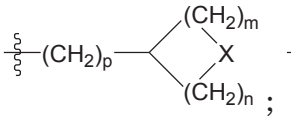
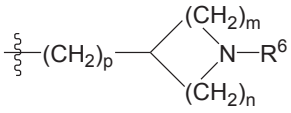
, at least one ring nitrogen atom which is adjacent to a carbonyl group is substituted.

In this specific example directly above, where a group or moiety is optionally substituted with one or more halo groups, it may be substituted for example with one, two, three, four, five or six halo groups.

In this specific example directly above, the parent phenyl or 5- or 6-membered heteroaryl group of R^2 may be selected from phenyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl.

In this specific example directly above, R^1 may optionally be substituted with one or more (such as one, two or three) substituents independently selected from halo; C_1-C_6

alkyl; C_1-C_6 haloalkyl; C_2-C_6 alkenyl; C_2-C_6 haloalkenyl; C_2-C_6 alkynyl; C_2-C_6 haloalkynyl; -R^5-CN; -R^5-N_3; -R^5-NO_2; -R^5-$N(R^6)_2$; -R^5-OR^6; -R^5-SR^6; -R^5-$Si(R^6)_3$; -R^5-O-$Si(R^6)_3$; -R^5-COR^6; -R^5-$COOR^6$; -R^5-CO-R^5-OR^6; -R^5-$CON(R^6)_2$; -R^5-CO-R^5-$N(R^6)_2$; -R^5-$C(=NR^6)R^6$; -R^5-$C(=NR^6)N(R^6)_2$; -R^5-$C(=NOH)R^6$; -R^5-SO_2R^6; -R^5-phenyl; -R^5-(Het);

; oxo (=O); $-CH_2CH_2-$; $-CH_2CH_2CH_2-$; $-CH_2CH_2CH_2CH_2-$; $-CH=CH-CH=CH_2-$; or -R^5-(C_3-C_6 cycloalkyl) wherein the C_3-C_6 cycloalkyl group is optionally substituted with one or two substituents independently selected from C_1-C_3 alkyl; wherein

R^5 is independently selected from a bond or C_1-C_5 alkylene;

R^6 is independently selected from hydrogen, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_3-C_6 cycloalkyl, -CO-(C_1-C_3 alkyl), -COO-(C_1-C_4 alkyl) or benzyl;

Het is selected from a pyridinyl, 2-oxo-1,2-dihydropyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl or diazirinyl group, each of which may optionally be substituted with one or two substituents independently selected from halo, C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl;

X is selected from O, S, SO or SO_2;

m is 1, 2 or 3;

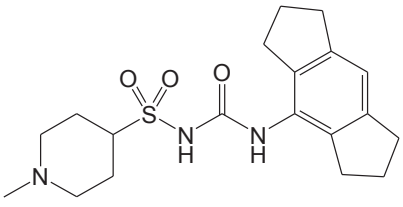
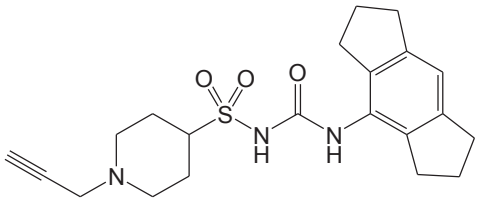
n is 1, 2 or 3; and

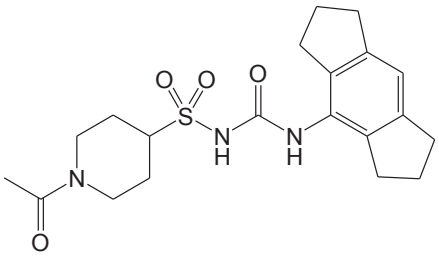
p is 0, 1 or 2.

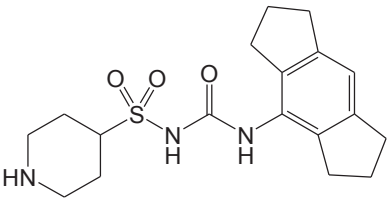
Typically, R^1 is substituted on one or more (such as one, two or three) ring nitrogen atoms with such a substituent.

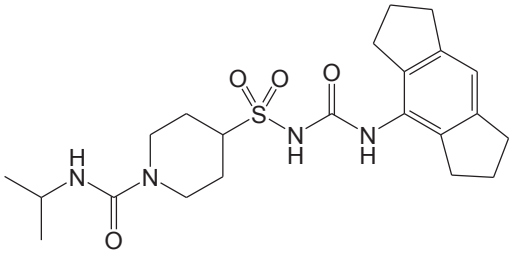
In one example of any of the above examples, the compound of formula (I) has a molecular weight of from 250 to 2000 Da. Typically, the compound of formula (I) has a molecular weight of from 280 to 900 Da. More typically, the compound of formula (I) has a molecular weight of from 310 to 550 Da.

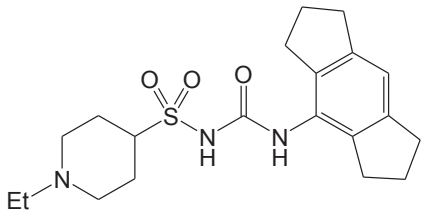
A second aspect of the disclosure provides a compound selected from the group consisting of:

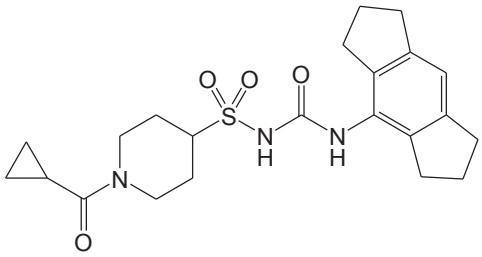



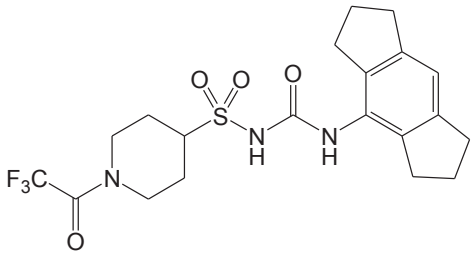


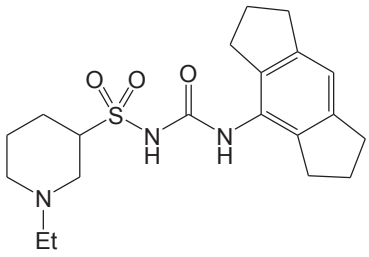


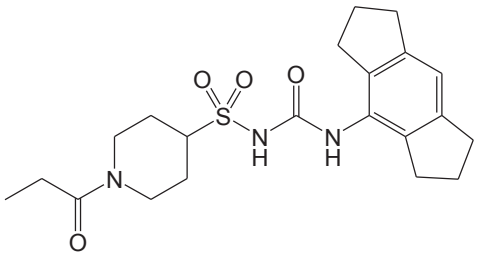


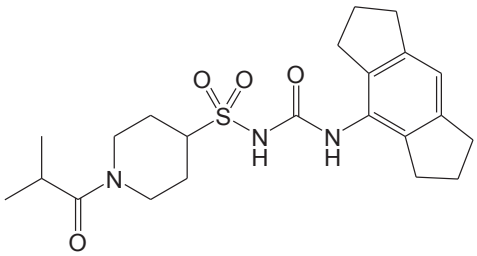


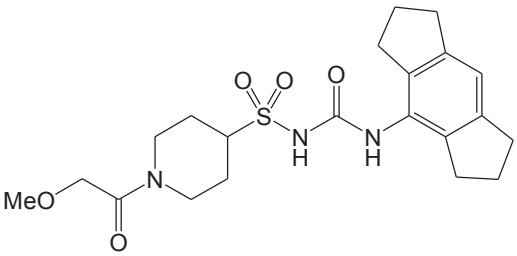


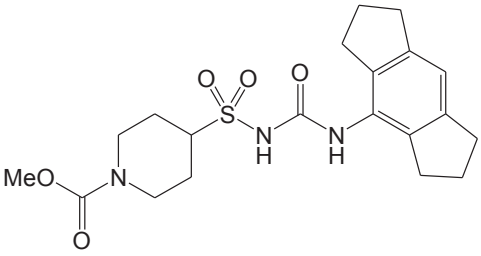


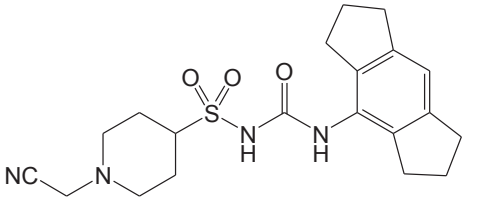












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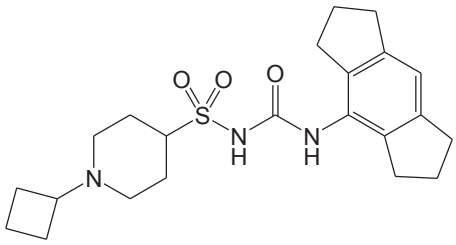

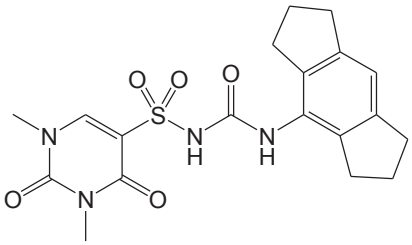

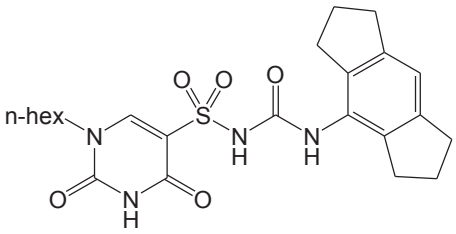
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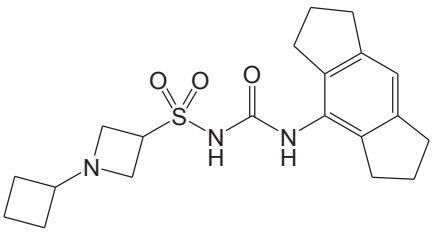

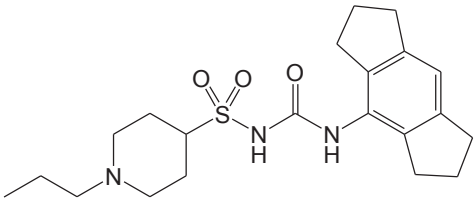

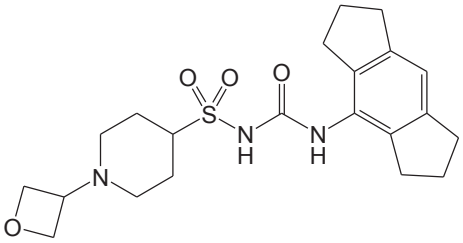

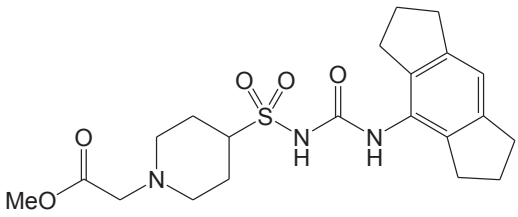
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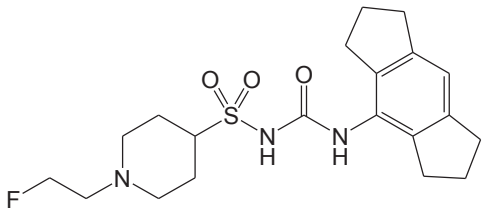
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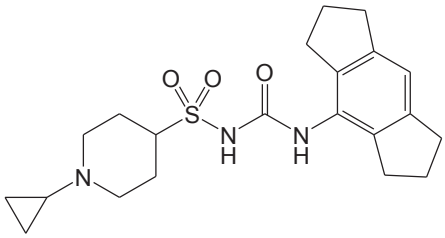

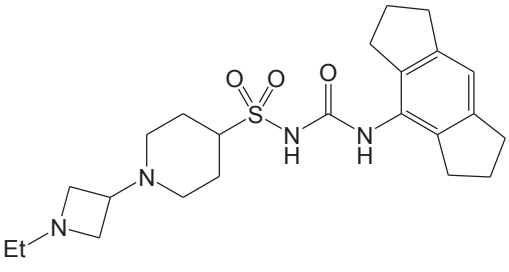
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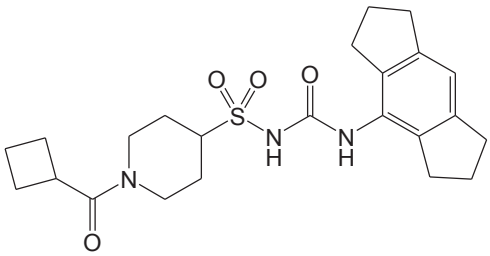

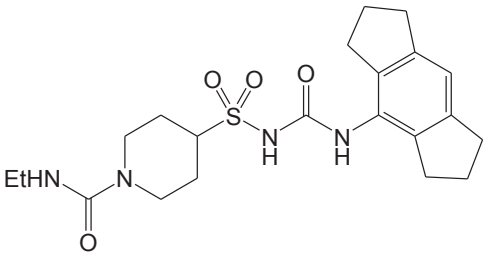
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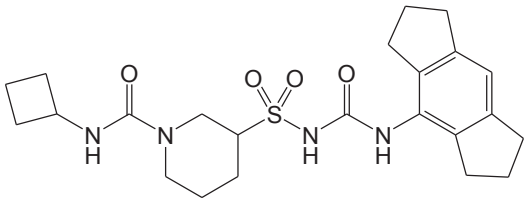

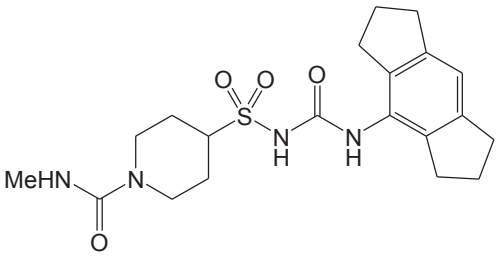
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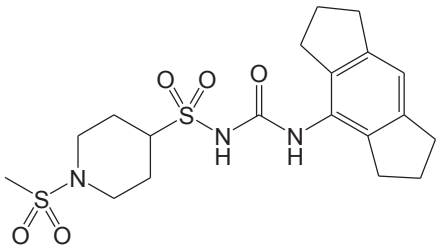

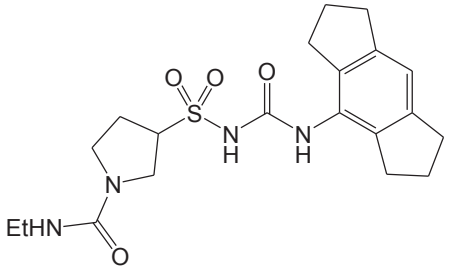
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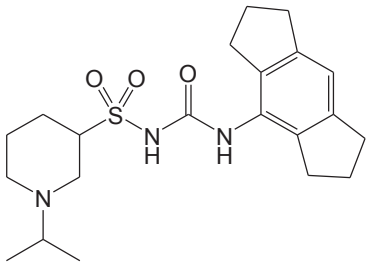

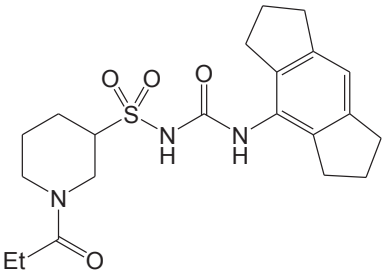
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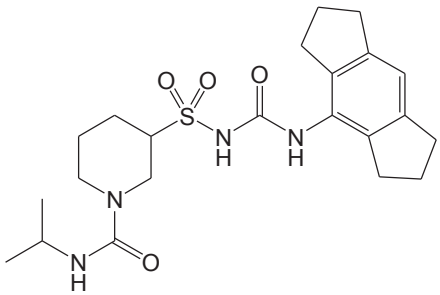

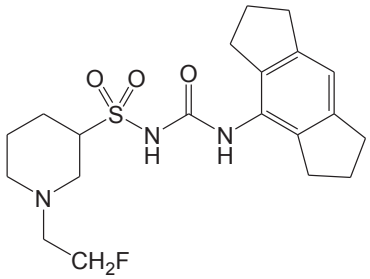
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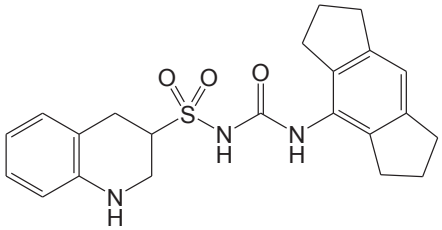

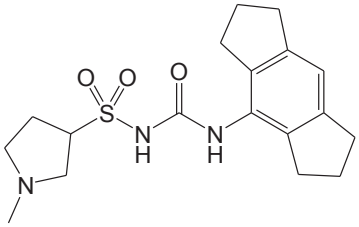

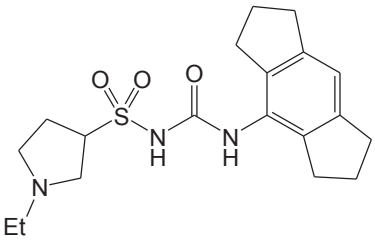
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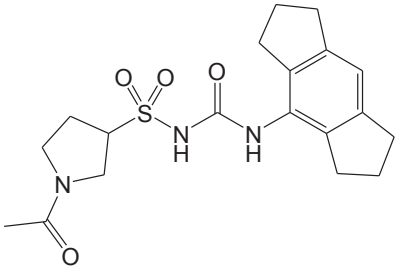

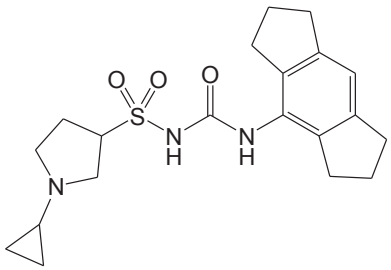

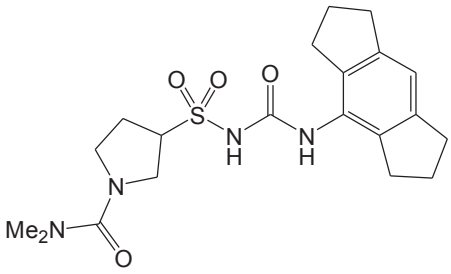

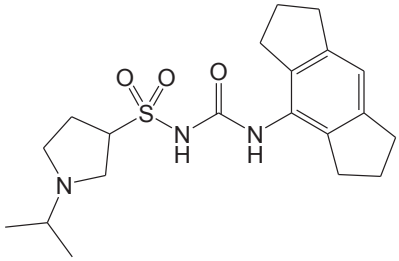

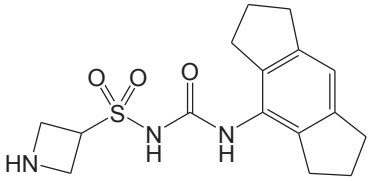

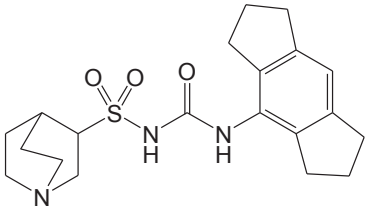

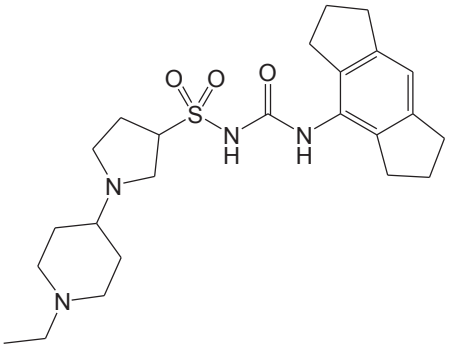

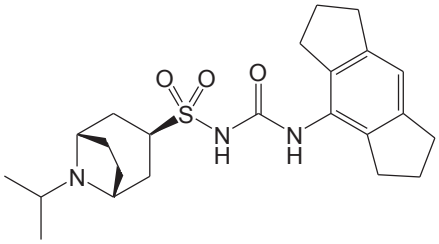

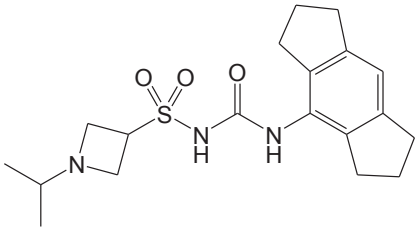

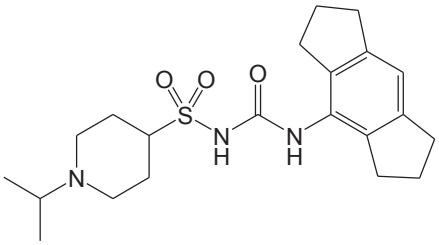

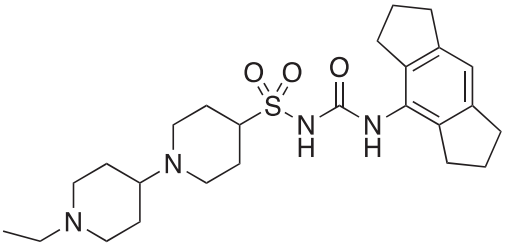

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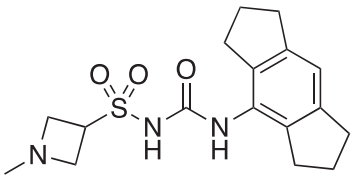

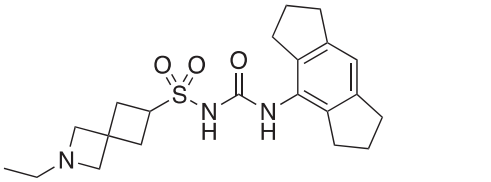

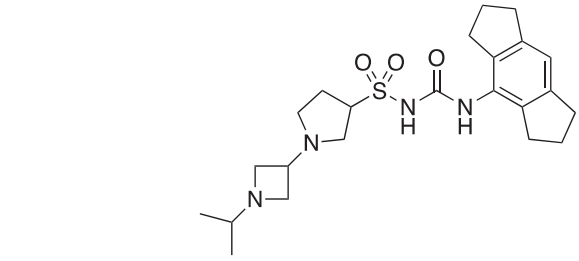

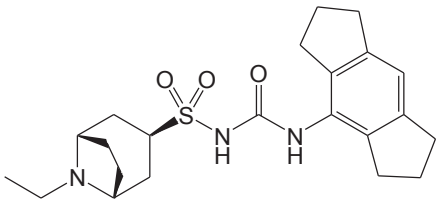

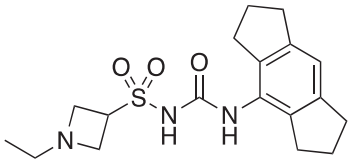

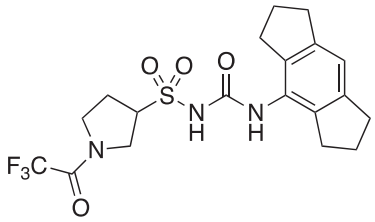

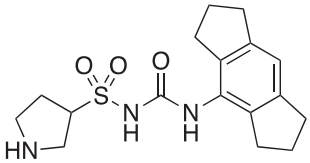

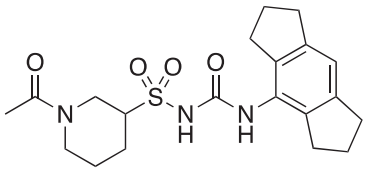

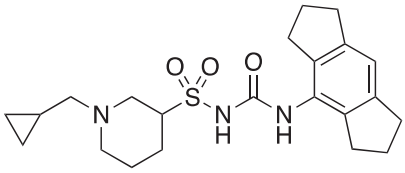

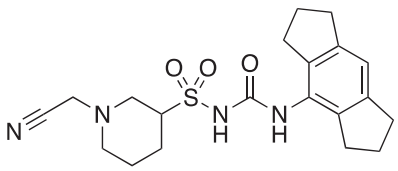

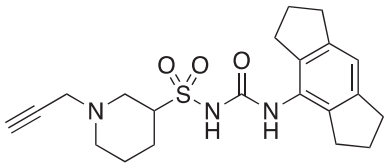

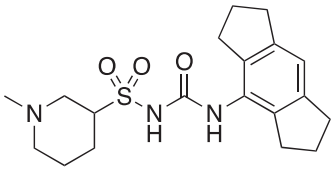

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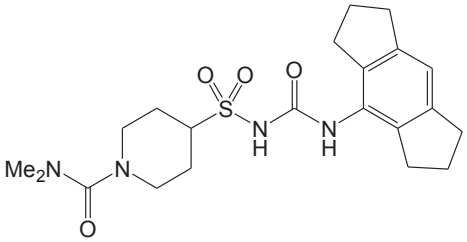

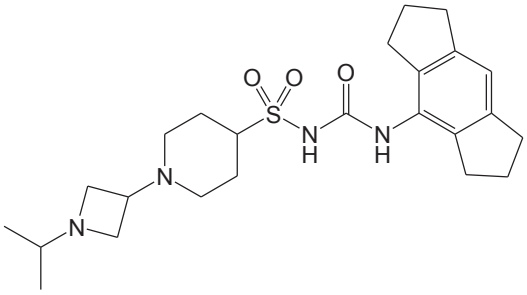

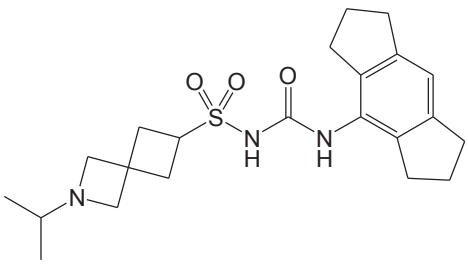

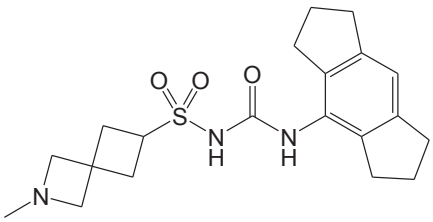

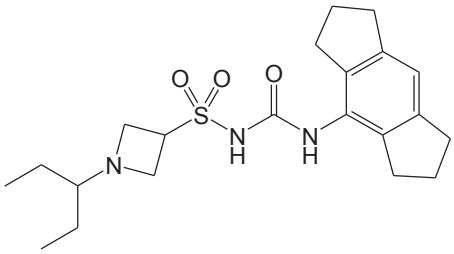

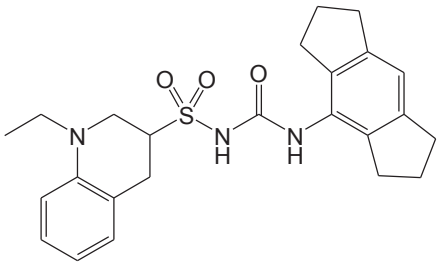

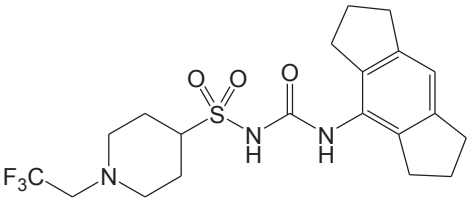

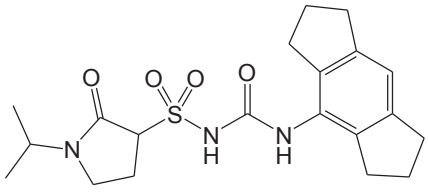

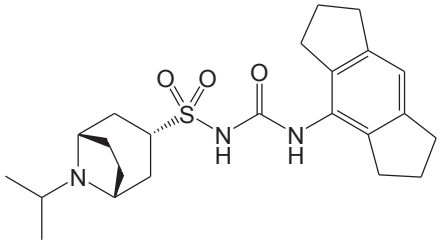

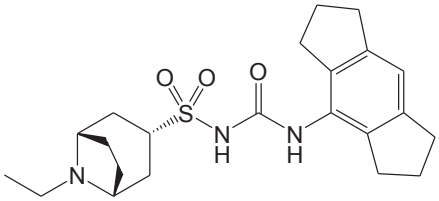

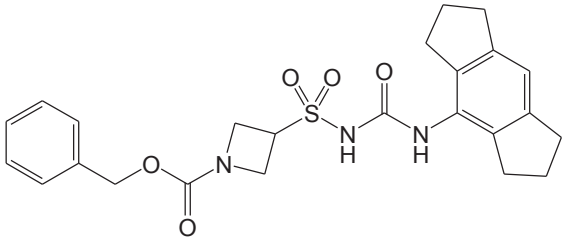

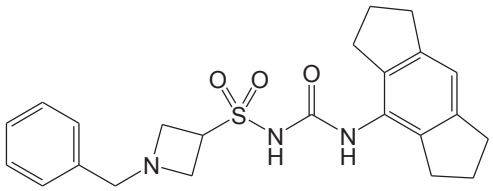

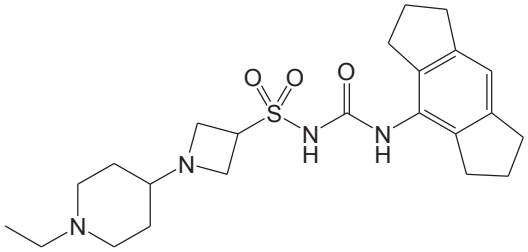

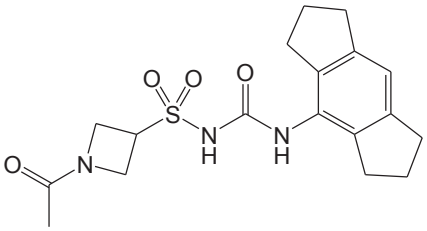

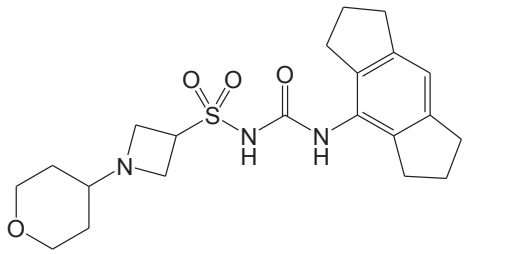

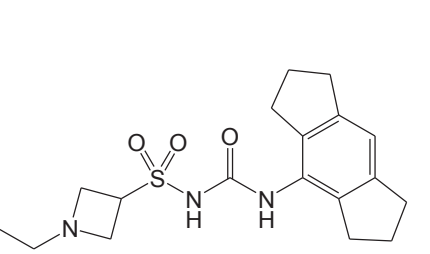

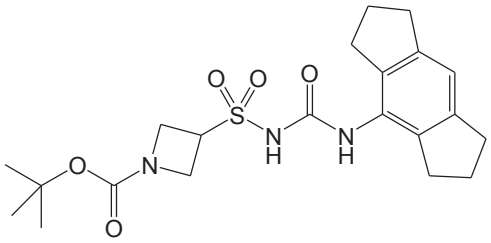

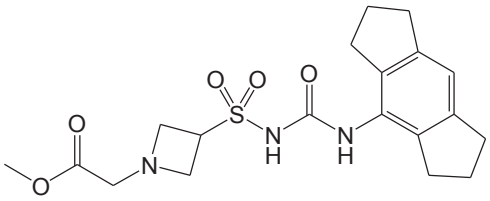

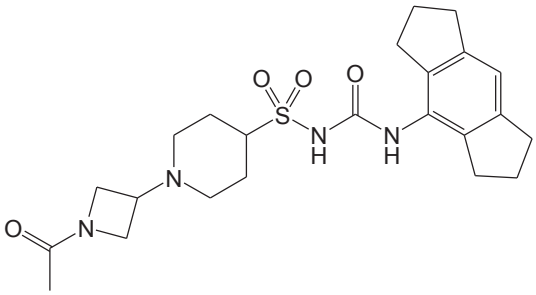

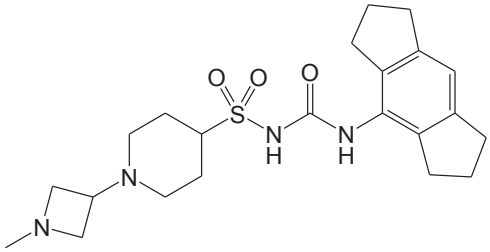

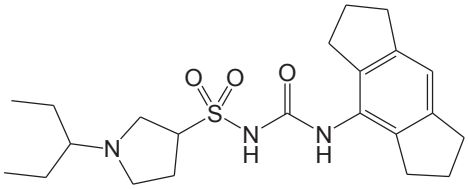

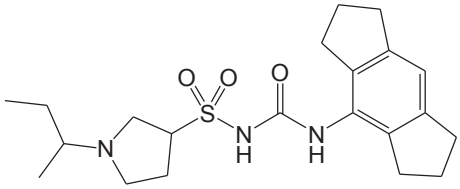

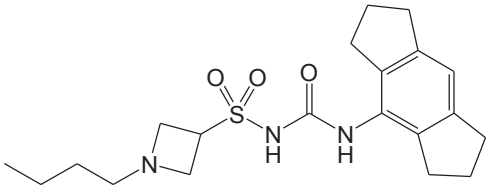

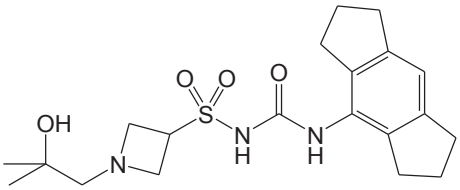

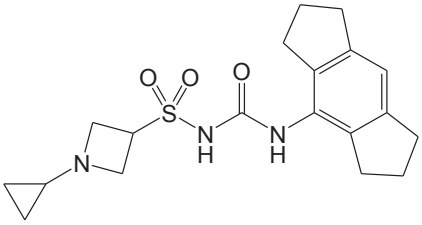

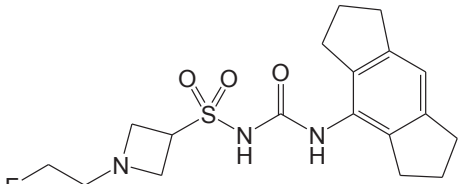

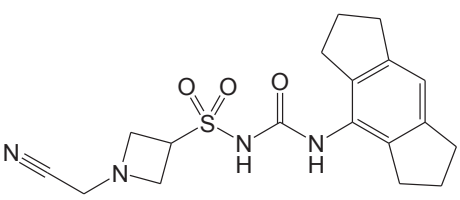

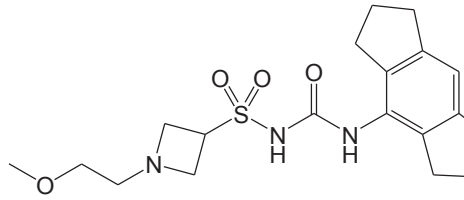

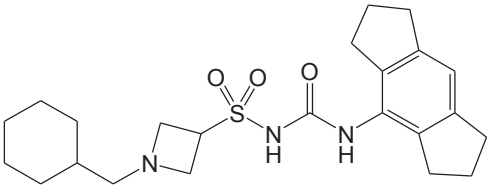

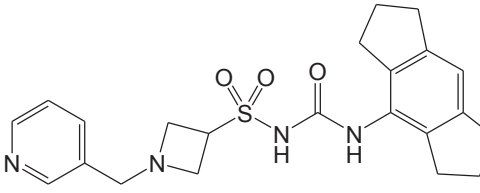

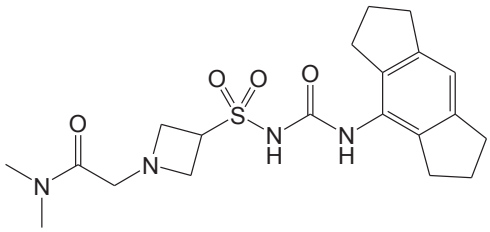

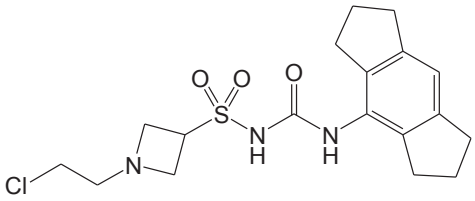

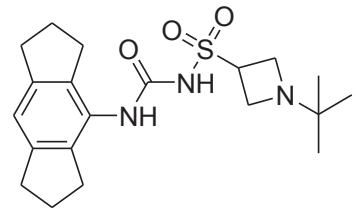

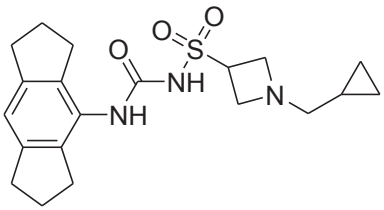

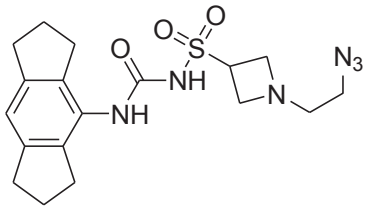

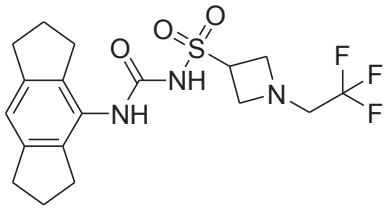

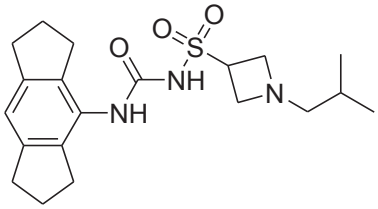

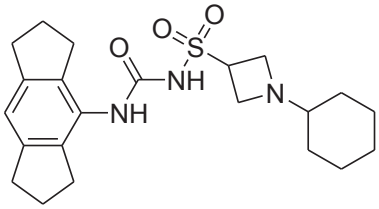

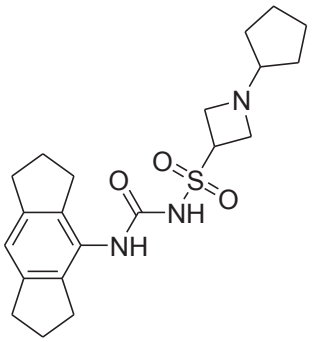

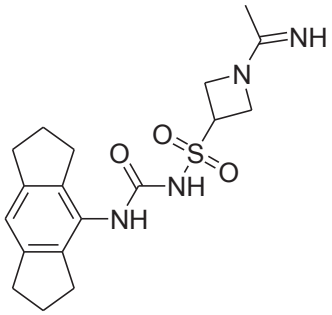

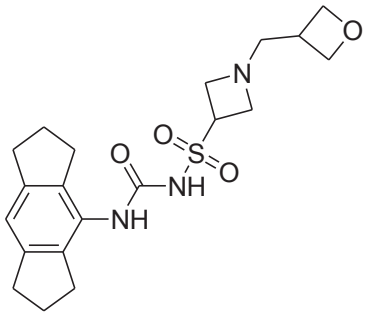

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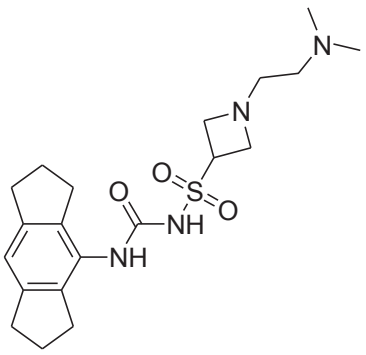

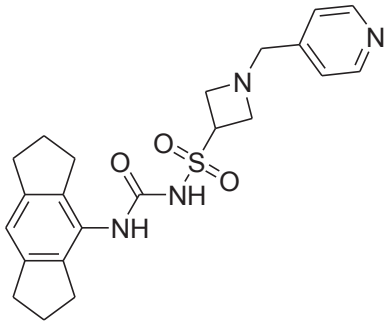

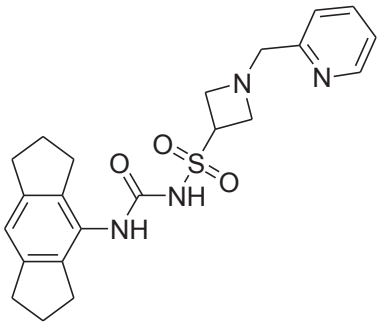

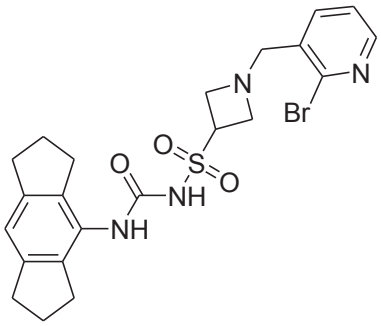

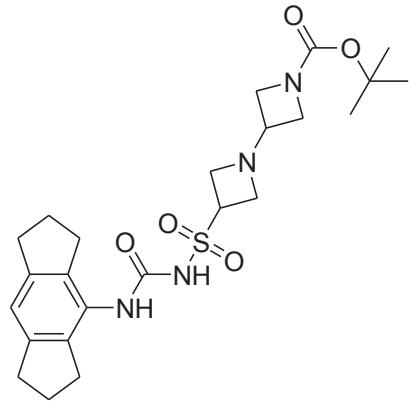

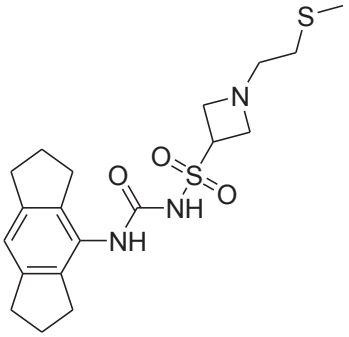

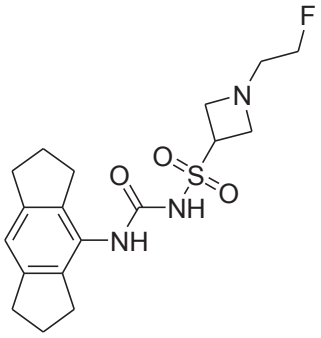

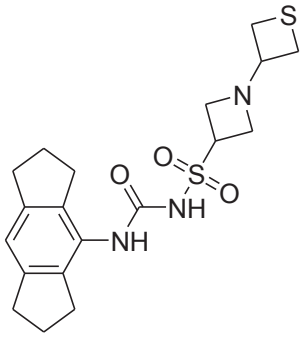

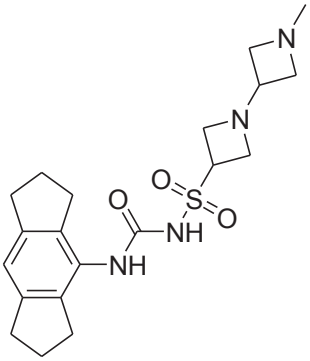

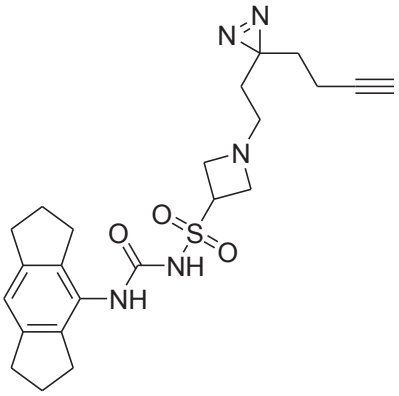

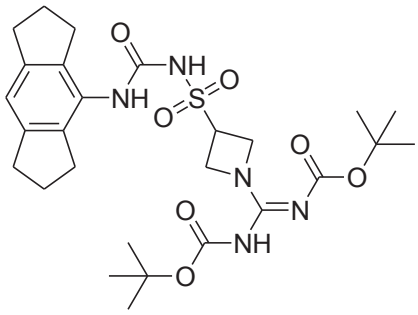

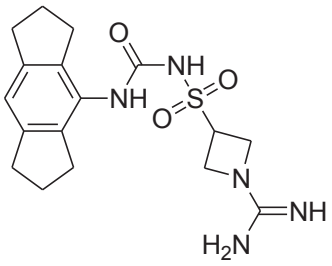

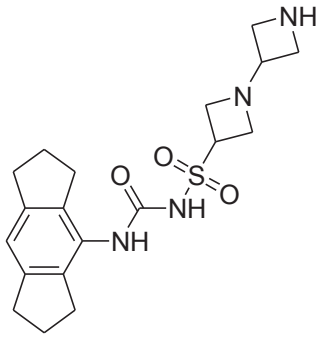

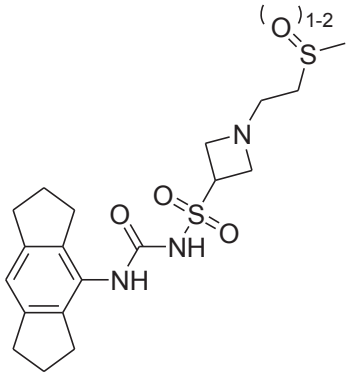

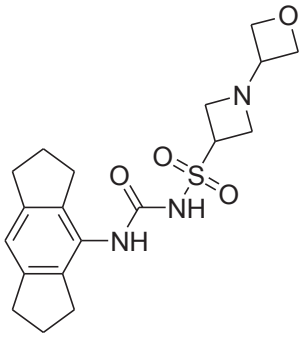

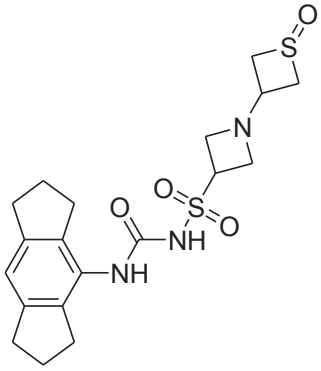

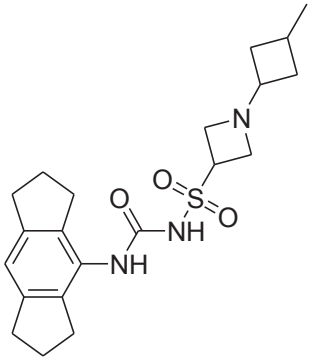

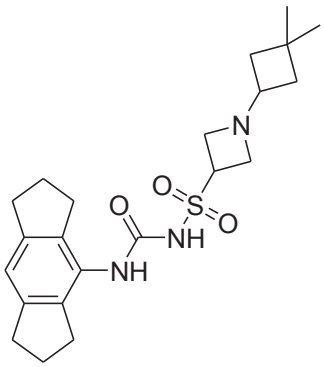

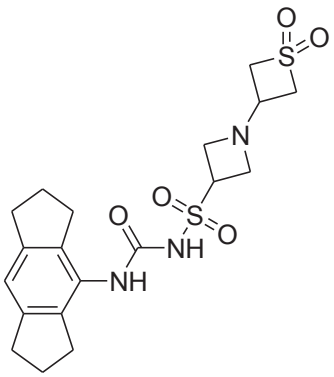

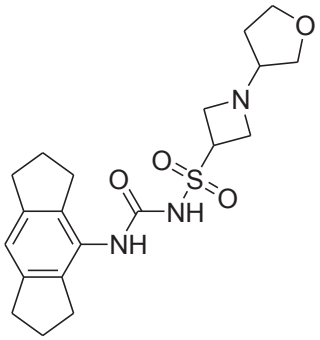

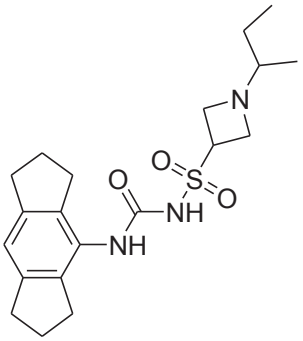

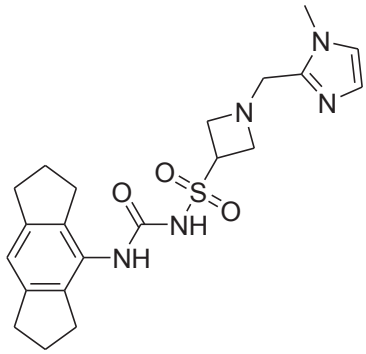

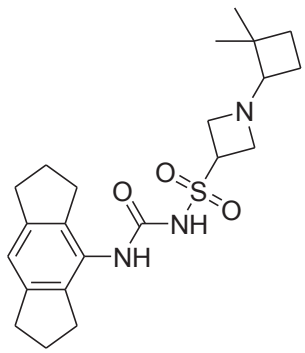

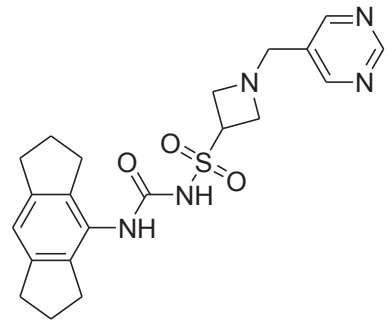

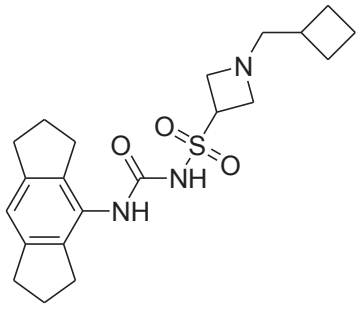

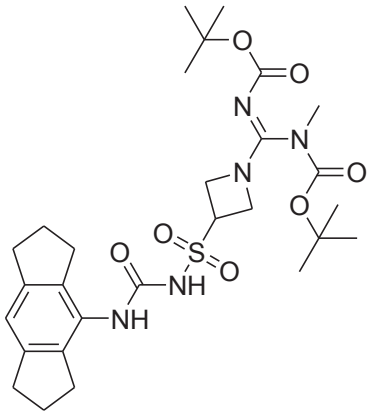

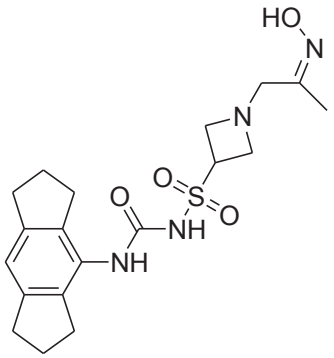

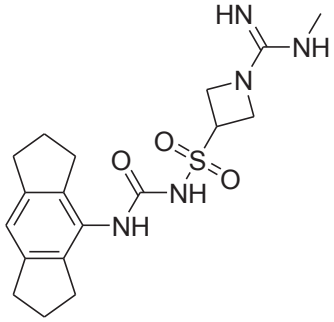

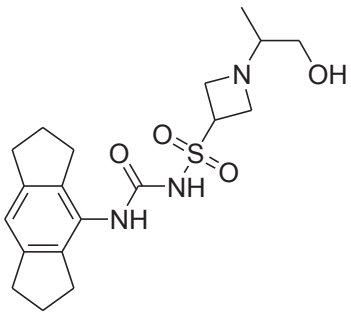

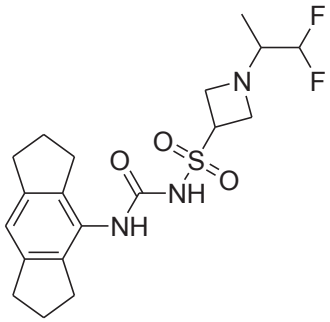

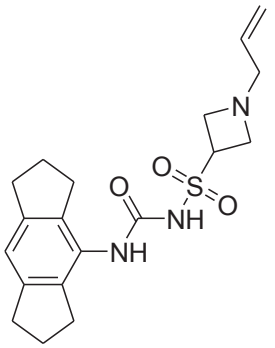

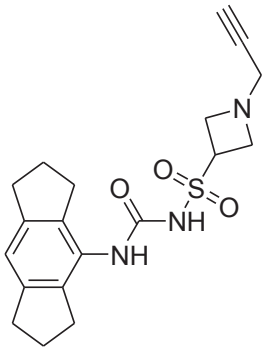

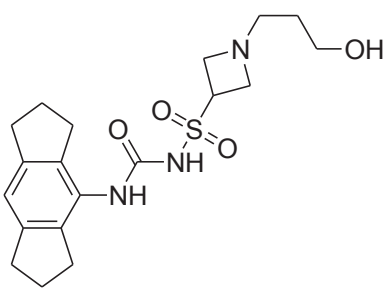

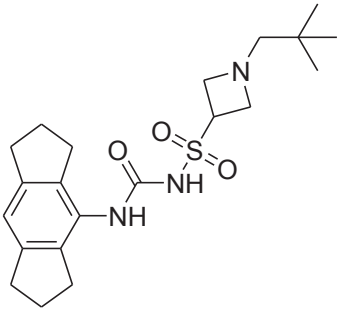

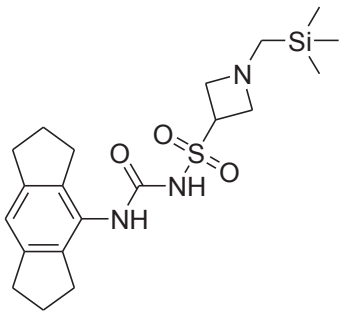

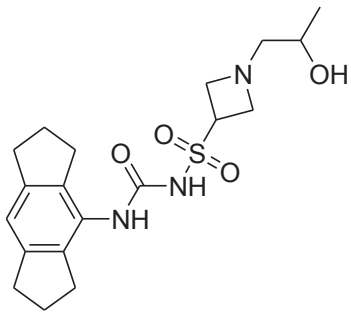

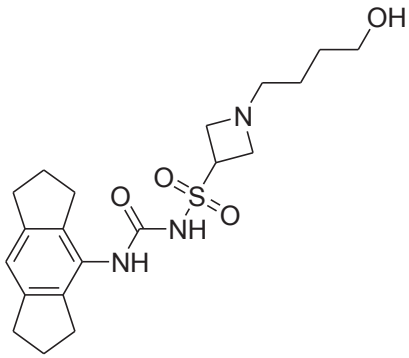

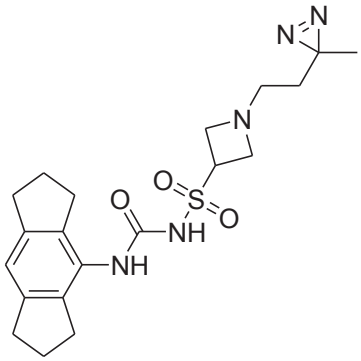

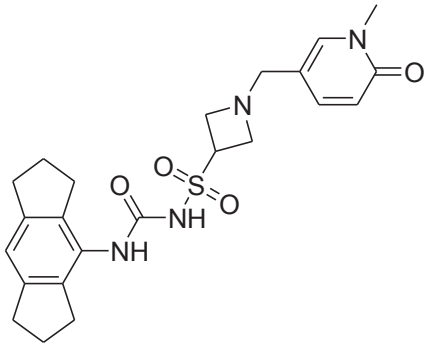

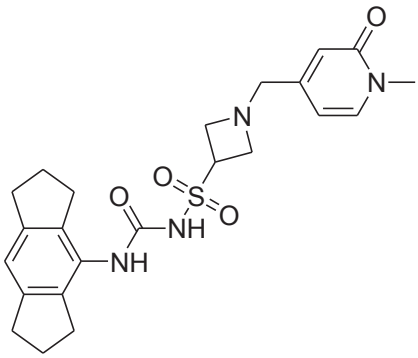

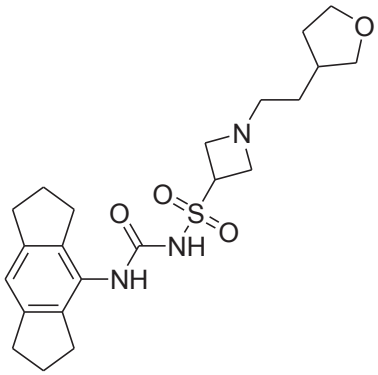

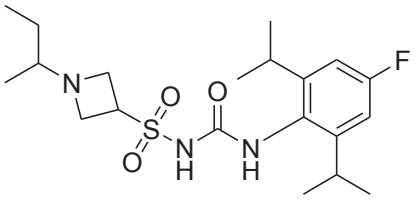

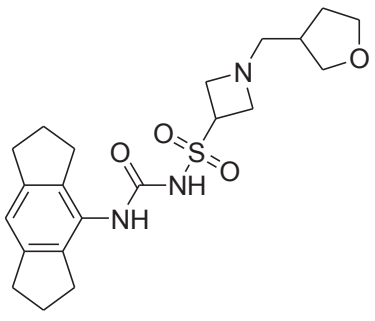

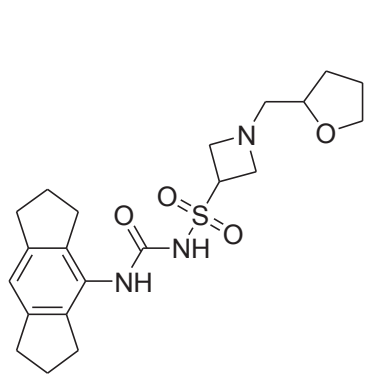

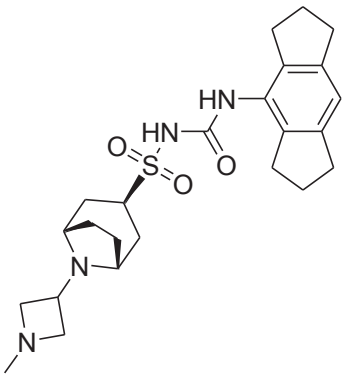

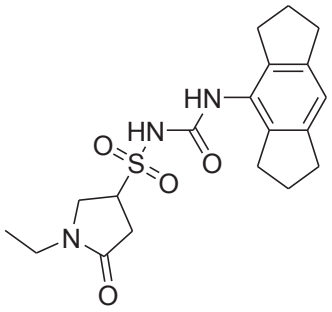

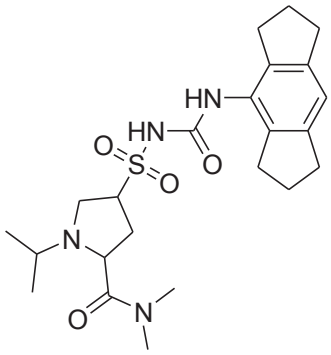

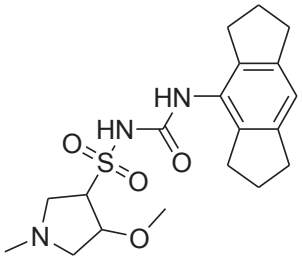

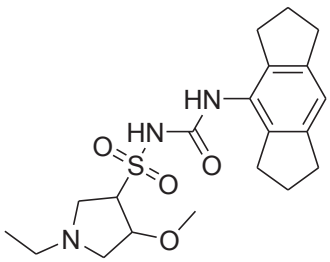

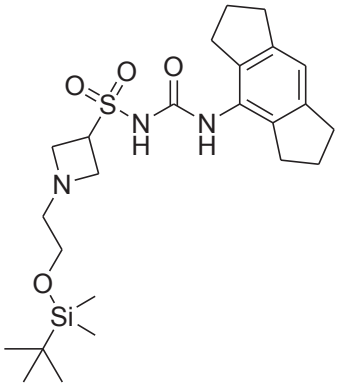

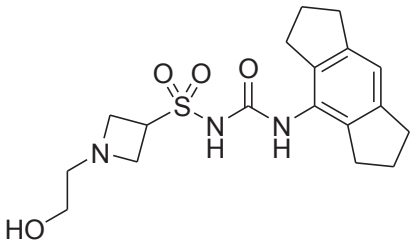

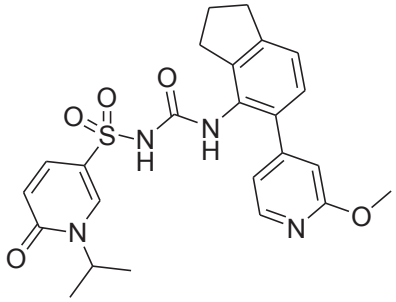

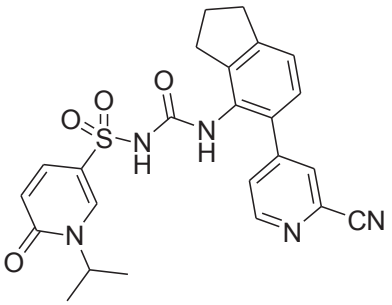

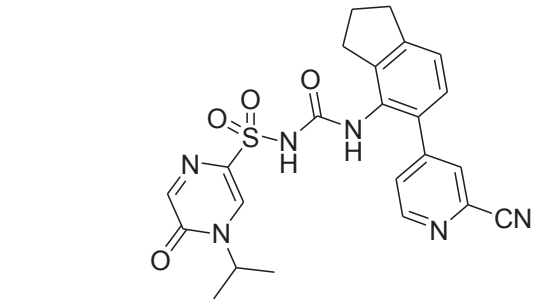

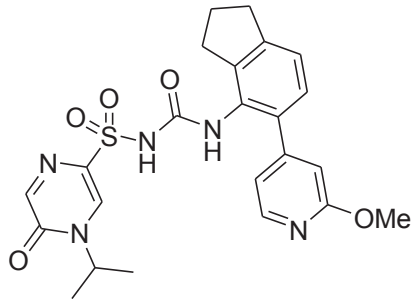

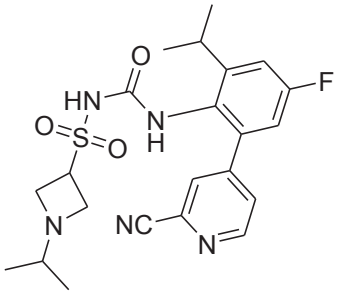

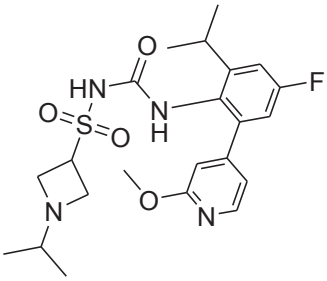

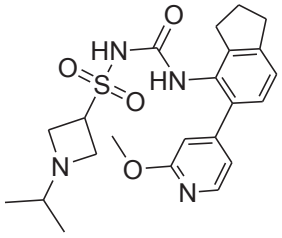

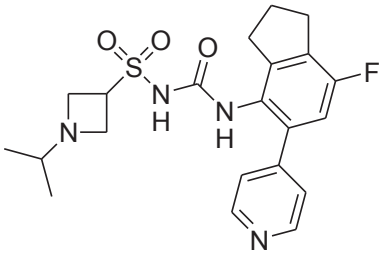

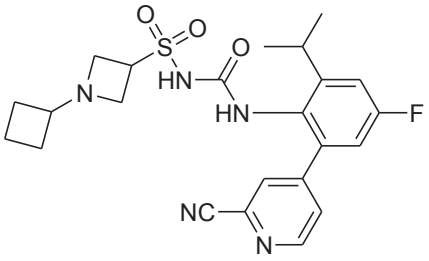

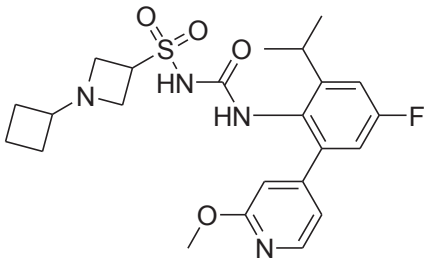

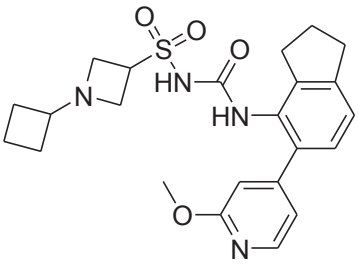

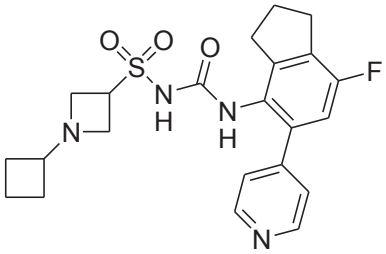

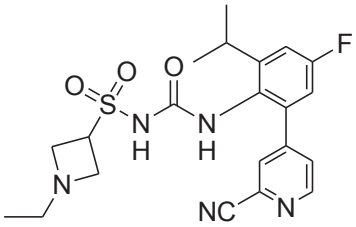

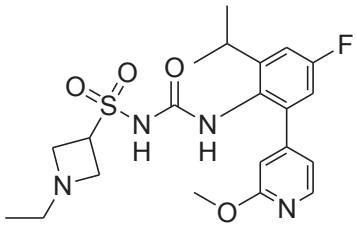

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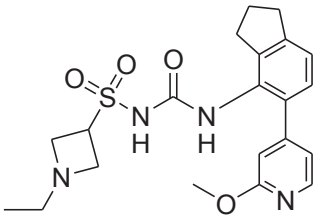

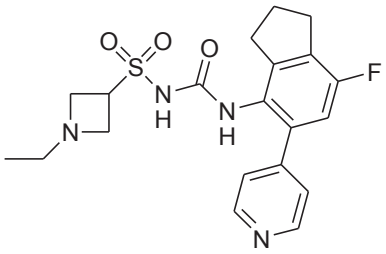

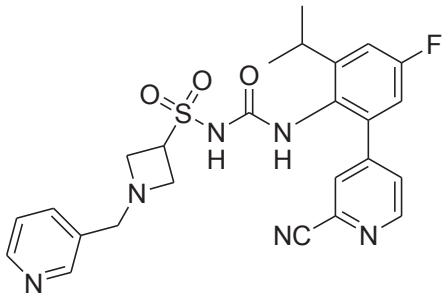

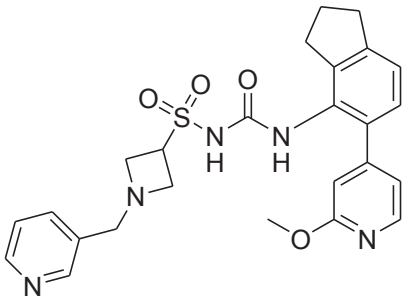

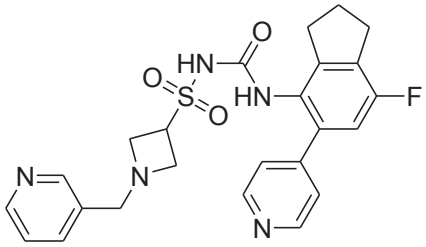

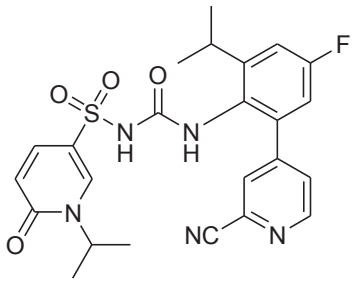

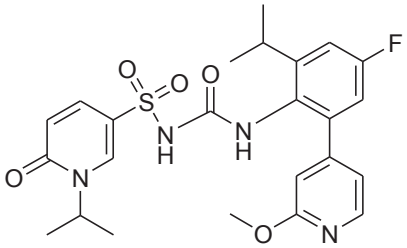

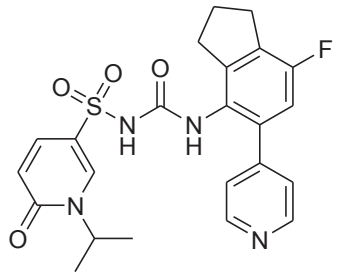

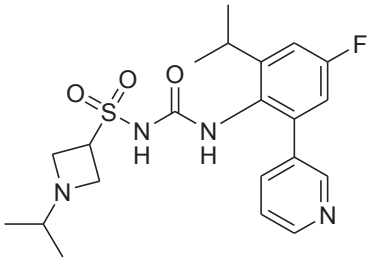

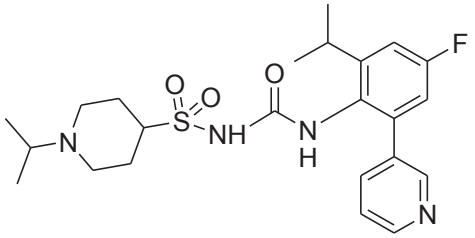

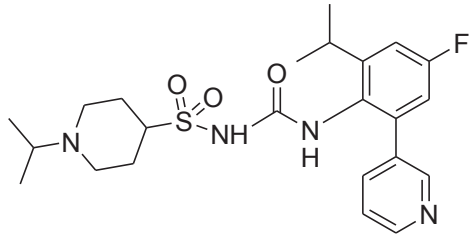

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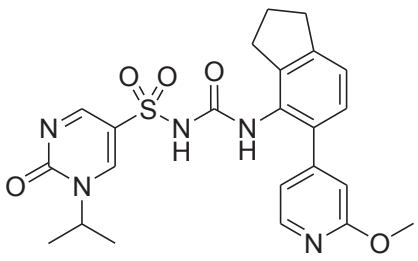

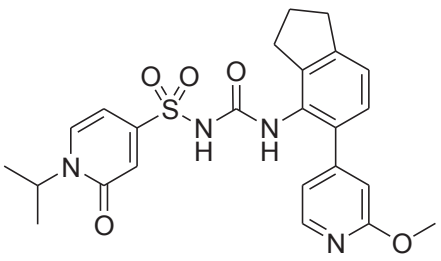

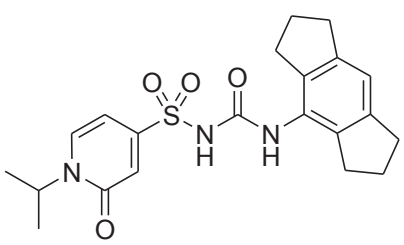

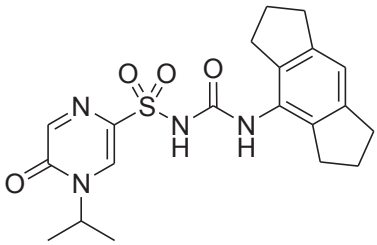

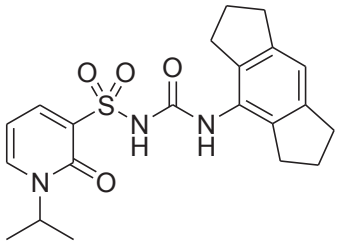

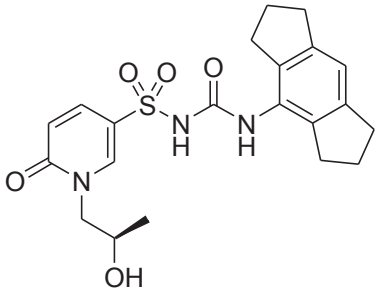

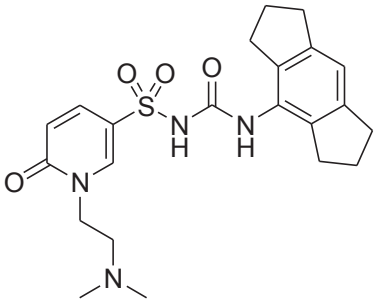

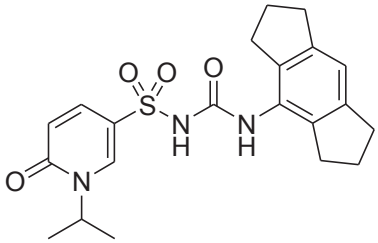

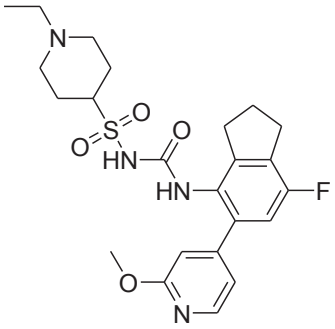

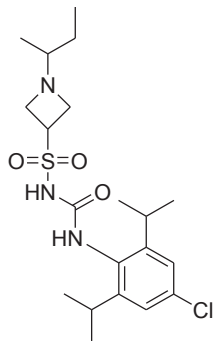

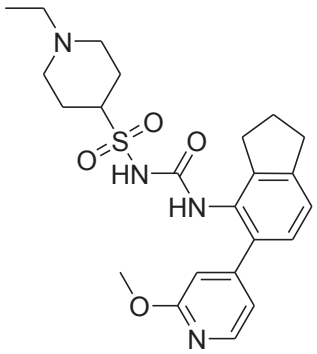

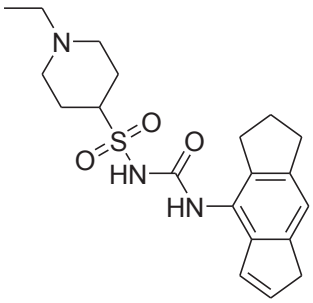

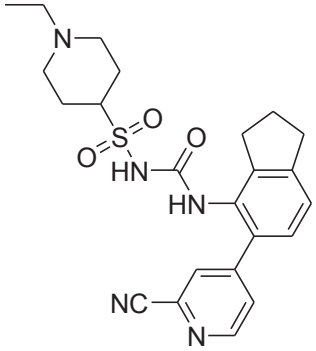

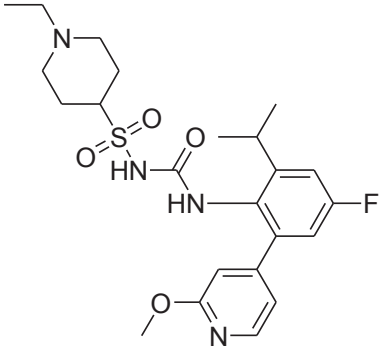

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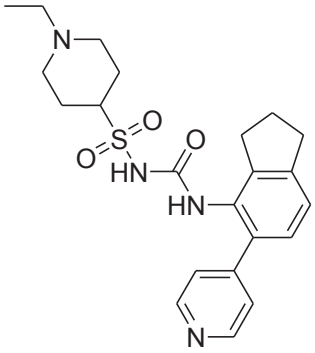

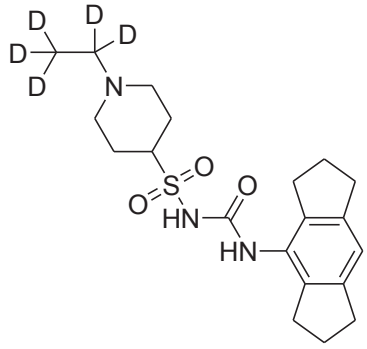

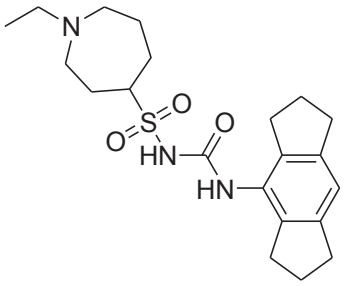

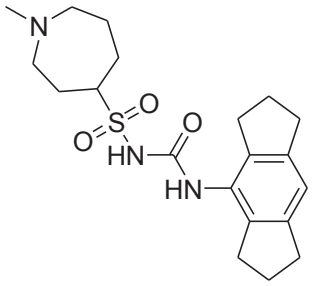

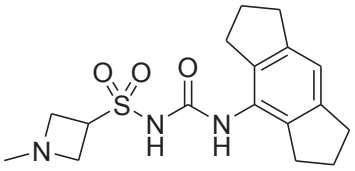

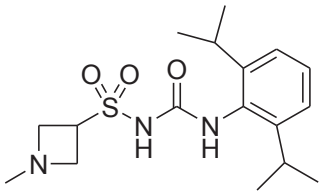

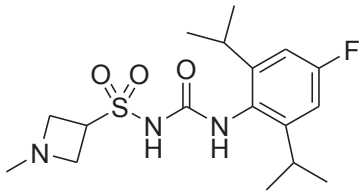

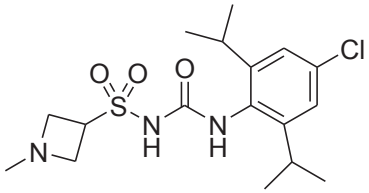

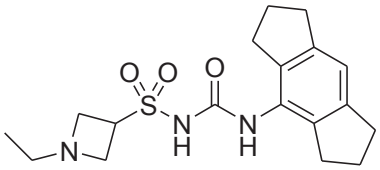

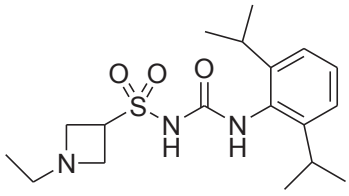

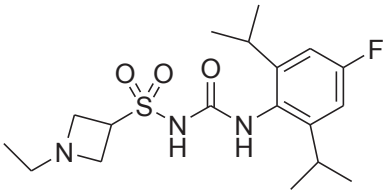

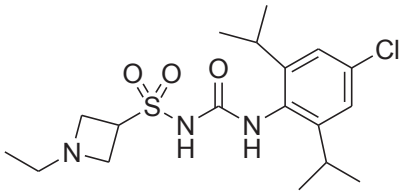

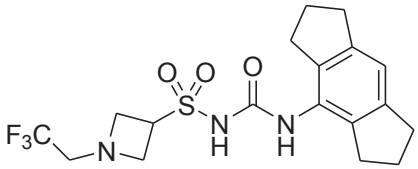

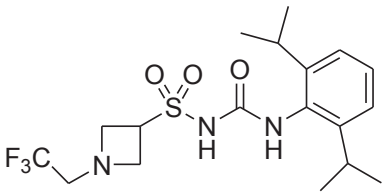

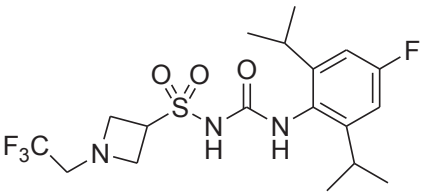

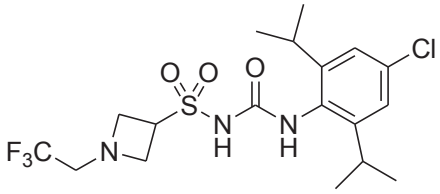

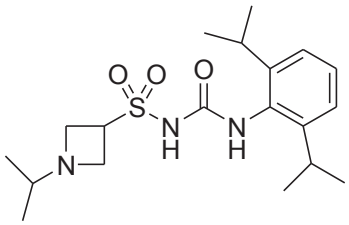

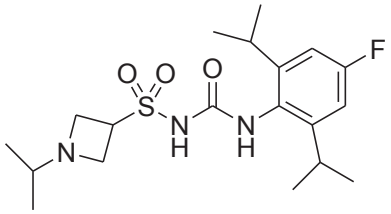

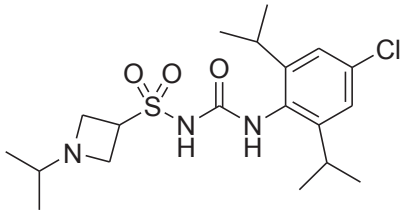

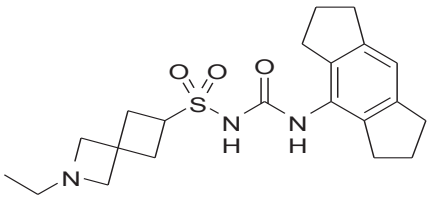

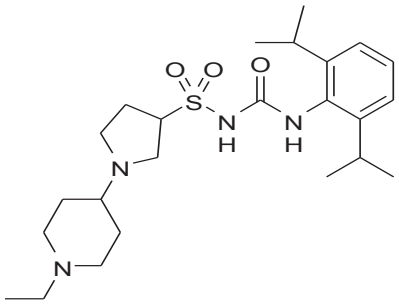

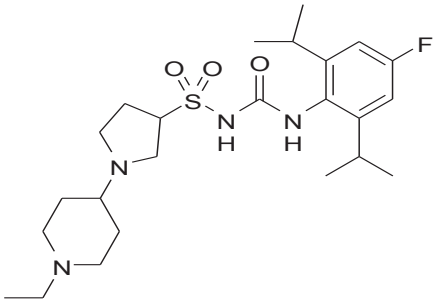

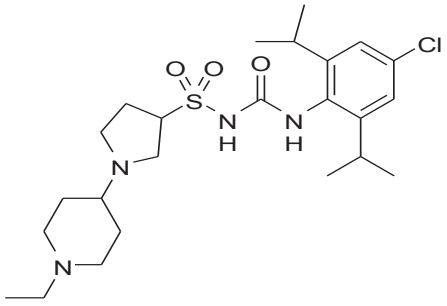

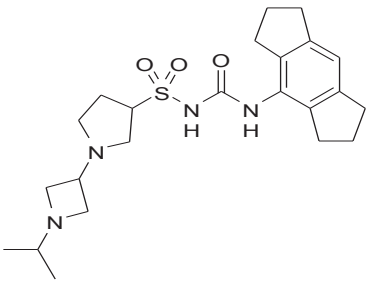

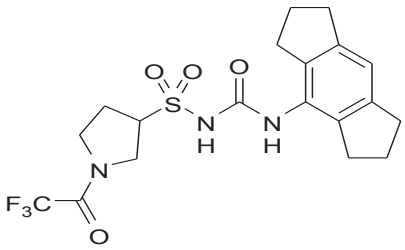

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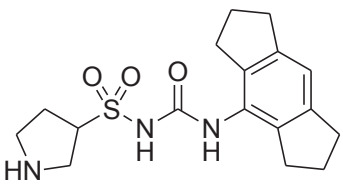

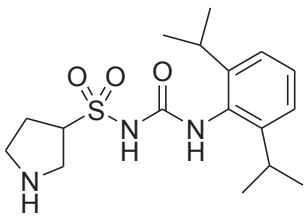

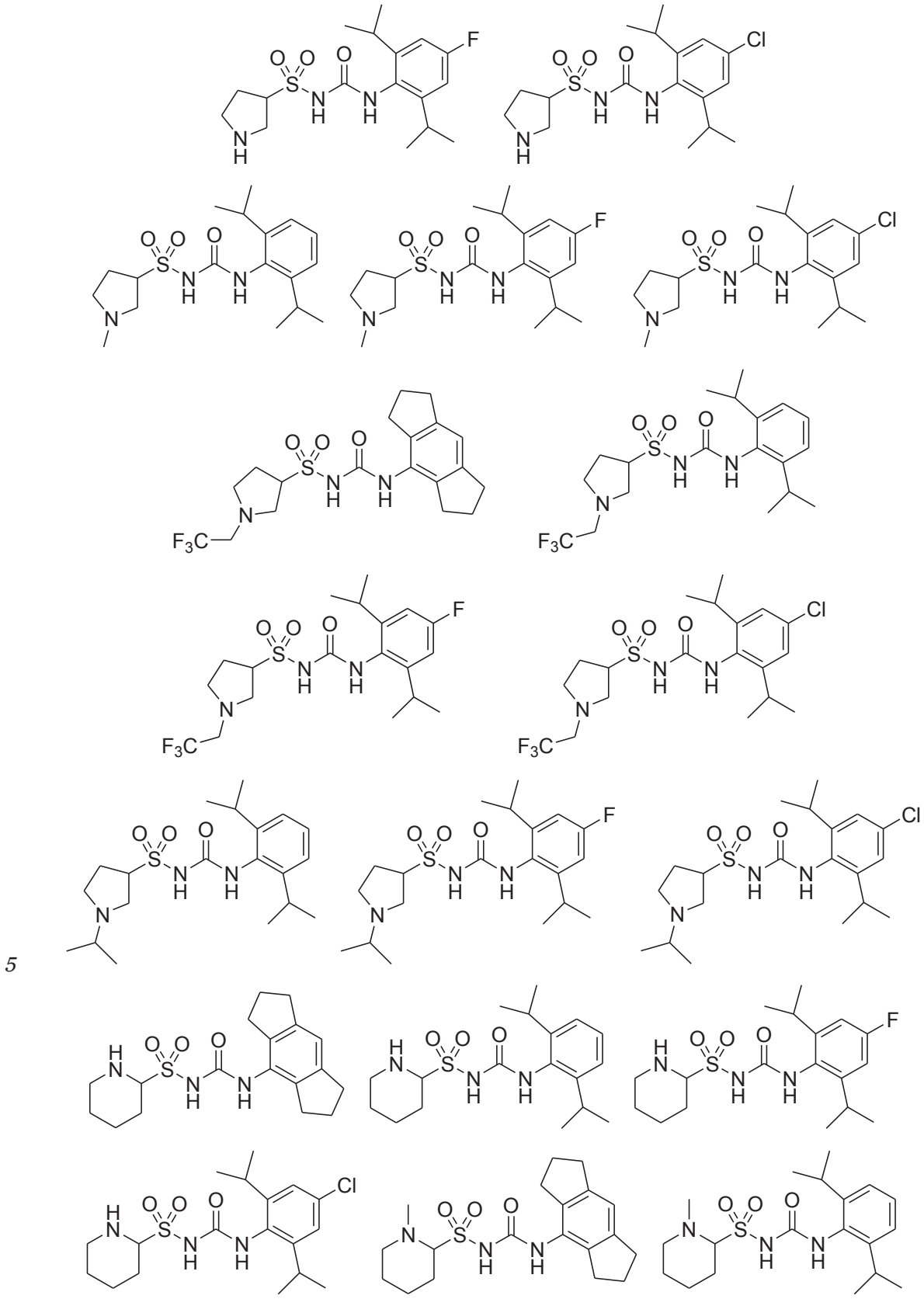

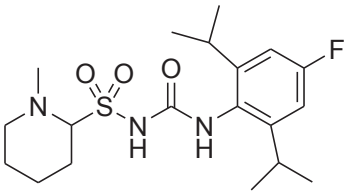
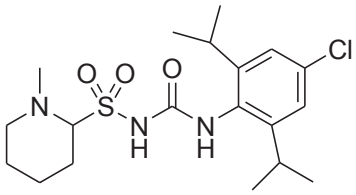
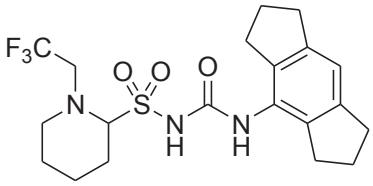
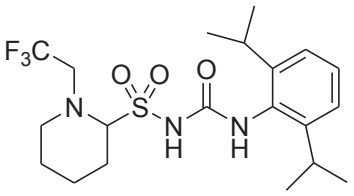
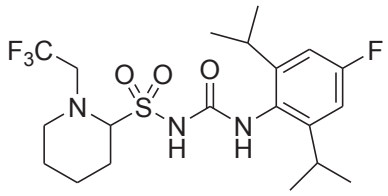
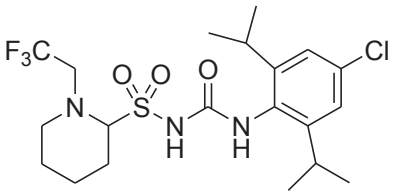
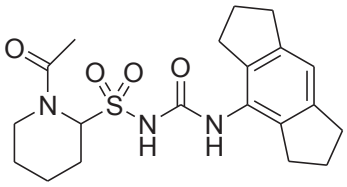
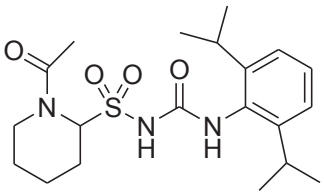
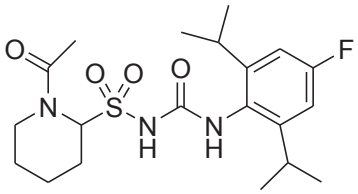
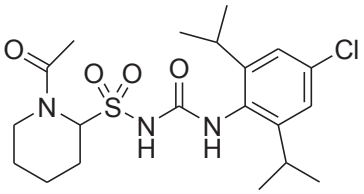
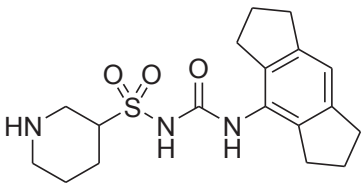
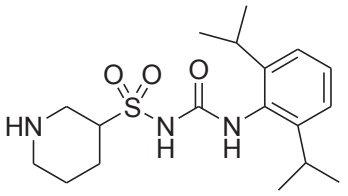
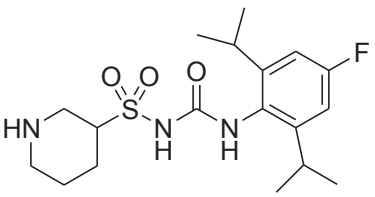
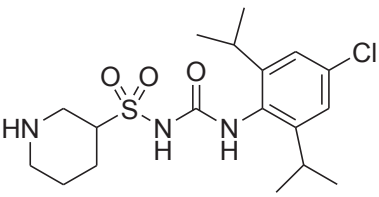
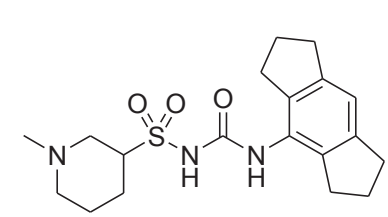
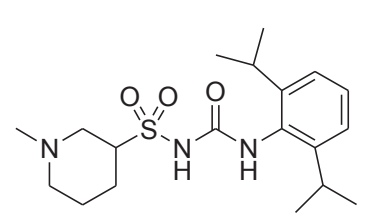
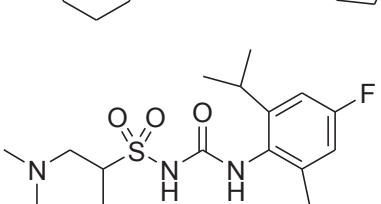
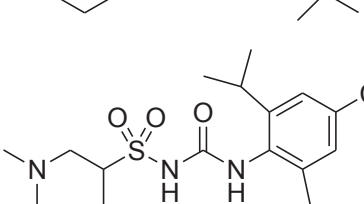
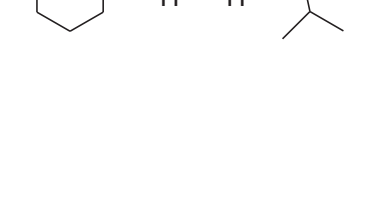
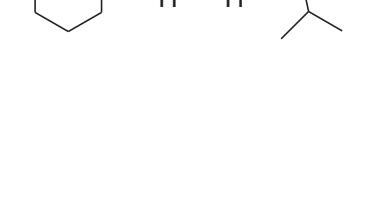

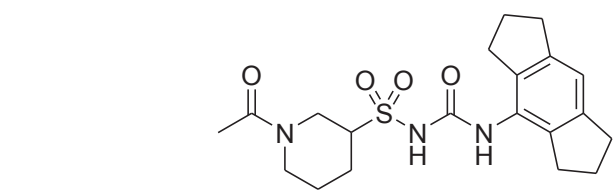
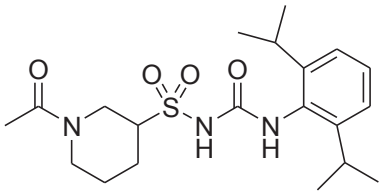
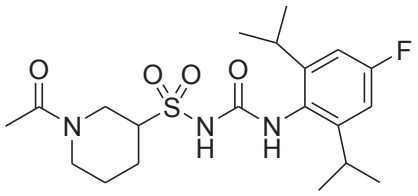
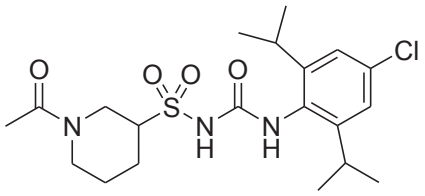
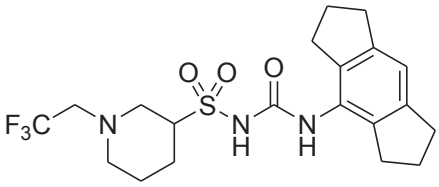
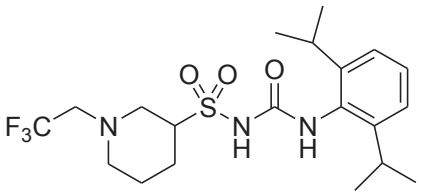
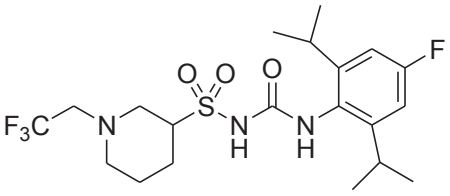
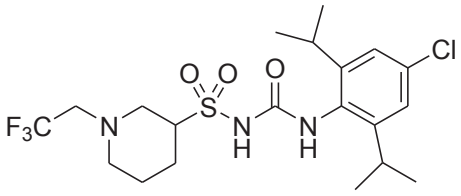
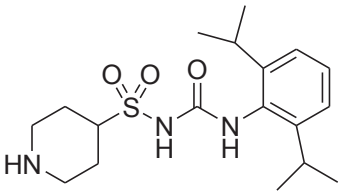
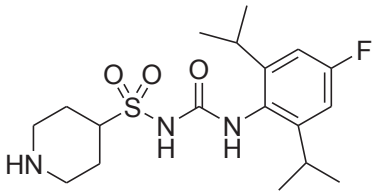
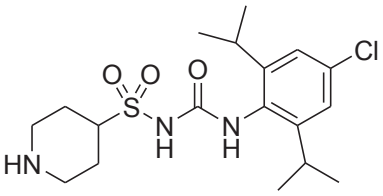
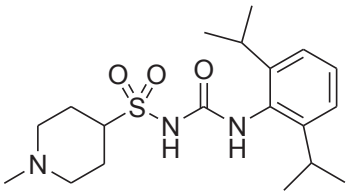
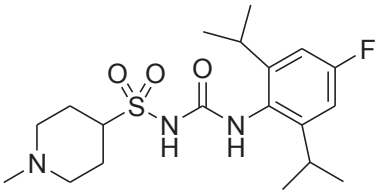
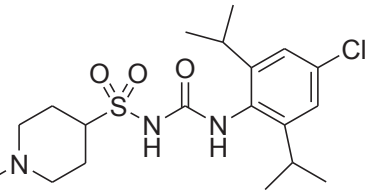
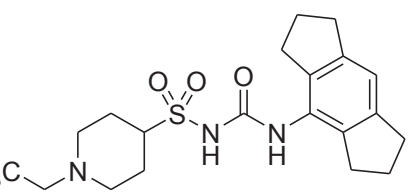
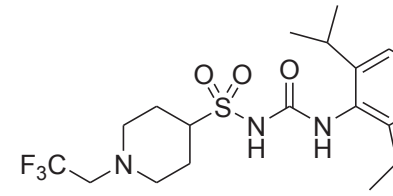

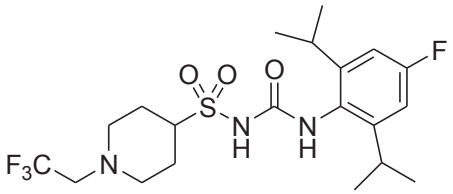

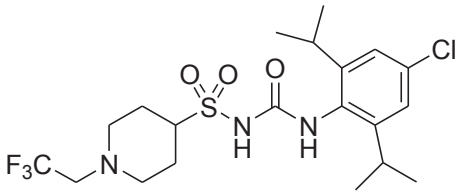

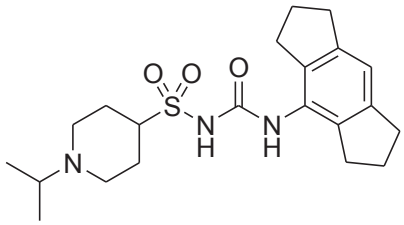

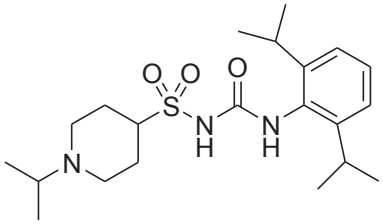

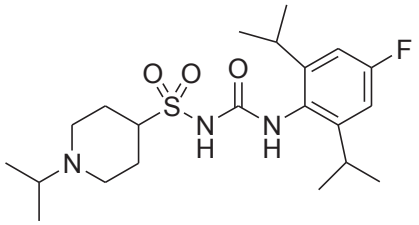

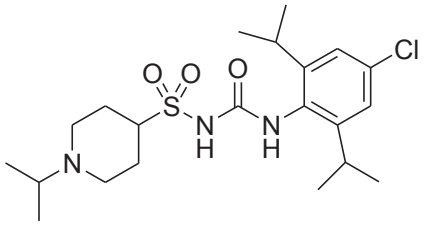

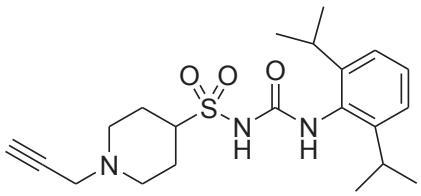

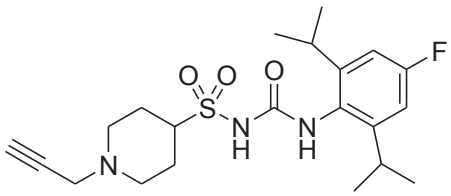

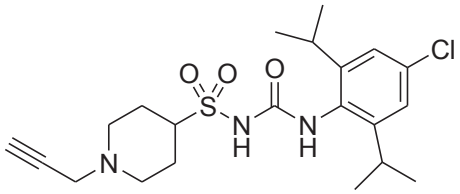

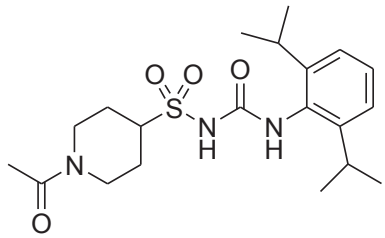

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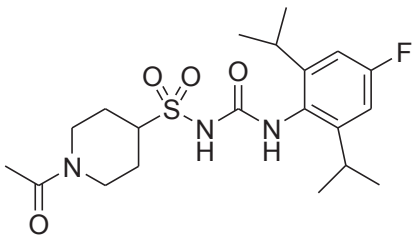

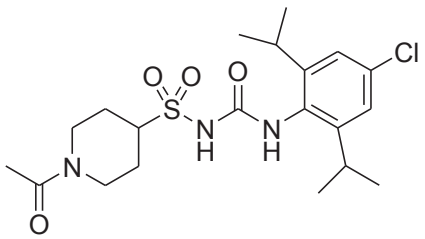

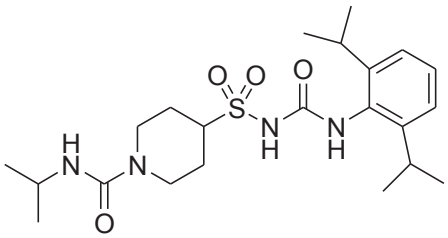

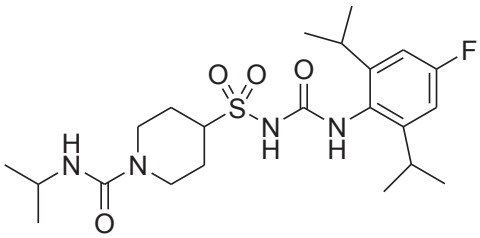

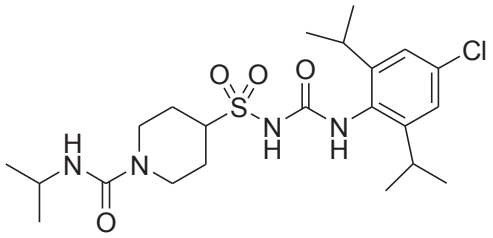

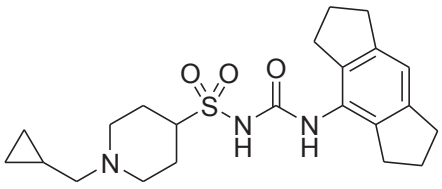

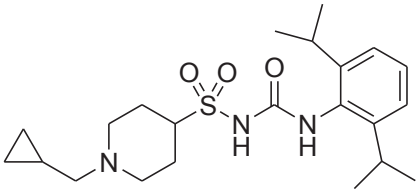

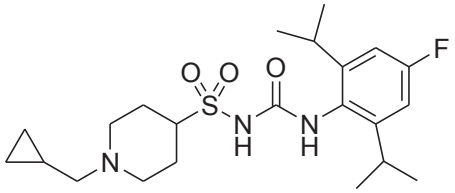

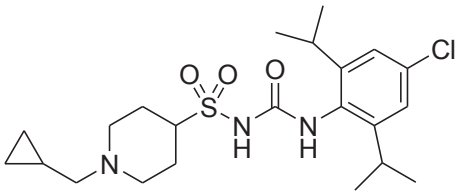

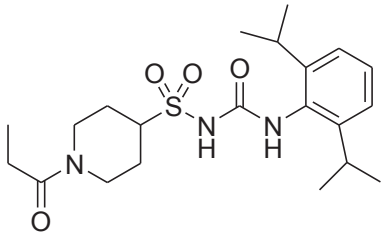

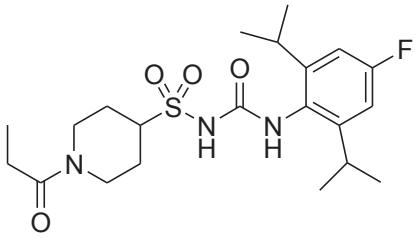

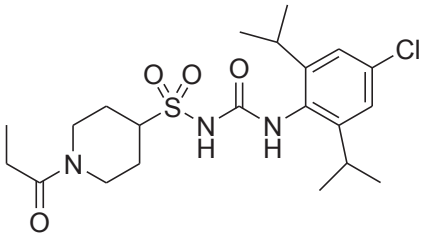

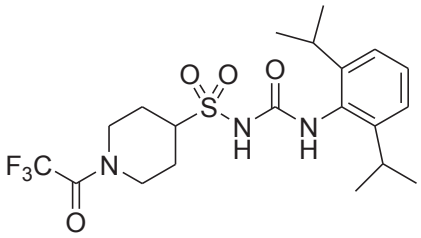

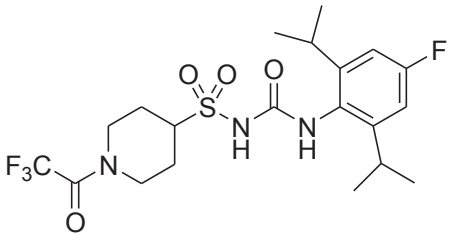

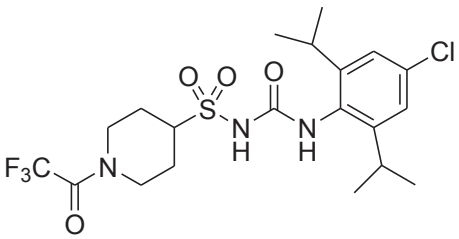

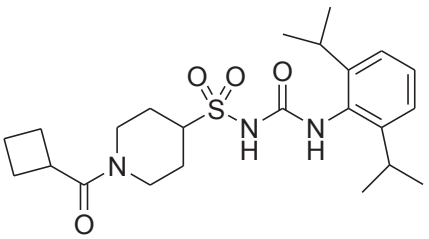

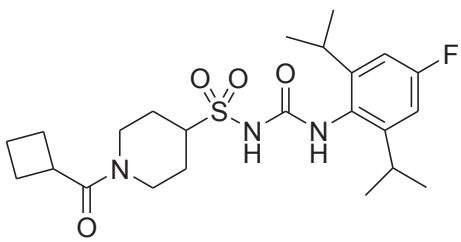

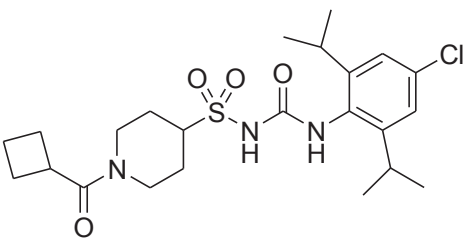

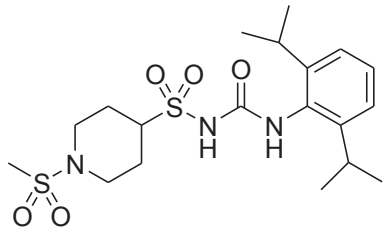
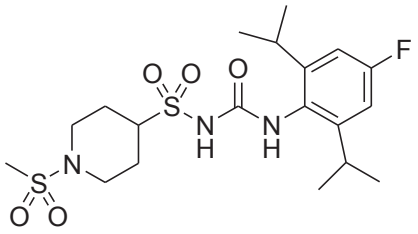
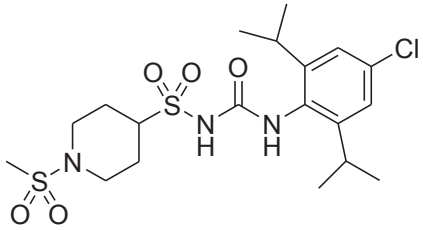

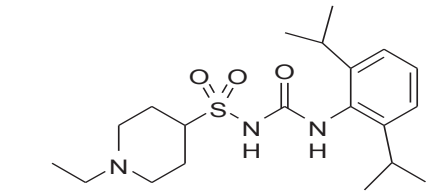

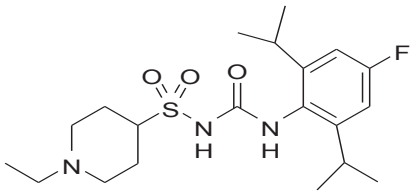

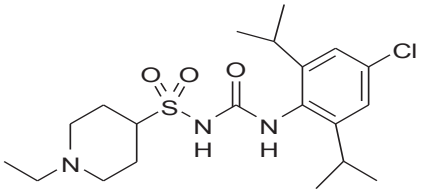

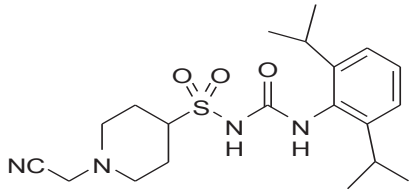

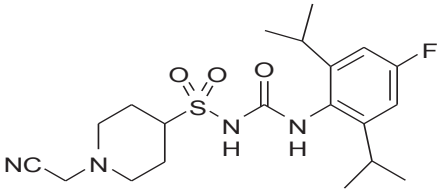

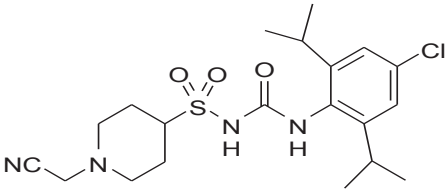

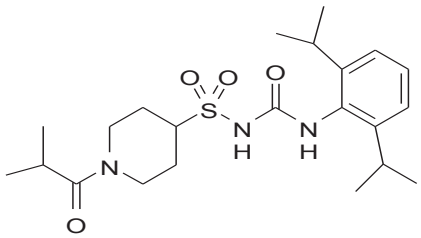

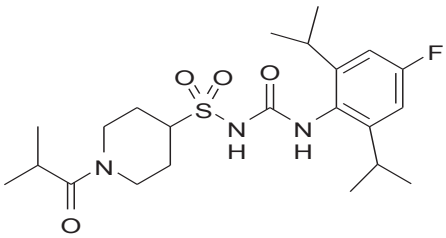

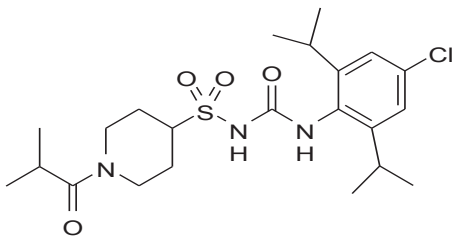

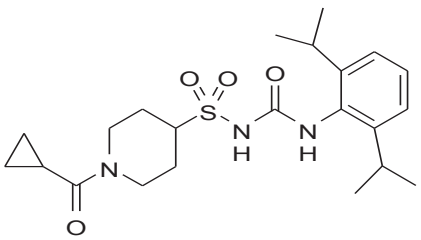

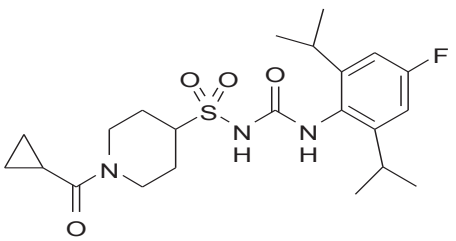

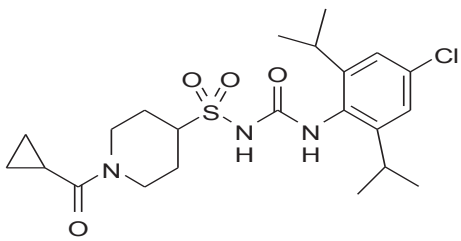

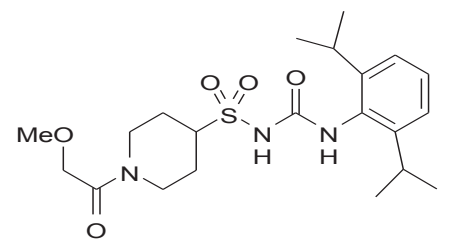

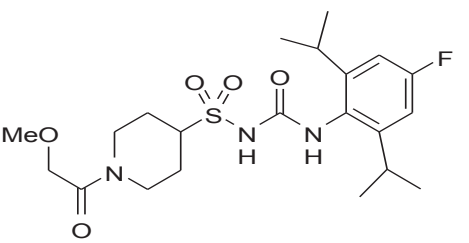

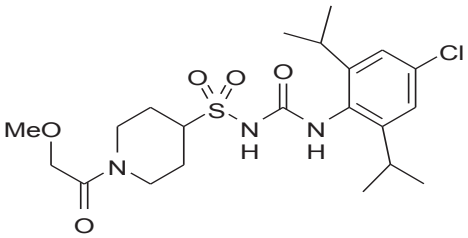
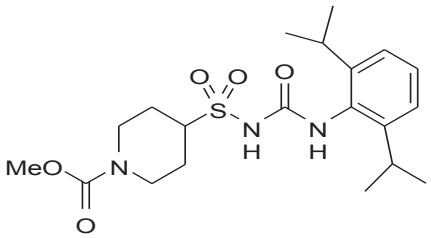
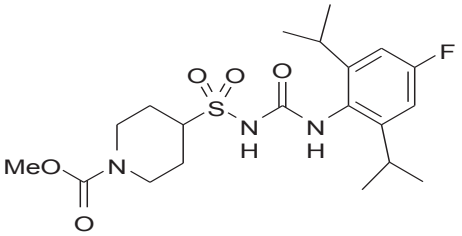
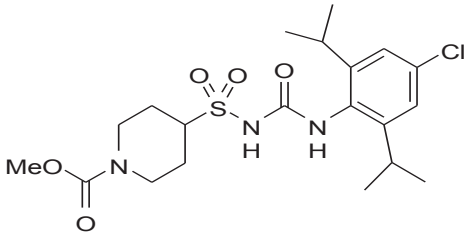
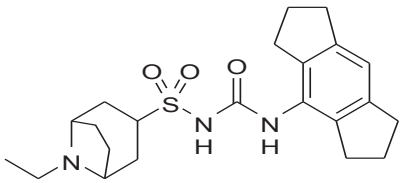
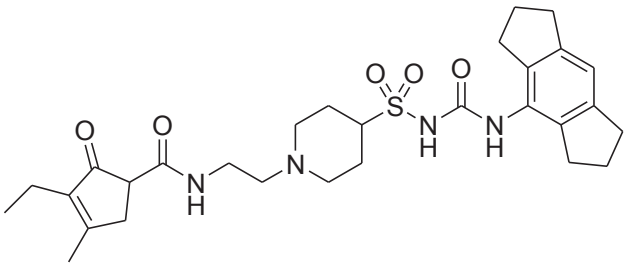
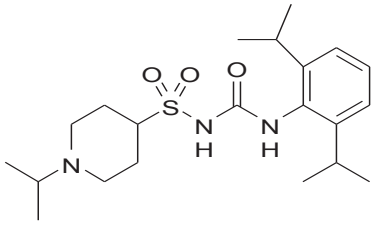
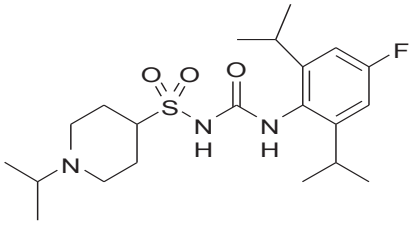
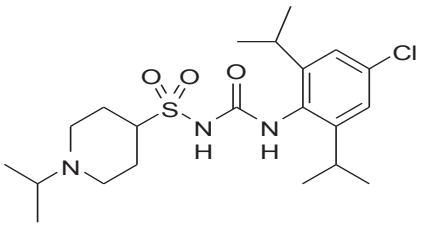
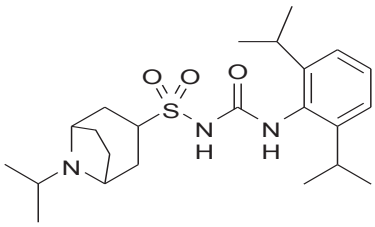
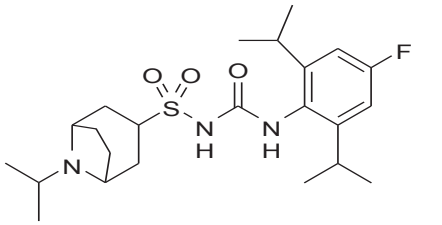
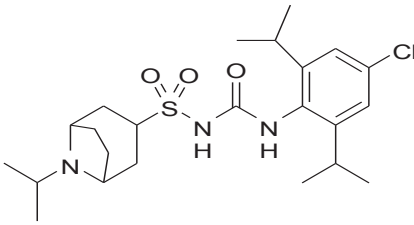
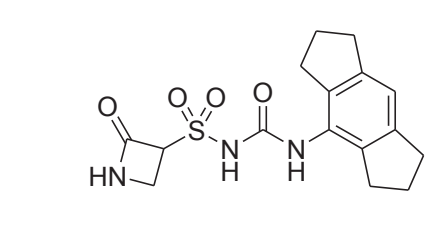
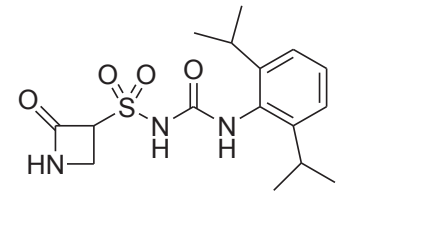

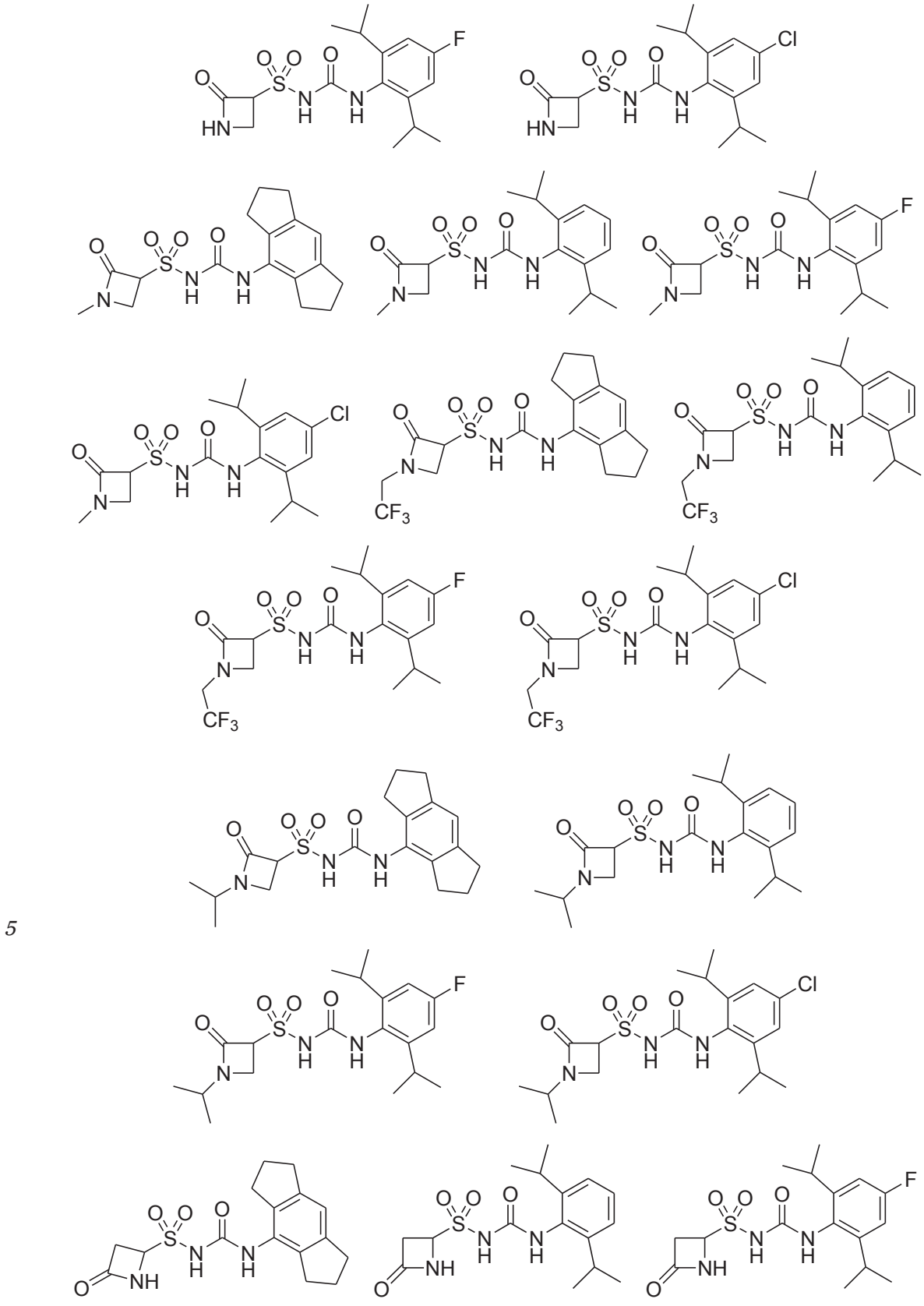

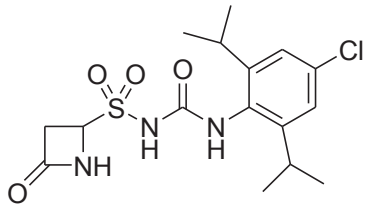

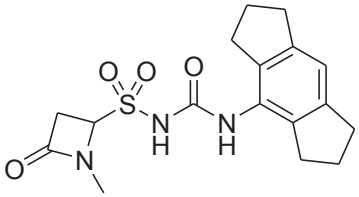

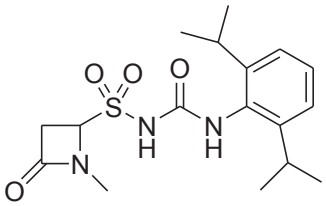

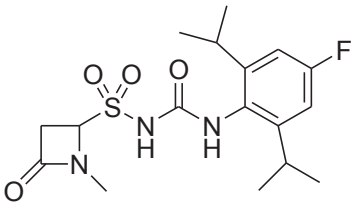

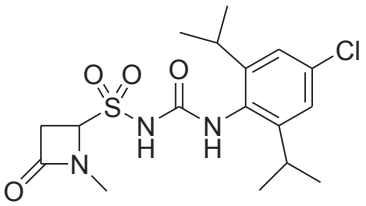

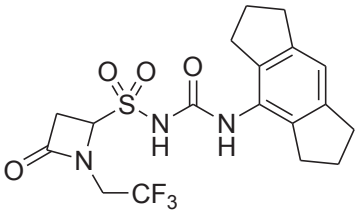

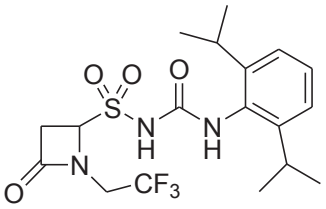

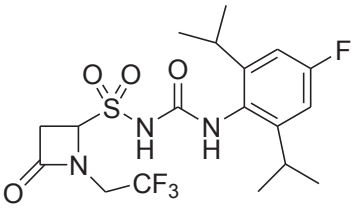

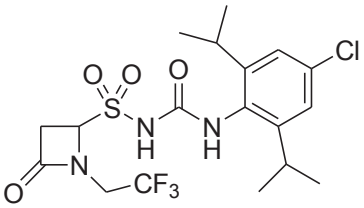

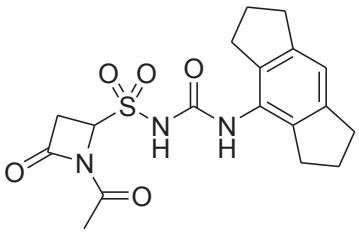

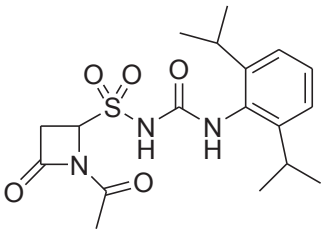

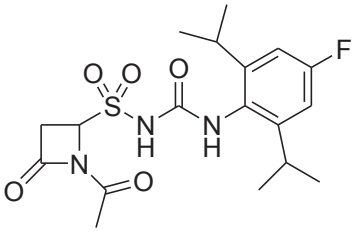

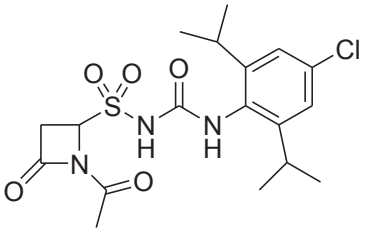

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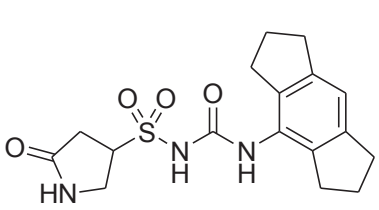

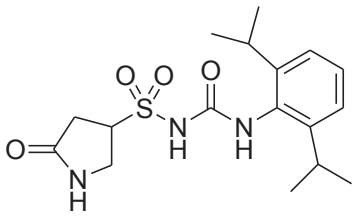

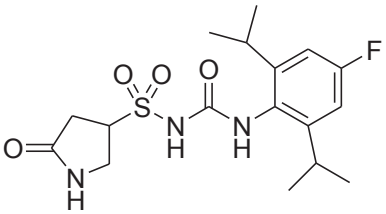

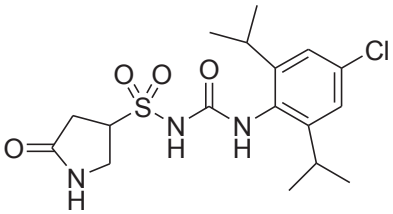

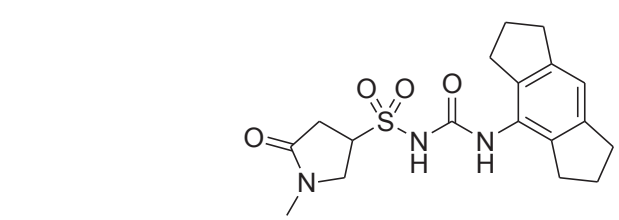
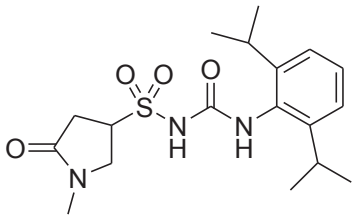
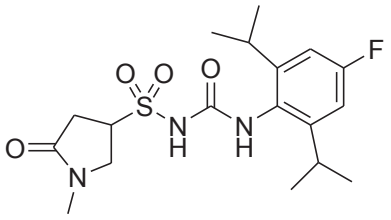
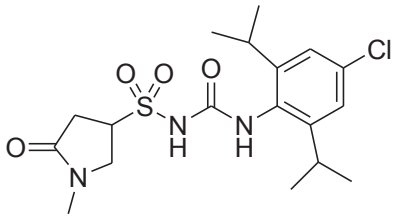
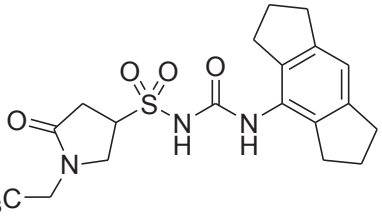
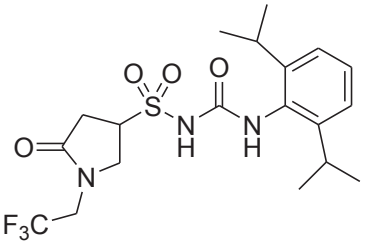
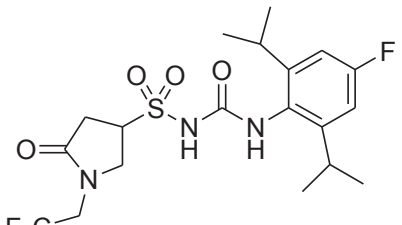
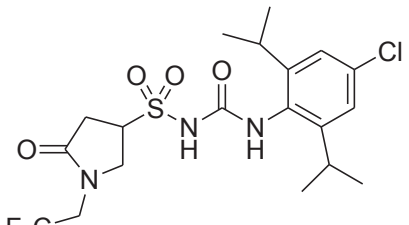
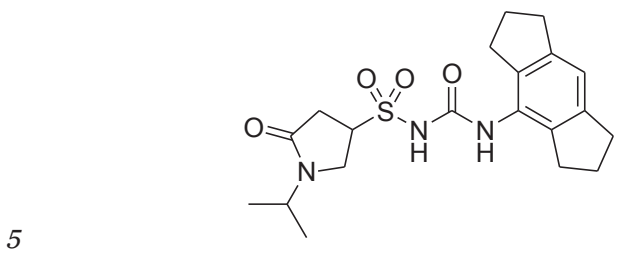
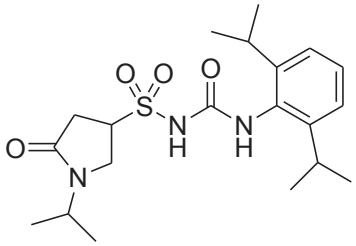
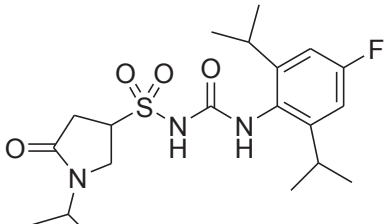
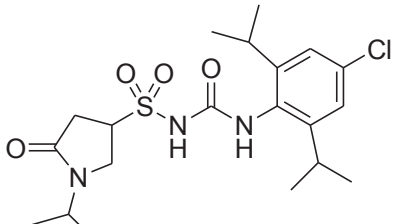
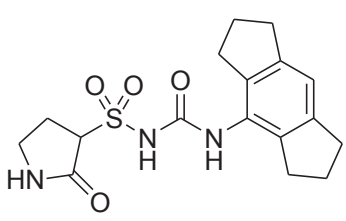
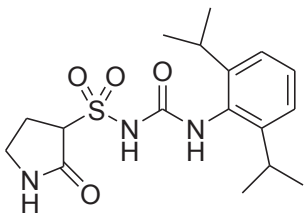
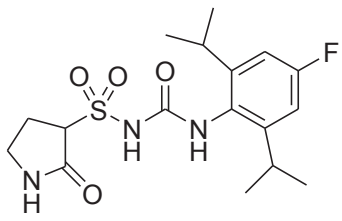

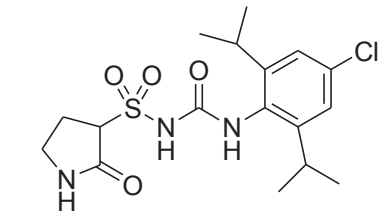
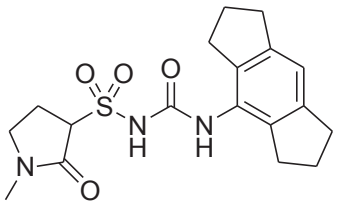
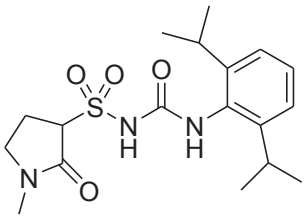
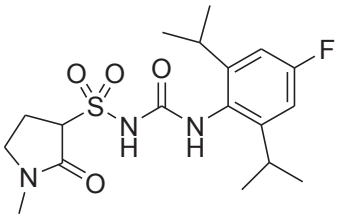
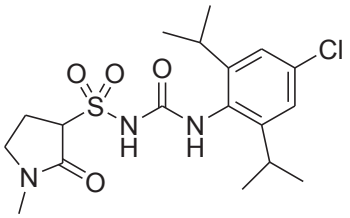
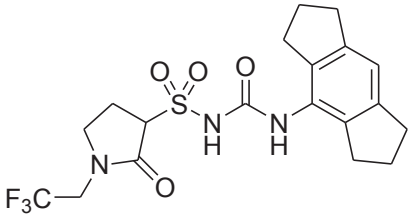
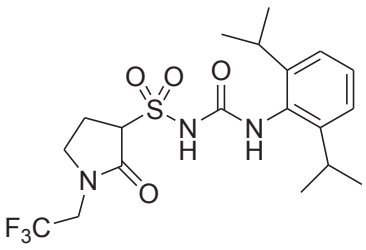
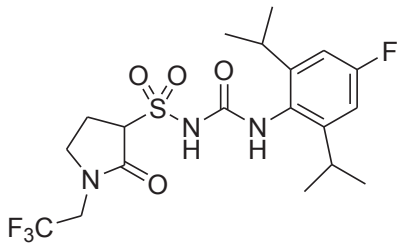
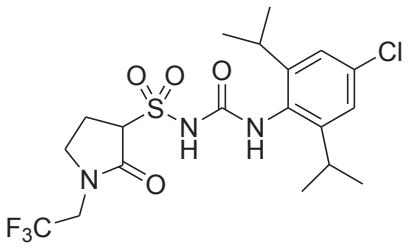
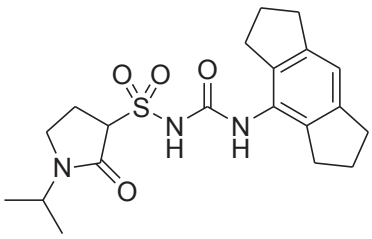
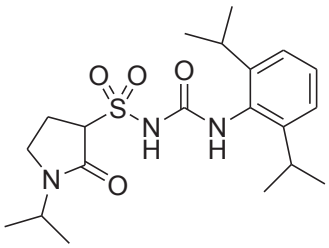
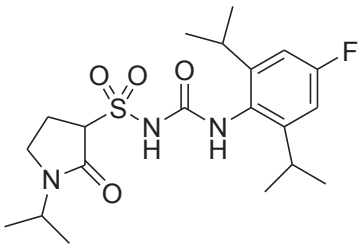
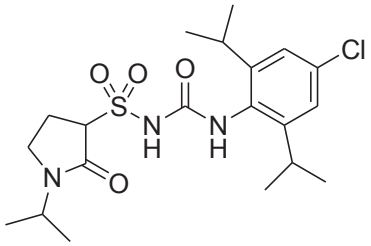
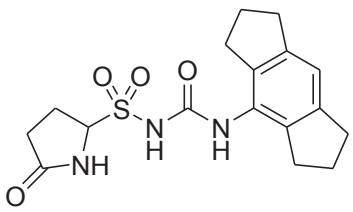
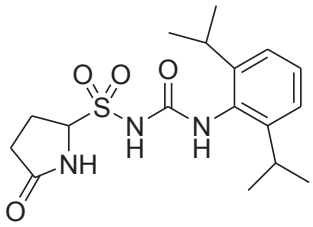
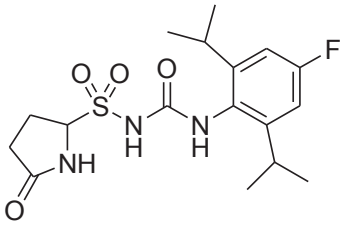
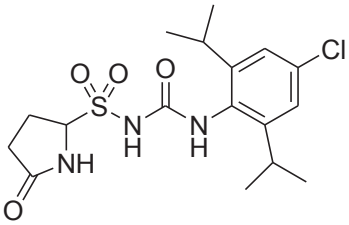
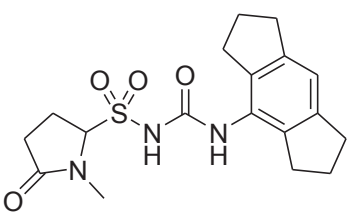

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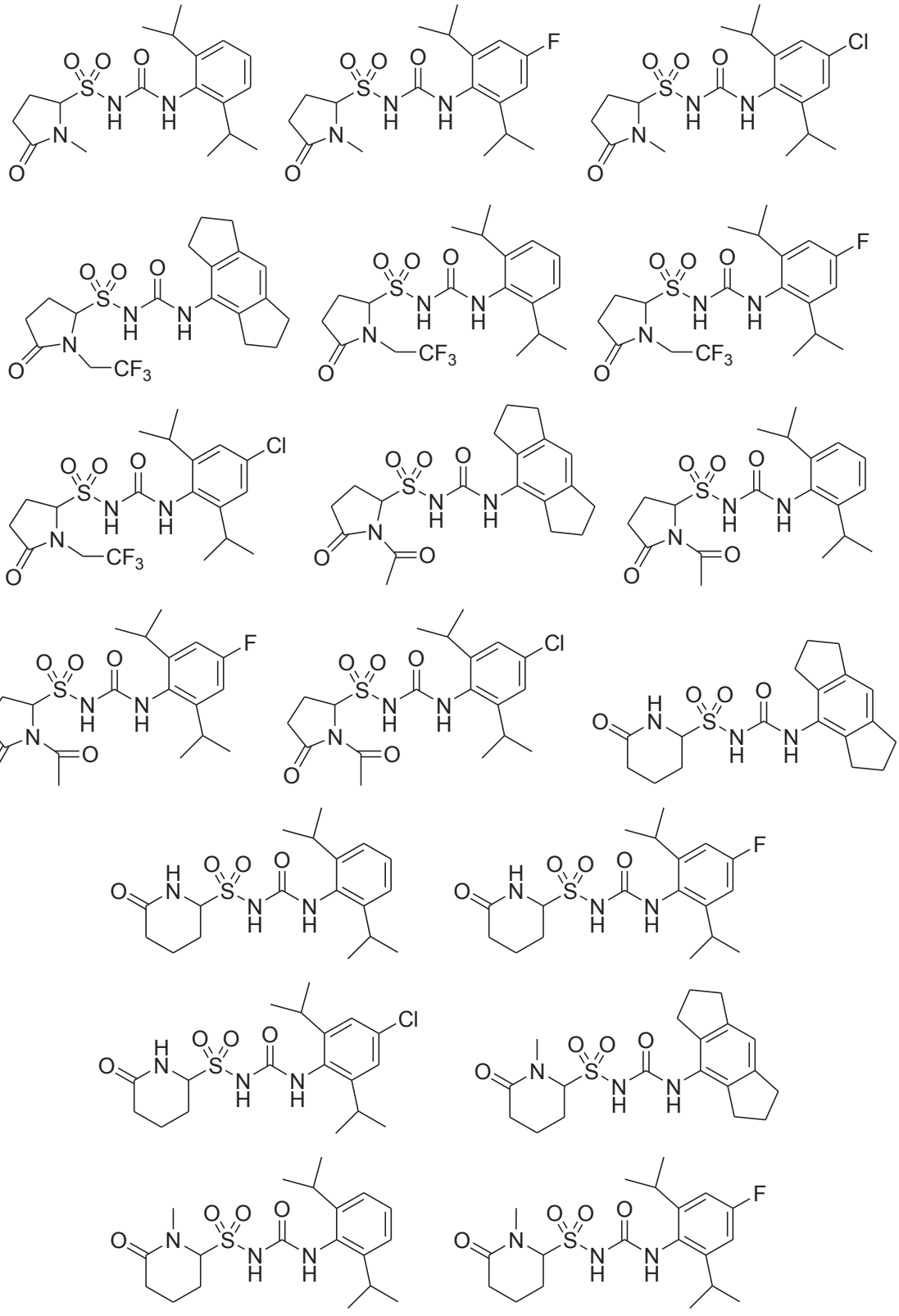

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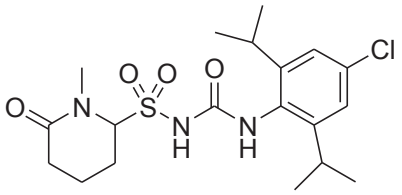
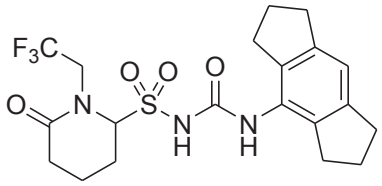
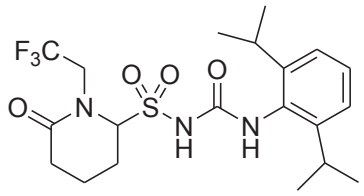
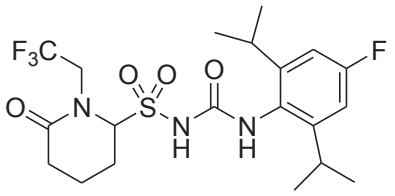
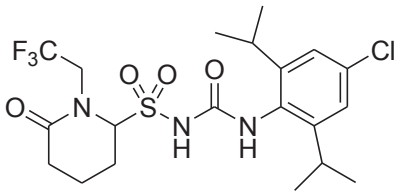
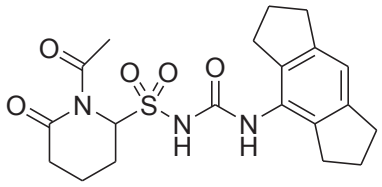
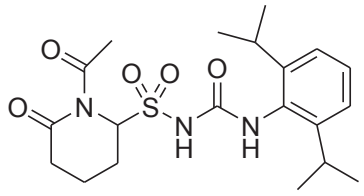
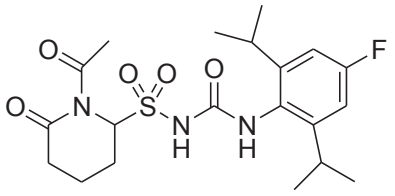
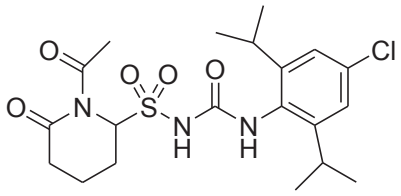
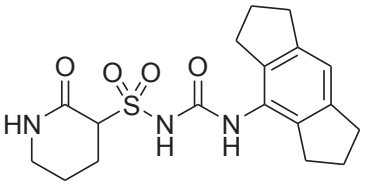
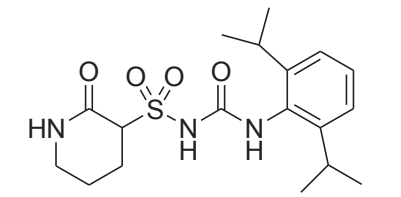
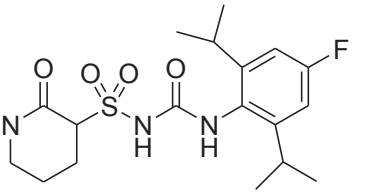
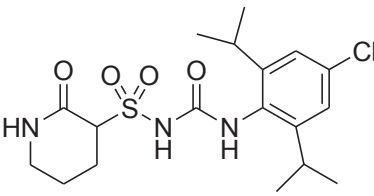
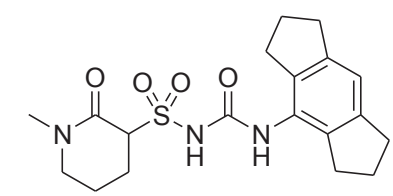
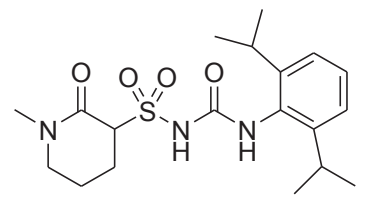
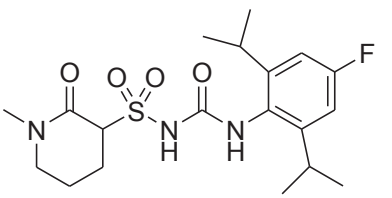

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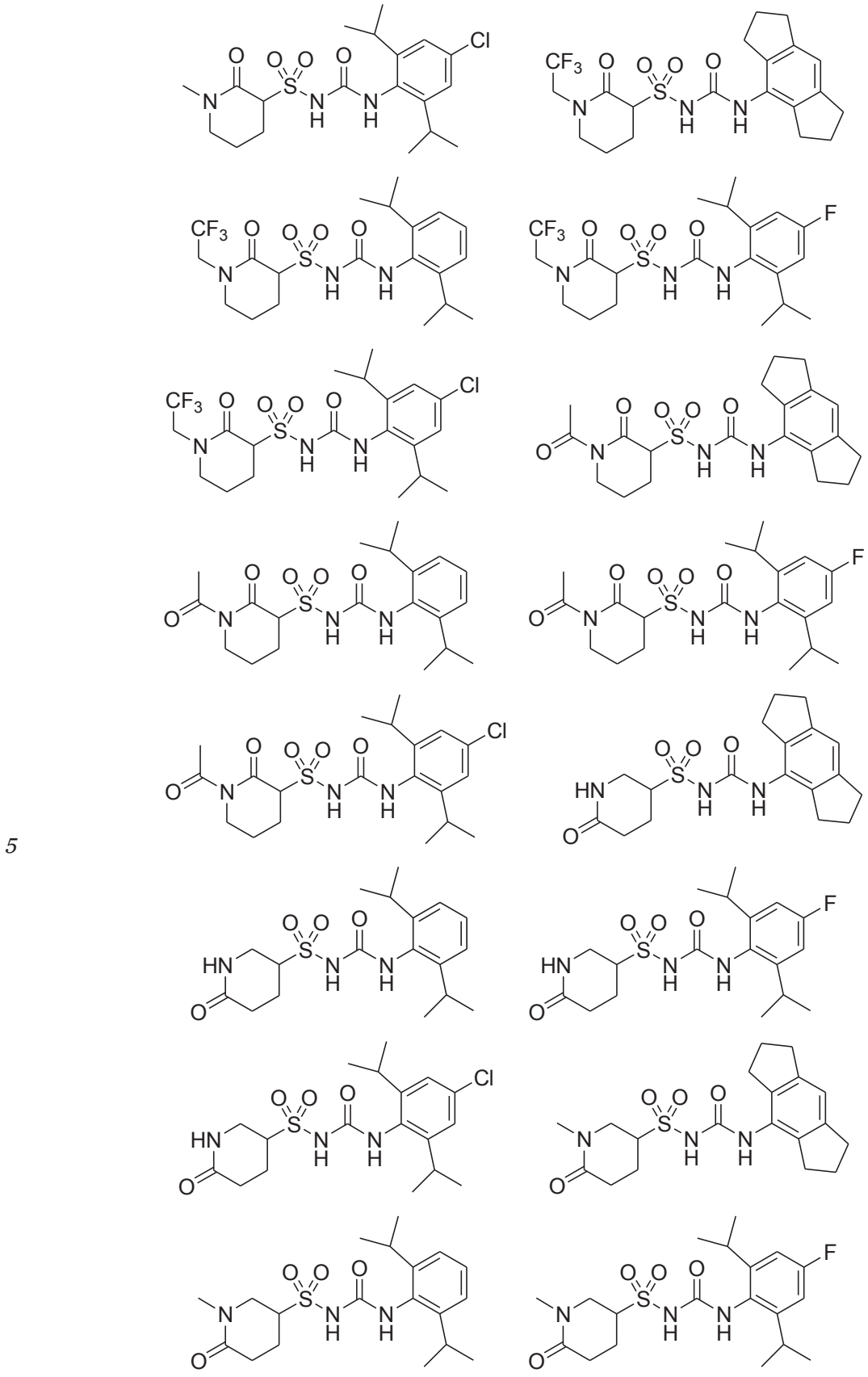

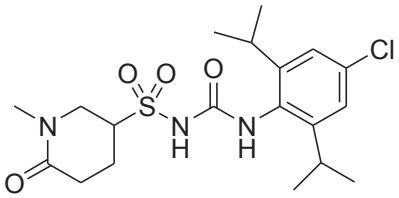
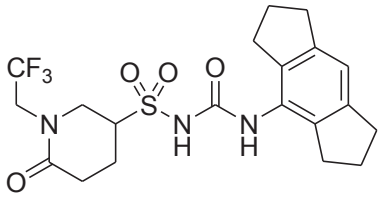
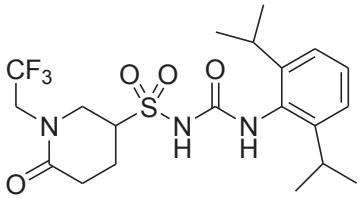
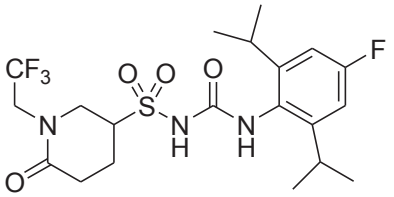
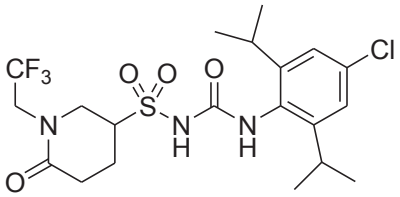
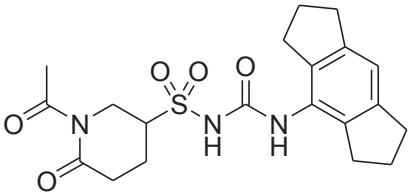
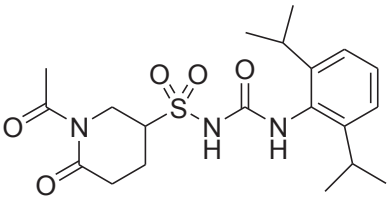
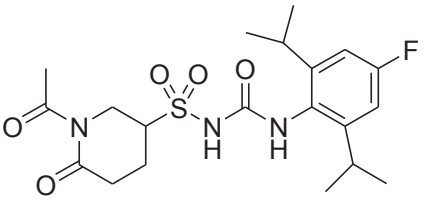
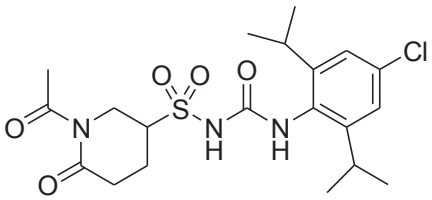
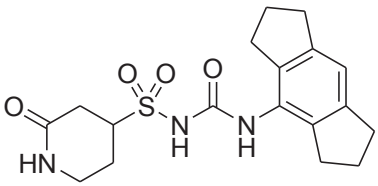
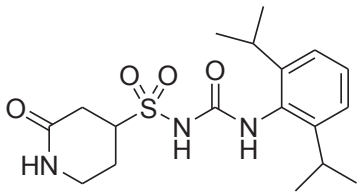
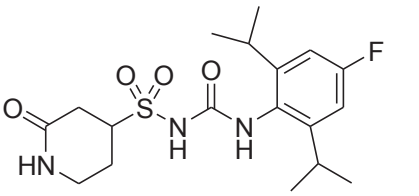
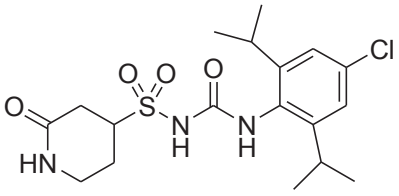

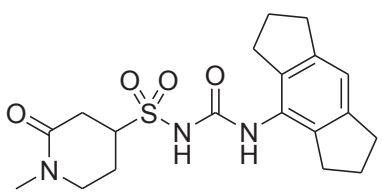
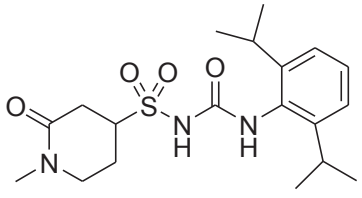
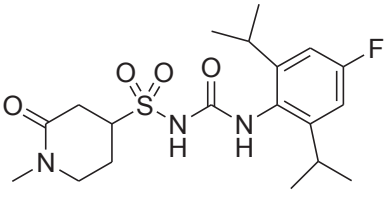

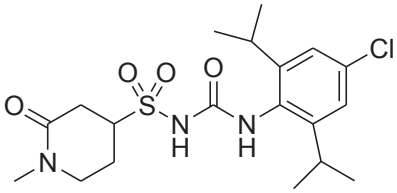

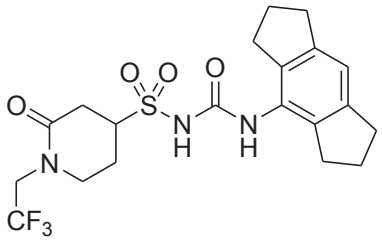

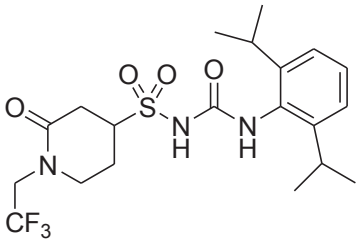

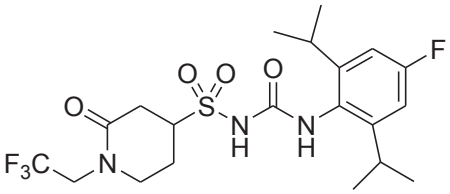

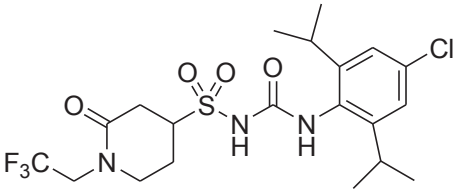

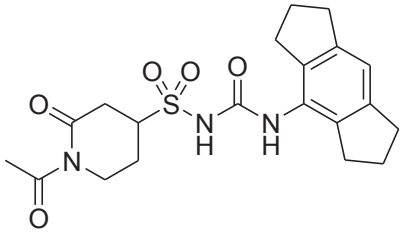

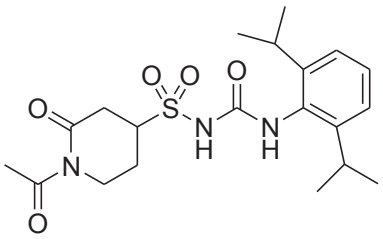

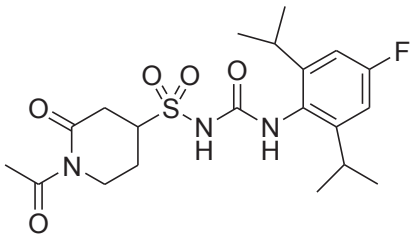

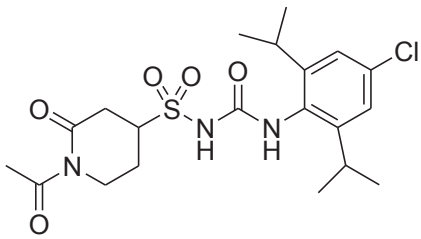

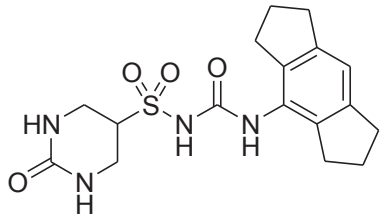

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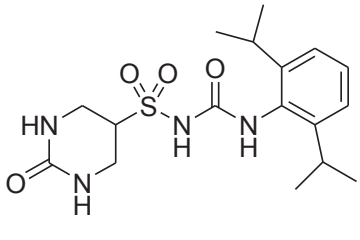

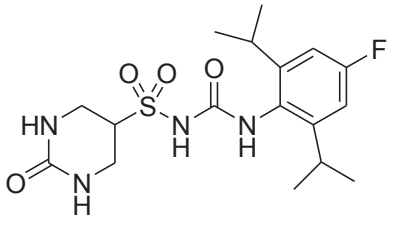

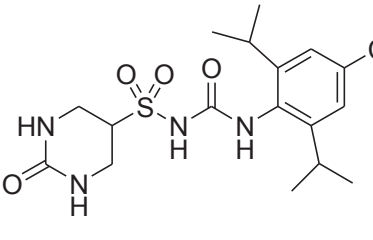

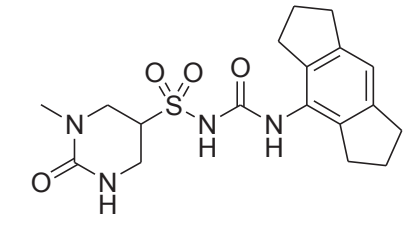

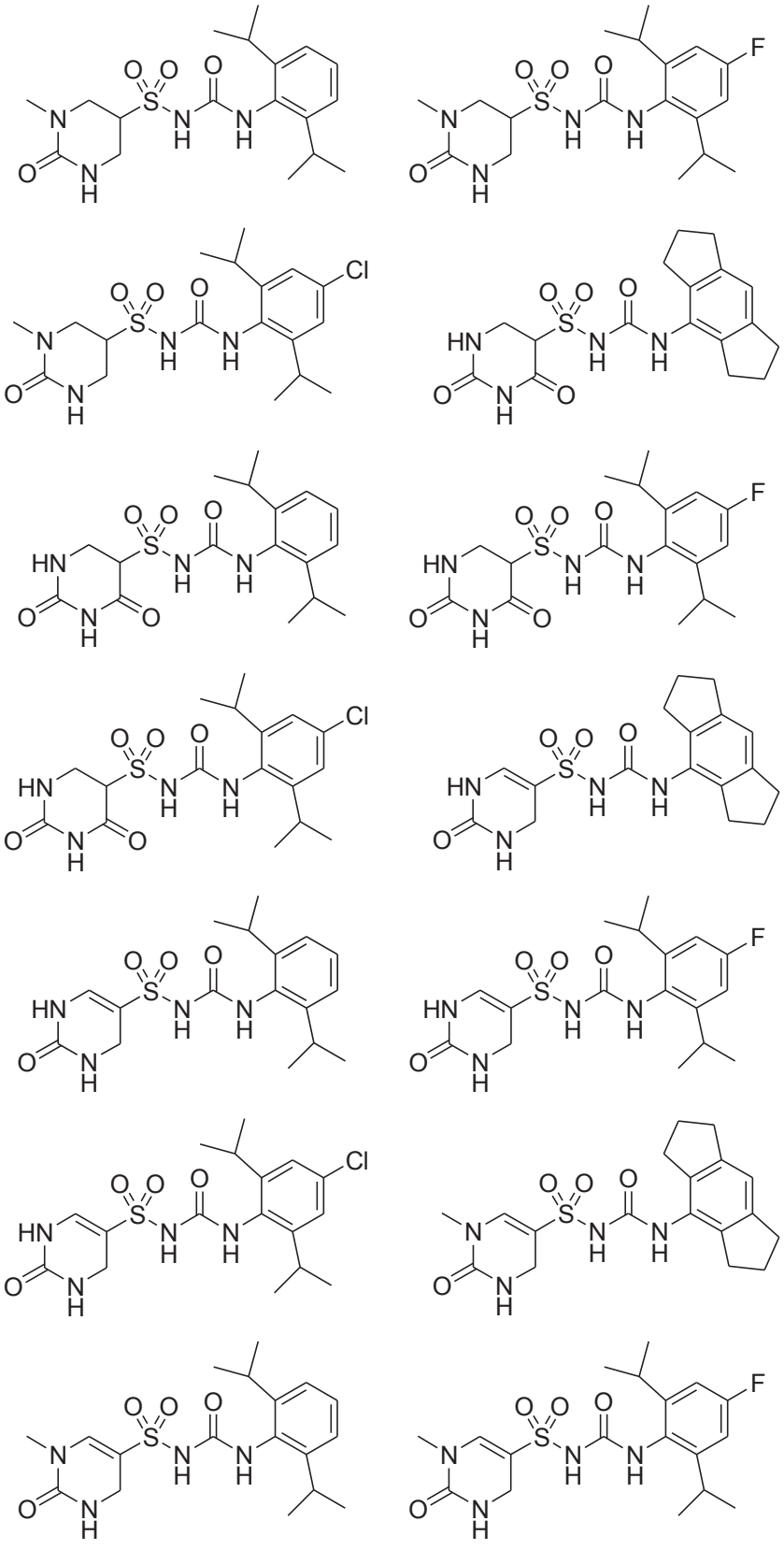

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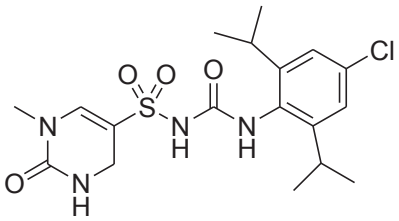

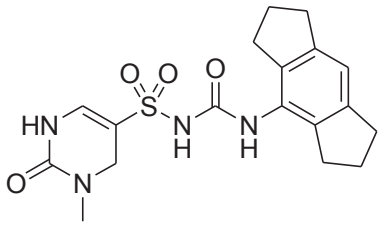

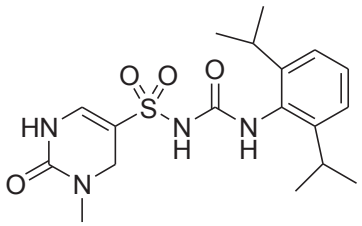

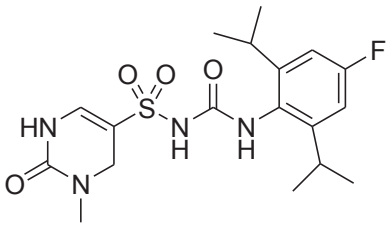

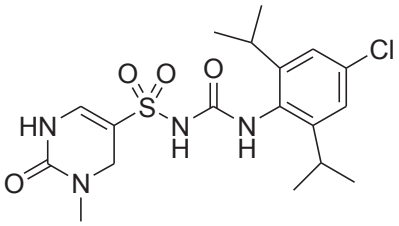

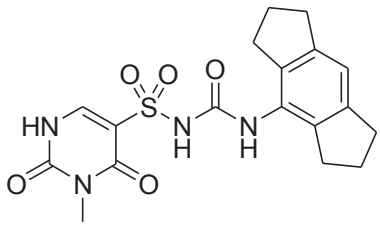

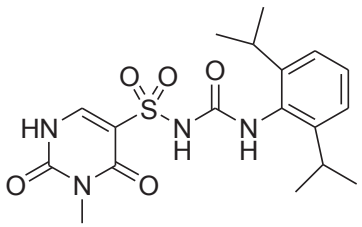

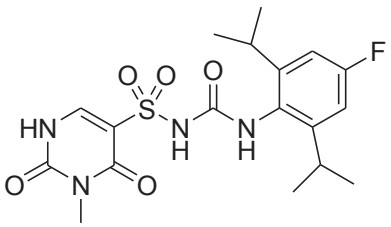

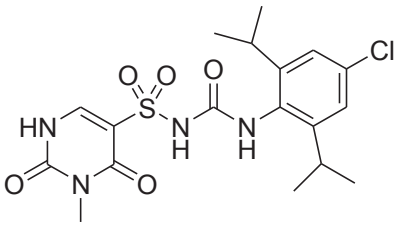

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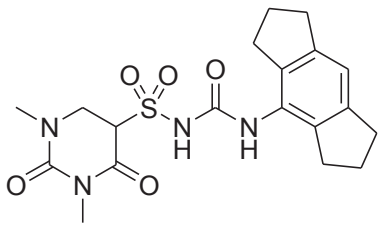

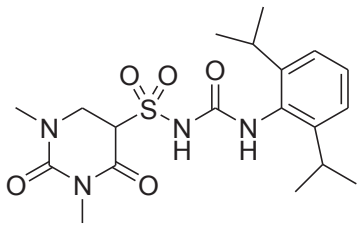

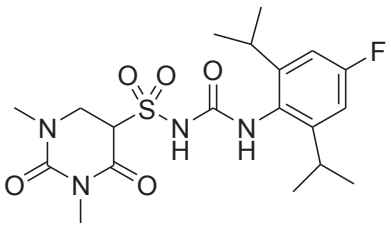

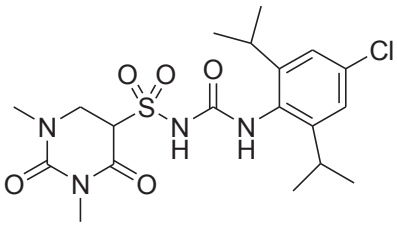

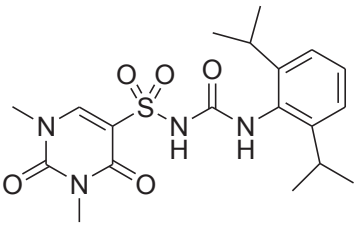

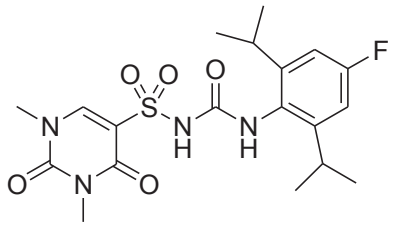
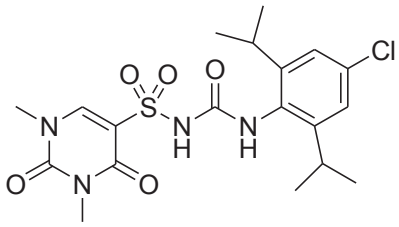
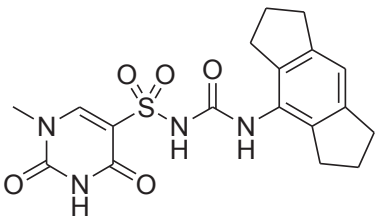
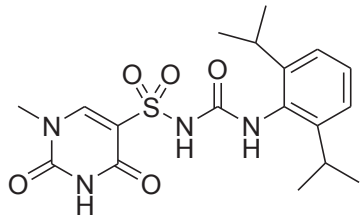
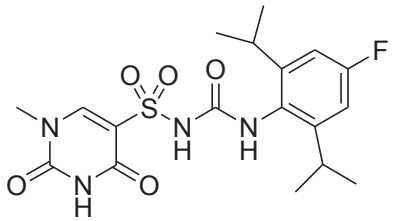
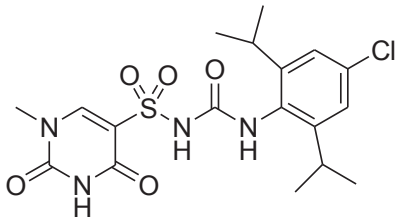
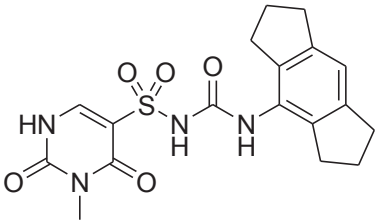
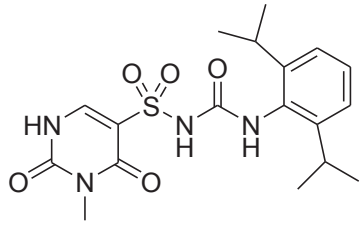
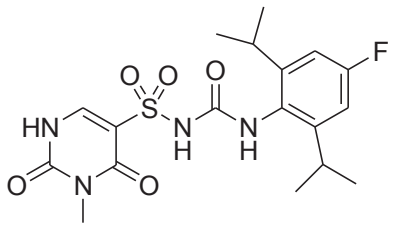
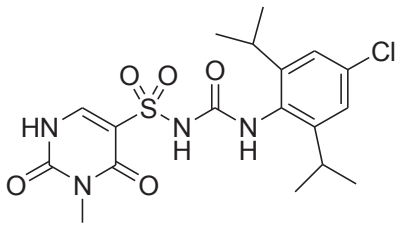

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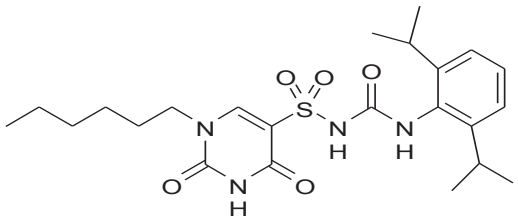
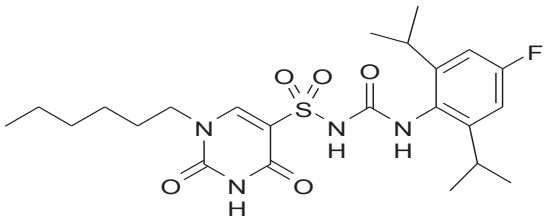
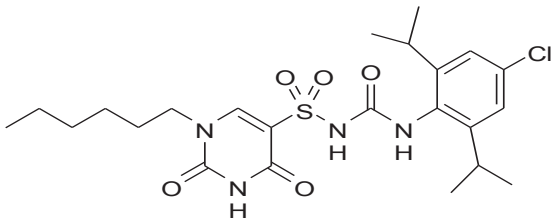




and .

A third aspect of the disclosure provides a pharmaceutically acceptable salt, solvate or

prodrug of any compound of the first or second aspect of the disclosure.

The compounds of the present disclosure can be used both in their free base form and their acid addition salt form. For the purposes of this disclosure, a “salt” of a compound of the present disclosure includes an acid addition salt. Acid addition salts are preferably pharmaceutically acceptable, non-toxic addition salts with suitable acids, including but not limited to inorganic acids such as hydrohalogenic acids (for example, hydrofluoric, hydrochloric, hydrobromic or hydroiodic acid) or other inorganic acids (for example, nitric, perchloric, sulfuric or phosphoric acid); or organic acids such as organic carboxylic acids (for example, propionic, butyric, glycolic, lactic, mandelic, citric, acetic, benzoic, salicylic, succinic, malic or hydroxysuccinic, tartaric, fumaric, maleic, hydroxymaleic, mucic or galactaric, gluconic, pantothenic or pamoic acid), organic sulfonic acids (for example, methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, toluene-p-sulfonic, naphthalene-2-sulfonic or camphorsulfonic acid) or amino acids (for example, ornithinic, glutamic or aspartic acid). The acid addition salt may be a mono-, di-, tri- or multi-acid addition salt. A preferred salt is a hydrohalogenic, sulfuric, phosphoric or organic acid addition salt. A preferred salt is a hydrochloric acid addition salt.

Where a compound of the disclosure includes a quaternary ammonium group, typically the compound is used in its salt form. The counter ion to the quaternary ammonium group may be any pharmaceutically acceptable, non-toxic counter ion. Examples of suitable counter ions include the conjugate bases of the protic acids discussed above in relation to acid-addition salts.

The compounds of the present disclosure can also be used both, in their free acid form and their salt form. For the purposes of this disclosure, a “salt” of a compound of the present disclosure includes one formed between a protic acid functionality (such as a carboxylic acid group) of a compound of the present disclosure and a suitable cation. Suitable cations include, but are not limited to lithium, sodium, potassium, magnesium, calcium and ammonium. The salt may be a mono-, di-, tri- or multi-salt. Preferably the salt is a mono- or di-lithium, sodium, potassium, magnesium, calcium or ammonium salt. More preferably the salt is a mono- or di-sodium salt or a mono- or di-potassium salt.

Preferably any salt is a pharmaceutically acceptable non-toxic salt. However, in

addition to pharmaceutically acceptable salts, other salts are included in the present disclosure, since they have potential to serve as intermediates in the purification or preparation of other, for example, pharmaceutically acceptable salts, or are useful for identification, characterisation or purification of the free acid or base.

The compounds and/or salts of the present disclosure may be anhydrous or in the form of a hydrate (e.g. a hemihydrate, monohydrate, dihydrate or trihydrate) or other solvate. Such solvates may be formed with common organic solvents, including but not limited to, alcoholic solvents e.g. methanol, ethanol or isopropanol.

In some examples of the present disclosure, therapeutically inactive prodrugs are provided. Prodrugs are compounds which, when administered to a subject such as a human, are converted in whole or in part to a compound of the disclosure. In most examples, the prodrugs are pharmacologically inert chemical derivatives that can be converted *in vivo* to the active drug molecules to exert a therapeutic effect. Any of the compounds described herein can be administered as a prodrug to increase the activity, bioavailability, or stability of the compound or to otherwise alter the properties of the compound. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include, but are not limited to, compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, and/or dephosphorylated to produce the active compound. The present disclosure also encompasses salts and solvates of such prodrugs as described above.

The compounds, salts, solvates and prodrugs of the present disclosure may contain at least one chiral centre. The compounds, salts, solvates and prodrugs may therefore exist in at least two isomeric forms. The present disclosure encompasses racemic mixtures of the compounds, salts, solvates and prodrugs of the present disclosure as well as enantiomerically enriched and substantially enantiomerically pure isomers. For the purposes of this disclosure, a “substantially enantiomerically pure” isomer of a compound comprises less than 5% of other isomers of the same compound, more typically less than 2%, and most typically less than 0.5% by weight.

The compounds, salts, solvates and prodrugs of the present disclosure may contain any stable isotope including, but not limited to ^{12}C, ^{13}C, ^{1}H, ^{2}H (D), ^{14}N, ^{15}N, ^{16}O, ^{17}O, ^{18}O, ^{19}F

and ^{127}I, and any radioisotope including, but not limited to ^{11}C, ^{14}C, ^{3}H (T), ^{13}N, ^{15}O, ^{18}F, ^{123}I, ^{124}I, ^{125}I and ^{131}I.

The compounds, salts, solvates and prodrugs of the present disclosure may be in any polymorphic or amorphous form.

A fourth aspect of the disclosure provides a pharmaceutical composition comprising 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, and a pharmaceutically acceptable excipient.

Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, “Aulton’s Pharmaceutics - The Design and Manufacture of Medicines”, M. E. Aulton and K. M. G. Taylor, Churchill Livingstone Elsevier, 4th Ed., 2013.

Pharmaceutically acceptable excipients including adjuvants, diluents or carriers that may be used in the pharmaceutical compositions of the disclosure are those conventionally employed in the field of pharmaceutical formulation, and include, but are not limited to, sugars, sugar alcohols, starches, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins such as human serum albumin, buffer substances such as phosphates, glycerine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinylpyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

In one example, the pharmaceutical composition of the fourth aspect of the disclosure additionally comprises one or more further active agents.

In a further example, the pharmaceutical composition of the fourth aspect of the 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, 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 refers to the use of a compound as described herein, or a pharmaceutically acceptable salt, solvate or prodrug 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 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 yet another aspect, the present disclosure refers to the use of a compound as described herein, or a pharmaceutically acceptable salt, solvate or prodrug 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 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).

The term "treatment" as used herein refers equally to curative therapy, and ameliorating or palliative therapy. The term includes obtaining beneficial or desired physiological results, which may or may not be established clinically. Beneficial or desired clinical results include, but are not limited to, the alleviation of symptoms, the prevention of symptoms, the diminishment of extent of disease, the stabilisation (i.e., not worsening) of a condition, the delay or slowing of progression/worsening of a condition/symptoms, the amelioration or palliation of the condition/symptoms, and remission (whether partial or total), whether detectable or undetectable. The term "palliation", and variations thereof, as used herein, means that the extent and/or undesirable manifestations of a physiological condition or symptom are lessened and/or time course of the progression is slowed or lengthened, as compared to not administering a compound, salt, solvate, prodrug or pharmaceutical composition of the present disclosure. The term "prevention" as used herein in relation to a disease, disorder or condition, relates to prophylactic or preventative therapy, as well as therapy to reduce the risk of developing the disease, disorder or condition. The term "prevention" includes both the avoidance of occurrence of the disease, disorder or

condition, and the delay in onset of the disease, disorder or condition. Any statistically 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 aspect 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 mutation may be, for example, a gain-of-function or other mutation resulting in increased NLRP3 activity. Typically, the use comprises the administration

of the compound, salt, solvate, prodrug or pharmaceutical composition to the individual. In one example, the use comprises the co-administration of one or more further active agents. The use may also comprise the diagnosis of an individual having a germline or somatic non-silent mutation in NLRP3, wherein the compound, salt, solvate, prodrug or pharmaceutical composition is administered to an individual on the basis of a positive diagnosis for the mutation. Typically, identification of the mutation in NLRP3 in the individual may be by any suitable genetic or biochemical means.

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 in an individual, wherein the individual has a germline or somatic non-silent mutation in NLRP3. The mutation may be, for example, a gain-of-function or other mutation resulting in increased NLRP3 activity. Typically, the treatment or prevention comprises the administration of the compound, salt, solvate, prodrug or medicament to the individual. In one example, the treatment or prevention comprises the co-administration of one or more further active agents. The treatment or prevention may also comprise the diagnosis of an individual having a germline or somatic non-silent mutation in NLRP3, wherein the compound, salt, solvate, prodrug or medicament is administered to an individual on the basis of a positive diagnosis for the mutation. Typically, identification of the mutation in NLRP3 in the individual may be by any suitable genetic or biochemical means.

Afurther example of the disclosure provides a method of treatment or prevention of a disease, disorder or condition, the method comprising the steps of diagnosing of an individual having a germline or somatic non-silent mutation in NLRP3, and 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 the positively diagnosed individual, 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.

In general examples, the disease, disorder or condition may be a disease, disorder or condition of the immune system, the cardiovascular system, the endocrine system, the gastrointestinal tract, the renal system, the hepatic system, the metabolic system, the

respiratory system, the central nervous system, may be a cancer or other malignancy, and/or may be caused by or associated with a pathogen.

It will be appreciated that these general examples defined according to broad categories of diseases, disorders and conditions are not mutually exclusive. In this regard any particular disease, disorder or condition may be categorized according to more than one of the above general examples. A non-limiting example is type I diabetes which is an autoimmune disease and a disease of the endocrine system.

In one example of the present disclosure, the disease, disorder or condition is responsive to NLRP3 inhibition. As used herein, the term "NLRP3 inhibition" refers to the complete or partial reduction in the level of activity of NLRP3 and includes, for example, the inhibition of active NLRP3 and/or the inhibition of activation of NLRP3.

There is evidence for a role of NLRP3-induced IL-1 and IL-18 in the inflammatory responses occurring in connection with, or as a result of, a multitude of different disorders (Menu *et al.,* Clinical and Experimental Immunology, 166: 1–15, 2011; Strowig *et al.,* Nature, 481:278-286, 2012).

NLRP3 has been implicated in a number of autoinflammatory diseases, including Familial Mediterranean fever (FMF), TNF receptor associated periodic syndrome (TRAPS), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), Sweet's syndrome, chronic nonbacterial osteomyelitis (CNO), and acne vulgaris (Cook *et al.,* Eur. J. Immunol., 40: 595–653, 2010). In particular, NLRP3 mutations have been found to be responsible for a set of rare autoinflammatory diseases known as CAPS (Ozaki *et al.,* J. Inflammation Research, 8:15-27, 2015; Schroder *et al.,* Cell, 140: 821-832, 2010; and Menu *et al.*, Clinical and Experimental Immunology, 166: 1–15, 2011). CAPS are heritable diseases characterized by recurrent fever and inflammation and are comprised of three autoinflammatory disorders that form a clinical continuum. These diseases, in order of increasing severity, are familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile cutaneous neurological articular syndrome (CINCA; also called neonatal-onset multisystem inflammatory disease, NOMID), and all have been shown to result from gain-of-function mutations in the NLRP3 gene, which leads to increased secretion of IL-1β.

A number of autoimmune diseases have been shown to involve NLRP3 including, in particular, multiple sclerosis, type-1 diabetes (T1D), psoriasis, rheumatoid arthritis (RA), Behcet's disease, Schnitzler syndrome, macrophage activation syndrome (Masters Clin. Immunol. 2013; Braddock *et al.* Nat. Rev. Drug Disc. 2004 3: 1-10; Inoue *et al.,* Immunology 139: 11-18, Coll *et al.* Nat. Med. 2015 21(3):248-55; and Scott *et al.* Clin. Exp. Rheumatol 2016 34(1): 88-93), systemic lupus erythematosus (Lu *et al.* J Immunol. 2017 198(3): 1119-29), and systemic sclerosis (Artlett *et al.* Arthritis Rheum. 2011; 63(11): 3563-74). NLRP3 has also been shown to play a role in a number of lung diseases including chronic obstructive pulmonary disorder (COPD), asthma (including steroid-resistant asthma), asbestosis, and silicosis (De Nardo *et al.,* Am. J. Pathol., 184: 42-54, 2014 and Kim *et al.* Am J Respir Crit Care Med. 2017 196(3): 283-97). NLRP3 has also been suggested to have a role in a number of central nervous system conditions, including Parkinson's disease (PD), Alzheimer's disease (AD), dementia, Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis (Walsh *et al.,* Nature Reviews, 15: 84-97, 2014, and Dempsey *et al.* Brain. Behav. Immun. 2017 61: 306-316), intracranial aneurysms (Zhang *et al.* J. Stroke & Cerebrovascular Dis. 2015 24; 5: 972–979), and traumatic brain injury (Ismael et al. J Neurotrauma. 2018 Jan 2). NRLP3 activity has also been shown to be involved in various metabolic diseases including type 2 diabetes (T2D), atherosclerosis, obesity, gout, pseudo-gout, metabolic syndrome (Wen *et al.,* Nature Immunology, 13: 352-357, 2012; Duewell *et al.,* Nature, 464: 1357-1361, 2010; Strowig *et al.,* Nature, 481: 278-286, 2012), and non-alcoholic steatohepatitis (Mridha *et al.* J Hepatol. 2017 66(5): 1037-46). A role for NLRP3 via IL-1β has also been suggested in atherosclerosis, myocardial infarction (van Hout *et al.* Eur. Heart J 2017 38(11): 828-36), heart failure (Sano *et al.* J AM. Coll. Cardiol. 2018 71(8): 875-66), aortic aneurysm and dissection (Wu *et al.* Arterioscler. Thromb. Vasc. Biol. 2017 37(4): 694–706), and other cardiovascular events (Ridker et al, N Engl J Med., doi: 10.1056/ NEJMoa1707914, 2017). Other diseases in which NLRP3 has been shown to be involved include: ocular diseases such as both wet and dry age-related macular degeneration (Doyle *et al.*, Nature Medicine, 18: 791-798, 2012 and Tarallo *et al.* Cell 2012 149(4): 847-59), diabetic retinopathy (Loukovaara *et al.* Acta Ophthalmol. 2017; 95(8): 803-808) and optic nerve damage (Puyang *et al.* Sci Rep. 2016 Feb 19;6:20998); liver diseases including non-alcoholic steatohepatitis (NASH) (Henao-Meija *et al.,* Nature, 482: 179-185, 2012); inflammatory reactions in the lung and skin (Primiano *et al.* J Immunol. 2016 197(6): 2421-33) including contact hypersensitivity (such as bullous pemphigoid (Fang *et al.* J Dermatol Sci. 2016; 83(2): 116-23)), atopic dermatitis (Niebuhr *et al.*

Allergy 2014 69(8): 1058-67), Hidradenitis suppurativa (Alikhan *et al.* 2009 J Am Acad Dermatol 60(4): 539-61), acne vulgaris (Qin *et al.* J Invest. Dermatol. 2014 134(2): 381-88), and sarcoidosis (Jager *et al.* Am J Respir Crit Care Med 2015 191: A5816); inflammatory reactions in the joints (Braddock *et al.,* Nat. Rev. Drug Disc., 3: 1-10, 2004); amyotrophic lateral sclerosis (Gugliandolo *et al.* Inflammation 2018 41(1): 93-103); cystic fibrosis (Iannitti *et al.* Nat. Commun. 2016 7: 10791); stroke (Walsh *et al.,* Nature Reviews, 15: 84-97, 2014); chronic kidney disease (Granata *et al.* PLoS One 2015 10(3): e0122272); and inflammatory bowel diseases including ulcerative colitis and Crohn's disease (Braddock *et al.,* Nat. Rev. Drug Disc., 3: 1-10, 2004, Neudecker *et al.* J Exp. Med. 2017 214(6): 1737-52, and Lazaridis *et al.* Dig. Dis. Sci. 2017 62(9): 2348-56). The NLRP3 inflammasome has been found to be activated in response to oxidative stress, and UVB irradiation (Schroder et al., Science, 327: 296-300, 2010). NLRP3 has also been shown to be involved in inflammatory hyperalgesia (Dolunay *et al.*, Inflammation, 40: 366-386, 2017).

The inflammasome, and NLRP3 specifically, has also been proposed as a target for modulation by various pathogens including viruses such as DNA viruses (Amsler et al., Future Virol. (2013) 8(4), 357–370).

NLRP3 has also been implicated in the pathogenesis of many cancers (Menu *et al.,* Clinical and Experimental Immunology 166: 1-15, 2011; and Masters Clin. Immunol. 2013). For example, several previous studies have suggested a role for IL-1β in cancer invasiveness, growth and metastasis, and inhibition of IL-1β with canakinumab has been shown to reduce the incidence of lung cancer and total cancer mortality in a randomised, double-blind, placebo-controlled trial (Ridker *et al.* Lancet, S0140-6736(17)32247-X, 2017). Inhibition of the NLRP3 inflammasome or IL-1β has also been shown to inhibit the proliferation and migration of lung cancer cells *in vitro* (Wang *et al.* Oncol Rep. 2016; 35(4): 2053-64). A role for the NLRP3 inflammasome has been suggested in myelodysplastic syndromes (Basiorka *et al.* Blood. 2016 Dec 22;128(25):2960-2975) and also in the carcinogenesis of various other cancers including glioma (Li *et al.* Am J Cancer Res. 2015; 5(1): 442-449), inflammation-induced tumours (Allen *et al.* J Exp Med. 2010; 207(5): 1045-56 and Hu *et al.* PNAS. 2010; 107(50): 21635-40), multiple myeloma (Li *et al.* Hematology 2016 21(3): 144-51), and squamous cell carcinoma of the head and neck (Huang *et al.* J Exp Clin Cancer Res. 2017 2; 36(1): 116). Activation of the NLRP3 inflammasome has also been shown to mediate chemoresistance of tumour cells to 5-Fluorouracil (Feng et al. J Exp Clin

Cancer Res. 2017 21; 36(1): 81), and activation of NLRP3 inflammasome in peripheral nerve contributes to chemotherapy-induced neuropathic pain (Jia *et al.* Mol Pain. 2017; 13: 1-11).

NLRP3 has also been shown to be required for the efficient control of viral, bacterial, fungal, and helminth pathogen infections (Strowig *et al.,* Nature, 481:278-286, 2012).

Accordingly, examples of diseases, disorders or conditions which may be responsive to NLRP3 inhibition and which may be treated or prevented in accordance with the examples of the present disclosure include:

(i) inflammation, including inflammation occurring as a result of an inflammatory disorder, e.g. an autoinflammatory disease, inflammation occurring as a symptom of a non-inflammatory disorder, inflammation occurring as a result of infection, or inflammation secondary to trauma, injury or autoimmunity;

(ii) auto-immune diseases such as acute disseminated encephalitis, Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome (APS), anti-synthetase syndrome, aplastic anemia, autoimmune adrenalitis, autoimmune hepatitis, autoimmune oophoritis, autoimmune polyglandular failure, autoimmune thyroiditis, Coeliac disease, Crohn's disease, type 1 diabetes (T1D), Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, idiopathic thrombocytopenic purpura, Kawasaki's disease, lupus erythematosus including systemic lupus erythematosus (SLE), multiple sclerosis (MS) including primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS) and relapsing remitting multiple sclerosis (RRMS), myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, pemphigus, pernicious anaemia, polyarthritis, primary biliary cirrhosis, rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis or Still's disease, refractory gouty arthritis, Reiter's syndrome, Sjögren's syndrome, systemic sclerosis a systemic connective tissue disorder, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis, Behçet's disease, Chagas' disease, dysautonomia, endometriosis, hidradenitis suppurativa (HS), interstitial cystitis, neuromyotonia, psoriasis, sarcoidosis, scleroderma, ulcerative colitis, Schnitzler syndrome, macrophage activation syndrome, Blau syndrome, vitiligo or vulvodynia;

(iii) cancer including lung cancer, pancreatic cancer, gastric cancer, myelodysplastic syndrome, leukaemia including acute lymphocytic leukaemia (ALL) and acute myeloid leukaemia (AML), adrenal cancer, anal cancer, basal and squamous cell skin cancer,

bile duct cancer, bladder cancer, bone cancer, brain and spinal cord tumours, breast cancer, cervical cancer, chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), chronic myelomonocytic leukaemia (CMML), colorectal cancer, endometrial cancer, oesophagus cancer, Ewing family of tumours, eye cancer, gallbladder cancer, gastrointestinal carcinoid tumours, gastrointestinal stromal tumour (GIST), gestational trophoblastic disease, glioma, Hodgkin lymphoma, Kaposi sarcoma, kidney cancer, laryngeal and hypopharyngeal cancer, liver cancer, lung carcinoid tumour, lymphoma including cutaneous T cell lymphoma, malignant mesothelioma, melanoma skin cancer, Merkel cell skin cancer, multiple myeloma, nasal cavity and paranasal sinuses cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, penile cancer, pituitary tumours, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, stomach cancer, testicular cancer, thymus cancer, thyroid cancer including anaplastic thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumour;

(iv) infections including viral infections (e.g. from influenza virus, human immunodeficiency virus (HIV), alphavirus (such as Chikungunya and Ross River virus), flaviviruses (such as Dengue virus and Zika virus), herpes viruses (such as Epstein Barr Virus, cytomegalovirus, Varicella-zoster virus, and KSHV), poxviruses (such as vaccinia virus (Modified vaccinia virus Ankara) and Myxoma virus), adenoviruses (such as Adenovirus 5), or papillomavirus), bacterial infections (e.g. from *Staphylococcus aureus, Helicobacter pylori, Bacillus anthracis, Bordatella pertussis, Burkholderia pseudomallei, Corynebacterium diptheriae, Clostridium tetani, Clostridium botulinum, Streptococcus pneumoniae, Streptococcus pyogenes*, *Listeria monocytogenes*, *Hemophilus influenzae, Pasteurella multicida, Shigella dysenteriae, Mycobacterium tuberculosis, Mycobacterium leprae, Mycoplasma pneumoniae, Mycoplasma hominis, Neisseria meningitidis, Neisseria gonorrhoeae, Rickettsia rickettsii, Legionella pneumophila, Klebsiella pneumoniae, Pseudomonas aeruginosa, Propionibacterium acnes, Treponema pallidum, Chlamydia trachomatis, Vibrio cholerae, Salmonella typhimurium, Salmonella typhi, Borrelia burgdorferi* or *Yersinia pestis*), fungal infections (e.g. from Candida or Aspergillus species), protozoan infections (e.g. from Plasmodium, Babesia, Giardia, Entamoeba, Leishmania or Trypanosomes), helminth infections (e.g. from schistosoma, roundworms, tapeworms or flukes) and prion infections;

(v) central nervous system diseases such as Parkinson's disease, Alzheimer's

disease, dementia, motor neuron disease, Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis, intracranial aneurysms, traumatic brain injury, and amyotrophic lateral sclerosis;

(vi) metabolic diseases such as type 2 diabetes (T2D), atherosclerosis, obesity, gout, and pseudo-gout;

(vii) cardiovascular diseases such as hypertension, ischaemia, reperfusion injury including post-MI ischemic reperfusion injury, stroke including ischemic stroke, transient ischemic attack, myocardial infarction including recurrent myocardial infarction, heart failure including congestive heart failure and heart failure with preserved ejection fraction, embolism, aneurysms including abdominal aortic aneurysm, and pericarditis including Dressler's syndrome;

(viii) respiratory diseases including chronic obstructive pulmonary disorder (COPD), asthma such as allergic asthma and steroid-resistant asthma, asbestosis, silicosis, nanoparticle induced inflammation, cystic fibrosis and idiopathic pulmonary fibrosis;

(ix) liver diseases including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) including advanced fibrosis stages F3 and F4, alcoholic fatty liver disease (AFLD), and alcoholic steatohepatitis (ASH);

(x) renal diseases including chronic kidney disease, oxalate nephropathy, nephrocalcinosis, glomerulonephritis, and diabetic nephropathy;

(xi) ocular diseases including those of the ocular epithelium, age-related macular degeneration (AMD) (dry and wet), uveitis, corneal infection, diabetic retinopathy, optic nerve damage, dry eye, and glaucoma;

(xii) skin diseases including dermatitis such as contact dermatitis and atopic dermatitis, contact hypersensitivity, sunburn, skin lesions, hidradenitis suppurativa (HS), other cyst-causing skin diseases, and acne conglobata;

(xiii) lymphatic conditions such as lymphangitis and Castleman's disease;

(xiv) psychological disorders such as depression and psychological stress;

(xv) graft versus host disease;

(xvi) allodynia including mechanical allodynia; and

(xvii) any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

In one example, the disease, disorder or condition is selected from:

(i) cancer;

(ii) an infection;

(iii) a central nervous system disease;

(iv) a cardiovascular disease;

(v) a liver disease;

(vi) an ocular diseases; or

(vii) a skin disease.

More typically, the disease, disorder or condition is selected from:

(i) cancer;

(ii) an infection;

(iii) a central nervous system disease; or

(iv) a cardiovascular disease.

In one example, the disease, disorder or condition is selected from:

(i) acne conglobata;

(ii) atopic dermatitis;

(iii) Alzheimer's disease;

(iv) amyotrophic lateral sclerosis;

(v) age-related macular degeneration (AMD);

(vi) anaplastic thyroid cancer;

(vii) cryopyrin-associated periodic syndromes (CAPS);

(viii) contact dermatitis;

(ix) cystic fibrosis;

(x) congestive heart failure;

(xi) chronic kidney disease;

(xii) Crohn's disease;

(xiii) familial cold autoinflammatory syndrome (FCAS);

(xiv) Huntington's disease;

(xv) heart failure;

(xvi) heart failure with preserved ejection fraction;

(xvii) ischemic reperfusion injury;

(xviii) juvenile idiopathic arthritis;

(xix) myocardial infarction;

(xx) macrophage activation syndrome;

(xxi) myelodysplastic syndrome;

(xxii) multiple myeloma;

(xxiii) motor neuron disease;

(xxiv) multiple sclerosis;

(xxv) Muckle-Wells syndrome;
(xxvi) non-alcoholic steatohepatitis (NASH);
(xxvii) neonatal-onset multisystem inflammatory disease (NOMID);
(xxviii) Parkinson's disease;
(xxix) systemic juvenile idiopathic arthritis;
(xxx) systemic lupus erythematosus;
(xxxi) traumatic brain injury;
(xxxii) transient ischemic attack; and
(xxxiii) ulcerative colitis.

In a further typical example of the disclosure, the disease, disorder or condition is inflammation. Examples of inflammation that may be treated or prevented in accordance with the examples of the present disclosure include inflammatory responses occurring in connection with, or as a result of:

(i) a skin condition such as contact hypersensitivity, bullous pemphigoid, sunburn, psoriasis, atopical dermatitis, contact dermatitis, allergic contact dermatitis, seborrhoetic dermatitis, lichen planus, scleroderma, pemphigus, epidermolysis bullosa, urticaria, erythemas, or alopecia;

(ii) a joint condition such as osteoarthritis, systemic juvenile idiopathic arthritis, adult-onset Still's disease, relapsing polychondritis, rheumatoid arthritis, juvenile chronic arthritis, gout, or a seronegative spondyloarthropathy (e.g. ankylosing spondylitis, psoriatic arthritis or Reiter's disease);

(iii) a muscular condition such as polymyositis or myasthenia gravis;

(iv) a gastrointestinal tract condition such as inflammatory bowel disease (including Crohn's disease and ulcerative colitis), gastric ulcer, coeliac disease, proctitis, pancreatitis, eosinopilic gastro-enteritis, mastocytosis, antiphospholipid syndrome, or a food-related allergy which may have effects remote from the gut (e.g., migraine, rhinitis or eczema);

(v) a respiratory system condition such as chronic obstructive pulmonary disease (COPD), asthma (including bronchial, allergic, intrinsic, extrinsic or dust asthma, and particularly chronic or inveterate asthma, such as late asthma and airways hyper-responsiveness), bronchitis, rhinitis (including acute rhinitis, allergic rhinitis, atrophic rhinitis, chronic rhinitis, rhinitis caseosa, hypertrophic rhinitis, rhinitis pumlenta, rhinitis sicca, rhinitis medicamentosa, membranous rhinitis, seasonal rhinitis e.g. hay fever, and vasomotor rhinitis), sinusitis, idiopathic pulmonary fibrosis (IPF), sarcoidosis, farmer's lung, silicosis, asbestosis, adult respiratory distress syndrome,

hypersensitivity pneumonitis, or idiopathic interstitial pneumonia;

(vi) a vascular condition such as atherosclerosis, Behcet's disease, vasculitides, or wegener's granulomatosis;

(vii) an autoimmune condition such as systemic lupus erythematosus, Sjogren's syndrome, systemic sclerosis, Hashimoto's thyroiditis, type I diabetes, idiopathic thrombocytopenia purpura, or Graves disease;

(viii) an ocular condition such as uveitis, allergic conjunctivitis, or vernal conjunctivitis;

(ix) a nervous condition such as multiple sclerosis or encephalomyelitis;

(x) an infection or infection-related condition, such as Acquired Immunodeficiency Syndrome (AIDS), acute or chronic bacterial infection, acute or chronic parasitic infection, acute or chronic viral infection, acute or chronic fungal infection, meningitis, hepatitis (A, B or C, or other viral hepatitis), peritonitis, pneumonia, epiglottitis, malaria, dengue hemorrhagic fever, leishmaniasis, streptococcal myositis, mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii pneumonia, orchitis/epidydimitis, legionella, Lyme disease, influenza A, epstein-barr virus, viral encephalitis/aseptic meningitis, or pelvic inflammatory disease;

(xi) a renal condition such as mesangial proliferative glomerulonephritis, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, uremia, or nephritic syndrome;

(xii) a lymphatic condition such as Castleman's disease;

(xiii) a condition of, or involving, the immune system, such as hyper IgE syndrome, lepromatous leprosy, familial hemophagocytic lymphohistiocytosis, or graft versus host disease;

(xiv) a hepatic condition such as chronic active hepatitis, non-alcoholic steatohepatitis (NASH), alcohol-induced hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease (AFLD), alcoholic steatohepatitis (ASH) or primary biliary cirrhosis;

(xv) a cancer, including those cancers listed above;

(xvi) a burn, wound, trauma, haemorrhage or stroke;

(xvii) radiation exposure; and/or

(xviii) obesity; and/or

(xix) pain such as inflammatory hyperalgesia.

In one example. of the present disclosure, the disease, disorder or condition is an

autoinflammatory disease such as cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), familial Mediterranean fever (FMF), neonatal onset multisystem inflammatory disease (NOMID), Tumour Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), deficiency of interleukin 1 receptor antagonist (DIRA), Majeed syndrome, pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), adult-onset Still's disease (AOSD), haploinsufficiency of A20 (HA20), pediatric granulomatous arthritis (PGA), PLCG2-associated antibody deficiency and immune dysregulation (PLAID), PLCG2-associated autoinflammatory, antibody deficiency and immune dysregulation (APLAID), or sideroblastic anaemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD).

Examples of diseases, disorders or conditions which may be responsive to NLRP3 inhibition and which may be treated or prevented in accordance with the examples of the present disclosure are listed above. Some of these diseases, disorders or conditions are substantially or entirely mediated by NLRP3 inflammasome activity, and NLRP3-induced IL-1β and/or IL-18. As a result, such diseases, disorders or conditions may be particularly responsive to NLRP3 inhibition and may be particularly suitable for treatment or prevention in accordance with the examples of the present disclosure. Examples of such diseases, disorders or conditions include cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), neonatal onset multisystem inflammatory disease (NOMID), familial Mediterranean fever (FMF), pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), Tumour Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS), systemic juvenile idiopathic arthritis, adult-onset Still’s disease (AOSD), relapsing polychondritis, Schnitzler’s syndrome, Sweet’s syndrome, Behcet’s disease, anti-synthetase syndrome, deficiency of interleukin 1 receptor antagonist (DIRA), and haploinsufficiency of A20 (HA20).

Moreover, some of the diseases, disorders or conditions mentioned above arise due to mutations in NLRP3, in particular, resulting in increased NLRP3 activity. As a result, such diseases, disorders or conditions may be particularly responsive to NLRP3 inhibition and may be particularly suitable for treatment or prevention in accordance with the examples of the present disclosure. Examples of such diseases, disorders or

conditions include cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), and neonatal onset multisystem inflammatory disease (NOMID).

In one example of the present disclosure, the disease, disorder or condition is not an ocular inflammatory disease or a symptom of an ocular inflammatory disease. In one example of the present disclosure, the disease, disorder or condition is not a skin disease. In one example of the present disclosure, the disease, disorder or condition is not a disease involving a chemokine receptor. In one example of the present disclosure, the disease, disorder or condition is not a dermatic disease. In one example of the present disclosure, the disease, disorder or condition is not dermatitis. In one example of the present disclosure, the disease, disorder or condition is not a disease involving an increase in eosinophils. In one example of the present disclosure, the disease, disorder or condition is not an allergic disease. In one example of the present disclosure, the disease, disorder or condition is not a disease susceptible to treatment with a chymase inhibitor. In one example of the present disclosure, the disease, disorder or condition is not fibrosis or extracellular matrix dysbolism. In one example of the present disclosure, the disease, disorder or condition is not a disease accompanied by abnormal vascular function. In one example of the present disclosure, the disease, disorder or condition is not a rheumatic disease. In one example of the present disclosure, the disease, disorder or condition is not a cardiac or circulatory system disease. In one example of the present disclosure, the disease, disorder or condition is not inflammatory bowel disease. In one example of the present disclosure, the disease, disorder or condition is not HCV infection. In one example of the present disclosure, the disease, disorder or condition is not cancer. In one example of the present disclosure, the disease, disorder or condition is not a disease susceptible to treatment with a hypoglycaemic agent.

An example of the disclosure provides a method of inhibiting NLRP3, the method comprising the use of 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, to inhibit NLRP3.

In an example of the present disclosure, the method comprises the use of 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, in combination with one or more further active agents.

In one example of the present disclosure, the method is performed *ex vivo* or *in vitro*, for example in order to analyse the effect on cells of NLRP3 inhibition.

In another example of the present disclosure, the method is performed *in vivo*. For example, the method may comprise 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 inhibit NLRP3. 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.

Alternately, the method as described in the disclosure may be a method of inhibiting NLRP3 in a non-human animal subject, the method comprising the steps of administering the compound, salt, solvate, prodrug or pharmaceutical composition to the non-human animal subject and optionally subsequently mutilating or sacrificing the non-human animal subject. Typically such a method further comprises the step of analysing one or more tissue or fluid samples from the optionally mutilated or sacrificed non-human animal subject. In one example, the method further comprises the step of co-administering an effective amount of one or more further active agents.

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 inhibition of NLRP3. Typically the use comprises the administration of the compound, salt, solvate, prodrug or pharmaceutical composition to a subject. In one example, the compound, salt, solvate, prodrug or pharmaceutical composition is co-administered with one or more further active agents.

A further example of the disclosure provides the use of a compound of the first or second aspect of the disclosure, or a pharmaceutically effective salt, solvate or prodrug of the third aspect of the disclosure, in the manufacture of a medicament for the inhibition of NLRP3. Typically, the inhibition comprises the administration of the compound, salt, solvate, prodrug or medicament to a subject. In one example, the

compound, salt, solvate, prodrug or medicament is co-administered with one or more further active agents.

In any examples of the present disclosure that comprises the use or co-administration of one or more further active agents, the one or more further active agents may comprise for example one, two or three different further active agents.

The one or more further active agents may be used or administered prior to, simultaneously with, sequentially with or subsequent to each other and/or to the compound of the first or second aspect of the disclosure, the pharmaceutically acceptable salt, solvate or prodrug of the third aspect of the disclosure, or the pharmaceutical composition of the fourth aspect of the disclosure. Where the one or more further active agents are administered simultaneously with the compound of the first or second aspect of the disclosure, or the pharmaceutically acceptable salt, solvate or prodrug of the third aspect of the disclosure, a pharmaceutical composition of the fourth aspect of the disclosure may be administered wherein the pharmaceutical composition additionally comprises the one or more further active agents.

In one example of the present disclosure that comprises the use or co-administration of one or more further active agents, the one or more further active agents are selected from:

(i) chemotherapeutic agents;
(ii) antibodies;
(iii) alkylating agents;
(iv) anti-metabolites;
(v) anti-angiogenic agents;
(vi) plant alkaloids and/or terpenoids;
(vii) topoisomerase inhibitors;
(viii) mTOR inhibitors;
(ix) stilbenoids;
(x) STING agonists;
(xi) cancer vaccines;
(xii) immunomodulatory agents;
(xiii) antibiotics;
(xiv) anti-fungal agents;
(xv) anti-helminthic agents; and/or

(xvi) other active agents.

It will be appreciated that these general examples defined according to broad categories of active agents are not mutually exclusive. In this regard any particular active agent may be categorized according to more than one of the above general examples. A non-limiting example is urelumab which is an antibody that is an immunomodulatory agent for the treatment of cancer.

In some examples, the one or more chemotherapeutic agents are selected from abiraterone acetate, altretamine, amsacrine, anhydrovinblastine, auristatin, azathioprine, adriamycin, bexarotene, bicalutamide, BMS 184476, bleomycin, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, cisplatin, carboplatin, carboplatin cyclophosphamide, chlorambucil, cachectin, cemadotin, cyclophosphamide, carmustine, cryptophycin, cytarabine, docetaxel, doxetaxel, doxorubicin, dacarbazine (DTIC), dactinomycin, daunorubicin, decitabine, dolastatin, etoposide, etoposide phosphate, enzalutamide (MDV3100), 5-fluorouracil, fludarabine, flutamide, gemcitabine, hydroxyurea and hydroxyureataxanes, idarubicin, ifosfamide, irinotecan, leucovorin, lonidamine, lomustine (CCNU), larotaxel (RPR109881), mechlorethamine, mercaptopurine, methotrexate, mitomycin C, mitoxantrone, melphalan, mivobulin, 3',4'-didehydro-4'-deoxy-8'-norvin-caleukoblastine, nilutamide, oxaliplatin, onapristone, prednimustine, procarbazine, paclitaxel, platinum-containing anti-cancer agents, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzene sulphonamide, prednimustine, procarbazine, rhizoxin, sertenef, streptozocin, stramustine phosphate, tretinoin, tasonermin, taxol, topotecan, tamoxifen, teniposide, taxane, tegafur/uracil, vincristine, vinblastine, vinorelbine, vindesine, vindesine sulfate, and/or vinflunine.

Alternatively or in addition, the one or more chemotherapeutic agents may be selected from CD59 complement fragment, fibronectin fragment, gro-beta (CXCL2), heparinases, heparin hexasaccharide fragment, human chorionic gonadotropin (hCG), interferon alpha, interferon beta, interferon gamma, interferon inducible protein (IP-10), interleukin-12, kringle 5 (plasminogen fragment), metalloproteinase inhibitors (TIMPs), 2-methoxyestradiol, placental ribonuclease inhibitor, plasminogen activator inhibitor, platelet factor-4 (PF4), prolactin 16 kD fragment, proliferin-related protein (PRP), various retinoids, tetrahydrocortisol-S, thrombospondin-1 (TSP-1), transforming growth factor-beta (TGF-β), vasculostatin, vasostatin (calreticulin

fragment), and/or cytokines (including interleukins, such as interleukin-2 (IL-2), or IL-10).

In some examples, the one or more antibodies may comprise one or more monoclonal antibodies. In some examples, the one or more antibodies are selected from abciximab, adalimumab, alemtuzumab, atlizumab, basiliximab, belimumab, bevacizumab, bretuximab vedotin, canakinumab, cetuximab, ceertolizumab pegol, daclizumab, denosumab, eculizumab, efalizumab, gemtuzumab, golimumab, ibritumomab tiuxetan, infliximab, ipilimumab, muromonab-CD3, natalizumab, ofatumumab, omalizumab, palivizumab, panitumuab, ranibizumab, rituximab, tocilizumab, tositumomab, and/or trastuzumab.

In some examples, the one or more alkylating agents may comprise an agent capable of alkylating nucleophilic functional groups under conditions present in cells, including, for example, cancer cells. In some examples, the one or more alkylating agents are selected from cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin. In some examples, the alkylating agent may function by impairing cell function by forming covalent bonds with amino, carboxyl, sulfhydryl, and/or phosphate groups in biologically important molecules. In some examples, the alkylating agent may function by modifying a cell's DNA.

In some examples, the one or more anti-metabolites may comprise an agent capable of affecting or preventing RNA or DNA synthesis. In some examples, the one or more anti-metabolites are selected from azathioprine and/or mercaptopurine.

In some examples, the one or more anti-angiogenic agents are selected from endostatin, angiogenin inhibitors, angiostatin, angioarrestin, angiostatin (plasminogen fragment), basement-membrane collagen-derived anti-angiogenic factors (tumstatin, canstatin, or arrestin), anti-angiogenic antithrombin III, and/or cartilage-derived inhibitor (CDI).

In some examples, the one or more plant alkaloids and/or terpenoids may prevent microtubule function. In some examples, the one or more plant alkaloids and/or terpenoids are selected from a vinca alkaloid, a podophyllotoxin and/or a taxane. In some examples, the one or more vinca alkaloids may be derived from the Madagascar periwinkle, Catharanthus roseus (formerly known as Vinca rosea), and may be selected

from vincristine, vinblastine, vinorelbine and/or vindesine. In some examples, the one or more taxanes are selected from taxol, paclitaxel, docetaxel and/or ortataxel. In some examples, the one or more podophyllotoxins are selected from an etoposide and/or teniposide.

In some examples, the one or more topoisomerase inhibitors are selected from a type I topoisomerase inhibitor and/or a type II topoisomerase inhibitor, and may interfere with transcription and/or replication of DNA by interfering with DNA supercoiling. In some examples, the one or more type I topoisomerase inhibitors may comprise a camptothecin, which may be selected from exatecan, irinotecan, lurtotecan, topotecan, BNP 1350, CKD 602, DB 67 (AR67) and/or ST 1481. In some examples, the one or more type II topoisomerase inhibitors may comprise an epipodophyllotoxin, which may be selected from an amsacrine, etoposid, etoposide phosphate and/or teniposide.

In some examples, the one or more mTOR (mammalian target of rapamycin, also known as the mechanistic target of rapamycin) inhibitors are selected from rapamycin, everolimus, temsirolimus and/or deforolimus.

In some examples, the one or more stilbenoids are selected from resveratrol, piceatannol, pinosylvin, pterostilbene, alpha-viniferin, ampelopsin A, ampelopsin E, diptoindonesin C, diptoindonesin F, epsilon-vinferin, flexuosol A, gnetin H, hemsleyanol D, hopeaphenol, trans-diptoindonesin B, astringin, piceid and/or diptoindonesin A.

In some examples, the one or more STING (Stimulator of interferon genes, also known as transmembrane protein (TMEM) 173) agonists may comprise cyclic di-nucleotides, such as cAMP, cGMP, and cGAMP, and/or modified cyclic di-nucleotides that may include one or more of the following modification features: 2'-O/3'-O linkage, phosphorothioate linkage, adenine and/or guanine analogue, and/or 2'-OH modification (e.g. protection of the 2'-OH with a methyl group or replacement of the 2'-OH by -F or $-N_3$).

In some examples, the one or more cancer vaccines are selected from an HPV vaccine, a hepatitis B vaccine, Oncophage, and/or Provenge.

In some examples, the one or more immunomodulatory agents may comprise an

immune checkpoint inhibitor. The immune checkpoint inhibitor may target an immune checkpoint receptor, or combination of receptors comprising, for example, CTLA-4, PD-1, PD-L1, PD-L2, T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), galectin 9, phosphatidylserine, lymphocyte activation gene 3 protein (LAG3), MHC class I, MHC class II, 4-1BB, 4-1BBL, OX40, OX40L, GITR, GITRL, CD27, CD70, TNFRSF25, TL1A, CD40, CD40L, HVEM, LIGHT, BTLA, CD160, CD80, CD244, CD48, ICOS, ICOSL, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2, TMIGD2, a butyrophilin (including BTNL2), a Siglec family member, TIGIT, PVR, a killer-cell immunoglobulin-like receptor, an ILT, a leukocyte immunoglobulin-like receptor, NKG2D, NKG2A, MICA, MICB, CD28, CD86, SIRPA, CD47, VEGF, neuropilin, CD30, CD39, CD73, CXCR4, and/or CXCL12.

In some examples, the immune checkpoint inhibitor is selected from urelumab, PF-05082566, MEDI6469, TRX518, varlilumab, CP-870893, pembrolizumab (PD1), nivolumab (PD1), atezolizumab (formerly MPDL3280A) (PD-L1), MEDI4736 (PD-L1), avelumab (PD-L1), PDR001 (PD1), BMS-986016, MGA271, lirilumab, IPH2201, emactuzumab, INCB024360, galunisertib, ulocuplumab, BKT140, bavituximab, CC-90002, bevacizumab, and/or MNRP1685A.

In some examples, the one or more antibiotics are selected from amikacin, gentamicin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, streptomycin, spectinomycin, geldanamycin, herbimycin, rifaximin, loracarbef, ertapenem, doripenem, imipenem, cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalothin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, telavancin, dalbavancin, oritavancin, clindamycin, lincomycin, daptomycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spiramycin, aztreonam, furazolidone, nitrofurantoin, linezolid, posizolid, radezolid, torezolid, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin G, penicillin V, piperacillin, temocillin, ticarcillin, calvulanate, ampicillin, subbactam, tazobactam, ticarcillin, clavulanate, bacitracin, colistin, polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine, sulfamethoxazole, sulfanamide, sulfasalazine,

sulfisoxazole, trimethoprim-sulfamethoxazole, sulfonamideochrysoidine, demeclocycline, minocycline, oytetracycline, tetracycline, clofazimine, dapsone, dapreomycin, cycloserine, ethambutol, ethionamide, isoniazid, pyrazinamide, rifampicin, rifabutin, rifapentine, streptomycin, arsphenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin, dalopristin, thiamphenicol, tigecycyline, tinidazole, trimethoprim, and/or teixobactin.

In some examples, the one or more antibiotics may comprise one or more cytotoxic antibiotics. In some examples, the one or more cytotoxic antibiotics are selected from an actinomycin, an anthracenedione, an anthracycline, thalidomide, dichloroacetic acid, nicotinic acid, 2-deoxyglucose, and/or chlofazimine. In some examples, the one or more actinomycins are selected from actinomycin D, bacitracin, colistin (polymyxin E) and/or polymyxin B. In some examples, the one or more antracenediones are selected from mitoxantrone and/or pixantrone. In some examples, the one or more anthracyclines are selected from bleomycin, doxorubicin (Adriamycin), daunorubicin (daunomycin), epirubicin, idarubicin, mitomycin, plicamycin and/or valrubicin.

In some examples, the one or more anti-fungal agents are selected from bifonazole, butoconazole, clotrimazole, econazole, ketoconazole, luliconazole, miconazole, omoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, albaconazole, efinaconazole, epoziconazole, fluconazole, isavuconazole, itraconazole, posaconazole, propiconazole, ravusconazole, terconazole, voriconazole, abafungin, amorolfin, butenafine, naftifine, terbinafine, anidulafungin, caspofungin, micafungin, benzoic acid, ciclopirox, flucytosine, 5-fluorocytosine, griseofulvin, haloprogin, tolnaflate, undecylenic acid, and/or balsam of Peru.

In some examples, the one or more anti-helminthic agents are selected from benzimidazoles (including albendazole, mebendazole, thiabendazole, fenbendazole, triclabendazole, and flubendazole), abamectin, diethylcarbamazine, ivermectin, suramin, pyrantel pamoate, levamisole, salicylanilides (including niclosamide and oxyclozanide), and/or nitazoxanide.

In some examples, other active agents are selected from growth inhibitory agents, anti-inflammatory agents (including nonsteroidal anti-inflammatory agents), anti-psoriatic agents (including anthralin and its derivatives), vitamins and vitamin-derivatives (including retinoinds, and VDR receptor ligands), corticosteroids, ion channel blockers

(including potassium channel blockers), immune system regulators (including cyclosporin, FK 506, and glucocorticoids), lutenizing hormone releasing hormone agonists (such as leuprolidine, goserelin, triptorelin, histrelin, bicalutamide, flutamide and/or nilutamide), and/or hormones (including estrogen).

Unless stated otherwise, in any examples of the disclosure, the subject may be any human or other animal. Typically, the subject is a mammal, more typically a human or a domesticated mammal such as a cow, pig, lamb, sheep, goat, horse, cat, dog, rabbit, mouse etc. Most typically, the subject is a human.

Any of the medicaments employed in the present disclosure can be administered by oral, parenteral (including intravenous, subcutaneous, intramuscular, intradermal, intratracheal, intraperitoneal, intraarticular, intracranial and epidural), airway (aerosol), rectal, vaginal or topical (including transdermal, buccal, mucosal and sublingual) administration.

Typically, the mode of administration selected is that most appropriate to the disorder, disease or condition to be treated or prevented. Where one or more further active agents are administered, the mode of administration may be the same as or different to the mode of administration of the compound, salt, solvate, prodrug or pharmaceutical composition of the disclosure.

For oral administration, the compounds, salts, solvates or prodrugs of the present disclosure will generally be provided in the form of tablets, capsules, hard or soft gelatine capsules, caplets, troches or lozenges, as a powder or granules, or as an aqueous solution, suspension or dispersion.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose. Corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatine. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material, such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Tablets may also be effervescent and/or

dissolving tablets.

Capsules for oral use include hard gelatine capsules in which the active ingredient is mixed with a solid diluent, and soft gelatine capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Powders or granules for oral use may be provided in sachets or tubs. Aqueous solutions, suspensions or dispersions may be prepared by the addition of water to powders, granules or tablets.

Any form suitable for oral administration may optionally include sweetening agents such as sugar, flavouring agents, colouring agents and/or preservatives.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For parenteral use, the compounds, salts, solvates or prodrugs of the present disclosure will generally be provided in a sterile aqueous solution or suspension, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride or glucose. Aqueous suspensions according to the disclosure may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate. The compounds of the disclosure may also be presented as liposome formulations.

For transdermal and other topical administration, the compounds, salts, solvates or prodrugs of the disclosure will generally be provided in the form of ointments, cataplasms (poultices), pastes, powders, dressings, creams, plasters or patches.

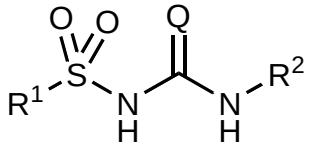
Suitable suspensions and solutions can be used in inhalers for airway (aerosol) administration.

The dose of the compounds, salts, solvates or prodrugs of the present disclosure will, of course, vary with the disorder, disease or condition to be treated or prevented. In general, a suitable dose will be in the range of 0.01 to 500 mg per kilogram body weight of the recipient per day. The desired dose may be presented at an appropriate interval such as once every other day, once a day, twice a day, three times a day or four times a day. The desired dose may be administered in unit dosage form, for example, containing 1 mg to 50 g of active ingredient per unit dosage form.

For the avoidance of doubt, insofar as is practicable any example of a given aspect of the present disclosure may occur in combination with any other example of the same aspect of the present disclosure. In addition, insofar as is practicable it is to be understood that any preferred, typical or optional example of any aspect of the present disclosure should also be considered as a preferred, typical or optional example of any other aspect of the present disclosure.

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, and wherein R^1 may optionally be substituted; and

R^2 is a cyclic group substituted at the α-position, 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.

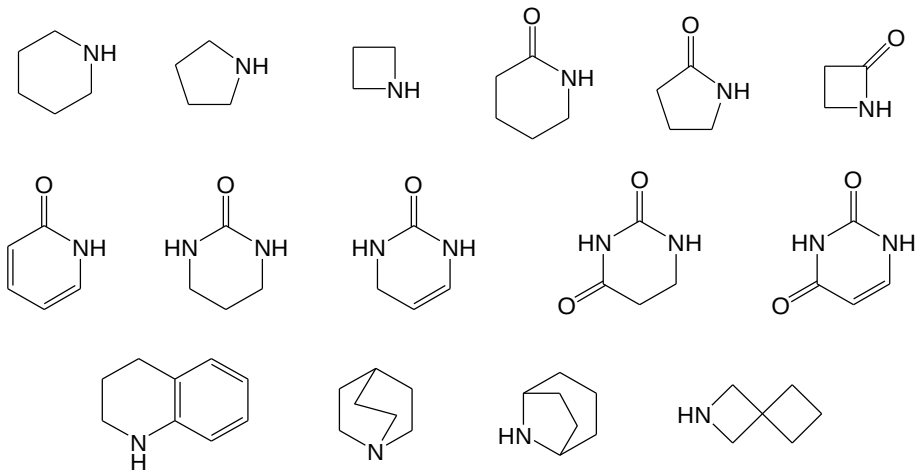
4. A compound as claimed in any one of claims 1 to 3, wherein the non-aromatic heterocyclic group of R^1 is fully saturated.

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:



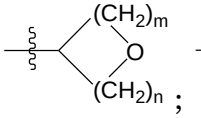
wherein R^1 is attached to the sulfur atom of the sulfonylurea group by a non-aromatic ring carbon atom, and wherein R^1 may optionally be substituted or further substituted.

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; $-R^\alpha-SR^\beta$; $-R^\alpha-SOR^\beta$; $-R^\alpha-SO_2H$; $-R^\alpha-SO_2R^\beta$; $-R^\alpha-SO_2NH_2$; $-R^\alpha-SO_2NHR^\beta$; $-R^\alpha-SO_2N(R^\beta)_2$; $-NH_2$; $-NHR^\beta$; $-N(R^\beta)_2$; $-R^\alpha-NH_2$; $-R^\alpha-NHR^\beta$; $-R^\alpha-N(R^\beta)_2$; -CHO; $-COR^\beta$; -COOH; $-COOR^\beta$; $-OCOR^\beta$; $-R^\alpha$-CHO; $-R^\alpha-COR^\beta$; $-R^\alpha$-COOH; $-R^\alpha-COOR^\beta$; $-R^\alpha-OCOR^\beta$; -NH-CHO; $-NR^\beta$-CHO; $-NH-COR^\beta$; $-NR^\beta-COR^\beta$; $-CONH_2$; $-CONHR^\beta$; $-CON(R^\beta)_2$; $-R^\alpha$-NH-CHO; $-R^\alpha-NR^\beta$-CHO; $-R^\alpha-NH-COR^\beta$; $-R^\alpha-NR^\beta-COR^\beta$; $-R^\alpha-CONH_2$; $-R^\alpha-CONHR^\beta$; $-R^\alpha-CON(R^\beta)_2$; $-O-R^\alpha$-OH; $-O-R^\alpha-OR^\beta$; $-O-R^\alpha-NH_2$; $-O-R^\alpha-NHR^\beta$; $-O-R^\alpha-N(R^\beta)_2$; $-NH-R^\alpha$-OH; $-NH-R^\alpha-OR^\beta$; $-NH-R^\alpha-NH_2$; $-NH-R^\alpha-NHR^\beta$; $-NH-R^\alpha-N(R^\beta)_2$; $-NR^\beta-R^\alpha$-OH; $-NR^\beta-R^\alpha-OR^\beta$; $-NR^\beta-R^\alpha-NH_2$; $-NR^\beta-R^\alpha-NHR^\beta$; $-NR^\beta-R^\alpha-N(R^\beta)_2$; 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 $-R^\beta$ 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;



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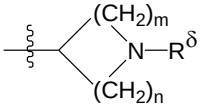


; oxo (=O); or a C_1-C_4 alkylene bridge;

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 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.

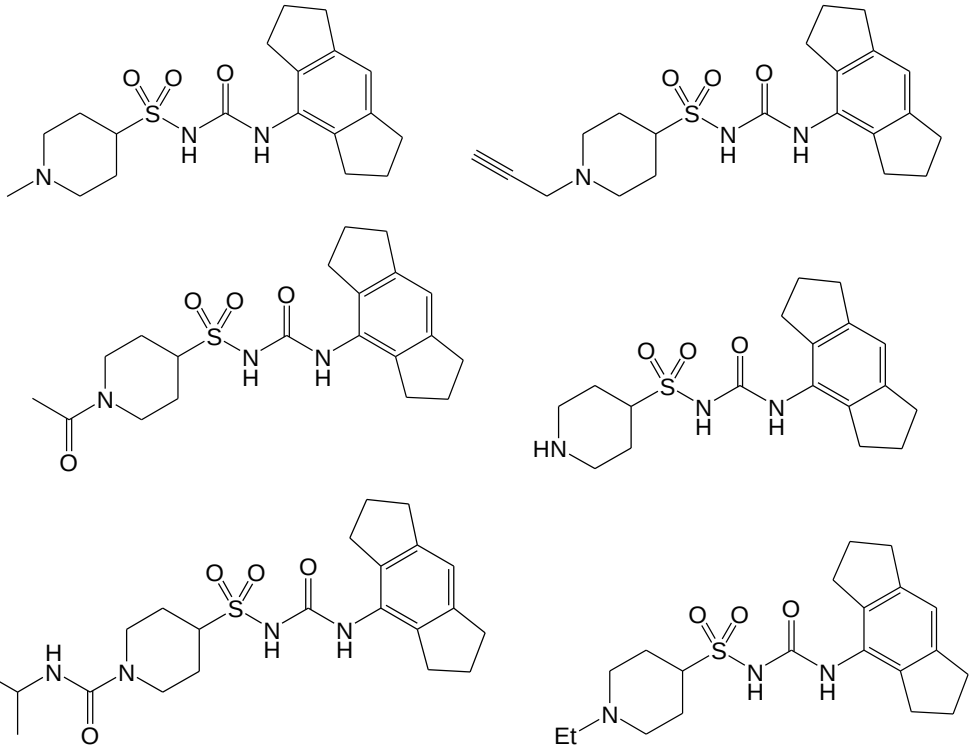
12. A compound as claimed in claim 11, wherein R^2 is an aryl or a heteroaryl group, wherein the aryl or the heteroaryl group is substituted at the α and α' positions, and wherein R^2 may optionally be further substituted.

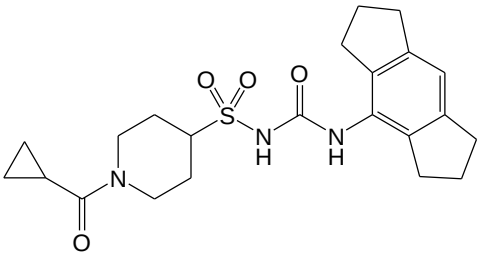
13. A compound as claimed in claim 12, wherein R^2 is a fused aryl or a fused heteroaryl group, wherein a first cycloalkyl, cycloalkenyl, non-aromatic heterocyclic, aryl or heteroaryl ring is fused to the aryl or heteroaryl group across the α,β positions and a second cycloalkyl, cycloalkenyl, non-aromatic 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.

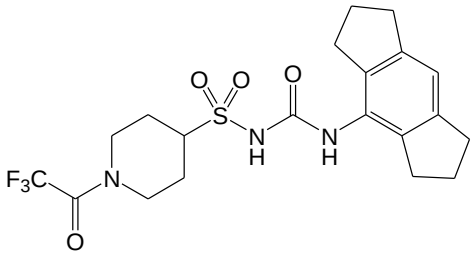
14. A compound as claimed in any one of claims 1 to 10, wherein R^2 is a cyclic group substituted at the α and α' positions, wherein R^2 may optionally be further substituted.

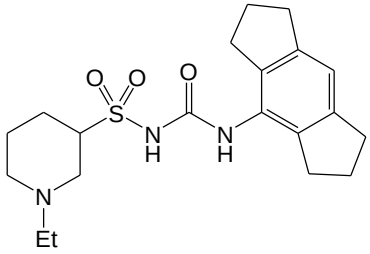
15. A compound as claimed in any one of claims 1 to 14, wherein Q is O.

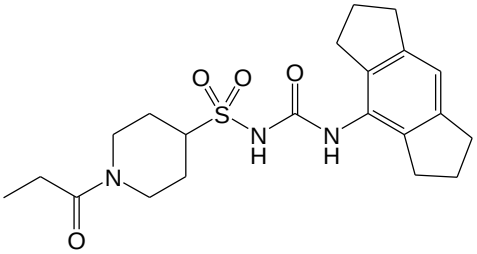
16. A compound selected from the group consisting of:

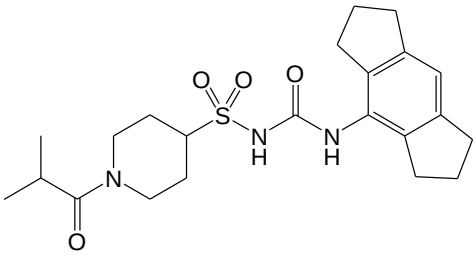


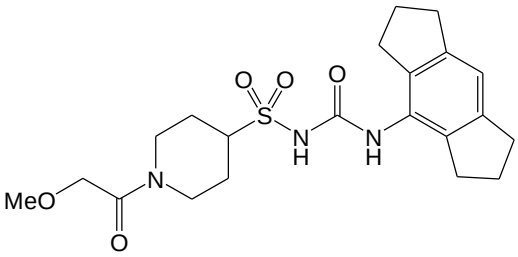


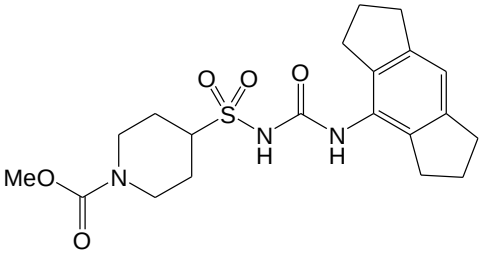


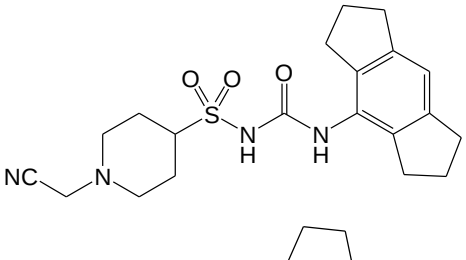


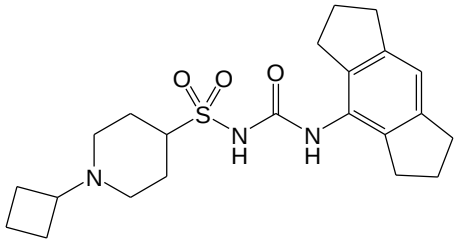


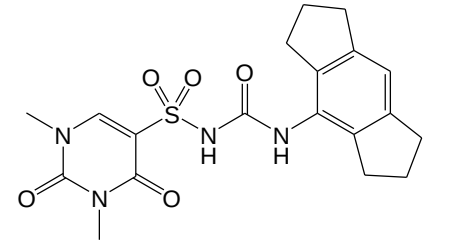


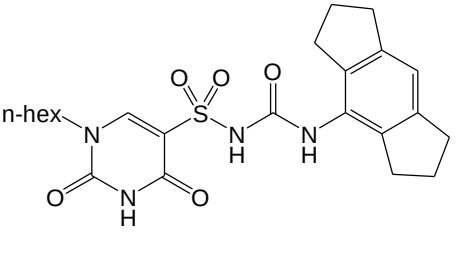


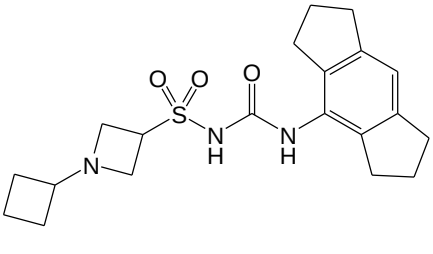


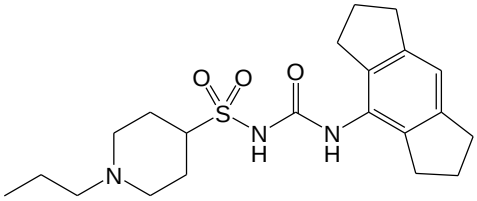


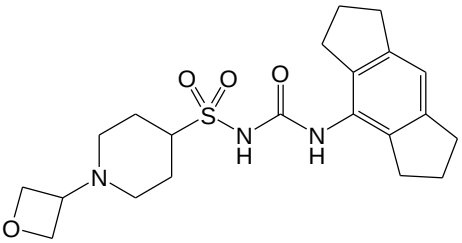


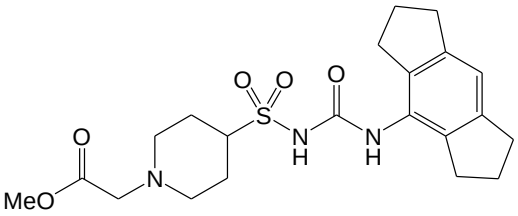


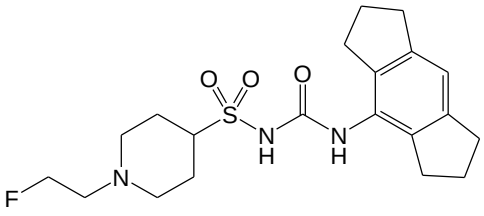


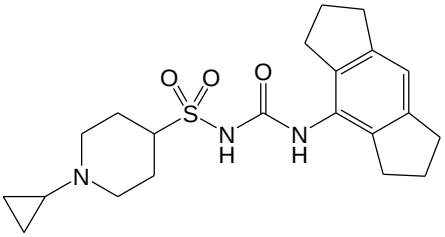


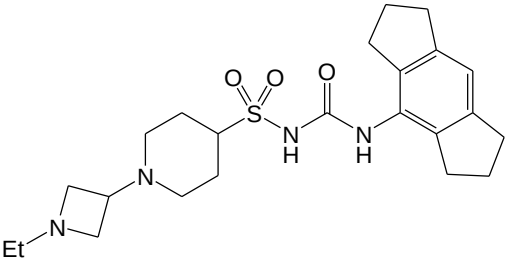


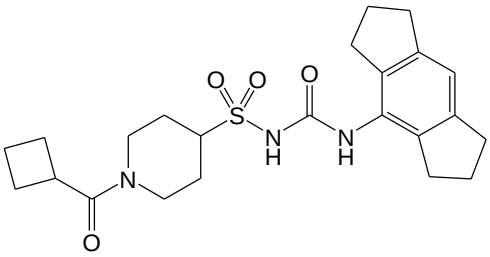


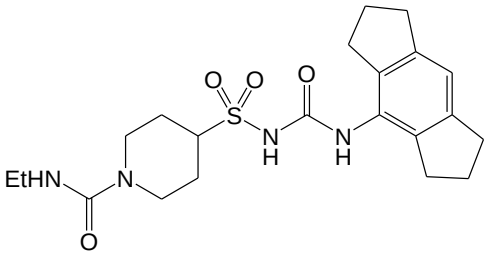


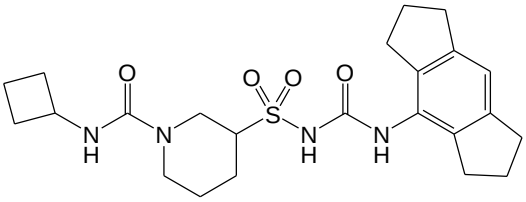


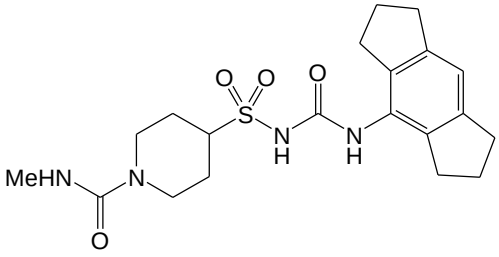












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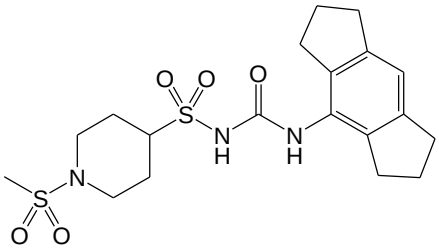

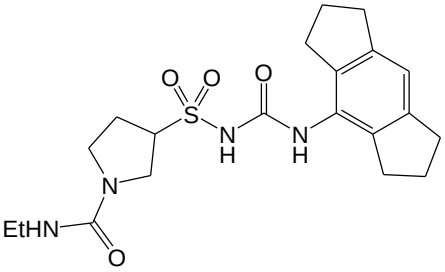

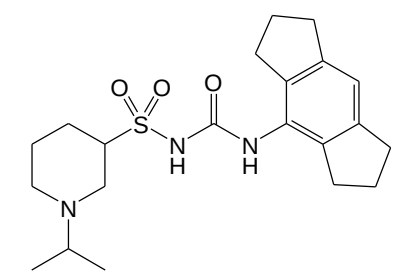

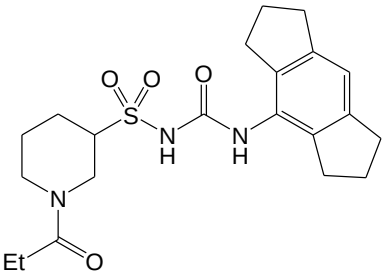

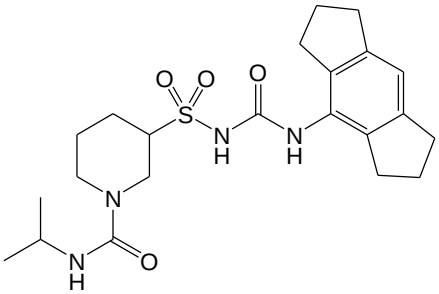

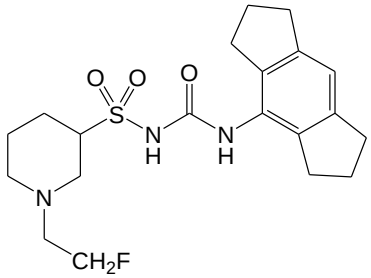

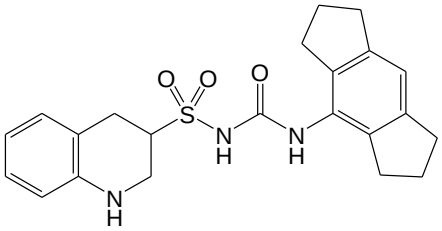

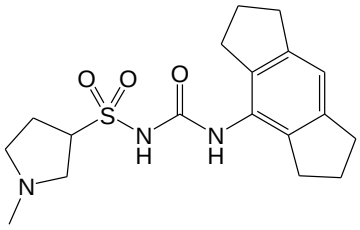

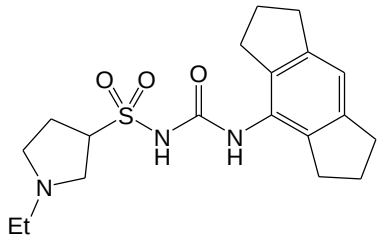

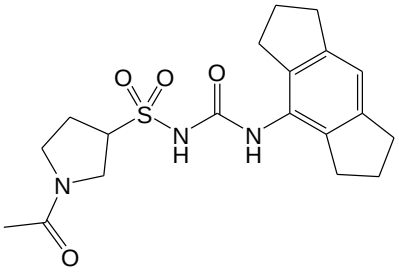

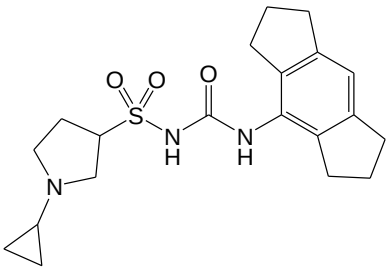

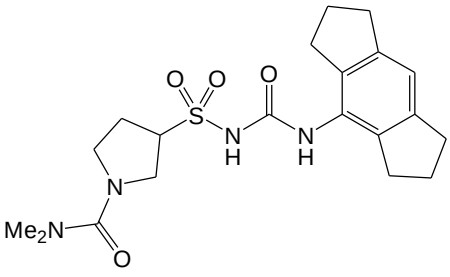

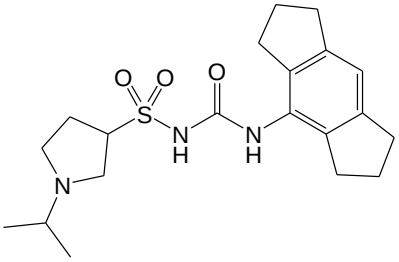

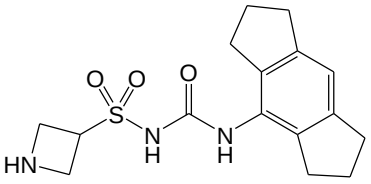

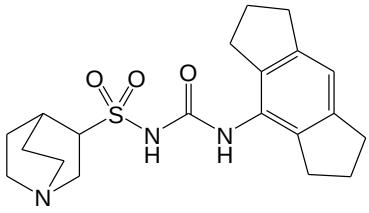

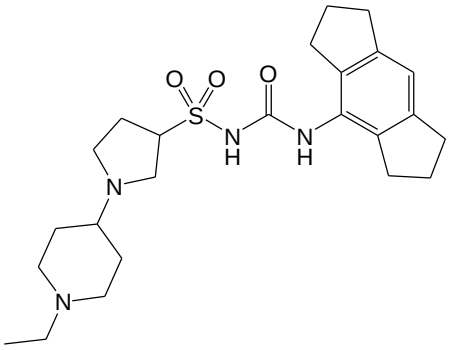

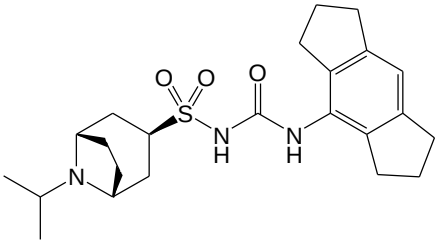

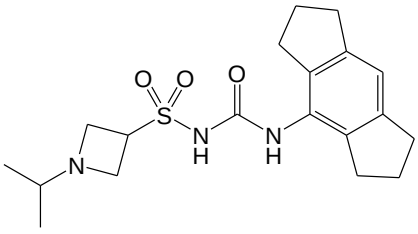

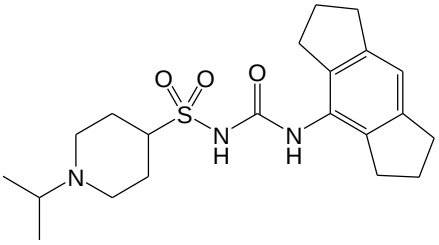

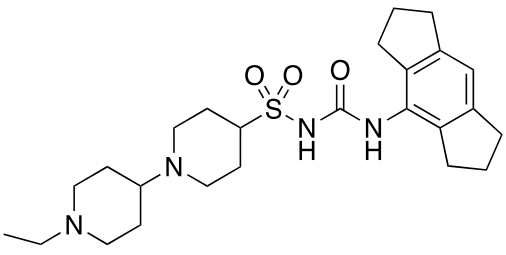

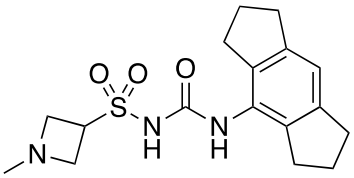

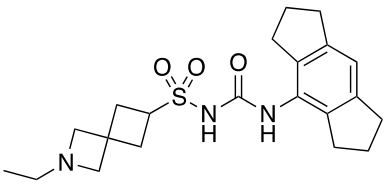

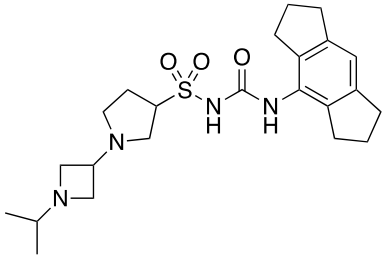

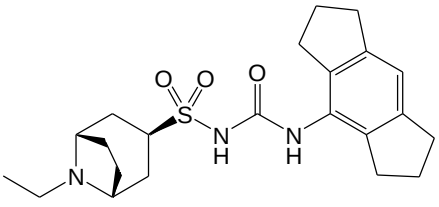

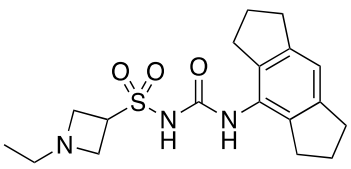

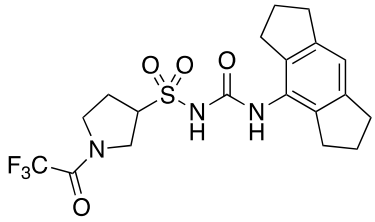

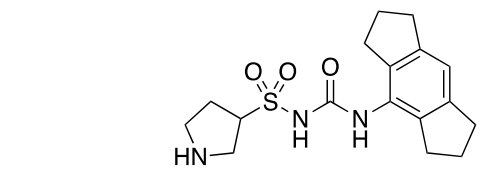
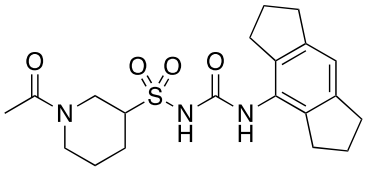
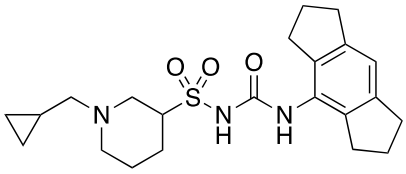
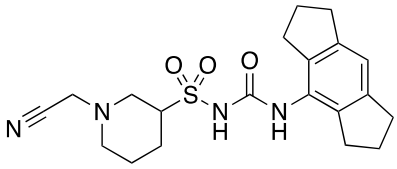
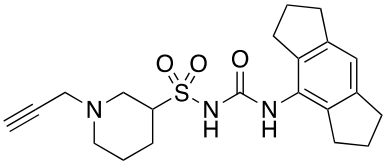
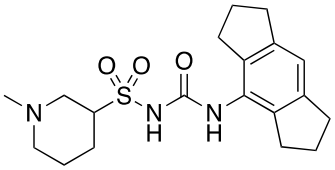
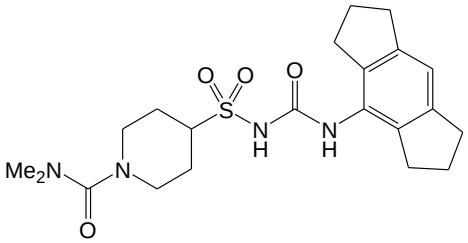
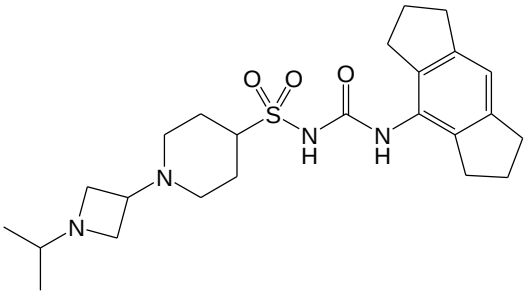
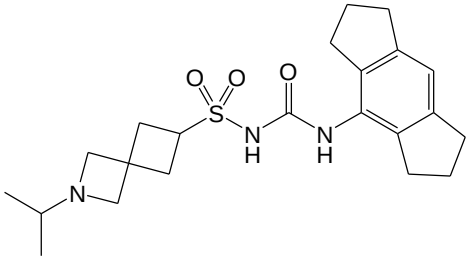
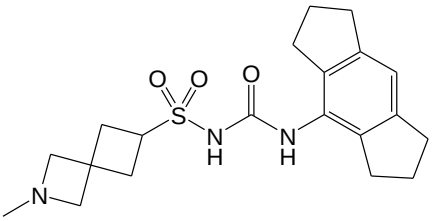
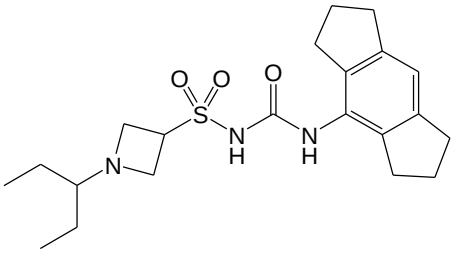
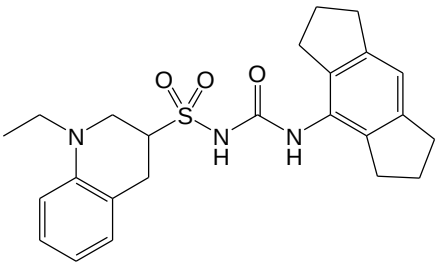
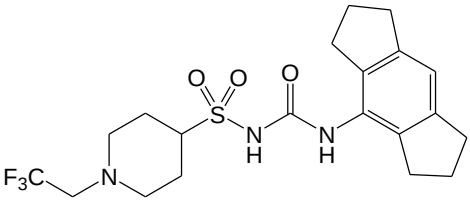
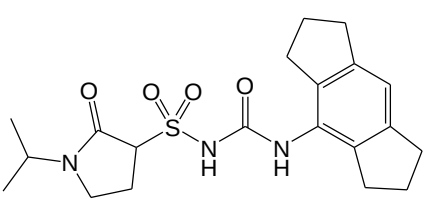

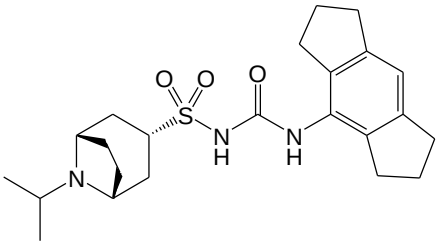

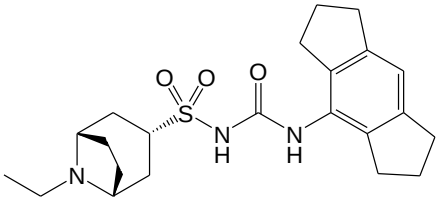

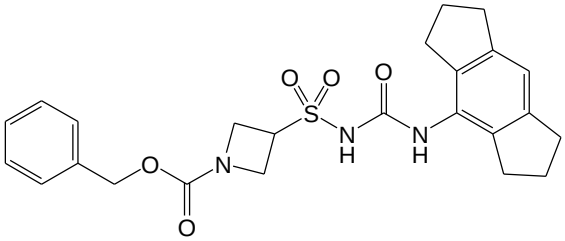

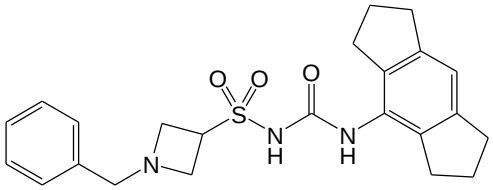

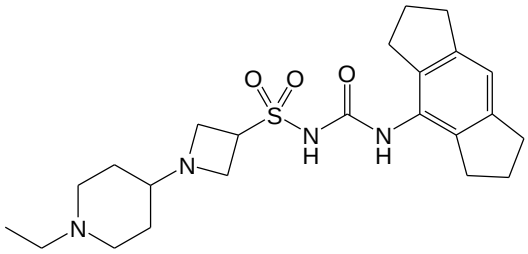

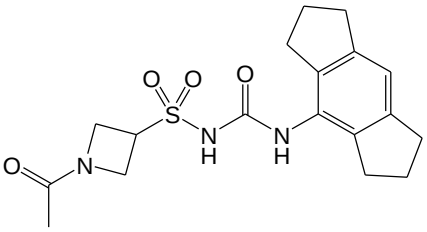

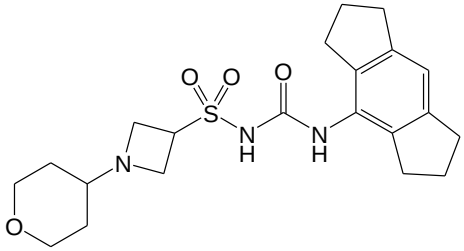

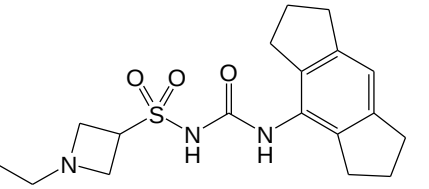

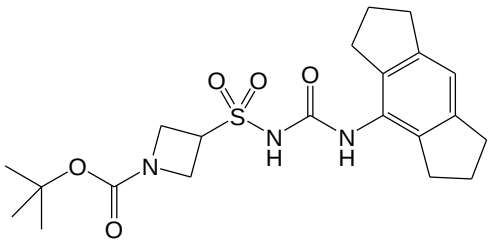

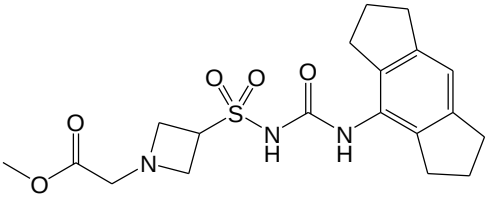

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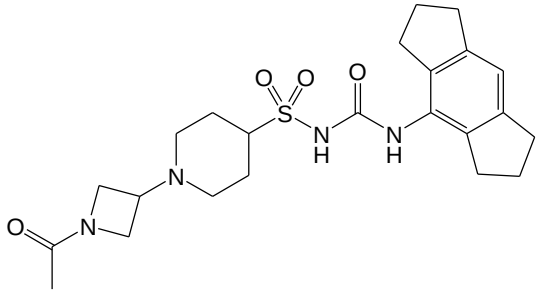

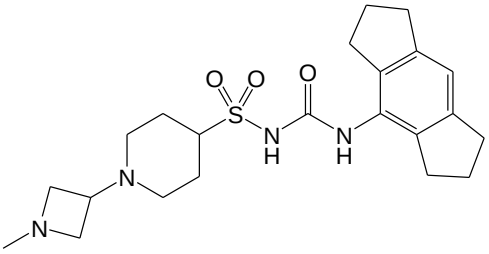

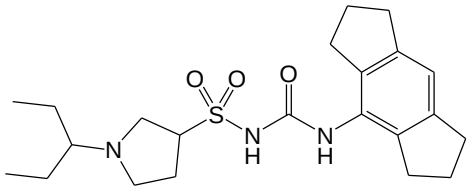

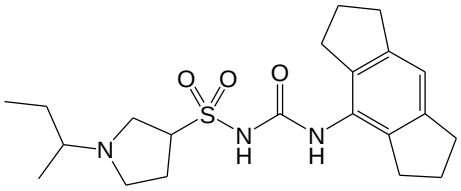

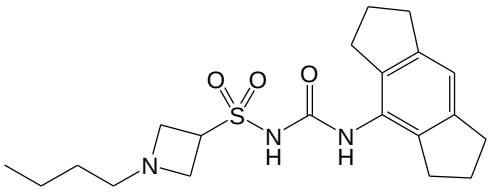

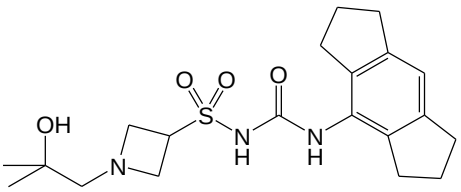

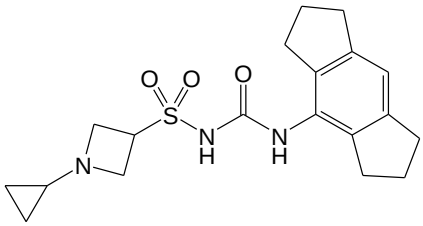

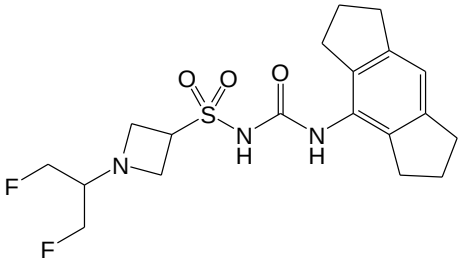

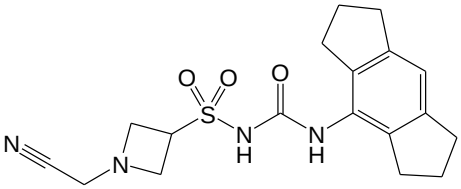

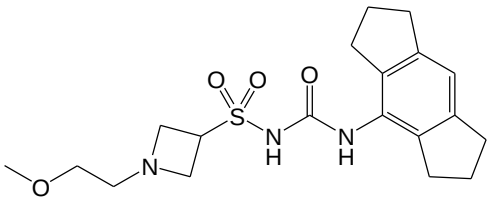

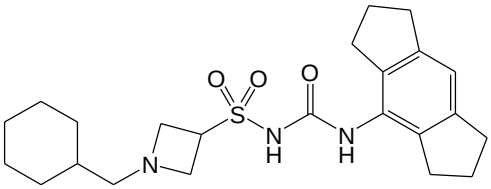

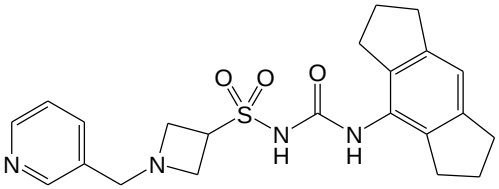

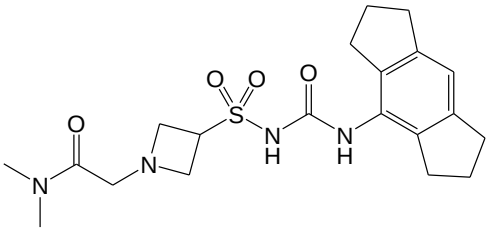

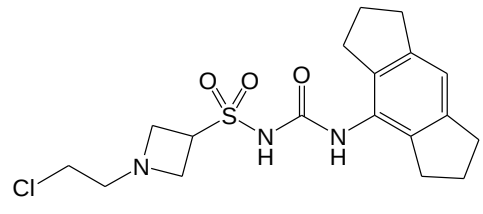

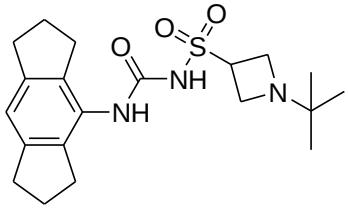

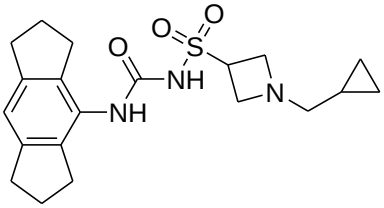

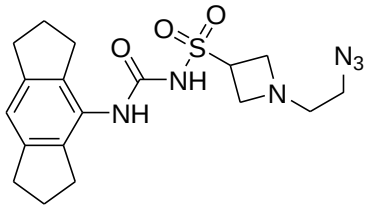

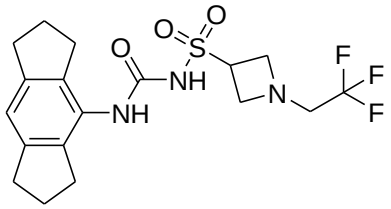

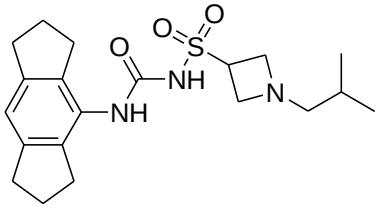

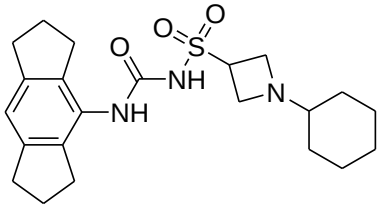

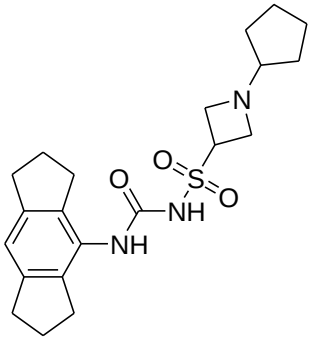

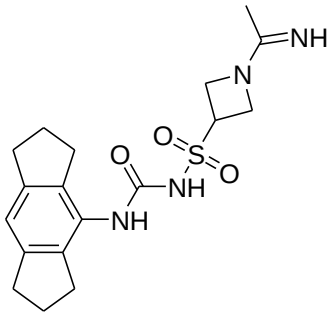

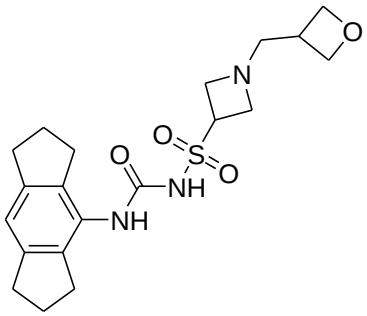

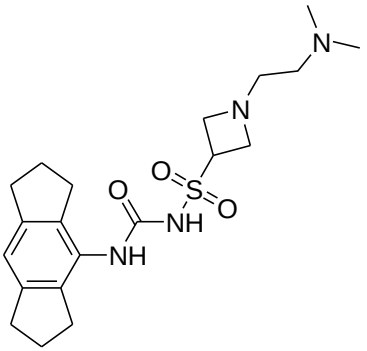

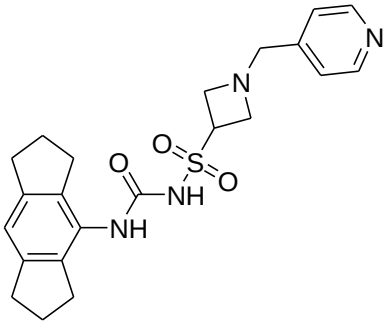

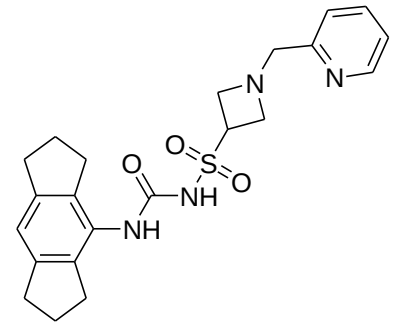

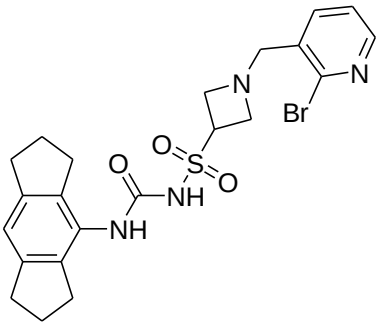

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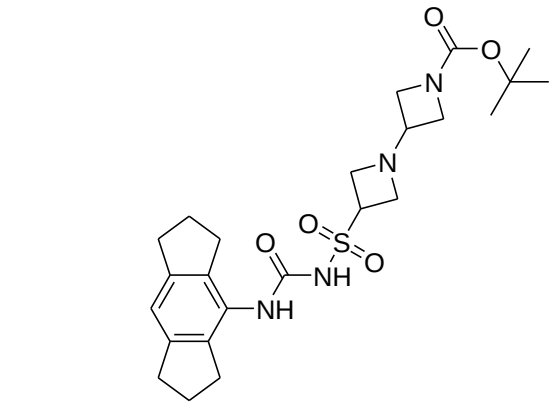

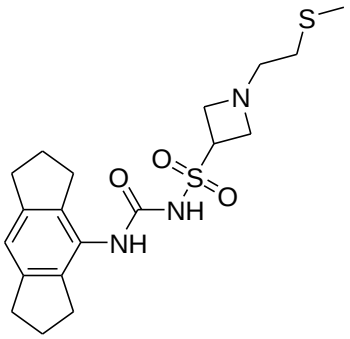

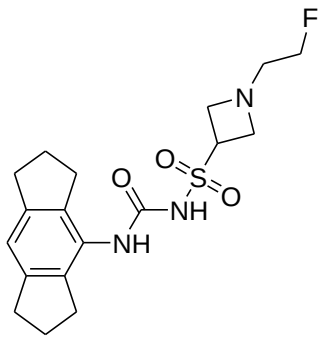

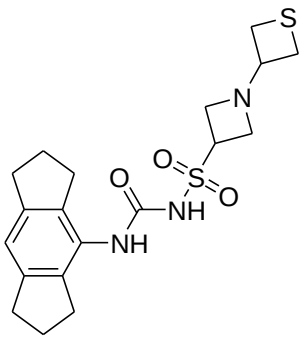

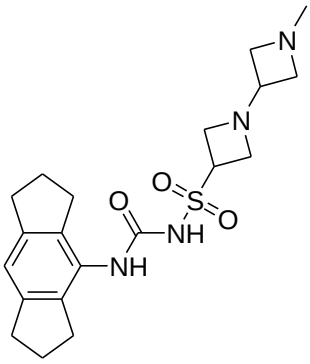

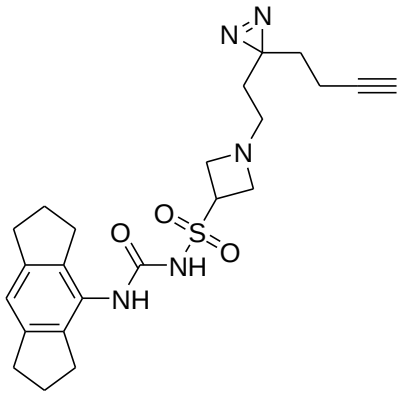

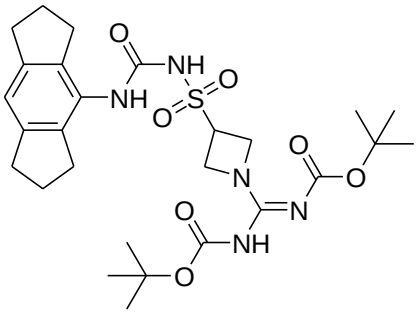

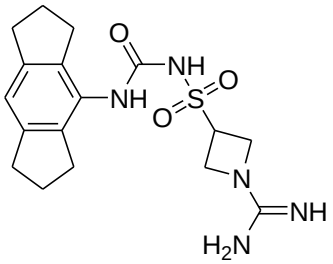

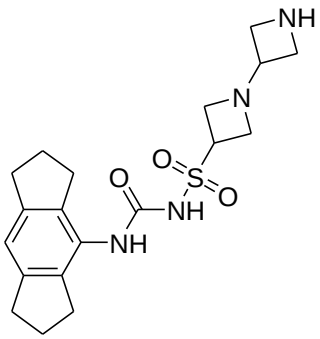

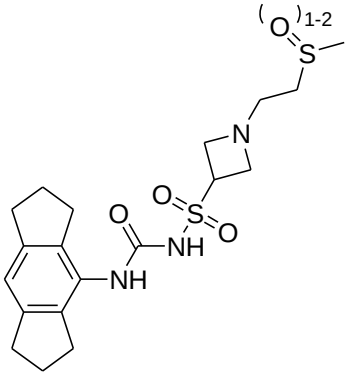

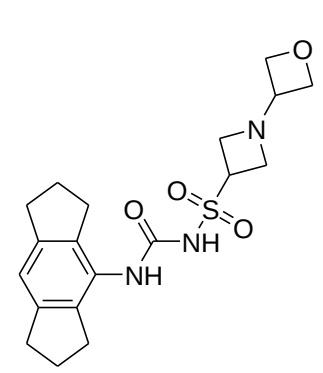
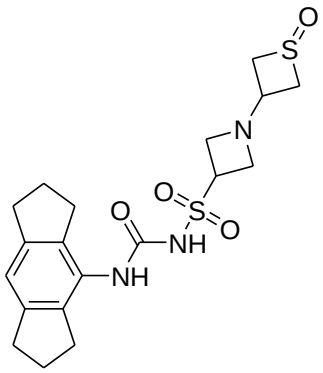
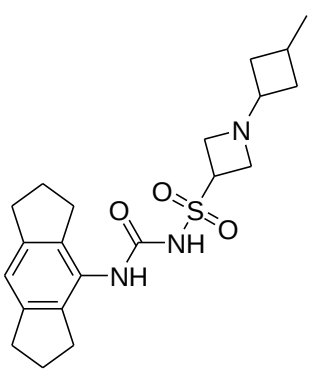
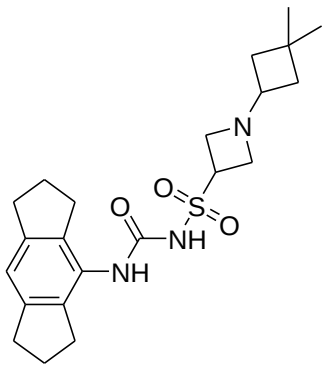
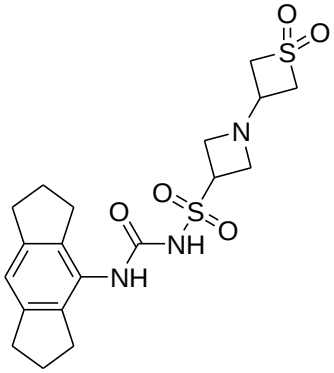
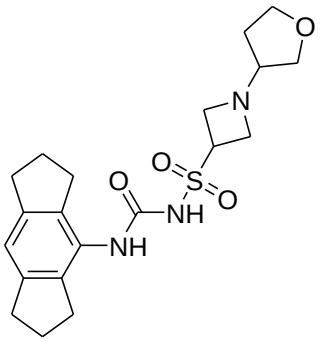
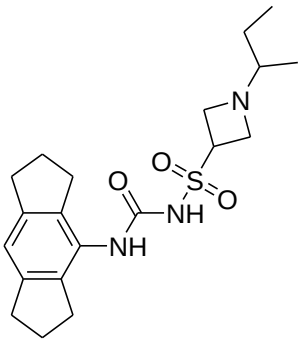
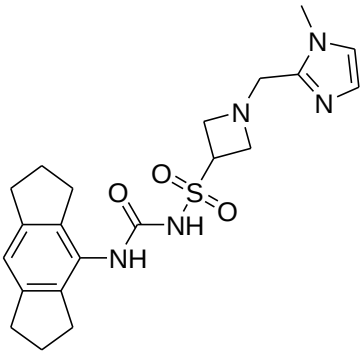
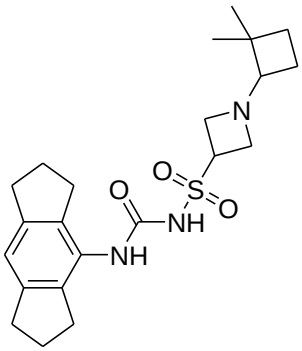
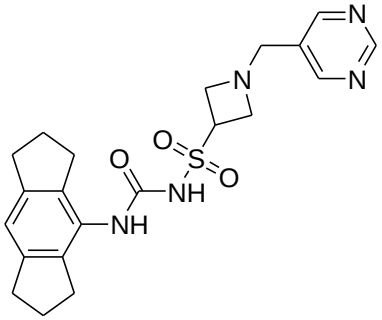
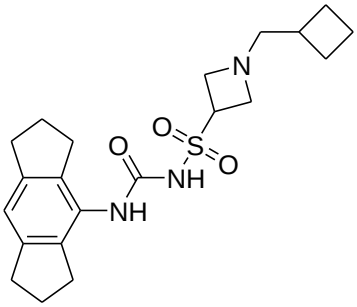

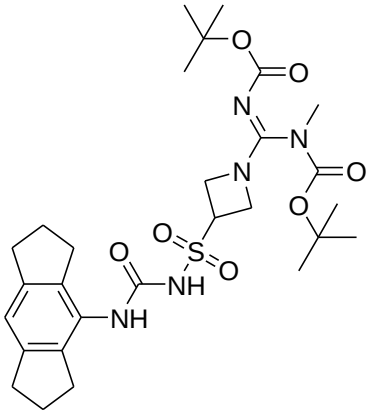

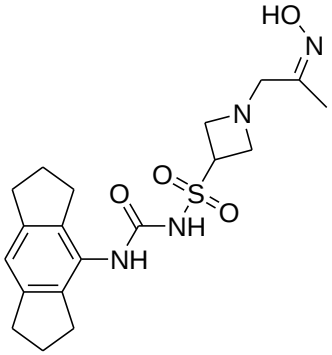

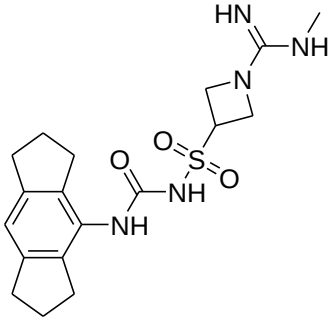

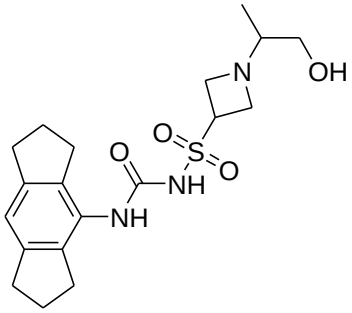

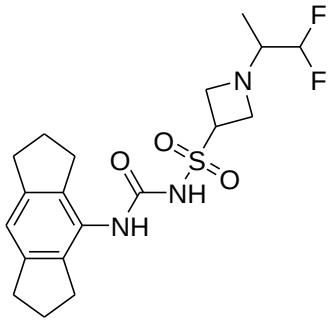

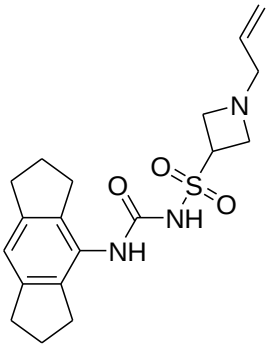

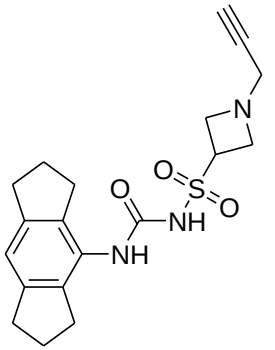

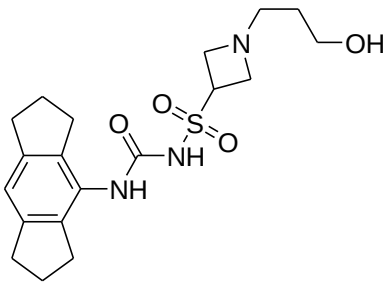

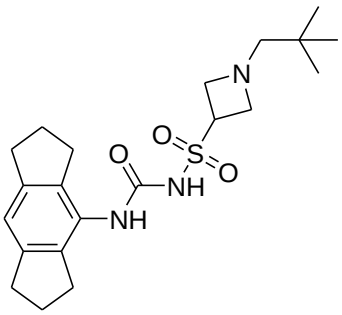

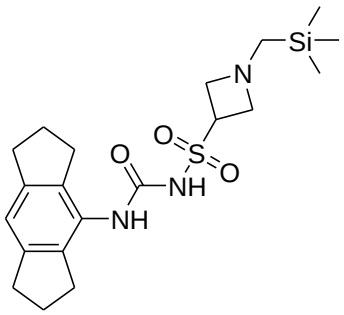

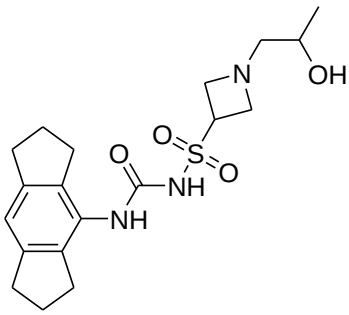

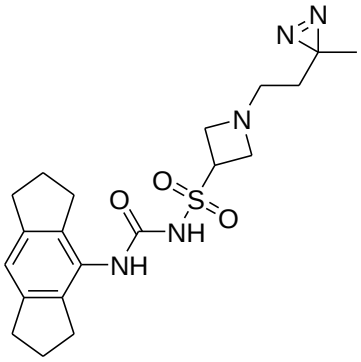

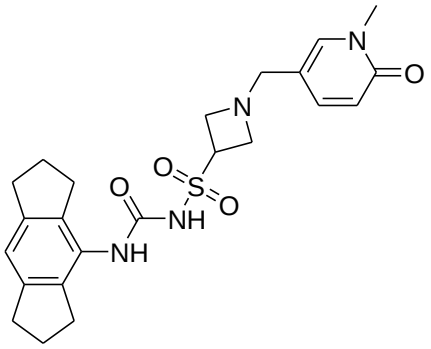

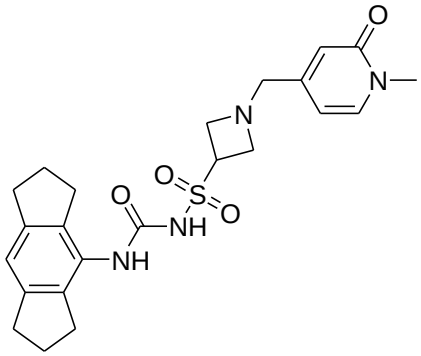

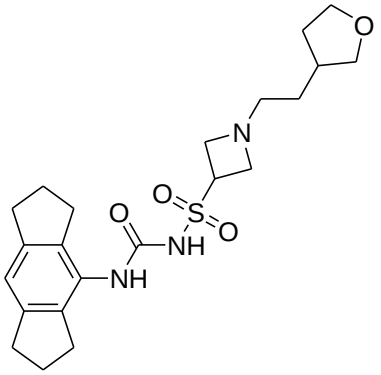

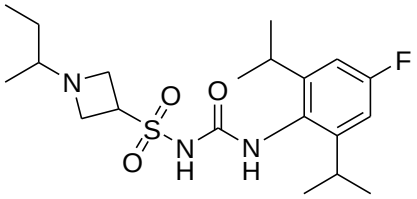

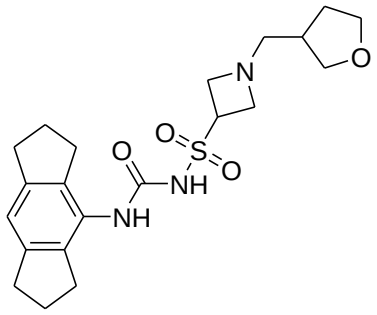

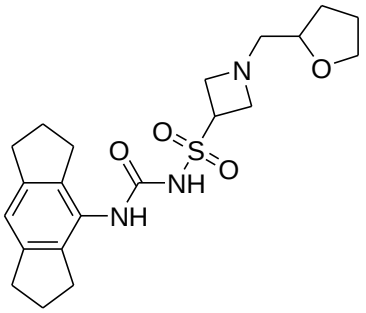

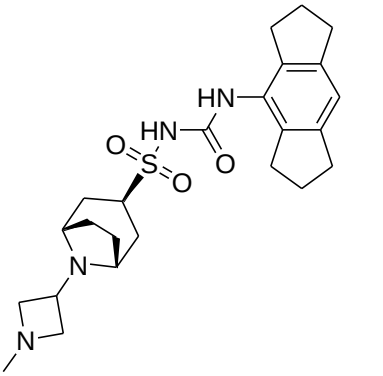

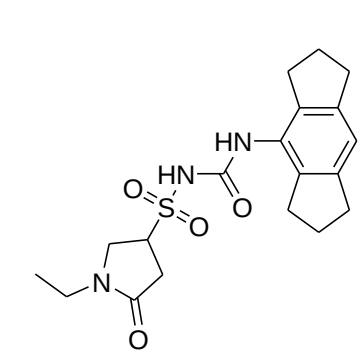

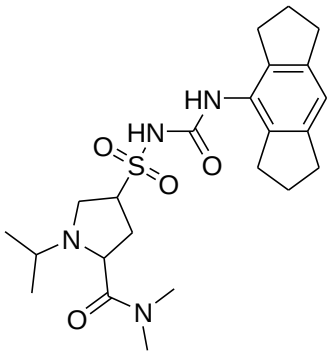

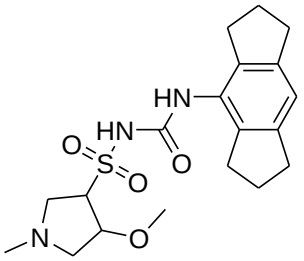

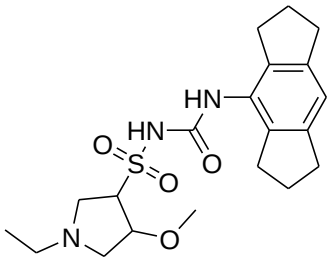

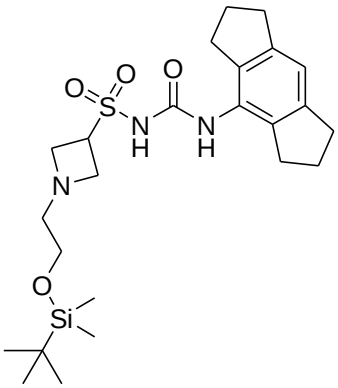

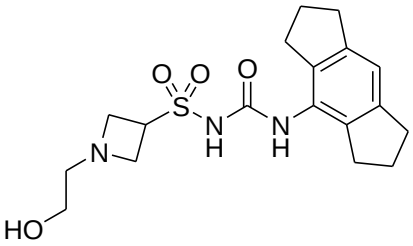

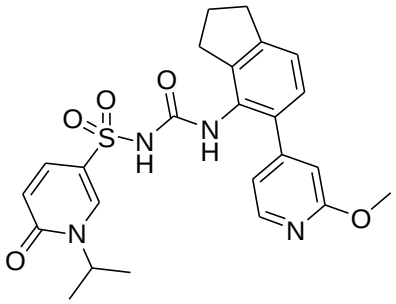

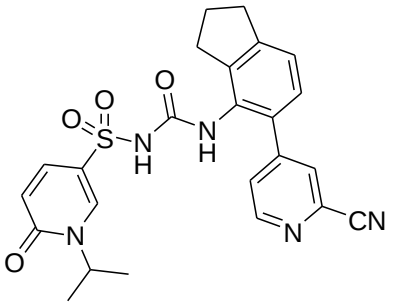

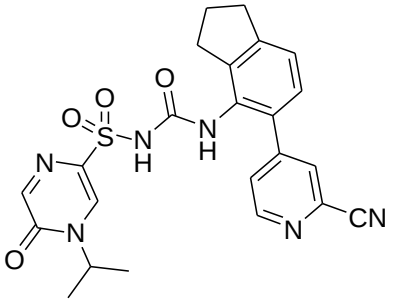

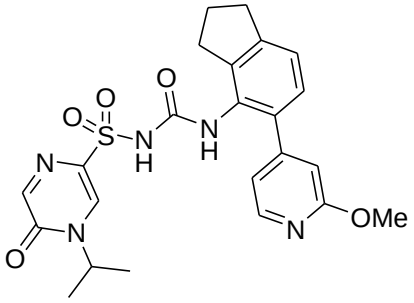

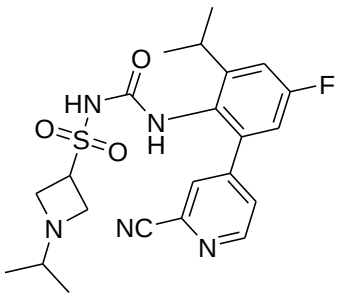

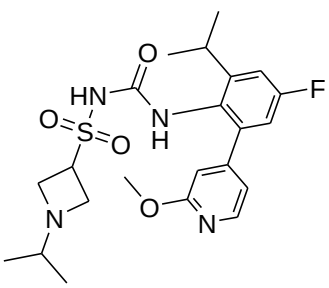

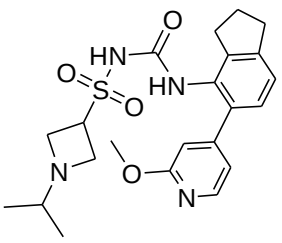

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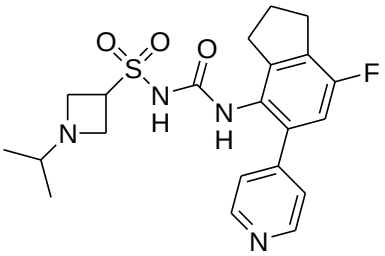

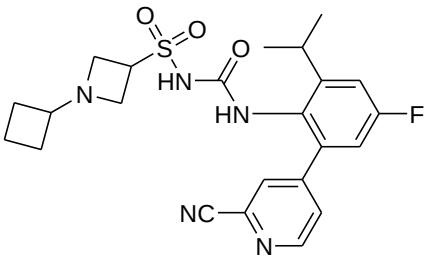

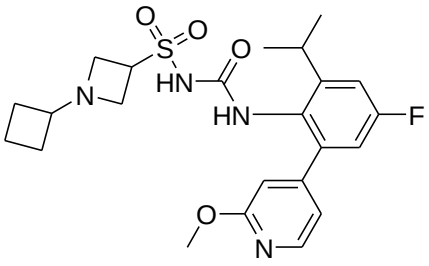

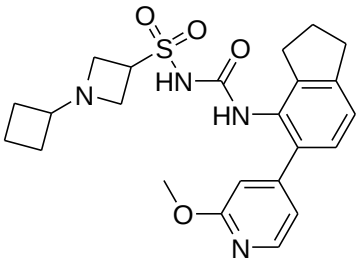

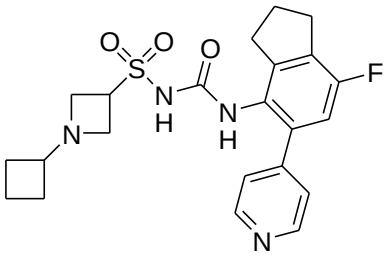

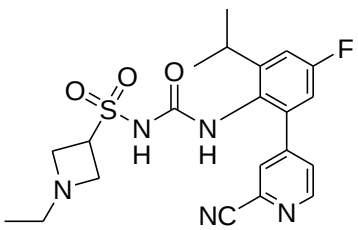

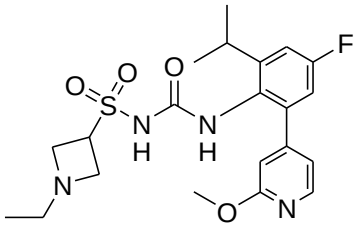

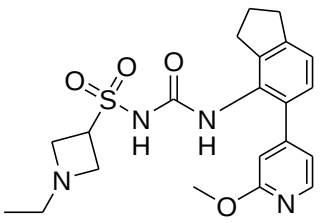

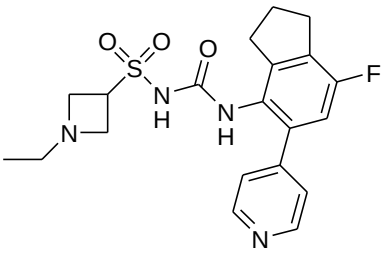

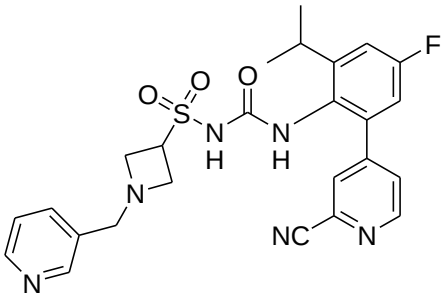

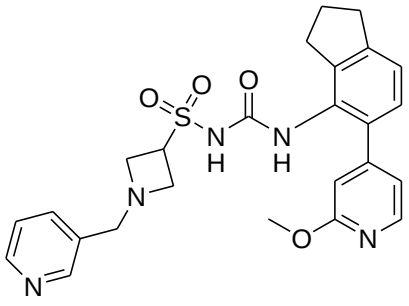

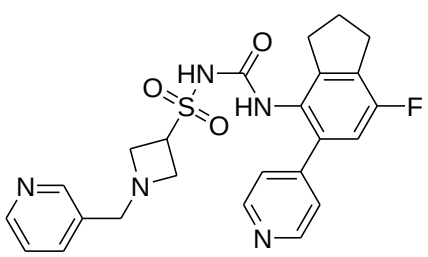

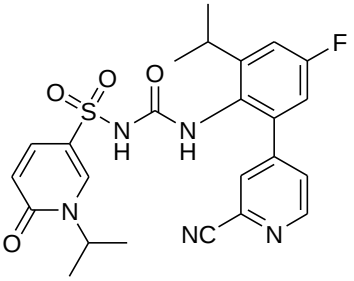

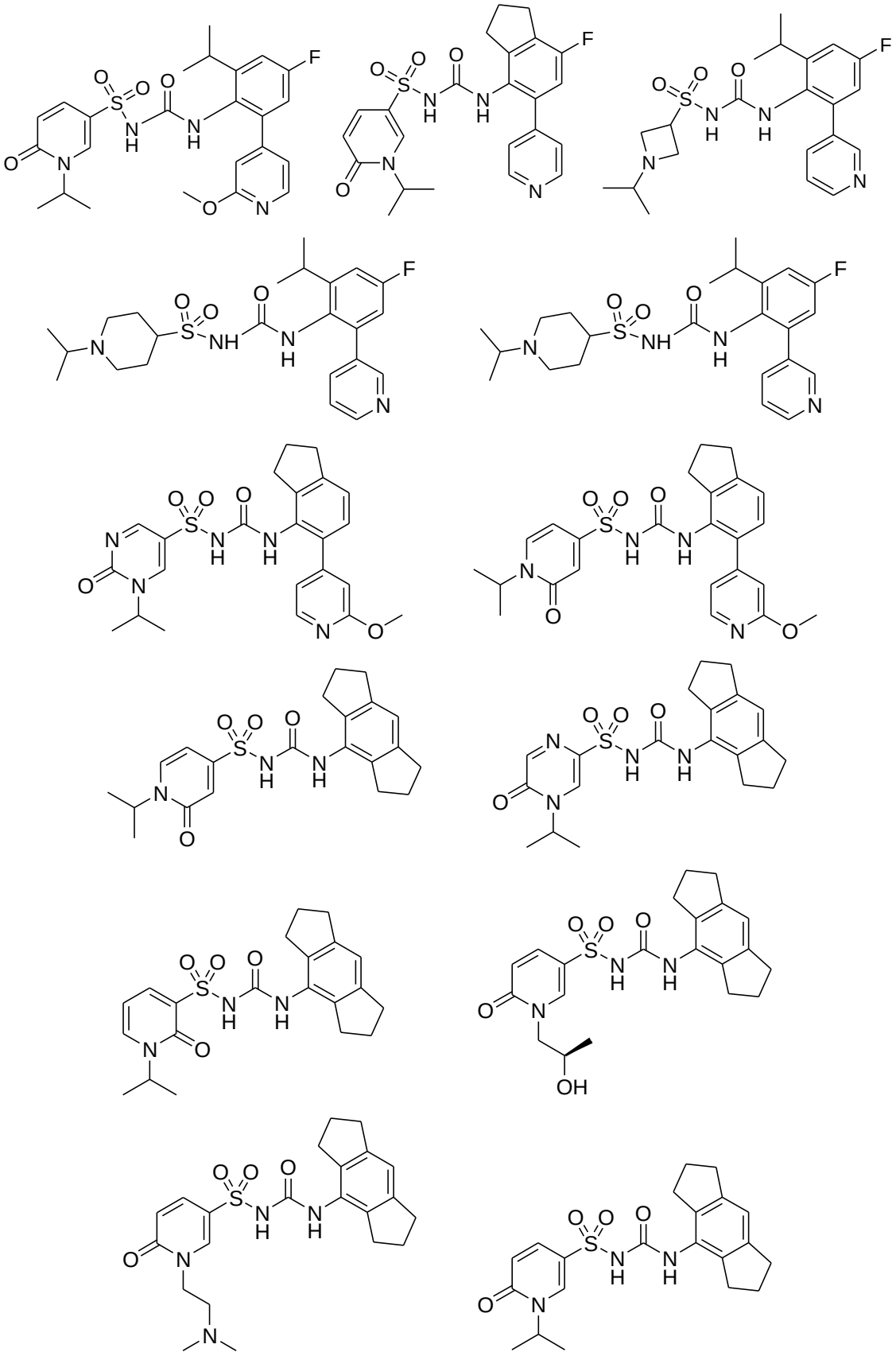

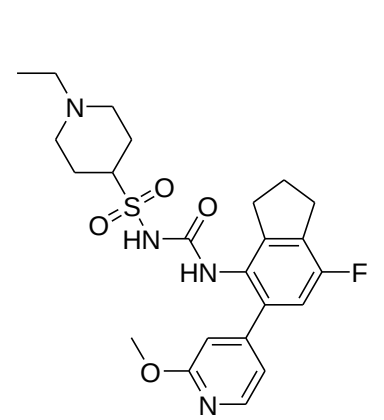
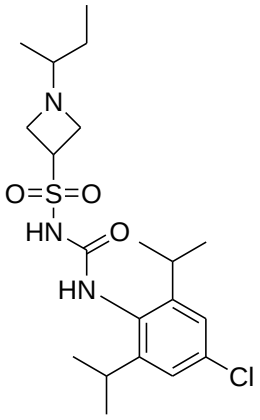
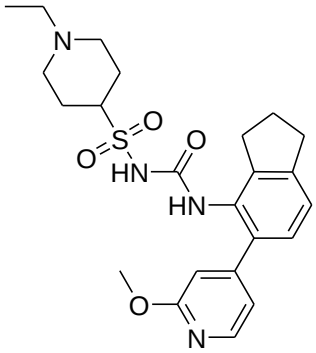
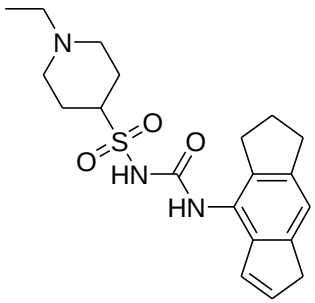
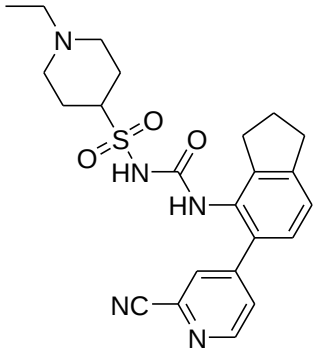
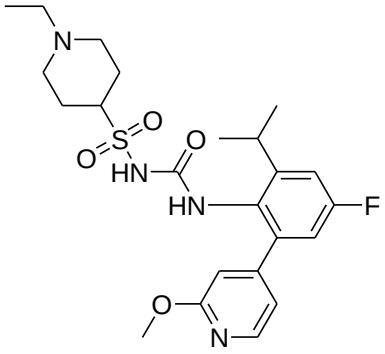
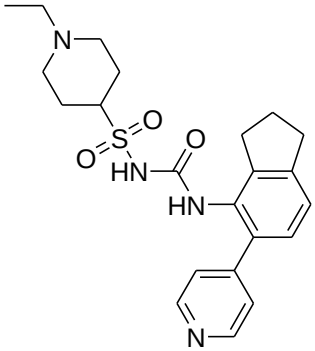
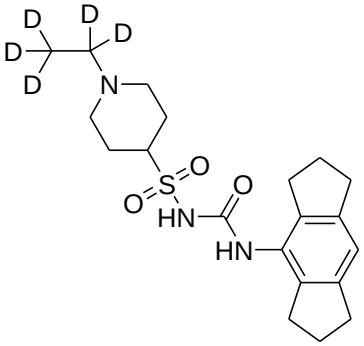
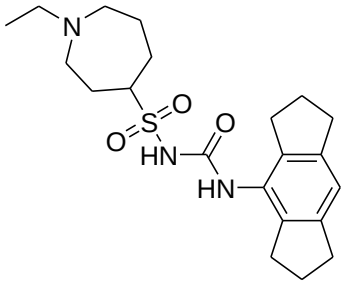
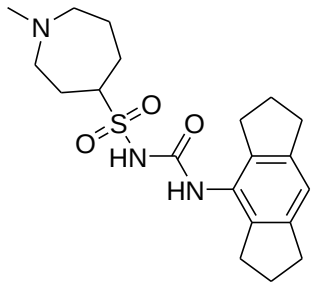

and .

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

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

claim 17, and a pharmaceutically acceptable excipient.

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

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

21. A compound, pharmaceutically acceptable salt, solvate, prodrug or pharmaceutical composition as claimed in claim 19 or 20, 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;
(xvi) allodynia; and
(xvii) any disease where an individual has been determined to carry a germline or somatic non-silent mutation in NLRP3.

22. A compound, pharmaceutically acceptable salt, solvate, prodrug or pharmaceutical composition as claimed in claim 19 or 20, 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).

23. A compound as claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt, solvate or prodrug as claimed in claim 17, or a pharmaceutical composition as claimed in claim 18, for use in inhibiting NLRP3.

24. Use of a compound as claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt, solvate or prodrug as claimed in claim 17, or a pharmaceutical composition as claimed in claim 18, 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.

25. Use of a compound as claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt, solvate or prodrug as claimed in claim 17, or a pharmaceutical composition as claimed in claim 18, 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).