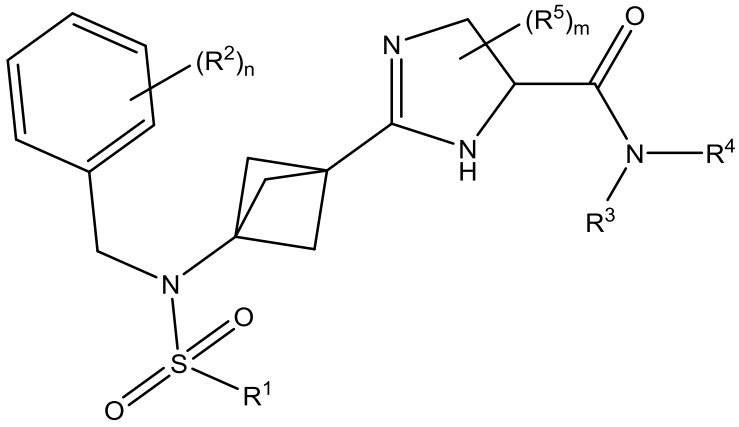
CLAIMS

1. A compound of formula (I):



(I)

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

R^1 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanol, -X-C_{3-8} cycloalkyl, haloC_{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, haloC_{1-6} alkyl, hydroxy, cyano, nitro, oxo, $CONR^xR^y$ or C_{3-8} cycloalkyl;

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, haloC_{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, haloC_{1-6} alkyl or -X-aryl,

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, haloC_{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,

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, haloC_{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

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.

2. A compound of formula (I) as defined in claim 1, wherein R^1 represents:

~~C_{1-6} alkyl (such as~~ methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl~~,~~ ~~or~~ i-pentyl~~);~~,

~~C_{1-6} alkoxy (such as~~ propoxy~~,);~~

~~-X-C_{3-8} cycloalkyl (such as~~ –(CH_2)-cyclopropyl, –$(CH_2)_2$-cyclopropyl, -cyclobutyl, -(CH_2)-cyclobutyl, -cyclopentyl~~,~~ ~~or~~ -cyclohexyl~~),~~,~~;~~

~~haloC_{1-6} 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 ~~–(CH_2)-cyclopropyl, –$(CH_2)_2$-cyclopropyl, -cyclobutyl, -(CH_2)-cyclobutyl, -~~cyclopentyl, ~~-~~cyclohexyl, phenyl, pyrrolidinyl, tetrahydropyranyl, furanyl, thiophenyl, pyrazolyl, pyridinyl or imidazolyl ~~cycloalkyl, aryl, heterocyclyl or heteroaryl~~ groups may be optionally substituted by one or more ~~(e.g. 1, 2, 3 or 4)~~ R^a groups~~, such as:~~.

3. A compound of formula (I) as defined in claim 1 or claim 2, wherein

~~haloC_{1-6} alkyl (such as~~ R^1 represents: trifluoromethyl, fluoropropyl, difluoropropyl, trifluoropropyl, fluorobutyl, difluorobutyl ~~or~~, trifluorobutyl~~,);~~

~~aryl (such as~~ phenyl~~,); or~~

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

wherein said phenyl, furanyl, thiophenyl, pyrazolyl, pyridinyl or imidazolyl ~~aryl or heteroaryl~~ groups may be optionally substituted by one or more ~~(e.g. 1, 2, 3 or 4)~~ R^a groups~~, in particular:~~.

4. A compound of formula (I) as defined in any one of claims 1 to 3, wherein

~~haloC_{1-6} alkyl (such as~~ R^1 represents fluoropropyl~~),~~,~~;~~

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

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

5. A compound of formula (I) as defined in any one of claims 1 to 3 wherein R^1 is substituted by 1, 2, 3, or 4 R^a groups.

6~~3~~. A compound of formula (I) as defined in any one of claims 1 to 5~~or claim 2~~, wherein R^a represents: ~~C_{1-6} alkyl (such as~~ methyl~~,), halogen (such as~~ fluorine~~,~~ ~~or~~ chlorine~~),~~ ~~haloC_{1-6}~~

alkyl (such as trifluoromethyl), hydroxy, cyano, nitro, oxo, $CONR^xR^y$ (such as $CONH_2$ or) or C_{3-8} cycloalkyl (such as cyclopropyl).

74. A compound of formula (I) as defined in any one of claims 1 to 63, wherein R^2 represents: halogen (such as fluorine, or chlorine), $halo C_{1-6}$ alkyl (such as difluoromethyl, or trifluoromethyl) or cyano, such as halogen (in particular fluorine or chlorine).

85. A compound of formula (I) as defined in any one of claims 1 to 73, wherein n represents an integer selected from 0 to 3; such as or 1 or 2;

6. A compound of formula (I) as defined in claim 5, wherein n represents an integer selected fromor 0.

97. A compound of formula (I) as defined in any one of claims 51 to 8 , wherein n represents 1 and R^2 represents halogen (such as fluorine, or chlorine), $halo C_{1-6}$ alkyl (such as difluoromethyl, or trifluoromethyl) or cyano.

10. A compound of formula (I) as defined in claim 9, wherein , such as n represents 1 and R^2 represents 3-fluorine, 4-fluorine, 3-chlorine, 4-chlorine, 4-difluoromethyl,4-trifluoromethyl or 4-cyano; or, in particular n represents 1 and R^2 represents 4-chlorine.

811. A compound of formula (I) as defined in any one of claims 1 to 85, wherein n represents 2 and R^2 represents halogen (such as fluorine, or chlorine), $halo C_{1-6}$ alkyl (such as trifluoromethyl,) or cyano.

12. A compound of formula (I) as defined in claim 11 wherein, such as n represents 2 and R^2 represents: 2-fluoro, 4-chloro; 3-fluoro, 4-chloro; 3-chloro, 4-fluoro; 3-fluoro, 4-trifluoromethyl; 3-chloro, 4-trifluoromethyl; 3-cyano, 4-chloro; 3,4-difluoro; or 3,4-dichloro; or, in particular n represents 2 and R^2 represents 3-fluoro, 4-chloro.

139. A compound of formula (I) as defined in any one of claim 51 to 8, wherein n represents 3 and R^2 represents halogen (such as fluorine, or chlorine, or), such as n represents 3 and R^2 represents 3,5-difluoro, 4-chloro.

140. A compound of formula (I) as defined in any one of claims 1 to 139, wherein R^3 represents:

Hydrogen; or

C_{1-6} 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); or

-X-C_{3-8} cycloalkyl (such as cyclopropyl, -CH_2-cyclopropyl, -$(CH_2)_2$-cyclopropyl, -cyclobutyl, -CH_2-cyclobutyl, -$(CH_2)_2$-cyclobutyl, -C(H)(CH_3)-cyclobutyl, cyclohexyl, -CH_2-cyclohexyl or bicyclo[1.1.1]pentanyl) optionally substituted by one or more C_{1-6} alkyl (such as methyl), C_{1-6} alkoxy (such as methoxy), haloC_{1-6} alkyl (such as difluoromethyl, trifluoromethyl or trifluoroethyl), halogen (such as fluorine), hydroxy or cyano groups; or

haloC_{1-6} alkyl (such as trifluoroethyl, difluoropropyl, trifluoropropyl, pentafluoropropyl, fluorobutyl, trifluorobutyl or trifluoropentyl) optionally substituted by one or more hydroxy groups; or

-X-aryl (such as -phenyl or -CH_2-phenyl) optionally substituted by one or more halogen (such as fluorine) groups;

or R^3 and R^4 together with the nitrogen atom to which they are attached join to form a heterocyclyl ring (such as azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, azepinyl, 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 C_{1-6} alkyl (such as methyl), haloC_{1-6} alkyl (such as difluoromethyl or trifluoromethyl) or halogen. (such as fluorine), such as:

15. A compound of formula (I) as defined claim 14, wherein R^3 represents -X-C_{3-8} cycloalkyl (such as cyclopropyl, -CH_2-cyclopropyl, -$(CH_2)_2$-cyclopropyl, -cyclobutyl, -CH_2-cyclobutyl, -$(CH_2)_2$-cyclobutyl, -C(H)(CH_3)-cyclobutyl, cyclohexyl, -CH_2-cyclohexyl or bicyclo[1.1.1]pentanyl) optionally substituted by one or more C_{1-6} alkyl (such as methyl), C_{1-6} alkoxy (such as methoxy), haloC_{1-6} alkyl (such as difluoromethyl, trifluoromethyl or trifluoroethyl), halogen (such as fluorine), hydroxy or cyano groups; or

haloC_{1-6} alkyl (such as trifluoroethyl, difluoropropyl, trifluoropropyl, pentafluoropropyl, fluorobutyl, trifluorobutyl or trifluoropentyl) optionally substituted by one or more hydroxy groups, in particular:.

16. A compound of formula (I) as defined in claim 15, wherein R^3 represents ~~-X-C_{3-8} cycloalkyl (such as~~ bicyclo[1.1.1]pentanyl~~, in particular unsubstituted bicyclo[1.1.1]pentanyl;~~ or ~~haloC_{1-6} alkyl (such as~~ trifluoropropyl~~, in particular unsubstituted trifluoropropyl)~~.

171. A compound of formula (I) as defined in any one of claims 1 to 1~~0~~6, wherein R^4 represents hydrogen, ~~C_{1-6} alkyl (such as~~ methyl~~, or~~ ethyl~~)~~ or ~~C_{3-8} cycloalkyl (such as~~ cyclopropyl~~), such as.~~

18. A compound of formula (I) as defined in claim~~s~~ 17 wherein R^4 represents hydrogen.

192. A compound of formula (I) as defined in any one of claims 1 to 1~~8~~1, wherein m represents an integer selected from 0 to 3; or~~, such as~~ 2~~;~~ or

~~13. A compound of formula (I) as defined in claim 12 wherein m represents~~ 0.

2014. A compound of formula (I) as defined in any one of claims 1 to 192, wherein R^5 represents; ~~C_{1-6} alkyl (such as~~ methyl, ethyl, n-propyl, i-propyl~~, or~~ i-butyl~~,)~~ or ~~-X-aryl (such as~~ -CH_2-phenyl~~);~~ or m represents 2 and said two R^5 groups join to form a ~~C_{3-8} cycloalkyl group (such as~~ cyclopropyl or cyclobutyl~~),~~.

21. A compound of formula (I) as defined in claim 20 ~~such as~~wherein R^5 represents ~~C_{1-6} alkyl (such as~~ methyl, ethyl, n-propyl, i-propyl or i-butyl~~), in particular R^5 represents C_{1-6} alkyl (such as methyl)~~.

22. A compound of formula (I) as defined in claim 21 wherein R^5 represents methyl.

21~~5~~3. A compound of formula (I) as defined in claim 192, wherein m represents 1 and R^5 represents ~~C_{1-6} alkyl (such as~~ methyl, n-propyl, i-propyl~~, or~~ i-butyl~~,)~~ or ~~-X-aryl (such as~~ -CH_2-phenyl~~)~~.

~~1~~246. A compound of formula (I) as defined in claim 192, wherein m represents 2 and R^5 represents ~~C_{1-6} alkyl (such as~~ methyl or ethyl~~)~~ or said two R^5 groups join to form a ~~C_{3-8} cycloalkyl group (such as~~ cyclopropyl or cyclobutyl~~), such as m represents 2 and R^5 represents C_{1-6} alkyl (such as methyl or ethyl), in particular m represents 2 and R^5 represents C_{1-6} alkyl (such as methyl)~~.

25. A compound of formula (I) as defined in claim 24, wherein m represents 2 and R^5 represents:
methyl or ethyl; or methyl.

2167. A compound of formula (I) as defined in claim 1920, wherein m represents 3 and R^5 represents ~~C_{1-6} alkyl (such as~~ methyl~~)~~.

2718. A compound of formula (I) as defined in any one of claims 1 to 2617, which is the free base of a compound of Examples 1-295~~, such as Example 1, Example 48 or Example 92,~~ or a pharmaceutically acceptable salt or solvate thereof.

1928. A pharmaceutical composition comprising a compound of formula (I) as defined in any of claims 1 to 2718.

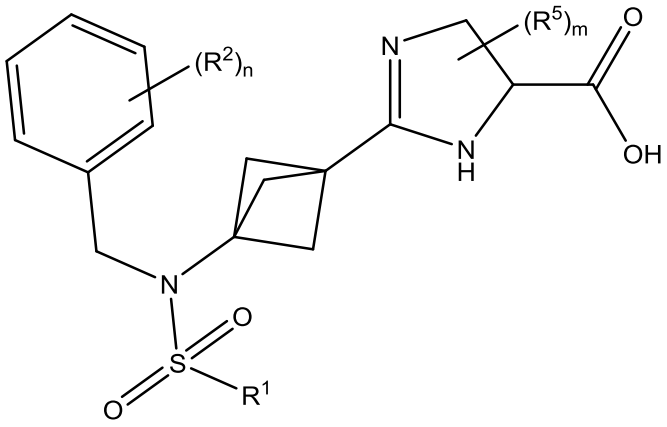
290. A pharmaceutical composition comprising a compound of formula (I) as defined in any of claims 1 to 2718, in combination with one or more therapeutic agents.

3021. A compound as defined in any of claims 1 to 2718 for use in therapy.

2312. A compound as defined in any of claims 1 to 2718 for use in the prophylaxis or treatment of ~~a disease or condition mediated by potassium channel inhibition, such as inhibition of Kv1.3, in particular~~ autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal ~~and~~ or metabolic mediated diseases.

232. A process for preparing a compound of formula (I) as herein defined in claim 1 which comprises:

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



(II)

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

(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).