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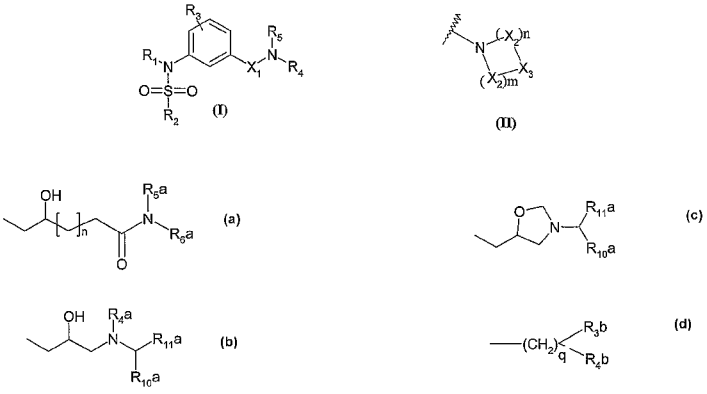
(54) Title: NOVEL POTASSIUM CHANNEL BLOCKERS



(57) Abstract: The present invention provides a compound of formula (I) or its salts or pharmaceutically acceptable derivatives thereof wherein; X_1 is selected from a group consisting of CH_2, C(=O), C(=NH), NC(=O), R_1 is selected from the group consisting of optionally substituted arylalkyl, and optionally substituted heteroarylalkyl R_2 is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl or heteroaryl or $NR_{24}R_{25}$, R_3 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxy, aryloxy, optionally substituted alkyl, optionally substituted amino, optionally substituted amino sulfonyl or nitrile; R_4 is selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted acyl, optionally substituted sulfonyl, optionally substituted sulfamoyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroaryl R_5 may be hydrogen, an optionally substituted alkyl, preferably CH_3 or, NR_4R_5 may form an optionally substituted saturated or partially saturated 4-7 membered ring with the general formula (II). Wherein; X_2 is C(=O), CH_2, $CH(R_6)$ or $C(R_6)(R_6)$, X_3 is CH_2, $CH(R_7)$, $C(R_7)(R_7)$, NH, $N(R_8)$, O or S Each R_6 independently represents optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl; Each R_7 independently represents optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted

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heteroaryl R_8 is optionally substituted acyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl; R_{24} and R_{25} are the same or different and each represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl, n = 1 or 2 m = 1, 2 or 3 With the proviso that when X_1 is C=O and R_5 is H then R_4 is not (a) or (b) or (c). Where R_4a, R_5a and R_6a are each independently H, C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl, or aryl-C_{1-6}alkyl; $R_{10}a$ is H or C_{1-6}alkyl; and $R_{11}a$ is C_{1-6}alkyl or aryl-C_{1-6}alkyl and when X_1 is C=O or CH_2 and R_5 is H then R_4 is not (d) Where q is 0 to 5, R_3b is H, OH or alkoxy and R_4b is NH_2, phenyl or a C_{3-10} heterocycle. The compounds are useful as potassium ion channel inhibitors.

NOVEL POTASSIUM CHANNEL BLOCKERS

FIELD OF THE INVENTION

The present invention relates to compounds of formula (I) which are potassium channel inhibitors. Compounds in this class may be useful as Kv1.3 inhibitors for immunomodulation and the treatment of autoimmune, chronic inflammatory, metabolic diseases and the like. Additionally, compounds in this class may also be useful as Kv1.5 inhibitors for the treatment or prevention of arrhythmias. Pharmaceutical compositions comprising the compounds and their use in the treatment of autoimmune and inflammatory diseases and in the treatment of arrhythmia are also provided.

BACKGROUND

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^+, Ca^{2+} and Cl^- can pass (Herbert, 1998). Potassium channels represent the largest and most diverse sub-group of ion channels and they play a central role in regulating the membrane potential and controlling cellular excitability (Armstrong & Hille, 1998). 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).

Compounds which modulate potassium channels have multiple therapeutic applications in several disease areas including autoimmune, inflammatory, cardiovascular, neuronal, auditory, renal and metabolic mediated diseases (Shieh *et al.*, 2000; Ford *et al.*, 2002, Xie *et al*, 2004, Cahalan *et al,* 1997). The potassium channel Kv1.3 is found in a number of tissues including neurons, blood cells, 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).

Kv1.3 Channel Blockers for Autoimmune Disorders

The role of autoreactive, late-stage, memory T-cells in the pathogenesis of a variety of autoimmune diseases including psoriasis, rheumatoid arthritis, multiple sclerosis, IBD and others is well established. Activation of T_{EM} cells is followed by substantial up-regulation of Kv1.3 channel expression and, as a result, Kv1.3 becomes the predominant route of potassium efflux from the cell. Thus, selective blockade of Kv1.3 causes membrane depolarisation and inhibition of Ca^{2+} influx, leading to inhibition of cytokine production and cell proliferation and function. Kv1.3 thus represents a novel therapeutic target of great interest for autoimmune disease control.

T-cells and Autoimmunity

T-cells are lymphocytes which play a central role in cell mediated immunity. One of the major forms of T-cell is the helper T-cell (T_H), also known as CD4+ cells which plays an essential role in the development of autoimmune diseases. Through the production of the cytokine interleukin 2 (IL-2), CD4+ T-cells can create the second main type of T-cell known as cytotoxic T-cells (CD8+). Naïve (inactive) CD4+ and CD8+ T-cells express both proteins (CCR7+CD45RA+) and use the chemokine receptor CCR7 as a key to gain entry into lymph nodes. Within lymph nodes, the naïve T-cells encounter antigen and through an activation process, change into "effector" T-cells that produce cytokines and proliferate. Once the ensuing immune response subsides, most naïve effectors die, but a few differentiate into long-lived central memory cells (T_{CM}). T_{CM} cells, like naïve cells, use CCR7 to home to the lymph nodes to encounter their cognate antigen. Upon antigenic stimulation, T_{CM} cells change into "T_{CM} effector" cells that produce cytokines and proliferate. They too suffer the same fate as naïve effectors, the majority dying after the immune response wanes, leaving a few long-lived survivors for further challenge. Repeated antigenic challenge, as might happen in autoimmune diseases or in chronic infections, causes T_{CM} cells to differentiate into short-lived "effector memory T-cells" (T_{EM}) that lack expression of both CCR7 and CD45RA, and do not need to home to lymph nodes for antigen-induced activation. A subset of CD8+ T_{EM} cells reacquire CD45RA and become CCR7-CD45RA+ T_{EMRA} cells. Upon activation, both CD4+ and CD8+ T_{EM} cells change into T_{EM} effectors that migrate rapidly to sites of inflammation and produce large amounts of the proinflammatory cytokines, interferon-γ (IFN-γ) and

tumor necrosis factor α (TNFα). In addition, CD8+ T_{EM} effectors carry large amounts of perforin and are therefore immensely destructive (Wulff *et al*, 2003, Beeton *et al*, 2005).

Functional Role of Kv1.3 in T-cells and Autoimmune Disorders

Human T-cells express two K^+ channels, Kv1.3 and IKCa1, that provide the counterbalance cation efflux necessary for the sustained elevation of cytosolic Ca^{2+} levels required for gene transcription, proliferation and cytokine secretion (Panyi *et al*, 2004, Chandy *et al*, 2004). The Kv1.3 and IKCa1 (also known as KCa3.1) channels regulate membrane potential and facilitate Ca^{2+} signalling in T-lymphocytes. Kv1.3 opens in response to membrane depolarisation and maintains the resting membrane potential (initiation phase), whereas IKCa1 opens in response to an increase in cytosolic Ca^{2+} and hyperpolarises the membrane potential (Beeton *et al*, 2001). Selective blockade of K^+ channels leads to membrane depolarisation, which in turn inhibits Ca^{2+} influx and shuts down cytokine production and cell proliferation. Early *in vitro* studies, using channel blocker toxins, clearly demonstrate that Kv1.3 channels are essential for the synthesis (gene activation) and secretion of the cytokine IL-2 after T-cell activation (Price *et al*, 1989) and provide a rationale for the potential therapeutic use of inhibitors of this channel in immunological disorders. The role of autoreactive T-cells in the pathogenesis of autoimmune diseases has clearly been demonstrated in animal models. Disease-specific, autoreactive T-cells in several other autoimmune diseases are also reported to exhibit a memory phenotype. Autoreactive T_{EM} cells are also implicated in psoriasis, rheumatoid arthritis, multiple sclerosis, IBD, vitiligo, uveitis, pemphigus, inflammatory myopathies, Hashimito disease, and scleroderma (Beeton *et al*, 2005). "Late" memory T- and B-cells have been implicated in the disease progression and tissue damage in a number of autoimmune diseases, in transplant rejection and chronic graft-versus-host disease. Modulators of the Kv1.3 channel may allow selective targeting of disease-inducing effector memory T-cells and memory B-cells without compromising the normal immune response and as a result are likely to have a preferred side-affect profile than agents that bring about more general immunosuppression.

The observation that the Kv1.3 blocker margatoxin (MgTX) effectively suppressed the delayed-type hypersensitivity (DTH) response *in vivo* was provided by Koo *et al*, 1999. In addition MgTX was also shown to inhibit primary antibody response in non-sensitised animals (secondary antibody response was not affected by MgTX. These latter results are in agreement with the notion that Kv1.3 channels are predominant in resting T lymphocytes and regulate their function, while IKCa1 channels are more important in pre-activated T lymphocytes. Correolide (Koo *et al*, 1999) and PAP-1 (Schmitz *et al*, 2005) are novel immunosuppressants which block Kv1.3 channels and are effective in the DTH model. Because the cellular components involved in DTH response are similar to those found in autoimmune diseases and allograft rejection, the results obtained are very promising for the development of Kv1.3 channel blockers as new immunosuppressants.

In the early 1980's a number of compounds were reported to block Kv1.3 channels at micromolar to millimolar concentrations as described by Triggle *et al,* in "Voltage Gated Ion Channels as Drug Targets" these include classical Kv channel inhibitors such as 4-aminopyridine and tetramethylammonium, and other non specific compounds such as the calcium activated potassium channel blockers quinine and ceteidil, the phenothiazine antipscychotics chloropromazine and trifluoroperazine, the classical calcium channel inhibitors verapamil, diltiazem, nifedipine and nitrendipine, and the beta blocker propranolol.

Also in the 1980's natural products extracted from scorpions, snakes and other marine organisms were found to be potent inhibitors of Kv1.3 channels, these were primarily short peptides (<70 residues) that are stabilised by multiple sulphide bonds. The first of these potent inhibitors was isolated from the venom of the scorpion *Leiurus quinquestriatus hebraeus* and was named charybdotoxin (ChTX) (Sands *et al*, 1989), there after screening of other scorpion venoms led to the identification of more potent Kv1.3 blocking toxins, these include margatoxin (MgTX) (Garcia *et al*, 1993), agitoxin-2 (Garcia *et al*, 1994), hongotoxin (Koshchak *et al*, 1998), pandinus imperator toxin 2 (Pi2) (Peter *et al*, 2001) and orthochirus scrobiculosus (OSK1)

(Mouhat *et al*, 2005) among others. With the exception of OSK1 (300 fold selective over the nearest related channel) none of the scorpion toxins were selective for Kv1.3

One of the most potent and selective Kv1.3 blockers to date, which was extracted from sea anemone is stichodactyla helianthus toxin (Shk) (Pennington *et al*, 1996) this has been reported for the treatment of autoimmune disease through the blockade of Kv1.3 (US 6,077,680). Shk and its synthetic derivative Shk-Dap^{22} with improved selectivity profile display pico molar activity (Pennington *et al*, 1998) however, these peptides proved to have unfavourable properties for further development.

Recently more novel and selective small molecule Kv1.3 channel blockers have been reported for the management of autoimmune disorders. These include the iminodihydroquinolines WIN173173 and CP339818 (Nguyen *et al.*, 1996), the benzhydryl piperidine UK-78,282 (Hanson *et al.* 1999), correolide (Felix *et al.*, 1999), cyclohexyl-substituted benzamide PAC (US-06194458, WO0025774), sulfamidebenzamidoindane (US-06083986), Khellinone (Baell *et al.*, 2004), dichloropenylpyrazolopyrimidine (WO-00140231) and psoralens (Wulff *et al.*, 1998., Vennekamp *et al.*, 2004, Schmitz *et al.*, 2005).

Sulfonamides have been reported to be useful as inhibitors of 11-beta-hydroxysteroid dehydrogenase type1, CCR5, H3 receptor and mitotic kinesins amongst others.

Substituted aryl tertiary sulfonamides, wherein position 4 is substituted with an amide have been claimed as inhibitors of 11-betehydroxysteroid dehydrogenase type1, for the treatment and prevention of hyperglycemia in diseases such as type-2 diabetes (WO2004065351).

Substituted aryl tertiary sulfonamides, wherein position 3 is optionally substituted with substituted alky, alkoxyamino, sulfonyl, acyl, alkoxy carbonyl or aminocarbonyl have been claimed as inhibitors of mitotic kinesins as effective anti cancer agents (WO2007056078).

Substituted 1-3 phenyl sulfonamides bearing a benzyl group and an amido group have been claimed as useful for the treatment and/or prophylaxis of viral diseases, in particular for the treatment of Hepatitis C (WO 2007/110171)

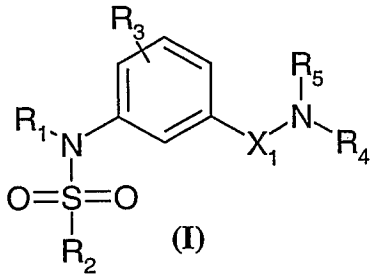
Elsewhere, arylsulophonylaminobenzene derivatives bearing an alkylamino group *meta* to the sulfonamide were found to be inhibitors of Factor Xa and useful in the treatment of arterial and venous thrombotic occlusive disorders, inflammation, cancer and neurodegenerative diseases (WO 96/40100).

Substituted 1,3 phenylsulfonamides containing an amido group *meta* to the sulfonamide have been claimed as inhibitors of BACE as an effective means for treating and preventing Alzheimer's and related diseases caused by the production of beta-amyloid (WO 2005/030709).

Substituted 1,3 phenylsulfonamides containing an ether group *meta* to the sulfonamide have also been claimed as liver X receptor (LXR) modulators useful for the treatment or prevention of diseases associated with the activity of LXR's (WO2003082205)

It has now surprisingly been found that compounds of general formula (I) set out below act as inhibitors of potassium channels. These compounds are particularly useful for inhibiting the potassium channel Kv1.3 and treating diseases associated with the inhibition of the potassium channel Kv1.3. This invention is not limited to treating diseases mediated by Kv1.3, the compounds also being useful to treat diseases which require Kv1.5 potassium channel inhibition for example atrial fibrillation (Marban, 2002, Brendel and Peukert, 2002).

Thus, in a first aspect, the present invention provides a compound of formula (I)



(I)

or its salts or pharmaceutically acceptable derivatives thereof wherein;

X_1 is selected from a group consisting of CH_2, C(=O), C(=NH), NC(=O),

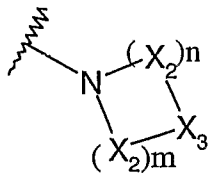
R_1 is selected from the group consisting of optionally substituted arylalkyl, and optionally substituted heteroarylalkyl

R_2 is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl or heteroaryl or $NR_{24}R_{25}$

R_3 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxy, aryloxy, optionally substituted alkyl, optionally substituted amino, optionally substituted amino sulfonyl or nitrile;

R_4 is selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted acyl, optionally substituted sulfonyl, optionally substituted sulfamoyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroaryl

R_5 is may be hydrogen, an optionally substituted alkyl, preferably CH_3 or, NR_4R_5 may form an optionally substituted saturated or partially saturated 4-7 membered ring with the general formula (II).



(II)

Wherein;

X_2 is C(=O), or $C(R_6)_2$,

X_3 is $C(R_7)_2$, NH, $N(R_8)$, O or S

R_6 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_7 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

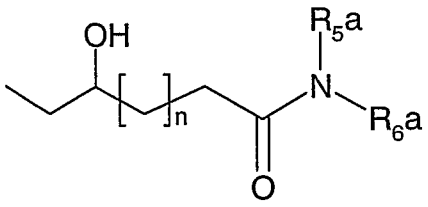
R_8 is optionally substituted acyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

R_{24} and R_{25} are the same or different and each represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl,

n = 1 or 2

m = 1, 2 or 3

With the proviso that when X_1 is C=O and R_5 is H then R_4 is not:



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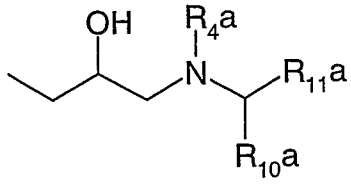

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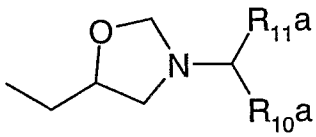
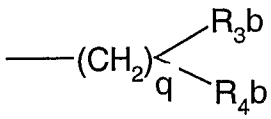


Where R_4a, R_5a and R_6a are each independently H, C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl, or aryl-C_{1-6}alkyl;

$R_{10}a$ is H or C_{1-6}alkyl; and

$R_{11}a$ is C_{1-6}alkyl or aryl-C_{1-6}alkyl

and when X_1 is C=O or CH_2 and R_5 is H then R_4 is not:



Where q is 0 to 5,

R_3b is H, OH or alkoxy and

R_4b is NH_2, phenyl or a C_{3-10} heterocycle.

As used herein, the following definitions shall apply unless otherwise indicated.

The term "optionally substituted" means that a group may be substituted by one or more substituents which may be the same or different. When otherwise not specified, these substituents are selected from alkyl, cycloalkyl, -O-C(halogen)$_3$ preferably –OCF_3, biaryl, carbocyclic aryl, heteroalicyclic, heteroaryl, acyl, amidino, amido, amino, alkyoxyamino, carbamoyl, carboxy, cyano, ether, hydroxyl, imino, halo, nitro, sulphamoyl, sulfonyl, sulphinyl, sulphenyl, sulfonamido or urea.

The term "alkyl group" as used herein, is typically a linear or branched alkyl group or moiety containing from 1 to 6 carbon atoms, preferably 2, 3, 4, or 5 carbon atoms such as a C_{1-4} alkyl group or moiety, for example methyl, ethyl, *n*-propyl, *i*-propyl, butyl, *i*-butyl and *t*-butyl. An alkyl group or moiety may be unsubstituted or substituted at any position. Typically, it is unsubstituted or carries one two or three substituents. Suitable substituents include cyano, halogen, hydroxyl, alkylamino, dialkylamino, amido, alkylamido, dialkylamido, alkanoyl, alkoxy, sulfonamido, nitro, aryl and heteroaryl. The alkyl moiety may also be an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond. An "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond.

The term "cycloalkyl" as used herein refers to mono- or bicyclic ring or ring systems consisting of 3 to 11 carbon atoms i.e. 3, 4, 5, 6, 7, 8, 9, 10 or 11 carbon atoms. The ring system may be a "saturated ring", which means that the ring does not contain any alkene or alkyne moieties. The cycloalkyl group may also be an "unsaturated ring" which means that it contains at least one alkene or alkyne moiety and the ring system is not aromatic. The cycloalkyl group may be unsubstituted or substituted as defined herein. In addition to the above mentioned substituents one or more ring carbon atoms may also be bonded *via* a double bond to a group selected from NH, S and O. The cycloalkyl substituent may be bonded *via* a linker group such as a C_{1-6} alkyl group, except where the optional substituent is alkyl. One or more hydrogens of the alkyl group in the linker may be replaced by a moiety selected from the group consisting of hydroxy, halo, cyano, amino, thiol, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino and C_{1-6}dialkylamino.

The term "aryl group" as used herein, is typically a C_{6-10} aryl group such as phenyl or naphthyl. A preferred aryl group is phenyl. An aryl group may be unsubstituted or substituted at any position. Typically, it carries 1, 2, 3 or 4 substituents. Suitable substituents include cyano, halogen, hydroxyl, nitro, trifluoromethyl, alkyl, alkylthio,

alkoxy, amino, alkylamino, dialkylamino, alkanoyl, amido, *N*-alkylamido, *NN*-dialkylamino, sulfonamido, aryl and heteroaryl.

The term "carbocyclic" refers to a compound which contains one or more covalently closed ring structures and the atoms forming the backbone of the ring(s) are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings. Carbocyclic groups include both, a "cycloalkyl group", which means a non-aromatic carbocycle, and a "carbocyclic aryl" group, which means an aromatic carbocycle. The carbocyclic group may optionally be substituted as defined herein.

The term "heterocyclic" or "heterocyclo" as used herein refers to mono- or bicyclic rings or ring systems which include one or more heteroatoms selected from N, S and O. The rings or ring systems include 1 to 6 carbon atoms in addition to the heteroatom(s) i.e. 1, 2, 3, 4, 5, or 6 carbon atoms. The term heterocyclic group include both a "heteroalicyclic" group, which means a non-aromatic heterocycle and a "heteroaryl" group, which means an aromatic heterocycle. The heterocyclic moiety may be unsubstituted or substituted as defined herein and the substituents, when positioned adjacent to one another, may combine to form cycloalkyl or heteroalicyclic ring systems for example methylendioxy or difluoromethylendioxy. The heterocyclic substituent may be bonded *via* a carbon atom or a heteroatom. The heterocyclic group may also include the oxides of nitrogen and sulfur if nitrogen or sulfur are present in the ring.

The term "heteroaryl" as used herein refers to mono- or bicyclic ring or ring systems which include one or more heteroatoms selected from N, S and O. The rings or ring systems include 1 to 13 carbon atoms (i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 carbon atoms) in addition to the heteroatom(s) and contain at least one aromatic ring with a heteroatom. The heteroaryl group may also include the oxides of nitrogen and sulfur if nitrogen or sulfur is present. Examples of monocyclic heteroaryl groups include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl and triazinyl. Examples of bicyclic

heterocycles include but are not limited to indolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, isoquinolinyl, quinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, benzotriazinyl and the like. Examples of tricyclic heterocycles include but are not limited to thianthrenyl, xanthenyl, phenoxathiinyl, carbazolyl, carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl and phenoxazinyl. The heteroaryl group may be unsubstituted or substituted as defined herein. The substituents, when positioned adjacent to one another, may combine to form a cycloalkyl or heteroalicyclic ring for example methylendioxy and difluoromethylendioxy. The heteroaryl substituent may be bonded *via* a carbon atom or a heteroatom.

The term "arylalkyl", as used herein, refers to a chemical moiety of formula aryl-C_{1-6}alkyl or C_{1-6}alkyl- aryl as those terms are defined herein.

The term "heteroarylalkyl", used as herein, refers to a chemical moiety of formula heteroaryl-C_{1-6}alkyl or C_{1-6}alkyl- heteroaryl as those terms are defined herein.

The term "acyl", as used herein, refers to a chemical moiety of formula (CH_2)yC(=O)Rz wherein y is 1-6, i.e. 1, 2, 3, 4, 5, or 6.

The term "amidino" refers to a chemical moiety with the formula (CH_2)yC(=NH)NRzR'z wherein y is 1-6, i.e. 1, 2, 3, 4, 5, or 6.

The term "amido" refers to both, a "C-amido" group which means a chemical moiety with the formula -C(=O)NRzR'z and a "N-amido" group which means a chemical moiety with the formula -NRzC(=O)R'z.

The term "amine" or "amino" refers to a chemical moiety of formula -NRzR'z. The definition of an amine is also understood to include their N-oxides.

A "cyano" group refers to a chemical moiety of formula -CN.

The term "hydroxy" or "hydroxyl" as used herein, refers to a chemical moiety of formula -OH.

The term "halogen" or "halo" refers to an atom selected from the group consisting of fluorine, chlorine, bromine and iodine.

The term "alkanoyl", as used herein, refers to a chemical moiety with the formula -C(=O)Rz.

The term "sulfone" or "sulfonyl" refers to a chemical moiety with the formula $-S(=O)_2Rz$.

The term "sulfinyl" refers to a chemical moiety with the formula -S(=O)Rz.

The term "sulfenyl" refers to a chemical moiety with the formula -SRz.

A "sulfamoyl" group refers to a chemical moiety with the formula $-NRz-S(=O)_2NRzR'z$.

The term "sulfonamido" refers to both an "S-sulfonamido" group which means a chemical moiety with the formula $-S(=O)_2NRzR'z$ and an "N-sulfonamido" group which means a chemical moiety with the formula $-N-S(=O)_2R'z$.

The term "thiocarbonyl" refers to a chemical moiety with the formula $(CH_2)yC(=S)Rz$ wherein y is 1-6, i.e. 1, 2, 3, 4, 5, or 6.

The term "thio" or "thiol", as used herein, refers to a chemical moiety of formula -SH.

The term "thioamide" refers to both a "C-thioamido" group which means a chemical moiety with the formula $(CH_2)yC(=S)NRzR'z$ and a "N-thioamido" group which means a chemical moiety with the formula $(CH_2)yNRzC(=S)R'z$ wherein y is 1-6, i.e. 1, 2, 3, 4, 5, or 6.

An "urea" group refers to a chemical moiety of formula -NRzC(=O)NRzR'z.

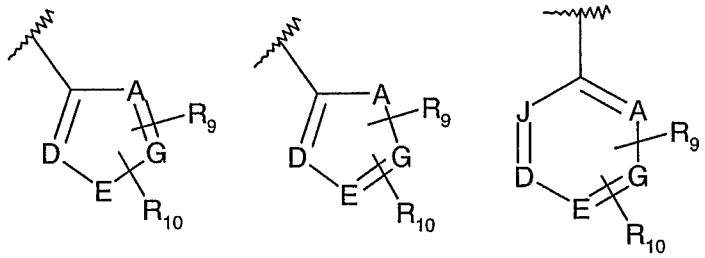
Rz and R'z are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, C_{1-6}alkoxy, aryl-C_{1-6}alkyl , aryl and heteroaryl.

In a preferred embodiment;

X_1 is C(=O).

R_2 is selected from $NR_{24}R_{25}$. Preferably R_{24} and R_{25} are the same or different and each represents hydrogen, or optionally substituted C_{1-3} alkyl. More preferably, R_{24} and R_{25} are CH_3.

Alternatively, R_2 is selected from formula (III), (IV) or (V)



(III) (IV) (V)

Wherein;

A, D, E, G, and J are the same or different and each represents C, or N with the proviso that in each instance at least one of A, D, E, G, or J is N;

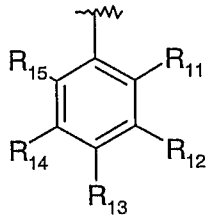
When R_2 is formula (III), E may also represent O or S; and

When R_2 is formula (IV), A may also represent O or S;

Preferred moities of formula (III), (IV) and (V) are Imidazole, Pyrazole, Pyrrole, Oxazole, Oxadiazole, Thiazole, Thiadiazole, Pyridine, Pyrimidine, Pyrazine, Pyridazine, and Triazine. More preferably R_2 is selected from Imidazole, Pyrazole, or Pyridine

R_9 and R_{10} are the same or different and each represents hydrogen, halogen, hydroxyl, nitrile, optionally substituted amino, optionally substituted acyl, optionally substituted C_{1-3} alkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl or may be taken together to form an optionally substituted saturated or partially saturated 5-7 membered heterocyclic or carbocyclic ring. Preferably R_9 and R_{10} are alkyl, more preferably CH_3.

Alternatively, R_2 is selected from compounds of formula (VI)

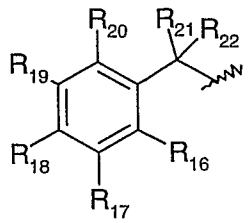


(VI)

R_{11}, R_{12}, R_{13}, R_{14}, and R_{15} are the same or different and each represents hydrogen, halogen, hydroxyl, optionally substituted amino, optionally substituted acyl, nitrile, optionally substituted C_{1-3} alkyl, any of the pairs R_{11} and R_{12}, or R_{12} and R_{13}, or R_{13} and R_{14}, or R_{14} and R_{15} or may be taken together to form an optionally substituted saturated or partially saturated 5-7 membered heterocyclic or carbocyclic ring.

Preferred moities of formula (VI) include phenyl, fluorophenyl, chlorophenyl, cyanophenyl, aminophenyl, acetamidophenyl, tetrahydrobenzofuran, benzopyran, dihydrobenzodioxin, benzoxazinone, benzooxadiazole, benzodioxole, indoline, indole, indazole, and benzomorpholine. More preferred moities are phenyl, fluorophenyl, cyanophenyl, tetrahydrobenzofuran, benzopyran, dihydrobenzodioxin, benzoxazinone, benzooxadiazole, benzodioxole, indoline, and benzomorpholine.

Perferably R^1 is



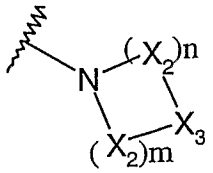
(VII)

Wherein R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are the same or different and each represents hydrogen, halogen, hydroxyl, optionally substituted amino, optionally substituted acyl, nitrile, optionally substituted C_{1-3} alkyl or optionally substituted alkoxy;
R_{21} and R_{22} are the same or different and each represents hydrogen, hydroxyl, and optionally substituted C_{1-3} alkyl. Preferably R_{17}, R_{18} and R_{19} are the same or different and each represents H, Cl, F, or CH_3. More preferably, R_{17}, R_{18} and R_{19} are the same or different and each represents H or Cl.

Preferably R_3 is H, F or CH_3. More preferably R_3 is H or F.

R_4 is preferably selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroaryl. Preferred examples include methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, 2-hydroxyethyl, hydroxypropyl, hydroxybutyl, propane-1,3-diol, methoxyethyl, phenyl, benzyl, phenethyl, 3-phenylpropyl, piperidinyl, pyrollidinyl, morpholinyl, piperazinyl, indazolyl, pyridyl, thiadiazolyl, and thiazolyl.

R_5 is preferably selected from hydrogen, optionally substituted alkyl, preferably CH_3 or NR_4R_5 may form an optionally substituted saturated or partially saturated 4-7 membered ring with the general formula (II). More preferably, R_5 is selected from hydrogen, CH_3 or NR_4R_5 may form an optionally substituted saturated or partially saturated 4-6 membered ring with the general formula (II) examples of which include azetidinyl, pyrrolidinyl, piperazinyl, piperidinyl.



(II)

Wherein;

X_2 is C(=O), or $C(R_6)_2$,

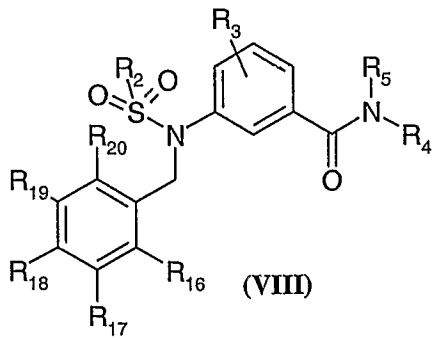
X_3 is $C(R_7)_2$, NH, $N(R_8)$, O or S

R_6 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_7 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_8 is optionally substituted acyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

More preferred compounds are those selected from compounds of formula (VIII);

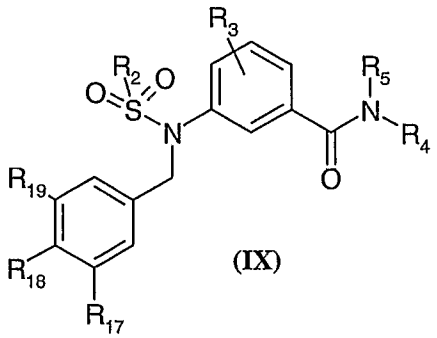


(VIII)

Wherein;

R_2 is selected from $NR_{24}R_{25}$ or formula (III), (IV) (V) or (VI), and R_3, R_4, R_5, R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are as defined above.

Most preferred compounds are those selected from compounds of formula (IX);



(IX)

Wherein;

R_2 is selected from $NR_{24}R_{25}$ or formula (III), (IV), (V) or (VI) as defined above; and R_3, R_4, R_5, R_{17}, R_{18}, and R_{19} are as defined above.

Particularly preferred compounds of the invention include:

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-ethyl)-benzamide

N-Benzyl-3-[benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-benzamide

3-[Benzyl-(pyridine-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(1H-indazol-6-yl)-benzamide

3-[(4-Acetylamino-benzenesulfonyl)-benzyl-amino]-N-isopropyl-benzamide

5-[Benzyl-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-benzyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-isopropyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-phenethyl-benzamide

N-Benzyl-N-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide

N-Benzyl-N-[3-(3-phenyl-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide
N-Benzyl-N-[3-(2-phenyl-morpholine-4-carbonyl)-phenyl]-benzenesulfonamide
N-Benzyl-N-[3-(4-phenoxy-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide
3-(Benzenesulfonyl-benzyl-amino)-N-(3-phenyl-propyl)-benzamide
3-(Benzenesulfonyl-benzyl-amino)-N-methyl-benzamide
3-(benzenesulfonyl-benzyl-amino)-N-tert-butyl-benzamide
N-Benzyl-N-[3-(3-phenyl-piperidine-1-carbonyl)-phenyl]-methanesulfonamide
N-Benzyl-N-[3-(2-phenyl-morpholine-4-carbonyl)-phenyl]-methanesulfonamide
N-Benzyl-N-[3-(4-phenoxy-piperidine-1-carbonyl)-phenyl]-methanesulfonamide
N-Benzyl-N-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-methanesulfonamide
1-Methyl-1H-imidazole-4-sulfonic acid benzyl-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-amide
N-Benzyl-N-[3-(morpholine-4-carbonyl)-phenyl]-benzenesulfonamide
3-(Benzenesulfonyl-benzyl-amino)-N-pyridin-2-ylmethyl-benzamide
3-(Benzenesulfonyl-benzyl-amino)-N-(1H-indazol-5-yl)-benzamide
3-(Benzenesulfonyl-benzyl-amino)-N-(4-imidazol-1-yl-phenyl)-benzamide
3-(Benzenesulfonyl-benzyl-amino)-N-(4-pyrazol-1-yl-phenyl)-benzamide
3-(Benzenesulfonyl-benzyl-amino)-N-[1,3,4]thiadiazol-2-yl-benzamide
3-(Benzenesulfonyl-benzyl-amino)-N-thiazol-2-yl-benzamide
N-[4-(Aminocarbonyl)phenyl]-3-[benzyl(phenylsulfonyl)amino]benzamide
N-[3-(Aminocarbonyl)phenyl]-3-[benzyl(phenylsulfonyl)amino]benzamide
3-(Benzenesulfonyl-benzyl-amino)-N-phenyl-benzamide
1-Methyl-1H-imidazole-4-sulfonic acid benzyl-[3-(2-phenyl-morpholine-4-carbonyl)-phenyl]-amide
3-[Benzyl-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-N-isopropyl-benzamide
3-[Benzyl-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide
3-[Benzyl-(2,4-dimethyl-thiazole-5-sulfonyl)-amino]-N-isopropyl-benzamide
N-Benzyl-2-fluoro-N-[3-(morpholine-4-carbonyl)-phenyl]-benzenesulfonamide
3-[Benzyl-(2-fluoro-benzenesulfonyl)-amino]-N,N-dimethyl-benzamide
3-[Benzyl-(3-fluoro-benzenesulfonyl)-amino]-N,N-dimethyl-benzamide
N-Benzyl-4-fluoro-N-[3-(morpholine-4-carbonyl)-phenyl]-benzenesulfonamide
3-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-N,N-dimethyl-benzamide

3-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-N-isopropyl-benzamide

1-Methyl-1H-imidazole-4-sulfonic acid benzyl-{3-[4-(2-fluoro-phenyl)-piperazine-1-carbonyl]-phenyl}-amide

3-[Benzyl-(2-fluoro-benzenesulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(3-fluoro-benzenesulfonyl)-amino]-N-isopropyl-benzamide

1-Methyl-1H-imidazole-4-sulfonic acid benzyl-[3-(4-cyclohexylmethyl-piperazine-1-carbonyl)-phenyl]-amide

3-[Benzyl-(2,3-dihydro-benzofuran-5-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(2,2-dimethyl-chroman-6-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(2,3-dihydro-benzo[1,4]dioxine-6-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(1-Acetyl-2,3-dihydro-1H-indole-5-sulfonyl)-benzyl-amino]-N-isopropyl-benzamide

3-[Benzyl-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-N-isopropyl-benzamide

2,3-Dihydro-benzo[1,4]dioxine-6-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide

4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide

Benzo[1,2,5]oxadiazole-4-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide

Benzo[1,3]dioxole-5-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide

3-(Benzenesulfonyl-benzyl-amino)-N-cyclopropyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-cyclobutyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-cyclopentyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-1-methyl-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(1-hydroxymethyl-propyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-propyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-isobutyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-ethyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-methoxy-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-propyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(3-hydroxy-propyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(4-hydroxy-butyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-cyclopropylmethyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-1-hydroxymethyl-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-((R)-1-hydroxymethyl-propyl)-benzamide

5-[(Benzo[1,2,5]oxadiazole-4-sulfonyl)-benzyl-amino]-2-fluoro-N-isopropyl-benzamide

5-(Benzenesulfonyl-benzyl-amino)-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(2,3-dihydro-benzo[1,4]dioxine-6-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(4-cyano-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(2-cyano-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(Benzo[1,3]dioxole-5-sulfonyl)-benzyl-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(2,3-dihydro-benzofuran-5-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(pyridine-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-Acetylamino-benzenesulfonyl)-benzyl-amino]-2-fluoro-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-isopropyl-benzamide

5-[Benzyl-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-N-isopropyl-benzamide

5-[Benzyl-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(1-methyl-1H-pyrazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-ethyl)-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(1-hydroxymethyl-propyl)-benzamide

N-(4-Chloro-benzyl)-3-cyano-N-[4-fluoro-3-(3-hydroxy-azetidine-1-carbonyl)-phenyl]-benzenesulfonamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-1-hydroxymethyl-ethyl)-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-1-methyl-ethyl)-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-methoxy-ethyl)-benzamide

N-(4-Chloro-benzyl)-3-cyano-N-[4-fluoro-3-(3-hydroxy-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide

N-(4-Chloro-benzyl)-3-cyano-N-[4-fluoro-3-((R)-3-hydroxy-pyrrolidine-1-carbonyl)-phenyl]-benzenesulfonamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-hydroxy-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-hydroxy-1-methyl-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(1-hydroxymethyl-propyl)-benzamide

Pyridine-3-sulfonic acid (4-chloro-benzyl)-[3-(3-hydroxy-azetidine-1-carbonyl)-phenyl]-amide

Pyridine-3-sulfonic acid (4-chloro-benzyl)-[3-(3-hydroxy-piperidine-1-carbonyl)-phenyl]-amide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-methoxy-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-cyclopropyl-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-cyclopentyl-benzamide

Pyridine-3-sulfonic acid (4-chloro-benzyl)-[3-((R)-3-fluoro-pyrrolidine-1-carbonyl)-phenyl]-amide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-cyclobutyl-benzamide

Pyridine-3-sulfonic acid [3-(azetidine-1-carbonyl)-phenyl]-(4-chloro-benzyl)-amide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-methyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-ethyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-(2-methoxy-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-cyclopropyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-cyclopentyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-cyclobutyl-benzamide

1-Methyl-1H-imidazole-4-sulfonic acid [3-(azetidine-1-carbonyl)-phenyl]-(4-chloro-benzyl)-amide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-methyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-ethyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-methoxy-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-cyclopropyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-cyclobutyl-benzamide

1-Methyl-1H-pyrazole-3-sulfonic acid [3-(azetidine-1-carbonyl)-phenyl]-(4-chloro-benzyl)-amide

1-Methyl-1H-pyrazole-3-sulfonic acid (4-chloro-benzyl)-[3-(3-methyl-piperidine-1-carbonyl)-phenyl]-amide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-cyclopentyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-1-methyl-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(1-hydroxymethyl-propyl)-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

3-[(4-chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-cyclobutyl-benzamide

3-[(4-chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-cyclopentyl-benzamide

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulfonic, ethanesulfonic, benzenesulfonic or p-toluenesulfonic. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, arylalkyl amines or heterocyclic amines.

The compounds of the invention may contain one or more chiral centres. For the avoidance of doubt, the chemical structures depicted herein are intended to embrace all stereo isomers of the compounds shown, including racemic and non racemic mixtures and pure enantiomers and/or diastereoisomers.

As discussed herein, the compounds of the invention are useful in the treatment of various conditions. Thus, in a second aspect, the present invention provides a compound of formula (I) as defined herein for use in medicine. Preferably the compound is used to prevent or treat conditions which require inhibition of potassium channels, such as immunological disorders, including psoriasis, rheumatoid arthritis and multiple sclerosis.

In a further aspect the present invention provides a pharmaceutical formulation comprising at least one compound of formula (I) or as defined herein and optionally one or more excipients, carriers or diluents.

The compositions of the invention may be presented in unit dose forms containing a predetermined amount of each active ingredient per dose. Such a unit may be adapted to provide 5-100mg/day of the compound, preferably either 5-15mg/day, 10-30mg/day, 25-50mg/day 40-80mg/day or 60-100mg/day. For compounds of formula

I, doses in the range 100-1000mg/day are provided, preferably either 100-400mg/day, 300-600mg/day or 500-1000mg/day. Such doses can be provided in a single dose or as a number of discrete doses. The ultimate dose will depend on the condition being treated, the route of administration and the age, weight and condition of the patient and will be at the doctor's discretion.

The compositions of the invention may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For applications to the eye or other external tissues, for example the mouth and skin, the formulations are preferably applied as a topical ointment or cream. When

formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may

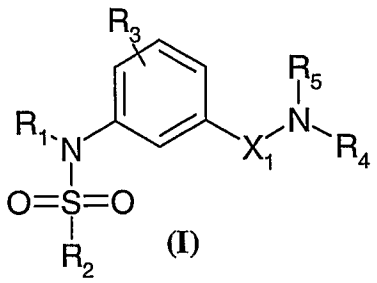
include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and *vial*s, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may also include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compositions of the invention can be used to treat conditions which require inhibition of potassium channels, for example in the treatment of immunological disorders. Thus, in further aspects, the present invention provides:

(i) A compound of formula (I)



(I)

Or its salts or pharmaceutically acceptable derivatives thereof wherein;

X_1 is selected from a group consisting of CH_2, C(=O), C(=NH), NC(=O),

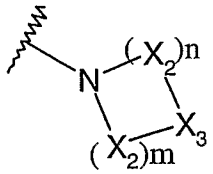
R_1 is selected from the group consisting of optionally substituted arylalkyl, and optionally substituted heteroarylalkyl

R_2 is selected from the group consisting of optionally substituted alkyl, preferably CH_3, optionally substituted aryl or heteroaryl or $NR_{24}R_{25}$

R_3 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxy, aryloxy, optionally substituted alkyl, optionally substituted amino, optionally substituted amino sulfonyl or nitrile;

R_4 is selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted acyl, optionally substituted sulfonyl, optionally substituted sulfamoyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroaryl

R_5 is may be hydrogen, an optionally substituted alkyl, preferably CH_3 or, NR_4R_5 may form an optionally substituted saturated or partially saturated 4-7 membered ring with the general formula (II).



(II)

Wherein;

X_2 is C(=O), or $C(R_6)_2$,

X_3 is $C(R_7)_2$, NH, $N(R_8)$, O or S

R_6 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_7 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_8 is optionally substituted acyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

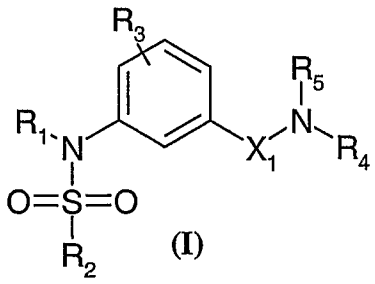
R_{24} and R_{25} are the same or different and each represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl,

n = 1 or 2

m = 1, 2 or 3

for use in the treatment or prophylaxis of psoriasis, rheumatoid arthritis, multiple sclerosis or other immunological disorders; and

(ii) A method for the prevention or treatment of a disorder which requires potassium channel inhibition, comprising administering to a subject an effective amount of at least one compound of formula (I)



(I)

Or its salts or pharmaceutically acceptable derivatives thereof wherein;

X_1 is selected from a group consisting of CH_2, C(=O), C(=NH), NC(=O),

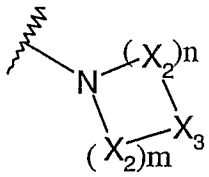
R_1 is selected from the group consisting of optionally substituted arylalkyl, and optionally substituted heteroarylalkyl

R_2 is selected from the group consisting of optionally substituted alkyl, preferably CH_3, optionally substituted aryl or heteroaryl or $NR_{24}R_{25}$

R_3 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxy, aryloxy, optionally substituted alkyl, optionally substituted amino, optionally substituted amino sulfonyl or nitrile;

R_4 is selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted acyl, optionally substituted sulfonyl, optionally substituted sulfamoyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroaryl

R_5 is may be hydrogen, an optionally substituted alkyl, preferably CH_3 or, NR_4R_5 may form an optionally substituted saturated or partially saturated 4-7 membered ring with the general formula (II).



(II)

Wherein;

X_2 is C(=O), or $C(R_6)_2$,

X_3 is $C(R_7)_2$, NH, $N(R_8)$, O or S

R_6 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_7 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_8 is optionally substituted acyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

R_{24} and R_{25} are the same or different and each represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl,

n = 1 or 2

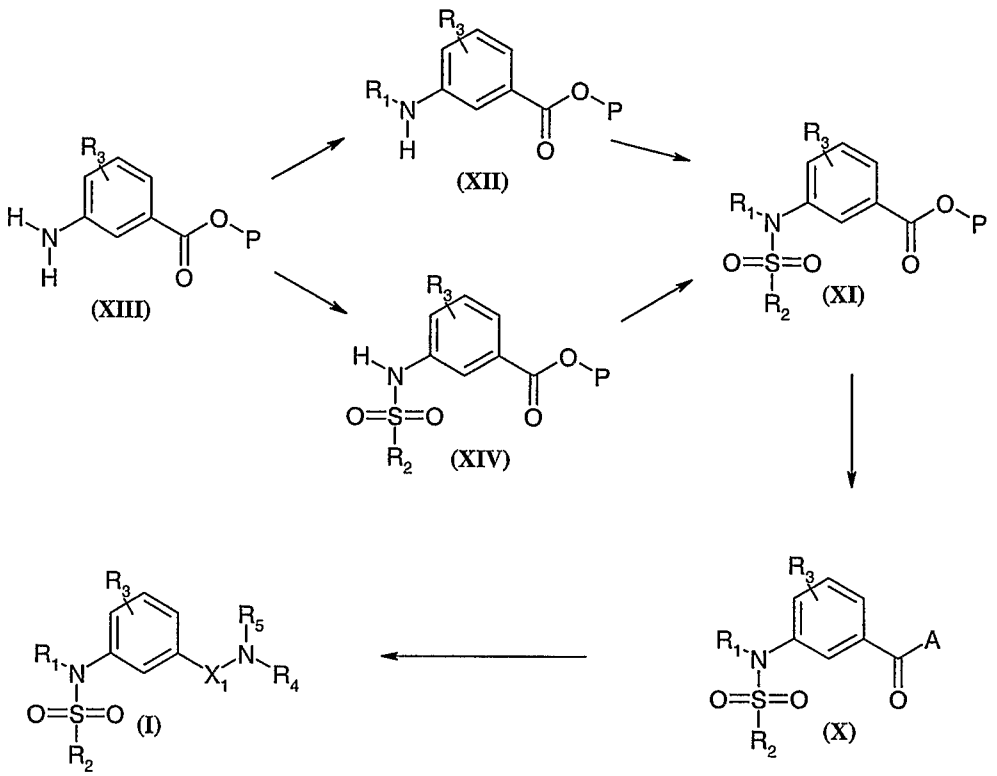
m = 1, 2 or 3

In particular, the medicament is for use in the treatment or prevention of psoriasis, rheumatoid arthritis, multiple sclerosis and other immunological disorders. The medicaments can also be used to treat arrhymias.

Preferred embodiments of the first aspect apply to all other aspects *mutatis mutandis*.

The compounds of formula (I) may be prepared by conventional routes, for example those set out in Schemes 1 to 6 shown below.

Scheme 1



Compounds of formula (I) where X_1 is C=O may be prepared from compounds of formula (X) where A is OH and amines of formula NHR_4R_5 together with a coupling reagent such as 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) or 2-(7-aza-1H-benztriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) utilising standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile or dimethylformamide at range of temperatures from ambient to reflux temperature optionally in the presence of a activating agent such as hydroxybenzotriazole (HOBT). Alternatively, compounds of formula (I) may be prepared from compounds of formula (X) where A is Cl and amines of formula NHR_4R_5 in the presence of a base for example triethylamine utilising standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile or dichloromethane at range of temperatures from ambient to reflux temperature. Compounds of formula NHR_4R_5 are available from commercial suppliers or may be prepared by standard published methods familiar to those skilled in the art.

Compounds of formula (X) where A is OH may be prepared from compounds of formula (XI) by removal of a suitable protecting group P. In a preferred instance P is a tertiary butyl group. Removal of this protecting group may be accomplished using standard methods of acidic or basic hydrolysis or *via* protolytic decomposition for example treatment with trifluoroacetic acid in solvent such as tetrahydrofuran, acetonitrile, dichloromethane or toluene at a range of temperatures from ambient to reflux temperature.

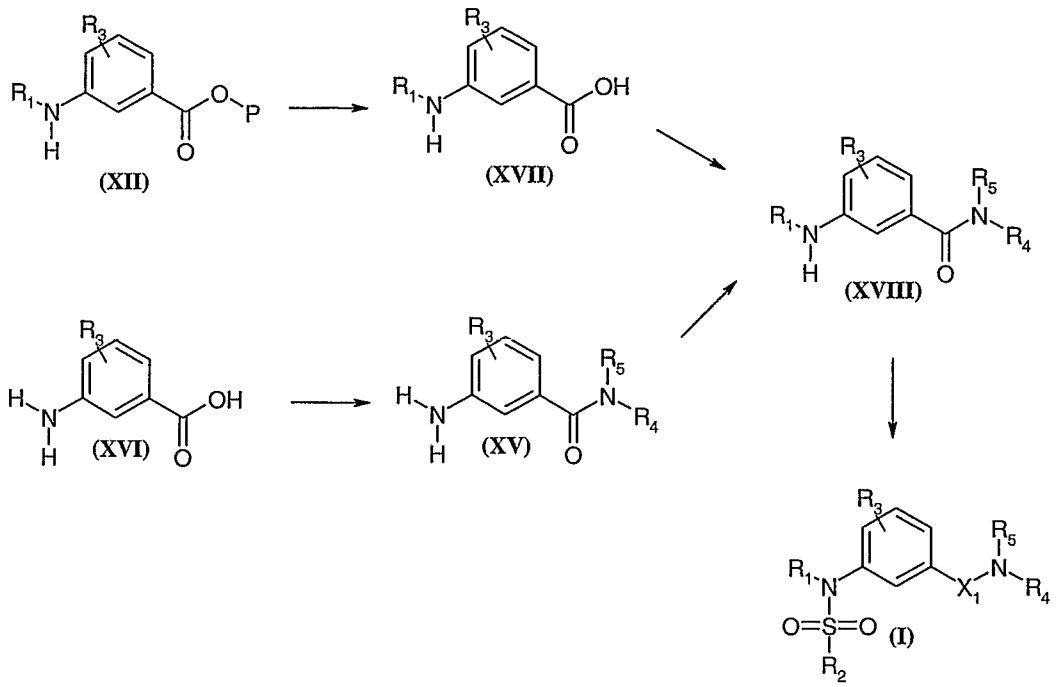
Compounds of formula (XI) may be prepared, from compounds of formula (XII) and sulfonyl chlorides or sulfamoyl chlorides of formula R_2SO_2Cl where R_2 is defined as above in the presence of a base, for example triethylamine, diisopropylamine or pyridine, utilizing standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile, dichloromethane or toluene at a range of temperatures from ambient to reflux temperature. Compounds of formula R_2SO_2Cl are either commercially available or may be prepared by standard published methods known to those skilled in the art.

Compounds of formula (XII) may be prepared from compounds of formula (XIII) *via* reductive amination of a ketone or aldehyde of formula R_1=O. The reaction may be performed in a one pot procedure with *in situ* formation and reduction of the imine or *via* a two stage process where the imine is isolated prior to reduction. Imine formation is performed under acid catalysis, suitable catalysts include acetic acid. Reduction may be performed using standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile, dichloromethane or toluene at a range of temperatures from ambient to reflux temperature with a suitable reductant such as sodium triacetoxyborohydride or sodium cyanoborohydride, the reduction may also be performed using catalytic hydrogenation. Compounds of formula (XIII) are either commercially available or may be prepared by standard published methods known to those skilled in the art.

Compounds of formula (XI) may also be prepared from compounds of formula (XIV) where P is a suitable protecting group, in a preferred instance a tertiary butyl group, *via* alkylation of the sulfonamide in a preferred instance with an alkyl bromide of formula R_1-Br in the presence of a base such as cesium carbonate or potassium carbonate, optionally in the presence of a phase transfer catalyst such as tetrabutylammonium bromide, utilizing standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile, dichloromethane, dimethylformamide or toluene at a range of temperatures from ambient to reflux temperature. Compounds of formula R_1-Br are either commercially available or may be prepared by standard published methods known to those skilled in the art.

Compounds of formula (XIV) may be prepared from compounds of formula (XIII) and sulfonyl chlorides of formula R_2SO_2Cl in the presence of a base, for example triethylamine, diisopropylamine or pyridine, utilizing standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile, dichloromethane or toluene at a range of temperatures from ambient to reflux temperature. Compounds of formula R_2SO_2Cl are either commercially available or may be prepared by standard published methods known to those skilled in the art.

Scheme 2



Compounds of formula (I) may also be prepared from compounds of formula (XVIII) and sulfonyl chlorides of formula R_2SO_2Cl in the presence of a base, for example triethylamine, diisopropylamine or pyridine, utilizing standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile, dichloromethane or toluene at a range of temperatures from ambient to reflux temperature. Compounds of formula R_2SO_2Cl are either commercially available or may be prepared by standard published methods known to those skilled in the art.

Compounds of formula (XVIII) may be prepared from the reaction of compounds of formula (XVII) and amines of formula NHR_4R_5 together with a coupling reagent such as 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) or 2-(7-aza-1H-benztriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) utilising standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile or dimethylformamide at range of temperatures from ambient to reflux temperature. Compounds of formula NHR_4R_5 are either

commercially available or may be prepared by standard published methods familiar to those skilled in the art.

Compounds of formula (XVII) may be prepared from compounds of formula (XII) by removal of a protecting group in a preferred instance a tertiary butyl group. This may be accomplished by standard methods of acidic or basic hydrolysis or *via* protolytic decomposition such as trifluoroacetic acid in solvent such as tetrahydrofuran, acetonitrile, dichloromethane or toluene at a range of temperatures from ambient to reflux temperature.

Compounds of formula (XVIII) may also be prepared from compounds of formula (XV) *via* reductive amination of a ketone or aldehyde of formula R_1=O. The reaction may be performed in a one pot procedure with *in situ* formation and reduction of the imine or *via* a two stage process where the imine is isolated and purified prior to reduction. Imine formation is performed under acid catalysis, suitable catalysts include acetic acid. Reduction may be performed using standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile, dichloromethane or toluene at a range of temperatures from ambient to reflux temperature with a suitable reductant such as sodium triacetoxyborohydride or sodium cyanoborohydride, the reduction may also be performed using catalytic hydrogenation.

Compounds of formula (XV) may be prepared from the reaction of compounds of formula (XVI) and amines of formula NHR_4R_5 together with a coupling reagent such as 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) or 2-(7-aza-1H-benztriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) utilising standard methods such as reaction in solvent such as tetrahydrofuran, acetonitrile or dimethylformamide at range of temperatures from ambient to reflux temperature. Compounds of formula NHR_4R_5 are either commercially available or may be prepared by standard published methods familiar to those skilled in the art. Compounds of formula (XVI) are either commercially available or may be prepared by standard published methods familiar to those skilled in the art.

As discussed herein, the compounds of the invention are useful in the treatment of various conditions. Thus, in a second aspect, the present invention provides a compound of formula I as defined herein for use in medicine. Preferably the compound is used to prevent or treat conditions which require inhibition of potassium channels.

In a further aspect the present invention provides a pharmaceutical formulation comprising at least one compound of formula I or as defined herein and optionally one or more excipients, carriers or diluents.

The compounds of the invention are found to be inhibitors of voltage gated potassium channels (K_v) and are therefore therapeutically useful. Such compounds are believed to be novel and the present invention also provides for these compounds. The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds.

Many of the starting materials referred to in the reactions described above are available from commercial sources or can be made by methods cited in the literature references.

Examples

The HPLC analysis was conducted using the following methods:

Solvent : [MeCN-0.05% HCO_2H : H_2O-0.1% HCO_2H], 10-95% gradient 3min, 95% 2.5min; Column: Phenomenex Gemini 50x4.6 mm i.d., C18 reverse phase; Flow rate: 0.75mL/min unless otherwise indicated.

Solvent : [MeCN-H_2O/0.01% HCO_2H], 5-95% gradient 5min, 95% 3min; Column: Phenomenex Gemini 50x4.6 mm i.d. , C18 reverse phase; Flow rate: 1.5mL/min unless otherwise indicated.

Solvent : [MeCN-H_2O/0.1% HCO_2H], 5-95% gradient 3.5min, 95% 2min; Column: Phenomenex Gemini 50x3 mm i.d. , C18 reverse phase; Flow rate: 1mL/min unless otherwise indicated.

Solvent : [MeCN-H_2O/0.1% HCO_2H], 5-95% gradient 6min, 95% 3min; Column: Phenomenex Gemini 50 x 4.6 mm i.d. , C18 reverse phase; Flow rate: 1mL/min unless otherwise indicated.

The preparative HPLC purification was conducted in the following manner:
Solvent : [MeCN-0.05% HCO_2H : H_2O-0.1% HCO_2H], 5-95% gradient 12min, 95% 3min; Waters X-Bridge 100x19 mm i.d. , C18 reverse phase; Flow rate: 16mL/min unless otherwise indicated.

Example 1) 3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-ethyl)-benzamide (Method A)

i) 3-(4-Chloro-benzylamino)-benzoic acid tert-butyl ester

A solution of 3-amino-*tert*-butylbenzoate (2 g, 0.01 mol), 4-chlorobenzaldehyde (1.4 g, 0.01 mol) and acetic acid (0.6 ml, 0.01 mol) in dichloromethane (80 ml) was stirred for 15 min. Sodium triacetoxyborohydride (4.2 g, 0.02 mol) was then added portion-wise over 10 min. The mixture was stirred at room temperature for 16 hrs. Water (50 ml) was added and the biphasic mixture stirred for 1 hr. The organic layer was separated, washed with saturated sodium bicarbonate solution (50 ml), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (dichloromethane / petroleum ether 80% to 100% v/v) to afford the title compound as a yellow solid (2.3 g). HPLC retention time 3.8 min. Mass spectrum (ES+) m/z 318 (M+H).

The following compounds were synthesised according to the method described using the appropriate starting materials:

5-Benzylamino-2-fluoro-N-isopropyl-benzamide

3-Benzylamino-benzoic acid tert-butyl ester

The following compounds were synthesised according to the method described using the appropriate starting materials with the the exception that the reaction was performed in the absence of acetic acid.

5-(4-Chloro-benzylamino)-2-fluoro-benzoic acid tert-butyl ester

The following compounds were synthesised according to the method described using the appropriate starting materials with the the exception that sodium borohydride was used as the reducing agent.

5-(4-chloro-benzylamino)-2-fluoro-N-isopropyl-benzamide

ii) 3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-benzoic acid tert-butyl ester

A solution of 3-(4-chloro-benzylamino)-benzoic acid *tert*-butyl ester (1 g, 0.03 mol), 1-Methyl-1H-Pyrazole-3-sulfonyl chloride (1.13 g, 0.06 mol) and pyridine (0.5 ml, 0.06 mol) in dichloromethane (40 ml) were refluxed for 48 hrs. On cooling, water (50 ml) was added with stirring, the organic layer was separated, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate/dichloromethane 0% to 10% v/v) to afford the title compound as a clear oil (1.33 g). Mass spectrum (ES+) m/z 49 (M+H).

The following compounds were synthesised according to the method described using the appropriate starting materials:

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-benzoic acid tert-butyl ester

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-benzoic acid tert-butyl ester

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-benzoic acid tert-butyl ester

3-(Benzenesulfonyl-benzyl-amino)-benzoic acid tert-butyl ester

3-[Benzyl-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-benzoic acid tert-butyl ester

3-[Benzyl-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-benzoic acid tert-butyl ester

3-[Benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-benzoic acid tert-butyl ester

3-[benzyl-(2-fluoro-benzenesulfonyl)-amino]-benzoic acid tert-butyl ester

3-[benzyl-(3-fluoro-benzenesulfonyl)-amino]-benzoic acid tert-butyl ester

3-[benzyl-(4-fluoro-benzenesulfonyl)-amino]-benzoic acid tert-butyl ester

3-(benzyl-methanesulfonyl-amino)-benzoic acid tert-butyl ester

iii) 3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-benzoic acid

A solution of 3-[(4-chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-benzoic acid *tert*-butyl ester (1.33 g, 0.02 mol) in a mixture of trifluoroacetic acid/dichloromethane (20 ml, 1:1 v/v) was stirred for 3 hrs. The reaction mixture was concentrated to dryness *in vacuo* to afford the title compound as a white solid (1.37 g). HPLC retention time 2.75 min. Mass spectrum (ES+) m/z 405.9 (M+).

The following compounds were synthesised according to the above method described using the appropriate starting materials:

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-benzoic acid

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-benzoic acid

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-benzoic acid

3-(benzenesulfonyl-benzyl-amino)-benzoic acid

3-[benzyl-(2-fluoro-benzenesulfonyl)-amino]-benzoic acid

3-[benzyl-(3-fluoro-benzenesulfonyl)-amino]-benzoic acid

3-[benzyl-(4-fluoro-benzenesulfonyl)-amino]-benzoic acid

The following compounds were synthesised according to the above method described using the appropriate starting materials with the following modifications;

A mixture of trifluoroacetic acid/dichloromethane (12.5 ml, 4:1 v/v) was used. On evaporation to dryness, the residue was treated with saturated sodium carbonate solution (50 ml) and partitioned with dichloromethane (50 ml). The basic aqueous solution was collected, acidified to pH 4-5 with glacial acetic acid and then extracted using ethyl acetate (2 x 50 ml). The organics were collected, dried over magnesium sulphate and concentrated to afford the following compounds:

3-[Benzyl-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-benzoic acid
3-[Benzyl-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-benzoic acid
3-[Benzyl-(2,4-dimethyl-thiazole-5-sulfonyl)-amino]-benzoic acid
3-[Benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-benzoic acid

***iv) 3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-ethyl)-benzamide* (1)**

A solution of 3-[(4-chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-benzoic acid (30 mg, 0.07 mmol), diisopropylethylamine (0.26 ml, 0.14 mmol), HATU (56 mg, 0.15 mmol) and 2-aminoethanol (9 μL, 0.14 mmol) were stirred in dry acetonitrile (3 ml) for 18 hrs. The reaction mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane (3 ml) and water (3 ml). The organic layer was separated and dried by passage through a hydrophobic frit, then concentrated *in vacuo*. The crude residue was purified by preparative HPLC to afford the title compound as an off white solid (11.9 mg). HPLC retention time 5.03 min. Mass spectrum (ES+) m/z 449 (M+H).

Other compounds prepared by Method A as described for Example 1 using the appropriate starting materials are listed in TABLE 1

Example 2) N-Benzyl-3-[benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-benzamide (Method B)

3-[Benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-benzoic acid (50 mg, 1.3 mmol), HATU (77 mg, 0.2 mmol), diisopropylethylamine (74 μL, 0.4 mmol) and benzylamine (22 μL, 0.2 mmol) were heated in dry acetonitrile under nitrogen at 60°C

for 18 hrs. After cooling, solvent was removed *in vacuo* and the residue purified by preparative TLC (100% ethyl acetate), to afford the title compound as a colourless oil (4.3 mg). HPLC retention time 5.46 min. Mass spectrum (ES+) m/z 462 (M+H).

Other compounds prepared by Method B as described for Example 2 using the appropriate starting materials are listed in TABLE 1

Example 3) 3-[Benzyl-(pyridine-3-sulfonyl)-amino]-N-isopropyl-benzamide

i) 3-(Pyridine-3-sulfonylamino)-benzoic acid tert-butyl ester

A solution of *tert*-butyl-3-aminobenzoate (100 mg, 0.5 mmol) and pyridine-3-sulfonylchloride (110 mg, 0.5 mmol) in pyridine (5 ml) was heated to 50°C for 90 min. On cooling, the reaction was diluted with toluene (100 ml) and concentrated *in vacuo*. This was repeated with further aliquots of toluene until all the pyridine had been removed to afford the title compound as a yellow oil (175 mg). HPLC retention time 4.27min. Mass spectrum (ES+) m/z 335 (M+H).

ii) 3-[Benzyl-(pyridine-3-sulfonyl)-amino]-benzoic acid

A solution of 3-(Pyridine-3-sulfonylamino)-benzoic acid *tert*-butyl ester (99 mg, 0.3 mmol), benzyl bromide (39 μL, 0.32 mmol) and Cesium Carbonate (145 mg, 0.4 mmol) in dimethylformamide (5 ml) was stirred for 16hrs. The reaction was diluted with ethyl acetate (50 ml) and washed with water (6 x 100 ml). The organic layer was separated, dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The oil was dissolved in trifluoroacetic acid/dichloromethane (1:5 v/v) (10 ml), stirred for 3 hrs and then concentrated *in vacuo* to afford the title compound as a white solid (58.7 mg). HPLC retention time 4.31 min. Mass spectrum (APCI+) m/z 369 (M+H).

***iii) 3-[Benzyl-(pyridine-3-sulfonyl)-amino]-N-isopropyl-benzamide* (3)**

3-[Benzyl-(pyridine-3-sulfonyl)-amino]-N-isopropyl-benzamide was prepared from 3-[benzyl-(pyridine-3-sulfonyl)-amino]-benzoic acid and isopropylamine according to the method described for Example 2. HPLC retention time 5.46min. Mass spectrum (APCI+) m/z 410 (M+H).

Example 4) 3-(Benzenesulfonyl-benzyl-amino)-N-(1H-indazol-6-yl)-benzamide (Method C)

A solution of 3-(benzenesulfonyl-benzyl-amino)-benzoic acid (25 mg, 0.068 mmol), 6-amino-1H-indazole (18 mg, 0.136 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (15 mg, 0.075 mmol), mercaptobenzothiazole (2 mg, 0.007 mmol) and triethylamine (24 μl, 0.17 mmol) in dry acetonitrile (2 ml) were stirred at room temperature for 15 hrs. The reaction mixture was quenched with water (10 ml) and extracted with dichloromethane (3 x 7 ml). The organics were combined, dried (PTFE frit) and concentrated *in vacuo*. The crude residue was purified by preparative TLC (10% diethyl ether in dichloromethane) to afford the title compound as a brown solid (15 mg, 45%). HPLC retention time 5.80min. Mass spectrum (ES+) m/z 483 (M+H).

Other compounds prepared by Method C as described for Example 4 using the appropriate starting materials are listed in TABLE 1

Example 5) 3-[(4-Acetylamino-benzenesulfonyl)-benzyl-amino]-N-isopropyl-benzamide (Method D)

i) 3-Benzylamino-benzoic acid

A solution of 3-benzylamino-benzoic acid tert-butyl ester (1g, 3 mmol) in trifluoroacetic acid/dichloromethane (1:5 v/v) (100 ml) was stirred for 16 hrs. The reaction was concentrated to dryness *in vacuo* to afford the title compound as a white solid. HPLC retention time 2.59 min. Mass spectrum (ES+) m/z 227.8 (M+).

The following compound was synthesised according to the above method described using the appropriate starting materials:

3-(4-Chloro-benzylamino)-benzoic acid

ii) 3-Benzylamino-N-isopropyl-benzamide

A solution of 3-benzylamino-benzoic acid (500 mg, 1.5 mmol), HATU (832 mg, 2 mmol), diisopropylethylamine (0.38 ml, 2 mmol) and isopropylamine (0.19 ml, 2 mmol) in acetonitrile was heated to 50°C for 16 hrs. On cooling, solvents were removed *in vacuo* and the residue partitioned between dichloromethane and water (50 ml/50 ml). The organic layer was separated, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate/dichloromethane 0% to 50% v/v) to afford the title compound as a white solid (242 mg). HPLC retention time 2.69 min. Mass spectrum (ES+) m/z 269.9 (M+H).

The following compound was synthesised according to the above method described using the appropriate starting materials:

3-(4-Chloro-benzylamino)-N-isopropyl-benzamide

***iii) 3-[(4-Acetylamino-benzenesulfonyl)-benzyl-amino]-N-isopropyl-benzamide* (5)**

3-Benzylamino-N-isopropyl-benzamide (20 mg, 0.07 mmol), pyridine (18 μL, 0.2 mmol) and 4-acetylamidobenzenesulfonyl chloride (50 mg, 0.2 mmol) were refluxed in dry dichloromethane for 18 hrs. On cooling, solvents were removed *in vacuo* and the residue purified by preparative LCMS to afford an off-white solid (0.5 mg). HPLC retention time 4.09 min. Mass spectrum (ES+) m/z 466 (M+H).

Other compounds prepared by Method D as described for Example 5 using the appropriate starting materials are listed in TABLE 1

Example 6) 5-[Benzyl-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide (Method E)

i) 5-Amino-2-fluoro-N-isopropyl-benzamide

A solution of 5-amino-2-fluorobenzoic acid (300 mg, 1.9 mmol), diisopropylethylamine (1 ml, 5.8 mmol), and isopropylamine (0.3 ml, 3.9 mmol) in acetonitrile was heated to 110°C in microwave for 45 min. This reaction was repeated 5 times and the crude products combined then concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2) eluting with ethyl acetate/dichloromethane

(0% to 10% v/v) to afford the title compound as a yellow solid (2.31 g). HPLC retention time 3.93min. Mass spectrum (ES+) m/z 197 (M+H).

ii) 5-Benzylamino-2-fluoro-N-isopropyl-benzamide

5-Benzylamino-2-fluoro-N-isopropyl-benzamide was synthesized from 5-amino-2-fluoro-N-isopropyl-benzamide and benzaldehyde according to the method described in Example 1

***iii) 5-[Benzyl-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide* (6)**

A solution of 5-benzylamino-2-fluoro-N-isopropyl-benzamide (30 mg, 0.1 mmol), diisopropylethylamine (37 μL, 0.2 mmol), and 3-oxo-3,4-dihydro-2H-1,4-benzooxazine-6-sulfonyl chloride (52 mg, 0.2 mmol) was refluxed in dry dichloromethane (3 ml) for 18 hrs. On cooling, water (10 ml) was added with stirring. The organic layer was separated, dried (PTFE frit), then concentrated *in vacuo*. The crude residue was purified by preparative TLC (10% v/v ethyl acetate/dichloromethane) to afford the title compound as an off white solid (23 mg). HPLC retention time 7.72 min. Mass spectrum (ES+) m/z 499 (M+H).

Other compounds prepared by Method E as described for Example 6 using the appropriate starting materials are listed in TABLE 1

Example 7) 3-[(4-Chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide (Method F)

3-(4-Chloro-benzylamino)-N-isopropyl-benzamide (30 mg, 0.1 mmol), diisopropylethylamine (35 μL, 0.2 mmol) and 1-methyl-1H-pyrazole-5-sulfonyl chloride (36 mg, 0.2 mmol) were stirred in dry dichloromethane (2 ml) at room temperature for 72 hrs. The reaction was diluted with dichloromethane (5 ml) and water (5 ml) with stirring. The organics were collected, dried (PTFE frit) and concentrated *in vacuo*. The residue was purified by preparative TLC (10% ethyl

acetate/dichloromethane) to yield the product as an off-white solid (11.9 mg). HPLC retention time 8.04 min. Mass spectrum (ES+) m/z 447 (M+H).

Other compounds prepared by Method F as described for Example 7 using the appropriate starting materials are listed in TABLE 1

Example 8

Kv1.3 Autopatch Electrophysiology Method

Cells stably transfected with cDNA for human Kv1.3 (in pcDNA3.1) were grown in Ex-cell 302 serum-free medium for CHO cells, supplemented with 10μl/ml [100x] glutamine, 500μg/ml G418 (gentimicin), and 1% HT supplement (50x, hypoxanthine and thymidine). Compounds were tested on these cells using the AutoPatch technology in whole cell mode.

The external bathing solution contained (in mM): 150 NaCl, 10 KCl, 1 $MgCl_2$, 3 $CaCl_2$, 10 HEPES, pH 7.4 with NaOH. Patch pipettes were filled with an electrode solution of composition (in mM): 100 K-Gluconate, 20 KCl, 1 $MgCl_2$, 1 $CaCl_2$, 10 HEPES, 11 EGTA, 5 ATP-Na_2, 2 Glutathione pH 7.2 with KOH.

Compounds were dissolved in DMSO (100%) and made up in the external bather at a concentration of 1μM immediately prior to use. All experiments were conducted at room temperature.

A cell suspension (10ml), with a density of $6x10^6$ cells, was aliquoted into a 15ml centrifuge tube and stored at 4°C before use. Prior to use a tube was taken and centrifuged at 1000 rpm for 4 mins at room temperature. The supernatant was then discarded, leaving a cell pellet at the bottom of the tube. The pellet was then resuspended using 1 ml of cold (4°C), filtered (0.22μm), 0.05 % BSA/bather solution (0.05g BSA/100ml bather). The bottom of the tube was manually agitated followed by gentle tituration. The cell suspension was then placed in the AutoPatch™ temperature controlled cell-hotel at 14°C and regularly titurated.

A length of Teflon capillary tubing was dipped into the cell suspension solution, and a column of fluid was taken up by negative pressure. The column of fluid was in

electrically connectivity with a Ag/AgCl reference electrode. Borosilicate glass patch pipettes (from 1.5mm OD, thin-walled filamented, GC150-TF capillary glass, Harvard) were pulled using a DMZ pipette puller (Zeitz Instruments), and were back-filled using the internal pipette solution, being careful that no bubbles remained at the tip or in the body of the pipette. Patch pipettes typically had resistances of 2.5-3.5 MΩ. Once filled, the pipette tip and a proportion of the shaft (~ 15mm) were dipped into Sigmacote (Sigma). The recording pipettes were placed in a multiwell array and mounted on the AutoPatch™ machine. Automated patch-clamping and drug-application was initiated by the operator, but thereafter AutoPatch.exe continued the experiment providing that pre-set conditions and criteria were satisfied.

Whole cell patch-clamp recordings were made using the AutoPatch™ rig, which incorporated an EPC9 or EPC10 amplifier (HEKA, Germany) under control of Pulse software (v8.54 or v8.76, HEKA, Germany), a cell applicator, automated drug application system (DAS), valve controller (VF1) and a suction device all at room temperature. This equipment was completely under the control of AutoPatch.exe and operator intervention was only made when there was a requirement to refill the bather reservoirs or to prevent the loss of a cell due to a technical error.

Qualification stages prior to perfusion and drug application ensured that the observed current met the criteria for the experiment. Cells were continuously perfused with external solution at a flow rate of ~2 ml/minute. The perfusion chamber had a working volume of 80-85µl that allowed for rapid exchange of drug solutions.

Electrophysiology voltage-step protocols and analysis of data was performed as follows. Data were sampled at 5kHz, and filtered with a –3dB bandwidth of 2.5kHz. Cells were held at a voltage of –80mV. Currents were evoked by a voltage step to +30mV for 500ms in duration applied every 15s. Online analysis of the hKv1.3 current during the application of compounds was performed by the Pulse (v8.54 or v8.76, HEKA, Germany), Excel (Microsoft, USA) and AutoPatch™ software, with

the total charge measured during the whole of voltage step. Inhibition of charge movement in the presence of drug was calculated relative to control.

Example 9

Kv1.5 Autopatch Electrophysiology Method

The external bathing solution contained (in mM): 150 NaCl, 10 KCl, 100 Potassium Gluconate, 3 $MgCl_2$, 1 $CaCl_2$, 10 HEPES, pH 7.4. Patch pipettes were filled with an electrode solution of composition (in mM): 160 KCl, 0.5 $MgCl_2$, 10 HEPES, 1 EGTA, pH 7.4 with KOH.

Compounds were dissolved in DMSO (100%) and made up in the external bather at a concentration of 1μM. All experiments were conducted at room temperature (22-24°C).

A cell suspension (10ml), with a density of 100,000 cells/ml, was aliquoted into a 15ml centrifuge tube and transferred to an incubator (37°C, 5% CO_2) for approximately one hour before use. Following 60 min incubation, a tube was taken and centrifuged at 1000 rpm for 4 mins at room temperature. 9.5ml supernatant was thence discarded, leaving a cell pellet at the bottom of the tube. The pellet was then resuspended using 100 μl of cold (4°C), filtered (0.22μm), 0.2 % BSA/bather solution (0.02g BSA/10ml bather). The bottom of the tube was manually agitated gently until the solution became cloudy with cells. The 100μl cell resuspension solution was then stored on the bench at 4°C (using a Peltier-based temperature control device) until used.

A length of capillary glass (1B150F-4, WPI) was dipped into the cell suspension solution, such that ~ 3cm column of fluid was taken up by capillary action. A Ag/AgCl wire was dropped into the non-dipped end of the capillary also. The outside of the solution-filled end of the capillary was then dried and the capillary was loaded into the AutoPatch™.

Borosilicate glass patch pipettes (from 1.5mm OD, thin-walled filamented, GC150-TF capillary glass, Harvard) were pulled using a DMZ pipette puller (Zeitz Instruments), and were back-filled using the internal pipette solution, being careful that no bubbles remain at the tip or in the body of the pipette. Patch pipettes typically had resistances of 2.3-3.5 MΩ. Once filled, the pipette tip and a proportion of the shaft (~ 15mm) were dipped into Sigmacote (Sigma). The recording pipette was then loaded into the AutoPatch™. Automated patch-clamping was initiated by the operator, but thereafter AutoPatch.exe continued the experiment providing that pre-set conditions and criteria were satisfied.

Whole cell patch-clamp recordings were made using the AutoPatch™ rig, which incorporated an EPC9 amplifier (HEKA, Germany) under control of Pulse software (v8.54, HEKA, Germany), a motion controller with 2 translators (Newport, UK), valve controller (VF1) and a c-level suction device all at room temperature (22-24°C). This equipment was completely under the control of AutoPatch.exe and operator intervention was only made when there was a requirement to refill the drug reservoirs or to prevent the loss of a cell due to a technical error. Cells with an R_{series} greater than 18 MΩ were discounted from the experiment.

Qualification stages prior to perfusion and drug application ensured that the observed current met the criteria for the experiment. Only those cells with an $I_K > 500$ pA were used for experiments. Cells were continuously perfused with external solution at a flow rate of 1.8-2 ml/minute. The perfusion chamber had a working volume of 80-85µl and allowed for rapid exchange of drug solutions. Online analysis of the $hK_v1.5$ current during the application of compounds was performed by the AutoPatch™ software. Voltage-step protocols and analysis of data was performed as described for conventional electrophysiology.

Electrophysiology voltage-step protocols and analysis of data was performed as follows. Data was sampled at 5kHz, and filtered with a –3dB bandwidth of 2.5kHz. Cells were held at a voltage of –80mV. Currents were evoked to a voltage step for

1000ms in duration at 0mV every 5s. Currents were analysed using Pulsefit software (v8.54, HEKA, Germany), with the total charge measured during the whole of the voltage step. All other plots were produced using Igor Pro (WaveMetrics)

TABLE 1

Summary of synthesis methods, characterisation data and biological activity

Example	Name	Method	LCMS Ret.n time	(ES+) *m/z* (M+H)	hKv1.3 %inh.	hKv1.5 %inh.
1	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-ethyl)-benzamide	A	5.0	449	86	48
2	N-Benzyl-3-[benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-benzamide	B	5.5	462	69	16
3	3-[Benzyl-(pyridine-3-sulfonyl)-amino]-N-isopropyl-benzamide	B	5.5	410	92	52
4	3-(Benzenesulfonyl-benzyl-amino)-N-(1H-indazol-6-yl)-benzamide	C	5.8	483	88	99
5	3-[(4-Acetylamino-benzenesulfonyl)-benzyl-amino]-N-isopropyl-benzamide	D	4.1	466	45	18
6	5-[Benzyl-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	7.7	499	84	46
7	3-[(4-Chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide	F	8.0	447	57	54
10	3-(Benzenesulfonyl-benzyl-amino)-N-benzyl-benzamide	B	4.7	457	94	83
11	3-(Benzenesulfonyl-benzyl-amino)-N-isopropyl-benzamide	B	4.5	409	89	61
12	3-(Benzenesulfonyl-benzyl-amino)-N-phenethyl-benzamide	B	4.7	471	100	98
13	N-Benzyl-N-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide	B	4.9	511	97	94
14	N-Benzyl-N-[3-(3-phenyl-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide	B	5.0	511	74	81
15	N-Benzyl-N-[3-(2-phenyl-morpholine-4-carbonyl)-phenyl]-benzenesulfonamide	B	5.0	513	91	64
16	N-Benzyl-N-[3-(4-phenoxy-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide	B	5.4	527	97	86
17	3-(Benzenesulfonyl-benzyl-amino)-N-(3-phenyl-propyl)-benzamide	B	5.6	484	97	92
18	3-(Benzenesulfonyl-benzyl-amino)-N-methyl-benzamide	B	4.2	381	74	20
19	3-(benzenesulfonyl-benzyl-amino)-N-tert-butyl-benzamide	C	7.5	423	89	67

20	N-benzyl-N-[3-(3-phenyl-piperidine-1-carbonyl)-phenyl]-methanesulfonamide	C	7.1	449	89	46
21	N-benzyl-N-[3-(2-phenyl-morpholine-4-carbonyl)-phenyl]-methanesulfonamide	C	6.7	451	47	16
22	N-benzyl-N-[3-(4-phenoxy-piperidine-1-carbonyl)-phenyl]-methanesulfonamide	C	6.9	465	63	15
23	N-benzyl-N-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-methanesulfonamide	C	7.1	449	62	13
24	1-Methyl-1H-imidazole-4-sulfonic acid benzyl-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-amide	B	5.9	515	61	13
25	N-Benzyl-N-[3-(morpholine-4-carbonyl)-phenyl]-benzenesulfonamide	B	5.7	437	66	19
26	3-(benzenesulfonyl-benzyl-amino)-N-pyridin-2-ylmethyl-benzamide	C	5.6	445	79	88
27	3-(benzenesulfonyl-benzyl-amino)-N-(1H-indazol-5-yl)-benzamide	C	5.7	483	95	81
28	3-(benzenesulfonyl-benzyl-amino)-N-(4-imidazol-1-yl-phenyl)-benzamide	C	5.8	509	98	98
29	3-(benzenesulfonyl-benzyl-amino)-N-(4-pyrazol-1-yl-phenyl)-benzamide	C	6.3	509	99	98
30	3-(benzenesulfonyl-benzyl-amino)-N-[1,3,4]thiadiazol-2-yl-benzamide	C	5.7	451	95	86
31	3-(benzenesulfonyl-benzyl-amino)-N-thiazol-2-yl-benzamide	C	6.1	450	93	95
32	N-[4-(aminocarbonyl)phenyl]-3-[benzyl(phenylsulfonyl)amino]benzamide	C	5.5	503 NH_3 salt	95	86
33	N-[3-(aminocarbonyl)phenyl]-3-[benzyl(phenylsulfonyl)amino]benzamide	C	5.5	503 NH_3 salt	92	85
34	3-(benzenesulfonyl-benzyl-amino)-N-phenyl-benzamide	C	6.4	443	91	84
35	1-Methyl-1H-imidazole-4-sulfonic acid benzyl-[3-(2-phenyl-morpholine-4-carbonyl)-phenyl]-amide	B	5.6	517	75	16
36	3-[Benzyl-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-N-isopropyl-benzamide	B	5.1	427	88	20
37	3-[Benzyl-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide	B	5.4	413	83	21
38	3-[Benzyl-(2,4-dimethyl-thiazole-5-sulfonyl)-amino]-N-isopropyl-benzamide	B	5.8	444	50	10

39	N-benzyl-2-fluoro-N-[3-(morpholine-4-carbonyl)-phenyl]-benzenesulfonamide	C	5.7	455	58	12
40	3-[benzyl-(2-fluoro-benzenesulfonyl)-amino]-N,N-dimethyl-benzamide	C	5.8	413	47	16
41	3-[benzyl-(3-fluoro-benzenesulfonyl)-amino]-N,N-dimethyl-benzamide	C	5.8	413	41	7
42	N-benzyl-4-fluoro-N-[3-(morpholine-4-carbonyl)-phenyl]-benzenesulfonamide	C	5.8	455	61	30
43	3-[benzyl-(4-fluoro-benzenesulfonyl)-amino]-N,N-dimethyl-benzamide	C	5.8	413	77	31
44	3-[benzyl-(4-fluoro-benzenesulfonyl)-amino]-N-isopropyl-benzamide	C	8.0	427	90	65
45	1-Methyl-1H-imidazole-4-sulfonic acid benzyl-{3-[4-(2-fluoro-phenyl)-piperazine-1-carbonyl]-phenyl}-amide	B	4.1	534	53	30
46	3-[benzyl-(2-fluoro-benzenesulfonyl)-amino]-N-isopropyl-benzamide	C	6.0	427	74	12
47	3-[benzyl-(3-fluoro-benzenesulfonyl)-amino]-N-isopropyl-benzamide	C	6.1	427	76	44
48	1-Methyl-1H-imidazole-4-sulfonic acid benzyl-[3-(4-cyclohexylmethyl-piperazine-1-carbonyl)-phenyl]-amide	B	2.8	536	59	10
49	3-[Benzyl-(2,3-dihydro-benzofuran-5-sulfonyl)-amino]-N-isopropyl-benzamide	D	4.6	451	99	98
50	3-[Benzyl-(2,2-dimethyl-chroman-6-sulfonyl)-amino]-N-isopropyl-benzamide	D	5.2	493	92	85
51	3-[Benzyl-(2,3-dihydro-benzo[1,4]dioxine-6-sulfonyl)-amino]-N-isopropyl-benzamide	D	4.6	467	97	98
52	3-[(1-Acetyl-2,3-dihydro-1H-indole-5-sulfonyl)-benzyl-amino]-N-isopropyl-benzamide	D	4.4	492	78	38
53	3-[Benzyl-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide	D	4.4	413	95	83
54	3-[Benzyl-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl)-amino]-N-isopropyl-benzamide	D	4.7	480	86	80
55	3-[Benzyl-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-N-isopropyl-benzamide	D	4.3	480	71	48
56	2,3-Dihydro-benzo[1,4]dioxine-6-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide	D	4.5	495	79	37

57	4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide	D	4.5	508	46	18
58	Benzo[1,2,5]oxadiazole-4-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide	D	4.7	479	41	25
59	Benzo[1,3]dioxole-5-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide	D	4.7	481	69	41
60	3-(Benzenesulfonyl-benzyl-amino)-N-cyclopropyl-benzamide	B	4.4	407	52	54
61	3-(Benzenesulfonyl-benzyl-amino)-N-cyclobutyl-benzamide	B	4.6	421	77	82
62	3-(Benzenesulfonyl-benzyl-amino)-N-cyclopentyl-benzamide	B	4.8	435	86	92
63	3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide	B	4.3	439	93	86
64	3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-1-methyl-ethyl)-benzamide	B	4.0	425	54	83
65	3-(Benzenesulfonyl-benzyl-amino)-N-(1-hydroxymethyl-propyl)-benzamide	B	4.1	439	90	47
66	3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-propyl)-benzamide	B	3.9	425	88	47
67	3-(Benzenesulfonyl-benzyl-amino)-N-isobutyl-benzamide	B	4.8	423	89	78
68	3-(Benzenesulfonyl-benzyl-amino)-N-ethyl-benzamide	B	4.3	395	80	43
69	3-(Benzenesulfonyl-benzyl-amino)-N-(2-methoxy-ethyl)-benzamide	B	4.2	425	82	43
70	3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-ethyl)-benzamide	B	3.8	411	81	38
71	3-(Benzenesulfonyl-benzyl-amino)-N-propyl-benzamide	B	4.6	409	92	75
72	3-(Benzenesulfonyl-benzyl-amino)-N-(3-hydroxy-propyl)-benzamide	B	3.9	425	78	57
73	3-(Benzenesulfonyl-benzyl-amino)-N-(4-hydroxy-butyl)-benzamide	B	4.0	439	89	45
74	3-(Benzenesulfonyl-benzyl-amino)-N-cyclopropylmethyl-benzamide	B	4.6	421	89	79
75	3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-1-hydroxymethyl-ethyl)-benzamide	B	3.6	441	69	37
76	3-(Benzenesulfonyl-benzyl-amino)-N-((R)-1-hydroxymethyl-propyl)-benzamide	B	4.2	439	85	72

77	5-[(Benzo[1,2,5]oxadiazole-4-sulfonyl)-benzyl-amino]-2-fluoro-N-isopropyl-benzamide	E	4.3	469	83	73
78	5-(Benzenesulfonyl-benzyl-amino)-2-fluoro-N-isopropyl-benzamide	E	4.3	427	98	74
79	5-[Benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	7.3	431	58	13
80	5-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	4.4	445	92	94
81	5-[Benzyl-(2,3-dihydro-benzo[1,4]dioxine-6-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	4.3	485	92	78
82	5-[Benzyl-(4-cyano-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	4.3	452	42	46
83	5-[Benzyl-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	4.3	452	100	96
84	5-[Benzyl-(2-cyano-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	4.2	452	80	58
85	5-[(Benzo[1,3]dioxole-5-sulfonyl)-benzyl-amino]-2-fluoro-N-isopropyl-benzamide	E	4.3	471	100	89
86	5-[Benzyl-(2,3-dihydro-benzofuran-5-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	4.7	469	97	78
87	5-[Benzyl-(pyridine-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	3.8	428	91	75
88	5-[(4-Acetylamino-benzenesulfonyl)-benzyl-amino]-2-fluoro-N-isopropyl-benzamide	E	3.9	484	52	45
89	3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-isopropyl-benzamide	E	7.9	444	99	87
90	3-[(4-Chloro-benzyl)-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-N-isopropyl-benzamide	F	7.8	514	80	69
91	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide	E	7.8	447	92	92
92	3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-isopropyl-benzamide	E	7.9	447	79	40

93	5-[Benzyl-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	7.7	431	74	28
94	3-[(4-Chloro-benzyl)-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-N-isopropyl-benzamide	F	8.4	514	76	82
95	3-[(4-Chloro-benzyl)-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-N-isopropyl-benzamide	F	7.5	461	94	83
96	5-[Benzyl-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	7.3	445	61	21
97	5-[Benzyl-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	E	7.9	431	48	17
98	5-[(4-chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	D	8.1	464	96	84
99	5-[(4-chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	D	8.0	465	98	87
100	5-[(4-chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	D	8.2	465	74	46
101	5-[(4-chloro-benzyl)-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	D	7.7	479	94	38
102	5-[(4-chloro-benzyl)-(1-methyl-1H-pyrazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide	D	7.9	465	75	55
103	5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-ethyl)-benzamide	A	7.6	488	100	99
104	5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(1-hydroxymethyl-propyl)-benzamide	A	7.9	516	101	98
105	N-(4-Chloro-benzyl)-3-cyano-N-[4-fluoro-3-(3-hydroxy-azetidine-1-carbonyl)-phenyl]-benzenesulfonamide	A	7.6	500	82	50
106	5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-1-hydroxymethyl-ethyl)-benzamide	A	7.4	518	94	77
107	5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-1-methyl-ethyl)-benzamide	A	7.7	502	98	99

108	5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide	A	8.0	516	100	99
109	5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-methoxy-ethyl)-benzamide	A	8.0	502	100	99
110	N-(4-Chloro-benzyl)-3-cyano-N-[4-fluoro-3-(3-hydroxy-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide	A	7.8	528	89	85
111	N-(4-Chloro-benzyl)-3-cyano-N-[4-fluoro-3-((R)-3-hydroxy-pyrrolidine-1-carbonyl)-phenyl]-benzenesulfonamide	A	7.6	514	53	41
112	3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-hydroxy-ethyl)-benzamide	A	7.0	446	91	65
113	3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-hydroxy-1-methyl-ethyl)-benzamide	A	7.1	460	95	70
114	3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(1-hydroxymethyl-propyl)-benzamide	A	7.4	474	77	45
115	Pyridine-3-sulfonic acid (4-chloro-benzyl)-[3-(3-hydroxy-azetidine-1-carbonyl)-phenyl]-amide	A	7.0	458	50	10
116	Pyridine-3-sulfonic acid (4-chloro-benzyl)-[3-(3-hydroxy-piperidine-1-carbonyl)-phenyl]-amide	A	7.3	486	38	13
117	3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide	A	7.5	474	95	91
118	3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-methoxy-ethyl)-benzamide	A	7.5	460	98	88
119	3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-cyclopropyl-benzamide	A	7.7	442	99	98
120	3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-cyclopentyl-benzamide	A	8.1	470	96	84
121	Pyridine-3-sulfonic acid (4-chloro-benzyl)-[3-((R)-3-fluoro-pyrrolidine-1-carbonyl)-phenyl]-amide	A	7.6	474	45	20
122	3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-cyclobutyl-benzamide	A	8.0	456	100	97

123	Pyridine-3-sulfonic acid [3-(azetidine-1-carbonyl)-phenyl]-(4-chloro-benzyl)-amide	A	7.6	442	75	52
124	3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-methyl-benzamide	A	7.1	419	73	10
125	3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-ethyl-benzamide	A	7.3	433	93	54
126	3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-(2-methoxy-ethyl)-benzamide	A	7.2	463	66	21
127	3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-cyclopropyl-benzamide	A	7.3	445	95	49
128	3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-cyclopentyl-benzamide	A	7.8	473	93	69
129	3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-cyclobutyl-benzamide	A	8.4	459	96	57
130	1-Methyl-1H-imidazole-4-sulfonic acid [3-(azetidine-1-carbonyl)-phenyl]-(4-chloro-benzyl)-amide	A	7.2	445	56	25
131	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-methyl-benzamide	A	5.4	419	99	78
132	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-ethyl-benzamide	A	5.6	433	100	99
133	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-methoxy-ethyl)-benzamide	A	5.4	463	98	84
134	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-cyclopropyl-benzamide	A	5.6	445	93	97
135	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-cyclobutyl-benzamide	A	5.9	459	99	99
136	1-Methyl-1H-pyrazole-3-sulfonic acid [3-(azetidine-1-carbonyl)-phenyl]-(4-chloro-benzyl)-amide	A	5.5	445	74	64
137	1-Methyl-1H-pyrazole-3-sulfonic acid (4-chloro-benzyl)-[3-(3-methyl-piperidine-1-carbonyl)-phenyl]-amide	A	6.2	487	84	69
138	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-cyclopentyl-benzamide	A	6.0	473	100	100

139	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-1-methyl-ethyl)-benzamide	A	5.2	463	82	50
140	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(1-hydroxymethyl-propyl)-benzamide	A	5.3	477	97	70
141	3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide	A	5.5	477	100	78
139	3-[(4-chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-cyclobutyl-benzamide	B	6.1	459	47	59
140	3-[(4-chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-cyclopentyl-benzamide	B	9.3	473	87	55

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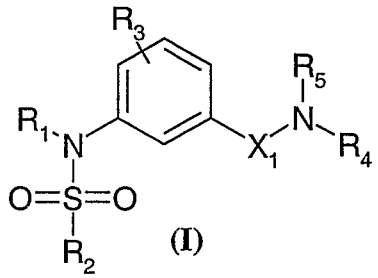
CLAIMS:

1. A compound of formula (I)



(I)

Or its salts or pharmaceutically acceptable derivatives thereof wherein;

X_1 is selected from a group consisting of CH_2, C(=O), C(=NH), NC(=O),

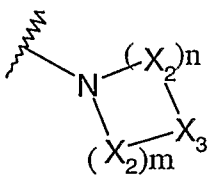
R_1 is selected from the group consisting of optionally substituted arylalkyl, and optionally substituted heteroarylalkyl

R_2 is selected from the group consisting of optionally substituted alkyl, preferably CH_3, optionally substituted aryl or heteroaryl or $NR_{24}R_{25}$

R_3 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxy, aryloxy, optionally substituted alkyl, optionally substituted amino, optionally substituted amino sulfonyl or nitrile;

R_4 is selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted acyl, optionally substituted sulfonyl, optionally substituted sulfamoyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroaryl

R_5 is may be hydrogen, an optionally substituted alkyl, preferably CH_3 or, NR_4R_5 may form an optionally substituted saturated or partially saturated 4-7 membered ring with the general formula (II).



(II)

Wherein;

X_2 is C(=O), or $C(R_6)_2$,

X_3 is $C(R_7)_2$, NH, $N(R_8)$, O or S

R_6 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_7 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

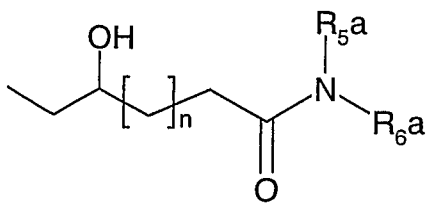
R_8 is optionally substituted acyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

R_{24} and R_{25} are the same or different and each represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl,

n = 1 or 2

m = 1, 2 or 3

With the proviso that when X_1 is C=O and R_5 is H then R_4 is not:



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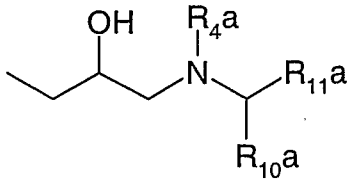

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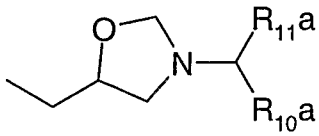
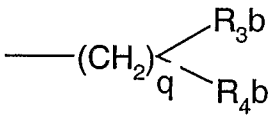


Where R_4a, R_5a and R_6a are each independently H, C_{1-6}alkyl, aryl, heteroaryl, cycloalkyl, or aryl-C_{1-6}alkyl;

$R_{10}a$ is H or C_{1-6}alkyl; and

$R_{11}a$ is C_{1-6}alkyl or aryl-C_{1-6}alkyl

and when X_1 is C=O or CH_2 and R_5 is H then R_4 is not:



Where q is 0 to 5,

R_3b is H, OH or alkoxy and

R_4b is NH_2, phenyl or a C_{3-10} heterocycle.

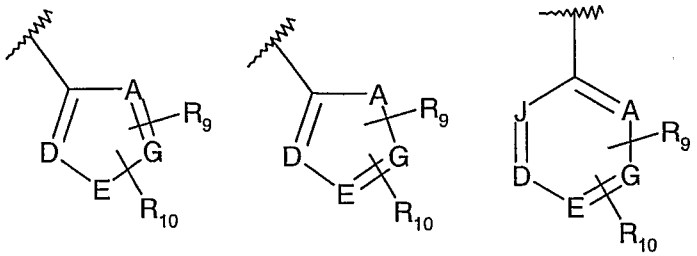
2. A compound according to claim 1 wherein X_1 is C(=O)

3. A compound according claim 2 wherein;

R_2 is selected from $NR_{24}R_{25}$.

4. A compound according to claim 2 wherein;

R_2 is selected from formula (III), (IV) or (V)



(III) (IV) (V)

Wherein;

A, D, E, G, and J are the same or different and each represents C, or N with the proviso that in each instance at least one of A, D, E, G, or J is N;

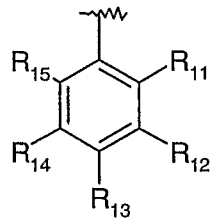
Where when R_2 is formula (III), E may also represent O or S; and

Where when R_2 is formula (IV), A may also represent O or S;

R_9 and R_{10} are the same or different and each represents hydrogen, halogen, hydroxyl, nitrile, optionally substituted amino, optionally substituted acyl, optionally substituted C_{1-3} alkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl or may be taken together to form an optionally substituted saturated or partially saturated 5-7 membered heterocyclic or carbocyclic ring.

5. A compound according to claim 2 wherein;

R_2 is formula (VI)

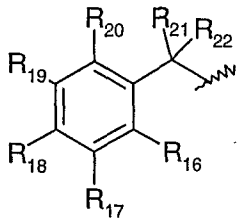


(VI)

Where R_{11}, R_{12}, R_{13}, R_{14}, and R_{15} are the same or different and each represents hydrogen, halogen, hydroxyl, optionally substituted amino, optionally substituted acyl, nitrile, optionally substituted C_{1-3} alkyl, any of the pairs R_{11} and R_{12}, or R_{12} and R_{13}, or R_{13} and R_{14}, or R_{14} and R_{15} or may be taken together to form an optionally substituted saturated or partially saturated 5-7 membered heterocyclic or carbocyclic ring.

6. A compound according to the preceding claims wherein R_1 has the formula;

(VII)



(VII)

Wherein;

R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are the same or different and each represents hydrogen, halogen, hydroxyl, optionally substituted amino, optionally substituted acyl, nitrile, optionally substituted C_{1-3} alkyl or optionally substituted alkoxy;

R_{21} and R_{22} are the same or different and each represents hydrogen, hydroxyl, and optionally substituted C_{1-3} alkyl.

7. A compound according to the preceding claims wherein;

R_3 is H, F or CH_3.

8. A compound according to the preceding claims wherein;

R_4 is selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroaryl.

9. A compound according to the preceding claims wherein;

R_5 is selected from hydrogen, optionally substituted alkyl, preferably CH_3 or NR_4R_5 may form an optionally substituted saturated or partially saturated 4-7 membered ring with the general formula (II)

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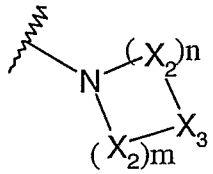


(II)

Wherein;

X_2 is C(=O), or $C(R_6)_2$,

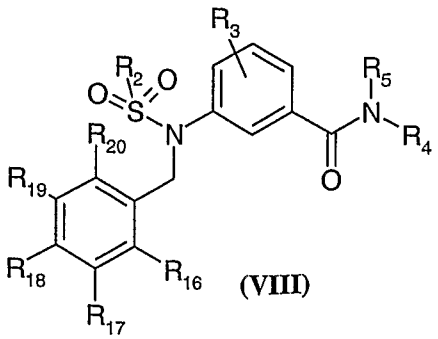
X_3 is $C(R_7)_2$, NH, $N(R_8)$, O or S

R_6 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_7 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl; and

R_8 is optionally substituted acyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl.

10. A compound according to the preceding claims with the Formula (VIII);

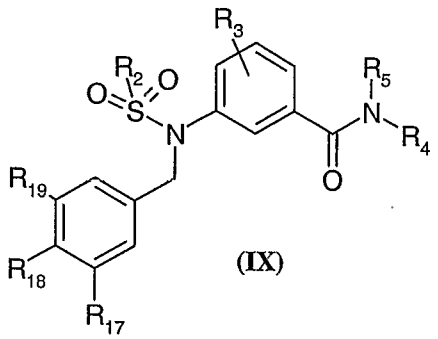


(VIII)

Wherein;

R_2 is selected from $NR_{24}R_{25}$ or formula (III), (IV) (V) or (VI), R_3, R_4, R_5, R_{16}, R_{17}, R_{18}, R_{19} and R_{20} are as defined above.

11. A compound according to the preceding claims with the Formula (IX);



(IX)

Wherein;

R_2 is selected from $NR_{24}R_{25}$ or formula (III), (IV), (V) or (VI) as defined above ; and

R_3, R_4, R_5, R_{17}, R_{18}, and R_{19} are as defined above.

12. A compound according to any of the preceding claims selected from:

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-ethyl)-benzamide

N-Benzyl-3-[benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-benzamide

3-[Benzyl-(pyridine-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(1H-indazol-6-yl)-benzamide

3-[(4-Acetylamino-benzenesulfonyl)-benzyl-amino]-N-isopropyl-benzamide

5-[Benzyl-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-benzyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-isopropyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-phenethyl-benzamide

N-Benzyl-N-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide

N-Benzyl-N-[3-(3-phenyl-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide

N-Benzyl-N-[3-(2-phenyl-morpholine-4-carbonyl)-phenyl]-benzenesulfonamide

N-Benzyl-N-[3-(4-phenoxy-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide

3-(Benzenesulfonyl-benzyl-amino)-N-(3-phenyl-propyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-methyl-benzamide

3-(benzenesulfonyl-benzyl-amino)-N-tert-butyl-benzamide

N-Benzyl-N-[3-(3-phenyl-piperidine-1-carbonyl)-phenyl]-methanesulfonamide

N-Benzyl-N-[3-(2-phenyl-morpholine-4-carbonyl)-phenyl]-methanesulfonamide

N-Benzyl-N-[3-(4-phenoxy-piperidine-1-carbonyl)-phenyl]-methanesulfonamide

N-Benzyl-N-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-methanesulfonamide

1-Methyl-1H-imidazole-4-sulfonic acid benzyl-[3-(4-phenyl-piperidine-1-carbonyl)-phenyl]-amide

N-Benzyl-N-[3-(morpholine-4-carbonyl)-phenyl]-benzenesulfonamide

3-(Benzenesulfonyl-benzyl-amino)-N-pyridin-2-ylmethyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(1H-indazol-5-yl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(4-imidazol-1-yl-phenyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(4-pyrazol-1-yl-phenyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-[1,3,4]thiadiazol-2-yl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-thiazol-2-yl-benzamide

N-[4-(Aminocarbonyl)phenyl]-3-[benzyl(phenylsulfonyl)amino]benzamide

N-[3-(Aminocarbonyl)phenyl]-3-[benzyl(phenylsulfonyl)amino]benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-phenyl-benzamide

1-Methyl-1H-imidazole-4-sulfonic acid benzyl-[3-(2-phenyl-morpholine-4-carbonyl)-phenyl]-amide

3-[Benzyl-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(2,4-dimethyl-thiazole-5-sulfonyl)-amino]-N-isopropyl-benzamide

N-Benzyl-2-fluoro-N-[3-(morpholine-4-carbonyl)-phenyl]-benzenesulfonamide

3-[Benzyl-(2-fluoro-benzenesulfonyl)-amino]-N,N-dimethyl-benzamide

3-[Benzyl-(3-fluoro-benzenesulfonyl)-amino]-N,N-dimethyl-benzamide

N-Benzyl-4-fluoro-N-[3-(morpholine-4-carbonyl)-phenyl]-benzenesulfonamide

3-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-N,N-dimethyl-benzamide

3-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-N-isopropyl-benzamide

1-Methyl-1H-imidazole-4-sulfonic acid benzyl-{3-[4-(2-fluoro-phenyl)-piperazine-1-carbonyl]-phenyl}-amide

3-[Benzyl-(2-fluoro-benzenesulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(3-fluoro-benzenesulfonyl)-amino]-N-isopropyl-benzamide

1-Methyl-1H-imidazole-4-sulfonic acid benzyl-[3-(4-cyclohexylmethyl-piperazine-1-carbonyl)-phenyl]-amide

3-[Benzyl-(2,3-dihydro-benzofuran-5-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(2,2-dimethyl-chroman-6-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(2,3-dihydro-benzo[1,4]dioxine-6-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(1-Acetyl-2,3-dihydro-1H-indole-5-sulfonyl)-benzyl-amino]-N-isopropyl-benzamide

3-[Benzyl-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonyl)-amino]-N-isopropyl-benzamide

3-[Benzyl-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-N-isopropyl-benzamide

2,3-Dihydro-benzo[1,4]dioxine-6-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide

4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide

Benzo[1,2,5]oxadiazole-4-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide

Benzo[1,3]dioxole-5-sulfonic acid benzyl-[3-(morpholine-4-carbonyl)-phenyl]-amide

3-(Benzenesulfonyl-benzyl-amino)-N-cyclopropyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-cyclobutyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-cyclopentyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-1-methyl-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(1-hydroxymethyl-propyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-propyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-isobutyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-ethyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-methoxy-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-propyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(3-hydroxy-propyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(4-hydroxy-butyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-cyclopropylmethyl-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-(2-hydroxy-1-hydroxymethyl-ethyl)-benzamide

3-(Benzenesulfonyl-benzyl-amino)-N-((R)-1-hydroxymethyl-propyl)-benzamide

5-[(Benzo[1,2,5]oxadiazole-4-sulfonyl)-benzyl-amino]-2-fluoro-N-isopropyl-benzamide

5-(Benzenesulfonyl-benzyl-amino)-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(2,3-dihydro-benzo[1,4]dioxine-6-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(4-cyano-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(2-cyano-benzenesulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(Benzo[1,3]dioxole-5-sulfonyl)-benzyl-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(2,3-dihydro-benzofuran-5-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(pyridine-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-Acetylamino-benzenesulfonyl)-benzyl-amino]-2-fluoro-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-isopropyl-benzamide

5-[Benzyl-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-6-sulfonyl)-amino]-N-isopropyl-benzamide

3-[(4-Chloro-benzyl)-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-N-isopropyl-benzamide

5-[Benzyl-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[Benzyl-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(1,2-dimethyl-1H-imidazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-chloro-benzyl)-(1-methyl-1H-pyrazole-4-sulfonyl)-amino]-2-fluoro-N-isopropyl-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-ethyl)-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(1-hydroxymethyl-propyl)-benzamide

N-(4-Chloro-benzyl)-3-cyano-N-[4-fluoro-3-(3-hydroxy-azetidine-1-carbonyl)-phenyl]-benzenesulfonamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-1-hydroxymethyl-ethyl)-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-1-methyl-ethyl)-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

5-[(4-Chloro-benzyl)-(3-cyano-benzenesulfonyl)-amino]-2-fluoro-N-(2-methoxy-ethyl)-benzamide

N-(4-Chloro-benzyl)-3-cyano-N-[4-fluoro-3-(3-hydroxy-piperidine-1-carbonyl)-phenyl]-benzenesulfonamide

N-(4-Chloro-benzyl)-3-cyano-N-[4-fluoro-3-((R)-3-hydroxy-pyrrolidine-1-carbonyl)-phenyl]-benzenesulfonamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-hydroxy-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-hydroxy-1-methyl-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(1-hydroxymethyl-propyl)-benzamide

Pyridine-3-sulfonic acid (4-chloro-benzyl)-[3-(3-hydroxy-azetidine-1-carbonyl)-phenyl]-amide

Pyridine-3-sulfonic acid (4-chloro-benzyl)-[3-(3-hydroxy-piperidine-1-carbonyl)-phenyl]-amide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-(2-methoxy-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-cyclopropyl-benzamide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-cyclopentyl-benzamide

Pyridine-3-sulfonic acid (4-chloro-benzyl)-[3-((R)-3-fluoro-pyrrolidine-1-carbonyl)-phenyl]-amide

3-[(4-Chloro-benzyl)-(pyridine-3-sulfonyl)-amino]-N-cyclobutyl-benzamide

Pyridine-3-sulfonic acid [3-(azetidine-1-carbonyl)-phenyl]-(4-chloro-benzyl)-amide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-methyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-ethyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-(2-methoxy-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-cyclopropyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-cyclopentyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-imidazole-4-sulfonyl)-amino]-N-cyclobutyl-benzamide

1-Methyl-1H-imidazole-4-sulfonic acid [3-(azetidine-1-carbonyl)-phenyl]-(4-chloro-benzyl)-amide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-methyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-ethyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-methoxy-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-cyclopropyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-cyclobutyl-benzamide

1-Methyl-1H-pyrazole-3-sulfonic acid [3-(azetidine-1-carbonyl)-phenyl]-(4-chloro-benzyl)-amide

1-Methyl-1H-pyrazole-3-sulfonic acid (4-chloro-benzyl)-[3-(3-methyl-piperidine-1-carbonyl)-phenyl]-amide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-cyclopentyl-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-1-methyl-ethyl)-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(1-hydroxymethyl-propyl)-benzamide

3-[(4-Chloro-benzyl)-(1-methyl-1H-pyrazole-3-sulfonyl)-amino]-N-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide

3-[(4-chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-cyclobutyl-benzamide

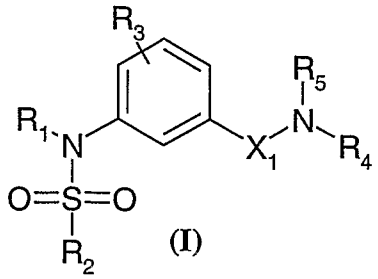
3-[(4-chloro-benzyl)-(2-methyl-2H-pyrazole-3-sulfonyl)-amino]-N-cyclopentyl-benzamide

13. A pharmaceutical composition comprising at least one compound as claimed in any one of claims 1 to 12 optionally together with one or more pharmaceutically acceptable excipients, diluents and/or carriers.

14. A compound as claimed in any one of claims 1 to 12 for use in medicine.

15. A compound according to claim 14 for use in the prevention or treatment of a disorder which requires potassium channel inhibition.

16. A compound of formula (I)



(I)

Or its salts or pharmaceutically acceptable derivatives thereof wherein;

X_1 is selected from a group consisting of CH_2, C(=O), C(=NH), NC(=O),

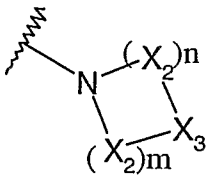
R_1 is selected from the group consisting of optionally substituted arylalkyl, and optionally substituted heteroarylalkyl

R_2 is selected from the group consisting of optionally substituted alkyl, preferably CH_3, optionally substituted aryl or heteroaryl or $NR_{24}R_{25}$

R_3 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxy, aryloxy, optionally substituted alkyl, optionally substituted amino, optionally substituted amino sulfonyl or nitrile;

R_4 is selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted acyl, optionally substituted sulfonyl, optionally substituted sulfamoyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroaryl

R_5 is may be hydrogen, an optionally substituted alkyl, preferably CH_3 or, NR_4R_5 may form an optionally substituted saturated or partially saturated 4-7 membered ring with the general formula (II).



(II)

Wherein;

X_2 is C(=O), or $C(R_6)_2$,

X_3 is $C(R_7)_2$, NH, $N(R_8)$, O or S

R_6 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_7 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_8 is optionally substituted acyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

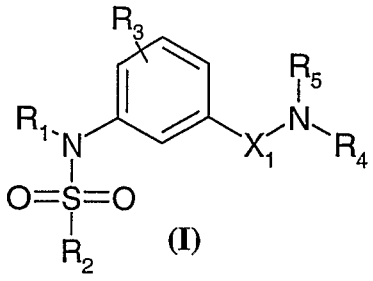
R_{24} and R_{25} are the same or different and each represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl,

n = 1 or 2

m = 1, 2 or 3

for use in the treatment or prophylaxis of psoriasis, rheumatoid arthritis, multiple sclerosis or other immunological disorders.

17. A method for the prevention or treatment of a disorder which requires potassium channel inhibition, comprising administering to a subject an effective amount of at least one compound of formula (I)



(I)

Or its salts or pharmaceutically acceptable derivatives thereof wherein;

X_1 is selected from a group consisting of CH_2, C(=O), C(=NH), NC(=O),

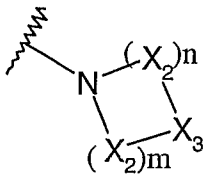
R_1 is selected from the group consisting of optionally substituted arylalkyl, and optionally substituted heteroarylalkyl

R_2 is selected from the group consisting of optionally substituted alkyl, preferably CH_3, optionally substituted aryl or heteroaryl or $NR_{24}R_{25}$

R_3 is selected from the group consisting of hydrogen, halogen, hydroxyl, alkoxy, aryloxy, optionally substituted alkyl, optionally substituted amino, optionally substituted amino sulfonyl or nitrile;

R_4 is selected from the group consisting of optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted acyl, optionally substituted sulfonyl, optionally substituted sulfamoyl, optionally substituted aryl, optionally substituted arylalkyl, and optionally substituted heteroaryl

R_5 is may be hydrogen, an optionally substituted alkyl, preferably CH_3 or, NR_4R_5 may form an optionally substituted saturated or partially saturated 4-7 membered ring with the general formula (II).



(II)

Wherein;

X_2 is C(=O), or $C(R_6)_2$,

X_3 is $C(R_7)_2$, NH, $N(R_8)$, O or S

R_6 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_7 for each occurrence independently represents hydrogen, optionally substituted amino, optionally substituted amino carbonyl, hydroxyl, optionally substituted acyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalky, optionally substituted aryl or optionally substituted heteroaryl;

R_8 is optionally substituted acyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

R_{24} and R_{25} are the same or different and each represents hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, optionally substituted aryl or optionally substituted heteroaryl,

n = 1 or 2

m = 1, 2 or 3

18. A method as claimed in claim 17 wherein the disorder is psoriasis, rheumatoid arthritis, multiple sclerosis or other immunological disorders.

19. A method as claimed in claim 17 wherein the disorder is arrhythmia

20. The use of a compound as defined in any one of claims 1 to 12 in the manufacture of a medicament for use in potassium channel inhibition.

21. The use as claimed in claim 20 wherein the medicament is for use in the treatment of psoriasis, rheumatoid arthritis, multiple sclerosis or other immunological disorders.

22. The use as claimed in claim 20 wherein the disorder is arrhythmia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/002078

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C311/21 C07D205/04 C07D211/08 C07D213/04 C07D231/00
C07D233/54 C07D265/28 C07D271/12 C07D277/32 C07D307/79
C07D311/70 C07D317/62 C07D319/18 A61K31/18 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/183768 A1 (J. FORD, ET AL.) 17 August 2006 (2006-08-17) claims 1, 7, 12, 14 -----	1-22
A	HANSON DOUGLAS C ET AL: "UK-78,282, a novel piperidine compound that potently blocks the Kv1.3 voltage-gated potassium channel and inhibits human T cell activation" BRITISH JOURNAL OF PHARMACOLOGY, NATURE PUBLISHING GROUP, BASINGSTOKE, HANTS, vol. 126, 1 January 1999 (1999-01-01), pages 1707-1716, XP008091174 ISSN: 0007-1188 cited in the application page 1709, right-hand column - page 1710, right-hand column; figure 1; table 1 ----- -/--	1-22

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2009	27/11/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	English, Russell

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 5 721 255 A (H.R. HOWARD, ET AL.) 24 February 1998 (1998-02-24) column 12, lines 42-63; claim 12; example 57	1,6,8-9, 13-18, 20-21
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