

Technical field

This invention relates to novel compounds, pharmaceutical compositions containing them
5 and their use as medicaments, in particular in the prophylaxis or treatment of progressive
myoclonic epilepsy, including PME associated with mutations in the KCNC1 gene, hearing
disorders, including hearing loss and tinnitus, as well as Fragile X syndrome, schizophrenia,
substance abuse disorders, and pain.

Background to the invention

The Kv3 voltage-gated potassium channel family includes four members, Kv3.1, Kv3.2,
Kv3.3, and Kv3.4. Kv3 channels are activated by depolarisation of the plasma membrane to
voltages more positive than -20mV; furthermore, the channels deactivate rapidly upon
repoliarisation of the membrane. These biophysical properties ensure that the channels open
15 towards the peak of the depolarising phase of the neuronal action potential to initiate
repoliarisation. 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 *et al.*, 2001). Kv3 subtypes are
20 predominant in the CNS, although Kv3.1, Kv3.3 and Kv3.4 channels are also found in spinal cord
(Brooke *et al.*, 2002; 2004; 2006). Kv3 channel subtypes are differentially expressed by sub-
classes of interneurons in cortical and hippocampal brain areas (e.g. Chow *et al.*, 1999; Martina
et al., 1998; McDonald *et al.*, 2006; Chang *et al.*, 2007), in the thalamus (e.g. Kasten *et al.*, 2007),
cerebellum (e.g. Sacco *et al.*, 2006; Puente *et al.*, 2010), and auditory brain stem nuclei (Li *et al.*,
25 2001).

Characterisation of mice in which one or more of the Kv3 subtypes has been deleted
shows that the absence of Kv3.1 gives rise to increased locomotor activity, altered
electroencephalographic activity, and a fragmented sleep pattern (Joho *et al.*, 1999). The deletion
of Kv3.2 leads to a reduction in seizure threshold and altered cortical electroencephalographic
30 activity (Lau *et al.*, 2000). Deletion of Kv3.3 is associated with mild ataxia and motor deficits
(McMahon *et al.*, 2004). Double deletion of Kv3.1 and Kv3.3 gives rise to a severe phenotype
characterised by spontaneous seizures, ataxia, and an increased sensitivity to the effects of
ethanol (Espinosa *et al.*, 2001; Espinosa *et al.*, 2008). A spontaneous mutation in the Kv3.1 gene
(KCNC1) in humans causes progressive myoclonic epilepsy (Muona *et al.*, 2014). Mutations of
35 the Kv3.3 gene (KCNC3) in humans is associated with spinocerebellar ataxia (SCA13) (Figuerola
et al., 2010).

Bipolar disorder, schizophrenia, are serious disorders of the central nervous system that have been associated with reduced function of parvalbumin-positive inhibitory interneurons in corticolimbic brain circuits (Reynolds *et al.*, 2004; Benes *et al.*, 2008; Brambilla *et al.*, 2003; Aroniadou-Anderjaska *et al.*, 2007; Ben-Ari, 2006). Parvalbumin positive basket cells express
5 Kv3 channels which allow these neurons to fire at high frequency to provide fast feedback inhibition within local circuits (Markram *et al.*, 2004). Accurate timing of this inhibitory feedback is necessary to sustain network synchronisation, for example, in the generation of gamma frequency field potential oscillations that have been associated with cognitive function (Fisahn *et al.*, 2005; Engel *et al.*, 2001). A reduction in gamma oscillations has been observed in patients with
10 schizophrenia (Spencer *et al.*, 2004), and evidence suggests reduced expression of Kv3.1, but not Kv3.2 in the dorsolateral prefrontal cortex of patients with schizophrenia (Yanagi *et al.*, 2014). Positive modulators of Kv3 channels enhance the firing of parvalbumin positive interneurons (Rosato-Siri *et al.*, 2015; Boddum *et al.*, 2017) leading to increased gamma oscillations (Andrade-Talavera *et al.*, 2020) and rescue deficits in cognitive and social behaviours in animal models
15 (Leger *et al.*, 2015). Furthermore, Kv3 positive modulators reduced abnormal behaviours in a mouse model of bipolar disorder (Parekh *et al.*, 2017)

Fragile X syndrome is a paediatric developmental disorder with autistic features that has also been linked to dysfunction of parvalbumin positive interneurons (e.g. Pirbhoy *et al.*, 2020) and alteration of Kv3.1 channel expression (Darnell *et al.*, 2001; Strumbos *et al.*, 2010). Kv3
20 channel modulators have been shown to rescue deficits in auditory brainstem function in vitro and in vivo in a mouse model of Fragile X syndrome (El-Hassar *et al.*, 2019).

Voltage-gated ion channels of the Kv3 family are expressed at high levels in auditory brainstem nuclei (Li *et al.*, 2001) where they permit the fast firing of neurons that transmit auditory information from the cochlear to higher brain regions. Phosphorylation of Kv3.1 and Kv3.3
25 channels in auditory brainstem neurons is suggested to contribute to the rapid physiological adaptation to sound levels that may play a protective role during exposure to noise (Desai *et al.*, 2008; Song *et al.*, 2005). Loss of Kv3.1 channel expression in central auditory neurons is observed in hearing impaired mice (von Hehn *et al.*, 2004); furthermore, a decline in Kv3.1 expression may be associated with loss of hearing in aged mice (Jung *et al.*, 2005), and loss of
30 Kv3 channel function may also follow noise-trauma induced hearing loss (Pilati *et al.*, 2012). Furthermore, pathological plasticity of auditory brainstem networks is likely to contribute to symptoms that are experienced by many people suffering from hearing loss of different types. Recent studies have shown that regulation of Kv3.1 channel function and expression has a major role in controlling auditory neuron excitability (Kaczmarek *et al.*, 2005; Anderson *et al.*, 2018; Gkait
35 *et al.*, 2018; Olsen *et al.*, 2018; Chambers *et al.*, 2017), suggesting that this mechanism could account for some of the plastic changes that give rise to hearing-related disorders such as tinnitus.

Recently, Kv3.4 channels have become a target of interest for the treatment of chronic pain. Kv3.4 channels are expressed on neurons of the dorsal root ganglia (Ritter *et al.*, 2012; Chien *et al.*, 2007), where they are predominantly expressed on sensory C-fibres (Chien *et al.*, 2007). Kv3 channels are also expressed by specific subsets of neurons in the spinal cord. Specifically, Kv3.1b (Deuchars *et al.*, 2001; Brooke *et al.*, 2002), Kv3.3 (Brooke *et al.*, 2006), and Kv3.4 subunits (Brooke *et al.*, 2004) have been identified in rodent spinal cord, although not always in association with circuits involved with sensory processing. It is likely that Kv3 channels shape the firing properties of spinal cord neurons, including motoneurons.

In addition recent studies showed the Kv3.4 channels expressed in DRG nociceptors have a significant impact on glutamatergic synaptic transmission (Muqeem *et al.*, 2018). animal model data suggest a down-regulation of Kv3.4 channel surface expression in DRG neurons following spinal cord injury associated with hypersensitivity to painful stimuli (Ritter *et al.*, 2015; Zemel *et al.*, 2017; Zemel *et al.*, 2018). Similarly, it has been observed that there is a down-regulation of Kv3.4 expression in DRGs of rodents following spinal cord ligation (Chien *et al.*, 2007). This latter study also showed that intrathecal administration to rats of an antisense oligonucleotide to suppress the expression of Kv3.4 led to hypersensitivity to mechanical stimuli. It has been shown that Kv3.4 channel inactivation could be influenced by protein kinase C-dependent phosphorylation of the channels, and that this physiological mechanism might allow DRG neurons to alter their firing characteristics in response to painful stimuli (Ritter *et al.*, 2012). These studies suggest a causal relationship between the emergence of mechanical allodynia and reduced Kv3.4 channel expression or function. No evaluation of Kv3.1, Kv3.2, or Kv3.3 expression in SC or DRG neurons was conducted in any of these studies, and expression of these two subtypes has not been explicitly demonstrated on DRG neurons (although as mentioned above, they are abundant within specific regions of the spinal cord). The *in vivo* studies reported above provide a rationale for modulation of Kv3.4 as a novel approach to the treatment of certain neuropathic pain states.

Patent applications WO2011/069951, WO2012/076877, WO2012/168710, WO2013/175215, WO2013/083994, WO2013/182850, WO2017/103604, WO2018/020263, WO2018/109484 and WO2020/079422 disclose compounds which are modulators of Kv3.1 and Kv3.2. Further, the utility of such compounds is demonstrated in animal models of seizure, hyperactivity, sleep disorders, psychosis, hearing disorders and bipolar disorders.

Patent application WO2013/182851 discloses modulation of Kv3.3 channels by certain compounds.

Patent application WO2013/175211 discloses that modulation of Kv3.1, Kv3.2 and/or Kv3.3 channels has been found to be beneficial in preventing or limiting the establishment of a permanent hearing loss resulting from acute noise exposure. The benefits of such prevention may be observed even after administration of the Kv3.1, Kv3.2 and/or Kv3.3 modulator has ceased.

Patent application WO2017/098254 discloses that modulation of Kv3.1, Kv3.2 and/or Kv3.3 channels has been found to be beneficial in the prophylaxis or treatment of pain, in particular neuropathic or inflammatory pain.

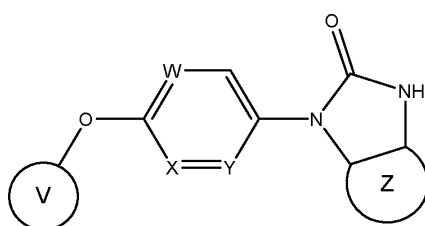
Patent applications WO2019/222816, WO2020/000065, WO2020/089262, WO2020/216919 and WO2020/216920 are said to describe compounds which activate Kv3 potassium channels.

Patent applications EP3901152 and WO2021214090, published after the priority date of the present application, are said to describe Kv3 enhancers for the treatment of cognitive disorders.

There remains a need for the identification of alternative modulators of Kv3.1, Kv3.2, Kv3.3 and/or Kv3.4 channels, in particular modulators of Kv3.1 and/or Kv3.2. Such modulators may demonstrate high *in vivo* potency, channel selectivity, an improved safety profile, or desirable pharmacokinetic parameters, for example high brain availability and/or low clearance rate that reduces the dose required for therapeutic effect *in vivo*. Alternative modulators may provide a benefit through having distinct metabolites from known modulators. Compounds which have balanced Kv3.1, Kv3.2, Kv3.3 and/or Kv3.4 modulatory properties may be desirable e.g. compounds which modulate Kv3.1 and Kv3.2 to the same, or a similar extent. For certain therapeutic indications, there is also a need to identify compounds with a different modulatory effect on Kv3.1, Kv3.2, Kv3.3 and/or Kv3.4 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):

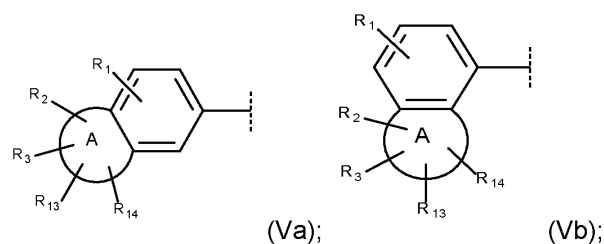


(I)

wherein:

V is group (Va), group (Vb) or group (Vc);

wherein group (Va) and group (Vb) are:



wherein:

R₁ is H, C₁₋₄alkyl, halo, haloC₁₋₄alkyl, CN, C₁₋₄alkoxy, or haloC₁₋₄alkoxy;

R₂ is H, C₁₋₄alkyl, C₃₋₅ spiro carbocyclyl, haloC₁₋₄alkyl or halo;

5 R₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₃ is absent;

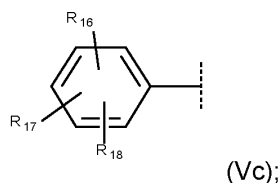
R₁₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₃ is absent;

R₁₄ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₄ 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;

10 wherein R₂ and R₃ may be attached to the same or a different ring atom; R₂ may be attached to a fused ring atom; and wherein R₁₃ and R₁₄ may be attached to the same or a different ring atom;

wherein group (Vc) is:



15

wherein:

R₁₆ is halo, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy or CN;

R₁₇ is H, halo, CN, C₁₋₄alkyl, C₁₋₄alkoxy or haloC₁₋₄alkoxy;

R₁₈ is H, halo, CN, C₁₋₄alkyl or C₁₋₄alkoxy;

20 W is N or CH;

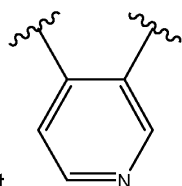
X is N or CH;

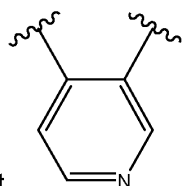
Y is N or CH;

wherein at least one of W, X and Y is CH, and when one of X and Y is N, the other is CH;

Z is a 5-membered heteroaryl comprising one or two nitrogen atoms, and wherein one of the nitrogen atoms and one of the carbon atoms may be independently optionally substituted by methyl; or Z is a 6-membered heteroaryl comprising one or two nitrogen atoms, wherein one of the carbon atoms may be optionally substituted by methyl; and

25



provided that Z is not  wherein one of the carbon atoms may be optionally substituted by methyl; or a salt and/or solvate and/or derivative thereof.

A compound of formula (I) may be provided in the form of a pharmaceutically acceptable salt and/or solvate and/or derivative thereof, such as a salt and/or solvate thereof, in particular a salt thereof. A compound of formula (I) may be provided in the form of a pharmaceutically acceptable salt and/or solvate thereof. In one embodiment of the invention a compound of formula (I) is provided in the form of a pharmaceutically acceptable salt.

The compounds of formula (I) may be used as medicaments, in particular for use in the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, substance abuse disorders, pain or Fragile X syndrome.

Further, there is provided a method for the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, substance abuse disorders, pain or Fragile X syndrome in a subject, the method comprising administering a compound of formula (I).

Compounds of formula (I) may be used in the manufacture of a medicament for the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, substance abuse disorders, pain or Fragile X syndrome.

The compounds of formula (I) may be used as medicaments in the prophylaxis or treatment of epilepsy, in particular progressive myoclonic epilepsy, including PME associated with mutations in the KCNC1 gene.

Further, there is provided a method for the prophylaxis or treatment of epilepsy, in particular progressive myoclonic epilepsy, including PME associated with mutations in the KCNC1 gene in a subject, the method comprising administering a compound of formula (I).

Compounds of formula (I) may be used in the manufacture of a medicament for the prophylaxis or treatment of epilepsy, in particular progressive myoclonic epilepsy, including PME associated with mutations in the KCNC1 gene.

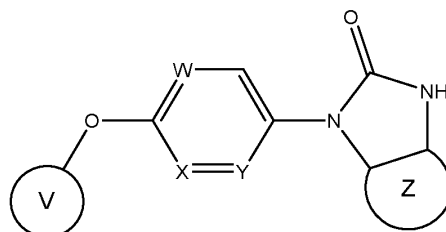
Also provided are pharmaceutical compositions containing a compound of formula (I) and a pharmaceutically acceptable carrier or excipient.

Also provided are processes for preparing compounds of formula (I) and novel intermediates of use in the preparation of compounds of formula (I).

Additionally provided are prodrug derivatives of the compounds of formula (I).

Detailed description of the invention

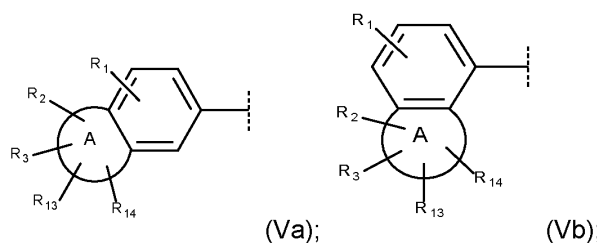
In one embodiment, the invention provides a compound of formula (I):



wherein:

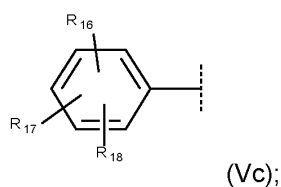
- 5 V is group (Va), group (Vb) or group (Vc);

wherein group (Va) and group (Vb) are:



wherein:

- R₁ is H, C₁₋₄alkyl, halo, haloC₁₋₄alkyl, CN, C₁₋₄alkoxy, or haloC₁₋₄alkoxy;
- 10 R₂ is H, C₁₋₄alkyl, C₃₋₅ spiro carbocyclyl, haloC₁₋₄alkyl or halo;
- R₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₃ is absent;
- R₁₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₃ is absent;
- R₁₄ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₄ is absent;
- A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom; which
- 15 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;
- wherein R₂ and R₃ may be attached to the same or a different ring atom; R₂ may be attached to a fused ring atom; and wherein R₁₃ and R₁₄ may be attached to the same or a different ring atom;
- 20 wherein group (Vc) is:



wherein:

R₁₆ is halo, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy or CN;

R₁₇ is H, halo, CN, C₁₋₄alkyl, C₁₋₄alkoxy or haloC₁₋₄alkoxy;

R₁₈ is H, halo, CN, C₁₋₄alkyl or C₁₋₄alkoxy;

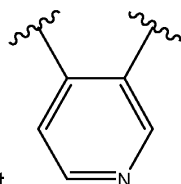
W is N or CH;

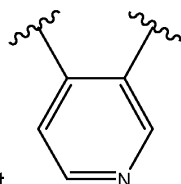
5 X is N or CH;

Y is N or CH;

wherein at least one of W, X and Y is CH, and when one of X and Y is N, the other is CH;

Z is a 5-membered heteroaryl comprising one or two nitrogen atoms, and wherein one of the nitrogen atoms and one of the carbon atoms may be independently optionally substituted by methyl;
10 or Z is a 6-membered heteroaryl comprising one or two nitrogen atoms, wherein one of the carbon atoms may be optionally substituted by methyl; and



provided that Z is not  wherein one of the carbon atoms may be optionally substituted by methyl.

The invention further provides a salt of a compound of formula (I). The invention further provides a pharmaceutically acceptable salt of a compound of formula (I). The invention further provides a solvate of a compound of formula (I). The invention further provides a pharmaceutically acceptable solvate of a compound of formula (I). The invention further provides a pharmaceutically acceptable salt and/or solvate of a compound of formula (I). The invention further provides a pharmaceutically acceptable salt and solvate of a compound of
20 formula (I) (i.e. a pharmaceutically acceptable solvate of a pharmaceutically acceptable salt).

Embodiments set out below relating to relative stereochemistry and the nature of groups, including V, W, X, Y, Z, A, R₁, R₂, R₃, R₁₃, R₁₄, R₁₆, R₁₇, R₁₈ and Z are envisaged as being independently, fully combinable with one another where appropriate to the circumstances (i.e. where chemically sensible) to form further embodiments of the invention. Such embodiments
25 apply equally to intermediates which may be of use in the synthesis of a compound of formula (I), such as compounds of formulae (II) and (III), (IV), (VI), (IX) and (X), e.g. compounds of formulae (II) and (III).

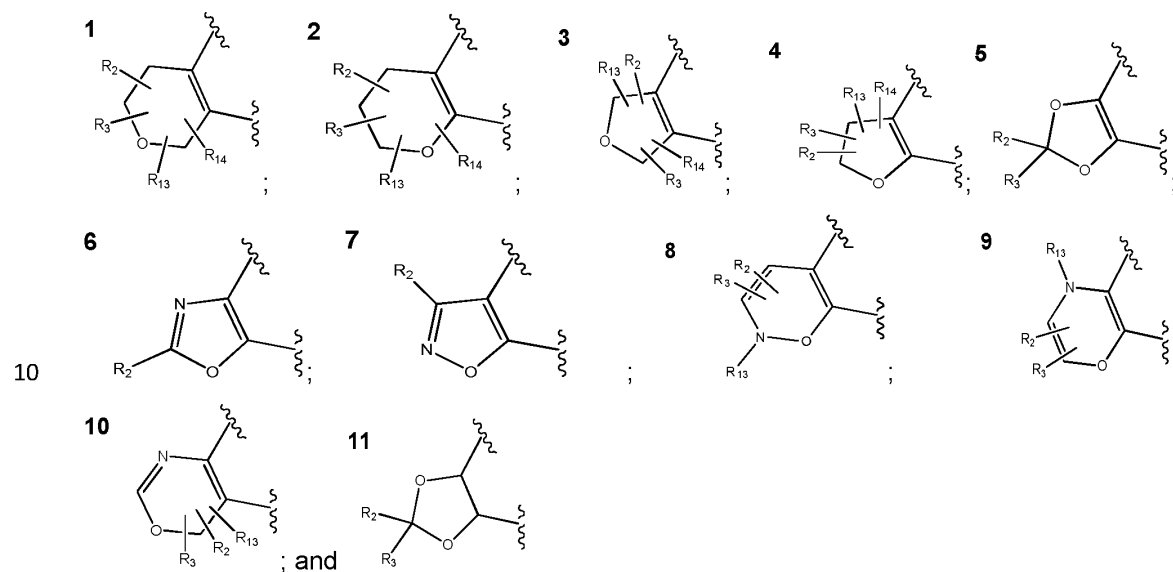
In one embodiment, V is group (Va). In a second embodiment, V is group (Vb). Groups (Va) and (Vb) both contain ring A and bear substituents R₁, R₂, R₁₃ and R₁₄.

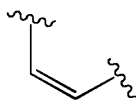
30 In one embodiment, ring A is a 5 membered saturated heterocycle, with at least one O atom; which heterocycle is optionally fused with a cyclopropyl group, or a cyclobutyl group, or a cyclopentyl group to form a tricycle when considered together with the phenyl.

Ring A may be a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom, suitably ring A may be a 5 membered saturated heterocycle, with at least one O atom.

In one embodiment, ring A contains one heteroatom which is oxygen. In one embodiment, ring A contains two heteroatoms, e.g. two oxygen atoms or one oxygen atom and one nitrogen atom. In one embodiment ring A is dihydrofuran, isoxazole, dihydropyran, 1,3-dioxolane, 1,3-oxazine or dihydropyran. Suitably, ring A is dihydrofuran or dihydropyran, in particular dihydrofuran.

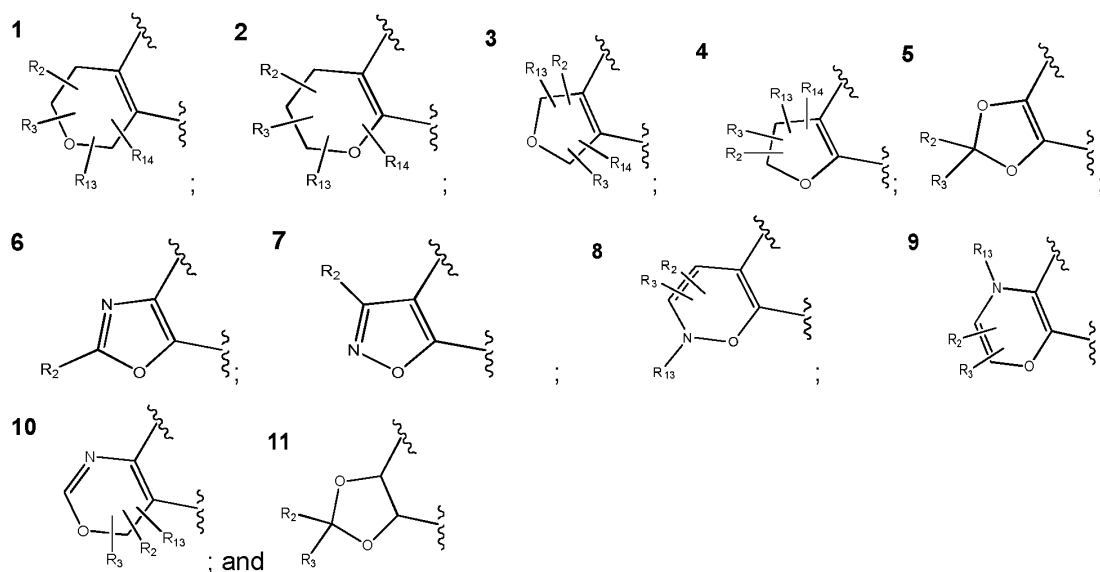
In one embodiment, ring A is selected from the group consisting of:

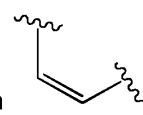


wherein  denotes a point at which ring A is fused to the phenyl ring.

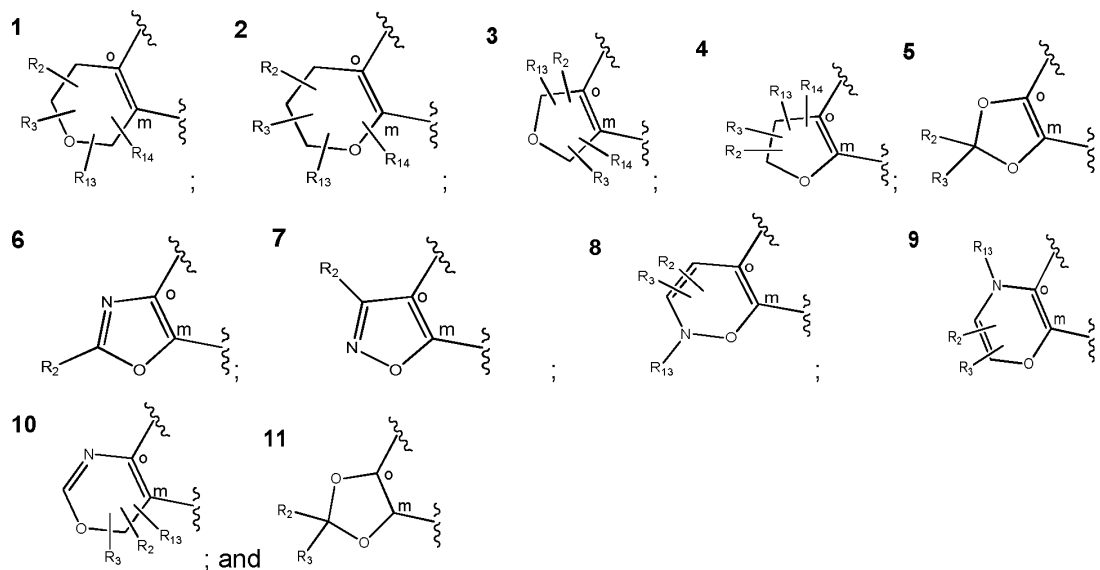
In one embodiment, ring A is selected from the group consisting of:

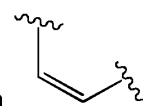
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wherein  denotes a point at which ring A is fused to the phenyl ring.

5 In one embodiment, ring A is selected from the group consisting of:

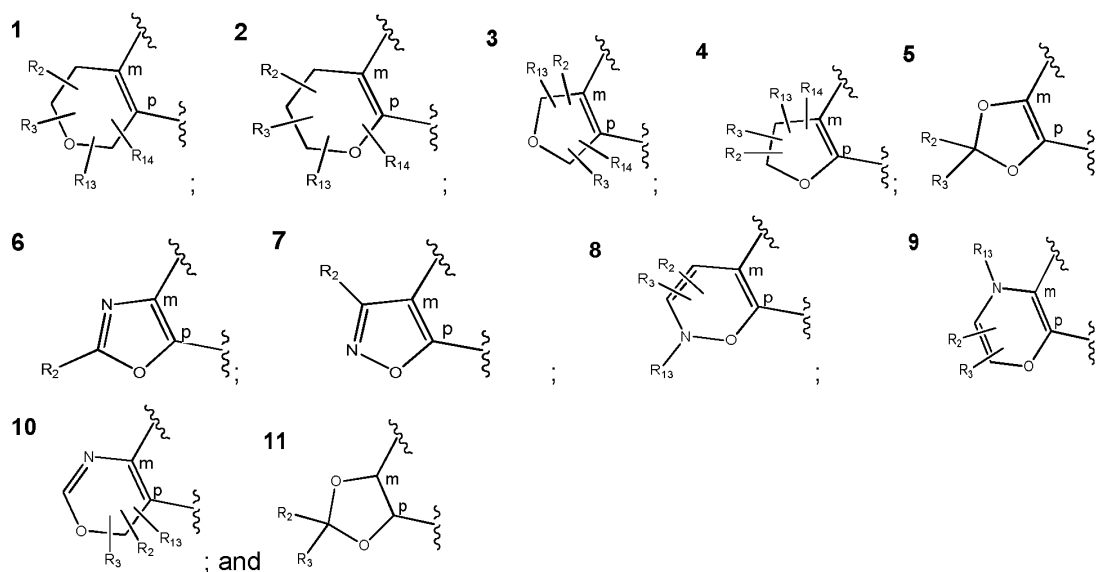


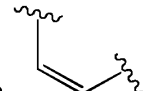
wherein  denotes a point at which ring A is fused to the phenyl ring, and "o" and "m" indicate the ortho- and meta-positions of the phenyl ring to which group A is fused.

10 In one embodiment, ring A is selected from the group consisting of:

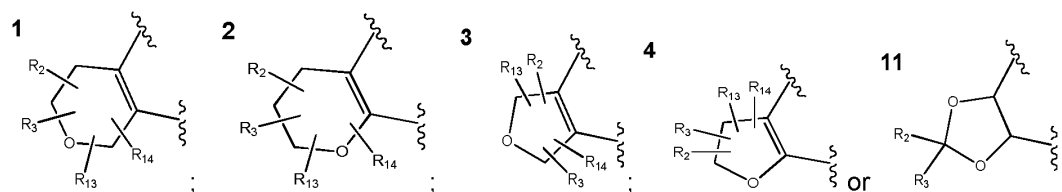
In one embodiment, ring A is selected from the group consisting of:

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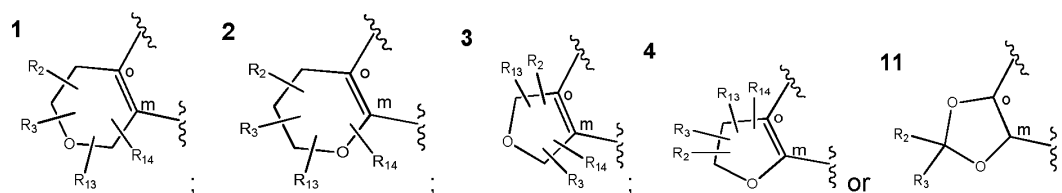


wherein  denotes a point at which ring A is fused to the phenyl ring, wherein “m” and “p” indicate the meta- and para-positions of the phenyl ring to which group A is fused.

Suitably, ring A is:

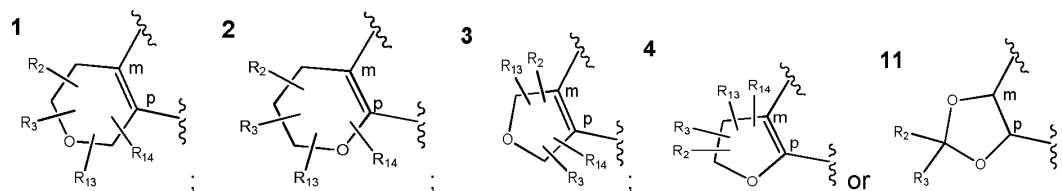


Suitably, ring A is:

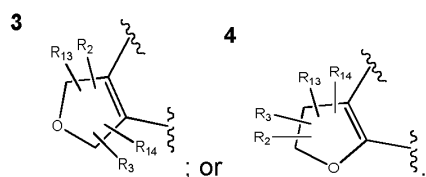


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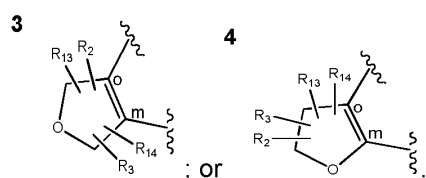
Suitably, ring A is:



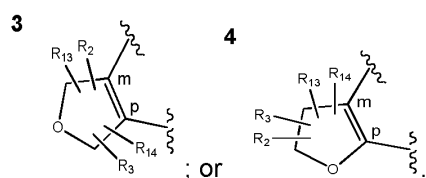
In particular, ring A is



In particular, ring A is



In particular, ring A is

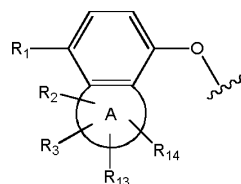


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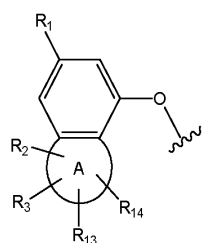
In one embodiment, when ring A is a 5 membered heterocycle containing one heteroatom which is oxygen, wherein suitably the oxygen atom is located at the phenolic position relative to the phenyl ring.

In one embodiment, R_1 is H, C_{1-4} alkyl, halo, halo C_{1-4} alkyl or CN, in particular C_{1-4} alkyl such as methyl. In one embodiment, R_1 is H or methyl. In one embodiment, R_1 is H. In one embodiment, R_1 is methyl.

In one embodiment, when V is group (Vb), R_1 is at the para position and is H or methyl:

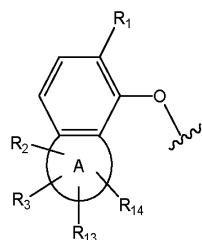


In one embodiment, when V is group (Vb), R_1 is in the meta position and is H or methyl:



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In one embodiment, when V is group (Vb), R_1 is in the ortho position and is H or methyl:



In one embodiment, R_2 is H, C_{1-4} alkyl, C_{3-5} spiro carbocyclyl or halo. In one embodiment, R_2 is C_{1-4} alkyl such as methyl or ethyl. In one embodiment R_2 is C_{3-5} spiro carbocyclyl such as C_3 spiro carbocyclyl. In one embodiment, R_2 is methyl. In one embodiment, R_2 is halo e.g. fluoro.

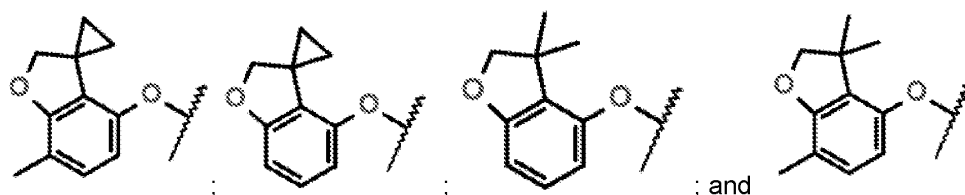
- 5 In one embodiment R_3 is H, C_{1-4} alkyl, halo C_{1-4} alkyl or halo. In one embodiment, R_3 is C_{1-4} alkyl such as methyl. In one embodiment, R_3 is methyl. In another embodiment R_3 is halo e.g. fluoro. In another embodiment R_3 is absent.

In one embodiment, R_2 and R_3 are located on the same ring A atom.

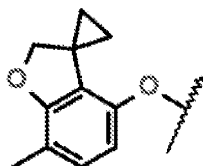
In one embodiment, R_{13} is H or is absent. Suitably, R_{13} is absent.

- 10 In one embodiment, R_{14} is H or is absent. Suitably, R_{14} is absent.

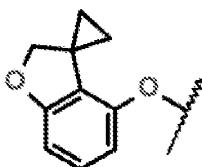
V may be selected from the group consisting of:



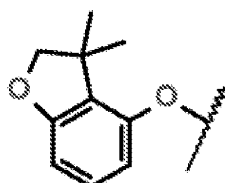
In one embodiment, V is

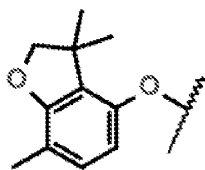


15 In one embodiment, V is



In one embodiment, V is





In one embodiment, V is

Group (Vc) bears substituents R₁₆, R₁₇ and R₁₈.

In one embodiment, R₁₆ is not in the para-position. In one embodiment, one of R₁₇ and R₁₈ is not H. In one embodiment, R₁₆ is in the meta-position. In one embodiment, R₁₇ is at the para position.

In one embodiment, R₁₆ is C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy or CN. In one embodiment, R₁₆ is C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl or haloC₁₋₄alkoxy. In one embodiment, R₁₆ is C₁₋₄alkyl, C₁₋₄alkoxy or haloC₁₋₄alkoxy. In one embodiment, R₁₆ is halo, C₁₋₄alkyl or C₁₋₄alkoxy. In one embodiment, R₁₆ is methyl, ethyl, propyl, butyl, cyclopropyl, chloro, fluoro, methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy or CN. In one embodiment, R₁₆ is trifluoromethoxy or methoxy. In one embodiment, R₁₆ is trifluoromethoxy. In one embodiment, R₁₆ is methoxy.

In one embodiment, R₁₇ is H, halo, CN, C₁₋₄alkyl or C₁₋₄alkoxy. In one embodiment, R₁₇ is H, CN, C₁₋₄alkyl, C₁₋₄alkoxy or haloC₁₋₄alkoxy. In one embodiment, R₁₇ is C₁₋₄alkyl or C₁₋₄alkoxy. In one embodiment, R₁₇ is H, CN or C₁₋₄alkyl. In one embodiment, R₁₇ is H, CN or methyl. In one embodiment, R₁₇ is methyl, ethyl, propyl, butyl, cyclopropyl, chloro, fluoro, methoxy, ethoxy, propoxy, trifluoromethoxy or CN. In one embodiment, R₁₇ is H. In one embodiment, R₁₇ is methyl or CN. In one embodiment, R₁₇ is methyl. In one embodiment, R₁₇ is CN.

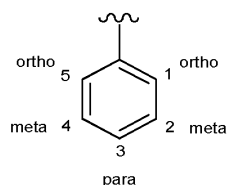
In one embodiment, R₁₈ is H.

In one embodiment, R₁₇ and R₁₈ are H. In one embodiment, R₁₆ is suitably at the ortho- or meta- position. In this embodiment, when R₁₆ is at the ortho position, it is suitably C₁₋₄ alkyl, for example methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl or *tert*-butyl. In one embodiment, when R₁₆ is at the meta position, it is suitably C₁₋₄alkyl for example methyl, ethyl, isopropyl or cyclopropyl; C₁₋₄alkoxy for example methoxy or ethoxy; or haloC₁₋₄alkoxy for example trifluoromethoxy. In one embodiment, R₁₆ is trifluoromethoxy at the meta position, and R₁₇ and R₁₈ are H. In one embodiment, R₁₆ is methoxy at the meta position, and R₁₇ and R₁₈ are H.

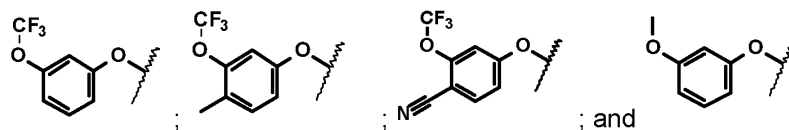
In one embodiment, R₁₈ is H and R₁₇ is not H. In one embodiment one of R₁₆ or R₁₇ is at the ortho position. In this embodiment, the substituent at the ortho position is suitably C₁₋₄ alkyl, for example methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl or *tert*-butyl. In another embodiment, one of R₁₆ and R₁₇ is at the ortho-position, and the other is at the meta-position. In this embodiment, the substituent at the ortho position is suitably C₁₋₄ alkyl, for example methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl or *tert*-butyl and the substituent at the meta position is suitably C₁₋₄alkyl for example methyl, ethyl, isopropyl or cyclopropyl; C₁₋₄alkoxy for example methoxy or ethoxy; or haloC₁₋₄alkoxy for example trifluoromethoxy. In one embodiment, one of

R₁₆ and R₁₇ is at the ortho-position, and the other is at the para-position. In one embodiment, one of R₁₆ and R₁₇ is at position 1-, and the other is at position 4-. In this embodiment, the substituent in the para position is suitably CN, fluoro or methyl. In one embodiment, both of R₁₆ and R₁₇ are at the ortho-positions. In this embodiment, the substituents at the ortho position are suitably the same, and are suitably C₁₋₄ alkyl, for example methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl or *tert*-butyl. In one embodiment R₁₆ is at the meta-position and R₁₇ is at the para-position. Within such an embodiment R₁₆ is suitably haloC₁₋₄alkyl, for example trifluoromethoxy, and R₁₇ is CN or C₁₋₄alkyl, for example, CN, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl or *tert*-butyl, and in particular R₁₇ is CN or methyl. In one embodiment, R₁₆ is trifluoromethoxy at the meta-position and R₁₇ is CN at the para-position. In one embodiment R₁₆ is trifluoromethoxy at the meta-position and R₁₇ is methyl at the para-position.

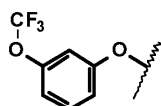
References to substituent position numbering and nomenclature are made in respect of the position of the phenyl ring to the oxygen moiety, for example:



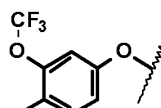
V may be selected from the group consisting of:



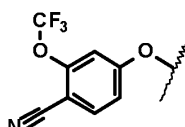
In one embodiment, V is:



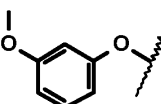
In one embodiment, V is:



In one embodiment, V is:



In one embodiment, V is



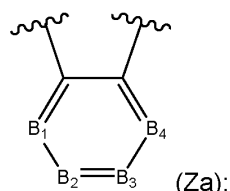
In one embodiment, W is N. In one embodiment, W is CH.

In one embodiment, X is N. In one embodiment, X is CH.

In one embodiment, Y is N. In one embodiment, Y is CH.

In one embodiment, W is N, and X and Y are CH. In one embodiment, W is N, X is N and Y is CH. In one embodiment, W is N, X is CH and Y is N. In one embodiment, W and X are CH, and Y is N.

In one embodiment, group Z is (Za):

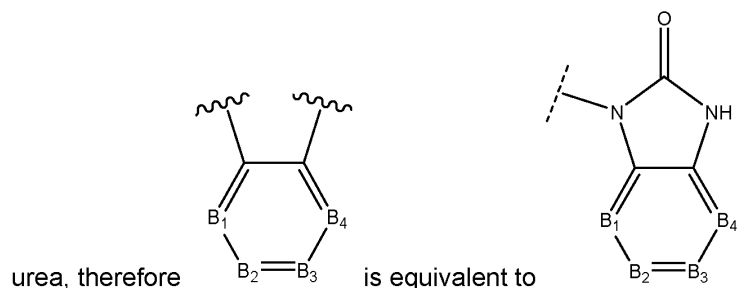


wherein:

B₁, B₂, B₃ and B₄ are each independently selected from N, CH and C(Me);

wherein one or two of B₁, B₂, B₃ and B₄ are N, and only one of B₁, B₂, B₃ and B₄ may be C(Me); and wherein when B₁, B₂ and B₄ are CH or C(Me), B₃ is not N.

Within such embodiments,  denotes the positions to which Z is fused to the cyclic



urea, therefore

is equivalent to

In one embodiment, B₁ is N. In one embodiment, B₁ is CH.

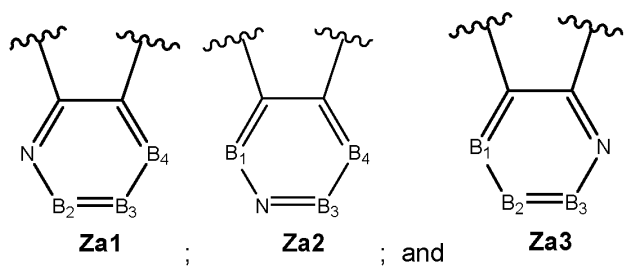
In one embodiment, B₂ is N. In one embodiment, B₂ is CH or C(Me). In one embodiment, B₂ is CH. In one embodiment, B₂ is C(Me).

In one embodiment, B₃ is CH or N. In one embodiment, B₃ is N. In one embodiment, B₃ is CH. In one embodiment, B₃ is C(Me).

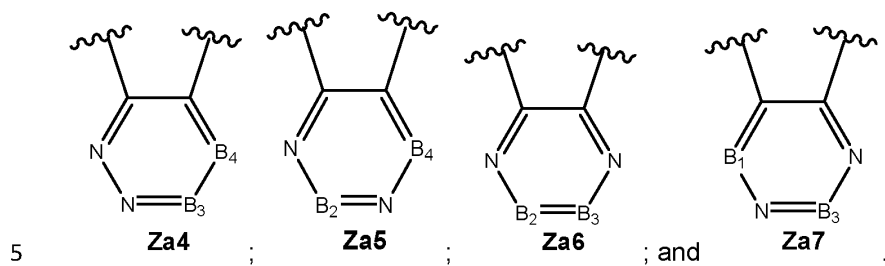
In one embodiment, B₄ is N. In one embodiment, B₄ is CH. In one embodiment, B₄ is C(Me).

In one embodiment, B₁ is N and B₂ is C(Me). In one embodiment, B₁ is N and B₃ is C(Me). In one embodiment, B₁ is N and B₄ is C(Me). In one embodiment, B₁ is N and B₂ is N. In one embodiment, B₁ is N and B₃ is N. In one embodiment, B₁ is N and B₄ is N. In one embodiment, B₁ and B₃ are N and B₂ is CH. In one embodiment, B₁ and B₃ are N and B₂ is C(Me). In one embodiment, B₁ is N, B₂ is C(Me), B₃ is N and B₄ is CH. In one embodiment, B₁ is N and B₂, B₃ and B₄ are each independently CH.

In one embodiment, (Za) is selected from the group consisting of:

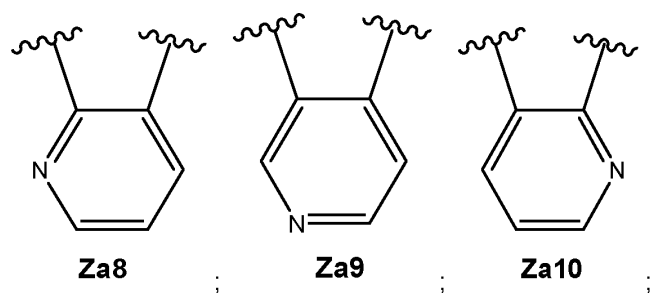


In one embodiment, (Za) is selected from the group consisting of:

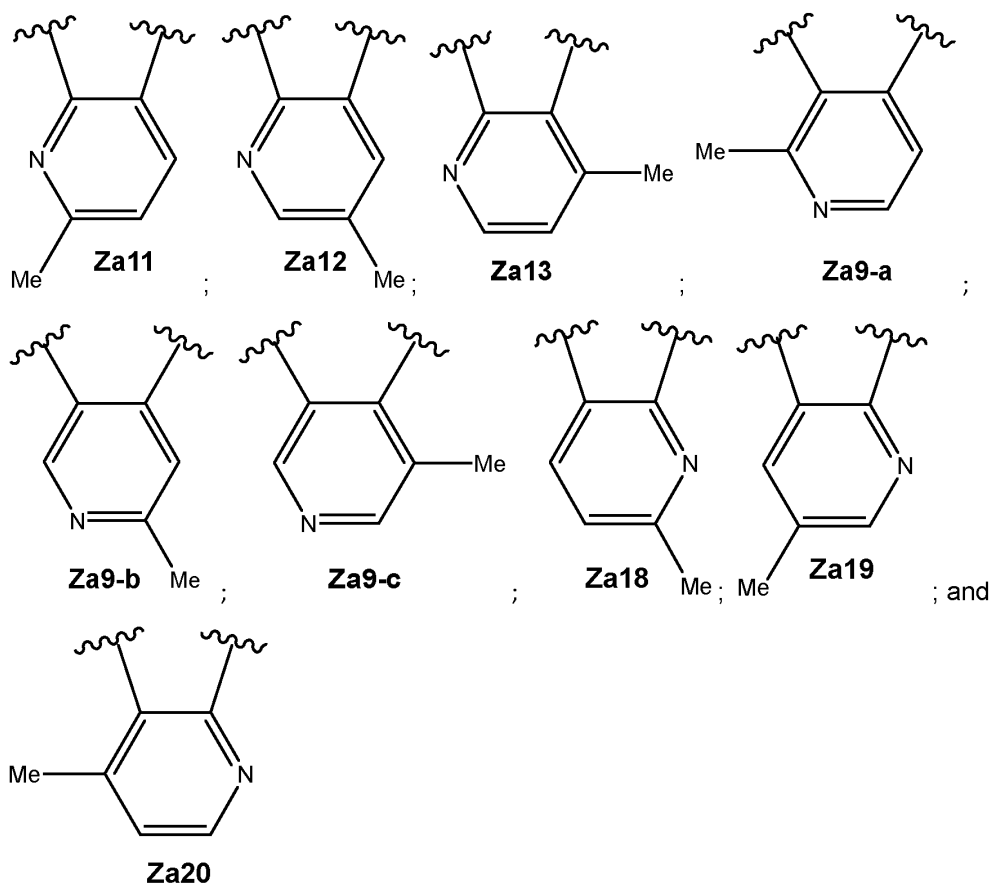


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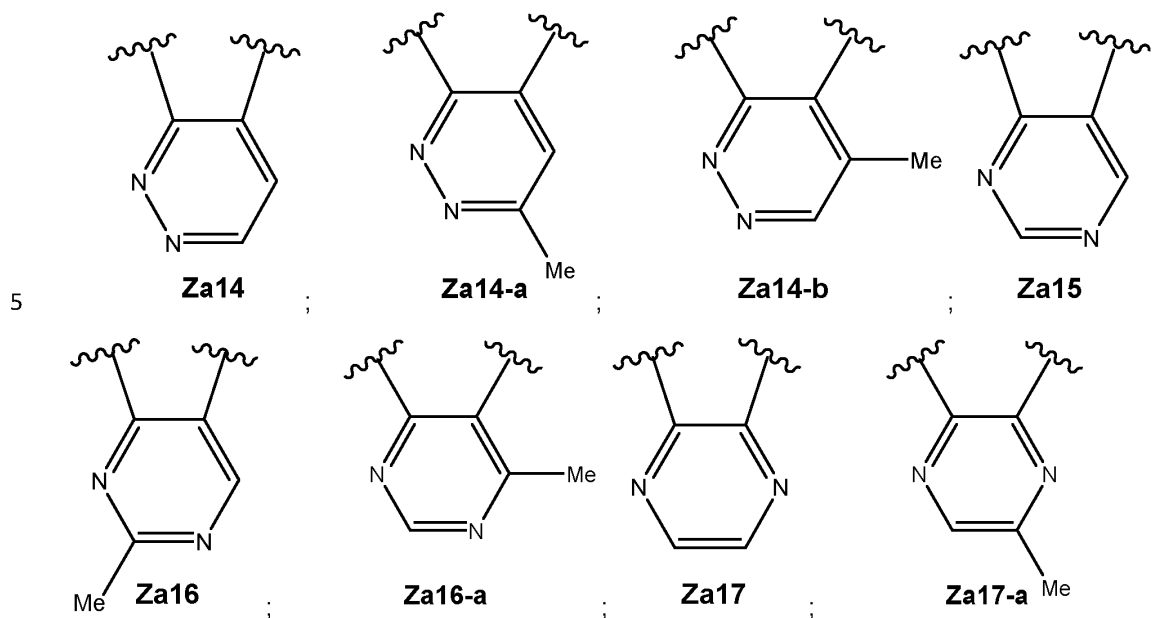
In one embodiment, (Za) is selected from the group consisting of:



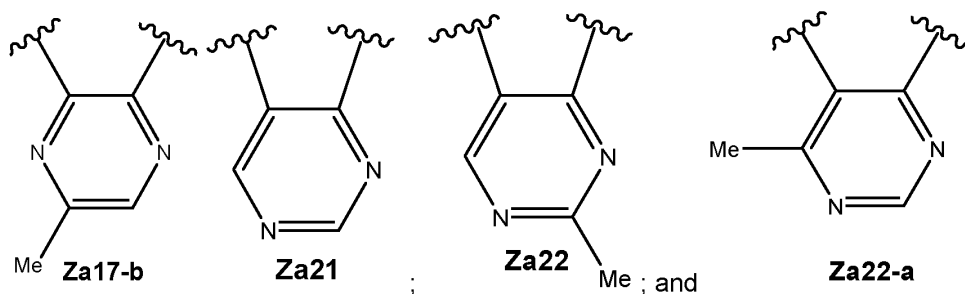
18



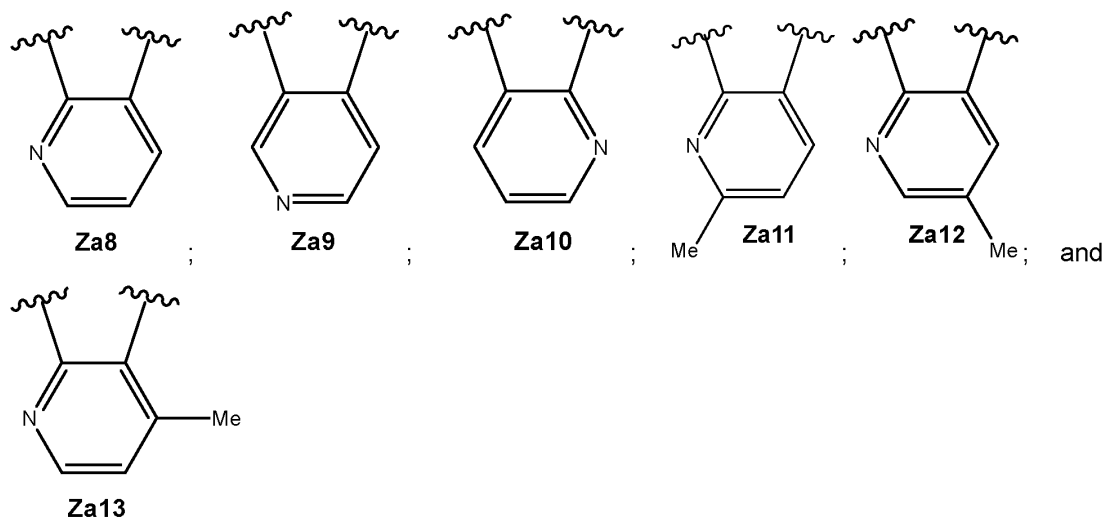
In one embodiment, (Za) is selected from the group consisting of:



19

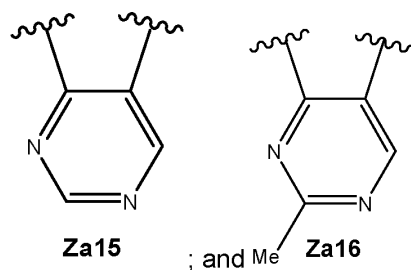


In one embodiment, (Za) is selected from the group consisting of:

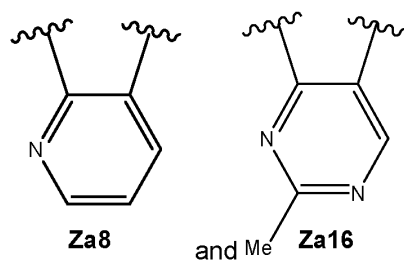


5

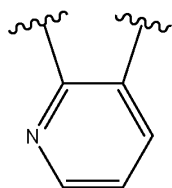
In one embodiment, (Za) is selected from the group consisting of:



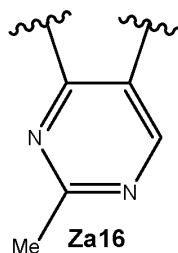
In one embodiment, (Za) is selected from the group consisting of:



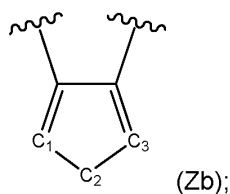
In one embodiment, (Za) is:

**Z8**

In one embodiment, (Za) is:

**Za16**

In one embodiment, group Z is group (Zb):



(Zb);

5

wherein:

C₁ and C₃ are each independently selected from CH, C(Me) and N; and

C₂ is NH or N(Me); and wherein when one of C₁ and C₃ is N, the other is CH or C(Me).

In one embodiment, C₁ is CH. In one embodiment, C₁ is C(Me). In one embodiment, C₁ is

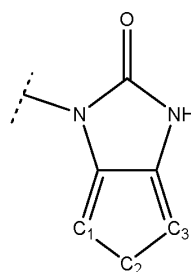
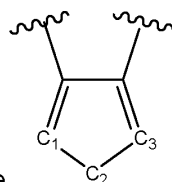
10 N.

In one embodiment, C₂ is NH. In one embodiment, C₂ is N(Me).

In one embodiment, C₃ is CH. In one embodiment, C₃ is C(Me). In one embodiment, C₃ is

N.

Within such embodiments,  denotes the positions to which Z is fused to the

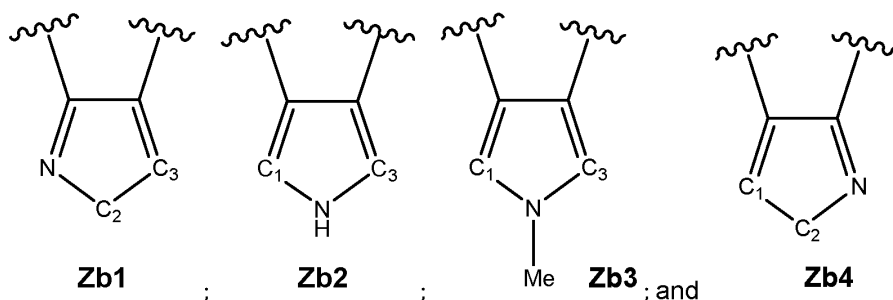


15 cyclic urea, therefore

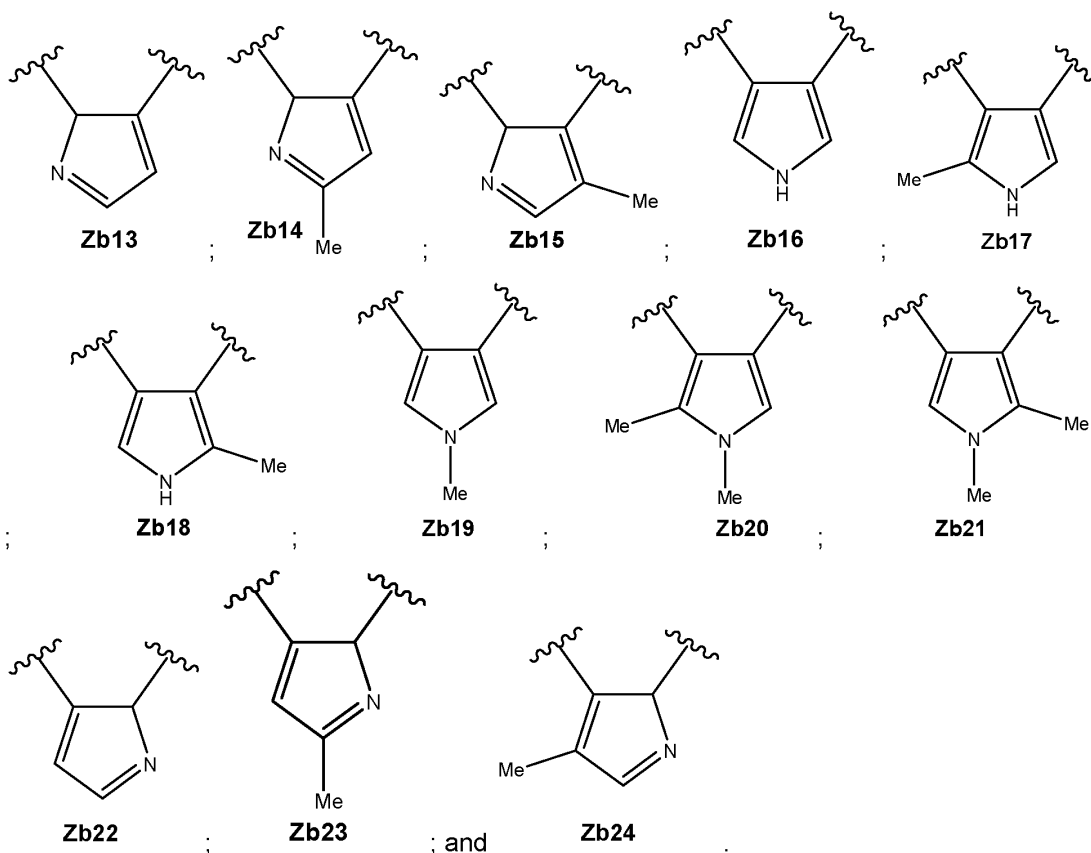
is equivalent to

In one embodiment, (Zb) is selected from the group consisting of:

21

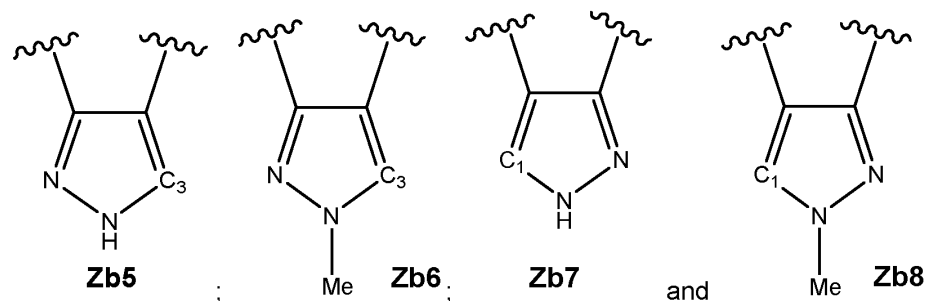


In one embodiment, (Zb) is selected from the group consisting of:

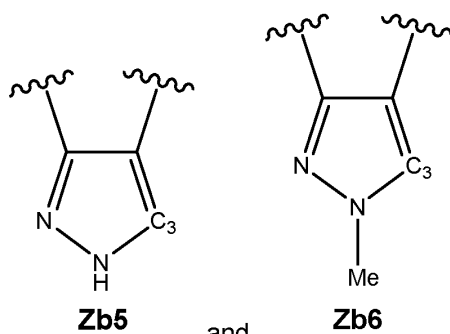


5

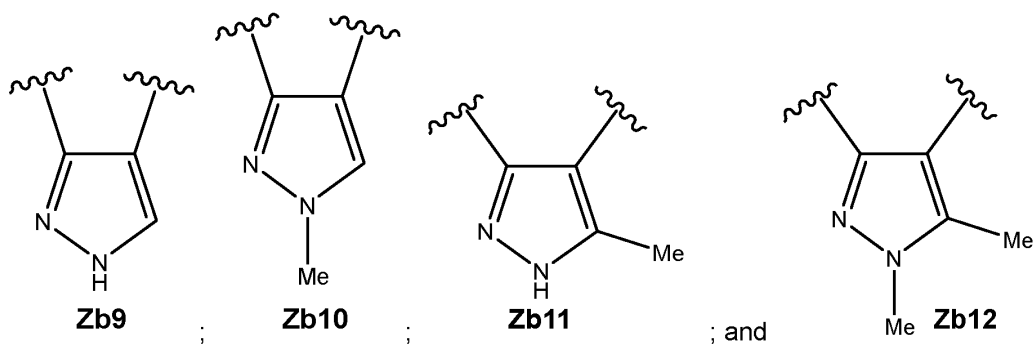
In one embodiment, (Zb) is selected from the group consisting of:



In one embodiment, (Zb) is selected from the group consisting of:

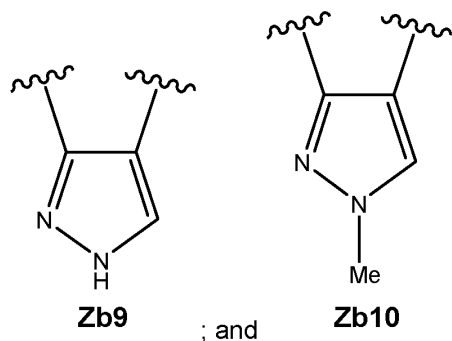


In one embodiment, (Zb) is selected from the group consisting of:

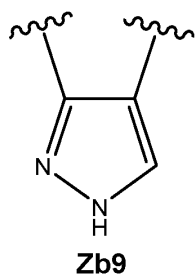


5

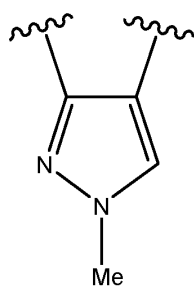
In one embodiment, (Zb) is selected from the group consisting of:



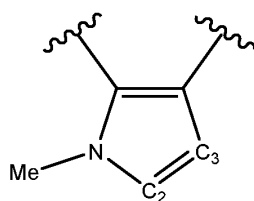
In one embodiment, (Zb) is:



In one embodiment, (Zb) is:

**Zb10**

In one embodiment, Z is group (Zc):

**Zc**

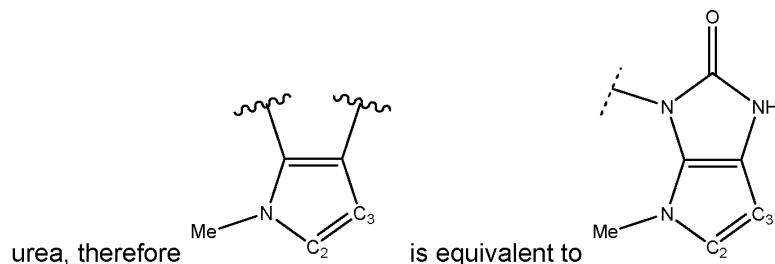
wherein:

- 5 C_2 is N, CH or C(Me) and C_3 is CH or C(Me); wherein when one of C_2 or C_3 is C(Me), the other is CH. In one embodiment C_2 is N. In a second embodiment C_2 is CH or C(Me).



Within such embodiments,

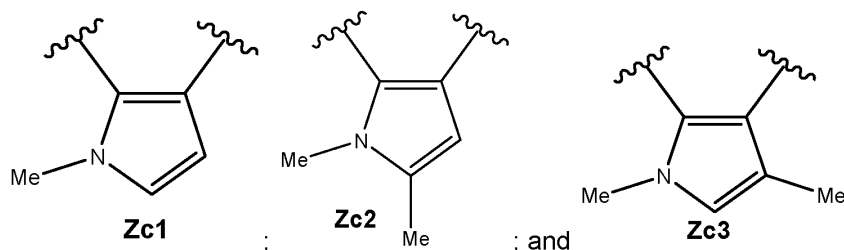
denotes the positions to which Z is fused to the cyclic



urea, therefore

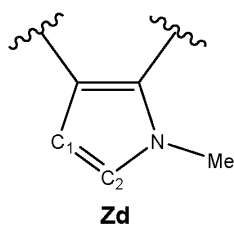
is equivalent to

- 10 In one embodiment, (Zc) is selected from the group consisting of:



In one embodiment, Z is group (Zd):

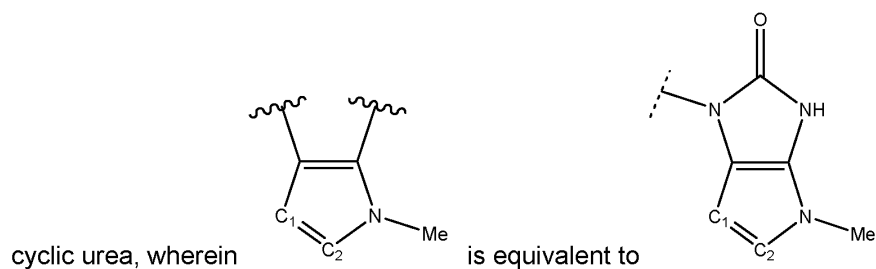
24



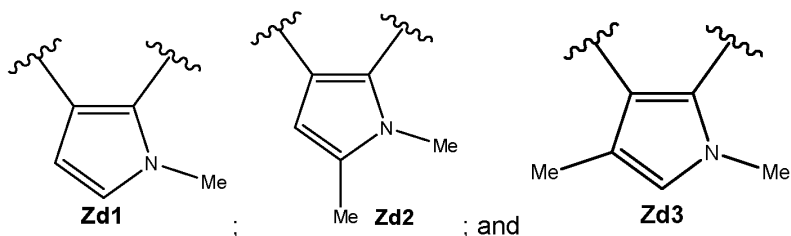
wherein:

C₁ is CH or C(Me) and C₂ is N, CH or C(Me); wherein when one of C₁ or C₂ is C(Me), the other is CH. In one embodiment C₂ is N. In a second embodiment C₂ is CH or C(Me).

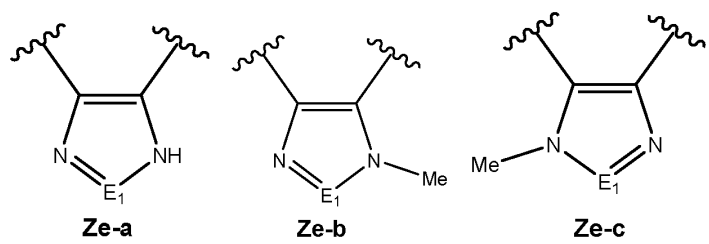
5 Within such embodiments,  denotes the positions to which Z is fused to the



In one embodiment, (Zd) is selected from the group consisting of:



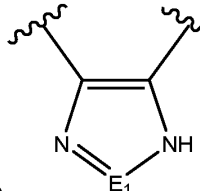
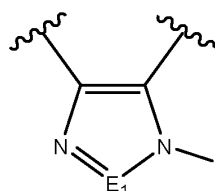
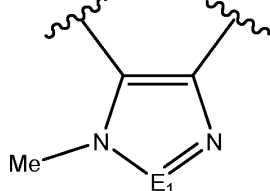
10 In one embodiment, Z is selected from the group consisting of (Ze-a), (Ze-b) and (Ze-c):

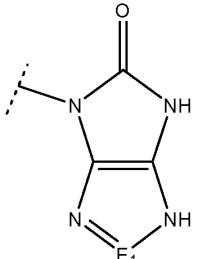
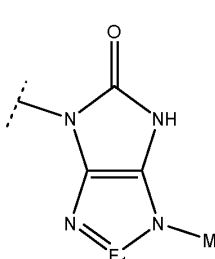
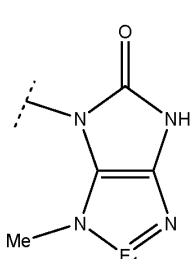


wherein:

E₁ is CH or C(Me).

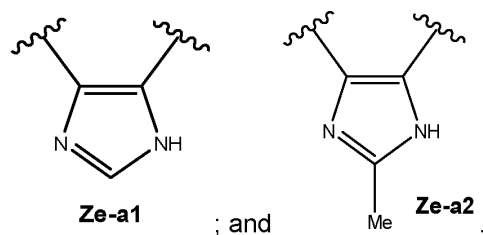
Within such embodiments,  denotes the positions to which Z is fused to the cyclic urea, therefore

, , and ;

, , and  respectively.

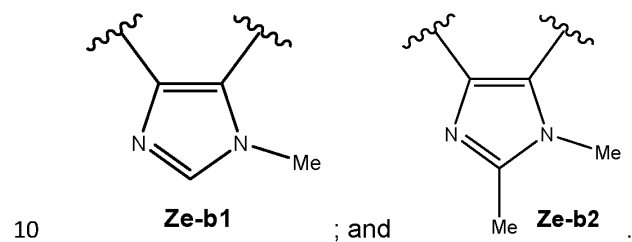
In one embodiment, Z is group (Ze-a).

5 In one embodiment, (Ze-a) is selected from the group consisting of:



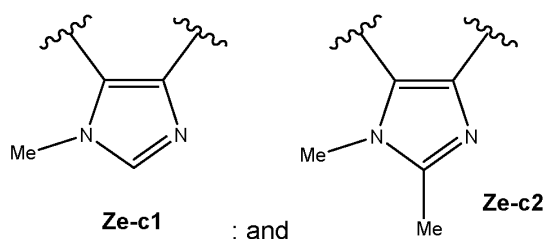
In one embodiment, Z is group (Ze-b).

In one embodiment, (Ze-b) is selected from the group consisting of:



In one embodiment, Z is group (Ze-c).

In one embodiment, (Ze-c) is selected from the group consisting of:



In one embodiment, there is provided a compound of formula (I) which is selected from the group consisting of:

- 3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;
- 7-methyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;
- 7-methyl-3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-yl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[5-[3-(trifluoromethoxy)phenoxy]pyrazin-2-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-(2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidin-5-yl)-1H,2H,3H-imidazo[4,5-b]pyridin-2-one;
- 4-[[5-(2-oxo-1H-imidazo[4,5-b]pyridin-3-yl)-2-pyridyl]oxy]-2-(trifluoromethoxy)benzonitrile;
- 7-methyl-3-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrimidin-5-yl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[2-(3-methoxyphenoxy)pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 2-methyl-6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-4H-imidazo[4,5-c]pyrazol-5-one;

- 2-methyl-6-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-4H-imidazo[4,5-c]pyrazol-5-one;
- 6-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-2-methyl-4H-imidazo[4,5-c]pyrazol-5-one;
- 5 2-methyl-6-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-4H-imidazo[4,5-c]pyrazol-5-one;
- 2-methyl-6-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrimidin-5-yl)-4H-imidazo[4,5-c]pyrazol-5-one;
- 10 3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-c]pyridin-2-one;
- 2-methyl-9-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one;
- 2-methyl-9-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-7H-purin-8-one;
- 2-methyl-9-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-7H-purin-8-one;
- 15 2-methyl-9-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one;
- 9-[6-(3-methoxyphenoxy)-3-pyridyl]-2-methyl-7H-purin-8-one;
- 9-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-7H-purin-8-one;
- 9-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-2-methyl-7H-purin-8-one;
- 20 3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]-1H-imidazo[4,5-b]pyridine-2-one;
- 3-[2-[4-methyl-3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 25 6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-2,4-dihydroimidazo[4,5-c]pyrazol-5-one;
- 3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-c]pyridin-2-one;
- 30 1-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-3H-imidazo[4,5-b]pyridin-2-one;
- 5-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-1H-imidazo[4,5-b]pyridin-2-one;
- 6-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-1H-imidazo[4,5-b]pyridin-2-one; and
- 35 3-[2-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one.

In one embodiment, there is provided a compound of formula (I) which is 2-methyl-9-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one.

In one embodiment, there is provided a compound of formula (I) which is 3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one.

5 In one embodiment, there is provided a compound of formula (I) which is 3-(2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidin-5-yl)-1H,2H,3H-imidazo[4,5-b]pyridin-2-one.

In one embodiment, there is provided a compound of formula (I) which is 3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one.

Such compounds may be provided in the form of a salt and/or solvate thereof and/or
10 derivative thereof, such as a salt and/or solvate thereof. Such compounds may also be provided in the form of a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof, such as a pharmaceutically acceptable salt and/or solvate thereof, in particular a pharmaceutically acceptable salt. Suitably, such compounds are not provided in the form of a salt.

The term "5-membered heteroaryl" as used herein refers to a 5-membered aromatic ring
15 including at least one heteroatom e.g. nitrogen. Examples of 5-membered heteroaryl include one nitrogen atom (pyrrole), two nitrogen atoms (imidazole or pyrazole) or three nitrogen atoms (triazole).

The term "6-membered heteroaryl" as used herein refers to a 6-membered aromatic ring including at least one heteroatom e.g. nitrogen. Examples of 6-membered heteroaryl include one
20 nitrogen atom (pyridine) or two nitrogen atoms (pyridazine, pyrimidine or pyrazine).

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 C₁₋₄alkyl group, whether alone or forming part of a larger group, e.g. C₁₋₄alkoxy, the alkyl group may be straight chain, branched, cyclic, or a combination
25 thereof. Examples of C₁₋₄alkyl are methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, and cyclobutyl. Reference to "propyl" includes *n*-propyl, isopropyl and cyclopropyl, and reference to "butyl" includes *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl and cyclobutyl. A particular group of exemplary C₁₋₄alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl. Examples of C₁₋₄alkoxy include methoxy, ethoxy, propoxy (which includes *n*-propoxy, isopropoxy and cyclopropoxy) and butoxy.
30

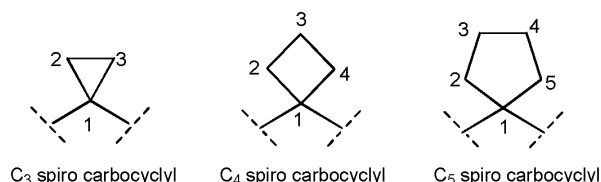
The term "C₁₋₄alkoxy" also extends to embodiments in which the oxygen atom is located within the alkyl chain, for example -CH₂CH₂OCH₃ or -CH₂OCH₃. Thus, in one embodiment the alkoxy is linked through carbon to the remainder of the molecule. In one embodiment the alkoxy is linked through oxygen to the remainder of the molecule, for example -OC₁₋₄alkyl.

35 The term 'haloC₁₋₄alkyl' 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 haloC₁₋₄ 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 'haloC₁₋₄alkoxy' 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 haloC₁₋₄ alkyl include methoxy and ethoxy groups substituted with one to three halo atoms, in particular one to three fluoro atoms.

The term 'C₃₋₅ spiro carbocyclyl' as used herein means a cyclic ring system containing 3 to 5 carbon atoms, for example, a cyclopropyl, cyclobutyl or cyclopentyl group, wherein the cyclic ring system is attached to a secondary carbon via a spirocentre such that the secondary carbon is one of the 3 to 5 carbon atoms in the cyclic ring as follows:



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 *et al.*. 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. Non-pharmaceutically acceptable salts may be used, for example, in the isolation of compounds of formula (I) and are included within the scope of this invention. For example, in one embodiment, there is provided a compound of formula (I) or salt thereof.

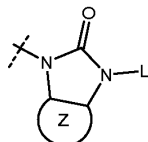
Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

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) and that these are included within the scope of the invention. As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable ester or salt of such ester of a compound of formula (I) which, upon administration to

the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof. Pharmaceutically acceptable derivatives include pharmaceutically acceptable prodrugs.

- A pharmaceutically acceptable prodrug may be formed by functionalising the secondary nitrogen of the urea, for example with a group "L" as illustrated below (wherein R₄ and R₅ are as described above):



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

- 10 $-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
- $-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- $-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
- $-\text{CH}(\text{R}^x)-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein R^x is hydrogen or C₁₋₃ alkyl,
- $-\text{CH}(\text{R}^x)-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- 15 $-\text{CH}(\text{R}^x)-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, and
- $-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2 \cdot \text{M}^+$.

- It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present
- 20 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.

- The present disclosure includes all isotopic forms of the compounds of the invention
- 25 provided herein, whether in a form (i) wherein all atoms of a given atomic number have a mass number (or mixture of mass numbers) which predominates in nature (referred to herein as the "natural isotopic form") or (ii) wherein one or more atoms are replaced by atoms having the same atomic number, but a mass number different from the mass number of atoms which predominates in nature (referred to herein as an "unnatural variant isotopic form"). It is understood that an atom
- 30 may naturally exist as a mixture of mass numbers. The term "unnatural variant isotopic form" also includes embodiments in which the proportion of an atom of given atomic number having a mass number found less commonly in nature (referred to herein as an "uncommon isotope") has been increased relative to that which is naturally occurring e.g. to the level of >20%, >50%, >75%, >90%, >95% or >99% by number of the atoms of that atomic number (the latter embodiment

referred to as an "isotopically enriched variant form"). The term "unnatural variant isotopic form" also includes embodiments in which the proportion of an uncommon isotope has been reduced relative to that which is naturally occurring. Isotopic forms may include radioactive forms (i.e. they incorporate radioisotopes) and non-radioactive forms. Radioactive forms will typically be
5 isotopically enriched variant forms.

An unnatural variant isotopic form of a compound may thus contain one or more artificial or uncommon isotopes such as deuterium (^2H or D), carbon-11 (^{11}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-15 (^{15}N), oxygen-15 (^{15}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), phosphorus-32 (^{32}P), sulphur-35 (^{35}S), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), fluorine-18 (^{18}F)
10 iodine-123 (^{123}I), iodine-125 (^{125}I) in one or more atoms or may contain an increased proportion of said isotopes as compared with the proportion that predominates in nature in one or more atoms.

Unnatural variant isotopic forms comprising radioisotopes may, for example, be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^3H , and
15 carbon-14, i.e. ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Unnatural variant isotopic forms which incorporate deuterium i.e. ^2H or D may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Further, unnatural variant isotopic forms may be prepared which
20 incorporate positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

In one embodiment, the compounds of the invention are provided in a natural isotopic form.

25 In one embodiment, the compounds of the invention are provided in an unnatural variant isotopic form. In a specific embodiment, the unnatural variant isotopic form is a form in which deuterium (i.e. ^2H or D) is incorporated where hydrogen is specified in the chemical structure in one or more atoms of a compound of the invention. In one embodiment, the atoms of the compounds of the invention are in an isotopic form which is not radioactive. In one embodiment,
30 one or more atoms of the compounds of the invention are in an isotopic form which is radioactive. Suitably radioactive isotopes are stable isotopes. Suitably the unnatural variant isotopic form is a pharmaceutically acceptable form.

In one embodiment, a compound of the invention is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In another embodiment, a compound
35 of the invention is provided whereby two or more atoms exist in an unnatural variant isotopic form.

Unnatural isotopic variant forms can generally be prepared by conventional techniques known to those skilled in the art or by processes described herein e.g. processes analogous to

those described in the accompanying Examples for preparing natural isotopic forms. Thus, unnatural isotopic variant forms could be prepared by using appropriate isotopically variant (or labelled) reagents in place of the normal reagents employed in the Examples. 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.

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.

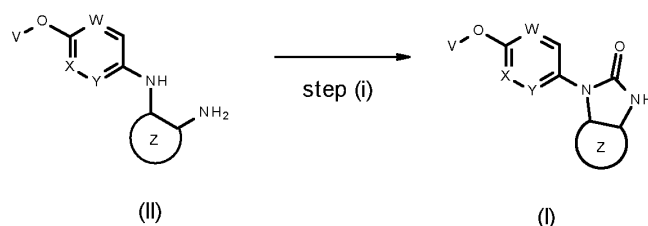
Patent applications WO2011/069951, WO2012/076877, WO2012/168710, WO2013/175215, WO2013/083994, WO2017/098254, WO2017/103604, WO2018/020263, WO2018/109484 and WO2020/079422 provide methods for the synthesis of intermediates which may be of use in the production of compounds of the present invention.

General Synthesis Schemes

The following schemes detail synthetic routes to compounds of the invention and intermediates in the synthesis of such compounds. In the following schemes reactive groups can be protected with protecting groups and deprotected according to established techniques well known to the skilled person.

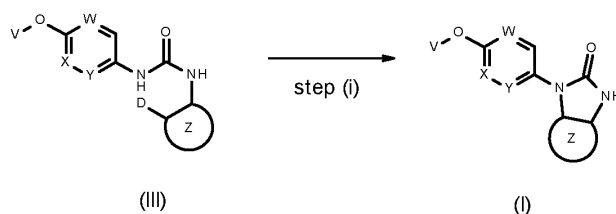
Compounds may be prepared by the general methods outlined hereinafter. In the following description, the groups V, W, X, Y and Z have the meanings as previously defined for unless otherwise stated.

Scheme 1a



Compounds of formula (I) can be prepared by cyclization of compounds of formula (II) in a suitable solvent e.g. dichloromethane with a carbonylating agent e.g. triphosgene preferentially
 5 prediluted in the same solvent and added in a second time at 0°C in presence of a suitable base e.g. triethylamine. Alternatively compounds of formula (I) can be prepared by cyclization of compounds of formula (II) using a carbonylating agent such as carbonyldiimidazole in a suitable solvent such as ethyl acetate in presence of a base such as triethylamine or DIPEA.

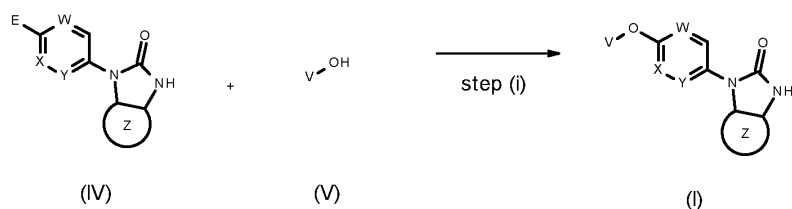
Scheme 1b



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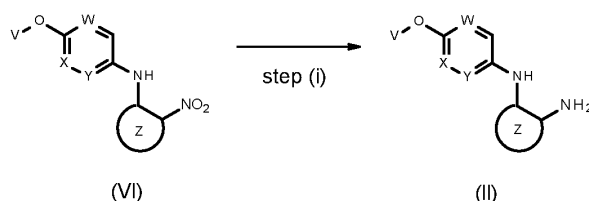
Compounds of formula (I) can be prepared by metal catalysed cross coupling reactions. In this reaction a aryl-halide derivative of formula (III) wherein typically D= Cl, Br or I is reacted in the presence of a metal catalyst such as diacetoxypalladium (palladium(II) acetate), a suitable ligand such as 5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (Xantphos) and a suitable base such as cesium carbonate in a suitable solvent e.g. in 1,4-
 15 dioxane, with conventional heating or microwave heating.

Scheme 1c



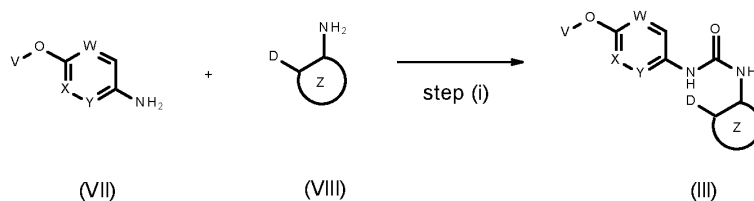
Compounds of formula (I) can be prepared by nucleophilic aromatic substitution. In this reaction an aryl-halide derivative of formula (IV) wherein typically E= F or Cl and a phenol of formula (V) are reacted in the presence of a suitable base such as potassium carbonate in a suitable solvent, e.g. in N,N-dimethylacetamide, in N,N-dimethylformamide or in dimethyl sulfoxide, with conventional heating or microwave heating.

Scheme 2



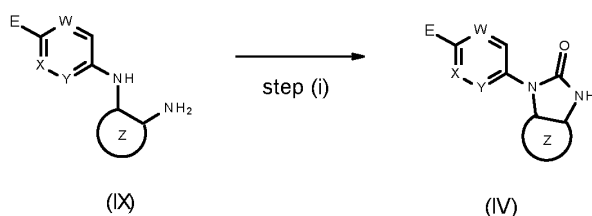
Anilines of formula (II) can be prepared by the reduction of nitro compounds of formula (VI). Suitable reactions conditions to transform (VI) into (II) are for example reduction in presence of Fe powder and ammonium chloride in a solvent such as a mixture ethanol/water for example at room temperature or with conventional heating.

Scheme 3



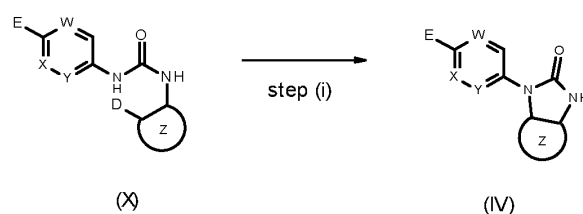
Ureas of formula (III) can be prepared by reaction of anilines of formula (VII) and anilines of formula (VIII) in a suitable solvent e.g. dichloromethane or ethyl acetate with a carbonylating agent e.g. triphosgene preferentially prediluted in the same solvent in presence of a suitable base e.g. triethylamine or diisopropylethylamine at temperature ranging from 0°C to room temperature.

Scheme 4a



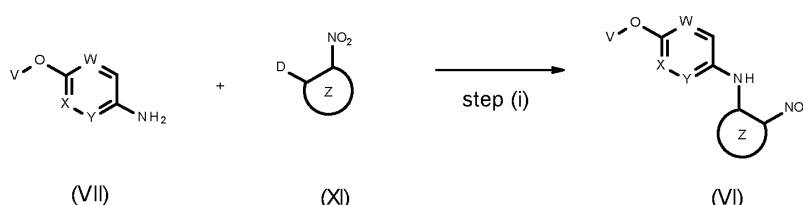
- Compounds of formula (IV) can be prepared by cyclization of compounds of formula (IX) in a suitable solvent *e.g.* dichloromethane with a carbonylating agent *e.g.* triphosgene preferentially prediluted in the same solvent and added in a second time at 0°C in presence of a suitable base *e.g.* triethylamine. Alternatively compounds of formula (I) can be prepared by
- 5 cyclization of compounds of formula (II) using a carbonylating agent such as carbonyldiimidazole in a suitable solvent such as ethyl acetate in presence of a base such as triethylamine or DIPEA.

Scheme 4b



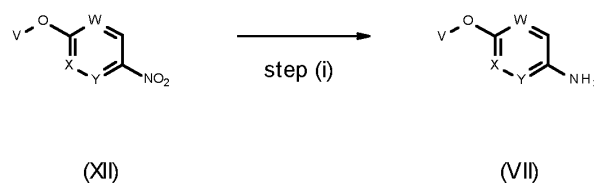
- Compounds of formula (IV) can be prepared by metal catalysed cross coupling reactions.
- 10 In this reaction a aryl-halide derivative of formula (X) wherein typically D= Cl, Br or I is reacted in the presence of a metal catalyst such as diacetoxypalladium (palladium(II) acetate), a suitable ligand such as 5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (Xantphos) and a suitable base such as cesium carbonate in a suitable solvent *e.g.* in 1,4-dioxane, with conventional heating or microwave heating.

15 Scheme 5



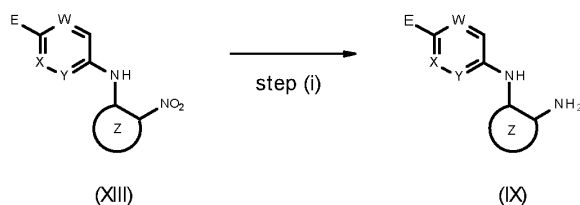
- Compounds of formula (VI) can be prepared by metal catalysed cross coupling reactions.
- In this reaction an aniline of formula (VII) and an aryl-halide derivative of formula (XI) wherein typically D= Cl, Br or I are reacted in the presence of a metal catalyst such as diacetoxypalladium (palladium(II) acetate), a suitable ligand such as 5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (Xantphos) and a suitable base such as cesium carbonate in a suitable solvent *e.g.* in 1,4-dioxane, with conventional heating or microwave heating.
- 20

Scheme 6



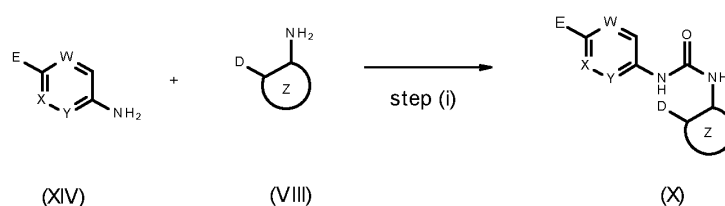
Anilines of formula (VII) can be prepared by the reduction of nitro compounds of formula (XII). Suitable reaction conditions to transform (XII) into (VII) are for example reduction in presence of Fe powder and ammonium chloride in a solvent such as a mixture ethanol/water for example at room temperature or with conventional heating.

Scheme 7



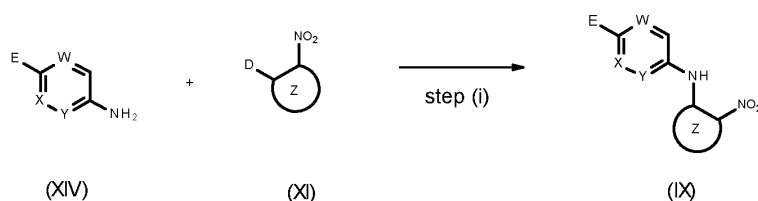
Anilines of formula (IX) can be prepared by the reduction of nitro compounds of formula (XIII). Suitable reaction conditions to transform (XIII) into (IX) are for example reduction in presence of Fe powder and ammonium chloride in a solvent such as a mixture ethanol/water for example at room temperature or with conventional heating.

Scheme 8



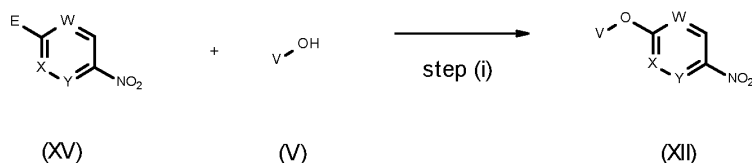
Ureas of formula (X) can be prepared by reaction of anilines of formula (XIV) and anilines of formula (VIII) in a suitable solvent e.g. dichloromethane or ethyl acetate with a carbonylating agent e.g. triphosgene preferentially prediluted in the same solvent in presence of a suitable base e.g. triethylamine or diisopropylethylamine at temperature ranging from 0°C to room temperature.

Scheme 9



Compounds of formula (IX) can be prepared by metal catalysed cross coupling reactions. In this reaction an aniline of formula (XIV) and an aryl-halide derivative of formula (XI) wherein typically D= Cl, Br or I are reacted in the presence of a metal catalyst such as diacetoxypalladium (palladium(II) acetate), a suitable ligand such as 5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (Xantphos) and a suitable base such as cesium carbonate in a suitable solvent e.g. in 1,4-dioxane, with conventional heating or microwave heating.

Scheme 10

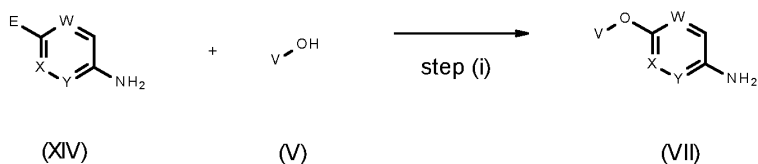


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Compounds of formula (XII) can be prepared by nucleophilic aromatic substitution. In this reaction a aryl-halide derivative of formula (XV) wherein typically E= F or Cl and a phenol of formula (V) are reacted in the presence of a suitable base such as potassium carbonate in a suitable solvent, e.g. in N,N-dimethylacetamide, in N,N-dimethylformamide or in dimethyl sulfoxide, with conventional heating or microwave heating.

15

Scheme 11



Compounds of formula (VII) can be prepared by metal catalysed cross coupling reactions. In this reaction an aniline of formula (XIV) wherein typically E= Br or I and a phenol derivative of formula (V) are reacted in the presence of a metal catalyst such as copper(I) iodide, a suitable

20

ligand such as pyridine-2-carboxylic acid and a suitable base such as cesium carbonate in a suitable solvent *e.g.* in *N,N*-dimethylacetamide, with conventional heating or microwave heating.

Alternatively, compounds of formula (VII) can be prepared by nucleophilic aromatic substitution. In this reaction an aryl-halide derivative of formula (XIV) wherein typically E= F or Cl and a phenol of formula (V) are reacted in the presence of a suitable base such as cesium carbonate in a suitable solvent, *e.g.* in dimethyl sulfoxide, with conventional heating or microwave heating.

Processes of the invention

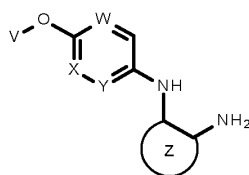
According to further aspects of the present invention are provided processes for the preparation of compounds of formula (I) or a salt, such as a pharmaceutically acceptable salt, and/or solvate thereof and/or derivative thereof, as well as processes for preparing intermediates or salts thereof in the synthesis of compounds of formula (I).

The processes of the invention are described above and include any individual step of a multi-step scheme.

Intermediates

The present invention also relates to novel intermediates in the synthesis of compounds of formula (I). Such novel intermediates include compounds of formulae (II), (II), (IV), (VI), (IX), (X) and (XIII). Thus, in one embodiment, there is provided a compound selected from the group consisting of:

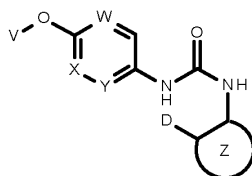
- a compound of formula (II):



(II)

wherein V, W, X, Y and Z are as defined for the compound of formula (I);

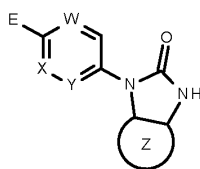
- a compound of formula (III):



(III)

wherein V, W, X, Y and Z are as defined for the compound of formula (I) and D is halo, such as Cl, Br or I;

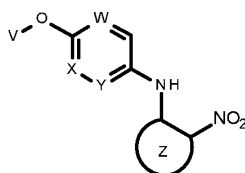
- a compound of formula (IV):



(IV)

- 5 wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl;

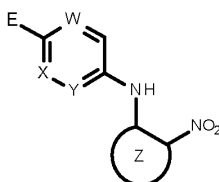
- a compound of formula (VI):



(VI)

wherein V, W, X, Y and Z are as defined for the compound of formula (I);

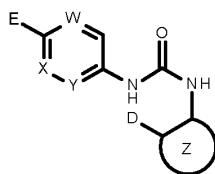
- 10 - a compound of formula (IX):



(IX)

wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl;

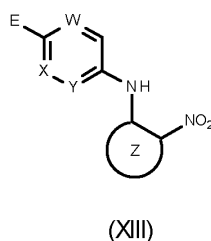
- a compound of formula (X):



(X)

wherein W, X, Y and Z are as defined for the compound of formula (I), E is halo, such as F or Cl and D is halo, such as Cl, Br or I; and

- a compound of formula (XIII):



- 5 wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl;

Salts, such as pharmaceutically acceptable salts, of such intermediates are also provided by the present invention.

10 Kv3.1, Kv3.2, Kv3.3 and/or Kv3.4 modulation

Compounds of formula (I) of the present invention are modulators of Kv3.1. Compounds of formula (I) may also be modulators of Kv3.2, Kv3.3 and/or Kv3.4. Compounds of the invention may be tested in the assay of Biological Example 1 to determine their modulatory properties for Kv3.1 and/or Kv3.2 and/or Kv3.3 and/or Kv3.4 channels.

- 15 A 'modulator' as used herein refers to a compound which is capable of producing at least 10% potentiation, and suitably at least 20% potentiation of whole-cell currents mediated by human Kv3.1 and/or human Kv3.2 and/or human Kv3.3 and/or human Kv3.4 channels recombinantly expressed in mammalian cells.

- 20 The term 'Kv3.1, Kv3.2, Kv3.3 and/or Kv3.4' shall be taken to mean the same as 'Kv3.1 and/or Kv3.2 and/or Kv3.3 and/or Kv3.4' and may also be referred to as 'Kv3.1/Kv3.2/Kv3.3/Kv3.4'.

- 25 In one embodiment the modulator is capable of producing at least 10% potentiation and suitably at least 20% potentiation of whole-cell currents mediated by human Kv3.1 channels recombinantly expressed in mammalian cells. Suitably the pEC₅₀ of the modulator is in the range of 4-8 (such as 5-7.5).

In one embodiment the modulator is capable of producing at least 10% potentiation and suitably at least 20% potentiation of whole-cell currents mediated by human Kv3.2 channels recombinantly expressed in mammalian cells. Suitably the pEC₅₀ of the modulator is in the range of 4-8 (such as 5-7.5).

- 30 In one embodiment the modulator is capable of producing at least 10% potentiation and suitably at least 20% potentiation of whole-cell currents mediated by human Kv3.3 channels

recombinantly expressed in mammalian cells. Suitably the pEC₅₀ of the modulator is in the range of 4-8 (such as 5-7.5).

In one embodiment the modulator is capable of producing at least 10% potentiation and suitably at least 20% potentiation of whole-cell currents mediated by human Kv3.4 channels recombinedly expressed in mammalian cells. Suitably the pEC₅₀ of the modulator is in the range of 4-8 (such as 5-7.5).

In another embodiment the modulator is capable of producing at least 10% potentiation and suitably at least 20% potentiation of whole-cell currents mediated by human Kv3.1 and Kv3.2 channels recombinedly expressed in mammalian cells.

In another embodiment the modulator is capable of producing at least 10% potentiation and suitably at least 20% potentiation of whole-cell currents mediated by human Kv3.1 and Kv3.3 channels recombinedly expressed in mammalian cells.

In another embodiment the modulator is capable of producing at least 10% potentiation and suitably at least 20% potentiation of whole-cell currents mediated by human Kv3.2 and Kv3.3 channels recombinedly expressed in mammalian cells.

In a further embodiment the modulator is capable of producing at least 10% potentiation and suitably at least 20% potentiation of whole-cell currents mediated by human Kv3.1, Kv3.2 and Kv3.3 channels recombinedly expressed in mammalian cells.

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives may be of use for the treatment or prophylaxis of a disease or disorder where a modulator of the Kv3.1 or Kv3.2 or Kv3.1 and Kv3.2 channels is required. As used herein, a modulator of Kv3.1 or Kv3.2 or Kv3.1 and Kv3.2 is a compound which alters the properties of these channels, either positively or negatively. In a particular aspect of the invention, the compound of formula (I) is a positive modulator. Compounds of the invention may be tested in the assay of Biological Example 1 to determine their modulatory properties.

In one embodiment of the invention the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives thereof are selective for modulation of Kv3.1 channels over modulation of Kv3.2 channels. By selective, is meant that compounds demonstrate, for example, at least a 2 fold, 5 fold or 10 fold activity for Kv3.1 channels than for Kv3.2 channels. The activity of a compound is suitably quantified by its potency as indicated by an EC₅₀ value.

In another embodiment of the invention, the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives thereof are selective for modulation of Kv3.2 channels over modulation of Kv3.1 channels. Once again, by selective is meant that compounds demonstrate, for example at least a 2 fold, 5 fold or 10 fold activity for Kv3.2 channels than for Kv3.1 channels.

In a particular embodiment of the invention the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives thereof demonstrate comparable activity between modulation of Kv3.1 and Kv3.2 channels, for example the activity for one 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 certain disorders it may be of benefit to utilise a modulator of Kv3.3 or Kv3.1, or Kv3.3 and 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.

In another embodiment of the invention, the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives thereof are selective for modulation of Kv3.1 channels over modulation of Kv3.3 channels. Once again, by selective is meant that compounds demonstrate, for example at least a 2 fold, 5 fold or 10 fold activity for Kv3.1 channels than for Kv3.3 channels.

In a particular embodiment of the invention, 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 certain disorders it may be of benefit to utilise a modulator of Kv3.3 or Kv3.2, or Kv3.3 and Kv3.2 which demonstrates a particular selectivity profile between the two channels. 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 another embodiment of the invention, the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives thereof are selective for modulation of Kv3.2 channels over modulation of Kv3.3 channels. Once again, by selective is meant that compounds demonstrate, for example at least a 2 fold, 5 fold or 10 fold activity for Kv3.2 channels than for Kv3.3 channels.

In another particular embodiment 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 a yet further particular embodiment of the invention 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 EC50 value.

Therapeutic methods

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof, for use in the treatment or prophylaxis of a disease or disorder where a modulator of Kv3.1, Kv3.2, Kv3.3 and/or Kv3.4 is required, for example those diseases and disorders mentioned herein below.

The invention provides a method of treating or preventing a disease or disorder where a modulator of Kv3.1, Kv3.2, Kv3.3 and/or Kv3.4 is required, for example those diseases and disorders mentioned herein below, which comprises administering to a subject a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof (e.g. salt) and/or derivative, in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder where a modulator of Kv3.1, Kv3.2, Kv3.3 and/or Kv3.4 is required, for example those diseases and disorders mentioned herein below.

In one embodiment is provided a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate thereof and/or derivative thereof for use as a medicament.

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.

A subject will typically be a subject in need of treatment or prophylaxis according to the invention. Suitably the subject is a human.

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

In one embodiment of the invention, the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives may be of use for the treatment or prophylaxis of a disease or disorder selected from the group consisting of hearing disorders, schizophrenia, depression and mood disorders, bipolar disorder, substance abuse disorders, anxiety disorders, sleep disorders, hyperacusis and disturbances of loudness perception, Ménière's disease, disorders of balance, and disorders of the inner ear, impulse control disorder, personality disorders, attention-deficit/hyperactivity disorder, autism spectrum disorders, eating disorders,

cognition impairment, ataxia, pain such as neuropathic pain, inflammatory pain and miscellaneous pain, Lewy body dementia and Parkinson's disease.

In one embodiment of the invention, the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives may be of use for the treatment or prophylaxis of a disease or disorder selected from the group consisting of hearing disorders including hearing loss and tinnitus, schizophrenia, substance abuse disorders, pain such as neuropathic pain, inflammatory pain and miscellaneous pain, Lewy body dementia and Parkinson's disease.

In one embodiment of the invention, the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives may be of use for the treatment or prophylaxis of a disease or disorder selected from the group consisting of Fragile-X, Rett's Disorder and Alzheimer's disease.

The invention provides a method for the prophylaxis or treatment of a disease or disorder selected from the group consisting of hearing disorders, schizophrenia, depression and mood disorders, bipolar disorder, substance abuse disorders, anxiety disorders, sleep disorders, hyperacusis and disturbances of loudness perception, Ménière's disease, disorders of balance, and disorders of the inner ear, impulse control disorder, personality disorders, attention-deficit/hyperactivity disorder, autism spectrum disorders, eating disorders, cognition impairment, ataxia, pain such as neuropathic pain, inflammatory pain and miscellaneous pain, Lewy body dementia and Parkinson's disease, which comprises administering to a subject a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof (e.g. salt) and/or derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder selected from the group consisting of hearing disorders, schizophrenia, depression and mood disorders, bipolar disorder, substance abuse disorders, anxiety disorders, sleep disorders, hyperacusis and disturbances of loudness perception, Ménière's disease, disorders of balance, and disorders of the inner ear, impulse control disorder, personality disorders, attention-deficit/hyperactivity disorder, autism spectrum disorders, eating disorders, cognition impairment, ataxia, pain such as neuropathic pain, inflammatory pain and miscellaneous pain, Lewy body dementia and Parkinson's disease.

In a particular embodiment of the invention, there is provided a compound of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof for use in the treatment or prophylaxis of hearing disorders. Hearing disorders include auditory neuropathy, auditory processing disorder, hearing loss, which includes sudden hearing loss, noise induced hearing loss, substance-induced hearing loss, and hearing loss in adults over 60, over 65, over 70 or over 75 years of age (presbycusis), and tinnitus.

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of Ménière's disease, disorders of balance, and disorders of the inner ear.

In a particular embodiment of the invention, there is provided a compound of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof for use in the treatment or prophylaxis of schizophrenia. Schizophrenia includes the subtypes Paranoid Type (295.30), Disorganised Type (295.10), Catatonic Type (295.20), Undifferentiated Type (295.90) and Residual Type (295.60); Schizophreniform Disorder (295.40); Schizoaffective Disorder (295.70) including the subtypes Bipolar Type and Depressive Type; Delusional Disorder (297.1) including the subtypes Erotomanic Type, Grandiose Type, Jealous Type, Persecutory Type, Somatic Type, Mixed Type and Unspecified Type; Brief Psychotic Disorder (298.8); Shared Psychotic Disorder (297.3); Psychotic Disorder Due to a General Medical Condition including the subtypes With Delusions and With Hallucinations; Substance-Induced Psychotic Disorder including the subtypes With Delusions (293.81) and With Hallucinations (293.82); and Psychotic Disorder Not Otherwise Specified (298.9).

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

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of Epilepsy, (including, but not limited to, localization-related epilepsies, generalized epilepsies, epilepsies with both generalized and local seizures, and the like), seizures associated with Lennox-Gastaut syndrome, seizures as a complication of a disease or condition (such as seizures associated with encephalopathy, phenylketonuria, juvenile Gaucher's disease, Lundborg's progressive myoclonic epilepsy, stroke, head trauma, stress, hormonal changes, drug use or withdrawal, alcohol use or withdrawal, sleep deprivation, fever, infection, and the like), essential tremor, restless limb syndrome, partial and generalised seizures (including tonic, clonic, tonic-clonic, atonic, myoclonic, absence seizures), secondarily generalized seizures, temporal lobe epilepsy, absence epilepsies

(including childhood, juvenile, myoclonic, photo- and pattern-induced), severe epileptic encephalopathies (including hypoxia-related and Rasmussen's syndrome), febrile convulsions, epilepsy partialis continua, progressive myoclonus epilepsies (including Unverricht-Lundborg disease and Lafora's disease), post-traumatic seizures/epilepsy including those related to head injury, simple reflex epilepsies (including photosensitive, somatosensory and proprioceptive, audiogenic and vestibular), metabolic disorders commonly associated with epilepsy such as pyridoxine-dependent epilepsy, Menkes' kinky hair disease, Krabbe's disease, epilepsy due to alcohol and drug abuse (e.g. cocaine), cortical malformations associated with epilepsy (e.g. double cortex syndrome or subcortical band heterotopia), chromosomal anomalies associated with seizures or epilepsy such as Partial monosomy (15Q) / Angelman syndrome).

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnesic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnesic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication

- Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30),
5 Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant
10 Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse
15 (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication
20 (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication
25 (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnesic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder
30 Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide.
- 35 The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of anxiety disorders including Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia

(300.01) and Panic Disorder with Agoraphobia (300.21); Agoraphobia; Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29, formerly Simple Phobia) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (Social Anxiety Disorder, 300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder, Separation Anxiety Disorder (309.21), Adjustment Disorders with Anxiety (309.24) and Anxiety Disorder Not Otherwise Specified (300.00).

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

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of hyperacusis and disturbances of loudness perception, including Fragile-X syndrome and autism.

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of Impulse control disorder including: Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), Impulse-Control Disorders Not Otherwise Specified (312.3), Binge Eating, Compulsive Buying, Compulsive Sexual Behaviour and Compulsive Hoarding.

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of Sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such

as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9); gender identity disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9).

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

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of Attention-Deficit/Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit /Hyperactivity Disorder Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23).

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of Autism Spectrum Disorders including Autistic Disorder (299.00), Asperger's Disorder (299.80), Rett's Disorder (299.80), Childhood Disintegrative Disorder (299.10) and Pervasive Disorder Not Otherwise Specified (299.80, including Atypical Autism).

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

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

10 The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of ataxia including ataxia, in particular spinocerebellar ataxia, especially ataxia associated with R420H, R423H or F448L mutations.

15 The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of pain including nociceptive, neuropathic, inflammatory or miscellaneous pain.

Nociceptive pain represents the normal response to noxious insult or injury of tissues such as skin, muscles, visceral organs, joints, tendons, or bones. Examples of nociceptive pain which form part of the invention include somatic pain: musculoskeletal (joint pain, myofascial pain) or cutaneous, which is often well localized; or visceral pain: hollow organs or smooth muscle.

20 Neuropathic pain is pain initiated or caused by a primary lesion or disease in the somatosensory nervous system. Sensory abnormalities range from deficits perceived as paraesthesia (numbness) to hypersensitivity (hyperalgesia or allodynia), and dysaesthesia (tingling and other sensations). Examples of neuropathic pain which form part of the invention include, but are not limited to, diabetic neuropathy, post-herpetic neuralgia, spinal cord injury pain, phantom limb (post-amputation) pain, and post-stroke central pain. Other causes of neuropathic pain include trauma, chemotherapy and heavy metal exposure.

30 Inflammatory pain occurs as a result of activation and sensitization of the nociceptive pain pathway by a variety of mediators released at a site of tissue inflammation. Mediators that have been implicated as key players in inflammatory pain are pro-inflammatory cytokines such IL-1-alpha, IL-1-beta, IL-6 and TNF-alpha, chemokines, reactive oxygen species, vasoactive amines, lipids, ATP, acid, and other factors released by infiltrating leukocytes, vascular endothelial cells, or tissue resident mast cells. Examples causes of inflammatory pain which form part of the invention include appendicitis, rheumatoid arthritis, inflammatory bowel disease, and herpes zoster.

35 Miscellaneous pain refers to pain conditions or disorders which are not easily classifiable. The current understanding of their underlying mechanisms is still rudimentary though specific

therapies for those disorders are well known; they include cancer pain, migraine and other primary headaches and wide-spread pain of the fibromyalgia type.

Suitably, specific pain indications that may be mediated by a modulator of Kv3.1 and/or Kv3.2 and/or Kv3.3 and/or Kv3.4 channels are neuropathic pain and/or inflammatory pain.

5 Pain is a subjective condition and in a clinical setting tends to be measured by a patient's self-assessment. Therefore it can be difficult to measure and quantify pain threshold. For chronic pain, typically a subjective 11-point rating scale is used where 0 is no pain and 10 is the worst pain imaginable. Subjects generally record their worst pain over a given period, usually a day. A minimum mean baseline score is also recorded and response to the medication is measured
10 relative to the baseline, for example, a reduction of at least 10%, 20%, 30%, 40% or 50% in pain from the baseline score may be observed.

Since individual responses to medicaments may vary, not all individuals may experience a reduction in pain from the baseline score. Consequently, suitably a reduction is observed in at least at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or all individuals tested.

15 Therefore, in one embodiment of the invention, a reduction of at least 10%, 20%, 30%, 40% or 50% in pain from the baseline score is observed upon administration of a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof to a subject.

Administration can occur before an anticipated onset of pain or after the onset of pain. In cases where it is anticipated that development of a disease or disorder may lead to an increase
20 in pain experienced by the subject, a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof can be administered. In cases where a subject is already experiencing pain a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may be administered to a subject.

Treatment of the subject may continue for as long as treatment is required, for example,
25 1 day, 1 week, 2 weeks, 3 weeks, 1 month, 6 months, 1 year, more than 1 year more than 2 years, more than 5 years or more than 10 years. Therefore in one embodiment of the invention a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof, is administered to a subject for 1 day to 1 month, 1 week to 3 months, 1 month to 6 months, 3 months to 1 year or more than 1 year.

30 Reduction in pain in a subject can be measured by assessing the response to an external stimuli such as mechanical or thermal (e.g. cold) stimuli (such as described in the Experimental section). The reduction can either be considered as a percentage reversal (calculated by measuring the pre- and post-dose thresholds of the affected pain site with a non-affected pain site, such as described in more detail under Data Analysis in the Experimental Section) or by
35 measuring withdrawal thresholds of the affected pain site. Preferably, the percentage reversal calculation is used.

Therefore, in one embodiment of the invention, the sensitivity to pain (such as neuropathic pain or inflammatory pain) is reversed by more than 20%, more than 30%, more than 40%, more than 50%, more than 60%, more than 70%, more than 80% or more than 90%, upon administration of a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof. Suitably, the sensitivity to pain is reversed by more than 80% or more than 90%.

Subjects may experience secondary benefits, such as one or more of improved function, mood, sleep, quality of life, reduced time off work.

In a particular embodiment, the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of neuropathic pain.

In a particular embodiment, the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of inflammatory pain.

In a particular embodiment, the compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates (e.g. salts) and/or derivatives thereof may be of use for the treatment or prophylaxis of miscellaneous pain.

In some embodiments the pain is chronic pain.

In one embodiment is provided a compound of formula (I) for use in the prophylaxis of acute noise-induced hearing loss.

In one embodiment is provided a method for the prophylaxis of acute noise-induced hearing loss, comprising administering to a subject a compound of formula (I).

In one embodiment is provided the use of a compound of formula (I) in the manufacture of a medicament for the prophylaxis of acute noise-induced hearing loss.

Acute noise-induced hearing loss may be caused by events such as exposure to loud noise or a blast. In these cases, where it is anticipated that a future event may result in acute noise-induced hearing loss, the compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may be administered before the event in order to prevent or reduce acute noise-induced hearing loss. The administration of compound (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may prevent any acute noise-induced hearing loss, or may reduce the severity of the acute noise-induced hearing loss or may mitigate other symptoms arising from acute noise-induced hearing loss, such as tinnitus.

“Acute hearing loss” is defined as hearing loss which occurs rapidly over a period of hours or days. For example, hearing loss may occur over a period of minutes, hours or days (for example over a period of up to 1 day, such as up to 2 days, 3 days, 4 days, 5 days, 6 days or 7 days). Acute hearing loss will typically be caused by exposure to loud sound or blast. Hearing loss caused by exposure to loud sound or blast is referred to herein as “noise-induced induced hearing

loss". "Acute noise induced hearing loss" is therefore hearing loss which occurs rapidly over a period of hours or days caused by exposure to loud sound or blast.

Important symptoms of acute hearing loss include:

1. a shift in the auditory threshold, i.e. an increase in the minimum sound level of a pure tone
5 that can be heard with no other sound present;
2. tinnitus; and
3. degradation in central auditory processing, for example impaired auditory temporal processing and/or speech understanding.

A "loud" noise or blast may be at least 90dB, for example, at least 100dB, at least 110dB,
10 at least 120 dB or at least 130 dB.

In one embodiment, administration of the compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof is initiated before an event which is anticipated to cause noise-induced acute hearing loss. For example, administration of the compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may be initiated
15 up to 2 weeks in advance, such as up to 1 week, 6 days, 5 days, 4 days, 3 days, 2 days, 24 h, 12 h, 6 h, 5 h, 4 h, 3 h, 2 h, 1 h, 30 minutes or up to 15 minutes in advance of an event which is anticipated to cause noise-induced acute hearing loss. The compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may be administered on multiple occasions before event which is anticipated to cause noise-induced acute hearing loss.

20 In one embodiment, a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof is administered in advance of potential exposure to a noise or blast which is anticipated to cause acute noise-induced hearing loss, for preventing or reducing the development of permanent tinnitus; for preventing or reducing the development of a permanent shift in auditory thresholds; or for preventing or reducing the development of
25 permanently degraded central auditory processing, including for example auditory temporal processing and/or speech understanding.

It will be appreciated that administration in advance may be in circumstances where the subject is considered to be at risk of exposure to a noise or blast which is anticipated to cause acute noise-induced hearing loss and is not limited to those circumstances where such exposure
30 ultimately occurs.

In one embodiment, administration of the compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof is initiated during an event which is anticipated to cause noise-induced acute hearing loss. The compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may be administered on multiple occasions
35 during an event which is anticipated to cause noise-induced acute hearing loss.

In one embodiment, a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof is initially administered during a noise or blast which is

anticipated to cause acute noise-induced hearing loss, for preventing or reducing the development of permanent tinnitus; for preventing or reducing the development of a permanent shift in the auditory threshold; or for preventing or reducing the development of permanently degraded central auditory processing, including for example auditory temporal processing and/or speech understanding.

In one embodiment, administration of the compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof is initiated after an event which is anticipated to cause acute noise-induced hearing loss.

Thus, in one embodiment, a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof is initially administered after a noise or blast which is anticipated to cause acute noise-induced hearing loss, for preventing or reducing the development of permanent tinnitus; for preventing or reducing the development of a permanent shift in the auditory threshold; or for preventing or reducing the development of permanently degraded central auditory processing, including for example auditory temporal processing and/or speech understanding.

When the compound of formula (I) is administered after an event which is anticipated to cause acute noise-induced hearing loss, such administration is normally undertaken during the "acute phase" i.e. before the hearing loss has become established.

In one embodiment, administration of the compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may be initiated up to 2 months after an event which is anticipated to cause noise-induced acute hearing loss, such as up to 1 month, 2 weeks, 1 week, 6 days, 5 days, 4 days, 3 days, 2 days, 24 h, 12 h, 6 h, 5 h, 4 h, 3 h, 2 h, 1 h, 30 minutes or up to 15 minutes after an event which is anticipated to cause acute noise-induced hearing loss. The compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may be administered on multiple occasions after an event which is anticipated to cause noise-induced acute hearing loss.

The compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may be administered over a period of up to 7 days (for example, up to 1 day, up to 2 days, up to 3 days, up to 4 days, up to 5 days, up to 6 days or up to 7 days), for 1-2 weeks (for example, 7-8 days, 7-9 days, 7-10 days, 7-11 days, 7-12 days, 7-13 days or 7-14 days), for 2-4 weeks (for example, 2-3 weeks or 2-4 weeks) or for 1-2 months (for example, 4-6 weeks or 4-8 weeks).

The compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may initially be administered up to 1 day in advance, such as up to 2 days in advance, up to 3 days in advance, up to 5 days in advance, up to 1 week in advance, up to 2 weeks in advance or up to 1 month in advance of a noise or blast which is anticipated to cause acute noise-induced hearing loss, administration which is initiated at any point in advance

exposure to a noise or blast which is anticipated to cause acute noise-induced hearing loss will typically continue for up to 2 months after exposure to the noise or blast which is anticipated to cause acute noise-induced hearing loss, such as for up to 1 month after, up to 3 weeks after, up to two weeks after, up to 1 week after, up to 5 days after, up to 3 days after, up to 2 days after, or
5 up to 1 day after.

In one embodiment is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof for use in preventing or reducing the development of a permanent shift in the auditory threshold, wherein the permanent shift in auditory threshold is reduced by at least 10dB, such as at least 15dB, at least 20dB, at least 30dB,
10 at least 40dB, or completely.

Pharmaceutical compositions

For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition
15 comprising a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof, and a pharmaceutically acceptable carrier or excipient.

In one embodiment, there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof, for use in the treatment or prevention of a disease or disorder selected from
20 the group consisting of hearing disorders, schizophrenia, depression and mood disorders, bipolar disorder, substance abuse disorders, anxiety disorders, sleep disorders, hyperacusis and disturbances of loudness perception, Ménière's disease, disorders of balance, and disorders of the inner ear, impulse control disorder, personality disorders, attention-deficit/hyperactivity disorder, autism spectrum disorders, eating disorders, cognition impairment, ataxia, pain such as
25 neuropathic pain, inflammatory pain and miscellaneous pain, Lewy body dementia and Parkinson's disease.

In a further embodiment, there is provided a method for the prophylaxis or treatment of a disease or disorder selected from the group consisting of hearing disorders, schizophrenia, depression and mood disorders, bipolar disorder, substance abuse disorders, anxiety disorders,
30 sleep disorders, hyperacusis and disturbances of loudness perception, Ménière's disease, disorders of balance, and disorders of the inner ear, impulse control disorder, personality disorders, attention-deficit/hyperactivity disorder, autism spectrum disorders, eating disorders, cognition impairment, ataxia, pain such as neuropathic pain, inflammatory pain and miscellaneous pain, Lewy body dementia and Parkinson's disease, which comprises
35 administering to a subject a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof.

The invention also provides the use of a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate thereof (e.g. salt) and/or derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder selected from the group consisting of hearing disorders, schizophrenia, depression and mood disorders, bipolar disorder, substance abuse disorders, anxiety disorders, sleep disorders, hyperacusis and disturbances of loudness perception, Ménière's disease, disorders of balance, and disorders of the inner ear, impulse control disorder, personality disorders, attention-deficit/hyperactivity disorder, autism spectrum disorders, eating disorders, cognition impairment, ataxia, pain such as neuropathic pain, inflammatory pain and miscellaneous pain, Lewy body dementia and Parkinson's disease.

The compounds of formula (I) or their pharmaceutically acceptable salts and/or solvates and/or derivatives 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 and/or derivatives 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 (such as a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof) 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 (such as a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof) 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 (such as a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (e.g. salt) and/or derivative thereof) 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 0.05 mg to 1000 mg, for example from 1.0 mg to 500 mg, of the active material, depending on the method of administration. The composition may contain from 50 mg to 1000 mg, for example from 100 mg to 400 mg 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 mg to 1000 mg, more suitably 1.0 mg to 500 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The dose provided to a subject will typically be a safe and effective dose, i.e. an amount providing an acceptable balance of desired benefits and undesired side effects. A "safe and effective amount" is intended to include an amount of a compound that is effective to achieve a desirable effect in treatment and/or prophylaxis of a disease-state. A desirable effect is typically clinically significant and/or measurable, for instance in the context of (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the

disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., slowing or arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state or a reduction in associated symptoms. The safe and effective amount may be one that is sufficient to achieve the desirable effect either when the compound is administered alone, or alternatively when it is administered in combination with one or more further APIs, which either are further compounds for use of the invention or are different from the compounds for use of the invention.

For avoidance of doubt, a "safe and effective amount" as recited herein can be achieved by any suitable dosage regimen, including but not limited to exemplary dosage regimens described elsewhere herein. Hence, for example, references herein to administering a safe and effective amount of a compound, such as by a particular administration route, include achieving the safe and effective amount via a single dose or by plural doses, such as administered by the specified administration route. For instance, orally administering a safe and effective amount includes both orally administering a single dose and orally administering any plural number of doses, provided that a safe and effective amount is thereby achieved by oral administration.

The invention provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable, salt, solvate and/or derivative thereof (e.g. a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof) together with a further pharmaceutically acceptable active ingredient or ingredients.

The invention provides a compound of formula (I), for use in combination with a further pharmaceutically acceptable active ingredient or ingredients.

When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route. Alternatively, the compounds may be administered separately.

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.

Suitably, a compound of formula (I) or a pharmaceutically acceptable, salt, solvate and/or derivative thereof is administered orally.

Suitably, a compound of formula (I) or a pharmaceutically acceptable, salt, solvate and/or derivative thereof is administered at 2 to 400 mg per day, such as 2 to 300 mg per day, especially
5 5 to 250 mg per day.

Suitably, a compound of formula (I) or a pharmaceutically acceptable, salt, solvate and/or derivative thereof is administered once or twice per day.

Suitably, a compound of formula (I) or a pharmaceutically acceptable, salt, solvate and/or derivative thereof is administered for a period of at least three months.

10 Desirably, a compound of formula (I) or a pharmaceutically acceptable, salt, solvate and/or derivative thereof is administered orally, once or twice per day, at 2 to 400 mg per day, such as 2 to 300 mg per day, especially 5 to 250 mg per day.

A human subject may be an adult, such as aged 18 to 65. Alternatively, a human subject may be 66 years old or older. A compound of formula (I) or a pharmaceutically acceptable, salt,
15 solvate and/or derivative thereof may be administered to a human subject of less than 18 years of age, such as 4 to 17 years old. Administration to a human subject of less than 18 years of age may be of particular relevance in the context of progressive myoclonic epilepsy and Fragile X syndrome.

For convenience and to assist with patient compliance, delivery technologies such as
20 patches or implants may be used to deliver a compound of formula (I) or a pharmaceutically acceptable, salt, solvate and/or derivative thereof over a sustained period of time e.g. at least one week or at least 4 weeks.

Experimental

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

Analytical Equipment

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

but may have been adapted from one reaction to another. The starting material may not necessarily have been prepared from the batch referred to. Compounds synthesised may have various purities, ranging from for example 85% to 99%. Calculations of number of moles and yield are in some cases adjusted for this.

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

Quality Control (3 minutes method): LC/MS-ES+ under acidic conditions was performed on a Zorbax SB C18 column (1.8 μ m 3 x 50 mm). Mobile phase: A: (H₂O + 0.05% TFA by vol.) /
10 B: (CH₃CN + 0.05% TFA by vol). Gradient: t = 0 min 0% (B), from 0 to 95% (B) in 2.5 min, 95% (B) for 0.2 min, from 95 to 100% (B) in 0.2 min, 100% (B) for 0.4 min, from 100% to 0% (B) in 0.1 min. Stop time 4 min. Column T = 60°C. Flow rate: 1.5 ml/min. Mass range ES+: (100-1000 amu, F=60). UV detection wavelengths: DAD 1A = 220.8, DAD 1B = 254.8. The use of this methodology is indicated by "QC_3_MIN" in the analytic characterization of the described
15 compounds.

It will be appreciated that retention times observed during chromatography can vary from preparation to preparation due to factors such as the age of column.

Chiral control: LC/MS-ES+ under acidic conditions was performed on a CHIRALCEL® OD-H (250 x 4,6 mm - 5 μ m). Mobile phase: A: (H₂O + 0.05% TFA by vol.) / B: (CH₃CN + 0.05%
20 TFA by vol). Gradient: t = 0 – 6 min 35% (B), t = 6 – 40 min from 35% to 50% (B), t = 40 – 45 min from 50% to 70% (B), t = 45 – 50 min from 70% to 35% (B), t = 50 – 55 min 35% (B). Stop time 60 min. Column T = 40°C. Flow rate: 1.0 ml/min. UV detection wavelengths: DAD 1A = 220.8, DAD 1B = 254.8.

Proton Magnetic Resonance (NMR) spectra were recorded either on Varian instruments
25 at 300, 400, 500 or 600 MHz, or on Bruker instruments at 400 MHz. Chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s (singlet), br.s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets) and m (multiplet). The NMR spectra were recorded at temperatures ranging from 25 to 60°C.

30 2D NMR NOESY experiments were acquired with a mixing time of 500 ms using a spectral width of 3355 Hz in both f1 and f2. A total of 256 increments were collected, processed to 1 K with linear prediction, 8 scans each. Data were processed with sine bell shift in both dimensions and with lb=0.3 Hz in f1. In a number of preparations, purification was performed using Biotage automatic flash chromatography (SP1 and SP4) or Flash Master Personal systems.

35 Flash chromatographies were carried out on silica gel 230-400 mesh (supplied by Merck AG Darmstadt, Germany) or on silica gel 300-400 mesh (supplied by Sinopharm Chemical

Reagent Co., Ltd.), Varian Mega Be-Si pre-packed cartridges, pre-packed Biotage silica cartridges (e.g. Biotage SNAP cartridge), pre-packed Modus silica cartridges.

Abbreviations

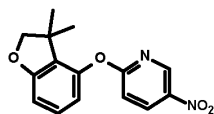
5	ACN	acetonitrile
	aq	aqueous
	Boc	tert-Butyloxycarbonyl
	DCM	dichloromethane
	DIPEA	N,N-diisopropylethylamine
10	EtOAc	ethyl acetate
	g	gram(s)
	h(rs)	hour(s)
	HATU	(O-7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluoro phosphate)
15	HCl	hydrogen chloride
	LC/MS	Liquid Chromatography–Mass Spectrometry
	Me	methyl
	mg	milligram(s)
	min	minute(s)
20	mL	millilitre(s)
	mmol	millimole
	m/z	mass to charge ratio
	NMR	Nuclear Magnetic Resonance
	MTBE	methyl <i>tert</i> -butyl ether
25	rt	room temperature
	T	temperature
	T3P	propanephosphonic acid anhydride
	TBTU	benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
	TEA	triethylamine
30	TFA	trifluoroacetic acid
	vol	volume
	wt.	weight

Experimental procedures

35

Intermediate 1

2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-5-nitro-pyridine

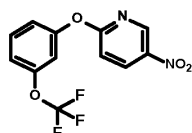


A mixture of 2-chloro-5-nitropyridine (60 mg, 0.38 mmol), 3,3-dimethyl-2H-benzofuran-4-ol (Intermediate 50 WO2012/076877, 8 mg, 0.42 mmol) and dipotassium carbonate (potassium carbonate) (79 mg, 0.58 mmol) in N,N-dimethylacetamide (1.5 mL) was stirred at 120 °C for 1 hour. The mixture was then diluted with water and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (30 mL), separated, dried over sodium sulfate, filtered and concentrated under vacuum to afford the title compound 2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-5-nitropyridine (105 mg) as a raw brown semi-solid.
LC/MS: QC_3_MIN: Rt = 2.54 min m/z 287 [M+H]⁺

10

Intermediate 2

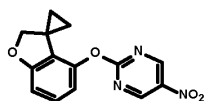
5-nitro-2-[3-(trifluoromethoxy)phenoxy]pyridine



Intermediate 2 was prepared using the methodology already described for Intermediate 1 replacing 3,3-dimethyl-2H-benzofuran-4-ol (Intermediate 50 WO2012/076877) with 3-(trifluoromethoxy)phenol.
LC/MS: QC_3_MIN: Rt = 2.54 min m/z 301 [M+H]⁺

Intermediate 3

5-nitro-2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidine



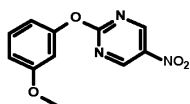
To a solution of 2-chloro-5-nitropyrimidine (250 mg, 1.57 mmol) in acetonitrile (2.5 mL), 2H-spiro[1-benzofuran-3,1'-cyclopropan]-4-ol (Intermediate 85 WO2012/076877, 280 mg, 1.73 mmol) and potassium carbonate (325 mg, 2.36 mmol) were added, and the mixture was stirred for 1 hour at 80 °C. The reaction crude was diluted with ethyl acetate (20 mL) and washed with brine (20 mL). The organic layer was dried over sodium sulphate, filtered and evaporated to dryness, affording the title compound 5-nitro-2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidine (430 mg) as a brown solid.

25

LC/MS: QC_3_MIN: Rt = 2.27 min m/z 286 [M+H]⁺

Intermediate 4

5-nitro-2-[3-(methoxy)phenoxy]pyrimidine



5

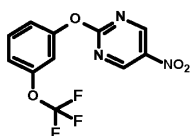
Intermediate 4 was prepared using the methodology already described for Intermediate 3 replacing 2H-spiro[1-benzofuran-3,1'-cyclopropan]-4-ol (Intermediate 85 WO2012/076877) with 3-methoxy phenol.

LC/MS: QC_3_MIN: Rt = 2.16 min m/z 248 [M+H]⁺

10

Intermediate 5

5-nitro-2-[3-(trifluoromethoxy)phenoxy]pyrimidine



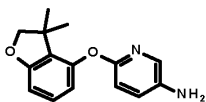
A mixture of 3-(trifluoromethoxy)phenol (2.4562g, 13.791mmol), 2-chloro-5-nitropyrimidine (2g, 12.537mmol) and dipotassium carbonate (potassium carbonate) (2.5991g, 18.805mmol) in acetonitrile (10mL) was stirred at rt for 5 h. The mixture was diluted with ethyl acetate (40 ml) and washed with brine (40 ml). Phases were separated and the organic layer was dried over Na₂SO₄, filtered and evaporated affording 5-nitro-2-[3-(trifluoromethoxy)phenoxy]pyrimidine (3.1g) that was used in the next step without further purification.

20

LC/MS: QC_3_MIN: Rt = 2.71min m/z 302 [M+H]⁺

Intermediate 6

6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyridin-3-amine



25

To a suspension of 2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-5-nitro-pyridine (Intermediate 1, 105 mg, 0.37 mmol) in ethanol (1.6 mL)/water(0.4 mL), iron (82 mg, 1.47 mmol) and ammonium chloride (79 mg, 1.47 mmol) were added and the reaction mixture was

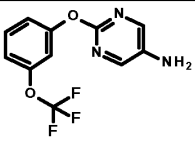
stirred at 80°C for 1h. The solids were filtered off and the filtrate was concentrated under vacuum. The residue was dissolved in ethyl acetate (20 mL) and washed with brine (20 mL). The organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by flash chromatography (Biotage System) on silica gel using a SFAR 5 g as column and cyclohexane/ethyl acetate from 80:20 to 30:70 as eluent affording 6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyridin-3-amine (60 mg) as a yellow solid.

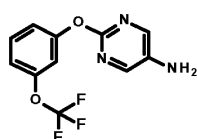
LC/MS: QC_3_MIN: $R_t = 1.95$ min m/z 257[M+H]⁺

Intermediate 6 may also be prepared as described for WO2012076877 Intermediate 59.

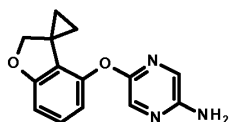
The following compounds were prepared using analogous methods to the foregoing methodology, replacing 2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-5-nitro-pyridine (Intermediate 1) with the appropriate nitro derivative. The reactions in the table were performed at room temperature (rt) with reaction times ranging from 16h to 24h. The conditions for each case are specified in the table. Final products were purified by flash-chromatography (Silica cartridge using Cyclohexane/EtOAc or DCM/Methanol as eluent or C-18 cartridge using water/acetonitrile as eluent).

Int.	Structure	Name	Nitro Derivative	T(°C) / h	LC-MS
7		2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidin-5-amine	5-nitro-2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidine (Intermediate 3)	rt for 24h	LC/MS: QC_3_MIN: $R_t = 1.93$ min m/z 256 [M+H] ⁺
8		2-(3-methoxyphenoxy)pyrimidin-5-amine	2-(3-methoxyphenoxy)-5-nitro-pyrimidine (Intermediate 4)	rt for 18h	LC/MS: QC_3_MIN: $R_t = 1.73$ min m/z 218 [M+H] ⁺
9		6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine	5-nitro-2-[3-(trifluoromethoxy)phenoxy]pyridine (Intermediate 2)	rt for 24h	LC/MS: QC_3_MIN: $R_t = 2.13$ min m/z 271 M+H] ⁺

Int.	Structure	Name	Nitro Derivative	T(°C) / h	LC-MS
10		6-[3-(trifluoromethoxy)phenoxy]pyrimidin-3-amine	5-nitro-2-[3-(trifluoromethoxy)phenoxy]pyrimidine (Intermediate 5)	rt for 16h	LC/MS: QC_3_MIN: Rt = 2.13 min m/z 272 [M+H] ⁺

Intermediate 10 (alternative route)**6-[3-(trifluoromethoxy)phenoxy]pyrimidin-3-amine**

- 5 A mixture of 2-chloro-5-aminopyrimidine (48mg, 0.3705mmol), 3-(Trifluoromethoxy)phenol (103.42mg, 0.5807mmol) (0.075mL), cesium carbonate (250mg, 0.7673mmol) and dimethyl sulfoxide (1mL) was stirred at 120°C for 16h. The reaction mixture was partitioned between saturated aqueous NaHCO₃ (30 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, then concentrated
- 10 in vacuo. The residue was purified by flash chromatography (Biotage System) on silica gel using a MODUS 12g as column and Cyclohexane: Ethyl acetate (0-100%) as eluent. The appropriate fractions were combined and evaporated to dryness. The residues were purified by reverse phase chromatography using a SNAP C-18 12g column, eluting with water and acetonitrile from 95:5 to 5:95. The appropriate fractions were combined and evaporated to dryness, producing 2-[3-
- 15 (trifluoromethoxy)phenoxy]pyrimidin-5-amine (26mg) as a colourless oil.
LC/MS: QC_3_MIN: Rt = 2.13 min m/z 272 [M+H]⁺

Intermediate 11**5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy pyrazin-2-amine**

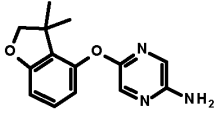
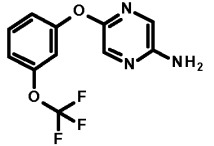
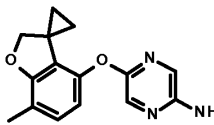
20

5-bromopyrazin-2-amine (600 mg, 3.45mmol), spiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (Intermediate 85 WO2012076877, 559 mg, 3.45 mmol), caesium carbonate (2.25 g, 6.90 mmol), copper(I) iodide (131 mg, 0.69 mmol) and pyridine-2-carboxylic acid (254 mg, 2.07 mmol) were mixed in N,N-dimethylacetamide (7 mL). The reaction mixture was split into two

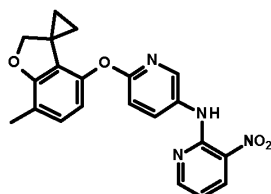
different vials and each vial was submitted to an argon-vacuum cycle and stirred at 120°C for 2 hours. The reaction mixtures were diluted with ethyl acetate (20 mL each) and filtered over cellulose. The filtrate was washed twice with a NH₄Cl saturated solution (20 mL), brine (20 mL), dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography (Biotage System) on silica gel using a SFAR 10 g as column and cyclohexane/ethyl acetate from 80:20 to 40:60 as eluent, affording the title compound 5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy pyrazin-2-amine (245 mg) as a brown powder.

LC/MS: QC_3_MIN: R_t = 2.08 min m/z 256[M+H]⁺

The following compounds were prepared using analogous methods to the foregoing methodology, replacing spiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (Intermediate 85 WO2012076877) with the appropriate phenol. Final products were purified by flash-chromatography (Silica cartridge using Cyclohexane/EtOAc or DCM/Methanol as eluent or C-18 cartridge using water/acetonitrile as eluent).

Int.	Structure	Name	Phenol Derivative	LC-MS
12		5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-amine	3,3-dimethyl-2H-benzofuran-4-ol (Intermediate 50 WO2012/076877)	LC/MS: QC_3_MIN: R _t = 2.15 min m/z 258 [M+H] ⁺
13		5-[3-(trifluoromethoxy)phenoxy]pyrazin-2-amine	3-trifluoromethoxy phenol	LC/MS: QC_3_MIN: R _t = 2.19 min m/z 272 [M+H] ⁺
14		5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy pyrazin-2-amine	7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (Intermediate 156 WO2012/076877)	LC/MS: QC_3_MIN: R _t = 2.12 min m/z 270 [M+H] ⁺

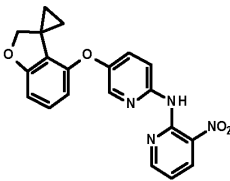
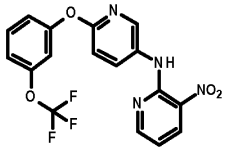
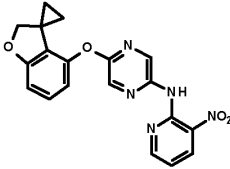
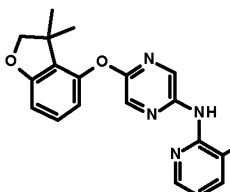
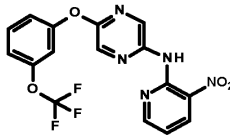
Intermediate 15

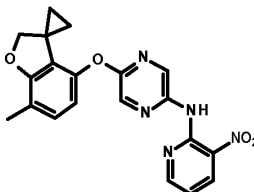
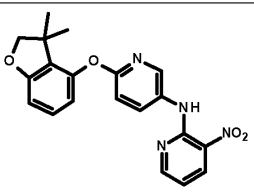
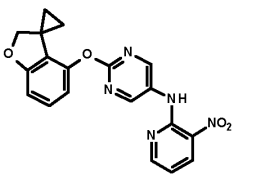
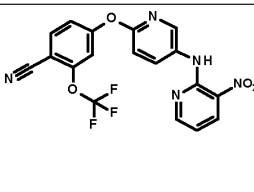
N-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-3-nitro-pyridin-2-amine

- 5 6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyridin-3-amine
(WO2012/076877 Intermediate 158, 50 mg, 0.19 mmol), caesium carbonate (122 mg, 0.37mmol)
and 2-chloro-3-nitro-pyridine (30 mg, 0.17mmol) were dissolved in 1,4-dioxane (2 mL) and
diacetoxypalladium (palladium(II) acetate) (42 mg, 0.19mmol) and (5-diphenylphosphanyl-9,9-
dimethyl-xanthen-4-yl)-diphenyl-phosphane (Xantphos) (9 mg, 0.01 mmol) were added. A
10 vacuum-argon cycle was applied three times and then, the mixture was stirred at 95 °C for 2
hours. After cooling, the reaction was diluted with EtOAc (20 mL) and washed with an NH₄Cl
saturated solution (20 mL). The two layers were separated and the organic one washed with brine
(20 mL), dried over Na₂SO₄, filtered and evaporated under vacuum affording the title compound
N-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-3-nitro-pyridin-2-
15 amine (82 mg) as a brown solid. The raw material was used in the next step without further
purification.
LC/MS: QC_3_MIN: Rt= 2.67 min m/z 391[M+H]⁺

- The following compounds were prepared using analogous methods to the foregoing methodology,
20 replacing 6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyridin-3-amine
(WO2012/076877 Intermediate 158) with the appropriate aniline and 2-chloro-3-nitro-pyridine with
the appropriate nitro derivative. This methodology can also be employed using nitrogen instead
of argon.

Int.	Structure	Name	Aniline	Nitro derivative	LC-MS
16		4-methyl-N-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-3-nitropyridin-2-amine	6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyridin-3-amine (WO2012/076877 Intermediate 158)	2-chloro-6-methyl-3-nitropyridine	LC/MS: QC_3_MIN: Rt = 2.71 min; m/z 405 [M+H] ⁺ .
17		3-nitro-N-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridin-2-amine	6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (WO2012/076877 Intermediate 87)	2-chloro-3-nitropyridine	LC/MS: QC_3_MIN: Rt = 2.55 min; m/z 377 [M+H] ⁺ .
18		N-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-3-nitropyridin-2-amine	6-[4-methyl-3-(trifluoromethoxy)phenoxy]pyridin-3-amine (WO2011/069951 Intermediate 147)	2-chloro-3-nitropyridine	LC/MS: QC_3_MIN: Rt = 2.74 min; m/z 407 [M+H] ⁺ .
19		4-methyl-3-nitro-N-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridin-2-amine	6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (WO2012/076877 Intermediate 87)	2-chloro-6-methyl-3-nitropyridine	LC/MS: QC_3_MIN: Rt = 2.59 min; m/z 391 [M+H] ⁺ .

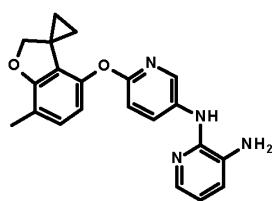
Int.	Structure	Name	Aniline	Nitro derivative	LC-MS
20		3-nitro-N-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)pyridin-2-amine	5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-2-amine (WO2017/103604 intermediate 24)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.53 min; m/z 377 [M+H] ⁺ .
21		3-nitro-N-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]pyridin-2-amine	6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine (Intermediate 9)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.66 min; m/z 393 [M+H] ⁺ .
22		N-(3-nitro-2-pyridyl)-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine	5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine (Intermediate 11)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.61 min; m/z 378 [M+H] ⁺ .
23		5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-N-(3-nitro-2-pyridyl)pyrazin-2-amine	5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-amine (Intermediate 12)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.76 min; m/z 380 [M+H] ⁺ .
24		N-(3-nitro-2-pyridyl)-5-[3-(trifluoromethoxy)phenoxy]pyrazin-2-amine	5-[3-(trifluoromethoxy)phenoxy]pyrazin-2-amine (Intermediate 13)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.85 min; m/z 394 [M+H] ⁺ .

Int.	Structure	Name	Aniline	Nitro derivative	LC-MS
25		5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-N-(3-nitro-2-pyridyl)pyrazin-2-amine	5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy pyrazin-2-amine (Intermediate 14)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.74 min; m/z 392 [M+H] ⁺ .
26		N-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-3-nitro-pyridin-2-amine	6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyridin-3-amine (Intermediate 6)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.66 min; m/z 379 [M+H] ⁺ .
27		N-(3-nitropyridin-2-yl)-2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidin-5-amine	2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidin-5-amine (Intermediate 7)	2-chloro-3-nitropyridine	LC/MS: QC_3_MIN: Rt =2.40 min; m/z 378 [M+H] ⁺ .
28		4-[[5-[(3-nitro-2-pyridyl)amino]-2-pyridyl]oxy]-2-(trifluoromethoxy)benzonitrile	4-[(5-amino-2-pyridyl)oxy]-2-(trifluoromethoxy)benzonitrile (WO2011/069951 Intermediate 161)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.56 min; m/z 418 [M+H] ⁺ .

Int.	Structure	Name	Aniline	Nitro derivative	LC-MS
29		N-(4-methyl-3-nitro-2-pyridyl)-2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrimidin-5-amine	2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrimidin-5-amine (Intermediate 7)	2-chloro-4-methyl-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.46 min; m/z 392 [M+H]+.
30		2-(3-methoxyphenoxy)-N-(3-nitro-2-pyridyl)pyrimidin-5-amine	2-(3-methoxyphenoxy)pyrimidin-5-amine (Intermediate 8)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt =2.31 min; m/z 340 [M+H]+.
31		N-(3-nitro-2-pyridyl)-2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-amine	6-[3-(trifluoromethoxy)phenoxy]pyrimidin-3-amine (Intermediate 10)	2-chloro-3-nitro-pyridine	LC/MS: QC_3_MIN: Rt = 2.61min m/z 394 [M+H]+

Intermediate 32

N2-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyridine-2,3-diamine



5

Iron (59 mg, 1.05 mmol), ammonium chloride (56 mg, 1.05 mmol) and N-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-3-nitro-pyridin-2-amine (Intermediate 15, 82 mg, 0.21 mmol) were suspended in a mixture ethanol (4 mL)/water (1 mL). The mixture was refluxed at 80°C for 1h. After cooling, the solids were filtered off and the filtrate was diluted with EtOAc (30 mL) and washed with brine (30 mL). The residue was purified by flash chromatography (Biotage System) on silica gel using a SFAR 10g as column

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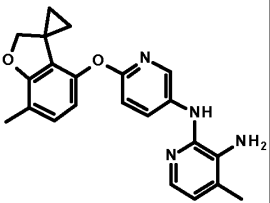
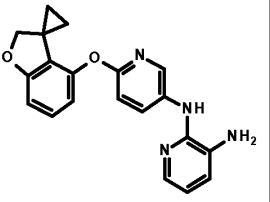
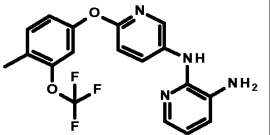
and Cyclohexane/Ethyl acetate from 80:20 to 30:70 as eluent, affording the title compound N2-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyridine-2,3-diamine (42 mg) as a white solid.

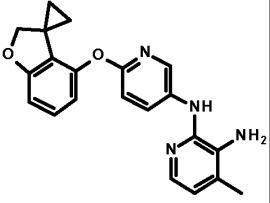
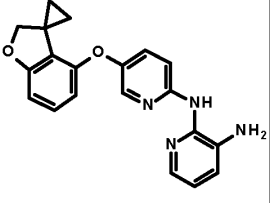
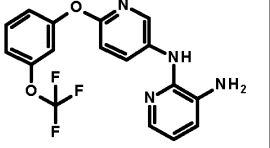
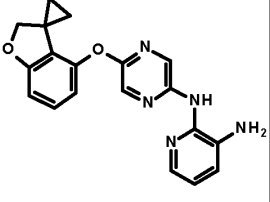
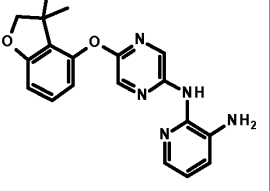
LC/MS: QC_3_MIN: Rt= 2.01 min m/z 361 [M+H]⁺

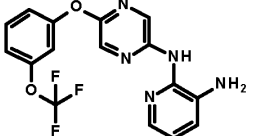
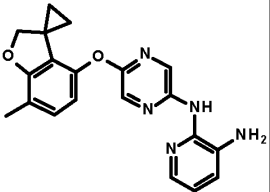
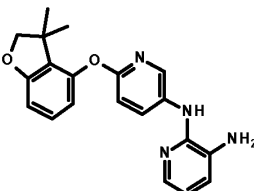
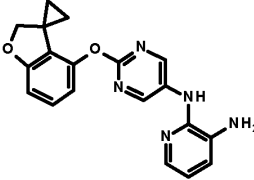
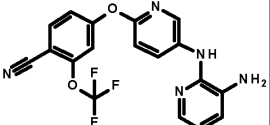
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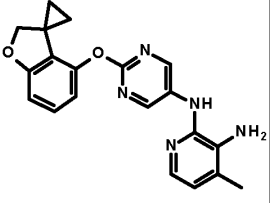
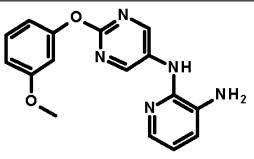
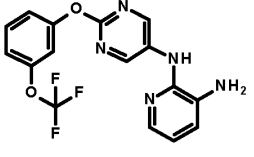
The following compounds were prepared using analogous methods to the foregoing methodology, replacing N-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-3-nitropyridin-2-amine (Intermediate 15) with the appropriate nitro derivative. The reactions were performed with temperatures ranging from room temperature (rt) to 80°C. The conditions for each case are specified in the table. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system) and/or reverse chromatography (C-18 cartridge; water/acetonitrile or other appropriate solvent system).

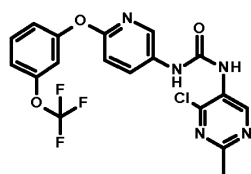
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Int	Structure	Name	Nitro derivative	T (°C) / h	LC-MS
33		4-methyl-N2-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyridine-2,3-diamine	4-methyl-N-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-3-nitropyridin-2-amine (Intermediate 16)	80°C for 1h	LC/MS: QC_3_MI N: Rt= 2.06 min [M+H] ⁺ = 375
34		N2-[6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridine-2,3-diamine	3-nitro-N-[6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridin-2-amine (Intermediate 17)	80°C for 1h	LC/MS: QC_3_MI N: Rt= 1.89 min [M+H] ⁺ = 347
35		N2-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]pyridine-2,3-diamine	N-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-3-nitropyridin-2-amine (Intermediate 18)	80°C for 1h	LC/MS: QC_3_MI N: Rt= 2.11 min [M+H] ⁺ = 377

Int	Structure	Name	Nitro derivative	T (°C) / h	LC-MS
36		4-methyl-N2-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridine-2,3-diamine	4-methyl-3-nitro-N-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridin-2-amine (Intermediate 19)	80°C for 1h	LC/MS: QC_3_MI N: Rt= 1.95 min [M+H] ⁺ = 361
37		N2-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)pyridine-2,3-diamine	3-nitro-N-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)pyridin-2-amine (Intermediate 20)	80°C for 2h	LC/MS: QC_3_MI N: Rt= 2.13 min [M+H] ⁺ = 347
38		N2-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]pyridine-2,3-diamine	3-nitro-N-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]pyridin-2-amine (Intermediate 21)	80°C for 1h	LC/MS: QC_3_MI N: Rt= 1.99 [M+H] ⁺ = 363
39		N2-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-yl)pyridine-2,3-diamine	N-(3-nitro-2-pyridyl)-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine (Intermediate 22)	rt for 18h	LC/MS: QC_3_MI N: Rt = 1.98 min [M+H] ⁺ = 348
40		N2-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]pyridine-2,3-diamine	5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-N-(3-nitro-2-pyridyl)pyrazin-2-amine (Intermediate 23)	rt for 18h	LC/MS: QC_3_MI N: Rt = 2.05 min [M+H] ⁺ = 350

Int	Structure	Name	Nitro derivative	T (°C) / h	LC-MS
41		N2-[5-[3-(trifluoromethoxy)phenoxy]pyrazin-2-yl]pyridine-2,3-diamine	N-(3-nitro-2-pyridyl)-5-[3-(trifluoromethoxy)phenoxy]pyrazin-2-amine (Intermediate 24)	rt for 18h	LC/MS: QC_3_MI N: Rt = 2.10 min [M+H] ⁺ = 364
42		N2-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy]pyrazin-2-yl]pyridine-2,3-diamine	5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-N-(3-nitro-2-pyridyl)pyrazin-2-amine (Intermediate 25)	rt for 18h	LC/MS: QC_3_MI N: Rt = 2.10 min [M+H] ⁺ = 362
43		N2-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]pyridine-2,3-diamine	N-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-3-nitro-pyridin-2-amine (Intermediate 26)	80°C for 1h	LC/MS: QC_3_MI N: Rt = 1.94 min [M+H] ⁺ = 349
44		N2-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy]pyrimidin-5-yl]pyridine-2,3-diamine	N-(3-nitropyridin-2-yl)-2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidin-5-amine (Intermediate 27)	rt overnight	LC/MS: QC_3_MI N: Rt = 1.74min [M+H] ⁺ = 348
45		4-[[5-[(3-amino-2-pyridyl)amino]-2-pyridyl]oxy]-2-(trifluoromethoxy)benzonitrile	4-[[5-[(3-nitro-2-pyridyl)amino]-2-pyridyl]oxy]-2-(trifluoromethoxy)benzonitrile (Intermediate 28)	80°C for 1h	LC/MS: QC_3_MI N: Rt = 1.97min [M+H] ⁺ = 388

Int	Structure	Name	Nitro derivative	T (°C) / h	LC-MS
46		4-methyl-N2-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrimidin-5-ylpyridine-2,3-diamine	N-(4-methyl-3-nitro-2-pyridyl)-2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrimidin-5-amine (Intermediate 29)	rt for 18h	LC/MS: QC_3_MI N: Rt = 1.84min [M+H] ⁺ = 362
47		N2-[2-(3-methoxyphenoxy)pyrimidin-5-yl]pyridine-2,3-diamine	2-(3-methoxyphenoxy)-N-(3-nitro-2-pyridyl)pyrimidin-5-amine (Intermediate 30)	rt for 16h, then 50°C for 1h and then 60°C for 1h	LC/MS: QC_3_MI N: Rt = 1.70 min [M+H] ⁺ = 310
48		N2-[2-(3-trifluoromethoxyphenoxy)pyrimidin-5-yl]pyridine-2,3-diamine	N-(3-nitro-2-pyridyl)-2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-amine (Intermediate 31)	rt for 16h	LC/MS: QC_3_MI N: Rt = 2.36 min [M+H] ⁺ = 364

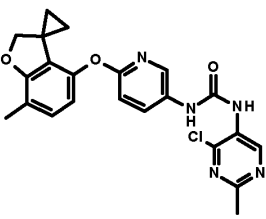
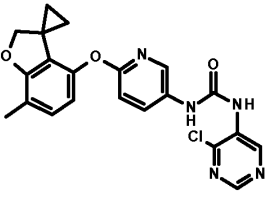
Intermediate 491-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]urea

5 Method 1:

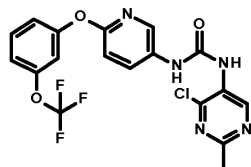
A mixture of bis(trichloromethyl) carbonate (90mg, 0.3033mmol) in dichloromethane (2mL) was cooled to 0 °C. A solution of 6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine (intermediate 9, 200mg, 0.7402mmol) and N,N-diisopropylethylamine (371mg, 2.8706mmol) (0.50 mL) in dichloromethane (3mL) was then added dropwise and the reaction mixture was left to stir at 0 °C for 30 minutes. Vacuum was applied for several minutes to remove excess phosgene and then a solution of 4-(dimethylamino)pyridine (100mg, 0.8185mmol) in dichloromethane (1mL)

- was added dropwise and the reaction mixture was left to stir at 0 °C for 5 minutes. 4-chloro-2-methyl-pyrimidin-5-amine (115mg, 0.8010mmol) was added and the reaction mixture was left to stir at 0 °C for 1 hour. The reaction mixture was diluted with DCM (15 mL) and washed with a 0.4 M aqueous solution of HCl (10 mL) and brine (15 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated under vacuum. The crude material was then purified by Reverse Phase flash chromatography (Biotage System) on silica gel using a SNAP C-18 12 g column eluting Water:Acetonitrile from 95:5 to 5:95. The desired fractions were collected and concentrated under vacuum to afford the title compound 1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]urea (74mg) as a white solid.
- LC/MS: QC_3_MIN: Rt = 2.42 min; m/z 440 & 442 [M+H]⁺.

- The following compounds were prepared using analogous methods to the foregoing methodology, replacing 6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine (intermediate 9) with the appropriate amine intermediate. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system) and/or reverse chromatography (C-18 cartridge; water/acetonitrile or other appropriate solvent system).

Int.	Structure	Name	Amine intermediate	LCMS
50		1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]urea	6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyridin-3-amine (WO2012/076877 Intermediate 158)	LC/MS: QC_3_MIN: Rt = 2.22 min; m/z 438, 440 [M+H] ⁺ .
51		1-(4-chloropyrimidin-5-yl)-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]urea	6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyridin-3-amine (WO2012/076877 Intermediate 158)	LC/MS: QC_3_MIN: Rt = 2.48 min; m/z 424 & 426 [M+H] ⁺ .

Int.	Structure	Name	Amine intermediate	LCMS
52		1-(4-chloro-2-methylpyrimidin-5-yl)-3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)urea	6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (WO2012/076877 Intermediate 87)	LC/MS: QC_3_MIN: Rt = 2.10 min; m/z 424 & 426 [M+H] ⁺ .
53		1-(4-chloro-2-methylpyrimidin-5-yl)-3-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]urea	6-[4-methyl-3-(trifluoromethoxy)phenoxy]pyridin-3-amine (WO2011/069951 Intermediate 147)	LC/MS: QC_3_MIN: Rt = 2.53 min; m/z 454 & 456 [M+H] ⁺ .
54		1-(4-chloro-2-methylpyrimidin-5-yl)-3-[6-(3-methoxyphenoxy)-3-pyridyl]urea	6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine	LC/MS: QC_3_MIN: Rt = 2.53 min; m/z 440 & 442 [M+H] ⁺ .

Intermediate 491-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]urea

5 Method 2:

- A mixture of bis(trichloromethyl) carbonate (58mg, 0.1955mmol) in ethyl acetate (3mL) was cooled to 0 °C. A solution of 6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine (Intermediate 9, 105mg, 0.3886mmol) and N,N-diisopropylethylamine (148.4mg, 1.1483mmol) (0.2mL) in ethyl acetate (3mL) was added dropwise and the reaction mixture was left to stir at 0 °C for 15 minutes.
- 10 Vacuum was applied for several minutes to remove excess phosgene and then 4-(dimethylamino)pyridine (48mg, 0.3929mmol) in ethyl acetate (0.5mL) and dichloromethane (0.5 mL) was added and stirred at 0 °C for 5 minutes. 4-chloro-2-methyl-pyrimidin-5-amine (62mg, 0.4318mmol) was added and the reaction mixture was left to stir at room temperature for 1 hour. The reaction mixture was then quenched with 0.2 N HCl (20mL) and extracted with ethyl acetate

(20mL). The organic layer was dried over Na₂SO₄, filtered then concentrated in vacuo. The residue was purified using Flash column chromatography (Biotage system) using a MODUS 12g column and cyclohexane:ethyl acetate from 90:10 to 50:50 as eluent, followed by reverse phase chromatography using a C-18 12g column and water:acetonitrile from 95:5 to 15:85 as eluent to afford the title compound 1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]urea (25mg) as a white solid.

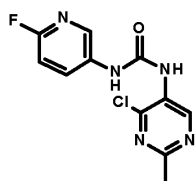
LC/MS: QC_3_MIN: Rt = 2.53 min; m/z 440 & 442 [M+H]⁺.

The following compounds were prepared using analogous methods to the foregoing methodology, replacing 6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine (Intermediate 9) with the appropriate amine intermediate. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system) and/or reverse chromatography (C-18 cartridge; water/acetonitrile or other appropriate solvent system).

Int.	Structure	Name	Amine intermediate	LCMS
52		1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-(6-(6-(3-(trifluoromethoxy)phenoxy)cyclopropyl)benzofuran-3,1'-yl)oxy-3-pyridyl)urea	6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (WO2012/076877 Intermediate 87)	LC/MS: QC_3_MIN: Rt = 2.37 min; m/z 424 & 426 [M+H] ⁺ .

Intermediate 55

1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-(6-fluoro-3-pyridyl)urea



A mixture of bis(trichloromethyl) carbonate (260mg, 0.8762mmol) in dichloromethane (4mL) was cooled to 0 °C. A solution of 5-amino-2-fluoropyridine (190mg, 1.6948mmol) and N,N-diisopropylethylamine (742mg, 5.7413mmol) (1mL) in dichloromethane (4mL) was added dropwise and the reaction mixture was left to stir at 0 °C for 15 minutes. Vacuum was applied for several minutes to remove excess phosgene and then 4-(dimethylamino)pyridine (214mg, 1.7517mmol) in dichloromethane (1mL) was added and stirred at 0 °C for 5 minutes. 4-chloro-2-

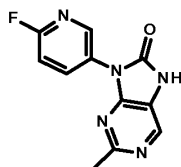
methyl-pyrimidin-5-amine (242mg, 1.68mmol) in dichloromethane (2mL) was added portionwise and the reaction mixture was left to stir at room temperature for 1.5 hours. The reaction mixture was then quenched with 0.2 N HCl (20mL) and extracted with ethyl acetate (20mL). The organic layer was dried over Na₂SO₄, filtered then concentrated in vacuo. The residue was purified
5 reverse phase chromatography using a C-18 12g column and water:acetonitrile from 95:5 to 60:40 as eluent to afford the title compound (isolated in two btches) 1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-(6-fluoro-3-pyridyl)urea (94mg) as a yellow solid and 1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-(6-fluoro-3-pyridyl)urea (180mg) as a white solid.

LC/MS: QC_3_MIN: Rt = 1.83 min; m/z 281 & 283 [M+H]⁺

10

Intermediate 56

9-(6-fluoro-3-pyridyl)-2-methyl-7H-purin-8-one

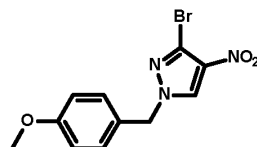


A mixture of 1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-(6-fluoro-3-pyridyl)urea (Intermediate
15 55, 94mg, 0.3337mmol), cesium carbonate (215mg, 0.66mmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (Xantphos) (22mg, 0.038mmol), and diacetoxypalladium (palladium(II) acetate) (7mg, 0.0312mmol) in 1,4-dioxane (5mL) was put under a vacuum-nitrogen flush and stirred at 95 °C for 2 hours. The reaction was filtered and concentrated in vacuo then purified by reverse phase chromatography (Biotage system) using a
20 C-18 25g column and water:acetonitrile from 95:5 to 80:20 as eluent to afford the title compound 9-(6-fluoro-3-pyridyl)-2-methyl-7H-purin-8-one (12mg) as a white solid.

LC/MS: QC_3_MIN: Rt = 1.45 min; m/z 245 [M]

Intermediate 57

4-bromo-1-[(4-methoxyphenyl)methyl]-3-nitro-pyrazole



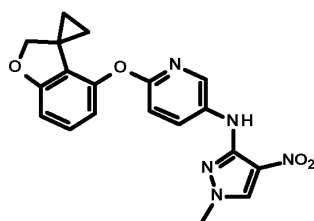
4-bromo-3-nitro-1H-pyrazole (135 mg, 0.70 mmol) was dissolved in N,N-dimethylformamide (2 mL). sodium hydride 60% dispersion in mineral oil (34 mg, 0.84 mmol) and

1-(bromomethyl)-4-methoxy-benzene (156 mg, 0.77 mmol) were added. The reaction mixture was stirred at rt for 2h. The reaction was quenched with water (15 mL) and diluted with ethyl acetate (20 mL). The two phases were separated and the organic one washed with brine (20 mL), dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography (Biotage System) on silica gel using a SFAR 5 g as column and cyclohexane/ethyl acetate from 100:0 to 70:30 as eluent, affording the title compound 4-bromo-1-[(4-methoxyphenyl)methyl]-3-nitro-pyrazole (197 mg) as a yellow oil.

LC/MS: QC_3_MIN: Rt = 2.30 min; m/z

10 Intermediate 58

N-(1-methyl-4-nitro-pyrazol-3-yl)-6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine



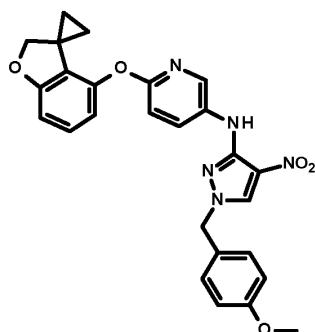
6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (WO2012/076877 Intermediate 87, 394mg, 1.55mmol), cesium carbonate (1.01g, 3.09mmol), 3-chloro-1-methyl-4-nitropyrazole (250mg, 1.55mmol) were dissolved in 1,4-dioxane (5mL), Xantphos (67mg, 0.12mmol) and Pd(OAc)₂ (17mg, 0.08mmol) were added. Three times cycle Argon-vacuum was applied and the mixture was stirred at 110°C for 7h. Then, further Xantphos (35mg) and Pd(OAc)₂ (10mg) were added and the reaction mixture was stirred at 110°C for further 2h. The reaction was quenched with NH₄Cl (50ml) and EtOAc (50ml) was added. The two layers were shaken, separated and the organic one was collected, washed with Brine(50ml), dried with Na₂SO₄, filtered and evaporated. The crude was suspended in MTBE (10Volumes), and the mixture was stirred 1h at 50°C and 3h at RT. The solid was filtered under vacuum affording N-(1-methyl-4-nitro-pyrazol-3-yl)-6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (1g) as brown solid used in the next step without further purification.

LC/MS: QC_3_MIN: Rt = 2.49 min; m/z 380 [M+H]⁺.

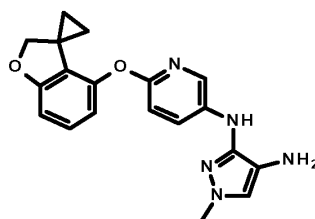
The following compounds were prepared using analogous methods to the foregoing methodology, replacing 6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (WO2012/076877 Intermediate 87) with the appropriate amine intermediate. Products were either isolated crude or were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or

other appropriate solvent system) and/or reverse chromatography (C-18 cartridge; water/acetonitrile or other appropriate solvent system).

Int.	Structure	Name	Amine intermediate	LCMS
59		N-(1-methyl-4-nitro-pyrazol-3-yl)-6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyridin-3-amine	6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyridin-3-amine (WO2012/076877 Intermediate 158).	LC/MS: QC_3_MIN: Rt = 2.54 min; m/z 394 [M+H] ⁺ , 809 [2M+Na] ⁺
60		6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-N-(1-methyl-4-nitropyrazol-3-yl)pyridin-3-amine	6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyridin-3-amine (Intermediate 6)	LC/MS: QC_3_MIN: Rt = 2.49 min; m/z 382 [M+H] ⁺
61		N-(1-methyl-4-nitro-pyrazol-3-yl)-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine	5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine (Intermediate 11)	LC/MS: QC_3_MIN: Rt = 2.55 min; m/z 381 [M+H] ⁺
62		N-(1-methyl-4-nitro-pyrazol-3-yl)-2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrimidin-5-amine	N-(4-methyl-3-nitro-2-pyridyl)-2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrimidin-5-amine (Intermediate 29)	LC/MS: QC_3_MIN: Rt = 2.36 min; m/z 381 [M+H] ⁺ , 783 [2M+Na] ⁺

Intermediate 63N-[1-[(4-methoxyphenyl)methyl]-4-nitro-pyrazol-3-yl]-6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine

- 5 Intermediate 59 was prepared using the same methodology described for the synthesis of Intermediate 55 replacing 3-chloro-1-methyl-4-nitropyrazole with 4-bromo-1-[(4-methoxyphenyl)methyl]-3-nitro-pyrazole (intermediate 57).
LC/MS: QC_3_MIN: Rt = 2.71 min; m/z 486 [M+H]⁺.

10 Intermediate 641-methyl-N3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyrazole-3,4-diamine

- 15 Iron (74mg, 1.32mmol), ammonium chloride (70 mg, 1.32mmol) and N-(1-methyl-4-nitro-pyrazol-3-yl)-6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (Intermediate 58, 100mg, 0.26mmol) were suspended on a mixture ethanol (2mL) water (0.5000mL). The mixture was refluxed at 80°C for 1h. After cooling, the solids were filtered and the mixture was diluted with EtOAc (30 mL) and washed with brine (50 mL). The residue was purified by flash chromatography (Biotage System) on silica gel using a SFAR 10g as column and DCM/MeOH
20 from 99/1: to 90/10 as eluent, affording the title compound 1-methyl-N3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyrazole-3,4-diamine (40mg) as a white solid.
LC/MS: QC_3_MIN: Rt = 1.92 min; m/z 350 [M+H]⁺, 722 [2M+Na]⁺

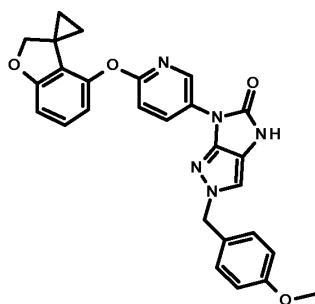
The following compounds were prepared using analogous methods to the foregoing methodology, replacing N-(1-methyl-4-nitro-pyrazol-3-yl)-6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (Intermediate 58) with the appropriate nitro derivative intermediate. The reactions were performed with temperatures ranging from room temperature (rt) to 80°C and reaction times ranging from 1h to 64h. The conditions for each case are specified in the table. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system) and/or reverse chromatography (C-18 cartridge; water/acetonitrile or other appropriate solvent system).

Int.	Structure	Name	Nitro derivative intermediate	T (°C) / h	LCMS
65		1-methyl-N3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyrazole-3,4-diamine	N-(1-methyl-4-nitro-pyrazol-3-yl)-6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyridin-3-amine (Intermediate 59)	80°C for 1h	LC/MS: QC_3_MI N: Rt = 2.00 min; m/z 364 [M+H] ⁺ .
66		N3-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-1-methyl-pyrazole-3,4-diamine	6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-N-(1-methyl-4-nitropyrazol-3-yl)pyridin-3-amine (Intermediate 60)	rt for 18h	LC/MS: QC_3_MI N: Rt = 1.94 min; m/z 352 [M+H] ⁺
67		1-methyl-N3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl]pyrazole-3,4-diamine	N-(1-methyl-4-nitro-pyrazol-3-yl)-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine (intermediate 61)	rt for 64h	LC/MS: QC_3_MI N: Rt = 1.86 min; m/z 351[M+H] ⁺

Int.	Structure	Name	Nitro derivative intermediate	T (°C) / h	LCMS
68		1-methyl-N3-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrimidin-5-yl)pyrazole-3,4-diamine	N-(1-methyl-4-nitro-pyrazol-3-yl)-2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrimidin-5-amine (Intermediate 62)	50°C for 4h	LC/MS: QC_3_MI N: Rt = 1.84 min; m/z 351 [M+H] ⁺ , 723 [2M+Na] ⁺
69		1-[(4-methoxyphenyl)methyl]-N3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyrazole-3,4-diamine	N-[1-[(4-methoxyphenyl)methyl]-4-nitro-pyrazol-3-yl]-6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyridin-3-amine (Intermediate 63)	rt for 18h and then 60°C for 1h	LC/MS: QC_3_MI N: Rt = 2.19 min; m/z 456 [M+H] ⁺

Intermediate 70

2-[4-(4-methoxyphenyl)methyl]-6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-4H-imidazo[4,5-c]pyrazol-5-one



5

To a solution of 1-[(4-methoxyphenyl)methyl]-N3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyrazole-3,4-diamine (Intermediate 69, 20 mg, 0.044 mmol) and triethylamine (0.008 mL, 0.058 mmol) in ethyl acetate (4 mL), 1-1'-carbonyldiimidazole (10 mg, 0.064 mmol) was added and the reaction mixture was stirred at room temperature for 2h. The reaction was diluted with ethyl acetate (30 mL) and washed with HCl 0.2M solution (20 mL). The

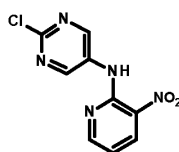
10

two phases were separated and the organic one was collected, washed with brine (20 mL), dried over sodium sulphate, filtered and evaporated to dryness. The residue was purified by flash chromatography (Biotage System) on silica gel using a SFAR 5 g as column and Cyclohexane/Ethyl acetate from 60:40 to 10:90 as eluent, affording the title compound 2-[(4-methoxyphenyl)methyl]-6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-4H-imidazo[4,5-c]pyrazol-5-one (7 mg) as a red oil.

LC/MS: QC_3_MIN: $R_t = 2.48$ min m/z 482 $[M+H]^+$

Intermediate 71

10 2-chloro-N-(3-nitro-2-pyridyl)pyrimidin-5-amine

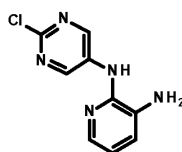


To a solution of 2-chloropyrimidin-5-amine (800 mg, 6.20 mmol) in dry dioxane (20 mL), 2-chloro-3-nitropyridine (1.96 g, 12.40 mmol), cesium carbonate (4.04 g, 12.4 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (270 mg, 0.47 mmol) and Palladium (II) acetate (69 mg, 0.31 mmol) were added and an argon-vacuum cycle was applied 3 times. The reaction mixture was stirred for 1 hour at 80°C. The mixture was diluted with ethyl acetate (30 mL) and the solids were filtered off. The resulting liquid phase was washed with water (20 mL) and brine (20 mL), dried over sodium sulphate, filtered and evaporated to dryness affording the title compound 2-chloro-N-(3-nitro-2-pyridyl)pyrimidin-5-amine (1.56 g) as a red-brown solid.

20 LC/MS: QC_3_MIN: $R_t = 2.09$ min m/z 252 $[M+H]^+$

Intermediate 72

N2-(2-chloropyrimidin-5-yl)pyridine-2,3-diamine



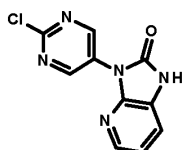
25 To a solution of 2-chloro-N-(3-nitropyridin-2-yl)pyrimidin-5-amine (Intermediate 71, 1.56 g, 5.49 mmol) in absolute ethanol (20 mL) and water (5 mL), ammonium chloride (588 mg, 11 mmol) and Iron Powder (615 mg, 11 mmol) were added and the reaction mixture was stirred for 16 hours at room temperature. The solids were filtered off and the filtrate was concentrated under vacuum. The residue was dissolved in ethyl acetate (30 mL) and washed with brine (50 mL). The organic

layer was dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by flash chromatography (Biotage System) on silica gel using a SFAR 25 g as column and Cyclohexane/Ethyl acetate from 80:20 to 20:80 as eluent affording the title compound N2-(2-chloropyrimidin-5-yl)pyridine-2,3-diamine (800 mg) as a brown solid.

5 LC/MS: QC_3_MIN: R_t = 1.29 min m/z 222 [M+H]⁺

Intermediate 73

3-(2-chloropyrimidin-5-yl)-1H-imidazo[4,5-b]pyridin-2-one



10 To a solution of N2-(2-chloropyrimidin-5-yl)pyridine-2,3-diamine (Intermediate 72, 800 mg, 3.62 mmol) in dichloromethane (20 mL), triethylamine (1.32 mL, 7.24 mmol) was added, and the mixture was cooled to 0°C. Triphosgene (429 mg, 1.45 mmol) was added dropwise as a dichloromethane (15 mL) solution. The mixture was stirred at 0°C for 10 minutes. The mixture was diluted with dichloromethane (30 mL) and washed with HCl 0.2 M solution (20 mL) and brine

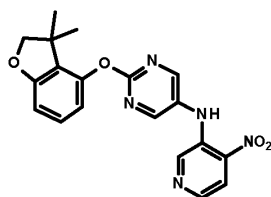
15 (5 mL). The organic layer was dried over sodium sulphate, filtered and evaporated to dryness affording an insoluble solid that was suspended in ethyl acetate (15 mL) and stirred overnight. After filtration, the solid was collected and dried affording the title compound 3-(2-chloropyrimidin-5-yl)-1H-imidazo[4,5-b]pyridin-2-one (140 mg) as light brown solid.

LC/MS: QC_3_MIN: R_t = 1.75 min m/z 248 [M+H]⁺

20

Intermediate 74

2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-N-(4-nitro-3-pyridyl)pyrimidin-5-amine



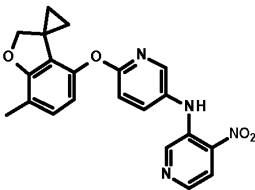
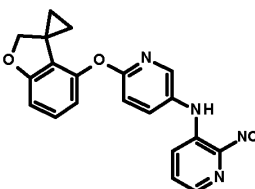
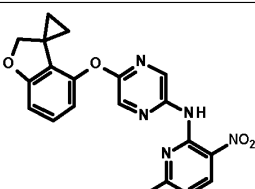
A mixture of 2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-amine

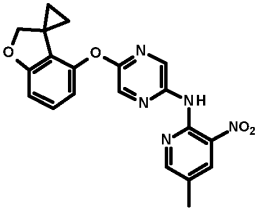
25 (WO2012/076877 Intermediate 65, 50mg, 0,19 mmol), 3-bromo-4-nitro-pyridine (43 mg, 0,21 mmol), Xantphos (17mg, 0,03 mmol), cesium carbonate (127mg, 0,39 mmol) and Pd(OAc)₂ (4 mg, 0,02 mmol) in 1,4-dioxane (2mL) was put under a vacuum-nitrogen flush and stirred at 95 °C for 1.5 hours. The mixture was then diluted in EtOAc (15 mL) and washed with water (20 mL) and

then brine (20 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated under vacuum affording the title compound 2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-N-(4-nitro-3-pyridyl)pyrimidin-5-amine (104mg) which was used in the next step without further purifications.

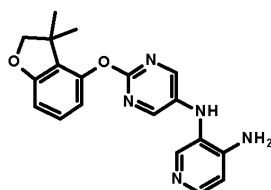
5 LC/MS: QC_3_MIN: R_t = 2.47 min m/z 380 [M+H]⁺

The following compounds were prepared using analogous methods to the foregoing methodology, replacing 2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-amine (WO2012/076877 Intermediate 65) with the appropriate aniline and 3-bromo-4-nitro-pyridine with the appropriate nitro derivative. Reactions were heated at 95°C for 1.5 to 2h. Products were either isolated crude or were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system) and/or reverse chromatography (C-18 cartridge; water/acetonitrile or other appropriate solvent system).

Int.	Structure	Name	Aniline	Nitro derivative	LC-MS
75		6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-N-(4-nitro-3-pyridyl)pyridin-3-amine	6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyridin-3-amine (WO2012/076877 Intermediate 158)	3-bromo-4-nitro-pyridine	LC/MS not available.
76		2-nitro-N-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl)pyridin-3-amine	6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyridin-3-amine (WO2012/076877 Intermediate 87)	3-bromo-2-nitro-pyridine	LC/MS not available.
77		N-(6-methyl-3-nitro-2-pyridyl)-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazin-2-amine	5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazin-2-amine (Intermediate 11)	2-chloro-6-methyl-3-nitro-pyridine	LC/MS not available.

Int.	Structure	Name	Aniline	Nitro derivative	LC-MS
78		N-(5-methyl-3-nitro-2-pyridyl)-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine	5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine (Intermediate 11)	2-chloro-5-methyl-3-nitro-pyridine	LC/MS not available.

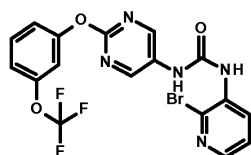
Intermediate 79

N3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]pyridine-3,4-diamine

- 5 A mixture of 2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-N-(4-nitro-3-pyridyl)pyrimidin-5-amine (Intermediate 74, 104mg, 0,27 mmol), iron (61mg, 1,1 mmol) and ammonium chloride (59mg, 1.1mmol) in ethanol (4mL) and water (1mL) was stirred at RT for 16 hours. The reaction mixture was filtered and the solid washed with EtOAc (10ml). The organic filtrate was collected and washed with water (10ml) and then brine (10ml). The organic layer was separated, dried over
- 10 Na₂SO₄, filtered and concentrated under vacuum. The crude was then purified by Reverse Phase flash chromatography (Biotage System) on C-18 stationary phase using a SNAP C-18 12 g column eluting Water:Acetonitrile from 95:5 to 0:100. The desired fractions were collected and concentrated under vacuum to afford the title compound N3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]pyridine-3,4-diamine (23mg) as a white solid.
- 15 LC/MS: QC_3_MIN: R_t = 2.07 min m/z 350 [M+H]⁺

- The following compounds were prepared using analogous methods to the foregoing methodology, replacing 2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-N-(4-nitro-3-pyridyl)pyrimidin-5-amine (Intermediate 72) with the appropriate nitro derivative. The reactions were performed
- 20 with temperatures ranging from room temperature (rt) to 90°C. The conditions for each case are specified in the table. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system) and/or reverse chromatography (C-18 cartridge; water/acetonitrile or other appropriate solvent system).

Int	Structure	Name	Nitro derivative	T (°C) / h	LC-MS
80		N3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyridine-3,4-diamine	6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-N-(4-nitro-3-pyridyl)pyridin-3-amine (Intermediate 75)	90°C for 16h	LC/MS: QC_3_MI N: Rt= 1.88 min [M+H] ⁺ = 361
81		N3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridine-2,3-diamine	2-nitro-N-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridin-3-amine (Intermediate 76)	rt for 18h	LC/MS: QC_3_MI N: Rt= 1.96 min [M+H] ⁺ = 347
82		6-methyl-N2-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-yl)pyridine-2,3-diamine	N-(6-methyl-3-nitro-2-pyridyl)-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine (Intermediate 77)	rt for 19h then 60°C for 2h	LC/MS: QC_3_MI N: Rt= 2.06 min [M+H] ⁺ = 362
83		5-methyl-N2-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-yl)pyridine-2,3-diamine	N-(5-methyl-3-nitro-2-pyridyl)-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-amine (Intermediate 78)	rt for 24h, then 55°C for 2h, then 60°C for 2h and then rt for 96h.	LC/MS: QC_3_MI N: Rt= 2.08 min [M+H] ⁺ = 362

Intermediate 841-(2-bromo-3-pyridyl)-3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]urea

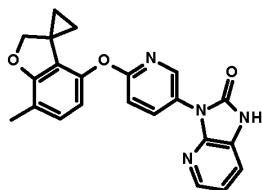
A mixture of bis(trichloromethyl) carbonate (32mg, 0.1078mmol) in dichloromethane (1.5mL) was cooled to 0 °C. A solution of 2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-amine (Intermediate 10, 75mg, 0.2765mmol) and N,N-diisopropylethylamine (148mg, 1.1452mmol) (0.20 mL) in dichloromethane (1,5mL) was then added dropwise and the reaction mixture was left to stir at 0 °C for 1 hour. Vacuum was applied for several minutes to remove excess phosgene and then a solution of 4-(dimethylamino)pyridine (35mg, 0.2865mmol) in dichloromethane (0.5000mL) was added dropwise and the reaction mixture was left to stir at 0 °C for 5 minutes. 2-bromopyridin-3-amine (55mg, 0.3179mmol) was added and the reaction mixture was left to stir at 0 °C for 1 hour. The mixture was concentrated under vacuum and the crude material was then purified by Reverse Phase flash chromatography (Biotage System) on silica gel using a SNAP C-18 12 g column eluting Water:Acetonitrile from 95:5 to 30:70. The desired fractions were collected and concentrated under vacuum to afford 1-(2-bromo-3-pyridyl)-3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]urea (18mg) as a white solid.

LC/MS: QC_3_MIN: Rt= 2.04min m/z 470 & 472 [M+H]⁺

15

Example 1

3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one



To a solution of N2-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyridine-2,3-diamine (Intermediate 32, 21 mg, 0.06 mmol) (Intermediate 29) in EtOAc (4 mL), 1-1'-carbonyldiimidazole (10.4 mg, 0.06 mmol) was added and the reaction mixture was stirred at room temperature for 2h. The reaction was diluted with EtOAc (30 mL) and washed with HCl 0.2 M solution (20 mL). The two phases were separated and the organic one was collected, washed with brine (20 mL), dried over sodium sulphate, filtered, and evaporated to dryness. The residue was purified by flash chromatography on C-18 using a SNAP 10g as column and H₂O/ACN from 95:5 to 20:80 as eluent. The desired fractions were collected and the solvent was removed under vacuum affording the title compound 3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one (17 mg as a white solid).

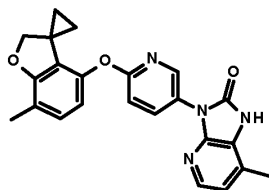
LC/MS: QC_3_MIN: Rt= 2.32min m/z 387 [M+H]⁺

30

¹H-NMR (400 MHz; DMSO-d₆): δ ppm 11.44 (bs, 1H), 8.37 (d, 1H), 8.07 (dd, 1H), 7.90 (dd, 1H), 7.35-7.41 (m, 1H), 7.05-7.11 (m, 2H), 6.90 (d, 1H), 6.43 (d, 1H), 4.42 (s, 2H), 2.11 (s, 3H), 1.07-1.20 (m, 2H), 0.83-0.88 (m, 2H).

5 Example 2

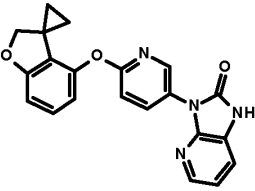
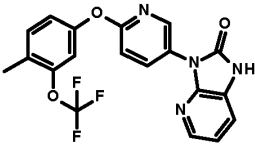
7-methyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one

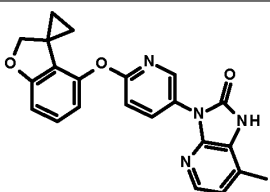
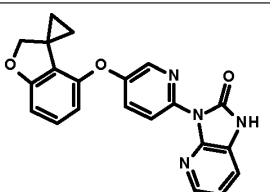
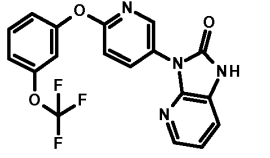


4-methyl-N2-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyridine-2,3-diamine (Intermediate 33, 25 mg, 0.07 mmol) and triethylamine (20 μL, 0.17 mmol) were mixed in dichloromethane (5 mL) and the mixture cooled to 0°C. A solution of triphosgene (8 mg, 0.03 mmol) in dichloromethane (2 mL) was slowly added and the reaction mixture was stirred at 0°C for 30 min. The reaction was diluted with ethyl acetate (30 mL) and washed with an aqueous 0.2 M HCl solution (20 mL). The two phases were separated and the organic one washed with brine (20 mL), dried over sodium sulphate, filtered and evaporated to dryness. The residue was purified by flash chromatography on silica gel (BIOTAGE SYSTEM) using a SFAR 5g as column and DCM/MeOH from 99.5:0.5 to 95:5 as eluent. The desired fractions were collected and the solvent was removed under vacuum affording the title compound 7-methyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one (9 mg) (Example 2) as a white solid.

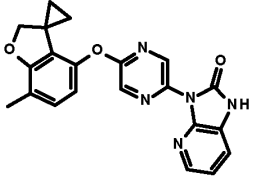
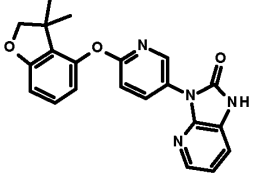
LC/MS: QC_3_MIN: Rt= 2.39 min m/z 401 [M+H]⁺ 401 & 823 [2M+Na]⁺.

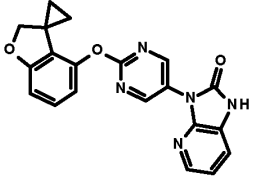
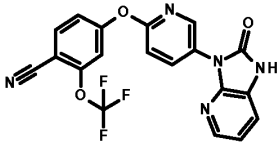
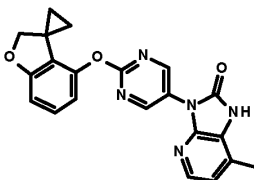
The following compounds were prepared using analogous methods to the foregoing methodology, replacing 4-methyl-N2-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyridine-2,3-diamine (Intermediate 33) with the appropriate diamine. Final products were purified by flash-chromatography (Silica cartridge using Cyclohexane/EtOAc or DCM/Methanol as eluent and/or C-18 cartridge using water/acetonitrile as eluent).

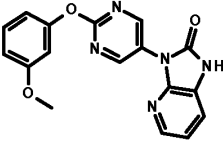
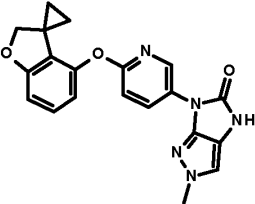
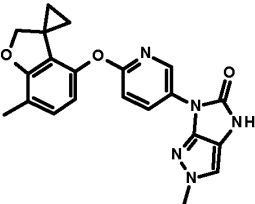
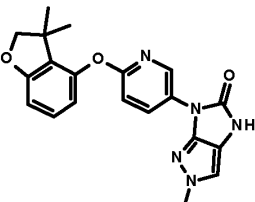
Ex	Structure	Name	Diamine	NMR	LC-MS
3		3-(6-(spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one	N2-(6-(spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridine-2,3-diamine (Intermediate 34)	¹ H-NMR (400 MHz; DMSO-d ₆): δ ppm 11.45 (s, 1H), 8.40 (dd, 1H), 8.10 (dd, 1H), 7.90 (dd, 1H), 7.38 (dd, 1H), 7.13 (dd, 1H), 7.04- 7.10 (m, 2H), 6.64 (dd, 1H), 6.51 (dd, 1H), 4.43 (s, 2H), 1.11-1.20 (m, 2H), 0.87-0.93 (m, 2H)	LC/MS: QC_3_MIN: Rt = 2.22 min m/z 373 [M+H] ⁺
4		3-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one	N2-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]pyridine-2,3-diamine (Intermediate 35)	¹ H-NMR (400 MHz; DMSO-d ₆): δ ppm 11.45 (s, 1H), 8.39 (d, 1H), 8.13 (dd, 1H), 7.90 (dd, 1H), 7.40-7.46 (m, 1H), 7.38 (dd, 1H), 7.18-7.24 (m, 2H), 7.15 (dd, 1H), 7.08 (dd, 1H), 2.26 (s, 3H)	LC/MS: QC_3_MIN: Rt= 2.42 min m/z 403 [M+H] ⁺

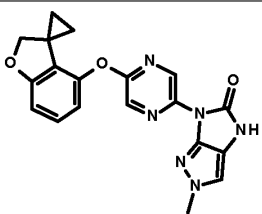
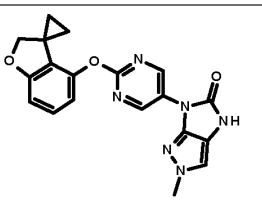
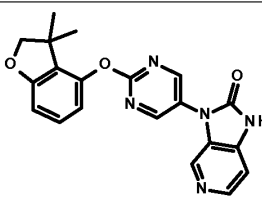
Ex	Structure	Name	Diamine	NMR	LC-MS
5		7-methyl-3-(6-(spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one	4-methyl-N2-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridine-2,3-diamine (Intermediate 36)	-	LC/MS: QC_3_MIN: Rt= 2.27 min m/z 387 [M+H] ⁺ m/z 795 [2M+Na] ⁺
6		3-(5-(spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one	N2-(5-(spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)pyridine-2,3-diamine (Intermediate 37)	-	LC/MS: QC_3_MIN: Rt= 2.15 min m/z 373[M+H] ⁺ m/z 767 [2M+Na] ⁺
7		3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one	N2-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]pyridine-2,3-diamine (Intermediate 38)	-	LC/MS: QC_3_MIN: Rt= 2.33 min m/z 387[M+H] ⁺ m/z 799 [2M+Na] ⁺

Ex	Structure	Name	Diamine	NMR	LC-MS
8		3-(5-(2-((1H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-yl)oxy)spiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)pyridine-2,3-diamine (Intermediate 39)	N2-(5-(2-((1H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-yl)pyridine-2,3-diamine (Intermediate 39)	¹ H-NMR (400 MHz; DMSO-d ₆): δ ppm 11.50 (s, 1H), 8.58 (d, 1H), 8.46 (d, 1H), 7.89 (dd, 1H), 7.41 (dd, 1H), 7.06-7.12 (m, 2H), 6.68 (dd, 1H), 6.62 (dd, 1H), 4.45 (s, 2H), 1.13-1.19 (m, 2H), 0.91-0.97 (m, 2H)	LC/MS: QC_3_MIN: Rt= 2.14 m/z 374 [M+H] ⁺
9		3-(5-((3,3-dimethyl-2H-benzofuran-4-yl)oxy)pyridin-2-yl)-1H-imidazo[4,5-b]pyridin-2-one (Intermediate 40)	N2-(5-((3,3-dimethyl-2H-benzofuran-4-yl)oxy)pyridin-2-yl)pyridine-2,3-diamine (Intermediate 40)	-	LC/MS: QC_3_MIN: Rt = 2.20 min m/z 376 [M+H] ⁺
10		3-(5-(3-(trifluoromethoxy)phenoxy)pyridin-2-yl)-1H-imidazo[4,5-b]pyridin-2-one (Intermediate 41)	N2-(5-(3-(trifluoromethoxy)phenoxy)pyridin-2-yl)pyridine-2,3-diamine (Intermediate 41)	¹ H-NMR (400 MHz; DMSO-d ₆): δ ppm 11.49 (s, 1H), 8.65 (d, 1H), 8.46 (d, 1H), 7.89 (dd, 1H), 7.59 (t, 1H), 7.42-7.45 (m, 1H), 7.41 (dd, 1H), 7.33-7.37 (m, 1H), 7.27-7.32 (m, 1H), 7.10 (dd, 1H)	LC/MS: QC_3_MIN: Rt = 2.29 min m/z 390 [M+H] ⁺

Ex	Structure	Name	Diamine	NMR	LC-MS
11		3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-1H-imidazo[4,5-b]pyridin-2-one	N2-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)pyridine-2,3-diamine (Intermediate 42)	¹ H-NMR (400 MHz; DMSO-d ₆): δ ppm 11.49 (s, 1H), 8.54 (s, 1H), 8.44 (s, 1H), 7.89 (d, 1H), 7.37-7.43 (m, 1H), 7.09 (dd, 1H), 6.93 (d, 1H), 6.53 (d, 1H), 4.44 (s, 2H), 2.12 (s, 3H), 1.08-1.14 (m, 2H), 0.89-0.95 (m, 2H).	LC/MS: QC_3_MIN: Rt = 2.24 min m/z 388 [M+H] ⁺
12		3-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one	N2-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]pyridine-2,3-diamine (Intermediate 43)	¹ H-NMR (400 MHz; DMSO-d ₆): δ ppm 11.44 (s, 1H), 8.41 (d, 1H), 8.10 (dd, 1H), 7.90 (dd, 1H), 7.38 (dd, 1H), 7.18 (d, 1H), 7.05-7.15 (m, 2H), 6.63 (d, 1H), 6.56 (s, 1H), 4.19 (s, 2H), 1.27 (s, 6H)	LC/MS: QC_3_MIN: Rt = 2.21 min m/z 375 [M+H] ⁺

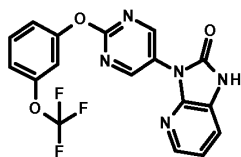
Ex	Structure	Name	Diamine	NMR	LC-MS
13		3-(2-((2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy)pyrimidin-5-yl)-1H,2H,3H-imidazo[4,5-b]pyridin-2-one	N2-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)pyridine-2,3-diamine (Intermediate 44)	¹ H-NMR (400 MHz; DMSO-d ₆): δ ppm 11.56 (s, 1H), 8.96 (s, 2H), 7.93 (dd, 1H), 7.41 (dd, 1H), 7.06-7.14 (m, 2H), 6.68 (dd, 1H), 6.62 (dd, 1H), 4.43 (s, 2H), 1.06-1.11 (m, 2H), 0.89-0.94 (m, 2H)	LC/MS: QC_3_MIN: Rt = 2.12 min m/z 374 [M+H] ⁺
14		4-[[5-(2-oxo-1H-imidazo[4,5-b]pyridin-3-yl)-2-pyridyl]oxy]-2-(trifluoromethoxy)benzonitrile	4-[[5-[(3-amino-2-pyridyl)amino]-2-pyridyl]oxy]-2-(trifluoromethoxy)benzonitrile (Intermediate 45)	-	LC/MS: QC_3_MIN: Rt = 2.27 min m/z 414 [M+H] ⁺
15		7-methyl-3-(2-((2H-spiro[2H-benzofuran-3,1'-cyclopropane]oxy)pyrimidin-5-yl)-1H-imidazo[4,5-b]pyridin-2-one	4-methyl-N2-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)pyridine-2,3-diamine (Intermediate 46)	-	LC/MS: QC_3_MIN: Rt = 2.19 min m/z 388 [M+H] ⁺

Ex	Structure	Name	Diamine	NMR	LC-MS
16		3-[2-(3-methoxyphenoxy)pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one	N2-[2-(3-methoxyphenoxy)pyrimidin-5-yl]pyridine-2,3-diamine (Intermediate 47)	-	LC/MS: QC_3_MIN: Rt = 2.09min m/z 336 [M+H] ⁺
18		2-methyl-6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-4H-imidazo[4,5-c]pyrazol-5-one	1-methyl-N3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyrazole-3,4-diamine (Intermediate 64)	-	LC/MS: QC_3_MIN: Rt = 2.23min m/z 376 [M+H] ⁺
19		2-methyl-6-[6-(7-methylspiro[2Hbenzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-4H-imidazo[4,5-c]pyrazol-5-one	1-methyl-N3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyrazole-3,4-diamine (Intermediate 65)	-	LC/MS: QC_3_MIN: Rt = 2.29 min; m/z 390 [M+H] ⁺ .
20		6-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-2-methyl-4H-imidazo[4,5-c]pyrazol-5-one	N3-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-1-methyl-pyrazole-3,4-diamine (Intermediate 66)	-	LC/MS: QC_3_MIN: Rt = 2.24 min; m/z 378 [M+H] ⁺ .

Ex	Structure	Name	Diamine	NMR	LC-MS
21		2-methyl-6-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-4H-imidazo[4,5-c]pyrazol-5-one	1-methyl-N3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)pyrazole-3,4-diamine (Intermediate 67)	-	LC/MS: QC_3_MIN: Rt = 2.13 min; m/z 377 [M+H] ⁺ .
22		2-methyl-6-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrimidin-5-yl)-4H-imidazo[4,5-c]pyrazol-5-one	1-methyl-N3-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrimidin-5-yl)pyrazole-3,4-diamine (Intermediate 68)	-	LC/MS: QC_3_MIN: Rt = 2.10 min; m/z 377 [M+H] ⁺ , 775 [2M+Na] ⁺
23		3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-c]pyridin-2-one	N3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]pyridine-3,4-diamine (Intermediate 79)	-	LC/MS: QC_3_MIN: Rt = 2.10 min; m/z 376 [M+H] ⁺ .

Example 17

3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one



To a solution of N2-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]pyridine-2,3-diamine (Intermediate 48, 786mg, 2.1636mmol) in ethyl acetate (5mL), were added 1-1'-carbonyldiimidazole (491.15mg, 3.029mmol) and triethylamine (580.4mg, 5.7357mmol) the reaction mixture was stirred at room temperature for 4hs. The reaction was diluted with ethyl acetate (50 ml) and washed with an aqueous 0.2N solution of HCl (30 ml). The two phases were separated and the organic one was collected, washed with brine (30ml), dried over sodium sulphate, filtered and evaporated to dryness. The residue was suspended in iPrOH (10 Volumes) and the mixture was stirred at 80C until the complete dissolution and then overnight at RT. The solid was filtered off under vacuum and the filtrate was evaporated on vacuum, dissolved in EtOAc and filtered on a SFAR silica column 10g. This filtrate was put together to the previous solid and the crude was suspended in EtOAc (10 Volumes). The mixture was stirred at 70C until the complete dissolution and then Cyclohexane (10 Volumes) was added. The heating was switched off and the mixture was stirred for 2h at RT. the solid was filtered under vacuum affording 3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one (424mg) as light pink solid.

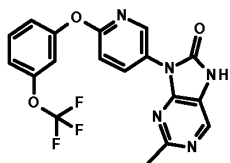
LC/MS: QC_3_MIN: Rt = 2.63 min; m/z 390 [M+H]⁺

¹H-NMR (400 MHz; DMSO-d₆): δ ppm 11.56 (s, 1H), 8.98 (s, 2H), 7.93 (dd, 1H), 7.58 (t, 1H), 7.40-7.44 (m, 2H), 7.35 (ddd, 1H), 7.26-7.32 (m, 1H), 7.11 (dd, 1H)

20

Example 24

2-methyl-9-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one



A mixture of 1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]urea (Intermediate 49, 27mg, 0.0614mmol), cesium carbonate (140mg, 0.4297mmol), Xantphos (24mg, 0.0415mmol), and Pd(OAc)₂ (5mg, 0.0223mmol) in 1,4-dioxane (1mL) was put under a vacuum-nitrogen flush and stirred at 95 °C for 2 hours. The reaction mixture was quenched with NH₄Cl (10mL) and water (10mL), then extracted with ethyl acetate

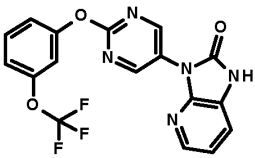
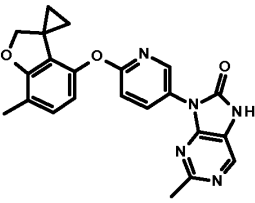
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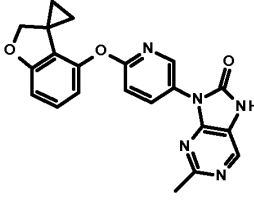
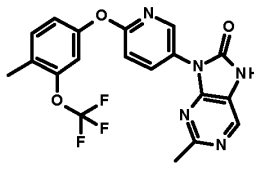
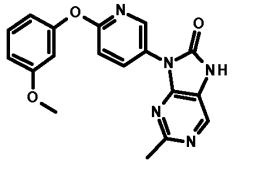
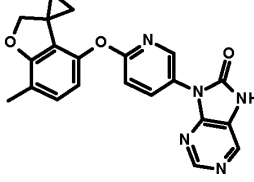
(15mL). The organic layer was washed with brine (15mL), dried over Na₂SO₄, filtered then concentrated in vacuo. Flash chromatography (Biotage system) was used to purify the residue using a MODUS 5g column and cyclohexane:ethyl acetate from 90:10 to 0:100 followed by DCM:Methanol 80:20. The fractions were concentrated in vacuo and further purified by reverse phase chromatography using a C-18 12g column and water:acetonitrile from 95:5 to 40:60 as eluent to afford the title compound 2-methyl-9-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one (1mg) as a white solid.

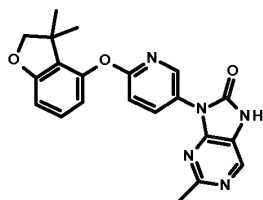
LC/MS: QC_3_MIN: Rt = 2.19 min; m/z 404 [M+H]⁺

¹H-NMR (400 MHz; CDCl₃): δ ppm 9.11 (s, 1H), 8.58 (dd, 1H), 8.30 (s, 1H), 8.10 (dd, 1H), 7.42-7.47 (m, 1H), 7.13-7.18 (m, 2H), 7.09-7.13 (m, 2H), 2.66 (s, 3H).

The following compounds were prepared using analogous methods to the foregoing methodology, replacing 1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]urea with the appropriate urea intermediate. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system) and/or reverse chromatography (C-18 cartridge; water/acetonitrile or other appropriate solvent system).

Ex.	Structure	Name	Urea intermediate	LCMS
17		3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one	1-(2-bromo-3-pyridyl)-3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]urea (Intermediate 84)	LC/MS: QC_3_MIN: Rt = 1.94 min; m/z 390 [M+H] ⁺
25		2-methyl-9-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-7H-purin-8-one	1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]urea (Intermediate 50)	LC/MS: QC_3_MIN: Rt = 1.98 min; m/z 402 [M+H] ⁺

Ex.	Structure	Name	Urea intermediate	LCMS
26		2-methyl-9-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-7H-purin-8-one	1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)urea (Intermediate 52)	LC/MS: QC_3_MIN: Rt = 2.04 min; m/z 388 [M+H] ⁺
27		2-methyl-9-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one	1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]urea (Intermediate 53)	LC/MS: QC_3_MIN: Rt = 2.23 min; m/z 418 [M+H] ⁺
28		9-[6-(3-methoxyphenoxy)-3-pyridyl]-2-methyl-7H-purin-8-one	1-(4-chloro-2-methyl-pyrimidin-5-yl)-3-[6-(3-methoxyphenoxy)-3-pyridyl]urea (Intermediate 54)	LC/MS: QC_3_MIN: Rt = 1.89 min; m/z 350 [M+H] ⁺
29		9-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-7H-purin-8-one	1-(4-chloropyrimidin-5-yl)-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]urea (Intermediate 51)	LC/MS: QC_3_MIN: Rt = 2.23 min; m/z 388 [M+H] ⁺

Example 30**9-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-2-methyl-7H-purin-8-one**

- 5 A mixture of 9-(6-fluoro-3-pyridyl)-2-methyl-7H-purin-8-one (Intermediate 56, 12mg, 0.0489mmol), dipotassium carbonate (11mg, 0.0796mmol) and 3,3-dimethyl-2H-benzofuran-4-ol (Intermediate 50 WO2012/076877, 8.5mg, 0.0518mmol), in dimethyl sulfoxide (5mL) was put

under a vacuum-nitrogen flush and stirred at 120 °C for 1 hour, then 135 °C for 4 hours. 3,3-dimethyl-2H-benzofuran-4-ol (2mg) was added and the reaction mixture was stirred at 135 °C for 4 hours. The reaction was filtered and concentrated *in vacuo*. The residue was then diluted with ethyl acetate (20mL) then washed with water (5 x 20mL). The organic layer was then dried over Na₂SO₄ then concentrated *in vacuo*.

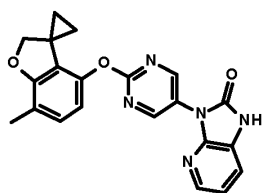
In a separate vial, a mixture of 9-(6-fluoro-3-pyridyl)-2-methyl-7H-purin-8-one (Intermediate 56, 17mg, 0.0693mmol), dipotassium carbonate (potassium carbonate) (14mg, 0.1013mmol), 3,3-dimethyl-2H-benzofuran-4-ol (12mg, 0.0731mmol), and in dimethyl sulfoxide (1mL) was put under a vacuum-nitrogen flush and stirred at 120 °C for 1 hour, then 135 °C for 4 hours. 3,3-dimethyl-2H-benzofuran-4-ol (2mg) was added and the reaction mixture was stirred at 135 °C for 24 hours. The reaction mixture was quenched with water (10mL) then extracted with ethyl acetate (2 x 10 mL). The organic layer was then washed with water (2 x 10mL) then brine (10mL), dried over Na₂SO₄, filtered then concentrated *in vacuo*. At this point, both reaction vials were combined for the purification. The residue was then purified by flash column chromatography (Biotage system) using a MODUS 12g column and DCM:Methanol from 99:1 to 95:5 as eluent, followed by reverse phase chromatography (Biotage system) using a C-18 25g column and water:acetonitrile from 95:5 to 55:45. The title compound 9-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-2-methyl-7H-purin-8-one (1.2mg) was isolated as a white solid.

LC/MS: QC_3_MIN: Rt = 2.07 min; m/z 390 [M+H]⁺

20

Example 31

3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrimidin-5-yl]-1H-imidazo[4,5-b]pyridine-2-one



To a solution of 3-(2-chloropyrimidin-5-yl)-1H-imidazo[4,5-b]pyridin-2-one (Intermediate 73, 15 mg, 0.061 mmol) in N,N-Dimethylformamide (1 mL), 7-methyl-2H-spiro[1-benzofuran-3,1'-cyclopropan]-4-ol (Intermediate 156 WO2012/076877, 12 mg, 0.067 mmol) and potassium carbonate (13 mg, 0.092mmol) were added, and the mixture was stirred for 20 hours at 90°C. The mixture was diluted with ethyl acetate (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried over sodium sulphate, filtered and evaporated to dryness. The residue was purified by flash chromatography (Biotage System) on silica gel using a SFAR 10 g as column and cyclohexane/ethyl acetate from 60:40 to 0:100 as eluent. The obtained residue

30

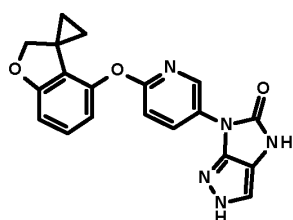
was further purified by reverse phase flash chromatography (Biotage system) on C18 stationary phase using a SNAP 12 g as column and water/acetonitrile from 70:30 to 10:90 as eluent affording the title compound 3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one (3.80 mg) as a white solid.

5 LC/MS: QC_3_MIN: $R_t = 2.26$ m/z 388 [M+H]⁺

The following compounds were prepared using analogous methods to the foregoing methodology, replacing 7-methyl-2H-spiro[1-benzofuran-3,1'-cyclopropan]-4-ol (Intermediate 156 WO2012/076877) with the appropriate phenol. Final products were purified by flash-
10 chromatography (Silica cartridge using Cyclohexane/EtOAc or DCM/Methanol as eluent or C-18 cartridge using water/acetonitrile as eluent).

Ex	Structure	Name	Phenol	NMR	LC-MS
32		3-[2-[4-methyl-3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one	4-methyl-3-(trifluoromethoxy)phenol (Intermediate 116 WO2011/069951)	¹ H-NMR (400 MHz; DMSO-d ₆): δ ppm 11.56 (s, 1H), 8.96 (s, 2H), 7.92 (dd, 1H), 7.45 (dd, 1H), 7.41 (dd, 1H), 7.34 (dt, 1H), 7.25 (dd, 1H), 7.10 (dd, 1H), 2.27 (s, 3H)	LC/MS: QC_3_MIN: $R_t = 2.36$ min m/z 404 [M+H] ⁺
17		3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one	3-(trifluoromethoxy)phenol	-	LC/MS: QC_3_MIN: $R_t = 2.29$ min m/z 390 [M+H] ⁺
33		3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one	3,3-dimethyl-2H-benzofuran-4-ol (Intermediate 50 WO2012/076877)	¹ H-NMR (400 MHz; DMSO-d ₆): δ ppm 11.56 (s, 1H), 8.97 (s, 2H), 7.93 (d, 1H), 7.41 (d, 1H), 7.08-7.18 (m, 2H), 6.67 (d,	LC/MS: QC_3_MIN: $R_t = 2.20$ min m/z 376 [M+H] ⁺

				2H), 4.19 (s, 2H), 1.24 (s, 6H)	
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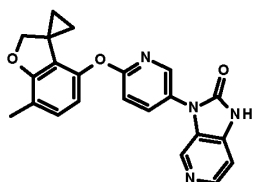
Example 34**6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-2,4-dihydroimidazo[4,5-c]pyrazol-5-one**

5

2-[(4-methoxyphenyl)methyl]-6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-4H-imidazo[4,5-c]pyrazol-5-one (Intermediate 70, 8 mg, 0.017 mmol) was dissolved in trifluoroacetic acid (1 mL, 10 mmol) and the reaction mixture was stirred at 70°C for 5 days. The solvent was evaporated and the residue was purified by reverse phase flash chromatography (Biotage System) on C18 stationary phase using a SFAR 12 g as column and water/acetonitrile from 80:20 to 75:25 as eluent, affording the title compound 6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-2,4-dihydroimidazo[4,5-c]pyrazol-5-one (1.2mg) as a white solid.

15

LC/MS: QC_3_MIN: $R_t = 2.07$ m/z 362 [M+H]⁺

Example 35**3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-c]pyridin-2-one**

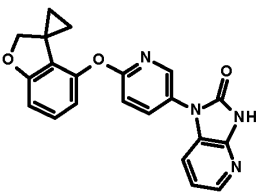
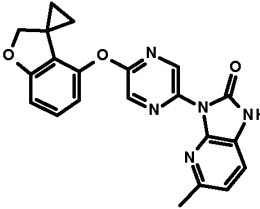
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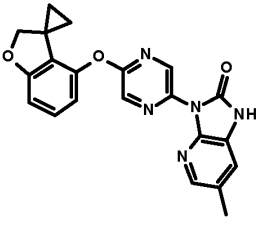
A mixture of N3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyridine-3,4-diamine (Intermediate 80, 30mg, 0.0832mmol) and N,N-

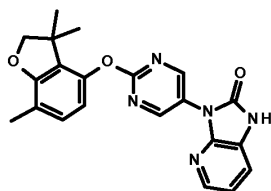
diisopropylethylamine (22,26mg, 0.1722mmol) (0.03 mL) in dichloromethane (1mL) was cooled to 0 °C. A solution of bis(trichloromethyl) carbonate (10mg, 0.0337mmol) in dichloromethane (0.5000mL) was added dropwise and the reaction mixture was left to stir at 0 °C for 1 hour. The reaction mixture was diluted in EtOAc (15 mL) and washed with a 0.4 M aqueous solution of HCl (10 mL) and brine (15 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated under vacuum. The reaction mixture was concentrated under vacuum and then purified by Reverse Phase flash chromatography (Biotage System) on silica gel using a SNAP C-18 12 g column eluting Water:Acetonitrile from 95:5 to 40:60. The desired fractions were collected and concentrated under vacuum to afford 3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-c]pyridin-2-one (19mg) as an orange solid.

LC/MS: QC_3_MIN: R_t = 1.85 m/z 387 [M+H]⁺

The following compounds were prepared using analogous methods to the foregoing methodology, replacing 4-methyl-N2-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]pyridine-2,3-diamine (Intermediate 75) with the appropriate diamine. Reactions were carried out at temperatures ranging between 0°C and room temperature. Final products were purified by flash-chromatography (Silica cartridge using Cyclohexane/EtOAc or DCM/Methanol as eluent or C-18 cartridge using water/acetonitrile as eluent).

Ex	Structure	Name	Diamine	LC-MS
36		1-(6-(spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-3H-imidazo[4,5-b]pyridin-2-one	N3-(6-(spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)pyridine-2,3-diamine (Intermediate 81)	LC/MS: QC_3_MIN: R _t = 2.23 min m/z 373 [M+H] ⁺
37		5-methyl-3-(5-(spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one	6-methyl-N2-(5-(spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)pyridine-2,3-diamine (Intermediate 82)	LC/MS: QC_3_MIN: R _t = 2.26 min m/z 388 [M+H] ⁺

38		6-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-1H-imidazo[4,5-b]pyridin-2-one	5-methyl-N2-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyridine-2,3-diamine (Intermediate 83)	LC/MS: QC_3_MIN: Rt = 2.27 min m/z 388 [M+H] ⁺
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Example 393-[2-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one

5

A mixture of 3-(2-chloropyrimidin-5-yl)-1H-imidazo[4,5-b]pyridin-2-one (Intermediate 73, 40mg, 0.1615mmol), 3,3,7-trimethyl-2H-benzofuran-4-ol (Intermediate 184 WO2012076877, 80mg, 0.2244mmol) and dipotassium carbonate (potassium carbonate) (48mg, 0.3473mmol) in dimethyl sulfoxide (5mL) was stirred at 120 °C for 2 hours. The mixture was then diluted with water (20 mL) and extracted in EtOAc (15 mL x 3). The combined organic layers were washed with brine (30 mL), separated, dried over MgSO₄, filtered and concentrated under vacuum. The crude residue was then purified by flash column chromatography (Biotage) using a MODUS 12g silica column eluting 0-100% EtOAc in DCM. The desired fractions were collected and concentrated. This residue was then purified further by reverse phase column chromatography (Biotage) using a SNAP 30g C-18 column eluting 5-95% acetonitrile in water. The desired fractions were collected and concentrated to give 3-[2-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one (7mg) as a white solid.

LC/MS: QC_3_MIN: R_t = 2.01 m/z 390 [M+H]⁺

20 Biological ExamplesBiological Example 1: Measurement of Kv3 channel modulation

The ability of the compounds of the invention to modulate the voltage-gated potassium channel subtypes Kv3.4/Kv3.3/Kv3.2/Kv3.1 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

5 To assess compound effects on human Kv3.3 channels (hKv3.3), a stable cell line expressing human Kv3.3 channels is created by transfecting Chinese Hamster Ovary (CHO)-K1 cells with a pBacMire_KCNC-3 vector. Cells are 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 are grown and maintained at 37 °C in a humidified environment
10 containing 5% CO₂ in air.

To assess compound effects on human Kv3.2 channels (hKv3.2), a stable cell line expressing human Kv3.2 channels (hKv3.2) is created by transfecting CHO-K1 cells with a pCIH5-hKv3.2 vector. Cells are cultured in DMEM/F12 medium supplemented by 10% Foetal Bovine Serum, 1X non-essential amino acids (Invitrogen) and 500ug/ml of Hygromycin-B (Invitrogen).
15 Cells are grown and maintained at 37 °C in a humidified environment containing 5% CO₂ in air.

To assess compound effects on human Kv3.1 channels (hKv3.1):
Human embryonic kidney (HEK)-hKv3.1 cell line is generated by transfecting HEK-293 cells with an expression vector with human Kv3.1 (NM_004976.4). Cells are cultured with MEM supplemented with 10% Heat-Inactivated FBS, 2 mM L-glutamine, 1% Penicillin-Streptomycin,
20 and 0.6 mg/ml of Geneticin (G418). HEK-hKv3.1b cells were amplified in T175 cm² flask at 37°C with 5% CO₂, using MEM amplification medium, containing the G418 selection antibiotic (0.6mg/ml). Cells were detached every 3-4 days, using DPBS to wash twice the flask, then TrypLE to dislodge the cells, and re-plated at a density of 2-4x10⁶ cells/flask.

To assess compound effects on human Kv3.4 channels (hKv3.4):

25 Human embryonic kidney (HEK)-hKv3.4 cell line is generated by transfecting HEK-293 cells with an expression vector with human Kv3.4 (NM_004978). Cells are cultured with MEM supplemented with 10% Heat-Inactivated FBS, 2 mM L-glutamine, 1% Penicillin-Streptomycin, and 0.6 mg/ml of Geneticin (G418). HEK-hKv3.4 cells were amplified in T175 cm² flask at 37°C with 5% CO₂, using MEM amplification medium, containing the G418 selection antibiotic
30 (0.6mg/ml). Cells were detached every 3-4 days, using DPBS to wash twice the flask, then TrypLE to dislodge the cells, and re-plated at a density of 4-8x10⁶ cells/flask.

Cell preparation for IonWorks Quattro™ experiments

The day of the experiment, cells are removed from the incubator and the culture medium
35 removed. Cells are 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 is tapped to dislodge cells and 10 ml of DPBS containing calcium

and magnesium is added to prepare a cell suspension. The cell suspension is then placed into a 15 ml centrifuge tube and centrifuged for 2 min at 1200 rpm. After centrifugation, the supernatant is removed and the cell pellet re-suspended in 4 ml of DPBS containing calcium and magnesium using a 5 ml pipette to break up the pellet. Cell suspension volume is then corrected to give a cell concentration for the assay of approximately 3 million cells per ml.

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

Electrophysiology

Experiments are conducted at r.t. using IonWorks Quattro™ planar array electrophysiology technology (Molecular Devices Corp.) with PatchPlate™ PPC. Stimulation protocols and data acquisition are carried out using a microcomputer (Dell Pentium 4). Planar electrode hole resistances (R_p) are determined by applying a 10 mV voltage step across each well. These measurements are performed before cell addition. After cell addition and seal formation, a seal test is performed by applying a voltage step from -80 mV to -70 mV for 160 ms. Following this, amphotericin-B solution is added to the intracellular face of the electrode to achieve intracellular access. Cells are held at -70 mV. Leak subtraction is 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 at -15 mV was applied for 100 ms and after 100 ms at -70 mV a second pulse at +40 mV was applied for 50 ms. Cells were then maintained for 100 ms at -100 mV and another pulse from -70 mV to +40 mV (duration 50 ms) was applied to clamp later the voltage at -40 mV during 200 ms.

For hKv3.3 assays, from the holding potential of -70 mV, a first test pulse to 0 mV is applied for 500 ms and following a further 100 ms at -70 mV, a second pulse to 40 mV is applied for 200 ms. These longer test pulses are 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.

For hKv3.4, assays from the holding potential of -70 mV, a first test pulse at -15 mV was applied for 100 ms and after 200 ms at -70 mV a second pulse was applied at 0 mV for 100 ms then after 200 ms at -70 mV a third pulse was applied at +40 mV during 200 ms.

Solutions and drugs

The intracellular solution contains the following (in mM): K-gluconate 100, KCl 54, $MgCl_2$ 3.2, HEPES 5, adjusted to pH 7.3 with KOH. Amphotericin-B solution is prepared as 50 mg/ml stock solution in DMSO and diluted to a final working concentration of 0.1 mg/ml in intracellular solution. The external solution is Dulbecco's Phosphate Buffered Saline (DPBS) and contained

the following (in mM): CaCl₂ 0.90, KCl 2.67, KH₂PO₄ 1.47, MgCl₂·6H₂O 0.493, NaCl 136.9, Na₃PO₄ 8.06, with a pH of 7.4.

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

Data analysis

The recordings are analysed and filtered using both seal resistance (>20 MΩ) and peak current amplitude (>500 pA 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 are used to determine the positive modulation effect of each compound. Kv3 channel-mediated outward currents are measured determined from the mean amplitude of the current over the final 10 ms of the -15 mV voltage pulse minus the mean baseline current at -70 mV over a 10 ms period just prior to the -15 mV step. These Kv3 channel currents following addition of the test compound are then compared with the currents recorded prior to compound addition. Data are normalised to the maximum effect of the reference compound (50µM 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 are 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) is 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 are measured for the 0mV step, considering the peak current and the decay (inactivation) of the current over the duration of the 0mV test pulse (500 ms).

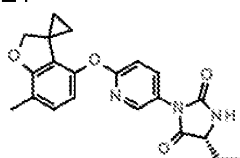
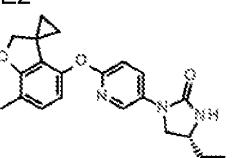
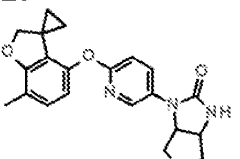
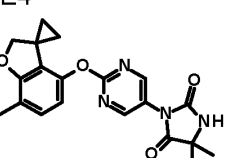
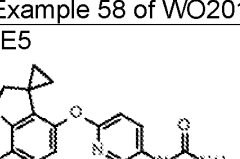
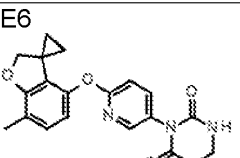
N-cyclohexyl-*N*-[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-*N'*-phenylurea is obtained from ASINEX (Registry Number: 552311-06-5).

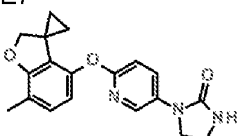
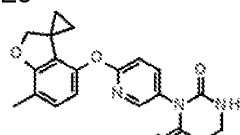
Results

The structures of a number of Reference Examples are provided in Table 1. Reference Example 1 has a hydantoin joined to a central pyridinyl ring, whilst Reference Examples 2 to 8 have various alternative heterocyclic groups joined to a central pyridinyl ring. Data for all Reference Examples 1 to 8 tested in the assay described above are also shown in Table 1.

Reference Example 1 was synthesised as outlined in WO2012/076877. Reference Examples 2 to 9 were synthesised using similar procedures to those disclosed herein.

Table 1: Kv3.1 assay results

Reference Example	Kv3.1 pEC ₅₀	Kv3.1 max R%
RE1  (Example 62 of WO2012/076877)	6.1	157
RE2 	4.7	92
RE3 	<4.3	30
RE4  (Example 58 of WO2012/076877)	5.14	158
RE5 	4.95	90
RE6 	4.6	111

Reference Example	Kv3.1 pEC ₅₀	Kv3.1 max R%
RE7 	4.4	29
RE8 	4.6	140

The data in Table 1 demonstrate that modification of the ethyl substituted hydantoin ring (Reference Example 1) to the corresponding ethyl substituted urea (Reference Example 2) or a fused oxygen containing 5,5-bicyclic urea (Reference Example 3) results in a significant
5 reduction in pEC₅₀ and max R properties in the Kv3.1 assay. Similarly, modification of the hydantoin ring of Reference Example 4 to the corresponding dihydrouracil (Reference Example 5) and *gem*-dimethyl isomer (Reference Example 6) results in a significant reduction in pEC₅₀ and max R properties in the Kv3.1 assay. Removal of substitution of the urea or dihydrouracil leads to further reduction of potency (Reference Examples 7 and 8).

10

Data for all Example compounds tested in the assay described above are presented in Table 2.

Table 2: Kv3.1 assay results

Example Compound	Kv3.1 pEC ₅₀	Kv3.1 max R%	Example Compound	Kv3.1 pEC ₅₀	Kv3.1 max R%
Example 1	6.7	148	Example 21	5.0	96
Example 2	6.8	83	Example 22	6.3	166
Example 3	7.0	197	Example 23	5.0 (n=4) 5.1 (n=2)	101 107
Example 4	5.9	111	Example 24	6.0	144
Example 5	6.5	132	Example 25	6.5	190
Example 6	5.7	221	Example 26	7.3	135
Example 7	6.3 (n=4) 6.4 (n=2)	89 96	Example 27	5.8 (n=6) 5.9 (n=4)	134 138
Example 8	6.7	204	Example 28	5.4	140

Example Compound	Kv3.1 pEC ₅₀	Kv3.1 max R%	Example Compound	Kv3.1 pEC ₅₀	Kv3.1 max R%
Example 9	5.9	147	Example 29	6.8	117
Example 10	5.7	94	Example 30	6.9	123
Example 11	6.5	205	Example 31	6.7	217
Example 12	6.5	164	Example 32	5.8	174
Example 13	6.7	194	Example 33	6.1	194
Example 14	6.0	124	Example 34	5.0 (n=4) 5.0 (n=2)	128 131
Example 15	6.0	201	Example 35	6.0	225
Example 16	5.5	124	Example 36	6.2	113
Example 17	5.9 (n=14) 6.0 (n=6)	103 125	Example 37	6.9	124
Example 18	6.6	148	Example 38	6.7	122
Example 19	6.5	99	Example 39	5.8	215
Example 20	6.1 (n=6) 6.2 (n=4)	145 155			

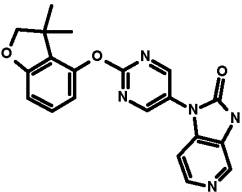
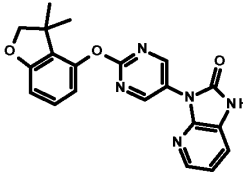
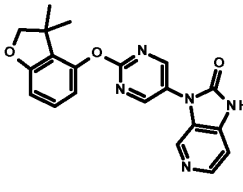
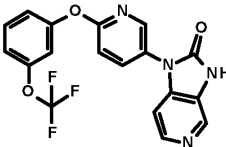
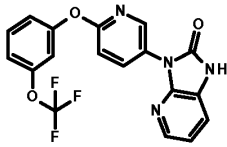
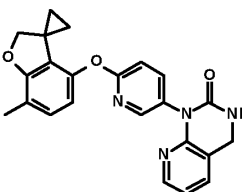
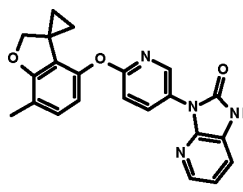
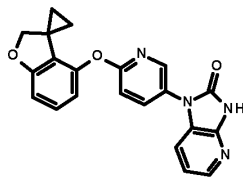
* Data are rounded to one decimal place

The data in Table 2 show that a 5-membered urea fused to a 5- or 6-membered heteroaromatic ring results in compounds displaying good pEC₅₀ properties in the Kv3.1 assay.

5

Data for Reference Examples comprising a 5-membered urea fused to a 3-pyridinyl ring, or a 6-membered urea fused to a 6-membered heterocyclic ring and their corresponding Example compounds are presented in Table 3.

Table 3: Kv3.1 assay results

Reference Example	Kv3.1 pEC ₅₀	Example	Kv3.1 pEC ₅₀
RE9 	<4.3	Example 33 	6.2
		Example 23 	5.1
RE10 	5.6	Example 7 	6.4
RE11 	5.7	Example 1 	6.7
		Example 36 	6.2

* Data are rounded to one decimal place

The data in Table 3 show that Reference Example 9 comprising a 5-membered urea fused to a 3-pyridinyl group is less potent than its corresponding 1-pyridinyl compound (Examples 33) and 2-pyridinyl compound (Example 23). Reference Example 10 comprising a 5-membered urea fused to a 3-pyridinyl group is less potent than its corresponding 1-pyridinyl compound (Examples 7). Reference Example 11 comprising a 6-membered urea fused to a 1-pyridinyl group is less potent than its corresponding 5-membered urea fused to a 1-pyridinyl group (Example 1) and 5-membered urea fused to a 4-pyridinyl group (Example 36).

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, Kv3.2 and Kv3.3 currents following the start of the -15mV depolarising voltage pulse.

$$Y = (Y_0 - Y_{\text{max}}) * \exp(-K * X) + Y_{\text{max}}$$

where:

Y_0 is the current value at the start of the depolarising voltage pulse;

Y_{max} is the plateau current;

K is the rate constant, and Tau_{act} is the activation time constant, which is the reciprocal of K .

Similarly, the effect of the compounds on the time taken for Kv3.1, 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 ($\text{Tau}_{\text{deact}}$) 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 action potentials at high frequency (Rudy *et al.*, 2001). 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
5 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 certain compounds 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} can reduce the ability of neurons in native tissues to fire at high frequency.

10

Biological Example 2: Determination of *in vivo* pharmacokinetic parameters

Materials and Methods

Adult male rats (Charles River, Italy) are dosed with test compound orally at 1mg/kg (5
15 ml/kg, in 5% v/v DMSO, 0.5% w/v HPMC in water) and intravenously at 0.5mg/kg (2ml/kg, in 5% v/v DMSO 40% w/v PEG400 in saline). After oral administration, blood samples are collected under deep Isoflurane anesthesia from the portal vein and heart of each rat (1 rat per time point). After intravenous administration, serial blood samples are collected from the lateral tail vein of each rat. Blood and brain samples are collected at a single timepoint of 0.5 h after dose
20 administration for these animals. In all cases, blood samples are collected into potassium EDTA tubes.

A further group of rats (n=1 per test compound) receive a single intravenous administration of the PgP transport inhibitor, Elacridar (3 mg/kg) shortly before the oral administration of the test compound at 1 mg/kg, as above.

25 Blood and brain samples can be assayed for test compound concentration using a method based on protein precipitation with acetonitrile followed by HPLC/MS-MS analysis with an optimized analytical method.

Analysis

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

Intravenous dosing: Maximum concentration over time (C_{max}), integrated concentration
35 over time (AUC), clearance (Cl_b), volume of distribution (V_{ss}), half-life ($t_{1/2}$) and Brain/Heart Blood conc @0.5hr.

Oral dosing: C_{max}, time of maximum concentration (T_{max}), AUC, bioavailability (F%), fraction absorbed (F_a%), blood to brain ratio (AUC B/B), and Fold-change in AUC B/B in the presence of Elacridar.

5 **Table 4: Test compound AUC and concentrations**

Example	AUC B/B (brain/blood) ratio	Brain/Heart Blood conc @0.5hr
8	<0.1	<0.1
13	0.12	0.13
17	0.45	0.76
24	0.29	0.33
26	<0.1	<0.1
33	0.65	0.63

Biological Example 3: Further Determination of *in vivo* pharmacokinetic parameters

Determination of blood and brain tissue binding

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

15 An appropriate amount of test compound is dissolved in DMSO to give a 10 millimolar solution. Further dilutions, to obtain a 166.7 micromolar working solution are then prepared using 50% acetonitrile in MilliQ water. This working solution is used to spike the blood to obtain a final concentration of 0.5 micromolar in whole blood. Similarly, the working solution is used to spike brain samples to obtain a final concentration of 5 micromolar in whole brain. From these spiked blood and brain preparations, control samples (n=3), are immediately extracted and used to
20 calculate the initial recovery of the test items.

150 microL of compound-free buffer (isotonic phosphate buffer for blood or artificial CSF buffer for brain) is dispensed in one half-well and 150 microL of spiked matrix (blood or brain) is loaded in the other half-well, with the two halves separated by a semi-permeable membrane. After an equilibration period of 5 h at 37°C, 50 microL of dialysed matrix (blood or brain) is added
25 to 50 microL of corresponding compound-free buffer, and vice-versa for buffer, such that the volume of buffer to matrix (blood or brain) remains the same. Samples are then extracted by protein precipitation with 300 microL of acetonitrile containing rolipram (control for positive ionization mode) or diclofenac (control for negative ionization mode) as internal standards and centrifuged for 10min at 3000rpm. Supernatants are collected (100 microL), diluted with 27% AcN

in MilliQ water (200 microL) and then injected into an HPLC-MS/MS or UPLC-MS/MS system to determine the concentration of test compound present.

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

5
$$Afu = \text{Buffer/Blood or } Afu = \text{CSF/Brain}$$

where Afu = apparent fraction unbound; Buffer= analyte/internal standard ratio determined in the buffer compartment; Blood= analyte/internal standard ratio determined in the blood compartment; Brain= analyte/internal standard ratio determined in the brain compartment.

10

$$Fucr = \frac{1/D}{[(1/Afu - 1) + 1/D]}$$

where: fucr = Fraction unbound corrected; D =matrix dilution factor (D=2 for blood and D=3 for brain).

15

then:

$$\% \text{Binding} = (1 - fucr) \times 100$$

$$\% \text{Unbound} = 100 - \% \text{Bound}$$

20 *In Vitro Metabolic Stability Study in Hepatocytes*

The objective of this study was to determine metabolic stability of test items in rat and human liver microsomes. Verapamil and dextromethorphan were used as positive controls for microsomal incubation.

25 Incubation medium was prepared by combining 11.2 mL of potassium phosphate monobasic and 38.8 mL of potassium phosphate dibasic, diluted to 1 L with water. Cryopreserved microsomes were thawed and kept on ice until use. Microsomes were then diluted in incubation to a protein concentration of 0.56 mg/mL. Cells were centrifuged, re-suspended in medium and counted by means of a haemocytometer. Cell viability was measured using the Trypan Blue exclusion test.

30 NADPH regenerating system solution was prepared by dissolving 1.7 mg of NADP, 7.8 mg of G6P and 6 units of G6P-Dehydrogenase in 1 mL of 2% sodium bicarbonate solution (prepared by dissolving 20 g of NaHCO₃ in 1 L of water).

35 Test compounds were separately dissolved in DMF to obtain 10 mM stock solutions that were further diluted in water/acetonitrile 50/50 (v/v) to obtain the corresponding 50 uM working solutions. Verapamil and dextromethorphan were dissolved in DMF in order to obtain a 10 mM verapamil solution and 10 mM dextromethorphan solution. These solutions were then diluted in

the incubation medium in order to obtain a 50 μ M verapamil working solution and a 50 μ M dextromethorphan working solution.

800 μ L-aliquots of NADPH regenerating system were pre-warmed at 37°C for 5 minutes. 5 μ L of 50 μ M test compounds, verapamil or dextromethorphan were added to 445 μ L of the
 5 0.56 mg/mL microsomes solution and the incubation mixture was pre-warmed in a 96 deep well 2 mL plate (incubation plate) at 37°C for 5 minutes. The incubation reactions were initiated by adding 50 μ L of pre-warmed NADPH regenerating system to the incubation mixtures. 50 μ L aliquots were taken from incubation mixtures at: 0, 3, 6, 9, 15, and 30 minutes and the reactions were stopped by adding 100 μ L of aceontrile with the corresponding internal standard. Samples
 10 were then diluted with 120 μ L of water (final organic solvent percentage at 37%) and centrifuged at 3000 rpm for 10 minutes, prior the LC-MS/MS analysis.

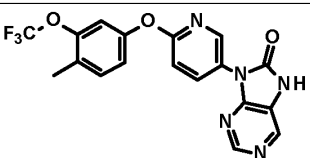
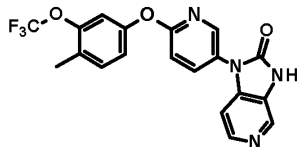
Metabolic stability was calculated from the peak area ratio of the remaining test compound with internal standard versus time. The intrinsic clearance (CL_{int}) was determined from the first order elimination constant k (min⁻¹) (obtained from GraphPad by plotting the natural logarithm of
 15 the peak area ratio of the remaining test item with internal standard versus time), using the actual volume of the incubation V (mL), the amount of hepatocytes in the incubation M (million cells) and the hepatocellularity number per g liver H_n (120 for human).

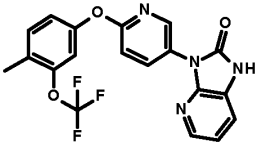
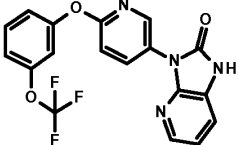
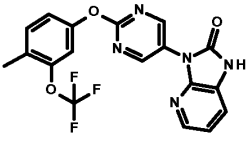
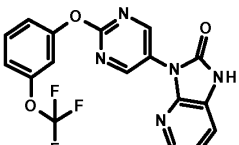
$$CL_{int} = k * \frac{V}{M} * \frac{H_n \times 10^6 \text{ cells}}{g \text{ liver}}$$

Values for CL_{int} were expressed as mL/min/g liver as shown in Table 5:

20

Table 5: Test compound pharmacokinetic parameters

Example	Kv3.1 pEC50	%FU Blood	%FU Brain	CLi rat (mL/min/g)	CLi human (mL/min/g)
 RE12 (Example 25 of WO2021214090)	5.2*	0.7	0.6	1.5	1.7
 RE13 (Example 47 of WO2021214090)	5.6**	1.3	0.5	1.3	0.6

Example	Kv3.1 pEC ₅₀	%FU Blood	%FU Brain	Cli rat (mL/min/g)	Cli human (mL/min/g)
Example 4 	5.9	0.2	0.3	0.9	0.7
Example 7 	6.4	-	-	-	-
Example 32 	5.8	1.0	0.6	0.9	0.8
Example 17 	6.0	1.6	1.6	<0.5	<0.5

* Based on EC₅₀ value of 5.9 as reported in WO2021214090. Reference Example 12 was prepared by analogous methods to the Examples - LC/MS: QC_3_MIN: Rt= 2.04 min m/z 404 [M+H]⁺.

** Based on EC₅₀ value of 2.4 as reported in WO2021214090. Reference Example 13 was prepared by analogous methods to the Examples - LC/MS: QC_3_MIN: Rt= 2.07 min m/z 403 [M+H]⁺.

The data in Table 5 show that Example 17 demonstrates a plurality of desirable properties - while maintaining good potency (pEC₅₀ 6.0), Example 17 also has good fraction unbound (1.6% in blood and brain) and good clearance (Cli <0.5 in humans and rats). These properties compare favourably with compounds such as Examples 4 and 32, and Reference Examples 12 and 13 (Example 25 and 27 of WO2021214090).

Formulation Example 1 - tablet:

5 A compound of formula (I), or a pharmaceutically acceptable salt and/or solvate and/or derivative thereof, can be used in a manner known *per se* as the active ingredient for the production of tablets of the following composition:

	Per tablet
Active ingredient	200 mg
10 Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	20 mg
	425 mg

15

Formulation Example 2 - capsule:

20 A compound of formula (I), or a pharmaceutically acceptable salt and/or solvate and/or derivative thereof, can be used in a manner known *per se* as the active ingredient for the production of capsules of the following composition:

	Per capsule
Active ingredient	100.0 mg
Com starch	20.0 mg
25 Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg
	220.0 mg

30 Additional animal models

Patent applications WO2011/069951, WO2012/076877, WO2012/168710, WO2013/175215 WO2013/182851, WO2013/083994, WO2013/182850, WO2017/103604, WO2018/020263, WO2018/109484 and WO2020/079422 (all incorporated by reference) demonstrate the activity of compounds which are modulators of Kv3.1 and Kv3.2 in animal models of seizure, hyperactivity, sleep disorders, psychosis, hearing disorders, bipolar disorders and pain.

35

Patent application WO2013/175211 (incorporated by reference) demonstrates the efficacy of a compound which is a modulator of Kv3.1 and Kv3.2 in a model of acute noise-induced hearing loss in the chinchilla, and also evaluates the efficacy of the compound in a model of central auditory processing deficit and in a model of tinnitus.

5

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.

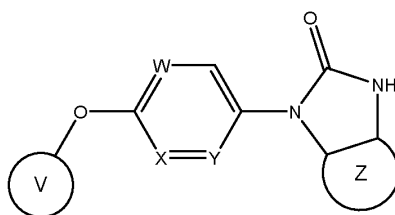
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The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described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

15

Clauses of the invention

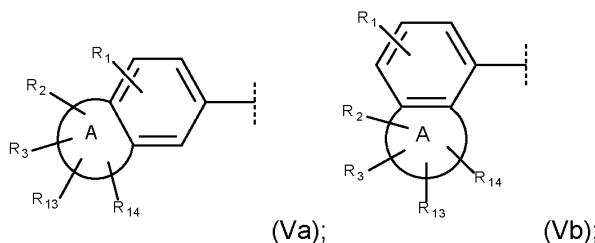
Clause 1. A compound of formula (I):



20 wherein:

V is group (Va), group (Vb) or group (Vc);

wherein group (Va) and group (Vb) are:



wherein:

25 R₁ is H, C₁₋₄alkyl, halo, haloC₁₋₄alkyl, CN, C₁₋₄alkoxy, or haloC₁₋₄alkoxy;

R₂ is H, C₁₋₄alkyl, C₃₋₅ spiro carbocyclyl, haloC₁₋₄alkyl or halo;

R₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₃ is absent;

R₁₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₃ is absent;

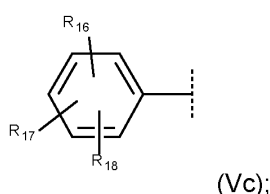
R₁₄ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₄ is absent;

A is a 5 or 6 membered saturated or unsaturated heterocycle, with at least one O atom; which

- 5 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;

wherein R₂ and R₃ may be attached to the same or a different ring atom; R₂ may be attached to a fused ring atom; and wherein R₁₃ and R₁₄ may be attached to the same or a different ring atom;

- 10 wherein group (Vc) is:



wherein:

R₁₆ is halo, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy or CN;

R₁₇ is H, halo, CN, C₁₋₄alkyl, C₁₋₄alkoxy or haloC₁₋₄alkoxy;

- 15 R₁₈ is H, halo, CN, C₁₋₄alkyl or C₁₋₄alkoxy;

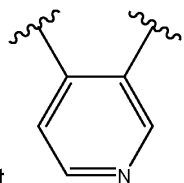
W is N or CH;

X is N or CH;

Y is N or CH;

wherein at least one of W, X and Y is CH, and when one of X and Y is N, the other is CH;

- 20 Z is a 5-membered heteroaryl comprising one or two nitrogen atoms, and wherein one of the nitrogen atoms and one of the carbon atoms may be independently optionally substituted by methyl; or Z is a 6-membered heteroaryl comprising one or two nitrogen atoms, wherein one of the carbon atoms may be optionally substituted by methyl; and

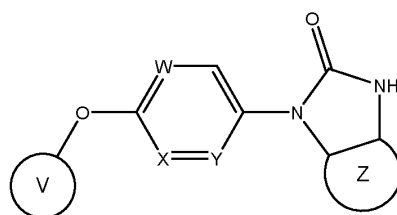


provided that Z is not ;

- 25 or a salt and/or solvate and/or derivative thereof.

Clause 2. A compound of formula (I):

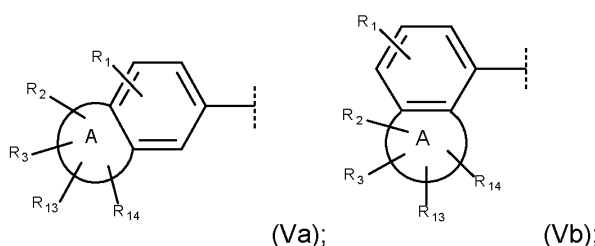
123



wherein:

V is group (Va), group (Vb) or group (Vc);

wherein group (Va) and group (Vb) are:



wherein:

R₁ is H, C₁₋₄alkyl, halo, haloC₁₋₄alkyl, CN, C₁₋₄alkoxy, or haloC₁₋₄alkoxy;

R₂ is H, C₁₋₄alkyl, C₃₋₅ spiro carbocyclyl, haloC₁₋₄alkyl or halo;

R₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₃ is absent;

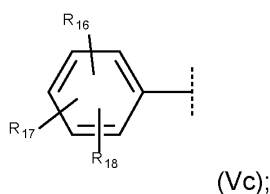
10 R₁₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₃ is absent;

R₁₄ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₄ 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;

15 wherein R₂ and R₃ may be attached to the same or a different ring atom; R₂ may be attached to a fused ring atom; and wherein R₁₃ and R₁₄ may be attached to the same or a different ring atom;

wherein group (Vc) is:



20 wherein:

R₁₆ is halo, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy or CN;

R₁₇ is H, halo, CN, C₁₋₄alkyl, C₁₋₄alkoxy or haloC₁₋₄alkoxy;

R₁₈ is H, halo, CN, C₁₋₄alkyl or C₁₋₄alkoxy;

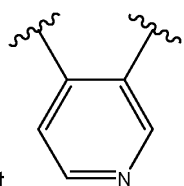
W is N or CH;

X is N or CH;

Y is N or CH;

wherein at least one of W, X and Y is CH, and when one of X and Y is N, the other is CH;

- 5 Z is a 5-membered heteroaryl comprising one or two nitrogen atoms, and wherein one of the nitrogen atoms and one of the carbon atoms may be independently optionally substituted by methyl; or Z is a 6-membered heteroaryl comprising one or two nitrogen atoms, wherein one of the carbon atoms may be optionally substituted by methyl; and



provided that Z is not ;

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

Clause 3. The compound or pharmaceutically acceptable salt and/or solvate thereof according to clause 2.

Clause 4. The compound or solvate thereof according to clause 3.

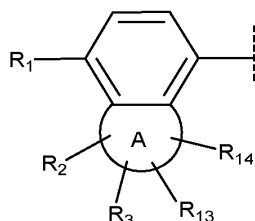
- 15 Clause 5. The compound or a pharmaceutically acceptable salt thereof according to clause 2.

Clause 6. The compound according to clause 1 or 2.

Clause 7. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6, wherein V is group (Va).

- 20 Clause 8. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6, wherein V is group (Vb).

Clause 9. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 8, wherein (Vb) is:



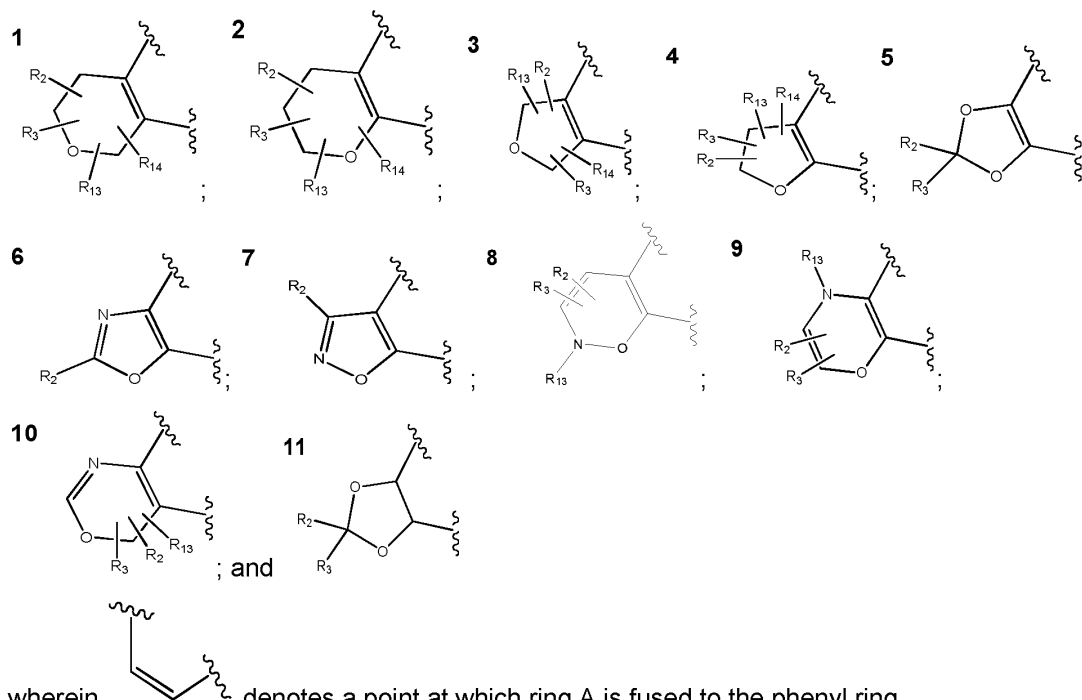
- 25 Clause 10. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 9, wherein R₁ is H, C₁₋₄alkyl, halo, haloC₁₋₄alkyl or CN, in particular C₁₋₄alkyl such as methyl.

Clause 11. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 10, wherein R₁ is H.

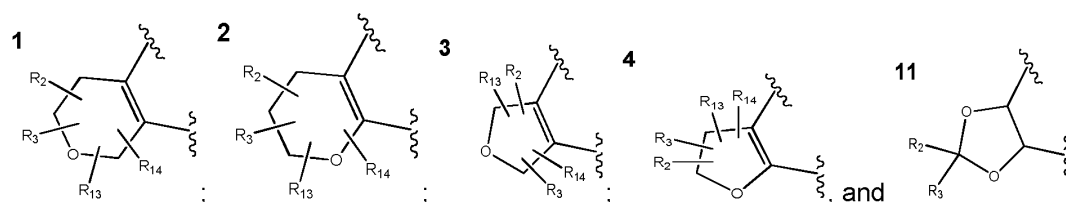
Clause 12. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 10, wherein R_1 is methyl.

Clause 13. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 12, wherein ring A is selected from the

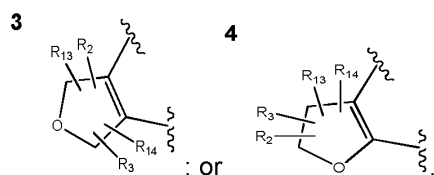
5 group consisting of:



10 Clause 14. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 13, wherein ring A is selected from the group consisting of:



15 Clause 15. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 14, wherein ring A is:



- Clause 16. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 15, wherein R_2 is H, C_{1-4} alkyl, C_{3-5} spiro carbocyclyl or halo; in particular C_{1-4} alkyl or C_{3-5} spiro carbocyclyl.
- Clause 17. The compound, pharmaceutically acceptable salt thereof, solvate thereof,
5 and/or derivative thereof according to clause 16, wherein R_2 is C_3 spiro carbocycle.
- Clause 18. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 17, wherein R_2 is methyl or halo e.g. fluoro.
- Clause 19. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 18, wherein R_2 is methyl.
- 10 Clause 20. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 19, wherein R_3 is H, C_{1-4} alkyl, halo C_{1-4} alkyl or halo.
- Clause 21. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 20, wherein R_3 is methyl or halo e.g. fluoro.
- 15 Clause 22. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 21, wherein R_3 is methyl.
- Clause 23. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 22, wherein R_{13} is H or is absent and is suitably absent.
- 20 Clause 24. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 23, wherein R_{14} is H or is absent and is suitably absent.
- Clause 25. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6, wherein V is group (Vc).
- 25 Clause 26. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 or 25, wherein R_{16} is C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl, halo C_{1-4} alkoxy or CN.
- Clause 27. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 26, wherein R_{16} is methyl, ethyl, propyl, butyl, cyclopropyl,
30 chloro, fluoro, methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy or CN.
- Clause 28. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 27, wherein R_{16} is trifluoromethoxy or methoxy.
- Clause 29. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 or 25 to 28, wherein R_{16} is at the meta-
35 position.

Clause 30. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 or 25 to 29, wherein R_{17} is H, halo, CN, C_{1-4} alkyl or C_{1-4} alkoxy.

Clause 31. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 30, wherein R_{17} is H.

Clause 32. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 31, wherein R_{17} is methyl, ethyl, propyl, butyl, cyclopropyl, chloro, fluoro, methoxy, ethoxy, propoxy, trifluoromethoxy or CN.

Clause 33. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 32, wherein R_{17} is methyl or CN.

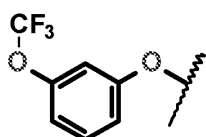
Clause 34. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 or 30 to 33, wherein R_{17} is at the para-position.

Clause 35. The compound, pharmaceutically acceptable salt thereof, solvate thereof, or derivative thereof according to any one of clauses 1 to 6 or 25 to 34, wherein R_{18} is H.

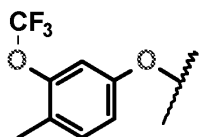
Clause 36. The compound, pharmaceutically acceptable salt thereof, solvate thereof, or derivative thereof according to any one of clauses 1 to 6 or 25 to 29, wherein R_{17} is H and R_{18} is H.

Clause 37. The compound, pharmaceutically acceptable salt thereof, solvate thereof, or derivative thereof according to clause 36, wherein R_{16} is at the meta-position.

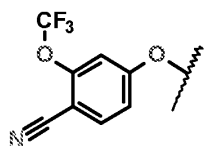
Clause 38. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 or 25 to 37, wherein V is:



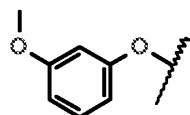
Clause 39. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 or 25 to 37, wherein V is:



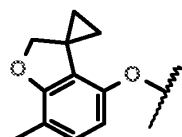
Clause 40. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 or 25 to 37, wherein V is:



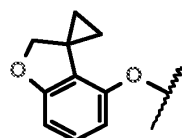
Clause 41. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 or 25 to 37, wherein V is:



- 5 Clause 42. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 24, wherein V is:

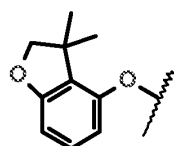


Clause 43. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 24, wherein V is:



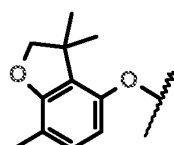
10

Clause 44. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 24, wherein V is:



Clause 45. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 24, wherein V is:

15



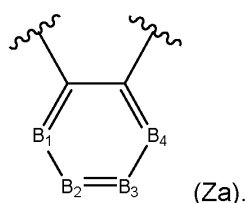
Clause 46. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 45, wherein W is N, and X and Y are CH.

Clause 47. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 45, wherein W is N, X is N and Y is CH.

5 Clause 48. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 45, wherein W is N, X is CH and Y is N.

Clause 49. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 45, wherein W and X are CH, and Y is N.

10 Clause 50. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 49, wherein Z is group (Za):



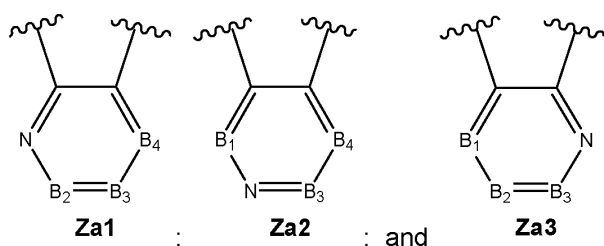
Clause 51. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 50, wherein B₁ is N.

15 Clause 52. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 50, wherein B₂ is N.

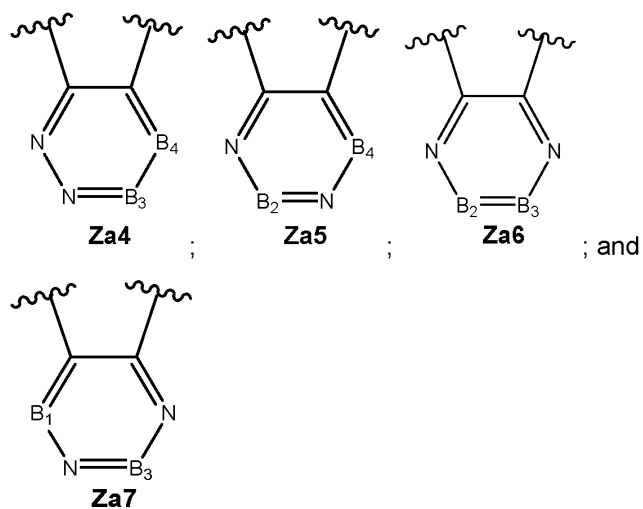
Clause 53. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 50, wherein B₃ is N.

Clause 54. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 50, wherein B₄ is N.

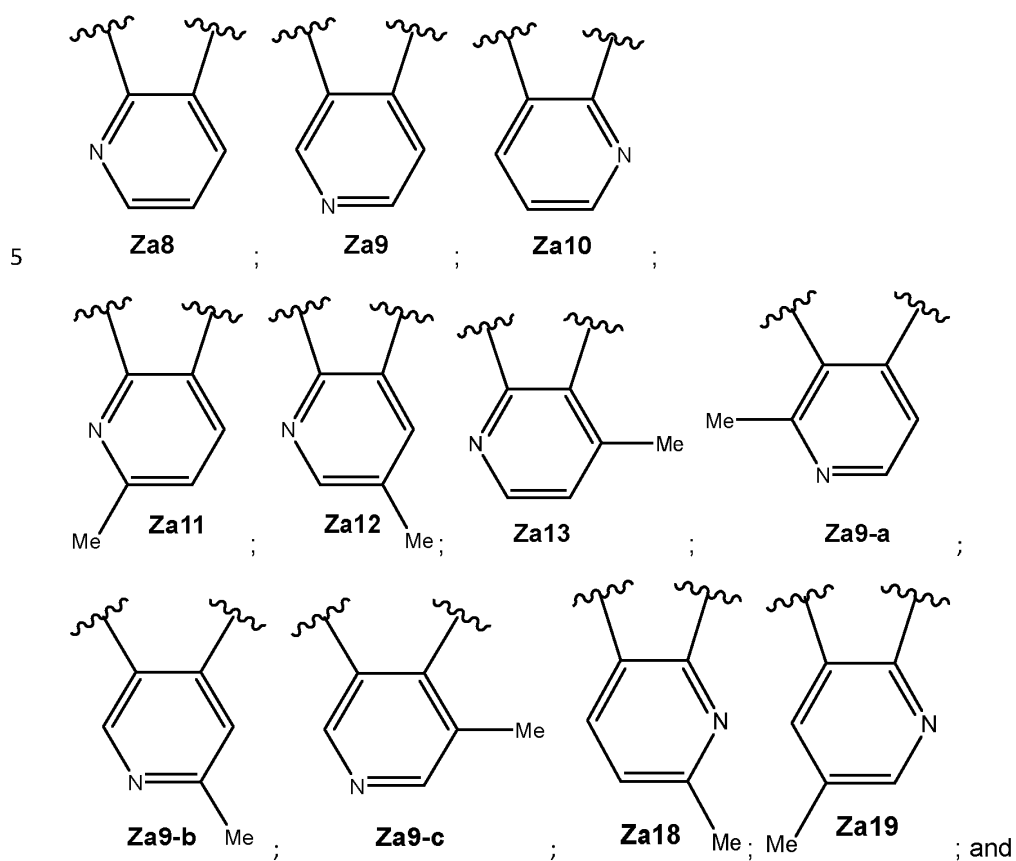
20 Clause 55. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 50, wherein (Za) is selected from the group consisting of:

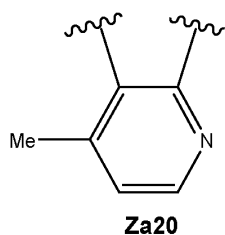


Clause 56. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 50, wherein (Za) is selected from the group consisting of:

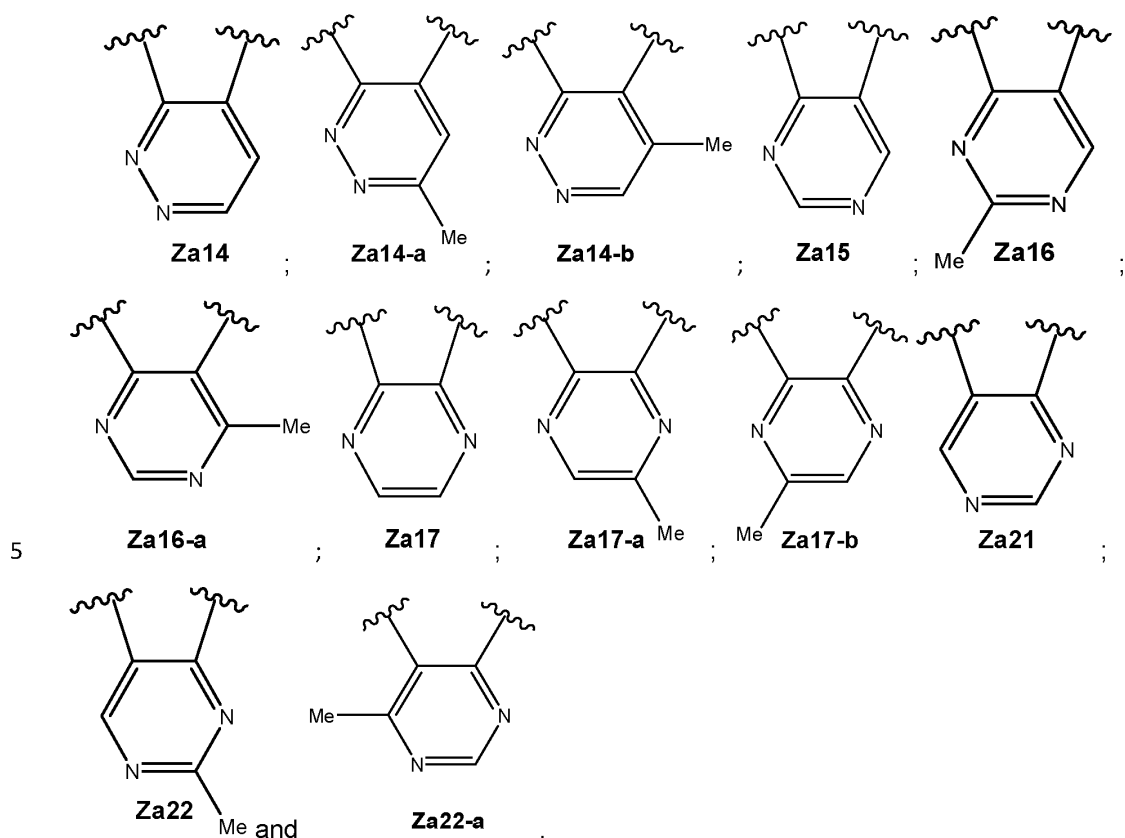


Clause 57. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 55, wherein (Za) is selected from the group consisting of:

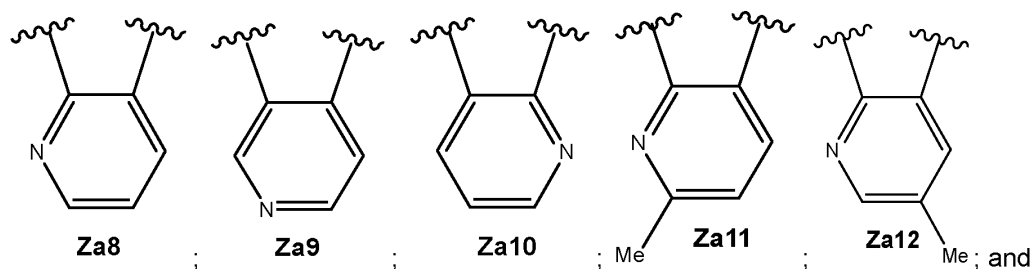


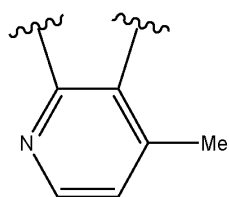


Clause 58. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 56, wherein (Za) is selected from the group consisting of:

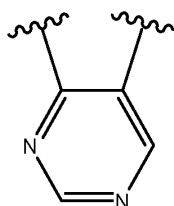
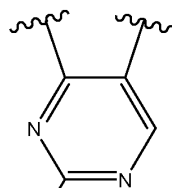


Clause 59. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 57, wherein (Za) is selected from the group consisting of:



**Za13**

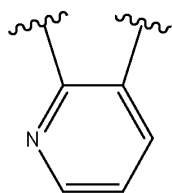
Clause 60. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 58, wherein (Za) is selected from the group consisting of:

**Za15****Za16**

; and Me

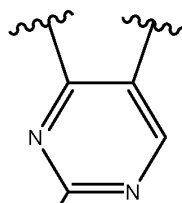
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Clause 61. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 59, wherein (Za) is:

**Za8**

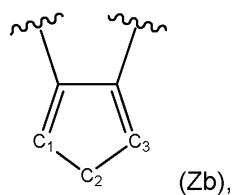
Clause 62. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 60, wherein (Za) is:

10

**Za16**

Clause 63. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 49, wherein Z is group (Zb):

133

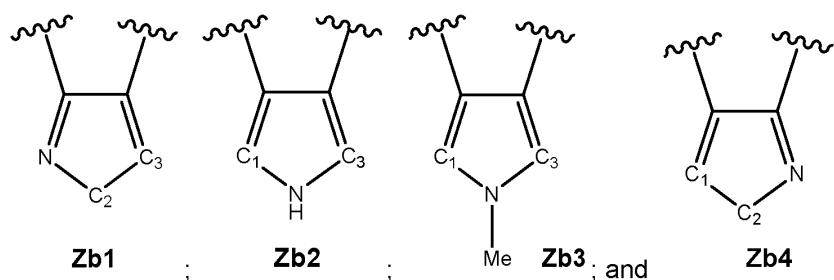


wherein:

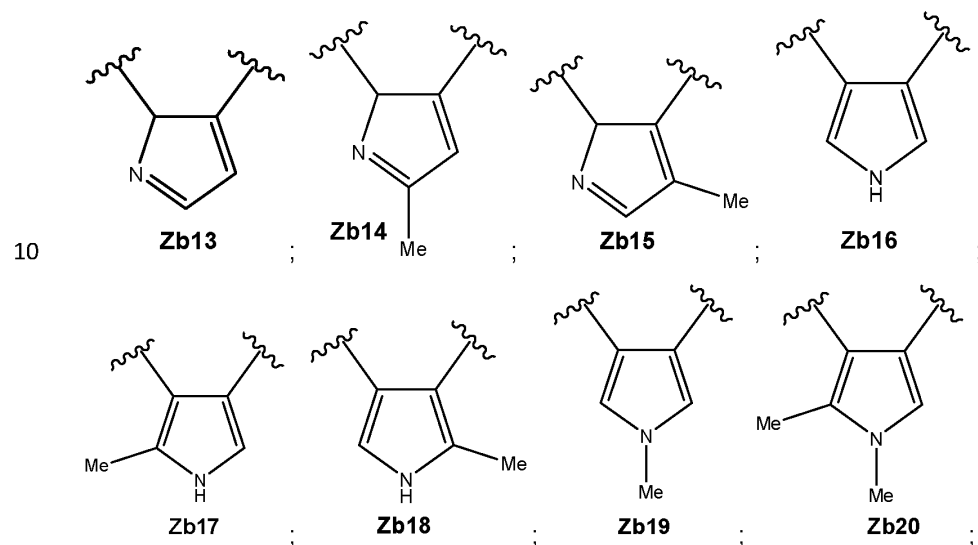
C₁ and C₃ are each independently selected from CH, C(Me) and N; and

C₂ is NH or N(Me); and wherein when one of C₁ and C₃ is N, the other is CH or C(Me).

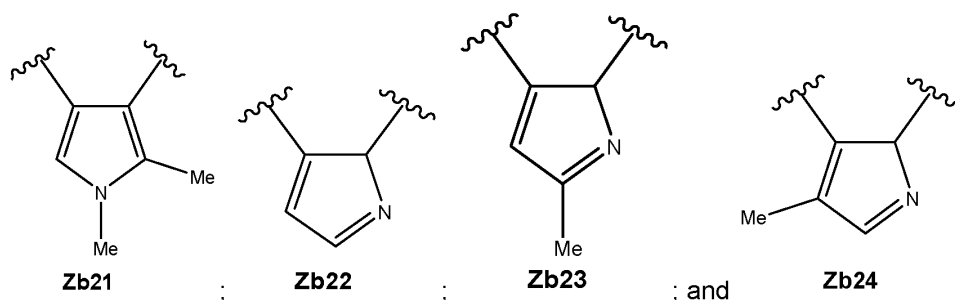
- 5 Clause 64. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 63, wherein (Zb) is selected from the group consisting of:



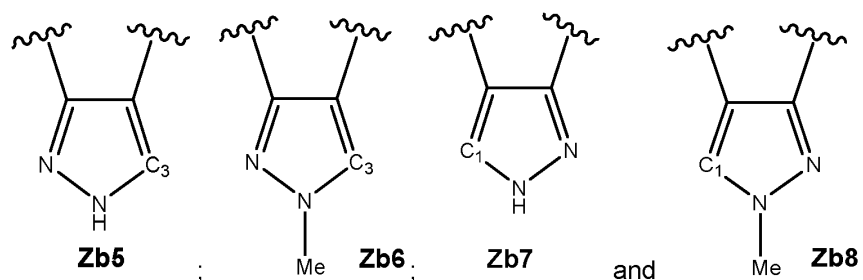
- Clause 65. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 63, wherein (Zb) is selected from the group consisting of:



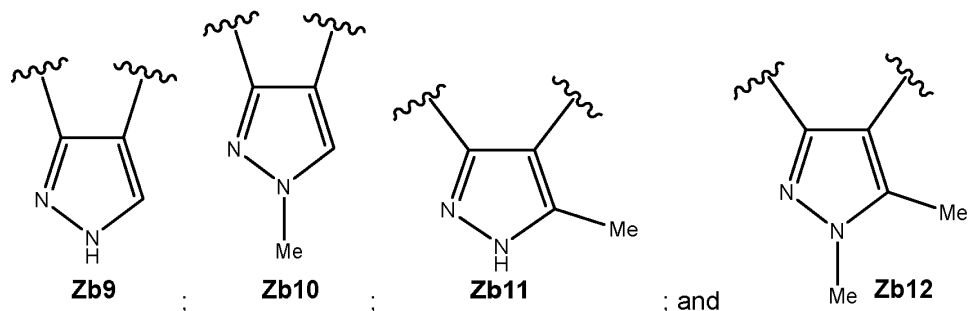
134



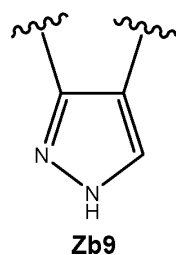
Clause 66. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 63, wherein (Zb) is selected from the group consisting of:



- 5 Clause 67. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 66, wherein (Zb) is selected from the group consisting of:

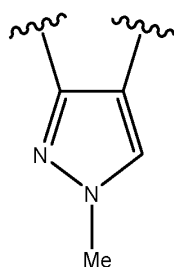


Clause 68. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 67, wherein (Zb) is:

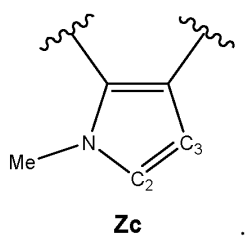


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Clause 69. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 68, wherein (Zb) is:

**Zb10**

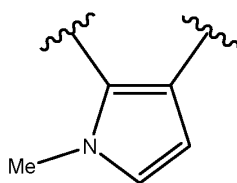
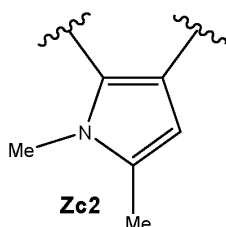
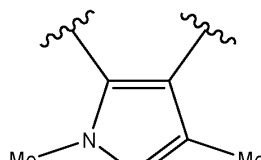
Clause 70. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 49, wherein Z is group (Zc):

**Zc**

5 wherein:

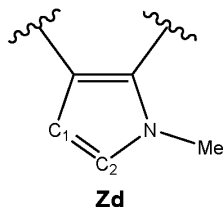
C₂ is N, CH or C(Me) and C₃ is CH or C(Me); wherein when one of C₂ or C₃ is C(Me), the other is CH.

Clause 71. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 70, wherein Zc is selected from the group consisting of:

**Zc1****Zc2****Zc3**

10

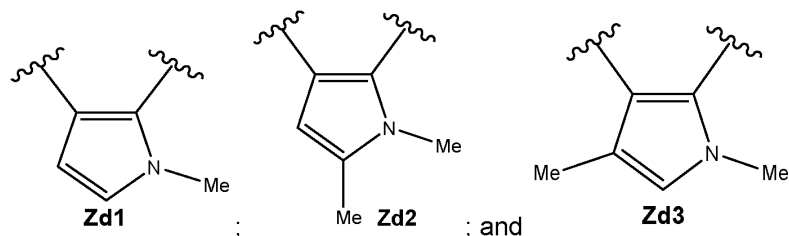
Clause 72. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 49, wherein Z is group (Zd):

**Zd**

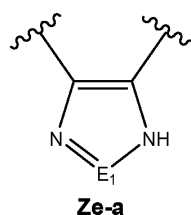
wherein:

15 C₁ is CH or C(Me) and C₂ is N, CH or C(Me); wherein when one of C₁ or C₂ is C(Me), the other is CH.

Clause 73. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 72, wherein (Zd) is selected from the group consisting of:



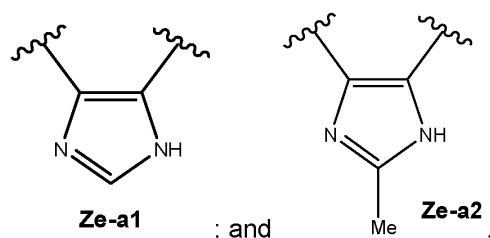
Clause 74. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 49, wherein Z is group (Ze-a):



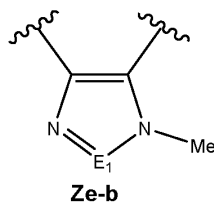
wherein:

E₁ is CH or CMe.

Clause 75. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 74, wherein (Ze-a) is selected from the group consisting of:



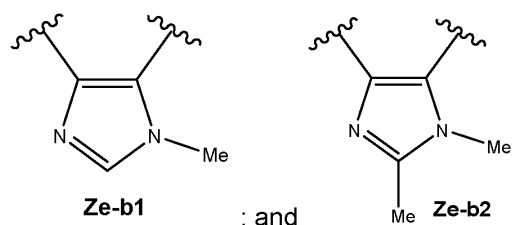
Clause 76. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 49, wherein Z is group (Ze-b):



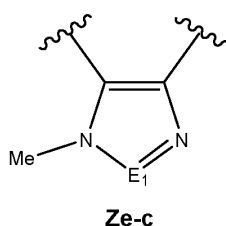
wherein

E₁ is CH or C(Me).

Clause 77. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 76, wherein (Ze-b) is selected from the group consisting of:



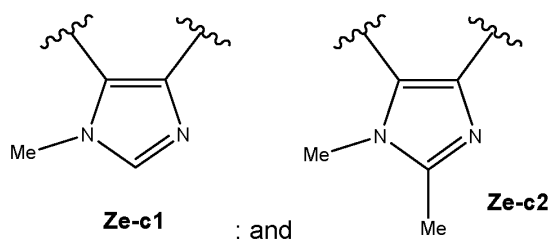
- 5 Clause 78. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 49, wherein Z is group (Ze-c):



wherein:

E₁ is CH or C(Me).

- 10 Clause 79. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to clause 76, wherein (Ze-c) is selected from the group consisting of:



- 15 Clause 80. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6, which is selected from the group consisting of:

3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;

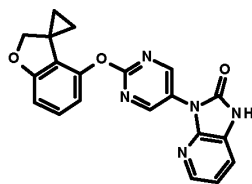
- 20 7-methyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;

3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one;

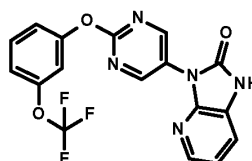
3-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;

- 7-methyl-3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;
- 5 3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[5-[3-(trifluoromethoxy)phenoxy]pyrazin-2-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 10 b]pyridin-2-one;
- 3-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-(2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidin-5-yl)-1H,2H,3H-imidazo[4,5-b]pyridin-2-one;
- 4-[[5-(2-oxo-1H-imidazo[4,5-b]pyridin-3-yl)-2-pyridyl]oxy]-2-(trifluoromethoxy)benzonitrile;
- 15 7-methyl-3-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrimidin-5-yl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[2-(3-methoxyphenoxy)pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 2-methyl-6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-4H-imidazo[4,5-c]pyrazol-5-one;
- 20 c]pyrazol-5-one;
- 2-methyl-6-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-4H-imidazo[4,5-c]pyrazol-5-one;
- 6-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-2-methyl-4H-imidazo[4,5-c]pyrazol-5-one;
- 2-methyl-6-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)-4H-imidazo[4,5-c]pyrazol-5-one;
- 25 c]pyrazol-5-one;
- 2-methyl-6-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrimidin-5-yl)-4H-imidazo[4,5-c]pyrazol-5-one;
- 3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-c]pyridin-2-one;
- 2-methyl-9-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one;
- 30 2-methyl-9-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-7H-purin-8-one;
- one;
- 2-methyl-9-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-7H-purin-8-one;
- 2-methyl-9-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one;
- 9-[6-(3-methoxyphenoxy)-3-pyridyl]-2-methyl-7H-purin-8-one;
- 35 9-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-7H-purin-8-one;
- 9-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-2-methyl-7H-purin-8-one;

- 3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridine-2-one;
- 3-[2-[4-methyl-3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridine-2-one;
- 3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridine-2-one;
- 5 6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-2,4-dihydroimidazo[4,5-c]pyrazol-5-one;
- 3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-c]pyridine-2-one;
- 1-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-3H-imidazo[4,5-b]pyridine-2-one;
- 10 5-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-1H-imidazo[4,5-b]pyridine-2-one;
- 6-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-1H-imidazo[4,5-b]pyridine-2-one; and
- 3-[2-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridine-2-one.
- 15 Clause 81. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6, which is 3-(2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidin-5-yl)-1H,2H,3H-imidazo[4,5-b]pyridine-2-one:

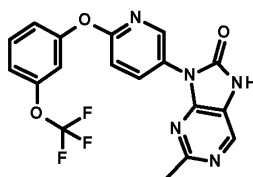


- Clause 82. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6, which is 3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridine-2-one:
- 20

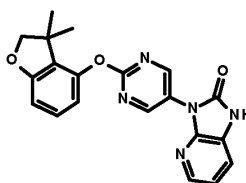


- Clause 83. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 which is 2-methyl-9-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one:
- 25

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Clause 84. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 6 which is 3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one:



5

Clause 85. The compound according to any one of clauses 81 to 84, wherein the compound is in the form of a pharmaceutically acceptable salt.

Clause 86. The compound according to any one of clauses 81 to 84, wherein the compound is not in the form of a salt.

10 Clause 87. A pharmaceutical composition comprising the compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 86 and a pharmaceutically acceptable carrier or excipient.

Clause 88. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 86 or the pharmaceutical composition
15 according to clause 87 for use as a medicament.

Clause 89. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 86 or the pharmaceutical composition for use according to clause 87 for use in the prophylaxis or treatment of a disease or disorder selected from the group consisting of hearing disorders, schizophrenia, depression and mood disorders, bipolar disorder, substance abuse disorders, anxiety disorders, sleep disorders, hyperacusis and disturbances of loudness perception, Ménière's disease, disorders of balance, and disorders of the inner ear, impulse control disorder, personality disorders, attention-deficit/hyperactivity disorder, autism spectrum disorders, eating disorders, cognition impairment, ataxia, pain such as neuropathic pain, inflammatory pain and miscellaneous pain, Lewy body
20 dementia and Parkinson's disease.

25 Clause 90. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 86 or the pharmaceutical composition for use according to clause 87 for use in the prophylaxis or treatment of progressive myoclonic

epilepsy, including PME associated with mutations in the KCNC1 gene, hearing disorders, including hearing loss and tinnitus, Fragile X syndrome, schizophrenia, substance abuse disorders, or pain.

5 Clause 91. Use of a compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 86 or the pharmaceutical composition for use according to clause 87 in the manufacture of a medicament.

Clause 92. Use of according to clause 91, in the manufacture of a medicament for the prophylaxis or treatment of progressive myoclonic epilepsy, including PME associated with mutations in the KCNC1 gene, hearing disorders, including hearing loss and tinnitus, Fragile X
10 syndrome, schizophrenia, substance abuse disorders, or pain.

Clause 93. A method for the prophylaxis or treatment of progressive myoclonic epilepsy, including PME associated with mutations in the KCNC1 gene, hearing disorders, including hearing loss and tinnitus, Fragile X syndrome, schizophrenia, substance abuse disorders, or pain, said method comprising administering a compound, pharmaceutically acceptable salt
15 thereof, solvate thereof, and/or derivative thereof according to any one of clauses 1 to 86 or the pharmaceutical composition for use according to clause 87 to a subject.

Clause 94. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 93, for use in the prophylaxis or treatment of progressive myoclonic
20 epilepsy.

Clause 95. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 91, for use in the prophylaxis or treatment of progressive myoclonic epilepsy associated with mutations in the KCNC1 gene.

25 Clause 96. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to to clause 94, for use in the prophylaxis or treatment of juvenile progressive myoclonic epilepsy.

Clause 97. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to
30 any one of clauses 1 to 93, for use in the prophylaxis or treatment of hearing loss.

Clause 98. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 93, for use in the prophylaxis or treatment of tinnitus.

Clause 99. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or
35 derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 93, for use in the prophylaxis or treatment of Fragile X syndrome.

Clause 100. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 93, for use in the prophylaxis or treatment of schizophrenia.

Clause 101. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or
5 derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 93, for use in the prophylaxis or treatment of substance abuse disorders.

Clause 102. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or
10 derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 93, for use in the prophylaxis or treatment of pain, such as neuropathic pain, inflammatory pain or miscellaneous pain.

Clause 103. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 102, for use in prophylaxis.

15 Clause 104. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 103, for use in treatment.

Clause 105. The derivative according to any one of clauses 1 to 104, functionalised at the secondary nitrogen of the urea with a group L, wherein L is selected from:

20 $-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,

$-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,

$-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,

$-\text{CH}(\text{R}^x)-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein R^x is hydrogen or C_{1-3} alkyl,

$-\text{CH}(\text{R}^x)-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,

25 $-\text{CH}(\text{R}^x)-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, and

$-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2 \cdot \text{M}^+$.

Clause 106. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 105, for use in a human.

30 Clause 107. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to clause 106, for use in a human of less than 18 years of age.

Clause 108. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to

35 clause 107, for use in a human 4 to 17 years old.

Clause 109. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to clause 106, for use in a human aged 18 to 65.

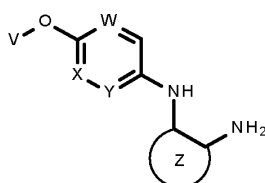
Clause 110. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to clause 106, for use in a human aged 66 years old or older.

Clause 111. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 110, for administration at 5 to 250 mg per day.

Clause 112. The compound, pharmaceutically acceptable salt thereof, solvate thereof, and/or derivative thereof, the pharmaceutical composition, use or method according to according to any one of clauses 1 to 111, for administration for a period of at least three months.

Clause 113. A compound or salt thereof selected from the group consisting of:

- a compound of formula (II):

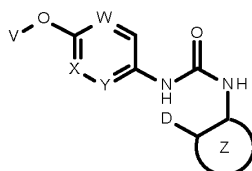


(II)

15

wherein V, W, X, Y and Z, B₁, B₂, B₃ and B₄ are as defined for the compound of formula (I);

- a compound of formula (III):



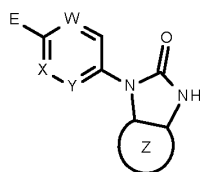
(III)

wherein V, W, X, Y and Z are as defined for the compound of formula (I) and D is halo, such as Cl, Br or I;

20

- a compound of formula (IV):

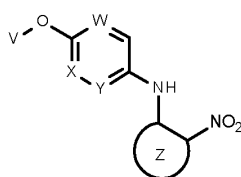
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(IV)

wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl;

- a compound of formula (VI):

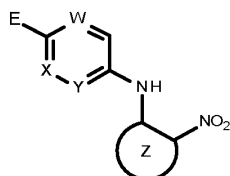


(VI)

5

wherein V, W, X, Y and Z are as defined for the compound of formula (I);

- a compound of formula (IX):

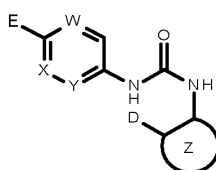


(IX)

wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl;

10

- a compound of formula (X):



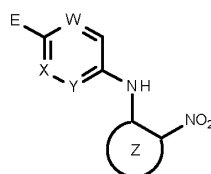
(X)

wherein W, X, Y and Z are as defined for the compound of formula (I), E is halo, such as F or Cl and D is halo, such as Cl, Br or I; and

15

- a compound of formula (XIII):

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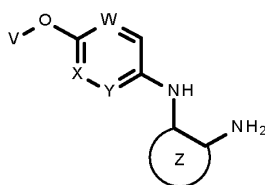


(XII)

wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl;

or a salt thereof, such as a pharmaceutically acceptable salt thereof.

- 5 Clause 114. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate and/or derivative thereof, which comprises reacting a compound of formula (II):

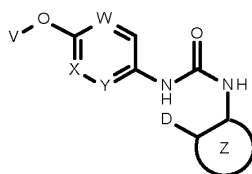


(II)

or a salt thereof, wherein V, W, X, Y and Z are as defined for the compound of formula (I), with a carbonylating agent such as triphosgene or carbonyldiimidazole.

10

Clause 115. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate and/or derivative thereof, which comprises reacting a compound of formula (III):

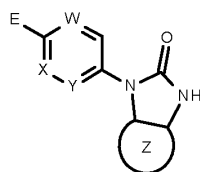


(III)

- 15 or a salt thereof, wherein V, W, X, Y and Z are as defined for the compound of formula (I), and D is halo, such as Cl, Br or I, under metal catalysed cross-coupling conditions.

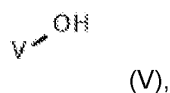
Clause 116. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt and/or solvate and/or derivative thereof, which comprises reacting a compound of formula (III):

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(IV)

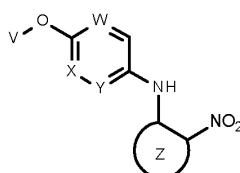
or a salt thereof, wherein W, X, Y and Z are as defined for the compound of formula (I), and E is halo, such as F or Cl, with a compound of formula (V):



(V),

- 5 or a salt thereof, wherein V is as defined in claim 1.

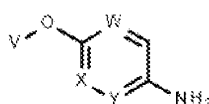
Clause 117. A process for the preparation for a compound of formula (II), or a salt thereof, which comprises reacting a compound of formula (VI):



(VI)

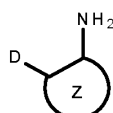
- 10 or a salt thereof, wherein V, W, X, Y and Z are as defined for the compound of formula (I), under reduction conditions (e.g. in the presence of Fe powder and ammonium chloride).

Clause 118. A process for the preparation of a compound of formula (III), or a salt thereof, which comprises reacting a compound of formula (VII):



(VII)

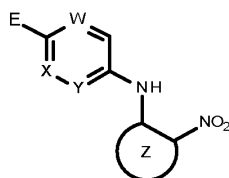
- 15 or a salt thereof, wherein V, W, X and Y are as defined for the compound of formula (I), with a compound of formula (VIII):



(VIII)

or a salt thereof, wherein Z is as defined for the compound of formula (I) and D is halo, such as Cl, Br or I.

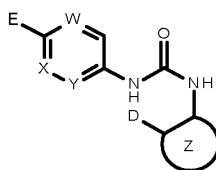
Clause 119. A process for the preparation of a compound of formula (IV), or a salt thereof, which comprises reacting a compound of formula (IX):



(IX)

or a salt thereof, wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as Cl or F, with a carbonylating agent such as triphosgene or carbonyldiimidazole.

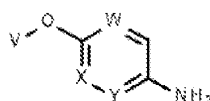
Clause 120. A process for the preparation of a compound of formula (IV), or a salt thereof, which comprises reacting a compound of formula (X):



(X)

or a salt thereof, wherein W, X, Y and Z are as defined for the compound of formula (I), E is halo, such as F or Cl and D is halo, such as Cl, Br or I, under metal catalysed cross-coupling conditions.

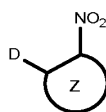
Clause 121. A process for the preparation of a compound of formula (VI), or a salt thereof, which comprises reacting a compound of formula (VII):



(VII)

or a salt thereof, wherein V, W, X and Y are as defined for the compound of formula (I), with a compound of formula (XI):

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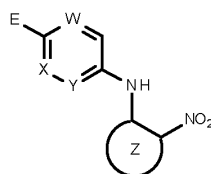


(XI)

or a salt thereof, wherein Z is as defined for the compound of formula (I) and D is halo, such as Cl, Br or I.

Clause 122. A process for the preparation of a compound of formula (IX), or a salt thereof,

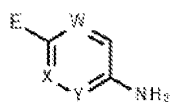
5 which comprises reacting a compound of formula (XII):



(XII)

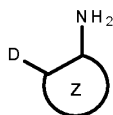
or a salt thereof, wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl, under reduction conditions (e.g. in the presence of Fe powder and ammonium chloride).

10 Clause 123. A process for the preparation of a compound of formula (X), or a salt thereof, which comprises reacting a compound of formula (XIV):



(XIV)

or a salt thereof, wherein W, X and Y are as defined for the compound of formula (I) and E is halo, such as F or Cl, with a compound of formula (VIII):



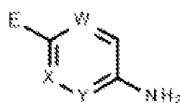
(VIII)

15

or a salt thereof, wherein Z is as defined in clause 1 and D is halo, such as Cl, Br or I.

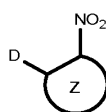
Clause 124. A process for the preparation of a compound of formula (IX), or a salt thereof, which comprises reacting a compound of formula (XIV):

149



(XIV)

or a salt thereof, wherein W, X and Y are as defined for the compound of formula (I) and E is halo, such as F or Cl, with a compound of formula (XI):



(XI)

- 5 or a salt thereof, wherein Z is as defined for the compound of formula (I) and D is halo, such as Cl, Br or I.

References

- 10 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.
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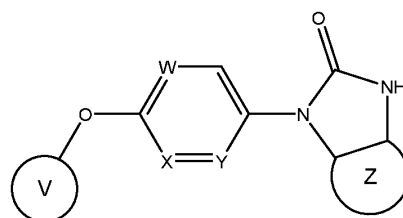
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Claims

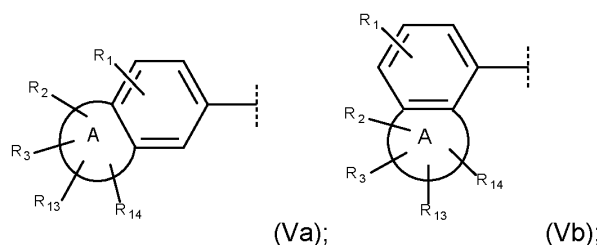
1. A compound of formula (I):



- 5 wherein:

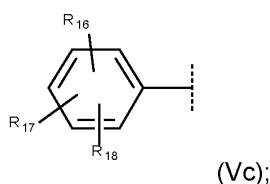
V is group (Va), group (Vb) or group (Vc);

wherein group (Va) and group (Vb) are:



wherein:

- 10 R₁ is H, C₁₋₄alkyl, halo, haloC₁₋₄alkyl, CN, C₁₋₄alkoxy, or haloC₁₋₄alkoxy;
 R₂ is H, C₁₋₄alkyl, C₃₋₅ spiro carbocyclyl, haloC₁₋₄alkyl or halo;
 R₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₃ is absent;
 R₁₃ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₃ is absent;
 R₁₄ is H, C₁₋₄alkyl, haloC₁₋₄alkyl, halo; or R₁₄ is absent;
 15 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;
 wherein R₂ and R₃ may be attached to the same or a different ring atom; R₂ may be attached to a fused ring atom; and wherein R₁₃ and R₁₄ may be attached to the same or a different ring
 20 atom;
 wherein group (Vc) is:



wherein:

R₁₆ is halo, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl, haloC₁₋₄alkoxy or CN;

R₁₇ is H, halo, CN, C₁₋₄alkyl, C₁₋₄alkoxy or haloC₁₋₄alkoxy;

R₁₈ is H, halo, CN, C₁₋₄alkyl or C₁₋₄alkoxy;

W is N or CH;

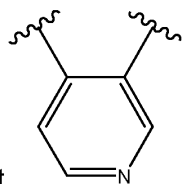
5 X is N or CH;

Y is N or CH;

wherein at least one of W, X and Y is CH, and when one of X and Y is N, the other is CH;

Z is a 5-membered heteroaryl comprising one or two nitrogen atoms, and wherein one of the nitrogen atoms and one of the carbon atoms may be independently optionally substituted by

10 methyl; or Z is a 6-membered heteroaryl comprising one or two nitrogen atoms, wherein one of the carbon atoms may be optionally substituted by methyl; and



provided that Z is not
or a salt and/or solvate and/or derivative thereof.

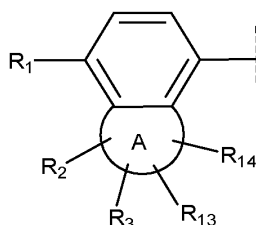
15 2. The pharmaceutically acceptable salt and/or solvate and/or derivative of the compound of formula (I) according to claim 1.

3. The pharmaceutically acceptable salt of the compound of formula (I) according to claim 1.

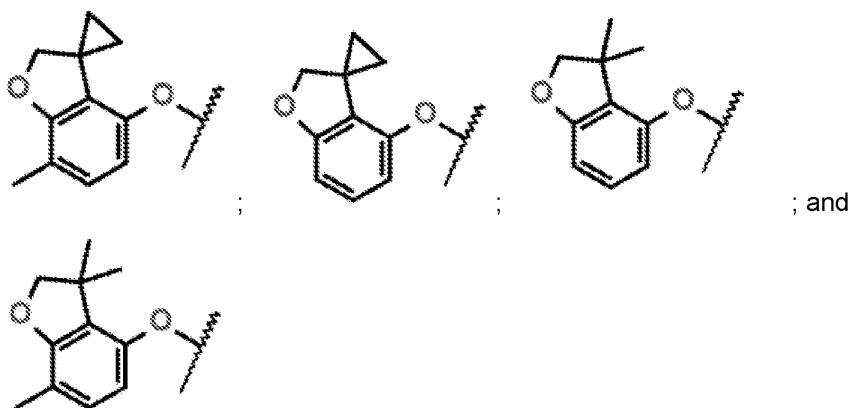
20 4. The pharmaceutically acceptable solvate of the compound of formula (I) according to claim 1.

5. The compound of formula (I) according to claim 1.

25 6. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to any one of claims 1 to 5, wherein V is group (Vb) and wherein (Vb) is:

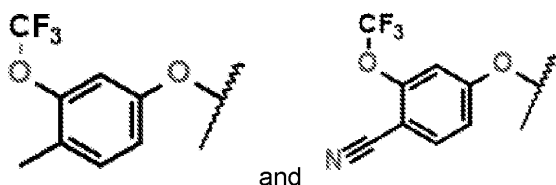


7. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to claim 6, wherein R_1 is H or methyl.
8. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to either claim 6 or 7, wherein R_2 is C_3 spiro carbocycle.
9. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to either claim 6 or 7, wherein R_2 is methyl and R_3 is methyl.
10. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to any one of claims 1 to 6, wherein V is selected from the group consisting of:



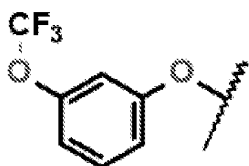
11. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to any one of claims 1 to 5, wherein V is group (Vc).
12. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to claim 11, wherein R_{16} is methyl, ethyl, propyl, butyl, cyclopropyl, chloro, fluoro, methoxy, ethoxy, propoxy, trifluoromethyl, trifluoromethoxy or CN, in particular R_{16} is trifluoromethoxy or methoxy, and R_{17} is methyl, ethyl, propyl, butyl, cyclopropyl, chloro, fluoro, methoxy, ethoxy, propoxy, trifluoromethoxy or CN, in particular R_{17} is H or methyl or CN.
13. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to claim 11, wherein R_{17} is H and R_{18} is H.
14. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to clause 13, wherein R_{16} is at the meta-position.

15. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to claim 11, wherein V is selected from the group consisting of:



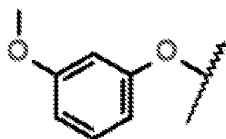
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16. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to claim 11, wherein V is:



17. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to claim 11, wherein V is:

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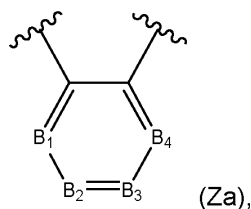
18. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to any one of claims 1 to 17, wherein W is N, and X and Y are CH.

15

19. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to any one of claims 1 to 17, wherein W is N, X is N and Y is CH.

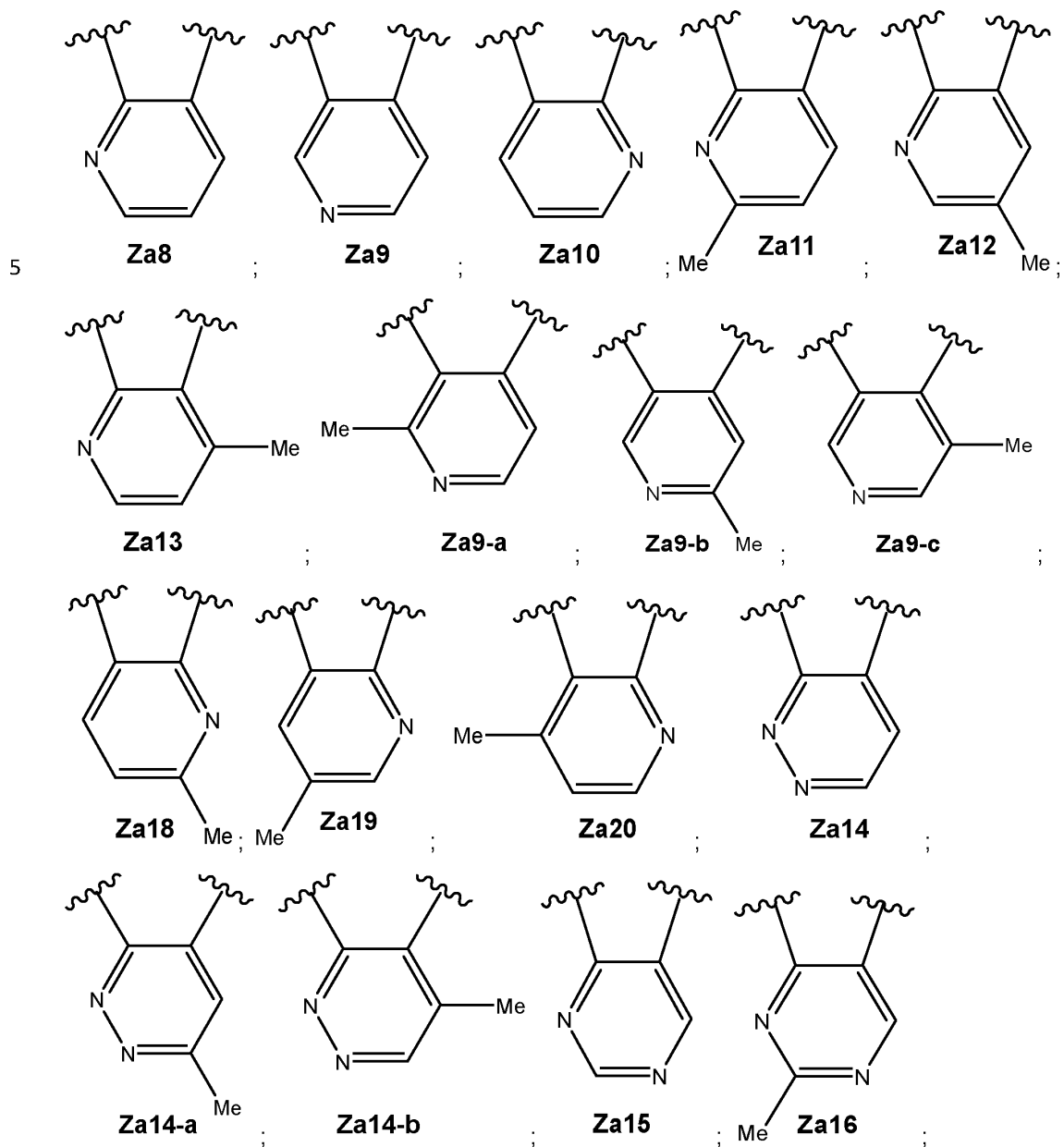
20. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to any one of claims 1 to 19, wherein Z is group (Za):

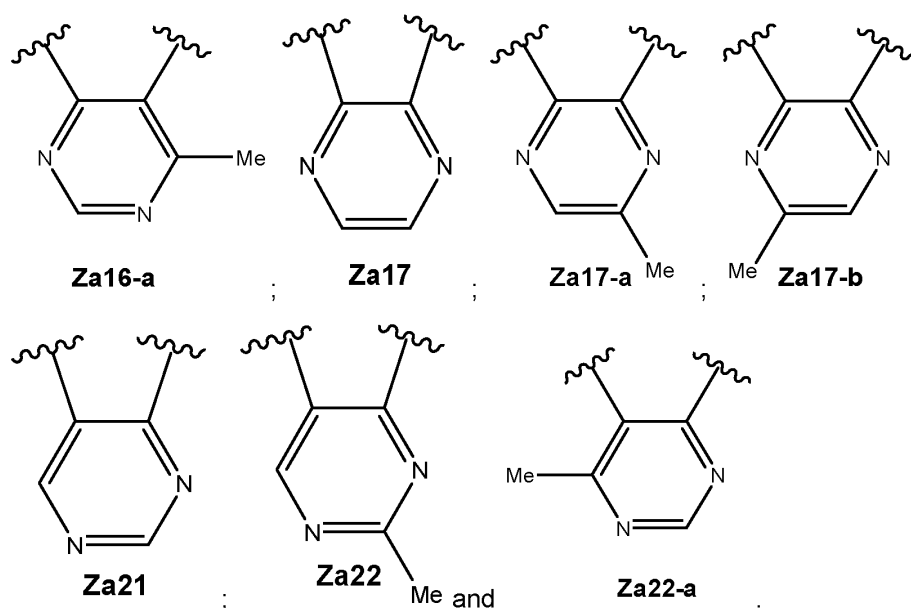
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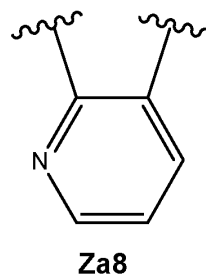
wherein:

B₁, B₂, B₃ and B₄ are each independently selected from N, CH and C(Me);
 wherein one or two of B₁, B₂, B₃ and B₄ are N, and only one of B₁, B₂, B₃ and B₄ may be C(Me);
 and wherein when B₁, B₂ and B₄ are CH or C(Me), B₃ is not N;
 and wherein (Za) is selected from the group consisting of:

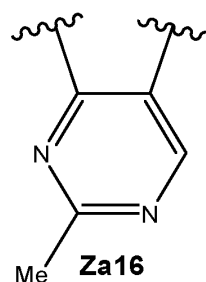




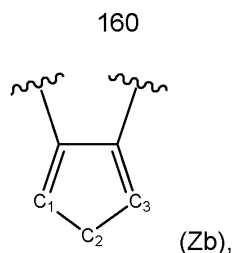
21. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to claim 20, wherein (Za) is:



22. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to claim 20, wherein (Za) is:



23. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according to any one of claims 1 to 19, wherein Z is group (Zb):

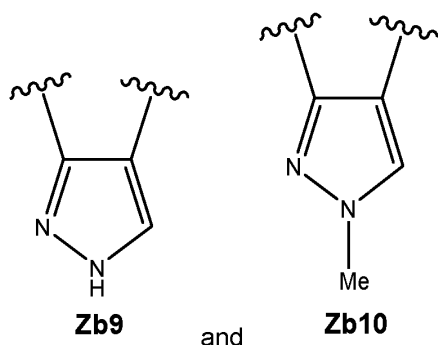


wherein:

C₁ and C₃ are each independently selected from CH, C(Me) and N;

C₂ is NH or N(Me); and wherein when one of C₁ and C₃ is N, the other is CH or C(Me);

5 suitably wherein Zb is selected from the group consisting of:

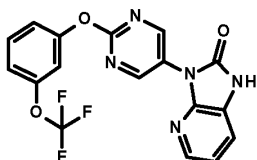


24. The compound claim 5, which is selected from the group consisting of:
- 3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-
- 10 b]pyridin-2-one;
- 7-methyl-3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-
- imidazo[4,5-b]pyridin-2-one;
- 3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;
- 15 7-methyl-3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-1H-imidazo[4,5-
- b]pyridin-2-one;
- 3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-2-pyridyl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazin-2-yl)-1H-imidazo[4,5-b]pyridin-2-
- 20 one;
- 3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[5-[3-(trifluoromethoxy)phenoxy]pyrazin-2-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-1H-imidazo[4,5-
- b]pyridin-2-one;
- 25 3-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-1H-imidazo[4,5-b]pyridin-2-one;

- 3-(2-{2H-spiro[1-benzofuran-3,1'-cyclopropane]oxy}pyrimidin-5-yl)-1H,2H,3H-imidazo[4,5-b]pyridin-2-one;
- 4-[[5-(2-oxo-1H-imidazo[4,5-b]pyridin-3-yl)-2-pyridyl]oxy]-2-(trifluoromethoxy)benzonitrile;
- 7-methyl-3-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrimidin-5-yl)-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[2-(3-methoxyphenoxy)pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 2-methyl-6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-4H-imidazo[4,5-c]pyrazol-5-one;
- 2-methyl-6-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-4H-imidazo[4,5-c]pyrazol-5-one;
- 6-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-2-methyl-4H-imidazo[4,5-c]pyrazol-5-one;
- 2-methyl-6-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-4H-imidazo[4,5-c]pyrazol-5-one;
- 2-methyl-6-(2-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrimidin-5-yl)-4H-imidazo[4,5-c]pyrazol-5-one;
- 3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-c]pyridin-2-one;
- 2-methyl-9-[6-[3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one;
- 2-methyl-9-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-7H-purin-8-one;
- 2-methyl-9-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-7H-purin-8-one;
- 2-methyl-9-[6-[4-methyl-3-(trifluoromethoxy)phenoxy]-3-pyridyl]-7H-purin-8-one;
- 9-[6-(3-methoxyphenoxy)-3-pyridyl]-2-methyl-7H-purin-8-one;
- 9-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-7H-purin-8-one;
- 9-[6-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]-3-pyridyl]-2-methyl-7H-purin-8-one;
- 3-[2-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy]pyrimidin-5-yl)-1H-imidazo[4,5-b]pyridine-2-one;
- 3-[2-[4-methyl-3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 3-[2-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one;
- 6-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-2,4-dihydroimidazo[4,5-c]pyrazol-5-one;
- 3-[6-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-3-pyridyl]-1H-imidazo[4,5-c]pyridin-2-one;
- 1-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)-3H-imidazo[4,5-b]pyridin-2-one;
- 5-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-1H-imidazo[4,5-b]pyridin-2-one;

6-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy)pyrazin-2-yl)-1H-imidazo[4,5-b]pyridin-2-one; and
 3-[2-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one.

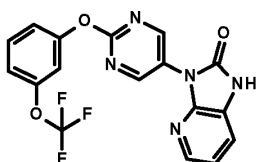
- 5 25. 3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one:



, or a salt and/or solvate thereof.

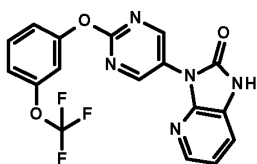
26. 3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one:

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27. A pharmaceutically acceptable salt of 3-[2-[3-(trifluoromethoxy)phenoxy]pyrimidin-5-yl]-1H-imidazo[4,5-b]pyridin-2-one:

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28. The derivative according to any one of claims 1 or 6 to 23, functionalised at the secondary nitrogen of the urea with a group L, wherein L is selected from:

- 20 -PO(OH)O⁻ • M⁺, wherein M⁺ is a pharmaceutically acceptable monovalent counterion,
 -PO(O⁻)₂ • 2M⁺,
 -PO(O⁻)₂ • D²⁺, wherein D²⁺ is a pharmaceutically acceptable divalent counterion,
 -CH(R^X)-PO(OH)O⁻ • M⁺, wherein R^X is hydrogen or C₁₋₃ alkyl,
 -CH(R^X)-PO(O⁻)₂ • 2M⁺,

$-\text{CH}(\text{R}^X)-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, and
 $-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2 \cdot \text{M}^+$.

29. The compound, salt thereof and/or solvate thereof, and/or derivative thereof according
5 to any one of claims 1 to 28 for use as a medicament.

30. Use of a compound, salt thereof and/or solvate thereof, and/or derivative thereof
according to any one of claims 1 to 28 in the manufacture of a medicament.

10 31. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use
according to any one of claims 1 to 30 for use in the treatment or prophylaxis of progressive
myoclonic epilepsy.

32. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use
15 according to claim 31 for use in the treatment or prophylaxis of progressive myoclonic epilepsy.

33. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use
according to claim 31 for use in the treatment or prophylaxis of juvenile progressive myoclonic
epilepsy.

20

34. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use
according to any one of claims 1 to 33 for use in a human.

35. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use
25 according to claim 34, for use in a human of less than 18 years of age.

36. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use
according to claim 35, for use in a human 4 to 17 years old.

30 37. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use
according to claim 34, for use in a human aged 18 to 65.

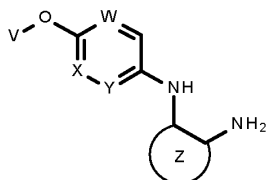
38. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use
according to claim 34, for use in a human aged 66 years old or older.

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39. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use
according to any one of claims 29 to 38, for administration at 5 to 250 mg per day.

40. The compound, salt thereof and/or solvate thereof, and/or derivative thereof or use according to any one of claims 29 to 39, for administration for a period of at least three months.

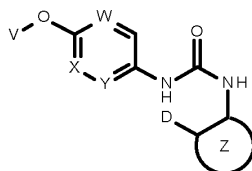
- 5 41. A compound or salt thereof selected from the group consisting of:
- a compound of formula (II):



(II)

wherein V, W, X, Y and Z, B₁, B₂, B₃ and B₄ are as defined for the compound of formula (I);

- a compound of formula (III):

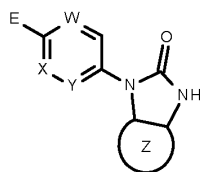


(III)

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wherein V, W, X, Y and Z are as defined for the compound of formula (I) and D is halo, such as Cl, Br or I;

- a compound of formula (IV):

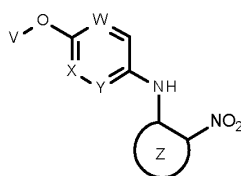


(IV)

- 15 wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl;

- a compound of formula (VI):

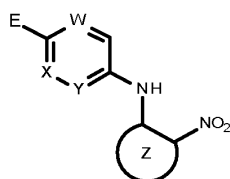
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(VI)

wherein V, W, X, Y and Z are as defined for the compound of formula (I);

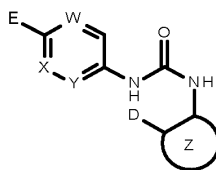
- a compound of formula (IX):



(IX)

- 5 wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl;

- a compound of formula (X):

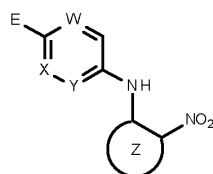


(X)

wherein W, X, Y and Z are as defined for the compound of formula (I), E is halo, such as F or Cl

- 10 and D is halo, such as Cl, Br or I; and

- a compound of formula (XIII):



(XIII)

wherein W, X, Y and Z are as defined for the compound of formula (I) and E is halo, such as F or Cl;

- 15 or a salt thereof, such as a pharmaceutically acceptable salt thereof.