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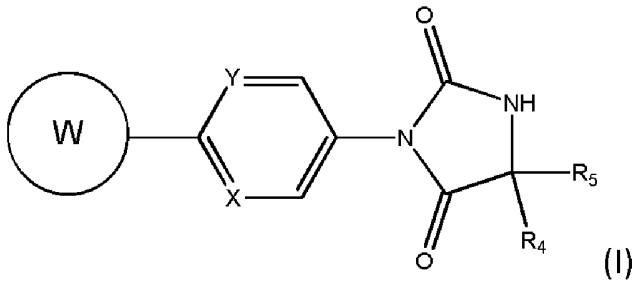

(I)

(57) Abstract: The present invention relates to the prophylaxis or treatment of diseases and disorders wherein a modulator of Kv3.3 channels is required, including spinocerebellar ataxia, by administering a compound of formula (I):

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PROPHYLAXIS OR TREATMENT OF DISEASES WHERE A MODULATOR OF KV3.3 CHANNELS IS REQUIRED

Technical field

This invention relates to compounds and pharmaceutical compositions containing such compounds for use in the prophylaxis or treatment of diseases and disorders wherein a modulator of Kv3.3 channels is required, including spinocerebellar ataxia.

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.Physiol. 584, 565-582), cerebellum (Sacco et al., 2006, Mol. Cell. Neurosci. 33, 170-179; Puente et al., 2010, Histochem. Cell Biol. 134, 403-409), and auditory brain stem nuclei (Li et al., 2001, J. Comp. Neurol. 437, 196-218).

Kv3 channels are important determinants of the function of the cerebellum, a region of the brain important for motor control (Joho and Hurlock, 2009, Cerebellum 8, 323–333). Characterisation of mice in which specific Kv3 subtypes have been deleted shows that the absence of Kv3.3 channels gives rise to a phenotype characterised by mild ataxia and motor deficits (McMahon et al., 2004, Eur. J.Neurosci. 19, 3317-3327). Likely underlying these behavioural deficits, Purkinje neurons in the cerebellum show increased excitability in the Kv3.3 knockout mice (Zagha et al., 2010, J.Neurophysiol. 103, 3516-25). Double deletion of Kv3.3 and Kv3.1 channels gives rise to a severe phenotype characterised by spontaneous seizures, ataxia, and an increased sensitivity to the effects of ethanol on motor coordination (Espinosa et al., 2001, J.Neurosci. 21, 6657-6665; Espinosa et al., 2008, J.Neurosci. 28, 5570-5581).

Spinocerebellar ataxia type 13 (SCA13) is a human autosomal dominant disease caused by mutations in the KCNC3 gene that encodes the Kv3.3 channel. SCA13 is either a neurodevelopmental disorder that is evident in infancy or a progressive neurodegenerative disease that emerges during

adulthood (Figueroa et al., 2010, Hum Mutat. 31, 191–196). The known mutations in the KCNC3 gene have been shown to cause a reduction in function of the channels in some cases (Waters et al., 2006, Nat. Genet. 38, 447-451; Minassian et al., 2012, J Physiol. 590.7, 1599-1614), and a gain of function in other cases (Figueroa et al., 2011, PLoS ONE 6, e17811). For example, an F448L mutation alters channel gating and causes early-onset SCA13, whereas R420H and R423H mutations are associated with reduced Kv3 current amplitude by a dominant negative mechanism (Figueroa et al., 2010, Hum Mutat. 31, 191–196; Minassian et al., 2012, J Physiol. 590.7, 1599-1614). R420H leads to an adult form of SCA13, whereas R423H is associated with an early-onset ataxia. Early onset forms of SCA13 may be associated with deficits in the development of the cerebellum (Issa et al., 2012, Dis Model Mech. 5, 921-929), which are secondary to loss of Kv3.3 function.

Small molecule modulators of Kv3.3, which are able to correct the deficits observed in the mutant channels, might be beneficial in the treatment of spinocerebellar ataxia, in particular SCA13.

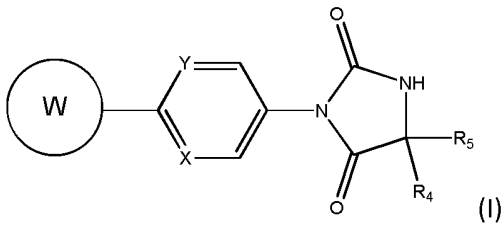
Hearing loss represents an epidemic that affects approximately 16% of the population in Europe and the US (Goldman and Holme, 2010, Drug Discovery Today 15, 253-255), with a prevalence estimated at 250 million people worldwide (B.Shield, 2006, Evaluation of the social and economic costs of hearing impairment. A report for Hear-It AISBL: www.hear-it.org/multimedia/Hear_It_Report_October_2006.pdf). Kv3.3 channels are expressed at high levels in auditory brainstem nuclei (Li et al., 2001, J. Comp. Neurol. 437, 196-218), where they contribute to the activity of neurons that transmit auditory information from the brainstem to higher brain regions. Phosphorylation of Kv3.3 channels in auditory brainstem neurons is suggested to contribute to the physiological adaptation to sound (Desai et al., 2008, J.Biol. Chem. 283, 22283–22294). Furthermore, a loss of Kv3 channel function, which likely includes a loss of Kv3.3 channel function, has been shown to be associated with noise-trauma induced hearing loss (Pilati et al., 2012, Hear Res. 283, 98-106). These data support the hypothesis that modulation of Kv3.3 channels in auditory brainstem nuclei could have a therapeutic benefit in patients suffering from hearing loss.

Patent applications WO2011/069951, WO2012/076877 and WO2012/168710 (application number PCT/GB2012/051278) 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, hearing disorders and bipolar disorders.

There remains a need for the identification of alternative modulators of Kv3 channels, in particular modulators of the Kv3.3 channel, which may demonstrate high *in vivo* potency, channel selectivity or desirable pharmacokinetic parameters that reduce the dose required for therapeutic effect *in vivo*. For certain therapeutic indications, there is also a need to identify compounds with a different modulatory effect on Kv3 channels, for example, compounds that alter the kinetics of channel gating or channel inactivation, and which may behave *in vivo* as negative modulators of the channels.

Summary of the invention

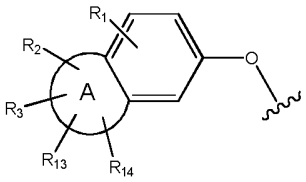
The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, for use in the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required:



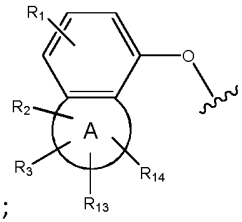
(I)

wherein:

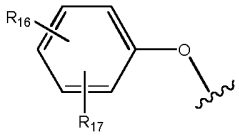
W is group (Wa), group (Wb) or group (Wc):



(Wa);



(Wb);



(Wc);

wherein:

R_1 is H, $C_{1\text{-}4}$alkyl, halo, halo$C_{1\text{-}4}$alkyl, CN, $C_{1\text{-}4}$alkoxy, or halo$C_{1\text{-}4}$alkoxy;
R_2 is H, $C_{1\text{-}4}$alkyl, $C_{3\text{-}5}$ spiro carbocyclyl, halo$C_{1\text{-}4}$alkyl or halo;
R_3 is H, $C_{1\text{-}4}$alkyl, halo$C_{1\text{-}4}$alkyl, halo; or R_3 is absent;
R_{13} is H, $C_{1\text{-}4}$alkyl, halo$C_{1\text{-}4}$alkyl, halo; or R_{13} is absent;
R_{14} is H, $C_{1\text{-}4}$alkyl, halo$C_{1\text{-}4}$alkyl, halo; or R_{14} is absent;
A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group, or a cyclobutyl group, or a cyclopentyl group to form a tricycle when considered together with the phenyl;
X is CH or N;
Y is CR_{15} or N;
R_{15} is H or $C_{1\text{-}4}$alkyl;
R_{16} is halo, $C_{1\text{-}4}$ alkyl, $C_{1\text{-}4}$ alkoxy, halo-$C_{1\text{-}4}$alkyl, halo-$C_{1\text{-}4}$alkoxy, or CN;
R_{17} is H, halo, cyano, $C_{1\text{-}4}$ alkyl or $C_{1\text{-}4}$ alkoxy; with the proviso that when R_{17} is H, R_{16} is not in the para position;
R_4 is $C_{1\text{-}4}$ alkyl;
R_5 is H or $C_{1\text{-}4}$ alkyl;
or R_4 and R_5 can be fused to form $C_{3\text{-}4}$ spiro carbocyclyl;

wherein R_2 and R_3 may be attached to the same or a different ring atom; R_2 may be attached to a fused ring atom; and wherein R_{13} and R_{14} may be attached to the same or a different ring atom.

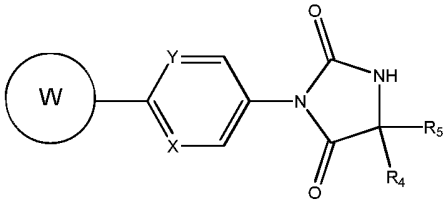
Also provided is a method of prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required, by administering to a subject a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, as defined above.

Further provided is the use of compounds of formula (I) as defined above in the manufacture of a medicament for the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required.

A disorder where a modulator of Kv3.3 channels is required is spinocerebellar ataxia, such as spinocerebellar ataxia type 13.

Detailed description of the invention

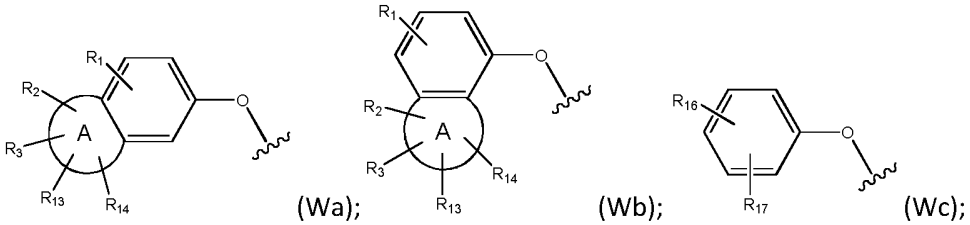
The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, for use in the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required:



(I)

wherein:

W is group (Wa), group (Wb) or group (Wc):



(Wa);

(Wb);

(Wc);

wherein:

R_1 is H, C_{1-4}alkyl, halo, haloC_{1-4}alkyl, CN, C_{1-4}alkoxy, or haloC_{1-4}alkoxy;
R_2 is H, C_{1-4}alkyl, C_{3-5} spiro carbocyclyl, haloC_{1-4}alkyl or halo;
R_3 is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_3 is absent;
R_{13} is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_{13} is absent;
R_{14} is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_{14} is absent;
A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group, or a cyclobutyl group, or a cyclopentyl group to form a tricycle when considered together with the phenyl;
X is CH or N;
Y is CR_{15} or N;
R_{15} is H or C_{1-4}alkyl;
R_{16} is halo, C_{1-4} alkyl, C_{1-4} alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy or CN;
R_{17} is H, halo, cyano, C_{1-4} alkyl or C_{1-4} alkoxy; with the proviso that when R_{17} is H, R_{16} is not in the para position;
R_4 is C_{1-4} alkyl;

R_5 is H or C_{1-4} alkyl;

or R_4 and R_5 can be fused to form C_{3-4} spiro carbocyclyl;

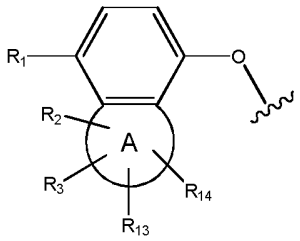
wherein R_2 and R_3 may be attached to the same or a different ring atom; R_2 may be attached to a fused ring atom; and wherein R_{13} and R_{14} may be attached to the same or a different ring atom.

The present invention also provides a method of prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required, by administering to a subject a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required.

Suitably, R_1 is H, C_{1-4}alkyl, halo or haloC_{1-4}alkyl. In another embodiment of the invention R_1 is H or methyl. In one embodiment of the invention R_1 is H. In another embodiment of the invention R_1 is C_{1-4}alkyl, in particular methyl. When W is group (Wa), suitably R_1 is H. When W is group (Wb), suitably R_1 is H or methyl.

When W is group (Wb), suitably R_1 is positioned at the para position of the phenyl ring, as illustrated below:



Suitably R_2 is H, C_{1-4}alkyl, C_{3-5}spiro carbocyclyl, or haloC_{1-4}alkyl. In one embodiment of the invention R_2 is C_{1-4}alkyl, in particular methyl, ethyl, isopropyl, tert-butyl or cyclopropyl, especially methyl, ethyl, isopropyl or tert-butyl. In one embodiment of the invention R_2 is C_{3-5}spiro carbocyclyl. In one embodiment of the invention R_2 is C_3spiro carbocyclyl. In another embodiment of the invention R_2 is C_4 spiro carbocyclyl. In a further embodiment of the invention R_2 is C_5spiro carbocyclyl. In one embodiment of the invention R_2 is haloC_{1-4}alkyl, in particular trifluoromethyl or 2,2,2-trifluoroethyl. In one embodiment of the invention R_2 is halo, in particular fluoro. In another embodiment of the invention R_2 is H.

In one embodiment of the invention R_3 is H, C_{1-4}alkyl, haloC_{1-4}alkyl or halo. Alternatively, R_3 is H, C_{1-4}alkyl, or haloC_{1-4}alkyl. Suitably R_3 is H or C_{1-4}alkyl. In one embodiment of the invention R_3 is H. In one embodiment of the invention R_3 is C_{1-4}alkyl, in particular methyl, ethyl, isopropyl, tert-butyl or cyclopropyl, especially methyl, ethyl, isopropyl or tert-butyl, such as methyl or ethyl. In one embodiment of the invention, R_3 is haloC_{1-4}alkyl, in particular trifluoromethyl or 2,2,2-trifluoroethyl. In one embodiment of the invention R_3 is halo, in particular fluoro. The skilled person will appreciate that, depending on the size, presence of heteroatoms and the degree of unsaturation of the A ring, R_3 may be

absent. Consequently, in another embodiment of the invention R_3 is absent. Suitably R_3 is H, methyl or trifluoromethyl.

In one embodiment of the invention R_2 may be H, C_{1-4}alkyl, haloC_{1-4}alkyl or C_{3-5}spiro carbocycyl and R_3 may be H, C_{1-4}alkyl, or haloC_{1-4}alkyl. In a particular embodiment of the invention, R_2 may be methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, C_{3-5}spiro carbocyclyl, trifluoromethyl or 2,2,2-trifluoroethyl and R_3 may be H, methyl, ethyl or trifluoromethyl. In certain embodiments of the invention R_3 is H and R_2 is H, methyl, ethyl, isopropyl or C_{3-4} spiro carbocyclyl. In further embodiments of the invention R_3 and R_2 are both fluoro (such as attached to the same ring carbon atom). In one embodiment of the invention R_2 is C_{1-4}alkyl and R_3 is H, for example R_2 is methyl, ethyl, tert-butyl or cyclopropyl. In one embodiment of the invention R_2 is C_{1-4}alkyl and R_3 is C_{1-4}alkyl, for example R_2 is methyl and R_3 is methyl, R_2 is ethyl and R_3 is ethyl or R_2 is methyl and R_3 is ethyl. In another embodiment of the invention R_2 is trifluoromethyl and R_3 is methyl.

In one embodiment of the invention R_2 and R_3 are attached to the same ring atom. In an alternative embodiment of the invention R_2 and R_3 are attached to different ring atoms.

In one embodiment of the invention R_{13} is H, F or methyl. In one embodiment of the invention R_{13} is H. In another embodiment of the invention R_{13} is C_{1-4}alkyl, in particular methyl. In a further embodiment of the invention R_{13} is halo, in particular fluoro. In an additional embodiment of the invention R_{13} is haloC_{1-4}alkyl, such as trifluoromethyl. The skilled person will appreciate that, depending on the size, presence of heteroatoms and the degree of unsaturation of the A ring, R_{13} may be absent. Consequently, in another embodiment of the invention R_{13} is absent.

In one embodiment of the invention R_{14} is H, F or methyl. In one embodiment of the invention R_{14} is H. in another embodiment of the invention R_{14} is C_{1-4}alkyl, in particular methyl. In a further embodiment of the invention R_{14} is halo, in particular fluoro. In an additional embodiment of the invention R_{13} is haloC_{1-4}alkyl, such as trifluoromethyl. The skilled person will appreciate that, depending on the size, presence of heteroatoms and the degree of unsaturation of the A ring, R_{14} may be absent. Consequently, in another embodiment of the invention R_{14} is absent.

In one embodiment of the invention R_{13} and R_{14} are attached to the same ring atom. In an alternative embodiment of the invention R_{13} and R_{14} are attached to different ring atoms.

In certain embodiments of the invention R_2, R_3, R_{13} and R_{14} are each independently selected from H, C_{1-4}alkyl, haloC_{1-4}alkyl and halo, such as H, C_{1-4}alkyl and haloC_{1-4}alkyl. Suitably R_2, R_3, R_{13} and R_{14} are each independently selected from H, F, methyl and trifluoromethyl.

Suitably, A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group to form a tricycle when considered together with the phenyl. In one embodiment of the invention A is a 5 membered saturated or unsaturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group, a cyclobutyl group or a cyclopentyl group to form a tricycle when considered together with the phenyl. In another embodiment of the invention A is a 6 membered saturated or unsaturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group, a cyclobutyl group or a cyclopentyl group to form a tricycle when considered together with the phenyl.

In one embodiment of the invention A is a 5 membered saturated or unsaturated heterocycle with at least one O atom, which heterocycle is fused with a cyclopropyl group to form a tricycle when considered together with the phenyl. In another embodiment of the invention A is a 6 membered saturated or unsaturated heterocycle with at least one O atom, which heterocycle is fused with a cyclopropyl group to form a tricycle when considered together with the phenyl. In one embodiment of the invention A is a 5 membered saturated or unsaturated heterocycle with at least one O atom. In one embodiment of the invention A is a 6 membered saturated or unsaturated heterocycle with at least one O atom.

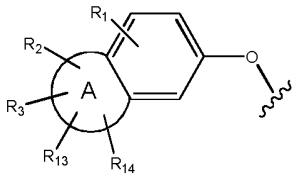
In certain embodiments of the invention the ring A contains one heteroatom. In other embodiments of the invention the ring A contains two heteroatoms (e.g. two oxygen atoms, one oxygen atom and one nitrogen atom, or one oxygen atom and one sulphur atom), in particular two oxygen atoms or one oxygen atom and one nitrogen atom.

Suitably, A is dihydrofuran, isoxazole, dihydropyran, 1,3-dioxolane, 1,3-oxazine or dihydropyran fused with a cyclopropyl group.

In one embodiment of the invention A is dihydrofuran. In one embodiment of the invention A is dihydropyran. In another embodiment of the invention A is dihydrofuran fused with a cyclopropyl group, a cyclobutyl group or a cyclopentyl group. In another embodiment of the invention A is dihydropyran fused with a cyclopropyl group, a cyclobutyl group or a cyclopentyl group. In a further embodiment the invention A is dihydrofuran fused with a cyclopropyl group. In still further embodiment the invention A is dihydropyran fused with a cyclopropyl group.

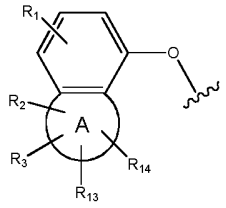
In one embodiment of the invention A is fused with a cyclopropyl group. In another embodiment A is fused with a cyclobutyl group. In a further embodiment of the invention A is fused with a cyclopentyl group. In one embodiment of the invention A is not fused with a cyclopropyl group, a cyclobutyl group or a cyclopentyl group.

In one embodiment of the invention W is group (Wa):



(Wa).

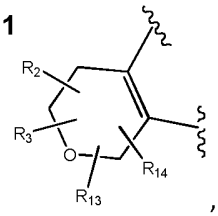
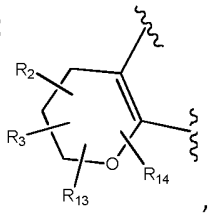
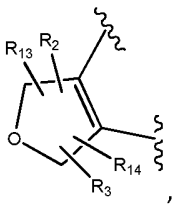
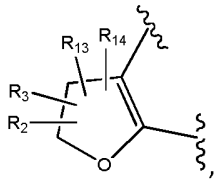
In one embodiment of the invention W is group (Wb):

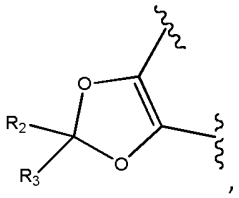
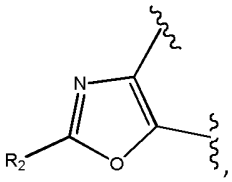
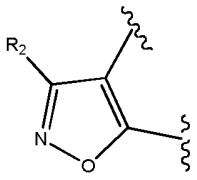
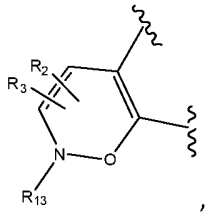


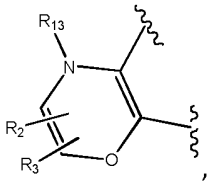
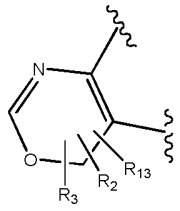
(Wb).

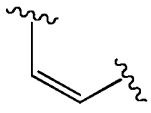
In one embodiment of the invention A is dihydrofuran, dihydropyran, furan, pyran, oxazole, isoxazole, oxazine, dioxine or 1,3-dioxalane. In another embodiment A is dihydrofuran, dihydropyran or 1,3-dioxalane.

In one embodiment of the invention A is:

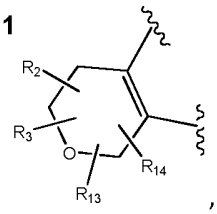
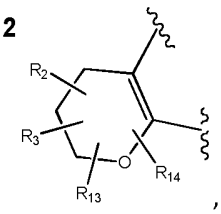
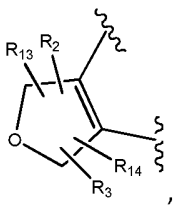
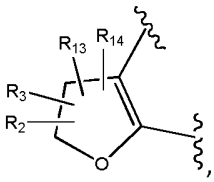
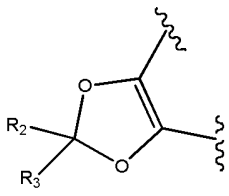
1  , 2  , 3  , 4  ,

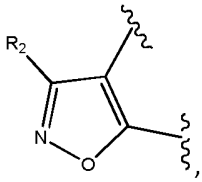
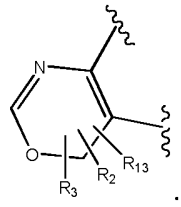
5  , 6  , 7  , 8  ,

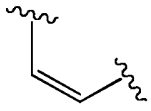
9  , or 10 

wherein  denotes a portion of the phenyl ring to which ring A is fused.

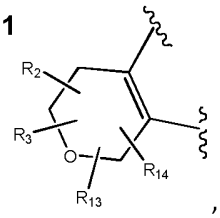
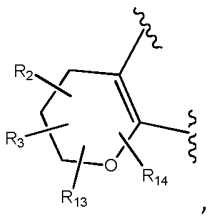
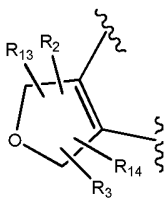
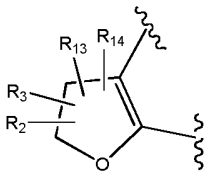
In another embodiment of the invention A is:

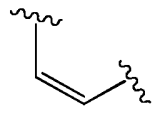
1  , 2  , 3  , 4  , 5  ,

7  , or . 10  .

wherein  denotes a portion of the phenyl ring to which ring A is fused.

In a further embodiment of the invention A is:

1  , 2  , 3  or 4 

wherein  denotes a portion of the phenyl ring to which ring A is fused.

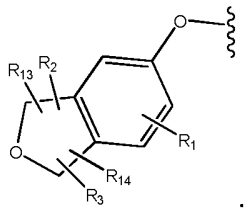
When A contains a 5 membered heterocycle containing one oxygen atom, suitably the heterocycle is dihydrofuran.

When A is a 5 membered heterocycle containing one oxygen atom, suitably the oxygen atom is located at the benzylic position relative to the phenyl ring.

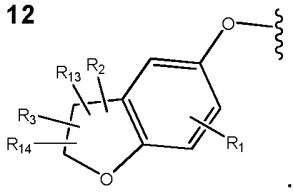
When W is group (Wa), suitably A is a 5 membered heterocycle containing one heteroatom, wherein the oxygen atom is located at the benzylic or para position relative to the phenyl ring.

When W is group (Wb), suitably A is a 5 membered heterocycle containing one heteroatom, wherein the oxygen atom is located at the benzylic or meta position relative to the phenyl ring.

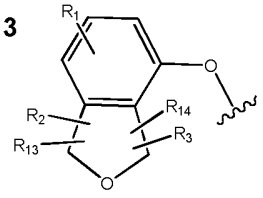
When W is group (Wa), in one embodiment of the invention, group (Wa) is:

11  .

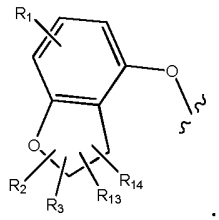
When W is group (Wa), in another embodiment or the invention, group (Wa) is:

12  .

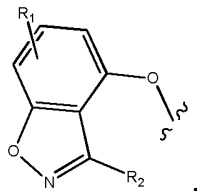
When W is group (Wb), in one embodiment of the invention, group (Wb) is:

13  .

When W is group (Wb), in another embodiment of the invention, (Wb) is:

14 

When W is group (Wb) in a further embodiment of the invention, group (Wb) is:

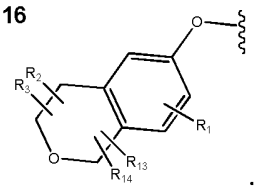
15 

When A contains a 6 membered heterocycle containing one oxygen atom, suitably the heterocycle is dihydropyran.

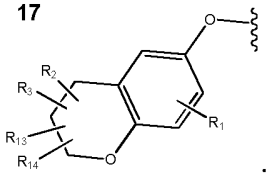
When W is group (Wa), suitably A is a 6 membered heterocycle containing one oxygen atom, wherein the oxygen atom is located at the para position relative to the phenyl ring.

When W is group (Wb), suitably A contains a 6 membered heterocycle containing one oxygen atom, wherein the oxygen atom is located at the meta position relative to the phenyl ring.

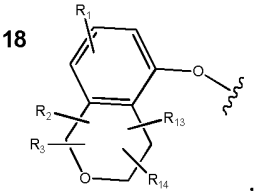
When W is group (Wa), in one embodiment of the invention, group (Wa) is:

16 

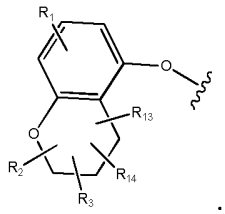
When W is group (Wa), in another embodiment of the invention, group (Wa) is:

17 

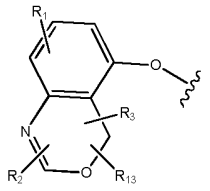
When W is group (Wb), in one embodiment of the invention, group (Wb) is:

18 

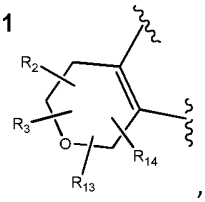
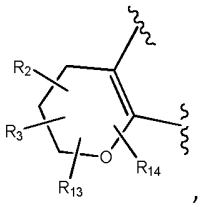
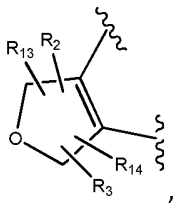
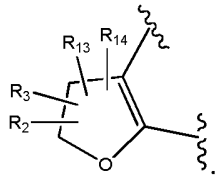
When W is group (Wb), in one embodiment of the invention, group (Wb) is:

19  .

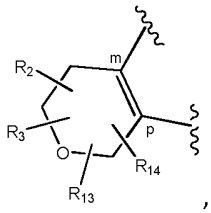
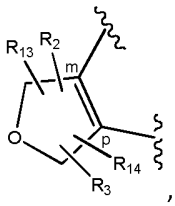
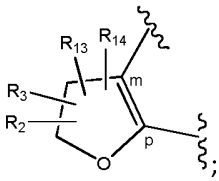
When W is group (Wb), in one embodiment of the invention, group (Wb) is:

20 

When W is group (Wa), in one embodiment of the invention, A is:

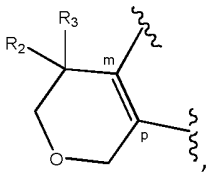
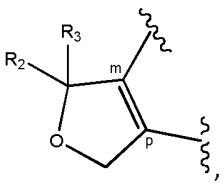
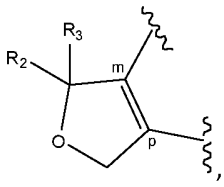
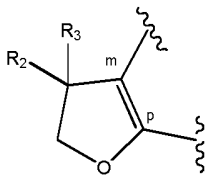
1  , 2  , 3  , or 4  .

When W is group (Wa), in one embodiment of the invention, A is:

21  , 22  , or 23  ;

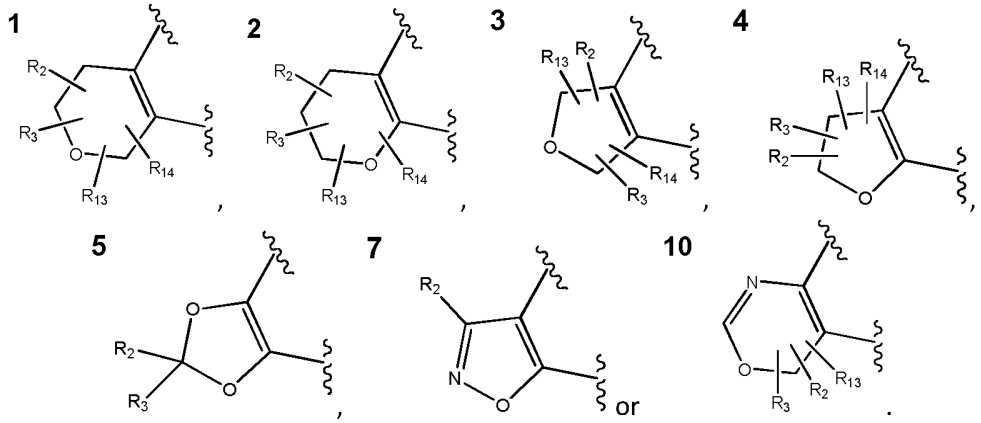
wherein m and p denote the meta and para positions, respectively, of ring A relative to the phenyl ring.

When W is group (Wa), in a further embodiment of the invention, A is selected from the group consisting of:

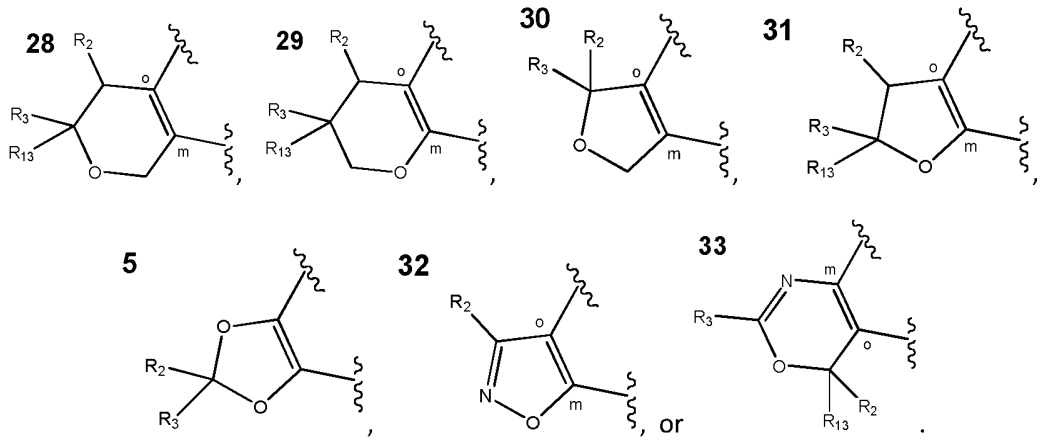
24  , 25  , 26  , and 27 

wherein m and p denote the meta and para positions, respectively, of ring A relative to the phenyl ring.

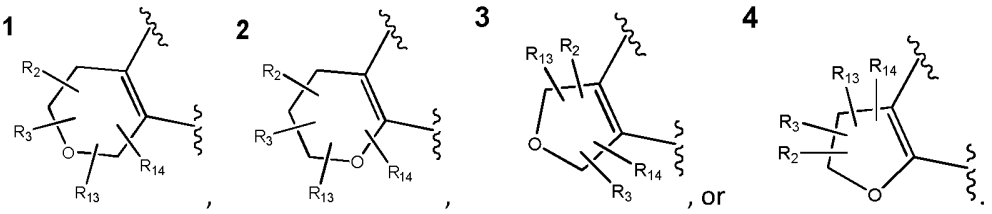
When W is group (Wb), in one embodiment of the invention, A is:



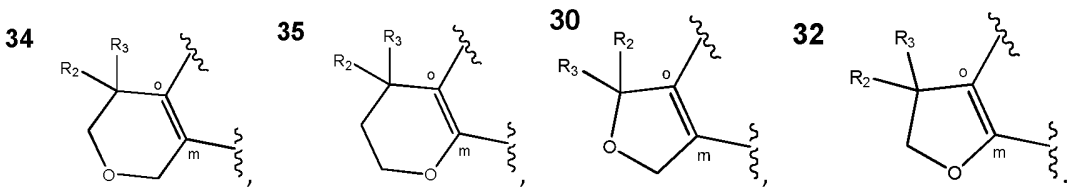
When W is group (Wb), in one embodiment of the invention, A is:



When W is group (Wb), in one embodiment of the invention, A is:



When W is group (Wb), in another embodiment of the invention, A is:



In one embodiment W is the group Wc.

When W is group (Wc), in one embodiment of the invention R_{16} is C_{1-4}alkoxy. In another embodiment of the invention R_{16} is methoxy. In one embodiment of the invention R_{16} is C_{1-4}alkyl. In another embodiment of the invention R_{16} is methyl. In a further embodiment of the invention R_{16} is ethyl. In a

yet further embodiment of the invention R_{16} is propyl. In a yet further embodiment of the invention R_{16} is butyl. In one embodiment of the invention R_{16} is halo. In another embodiment of the invention R_{16} is chloro. In a further embodiment of the invention R_{16} is fluoro. In one embodiment of the invention R_{16} is halo-C_{1-4}alkoxy. In another embodiment of the invention R_{16} is trifluoromethoxy. In one embodiment of the invention R_{16} is halo-C_{1-4}alkyl. In another embodiment of the invention R_{16} is trifluoromethyl. In one embodiment of the invention R_{16} is cyano.

In one embodiment of the invention, R_{17} is H. In one embodiment of the invention R_{17} is C_{1-4}alkyl. In another embodiment of the invention R_{17} is methyl. In one embodiment of the invention R_{17} is halo. In another embodiment of the invention, R_{17} is chloro. In a further embodiment of the invention R_{17} is fluoro. In one embodiment of the invention R_{17} is C_{1-4}alkyl. In one embodiment of the invention R_{17} is cyano.

In one embodiment of the invention R_{16} is C_{1-4}alkyl, C_{1-4}alkoxy, or halo-C_{1-4}alkoxy; R_{17} is H, cyano or alkyl; X is N, Y is N or CR_{15}, R_4 is C_{1-4}alkyl, and R_5 is C_{1-4}alkyl or H. In one embodiment of the invention R_{16} is propyl, butyl, methoxy, propoxy, or trifluoromethoxy; R_{17} is H, cyano or methyl; X is N, Y is N or CR_{15}, R_4 is ethyl, and R_5 is methyl or H.

In one embodiment, one of R_{16} and R_{17} is in the para position and the remaining R_{16} or R_{17} is in the meta position. In one embodiment, one of R_{16} and R_{17} is in the para position and the remaining R_{16} or R_{17} is in the ortho position.

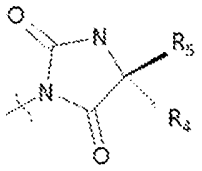
In one embodiment of the invention R_{16} is C_{1-4}alkoxy and R_{17} is C_{1-4}alkyl. In one embodiment of the invention R_{16} is methoxy and R_{17} is methyl. In one embodiment of the invention R_{16} is C_{1-4}alkoxy in the meta position and R_{17} is C_{1-4}alkyl in the para position. In a further embodiment of the invention R_{16} is methoxy in the meta position, R_{17} is methyl in the para position, R_4 is C_{1-4}alkyl, R_5 is H, R_4 is in the R configuration. In a yet further embodiment of the invention R_{16} is methoxy in the meta position, R_{17} is methyl in the para position, X is N, Y is C, R_4 is C_{1-4}alkyl, R_5 is H and the absolute configuration of the stereogenic centre is R. In a still further embodiment of the invention R_{16} is methoxy in the meta position, R_{17} is methyl in the para position, X is N, Y is C, R_4 is ethyl, R_5 is H and the absolute configuration of the stereogenic centre is R.

Suitably, R_4 is methyl, ethyl, isopropyl or t-butyl. In one embodiment of the invention R_4 is methyl. In another embodiment of the invention R_4 is ethyl. In a further embodiment of the invention R_4 is propyl, such is isopropyl. In a yet further embodiment of the invention R_4 is butyl, such as t-butyl.

Suitably, R_5 is H or methyl. In one embodiment of the invention R_5 is H. In a second embodiment of the invention R_5 is C_{1-4}alkyl, in particular R_5 is methyl.

In one embodiment of the invention R_4 and R_5 together form a C_3 spiro carbocycle. In a second embodiment of the invention R_4 and R_5 together form a C_4 spiro carbocycle. In a further embodiment of the invention R_4 is methyl and R_5 is methyl. In an embodiment of particular interest, R_4 is ethyl and R_5 is methyl. In another embodiment, R_4 is ethyl and R_5 is ethyl. In an additional embodiment, R_4 is ethyl and R_5 is H.

Suitably, R_4 and R_5 have the stereochemical arrangement:



In one embodiment of the invention X is CH. In another embodiment of the invention X is N.

In one embodiment of the invention Y is CR_{15}. In another embodiment of the invention Y is N. In a further embodiment of the invention Y is CR_{15}, wherein R_{15} is H. In a still further embodiment of the invention Y is CR_{15}, wherein R_{15} is C_{1-4}alkyl, in particular methyl.

In one embodiment of the invention X is CH and Y is CR_{15}, wherein R_{15} is H. In another embodiment of the invention X is N and Y is CR_{15}, wherein R_{15} is H. In a further embodiment of the invention X is N and Y is CR_{15}, wherein R_{15} is methyl. In a further embodiment of the invention X is CH and Y is CR_{15}, wherein R_{15} is methyl. In a still further embodiment of the invention X is N and Y is N.

When W is group (Wc), suitably the compound of formula (I) is selected from:
(5*R*)-5-methyl-3-{4-[(3-methylphenyl)oxy]phenyl}-2,4-imidazolidinedione;
(5R)-5-methyl-3-(4-{[3-(methyloxy)phenyl]oxy}phenyl)-2,4-imidazolidinedione;
(5*R*)-3-(4-{[3-(ethyloxy)phenyl]oxy}phenyl)-5-methyl-2,4-imidazolidinedione;
(5*R*)-3-{4-[(3-chloro-5-fluorophenyl)oxy]phenyl}-5-methyl-2,4-imidazolidinedione;
(5*R*)-3-{4-[(3-chloro-4-fluorophenyl)oxy]phenyl}-5-methyl-2,4-imidazolidinedione;
(5*S*)-3-{4-[(3-chloro-4-fluorophenyl)oxy]phenyl}-5-methyl-2,4-imidazolidinedione;
(5*R*)-5-methyl-3-(4-{[2-methyl-5-(methyloxy)phenyl]oxy}phenyl)-2,4-imidazolidinedione;
(5*R*)-5-methyl-3-(4-{[4-methyl-3-(methyloxy)phenyl]oxy}phenyl)-2,4-imidazolidinedione;
(5*R*)-5-methyl-3-(6-{[3-(1-methylethyl)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
(5*R*)-5-methyl-3-[6-({3-[(1-methylethyl)oxy]phenyl}oxy)-3-pyridinyl]-2,4-imidazolidinedione;
(5*R*)-3-{6-[(2,5-dimethylphenyl)oxy]-3-pyridinyl}-5-methyl-2,4-imidazolidinedione;
(5*R*)-3-{6-[(2,3-dimethylphenyl)oxy]-3-pyridinyl}-5-methyl-2,4-imidazolidinedione;
(5*R*)-3-{6-[(2,6-dimethylphenyl)oxy]-3-pyridinyl}-5-methyl-2,4-imidazolidinedione;
(5*R*)-3-{6-[(2-ethylphenyl)oxy]-3-pyridinyl}-5-methyl-2,4-imidazolidinedione;
(5*R*)-5-methyl-3-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;

(5*R*)-5-methyl-3-(6-{[2-methyl-5-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
(5*R*)-5-methyl-3-(6-{[2-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
(5*R*)-5-ethyl-3-(4-{[3-(methyloxy)phenyl]oxy}phenyl)-2,4-imidazolidinedione;
(5*R*)-5-ethyl-3-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
(5*S*)-5-ethyl-3-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
(5*R*)-5-ethyl-3-(6-{[3-(1-methylethyl)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
5,5-dimethyl-3-(4-{[3-(methyloxy)phenyl]oxy}phenyl)-2,4-imidazolidinedione;
3-{4-[(2,3-dimethylphenyl)oxy]phenyl}-5,5-dimethyl-2,4-imidazolidinedione;
3-{6-[(2-ethylphenyl)oxy]-3-pyridinyl}-5,5-dimethyl-2,4-imidazolidinedione;
3-{6-[(2,6-dimethylphenyl)oxy]-3-pyridinyl}-5,5-dimethyl-2,4-imidazolidinedione;
(5*R*)-5-(1-methylethyl)-3-(4-{[4-methyl-3-(methyloxy)phenyl]oxy}phenyl)-2,4-imidazolidinedione;
(5*R*)-5-methyl-3-(2-{[3-(1-methylethyl)phenyl]oxy}-5-pyrimidinyl)-2,4-imidazolidinedione;
(5*R*)-5-ethyl-3-(2-{[3-(ethyloxy)-4-methylphenyl]oxy}-5-pyrimidinyl)-2,4-imidazolidinedione;
(5*R*)-5-(1,1-dimethylethyl)-3-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
(5*R*)-5-ethyl-5-methyl-3-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
7-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-5,7-diazaspiro[3.4]octane-6,8-dione;
6-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-4,6-diazaspiro[2.4]heptane-5,7-dione;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-2-(1-methylethyl)benzonitrile;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-2-[(trifluoromethyl)oxy]benzonitrile;
3-{6-[(4-fluoro-3-methylphenyl)oxy]-3-pyridinyl}-5,5-dimethyl-2,4-imidazolidinedione;
3-{6-[(4-fluoro-2-methylphenyl)oxy]-3-pyridinyl}-5,5-dimethyl-2,4-imidazolidinedione;
5,5-dimethyl-3-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
(5R)-5-(1-methylethyl)-3-(6-{[4-methyl-3-(methyloxy)phenyl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
3-(6-{[2-(1,1-dimethylethyl)phenyl]oxy}-3-pyridinyl)-5,5-dimethyl-2,4-imidazolidinedione;
3-(2-{[2-(1,1-dimethylethyl)phenyl]oxy}-5-pyrimidinyl)-5,5-dimethyl-2,4-imidazolidinedione;
(5R)-5-ethyl-5-methyl-3-(2-{[4-methyl-3-(methyloxy)phenyl]oxy}-5-pyrimidinyl)-2,4-imidazolidinedione;
(5R)-5-ethyl-3-(2-{[3-(ethyloxy)-4-methylphenyl]oxy}-5-pyrimidinyl)-5-methyl-2,4-imidazolidinedione;
5,5-dimethyl-3-[6-({3-[(trifluoromethyl)oxy]phenyl}oxy)-3-pyridinyl]-2,4-imidazolidinedione;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-3-ethylbenzonitrile;
2-chloro-4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}benzonitrile;
5,5-dimethyl-3-[6-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-3-pyridinyl]-2,4-imidazolidinedione;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-2-(methyloxy)benzonitrile;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-3-methylbenzonitrile;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-3-(trifluoromethyl)benzonitrile;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-2-ethylbenzonitrile;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyrimidinyl]oxy}-2-ethylbenzonitrile;
3-cyclopropyl-4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}benzonitrile;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-3-(1,1-dimethylethyl)benzonitrile;
2-[(cyclopropylmethyl)oxy]-4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}benzonitrile;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-2-(ethyloxy)benzonitrile;
2-cyclopropyl-4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}benzonitrile;
5,5-dimethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione;
4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyrimidinyl]oxy}-3-(1,1-dimethylethyl)benzonitrile;

4-{[5-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)-2-pyridinyl]oxy}-2-[(1-methylethyl)oxy]benzonitrile;
4-({5-[(4R)-4-ethyl-4-methyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)-2-[(1-methylethyl)oxy]benzonitrile;
3-cyclopropyl-4-({5-[(4R)-4-ethyl-4-methyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)benzonitrile;
4-({5-[(4R)-4-ethyl-4-methyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)-2-[(trifluoromethyl)oxy]benzonitrile;
2-cyclopropyl-4-({5-[(4R)-4-ethyl-4-methyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)benzonitrile;
(5R)-5-ethyl-5-methyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione;
3-(1,1-dimethylethyl)-4-({5-[(4R)-4-ethyl-4-methyl-2,5-dioxo-1-imidazolidinyl]-2-pyrimidinyl}oxy)benzonitrile;
3-(1,1-dimethylethyl)-4-({5-[(4R)-4-ethyl-4-methyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)benzonitrile;
4-{[4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)phenyl]oxy}-2-(methyloxy)benzonitrile;
4-{[4-(4,4-dimethyl-2,5-dioxo-1-imidazolidinyl)phenyl]oxy}-2-(ethyloxy)benzonitrile;
4-({4-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]phenyl}oxy)-2-(ethyloxy)benzonitrile;
3-cyclopropyl-4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)benzonitrile;
3-(1,1-dimethylethyl)-4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)benzonitrile;
4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)-2-(methyloxy)benzonitrile;
4-({4-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]phenyl}oxy)-2-(methyloxy)benzonitrile;
2-[(cyclopropylmethyl)oxy]-4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)benzonitrile;
(5R)-5-ethyl-3-[6-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-3-pyridinyl]-2,4-imidazolidinedione;
2-cyclopropyl-4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)benzonitrile;
4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)-2-(1-methylethyl)benzonitrile;
4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)-2-(1-methylethyl)benzonitrile;
(5R)-5-ethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione;
4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)-2-[(1-methylethyl)oxy]benzonitrile;
4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)-3-methylbenzonitrile;
4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)-2-[(trifluoromethyl)oxy]benzonitrile;
3-ethyl-4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyrimidinyl}oxy)benzonitrile;
4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyrimidinyl}oxy)-3-methylbenzonitrile;
3-(1,1-dimethylethyl)-4-({5-[(4R)-4-ethyl-2,5-dioxo-1-imidazolidinyl]-2-pyrimidinyl}oxy)benzonitrile and
4-({5-[(4R)-4-ethyl-4-methyl-2,5-dioxo-1-imidazolidinyl]-2-pyridinyl}oxy)-2-(1-methylethyl)benzonitrile;
or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

When W is group (Wb), suitably the compound of formula (I) is selected from:
(5R)-3-[4-(1,3-dihydro-2-benzofuran-4-yloxy)phenyl]-5-methyl-2,4-imidazolidinedione;
(5R)-5-methyl-3-{4-[(3-methyl-1,2-benzisoxazol-4-yl)oxy]phenyl}-2,4-imidazolidinedione;
(5R)-3-{4-[(3,6-dimethyl-1,2-benzisoxazol-4-yl)oxy]phenyl}-5-methyl-2,4-imidazolidinedione;
5,5-dimethyl-3-{4-[(3-methyl-1,2-benzisoxazol-4-yl)oxy]phenyl}-2,4-imidazolidinedione;
(5R)-5-ethyl-3-{6-[(3-ethyl-1,2-benzisoxazol-4-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione;
(5R)-5-ethyl-3-(6-{[3-(1-methylethyl)-1,2-benzisoxazol-4-yl]oxy}-3-pyridinyl)-2,4-imidazolidinedione;
(5R)-3-{4-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]phenyl}-5-methyl-2,4-imidazolidinedione;
(5R)-3-{6-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-3-pyridinyl}-5-methyl-2,4-imidazolidinedione;

(5R)-3-{6-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-3-pyridinyl}-5-ethyl-2,4-imidazolidinedione;
(5R)-3-{2-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-5-pyrimidinyl}-5-ethyl-2,4-imidazolidinedione;
7-{6-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-3-pyridinyl}-5,7-diazaspiro[3.4]octane-6,8-dione;
6-{6-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-3-pyridinyl}-4,6-diazaspiro[2.4]heptane-5,7-dione;
3-{6-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-3-pyridinyl}-5,5-dimethyl-2,4-imidazolidinedione;
(5R)-3-{2-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-5-pyrimidinyl}-5-(1,1-dimethylethyl)-2,4-imidazolidinedione;
(5R)-5-ethyl-3-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione;
5,5-dimethyl-3-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione;
(5R)-5-ethyl-5-methyl-3-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione;
(5R)-5-ethyl-3-(6-{[(3S/R)-3-methyl-1,3-dihydro-2-benzofuran-4-yl]oxy}-3-pyridinyl)-2,4-imidazolidinedione (diastereoisomeric mixture);
(5R)-5-ethyl-3-{6-[(3-methyl-1,3-dihydro-2-benzofuran-4-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione (diastereoisomers 1 and 2);
(5R)-5-ethyl-3-{6-[(3-ethyl-1,3-dihydro-2-benzofuran-4-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione (distereoisomeric mixture);
(5R)-5-ethyl-3-{6-[(3-ethyl-1,3-dihydro-2-benzofuran-4-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione (diastereoisomers 1 and 2);
5,5-dimethyl-3-{6-[(3-methyl-3,4-dihydro-2H-chromen-5-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione (racemate mixture);
5,5-dimethyl-3-{6-[(3-methyl-3,4-dihydro-2H-chromen-5-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione (enantiomers 1 and enantiomer 2);
5,5-dimethyl-3-{6-[(1a-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromen-7-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione;
5,5-dimethyl-3-{6-[(1a-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromen-7-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione (enantiomer 1 and enantiomer 2);
(5R)-5-ethyl-5-methyl-3-[6-(1H-spiro[2-benzopyran-4,1'-cyclopropan]-5-yloxy)-3-pyridinyl]-2,4-imidazolidinedione;
3-{2-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-5-pyrimidinyl}-5,5-dimethyl-2,4-imidazolidinedione;
(5R)-3-{2-[(3,3-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-5-pyrimidinyl}-5-(1-methylethyl)-2,4-imidazolidinedione;
(5R)-3-{6-[(2,2-dimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-3-pyridinyl}-5-ethyl-2,4-imidazolidinedione;
5,5-dimethyl-3-[6-(1H-spiro[2-benzopyran-4,1'-cyclopropan]-5-yloxy)-3-pyridinyl]-2,4-imidazolidinedione;
(5R)-3-[2-(2,3-dihydrospiro[chromene-4,1'-cyclopropan]-5-yloxy)-5-pyrimidinyl]-5-ethyl-5-methyl-2,4-imidazolidinedione;
5,5-dimethyl-3-{6-[(4-methyl-3,4-dihydro-2H-chromen-5-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione (racemate mixture, enantiomer 1, enantiomer 2);

(5R)-5-ethyl-5-methyl-3-{6-[(3-methyl-3,4-dihydro-2H-chromen-5-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione (diastereoisomeric mixture, diastereoisomer 1, diastereoisomer 2);
(5R)-5-ethyl-5-methyl-3-[6-(1,1a,2,7b-tetrahydrocyclopropa[c]chromen-7-yloxy)-3-pyridinyl]-2,4-imidazolidinedione (diastereoisomeric mixture, diastereoisomer 1, diastereoisomer 2);
3-{6-[(3-ethyl-1,3-dihydro-2-benzofuran-4-yl)oxy]-3-pyridinyl}-5,5-dimethyl-2,4-imidazolidinedione (racemate mixture, enantiomer 1, enantiomer 2);
(5R)-5-ethyl-5-methyl-3-[2-(4-methylchroman-5-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomeric mixture, diastereoisomer 1, diastereoisomer 2);
(5R)-5-ethyl-5-methyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-3-[2-(3,3-dimethylisochroman-5-yl)oxypyrimidin-5-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[2-(7-methylspiro[1H-isobenzofuran-3,1'-cyclobutane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-{2-[(3,3,7-trimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-5-pyrimidinyl}-2,4-imidazolidinedione;
(5R)-3-{2-[(2,2-difluoro-7-methyl-1,3-benzodioxol-4-yl)oxy]-5-pyrimidinyl}-5-ethyl-5-methyl-2,4-imidazolidinedione;
(5R)-3-{2-[(2,2-difluoro-1,3-benzodioxol-4-yl)oxy]-5-pyrimidinyl}-5-ethyl-5-methyl-2,4-imidazolidinedione;
(5R)-5-ethyl-5-methyl-3-{2-[(2,4,4-trimethyl-4H-3,1-benzoxazin-5-yl)oxy]-5-pyrimidinyl}-2,4-imidazolidinedione;
5,5-dimethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione;
3-[2-(3,3-dimethylisochroman-5-yl)oxypyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione;
5,5-dimethyl-3-[2-(7-methylspiro[1H-isobenzofuran-3,1'-cyclobutane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-{6-[(3,3,7-trimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-3-pyridinyl}-2,4-imidazolidinedione;
(5R)-5-ethyl-3-{2-[(3,3,7-trimethyl-2,3-dihydro-1-benzofuran-4-yl)oxy]-5-pyrimidinyl}-2,4-imidazolidinedione;
(5R)-5-ethyl-5-methyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]imidazolidine-2,4-dione;
(5R)-3-[6-(3,3-dimethylisochroman-5-yl)oxy-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
(5R)-3-[6-[(3,3-diethyl-1H-isobenzofuran-4-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[6-[(2,4,4-trimethyl-3,1-benzoxazin-5-yl)oxy]-3-pyridyl]imidazolidine-2,4-dione;
(5R)-3-{6-[(3,3-dimethyl-1,3-dihydro-2-benzofuran-4-yl)oxy]-3-pyridinyl}-5-ethyl-5-methyl-2,4-imidazolidinedione;
5,5-dimethyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]imidazolidine-2,4-dione;

or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

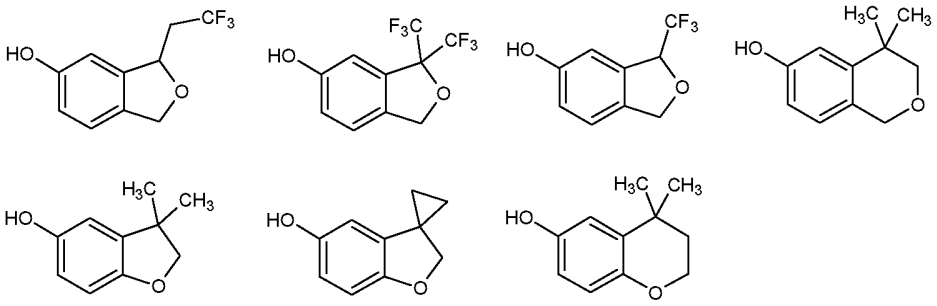
When W is group (Wa), suitably the compound of formula (I) is selected from:
3-[2-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione;
3-[2-[(3,3-diethyl-1H-isobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione;
3-[2-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1);
3-[2-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 2);
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);
3-[2-[(3-ethyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1);
3-[2-[(3-ethyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 2);
3-[2-[(3-cyclopropyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1);
3-[2-[(3-cyclopropyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 2);
5,5-dimethyl-3-(2-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxypyrimidin-5-yl)imidazolidine-2,4-dione;
5,5-dimethyl-3-(2-spiro[1H-isobenzofuran-3,1'-cyclopentane]-5-yloxypyrimidin-5-yl)imidazolidine-2,4-dione;
5,5-dimethyl-3-[2-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-[2-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 2);
3-[2-[(3,3-dimethyl-2H-benzofuran-5-yl)oxy]pyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione;
3-[2-(4,4-dimethylisochroman-6-yl)oxypyrimidin-5-yl]-5,5-dimethyl-imidazolidine-2,4-dione;
(5R)-3-[2-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
(5R)-3-[2-[(3,3-diethyl-1H-isobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
(5R)-3-[2-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-3-[2-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-5-methyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-5-methyl-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-[(3-ethyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5-methyl-imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-3-[2-[(3-ethyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5-methyl-imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-3-[2-[(3-cyclopropyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-3-[2-[(3-cyclopropyl-1,3-dihydroisobenzofuran-5-yl)oxy]pyrimidin-5-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-5-methyl-3-(2-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxypyrimidin-5-yl)imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-(2-spiro[1H-isobenzofuran-3,1'-cyclopentane]-5-yloxypyrimidin-5-yl)imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[2-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-5-methyl-3-[2-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-3-[2-[(3,3-dimethyl-2H-benzofuran-5-yl)oxy]pyrimidin-5-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
(5R)-3-[2-(4,4-dimethylisochroman-6-yl)oxypyrimidin-5-yl]-5-ethyl-5-methyl-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;
(5R)-3-[6-[(3,3-diethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
(5R)-3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-5-methyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-5-methyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-3-[6-[(3-ethyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5-methyl-imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-3-[6-[(3-ethyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5-methyl-imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-3-[6-[(3-cyclopropyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-3-[6-[(3-cyclopropyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-5-methyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclopentane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;

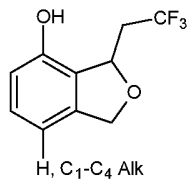
(5R)-5-ethyl-5-methyl-3-[6-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-5-methyl-3-[6-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-3-[6-[(3,3-dimethyl-2H-benzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
(5R)-3-[6-(4,4-dimethylisochroman-6-yl)oxy-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
3-[6-[(3,3-diethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-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);
3-[6-[(3-ethyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1);
3-[6-[(3-ethyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 2);
3-[6-[(3-cyclopropyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1);
3-[6-[(3-cyclopropyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-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;
5,5-dimethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclopentane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
5,5-dimethyl-3-[6-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-[6-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 2);
3-[6-[(3,3-dimethyl-2H-benzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione;
3-[6-(4,4-dimethylisochroman-6-yl)oxy-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione;
(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-5-methyl-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[5-methyl-6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-5-methyl-3-[5-methyl-6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2);
(5R)-5-ethyl-5-methyl-3-(5-methyl-6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[5-methyl-6-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1);
(5R)-5-ethyl-5-methyl-3-[5-methyl-6-[[3-(trifluoromethyl)-1,3-dihydroisobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2);

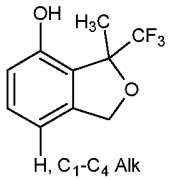
5,5-dimethyl-3-(5-methyl-6-{[3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl]oxy}pyridin-3-yl)imidazolidine-2,4-dione (enantiomer 1);
5,5-dimethyl-3-(5-methyl-6-{[3-(trifluoromethyl)-1,3-dihydro-2-benzofuran-5-yl]oxy}pyridin-3-yl)imidazolidine-2,4-dione (enantiomer 2);
(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione;
(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[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione;
(5R)-3-[6-[(3,3-dimethyl-2H-benzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-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;
(5R)-3-{4-[(3,3-dimethyl-1,3-dihydro-2-benzofuran-5-yl)oxy]phenyl}-5-ethyl-5-methyl-2,4-imidazolidinedione; and
(5R)-3-[4-(1,3-dihydro-2-benzofuran-5-yloxy)phenyl]-5-methyl-2,4-imidazolidinedione;
or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof.

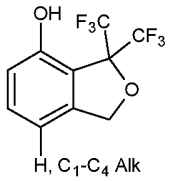
Suitably, the compound of formula (I) contains a (Wa) group corresponding to one of the following phenol groups:

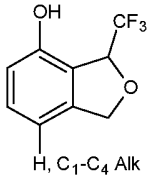


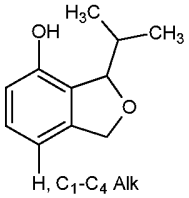
Suitably, the compound of formula (I) contains a (Wb) group corresponding to one of the following phenol groups:

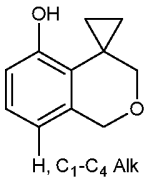


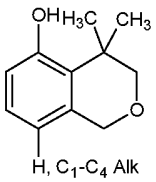


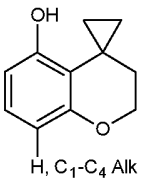


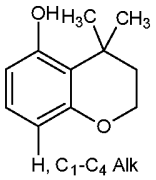




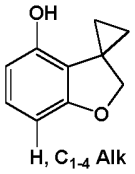


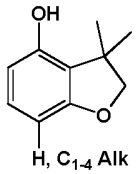






Alternatively, when the compound of formula (I) contains a (Wb) group corresponding to one of the following phenol groups:





For the avoidance of doubt, the embodiments of any one feature of the compounds of the invention may be combined with any embodiment of another feature of compounds of the invention to create a further embodiment.

The term 'halo' or 'halogen' as used herein, refers to a fluorine, chlorine, bromine or iodine atom. Particular examples of halo are fluorine and chlorine, especially fluorine.

When the compound contains a C_{1-4}alkyl group, whether alone or forming part of a larger group, e.g. C_{1-4}alkoxy, the alkyl group may be straight chain, branched, cyclic, or a combination thereof. Examples of C_{1-4}alkyl are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl and cyclobutyl. A particular group of exemplary C_{1-4}alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl. An example of C_{1-4}alkoxy is methoxy.

The term 'haloC_{1-4}alkyl' as used herein, includes straight chain, branched chain or cyclic alkyl groups containing 1 to 4 carbon atoms substituted by one or more halo atoms, for example fluoromethyl, difluoromethyl and trifluoromethyl. A particular group of exemplary haloC_{1-4} alkyl include methyl and ethyl groups substituted with one to three halo atoms, in particular one to three fluoro atoms, such as trifluoromethyl or 2,2,2-trifluoroethyl.

The term 'haloC_{1-4}alkoxy' as used herein, includes straight chain, branched chain or cyclic alkoxy groups containing 1 to 4 carbon atoms substituted by one or more halo atoms, for example fluoromethoxy,

difluoromethoxy and trifluoromethoxy. A particular group of exemplary haloC_{1-4} alkyl include methoxy and ethoxy groups substituted with one to three halo atoms, in particular one to three fluoro atoms.

The term '5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom' includes for example dihydrofuran, dihydropyran, furan, pyran, oxazole, isoxazole, oxazine, dioxine, morpholine or 1,3-dioxalane.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) 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 formula (I) and are included within the scope of this invention.

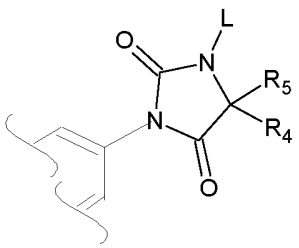
Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) 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 formula (I) for use the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required, for use in a method of preventing or treating a disease or disorder where a modulator of Kv3.3 channels is required, and for use in the manufacture of a medicament for the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required.

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

Suitably, a pharmaceutically acceptable prodrug is formed by functionalising the secondary nitrogen of the hydantoin, for example with a group "L" as illustrated below:



A compound of formula (I) may be functionalised via the secondary nitrogen of the hydantoin with a group L, wherein L is selected from:

a) $-PO(OH)O^- \bullet M^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
b) $-PO(O^-)_2 \bullet 2M^+$,
c) $-PO(O^-)_2 \bullet D^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
d) $-CH(R^X)-PO(OH)O^- \bullet M^+$, wherein R^X is hydrogen or C_{1-3} alkyl,
e) $-CH(R^X)-PO(O^-)_2 \bullet 2M^+$,
f) $-CH(R^X)-PO(O^-)_2 \bullet D^{2+}$
g) $-SO_3^- \bullet M^+$,
h) $-CH(R^X)-SO_3^- \bullet M^+$, and
i) $-CO-CH_2CH_2-CO_2 \bullet M^+$.

All isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures) are contemplated for the uses and method of the invention. Where additional chiral centres are present in compounds of formula (I), 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.

Isotopically-labelled compounds which are identical to those recited in formula (I) but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature, or in which the proportion of an atom having an atomic mass or mass number found less commonly in nature has been increased (the latter concept being referred to as "isotopic enrichment") are also contemplated for the uses and method of the invention. 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 ^2H (deuterium), ^3H, ^{11}C, ^{13}C, ^{14}C, ^{18}F, ^{123}I or ^{125}I, which may be naturally occurring or non-naturally occurring isotopes.

Compounds of formula (I) and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are contemplated for use for the uses and method of the present invention. Isotopically labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H or ^{14}C have been incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e. ^3H, 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 formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are 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 formula (I) may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth below, those in the Examples, and modifications thereof.

Compounds of formula (I), and salts and solvates thereof wherein W is group (Wc) may be prepared by the general methods outlined in WO2011/069951.

Compounds of formula (I), and salts and solvates thereof wherein W is group (Wb) may be prepared by the general methods outlined in WO2012/076877.

Compounds of formula (I), and salts and solvates thereof wherein W is group (Wa) may be prepared by the general methods outlined in WO2012/168710.

The compounds of formula (I) 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 Kv3.3 channel is required. As used herein, a modulator of Kv3.3 is a compound which alters the properties of this channel, either positively or negatively. Compounds of the invention may be tested in the assay of Biological Example 1 to determine their modulatory properties.

As described in Biological Example 1, the following compounds of formula (I) wherein W is group (Wc) were investigated as Kv3.3 channel modulators in a recombinant cell assay:

5,5-dimethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione (Example 57 of WO2011/069951);

(5R)-5-ethyl-5-methyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione (Example 64 of WO2011/069951);

(5R)-5-ethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione (Example 79 of WO2011/069951).

As described in Biological Example 1, the following compounds of formula (I) wherein W is group (Wb) were investigated as Kv3.3 channel modulators in a recombinant cell assay:

(5R)-5-ethyl-3-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione (Example 15 of WO2012/076877);

5,5-dimethyl-3-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione (Example 16 of WO2012/076877);

5,5-dimethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione (Example 58 of WO2012/076877);

5,5-dimethyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]imidazolidine-2,4-dione (Example 70 of WO2012/076877).

As described in Biological Example 1, the following compounds of formula (I) wherein W is group (Wa) were investigated as Kv3.3 channel modulators in a recombinant cell assay:

5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 1) (Example 5 of WO2012/168710);

5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 2) (Example 6 of WO2012/168710);

(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (Example 33 of WO2012/168710);

5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 1) (Example 52 of WO2012/168710);

5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 2) (Example 53 of WO2012/168710);
5,5-dimethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione (Example 58 of WO2012/168710);
(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-5-methyl-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione (Example 64 of WO2012/168710);
(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione (Example 72 of WO2012/168710);
(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1) (Example 73 of WO2012/168710);
(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2) (Example 74 of WO2012/168710);
(5R)-5-ethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione (Example 75 of WO2012/168710);
3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1) (Example 50 of WO2012/168710);
3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (Example 51 of WO2012/168710).

In certain disorders it may be of benefit to utilise a modulator of Kv3.3 or Kv3.1 which demonstrates a particular selectivity profile between the two channels. For example a compound may be selective for modulation of Kv3.3 channels over modulation of Kv3.1 channels demonstrating, for example, at least a 2 fold, 5 fold or 10 fold activity for Kv3.3 channels than for Kv3.1 channels. Alternatively, a compound may be selective for modulation of Kv3.3 channels over modulation of Kv3.2 channels demonstrating, for example, at least a 2 fold, 5 fold or 10 fold activity for Kv3.3 channels than for Kv3.2 channels. In other cases a compound may demonstrate comparable activity between modulation of Kv3.3 and Kv3.1 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. In other cases a compound may demonstrate comparable activity between modulation of Kv3.3 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. In other cases a compound may demonstrate comparable activity between modulation of Kv3.3, Kv3.2 and Kv3.1 channels, for example the activity for each channel is less than 2 fold that for any 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 Kv3.3 channels may be selected from:

- ataxia, in particular spinocerebellar ataxia, especially ataxia associated with R420H, R423H or F448L mutations;
- hearing disorders, including hearing disorders affecting central auditory processing, and tinnitus.

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates may be of use for the prophylaxis or treatment of spinocerebellar ataxia, including spinocerebellar ataxia type 13, and in particular spinocerebellar ataxia associated with R420H, R423H or F448L mutations of the Kv3.3

channel. In one embodiment of the invention the disorder to be treated results from a R420H mutation of the Kv3.3 channel. In another embodiment of the invention the disorder to be treated results from a R423H mutation of the Kv3.3 channel. In a further embodiment of the invention the disorder to be treated results from a F448L mutation of the Kv3.3 channel.

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.

Symptoms of spinocerebellar ataxia which may be impacted by treatment or prophylaxis according to the present invention include the loss of motor coordination and the consequential impact on movement, balance and/or speech.

The invention also provides a method of preventing or treating a disease or disorder where a modulator of Kv3.3 channels 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 formula (I) or a pharmaceutically acceptable salt and/or solvate thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof, for use in the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required, for example those diseases and disorders mentioned hereinabove.

The invention also provides the use of a compound of formula (I), 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 Kv3.3 channels is required, for example those diseases and disorders mentioned hereinabove.

For use in therapy the compounds of formula (I) are usually administered as a pharmaceutical composition. Also provided is a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof, and a pharmaceutically acceptable carrier.

The compounds of formula (I) 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 formula (I) 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 50 mg to 1000 mg, 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 1000 mg, 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.

Also provided is a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof together with a further therapeutic agent or agents.

Also provided is a compound of formula (I), 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 formula (I) 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.

For use in therapy the Kv3.3 modulators are usually administered as a pharmaceutical composition for example a composition comprising a Kv3.3 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 formula (I) or a pharmaceutically acceptable salt thereof, are described hereinabove. Such compositions and methods of administration may also be used for other Kv3.3 modulators or pharmaceutically acceptable salts and/or solvates thereof, in the treatment of spinocerebellar ataxia.

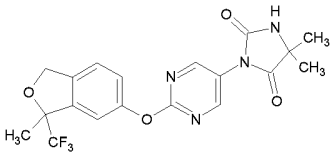
Experimental

The invention is illustrated by the compounds described below.

The following compounds of formula (I) wherein W is group (Wa) may be synthesised according to the procedures described in WO2012/168710:

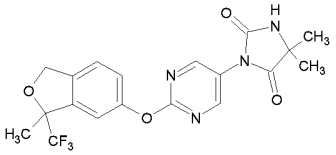
Compound 1

5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 1) - Example 5 of WO2012/168710



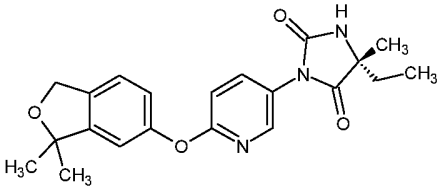
Compound 2

5,5-dimethyl-3-[2-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]pyrimidin-5-yl]imidazolidine-2,4-dione (enantiomer 2) - Example 6 of WO2012/168710



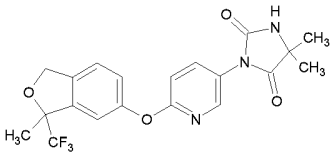
Compound 3

(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione - Example 33 of WO2012/168710



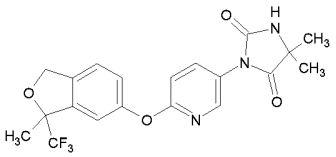
Compound 4

5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 1) - Example 52 of WO2012/168710



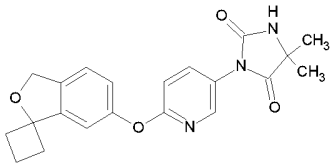
Compound 5

5,5-dimethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (enantiomer 2) - Example 53 of WO2012/168710



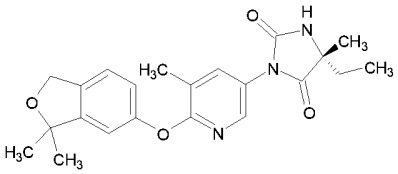
Compound 6

5,5-dimethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione - Example 58 of WO2012/168710



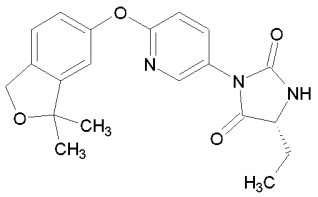
Compound 7

(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-5-methyl-3-pyridyl]-5-ethyl-5-methyl-imidazolidine-2,4-dione - Example 64 of WO2012/168710



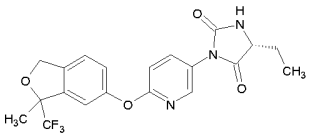
Compound 8

(5R)-3-[6-[(3,3-dimethyl-1H-isobenzofuran-5-yl)oxy]-3-pyridyl]-5-ethyl-imidazolidine-2,4-dione - Example 72 of WO2012/168710



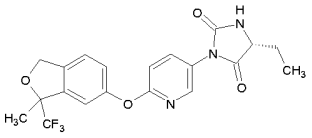
Compound 9

(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 1) - Example 73 of WO2012/168710



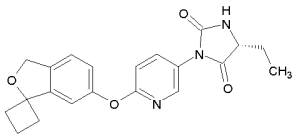
Compound 10

(5R)-5-ethyl-3-[6-[[3-methyl-3-(trifluoromethyl)-1H-isobenzofuran-5-yl]oxy]-3-pyridyl]imidazolidine-2,4-dione (diastereoisomer 2) - Example 74 of WO2012/168710



Compound 11

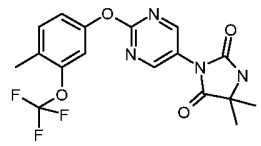
(5R)-5-ethyl-3-(6-spiro[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)imidazolidine-2,4-dione - Example 75 of WO2012/168710



The following compounds of formula (I) wherein W is group (Wc) may be synthesised according to the procedures described in WO2011/069951:

Compound 12

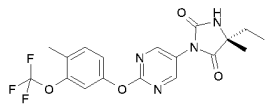
5,5-Dimethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione (Example 57 of WO2011/069951)



;

Compound 13

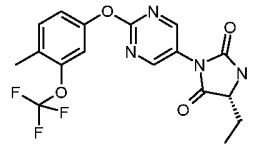
(5R)-5-ethyl-5-methyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione (Example 64 of WO2011/069951)



;

Compound 14

(5R)-5-ethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione (Example 79 of WO2011/069951)

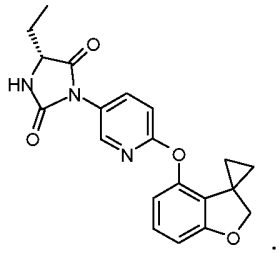


.

The following compounds of formula (I) wherein W is group (Wb) may be synthesised according to the procedures described in WO2012/076877:

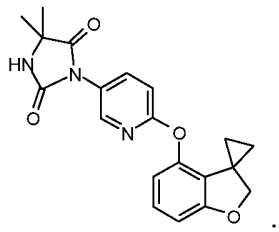
Compound 15

(5R)-5-ethyl-3-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione (Example 15 of WO2012/076877)


;

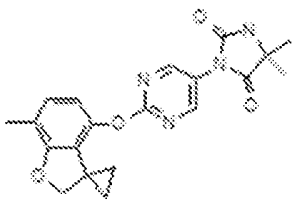
Compound 16

5,5-dimethyl-3-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione (Example 16 of WO2012/076877)


;

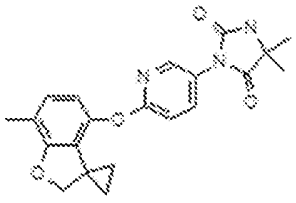
Compound 17

5,5-dimethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione (Example 58 of WO2012/076877)


;

Compound 18

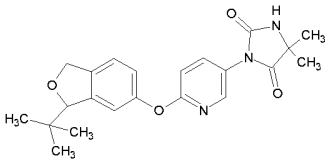
5,5-dimethyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]imidazolidine-2,4-dione (Example 70 of WO2012/076877)


.

The following compounds of formula (I) wherein W is group (Wa) may be synthesised according to the procedures described in WO2012/168710:

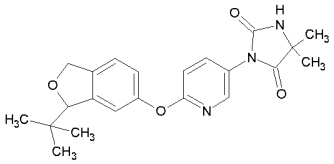
Compound 19

3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione (enantiomer 1) - Example 50 of WO2012/168710



Compound 20

3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione - Example 51 of WO2012/168710



Biological Example 1

The ability of the compounds of the invention to modulate the voltage-gated potassium channel subtypes Kv3.3/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.

Cell biology

To assess compound effects on human Kv3.3 channels (hKv3.3), a stable cell line expressing human Kv3.3 channels was created by transfecting Chinese Hamster Ovary (CHO)-K1 cells with a pBacMire_KCNC-3 vector. Cells were cultured in DMEM/F12 (Gibco) supplemented with 10% Foetal Bovine Serum (Gibco), 1X non-essential amino acids (Invitrogen) and geneticin (G418) 400 microg/mL. Cells were grown and maintained at 37°C in a humidified environment containing 5% CO_2 in air.

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 CHO-K1 cells with a pCIH5-hKv3.2 vector. Cells were cultured in DMEM/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% CO_2 in air.

To assess compound effects on human Kv3.1 channels (hKv3.1), CHO/Gam/E1A-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-Gam1 protein and selection with Geneticin-G418, to generate a stable cell line, CHO/Gam-A3. CHO/Gam-A3 cells were transfected with pCDNA3-E1A-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. For hKv3.2 and hKv3.1 assays, 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. For hKv3.3 assays, from the holding potential of -70 mV, a first test pulse to 0 mV was applied for 500 ms and following a further 100 ms at -70 mV, a second pulse to 40 mV was applied for 200 ms. These longer test pulses were used to study inactivation of hKv3.3 channels. 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 m*M*): 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 m*M*): $CaCl_2$ 0.90, KCl 2.67, KH2PO4 1.47, MgCl.6H2O 0.493, NaCl 136.9, Na_3PO_4 8.06, with a pH of 7.4.

Compounds of the invention (or reference compounds such as *N*-cyclohexyl-*N*-[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-*N*'-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. For hKv3.2 and hKv3.1 assays, paired comparisons of evoked currents 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 measured 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 (50microM of *N*-cyclohexyl-*N*-[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-*N*'-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. For hKv3.3 assays, paired comparisons of evoked currents between pre- and post-drug additions were measured for the 0mV step, considering the peak current and the decay (inactivation) of the current over the duration of the 0mv test pulse (500ms).

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

All of the Example compounds were tested in the above hKv3.1 and hKv3.2 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 50microM *N*-cyclohexyl-*N*-[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-*N*'-phenylurea. Thus, in the recombinant cell assays of Biological Example 1, all of the Example compounds act as positive modulators.

Compound 13 at 12.5 micromolar produced a mean 113% increase in human Kv3.3 peak current at 0mV (n=4). Compound 18 at 12.5 micromolar produced a mean 192% increase in human Kv3.3 peak current at 0mV (n=2).

A secondary analysis of the data from the hKv3.1, hKv3.2, and hKv3.3 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 voltage 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.

$Y = (Y0 - Ymax) * exp(-K*X) + Ymax$

where:

Y0 is the current value at the start of the depolarising voltage pulse;

Ymax 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, Kv3.2 or Kv3.3 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, Kv3.2, and Kv3.3 channels must activate and deactivate very rapidly in order to allow neurons to fire actions potentials at high frequency (Rudy and McBain, 2001, Trends in Neurosciences 24, 517-526). 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, and/or Kv3.3 channels will effectively behave as negative modulators of the channels, leading to a slowing of neuronal firing. This latter effect has been shown for certain of the compounds disclosed in WO2011/069951, where marked increases in Tau_{act} can be observed from recordings made from "fast-firing" interneurons in the cortex of rat brain, using electrophysiological techniques, *in vitro*. 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 act as positive modulators in the recombinant cell assay of Biological Example 1, those compounds which markedly increase the value of Tau_{act} reduce the ability of neurons in native tissues to fire at high frequency.

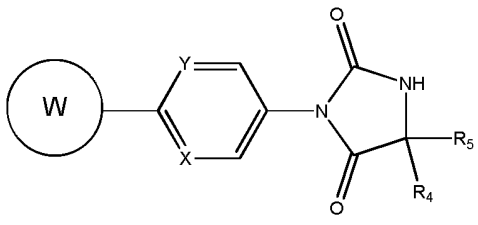
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

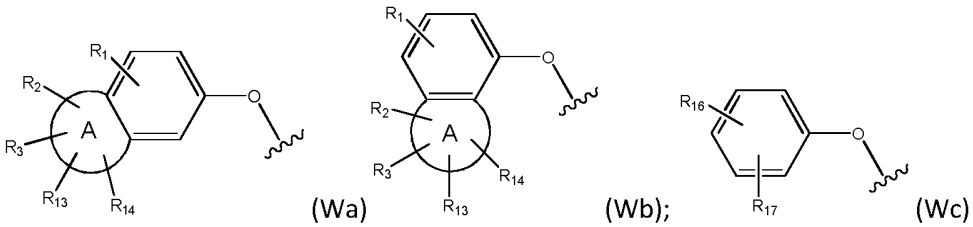
1. A compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, for use in the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required:



(I)

wherein:

W is group (Wa), group (Wb) or group (Wc):



(Wa) (Wb); (Wc)

wherein:

R_1 is H, C_{1-4}alkyl, halo, haloC_{1-4}alkyl, CN, C_{1-4}alkoxy, or haloC_{1-4}alkoxy;

R_2 is H, C_{1-4}alkyl, C_{3-5} spiro carbocyclyl, haloC_{1-4}alkyl or halo;

R_3 is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_3 is absent;

R_{13} is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_{13} is absent;

R_{14} is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_{14} is absent;

A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group, or a cyclobutyl group, or a cyclopentyl group to form a tricycle when considered together with the phenyl;

X is CH or N;

Y is CR_{15} or N;

R_{15} is H or C_{1-4}alkyl;

R_{16} is halo, C_{1-4} alkyl, C_{1-4} alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, or CN;

R_{17} is H, halo, cyano, C_{1-4} alkyl or C_{1-4} alkoxy; with the proviso that when R_{17} is H, R_{16} is not in the para position;

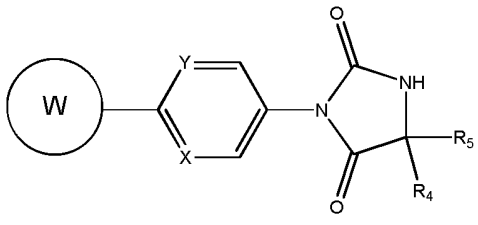
R_4 is C_{1-4} alkyl;

R_5 is H or C_{1-4} alkyl;

or R_4 and R_5 can be fused to form C_{3-4} spiro carbocyclyl;

wherein R_2 and R_3 may be attached to the same or a different ring atom; R_2 may be attached to a fused ring atom; and wherein R_{13} and R_{14} may be attached to the same or a different ring atom.

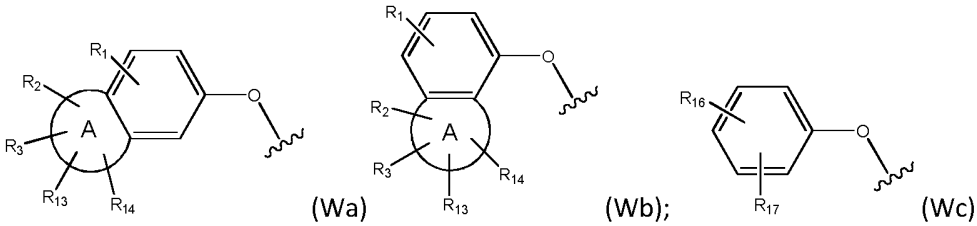
2. A method for the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required, by administering to a subject a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof:



(I)

wherein:

W is group (Wa), group (Wb) or group (Wc):



(Wa) (Wb); (Wc)

wherein:

R_1 is H, C_{1-4}alkyl, halo, haloC_{1-4}alkyl, CN, C_{1-4}alkoxy, or haloC_{1-4}alkoxy;

R_2 is H, C_{1-4}alkyl, C_{3-5} spiro carbocyclyl, haloC_{1-4}alkyl or halo;

R_3 is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_3 is absent;

R_{13} is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_{13} is absent;

R_{14} is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_{14} is absent;

A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group, or a cyclobutyl group, or a cyclopentyl group to form a tricycle when considered together with the phenyl;

X is CH or N;

Y is CR_{15} or N;

R_{15} is H or C_{1-4}alkyl;

R_{16} is halo, C_{1-4} alkyl, C_{1-4} alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, or CN;

R_{17} is H, halo, cyano, C_{1-4} alkyl or C_{1-4} alkoxy; with the proviso that when R_{17} is H, R_{16} is not in the para position;

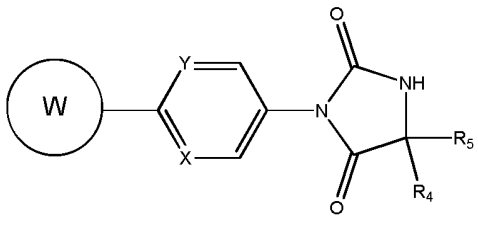
R_4 is C_{1-4} alkyl;

R_5 is H or C_{1-4} alkyl;

or R_4 and R_5 can be fused to form C_{3-4} spiro carbocyclyl;

wherein R_2 and R_3 may be attached to the same or a different ring atom; R_2 may be attached to a fused ring atom; and wherein R_{13} and R_{14} may be attached to the same or a different ring atom.

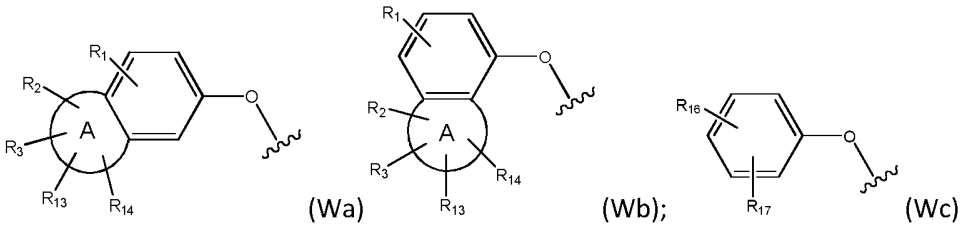
3. A compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, for use in the manufacture of a medicament for the prophylaxis or treatment of a disease or disorder where a modulator of Kv3.3 channels is required:



(I)

wherein:

W is group (Wa), group (Wb) or group (Wc):



(Wa) (Wb); (Wc)

wherein:

R_1 is H, C_{1-4}alkyl, halo, haloC_{1-4}alkyl, CN, C_{1-4}alkoxy, or haloC_{1-4}alkoxy;

R_2 is H, C_{1-4}alkyl, C_{3-5} spiro carbocyclyl, haloC_{1-4}alkyl or halo;

R_3 is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_3 is absent;

R_{13} is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_{13} is absent;

R_{14} is H, C_{1-4}alkyl, haloC_{1-4}alkyl, halo; or R_{14} is absent;

A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group, or a cyclobutyl group, or a cyclopentyl group to form a tricycle when considered together with the phenyl;

X is CH or N;

Y is CR_{15} or N;

R_{15} is H or C_{1-4}alkyl;

R_{16} is halo, C_{1-4} alkyl, C_{1-4} alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, or CN;

R_{17} is H, halo, cyano, C_{1-4} alkyl or C_{1-4} alkoxy; with the proviso that when R_{17} is H, R_{16} is not in the para position;

R_4 is C_{1-4} alkyl;

R_5 is H or C_{1-4} alkyl;

or R_4 and R_5 can be fused to form C_{3-4} spiro carbocyclyl;

wherein R_2 and R_3 may be attached to the same or a different ring atom; R_2 may be attached to a fused ring atom; and wherein R_{13} and R_{14} may be attached to the same or a different ring atom.

4. The compound, method or use of any one of claims 1 to 3, wherein the disease or disorder where a modulator of Kv3.3 is required is spinocerebellar ataxia.

5. The compound, method or use of claim 4, wherein the spinocerebellar ataxia is spinocerebellar ataxia type 13.

6. The compound, method or use of claim 4, wherein the spinocerebellar ataxia results from a R420H mutation of the Kv3.3 channel.

7. The compound, method or use of claim 4, wherein the spinocerebellar ataxia results from a R423H mutation of the Kv3.3 channel.

8. The compound, method or use of claim 4, wherein the spinocerebellar ataxia results from a F448L mutation of the Kv3.3 channel.

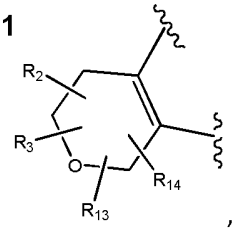
9. The compound, method or use of any one of claims 1 to 8, for use in the prophylaxis of a disease or disorder where a modulator of Kv3.3 channels is required.

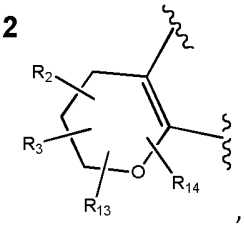
10. The compound, method or use of any one of claims 1 to 8, for use in the treatment of a disease or disorder where a modulator of Kv3.3 channels is required.

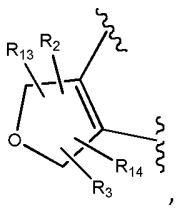
11. The compound, method or use of any one of claims 1 to 10, wherein W is group (Wa).

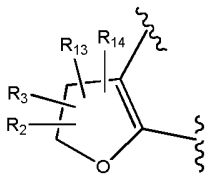
12. The compound, method or use of any one of claims 1 to 10, wherein W is group (Wb).

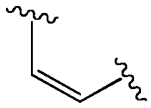
13. The compound, method or use according to any one of claims 1 to 12, wherein ring A is:

1 

, 2 

, 3 

, and 4 

wherein  denotes a point at which ring A is fused to the phenyl ring.

14. The compound, method or use according to any one of claims 1 to 13 wherein R_1 is H.

15. The compound, method or use according to any one of claims 1 to 13 wherein R_1 is methyl.

16. The compound, method or use according to any one of claims 1 to 15 wherein R_2 is H, C_{1-4}alkyl, C_{3-5}spiro carbocyclyl, or haloC_{1-4}alkyl.

17. The compound, method or use according to claim 16, wherein R_2 is methyl, ethyl, tert-butyl, cyclopropyl or C_{3-5}spiro carbocyclyl.

18. The compound, method or use according to any one of claims 1 to 17 wherein R_3 is H, C_{1-4}alkyl, haloC_{1-4}alkyl or halo.

19. The compound, method or use according to claim 18, wherein R_3 is H, methyl, ethyl or trifluoromethyl.

20. The compound, method or use according to one of claims 1 to 17, wherein R_3 is H or is absent.

21. The compound, method or use according to any one of claims 1 to 20 wherein R_{13} is H, methyl, trifluoromethyl or is absent.

22. The compound, method or use according to claim 21, wherein R_{13} is H or absent.

23. The compound, method or use according to any of claims 1 to 22 wherein R_{14} is H, methyl, trifluoromethyl or is absent.

24. The compound, method or use according to claim 23, wherein R_{14} is H or is absent.

25. The compound, method or use according to any one of claims 1 to 4, wherein W is group (Wc).

26. The compound, method or use according to claim 25, wherein R_{16} is halo, C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy or cyano and R_{17} is H, halo, C_{1-4}alkyl and C_{1-4}alkoxy; with the proviso that when R_{17} is H, R_{16} is not in the para position.

27. The compound, method or use according to claim 25 or claim 26, wherein R_{16} is halo, C_{1-4}alkyl or C_{1-4} alkoxy.

28. The compound, method or use according to claim 25 wherein R_{16} is C_{1-4}alkyl, C_{1-4}alkoxy, or halo-C_{1-4}alkoxy; and R_{17} is H, cyano or alkyl.

29. The compound, method or use according to claim 25, wherein R_{16} is propyl, butyl, methoxy, propoxy, or trifluoromethoxy; and R_{17} is H, cyano or methyl.

30. The compound, method or use according to any one of claims 25 to 29, wherein one of R_{16} and R_{17} is in the para position and the remaining one of R_{16} or R_{17} is in the meta position.

31. The compound, method or use according to any one of claims 25 to 29, wherein one of R_{16} and R_{17} is in the meta position and the remaining one of R_{16} or R_{17} is in the ortho position.

32. The compound, method or use according to any one of claims 1 to 31, wherein X is CH.

33. The compound, method or use according to any one of claims 1 to 31, wherein X is N.

34. The compound, method or use according to any one of claims 1 to 33, wherein Y is N.

35 The compound, method or use according to any one of claims 1 to 33, wherein Y is CR_{15} and R_{15} is H.

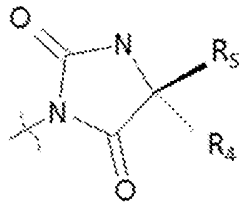
36. The compound, method or use according to any of claims 1 to 33, wherein Y is CR_{15} and R_{15} is methyl.

37. The compound, method or use according to any one of claims 1 to 36, wherein R_4 is methyl or ethyl.

38. The compound, method or use according to claim 37, wherein R_5 methyl.

39. The compound, method or use according to any one of claims 1 to 38, wherein R_5 is H.

40. The compound, method or use according to any one of claims 1 to 39, wherein R_4 and R_5 have the stereochemical arrangement:



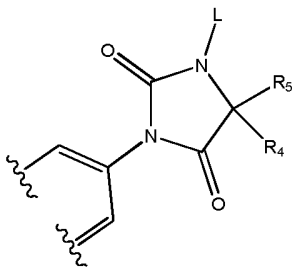
41. The compound, method or use according to any one of claims 1 to 10, wherein W is group (Wc) and the compound of formula (I) is selected from the group consisting of:
(5R)-5-ethyl-5-methyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione;
(5R)-5-ethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione; and
5,5-dimethyl-3-[2-({4-methyl-3-[(trifluoromethyl)oxy]phenyl}oxy)-5-pyrimidinyl]-2,4-imidazolidinedione.

42. The compound, method or use according to any one of claims 1 to 10, wherein W is group (Wb) and the compound of formula (I) is selected from the group consisting of:
(5R)-5-ethyl-3-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione;
5,5-dimethyl-3-[6-(spiro[1-benzofuran-3,1'-cyclopropan]-4-yloxy)-3-pyridinyl]-2,4-imidazolidinedione;
5,5-dimethyl-3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]imidazolidine-2,4-dione; and
5,5-dimethyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]imidazolidine-2,4-dione.

43. The compound, method or use according to any one of claims 1 to 10, wherein W is group (Wa) and the compound of formula (I) is selected from the group consisting of:
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;
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]-5-methyl-3-pyridyl]-5-ethyl-5-methyl-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[1H-isobenzofuran-3,1'-cyclobutane]-5-yloxy-3-pyridyl)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); and
3-[6-[(3-tert-butyl-1,3-dihydroisobenzofuran-5-yl)oxy]-3-pyridyl]-5,5-dimethyl-imidazolidine-2,4-dione.

44. A compound, method or use according to any one of claims 1 to 43, wherein the compound of formula (I) is a prodrug and is functionalised at the secondary nitrogen of the hydantoin, as illustrated below:



wherein L is selected from:

a) $-PO(OH)O^- \bullet M^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
b) $-PO(O^-)_2 \bullet 2M^+$,
c) $-PO(O^-)_2 \bullet D^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
d) $-CH(R^X)-PO(OH)O^- \bullet M^+$, wherein R^X is hydrogen or C_{1-3} alkyl,
e) $-CH(R^X)-PO(O^-)_2 \bullet 2M^+$,
f) $-CH(R^X)-PO(O^-)_2 \bullet D^{2+}$
g) $-SO_3^- \bullet M^+$,
h) $-CH(R^X)-SO_3^- \bullet M^+$, and
i) $-CO-CH_2CH_2-CO_2 \bullet M^+$.

Figure 1a: hKv3.2 currents recorded using the assay described in Biological Example 1, at two concentrations of the compound of Reference Example RE1

Figure 1a

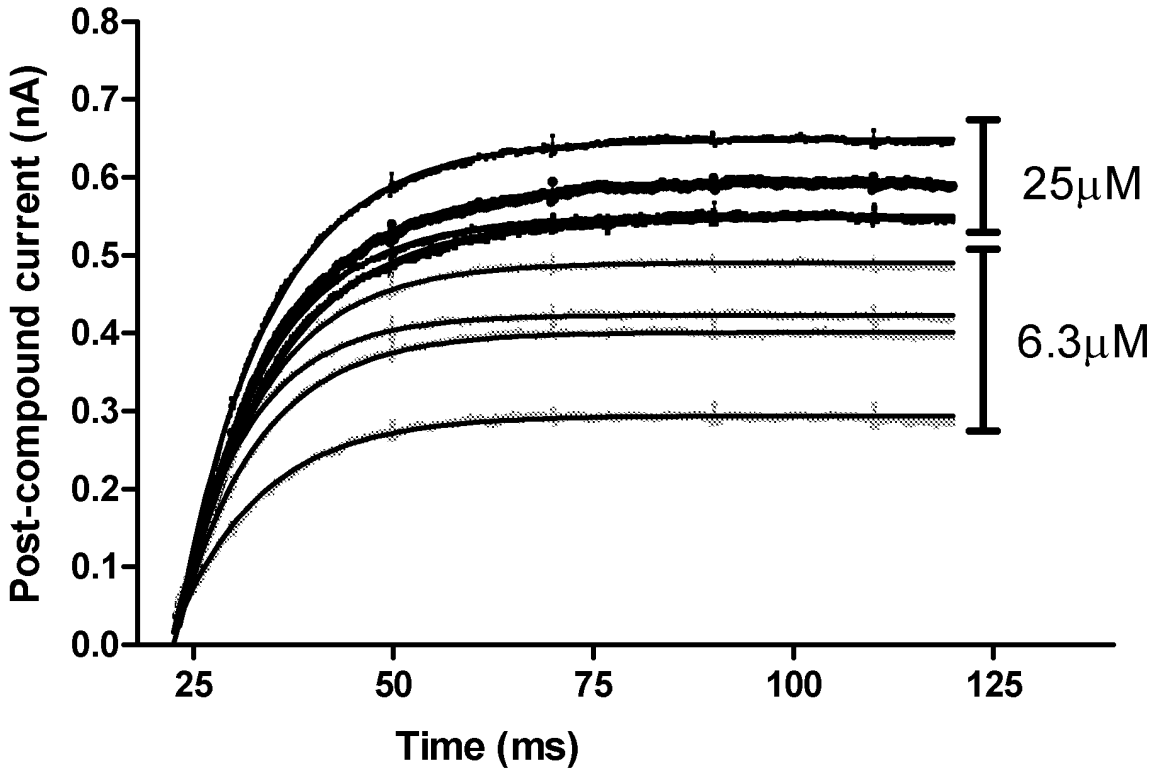
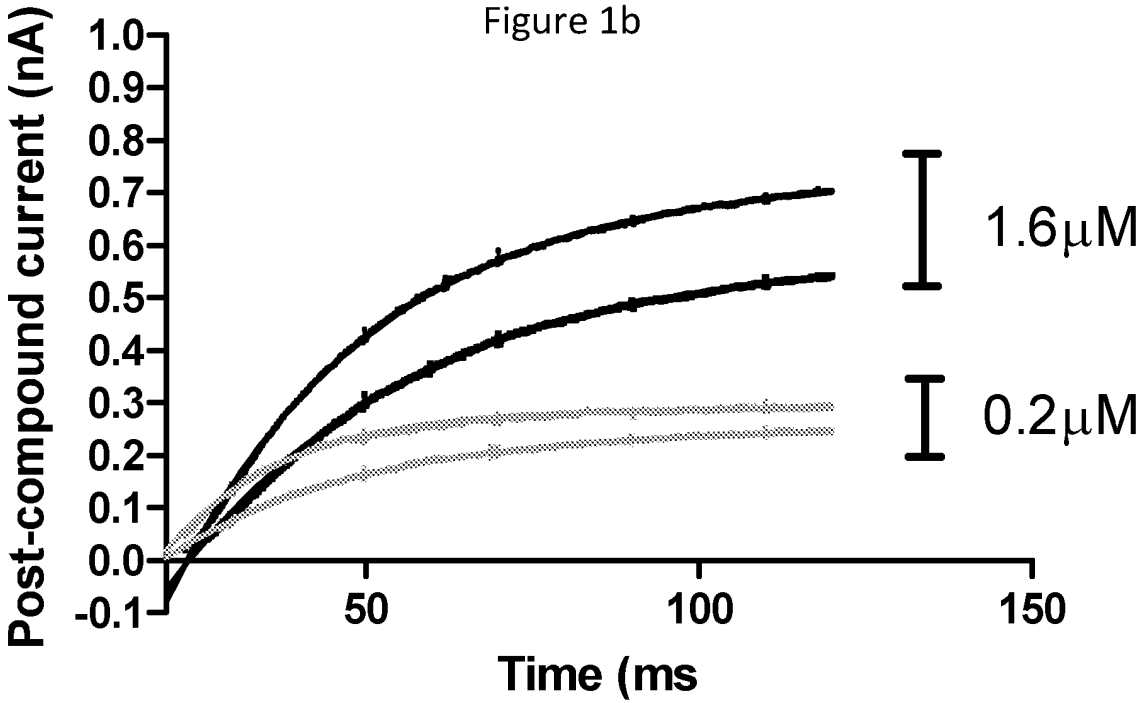


Figure 1b: hKv3.2 currents recorded using the assay described in Biological Example 1, at two concentrations of the compound of Reference Example RE3

Figure 1b



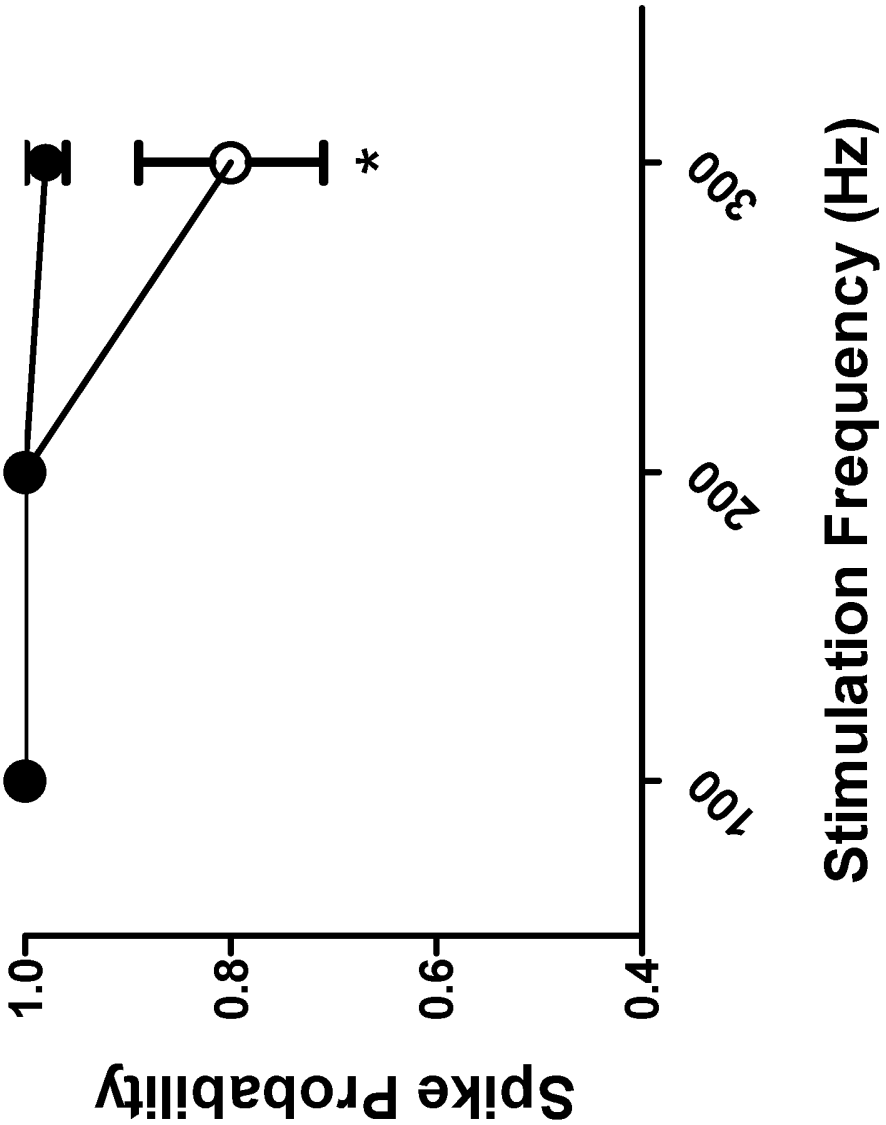

Spike Probability
1.0
0.8
0.6
0.4
100
200
300
Stimulation Frequency (Hz)
*

Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/051488

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4178 A61K31/4439 A61K31/506 A61P25/28 A61P27/16
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)
A61K

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2012/168710 A1 (AUTIFONY THERAPEUTICS LTD [GB]; ALVARO GIUSEPPE [IT]; DECOR ANNE [CA];) 13 December 2012 (2012-12-13) cited in the application	1-11, 13-24, 32-40, 43,44
A,P	the whole document, in particular page 33, lines 20-22	12, 25-31, 41,42

X,P	WO 2012/076877 A1 (AUTIFONY THERAPEUTICS LTD [GB]; ALVARO GIUSEPPE [IT]; DAMBRUOSO PAOLO) 14 June 2012 (2012-06-14) cited in the application	1-3,9, 10, 12-24, 32-40,42
A,P	the whole document, in particular the claims	4-8, 25-31, 41,43,44

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2013	31/07/2013

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

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/051488

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2013/083994 A1 (AUTIFONY THERAPEUTICS LTD [GB]) 13 June 2013 (2013-06-13) the whole document, in particular the claims and page 16, lines 27-29	1-4,9, 10,12, 13, 15-24, 32-35, 37-40, 42,44
X	WO 2011/069951 A1 (GLAXO GROUP LTD [GB]; ALVARO GIUSEPPE [IT]; DECOR ANNE [IT]; FONTANA S) 16 June 2011 (2011-06-16) cited in the application the whole document, in particular the claims	1-44
A	WO 2012/042042 A1 (ORYZON GENOMICS SA [ES]; MAES TAMARA [ES]; BUESA ARJOL CARLOS [ES]) 5 April 2012 (2012-04-05) the whole document	1-44
A	NATALI A. MINASSIAN ET AL: "Altered Kv3.3 channel gating in early onset spinocerebellar ataxia type 13", THE JOURNAL OF PHYSIOLOGY, vol. 590, no. 7, 30 January 2012 (2012-01-30), pages 1599-1614, XP055072783, ISSN: 0022-3751, DOI: 10.1113/jphysiol.2012.228205 cited in the application the whole document	1-44

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2013/051488

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012168710 A1	13-12-2012	NONE	
WO 2012076877 A1	14-06-2012	AU 2011340258 A1	30-05-2013
		CA 2817205 A1	14-06-2012
		SG 190203 A1	28-06-2013
		WO 2012076877 A1	14-06-2012
WO 2013083994 A1	13-06-2013	NONE	
WO 2011069951 A1	16-06-2011	AU 2010330048 A1	31-05-2012
		CA 2781685 A1	16-06-2011
		CN 102753533 A	24-10-2012
		EA 201290310 A1	30-01-2013
		EP 2509961 A1	17-10-2012
		JP 2013513564 A	22-04-2013
		KR 20120107490 A	02-10-2012
		US 2012289526 A1	15-11-2012
		WO 2011069951 A1	16-06-2011
WO 2012042042 A1	05-04-2012	NONE	