The invention provides compounds of the general type: (Formula (I)). Said compounds being modulators of Kv3 channels and of use in the prophylaxis or treatment of related disorders.
Technical field

This invention relates to novel compounds, pharmaceutical compositions containing them and their use in therapy, in particular as antipsychotic agents. Other uses of the compounds include the prophylaxis or treatment of hearing and hearing related disorders, including hearing loss and tinnitus, as well as schizophrenia, bipolar disorder, epilepsy, sleep disorders, and disorders where cognitive decline is a symptom.

Background to the invention

The Kv3 voltage-gated potassium channel family includes four members, Kv3.1, Kv3.2, Kv3.3, and Kv3.4. Genes for each of these subtypes can generate multiple isoforms by alternative splicing, producing versions with different C-terminal domains. Thirteen isoforms have been identified in mammals to date, but the currents expressed by these variants appear similar (Rudy and McBain, 2001, Trends in Neurosciences 24, 517-526). Kv3 channels are activated by depolarisation of the plasma membrane to voltages more positive than -20mV; furthermore, the channels deactivate rapidly upon repolarisation of the membrane. These biophysical properties ensure that the channels open towards the peak of the depolarising phase of the neuronal action potential to initiate repolarisation. Rapid termination of the action potential mediated by Kv3 channels allows the neuron to recover more quickly to reach sub-threshold membrane potentials from which further action potentials can be triggered. As a result, the presence of Kv3 channels in certain neurons contributes to their ability to fire at high frequencies (Rudy and McBain, 2001, Trends in Neurosci. 24, 517-526). Kv3.1-3 subtypes are predominant in the CNS, whereas Kv3.4 channels are found predominantly in skeletal muscle and sympathetic neurons (Weiser et al., 1994, J.Neurosci. 14, 949-972). Kv3.1-3 channel subtypes are differentially expressed by sub-classes of interneurons in cortical and hippocampal brain areas (e.g. Chow et al., 1999, J.Neurosci. 19, 9332-9345; Martina et al., 1998, J.Neurosci. 18, 8111-8125; McDonald and Mascagni, 2006, Neurosci. 138, 537-547, Chang et al., 2007, J. Comp. Neurol. 502, 953-972), in the thalamus (e.g. Kasten et al., 2007, J.Physirol. 584, 565-582), cerebellum (e.g. Sacco et al., 2006, Mol. Cell. Neurosci. 33, 170-179), and auditory brain stem nuclei (Li et al., 2001, J. Comp. Neurol. 437, 196-218).

Characterisation of mice in which one or more of the Kv3 subtypes has been deleted shows that the absence of Kv3.1 gives rise to increased locomotor activity, altered electroencephalographic activity, and a fragmented sleep pattern (Joho et al., 1999, J.Neurophysiol. 82, 1855-1864). The deletion of Kv3.2 leads to a reduction in seizure threshold and altered cortical electroencephalographic activity (Lau et al., 2000, J.Neurosci. 20, 9071-9085). Deletion of Kv3.3 is associated with mild ataxia and motor

The known pharmacology of Kv3 channels is limited. Tetraethylammonium (TEA) has been shown to inhibit the channels at low millimolar concentrations (Rudy and McBain, 2001, Trends in Neurosci. 24, 517-526), and blood-depressing substance (BDS) toxins from the sea anemone, Anemone sulcata (Diochot et al., 1998, J. Biol. Chem. 273, 6744-6749), have been shown to selectively inhibit Kv3 channels with high affinity (Yeung et al., 2005, J. Neurosci. 25, 8735-8745). In addition to compounds acting directly on Kv3 channels, agonists of receptors that activate protein kinase A (PKA) and protein kinase C (PKC) have been shown to modulate Kv3-mediated currents in specific brain areas, leading to a reduction in the ability of the neurons to fire at high frequency (Atzori et al., 2000, Nat. Neurosci. 3, 791-798; Song et al., 2005, Nat Neurosci. 8, 1335-1342); these studies suggest that PKA and PKC can specifically phosphorylate Kv3 channels in a neuron-specific manner, causing a reduction in Kv3-mediated currents.

Bipolar disorder, schizophrenia, anxiety, and epilepsy are serious disorders of the central nervous system that have been associated with reduced function of inhibitory interneurons and gamma-aminobutyric acid (GABA) transmission (Reynolds et al., 2004, Neurotox. Res. 6, 57-61; Benes et al., 2008, PNAS, 105, 20935-20940; Brambilla et al., 2003, Mol. Psychiatry. 8, 721-37, 715; Aroniadou-Anderjaska et al., 2007, Amino Acids 32, 305-315; Ben-Ari, 2006, Crit. Rev. Neurobiol. 18, 135-144). Parvalbumin positive basket cells that express Kv3 channels in the cortex and hippocampus play a key role in generating feedback inhibition within local circuits (Markram et al., 2004, Nat Rev Neurosci. 5, 793-807). Given the relative dominance of excitatory synaptic input over inhibitory input to glutamatergic pyramidal neurons in these circuits, fast-firing of interneurons supplying inhibitory input is essential to ensure balanced inhibition. Furthermore, accurate timing of inhibitory input is necessary to sustain network synchronisation, for example, in the generation of gamma frequency field potential oscillations that have been associated with cognitive function (Fisahn et al., 2005, J Physiol 562, 65-72; Engel et al., 2001, Nat Rev Neurosci. 2, 704-716). Notably, a reduction in gamma oscillations has been observed in patients with schizophrenia (Spencer et al., 2004, PNAS 101, 17288-17293). Consequently, positive modulators of Kv3 channels might be expected to enhance the firing capabilities of specific
groups of fast-firing neurons in the brain. These effects may be beneficial in disorders associated with abnormal activity of these neuronal groups.

In addition, Kv3.2 channels have been shown to be expressed by neurons of the suprachiasmatic nucleus (SCN) the main circadian pacemaker in the CNS (Schulz and Steimer, 2009, CNS Drugs 23 Suppl 2, 3-13).

Hearing loss represents an epidemic that affects approximately 16% of the population in Europe and the US (Goldman and Holme, 2010, Drug Discovery Today 15, 253-255), with a prevalence estimated at 250 million people worldwide (B. Shield, 2006, Evaluation of the social and economic costs of hearing impairment. A report for Hear-It AISBL: www.hear-it.org/multimedia/Hear_It_Report_October_2006.pdf). As life expectancy continues to increase, so too will the number of people suffering from hearing disorders. Furthermore, it is believed that modern lifestyles may exacerbate this burden as the younger generation ages. Hearing conditions, including tinnitus have a profound effect on the quality of life, causing social isolation, depression, work and relationship difficulties, low self-esteem, and prejudice. Voltage-gated ion channels of the Kv3 family are expressed at high levels in auditory brainstem nuclei (Li et al., 2001, J. Comp. Neurol. 437, 196-218) where they permit the fast firing of neurons that transmit auditory information from the cochlea to higher brain regions. Loss of Kv3.1 channel expression in central auditory neurons is observed in hearing impaired mice (von Hehn et al., 2004, J. Neurosci. 24, 1936-1940), furthermore, a decline in Kv3.1 expression may be associated with loss of hearing in aged mice (Jung et al. 2005 Neurol. Res. 27, 436-440), and loss of Kv3 channel function may also follow noise-trauma induced hearing loss (Pilati et al., Hear Res. 2012 Jan 283(l2):98-106). Furthermore, pathological plasticity of auditory brainstem networks is likely to contribute to symptoms that are experienced by many people suffering from hearing loss of different types. Recent studies have shown that regulation of Kv3.1 channel function and expression has a major role in controlling auditory neuron excitability (Kaczmarek et al., 2005, Hearing Res. 206, 133-145), suggesting that this mechanism could account for some of the plastic changes that give rise to tinnitus. These data support the hypothesis that positive modulation of Kv3 channels in auditory brainstem nuclei could have a therapeutic benefit in patients suffering from hearing loss. Finally, Fragile X syndrome and autism are frequently associated with hypersensitivity to sensory input, including auditory stimuli. Recent findings suggest that the protein coded by the FMR1 gene, whose mutation or absence gives rise to Fragile X syndrome, may directly regulate the expression of Kv3.1 channels in the auditory brainstem nuclei (Strumbos et al., 2010, J. Neuroscience, in press), suggesting that mis-regulation of Kv3.1 channels could give rise to hyperacusis in patients suffering from Fragile X or autism. Consequently, we propose that small molecule modulators of Kv3 channels in auditory
brainstem nuclei could have a benefit in the treatment of disorders of hearing, including tinnitus and auditory hyper-acuity associated with Fragile X syndrome and autism.

Spinocerebellar ataxia type 13 (SCA13) is a human autosomal dominant disease caused by mutations in the KCNC3 gene that encodes the Kv3.3 channel. These mutations have been shown to cause a reduction in function of the channels (Waters et al., 2006, Nat. Genet. 38, 447-451; Minassian et al., 2012, J Physiol. 590.7, 1599-1614). Coexpression of Kv3.1 and Kv3.3 in many brain areas, including the cerebellum suggests some redundancy or the ability of one subtype to compensate for the absence of the other, indeed the phenotype of the Kv3.1/Kv3.3 double knockout mice is markedly more severe than either of the two single knockouts (e.g. Espinosa et al., 2008, J. Neurosci. 28, 5570-5581).

Furthermore, it is possible that Kv3.1 and Kv3.3 proteins assemble to form heteromeric channels in some neurons. The ability of Kv3.1 to compensate for a loss of function of Kv3.3 may explain why certain mutations in the latter are only associated with an onset of spinocerebellar ataxia later in adult life, rather than from birth (Minassian et al., 2012, J Physiol. 590.7, 1599-1614). Consequently, we propose that small molecule modulators of either Kv3.3 or Kv3.1 might be beneficial in the treatment of spinocerebellar ataxia, in particular SCA13.

Patent applications WO2011/069951, WO2012/076877 (application number PCT/GB2011/052414) and WO2012/168710 disclose compounds which are modulators of Kv3.1 and Kv3.2. Further, the value of such compounds is demonstrated in animal models of seizure, hyperactivity, sleep disorders, psychosis, cognitive deficit, bipolar disorder and hearing disorders.

There remains a need for the identification of alternative modulators of Kv3.1 and Kv3.2, in particular modulators of Kv3.1 and Kv3.2 which may demonstrate certain channel selectivity profiles or desirable pharmacokinetic parameters, for example high brain availability. Other desirable parameters which may be demonstrated include good bioavailability, good brain penetration, high fraction unbound in blood and brain, and good metabolic stability.

Summary of the invention

The present invention provides a compound selected from:

5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione;

(5R)-3-[6-[[3,3-dimethyl-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;

3-[6-[[3-tert-butyl-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione;
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione;
5,5-dimethyl-3-(6-spiro[1H-isobenzofuran-34'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-3-[6-[[33-dimethyl-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-(6-spiro[1H-isobenzofuran-34'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-(2-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy)pyrimidine-5-yl]imidazolidine-2,4-dione;
or
(5R)-3-{4-[[3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl]oxy]phenyl}-5-ethyl-5-methyl-2,4-imidazolidinedione.

In particular, the present invention provides a compound selected from:
5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 2);
(5R)-3-[6-[[3,3-dimethyl-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
3-[6-[[3-tert-butyl-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1);
3-[6-[[3-tert-butyl-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 2);
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 2);
5,5-dimethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-3-[6-[[3,3-dimethyl-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[6-[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-3-(6-spiro[lH-isobenzofuran]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-3-(2-spiro[lH-isobenzofuran-3,l'-cyclobutane]-5-yloxy)imidazolidine-2,4-dione; or
(5R)-3-{4-[[3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl]oxy]phenyl}-5-ethyl-5-methyl-2,4-imidazolidinedione.

Such compounds being referred to herein as 'compounds of the invention'.

A compound of the invention may be provided in the form of a pharmaceutically acceptable salt and/or solvate thereof. In one embodiment of the invention a compound of the invention is provided in the form of a pharmaceutically acceptable salt.

The compounds of the invention may be used as medicaments, in particular for the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, bipolar disorder, epilepsy, sleep disorders, cognition impairment or ataxia.

Further, there is provided a method for the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, bipolar disorder, epilepsy, sleep disorders, cognition impairment or ataxia by administering to a subject a compound of the invention.

Compounds of the invention may be used in the manufacture of a medicament for the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, bipolar disorder, epilepsy, sleep disorders, cognition impairment or ataxia.

Also provided are pharmaceutical compositions containing a compound of the invention and a pharmaceutically acceptable carrier or excipient.

Additionally provided are prodrug derivatives of the compounds of the invention.

**Detailed description of the invention**

The present invention provides a compound selected from:
5.5-dimethyl-3-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione;
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione;
5,5-dimethyl-3-[6-spiro[1H-isobenzofuran-3,4'-cyclobutane]-5-yloxy-3-pyridyl]imidazolidine-2,4-dione;
(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-3-{4-[(3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]phenyl}-5-ethyl-5-methyl-2,4-imidazolidinedione;
or a pharmaceutically acceptable salt and/or solvate thereof.

In particular, the present invention provides a compound selected from:
5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 2);
(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1);
3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 2);
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 2); 
5,5-dimethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1);

(5R)-5-ethyl-3-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2);

(5R)-5-ethyl-3-[6-spiro[lH-isobenzofuran-3,l'-cyclobutane]-5-yloxy-3-pyridyl]imidazolidine-2,4-dione;

(5R)-5-ethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 1);

(5R)-5-ethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 2);

(5R)-5-ethyl-3-[2-spiro[lH-isobenzofuran-3,l'-cyclobutane]-5-yloxy]pyrimidin-5-yl]imidazolidine-2,4-dione;

(5R)-3-{4-[[3,3-dimethyl-l,3-dihydro-2-benzofuran-5-yl]oxy]phenyl}-5-ethyl-5-methyl-2,4-imidazolidinedione;

or a pharmaceutically acceptable salt and/or solvate thereof.

It will be appreciated that for use in medicine the salts of the compounds of the invention should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse J.Pharm.Sci. (1977) 66, pp 1-19. Such pharmaceutically acceptable salts include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates or formates, may be used, for example in the isolation of compounds of the invention and are included within the scope of this invention.

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

The compounds of the invention may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope stoichiometric solvates (e.g. hydrates) as well as compounds containing variable amounts of solvent (e.g. water).

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of the invention and that these are included within the scope of the invention.
As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable prodrug such as an ester or salt of such ester of a compound of the invention which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of the invention or an active metabolite or residue thereof.

Suitably, a pharmaceutically acceptable prodrug is formed by functionalising the secondary nitrogen of the hydantoin, for example with a group "L" as illustrated below (wherein \( R_4 \) and \( R_5 \) correspond to the functionalities of the compounds of the invention):

![Chemical structure](image)

In one embodiment of the invention, a compound of the invention is functionalised via the secondary nitrogen of the hydantoin with a group \( L \), wherein \( L \) is selected from:

- a) \(-\text{PO(OH)}_\circ \cdot \ M^+, \) wherein \( M^+ \) is a pharmaceutically acceptable monovalent counterion,
- b) \(-\text{PO(O)}_\circ \cdot 2 M^+, \)
- c) \(-\text{PO(O)}_\circ \cdot D^+ \), wherein \( D^+ \) is a pharmaceutically acceptable divalent counterion,
- d) \(-\text{CH(R)}^+\cdot\text{PO(OH)}_\circ \cdot M^+, \) wherein \( R \) is hydrogen or \( C_{3-3} \) alkyl,
- e) \(-\text{CH(R)}^+\cdot\text{PO(O)}_\circ \cdot 2 M^+, \)
- f) \(-\text{CH(R)}^+\cdot\text{PO(O)}_\circ \cdot D^+, \)
- g) \(-\text{SO}_\circ \cdot M^+, \)
- h) \(-\text{CH(R)}^+\cdot\text{SO}_\circ \cdot M^+, \) and
- i) \(-\text{CO-CH}_2\text{CH}_2\text{C}_\circ \cdot M^+. \)

It is to be understood that the present invention encompasses all isomers of the compounds of the invention and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of the invention, the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.
The subject invention also includes isotopically-labelled compounds which are identical to those recited as compounds of the invention but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. The skilled person will appreciate that in many circumstances the proportion of an atom having an atomic mass or mass number found less commonly in nature can also be increased (referred to as “isotopic enrichment”). Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, iodine and chlorine such as $^3$H, $^{11}$C, $^{14}$C, $^{18}$F, $^{123}$I or $^{125}$I. Another isotope of interest is $^{13}$C. Another isotope of interest is $^2$H (deuterium).

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically labelled compounds of the present invention, for example those into which radioactive isotopes such as $^3$H or $^{14}$C have been incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e. $^3$H, and carbon-14, i.e. $^{14}$C, isotopes are particularly preferred for their ease of preparation and detectability. $^{11}$C and $^{18}$F isotopes are particularly useful in PET (positron emission tomography).

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

In general, the compounds of the invention may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the methods set forth in the Examples, WO2012/168710 and modifications thereof.

The present invention provides compounds of the invention or a pharmaceutically acceptable salt thereof for use in therapy.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of a disease or disorder where a modulator of the Kv3.1 or Kv3.2 or Kv3.1 and Kv3.2 channels is required. As used herein, a modulator of Kv3.1 or Kv3.2 or Kv3.1 and Kv3.2 is a compound which alters the properties of these channels, either positively or negatively. Compounds of the invention may be tested in the assay of Biological Example 1 to determine their modulatory properties.
In certain disorders it may be of benefit to utilise a modulator of Kv3.1 or Kv3.2 which demonstrates a particular selectivity profile between the two channels. For example a compound may be selective for modulation of Kv3.1 channels over modulation of Kv3.2 channels demonstrating, for example, at least a 2 fold, 5 fold or 10 fold activity for Kv3.1 channels than for Kv3.2 channels. Alternatively, a compound may be selective for modulation of Kv3.2 channels over modulation of Kv3.1 channels demonstrating, for example, at least a 2 fold, 5 fold or 10 fold activity for Kv3.2 channels than for Kv3.1 channels. In other cases a compound may demonstrate comparable activity between modulation of Kv3.1 and Kv3.2 channels, for example the activity for each channel is less than 2 fold that for the other channel, such as less than 1.5 fold or less than 1.2 fold. The activity of a compound is suitably quantified by its potency as indicated by an \( EC_{50} \) value.

Diseases or conditions that may be mediated by modulation of Kv3.1 and/or Kv3.2 channels may be selected from the list below. The numbers in brackets after the listed diseases below refer to the classification code in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10).

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90);

Seasonal affective disorder.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of schizophrenia including the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Bipolar Type and Depressive Type; Delusional Disorder (297.1) including the subtypes Erotomaniac Type,
Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced Psychotic Disorder including the subtypes With Delusions (293.81) and With Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of anxiety disorders including Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia (300.01) and Panic Disorder with Agoraphobia (300.21); Agoraphobia; Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29, formerly Simple Phobia) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (Social Anxiety Disorder, 300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.2), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder, Separation Anxiety Disorder (309.21), Adjustment Disorders with Anxiety (309.24) and Anxiety Disorder Not Otherwise Specified (300.00).

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnestic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as
Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep
Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the enhancement of cognition including the treatment of cognition impairment in other diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with cognitive impairment, e.g. Alzheimer's disease. Alternatively, the compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the prophylaxis of cognition impairment, such as may be associated with diseases such as schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with cognitive impairment, e.g. Alzheimer's disease.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of sleep disorders including primary sleep disorders such as Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition, in particular sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, Hypersomnia Type, Parasomnia Type and Mixed Type; sleep apnea and jet-lag syndrome.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of eating disorders such as Anorexia Nervosa (307.1) including the subtypes Restricting Type and Binge-Eating/Purging Type; Bulimia Nervosa (307.51) including the subtypes Purging Type and Nonpurging Type; Obesity; Compulsive Eating Disorder; Binge Eating Disorder; and Eating Disorder Not Otherwise Specified (307.50).

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of Autism Spectrum Disorders including Autistic Disorder (299.00), Asperger's Disorder (299.80), Rett's Disorder (299.80), Childhood Disintegrative Disorder (299.10) and Pervasive Disorder Not Otherwise Specified (299.80, including Atypical Autism).
The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of Attention-Deficit/Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit /Hyperactivity Disorder Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23).

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of Personality Disorders including the subtypes Paranoid Personality Disorder (301.0), Schizoid Personality Disorder (301.20), Schizotypal Personality Disorder (301.22), Antisocial Personality Disorder (301.7), Borderline Personality Disorder (301.83), Histrionic Personality Disorder (301.50), Narcissistic Personality Disorder (301.81), Avoidant Personality Disorder (301.82), Dependent Personality Disorder (301.6), Obsessive-Compulsive Personality Disorder (301.4) and Personality Disorder Not Otherwise Specified (301.9).

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of Sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9); gender identity disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9).

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of Impulse control disorder including: Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), Impulse-Control Disorders Not Otherwise Specified (312.3), Binge Eating, Compulsive Buying, Compulsive Sexual Behaviour and Compulsive Hoarding.
The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of hearing disorders including auditory neuropathy, auditory processing disorder, hearing loss, which includes sudden hearing loss, noise induced hearing loss, substance-induced hearing loss, and hearing loss in adults over 60 (presbycusis), and tinnitus.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of Meniere's disease, disorders of balance, and disorders of the inner ear.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of hyperacusis and disturbances of loudness perception, including Fragile-X syndrome and autism.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates may be of use for the treatment or prophylaxis of Epilepsy, (including, but not limited to, localization-related epilepsies, generalized epilepsies, epilepsies with both generalized and local seizures, and the like), seizures associated with Lennox-Gastaut syndrome, seizures as a complication of a disease or condition (such as seizures associated with encephalopathy, phenylketonuria, juvenile Gaucher's disease, Lundborg's progressive myoclonic epilepsy, stroke, head trauma, stress, hormonal changes, drug use or withdrawal, alcohol use or withdrawal, sleep deprivation, fever, infection, and the like), essential tremor, restless limb syndrome, partial and generalised seizures (including tonic, clonic, tonic-clonic, atonic, myoclonic, absence seizures), secondarily generalized seizures, temporal lobe epilepsy, absence epilepsies (including childhood, juvenile, myoclonic, photo- and pattern-induced), severe epileptic encephalopathies (including hypoxia-related and Rasmussen's syndrome), febrile convulsions, epilepsy partialis continua, progressive myoclonus epilepsies (including Unverricht-Lundborg disease and Lafora's disease), post-traumatic seizures/epilepsy including those related to head injury, simple reflex epilepsies (including photosensitive, somatosensory and proprioceptive, audiogenic and vestibular), metabolic disorders commonly associated with epilepsy such as pyridoxine-dependent epilepsy, Menkes' kinky hair disease, Krabbe's disease, epilepsy due to alcohol and drug abuse (e.g. cocaine), cortical malformations associated with epilepsy (e.g. double cortex syndrome or subcortical band heterotopia), chromosomal anomalies associated with seizures or epilepsy such as Partial monosomy (15Q) / Angelman syndrome.

In one embodiment of the invention, there is provided a compound of the invention or a pharmaceutically acceptable salt and/or solvate thereof for the treatment or prophylaxis of depression and mood disorders, hearing disorders, schizophrenia, substance abuse disorders, sleep disorders or epilepsy.
In one embodiment of the invention, there is provided a compound of the invention or a pharmaceutically acceptable salt and/or solvate thereof for the treatment or prophylaxis of bipolar disorder or mania.

In one embodiment of the invention, there is provided a compound of the invention or a pharmaceutically acceptable salt and/or solvate thereof for the treatment or prophylaxis of ataxia, such as spinocerebellar ataxia.

In one embodiment of the invention, there is provided a compound of the invention or a pharmaceutically acceptable salt and/or solvate thereof for the treatment or prophylaxis of cognition impairment.

The term "treatment" or "treating" as used herein includes the control, mitigation, reduction, or modulation of the disease state or its symptoms.

The term "prophylaxis" is used herein to mean preventing symptoms of a disease or disorder in a subject or preventing recurrence of symptoms of a disease or disorder in an afflicted subject and is not limited to complete prevention of an affliction.

The invention also provides a method of treating or preventing a disease or disorder where a modulator of Kv3 is required, for example those diseases and disorders mentioned hereinabove, which comprises administering to a subject in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt and/or solvate thereof.

The invention also provides a compound of the invention, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the treatment or prophylaxis of a disease or disorder where a modulator of Kv3 is required, for example those diseases and disorders mentioned hereinabove.

The invention also provides the use of a compound of the invention, or a pharmaceutically acceptable salt and/or solvate thereof, in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder where a modulator of Kv3 is required, for example those diseases and disorders mentioned hereinabove.

The invention also provides a method of treating depression and mood disorders, schizophrenia, substance abuse disorders, sleep disorders or epilepsy, for example for those indications mentioned hereinabove, which comprises administering to a subject in need thereof an effective amount of a Kv3 modulator or a pharmaceutically acceptable salt and/or solvate thereof.
For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt and/or solvate thereof, and a pharmaceutically acceptable carrier.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates thereof may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly. Other possible routes of administration include intratympanic and intracochlear.

The compounds of the invention or their pharmaceutically acceptable salts and/or solvates thereof which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill
for use with an atomising device. Alternatively the sealed container may be a disposable dispensing
device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where
the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed
gas e.g. air, or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. Aerosol
dosage forms can also take the form of pump-atomisers.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles
where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin
and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a
conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

In one embodiment the composition is in unit dose form such as a tablet, capsule or ampoule.

The composition may contain from 0.1% to 100% by weight, for example from 10 to 60% by weight, of
the active material, depending on the method of administration. The composition may contain from 0%
to 99% by weight, for example 40% to 90% by weight, of the carrier, depending on the method of
administration. The composition may contain from 0.05mg to 1000mg, for example from 1.0mg to
500mg, of the active material, depending on the method of administration. The composition may
contain from 50mg to 1000mg, for example from 100mg to 400mg of the carrier, depending on the
method of administration. The dose of the compound used in the treatment of the aforementioned
disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and
other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000mg, more
suitably 1.0 to 500mg, and such unit doses may be administered more than once a day, for example two
or three a day. Such therapy may extend for a number of weeks or months.

The invention provides, in a further aspect, a combination comprising a compound of the invention or a
pharmaceutically acceptable salt, solvate and/or derivative thereof together with a further therapeutic
agent or agents.

The invention provides a compound of the invention, for use in combination with a further therapeutic
agent or agents.

When the compounds are used in combination with other therapeutic agents, the compounds may be
administered either sequentially or simultaneously by any convenient route.
The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. The individual components of combinations may also be administered separately, through the same or different routes.

When a compound of the invention or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

The present invention also provides Kv3 modulators, or their pharmaceutically acceptable salts and/or solvates thereof, for use in the treatment or prophylaxis of depression and mood disorders, hearing disorders, schizophrenia, substance abuse disorders, sleep disorders or epilepsy.

In particular Kv3 modulators or their pharmaceutically acceptable salts and/or solvates may be particularly useful in the treatment or prophylaxis of depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90), Seasonal affective disorder.

The invention also provides a method of treating depression and mood disorders, hearing disorders, schizophrenia, substance abuse disorders, sleep disorders or epilepsy, including for example those
disorders mentioned hereinabove, which comprises administering to a subject in need thereof an effective amount of Kv3 modulator or a pharmaceutically acceptable salt and/or solvate thereof.

The invention also provides a Kv3 modulator, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the treatment or prophylaxis of depression and mood disorders, hearing disorders, schizophrenia, substance abuse disorders, sleep disorders or epilepsy, including for example those disorders mentioned hereinabove.

The invention also provides the use of a Kv3 modulator, or a pharmaceutically acceptable salt and/or solvate thereof, in the manufacture of a medicament for the treatment or prophylaxis of depression and mood disorders, hearing disorders, schizophrenia, substance abuse disorders, sleep disorders or epilepsy, including for example those disorders mentioned hereinabove.

For use in therapy the Kv3 modulators are usually administered as a pharmaceutical composition for example a composition comprising a Kv3 modulator or a pharmaceutically acceptable salt and/or solvate thereof, and a pharmaceutically acceptable carrier. Examples of such compositions, and methods of administration thereof, which compositions comprise a compound of the invention or a pharmaceutically acceptable salt thereof, are described hereinabove. Such compositions and methods of administration may also be used for other Kv3 modulators or pharmaceutically acceptable salts and/or solvates thereof, in the treatment of depression and mood disorders, hearing disorders, schizophrenia, substance abuse disorders, sleep disorders or epilepsy, including for example those disorders mentioned hereinabove.

Furthermore, the invention relates to a method for manufacturing compounds of the invention, to novel intermediates of use in the manufacture of compounds of the invention and to the manufacture of such intermediates.

Particular intermediates of interest include:

3-/-/-spiro[2-benzofuran-l,l'-cyclobutan]-6-ol

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3-ferf-butyl-l,3-dihydro-2-benzofuran-5-ol (including 3-ferf-butyl-l,3-dihydro-2-benzofuran-5-ol enantiomer 1 and 3-ferf-butyl-l,3-dihydro-2-benzofuran-5-ol enantiomer 2)
3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol (including 3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol enantiomer 1 and 3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol enantiomer 2)

Especially of interest are the anilines:

6-[(3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine

6-[(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine

including 6-[(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine (enantiomer 1) and

6-[(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine (enantiomer 2);

6-(3/-/spirol2-benzofuran-1,l'-cyclobutan]-6-yloxy)pyridin-3-amine

2-(3/-/spirol2-benzofuran-1,l'-cyclobutan]-6-yloxy)pyrimidin-5-amine
Experimental

The invention is illustrated by the compounds described below. The following examples describe the laboratory synthesis of specific compounds of the invention and are not meant to limit the scope of the invention in any way with respect to compounds or processes. It is understood that, although specific reagents, solvents, temperatures and time periods are used, there are many possible equivalent alternatives that can be used to produce similar results. This invention is meant to include such equivalents.

Analytical Equipment

Starting materials, reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Unless otherwise stated, all compounds with chiral centres are racemic. Where reactions are described as having been carried out in a similar manner to earlier, more completely described reactions, the general reaction conditions used were essentially the same.

Work up conditions used were of the types standard in the art, but may have been adapted from one reaction to another. The starting material may not necessarily have been prepared from the batch referred to. Compounds synthesised may have various purities ranging from for example 85% to 98%. Calculations of number of moles and yield are in some cases adjusted for this.
Proton Magnetic Resonance (indicated by \(^{1}H-NMR\)) spectra or Carbon Nuclear Magnetic Resonance (indicated by \(^{13}C-NMR\)) were recorded either on Varian instruments at 200, 300, 400, 500 or 600 MHz, or on Bruker instruments at 400 MHz. Chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s (singlet), br.s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets) and m (multiplet). The NMR spectra were recorded at temperatures ranging from 25 to 60°C.

HPLC-Mass spectra (HPLC-MS) were taken on an Agilent 1100 Series LC/MSD Mass Spectrometer coupled with HPLC instrument Agilent 1100 Series, operating in positive electrospray ionization mode and in acidic gradient conditions.

**Quality Control (8 minutes method):** LC/MS-ES+ under acidic conditions was performed on a Phenomenex Luna C18 column (3.0 µm 2 x 50 mm). Mobile phase: A: (H2O + 0.05% TFA by vol.) / B: (CH₃CN + 0.05% TFA by vol). Gradient: t = 0 min 0% (B). From 0 to 95% (B) in 8 min. 95% (B) for 0.5 min. From 95 to 100% (B) in 0.5 min. 100% (B) for 0.5 min. From 100% to 0% (B) in 0.1 min. Stop time 11 min. Column T = 40°C. Flow rate: 1.0 ml/min. Mass range ES+: (100-1000 amu, F=60). UV detection wavelengths: DAD 1A = 220.8, DAD I B = 254.8. The use of this methodology is indicated by "LC/MS: QC_8_M IN" in the analytic characterization of the described compounds.

**Quality Control (3 minutes method):** LC/MS-ES+ under acidic conditions was performed on a Zorbax SB C18 column (1.8 µm 3 x 50 mm). Mobile phase: A: (H₂O + 0.05% TFA by vol.) / B: (CH₃CN + 0.05% TFA by vol). Gradient: t = 0 min 0% (B), from 0 to 95% (B) in 2.5 min. 95% (B) for 0.2 min, from 95 to 100% (B) in 0.2 min, 100% (B) for 0.4 min, from 100% to 0% (B) in 0.1 min. Stop time 4 min. Column T = 60°C. Flow rate: 1.5 ml/min. Mass range ES+: (100-1000 amu, F=60). UV detection wavelengths: DAD 1A = 220.8, DAD I B = 254.8. The use of this methodology is indicated by "LC/MS: QC_3_M IN" in the analytic characterization of the described compounds.

**Ultra Performance Liquid Chromatography with an acidic gradient:**

Total ion current (TIC) and DAD UV chromatographic traces together with MS and UV spectra associated with the peaks were taken on a UPLC/MS Acquity™ system equipped with 2996 PDA detector and coupled to a Waters Micromass ZQ™ mass spectrometer operating in positive or negative electrospray ionisation mode [LC/MS + ES (+ or -): analyses were performed using an Acquity™ UPLC BEH C18 column (50 x 2.1 mm, 1.7 µm particle size). **Generical Method:** Mobile phase: A: (water + 0.1% HCO₃H) / B: (CH₃CN + 0.06% HCO₂H). Gradient: t = 0 min 3% (B), t = 0.05 min 6% (B), t = 0.57 min 70% (B), t = 1.06 min 99% (B) lasting for 0.389 min, t = 1.45 min 3% (B), stop time 1.5 min. Column T = 40°C. Flow rate = 1.0 ml/min. Mass range: ES (+): 100-1000 amu. ES (-): 100-800 amu. UV detection range: 210-350 nm. The
Ultra Performance Liquid Chromatography with a basic gradient:

Total ion current (TIC) and DAD UV chromatographic traces together with MS and UV spectra associated with the peaks were taken on a UPLC/MS Acquity™ system equipped with PDA detector and coupled to a Waters SQD mass spectrometer operating in positive and negative alternate electrospray ionisation mode [LC/MS - ES+/-]. Analyses were performed using an Acquity™ UPLC BEH C18 column (50 x 2.1 mm, 1.7 µm particle size). Mobile phase: A: (10 mM aqueous solution of NH₄HCO₃ (adjusted to pH 10 with ammonia)) / B: CH₃CN. Gradient: t = 0 min 3% (B), t = 1.06 min 99% (B) lasting for 0.39 min, t = 1.46 min 3% (B), stop time 1.5 min. Column T = 40 °C. Flow rate = 1.0 mL/min. Mass range: ES (+): 100-1000 amu. ES (-): 100-1000 amu. UV detection range: 220-350 nm. The use of this methodology is indicated by "UPLC_B" in the analytic characterization of the described compounds.

In a number of preparations, purification was performed using manual flash chromatography, semi automatic flash chromatography (Biotage Flash Master Personal) or automatic flash chromatography (Biotage SP1 and SP4) apparatus.

Flash chromatographies on silica gel were carried out on pre-packed Biotage silica cartridges (e.g. Biotage SNAP cartridge KP-Si). Reverse phase C18 flash chromatographies were carried out using VARIAN MEGA BE-C18 cartridges, or pre-packed Biotage C18 cartridges (e.g. Biotage SNAP cartridge KP-C18-HS).

SPE-SCX cartridges are ion exchange solid phase extraction columns supplied by Varian. The eluent used with SPE-SCX cartridges is DCM and MeOH or only MeOH followed by ammonia solution in MeOH. The collected fractions are those eluted with the ammonia solution in MeOH.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>Boc</td>
<td>t-butyloxy carbonyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>butyllithium</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>CDI</td>
<td>I,1'-Carbonyldiimidazole</td>
</tr>
<tr>
<td>(CH₂O)ₙ</td>
<td>paraformaldehyde</td>
</tr>
<tr>
<td>cHex</td>
<td>cyclohexane</td>
</tr>
<tr>
<td>CV</td>
<td>column volume</td>
</tr>
</tbody>
</table>
DCM    dichloromethane
DIPEA  N,N-diisopropylethylamine
DMAP    4-dimethylaminopyridine
DMF     N,N-dimethylformamide
DMSO    dimethylsulfoxide
DMSO-d$_6$ deutrated dimethylsulfoxide
Et$_2$O  diethyl ether
EtOAc   ethyl acetate
h       hours
H$_2$    gaseous hydrogen
HATU    (0-7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluoro
        phosphate)
HC$_2$O$_2$H formic acid
HCl     hydrogen chloride
H$_2$S$_0$$_4$ sulfuric acid
K$_2$CO$_3$ potassium carbonate
KHDMS   potassium hexamethyldisilazide
KOH     potassium hydroxide
MeCN    acetonitrile
MeOH    methanol
MeOD    deuterated methanol
MOM     methoxymethyl
N$_2$    gaseous nitrogen
NaHCO$_3$ sodium hydrogen carbonate
Na$_2$CO$_3$ sodium carbonate
NaOH    sodium hydroxide
NaOMe   sodium methoxide
NMR     Nuclear Magnetic Resonance
Pd/C    palladium on charcoal
PE      petroleum ether
r.t.    room temperature
T$_3$P   propylphosphonic anhydride
tBuOK   potassium tert-butoxide
TBDMS   (1,1-dimethylethyl)dimethylsilyl
Intermediate 1

3,3-dimethyl-1H-isobenzofuran-5-ol

![3,3-dimethyl-1H-isobenzofuran-5-ol](image)

10 To a solution of 2-[5-[tert-butyl(dimethyl)silyl]oxy-2-(hydroxymethyl)phenyl]propan-2-ol (WO2012/168710 Intermediate 10, 1.344g, 4.533mmol) in THF (5mL) at 0°C butyllithium 1.6M in hexane (3.116mL, 4.98mmol) was added and the reaction mixture was stirred for 5 minutes at the same temperature. 4-methylbenzenesulfonyl chloride (1.04g, 5.44mmol) dissolved in 1 mL of THF was added followed by the addition of butyllithium 1.6M in hexane (3.116mL, 4.98mmol). After 10 minutes at the same temperature tetrabutylammonium fluoride (9.066mL, 9.066mmol) was added and the reaction mixture stirred for additional 10 min. Then, it was quenched with ammonium chloride (50 mL) and extracted with ethyl acetate (100 mL). The organic phase was washed with brine (2x100mL), dried with Na2SO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (Biotage system) using a SNAP 50g as column and cyclohexane/ethyl acetate from 100:0 to 70:30 to afford the title compound (500mg) as white solid.

LC/MS: QC_3_MIN: Rf = 1.772 min; m/z 147 [(M-H2O)+H]+.

The following compounds were prepared using the foregoing methodology, replacing 2-[5-[tert-butyl(dimethyl)silyl]oxy-2-(hydroxymethyl)phenyl]propan-2-ol (WO2012/168710 Intermediate 10) with the appropriate dihydroxy compound. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system).

<table>
<thead>
<tr>
<th>Int.</th>
<th>Structure</th>
<th>Name</th>
<th>Dihydroxy compound</th>
<th>LCMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intermediate 5 (enantiomer 1) and Intermediate 6 (enantiomer 2)

3-tert-butyl-1,3-dihydro-2-benzofuran-5-ol
Two enantiomers were obtained by chiral separation of racemic mixture (WO2012/168710 Intermediate 20, 300mg):

Preparative method:

<table>
<thead>
<tr>
<th>Column</th>
<th>Chiralpak AD-H (25 x 2.0 cm), 5 μ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile phase</td>
<td>n-Hexane/2-Propanol 90/10 % v/v</td>
</tr>
<tr>
<td>Flow rate (ml/min)</td>
<td>17 ml/min</td>
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<tr>
<td>DAD detection</td>
<td>220 nm</td>
</tr>
<tr>
<td>Loop</td>
<td>1000 μL</td>
</tr>
<tr>
<td>Solubilisation</td>
<td>300 mg in 20 ml EtOH/n-Hexane 3/1 = 15 mg/ml</td>
</tr>
<tr>
<td>Injection</td>
<td>15 mg (each injection)</td>
</tr>
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</table>

Analytical characterization:

<table>
<thead>
<tr>
<th>Column</th>
<th>Chiralpak AD-H (25 x 0.46 cm), 5 μ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile phase</td>
<td>n-Hexane/2-Propanol 90/10 % v/v</td>
</tr>
<tr>
<td>Flow rate (ml/min)</td>
<td>1 ml/min</td>
</tr>
<tr>
<td>DAD detection</td>
<td>220 nm</td>
</tr>
<tr>
<td>Loop</td>
<td>20 μL</td>
</tr>
</tbody>
</table>

Intermediate 5 (enantiomer 1) : 130mg; Rt = 7.2 minutes.

Intermediate 6 (enantiomer 2) : 130mg; Rt = 9.3 minutes.

Intermediate 7 (enantiomer 1) and Intermediate 8 (enantiomer 2).

3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol
Two enantiomers were obtained by chiral separation of racemic mixture (WO2012/168710 Intermediate 21, 600mg):

Preparative method:

<table>
<thead>
<tr>
<th>Column</th>
<th>Chiralcel OJ-H (25 x 3.0 cm), 5 µ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile phase</td>
<td>n-Hexane/2-Propanol 88/12 % v/v</td>
</tr>
<tr>
<td>Flow rate (ml/min)</td>
<td>40 ml/min</td>
</tr>
<tr>
<td>DAD detection</td>
<td>220 nm</td>
</tr>
<tr>
<td>Loop</td>
<td>1000 µL</td>
</tr>
<tr>
<td>Solubilisation</td>
<td>300 mg in 10 ml EtOH/n-Hexane 3/2 = 30 mg/ml</td>
</tr>
<tr>
<td>Injection</td>
<td>30 mg (each injection)</td>
</tr>
</tbody>
</table>

Analytical characterization:

<table>
<thead>
<tr>
<th>Column</th>
<th>Chiralcel OJ-H (25 x 0.46 cm), 5 µ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile phase</td>
<td>n-Hexane/2-Propanol 88/12 % v/v</td>
</tr>
<tr>
<td>Flow rate (ml/min)</td>
<td>1 ml/min</td>
</tr>
<tr>
<td>DAD detection</td>
<td>220 nm</td>
</tr>
<tr>
<td>Loop</td>
<td>10 µL</td>
</tr>
</tbody>
</table>

Intermediate 7 (enantiomer 1): 280mg; Rt= 8.4 minutes.

Intermediate 8 (enantiomer 2): 280mg; Rt= 11.6 minutes.

Intermediate 9

6-[(3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine
To a solution of 3,3-dimethyl-1H-isobenzofuran-5-ol (Intermediate 1, 30mg, 0.18mmol) and 2-chloro-5-nitro-pyridine (27.5mg, 0.1736mmol) in DMF (1mL) dipotassium carbonate (37.8mg, 0.2741mmol) was added and the reaction mixture was stirred for 1.5 hours at 80°C. After cooling the reaction was quenched with water (1mL), diluted with brine (5mL) and extracted with ethyl acetate (2x10mL). The organic layer was dried (Na₂SO₄), filtered and evaporated and the residue was dissolved in ethanol (3mL)/water (1mL). Iron (61.2mg, 1.1mmol) and an aqueous 6M solution of hydrogen chloride (0.03 mL, 0.18mmol) were added and the reaction mixture was stirred for 4 hours at 50°C. The catalyst was filtered off and the resulting solution was diluted with a saturated solution of NaHCO₃ (15mL) and extracted with ethyl acetate (2x20mL). The organic layer was dried (Na₂SO₄), filtered and evaporated and the residue was purified by flash chromatography (Biotage system) on silica gel using a SNAP 10g as column and cyclohexane/ethyl acetate from 80:20 to 30:70 as eluent affording the title compound (20 mg) as colourless oil.

LC/MS: QC_3_MIN: Rt = 1.754 min; m/z 257 [M+H]+.

The following compounds were prepared using the foregoing methodology, replacing 3,3-dimethyl-1H-isobenzofuran-5-ol (Intermediate 1) with the appropriate phenol. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system).

<table>
<thead>
<tr>
<th>Int.</th>
<th>Structure</th>
<th>Name</th>
<th>Phenol</th>
<th>LCMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>6-[(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine (enantiomer 1)</td>
<td>3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol (Intermediate 7 enantiomer 1)</td>
<td>LC/MS: QC_3_MIN: Rt = 2.123 min; m/z 311 [M+H]+.</td>
</tr>
<tr>
<td>11</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>6-[(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine (enantiomer 2)</td>
<td>3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol (Intermediate 7 enantiomer 2)</td>
<td>LC/MS: QC_3_MIN: Rt = 1.989 min; m/z</td>
</tr>
</tbody>
</table>
**benzofuran-5-vloxvlpvridin-3-amine** (enantiomer 2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Form</th>
<th>Retention Time (min)</th>
<th>M/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzofuran-5-ol</td>
<td>(Intermediate 8 enantiomer 2)</td>
<td>311 [M+H]+</td>
<td></td>
</tr>
</tbody>
</table>
| 6-(3H-spiro[2-benzofuran-l,1'-cyclobutan-6-yloxy]pyrimidin-5-amine | (Intermediate 4) | LC/MS: QC_3_MIN: R_t = 1.875 min; m/z 270 [M+H]+.

5 2-(3H-spiro[2-benzofuran-l,1'-cyclobutan-6-yloxy]pyrimidin-5-amine

To a solution of spiro[iH-isobenzofuran-3,l'-cyclobutane]-5-ol (Intermediate 4, 50mg, 0.28mmol) in dry acetonitrile (4mL) dipotassium carbonate (58.8mg, 0.43mmol) and then 2-chloro-5-nitro-pyrimidine (43.0mg, 0.27mmol) were added and the reaction mixture was stirred for 4 hours at room temperature. The reaction was diluted with ethyl acetate (20ml) and washed with an aqueous saturated solution of ammonium chloride (2x10ml). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was dissolved in ethanol (5mL)/water (1mL). Iron (95.0mg, 1.7mmol) and an aqueous 6M solution of hydrogen chloride (0.05ml, 0.3mmol) were added and the reaction mixture was stirred at 50°C for 3 hours. The catalyst was filtered off and the solution was diluted with an aqueous saturated solution of NaHCO_3 (10ml) and extracted with ethyl acetate (2x15ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue was purified by flash chromatography (Biotage system) on silica gel using a SNAP 10g as column and cyclohexane/ethyl acetate from 60:40 to 0:100 as eluent affording the title compound (24mg) as a light yellow solid.

LC/MS: QC_3_MIN: R_t = 1.875 min; m/z 270 [M+H]+.
The following compounds were prepared using the foregoing methodology, replacing 3H-spiro[2-benzofuran-l,l'-cyclobutan]-6-ol (Intermediate 24) with the appropriate phenol. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system).

<table>
<thead>
<tr>
<th>Int.</th>
<th>Structure</th>
<th>Name</th>
<th>Phenol</th>
<th>LCMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td><img src="image1" alt="Structure" /></td>
<td>2-<a href="image2">(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yloxy)pyrimidin-5-amine (enantiomer 1)</a></td>
<td>3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol (Intermediate 7 enantiomer 1)</td>
<td>LC/MS: QC_3_MIN: Rt = 2.045 min; m/z 312 [M+H]+</td>
</tr>
<tr>
<td>15</td>
<td><img src="image3" alt="Structure" /></td>
<td>2-<a href="image4">(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yloxy)pyrimidin-5-amine (enantiomer 2)</a></td>
<td>3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol (Intermediate 8 enantiomer 2)</td>
<td>LC/MS: QC_3_MIN: Rt = 2.002 min; m/z 312 [M+H]+</td>
</tr>
</tbody>
</table>

Intermediate 16

4-[(3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yloxy)aniline

![Structure](image5)

I,1-Dimethyl-6-(4-nitrophenoxy)-1,3-dihydro-2-benzofuran (WO2012/168710 Intermediate 69, 280 mg, 0.98 mmol) was dissolved in ethanol (5ml), 5% w/w Pd/C was added and the reaction mixture was stirred for 4 hours under hydrogen atmosphere (2 bar). The catalyst was filtered off and the solvent evaporated to dryness to afford a pale yellow solid, which was purified by re-slurry in B_2O, to afford the title compound (80 mg) as off-white solid.
UPLC_A: $R_t = 0.67$ min, m/z 256 [M+H]+.

$^1$H NMR (400 MHz, DMSO-d6): $\delta$ ppm 7.14 (d, 1H), 6.78-6.73 (m, 3H), 6.70 (dd, 1H), 6.60-6.56 (m, 2H), 4.96 (s, 2H), 4.88 (s, 2H), 1.37 (s, 6H).

$^{13}$C NMR (200 MHz, DMSO-d6): $\delta$ ppm 158.6, 148.8, 145.9, 145.3, 131.5, 122.0, 120.6, 115.6, 114.8, 109.1, 84.8, 69.4, 28.0.

5 Example 1

5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-imidazolidine-2,4-dione (enantiomer 1)]

![Chemical Structure]

To a solution of 3-methyl-3-(trifluoromethyl)-IH-isobenzofuran-5-ol (enantiomer 1) (Intermediate 7, 20mg, 0.0917mmol) and 3-(2-chloropyrimidin-5-yl)-5,5-dimethyl-imidazolidine-2,4-dione (WO2012/168710 Intermediate 1, 19.855mg, 0.0825mmol) in DME (0.5000mL) dipotassium carbonate (25.34mg, 0.1833mmol) was added and the reaction mixture was stirred for 2 hours at 80°C. After cooling the mixture was diluted with water (5ml) and extracted with ethyl acetate (2x10ml). The organic layer was dried (Na2SO4), filtered and evaporated and the residue was purified by flash chromatography (Biotage system) on silica gel using a SNAP IQg as column and cyclohexane/ethyl acetate from 70:30 to 20:80 as eluent affording the title compound (15mg) as white solid.

$^1$H NMR (400 MHz, DMSO-d6): $\delta$ ppm 8.74 (s, 1H), 8.72 (s, 2H), 7.47 (d, 1H), 7.38-7.42 (m, 1H), 7.35 (dd, 1H), 5.12-5.23 (m, 2H), 1.66 (s, 3H), 1.42 (s, 6H)

LC/MS: QC_3_M IN: $R_t = 2.228$ min; m/z 423 [M+H]+.

The following compounds were prepared using the foregoing methodology, replacing 3,3-dimethyl-IH-isobenzofuran-5-ol (Intermediate 7) with the appropriate Phenol. Final products were purified by flash chromatography (Silica cartridge; cyclohexane/ethyl acetate or other appropriate solvent system).

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>Phenol</th>
<th>LCMS</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>5,5-dimethyl-3-[2-[3-methyl-3-(trifluoromethyl)-1H-imidazolidine-2,4-dione (enantiomer 1)] (trifluoromethyl)</td>
<td>3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-pyrimidin</td>
<td>LC/MS: QC_3_M IN: $R_t = 2.249$ min; m/z 423 [M+H]+</td>
<td>$^1$H NMR (400 MHz, DMSO-d6): $\delta$ ppm 8.74 (s, 1H)</td>
</tr>
</tbody>
</table>
Example 3

(5R)-3-[6-[(33-dimethyl-1H-isobenzofuran-5-yl)oxy]-1-3-pyridyl]-1-5-ethyl-5-methyl-imidazolidine-2,4-dione

To a solution of 3,3-dimethyl-1H-isobenzofuran-5-ol (Intermediate 1, 45mg, 0.2741mmol) in DMF (1ml) (5R)-5-ethyl-3-(6-fluoro-3-pyridyl)-5-methyl-imidazolidine-2,4-dione (WO2012/168710 Intermediate 4, 45.51mg, 0.1918mmol) and dipotassium carbonate (75.755mg, 0.5481mmol) were added. The reaction mixture was stirred at 100°C for 12 hours. The reaction was quenched with an aqueous saturated solution of ammonium chloride (5 ml) and extracted with ethyl acetate (10ml). The organic layer was washed with brine (3x10 ml) dried over sodium sulphate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (Biotage system) using a SNAP 10g as column and cyclohexane/ethyl acetate from 75:25 to 30:70 as eluent to afford the title compound (25mg).

LC/MS: QC_3_MIN: R_t = 1.857 min; m/z 382 [M+H]+.

H-NMR (400 MHz, DMSO-d6): δ ppm 8.58 (s, IH), 7.85 (dd, IH), 7.29 (d, IH), 7.09-7.15 (m, 2H), 7.04 (dd, IH), 4.96 (s, 2H), 1.72-1.83 (m, IH), 1.59-1.70 (m, IH), 1.42 (s, 6H), 1.39 (s, 3H), 0.86 (t, 3H).

The following compounds were prepared using the foregoing methodology, replacing 3,3-dimethyl-1H-isobenzofuran-5-ol (Intermediate 1) with the appropriate phenol. Final products were purified by flash-
chromatography (Silica cartridge using cyclohexane/EtOAc as eluents or reverse phase C18 column using water/acetonitrile as eluents).

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Name</th>
<th>Phenol</th>
<th>LCMS</th>
<th>NM R</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image1" alt="Structure" /></td>
<td>3-f6-f(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxyl-3-dimethylimidazolidine-2,4-dione (enantiomer 1)</td>
<td>3-ferf-butyl-l,3-dihydro-2-benzofuran-5-ol (Intermediate 5 enantiomer 1)</td>
<td>LC/MS: QC 3 MIN: Rt = 2.054 min; m/z 396 [M+H]+.</td>
<td>[^1^H]NMR (400 MHz, DMSO-d$_6$): δ ppm 8.61 (s, 1H), 8.15 (d, 1H), 7.88 (dd, 1H), 7.34 (d, 1H), 7.05-7.15 (m, 3H), 5.02-5.09 (m, 1H), 4.93-4.99 (m, 1H), 4.93-4.97 (m, 1H), 1.40 (s, 6H), 0.90 (s, 9H).</td>
</tr>
<tr>
<td>5</td>
<td><img src="image2" alt="Structure" /></td>
<td>3-f6-f(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxyl-3-dimethylimidazolidine-2,4-dione (enantiomer 2)</td>
<td>3-ferf-butyl-l,3-dihydro-2-benzofuran-5-ol (Intermediate 6 enantiomer 2)</td>
<td>LC/MS: QC 3 MIN: Rt = 2.147 min; m/z 396 [M+H]+, 813 [2M+Na]+.</td>
<td>[^1^H]NMR (400 MHz, DMSO-d$_6$): δ ppm 8.61 (s, 1H), 8.15 (d, 1H), 7.88 (dd, 1H), 7.34 (d, 1H), 7.05-7.15 (m, 3H), 5.02-5.09 (m, 1H), 4.93-4.99 (m, 1H), 4.93-4.97 (m, 1H), 1.40 (s, 6H), 0.90 (s, 9H).</td>
</tr>
<tr>
<td>Compound</td>
<td>Structure</td>
<td>LC/MS: QC_3_MIN: Rt = 2.388 min; m/z 422 [M+H]+.</td>
<td>¹H-NMR (400 MHz, DMSO-d$_6$): δ ppm 8.62 (br.s, 1H), 8.16 (d, 1H), 7.91 (dd, 1H), 7.45 (d, 1H), 7.23-7.29 (m, 2H), 7.18 (d, 1H), 5.11-5.22 (m, 2H), 1.65 (s, 3H), 1.40 (s, 6H).</td>
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<tr>
<td>5,5-dimethyl-3-[[6-[[3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol (Intermed 7 enantiomer 1)]]] isobenzofuran-5-vloxyl-3-pyridylimidazolidine-2,4-dione (enantiomer 1)</td>
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<tr>
<td>5,5-dimethyl-3-[[6-[[3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol (Intermed 8 enantiomer 2)]]] isobenzofuran-5-vloxyl-3-pyridylimidazolidine-2,4-dione (enantiomer 2)</td>
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<td></td>
</tr>
<tr>
<td>5,5-dimethyl-3-[[6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-vloxyl-3-pyridylimidazolidine-2,4-dione]</td>
<td></td>
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<tr>
<td>3H-spiro[2-benzofuran-1,1'-cyclobutan]-6-ol (Intermed 4)</td>
<td></td>
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</tbody>
</table>

LC/MS: QC_3_MIN: Rt = 1.888 min; m/z 380 [M+H]+, 781 [2M+Na]+. ¹H-NMR (400 MHz, DMSO-d$_6$): δ ppm 8.62 (s, 1H), 8.16 (d, 1H), 7.88 (dd, 1H), 7.36 (d, 1H), 7.29 (d, 1H), 7.15 (d, 1H), 7.06 (dd, 1H), 4.96 (s, 2H), 2.42-2.52 (m, 2H), 2.28-2.38.
Example 9

(5R)-3-[6-[(33-dimethyl-lH-isobenzofuran-5-yl)oxy]-1-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione

To a solution of (2R)-2-amino-N-[6-[(3,3-dimethyl-lH-isobenzofuran-5-yl)oxy]-3-pyridyl]butanamide (WO2012/168710 Intermediate 61, 18mg, 0.0527mmol) in DCM (4mL) N,N-diethylthalamine (0.022ml, 0.16mmol) was added and the reaction mixture was cooled to 0°C. A solution of bis(trichloromethyl) carbonate (7.8mg, 0.026mmol) in DCM (1mL) was slowly added and the reaction mixture was stirred for 30 minutes at the same temperature. The reaction was diluted with DCM (5ml) and washed with an aqueous saturated solution of NH₄Cl (10ml). The organic layer was dried (Na₂SO₄), filtered and evaporated and the residue was purified by flash chromatography (Biotage system) on silica gel using a SNAP IOg as column and cyclohexane/ethyl acetate from 80:20 to 10:90 as eluent affording the title compound (16mg) as white solid.

LC/MS: QC_3_M: Rₜ = 2.159 min; m/z 368 [M+H]+.

1H-NMR (400 MHz, DMSO-d₆): δ ppm 8.60 (br.s, IH), 8.12 (d, IH), 7.84 (dd, IH), 7.29 (d, IH), 7.13 (d, IH), 7.11 (d, IH), 7.04 (dd, IH), 4.96 (s, 2H), 4.18-4.23 (m, IH), 1.75-1.85 (m, IH), 1.65-1.75 (m, IH), 1.42 (s, 6H), 0.95 (t, 3H).

The following compounds were prepared using the foregoing methodology, replacing (2R)-2-amino-N-[6-[(3,3-dimethyl-lH-isobenzofuran-5-yl)oxy]-3-pyridyl]butanamide (WO2012/168710 Intermediate 61) with the appropriate amino amide. Final products were purified by flash-chromatography (Silica cartridge; cyclohexane/EtOAc, dichloromethane/methanol or other appropriate solvent system).

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Name</th>
<th>Amino amide</th>
<th>LCMS</th>
<th>N M R</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>10</td>
<td>(5R)-5-ethyl-3-i6-rr3-methyl-3-(trifluoromethyl)-IH-isobenzofuran-5-vloxvl-3-pyridvllimidazolidine-2,4-dione (diastereoisome r 1)</td>
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<td>----------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td></td>
<td>(2R)-2-amino-N-(6-((3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yloxy)pyridin-3-y1)butanamide (diastereoisome r 1)</td>
<td></td>
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<tr>
<td></td>
<td>LC/MS: QC_3_MIN: Rt = 2.330 min; m/z 422 [M+H]+. 1H-NMR (400 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt;): δ ppm 8.61 (br.s, 1H), 8.13 (d, 1H), 7.87 (dd, 1H), 7.44 (d, 1H), 7.24-7.30 (m, 2H), 7.18 (d, 1H), 5.11-5.21 (m, 2H), 4.18-4.23 (m, 1H), 1.76-1.86 (m, 1H), 1.65-1.75 (m, 1H), 1.65 (s, 3H), 0.95 (t, 3H).</td>
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</table>

<table>
<thead>
<tr>
<th>11</th>
<th>(5R)-5-ethyl-3-f6-ff3-methyl-3-(trifluoromethyl)-IH-isobenzofuran-5-vloxvl-3-pyridvllimidazolidine-2,4-dione (diastereoisome r 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2R)-2-amino-N-(6-((3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yloxy)pyridin-3-y1)butanamide (diastereoisome r 2)</td>
</tr>
<tr>
<td></td>
<td>LC/MS: QC_3_MIN: Rt = 2.266 min; m/z 422 [M+H]+. 1H-NMR (400 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt;): δ ppm 8.61 (br.s, 1H), 8.13 (d, 1H), 7.87 (dd, 1H), 7.44 (d, 1H), 7.24-7.30 (m, 2H), 7.18 (d, 1H), 5.11-5.21 (m, 2H), 4.18-4.23 (m, 1H), 1.76-1.86 (m, 1H), 1.65-1.75 (m, 1H), 1.65 (s, 3H), 0.95 (t, 3H).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>12</th>
<th>(5R)-5-ethyl-3-6-SDirolffH-isobenzofuran-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2R)-2-amino-N-(6-(3H-spiro[2 QC_3_M IN: Rt = 2.254 min; m/z 422 [M+H]+. 1H-NMR (400 MHz, DMSO-d&lt;sub&gt;6&lt;/sub&gt;): δ ppm 8.60 (br.s,</td>
</tr>
<tr>
<td>13</td>
<td>3,1'-cyclobutane-5-vloxv-3-Pyridin-Dimidazolidine-2,4-dione</td>
</tr>
<tr>
<td>14</td>
<td>(5R)-5-ethyl-3-[2 trifluoromethyl]-IH-isobenzofuran-5-3-vloxv-pyrimidine-2,4-dione (diastereoisomer r1)</td>
</tr>
</tbody>
</table>

**LC/MS:** QC_3_MIN: Rf = 2.199 min; m/z 423 [M+H]+. $^1$H-NMR (400 MHz, DMSO-d6): δ ppm 8.74 (br.s, 1H), 7.47 (d, 1H), 8.70 (s, 2H).
<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Properties</th>
</tr>
</thead>
</table>
| 5-yl-
  oxypyrimidine | ![Structure](image) | 7.38-7.41 (m, 1H), 7.35 (dd, 1H), 5.12-5.22 (m, 2H), 4.20-4.26 (m, 1H), 1.77-1.88 (m, 1H), 1.66-1.77 (m, 1H), 1.65 (s, 3H), 0.96 (t, 3H). |
| N-5-yl-
  limidazolidine | | |
| -2,4-dione | | |
| (diastereoisome 2) | | |
| (WO2012/1687 10 Intermediate 67) | | |
| (5R)-5-ethyl-3-(2,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy)phenyl)-5-ethyl-5-methyl-2,4-imidazolidinedione | ![Structure](image) | LC/MS: QC3_MIN: Rt = 2.107 min; m/z 381 [M+H]+. 
^1H-NMR (400 MHz, DMSO-d_6): δ ppm 8.73 (br.s, 3H), 8.69 (s, 2H), 7.45 (dd, 1H), 7.31 (d, 1H), 7.15 (dd, 1H), 4.97 (s, 2H), 4.21-4.26 (m, 1H), 2.43-2.53 (m, 2H), 2.28-2.38 (m, 2H), 1.63-1.98 (m, 4H), 0.97 (t, 3H). |

Example 6

(5R)-3-(4-(3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy)phenyl)-5-ethyl-5-methyl-2,4-imidazolidinedione
(2R)-2-amino-N-[4-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]phenyl]-2-methybutanamide

(WO2012/168710 Intermediate 71, 140 mg, 0.39 mmol) was dissolved in ethyl acetate (2 mL) and the resulting solution was added drop wise to a suspension of CDI (1.4 equiv) in ethyl acetate (0.5 mL). The resulting suspension was stirred overnight. A new solution of CDI was freshly prepared (60 mg in 0.5 mL of ethyl acetate) and added drop wise to the mixture. A third portion of CDI (50 mg) was added and the reaction mixture was left stirring over week-end at room temperature. The mixture was treated with 10 % w/w aqueous citric acid solution, two layers were separated and the organic layer washed with water and brine, then dried over Na₂SO₄ and evaporated to dryness. The residue was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate from 80:20 to 60:40 as eluent. The fractions containing the product were combined, evaporated to dryness and further purified by crystallization from ethyl acetate/n-heptane. The slurry was stirred for 2 hours, and then the solid collected, washed with n-heptane and dried under vacuum. The residue was re-purified by flash chromatography on silica gel using dichloromethane/methanol from 100:0 to 90:10. The fractions containing the product were combined, evaporated to dryness and the residue further purified by crystallization from methyl tertbutyl ether/n-heptane to afford the title compound (47 mg) as white solid.

UPLC_A: Rt = 1.02 min, m/z 381 [M+H]+, 761 [2M+H]+.

¹H-NMR (400 MHz, DMSO-d₆): δ ppm 8.47 (s, 1H), 7.34-7.30 (m, 2H), 7.28 (d, 1H), 7.07-7.03 (m, 3H), 6.94 (dd, 1H), 4.94 (s, 2H), 1.81-1.72 (m, 1H), 1.69-1.59 (m, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 0.85 (t, 3H). ¹³C-NMR (200 MHz, DMSO-d₆): δ ppm 175.9, 156.7, 155.5, 154.8, 149.3, 134.0, 128.5, 126.8, 122.6, 118.4, 117.8, 112.1, 85.0, 69.5, 61.3, 30.5, 28.0, 23.2, 7.7.

Biological Example 1

The ability of the compounds of the invention to modulate the voltage-gated potassium channel subtypes Kv3.2/3.1 may be determined using the following assay. Analogous methods may be used to investigate the ability of the compounds of the invention to modulate other channel subtypes, including Kv3.3 and Kv3.4.

Cell biology

To assess compound effects on human Kv3.2 channels (hKv3.2), a stable cell line expressing human Kv3.2 channels (hKv3.2) was created by transfecting Chinese Hamster Ovary (CHO)-KI cells with a pCI H5-hKv3.2 vector. Cells were cultured in DM EM/F12 medium supplemented by 10% Foetal Bovine
Serum, 1X non-essential amino acids (Invitrogen) and 500ug/ml of Hygromycin-B (Invitrogen). Cells were grown and maintained at 37°C in a humidified environment containing 5% CO₂ in air.

To assess compound effects on human Kv3.1 channels (hKv3.1), CHO/Gam/EIA-clone22 alias CGE22 cells were transduced using a hKv3.1 BacMam reagent. This cell line was designed to be an improved CHO-K1-based host for enhanced recombinant protein expression as compared to wild type CHO-K1. The cell line was generated following the transduction of CHO-K1 cells with a BacMam virus expressing the Adenovirus-GamiI protein and selection with Geneticin-G418, to generate a stable cell line, CHO/Gam-A3. CHO/Gam-A3 cells were transfected with pCDNA3-EIA-Hygro, followed by hygromycin-B selection and FACS sorting to obtain single-cell clones. BacMam-Luciferase and BacMam-GFP viruses were then used in transient transduction studies to select the clone based on highest BacMam transduction and recombinant protein expression. CGE22 cells were cultured in the same medium used for the hKv3.2 CHO-K1 stable cell line with the addition of 300ug/ml hygromycin-B and 300ug/ml G418. All other conditions were identical to those for hKv3.2 CHO-K1 cells. The day before an experiment 10 million CGE22 cells were plated in a T175 culture flask and the hKv3.1 BacMam reagent (pFBM/human Kv3.1) was added (MOI of 50). Transduced cells were used 24 hours later.

Cell preparation for IonWorks Quattro™ experiments

The day of the experiment, cells were removed from the incubator and the culture medium removed. Cells were washed with 5 ml of Dulbecco's PBS (DPBS) calcium and magnesium free and detached by the addition of 3 ml Versene (Invitrogen, Italy) followed by a brief incubation at 37°C for 5 minutes. The flask was tapped to dislodge cells and 10 ml of DPBS containing calcium and magnesium was added to prepare a cell suspension. The cell suspension was then placed into a 15 ml centrifuge tube and centrifuged for 2 min at 1200 rpm. After centrifugation, the supernatant was removed and the cell pellet re-suspended in 4 ml of DPBS containing calcium and magnesium using a 5ml pipette to break up the pellet. Cell suspension volume was then corrected to give a cell concentration for the assay of approximately 3 million cells per ml.

All the solutions added to the cells were pre-warmed to 37°C.

Electrophysiology

Experiments were conducted at room temperature using IonWorks Quattro™ planar array electrophysiology technology (Molecular Devices Corp.) with PatchPlate™ PPC. Stimulation protocols and data acquisition were carried out using a microcomputer (Dell Pentium 4). Planar electrode hole resistances(Rp) were determined by applying a 10 mV voltage step across each well. These
measurements were performed before cell addition. After cell addition and seal formation, a seal test was performed by applying a voltage step from -80 mV to -70 mV for 160 ms. Following this, amphotericin-B solution was added to the intracellular face of the electrode to achieve intracellular access. Cells were held at -70mV. Leak subtraction was conducted in all experiments by applying 50 ms hyperpolarizing (10 mV) prepulses to evoke leak currents followed by a 20 ms period at the holding potential before test pulses. From the holding potential of -70 mV, a first test pulse to -15 mV was applied for 100 ms and following a further 100 ms at -70 mV, a second pulse to 40 mV was applied for 50 ms. Cells were then maintained for a further 100 ms at -100 mV and then a voltage ramp from -100 mV to 40 mV was applied over 200 ms. Test pulses protocol may be performed in the absence (pre-read) and presence (post-read) of the test compound. Pre- and post-reads may be separated by the compound addition followed by a 3 minute incubation.

Solutions and drugs

The intracellular solution contained the following (in mW): K-gluconate 100, KCl 54, MgCl2 3.2, HEPES 5, adjusted to pH 7.3 with KOH. Amphotericin-B solution was prepared as 50mg/ml stock solution in DMSO and diluted to a final working concentration of 0.1 mg/ml in intracellular solution. The external solution was Dulbecco’s Phosphate Buffered Saline (DPBS) and contained the following (in mW): CaCl2 0.90, KCl 2.67, KH2P04 1.47, MgCl2.6H2O 0.493, NaCl 136.9, Na3P04 8.06, with a pH of 7.4.

Compounds of the invention (or reference compounds such as 1-V-cyclohexyl-1-V-(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-1-V-phenylurea were dissolved in dimethylsulfoxide (DMSO) at a stock concentration of 10 mM. These solutions were further diluted with DMSO using a Biomek FX (Beckman Coulter) in a 384 compound plate. Each dilution (1 µL) was transferred to another compound plate and external solution containing 0.05% pluronic acid (66 µL) was added. 3.5 µL from each plate containing a compound of the invention was added and incubated with the cells during the IonWorks Quattro™ experiment. The final assay dilution was 200 and the final compound concentrations were in the range 50 µM to 50 nM.

Data analysis

The recordings were analysed and filtered using both seal resistance (>20 MΩ) and peak current amplitude (>500pA at the voltage step of 40 mV) in the absence of compound to eliminate unsuitable cells from further analysis. Paired comparisons between pre- and post-drug additions measured for the -15 mV voltage step were used to determine the positive modulation effect of each compound. Kv3 channel-mediated outward currents were determined from the mean amplitude of the current over the final 10ms of the -15mV voltage pulse minus the mean baseline current at -70mV over a 10ms period.
just prior to the -15mV step. These Kv3 channel currents following addition of the test compound were then compared with the currents recorded prior to compound addition. Data were normalised to the maximum effect of the reference compound (50µM of 1/V-cyclohexyl-V\{[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-V'/phenylurea) and to the effect of a vehicle control (0.5% DMSO). The normalised data were analysed using ActivityBase or Excel software. The concentration of compound required to increase currents by 50% of the maximum increase produced by the reference compound (EC50) was determined by fitting of the concentration-response data using a four parameter logistic function in ActivityBase.

\(1/V\)-cyclohexyl-V\{[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-V'/phenylurea was obtained from ASINEX (Registry Number: 552311-06-5).

All of the Example compounds were tested in the above assay measuring potentiation of Kv3.1 or Kv3.2 or Kv3.1 and Kv.3.2 (herein after “Kv3.1 and/or Kv3.2”). Kv3.1 and/or Kv3.2 positive modulators produce in the above assay an increase of whole-cell currents of, on average, at least 20% of the increase observed with 50µM A\(1/V\)-cyclohexyl-V\{[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-V'/phenylurea. Thus, in the recombinant cell assays of Biological Example 1, all of the Example compounds act as positive modulators. As used herein, a Kv3.1 and/or Kv3.2 positive modulator is a compound which has been shown to produce at least 20% potentiation of whole-cell currents mediated by human Kv3.1 and/or human Kv3.2 channels recombinantly expressed in mammalian cells, as determined using the assays described in Biological Example 1 (Biological Assays).

Furthermore, all Examples were found to demonstrate a more balanced activity between Kv3.1 and Kv3.2 channels as compared to similar compounds of the prior art such as (5R)-5-ethyl-3-[6-(spiro[l-benzofuran-3,1'-cyclopropan]-4-yl oxy)-3-pyridinyl]-2,4-imidazolidinedione (Reference Example 87 of WO2011069951A1) and 5,5-dimethyl-3-[6-(spiro[l-benzofuran-3,1'-cyclopropan]-4-yl oxy)-3-pyridinyl]-2,4-imidazolidinedione (Reference Example 88 of WO2011069951A1). (5R)-5-ethyl-3-[6-(spiro[l-benzofuran-3,1'-cyclopropan]-4-yl oxy)-3-pyridinyl]-2,4-imidazolidinedione and 5,5-dimethyl-3-[6-(spiro[l-benzofuran-3,1'-cyclopropan]-4-yl oxy)-3-pyridinyl]-2,4-imidazolidinedione both demonstrate a 0.7 log unit difference in pEC\textsubscript{50} values between the two channels, whereas all example compounds demonstrate more comparable activities between channels and with a maximum difference in average pEC\textsubscript{50} values of only 0.42 log units. Locating the A ring in the meta/para position, which is a feature of all compounds of the present invention, therefore helps ensure comparable activities between Kv3.1 and Kv3.2 channels.
A secondary analysis of the data from the assays described in Biological Example 1 may be used to
investigate the effect of the compounds on rate of rise of the current from the start of the depolarising
time pulses. The magnitude of the effect of a compound can be determined from the time constant
(Tau$_{act}$) obtained from a non-linear fit, using the equation given below, of the rise in Kv3.1 or Kv3.2
currents following the start of the -15mV depolarising voltage pulse.

\[ Y = (Y_0 - Y_{max}) \times \exp(-K'X) + Y_{max} \]

where:

- $Y_0$ is the current value at the start of the depolarising voltage pulse;
- $Y_{max}$ is the plateau current;
- $K'$ is the rate constant, and Tau$_{act}$ is the activation time constant, which is the reciprocal of $K$.

Similarly, the effect of the compounds on the time taken for Kv3.1 and Kv3.2 currents to decay on
closing of the channels at the end of the -15mV depolarising voltage pulses can also be investigated. In
this latter case, the magnitude of the effect of a compound on channel closing can be determined from
the time constant (Tau$_{deact}$) of a non-linear fit of the decay of the current ("tail current") immediately
following the end of the depolarising voltage pulse.

Kv3.1 and Kv3.2 channels must activate and deactivate very rapidly in order to allow neurons to fire
Slowing of activation is likely to delay the onset of action potential repolarisation; slowing of
deactivation could lead to hyperpolarising currents that reduce the excitability of the neuron and delay
the time before the neuron can fire a further action potential. Together these two slowing effects on
channel activation and deactivation are likely to lead to a reduction rather than a facilitation of the
neurons ability to fire at high frequencies. Thus compounds that have this slowing effect on the Kv3.1
and/or Kv3.2 channels will effectively behave as negative modulators of the channels, leading to a
slowing of neuronal firing. This latter effect has been shown on "fast-firing" interneurons in the cortex
of rat brain, using electrophysiological techniques, in vitro, for certain compounds disclosed in
WO2011/069951, which produced a marked increases in Tau$_{act}$ in the Kv3.1 and Kv3.2 assays described
above. The addition of the relevant compounds reduces the ability of the neurons to fire in response to
trains of depolarising pulses at 300Hz.
Therefore, although compounds of the invention may be identified as positive modulators in the recombinant cell assay of Biological Example 1, those compounds which markedly increase the value of \( \text{Tau}_{\text{act}} \) reduce the ability of neurons in native tissues to fire at high frequency.

**Biological Example 2**

**Determination of blood and brain tissue binding**

**Materials and Methods**

Rat whole blood, collected on the week of the experiment using K3-EDTA as an anti-coagulant, was diluted with isotonic phosphate buffer 1:1 (v/v). Rat whole brain, stored frozen at -20 °C, was thawed and homogenised in artificial cerebrospinal fluid (CSF) 1:2 (w/v).

An appropriate amount of test compound was dissolved in DMSO to give a 5 millimolar solution. Further dilutions, to obtain a 166.7 micromolar working solution was then prepared using 50% acetonitrile in MilliQ water. This working solution was used to spike the blood to obtain a final concentration of 0.5 micromolar in whole blood. Similarly, the working solution was used to spike brain samples to obtain a final concentration of 5 micromolar in whole brain. From these spiked blood and brain preparations, control samples (n=3), were immediately extracted and used to calculate the initial recovery of the test items.

150 microL of compound-free buffer (isotonic phosphate buffer for blood or artificial CSF buffer for brain) was dispensed in one half-well and 150 microL of spiked matrix (blood or brain) was loaded in the other half-well, with the two halves separated by a semi-permeable membrane. After an equilibration period of 5 hours at 37°C, 50 microL of dialysed matrix (blood or brain) was added to 50 microL of corresponding compound-free buffer, and vice-versa for buffer, such that the volume of buffer to matrix (blood or brain) remained the same. Samples were then extracted by protein precipitation with 300 microL of acetonitrile containing rolipram (control for positive ionization mode) or diclofenac (control for negative ionization mode) as internal standards and centrifuged for 10 min at 2800 rpm. Supernatants were collected (100 microL), diluted with 18% ACN in MilliQ water (200 microL) and then injected into an HPLC-MS/MS or UPLC-MS/MS system to determine the concentration of test compound present.

**Analysis**

Blood and brain tissue binding were then determined using the following formulas:

\[ \text{Afu}=\frac{\text{Buffer/Blood}}{\text{CSF/Brain}} \]
Where \( A_{fu} \) = apparent fraction unbound; Buffer = analyte/internal standard ratio determined in the buffer compartment; Blood = analyte/internal standard ratio determined in the blood compartment; Brain = analyte/internal standard ratio determined in the brain compartment.

\[
F_{ucr} = \frac{1}{D} \times \left( \frac{1}{A_{fu}} - 1 \right) + \frac{1}{D}
\]

where: \( f_{ucr} \) = Fraction unbound corrected; \( D \) = matrix dilution factor (\( D = 2 \) for blood and \( D = 3 \) for brain).

Then:

\[
\text{%Binding} = (1 - f_{ucr}) \times 100
\]

\[
\text{%Unbound} = 100 - \text{%Bound}
\]

10 **Brain/Blood partition ratio (Kbb) Determination**

For compounds freely permeable across the blood/brain barrier (BBB), the unbound concentrations in blood and brain would be equivalent under steady-state distribution conditions. Therefore, the Kbb value could be calculated as:

\[
F_{u(\text{blood})}/F_{u(\text{brain})}
\]

which is expected to be equivalent to the brain-to-blood concentration ratio \( (C_{t(\text{brain})}/C_{t(\text{blood})}) \) if efflux pump transporters are not involved.

**Materials and Methods**

Adult male rats (Charles River, Italy) were dosed with test compound orally at 1mg/kg (5 ml/kg, in 5% v/v DMSO, 0.5% w/v HPMC in water) and intravenously at 0.5mg/kg (2ml/kg, in 5% v/v DMSO 40% w/v PEG400 in saline). After oral administration, blood samples were collected under deep Isoflurane anesthesia from the portal vein and heart of each rat (1 rat per time point). After intravenous administration, serial blood samples were collected from the lateral tail vein of each rat. A further group of rats (\( n=1 \) per test compound) received a single intravenous administration of the Pgp transport inhibitor, Elacridar (3 mg/kg) shortly before the oral administration of the test compound at 1 mg/kg, as above. Blood and brain samples were collected at a single timepoint of 0.5 h after dose administration for these animals. In all cases, blood samples were collected into potassium EDTA tubes.
Blood and brain samples were assayed for test compound concentration using a method based on protein precipitation with acetonitrile followed by HPLC/MS-MS analysis with an optimized analytical method.

**Analysis**

The concentrations of test compound in blood (expressed as ng/ml) and brain (expressed as ng/g) at the different time points following either oral or intravenous dosing were analysed using a non-compartmental pharmacokinetic model using WinNonLin Professional version 4.1. The following parameters were derived:

- **Intravenous dosing**: Maximum concentration over time (Cmax), integrated concentration over time (AUC), clearance (Clb), volume of distribution (Vss) and half-life (tl/2).
- **Oral dosing**: Cmax, time of maximum concentration (Tmax), AUC, bioavailability (F%), fraction absorbed (Fa%), blood to brain ratio (AUC BB), and Fold-change in AUC BB in the presence of Elacridar.

In the above *in vivo* pharmacokinetic assay, Examples 3, 4, 6 and 8 were each found to demonstrate AUC BB values of at least 1.7 fold that of (5R)-5-ethyl-3-[6-(spiro[l-benzofuran-3,l'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione (Reference Example 87 of WO2011/069951A1) and 5,5-dimethyl-3-[6-(spiro[l-benzofuran-3,l'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione (Reference Example 88 of WO2011/069951A1).

Examples 3, 4, 6 and 8 show limited change in AUC BB in the presence of Elacridar, indicating an absence of notable p-glycoprotein interactions.

Consequently, compounds of the invention, especially those having an oxygen atom located in the benzylic position of the ring A, may be expected to demonstrate good availability in brain tissue.

**Biological Example 3**

Activity of modulators of Kv3 in a mouse model of amphetamine induced hyperlocomotion

Example 3 was tested in the mouse model of amphetamine induced hyperlocomotion described in Example 93 of WO2011/069951A1. At a dose of 60 mg/kg, Example 3 completely prevented (P<0.01) the increase in locomotor activity induced by amphetamine measured over a 60 minute period following the amphetamine administration.
Evaluation of the efficacy of modulators of Kv3 channels in a model of noise-induced hearing loss in the Chinchilla

The otoprotective efficacy of an exemplary Kv3 modulator described within WO2011069951A1, referred to herein as "COMPOUND X", was investigated using a chinchilla model of noise-induced hearing loss, as follows:

Materials and Methods

Subjects comprised male, 3 year old chinchillas (Laniger), 10 animals per group. Chinchillas were housed in the study facility for a minimum of 5 days prior to noise exposure. Food and water were available ad libitum. Animals were maintained at 21°C on a 12/12 light/dark cycle.

Vehicle and Drug Preparation and Administration

Vehicle (20% Captisol®, 0.5% w/v HPMC K15M and 0.5% w/v Tween 80™) was prepared using autoclaved deionized water not more than one week prior to use. A suspension of COMPOUND X in the vehicle at 10 mg/ml was prepared less than 24 hours prior to administration. COMPOUND X was administered at 60 mg/kg via the intraperitoneal route, with doses 12 hours apart. Five injections were given pre-noise exposure and five post-noise exposure. On the day of noise exposure, injections were given 1.5 hours before the start of noise exposure and one hour after completion of the noise exposure protocol.

Noise Exposure

Animals were placed in a sound-attenuated booth for 15 minutes prior to noise exposure. Noise exposure consisted of a 105 dB SPL octave-band noise centered at 4 kHz (TDT GNS 40X white noise generator) for 6 hours duration. The noise was routed through an attenuator (TDT PA3), a filter (Krohn-Hite 3384) and a power amplifier (Sony 55ES) to a custom-built acoustic exponential horn with a maximum output at 4 kHz using an Altec 209E driver. The loudspeaker was suspended directly above the cage. During noise exposure, animals had access to water, but not food.

Auditory Brainstem Response

Auditory brainstem responses (ABRs) were collected prior to noise exposure and 21 days after noise exposure. All animals were anesthetized throughout the ABR procedure and prior to sacrifice with a 0.3 ml/kg IM injection of 50 mg/m L-ketamine, 5 mg/m L-xylazine, and 1mg/kg acepromazine. Thresholds were measured in response to tone-bursts with 1 ms rise/fall and a 0 ms plateau gated by a Blackman envelope and centred at the frequencies of 2, 4, 6 and 8 kHz, presented at 30/s. Two intensity series
were obtained for each animal from 100 to 0 dB peak SPL in 10 dB decrements with 512 sweeps per average. The recording epoch was 15 ms following stimulus onset. Responses were analogue filtered with a 30 - 3000 Hz band pass. Threshold is defined as the lowest intensity capable of eliciting a replicable, visually detectable auditory brainstem response in both intensity series.

Further details of these methods can also be found in Campbell et al. (2011) Hearing Research 282, 138-144.

Data Analysis

The thresholds for ABRs at the four different sound frequencies at day 21 post-noise exposure were compared to the thresholds at baseline, prior to noise exposure in order to determine a threshold shift for each animal. The data were then analysed using a 2-way ANOVA, with treatment and frequency as main factors.

Results

In this assay, COMPOUND X significantly reduced the permanent threshold shift in ABR observed 21 days after noise exposure (p<0.01). These results support the potential efficacy of COMPOUND X and of small molecule Kv3 channel modulators in general in the treatment of hearing disorders, in particular noise-induced hearing loss.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.
Claims

1). A compound selected from:

5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione;

(5R)-3-[[3,3-dimethyl-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;

3-[[3-tert-butyl-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione;

5,5-dimethyl-3-[[6-spiro[1H-isobenzofuran-3,4'-cyclobutane]-5-yloxy]-3-pyridyl]imidazolidine-2,4-dione;

(5R)-3-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;

(5R)-5-ethyl-3-[[6-spiro[1H-isobenzofuran-3,4'-cyclobutane]-5-yloxy]-3-pyridyl]imidazolidine-2,4-dione;

(5R)-3-[[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione;

(5R)-3-4-[[3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl]oxy]phenyl]-5-ethyl-5-methyl-2,4-imidazolidinedione;

or a pharmaceutically acceptable salt and/or solvate thereof.

2. The compound according to claim 1, selected from:

5,5-dimethyl-3-[[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 1);

5,5-dimethyl-3-[[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 2);

(5R)-3-[[6-[[3,3-dimethyl-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;

3-[[6-[[3-tert-butyl-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1);

3-[[6-[[3-tert-butyl-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 2);
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-lH-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-lH-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 2);
5,5-dimethyl-3-(6-spiro[lH-isobenzofuran-3,4'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione (diastereoisomer 1);
5,5-dimethyl-3-(6-spiro[lH-isobenzofuran-3,4'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-3-[[33-dimethyl-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-3-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-3-[[2-[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-3-[[2-[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-3-[[2-spiro[lH-isobenzofuran-3,1'-cyclobutane]-5-yloxypyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-3-[[4-[[3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl]oxy]phenyl]-5-ethyl-5-methyl-2,4-imidazolidinedione;
or a pharmaceutically acceptable salt and/or solvate thereof.

3). The compound according to claim 2, which is:
5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 2);
(5R)-3-[[3,3-dimethyl-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
3-[[3-tert-butyl-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1);
3-[[3-tert-butyl-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 2);
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 2); 
5,5-dimethyl-3-(6-spiro[1H-isobenzofuran-3,4'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-3-[6-[[33-dimethyl-1H-isobenzofuran-5-yl]oxy]-3'-pyridyl]-5-ethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1); 
(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2); 
(5R)-5-ethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-3-(2-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxypyrimidin-5-yl)imidazolidine-2,4-dione; 
or
(5R)-3-{4-[[3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl]oxy]phenyl}-5-ethyl-5-methyl-2,4-imidazolidinedione.

4). A compound according to any one of claims 1 to 3, for use as a medicament.

5). A compound according to claim 4, for use in the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, bipolar disorder, epilepsy, sleep disorders, cognition impairment or ataxia.

6). A compound according to claim 5, for use in the prophylaxis or treatment of hearing loss or tinnitus.

7). A compound according to any one of claims 4 to 6, for use in conjunction with a further pharmaceutically active agent.

8). A method for the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, bipolar disorder, epilepsy, sleep disorders, cognition impairment or ataxia by administering to a subject a compound according to any one of claims 1 to 3.

9). Use of a compound according to any one of claims 1 to 3 in the manufacture of a medicament for the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, bipolar disorder, epilepsy, sleep disorders, cognition impairment or ataxia.
10). A pharmaceutical composition comprising a compound according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier or excipient.

11). A compound selected from:

- 3/-/-spiro[2-benzofuran-1,1'-cyclobutan]-6-ol

- 3-ferf-butyl-1,3-dihydro-2-benzofuran-5-ol (including 3-ferf-butyl-1,3-dihydro-2-benzofuran-5-ol enantiomer 1 and 3-ferf-butyl-1,3-dihydro-2-benzofuran-5-ol enantiomer 2)

- 3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol (including 3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol enantiomer 1 and 3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-ol enantiomer 2)

12). A compound selected from:

- 6-[(3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine

- 6-[(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine (enantiomer 1) and

- 6-[(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl)oxy]pyridin-3-amine (enantiomer 2)

- 6-(3/-/-spiro[2-benzofuran-1,1'-cyclobutan]-6- yloxy)pyridin-3-amine
2-(3H-spiro[2-benzofuran-1,1’-cyclobutan]-6-yloxy)pyrimidin-5-amine

24-[3-methyl-3-(trifluoromethyl)-13-dihydro-2-benzofuran-5-yl]oxy)pyrimidin-5-amine

, including 2-[(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl]oxy)pyrimidin-5-amine (enantiomer 1) and 2-[(3-methyl-3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl]oxy)pyrimidin-5-amine (enantiomer 2); and

4-[(3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]aniline

A derivative of a compound according to any one of claims 1 to 3, which derivative is functionalised via the secondary nitrogen of the hydantoin with a group \(L\), wherein \(L\) is selected from:

- \(-\text{PO(OH)}0^\cdot M^+\), wherein \(M^+\) is a pharmaceutically acceptable monovalent counterion,
- \(-\text{PO(0}^\cdot M^+\),
- \(-\text{PO(0}^\cdot \text{D}^2\cdot M^+\), wherein \(\text{D}^2\) is a pharmaceutically acceptable divalent counterion,
- \(-\text{CH(R')}^\cdot \text{PO(OH)}0^\cdot M^+\), wherein \(R'\) is hydrogen or \(C_{1-3}\) alkyl,
- \(-\text{CH(R')}^\cdot \text{PO(0}^\cdot M^+\)
- \(-\text{CH(R')}^\cdot \text{SO}3^\cdot M^+\),
- \(-\text{CH(R')}^\cdot \text{S}03^\cdot M^+\), and
- \(-\text{CO-CH}2\text{CH}2\text{CO}2\cdot M^+\).
INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/051487

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/14 C07D405/12 A61K31/343 A61K31/4178 A61P25/00
ADD.

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)
C07D

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 practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>A</td>
<td>NEIL A CASTLE: &quot;Pharmacological modulation of voltage-gated potassium channel as a therapeutic strategy&quot;, CURRENT OPINION IN THERAPEUTIC PATENTS, XX, XX, vol. 20, no. 11, 1 November 2010 (2010-11-01), pages 1471-1503, XP008163260, ISSN: 0962-2594, DOI: 10.1517/13543776.2010.513384 page 11; figure 4 page 19</td>
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Further documents are listed in the continuation of Box C. X See patent family annex.

* Special categories of cited documents:

**A** document defining the general state of the art which is not considered to be of particular relevance

**E** earlier application or patent but published on or after the international filing date

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**P** document published prior to the international filing date but later than the priority date claimed

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**X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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**S** document member of the same patent family

Date of the actual completion of the international search
11 July 2013

Date of mailing of the international search report
17/07/2013

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Authorized officer
Koch, Kristian
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