

HETEROCYCLIC SULFONAMIDE DERIVATIVES AND PHARMACEUTICAL USES THEREOF**FIELD OF THE INVENTION**

The invention relates to heterocyclic sulfonamide derivatives and their use in the treatment
5 and prophylaxis of autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and
metabolic mediated diseases, and to compositions containing said derivatives and
processes for their preparation.

BACKGROUND OF THE INVENTION

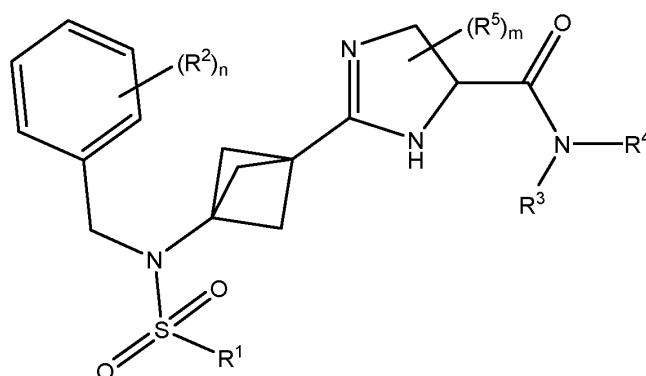
10 Ion channels are proteins that span the lipid bilayer of the cell membrane and provide an
aqueous pathway through which specific ions such as Na⁺, K⁺, Ca²⁺ and Cl⁻ can pass
(Herbert (1998) Am. J. Med 104, 87- 98). Potassium channels represent the largest and
most diverse subgroup of ion channels and they play a central role in regulating the
membrane potential and controlling cellular excitability (Armstrong & Hille (1998) Neuron 20,
15 371-380). Potassium channels have been categorized into gene families based on their
amino acid sequence and their biophysical properties (for nomenclature see Gutman *et al.*
(2003) Pharmacol Rev. Dec 55(4), 583-586).

Compounds which modulate potassium channels have multiple therapeutic applications in
20 several disease areas including autoimmune, inflammatory, cardiovascular, neuronal,
auditory, renal and metabolic mediated diseases (Shieh *et al* (2000) Pharmacol Rev 52(4),
557-594; Ford *et al* (2002) Prog Drug Res 58, 133- 168, Xie *et al* (2004) Current Drug
Discovery, 31-33; Cahalan *et al* (1997) Current Opinion in Biotechnology 8, 749-756). The
potassium channel Kv1.3 is found in a number of tissues including neurons, blood cells,
25 osteoclasts, macrophages, epithelia, and T- and B-lymphocytes. Furthermore, Kv1.3
inhibition has been shown to modulate T-cell function which has implications in many
autoimmune diseases including psoriasis, rheumatoid arthritis, multiple sclerosis, obesity,
diabetes and inflammatory bowel disease (Beeton *et al* (2006) PNAS 46, 103, 17414-
17419).

30 There is therefore a need to provide effective Kv1.3 inhibitors for the treatment of
autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated
diseases.

35 SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a compound of formula (I):



(I)

or a tautomeric or a stereochemically isomeric form, a pharmaceutically acceptable salt or a solvate thereof, wherein:

- 5 R^1 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanol, $-X-C_{3-8}$ cycloalkyl, halo C_{1-6} alkyl, aryl, heterocyclyl or heteroaryl, wherein said cycloalkyl, aryl, heterocyclyl or heteroaryl groups may be optionally substituted by one or more (e.g. 1, 2, 3 or 4) R^a groups;
 R^a represents C_{1-6} alkyl, halogen, halo C_{1-6} alkyl, hydroxy, cyano, nitro, oxo, $CONR^xR^y$ or C_{3-8} cycloalkyl;
- 10 R^x and R^y independently represent hydrogen or C_{1-6} alkyl;
 X represents a bond, $-CH_2-$ or $-(CH_2)_2-$;
 R^2 represents halogen, halo C_{1-6} alkyl or cyano;
 n represents an integer selected from 0 to 4;
 R^3 represents hydrogen, C_{1-6} alkyl, $-X-C_{3-8}$ cycloalkyl, halo C_{1-6} alkyl or $-X$ -aryl,
- 15 wherein said alkyl may be optionally substituted by one or more cycloalkyl groups,
 wherein said cycloalkyl may be optionally substituted by one or more C_{1-6} alkyl, C_{1-6} alkoxy, halo C_{1-6} alkyl, halogen, hydroxy or cyano groups,
 wherein said haloalkyl may be optionally substituted by one or more hydroxy groups,
 wherein said aryl may be optionally substituted by one or more halogen groups,
- 20 wherein R^3 and R^4 together with the nitrogen atom to which they are attached may join to form a heterocyclyl ring optionally substituted by one or more C_{1-6} alkyl, halo C_{1-6} alkyl, or halogen;
 R^4 represents hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;
 R^5 represents C_{1-6} alkyl or $-X$ -aryl; and
- 25 m represents an integer selected from 0 to 4, such that when m represents 2, said R^5 groups may join to form a C_{3-8} cycloalkyl group.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term 'halo' or 'halogen' as used herein refers to fluorine, chlorine, bromine or iodine.

The term 'cyano' as used herein refers to a group where a carbon atom is triple bonded to a nitrogen atom.

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The term 'C₁₋₆ alkyl' as used herein as a group or part of a group refers to a linear or branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl and the like.

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The term 'C₁₋₆ alkoxy' as used herein as a group or part of a group refers to a C₁₋₆ alkyl group which contains one or more oxygen atoms wherein C₁₋₆ alkyl is as defined herein. Examples of such groups include methoxy, ethoxy or propoxy.

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The term 'haloC₁₋₆ alkyl' as used herein as a group or part of a group refers to a C₁₋₆ alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a halogen. The term 'haloC₁₋₆ alkyl' therefore includes monohaloC₁₋₆ alkyl and also polyhaloC₁₋₆ alkyl. There may be one, two, three or more hydrogen atoms replaced with a halogen, so the haloC₁₋₆ alkyl may have one, two, three or more halogens. Examples of such groups include

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fluoroethyl, fluoromethyl, trifluoromethyl or trifluoroethyl and the like.

The term 'oxo' as used herein refers to the group =O.

The term 'nitro' as used herein refers to the group -N(=O)₂.

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The term 'hydroxy' or 'hydroxyl' as used herein refers to the group OH.

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The term "C₁₋₆ alkanol" as used herein as a group or part of a group refers to a C₁₋₆ alkyl group which contains a hydroxyl group wherein C₁₋₆ alkyl is as defined herein. An example of a C₁₋₆ alkanol group includes -CH₂OH.

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The term "C₃₋₈ cycloalkyl" as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term 'aryl' as used herein refers to a carbocyclic monocyclic or bicyclic aromatic, unsaturated ring system containing for example 3 to 12 ring members. Examples of aryl rings include phenyl and naphthyl.

- 5 The term 'heteroaryl' as used herein refers to a monocyclic or bicyclic aromatic, unsaturated ring system containing for example 3 to 12 ring members. Each ring may contain up to five heteroatoms typically selected from nitrogen, sulfur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom.

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Examples of five membered heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, thiadiazole, isothiazole, pyrazole, triazole and tetrazole groups.

- 15 Examples of six membered heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine.

A bicyclic heteroaryl group may be, for example, a group selected from:

- 20 a) a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;
- b) a pyridine ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
- c) a pyrimidine ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- 25 d) a pyrrole ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
- e) a pyrazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- f) an imidazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- 30 g) an oxazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- h) an isoxazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- 35 i) a thiazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;

- j) an isothiazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- k) a thiophene ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
- 5 l) a furan ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
- m) a cyclohexyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; and
- 10 n) a cyclopentyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms.

Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole (e.g. imidazo[2,1-b]thiazole) and imidazoimidazole (e.g. imidazo[1,2-a]imidazole).

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Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzothiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzothiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine (e.g. pyrazolo[1,5-a]pyrimidine), triazolopyrimidine (e.g. [1,2,4]triazolo[1,5-a]pyrimidine), benzodioxole, imidazopyridine and pyrazolopyridine (e.g. pyrazolo[1,5-a]pyridine) groups.

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Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, isochroman, chromene, isochromene, benzodioxan, quinolizine, benzoxazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups.

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Examples of polycyclic heteroaryl groups containing an aromatic ring and a non-aromatic ring include, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzthiophene, dihydrobenzofuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, tetrahydrotriazolopyrazine (e.g. 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine), chroman, thiochroman, isochroman, chromene, isochromene, benzodioxan, benzoxazine, benzodiazepine, and indoline groups.

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The term 'heterocyclyl' as used herein refers to a monocyclic or bicyclic non-aromatic, partially saturated or fully saturated ring system containing for example 3 to 12 ring

members. Each ring may contain up to five heteroatoms typically selected from nitrogen, sulfur and oxygen.

Particular examples of 'heterocyclyl' include morpholine, piperidine (e.g. piperidin-1-yl, piperidin-2-yl, piperidin-3-yl and piperidin-4-yl), piperidinone, pyrrolidine (e.g. pyrrolidin-1-yl, pyrrolidin-2-yl and pyrrolidin-3-yl), pyrrolidone, azetidine, pyran (2H-pyran or 4H-pyran), dihydrothiophene, oxetanyl, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. tetrahydropyran-4-yl), imidazoline, imidazolidinone, oxazoline, thiazoline, pyrazolin-2-yl, pyrazolidine, piperazinone and piperazine.

It will be appreciated that the term 'heterocyclyl' includes reference to spiro and bridged heterocyclic derivatives. Examples of such spiro and bridged heterocyclic derivatives include: 1-azaspiro[3.3]heptyl, 5-azaspiro[2.4]heptyl, 5-azaspiro[3.4]octyl, 8-azabicyclo[3.2.1]octyl, 3-azabicyclo[3.1.0]hexyl, octahydrocyclopenta[c]pyrrolyl, 2-azaspiro[3.3]heptyl, 3-azabicyclo[3.2.1]octyl, 6-azaspiro[3.4]octyl, 5-azaspiro[2.5]octyl or 2-oxa-6-azaspiro[3.4]octyl, hexahydropyrrolo[2,3-c]pyrrolidinyl, oxaspiro[3.3]heptanyl, diazaspiro[3.4]octanyl, diazaspiro[4.4]nonyl, oxa-azaspiro[3.4]octanyl, oxa-azaspiro[4.4]nonyl, tetrahydrofuro[3,4-c]pyrrolidinyl, oxa-azaspiro[3.3]heptyl, diazaspiro[4.5]decanyl, diazaspiro[3.4]octanyl, octahydro-naphthyridinyl, tetrahydropyrazino-oxazinyl, oxadiazospiro[5.5]undecanyl and oxabicyclo[2.2.1]heptanyl.

The term 'optionally substituted' as used herein refers to a group which may be substituted or unsubstituted by a substituent as herein defined.

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Embodiments

In one embodiment, R¹ represents:

- C₁₋₆ alkyl (such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl or i-pentyl);
- C₁₋₆ alkoxy (such as propoxy);
- X-C₃₋₈ cycloalkyl (such as -(CH₂)-cyclopropyl, -(CH₂)₂-cyclopropyl, -cyclobutyl, -(CH₂)-cyclobutyl, -cyclopentyl or -cyclohexyl);
- haloC₁₋₆ alkyl (such as trifluoromethyl, fluoropropyl, difluoropropyl, trifluoropropyl, fluorobutyl, difluorobutyl or trifluorobutyl);
- aryl (such as phenyl);
- heterocyclyl (such as pyrrolidinyl or tetrahydropyranyl); or
- heteroaryl (such as furanyl, thiophenyl, pyrazolyl, pyridinyl or imidazolyl);

wherein said cycloalkyl, aryl, heterocyclyl or heteroaryl groups may be optionally substituted by one or more (e.g. 1, 2, 3 or 4) R^a groups.

5 In a further embodiment, R¹ represents:

haloC₁₋₆ alkyl (such as trifluoromethyl, fluoropropyl, difluoropropyl, trifluoropropyl, fluorobutyl, difluorobutyl or trifluorobutyl);

aryl (such as phenyl); or

heteroaryl (such as furanyl, thiophenyl, pyrazolyl, pyridinyl or imidazolyl);

10 wherein said aryl or heteroaryl groups may be optionally substituted by one or more (e.g. 1, 2, 3 or 4) R^a groups.

In a further embodiment, R¹ represents:

heteroaryl (such as pyridinyl);

15 wherein said heteroaryl groups may be optionally substituted by one or more (e.g. 1, 2, 3 or 4) R^a groups.

In a yet further embodiment, R¹ represents:

haloC₁₋₆ alkyl (such as fluoropropyl);

20 aryl (such as phenyl, in particular unsubstituted phenyl); or

heteroaryl (such as pyridinyl, in particular unsubstituted pyridyl).

In one embodiment, R^a represents C₁₋₆ alkyl (such as methyl), halogen (such as fluorine or chlorine), haloC₁₋₆ alkyl (such as trifluoromethyl), hydroxy, cyano, nitro, oxo, CONR^xR^y (such

25 as CONH₂) or C₃₋₈ cycloalkyl (such as cyclopropyl).

In one embodiment, R² represents halogen (such as fluorine or chlorine), haloC₁₋₆ alkyl (such as difluoromethyl or trifluoromethyl) or cyano. In a further embodiment, R² represents halogen (such as fluorine or chlorine).

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In one embodiment, n represents an integer selected from 0 to 3.

In a further embodiment, n represents 0.

35 In a yet further embodiment, n represents 1 or 2.

In an alternative embodiment, n represents 1 and R² represents halogen (such as fluorine or chlorine), haloC₁₋₆ alkyl (such as difluoromethyl or trifluoromethyl) or cyano. In a further embodiment, n represents 1 and R² represents 3-fluorine, 4-fluorine, 3-chlorine, 4-chlorine, 4-difluoromethyl, 4-trifluoromethyl or 4-cyano. In a yet further embodiment, n represents 1
5 and R² represents 4-chlorine.

In an alternative embodiment, n represents 2 and R² represents halogen (such as fluorine or chlorine), haloC₁₋₆ alkyl (such as trifluoromethyl) or cyano. In a further embodiment, n represents 2 and R² represents: 2-fluoro, 4-chloro; 3-fluoro, 4-chloro; 3-chloro, 4-fluoro; 3-
10 fluoro, 4-trifluoromethyl; 3-chloro, 4-trifluoromethyl; 3-cyano, 4-chloro; 3,4-difluoro; or 3,4-dichloro. In a yet further embodiment, n represents 2 and R² represents 3-fluoro, 4-chloro.

In an alternative embodiment, n represents 3 and R² represents halogen (such as fluorine or chlorine). In a further embodiment, n represents 3 and R² represents 3,5-difluoro, 4-chloro.
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In one embodiment, R³ represents:

hydrogen;

C₁₋₆ alkyl (such as methyl, n-propyl, i-propyl, dimethylpropyl, n-butyl or t-butyl) optionally substituted by one or more cycloalkyl groups (such as cyclopropyl);
20 -X-C₃₋₈ cycloalkyl (such as cyclopropyl, -CH₂-cyclopropyl, -(CH₂)₂-cyclopropyl, -cyclobutyl, -CH₂-cyclobutyl, -(CH₂)₂-cyclobutyl, -C(H)(CH₃)-cyclobutyl, cyclohexyl, -CH₂-cyclohexyl or bicyclo[1.1.1]pentanyl optionally substituted by one or more C₁₋₆ alkyl (such as methyl), C₁₋₆ alkoxy (such as methoxy), haloC₁₋₆ alkyl (such as difluoromethyl, trifluoromethyl or trifluoroethyl), halogen (such as fluorine), hydroxy or cyano groups;

25 haloC₁₋₆ alkyl (such as trifluoroethyl, difluoropropyl, trifluoropropyl, pentafluoropropyl, fluorobutyl, trifluorobutyl or trifluoropentyl) optionally substituted by one or more hydroxy groups;

-X-aryl (such as -phenyl or -CH₂-phenyl) optionally substituted by one or more halogen (such as fluorine) groups;
30 or R³ and R⁴ together with the nitrogen atom to which they are attached join to form a heterocyclyl ring (such as azetidiny, pyrrolidiny, piperidiny, morpholiny, azepiny, 1-azaspiro[3.3]heptyl, 5-azaspiro[2.4]heptyl, 5-azaspiro[3.4]octyl, 8-azabicyclo[3.2.1]octyl, 3-azabicyclo[3.1.0]hexyl, octahydrocyclopenta[c]pyrrolyl, 2-azaspiro[3.3]heptyl, 3-azabicyclo[3.2.1]octyl, 6-azaspiro[3.4]octyl, 5-azaspiro[2.5]octyl or 2-oxa-6-azaspiro[3.4]octyl) optionally substituted by one or more C₁₋₆ alkyl (such as methyl), haloC₁₋₆ alkyl (such as difluoromethyl or trifluoromethyl) or halogen (such as fluorine).
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In a further embodiment, R³ represents:

-X-C₃₋₈ cycloalkyl (such as cyclopropyl, -CH₂-cyclopropyl, -(CH₂)₂-cyclopropyl, -cyclobutyl, -CH₂-cyclobutyl, -(CH₂)₂-cyclobutyl, -C(H)(CH₃)-cyclobutyl, cyclohexyl, -CH₂-cyclohexyl or bicyclo[1.1.1]pentanyl) optionally substituted by one or more C₁₋₆ alkyl (such as methyl), C₁₋₆ alkoxy (such as methoxy), haloC₁₋₆ alkyl (such as difluoromethyl, trifluoromethyl or trifluoroethyl), halogen (such as fluorine), hydroxy or cyano groups; or

haloC₁₋₆ alkyl (such as trifluoroethyl, difluoropropyl, trifluoropropyl, pentafluoropropyl, fluorobutyl, trifluorobutyl or trifluoropentyl) optionally substituted by one or more hydroxy groups.

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In a yet further embodiment, R³ represents:

-X-C₃₋₈ cycloalkyl (such as bicyclo[1.1.1]pentanyl, in particular unsubstituted bicyclo[1.1.1]pentanyl; or

haloC₁₋₆ alkyl (such as trifluoropropyl, in particular unsubstituted trifluoropropyl).

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In one embodiment, R⁴ represents hydrogen, C₁₋₆ alkyl (such as methyl or ethyl) or C₃₋₈ cycloalkyl (such as cyclopropyl). In a further embodiment, R⁴ represents hydrogen.

In one embodiment, m represents an integer selected from 0 to 3.

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In one embodiment, R⁵ represents C₁₋₆ alkyl (such as methyl, ethyl, n-propyl, i-propyl or i-butyl) or -X-aryl (such as -CH₂-phenyl) or m represents 2 and said two R⁵ groups join to form a C₃₋₈ cycloalkyl group (such as cyclopropyl or cyclobutyl). In a further embodiment, R⁵ represents C₁₋₆ alkyl (such as methyl, ethyl, n-propyl, i-propyl or i-butyl). In a yet further embodiment, R⁵ represents C₁₋₆ alkyl (such as methyl).

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In one embodiment, m represents 0.

In a further embodiment, m represents 2.

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In an alternative embodiment, m represents 1 and R⁵ represents C₁₋₆ alkyl (such as methyl, n-propyl, i-propyl or i-butyl) or -X-aryl (such as -CH₂-phenyl).

In an alternative embodiment, m represents 2 and R⁵ represents C₁₋₆ alkyl (such as methyl or ethyl) or said two R⁵ groups join to form a C₃₋₈ cycloalkyl group (such as cyclopropyl or cyclobutyl).

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In a further embodiment, m represents 2 and R⁵ represents C₁₋₆ alkyl (such as methyl or ethyl). In a yet further embodiment, m represents 2 and R⁵ represents C₁₋₆ alkyl (such as methyl).

- 5 In an alternative embodiment, m represents 3 and R⁵ represents C₁₋₆ alkyl (such as methyl).

In one embodiment, the invention provides a compound of formula (I) which is the free base of a compound of Examples 1-295 or a pharmaceutically acceptable salt or solvate thereof.

- 10 In one embodiment, the invention provides a compound of formula (I) which is the free base of a compound of Example 1, Example 48 or Example 92 or a pharmaceutically acceptable salt or solvate thereof.

- A reference to a compound of the formula (I) and sub-groups thereof also includes ionic forms, salts, solvates, isomers (including geometric and stereochemical isomers), tautomers, N-oxides, esters, prodrugs, isotopes and protected forms thereof, for example, as discussed below; preferably, the salts or tautomers or isomers or N-oxides or solvates thereof; and more preferably, the salts or tautomers or N-oxides or solvates thereof, even more preferably the salts or tautomers or solvates thereof. Hereinafter, compounds and their ionic forms, salts, solvates, isomers (including geometric and stereochemical isomers), tautomers, N-oxides, esters, prodrugs, isotopes and protected forms thereof as defined in any aspect of the invention (except intermediate compounds in chemical processes) are referred to as "compounds of the invention".

25 **Salts**

- Certain compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulfonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds.

- 30 The salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods such as methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002.
- 35 Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water or in an organic solvent, or in a

mixture of the two; generally, non-aqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

Acid addition salts (*mono-* or *di-*salts) may be formed with a wide variety of acids, both
5 inorganic and organic. Examples of acid addition salts include *mono-* or *di-*salts formed with
an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic,
ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulfonic, benzoic, 4-acetamidobenzoic,
butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, capric, caproic,
caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-
10 hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic,
glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α -oxoglutaric, glycolic, hippuric,
hydrohalic acids (e.g. hydrobromic, hydrochloric, hydriodic), isethionic, lactic (e.g. (+)-L-
lactic, ($\pm$)-DL-lactic), lactobionic, maleic, malic, (-)-L-malic, malonic, ($\pm$)-DL-mandelic,
methanesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic, 1-hydroxy-2-naphthoic,
15 nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, pyruvic, L-
pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, (+)-L-
tartaric, thiocyanic, p-toluenesulfonic, undecylenic and valeric acids, as well as acylated
amino acids and cation exchange resins.

20 One particular group of salts consists of salts formed from acetic, hydrochloric, hydriodic,
phosphoric, nitric, sulfuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric,
benzenesulfonic, toluenesulfonic, methanesulfonic (mesylate), ethanesulfonic,
naphthalenesulfonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic
acids. One particular salt is the hydrochloride salt.

25 Where the compounds of the formula (I) contain an amine function, these may form
quaternary ammonium salts, for example by reaction with an alkylating agent according to
methods well known to the skilled person. Such quaternary ammonium compounds are
within the scope of formula (I).

30 The compounds of the invention may exist as *mono-* or *di-*salts depending upon the pK_a of
the acid from which the salt is formed.

It will be appreciated that for use in medicine the salts of the compounds of formula (I)
35 should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be
apparent to those skilled in the art. Pharmaceutically acceptable salts include those
described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.* **1977**, 66, pp. 1-19. Such

pharmaceutically acceptable salts include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates or formates may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts. Such non-pharmaceutically acceptable salts forms, which may be useful, for example, in the purification or separation of the compounds of the invention, also form part of the invention.

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Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

15 **Solvates**

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Pharmaceutically acceptable solvates of the compound of the invention are within the scope of the invention. In one embodiment, the pharmaceutically acceptable solvates of the compounds of the invention include the hydrate thereof.

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It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

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As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

30

N-Oxides

Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide.

35

Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle.

- 5 N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a *per*-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Commun.* **1977**, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.
- 10

Prodrugs

- It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All such prodrugs of compounds of the invention are included within the scope of the invention. Examples of pro-drug functionality suitable for the compounds of the present invention are described in *Drugs of Today*, 19, 9, **1983**, 499-538 and in *Topics in Chemistry*, Chapter 31, pp. 306-316 and in "*Design of Prodrugs*" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "*Design of Prodrugs*" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within compounds of the invention.
- 15
- 20
- 25
- 30

- Also included within the scope of the compound and various salts of the invention are polymorphs thereof.

Enantiomers

- The compounds of formula (I) may be achiral or *R* or *S* enantiomers. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible enantiomers and diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by
- 35

stereospecific or asymmetric syntheses. The invention also extends to any tautomeric forms or mixtures thereof.

Isotopes

5 The subject invention also includes all pharmaceutically acceptable isotopically-labelled compounds which are identical to those recited in formula (I) but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature.

10 Examples of isotopes suitable for inclusion in the compounds of the invention comprise isotopes of hydrogen, such as ^2H (D) and ^3H (T), carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I , ^{125}I and ^{131}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulfur, such as ^{35}S .

15 Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The compounds of formula (I) can also have valuable diagnostic properties in that they can be used for detecting or identifying the formation of a complex between a labelled compound and other molecules, peptides, proteins, enzymes or receptors. The detecting or identifying
20 methods can use compounds that are labelled with labelling agents such as radioisotopes, enzymes, fluorescent substances, luminous substances (for example, luminol, luminol derivatives, luciferin, aequorin and luciferase) *etc.* The radioactive isotopes tritium, *i.e.* ^3H (T), and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

25 Substitution with heavier isotopes such as deuterium, *i.e.* ^2H (D), may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

30 Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining target occupancy.

Isotopically-labelled compounds of formula (I) can generally be prepared by conventional
35 techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using appropriate isotopically-labelled reagents in place of the non-labelled reagent previously employed.

Purity

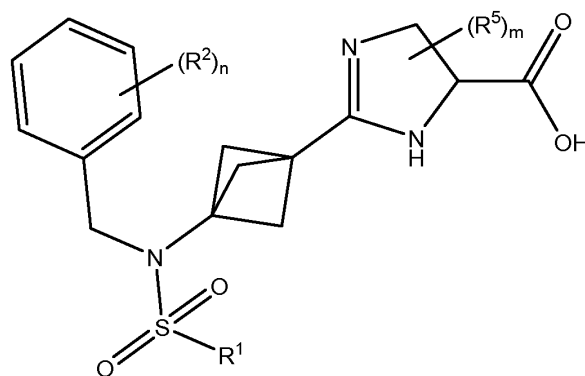
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are given on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

10 **Processes**

According to a further aspect of the present invention there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following schemes are examples of synthetic schemes that may be used to synthesise the compounds of the invention. In the following schemes reactive groups can be protected with protecting groups and de-protected according to well established techniques.

According to a further aspect of the invention there is provided a process for preparing a compound of formula (I) as herein defined which comprises:

- 20 (a) reacting a compound of formula (II):



(II)

wherein R^1 , R^2 , n , R^5 and m are as defined herein, with a compound of formula HNR^3R^4 ;

- 25 (b) deprotection of a protected derivative of a compound of formula (I);
- (c) interconversion of a compound of formula (I) or protected derivative thereof to a further compound of formula (I) or protected derivative thereof; and

(d) optional formation of a pharmaceutically acceptable salt of a compound of formula (I).

Process (a) typically comprises dissolving a compound of formula (II) in suitable reagents, such as MeCN and DIEA, followed by addition of a compound of formula HNR^3R^4 in the presence of a suitable reagent such as COMU.

Compounds of formula (II) may be prepared in accordance with the Schemes and experimental procedures provided in Examples 1 to 5 herein.

Compounds of formula HNR^3R^4 are either known or may be prepared in accordance with known procedures.

A wide range of well known functional group interconversions for process (c) are known by a person skilled in the art for converting a precursor compound to a compound of formula (I) and are described in Advanced Organic Chemistry by Jerry March, 4th Edition, John Wiley & Sons, 1992. For example possible metal catalysed functionalisations such as using organotin reagents (the Stille reaction), Grignard reagents and reactions with nitrogen nucleophiles are described in 'Palladium Reagents and Catalysts' [Jiro Tsuji, Wiley, ISBN 0-470-85032-9] and Handbook of OrganoPalladium Chemistry for Organic Synthesis [Volume 1, Edited by Ei-ichi Negishi, Wiley, ISBN 0-471-31506-0].

If appropriate, the reactions described herein are followed or preceded by one or more reactions known to the skilled of the art and are performed in an appropriate order to achieve the requisite substitutions on R^1 , R^2 , R^3 , R^4 and R^5 defined herein to afford other compounds of formula (I). Non-limiting examples of such reactions whose conditions can be found in the literature include:

protection of reactive functions,
deprotection of reactive functions,
halogenation,
dehalogenation,
dealkylation,
alkylation of amine, aniline, alcohol and phenol,
Mitsunobu reaction on hydroxyl groups,
cycloaddition reactions on appropriate groups,
reduction of nitro, esters, cyano, aldehydes,
transition metal-catalyzed coupling reactions,
acylation,

- sulfonylation/introduction of sulfonyl groups,
saponification/hydrolysis of esters groups,
amidification or transesterification of ester groups,
esterification or amidification of carboxylic groups,
5 halogen exchange,
nucleophilic substitution with amine, thiol or alcohol,
reductive amination,
oxime formation on carbonyl and hydroxylamine groups,
S-oxidation,
10 N-oxidation,
salification.

It is recognised that the sequence of reactions involving aryl coupling and reduction may be varied. It is also recognised that a wide range of palladium based catalysts are suitable for
15 conducting aryl coupling reactions.

It may also be recognised that isomer separation may occur at any suitable stage in the synthetic sequence. It should be stressed that such chiral separation forms a key aspect of the invention and that such separation may be conducted in accordance with the
20 methodology described herein or may be conducted in accordance with known methodology. It is also recognised that it may be beneficial to temporarily form a protected derivative of an intermediate in the synthesis, for example, a Boc-protected amine, or SEM-protected amide, in order to facilitate chromatographic separation, chiral resolution or to give improved solubility or yields in particular steps.

25 In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and de-protecting functional groups, can be found in Protective Groups in Organic Synthesis (T. Green and P. Wuts; 4th
30 Edition; John Wiley and Sons, 2007).

A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a *tert*-butyl ether; a tetrahydropyranyl (THP) ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or *tert*-butyldimethylsilyl
35 ether; or an acetyl ester (-OC(=O)CH₃).

An amine group may be protected, for example, as an amide (-NRCO-R) or a carbamate (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH₃); a benzyl carbamate (-NHCO-OCH₂C₆H₅, -NH-Cbz or NH-Z); as a *tert*-butyl carbamate (-NHCOOC(CH₃)₃, NH-Boc); a 2-biphenyl-2-propyl carbamate (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, NH-Boc), as a 9-fluorenylmethyl carbamate (-NH-Fmoc), as a 6-nitroveratryl carbamate (-NH-Nvoc), as a 2-trimethylsilylethyl carbamate (-NH-Teoc), as a 2,2,2-trichloroethyl carbamate (-NH-Troc), as an allyl carbamate (-NH-Alloc), or as a 2(-phenylsulfonyl)ethyl carbamate (-NH-Psec).

Other protecting groups for amines, such as cyclic amines and heterocyclic N-H groups, include toluenesulfonyl (tosyl) and methanesulfonyl (mesyl) groups, benzyl groups such as a *para*-methoxybenzyl (PMB) group and tetrahydropyranyl (THP) groups.

A carboxylic acid group may be protected as an ester for example, as: an C₁₋₇ alkyl ester (e.g. a methyl ester; a *tert*-butyl ester); a C₁₋₇ haloalkyl ester (e.g. a C₁₋₇ trihaloalkyl ester); a triC₁₋₇ alkylsilyl-C₁₋₇ alkyl ester; or a C₅₋₂₀ aryl-C₁₋₇ alkyl ester (e.g. a benzyl ester; a nitrobenzyl ester; *para*-methoxybenzyl ester).

It will be understood by those skilled in the art that certain compounds of the invention can be converted into other compounds of the invention according to standard chemical methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

25 ***Therapeutic Utility***

The compounds of the invention, subgroups and examples thereof, are potassium channel inhibitors, and which may be useful in preventing or treating disease states or conditions described herein. In addition, the compounds of the invention, and subgroups thereof, will be useful in preventing or treating diseases or condition mediated by potassium channel inhibition, in particular inhibition of the potassium channel Kv1.3.

Examples of diseases or conditions mediated by potassium channel inhibition include: autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated diseases.

Thus, according to a further aspect of the invention there is provided a compound of formula (I) as defined herein for use in therapy.

According to a further aspect of the invention there is provided a compound of formula (I) as defined herein for use in preventing or treating diseases or condition mediated by potassium channel inhibition, in particular inhibition of the potassium channel Kv1.3.

5

According to a further aspect of the invention there is provided the use of a compound of formula (I) as defined herein in the manufacture of a medicament for preventing or treating diseases or condition mediated by potassium channel inhibition, in particular inhibition of the potassium channel Kv1.3.

10

According to a further aspect of the invention there is provided a compound of formula (I) as defined herein for use in preventing or treating autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated diseases.

15 According to a further aspect of the invention there is provided the use of a compound of formula (I) as defined herein in the manufacture of a medicament for preventing or treating autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated diseases.

20 The compounds of the present invention may be useful for the treatment of the adult population. The compounds of the present invention may be useful for the treatment of the pediatric population.

Examples of autoimmune disorders include: rheumatoid arthritis and multiple sclerosis.

25

One particular example of cardiovascular diseases includes arrhythmias.

Examples of specific diseases or conditions mediated by potassium channels, such as Kv1.3 include: psoriasis, psoriatic arthritis, autoimmune thyroiditis, Hashimoto's disease, Grave's disease, rheumatoid arthritis, vitiligo, Crohn's disease, ulcerative colitis, inflammatory bowel disease, ankylosing spondylitis (Morbus Bechterew), periodontal disease, diabetes type I, multiple sclerosis, systemic lupus erythematosus, anti-glomerular basement membrane glomerulonephritis, rapidly progressive glomerulonephritis, advanced chronic renal failure, chronic kidney disease, renal fibrosis, uveitis, pars planitis, asthma, pemphigus foliaceus, inclusion body myositis, dermatomyositis, scleroderma, Behcet disease, atopic dermatitis, allergic and irritant contact dermatitis, Lichen planus, Sjogren's syndrome, Graft-versus-Host-Reaction, Host-versus-Graft-Reaction, transplant rejection, end-stage renal disease,

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vascularized composite allotransplantation rejection, alopecia areata, inflammatory bone resorption disease, anti-neutrophil cytoplasmic autoantibody-associated vasculitis, osteoarthritis, diseases associated with intimal hyperplasia, breast cancer, leukemia, chronic lymphocytic leukemia, human lung adenocarcinoma, cutaneous T-cell lymphoma,
5 osteosarcoma, neuroblastoma, ovarian cancer and melanoma, neuroinflammatory disorders, neurodegeneration, HIV- 1 -associated neurocognitive disorders (HAND), microglia-induced oxidative stress in Alzheimer's disease, obesity, and insulin resistance, restenosis/neointimal hyperplasia, atherosclerosis (arteriosclerotic vascular disease or ASVD), acute coronary syndrome, acute ischemic stroke, hypertension.

10

In one embodiment, the disease or condition mediated by potassium channels, such as Kv1.3 includes: psoriasis, rheumatoid arthritis, diabetes type I, multiple sclerosis, anti-glomerular basement membrane glomerulonephritis, rapidly progressive glomerulonephritis, advanced chronic renal failure, chronic kidney disease, renal fibrosis, allergic and irritant
15 contact dermatitis, transplant rejection, asthma, end-stage renal disease, vascularized composite allotransplantation rejection, alopecia areata, inflammatory bone resorption disease, human lung adenocarcinoma, melanoma, neuroinflammatory disorders, neurodegeneration, obesity, and insulin resistance, restenosis/neointimal hyperplasia, atherosclerosis (arteriosclerotic vascular disease or ASVD) and acute coronary syndrome.

20

In a further embodiment, the disease or condition mediated by potassium channels, such as Kv1.3 includes: psoriasis, atopic dermatitis, allergic and irritant contact dermatitis, rheumatoid arthritis, uveitis and multiple sclerosis, such as atopic dermatitis, allergic and irritant contact dermatitis, rheumatoid arthritis, uveitis and multiple sclerosis.

25

In one embodiment, the disease or condition mediated by potassium channels, such as Kv1.3, is one which requires an antiproliferative response, such as breast cancer, ovarian cancer, leukemia, chronic lymphocytic leukemia, osteosarcoma, neuroblastoma, human lung adenocarcinoma, melanoma, restenosis and neointimal hyperplasia.

30

In one embodiment, the disease or condition mediated by potassium channels, such as Kv1.3, is one which requires a neuroprotective response, such as neurodegeneration.

In one embodiment, the disease or condition mediated by potassium channels, such as
35 Kv1.3, is one which requires modulation of cellular metabolism, such as obesity and insulin resistance.

In one embodiment, the disease or condition mediated by potassium channels, such as Kv1.3, is one which is treatable by inhibition of Kv1.3^{high} phenotype cells, particularly Kv1.3^{high} phenotype immune system cells, more particularly class-switched memory B-cells and/or effector memory T-cells of the Kv1.3^{high} phenotype, even more particularly T-cell driven autoimmune disorders and chronic inflammation conditions, in particular selected from the group consisting of psoriatic arthritis, Type 1 diabetes, rheumatoid arthritis, multiple sclerosis, psoriasis, asthma, anti-glomerular basement membrane glomerulonephritis, acute coronary syndrome.

It will be appreciated that Kv1.3^{high} phenotype cells are cells wherein Kv1.3 expression numbers range from 750 to 2900, particularly 950 to 2900 Kv1.3 channels per cell, which can be determined either by immunohistochemical staining or patch-clamp analysis well known to the skilled person, and for example described in Wulff *et al.* (2003) J. Clin. Invest. 111, 1703; Rus *et al* (2005) PNAS 102, 11094.

It will be apparent to the skilled person that analysis of whether Kv1.3 expression in cells of a subject is high as defined herein, can particularly be determined by:

- (a) obtaining a sample from said subject;
- (b) optionally isolating cells wherein Kv1.3 expression is to be determined from said sample;
- (c) optionally culturing said cells in a suitable medium; and
- (d) determining the Kv1.3 expression in said cells.

In one embodiment, said sample is a fluid sample, particularly a synovial or cerebrospinal fluid sample, leukapheresis sample, or peripheral blood sample, e.g. from a subject suspected of suffering from rheumatoid arthritis, or a tissue sample, particularly a sample from the affected tissue, such as a psoriatic lesion, synovial tissue or brain infiltrate, from said subject.

In one embodiment, said cells wherein Kv1.3 expression is to be determined may be selected from: lymphocytes, B- cells, or T-cells, such as TEM cells; CD4⁺ T-cells or CD8⁺ T-cells.

In one embodiment, said cells wherein Kv1.3 expression is to be determined are isolated by techniques known in the art, particularly density gradient centrifugation and FACS (fluorescence activated cell sorting), wherein in particular such isolation is used in the case of fluid samples.

In one embodiment, said suitable medium is known in the art, e.g. Dulbecco's media, such as Iscove's modified Dulbecco's medium, which may be supplemented with the necessary additives, such as antibiotics.

5

In the embodiment wherein the sample comprises tissue samples, the isolation and culturing may in certain cases be replaced by a step of sample preparation, e.g. paraffin preparation.

It will be appreciated that the Kv1.3 expression in said cells is determined via art-known techniques, particularly by patch-clamp, such as the patch-clamp techniques referenced herein, or by subjecting said cells to immunohistochemical staining and determining Kv1.3 expression by fluorescence microscopy, such as described in the literature references included herein, wherein the corresponding Kv1.3 expression in said cells may be calculated from the results obtained by the aforementioned techniques via art-known methods, such as described in the literature references cited herein. Examples of such methods are described in e.g. PNAS 2006, 103, 17414; J. Clin. Invest. 2003, 111, 1703; J. Invest. Dermatol. 2011, 131, 118; PNAS 2005, 102, 11094.

Pharmaceutical Compositions

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation). In one embodiment this is a sterile pharmaceutical composition.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising (e.g. admixing) at least one compound of formula (I) (and sub-groups thereof as defined herein), together with one or more pharmaceutically acceptable excipients and optionally other therapeutic or prophylactic agents, as described herein.

The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents, fillers or bulking agents, granulating agents, coating agents, release-controlling agents, binding agents, disintegrants, lubricating agents, preservatives, antioxidants, buffering agents, suspending agents, thickening agents, flavouring agents, sweeteners, taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions. Examples of excipients for various types of pharmaceutical compositions are set out in more detail below.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a
5 reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical
10 Sciences, Mack Publishing Company, Easton, PA, USA.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, intrabronchial, sublingual, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can
15 be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery. The delivery can be by bolus injection, short term infusion or longer term infusion and can be via passive delivery or through the utilisation of a suitable infusion pump or syringe driver.

20 Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, co-solvents, surface active agents, organic solvent mixtures, cyclodextrin complexation agents, emulsifying agents (for forming and stabilizing emulsion formulations), liposome components for
25 forming liposomes, gellable polymers for forming polymeric gels, lyophilisation protectants and combinations of agents for, *inter alia*, stabilising the active ingredient in a soluble form and rendering the formulation isotonic with the blood of the intended recipient. Pharmaceutical formulations for parenteral administration may also take the form of aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents
30 (R. G. Strickly, Solubilizing Excipients in oral and injectable formulations, Pharmaceutical Research, Vol 21(2) 2004, p 201-230).

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules, vials and prefilled syringes, and may be stored in a freeze-dried
35 (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. In one embodiment, the formulation is provided as an active pharmaceutical ingredient in a bottle for subsequent reconstitution using an

appropriate diluent.

The pharmaceutical formulation can be prepared by lyophilising a compound of formula (I), or sub-groups thereof. Lyophilisation refers to the procedure of freeze-drying a composition.

- 5 Freeze-drying and lyophilisation are therefore used herein as synonyms.

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

- 10 Pharmaceutical compositions of the present invention for parenteral injection can also comprise pharmaceutically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use.
- 15 Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as sunflower oil, safflower oil, corn oil or olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of thickening or coating
- 20 materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

- The compositions of the present invention may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the
- 25 action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include agents to adjust tonicity such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate
- 30 and gelatin.

- In one particular embodiment of the invention, the pharmaceutical composition is in a form suitable for i.v. administration, for example by injection or infusion. For intravenous
- 35 administration, the solution can be dosed as is, or can be injected into an infusion bag (containing a pharmaceutically acceptable excipient, such as 0.9% saline or 5% dextrose), before administration.

In another particular embodiment, the pharmaceutical composition is in a form suitable for sub-cutaneous (s.c.) administration.

Pharmaceutical dosage forms suitable for oral administration include tablets (coated or
5 uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal patches.

Thus, tablet compositions can contain a unit dosage of active compound together with an
10 inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and
15 granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

20 Tablets may be designed to release the drug either upon contact with stomach fluids (immediate release tablets) or to release in a controlled manner (controlled release tablets) over a prolonged period of time or with a specific region of the GI tract.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the
25 active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated. Coatings may act either as a protective film (e.g. a polymer, wax or varnish) or as a mechanism for
30 controlling drug release or for aesthetic or identification purposes. The coating (e.g. a Eudragit TM type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum, duodenum, jejunum or colon.

35 Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to

release the compound in a controlled manner in the gastrointestinal tract. Alternatively the drug can be presented in a polymer coating e.g. a polymethacrylate polymer coating, which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding
5 coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. In another alternative, the coating can be designed to disintegrate under microbial action in the gut. As a further alternative, the active compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic
10 release and other delayed release or sustained release formulations (for example formulations based on ion exchange resins) may be prepared in accordance with methods well known to those skilled in the art.

The compound of formula (I) may be formulated with a carrier and administered in the form
15 of nanoparticles, the increased surface area of the nanoparticles assisting their absorption. In addition, nanoparticles offer the possibility of direct penetration into the cell. Nanoparticle drug delivery systems are described in "Nanoparticle Technology for Drug Delivery", edited by Ram B Gupta and Uday B. Kompella, Informa Healthcare, ISBN 9781574448573, published 13th March 2006. Nanoparticles for drug delivery are also described in J. Control.
20 Release, 2003, 91 (1-2), 167-172, and in Sinha *et al.*, Mol. Cancer Ther. August 1, (2006) 5, 1909.

The pharmaceutical compositions typically comprise from approximately 1% (w/w) to approximately 95% (w/w) active ingredient and from 99% (w/w) to 5% (w/w) of a
25 pharmaceutically acceptable excipient or combination of excipients. Particularly, the compositions comprise from approximately 20% (w/w) to approximately 90%,% (w/w) active ingredient and from 80% (w/w) to 10% of a pharmaceutically acceptable excipient or combination of excipients. The pharmaceutical compositions comprise from approximately 1% to approximately 95%, particularly from approximately 20% to approximately 90%, active
30 ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, pre-filled syringes, dragées, tablets or capsules.

The pharmaceutically acceptable excipient(s) can be selected according to the desired
35 physical form of the formulation and can, for example, be selected from diluents (e.g solid diluents such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), disintegrants, buffering agents, lubricants, flow aids, release controlling (e.g.

release retarding or delaying polymers or waxes) agents, binders, granulating agents, pigments, plasticizers, antioxidants, preservatives, flavouring agents, taste masking agents, tonicity adjusting agents and coating agents.

- 5 The skilled person will have the expertise to select the appropriate amounts of ingredients for use in the formulations. For example tablets and capsules typically contain 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents (depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w) antioxidants, 0-5% (w/w) pigments. Slow release tablets would in addition contain 0-99%
10 (w/w) release-controlling (e.g. delaying) polymers (depending on dose). The film coats of the tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

- Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents,
15 and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

- Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the
20 mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragee cores or capsules. It is also possible for them to be incorporated into a polymer or waxy matrix that allow the active ingredients to diffuse or be released in measured amounts.

- The compounds of the invention can also be formulated as solid dispersions. Solid
25 dispersions are homogeneous extremely fine disperse phases of two or more solids. Solid solutions (molecularly disperse systems), one type of solid dispersion, are well known for use in pharmaceutical technology (see (Chiou and Riegelman, J. Pharm. Sci., 60, 1281-1300 (1971)) and are useful in increasing dissolution rates and increasing the bioavailability of poorly water-soluble drugs.

- 30 This invention also provides solid dosage forms comprising the solid solution described above. Solid dosage forms include tablets, capsules, chewable tablets and dispersible or effervescent tablets. Known excipients can be blended with the solid solution to provide the desired dosage form. For example, a capsule can contain the solid solution blended with (a)
35 a disintegrant and a lubricant, or (b) a disintegrant, a lubricant and a surfactant. In addition a capsule can contain a bulking agent, such as lactose or microcrystalline cellulose. A tablet can contain the solid solution blended with at least one disintegrant, a lubricant, a surfactant,

a bulking agent and a glidant. A chewable tablet can contain the solid solution blended with a bulking agent, a lubricant, and if desired an additional sweetening agent (such as an artificial sweetener), and suitable flavours. Solid solutions may also be formed by spraying solutions of drug and a suitable polymer onto the surface of inert carriers such as sugar
5 beads ('non-pareils'). These beads can subsequently be filled into capsules or compressed into tablets.

The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack. Patient packs have
10 an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in patient prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.

15 Compositions for topical use and nasal delivery include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

20 Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound. Solutions of the active compound may also be used for rectal administration.

25 Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administered in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

30 The compounds of the formula (I) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within these ranges,
35 particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to

20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

10

Methods of Treatment

The compounds of the formula (I) and sub-groups as defined herein may be useful in the prophylaxis or treatment of a range of disease states or conditions mediated by potassium channel inhibition, in particular inhibition of the potassium channel Kv1.3. Thus, according to a further aspect of the invention there is provided a method of treating a disease state or condition mediated by potassium channel inhibition (e.g. Kv1.3) which comprises administering to a subject in need thereof a compound of formula (I) as described herein. Examples of such disease states and conditions are set out above, and in particular include autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated diseases.

20

The compounds are generally administered to a subject in need of such administration, for example a human or animal patient, particularly a human.

25

The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

30

The compounds may be administered over a prolonged term to maintain beneficial therapeutic effects or may be administered for a short period only. Alternatively they may be administered in a continuous manner or in a manner that provides intermittent dosing (e.g. a pulsatile manner).

35

A typical daily dose of the compound of formula (I) can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 5 nanograms to 25 milligrams per kilogram of bodyweight, and more usually 10 nanograms to 15 milligrams per kilogram (e.g. 10 nanograms to 10 milligrams, and more typically 1 microgram per kilogram to 20 milligrams per kilogram, for example 1 microgram to 10 milligrams per kilogram) per kilogram of bodyweight although higher or lower doses may be administered where required. The compound of the formula (I) can be administered on a daily basis or on a repeat basis every 2, or 3, or 4, or 5, or 6, or 7, or 10 or 14, or 21, or 28 days for example.

The compounds of the invention may be administered orally in a range of doses, for example 1 to 1500 mg, 2 to 800 mg, or 5 to 500 mg, e.g. 2 to 200 mg or 10 to 1000 mg, particular examples of doses including 10, 20, 50 and 80 mg. The compound may be administered once or more than once each day. The compound can be administered continuously (i.e. taken every day without a break for the duration of the treatment regimen). Alternatively, the compound can be administered intermittently (i.e. taken continuously for a given period such as a week, then discontinued for a period such as a week and then taken continuously for another period such as a week and so on throughout the duration of the treatment regimen). Examples of treatment regimens involving intermittent administration include regimens wherein administration is in cycles of one week on, one week off; or two weeks on, one week off; or three weeks on, one week off; or two weeks on, two weeks off; or four weeks on two weeks off; or one week on three weeks off - for one or more cycles, e.g. 2, 3, 4, 5, 6, 7, 8, 9 or 10 or more cycles.

In one particular dosing schedule, a patient will be given an infusion of a compound of the formula (I) for periods of one hour daily for up to ten days in particular up to five days for one week, and the treatment repeated at a desired interval such as two to four weeks, in particular every three weeks.

More particularly, a patient may be given an infusion of a compound of the formula (I) for periods of one hour daily for 5 days and the treatment repeated every three weeks.

In another particular dosing schedule, a patient is given an infusion over 30 minutes to 1 hour followed by maintenance infusions of variable duration, for example 1 to 5 hours, e.g. 3 hours.

In a further particular dosing schedule, a patient is given a continuous infusion for a period of 12 hours to 5 days, in particular a continuous infusion of 24 hours to 72 hours.

In another particular dosing schedule, a patient is given the compound orally once a week.

5 In another particular dosing schedule, a patient is given the compound orally once-daily for between 7 and 28 days such as 7, 14 or 28 days.

10 In another particular dosing schedule, a patient is given the compound orally once-daily for 1 day, 2 days, 3 days, 5 days or 1 week followed by the required amount of days off to complete a one or two week cycle.

In another particular dosing schedule, a patient is given the compound orally once-daily for 2 weeks followed by 2 weeks off.

15 In another particular dosing schedule, a patient is given the compound orally once-daily for 2 weeks followed by 1 week off.

In another particular dosing schedule, a patient is given the compound orally once-daily for 1 week followed by 1 week off.

20 Ultimately, however, the quantity of compound administered and the type of composition used will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

25 It will be appreciated that potassium channel inhibitors can be used as a single agent or in combination with other therapeutically active agents. Combination experiments can be performed, for example, as described in Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. Adv Enzyme Regulat 1984;22: 27–55.

30 The compounds as defined herein can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds (or therapies) for treatment of a particular disease state, for example autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated diseases. For the treatment of the above conditions, the compounds of the invention may be advantageously employed in
35 combination with one or more other therapeutically agents which support the therapy of the disease being treated.

Each of the compounds present in the combinations of the invention may be given in individually varying dose schedules and via different routes. As such, the posology of each of the two or more agents may differ: each may be administered at the same time or at different times. A person skilled in the art would know through his or her common general
5 knowledge the dosing regimes and combination therapies to use. For example, the compound of the invention may be using in combination with one or more other agents which are administered according to their existing combination regimen.

Where the compound of the formula (I) is administered in combination therapy with one, two,
10 three, four or more other therapeutic agents (particularly one or two, more particularly one), the compounds can be administered simultaneously or sequentially. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. When administered sequentially, they can be administered at closely spaced intervals (for example
15 over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s). These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

20 In one embodiment is provided a compound of formula (I) for the manufacture of a medicament for use in therapy wherein said compound is used in combination with one, two, three, or four other therapeutic agents. In another embodiment is provided a medicament for treating autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated
25 diseases which comprises a compound of formula (I) wherein said medicament is used in combination with one, two, three, or four other therapeutic agents.

It will be appreciated that the particular method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend
30 on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

35 The weight ratio of the compound according to the present invention and the one or more other therapeutic agent(s) when given as a combination may be determined by the person

skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other therapeutic agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of formula (I) and another therapeutic agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

In one embodiment the pharmaceutical composition comprises a compound of formula (I) together with a pharmaceutically acceptable carrier and optionally one or more therapeutic agent(s).

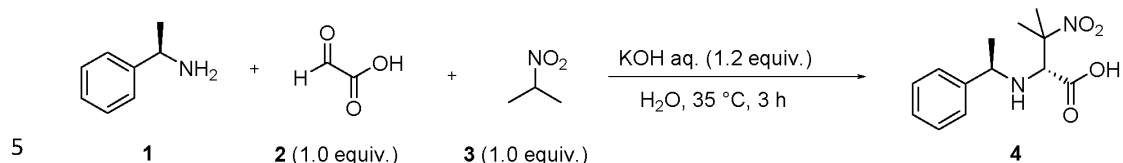
In another embodiment the invention relates to the use of a combination according to the invention in the manufacture of a pharmaceutical composition for preventing or treating autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated diseases.

In a further embodiment the invention relates to a product containing a compound of formula (I) and one or more additional therapeutic agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated diseases.

Examples of suitable additional therapeutic agents include: methotrexate, corticosteroids like prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, cortisone and the like; mycophenolate mofetil, tacrolimus, leflunomide or teriflunomide, cyclosporine A, cyclophosphamide, mitoxanthrone, fingolimod, azathioprine, glatiramer acetate, dimethyl fumarate, an IK-1 inhibitor like TRAM-34, a JAK-inhibitor like Tofacitinib or braticinip, a SYK-inhibitor like Fostamatinib, interferon-beta (IFN- β).

EXAMPLES

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

Synthesis of (2S)-3-methyl-3-nitro-2-[(1'S)-1'-phenylethyl]amino}butanoic acid (4)¹

2-Nitropropane (**3**, 3.7 mL, 40 mol, 1.0 equiv) and water (40 mL) were placed under argon in a 500 mL flask with a stir bar, potassium hydroxide (2.7 g, 48 mmol, and 1.2 equiv) was added all at once. The flask was placed in a regulated oil bath heated to 45 °C. (S)-(-)- α -Methybenzylamine (**1**, 4.8 g, 40 mmol) was added quickly. The reaction mixture was maintained at ca. 45 °C and stirred swiftly as glyoxylic acid (**2**, 50% aq, 3.7 g, 40 mmol, 1.0 equiv.) was added slowly dropwise (60 min, slowest for the last one-third) via a syringe. The reaction mixture became cloudy, then clear, and when the solid began forming again the addition was slowed down. After completion of the addition, the reaction was stirred for an additional 3 h under argon at 35 °C, and stirred swiftly as 3M aq hydrochloric acid (30.4 mL, 92 mmol) was added dropwise (over 30 min). The resulting thick off-white suspension was stirred for overnight at room temperature. The cooled suspension was filtered with suction filtration, and the filter cake was rinsed with diluted aqueous HCl, water and diethyl ether. The solid in the filter cake was dried by suction, and then dried under high vacuum for 3 h at 50 °C to get a slightly off-white power (5.4 g).

20

Purification of 3-methyl-3-nitro-(2S)-(1 (S)-phenylethyl-amino))-butyric acid (4)¹

3M HCl, water and acetic acid was placed in an Erlenmyer flask and stirred well as it as immersed in a 60°C bath and warmed to 40-50°C. When the solution was up to the temperature, dissolved **4** in the stirred warm DMSO solution (50 °C, dry, 40 mL) and added 25 mL of acetic acid to form a clear solution, then added the warm DMSO solution to the Erlenmeyer at an even dropwise rat. The suspension was then filtered through paper by suction and ethyl ether. The filter cake was then suction to compact "dryness" over 30 min. The solids then transferred to room temperature and dried under full vacuum for 12 hours.

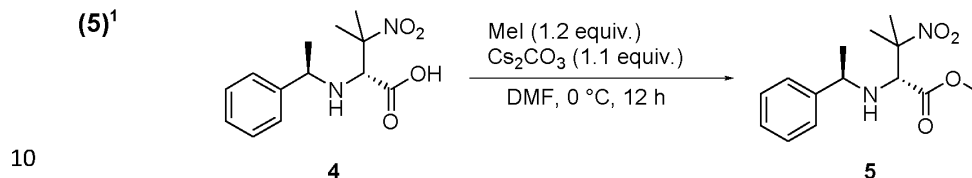
Second purification of 3-methyl-3-nitro-(2S)-(1 (S)-phenylethyl-amino))-butyric acid (4) (Procedure is similar to the first precipitation above)¹

A solution of diluted aq hydrochloric acid, water and acetic acid was placed in a 1 L Erlenmeyer flask and stirred well as it was immersed in a 45-60°C bath and warmed to 40 °C. Another flask, to a solution of the **4** in anhydrous DMSO (40 mL) was added acetic acid. The mixture was then warmed to 50°C and added dropwise to the Erlenmeyer flask. Upon complete addition, the suspension was stirred and placed in a 0 °C bath to cool room temperature. The suspension was then filtered through paper by suction and rinsed with dilute aq hydrochloric

acid, water, isopropanol and diethyl ether. The filter cake was then suctioned to compact "dryness" over 30 min. The filtered was then transferred to room temperature vacuum and dried under full vacuum for 14 hours. After that, the solids was dried at 50 °C under high vacuum for 3 hours to yield **4** as white powder (1.4 g, 13.2% yield).

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Synthesis of methyl (2S)-3-methyl-3-nitro-2-[[[1 'S)-1 '-phenylethyl]amino]butanoate (5)¹

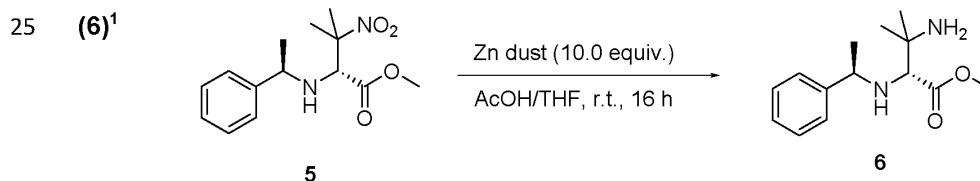


In an oven-dried 100 mL flask with a stir bar was charged with **4** (1.4 g, 5.3 mmol) and cesium carbonate (1.8 g, 5.6 mmol, 1.1 equiv) under argon with rapid string. Dimethylformamide (10 mL) was added rapidly and stirred for 10 min, with aid of sonication for 5 min. After the reaction mixture was cooled to 0°C, iodomethane (378.7 uL, 6.1 mmol, 1.2 equiv) was added dropwise over 15 min. The reaction mixture was stirred under argon and at 0 °C for 1 h then was allowed to warm to ambient temperature with stirring was continued for 12 h. The reaction was washed with EtOAc and water into a separatory funnel containing EtOAc, water and 3.0 M aq hydrochloric acid. The organic layer was separated. And the aqueous layer was adjusted pH to 7-8 and extracted with EtOAc. The combined organic phases were washed with 3% Li₂SO₄, half-saturated aq NaHCO₃ and brine and dried over anhydrous Na₂SO₄. The solvent was concentrated to give amber oil (1.5 g, quant.). The obtained **5** was used without further purification.

15

20

Synthesis of methyl (2S)-3-amino-3-methyl-2-[[[1 'S)-1 '-phenylethyl]amino]butanoate (6)¹



5 (1.5 g, 5.3 mmol) was dissolved in anhydrous THF (10 mL) and glacial acetic acid (12 mL) along with activated powdered molecular sieves 4A (1.8 g), and stirred mildly for 3 h under argon. The flask was then immersed in 0 °C bath and stirred well for 20 min. To the cold reaction mixture was added zinc dust (3.1 g, 52.9 mmol, 10.0 equiv). The mixture reaction was stirred at 0 °C for 2 h, and then allowed warm to ambient temperature with stirring continued for 16 h. The mixture was then diluted with THF and filtered through a celite pad with additional THF washing. The solution was rotary evaporated to yield a slightly yellow oily solid. This material was dissolved in 3:1 chloroform/ isopropanol and EDTA solutions at pH 10.5-11.0. Additional 4M NaOH solutions are added in portions to reach pH=10.5-11.0. The funnel

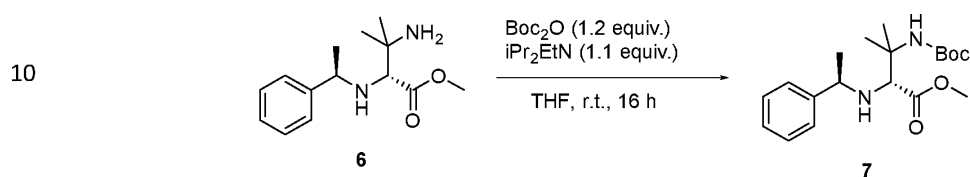
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contents were thoroughly shaken, and the aqueous phase separated. The organic phase was then washed with EDTA pH=10.5-11.0, brine, dried over Na₂SO₄, filtered and evaporated under reduced pressure, followed with additional heptane and evaporation to yield a light-amber oil. The obtained **6** was used without further purification.

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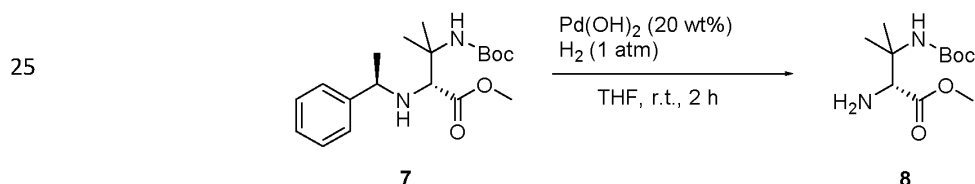
Synthesis of methyl(2S)-3-[[[(tert-butoxy)carbonyl]amino]-3-methyl-2-[[[(1'S)-1'-phenylethyl]amino]butanoate (7**)¹**



6 (5.3 mmol) was dissolved in anhydrous THF (10 mL) under argon, and diisopropylethylamine (1.0 mL, 5.8 mmol, 1.1 equiv) was added to this solution. tert-Butylpyrocarbonate (1.3 g, 5.9 mmol, 1.2 equiv) was added. After stirring at room temperature for 16 h, the reaction mixture was dissolved in EtOAc, and washed with water containing 1 eq HCl, half saturated NaHCO₃ solution, 14% NH₄OH, brine, dried over Na₂SO₄, filtered and contracted under reduced pressure to yield the BOC-diamino-ester residue, which was purified by CombiFlash (eluting with EtOAc in DCM 0-5%) to afford it as viscous oil (940.3 mg, 51% yield(3 steps)).

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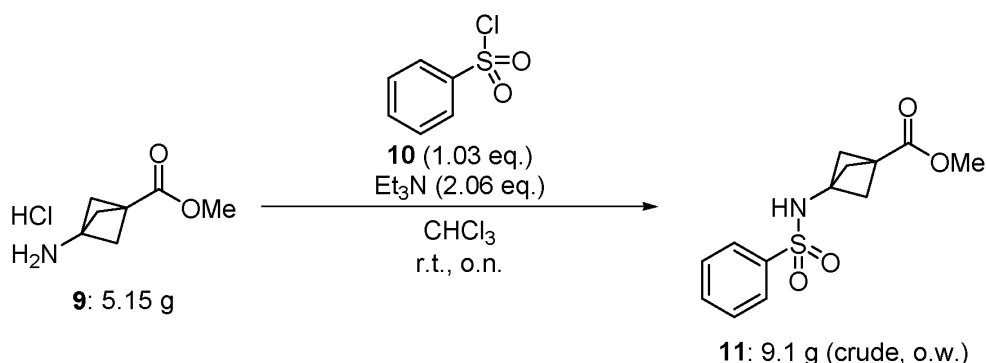
Synthesis of methyl (2S)-2-amino-3-[[[(tert-butoxy)carbonyl]amino]-3-methylbutanoate (8**)¹**



7 (0.6 g, 1.7 mmol) was dissolved in anhydrous THF (10 mL) in 50 mL flask and placed under argon. Palladium hydroxide catalyst (0.12 g, 20 wt%) was rapidly weight and added to the flask. The flask was then filled with hydrogen and refilled. After 2 h, LC/MS showed the reaction was completed. The mixture was filtered through a celite pad, and the filtrate was condensed to dryness. The residue was purified by CombiFlash (eluting with 0-5% MeOH in DCM) to afford **8** as white solid (451.7 mg, quant.)

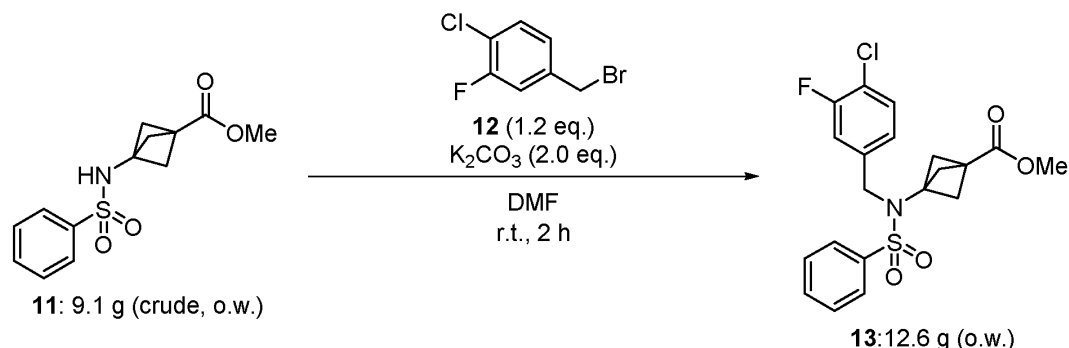
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Synthesis of methyl 3-(phenylsulfonamido)bicyclo[1.1.1]pentane-1-carboxylate (11**)**



To a stirred solution of methyl 3-aminobicyclo[1.1.1]pentane-1-carboxylate hydrochloride (9, 5.15 g) and Et₃N (8.36 mL, 2.06 eq.) in CHCl₃ (60 mL), phenylsulfonyl chloride (10, 5.30 g, 1.03 eq.) was added at 0 °C. The reaction mixture was stirred and warmed to ambient temperature for over night. After the reaction completion was checked by TLC, H₂O and 1N HCl was added to the reaction mixture, and the aqueous phase was extracted twice with AcOEt. The combined extract was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give methyl 3-(phenylsulfonamido)bicyclo[1.1.1]pentane-1-carboxylate (11, 9.07 g, , overweight). The obtained 2 was used without further purification.

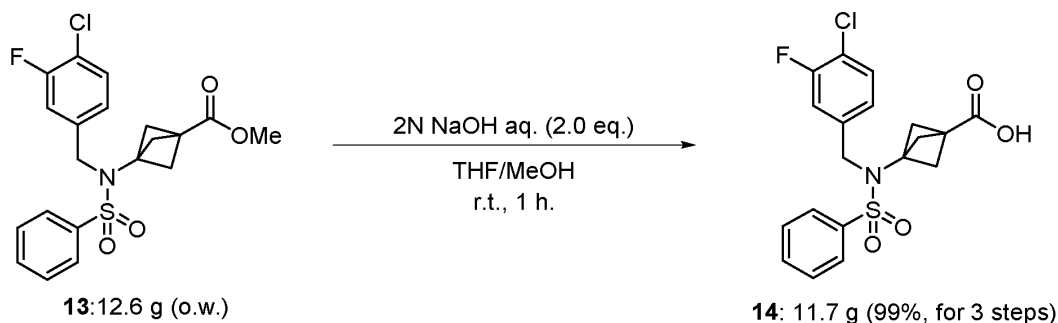
Synthesis of methyl 3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentane-1-carboxylate (13)



To a stirred solution of methyl 3-(phenylsulfonamido)bicyclo[1.1.1]pentane-1-carboxylate (11, 9.07 g) and 4-(bromomethyl)-1-chloro-2-fluorobenzene (12, 7.8 g, 1.2 eq.) in DMF (20 mL), K₂CO₃ (8.3 g, 2. eq.) was added at room temperature. The reaction mixture was stirred for 2 hours. After the reaction completion was checked by TLC, H₂O and 1N HCl was added to the reaction mixture, and the aqueous phase was extracted twice with AcOEt. The combined extract was washed twice with diluted HCl aq. and brine. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give crude product. The crude product was purified by column chromatography on silica-gel (eluent: *n*-hexane/ethyl

acetate) to give the 3-(N-(4-chloro-3-fluorobenzyl) phenylsulfonamido)bicyclo[1.1.1]pentane-1-carboxylate (**13**, 12.65 g, , overweight).

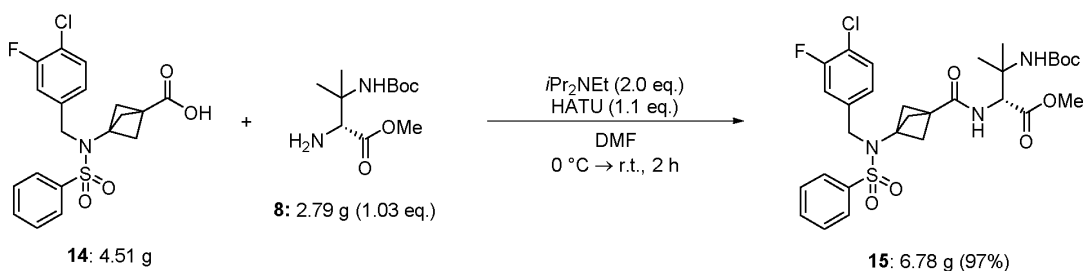
Synthesis of 3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentane-1-carboxylic acid (14)



To a stirred solution of 3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo [1.1.1]pentane-1-carboxylate (**13**, 12.65 g) in THF and MeOH (1 : 1, 60 mL), 2N NaOH aq. (60 mL, 2.0 eq.) was added at room temperature. The reaction mixture was stirred for 1

hour. After the reaction completion was checked by TLC, the reaction mixture was concentrated in vacuo, then 1N HCl aq. was added, and the aqueous phase was extracted twice with AcOEt. The combined extract was washed with brine. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give 3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentane-1-carboxylic acid (**14**, 11.75 g, 99% for 3 steps from **1**). The obtained **14** was used without further purification.

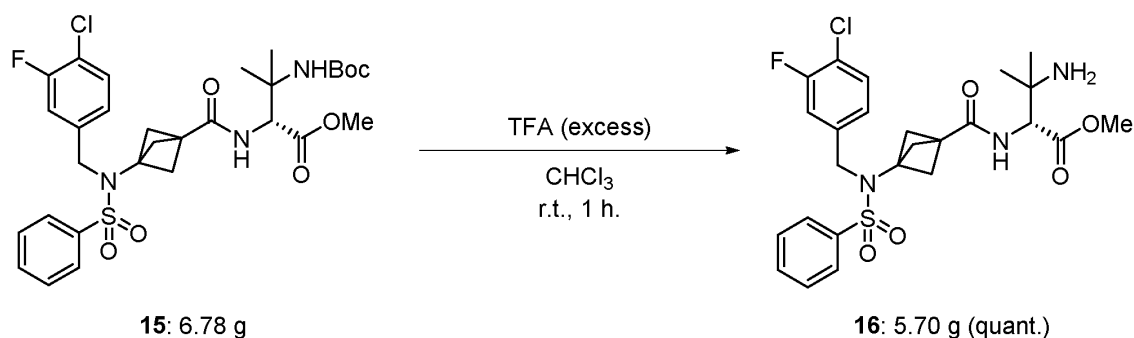
Synthesis of methyl (R)-3-((tert-butoxycarbonyl)amino)-2-(3-(N-(4-chloro-3-fluorobenzyl)phenyl)sulfonamido) bicyclo[1.1.1]pentane-1-carboxamido)-3-methylbutanoate (15)



To a stirred solution of 3-(N-(4-chloro-3-fluorobenzyl)phenyl)sulfonamido bicyclo[1.1.1]pentane-1-carboxylic acid (**14**, 4.5 g), methyl (R)-2-amino-3-((tert-butoxycarbonyl)amino)-3-methylbutanoate (**8**, 2.8 g, 1.03 eq.) and *i*Pr₂NEt (3.83 mL, 2.0 eq.) in DMF (20 mL), HATU (4.6 g, 1.1 eq.) was added at at 0 °C. The reaction mixture was stirred and warmed to ambient temperature for 2 hours. After the reaction completion was

checked by TLC, H₂O and 1N HCl was added to the reaction mixture, and the aqueous phase was extracted twice with AcOEt. The combined extract was washed twice with H₂O and brine. The combined extract was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give crude product. The crude product was purified by column chromatography on silica-gel (eluent: *n*-hexane/ethyl acetate) to give the methyl(R)-3-((tert-butoxycarbonyl)amino)-2-(3-(N-(4-chloro-3-fluorobenzyl)phenyl)sulfonamido)bicyclo[1.1.1]pentane-1-carboxamido)-3-methylbutanoate (**15**, 6.78 g, 97%). The obtained **6** was used without further purification.

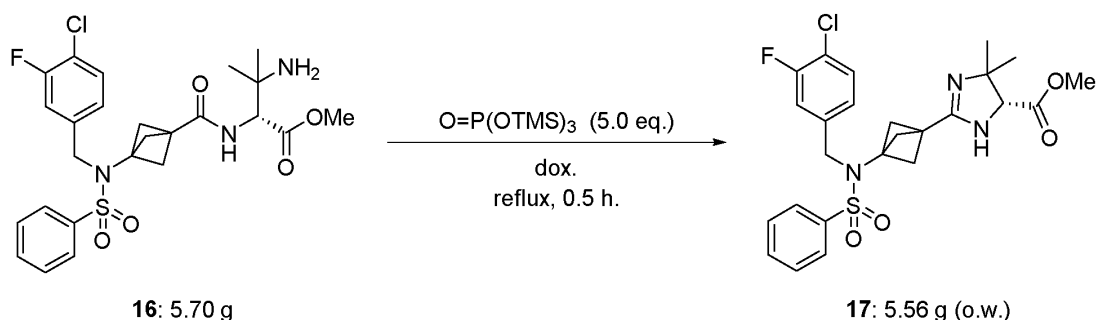
10 **Synthesis of methyl (R)-3-amino-2-(3-(N-(4-chloro-3-fluorobenzyl)phenyl)sulfonamido)bicyclo[1.1.1]pentane -1-carboxamido)-3-methylbutanoate (16)**



15 To a stirred solution of methyl (R)-3-((tert-butoxycarbonyl)amino)-2-(3-(N-(4-chloro- 3-
fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentane-1-carboxamido)-3-methylbutanoate
(**15**, 6.78 g) in CHCl₃ (20 mL), TFA (20 mL) was added at room temperature. The reaction
mixture was stirred for 1 hour. After the reaction completion was checked by TLC, the
reaction mixture was concentrated in vacuo, then sat. NaHCO₃ aq. was carefully added, and
20 the aqueous phase was extracted twice with AcOEt. The combined extract was washed with
brine. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in
vacuo to give methyl (R)-3-amino-2-(3-(N-(4-chloro-3-
fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentane-1-carboxamido)-3-methylbutanoate
(**7**, 5.70 g, quant.). The obtained **16** was used without further purification.

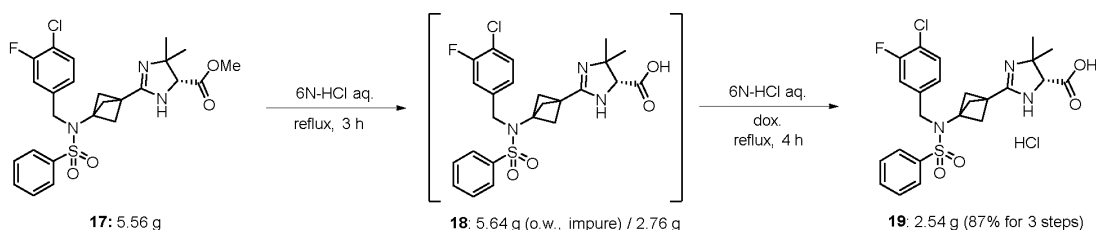
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Synthesis of methyl (R)-2-(3-(N-(4-chloro-3-fluorobenzyl)phenyl)sulfonamido)bicyclo[1.1.1]pentan-1-yl)-4,4- dimethyl-4,5-dihydro-1H-imidazole-5-carboxylate (17)



To a stirred solution of methyl (R)-2-(3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentan-1-carboxamido)-3-methylbutanoate (**16**, 5.70 g) in dioxane (100 mL), tris(trimethylsilyl) phosphate (17.4 mL, 5.0 eq.) was added at room temperature. The reaction mixture was refluxed for 30 min. After the reaction completion was checked by TLC, the reaction mixture was cooled to ambient temperature, then sat. NaHCO₃ aq. was carefully added at 0 °C, and the aqueous phase was extracted twice with AcOEt. The combined extract was washed with sat. NaHCO₃ aq. and brine. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give methyl (R)-2-(3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl-4,5-dihydro-1H-imidazole-5-carboxylate (**17**, 5.56 g, overweight). The obtained **17** was used without further purification.

Synthesis of (R)-2-(3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl-4,5-dihydro-1H-imidazole-5-carboxylic acid hydrochloride (19**)**



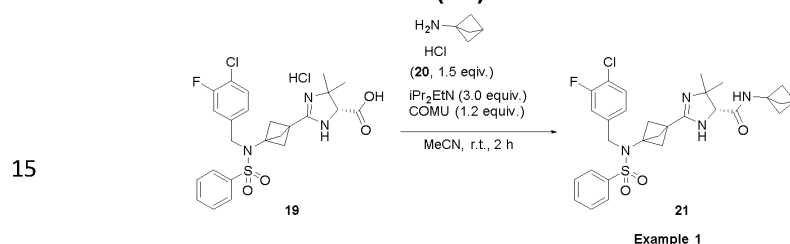
The stirred solution of methyl (R)-2-(3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl-4,5-dihydro-1H-imidazole-5-carboxylate (**17**, 5.56 g) in 6N HCl aq. (15 mL) was refluxed for 3 hours. After the reaction completion was checked by TLC, the reaction mixture was cooled to ambient temperature, then NaHCO₃ (7.56 g) was carefully added at 0 °C, and the aqueous phase was extracted twice with THF. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give crude product (**18**, 5.64 g, overweight) which contained small amount of **17**. The stirred solution of the same portion of obtained mixture (2.76 g) was in 6N HCl aq. (10 mL) and dioxane (10 mL) was refluxed for 4 hours. After the reaction completion was checked by LC-MS, the

reaction mixture was cooled to ambient temperature, the reaction mixture was concentrated in vacuo, then H₂O was added, and the aqueous phase was extracted twice with AcOEt. The combined extract was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo, then slurried by Et₂O to give (R)-2-(3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)

- 5 bicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl-4,5-dihydro-1H-imidazole-5-carboxylic acid (**19**, 2.54 g, 87% for 3 steps from **15**)

Example 1

- (R)-N-(Bicyclo[1.1.1]pentan-1-yl)-2-(3-(N-(4-chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl-4,5-dihydro-1H-imidazole-5-carboxamide (**E1**)



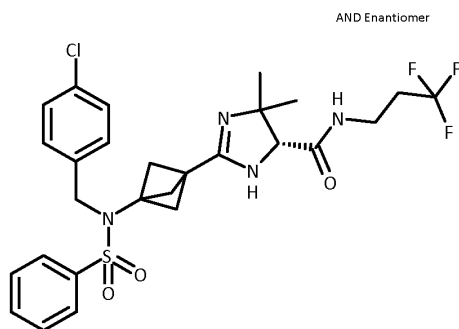
- (R)-2-(3-(N-(4-Chloro-3-fluorobenzyl)phenylsulfonamido)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethyl-4,5-dihydro-1H-imidazole-5-carboxylic acid hydrochloride (**19**, 500 mg, 0.92 mmol) was dissolved in MeCN, and DIEA (357.4 mg, 2.8 mmol, 3.0 equiv), bicyclo[1.1.1]pentan-3-amine hydrochloride (**20**, 165.3 mg, 1.4 mmol, 1.5 equiv), and COMU (473.7 mg, 1.1 mmol, 1.2 equiv) were added thereto. After stirring at room temperature for 2 h, the solvent was removed under reduced pressure and the residue was purified by preparative TLC (CHCl₃:MeOH = 9:1 (v/v)) to give **21** as white solid (198.0 mg, 37%).

25 MS: M/z Observed (m+H) 572.

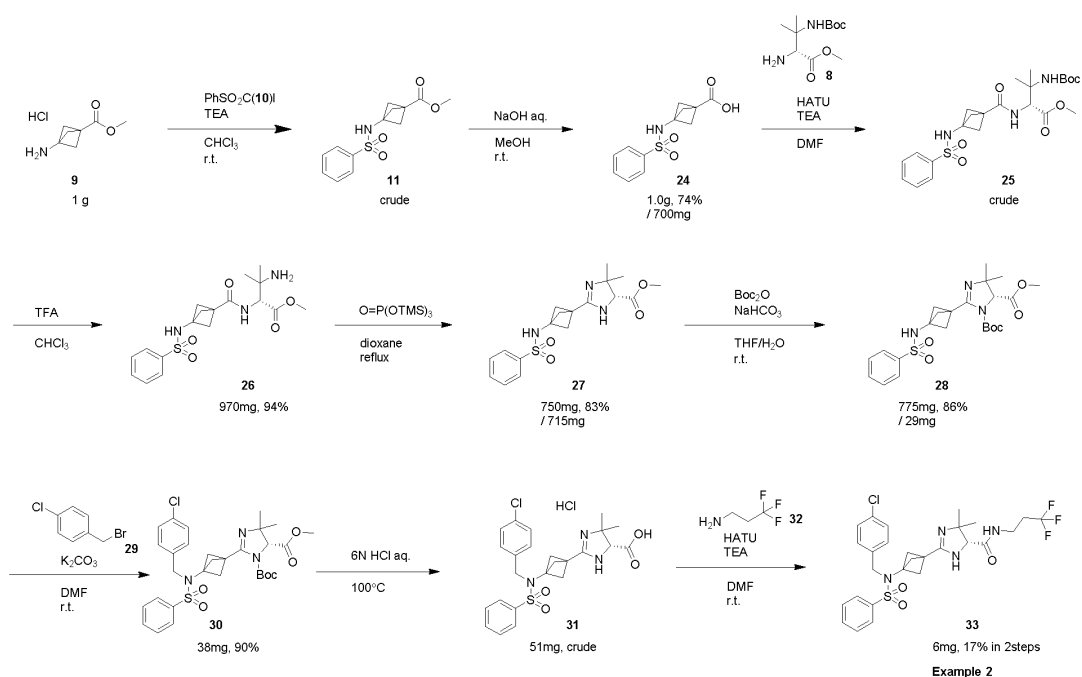
NMR: ¹H NMR (400 MHz, Methanol-*d*₄) δ 1.01 (s, 3H), 1.28 (s, 3H), 2.03 – 2.09 (m, 12H), 2.40 (s, 1H), 3.77 (s, 1H), 4.54 (s, 2H), 7.22 – 7.27 (m, 1H), 7.31 (dd, *J* = 10.2, 2.0 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.58 – 7.65 (m, 2H), 7.66 – 7.73 (m, 1H), 7.87 – 7.93 (m, 2H).

30

Example 2 (E2)

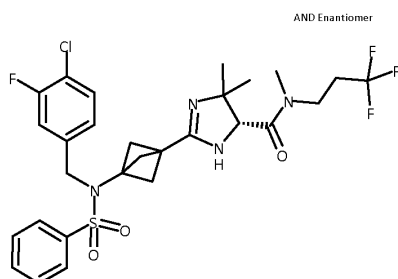


The compound of Example 2 was prepared in an analogous manner to the procedure described hereinbefore for Example 1 in accordance with the following Scheme:

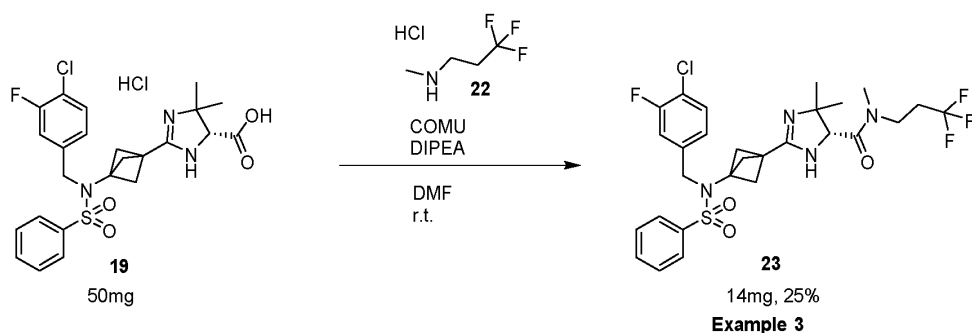


- 5 MS: M/z Observed (m+H) 584.

Example 3 (E3)



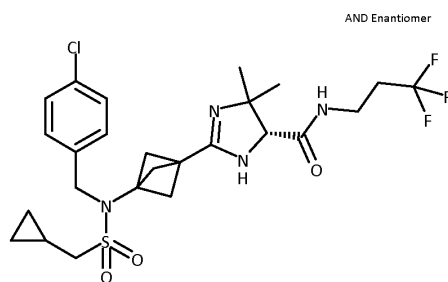
The compound of Example 3 was prepared in an analogous manner to the procedure described hereinbefore for Example 1 in accordance with the following Scheme:



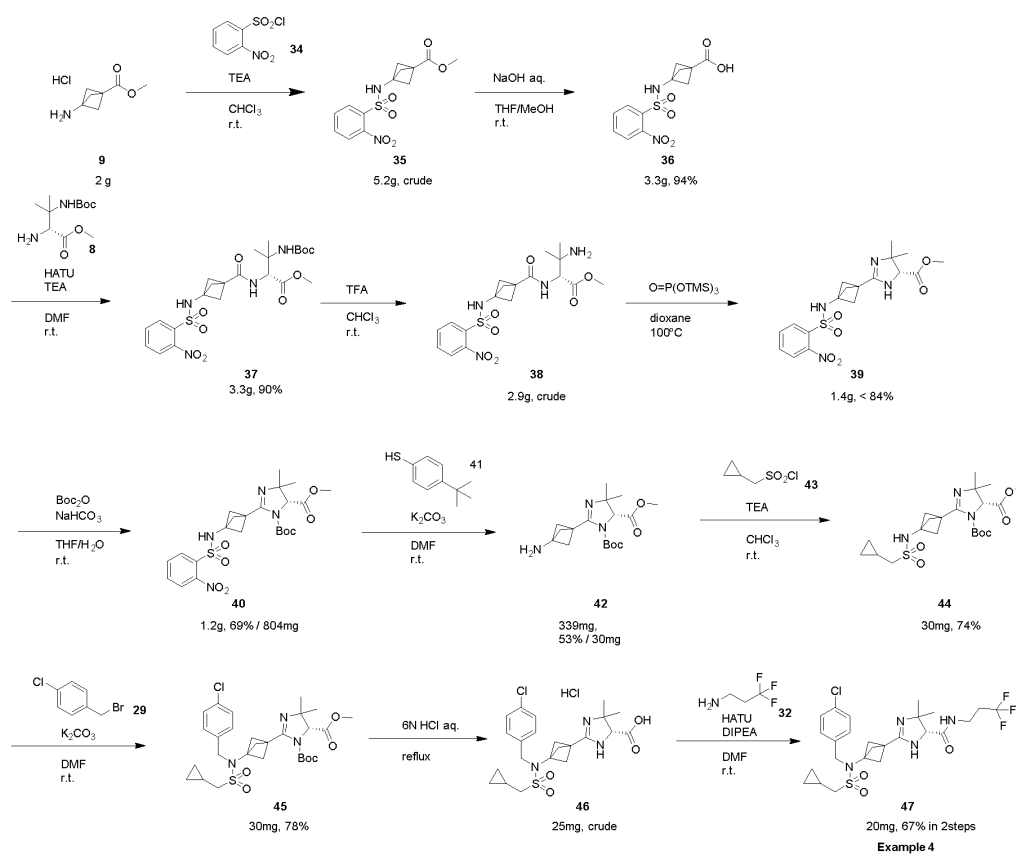
MS: M/z Observed (m+H) 616.

5

Example 4 (E4)

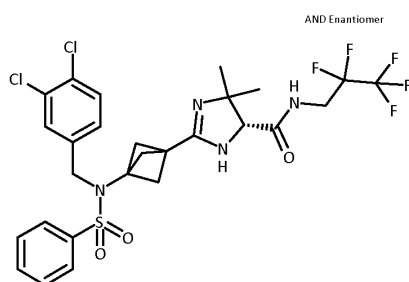


The compound of Example 4 was prepared in an analogous manner to the procedure described hereinbefore for Example 1 in accordance with the following Scheme:



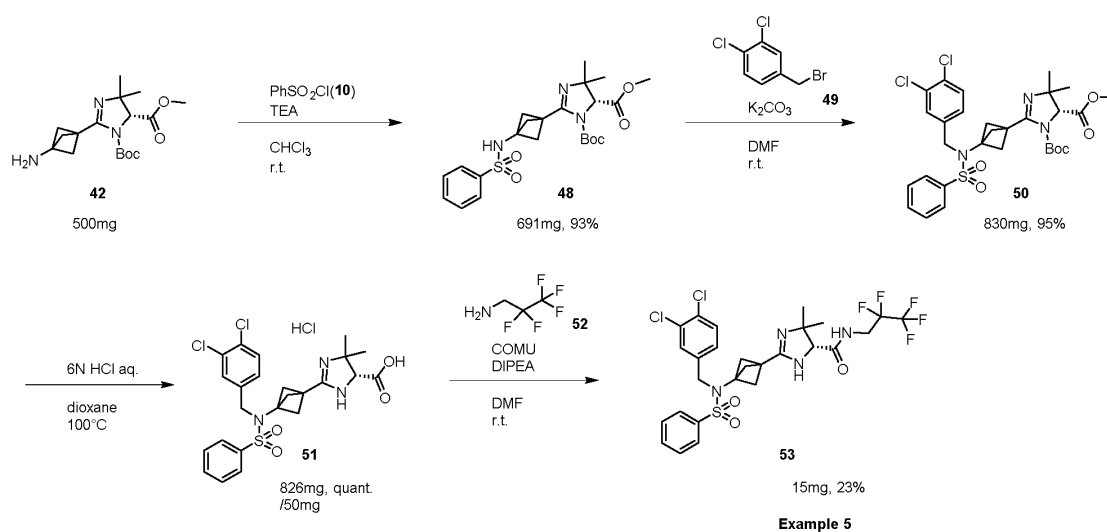
MS: M/z Observed (m+H) 562.

Example 5 (E5)



5

The compound of Example 5 was prepared in an analogous manner to the procedure described hereinbefore for Example 1 in accordance with the following Scheme:



MS: M/z Observed (m+H) 654.

Examples 6 to 295

- 5 The compounds of Examples 6 to 295 were prepared in an analogous manner to the procedure described hereinbefore for Example 1:

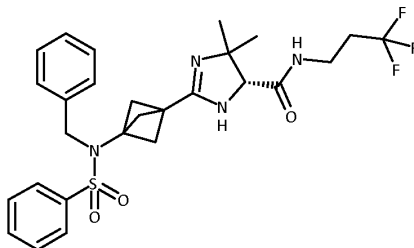
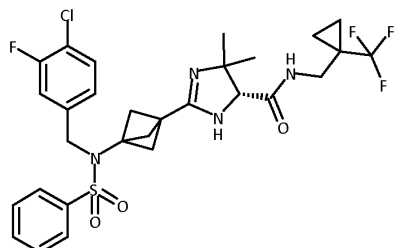
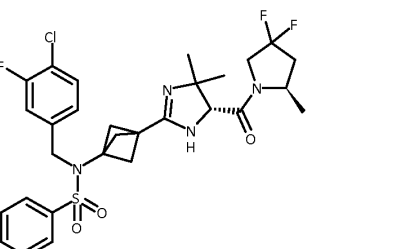
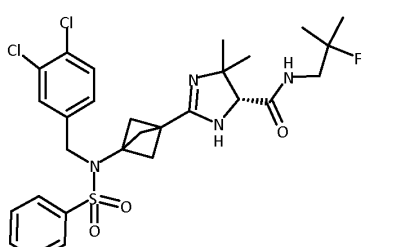
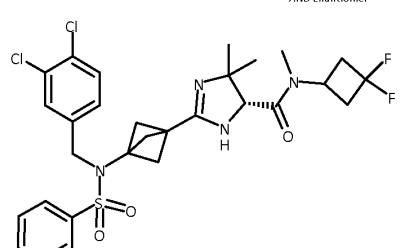
Example Number	Structure	Characterising Data
6	AND Enantiomer	MS: M/z Observed (m+H) 578
7	AND Enantiomer	MS: M/z Observed 550

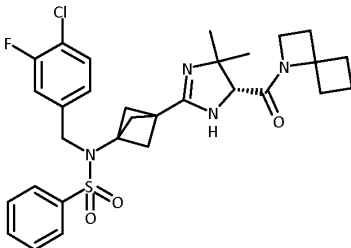
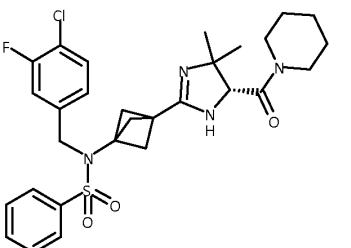
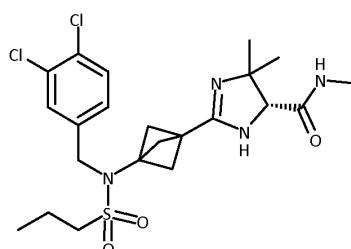
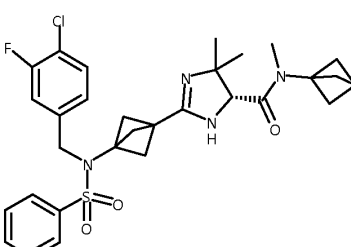
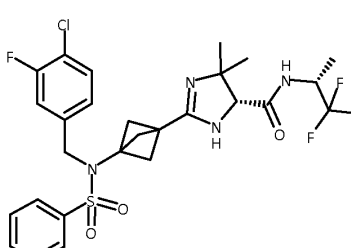
8	AND Enantiomer MS: M/z Observed 574
9	AND Enantiomer MS: M/z Observed 602
10	AND Enantiomer MS: M/z Observed 564
11	AND Enantiomer MS: M/z Observed 596

12	AND Enantiomer MS: M/z Observed 554	
13	AND Enantiomer MS: M/z Observed 602	
14	AND Enantiomer MS: M/z Observed 596	
15	AND Enantiomer MS: M/z Observed 584	

16	AND Enantiomer MS: M/z Observed 584	
17	AND Enantiomer MS: M/z Observed 602	
18	AND Enantiomer MS: M/z Observed 590	
19	AND Enantiomer MS: M/z Observed 548	

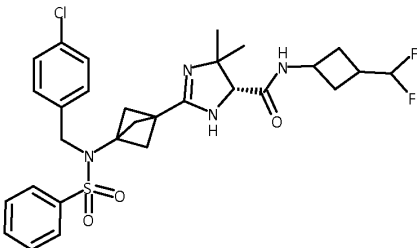
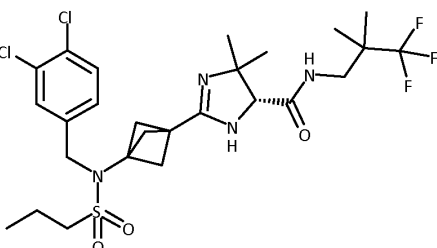
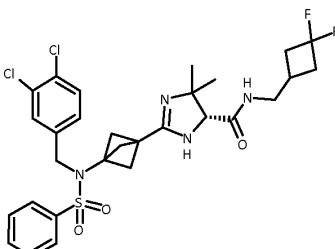
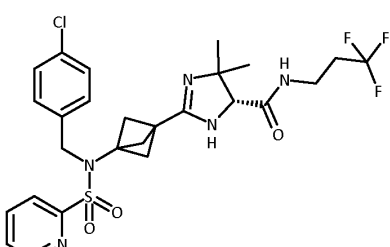
20	AND Enantiomer	MS: M/z Observed 574
21	AND Enantiomer	MS: M/z Observed 574
22	AND Enantiomer	MS: M/z Observed 596
23	AND Enantiomer	MS: M/z Observed 567
24	AND Enantiomer	MS: M/z Observed 585

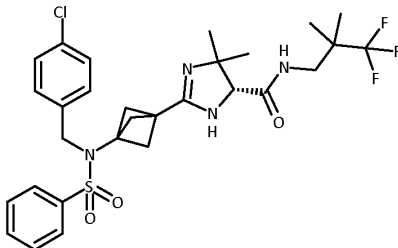
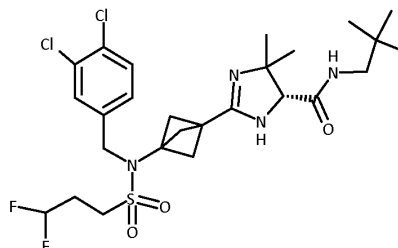
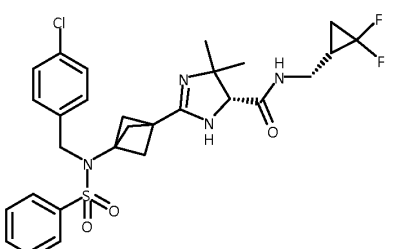
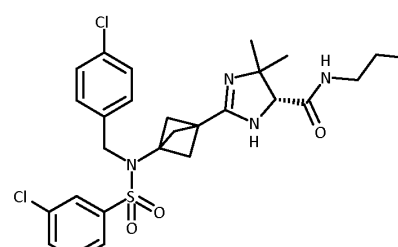
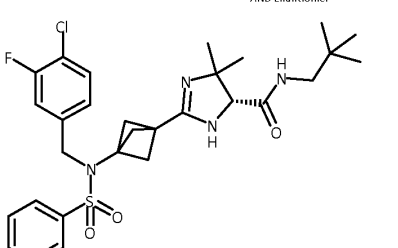
25	AND Enantiomer  MS: M/z Observed 549	
26	AND Enantiomer  MS: M/z Observed 628	
27	AND Enantiomer  MS: M/z Observed 610	
28	AND Enantiomer  MS: M/z Observed 596	
29	AND Enantiomer  MS: M/z Observed 626	

30	AND Enantiomer  MS: M/z Observed 586
31	AND Enantiomer  MS: M/z Observed 574
32	AND Enantiomer  MS: M/z Observed 554
33	AND Enantiomer  MS: M/z Observed 586
34	AND Enantiomer  MS: M/z Observed 602

35	AND Enantiomer MS: M/z Observed 580	
36	AND Enantiomer MS: M/z Observed 592	
37	AND Enantiomer MS: M/z Observed 592	
38	AND Enantiomer MS: M/z Observed 624	
39	AND Enantiomer MS: M/z Observed 578	

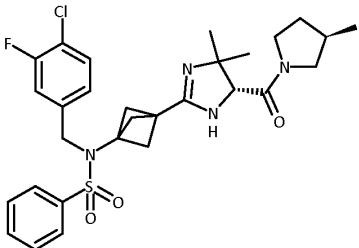
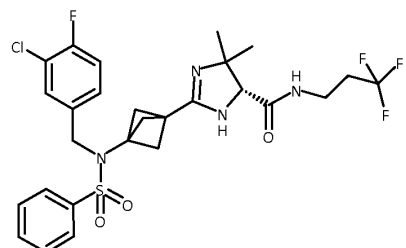
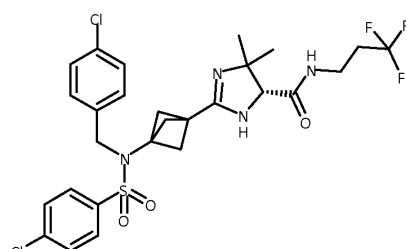
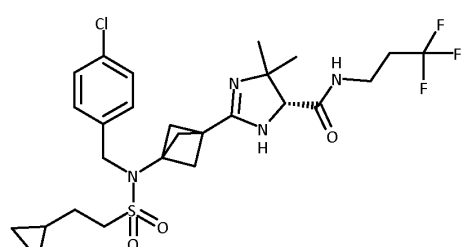
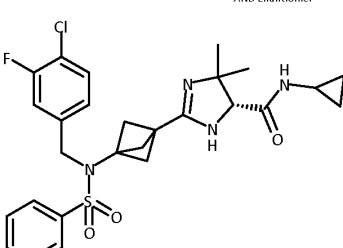
40	AND Enantiomer MS: M/z Observed 567
41	AND Enantiomer MS: M/z Observed 574
42	AND Enantiomer MS: M/z Observed 590
43	AND Enantiomer MS: M/z Observed 577
44	AND Enantiomer MS: M/z Observed 610

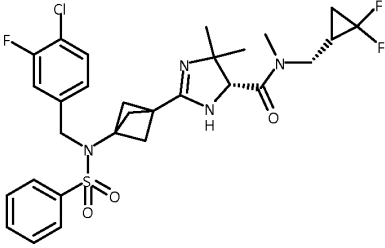
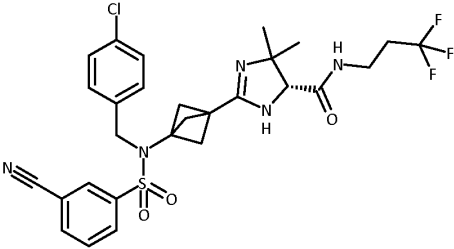
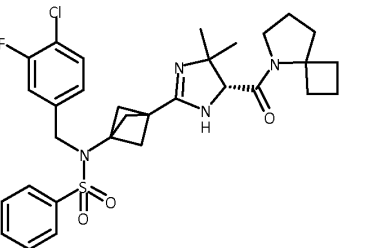
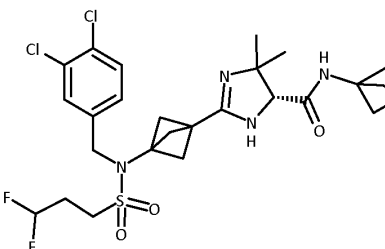
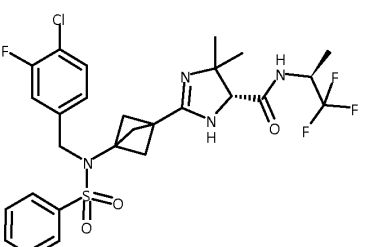
45	AND Enantiomer  MS: M/z Observed 592	
46	AND Enantiomer  MS: M/z Observed 612	
47	AND Enantiomer  MS: M/z Observed 626	
48	AND Enantiomer  MS: M/z Observed 585 NMR: ¹H-NMR (400 MHz, CHLOROFORM-D) δ 1.00 (s, 3H), 1.25 (s, 1H), 1.45 (s, 3H), 2.07 (s, 6H), 2.22-2.43 (m, 2H), 3.35-3.49 (m, 1H), 3.50-3.62 (m, 1H), 4.02 (s, 1H), 4.65 (s, 2H), 7.29-7.42 (m, 4H), 7.52 (ddd, J = 7.4, 4.7, 1.0 Hz, 1H), 7.93 (td, J = 7.8, 1.8 Hz, 1H), 7.97-8.05 (m, 1H), 8.67-8.76 (m, 1H)	

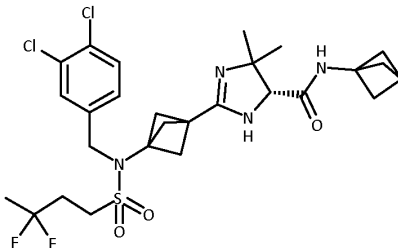
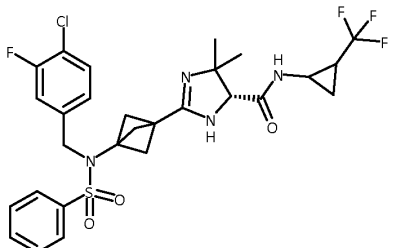
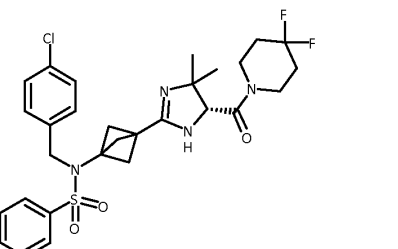
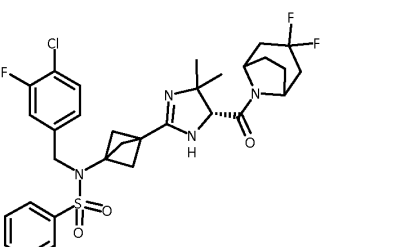
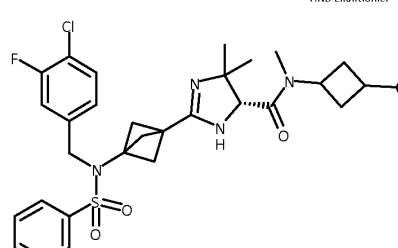
49	AND Enantiomer  MS: M/z Observed 612
50	AND Enantiomer  MS: M/z Observed 598
51	AND Enantiomer  MS: M/z Observed 578
52	AND Enantiomer  MS: M/z Observed 618
53	AND Enantiomer  MS: M/z Observed 576

54	AND Enantiomer MS: M/z Observed 564
55	AND Enantiomer MS: M/z Observed 582
56	AND Enantiomer MS: M/z Observed 560
57	AND Enantiomer MS: M/z Observed 586
58	AND Enantiomer MS: M/z Observed 610

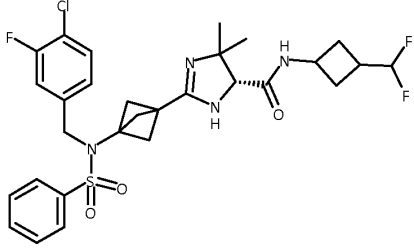
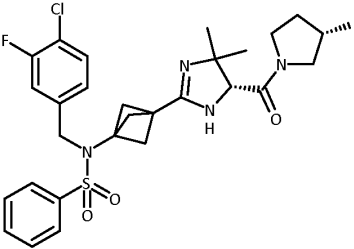
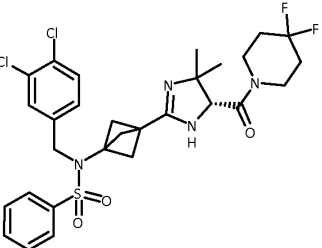
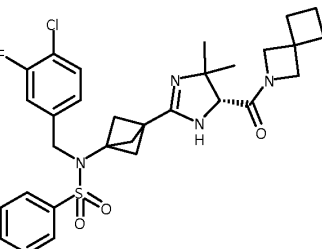
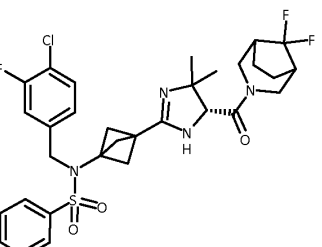
59	AND Enantiomer MS: M/z Observed 602	
60	AND Enantiomer MS: M/z Observed 560	
61	AND Enantiomer MS: M/z Observed 632	
62	AND Enantiomer MS: M/z Observed 618	
63	AND Enantiomer MS: M/z Observed 610	

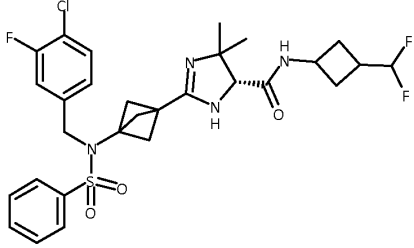
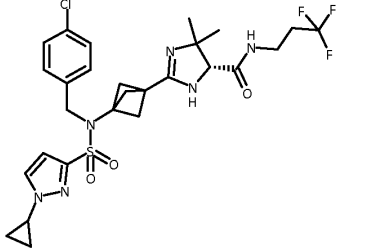
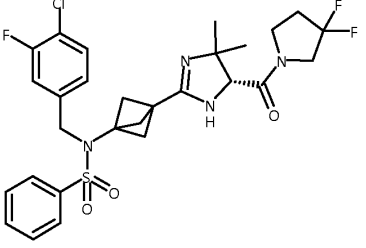
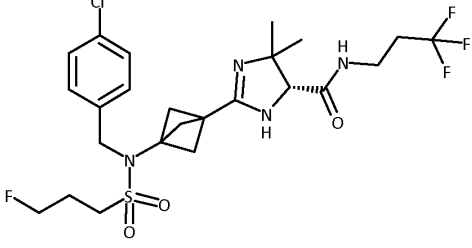
64	AND Enantiomer  MS: M/z Observed 574
65	AND Enantiomer  MS: M/z Observed 602
66	AND Enantiomer  MS: M/z Observed 618
67	AND Enantiomer  MS: M/z Observed 576
68	AND Enantiomer  MS: M/z Observed 546

69	AND Enantiomer 	MS: M/z Observed 610
70	AND Enantiomer 	MS: M/z Observed 609
71	AND Enantiomer 	MS: M/z Observed 600
72	AND Enantiomer 	MS: M/z Observed 590
73	AND Enantiomer 	MS: M/z Observed 602

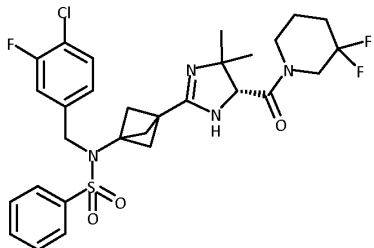
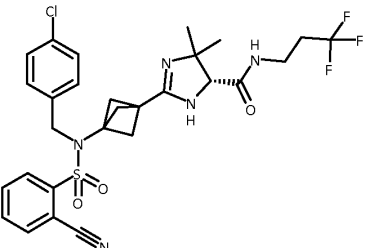
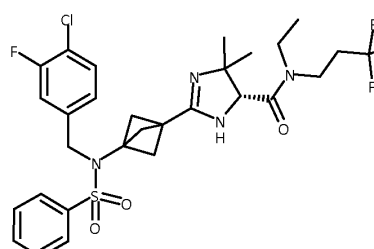
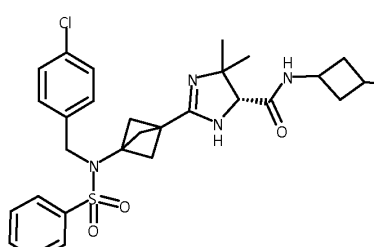
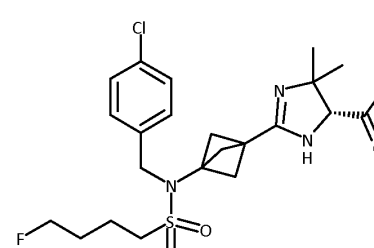
74	AND Enantiomer  MS: M/z Observed 604
75	AND Enantiomer  MS: M/z Observed 614
76	AND Enantiomer  MS: M/z Observed 592
77	AND Enantiomer  MS: M/z Observed 636
78	AND Enantiomer  MS: M/z Observed 624

79	AND Enantiomer MS: M/z Observed 584
80	AND Enantiomer MS: M/z Observed 578
81	AND Enantiomer MS: M/z Observed 572
82	AND Enantiomer MS: M/z Observed 636
83	AND Enantiomer MS: M/z Observed 610

84	AND Enantiomer 	MS: M/z Observed 610
85	AND Enantiomer 	MS: M/z Observed 574
86	AND Enantiomer 	MS: M/z Observed 626
87	AND Enantiomer 	MS: M/z Observed 586
88	AND Enantiomer 	MS: M/z Observed 636

89	AND Enantiomer 	MS: M/z Observed 610
90	AND Enantiomer 	MS: M/z Observed 614
91	AND Enantiomer 	MS: M/z Observed 596
92	AND Enantiomer 	MS: M/z Observed 568 NMR: ¹H-NMR (400 MHz, CHLOROFORM-D) δ 1.03 (s, 3H), 1.25 (s, 1H), 1.48 (s, 3H), 2.12-2.48 (m, 10H), 3.15 (t, J = 7.6 Hz, 2H), 3.36-3.52 (m, 1H), 3.52-3.66 (m, 1H), 4.05 (s, 1H), 4.45 (s, 2H), 4.52 (t, J = 5.5 Hz, 1H), 4.64 (t, J = 5.5 Hz, 1H), 7.15 (br s, 1H), 7.28-7.36 (m, 4H)

93	AND Enantiomer MS: M/z Observed 600	
94	AND Enantiomer MS: M/z Observed 622	
95	AND Enantiomer MS: M/z Observed 594	
96	AND Enantiomer MS: M/z Observed 592	
97	MS: M/z Observed 567	

98	AND Enantiomer  MS: M/z Observed 610
99	AND Enantiomer  MS: M/z Observed 609
100	AND Enantiomer  MS: M/z Observed 630
101	AND Enantiomer  MS: M/z Observed 592
102	AND Enantiomer  MS: M/z Observed 582

103	AND Enantiomer MS: M/z Observed 614	
104	AND Enantiomer MS: M/z Observed 624	
105	AND Enantiomer MS: M/z Observed 576	
106	AND Enantiomer MS: M/z Observed 594	
107	AND Enantiomer MS: M/z Observed 618	

108	AND Enantiomer MS: M/z Observed 616
109	AND Enantiomer MS: M/z Observed 600
110	AND Enantiomer MS: M/z Observed 585
111	AND Enantiomer MS: M/z Observed 618
112	AND Enantiomer MS: M/z Observed 620

113	AND Enantiomer MS: M/z Observed 640	
114	AND Enantiomer MS: M/z Observed 596	
115	AND Enantiomer MS: M/z Observed 612	
116	AND Enantiomer MS: M/z Observed 652	
117	AND Enantiomer MS: M/z Observed 648	

118	AND Enantiomer MS: M/z Observed 628
119	AND Enantiomer MS: M/z Observed 642
120	AND Enantiomer MS: M/z Observed 640
121	AND Enantiomer MS: M/z Observed 576
122	AND Enantiomer MS: M/z Observed 599

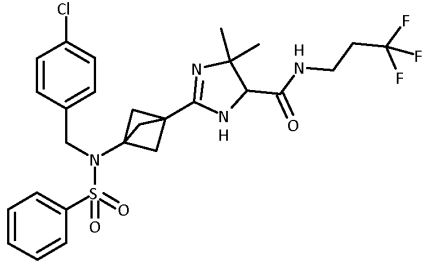
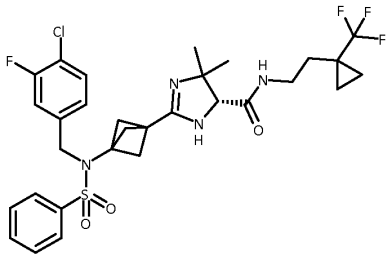
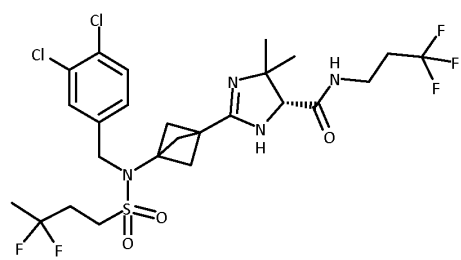
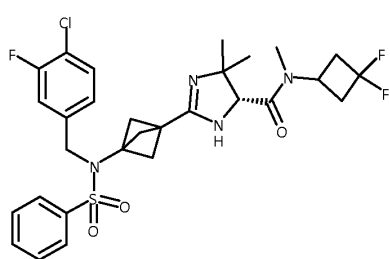
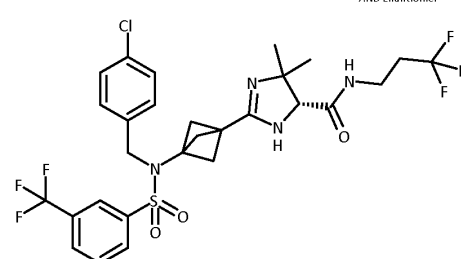
123	AND Enantiomer MS: M/z Observed 610
124	AND Enantiomer MS: M/z Observed 592
125	AND Enantiomer MS: M/z Observed 628
126	AND Enantiomer MS: M/z Observed 638
127	AND Enantiomer MS: M/z Observed 592

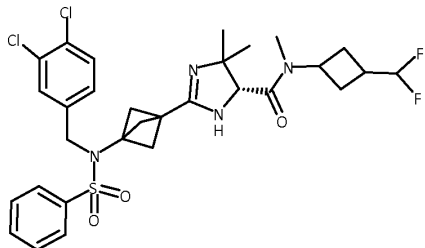
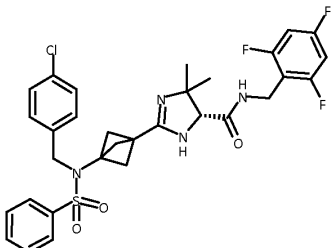
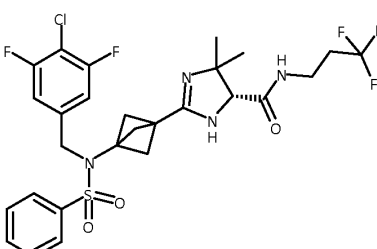
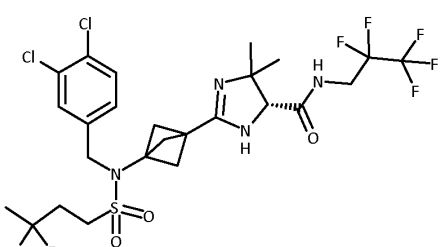
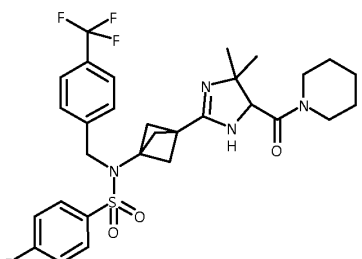
128	AND Enantiomer MS: M/z Observed 602
129	AND Enantiomer MS: M/z Observed 622
130	AND Enantiomer MS: M/z Observed 624
131	AND Enantiomer MS: M/z Observed 624
132	AND Enantiomer MS: M/z Observed 610

133	AND Enantiomer MS: M/z Observed 624	
134	AND Enantiomer MS: M/z Observed 638	
135	AND Enantiomer MS: M/z Observed 610	
136	AND Enantiomer MS: M/z Observed 584	
137	AND Enantiomer MS: M/z Observed 586	

138	AND Enantiomer MS: M/z Observed 617	
139	AND Enantiomer MS: M/z Observed 578	
140	AND Enantiomer MS: M/z Observed 588	
141	AND Enantiomer MS: M/z Observed 630	
142	AND Enantiomer MS: M/z Observed 638	

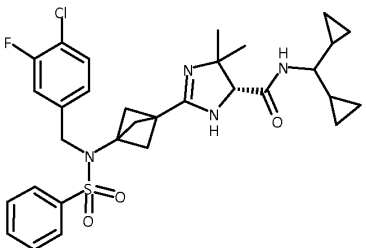
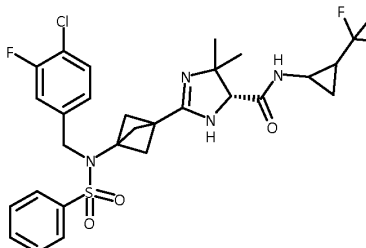
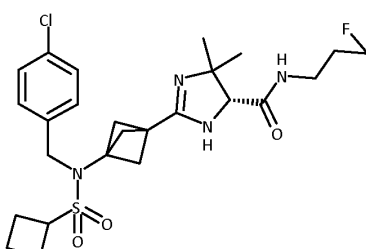
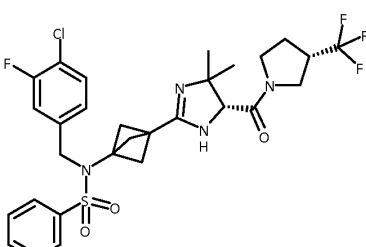
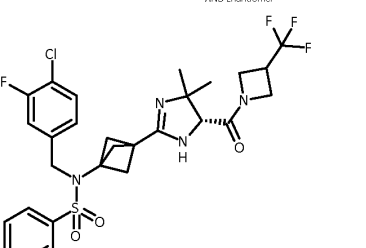
143	AND Enantiomer MS: M/z Observed 610
144	AND Enantiomer MS: M/z Observed 636
145	MS: M/z Observed 625
146	AND Enantiomer MS: M/z Observed 602
147	AND Enantiomer MS: M/z Observed 632

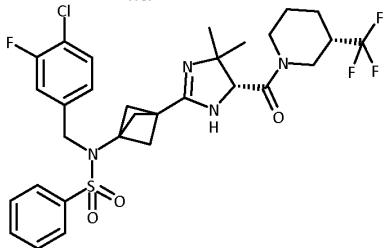
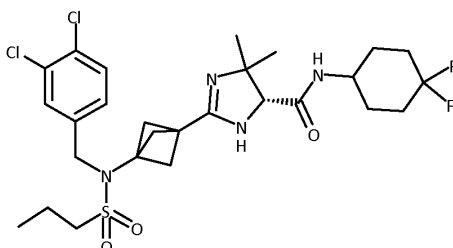
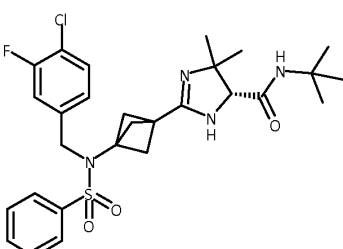
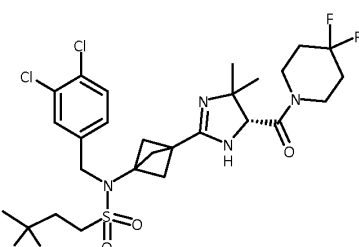
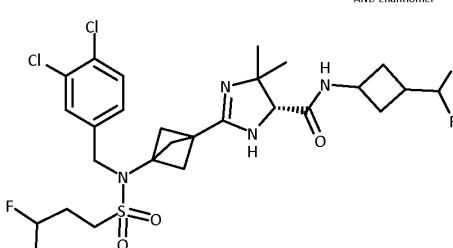
148		MS: M/z Observed 584
149	AND Enantiomer 	MS: M/z Observed 642
150	AND Enantiomer 	MS: M/z Observed 634
151	AND Enantiomer 	MS: M/z Observed 610
152	AND Enantiomer 	MS: M/z Observed 652

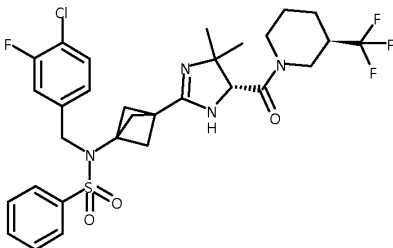
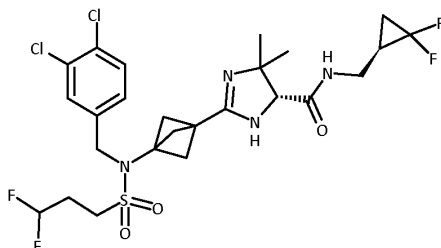
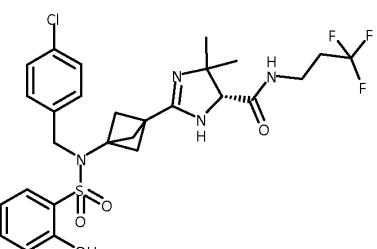
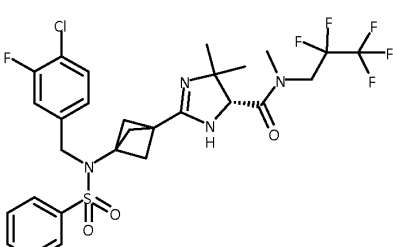
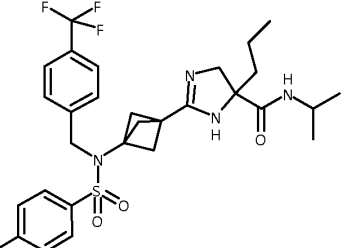
153	AND Enantiomer  MS: M/z Observed 640
154	AND Enantiomer  MS: M/z Observed 632
155	AND Enantiomer  MS: M/z Observed 620
156	AND Enantiomer  MS: M/z Observed 670
157	 MS: M/z Observed 607

158	AND Enantiomer MS: M/z Observed 642
159	AND Enantiomer MS: M/z Observed 612
160	AND Enantiomer MS: M/z Observed 630
161	MS: M/z Observed 629
162	AND Enantiomer MS: M/z Observed 642

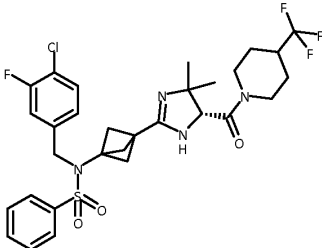
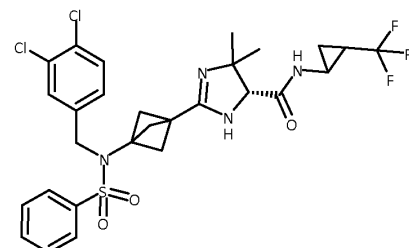
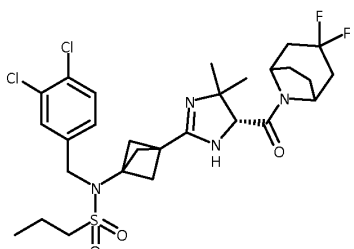
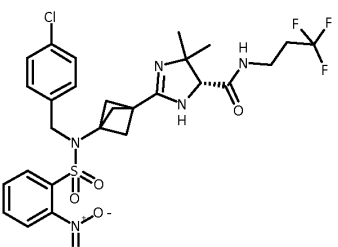
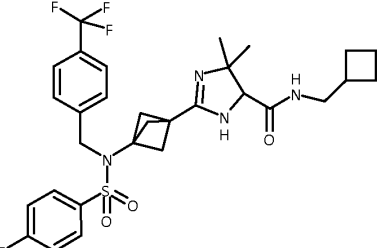
163	AND Enantiomer MS: M/z Observed 630
164	MS: M/z Observed 632
165	AND Enantiomer MS: M/z Observed 620
166	AND Enantiomer MS: M/z Observed 636
167	AND Enantiomer MS: M/z Observed 652

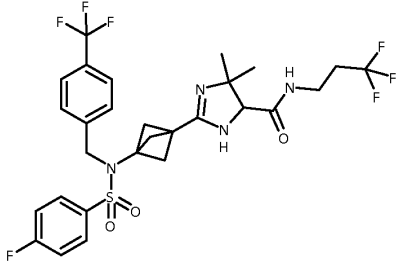
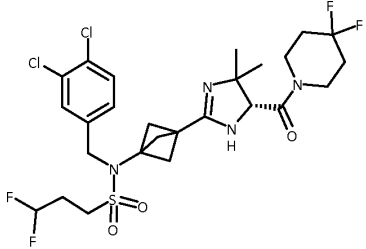
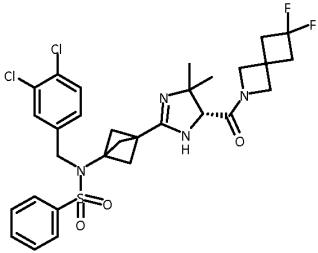
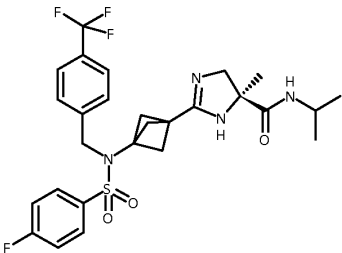
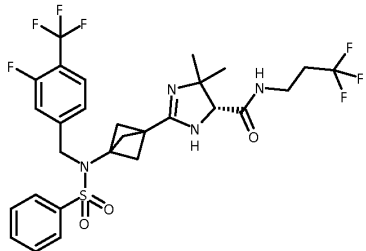
168	AND Enantiomer  MS: M/z Observed 600
169	AND Enantiomer  MS: M/z Observed 614
170	AND Enantiomer  MS: M/z Observed 562
171	AND Enantiomer  MS: M/z Observed 628
172	AND Enantiomer  MS: M/z Observed 614

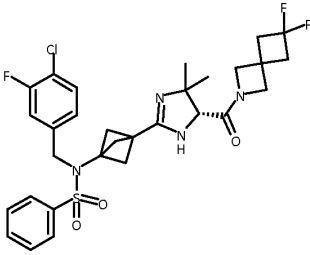
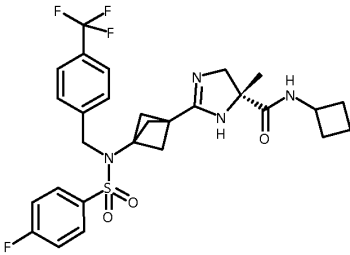
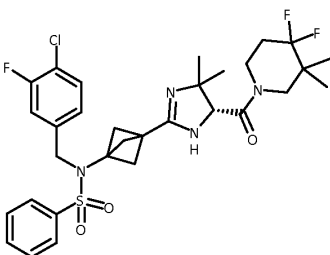
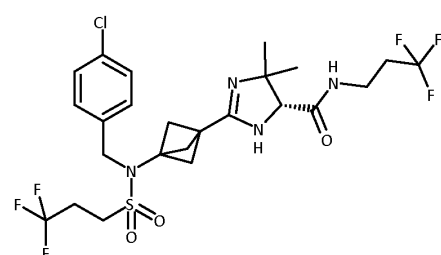
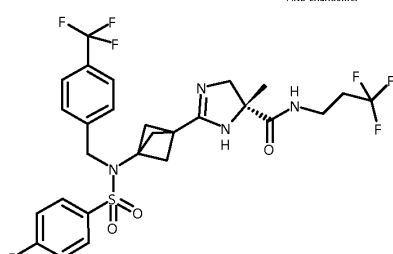
173	HCl AND Enantiomer 	MS: M/z Observed 678
174	AND Enantiomer 	MS: M/z Observed 606
175	AND Enantiomer 	MS: M/z Observed 562
176	AND Enantiomer 	MS: M/z Observed 642
177	AND Enantiomer 	MS: M/z Observed 628

178	AND Enantiomer  MS: M/z Observed 642
179	AND Enantiomer  MS: M/z Observed 614
180	AND Enantiomer  MS: M/z Observed 600
181	AND Enantiomer  MS: M/z Observed 652
182	 MS: M/z Observed 595

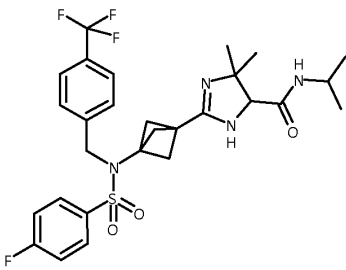
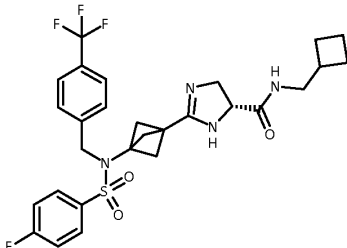
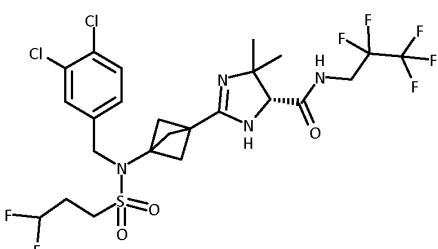
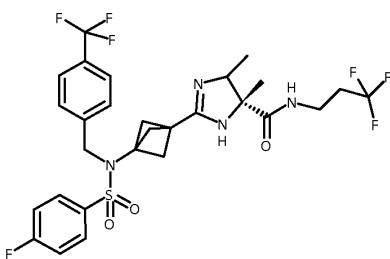
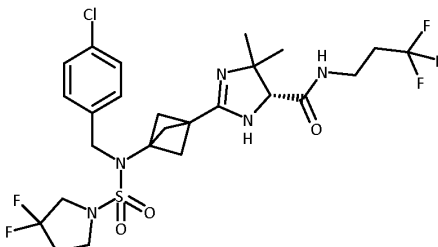
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184	AND Enantiomer MS: M/z Observed 607	
185	AND Enantiomer MS: M/z Observed 560	
186	MS: M/z Observed 643	
187	AND Enantiomer MS: M/z Observed 618	

188	AND Enantiomer 	MS: M/z Observed 642
189	AND Enantiomer 	MS: M/z Observed 630
190	AND Enantiomer 	MS: M/z Observed 618
191	AND Enantiomer 	MS: M/z Observed 629
192		MS: M/z Observed 607

193		MS: M/z Observed 635
194	AND Enantiomer 	MS: M/z Observed 628
195	AND Enantiomer 	MS: M/z Observed 638
196	AND Enantiomer 	MS: M/z Observed 567
197	AND Enantiomer 	MS: M/z Observed 635

198	AND Enantiomer 	MS: M/z Observed 622
199	AND Enantiomer 	MS: M/z Observed 579
200	AND Enantiomer 	MS: M/z Observed 638
201	AND Enantiomer 	MS: M/z Observed 604
202	AND Enantiomer 	MS: M/z Observed 621

203	AND Enantiomer MS: M/z Observed 608
204	AND Enantiomer MS: M/z Observed 628
205	AND Enantiomer MS: M/z Observed 628
206	AND Enantiomer MS: M/z Observed 618
207	AND Enantiomer MS: M/z Observed 634

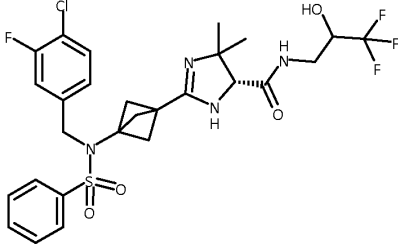
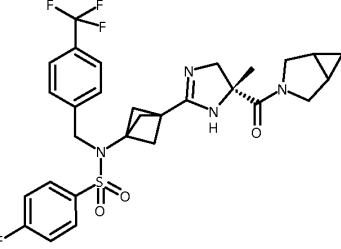
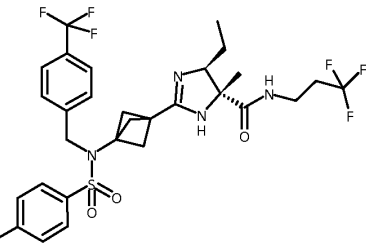
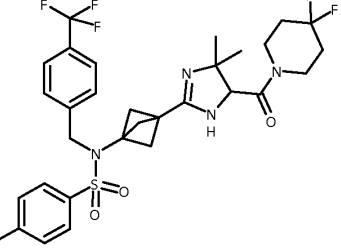
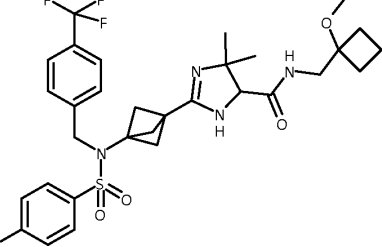
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209	AND Enantiomer 	MS: M/z Observed 579
210	AND Enantiomer 	MS: M/z Observed 656
211	AND Enantiomer 	MS: M/z Observed 635
212	AND Enantiomer 	MS: M/z Observed 613

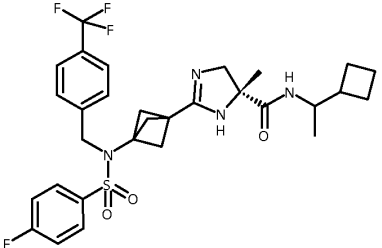
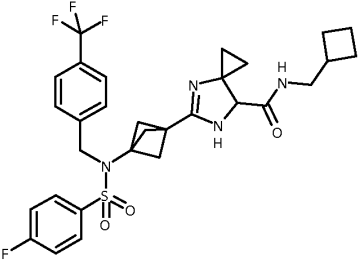
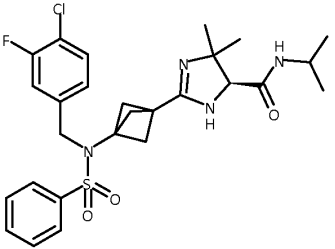
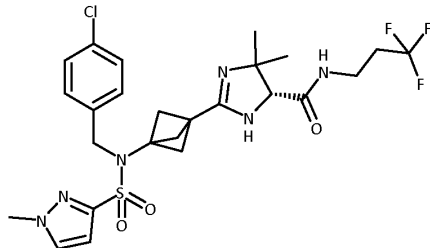
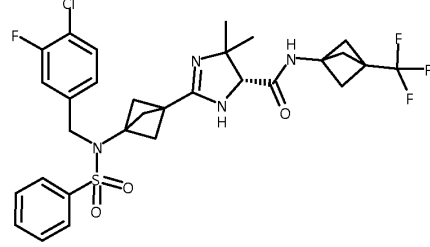
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216	AND Enantiomer MS: M/z Observed 598
217	AND Enantiomer MS: M/z Observed 635

218	AND Enantiomer MS: M/z Observed 579
219	AND Enantiomer MS: M/z Observed 598
220	MS: M/z Observed 617
221	AND Enantiomer MS: M/z Observed 652
222	AND Enantiomer MS: M/z Observed 654

223	AND Enantiomer MS: M/z Observed 609	
224	MS: M/z Observed 633	
225	AND Enantiomer MS: M/z Observed 618	
226	AND Enantiomer MS: M/z Observed 634	
227	AND Enantiomer MS: M/z Observed 629	

228	AND Enantiomer MS: M/z Observed 593
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232	MS: M/z Observed 607

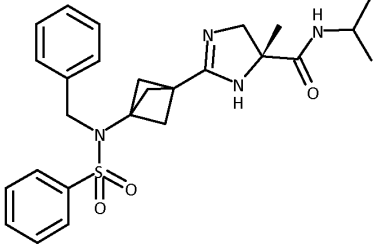
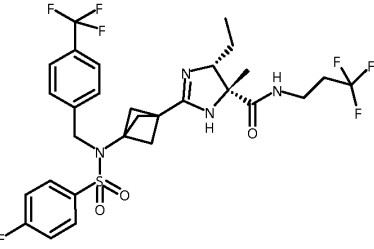
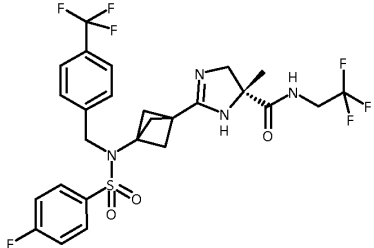
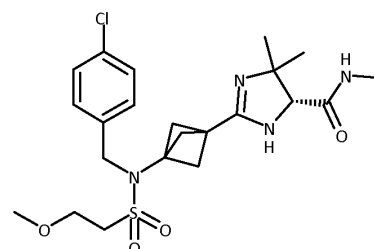
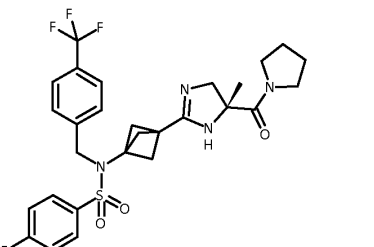
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234	AND Enantiomer 	MS: M/z Observed 591
235	AND Enantiomer HCl 	MS: M/z Observed 686
236		MS: M/z Observed 643
237		MS: M/z Observed 637

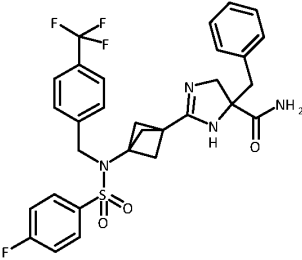
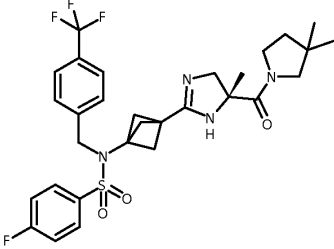
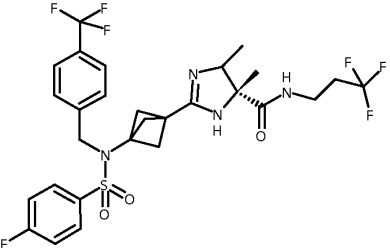
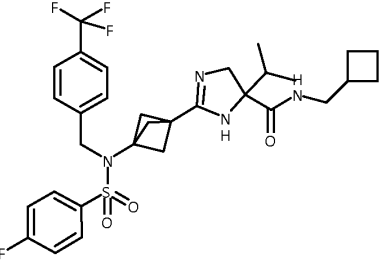
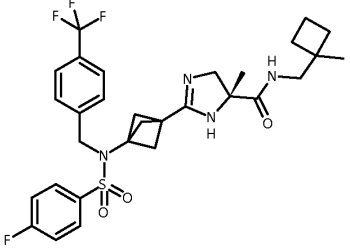
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239		MS: M/z Observed 605
240	AND Enantiomer 	MS: M/z Observed 548
241	AND Enantiomer 	MS: M/z Observed 588
242	AND Enantiomer 	MS: M/z Observed 640

243	AND Enantiomer MS: M/z Observed 499	
244	AND Enantiomer MS: M/z Observed 593	
245	AND Enantiomer MS: M/z Observed 607	
246	AND Enantiomer MS: M/z Observed 574	
247	AND Enantiomer MS: M/z Observed 593	

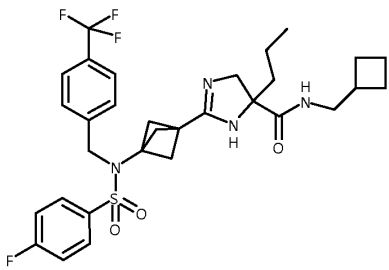
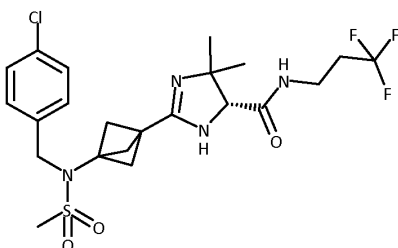
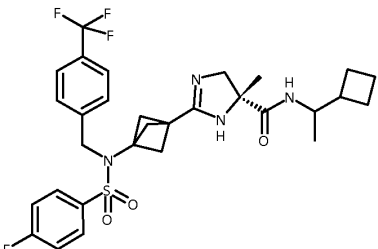
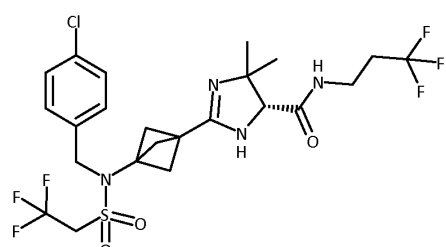
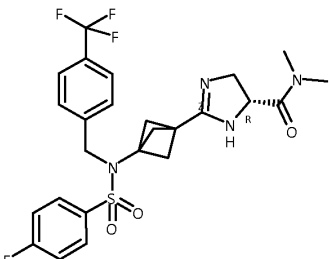
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249	AND Enantiomer MS: M/z Observed 622	
250	AND Enantiomer MS: M/z Observed 567	
251	AND Enantiomer MS: M/z Observed 635	
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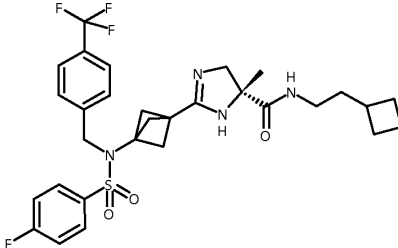
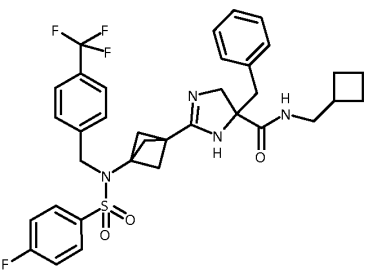
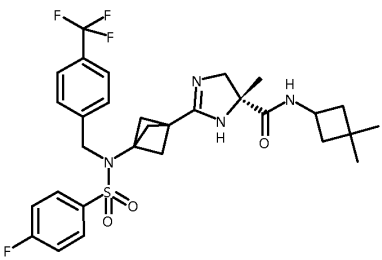
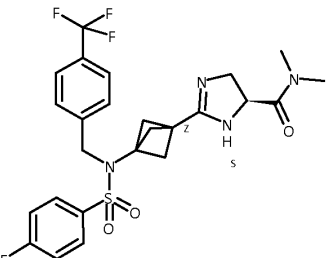
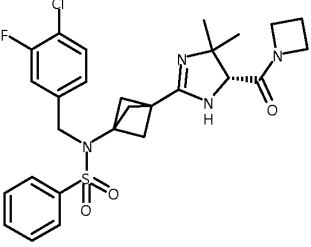
253	AND Enantiomer MS: M/z Observed 605
254	AND Enantiomer MS: M/z Observed 549
255	AND Enantiomer MS: M/z Observed 649
256	AND Enantiomer MS: M/z Observed 607
257	AND Enantiomer MS: M/z Observed 576

258	AND Enantiomer  MS: M/z Observed 481
259	AND Enantiomer HCl  MS: M/z Observed 686
260	AND Enantiomer  MS: M/z Observed 607
261	AND Enantiomer  MS: M/z Observed 566
262	AND Enantiomer  MS: M/z Observed 579

263		MS: M/z Observed 601
264	AND Enantiomer 	MS: M/z Observed 607
265	AND Enantiomer 	MS: M/z Observed 635
266		MS: M/z Observed 621
267	AND Enantiomer 	MS: M/z Observed 607

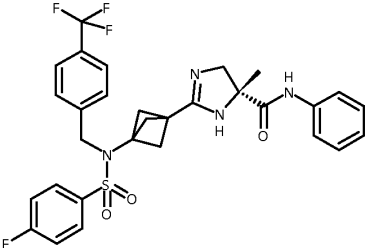
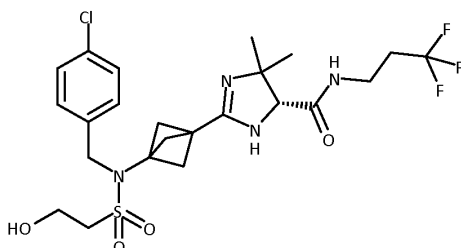
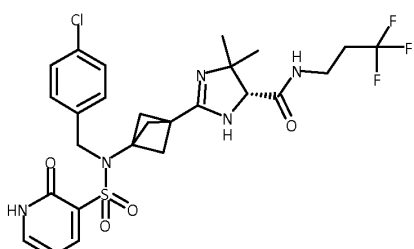
268	AND Enantiomer MS: M/z Observed 607
269	AND Enantiomer MS: M/z Observed 553
270	AND Enantiomer MS: M/z Observed 615
271	MS: M/z Observed 623
272	AND Enantiomer MS: M/z Observed 592

273		MS: M/z Observed 621
274	AND Enantiomer 	MS: M/z Observed 521
275	AND Enantiomer 	MS: M/z Observed 607
276	AND Enantiomer 	MS: M/z Observed 589
277		MS: M/z Observed 539

278	AND Enantiomer  MS: M/z Observed 607
279	 MS: M/z Observed 669
280	AND Enantiomer  MS: M/z Observed 607
281	 MS: M/z Observed 539
282	AND Enantiomer  MS: M/z Observed 546

283	AND Enantiomer MS: M/z Observed 618
284	MS: M/z Observed 635
285	AND Enantiomer MS: M/z Observed 621
286	AND Enantiomer MS: M/z Observed 668
287	AND Enantiomer MS: M/z Observed 564

288	AND Enantiomer MS: M/z Observed 601
289	AND Enantiomer MS: M/z Observed 621
290	AND Enantiomer MS: M/z Observed 621
291	AND Enantiomer MS: M/z Observed 574
292	AND Enantiomer MS: M/z Observed 627

293	AND Enantiomer 	MS: M/z Observed 601
294	AND Enantiomer 	MS: M/z Observed 552
295	AND Enantiomer 	MS: M/z Observed 601

BIOLOGICAL ASSAYS

K_v1.3 Potency evaluation

5 Electrophysiology recordings

A proprietary Chinese hamster ovary cell line stably expressing exogenous human α -subunits of K_v1.3 (CHO-K_v1.3) channel, validated biophysically and pharmacologically in house, was used to assess the ability of test compounds to block K_v1.3 currents using automated patch clamp electrophysiology. The QPatch HT system (Sophion Bioscience A/S, Denmark) was used with the conventional whole-cell configuration. This system is an automated, chip-based planar patch clamp device allowing for up to 48 parallel independent experiments in one experimental assay run. Cells are added to each well and drawn by suction onto a small aperture to obtain a Gigaohm seal between the cell membrane and treated silicon surface, and whole-cell recordings initiated after access is achieved by suction and/or voltage pulses. The QPatch HT uses static perfusion, whereby a small

volume of recording solution or drug is added to a reservoir on the chip and the solution perfuses across the cell through quartz-lined microfluidic channels; this solution is removed by capillary action when the next sample application is made.

- 5 CHO-K_v1.3 cells were prepared for experiments by dissociation from T175 cell culture flasks using trypsin-EDTA (0.05%), cells were kept in serum free media in the cell hotel on board the QPatch HT. These cells were sampled, washed and re-suspended in extracellular recording solution by the QPatch HT immediately before application to the recording well site on the chip. Experiments were performed using the following solutions; extracellular solution
10 contained (in mM); 150 NaCl, 10 KCl, 1 MgCl₂, 3 CaCl₂, 10 Glucose and 10 HEPES (pH 7.4, NaOH) and intracellular solution contained (in mM); 20 KCl, 120 KF, 10 HEPES, 10 EGTA, 5 ATP (pH 7.2, KOH,).

- The potency (Inhibitory Concentration 50%, IC₅₀) of synthesized compounds against K_v1.3
15 was determined from concentration-response relationships established by cumulatively applying four escalating concentrations of test compound to an individual cell and a minimum of N ≥ 3 individual cells of data per compound were used to generate the IC₅₀ value.

- 20 On achieving the whole-cell configuration; two additions of vehicle (0.1 – 0.3 % DMSO v/v) were applied to each cell in two bolus additions with a two minute recording period between each addition (four minutes total recording time). Following the vehicle period, four concentrations of test sample were applied as two bolus additions per test concentration at two minute intervals, and the effects on current measured during the four minute recording
25 period.

- Currents were elicited using a single step voltage protocol. From a holding potential of -80 mV the cell is depolarised to +30 mV (500 ms) resulting in an outward current before finally repolarising the cell by returning to the holding potential. The command voltage was applied
30 at a frequency of 0.067 Hz throughout the duration of the experiment. For each sweep of the voltage protocol membrane current and the passive properties of the individual cells were recorded by QPatch assay software (version 5.2). Cursors were placed to calculate the charge (integral of the current recorded during cursor interval) between 2 - 490 ms (0.4 - 99%) of the 500 ms step to +30 mV.

- 35 The % inhibition of charge for each test concentration application period was calculated as the reduction in mean charge at the end of each concentration test period relative to the

charge value measured at the end of the control (i.e. vehicle) period. Sigmoidal concentration response curves (four parameter logistic curve) were fitted to the % inhibition from which the IC₅₀ was determined. Curve fits were constrained at 0 and 100%.

- 5 The compounds of the invention were tested in the above referenced assay and the results are shown in Table 1:

Table 1: Kv1.3 Potency Values

Example Number	hK _v 1.3 IC ₅₀ μ M
1	0.035
2	0.030
3	0.061
4	0.079
5	0.138
6	0.02
7	0.026
8	0.027
9	0.028
10	0.028
11	0.028
12	0.03
13	0.037
14	0.033
15	0.033
16	0.035
17	0.035
18	0.036
19	0.037
20	0.037
21	0.038
22	0.039
23	0.04
24	0.04
25	0.04
26	0.054
27	0.04

28	0.04
29	0.04
30	0.041
31	0.042
32	0.043
33	0.043
34	0.047
35	0.044
36	0.045
37	0.045
38	0.045
39	0.045
40	0.046
41	0.046
42	0.046
43	0.046
44	0.046
45	0.046
46	0.047
47	0.047
48	0.048
49	0.048
50	0.048
51	0.048
52	0.049
53	0.049
54	0.05
55	0.05
56	0.05
57	0.05
58	0.05
59	0.051
60	0.051
61	0.051
62	0.052

63	0.052
64	0.052
65	0.053
66	0.053
67	0.053
68	0.055
69	0.055
70	0.056
71	0.057
72	0.057
73	0.058
74	0.058
75	0.059
76	0.06
77	0.06
78	0.06
79	0.06
80	0.061
81	0.061
82	0.061
83	0.061
84	0.061
85	0.062
86	0.062
87	0.063
88	0.063
89	0.063
90	0.064
91	0.064
92	0.064
93	0.064
94	0.064
95	0.064
96	0.065
97	0.066

98	0.066
99	0.067
100	0.067
101	0.067
102	0.068
103	0.068
104	0.069
105	0.069
106	0.07
107	0.071
108	0.071
109	0.071
110	0.072
111	0.072
112	0.072
113	0.072
114	0.073
115	0.073
116	0.073
117	0.073
118	0.074
119	0.074
120	0.074
121	0.075
122	0.075
123	0.075
124	0.075
125	0.075
126	0.076
127	0.077
128	0.077
129	0.078
130	0.078
131	0.078
132	0.078

133	0.078
134	0.079
135	0.081
136	0.082
137	0.082
138	0.084
139	0.084
140	0.084
141	0.084
142	0.084
143	0.085
144	0.087
145	0.088
146	0.088
147	0.088
148	0.089
149	0.089
150	0.09
151	0.09
152	0.091
153	0.091
154	0.091
155	0.092
156	0.092
157	0.094
158	0.095
159	0.095
160	0.097
161	0.098
162	0.098
163	0.098
164	0.099
165	0.099
166	0.099
167	0.099

168	0.099
169	0.1
170	0.101
171	0.102
172	0.103
173	0.103
174	0.103
175	0.104
176	0.104
177	0.104
178	0.105
179	0.105
180	0.106
181	0.106
182	0.108
183	0.108
184	0.109
185	0.109
186	0.11
187	0.11
188	0.112
189	0.112
190	0.113
191	0.114
192	0.115
193	0.115
194	0.121
195	0.124
196	0.125
197	0.126
198	0.126
199	0.129
200	0.129
201	0.131
202	0.134

203	0.134
204	0.135
205	0.136
206	0.137
207	0.137
208	0.143
209	0.144
210	0.144
211	0.148
212	0.149
213	0.152
214	0.159
215	0.159
216	0.163
217	0.167
218	0.168
219	0.168
220	0.169
221	0.169
222	0.17
223	0.177
224	0.178
225	0.182
226	0.185
227	0.186
228	0.19
229	0.199
230	0.201
231	0.205
232	0.208
233	0.209
234	0.211
235	0.212
236	0.213
237	0.217

238	0.221
239	0.23
240	0.235
241	0.243
242	0.248
243	0.251
244	0.252
245	0.253
246	0.258
247	0.262
248	0.275
249	0.28
250	0.286
251	0.307
252	0.317
253	0.323
254	0.333
255	0.341
256	0.342
257	0.348
258	0.362
259	0.365
260	0.37
261	0.386
262	0.395
263	0.4
264	0.404
265	0.408
266	0.415
267	0.424
268	0.441
269	0.481
270	0.485
271	0.494
272	0.524

273	0.552
274	0.559
275	0.571
276	0.575
277	0.593
278	0.595
279	0.608
280	0.615
281	0.632
282	0.706
283	0.749
284	0.787
285	0.802
286	0.859
287	0.976
288	1.02
289	1.058
290	1.064
291	1.119
292	2.946
293	4.082
294	10.508
295	21.426